CHEM 231: ORGANIC CHEMISTRY I TEXTBOOK



Sol Parajon Puenzo
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CHEM 231: Organic Chemistry I Textbook

Sol Parajon Puenzo

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Glossary

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1: STRUCTURE AND BONDING

Chapter Objectives

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

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

1.0: Why This Chapter?

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1.0: Why This Chapter?

We'll ease into the study of organic chemistry by first reviewing some ideas about atoms, bonds, and molecular geometry that you may recall from your general chemistry course. Much of the material in this chapter and the next is likely to be familiar to you, but it's nevertheless a good idea to make sure you understand it before moving on.

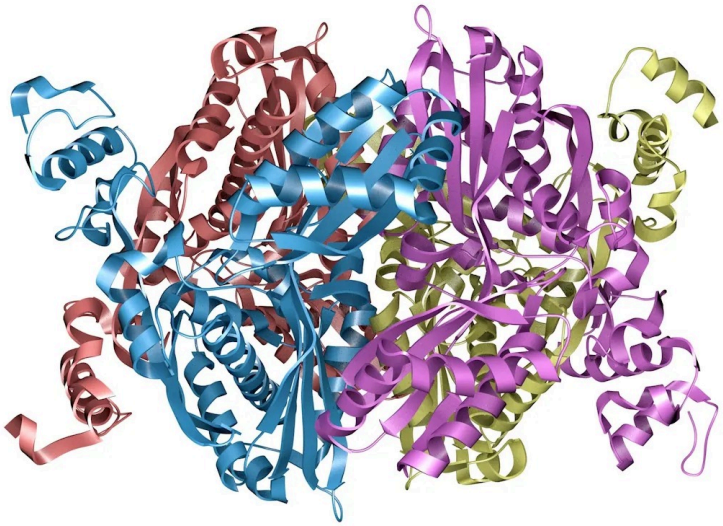
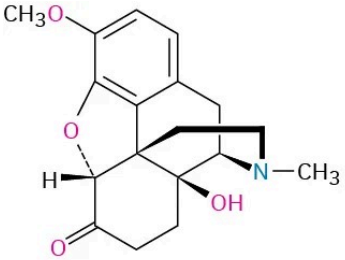
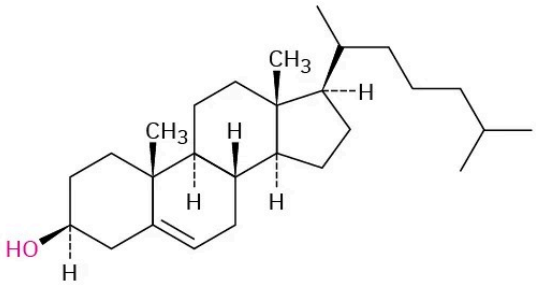


Figure 1.0.1: The enzyme HMG–CoA reductase, shown here as a so-called ribbon model, catalyzes a crucial step in the body's synthesis of cholesterol. Understanding how this enzyme functions has led to the development of drugs credited with saving millions of lives. (credit: image from the RCSB PDB (rcsb.org) of PBD ID 1HW9 (E.S. Istvan, J. Deisenhofer) (2001) Structural mechanism for statin inhibition of HMG-CoA reductase *Science* 292: 1160–1164/RCSB PDB, CC BY 1.0)

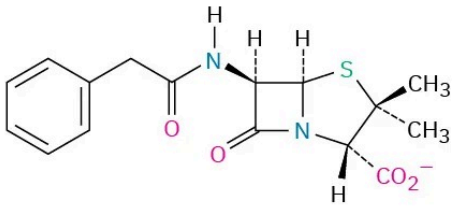
What is organic chemistry, and why should you study it? The answers to these questions are all around you. Every living organism is made of organic chemicals. The proteins that make up your hair, skin, and muscles; the DNA that controls your genetic heritage; the foods that nourish you; and the medicines that heal you are all organic chemicals. Anyone with a curiosity about life and living things, and anyone who wants to be a part of the remarkable advances taking place in medicine and the biological sciences, must first understand organic chemistry. Look at the following drawings for instance, which show the chemical structures of some molecules whose names might be familiar to you. Although the drawings may appear unintelligible at this point, don't worry. They'll make perfectly good sense before long, and you'll soon be drawing similar structures for any substance you're interested in.



Oxycodone (OxyContin)



Cholesterol



Benzylpenicillin

Historically, the term *organic chemistry* dates to the mid-1700s, when it was used to mean the chemistry of substances found in living organisms. Little was known about chemistry at that time, and the behavior of the "organic" substances isolated from plants and animals seemed different from that of the "inorganic" substances found in minerals. Organic compounds were generally low-melting solids and were usually more difficult to isolate, purify, and work with than high-melting inorganic compounds.

By the mid-1800s, however, it was clear that there was no fundamental difference between organic and inorganic compounds.

The only distinguishing characteristic of organic compounds is that all contain the element carbon.

Organic chemistry, then, is the study of carbon compounds. But why is carbon special? Why, of the more than 197 million presently known chemical compounds, do almost all of them contain carbon? The answers to these questions come from carbon's electronic structure and its consequent position in the periodic table (Figure 1.0.2). As a group 4A element, carbon can share four valence electrons and form four strong covalent bonds. Furthermore, carbon atoms can bond to one another, forming long chains and rings. Carbon, alone of all elements, is able to form an immense diversity of compounds, from the simple methane, with one carbon atom, to the staggeringly complex DNA, which can have more than *100 million* carbons.

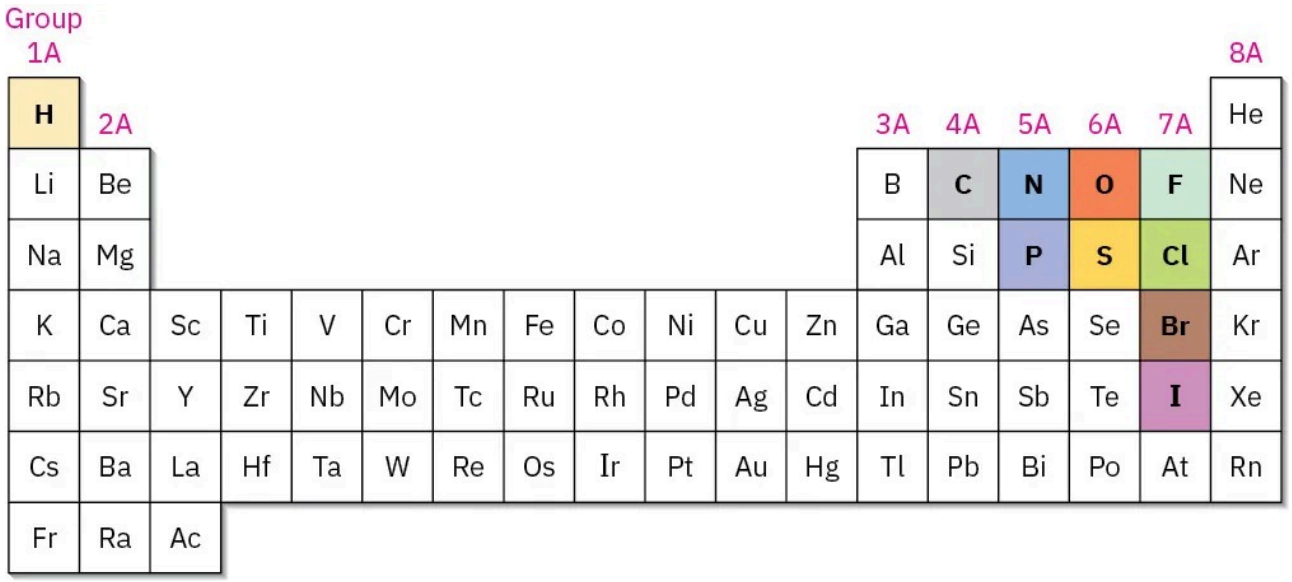


Figure 1.0.2: Carbon, hydrogen, and other elements commonly found in organic compounds are shown in the colors typically used to represent them.

Not all carbon compounds are derived from living organisms, however. Modern chemists have developed a remarkably sophisticated ability to design and synthesize new organic compounds in the laboratory—medicines, dyes, polymers, and a host of other substances. Organic chemistry touches the lives of everyone. Its study can be a fascinating undertaking.

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1.1: Atomic Structure - The Nucleus

As you might remember from your general chemistry course, an atom consists of a dense, positively charged nucleus surrounded at a relatively large distance by negatively charged electrons (Figure 1.1.1). The nucleus consists of subatomic particles called *neutrons*, which are electrically neutral, and *protons*, which are positively charged. Because an atom is neutral overall, the number of positive protons in the nucleus and the number of negative electrons surrounding the nucleus are the same.

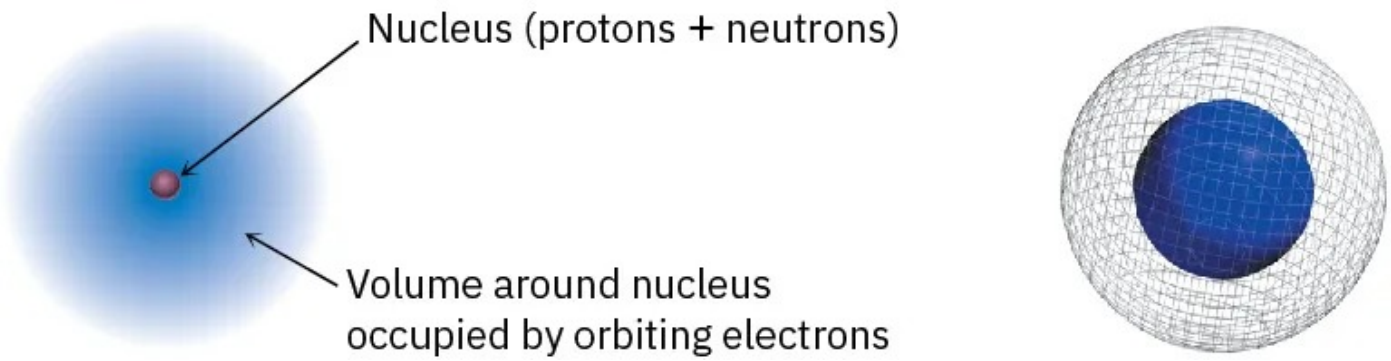


Figure 1.1.1: A schematic view of an atom. The dense, positively charged nucleus contains most of the atom's mass and is surrounded by negatively charged electrons. The three-dimensional view on the right shows calculated electron-density surfaces. Electron density increases steadily toward the nucleus and is 40 times greater at the **blue solid surface** than at the **gray mesh surface**.

Although extremely small—about 10^{-14} to 10^{-15} meter (m) in diameter—the nucleus nevertheless contains essentially all the mass of the atom. Electrons have negligible mass and circulate around the nucleus at a distance of approximately 10^{-10} m. Thus, the diameter of a typical atom is about 2×10^{-10} m, or 200 picometers (pm), where 1 pm = 10^{-12} m. To give you an idea of how small this is, a thin pencil line is about 3 million carbon atoms wide. Although most chemists throughout the world use the International System (SI) of units and describe small distances in picometers, many organic chemists and biochemists in the United States still use the unit angstrom (Å) to express atomic distances, where 1 Å = 100 pm = 10^{-10} m. As you probably did in your general chemistry course, however, we'll stay with SI units in this book.

A specific atom is described by its atomic number (*Z*), which gives the number of protons (or electrons) it contains, and its mass number (*A*), which gives the total number of protons and neutrons in its nucleus. All the atoms of a given element have the same atomic number: 1 for hydrogen, 6 for carbon, 15 for phosphorus, and so on; but they can have different mass numbers depending on how many neutrons they contain. Atoms with the same atomic number but different mass numbers are called isotopes. The element carbon, for instance, has three isotopes that occur naturally, with mass numbers of 12, 13, and 14. Carbon-12 has a natural abundance of 98.89%, carbon-13 has a natural abundance of 1.11%, and carbon-14 has only a negligible natural abundance.

The weighted-average of an element's naturally occurring isotopes is called **atomic weight** and is given in unified atomic mass units (u) or daltons (Da) where 1 u or 1 Da is defined as one twelfth the mass of one atom of carbon-12. Thus, the atomic weight is 1.008 u for hydrogen, 12.011 u for carbon, 30.974 u for phosphorus, and so on. Atomic weights of all elements are given in the periodic table in Appendix D.

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1.2: Atomic Structure - Orbitals

How are the electrons distributed in an atom? You might recall from your general chemistry course that, according to the *quantum mechanical model*, the behavior of a specific electron in an atom can be described by a mathematical expression called a *wave equation*—the same type of expression used to describe the motion of waves in a fluid. The solution to a wave equation is called a *wave function*, or orbital, and is denoted by the lowercase Greek letter psi (ψ).

When the square of the wave function, ψ^2, is plotted in three-dimensional space, an orbital describes the volume of space around a nucleus that an electron is most likely to occupy. You might therefore think of an orbital as looking like a photograph of the electron taken at a slow shutter speed. In such a photo, the orbital would appear as a blurry cloud, indicating the region of space where the electron has been. This electron cloud doesn't have a sharp boundary, but for practical purposes we can set the limits by saying that an orbital represents the space where an electron spends 90% to 95% of its time.

What do orbitals look like? There are four different kinds of orbitals, denoted *s, p, d,* and *f,* each with a different shape. Of the four, we'll be concerned primarily with *s* and *p* orbitals because these are the most common in organic and biological chemistry. An *s* orbital has a spherical shape, with the nucleus at its center; a *p* orbital has a dumbbell shape with two parts, or *lobes*; and four of the five *d* orbitals have a cloverleaf shape with four lobes, as shown in Figure 1.2.1. The fifth *d* orbital is shaped like an elongated dumbbell with a doughnut around its middle.

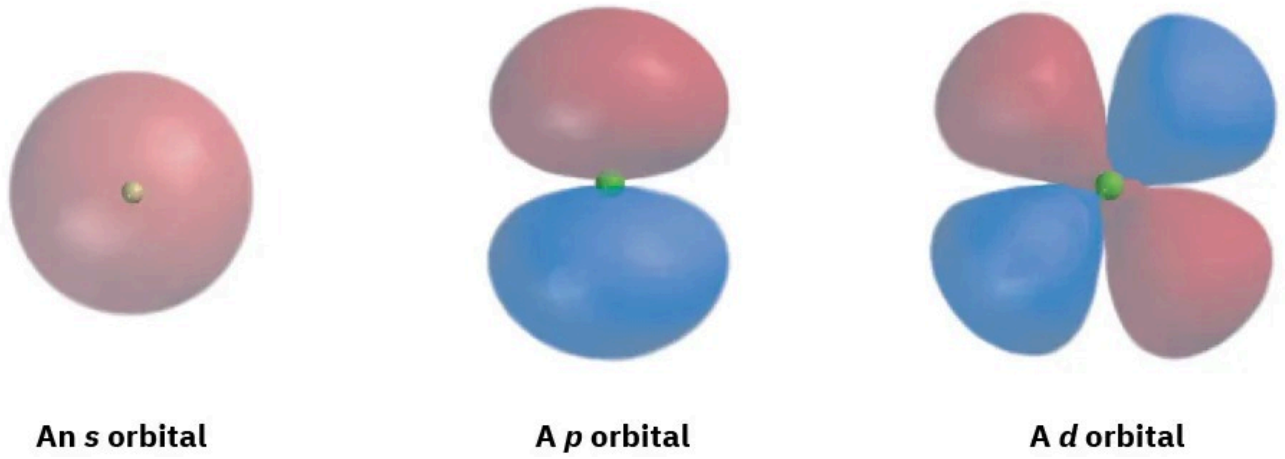


Figure 1.2.1: Representations of *s, p,* and *d* orbitals. An *s* orbital is spherical, a *p* orbital is dumbbell-shaped, and four of the five *d* orbitals are cloverleaf-shaped. Different lobes of p orbitals are often drawn for convenience as teardrops, but their actual shape is more like that of a doorknob, as indicated.

The orbitals in an atom are organized into different layers around the nucleus called electron shells, which are centered around the nucleus and have successively larger size and energy. Different shells contain different numbers and kinds of orbitals, and each orbital within a shell can be occupied by two electrons. The first shell contains only a single *s* orbital, denoted 1*s*, and thus holds only 2 electrons. The second shell contains one 2*s* orbital and three 2*p* orbitals and thus holds a total of 8 electrons. The third shell contains a 3*s* orbital, three 3*p* orbitals, and five 3*d* orbitals, for a total capacity of 18 electrons. These orbital groupings and their energy levels are shown in Figure 1.2.2.

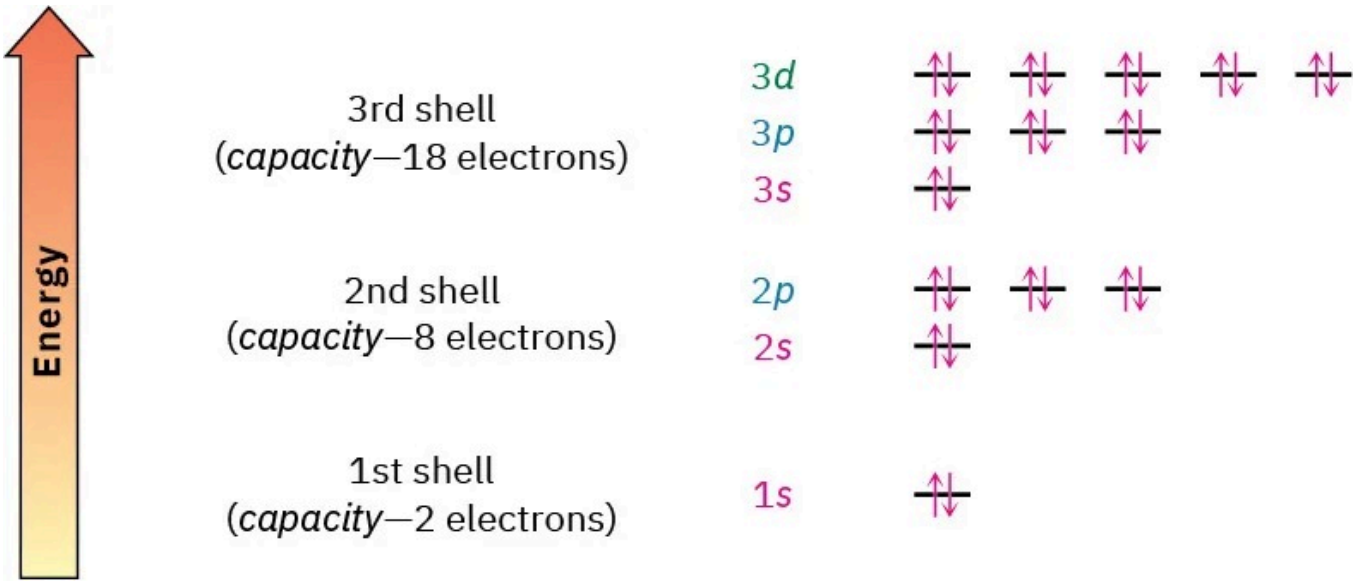


Figure 1.2.2: Energy levels of electrons in an atom. The first shell holds a maximum of 2 electrons in one **1s** orbital; the second shell holds a maximum of 8 electrons in one **2s** and three ***2p*** orbitals; the third shell holds a maximum of 18 electrons in one **3s**, three ***3p***, and ***3d*** orbitals; and so on. The two electrons in each orbital are represented by five up and down arrows, ⇅. Although not shown, the energy level of the **4s** orbital falls between ***3p*** and ***3d***.

The three different *p* orbitals within a given shell are oriented in space along mutually perpendicular directions, denoted p_x, p_y, and p_z. As shown in Figure 1.2.3, the two lobes of each *p* orbital are separated by a region of zero electron density called a node. Furthermore, the two orbital regions separated by the node have different algebraic signs, + and –, in the wave function, as represented by the different colors in Figure 1.2.1 and Figure 1.2.3. As we'll see in **Section 1.12**, these algebraic signs for different orbital lobes have important consequences with respect to chemical bonding and chemical reactivity.

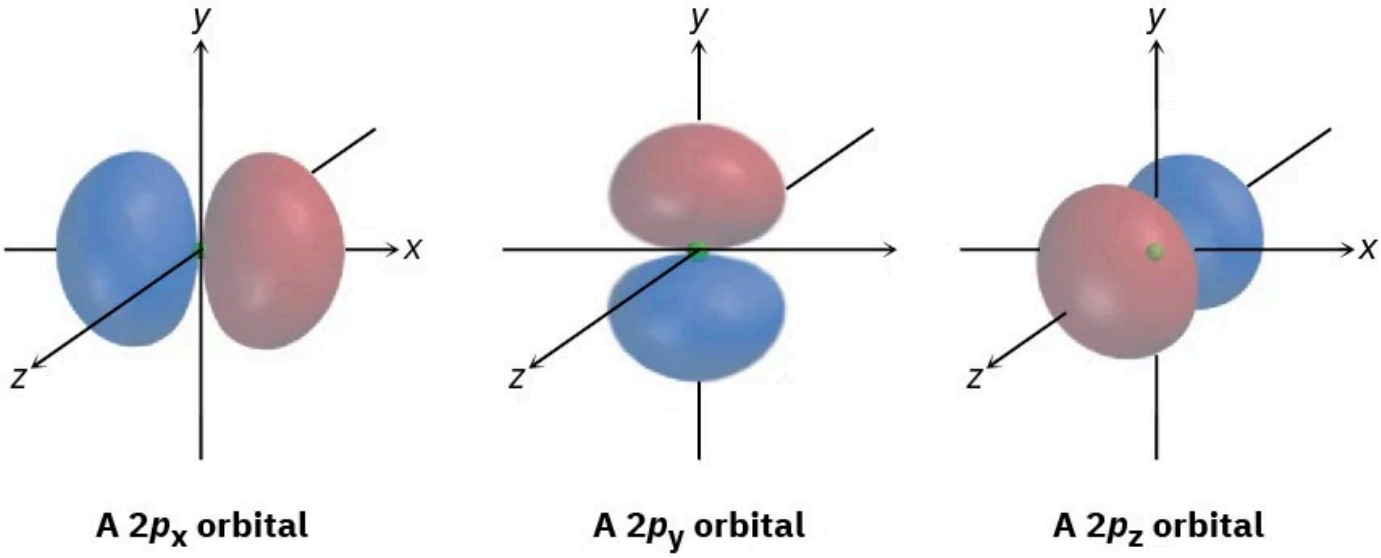


Figure 1.2.3: Shapes of the 2*p* orbitals. Each of the three mutually perpendicular, dumbbell-shaped orbitals has two lobes separated by a node. The two lobes have different algebraic signs in the corresponding wave function, as indicated by the different colors.

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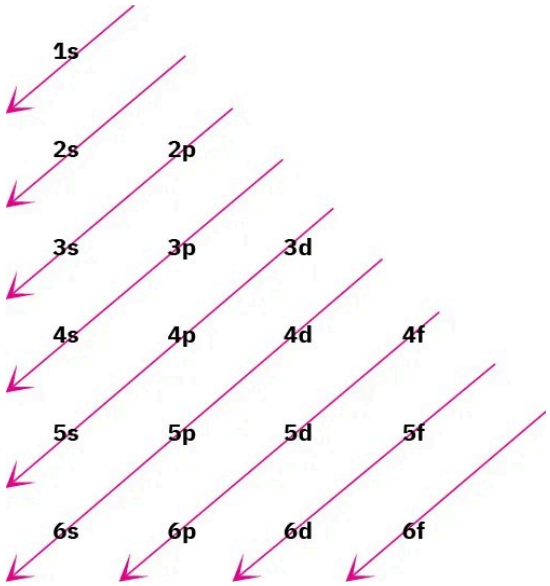
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1.3: Atomic Structure - Electron Configurations

The lowest-energy arrangement, or ground-state electron configuration, of an atom is a list of the orbitals occupied by its electrons. We can predict this arrangement by following three rules.

RULE 1

The lowest-energy orbitals fill up first, $1s \rightarrow 2s \rightarrow 2p \rightarrow 3s \rightarrow 3p \rightarrow 4s \rightarrow$3d, according to the following graphic, a statement called the *Aufbau principle*. Note that the 4s orbital lies between the 3*p* and 3*d* orbitals in energy.



RULE 2

Electrons act in some ways as if they were spinning around an axis, somewhat as the earth spins. This spin can have two orientations, denoted as up (↑) and down (↓). Only two electrons can occupy an orbital, and they must have opposite spins, a statement called the *Pauli exclusion principle*.

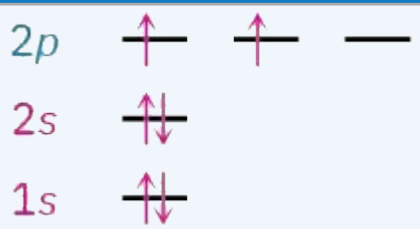
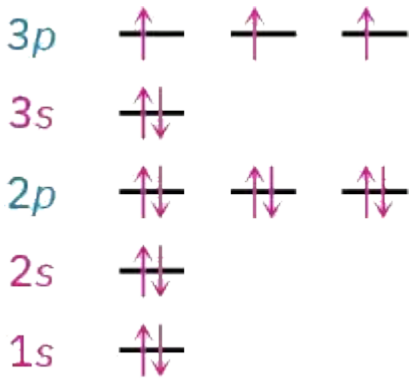
RULE 3

If two or more empty orbitals of equal energy are available, one electron occupies each with spins parallel until all orbitals are half-full, a statement called *Hund's rule*.

Some examples of how these rules apply are shown in Table 1.3.1. Hydrogen, for instance, has only one electron, which must occupy the lowest-energy orbital. Thus, hydrogen has a 1s ground-state configuration. Carbon has six electrons and the ground-state configuration $1s^2 2s^2 2p_x^1 2p_y^1$, and so forth. Note that a superscript is used to represent the number of electrons in a particular orbital.

Table 1.3.1: Ground-State Electron Configurations of Some Elements

Element	Atomic number	Configuration
Hydrogen	1	1s ↑

Element	Atomic number	Configuration
Carbon	6	
Phosphorus	15	

Exercise 1.3.1

What is the ground-state electron configuration of each of the following elements:

a. Oxygen
b. Nitrogen
c. Sulfur

Answer available at the end of this section.

Exercise 1.3.2

How many electrons does each of the following biological trace elements have in its outermost electron shell?

a. Magnesium
b. Cobalt
c. Selenium

Answer available at the end of this section.

Answers

Exercise 1.3.1

a. $1s^2\ 2s^2\ 2p^4$
b. $1s^2\ 2s^2\ 2p^3$
c. $1s^2\ 2s^2\ 2p^6\ 3s^2\ 3p^4$

Exercise 1.3.2

a. 2
b. 2
c. 6

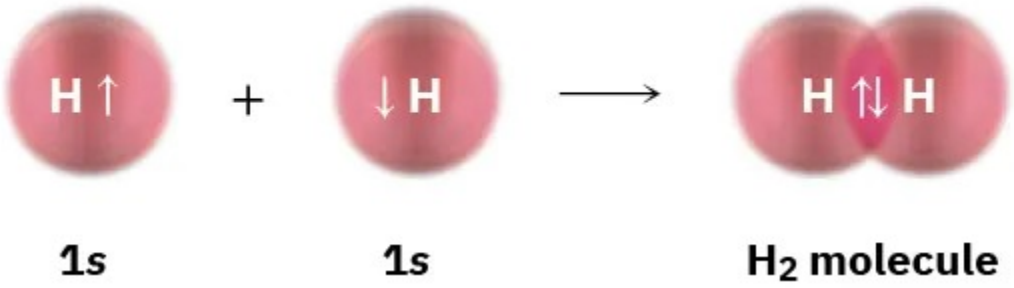
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1.4: Describing Chemical Bonds - Valence Bond Theory

How does electron sharing lead to bonding between atoms? Two models have been developed to describe covalent bonding: *valence bond theory* and *molecular orbital theory*. Each model has its strengths and weaknesses, and chemists tend to use them interchangeably depending on the circumstances. Valence bond theory is the more easily visualized of the two, so most of the descriptions we'll use in this book derive from that approach.

According to valence bond (VB) theory, a covalent bond forms when two atoms approach each other closely and a singly occupied orbital on one atom *overlaps* a singly occupied orbital on the other atom. The electrons are now paired in the overlapping orbitals and are attracted to the nuclei of both atoms, thus bonding the atoms together. In the H_2 molecule, for instance, the H–H bond results from the overlap of two singly occupied hydrogen 1s orbitals.



The overlapping orbitals in the H_2 molecule have the elongated egg shape we might get by pressing two spheres together. If a plane were to pass through the middle of the bond, the intersection of the plane and the overlapping orbitals would be a circle. In other words, the H–H bond is cylindrically symmetrical, as shown in Figure 1.4.1. Such bonds, which are formed by the head-on overlap of two atomic orbitals along a line drawn between the nuclei, are called sigma (σ) bonds.

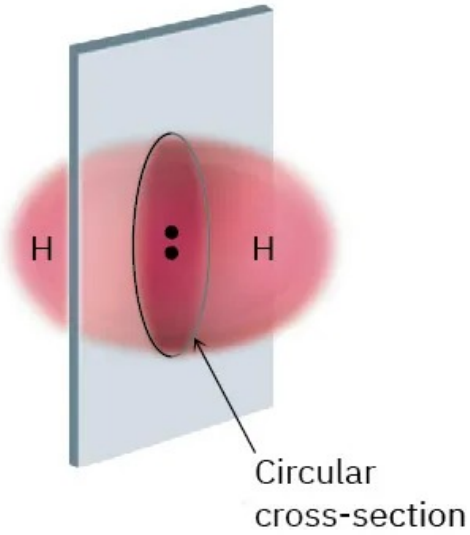


Figure 1.4.1: The cylindrical symmetry of the H–H σ bond in an H_2 molecule. The intersection of a plane cutting through the σ bond is a circle.

During the bond-forming reaction 2H• ⟶ H2, 436 kJ/mol (104 kcal/mol) of energy is released. Because the product H_2 molecule has 436 kJ/mol less energy than the starting 2 H• atoms, the product is more stable than the reactant and we say that the H–H bond has a bond strength of 436 kJ/mol. In other words, we would have to put 436 kJ/mol of energy into the H–H bond to break the H_2 molecule apart into two H atoms (Figure 1.4.2). For convenience, we'll generally give energies in both kilocalories (kcal) and the SI unit kilojoules (kJ): 1 kJ = 0.2390 kcal; 1 kcal = 4.184 kJ.

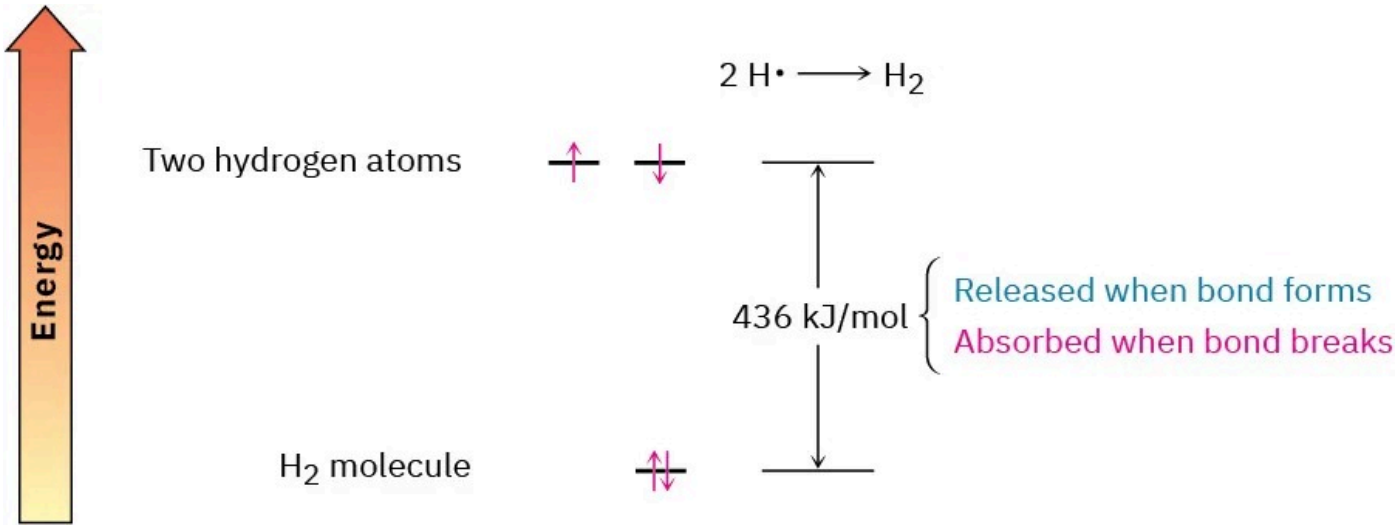


Figure 1.4.2: Relative energy levels of two H atoms and the H_2 molecule. The H_2 molecule has 436 kJ/mol (104 kcal/mol) less energy than the two separate H atoms, so 436 kJ/mol of energy is **released when the H–H bond forms**. Conversely, 436 kJ/mol is **absorbed when the H–H bond breaks**.

How close are the two nuclei in the H_2 molecule? If they are too close, they will repel each other because both are positively charged. Yet if they're too far apart, they won't be able to share the bonding electrons. Thus, there is an optimum distance between nuclei that leads to maximum stability (Figure 1.4.3). Called the bond length, this distance is 74 pm in the H–H molecule. Every covalent bond has both a characteristic bond strength and bond length.

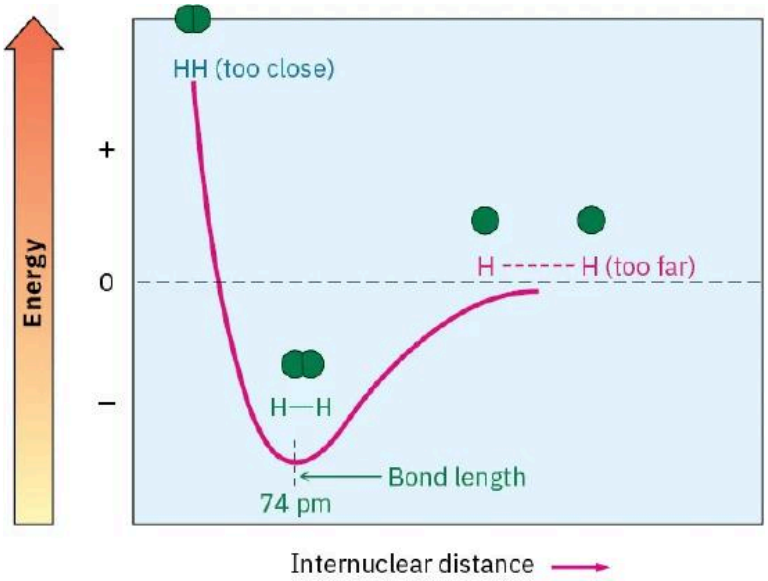


Figure 1.4.3: A plot of energy versus internuclear distance for two hydrogen atoms. The distance between nuclei at the minimum energy point is the **bond length.**

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1.5: Development of Chemical Bonding Theory

By the mid-1800s, the new science of chemistry was developing rapidly, especially in Europe, and chemists had begun to probe the forces holding compounds together. In 1858, the German chemist August Kekulé and the Scottish chemist Archibald Couper independently proposed that, in all organic compounds, carbon is *tetravalent*—it always forms four bonds when it joins other elements to form stable compounds. Furthermore, said Kekulé, carbon atoms can bond to one another to form extended chains of linked atoms. In 1865, Kekulé provided another major advance when he suggested that carbon chains can double back on themselves to form *rings* of atoms.

Although Kekulé and Couper were correct in describing the tetravalent nature of carbon, chemistry was still viewed in a two-dimensional way until 1874. In that year, the Dutch chemist Jacobus van 't Hoff and French chemist Joseph Le Bel added a third dimension to our ideas about organic compounds when they proposed that the four bonds of carbon are not oriented randomly but have specific spatial directions. Van't Hoff went even further and suggested that the four atoms to which carbon is bonded sit at the corners of a regular tetrahedron, with carbon in the center.

A representation of a tetrahedral carbon atom is shown in Figure 1.5.1. Note the conventions used to show three-dimensionality: solid lines represent bonds in the plane of the page, the heavy wedged line represents a bond coming out of the page toward the viewer, and the dashed line represents a bond receding back behind the page, away from the viewer. Get used to them; these representations will be used throughout the text.

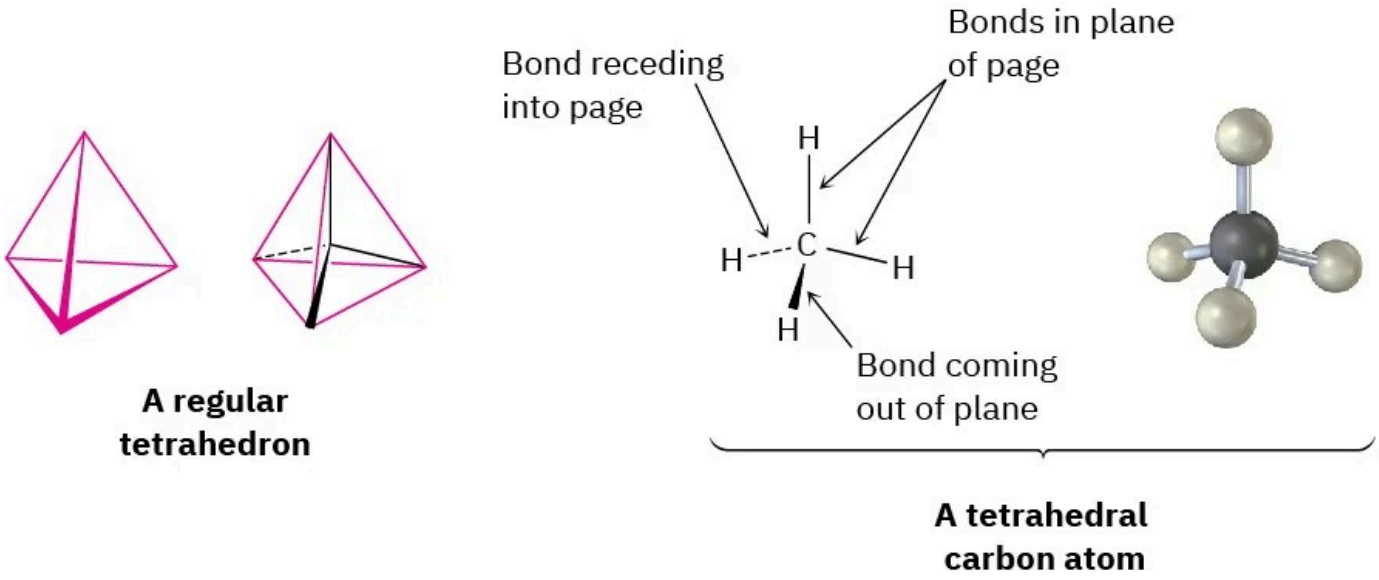


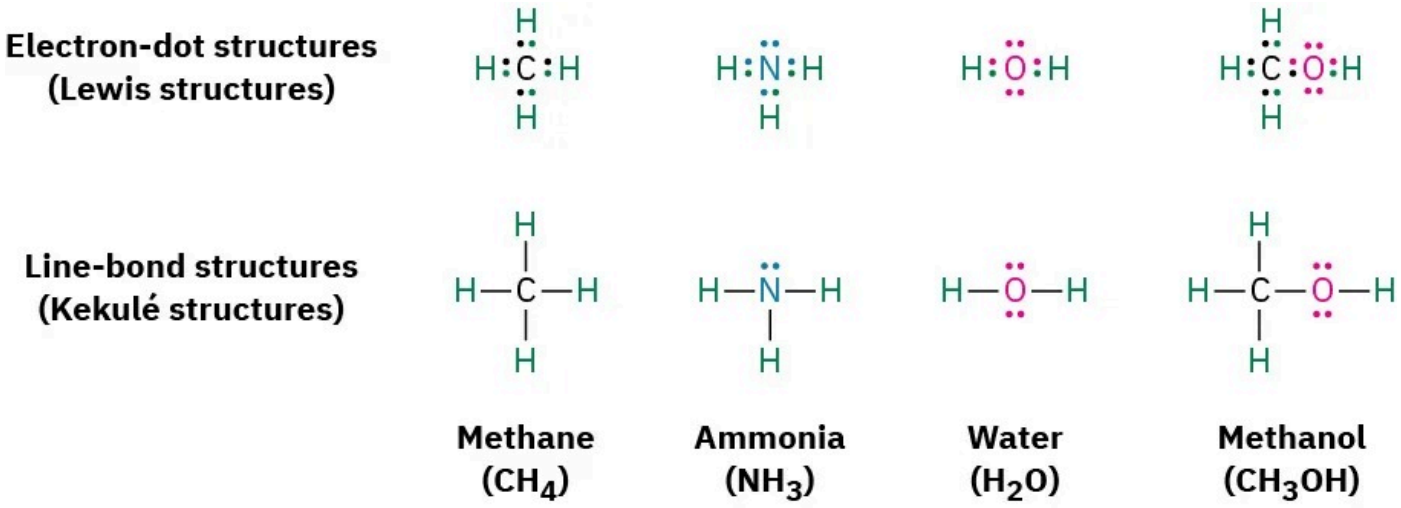
Figure 1.5.1: A representation of van't Hoff's tetrahedral carbon atom. The solid lines represent bonds in the plane of the paper, the heavy wedged line represents a bond coming out of the plane of the page toward the viewer, and the dashed line represents a bond going back behind the plane of the page away from the viewer.

Why, though, do atoms bond together, and how can chemical bonds be described electronically? The *why* question is relatively easy to answer: atoms bond together because the compound that results is more stable and lower in energy than the separate atoms. Energy—usually as heat—is always released and flows out of the chemical system when a bond forms. Conversely, energy is added to the chemical system when a bond breaks. Making bonds always releases energy, and breaking bonds always absorbs energy. The *how* question is more difficult. To answer it, we need to know more about the electronic properties of atoms.

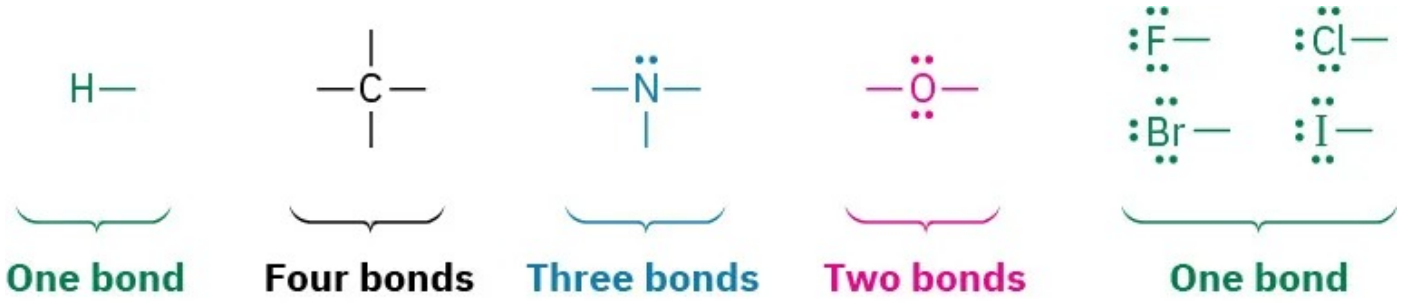
We know through observation that eight electrons (an electron *octet*) in an atom's outermost shell, or valence shell, impart special stability to the noble-gas elements in group 8A of the periodic table: Ne (2 + 8); Ar (2 + 8 + 8); Kr (2 + 8 + 18 + 8). We also know that the chemistry of the main-group elements on the left and right sides of the periodic table is governed by their tendency to take on the electron configuration of the nearest noble gas. The alkali metals such as sodium in group 1A, for example, achieve a noble-gas configuration by losing the single *s* electron from their valence shell to form a cation, while the halogens such as chlorine in group 7A achieve a noble-gas configuration by gaining a *p* electron to fill their valence shell and form an anion. The resultant ions are held together in compounds like $Na^+ Cl^-$ by the electrical attraction of unlike charges that we call an ionic bond.

But how do elements closer to the middle of the periodic table form bonds? Look at methane, CH_4, the main constituent of natural gas, for example. The bonding in methane is not ionic because it would take too much energy for carbon ($1s^2\ 2s^2\ 2p^2$) either to gain or lose four electrons to achieve a noble-gas configuration. Instead, carbon bonds to other atoms, not by gaining or losing electrons, but by *sharing* them. Such a shared-electron bond, first proposed in 1916 by the American chemist G. N. Lewis, is called a covalent bond. The neutral collection of atoms held together by covalent bonds is called a molecule. Ionic compounds such as sodium chloride, however, are not called molecules.

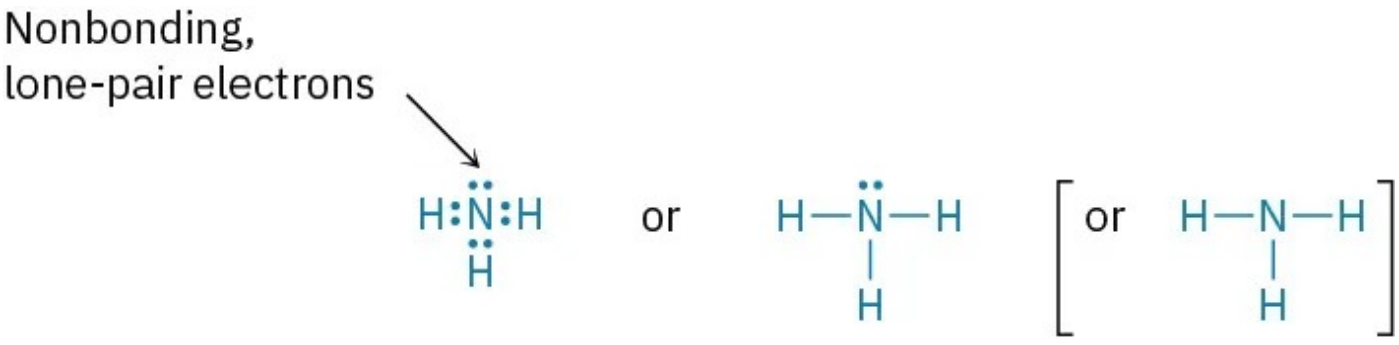
A simple way of indicating the covalent bonds in molecules is to use what are called Lewis structures, or electron-dot structures, in which the valence-shell electrons of an atom are represented as dots. Thus, hydrogen has one dot representing its 1s electron, carbon has four dots ($2s^2\ 2p^2$), oxygen has six dots ($2s^2\ 2p^4$), and so on. A stable molecule results whenever a noble-gas configuration of eight dots (an octet) is achieved for all main-group atoms or two dots for hydrogen. Even simpler than Lewis structures is the use of Kekulé structures, or line-bond structures, in which the two-electron covalent bonds are indicated as lines drawn between atoms.



The number of covalent bonds an atom forms depends on how many additional valence electrons it needs to reach a noble-gas configuration. Hydrogen has one valence electron (1s) and needs only one more to reach the helium configuration ($1s^2$), so it forms one bond. Carbon has four valence electrons ($2s^2\ 2p^2$) and needs four more to reach the neon configuration ($2s^2\ 2p^6$), so it forms four bonds. Nitrogen has five valence electrons ($2s^2\ 2p^3$), needs three more, and forms three bonds; oxygen has six valence electrons ($2s^2\ 2p^4$), needs two more, and forms two bonds; and the halogens have seven valence electrons, need one more, and form one bond.



Valence electrons that are not used for bonding remain as dots in structures and are called lone-pair electrons, or nonbonding electrons. The nitrogen atom in ammonia, NH_3, for instance, shares six valence electrons in three covalent bonds and has its remaining two valence electrons as two dots in a nonbonding lone pair. As a time-saving shorthand, nonbonding electrons are often omitted when drawing line-bond structures, but you still have to keep them in mind since they're often crucial in chemical reactions.



Ammonia

Worked Example 1.5.1: Predicting the Number of Bonds Formed by Atoms in Molecules

How many hydrogen atoms does phosphorus bond to in forming phosphine, $PH_?$?

Strategy

Identify the periodic group of phosphorus, and find from that how many electrons (bonds) are needed to make an octet.

Solution

Phosphorus is in group 5A of the periodic table and has five valence electrons. It thus needs to share three more electrons to make an octet and therefore bonds to three hydrogen atoms, giving PH_3.

Worked Example 1.5.2: Drawing Electron-Dot and Line-Bond Structures

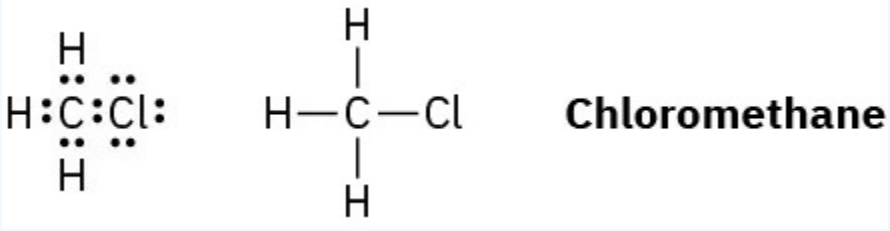
Draw both electron-dot and line-bond structures for chloromethane, CH_3Cl.

Strategy

Remember that a covalent bond—that is, a pair of shared electrons—is represented as a line between atoms.

Solution

Hydrogen has one valence electron, carbon has four valence electrons, and chlorine has seven valence electrons. Thus, chloromethane is represented as



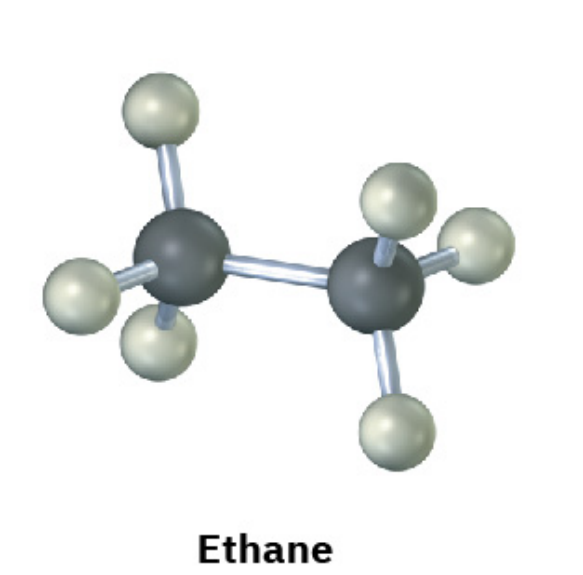
Exercise 1.5.1

Draw a molecule of chloroform, $CHCl_3$, using solid, wedged, and dashed lines to show its tetrahedral geometry.

Answer available at the end of this section.

Exercise 1.5.2

Convert the following representation of ethane, C_2H_6, into a conventional drawing that uses solid, wedged, and dashed lines to indicate tetrahedral geometry around each carbon (black = C, gray = H).



Answer available at the end of this section.

Exercise 1.5.3

What are likely formulas for the following substances?
(a) $CCl_?$ (b) $AlH_?$ (c) $CH_? Cl_2$ (d) $SiF_?$ (e) $CH_3NH_?$

Answer available at the end of this section.

Exercise 1.5.4

Write line-bond structures for the following substances, showing all nonbonding electrons:

a. $CHCl_3$, chloroform
b. H_2S, hydrogen sulfide
c. CH_3NH_2, methylamine
d. CH_3Li, methyllithium

Answer available at the end of this section.

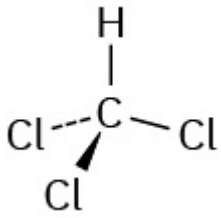
Exercise 1.5.5

Why can't an organic molecule have the formula C_2H_7 ?

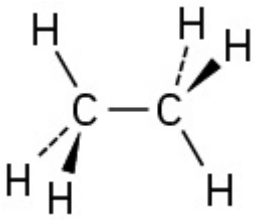
Answer available at the end of this section.

Answers

Exercise 1.5.1



Exercise 1.5.2

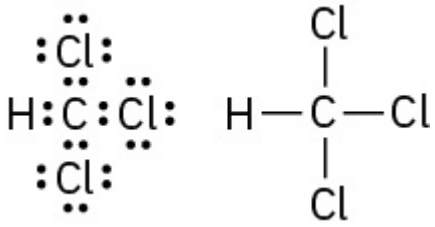


Exercise 1.5.3

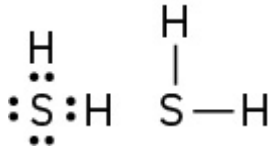
(a) CCl_4 (b) AlH_3 (c) CH_2Cl_2 (d) SiF_4 (e) CH_3NH_2

Exercise 1.5.4

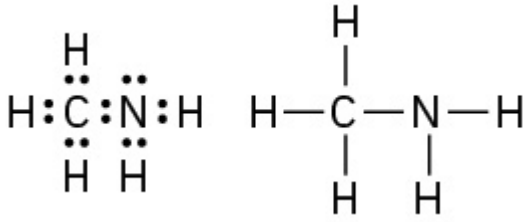
a.



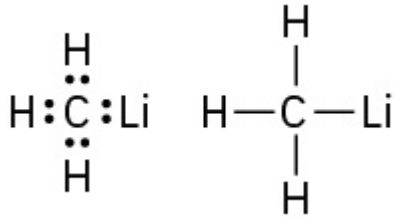
b.



c.



d.



Exercise 1.5.5

C_2H_7 has too many hydrogens for a compound with two carbons.

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1.6: The Shapes of Molecules

Learning Objective

- Determine the shape of simple organic molecules.

The Lewis electron-pair approach can be used to predict the number and types of bonds between the atoms in a substance, and it indicates which atoms have lone pairs of electrons. This approach gives no information about the actual arrangement of atoms in space, however. We continue our discussion of structure and bonding by introducing the **valence-shell electron-pair repulsion** (VSEPR) model (pronounced "vesper"), which can be used to predict the shapes of many molecules and polyatomic ions. Keep in mind, however, that the VSEPR model, like any model, is a limited representation of reality; the model provides no information about bond lengths or the presence of multiple bonds.

The VSEPR Model

The VSEPR model can predict the structure of nearly any molecule or polyatomic ion in which the central atom is a nonmetal, as well as the structures of many molecules and polyatomic ions with a central metal atom. The premise of the VSEPR theory is that electron pairs located in bonds and lone pairs repel each other and will therefore adopt the geometry that places electron pairs as far apart from each other as possible. This theory is very simplistic and does not account for the subtleties of orbital interactions that influence molecular shapes; however, the simple VSEPR counting procedure accurately predicts the three-dimensional structures of a large number of compounds, which cannot be predicted using the Lewis electron-pair approach.

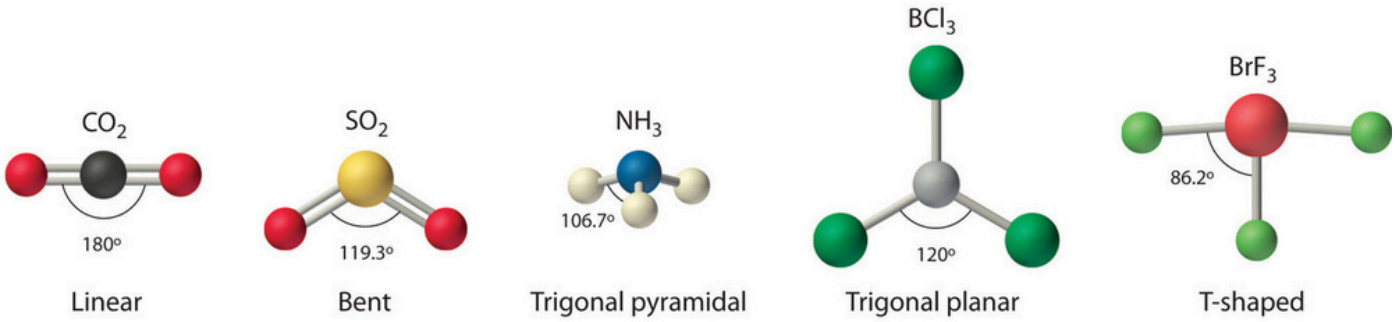


Figure 1.6.1: Common Structures for Molecules and Polyatomic Ions That Consist of a Central Atom Bonded to Two or Three Other Atoms.

We can use the VSEPR model to predict the geometry of most polyatomic molecules and ions by focusing only on the number of electron pairs around the *central atom*, ignoring all other valence electrons present. According to this model, valence electrons in the Lewis structure form **electron groups** (regions of electron density), which may consist of a single bond, a double bond, a triple bond, a lone pair of electrons, or even a single unpaired electron, which in the VSEPR model is counted as a lone pair. Because electrons repel each other electrostatically, the most stable arrangement of electron groups (i.e., the one with the lowest energy) is the one that minimizes repulsions. Groups are positioned around the central atom in a way that produces the molecular structure with the lowest energy, as illustrated in Figure 1.6.1.

Table 1.6.1 summarizes the shapes of molecules based on the number of electron groups and surrounding atoms.

Table 1.6.1: Summary of Electron Group Geometries and Molecular Structures

Number of Electron Groups on Central Atom	Number of Bonding Groups	Number of Lone Pairs of Electrons	Electron Group Geometry	Molecular Structure / Shape
2	2	0	linear	linear
3	3	0	trigonal planar	trigonal planar
3	2	1	trigonal planar	bent 120°

Number of Electron Groups on Central Atom	Number of Bonding Groups	Number of Lone Pairs of Electrons	Electron Group Geometry	Molecular Structure / Shape
4	4	0	tetrahedral	tetrahedral
4	3	1	tetrahedral	trigonal pyramidal
4	2	2	tetrahedral	bent 109°

It is important to note that electron group geometry around a central atom is *not* the same thing as its molecular structure. Electron group geometries describe ***all*** regions where electrons are located, bonds, as well as lone pairs. Molecular structure describes the location of the *atoms* alone, not including the lone pair electrons.

We differentiate between these two situations by naming the geometry that includes *all* electron pairs the **electron group geometry**. The structure that includes only the placement of the atoms in the molecule is called the **molecular structure** (or molecular shape). The electron group geometries will be the *same* as the molecular structures when there are no lone electron pairs around the central atom, but they will be *different* when there are lone pairs present on the central atom.

Predicting Electron Group Geometry and Molecular Structure

The following procedure uses VSEPR theory to determine electron group geometry and molecular structures:

1. Draw the Lewis structure of the molecule or polyatomic ion.
2. Count the number of electron groups or regions of electron density (lone pairs and bonds) around the central atom. A single, double, or triple bond counts as one electron group.
3. Determine the electron group geometry by placing the groups as far apart as possible.
4. Determine the molecular structure (looking at the bonded groups only).

Two Electron Groups: Linear

Any molecule with only two atoms is **linear**. A molecule whose central atom contains only two electron groups orients those two groups as far apart from each other as possible, which is 180° apart. When the two electron groups are 180° apart, the atoms attached to those electron groups are also 180° apart, so the overall molecular structure is linear. Examples include BeH_2 and CO_2:

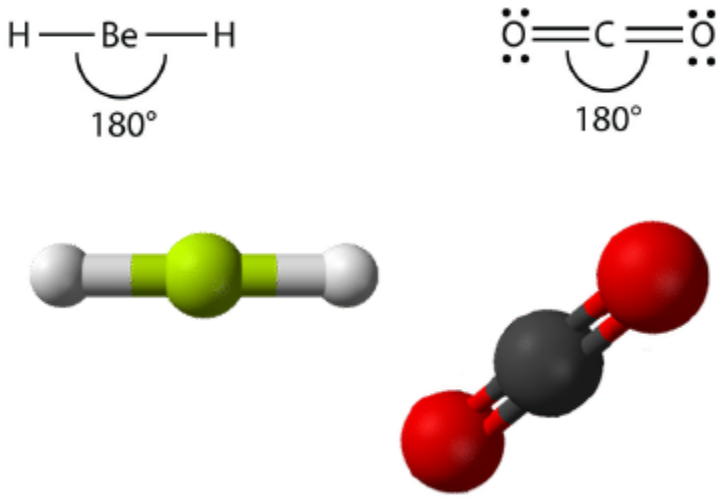


Figure 1.6.2: Bond-line representation and "ball and stick" model of Beryllium hydride and carbon dioxide bonding.

Three Electron Groups: Trigonal Planar

A molecule with three electron groups orients the three groups as far apart as possible. They adopt the positions of an equilateral triangle, 120° apart and in a plane. The shape of such molecules is **trigonal planar**. An example is BF_3 in Figure 1.6.3:

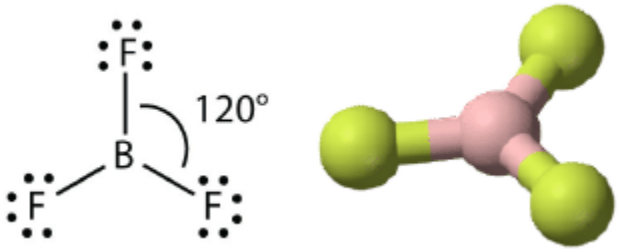


Figure 1.6.3: Boron trifluoride has 3 bonding groups. (CK12 Licence)

Some substances have a **trigonal planar** electron group distribution but have atoms bonded to only two of the three electron groups. An example is GeF_2 in Figure 1.6.4. From an electron group geometry perspective, GeF_2 has a **trigonal planar** shape, but its real shape is dictated by the positions of the atoms. This molecular structure is called **bent 120°** or angular.

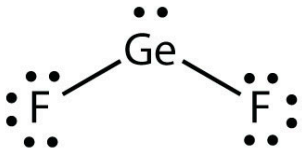


Figure 1.6.4: Germanium difluoride has 2 bonding groups and 1 lone pair of electrons.

Four Electron Groups: Tetrahedral

A molecule with four electron groups about the central atom orients the four groups in the direction of a tetrahedron with bond angles of approximately 109.5°. If there are four atoms attached to these electron groups, then the molecular structure is also **tetrahedral**. Methane (CH_4) is an example.

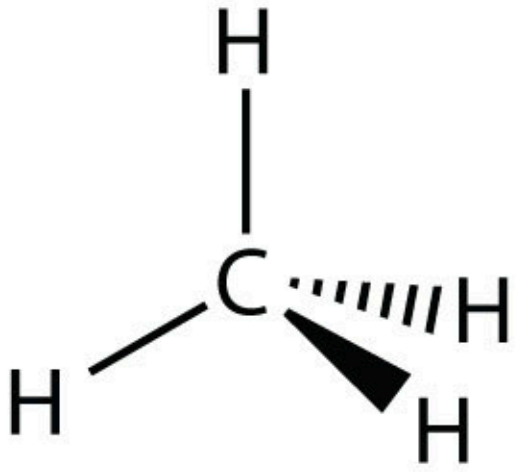


Figure 1.6.5: Tetrahedral structure of methane. Methane has carbon as the central atom with 4 bonding groups. (CK12 Licence)

This diagram of CH_4 illustrates the standard convention of displaying a three-dimensional molecule on a two-dimensional surface. The straight lines are in the plane of the page, the solid wedged line is coming out of the plane toward the reader, and the dashed wedged line is going out of the plane away from the reader.

NH_3 is an example of a molecule whose central atom has four electron groups, but only three of them are bonded to surrounding atoms. The electron groups are oriented in a **tetrahedral** shape. From a molecular geometry perspective, the shape of NH_3 is **trigonal pyramidal**.

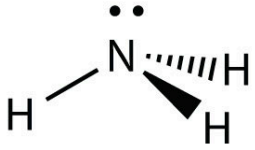


Figure 1.6.6: 3D representation of Ammonia. (CK12 Licence)

H_2O is an example of a molecule whose central atom has four electron groups, but only two of them are bonded to surrounding atoms. The electron groups are oriented in a **tetrahedral** shape. The shape of the molecule is **bent 109°** or angular. A molecule with four electron groups about the central atom, but only one electron group bonded to another atom, is linear because there are only two atoms in the molecule.

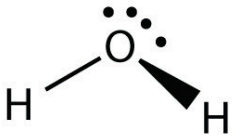


Figure 1.6.7: 3D representation of Water.

Shapes of Molecules with Double or Triple Bonds

Double or triple bonds count as a single electron group. The Lewis electron dot diagram of formaldehyde (CH_2O) is shown in Figure 1.6.8.

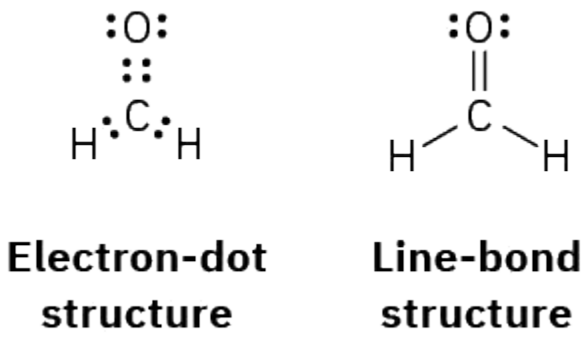


Figure 1.6.8: Electron-Dot Diagram and Line-Bond Representation of Formaldehyde.

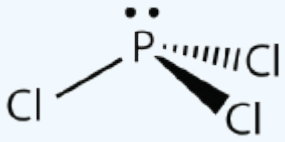
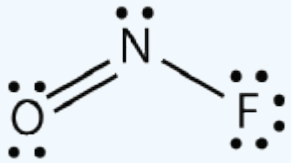
The central C atom has three electron groups around it because the double bond counts as one electron group. The three electron groups repel each other to adopt a *trigonal planar shape*. In the Bond-Line representation, the lone electron pairs on the O atom are omitted for clarity. The molecule will not be a perfect equilateral triangle because the C–O double bond is different from the two C–H bonds, but both planar and triangular describe the appropriate approximate shape of this molecule.

Example 1.6.1

What is the approximate shape of each molecule?

a. PCl_3
b. NOF

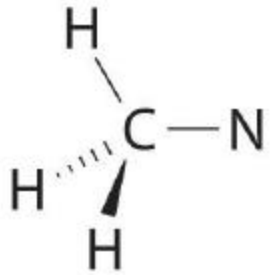
Solution

The first step is to draw the 3D electron dot diagram of the molecule. For PCl_3, the electron dot diagram is as follows:  The lone electron pairs on the Cl atoms are omitted for clarity. The P atom has four electron groups, with three of them bonded to surrounding atoms, so the molecular shape is trigonal pyramidal.	The 3D electron dot diagram for NOF is as follows:  The N atom has three electron groups on it, two of which are bonded to other atoms. The molecular shape is bent.

Molecules With Multiple Central Atoms

The VSEPR model can be used to predict the structure of somewhat more complex molecules with more than one central atom by using VSEPR as described above for each central atom individually. We will demonstrate with methyl isocyanate (CH_3–N=C=O), a volatile and highly toxic molecule that is used to produce the pesticide Sevin.

Start by looking at the electron groups around the first carbon atom at the left, which is connected to three H atoms and one N atom by single bonds. There are four groups or electrons or four bonds around the carbon. We can therefore predict the CH_3–N portion of the molecule to be roughly *tetrahedral*, similar to methane:



The nitrogen atom is connected to one carbon by a single bond and to the other carbon by a double bond, producing a total of three bonds, C–N=C. For nitrogen to have an octet of electrons, it must also have a lone pair:

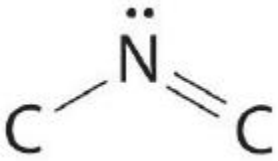


Figure 1.6.9: One carbon bonded to nitrogen and another carbon double bonded to the nitrogen. The nitrogen has one lone pair.

Because multiple bonds are not shown in the VSEPR model, the nitrogen is effectively surrounded by three electron groups. Thus according to the VSEPR model, the C–N=C fragment should be *bent* with an angle ~120°.

The carbon in the –N=C=O fragment is doubly bonded to both nitrogen and oxygen, which in the VSEPR model gives carbon a total of two electron pairs. The N=C=O angle should therefore be 180°, or linear. The three fragments combine to give the following structure:

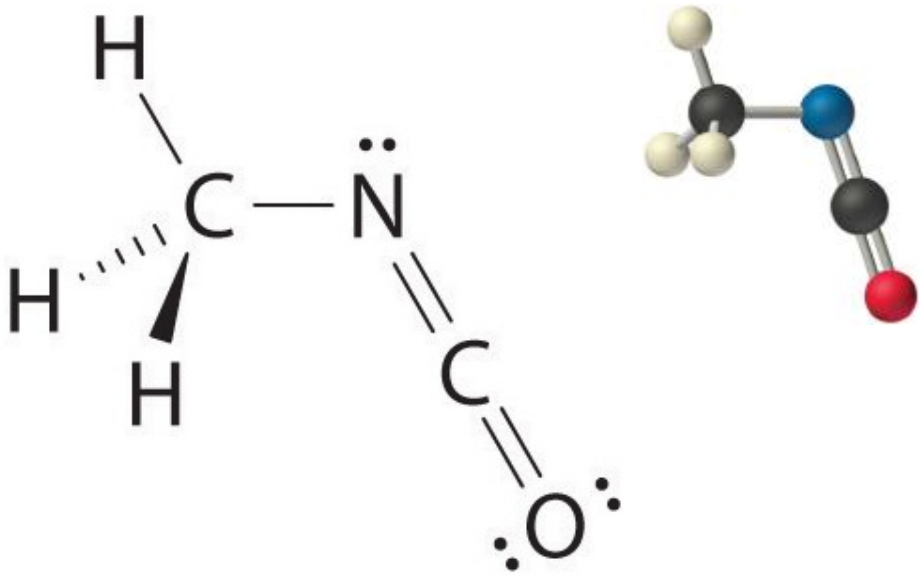


Figure 1.6.10. Left - 3D Bond-Line Structure of Methyl Isocyanate, (this representation is the simplest while allowing for three-dimensional perspective). Right - The Computational Determined 3D Structure of Methyl Isocyanate.

Certain patterns are seen in the structures of moderately complex molecules. For example, carbon atoms with four bonds (such as the carbon on the left in methyl isocyanate) are generally tetrahedral. Similarly, the carbon atom on the right has two double bonds that are similar to those in CO_2, so its geometry, like that of CO_2, is linear. Recognizing similarities to simpler molecules will help you predict the molecular geometries of more complex molecules.

Example 1.6.2

Use the VSEPR model to predict the molecular geometry of propyne ($H_3C–C{\equiv}CH$), a gas with some anesthetic properties.

Strategy:

Count the number of electron groups around each carbon, recognizing that in the VSEPR model, a multiple bond counts as a single group. Use Table 1.6.1 to determine the molecular geometry around each carbon atom and then deduce the structure of the molecule as a whole.

Solution:

Because the carbon atom on the left is bonded to four other atoms, we know that it is approximately tetrahedral. The next two carbon atoms share a triple bond, and each has an additional single bond. Because a multiple bond is counted as a single bond in the VSEPR model, each carbon atom behaves as if it had two electron groups. This means that both of these carbons are linear, with C–C≡C and C≡C–H angles of 180°.

Exercises

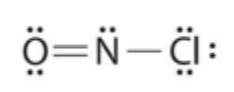
Exercise 1.6.1

What is the approximate molecular shape of $\mathrm{CH_2Cl_2}$?

Answer available at the end of this section.

Exercise 1.6.2

What is the molecular shape of nitrosyl chloride, a highly corrosive, reddish-orange gas? Its Lewis structure is shown below.



Answer available at the end of this section.

Exercise 1.6.3

Ethylene ($\mathrm{C_2H_4}$) has two central atoms. Determine the geometry around each central atom and the shape of the overall molecule. (Hint: Draw the Lewis structure, hydrogen is a terminal atom.)

Answer available at the end of this section.

Answer available at the end of this section.

Exercise 1.6.4

Predict the geometry of allene ($H_2C{=}C{=}CH_2$), a compound with narcotic properties that is used to make more complex organic molecules.

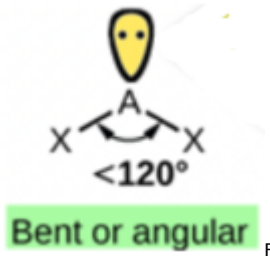
Answer available at the end of this section.

Answers

Exercise 1.6.1

Tetrahedral

Exercise 1.6.2



Focus on the central atom, N. It has a double bond to O, count this as one bond. It also has a single bond to Cl. Thus, N has 2 bonds and one lone pair. These 3 electron pairs will spread out 120 degrees from each other. But, since the shape is defined by the arrangement of the atoms only, the shape is bent or angular.

Exercise 1.6.3

Exercise 1.6.3

Trigonal planar about both central C atoms.

Exercise 1.6.4

The terminal carbon atoms are trigonal planar, the central carbon is linear, and the C–C–C angle is 180°.

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1.7: Describing Chemical Bonds - Molecular Orbital Theory

We said in Section 1.6 that chemists use two models for describing covalent bonds: valence bond theory and molecular orbital theory. Having now seen the valence bond approach, which uses hybrid atomic orbitals to account for geometry and assumes the overlap of atomic orbitals to account for electron sharing, let's look briefly at the molecular orbital approach to bonding. We'll return to this topic in Chapters 14, 15, and 30 for a more in-depth discussion.

Molecular orbital (MO) theory describes covalent bond formation as arising from a mathematical combination of atomic orbitals (wave functions) on different atoms to form *molecular orbitals,* so called because they belong to the entire molecule rather than to an individual atom. Just as an *atomic* orbital, whether unhybridized or hybridized, describes a region of space around an *atom* where an electron is likely to be found, so a *molecular* orbital describes a region of space in a *molecule* where electrons are most likely to be found.

Like an atomic orbital, a molecular orbital has a specific size, shape, and energy. In the H_2 molecule, for example, two singly occupied 1s atomic orbitals combine to form two molecular orbitals. There are two ways for the orbital combination to occur—an additive way and a subtractive way. The additive combination leads to formation of a molecular orbital that is lower in energy and roughly egg-shaped, while the subtractive combination leads to a molecular orbital that is higher in energy and has a node between nuclei (Figure 1.7.1). Note that the additive combination is a single, egg-shaped, molecular orbital; it is not the same as the two overlapping 1s atomic orbitals of the valence bond description. Similarly, the subtractive combination is a single molecular orbital with the shape of an elongated dumbbell.

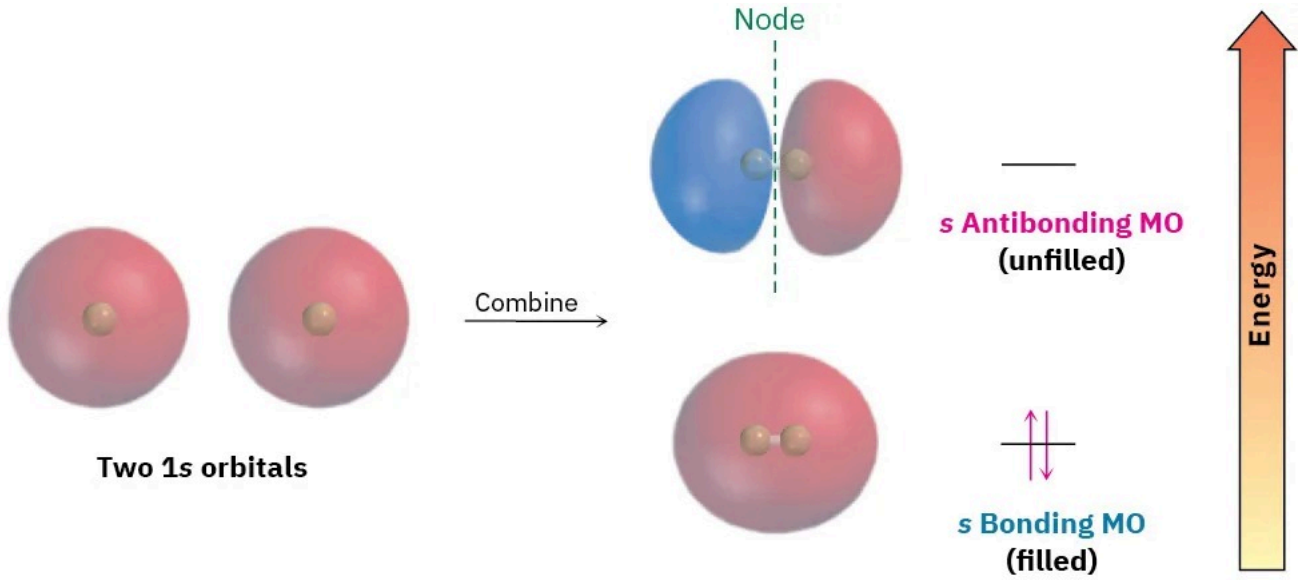


Figure 1.7.1: Molecular orbitals of H_2. Combination of two hydrogen 1s atomic orbitals leads to two H_2 molecular orbitals. The lower-energy, **bonding MO** is filled, and the higher-energy, **antibonding MO** is unfilled.

The additive combination is lower in energy than the two hydrogen 1s atomic orbitals and is called a bonding MO because electrons in this MO spend most of their time in the region between the two nuclei, thereby bonding the atoms together. The subtractive combination is higher in energy than the two hydrogen 1s orbitals and is called an antibonding MO because any electrons it contains *can't* occupy the central region between the nuclei, where there is a node, and thus can't contribute to bonding. The two nuclei therefore repel each other.

Just as bonding and antibonding σ molecular orbitals result from the head-on combination of two s atomic orbitals in H_2, so bonding and antibonding π molecular orbitals result from the sideways combination of two *p* atomic orbitals in ethylene. As shown in Figure 1.7.2, the lower-energy, π bonding MO has no node between nuclei and results from the combination of *p* orbital lobes with the same algebraic sign. The higher-energy, π antibonding MO has a node between nuclei and results from the combination of lobes with opposite algebraic signs. Only the bonding MO is occupied; the higher-energy, antibonding MO is vacant. We'll see in Chapters 14, 15, and 30 that molecular orbital theory is particularly useful for describing π bonds in compounds that have more than one double bond.

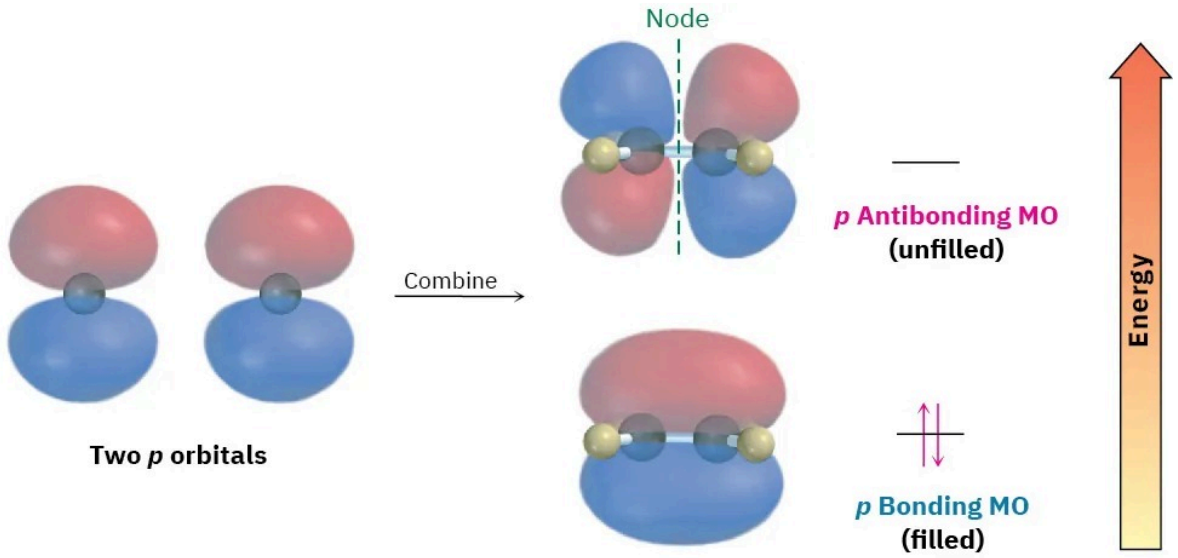


Figure 1.7.2: A molecular orbital description of the C–C π bond in ethylene. The lower-energy, ***π*** bonding MO results from an additive combination of *p* orbital lobes with the same algebraic sign and is filled. The higher-energy, ***π*** **antibonding MO** results from a subtractive combination of *p* orbital lobes with opposite algebraic signs and is unfilled.

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1.8: sp³ Hybrid Orbitals and the Structure of Methane

The bonding in the hydrogen molecule is fairly straightforward, but the situation is more complicated in organic molecules with tetravalent carbon atoms. Take methane, CH_4, for instance. As we've seen, carbon has four valence electrons ($2s^2\ 2p^2$) and forms four bonds. Because carbon uses two kinds of orbitals for bonding, 2*s* and 2*p,* we might expect methane to have two kinds of C–H bonds. In fact, though, all four C–H bonds in methane are identical and are spatially oriented toward the corners of a regular tetrahedron. How can we explain this?

An answer was provided in 1931 by Linus Pauling, who showed mathematically how an *s* orbital and three *p* orbitals on an atom can combine, or *hybridize,* to form four equivalent atomic orbitals with tetrahedral orientation. Shown in Figure 1.8.1, these tetrahedrally oriented orbitals are called sp^3 hybrid orbitals. Note that the superscript 3 in the name sp^3 tells how many of each type of atomic orbital combine to form the hybrid, not how many electrons occupy it.

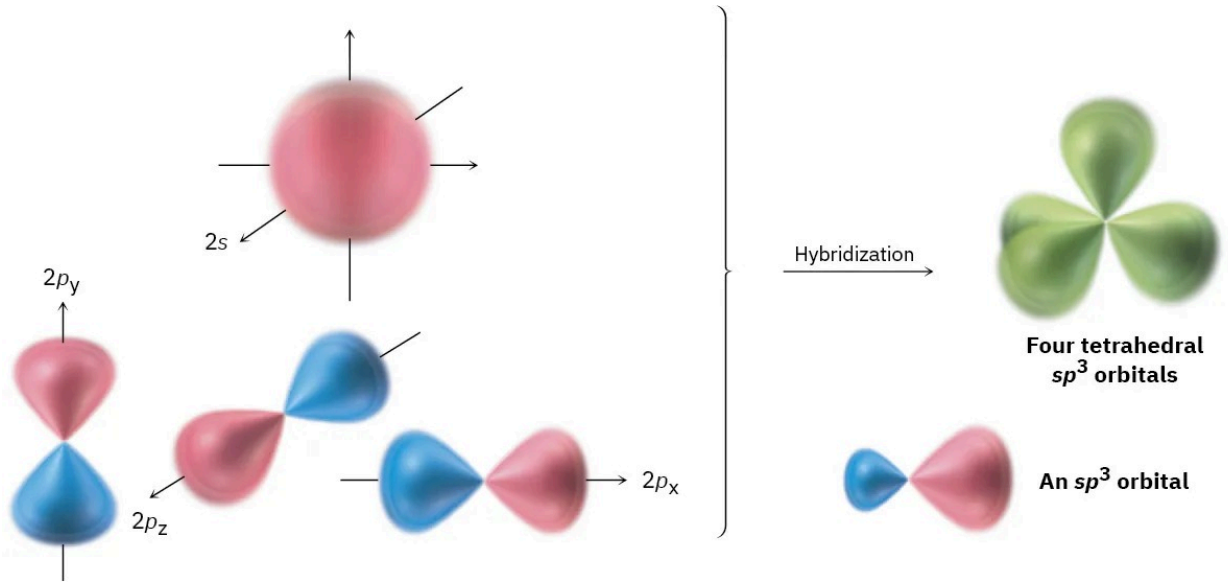


Figure 1.8.1: Four sp^3 hybrid orbitals , oriented toward the corners of a regular tetrahedron, are formed by the combination of an s orbital and three *p* orbitals (red/blue). The sp^3 hybrids have two lobes and are unsymmetrical about the nucleus, giving them a directionality and allowing them to form strong bonds to other atoms.

The concept of hybridization explains how carbon forms four equivalent tetrahedral bonds but not why it does so. The shape of the hybrid orbital suggests the answer to why. When an *s* orbital hybridizes with three *p* orbitals, the resultant sp^3 hybrid orbitals are unsymmetrical about the nucleus. One of the two lobes is larger than the other and can therefore overlap more effectively with an orbital from another atom to form a bond. As a result, sp^3 hybrid orbitals form stronger bonds than do unhybridized *s* or *p* orbitals.

The asymmetry of sp^3 orbitals arises because, as noted previously, the two lobes of a *p* orbital have different algebraic signs, + and –, in the wave function. Thus, when a *p* orbital hybridizes with an *s* orbital, the positive *p* lobe adds to the *s* orbital but the negative *p* lobe subtracts from the *s* orbital. The resultant hybrid orbital is therefore unsymmetrical about the nucleus and is strongly oriented in one direction.

When each of the four identical sp^3 hybrid orbitals of a carbon atom overlaps with the 1s orbital of a hydrogen atom, four identical C–H bonds are formed and methane results. Each C–H bond in methane has a strength of 439 kJ/mol (105 kcal/mol) and a length of 109 pm. Because the four bonds have a specific geometry, we also can define a property called the bond angle. The angle formed by each H–C–H is 109.5°, the so-called tetrahedral angle. Methane thus has the structure shown in Figure 1.8.2.

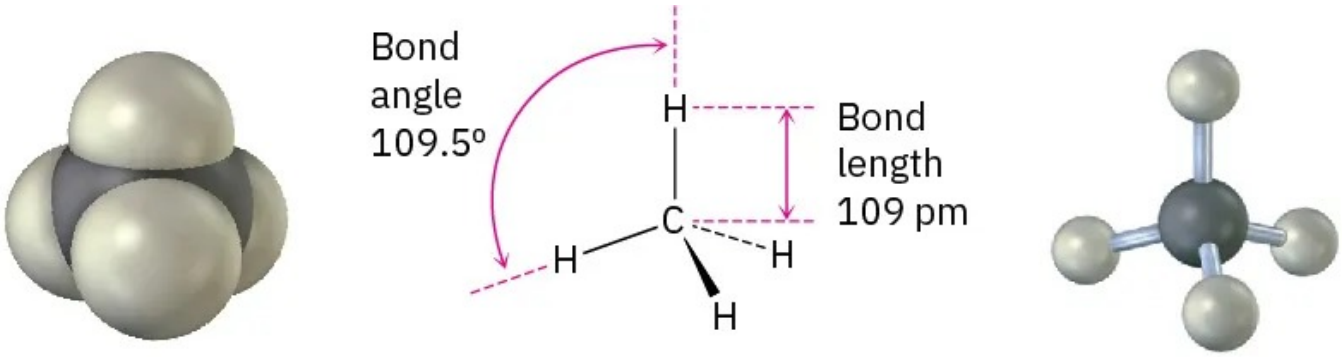


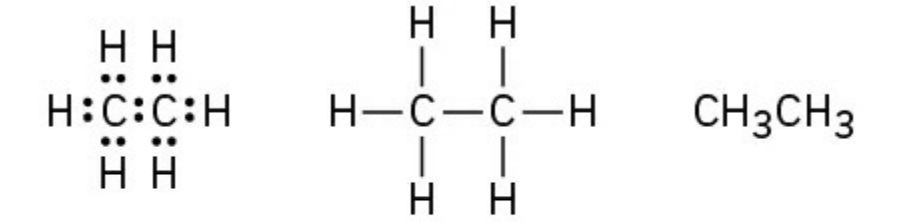
Figure 1.8.2: The structure of methane, showing its 109.5° bond angles.

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1.9: sp^3 Hybrid Orbitals and the Structure of Ethane

The same kind of orbital hybridization that accounts for the methane structure also accounts for the bonding together of carbon atoms into chains and rings to make possible many millions of organic compounds. Ethane, C_2H_6, is the simplest molecule containing a carbon–carbon bond.



Some representations of ethane

We can picture the ethane molecule by imagining that the two carbon atoms bond to each other by head-on sigma (σ) overlap of an sp^3 hybrid orbital from each (Figure 1.9.1). The remaining three sp^3 hybrid orbitals on each carbon overlap with the 1s orbitals of three hydrogens to form the six C–H bonds. The C–H bonds in ethane are similar to those in methane, although a bit weaker: 421 kJ/mol (101 kcal/mol) for ethane versus 439 kJ/mol for methane. The C–C bond is 153 pm in length and has a strength of 377 kJ/mol (90 kcal/mol). All the bond angles of ethane are near, although not exactly at, the tetrahedral value of 109.5°.

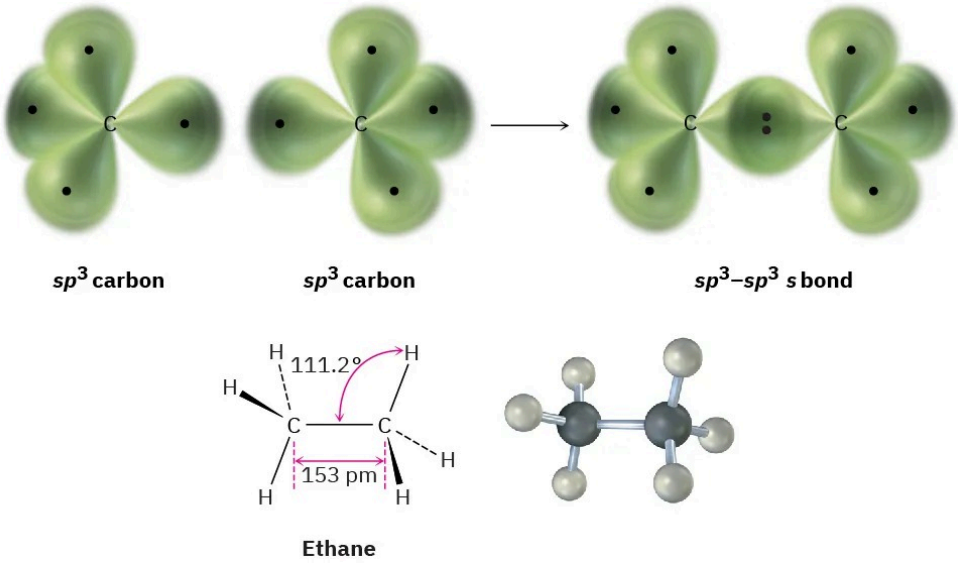


Figure 1.9.1: The structure of ethane. The carbon–carbon bond is formed by σ overlap of two ***sp*^{3} hybrid orbitals**. For clarity, the smaller lobes of the sp^3 hybrid orbitals are not shown.

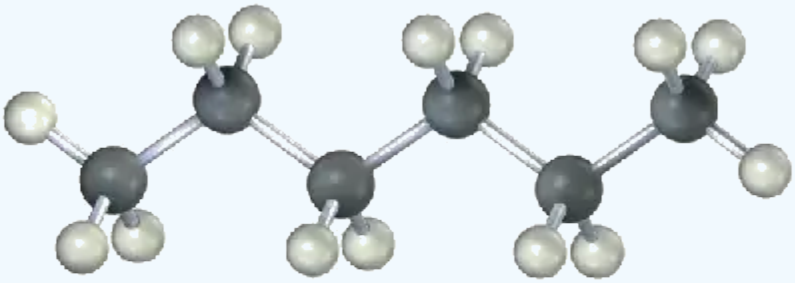
Exercise 1.9.1

Draw a line-bond structure for propane, $CH_3CH_2CH_3$. Predict the value of each bond angle, and indicate the overall shape of the molecule.

Answer available at the end of this section.

Exercise 1.9.2

Convert the following molecular model of hexane, a component of gasoline, into a line-bond structure (black = C, gray = H).

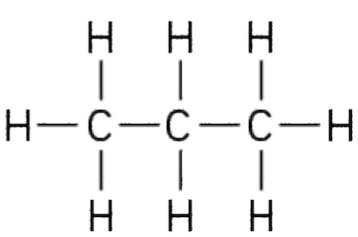


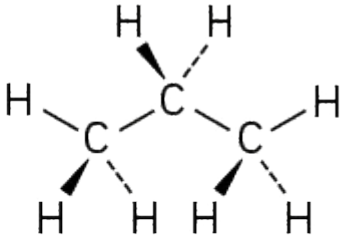
Hexane

Answer available at the end of this section.

Answers

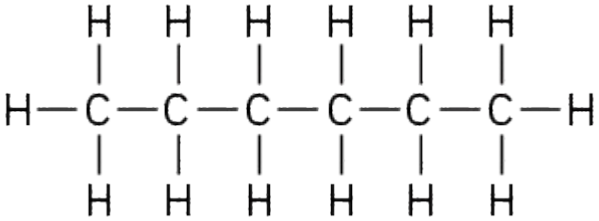
Exercise 1.9.1





All bond angles are near 109°.

Exercise 1.9.2



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1.10: sp^2 Hybrid Orbitals and the Structure of Ethylene

The bonds we've seen in methane and ethane are called *single bonds* because they result from the sharing of one electron pair between bonded atoms. It was recognized nearly 150 years ago, however, that carbon atoms can also form *double bonds* by sharing two electron pairs between atoms or *triple bonds* by sharing three electron pairs. Ethylene, for instance, has the structure $H_2C{=}CH_2$ and contains a carbon–carbon double bond, while acetylene has the structure HC≡CH and contains a carbon–carbon triple bond.

How are multiple bonds described by valence bond theory? When we discussed sp^3 hybrid orbitals in Section 1.6, we said that the four valence-shell atomic orbitals of carbon combine to form four equivalent sp^3 hybrids. Imagine instead that the 2*s* orbital combines with only *two* of the three available 2*p* orbitals. Three sp^2 hybrid orbitals result, and one 2*p* orbital remains unchanged. Like sp^3 hybrids, sp^2 hybrid orbitals are unsymmetrical about the nucleus and are strongly oriented in a specific direction so they can form strong bonds. The three sp^2 orbitals lie in a plane at angles of 120° to one another, with the remaining *p* orbital perpendicular to the sp^2 plane, as shown in Figure 1.10.1.

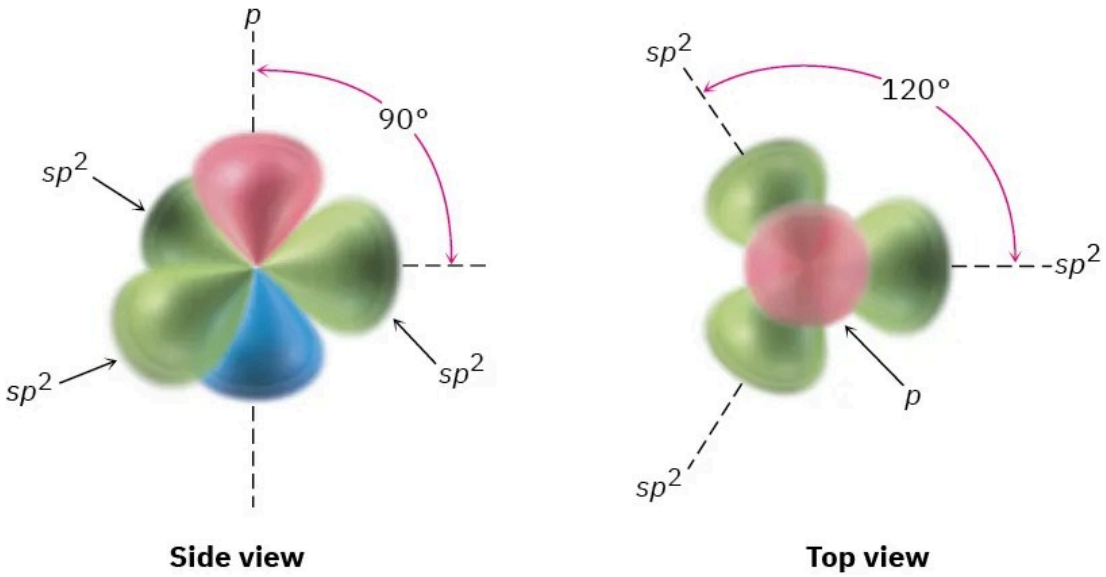


Figure 1.10.1: sp^2 Hybridization. The three equivalent ***sp*^{2} hybrid orbitals** lie in a plane at angles of 120° to one another, and a single unhybridized ***p* orbital (red/blue)** is perpendicular to the sp^2 plane.

When two carbons with sp^2 hybridization approach each other, they form a strong σ bond by sp^2–sp^2 head-on overlap. At the same time, the unhybridized *p* orbitals interact by sideways overlap to form what is called a pi (π) bond. The combination of an sp^2–sp^2 σ bond and a 2*p*–2*p* π bond results in the sharing of four electrons and the formation of a carbon–carbon double bond (Figure 1.10.2). Note that the electrons in the σ bond occupy the region centered between nuclei, while the electrons in the π bond occupy regions above and below a line drawn between nuclei.

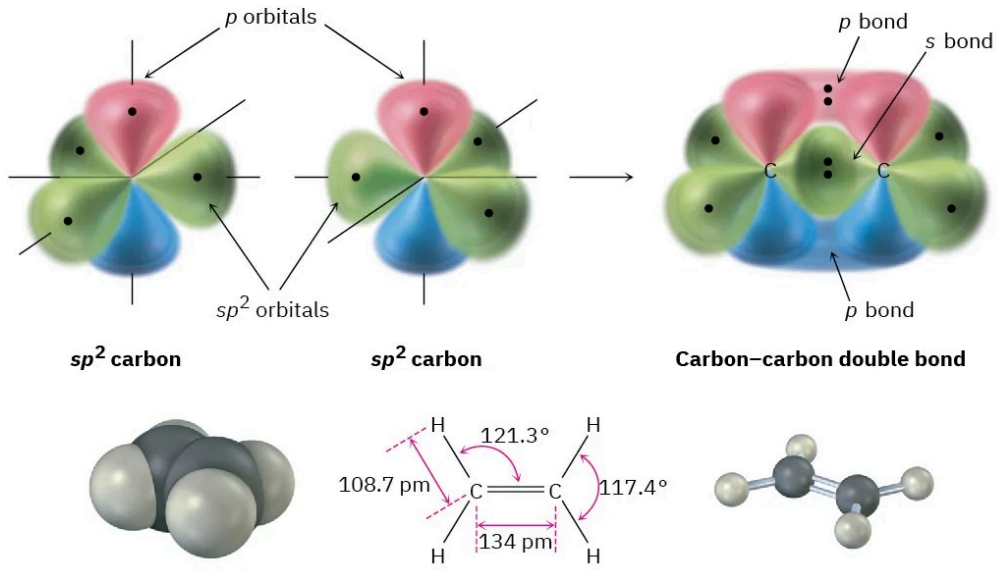


Figure 1.10.2: The structure of ethylene. One part of the double bond in ethylene results from σ (head-on) overlap of **sp^2 hybrid orbitals** , and the other part results from π (sideways) overlap of unhybridized ***p* orbitals (red/blue)**. The π bond has regions of electron density above and below a line drawn between nuclei.

To complete the structure of ethylene, four hydrogen atoms form σ bonds with the remaining four sp^2 orbitals. Ethylene thus has a planar structure, with H–C–H and H–C–C bond angles of approximately 120°. (The actual values are 117.4° for the H–C–H bond angle and 121.3° for the H–C–C bond angle.) Each C–H bond has a length of 108.7 pm and a strength of 464 kJ/mol (111 kcal/mol).

The carbon–carbon double bond in ethylene is both shorter and stronger than the single bond in ethane because it has four electrons bonding the nuclei together rather than two. Ethylene has a C=C bond length of 134 pm and a strength of 728 kJ/mol (174 kcal/mol) versus a C–C length of 153 pm and a strength of 377 kJ/mol for ethane. The carbon–carbon double bond is less than twice as strong as a single bond because the sideways overlap in the π part of the double bond is not as great as the head-on overlap in the σ part.

Worked Example 1.10.1: Drawing Electron-Dot and Line-Bond Structures

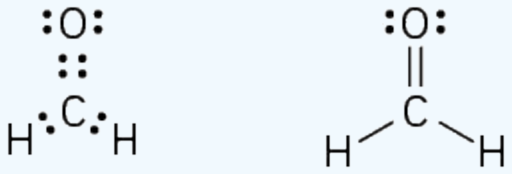
Commonly used in biology as a tissue preservative, formaldehyde, CH_2O, contains a carbon–*oxygen* double bond. Draw electron-dot and line-bond structures of formaldehyde, and indicate the hybridization of the carbon orbitals.

Strategy

We know that hydrogen forms one covalent bond, carbon forms four, and oxygen forms two. Trial and error, combined with intuition, is needed to fit the atoms together.

Solution

There is only one way that two hydrogens, one carbon, and one oxygen can combine:



Electron-dot structure

Line-bond structure

Like the carbon atoms in ethylene, the carbon atom in formaldehyde is in a double bond, and its orbitals are therefore sp^2-hybridized.

Exercises

Exercise 1.10.1

Draw a line-bond structure for propene, $CH_3CH{=}CH_2$. Indicate the hybridization of the orbitals on each carbon, and predict the value of each bond angle.

Answer available at the end of this section.

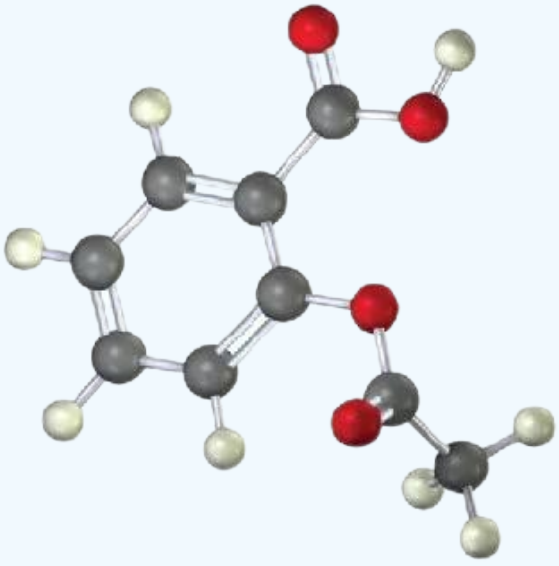
Exercise 1.10.2

Draw a line-bond structure for 1,3-butadiene, $H_2C{=}CH{-}CH{=}CH_2$. Indicate the hybridization of the orbitals on each carbon, and predict the value of each bond angle.

Answer available at the end of this section.

Exercise 1.10.3

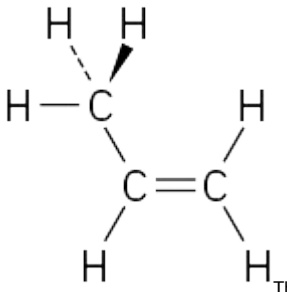
A molecular model of aspirin (acetylsalicylic acid) is shown. Identify the hybridization of the orbitals on each carbon atom in aspirin, and tell which atoms have lone pairs of electrons (black = C, red = O, gray = H).



Answer available at the end of this section.

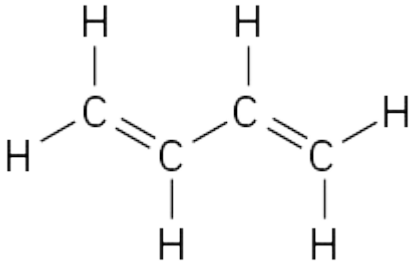
Answers

Exercise 1.10.1



The CH_3 carbon is sp^3; the double-bond carbons are sp^2; the C=C–C and C=C–H bond angles are approximately 120°; other bond angles are near 109°.

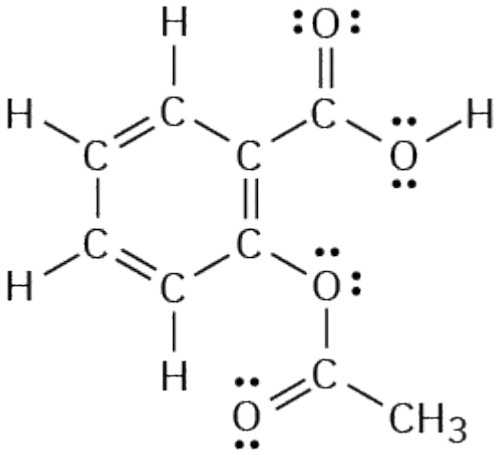
Exercise 1.10.2



All carbons are sp^2, the electron geometry is trigonal planar, and all bond angles are near 120°.

Exercise 1.10.3

All carbons except CH_3 are sp^2.



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1.11: sp Hybrid Orbitals and the Structure of Acetylene

In addition to forming single and double bonds by sharing two and four electrons, respectively, carbon can also form a triple bond by sharing six electrons. To account for the triple bond in a molecule such as acetylene, $\mathrm{H-C\equiv C-H}$, we need a third kind of hybrid orbital, an sp hybrid. Imagine that, instead of combining with two or three p orbitals, a carbon 2 s orbital hybridizes with only a single p orbital. Two sp hybrid orbitals result, and two p orbitals remain unchanged. The two sp orbitals are oriented 180° apart on the right-left (x) axis, while the p orbitals are perpendicular on the up-down (y) axis and the in-out (z) axis, as shown in Figure 1.11.1.

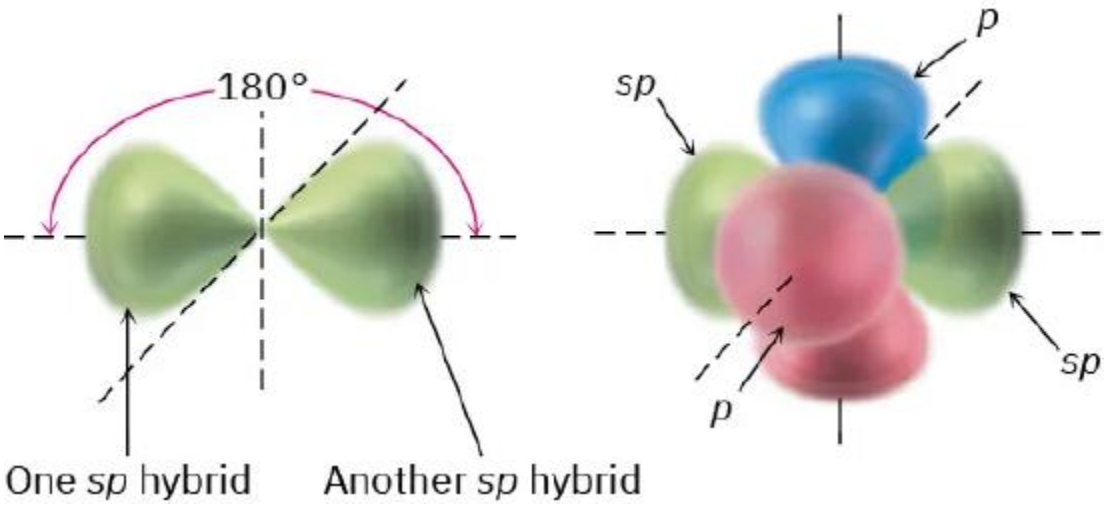


Figure 1.11.1: *sp* Hybridization. The two ***sp* hybrid orbitals** are oriented 180° away from each other, perpendicular to the two remaining ***p* orbitals (red/blue)**.

When two *sp*-hybridized carbon atoms approach each other, *sp* hybrid orbitals on each carbon overlap head-on to form a strong *sp*–*sp* σ bond. At the same time, the p_z orbitals from each carbon form a p_z–p_z π bond by sideways overlap, and the p_y orbitals overlap similarly to form a p_y–p_y π bond. The net effect is the sharing of six electrons and formation of a carbon–carbon triple bond. Each of the two remaining *sp* hybrid orbitals forms a σ bond with hydrogen to complete the acetylene molecule (Figure 1.11.2).

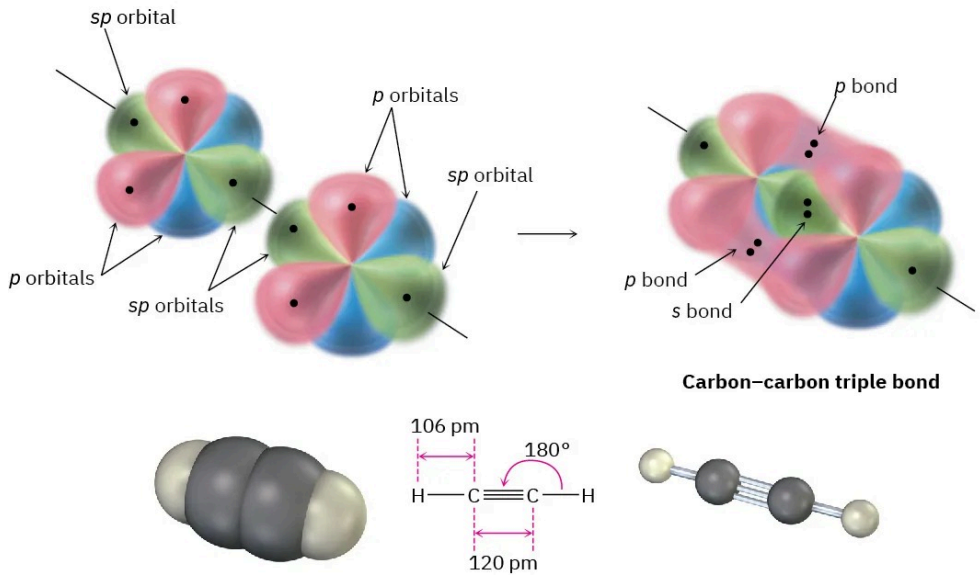


Figure 1.11.2: The structure of acetylene. The two carbon atoms are joined by one *sp*–*sp* σ bond and two *p*–*p* π bonds.

As suggested by *sp* hybridization, acetylene is a linear molecule with H–C–C bond angles of 180°. The C–H bonds have a length of 106 pm and a strength of 558 kJ/mol (133 kcal/mol). The C–C bond length in acetylene is 120 pm, and its strength is about 965 kJ/mol (231 kcal/mol), making it the shortest and strongest of any carbon–carbon bond. A comparison of *sp*, sp^2, and sp^3 hybridization is given in Table 1.11.1.

Table 1.11.1 *Comparison of C–C and C–H Bonds in Methane, Ethane, Ethylene, and Acetylene*

Molecule	Bond	Bond strength	Bond length (pm)	
		(kJ/mol)	(kcal/mol)	
Methane, CH_4	$(sp^3)\,C-H$	439	105	109
Ethane, CH_3CH_3	$(sp^3)\,C-C\,(sp^3)$	377	90	153
	$(sp^3)\,C-H$	421	101	109
Ethylene, $H_2C=CH_2$	$(sp^2)\,C=C\,(sp^2)$	728	174	134
	$(sp^2)\,C-H$	464	111	109
Acetylene, $HC\equiv CH$	$(sp)C\equiv C(sp)$	965	231	120
	$(sp)C-H$	558	133	106

Exercise 1.11.1

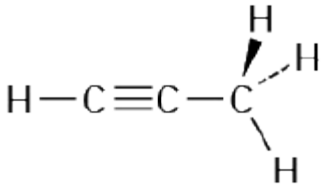
Draw a line-bond structure for propyne, $CH_3C{\equiv}CH$. Indicate the hybridization of the orbitals on each carbon, and predict a value for each bond angle.

Answer available at the end of this section.

Answers

Exercise 1.11.1

The CH_3 carbon is sp^3; the triple-bond carbons are *sp;* the C≡C–C and H–C≡C bond angles are approximately 180°.



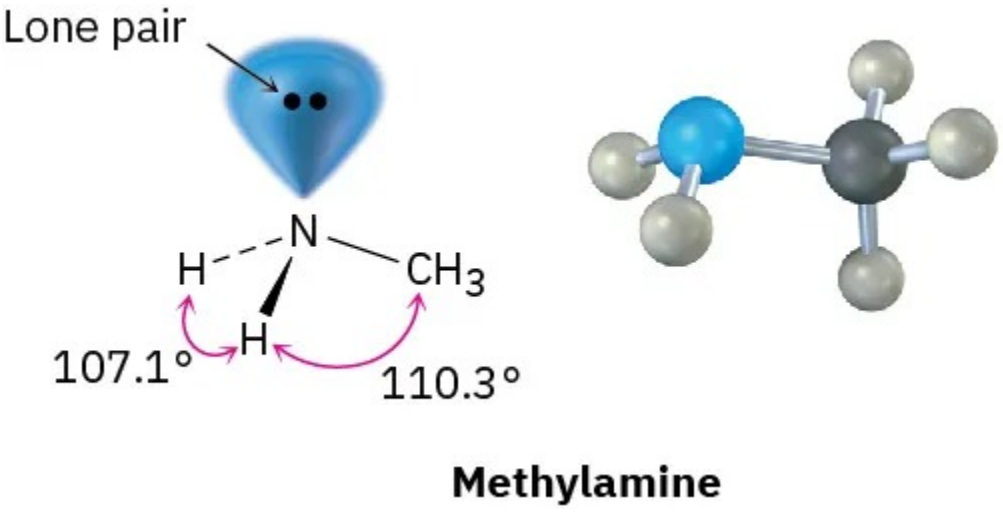
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1.12: Hybridization of Nitrogen, Oxygen, Phosphorus and Sulfur

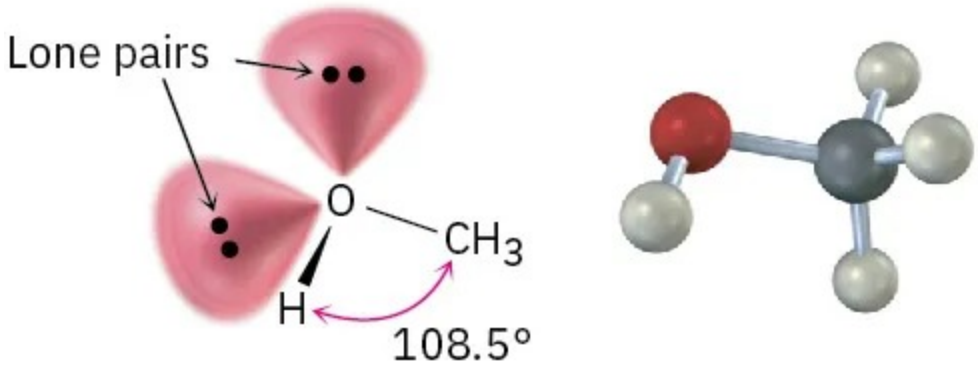
The valence-bond concept of orbital hybridization described in the previous four sections is not limited to carbon. Covalent bonds formed by other elements can also be described using hybrid orbitals. Look, for instance, at the nitrogen atom in methylamine (CH_3NH_2), an organic derivative of ammonia (NH_3) and the substance responsible for the odor of rotting fish.

The experimentally measured H–N–H bond angle in methylamine is 107.1°, and the C–N–H bond angle is 110.3°, both of which are close to the 109.5° tetrahedral angle found in methane. We therefore assume that nitrogen forms four sp^3-hybridized orbitals, just as carbon does. One of the four sp^3 orbitals is occupied by two nonbonding electrons (a lone pair), and the other three hybrid orbitals have one electron each. Overlap of these three half-filled nitrogen orbitals with half-filled orbitals from other atoms (C or H) gives methylamine. Note that the unshared lone pair of electrons in the fourth sp^3 hybrid orbital of nitrogen occupies as much space as an N–H bond does and is very important to the chemistry of methylamine and other nitrogen-containing organic molecules.



Methylamine

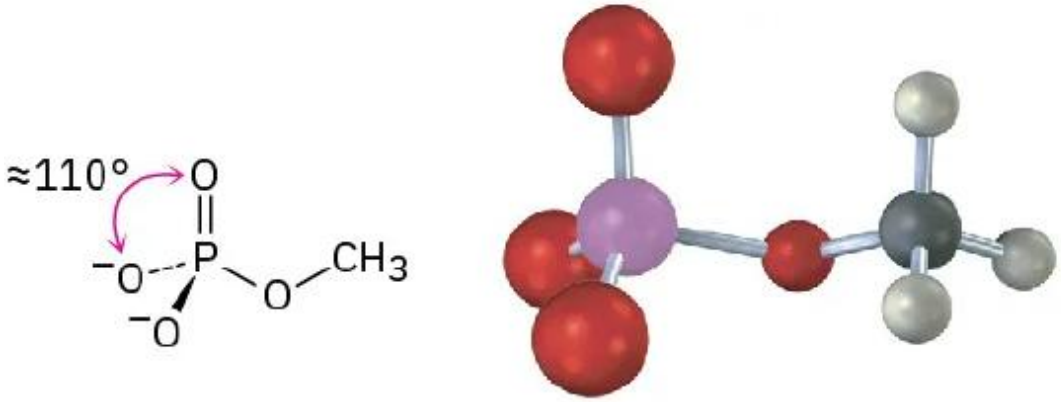
Like the carbon atom in methane and the nitrogen atom in methylamine, the oxygen atom in methanol (methyl alcohol) and many other organic molecules can be described as sp^3-hybridized. The C–O–H bond angle in methanol is 108.5°, very close to the 109.5° tetrahedral angle. Two of the four sp^3 hybrid orbitals on oxygen are occupied by nonbonding electron lone pairs, and two are used to form bonds.



Methanol
(methyl alcohol)

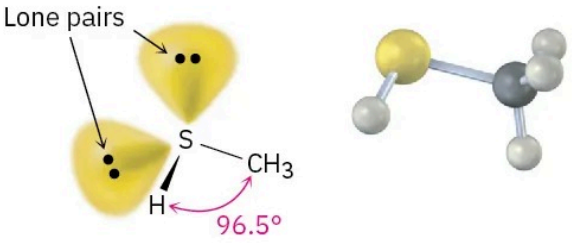
In the periodic table, phosphorus and sulfur are the third-row analogs of nitrogen and oxygen, and the bonding in both can be described using hybrid orbitals. Because of their positions in the third row, however, both phosphorus and sulfur can expand their outer-shell octets and form more than the typical number of covalent bonds. Phosphorus, for instance, often forms five covalent bonds, and sulfur often forms four.

Phosphorus is most commonly encountered in biological molecules in compounds called *organophosphates*, which contain a phosphorus atom bonded to four oxygens, with one of the oxygens also bonded to carbon. Methyl phosphate, $CH_3OPO_3^{2-}$, is the simplest example. The O–P–O bond angle in such compounds is typically in the range 110° to 112°, implying sp^3 hybridization for phosphorus orbitals.

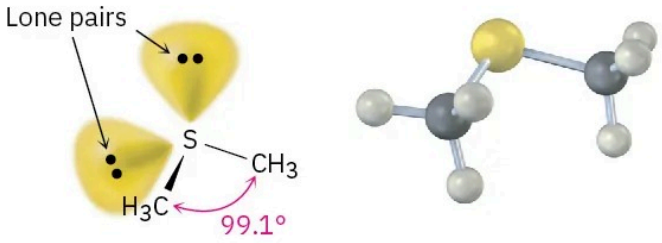


Methyl phosphate
(an organophosphate)

Sulfur is most commonly encountered in biological molecules either in compounds called *thiols,* which have a sulfur atom bonded to one hydrogen and one carbon, C–S–H or in *sulfides,* which have a sulfur atom bonded to two carbons, C–S–C. Produced by some bacteria, methanethiol (CH_3SH) is the simplest example of a thiol, and dimethyl sulfide, $H_3C–S–CH_3$, is the simplest example of a sulfide. Both can be described by approximate sp^3 hybridization around sulfur, although both have significant deviation from the 109.5° tetrahedral angle.



Methanethiol

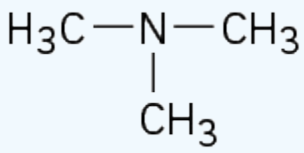


Dimethyl sulfide

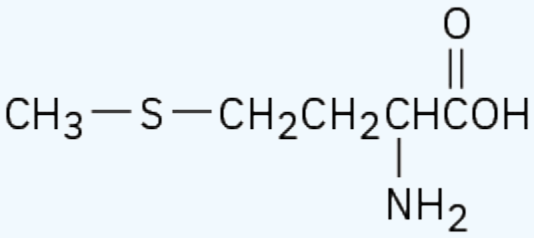
Exercise 1.12.1

Identify all lone pairs of electrons in the following molecules, and tell what geometry you expect for each of the indicated atoms.

a. The oxygen atom in dimethyl ether, $CH_3–O–CH_3$
b. The nitrogen atom in trimethylamine,



c. The phosphorus atom in phosphine, PH_3
d. The sulfur atom in the amino acid methionine,



Answer available at the end of this section.

Answers

Exercise 1.12.1

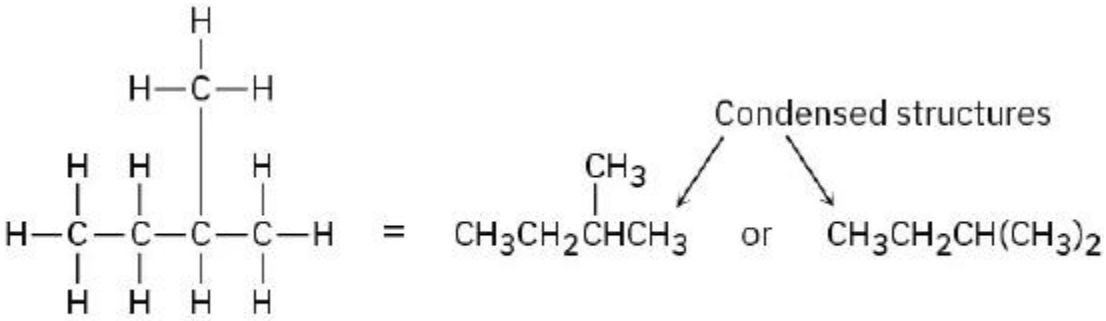
a. O has 2 lone pairs and is sp3-hybridized.
b. N has 1 lone pair and is sp3-hybridized.
c. P has 1 lone pair and is sp3-hybridized.
d. S has 2 lone pairs and is sp^3-hybridized.

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1.13: Drawing Chemical Structures

Let's cover just one more point before ending this introductory chapter. In the structures we've been drawing until now, a line between atoms has represented the two electrons in a covalent bond. Drawing every bond and every atom is tedious, however, so chemists have devised several shorthand ways for writing structures. In condensed structures, carbon–hydrogen and carbon–carbon single bonds aren't shown; instead, they're understood. If a carbon has three hydrogens bonded to it, we write CH_3; if a carbon has two hydrogens bonded to it, we write CH_2; and so on. The compound called 2-methylbutane, for example, is written as follows:



2-Methylbutane

Note that the horizontal bonds between carbons aren't shown in condensed structures—the CH_3, CH_2, and CH units are simply placed next to each other—but vertical carbon–carbon bonds like that of the first of the condensed structures drawn above are shown for clarity. Notice also in the second of the condensed structures that the two CH_3 units attached to the CH carbon are grouped together as $(CH_3)_2$. Even simpler than condensed structures are skeletal structures such as those shown in Table 1.13.1. The rules for drawing skeletal structures are straightforward.

RULE 1

Carbon atoms aren't usually shown. Instead, a carbon atom is assumed to be at each intersection of two lines (bonds) and at the end of each line. Occasionally, a carbon atom might be indicated for emphasis or clarity.

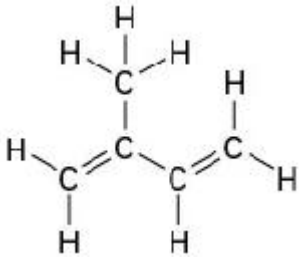
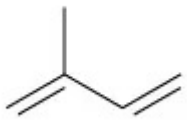
RULE 2

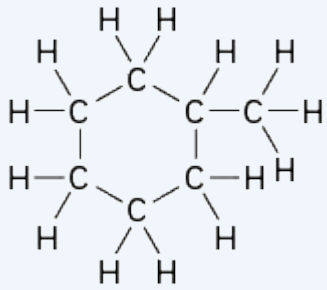
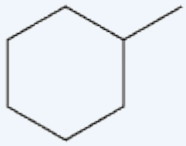
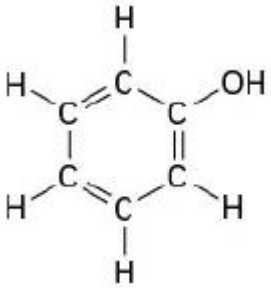
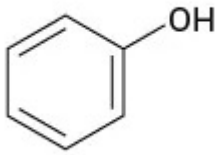
Hydrogen atoms bonded to carbon aren't shown. Because carbon always has a valence of 4, we mentally supply the correct number of hydrogen atoms for each carbon.

RULE 3

Atoms other than carbon and hydrogen *are* shown.

Table 1.13.1 *Line-bond and Skeletal Structures for Some Compounds*

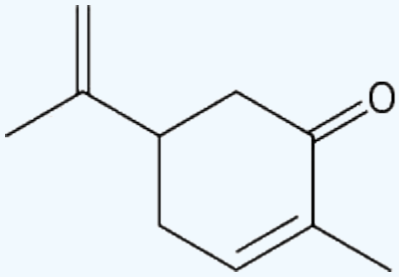
Compound	Line-bond structure	Skeletal structure
Isoprene, C_5H_8		

Compound	Line-bond structure	Skeletal structure
Methylcyclohexane, C_7H_{14}		
Phenol, C_6H_6O		

One further comment: Although such groupings as $-CH_3$, –OH, and $-NH_2$ are usually written with the C, O, or N atom first and the H atom second, the order of writing is sometimes inverted to H_3C-, HO–, and H_2N- if needed to make the bonding connections clearer. Larger units such as $-CH_2CH_3$ are not inverted, though; we don't write H_3CH_2C- because it would be confusing. There are, however, no well-defined rules that cover all cases; it's largely a matter of preference.

Worked Example 1.13.1: Interpreting a Line-Bond Structure

Carvone, a substance responsible for the odor of spearmint, has the following structure. Tell how many hydrogens are bonded to each carbon, and give the molecular formula of carvone.

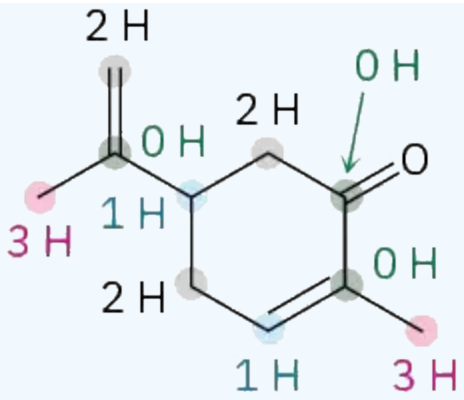


Carvone

Strategy

The end of a line represents a carbon atom with 3 hydrogens, CH_3; a two-way intersection is a carbon atom with 2 hydrogens, CH_2; a three-way intersection is a carbon atom with 1 hydrogen, CH; and a four-way intersection is a carbon atom with no attached hydrogens.

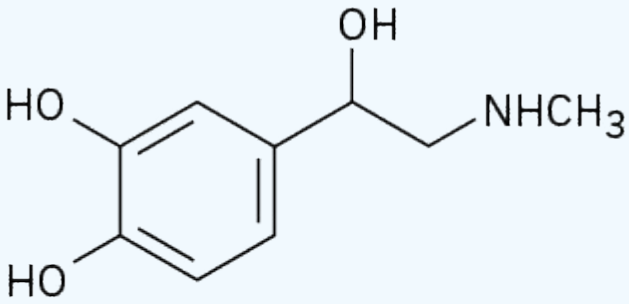
Solution



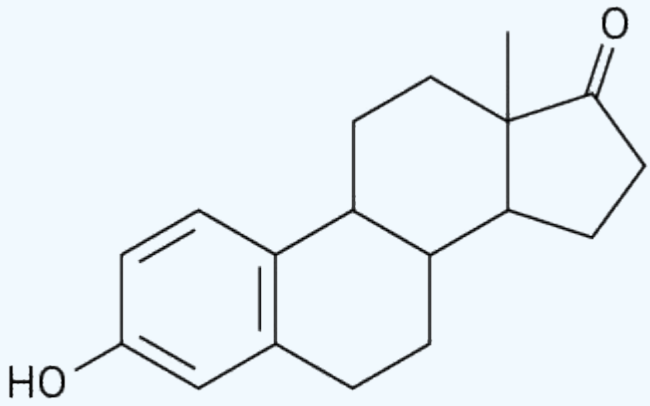
Carvone ($C_{10}H_{14}O$)

Exercise 1.13.1

How many hydrogens are bonded to each carbon in the following compounds, and what is the molecular formula of each substance?



a. **Adrenaline**



b. **Estrone (a hormone)**

Answer available at the end of this section.

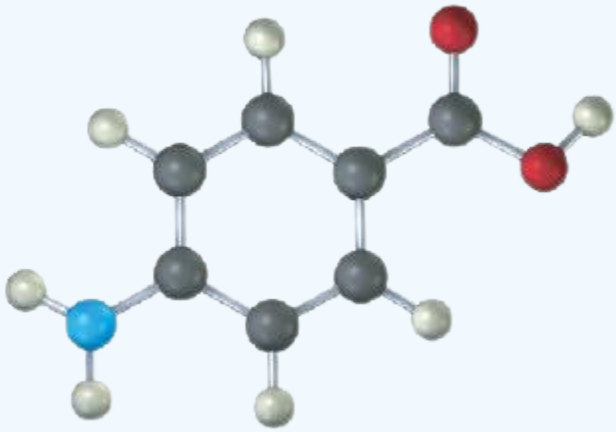
Exercise 1.13.2

Propose skeletal structures for compounds that satisfy the following molecular formulas: There is more than one possibility in each case.

a. C_5H_{12}
b. C_2H_7N
c. C_3H_6O
d. C_4H_9Cl

Answer available at the end of this section.

Exercise 1.13.3



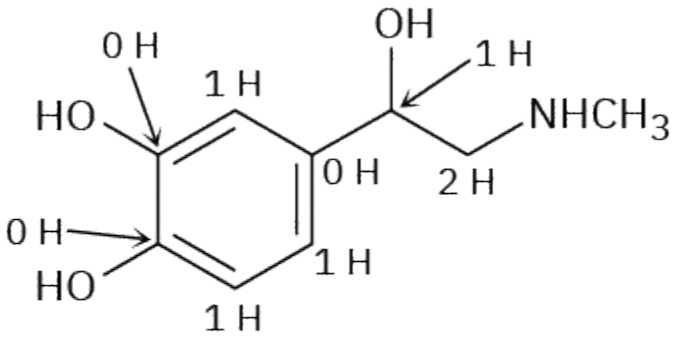
The following molecular model is a representation of *para*-aminobenzoic acid (PABA), the active ingredient in many sunscreens. Indicate the positions of the multiple bonds, and draw a skeletal structure (black = C, red = O, blue = N, gray = H).

Answer available at the end of this section.

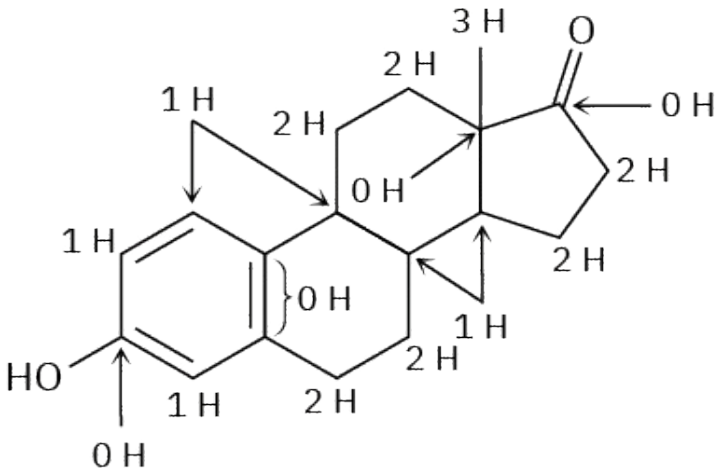
Answers

Exercise 1.13.1

a.



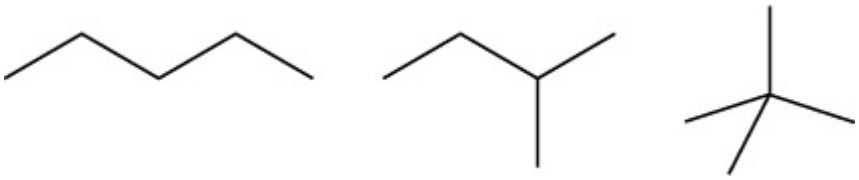
b. Adrenaline—$C_9H_{13}NO_3$



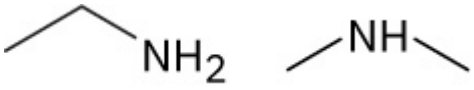
Estrone—$C_{18}H_{22}O_2$

Exercise 1.13.2

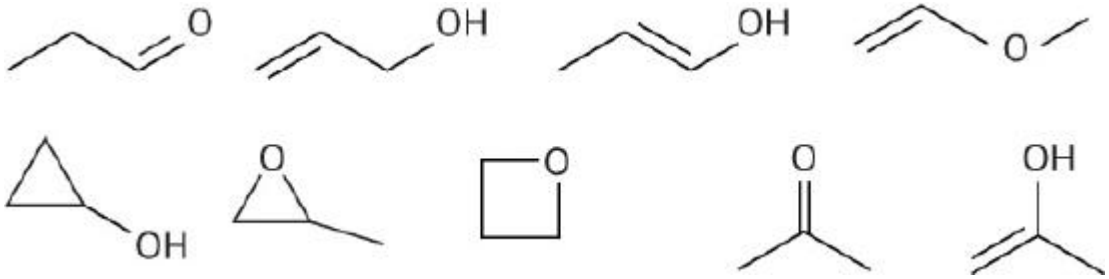
(a) There are numerous possibilities, such as:



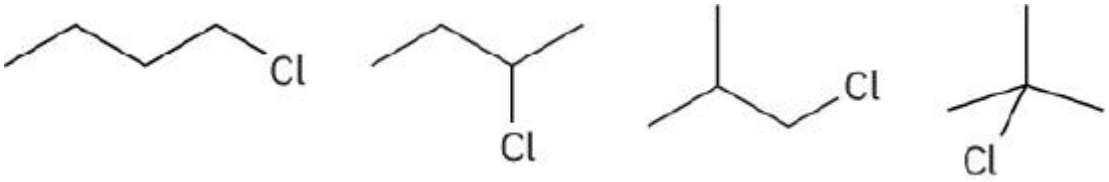
(b) There are numerous possibilities, such as:



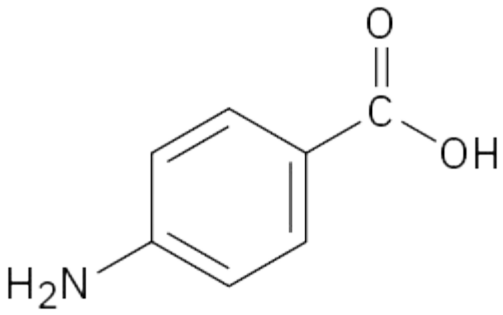
(c) There are numerous possibilities, such as:



(d) There are numerous possibilities, such as:



Exercise 1.13.3



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1.14: Chemistry Matters—Organic Foods- Risk versus Benefit

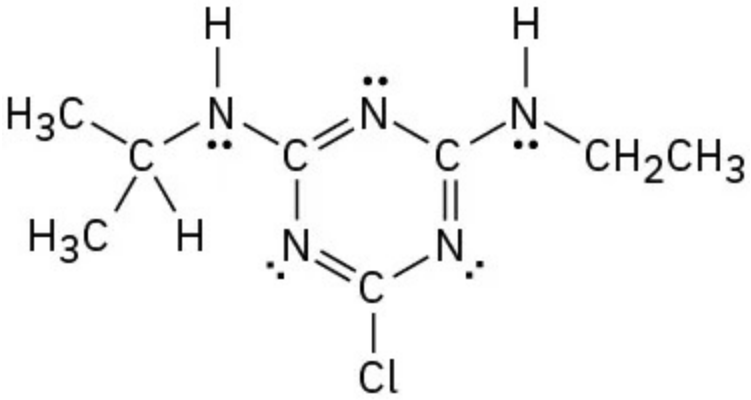
Contrary to what you may hear in supermarkets or on television, all foods are organic—that is, complex mixtures of organic molecules. Even so, when applied to food, the word *organic* has come to mean an absence of synthetic chemicals, typically pesticides, antibiotics, and preservatives. How concerned should we be about traces of pesticides in the food we eat? Or toxins in the water we drink? Or pollutants in the air we breathe?

Life is not risk-free—we all take many risks each day without even thinking about it. We decide to ride a bike rather than drive, even though there is a ten times greater likelihood per mile of dying in a bicycling accident than in a car. We decide to walk down stairs rather than take an elevator, even though 32,000 people die from falls each year in the United States. Some of us decide to smoke cigarettes, even though it increases our chance of getting cancer by 50%. But what about risks from chemicals like pesticides?



Figure 1.14.1: How dangerous is the pesticide being sprayed on this crop? (credit: "NRCSAR83001(265)" by USDA Natural Resources Conservation Service/Wikimedia Commons, Public Domain)

One thing is certain: without pesticides, whether they target weeds (herbicides), insects (insecticides), or molds and fungi (fungicides), crop production would drop significantly, food prices would increase, and famines would occur in less developed parts of the world. Take the herbicide atrazine, for instance. In the United States alone, approximately 100 million pounds of atrazine are used each year to kill weeds in corn, sorghum, and sugarcane fields, greatly improving the yields of these crops. Nevertheless, the use of atrazine continues to be a concern because traces persist in the environment. Indeed, heavy atrazine exposure *can* pose health risks to humans and some animals. Because of these risks, the United States Environmental Protection Agency (EPA) has decided not to ban its use because doing so would result in lower crop yields and increased food costs, and because there is no suitable alternative herbicide available.



Atrazine

How can the potential hazards from a chemical like atrazine be determined? Risk evaluation of chemicals is carried out by exposing test animals, usually mice or rats, to the chemical and then monitoring the animals for signs of harm. To limit the expense and time needed, the amounts administered are typically hundreds or thousands of times greater than those a person might normally encounter. The results obtained in animal tests are then distilled into a single number called an LD_{50}, the amount of substance per kilogram of body weight that is a lethal dose for 50% of the test animals. For atrazine, the LD_{50} value is between 1 and 4 g/kg depending on the animal species. Aspirin, for comparison, has an LD_{50} of 1.1 g/kg, and ethanol (ethyl alcohol) has an LD_{50} of 10.6 g/kg.

Table 1.14.1 lists the LD_{50} for some other familiar substances. The lower the value, the more toxic the substance. Note, though, that LD_{50} values only pertain to the effects of heavy exposure for a relatively short time. They say nothing about the risks of long-term exposure, such as whether the substance can cause cancer or interfere with development in the unborn.

Table 1.14.1: Some LD_{50} Values

Substance	LD_{50} (g/kg)	Substance	LD_{50} (g/kg)
Strychnine	0.005	Chloroform	1.2
Arsenic trioxide	0.015	Iron(II) sulfate	1.5
DDT	0.115	Ethyl alcohol	10.6
Aspirin	1.1	Sodium cyclamate	17

So, should we still use atrazine? All decisions involve tradeoffs, and the answer is rarely obvious. Does the benefit of increased food production outweigh possible health risks of a pesticide? Do the beneficial effects of a new drug outweigh a potentially dangerous side effect in a small number of users? Different people will have different opinions, but an honest evaluation of facts is surely the best way to start. As of June 2022, atrazine was still approved for continued use in the United States because the EPA believes that the benefits of increased food production outweigh possible health risks. At the same time, atrazine is little used, though not banned, in the European Union.

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1.A: Structure and Bonding (Summary)

Concepts & Vocabulary

1.0: Prelude to Structure and Bonding

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

1.1: Atomic Structure: The Nucleus

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

1.2: Atomic Structure: Orbitals

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

1.3: Atomic Structure: Electron Configurations

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

1.4: Development of Chemical Bonding Theory

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

1.5: The Nature of Chemical Bonds: Valence Bond Theory

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

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

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

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

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

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

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

1.9 sp Hybrid Orbitals and the Structure of Acetylene

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

1.10: Hybridization of Nitrogen, Oxygen, Phosphorus, and Sulfur

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

1.11: The Nature of Chemical Bonds: Molecular Orbital Theory

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

1.12: Drawing Chemical Structures

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

Skills to Master

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

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

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

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

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

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

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

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

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

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

Memorization Tasks (MT)

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

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

Contributors

- Dr. Kelly Matthews (Professor of Chemistry, Harrisburg Area Community College)

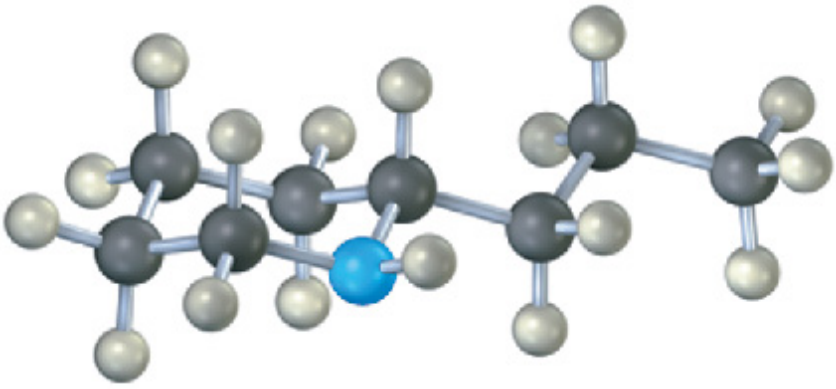
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1.B: Additional Problems

Visualizing Chemistry

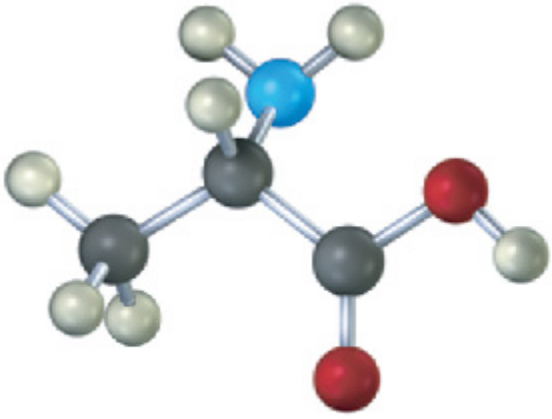
PROBLEM 1.18 Convert each of the following molecular models into a skeletal structure, and give the formula of each. Only the connections between atoms are shown; multiple bonds are not indicated (black = C, red = O, blue = N, gray = H).

(a)



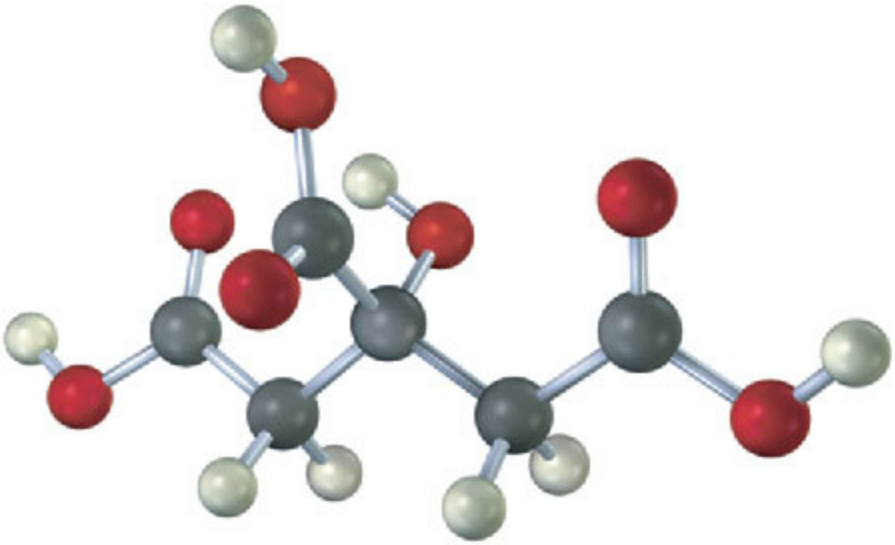
Coniine (the toxic substance in poison hemlock)

(b)

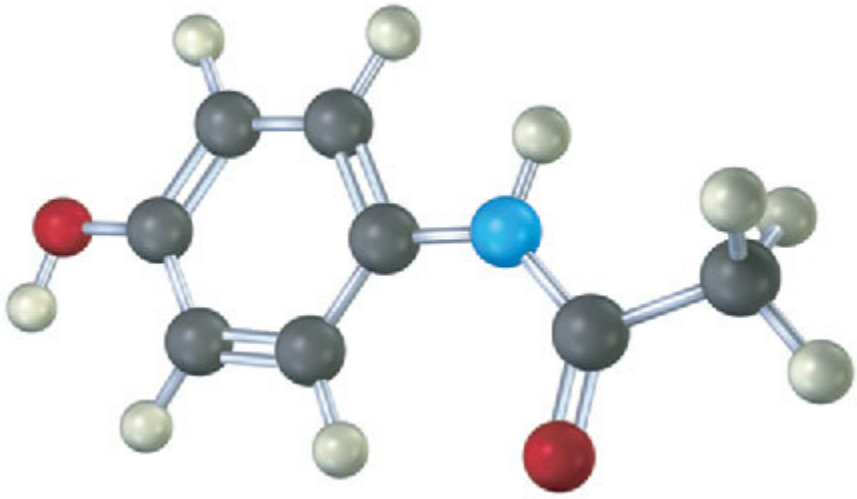


Alanine (an amino acid)

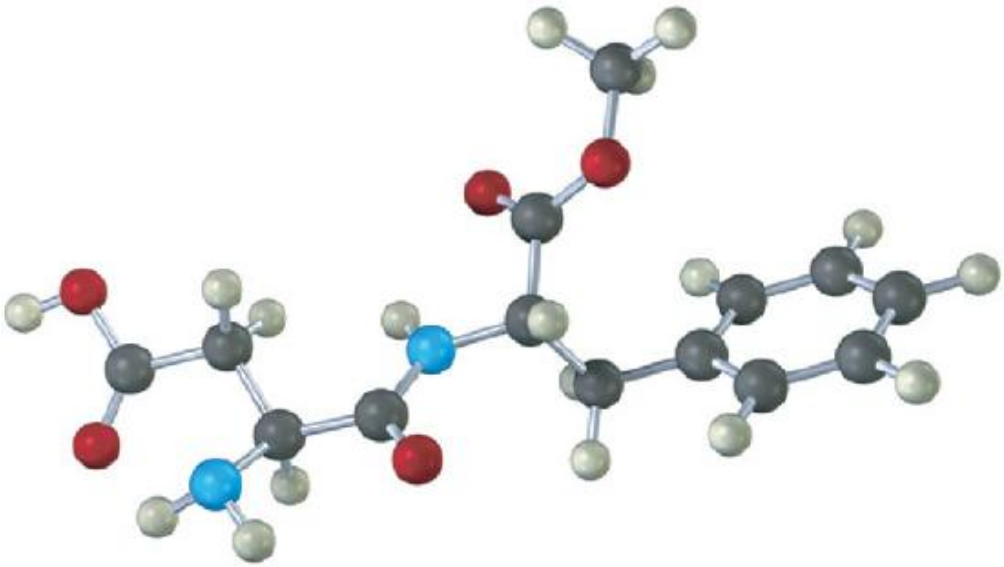
PROBLEM 1.19 The following model is a representation of citric acid, the key substance in the so-called citric acid cycle, by which food molecules are metabolized in the body. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure by indicating the positions of multiple bonds and lone-pair electrons (black = C, red = O, gray = H).



PROBLEM 1.20 The following model is a representation of acetaminophen, a pain reliever sold in drugstores under a variety of names, including Tylenol. Identify the hybridization of each carbon atom in acetaminophen, and tell which atoms have lone pairs of electrons (black = C, red = O, blue = N, gray = H).



PROBLEM 1.21 The following model is a representation of aspartame, $C_{14}H_{18}N_2O_5$, known commercially under many names, including NutraSweet. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure for aspartame, and indicate the positions of multiple bonds (black = C, red = O, blue = N, gray = H).



Electron Configurations

PROBLEM 1.22 How many valence electrons does each of the following dietary trace elements have?

(a) Zinc **(b)** Iodine **(c)** Silicon **(d)** Iron

PROBLEM 1.23 Give the ground-state electron configuration for each of the following elements:

(a) Potassium **(b)** Arsenic **(c)** Aluminum **(d)** Germanium

Electron-Dot and Line-Bond Structures

PROBLEM 1.24 What are likely formulas for the following molecules?

(a) $NH_?OH$ **(b)** $AlCl_?$ **(c)** $CF_2Cl_?$ **(d)** $CH_?O$

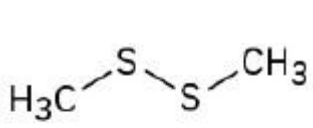
PROBLEM 1.25 Why can't molecules with the following formulas exist?

(a) CH_5 **(b)** C_2H_6N **(c)** $C_3H_5Br_2$

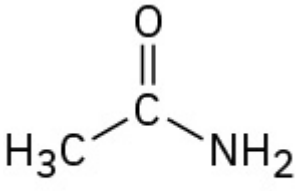
PROBLEM 1.26 Draw an electron-dot structure for acetonitrile, C_2H_3N, which contains a carbon–nitrogen triple bond. How many electrons does the nitrogen atom have in its outer shell? How many are bonding, and how many are nonbonding?

PROBLEM 1.27 Draw a line-bond structure for vinyl chloride, C_2H_3Cl, the starting material from which PVC poly(vinyl chloride) plastic is made.

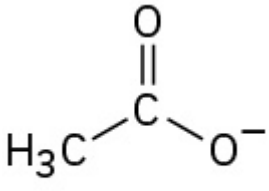
PROBLEM 1.28 Fill in any nonbonding valence electrons that are missing from the following structures:



(a) **Dimethyl disulfide**

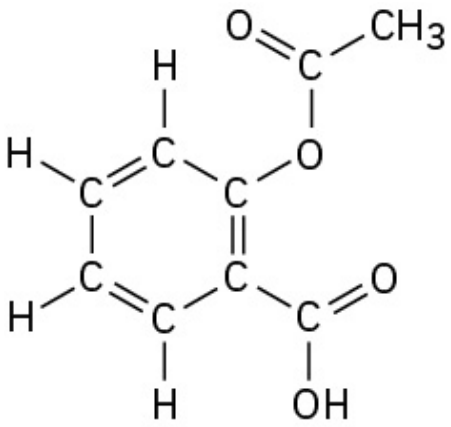


(b) **Acetamide**



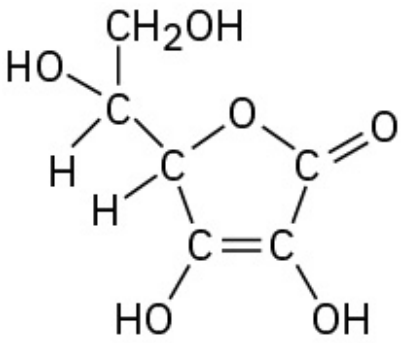
(c) **Acetate ion**

PROBLEM 1.29 Convert the following line-bond structures into molecular formulas:



Aspirin
(acetylsalicylic acid)

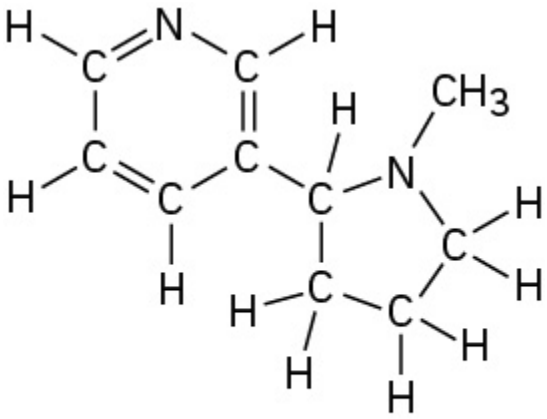
(a)



Vitamin C
(ascorbic acid)

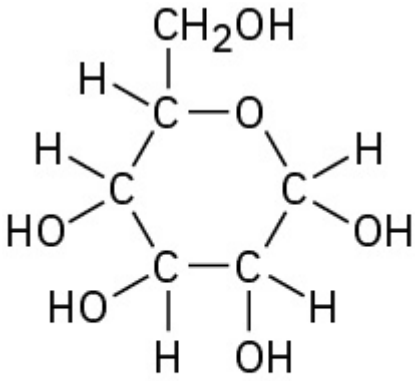
(b)

(c)



Nicotine

(d)



Glucose

PROBLEM 1.30 Convert the following molecular formulas into line-bond structures that are consistent with valence rules:

(a) C_3H_8 **(b)** CH_5N **(c)** C_2H_6O (2 possibilities)

(d) C_3H_7Br (2 possibilities) **(e)** C_2H_4O (3 possibilities) **(f)** C_3H_9N (4 possibilities)

PROBLEM 1.31 Draw a three-dimensional representation of the oxygen-bearing carbon atom in ethanol, CH_3CH_2OH, using the standard convention of solid, wedged, and dashed lines.

PROBLEM 1.32 Oxaloacetic acid, an important intermediate in food metabolism, has the formula $C_4H_4O_5$ and contains three C==O bonds and two O–H bonds. Propose two possible structures.

PROBLEM 1.33 Draw structures for the following molecules, showing lone pairs:

(a) Acrylonitrile, C_3H_3N, which contains a carbon–carbon double bond and a carbon–nitrogen triple bond

(b) Ethyl methyl ether, C_3H_8O, which contains an oxygen atom bonded to two carbons

(c) Butane, C_4H_{10}, which contains a chain of four carbon atoms

(d) Cyclohexene, C_6H_{10}, which contains a ring of six carbon atoms and one carbon–carbon double bond

Hybridization

PROBLEM 1.34 What is the hybridization of each carbon atom in acetonitrile (Problem 1-26)?

PROBLEM 1.35 What kind of hybridization do you expect for each carbon atom in the following molecules?

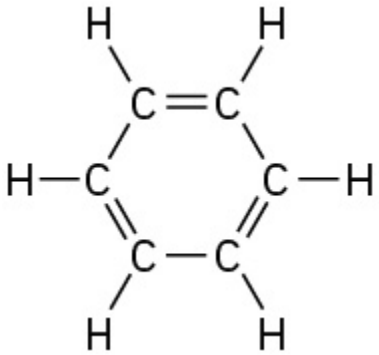
(a) Propane, $CH_3CH_2CH_3$

(b) 2-Methylpropene, $CH_3C(=CH_2)CH_3$

(c) Acetic acid, CH_3COOH

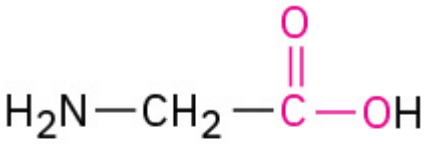
(d) But-1-en-3-yne, $H_2C{=}CH{-}C{\equiv}CH$

PROBLEM 1.36 What is the shape of benzene, and what hybridization do you expect for each carbon?

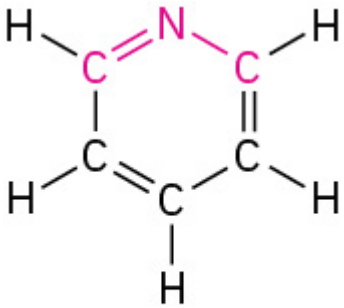


Benzene

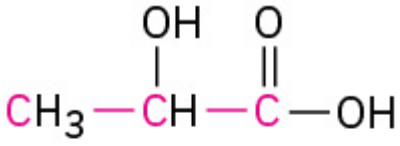
PROBLEM 1.37 What bond angle do you expect for each of the indicated atoms, and what kind of hybridization do you expect for the central atom in each molecule?



(a) **Glycine (an amino acid)**



(b) **Pyridine**



(c) **Lactic acid (in sour milk)**

PROBLEM 1.38 Propose structures for molecules that meet the following descriptions:

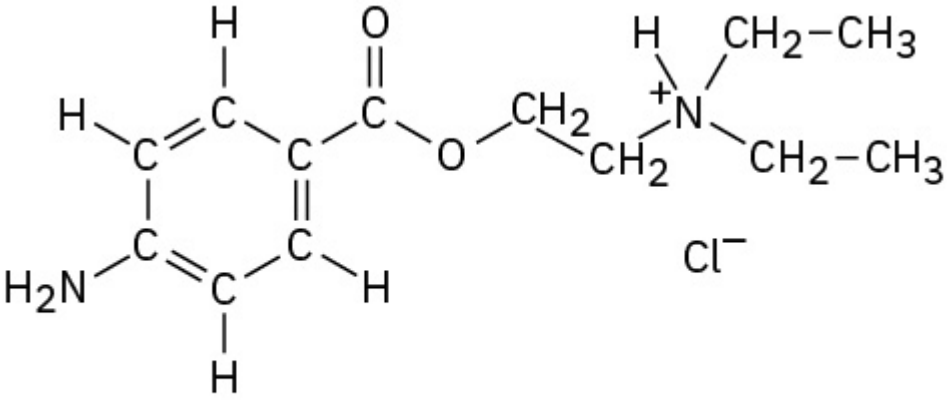
(a) Contains two sp^2-hybridized carbons and two sp^3-hybridized carbons

(b) Contains only four carbons, all of which are sp^2-hybridized

(c) Contains two *sp*-hybridized carbons and two sp^2-hybridized carbons

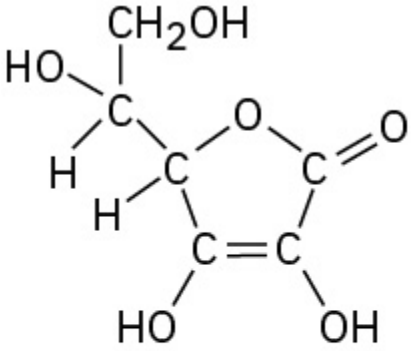
PROBLEM 1.39 What kind of hybridization do you expect for each carbon atom in the following molecules:

(a)



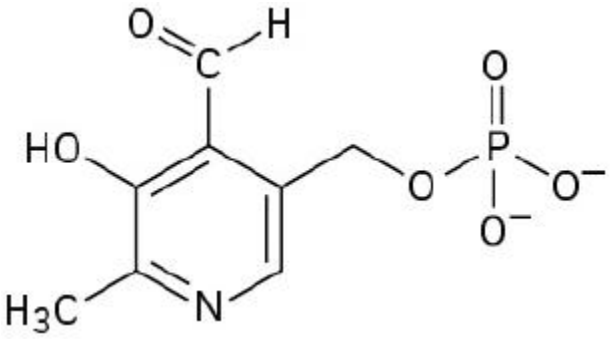
Procaine

(b)



Vitamin C
(ascorbic acid)

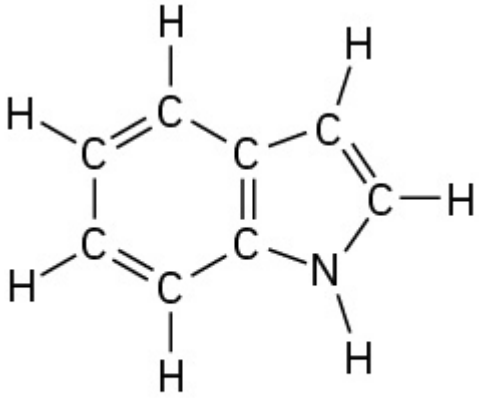
PROBLEM 1.40 Pyridoxal phosphate, a close relative of vitamin B_6, is involved in a large number of metabolic reactions. What is the hybridization and the bond angle for each nonterminal atom?



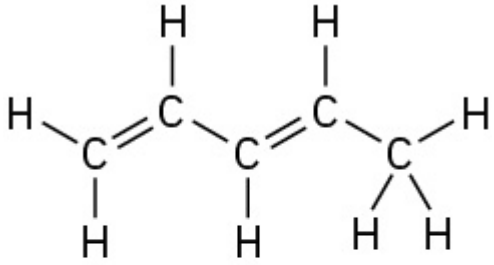
Pyridoxal phosphate

Skeletal Structures

PROBLEM 1.41 Convert the following structures into skeletal drawings:

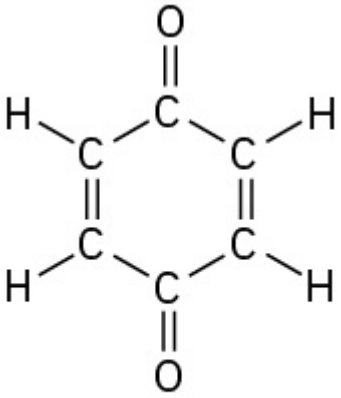


(a) Indole



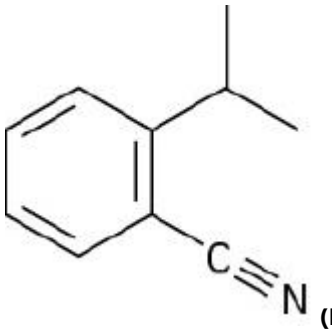
(b) 1,3-Pentadiene

(c) 1,2-Dichlorocyclopentane

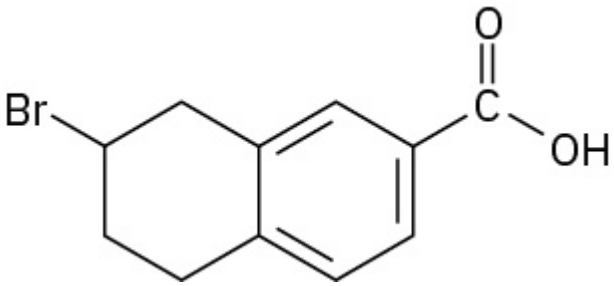


(d) Benzoquinone

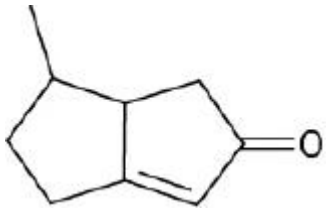
PROBLEM 1.42 How many hydrogens are bonded to each carbon atom in the following substances, and what is the molecular formula of each?



(a)

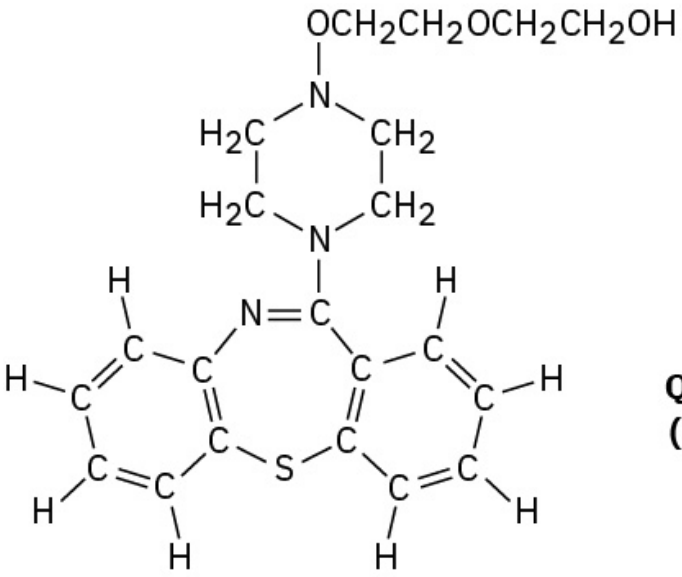


(b)



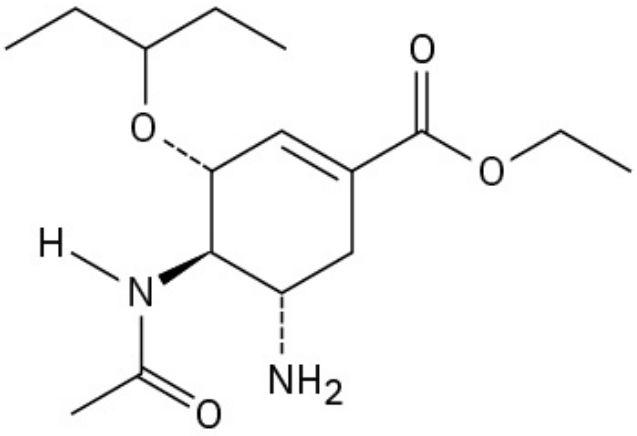
(c)

PROBLEM 1.43 Quetiapine, marketed as Seroquel, is a heavily prescribed antipsychotic drug used in the treatment of schizophrenia and bipolar disorder. Convert the following representation into a skeletal structure, and give the molecular formula of quetiapine.



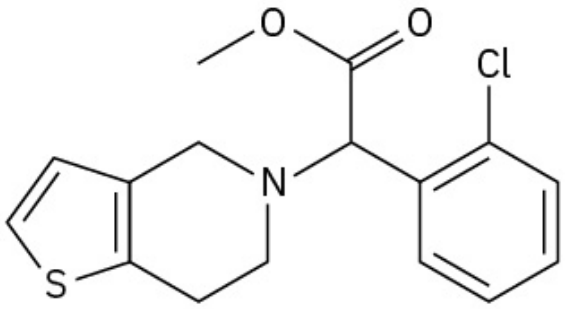
Quetiapine
(Seroquel)

PROBLEM 1.44 How many hydrogens are bonded to each carbon atom in (a) the antiinfluenza agent oseltamivir, marketed as Tamiflu, and (b) the platelet aggregation inhibitor clopidogrel, marketed as Plavix? Give the molecular formula of each.



Oseltamivir
(Tamiflu)

(a)



Clopidogrel
(Plavix)

(b)

General Problems

PROBLEM 1.45 Why do you suppose no one has ever been able to make cyclopentyne as a stable molecule?

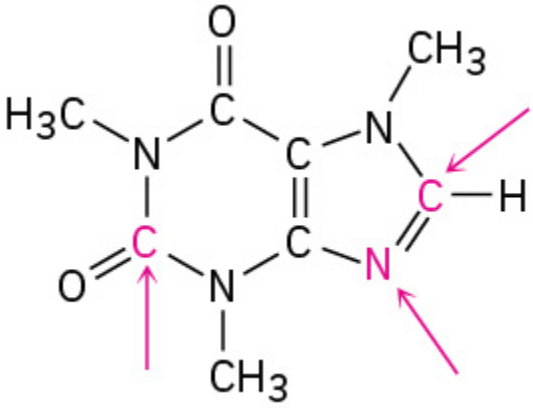


Cyclopentyne

PROBLEM 1.46 Allene, $H_2C{=}C{=}CH_2$, has two adjacent double bonds. Draw a picture showing the orbitals involved in the σ and π bonds of allene. Is the central carbon atom sp^2- or *sp*-hybridized? What about the hybridization of the terminal carbons? What shape do you predict for allene?

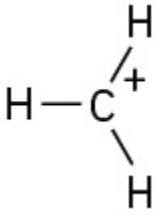
PROBLEM 1.47 Allene (see previous PROBLEM) is structurally related to carbon dioxide, CO_2. Draw a picture showing the orbitals involved in the σ and π bonds of CO_2, and identify the likely hybridization of carbon.

PROBLEM 1.48 Complete the electron-dot structure of caffeine, showing all lone-pair electrons, and identify the hybridization of the indicated atoms.



Caffeine

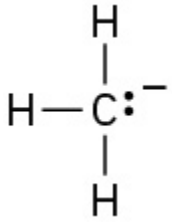
PROBLEM 1.49 Most stable organic species have tetravalent carbon atoms, but species with trivalent carbon atoms also exist. Carbocations are one such class of compounds.



A carbocation

1. How many valence electrons does the positively charged carbon atom have?
2. What hybridization do you expect this carbon atom to have?
3. What geometry is the carbocation likely to have?

PROBLEM 1.50 A *carbanion* is a species that contains a negatively charged, trivalent carbon.



A carbanion

a. What is the electronic relationship between a carbanion and a trivalent nitrogen compound such as NH_3?
b. How many valence electrons does the negatively charged carbon atom have?
c. What hybridization do you expect this carbon atom to have?
d. What geometry is the carbanion likely to have?

PROBLEM 1.51 Divalent carbon species called *carbenes* are capable of fleeting existence. For example, methylene, $:CH_2$, is the simplest carbene. The two unshared electrons in methylene can be either paired in a single orbital or unpaired in different orbitals. Predict the type of hybridization you expect carbon to adopt in singlet (spin-paired) methylene and triplet (spin-unpaired) methylene. Draw a picture of each, and identify the valence orbitals on carbon.

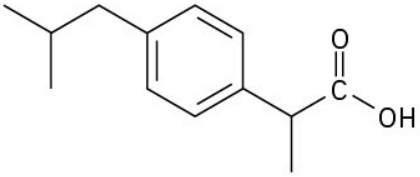
PROBLEM 1.52 Two different substances have the formula C_4H_{10}. Draw both, and tell how they differ.

PROBLEM 1.53 Two different substances have the formula C_3H_6. Draw both, and tell how they differ.

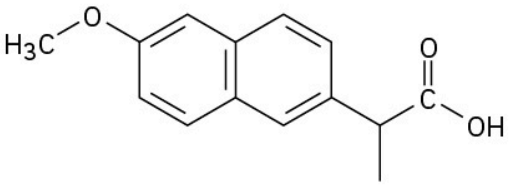
PROBLEM 1.54 Two different substances have the formula C_2H_6O. Draw both, and tell how they differ.

PROBLEM 1.55 Three different substances contain a carbon–carbon double bond and have the formula C_4H_8. Draw them, and tell how they differ.

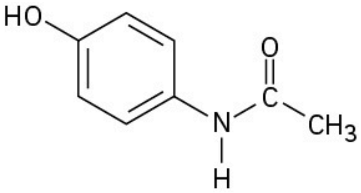
PROBLEM 1.56 Among the most common over-the-counter drugs you might find in a medicine cabinet are mild pain relievers such ibuprofen (Advil, Motrin), naproxen (Aleve), and acetaminophen (Tylenol).



Ibuprofen



Naproxen



Acetaminophen

a. How many sp^3-hybridized carbons does each molecule have?
b. How many sp^2-hybridized carbons does each molecule have?
c. What similarities can you see in their structures?

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2: POLAR COVALENT BONDS; ACIDS AND BASES

Chapter Objectives

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

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

2.0: Why This Chapter?

2.1: Polar Covalent Bonds - Electronegativity

2.2: Polar Covalent Bonds - Dipole Moments

2.3: Intermolecular Forces

2.4: Physical Properties of Organic Compounds

2.5: Formal Charges

2.6: Resonance

2.7: Drawing Resonance Forms

2.8: Acids and Bases - The Brønsted-Lowry Definition

2.9: Acid and Base Strength

2.10: Organic Acids and Organic Bases

2.11: Structural Effects on Acidity and Basicity

2.12: Acids and Bases - The Lewis Definition

2.13: Chemistry Matters—Alkaloids- From Cocaine to Dental Anesthetics

2.A: Polar Covalent Bonds; Acids and Bases (Summary)

2.B: Additional Problems

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2.0: Why This Chapter?

Understanding organic chemistry means knowing not just what happens but also why and how it happens at the molecular level. In this chapter, we'll look at some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation to understand the specific reactions discussed in subsequent chapters. Topics such as bond polarity, the acid–base behavior of molecules, and hydrogen-bonding are a particularly important part of that foundation.



Figure 2.0.1: The opium poppy is the source of morphine, one of the first "vegetable alkali," or *alkaloids*, to be isolated. (credit: "*Papaver somniferum*" by Liz West/Flickr, CC BY 2.0)

We saw in the previous chapter how covalent bonds between atoms are described, and we looked at the valence bond model, which uses hybrid orbitals to account for the observed shapes of organic molecules. Before going on to a systematic study of organic chemistry, however, we still need to review a few fundamental topics. In particular, we need to look more closely at how electrons are distributed in covalent bonds and at some of the consequences that arise when the electrons in a bond are not shared equally between atoms.

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2.1: Polar Covalent Bonds - Electronegativity

Up to this point, we've treated chemical bonds as either ionic or covalent. The bond in sodium chloride, for instance, is ionic. Sodium transfers an electron to chlorine to produce Na^+ and Cl^- ions, which are held together in the solid by electrostatic attractions between unlike charges. The C–C bond in ethane, however, is covalent. The two bonding electrons are shared equally by the two equivalent carbon atoms, resulting in a symmetrical electron distribution in the bond. Most bonds, however, are neither fully ionic nor fully covalent but are somewhere between the two extremes. Such bonds are called polar covalent bonds, meaning that the bonding electrons are attracted more strongly by one atom than the other so that the electron distribution between atoms is not symmetrical (Figure 2.1.1).

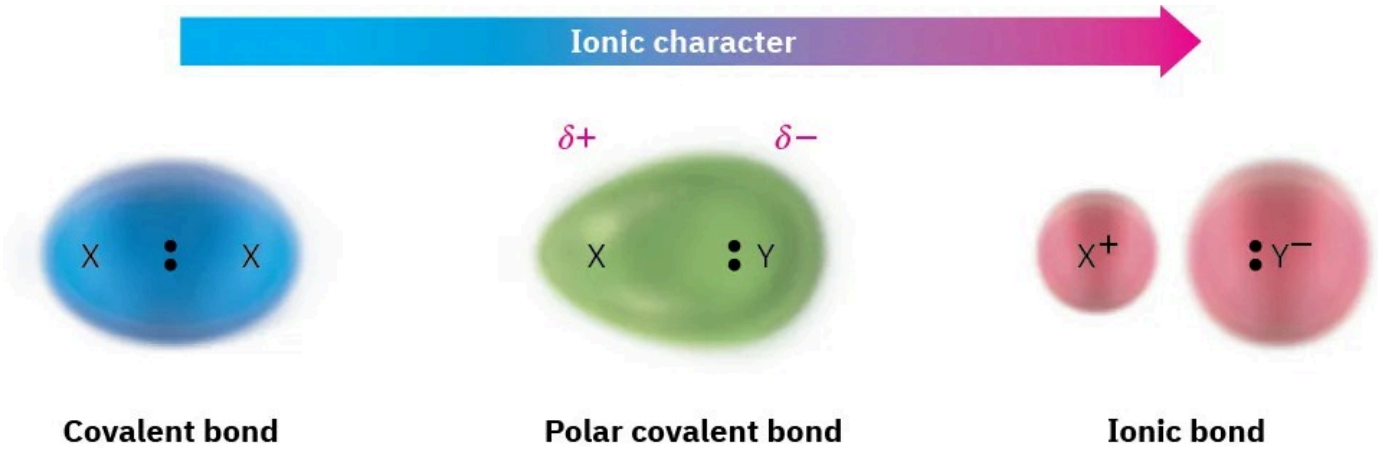


Figure 2.1.1: The continuum in bonding from covalent to ionic is a result of an unequal distribution of bonding electrons between atoms.

The symbol δ (lowercase Greek letter delta) means *partial* charge, either partial positive (δ+) for the electron-poor atom or partial negative (δ–) for the electron-rich atom.

Bond polarity is due to differences in electronegativity (EN), the intrinsic ability of an atom to attract the shared electrons in a covalent bond. As shown in Figure 2.1.2, electronegativities are based on an arbitrary scale, with fluorine the most electronegative (EN = 4.0) and cesium the least (EN = 0.7). Metals on the left side of the periodic table attract electrons weakly and have lower electronegativities, while oxygen, nitrogen, and halogens on the right side of the periodic table attract electrons strongly and have higher electronegativities. Carbon, the most important element in organic compounds, has an intermediate electronegativity value of 2.5.

H 2.1																He
Li 1.0	Be 1.6											B 2.0	C 2.5	N 3.0	O 3.5	F 4.0	Ne
Na 0.9	Mg 1.2											Al 1.5	Si 1.8	P 2.1	S 2.5	Cl 3.0	Ar
K 0.8	Ca 1.0	Sc 1.3	Ti 1.5	V 1.6	Cr 1.6	Mn 1.5	Fe 1.8	Co 1.9	Ni 1.9	Cu 1.9	Zn 1.6	Ga 1.6	Ge 1.8	As 2.0	Se 2.4	Br 2.8	Kr
Rb 0.8	Sr 1.0	Y 1.2	Zr 1.4	Nb 1.6	Mo 1.8	Tc 1.9	Ru 2.2	Rh 2.2	Pd 2.2	Ag 1.9	Cd 1.7	In 1.7	Sn 1.8	Sb 1.9	Te 2.1	I 2.5	Xe
Cs 0.7	Ba 0.9	La 1.0	Hf 1.3	Ta 1.5	W 1.7	Re 1.9	Os 2.2	Ir 2.2	Pt 2.2	Au 2.4	Hg 1.9	Tl 1.8	Pb 1.9	Bi 1.9	Po 2.0	At 2.1	Rn

Figure 2.1.2 Electronegativity values and trends. Electronegativity generally increases from left to right across the periodic table and decreases from top to bottom. The values are on an arbitrary scale, with F = 4.0 and Cs = 0.7. Elements in **red** are the most electronegative, those in **yellow** are medium, and those in **green** are the least electronegative.

As a rough guide, bonds between atoms whose electronegativities differ by less than 0.5 are nonpolar covalent, bonds between atoms whose electronegativities differ by 0.5 to 2 are polar covalent, and bonds between atoms whose electronegativities differ by more than 2 are largely ionic. Carbon–hydrogen bonds, for example, are relatively nonpolar because carbon (EN = 2.5) and hydrogen (EN = 2.1) have similar electronegativities. Bonds between carbon and more electronegative elements such as oxygen (EN = 3.5) and nitrogen (EN = 3.0), by contrast, are polarized so that the bonding electrons are drawn away from carbon toward the electronegative atom. This leaves carbon with a partial positive charge, δ–, and the electronegative atom with a partial negative charge, δ–. An example is the C–O bond in methanol, CH_3OH (Figure 2.1.3*a*). Bonds between carbon and less electronegative elements are polarized so that carbon bears a partial negative charge and the other atom bears a partial positive charge. An example is the C–Li bond in methyllithium, CH_3Li (Figure 2.1.3*b*).

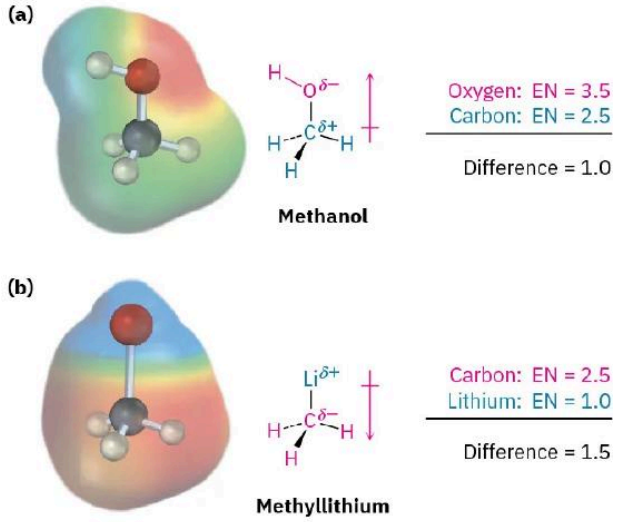


Figure 2.1.3: Polar covalent bonds. (a) Methanol, CH_3OH, has a polar covalent C–O bond, and **(b)** methyllithium, CH_3Li, has a polar covalent C–Li bond. The computer-generated representations, called electrostatic potential maps, use color to show calculated charge distributions, ranging from **red (electron-rich; *δ*–)** to **blue (electron-poor; *δ*+).**

Note in the representations of methanol and methyllithium in Figure 2.1.3 that a crossed arrow  is used to indicate the direction of bond polarity. By convention, electrons are displaced in the direction of the arrow. The tail of the arrow (which looks like a plus sign) is electron-poor (δ+), and the head of the arrow is electron-rich (δ–).

Note also in Figure 2.1.3 that calculated charge distributions in molecules can be displayed visually with what are called electrostatic potential maps, which use color to indicate electron-rich (red; δ–) and electron-poor (blue; δ+) regions. In methanol, oxygen carries a partial negative charge and is colored red, while the carbon and hydrogen atoms carry partial positive charges and are colored blue-green. In methyllithium, lithium carries a partial positive charge (blue), while carbon and the hydrogen atoms carry partial negative charges (red). Electrostatic potential maps are useful because they show at a glance the electron-rich and electron-poor atoms in molecules. We'll make frequent use of these maps throughout the text and will see many examples of how electronic structure correlates with chemical reactivity.

When speaking of an atom's ability to polarize a bond, we often use the term *inductive effect*. An inductive effect is simply the shifting of electrons in a σ bond in response to the electronegativity of nearby atoms. Metals, such as lithium and magnesium, inductively donate electrons, whereas reactive nonmetals, such as oxygen and nitrogen, inductively withdraw electrons. Inductive effects play a major role in understanding chemical reactivity, and we'll use them many times throughout this text to explain a variety of chemical observations.

Exercise 2.1.1

Which element in each of the following pairs is more electronegative?

a. Li or H
b. B or Br

c. Cl or I
d. C or H

Answer available at the end of this section.

Exercise 2.1.2

Use the $\delta+/\delta-$ convention to indicate the direction of expected polarity for each of the bonds indicated.

a. $H_3C–Cl$
b. $H_3C–NH_2$
c. $H_2N–H$
d. $H_3C–SH$
e. $H_3C–MgBr$
f. $H_3C–F$

Answer available at the end of this section.

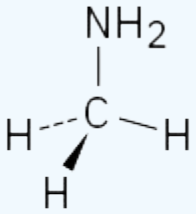
Exercise 2.1.3

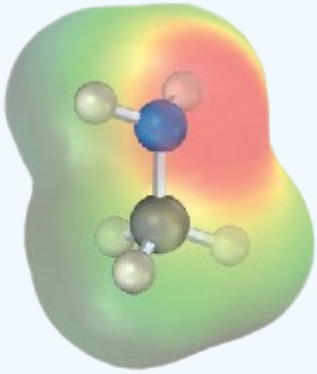
Use the electronegativity values shown in Figure 2.1.2 to rank the following bonds from least polar to most polar: $H_3C–Li$, $H_3C–K$, $H_3C–F$, $H_3C–MgBr$, $H_3C–OH$

Answer available at the end of this section.

Exercise 2.1.4

Look at the following electrostatic potential map of methylamine, a substance responsible for the odor of rotting fish, and tell the direction of polarization of the C–N bond:





Answer available at the end of this section.

Answers

Exercise 2.1.1

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

Exercise 2.1.2

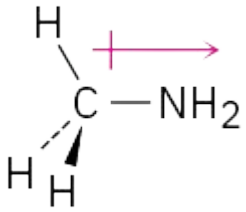
a. $\mathrm{H_3\overset{\delta+}{C}-\overset{\delta-}{Cl}}$
b. $\mathrm{H_3\overset{\delta+}{C}-\overset{\delta-}{N}H_2}$
c. $\mathrm{H_2\overset{\delta-}{N}-\overset{\delta+}{H}}$
d. $\mathrm{H_3C-SH}$ Carbon and sulfur have identical electronegativities.
e. $\mathrm{H_3\overset{\delta}{C}-\overset{\delta+}{MgBr}}$
f. $\mathrm{H_3{}^{\delta+}-\overset{\delta-}{F}}$

Exercise 2.1.3

$H_3C–OH < H_3C–MgBr < H_3C–Li = H_3C–F < H_3C–K$

Exercise 2.1.4

The nitrogen is electron-rich, and the carbon is electron-poor.



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2.2: Polar Covalent Bonds - Dipole Moments

Just as individual bonds are often polar, molecules as a whole are often polar as well. Molecular polarity results from the vector summation of all individual bond polarities and lone-pair contributions in the molecule. As a practical matter, strongly polar substances are often soluble in polar solvents like water, whereas less polar substances are insoluble in water.

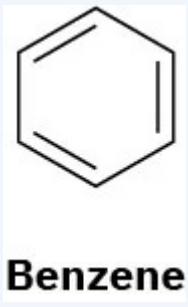
Net polarity is measured by a quantity called the *dipole moment* and can be thought of in the following way: assume that there is a center of mass of all positive charges (nuclei) in a molecule and a center of mass of all negative charges (electrons). If these two centers don't coincide, then the molecule has a net polarity.

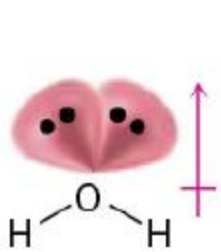
The dipole moment, μ (lowercase Greek letter mu), is defined as the magnitude of the charge Q at either end of the molecular dipole times the distance r between the charges, $\mu = Q \times r$. Dipole moments are expressed in *debyes* (D), where 1 D = 3.336×10^{-30} coulomb meters (C · m) in SI units. For example, the unit charge on an electron is 1.60×10^{-19} C. Thus, if one positive charge and one negative charge are separated by 100 pm (a bit less than the length of a typical covalent bond), the dipole moment is 1.60×10^{-29} C · m, or 4.80 D.

$$\begin{aligned} \mu &= Q \times r \\ \mu &= \left(1.60 \times 10^{-19}\text{C}\right)\left(100 \times 10^{-12}\text{ m}\right)\left(\frac{1\text{D}}{3.336 \times 10^{-35}\text{C} - \text{m}}\right) = 4.80\text{D} \end{aligned} \tag{2.2.1}$$

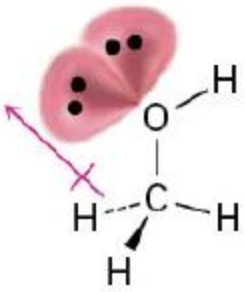
Dipole moments for some common substances are given in Table 2.2.1. Of the compounds shown in the table, sodium chloride has the largest dipole moment (9.00 D) because it is ionic. Even small molecules like water (μ = 1.85 D), methanol (CH_3OH; μ = 1.70 D), and ammonia (μ = 1.47 D), have substantial dipole moments, however, both because they contain strongly electronegative atoms (oxygen and nitrogen) and because all three molecules have lone-pair electrons. The lone-pair electrons on oxygen and nitrogen stick out into space away from the positively charged nuclei, giving rise to a considerable charge separation and making a large contribution to the dipole moment.

Table 2.2.1: Dipole Moments of Some Compounds

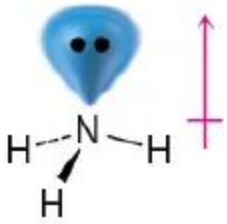
Compound	Dipole moment (D)	Compound	Dipole moment (D)
NaCl	9.00	NH_3	1.47
CH_2O	2.33	CH_3NH_2	1.31
CH_3Cl	1.87	CO_2	0
H_2O	1.85	CH_4	0
CH_3OH	1.70	CH_3CH_3	0
CH_3CO_2H	1.70	 Benzene	0
CH_3SH	1.52		



Water
(μ = 1.85 D)

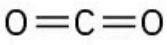


Methanol
(μ = 1.70 D)

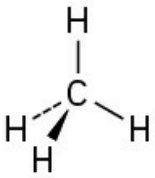


Ammonia
(μ = 1.47 D)

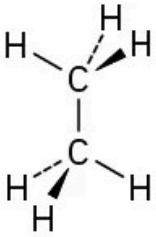
In contrast with water, methanol, and ammonia, molecules such as carbon dioxide, methane, ethane, and benzene have zero dipole moments. Because of the symmetrical structures of these molecules, the individual bond polarities and lone-pair contributions exactly cancel.



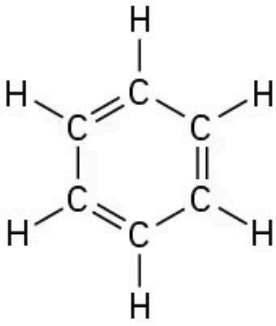
Carbon dioxide
(μ = 0)



Methane
(μ = 0)



Ethane
(μ = 0)



Benzene
(μ = 0)

Worked Example 2.2.1: Predicting the Direction of a Dipole Moment

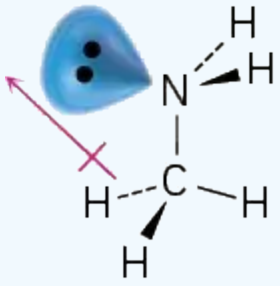
Make a three-dimensional drawing of methylamine, CH_3NH_2, and show the direction of its dipole moment (μ = 1.31).

Strategy

Look for any lone-pair electrons, and identify any atom with an electronegativity substantially different from that of carbon. (Usually, this means O, N, F, Cl, or Br.) Electron density will be displaced in the general direction of the electronegative atoms and the lone pairs.

Solution

Methylamine contains an electronegative nitrogen atom with a lone pair of electrons. The dipole moment thus points generally from $-CH_3$ toward the lone pair.



Methylamine
(μ = 1.31)

Exercise 2.2.1

Ethylene glycol, $HOCH_2CH_2OH$, may look nonpolar when drawn, but an internal hydrogen bond between the two –OH groups results in a dipole moment. Explain.

Answer available at the end of this section.

Exercise 2.2.2

Make three-dimensional drawings of the following molecules, and predict whether each has a dipole moment. If you expect a dipole moment, show its direction.

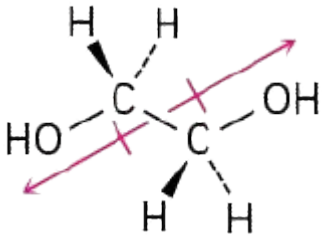
a. $H_2C{=}CH_2$
b. $CHCl_3$
c. CH_2Cl_2
d. $H_2C{=}CCl_2$

Answer available at the end of this section.

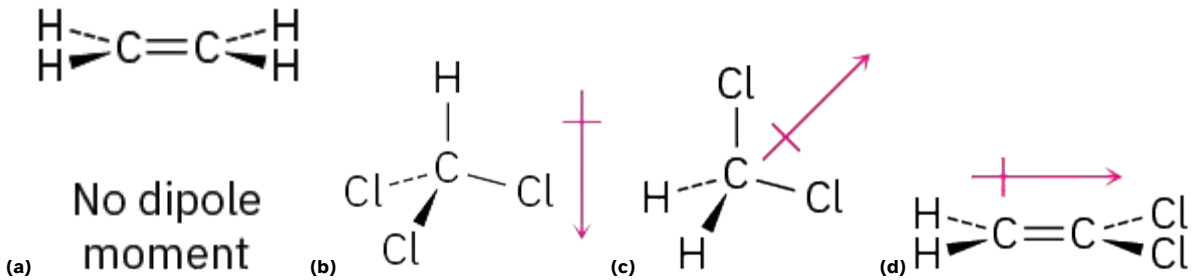
Answers

Exercise 2.2.1

The two C–O dipoles cancel because of the symmetry of the molecule:



Exercise 2.2.2



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2.3: Intermolecular Forces

Intermolecular Forces

In Organic Chemistry, understanding the physical properties of organic compounds, such as boiling point (b.p.), molecular polarity, and solubility, is crucial. It provides us with helpful information on how to deal with a substance properly. Those physical properties are essentially determined by the intermolecular forces involved. **Intermolecular forces** are the attractive forces ***between*** molecules that hold the molecules together; it is an electrical force in nature.

In this section, we will discuss the types of IMF in molecular compounds (from weakest to strongest):

- London dispersion forces
- Dipole-dipole interactions
- Hydrogen bonding
- Ion-Dipole
- Ionic Bond

London Dispersion Forces

Dispersion Forces (also called London Forces) result from the instantaneous dipole and induced dipole of the molecules. For nonpolar molecules, the constant shifting and distortion of electron density leads to a weak, short-lived dipole at a given moment, which is called an instantaneous dipole. Such temporary dipoles will induce the electrons in a neighboring molecule to get distorted as well, and to develop a corresponding transient dipole of its own, which is the induced dipole. At the end, all nonpolar molecules are attracted together via the temporary dipoles illustrated in Figure 2.3.1. The dispersion force is weak in nature and is the weakest intermolecular force. However, since it applies to all types of molecules (it is the only intermolecular force for nonpolar molecules), dispersion forces are also the most fundamental intermolecular force.

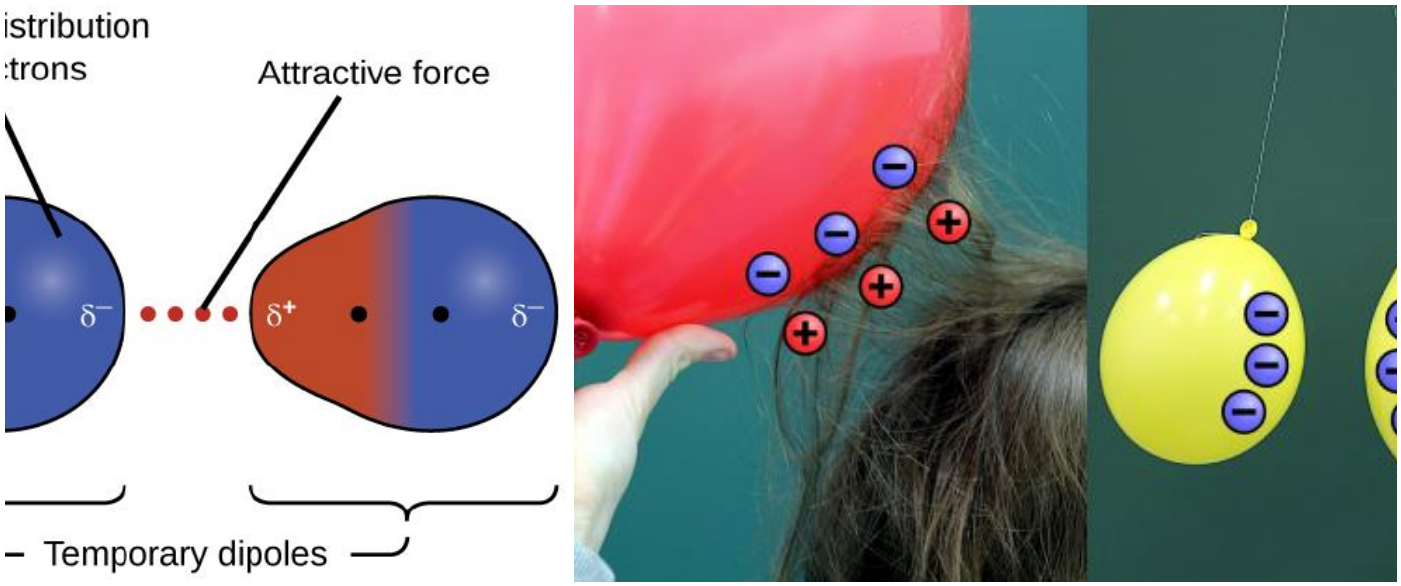


Figure 2.3.1: Dispersion forces result from the formation of temporary dipoles, as illustrated here for two nonpolar diatomic molecules.

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 2.3.2, 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.

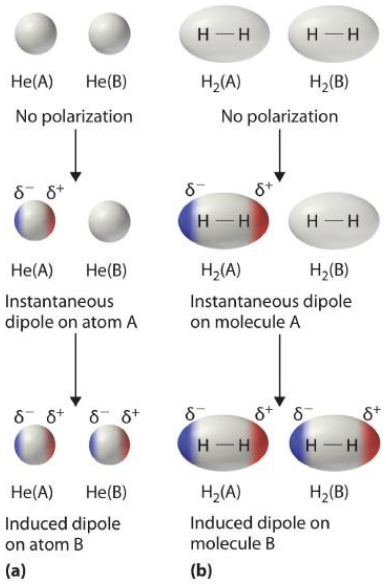


Figure 2.3.2: Instantaneous Dipole Moments. The formation of an instantaneous dipole moment on one He atom (a) or an H_2 molecule (b) results in the formation of an induced dipole on an adjacent atom or molecule.

Non-polar Molecules with non-polar bonds experience no other type of intermolecular interaction than dispersion forces. For Molecules with polar bonds, where the covalent bonds are oriented in space in such a way that the effect of the polar bonds in the molecules cancel each other out, the individual bonds are polar, but due to molecular symmetry, the overall molecule is ***nonpolar*.** Such molecules only experience London Forces. Carbon dioxide (CO_2) and carbon tetrachloride (CCl_4) are examples of such molecules (Figure 2.3.3).

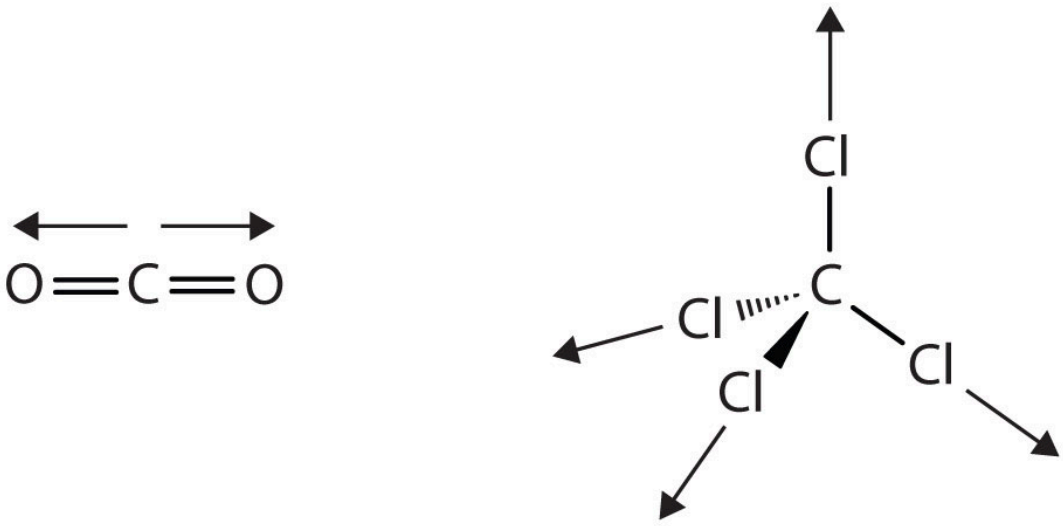


Figure 2.3.3: Nonpolar Molecules. Although the individual bonds in both CO_2 and CCl_4 are polar, their effects cancel out because of the spatial orientation of the bonds in each molecule. As a result, such molecules experience little or no dipole-dipole interaction.

The Magnitude of Dispersion Forces

depends on two factors:

- **Larger and heavier atoms and molecules.** The relative polarizability of electrons. The simple understanding of polarizability is how easily the electrons get distorted. For larger atoms, there are more electrons in a larger space, therefore the electrons are more loosely held and more easily polarized, so the dispersion force is stronger. Generally, the larger the molar mass of the molecule, the stronger the dispersion force.
- **The relative surface area of the molecule.** Molecules with longer, flatter, or cylindrical shapes have a greater surface area compared to the bulky, branched molecules, and therefore have a stronger dispersion force. Taking the two constitutional isomers of C_4H_{10}, butane, and isobutane, as an example, the dispersion force of butane is stronger than that of isobutane. Figure 2.3.4.

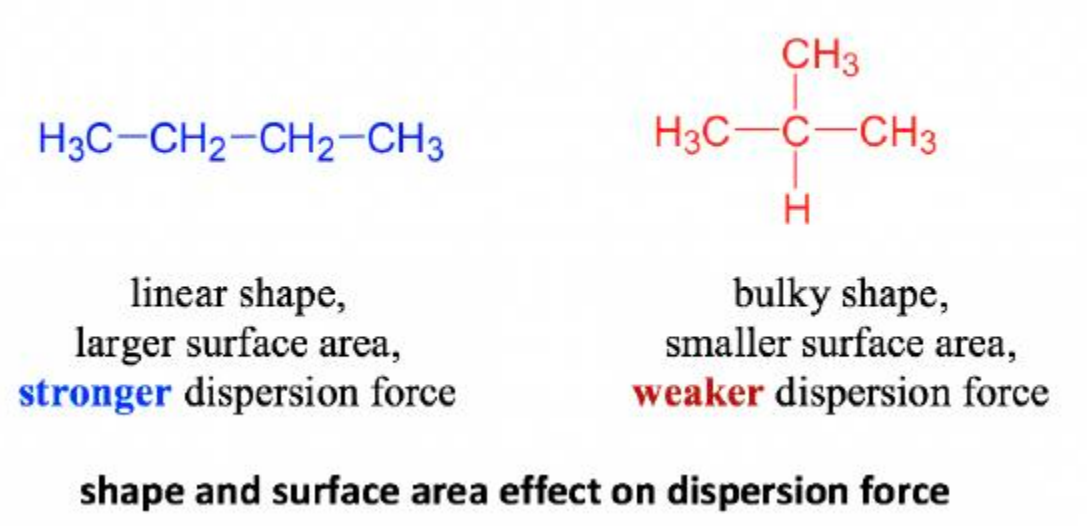


Figure 2.3.4: Shape and surface area effect on dispersion force

Dipole-Dipole Force

A covalent bond that has an unequal sharing of electrons is called a **polar covalent** bond. The charge separation in a **polar covalent bond** is not as extreme as is found in ionic compounds, but there is a related result: oppositely charged ends of different molecules will attract each other. This type of intermolecular interaction is called a **dipole-dipole interaction**. Most molecules with polar covalent bonds experience dipole-dipole interactions. HF is an example of a polar molecule, also known as a dipole.

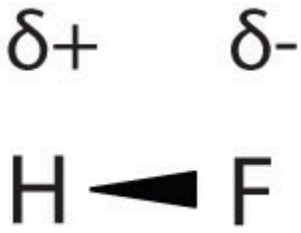


Figure 2.3.5: Polar Covalent Bonds.

The electrons in the HF molecule are not equally shared by the two atoms in the bond. The fluorine atom has nine protons in its nucleus, it attracts the negatively charged electrons in the bond more than the hydrogen atom does with its one proton in its nucleus. Thus, electrons are more strongly attracted to the fluorine atom, leading to an imbalance in the electron distribution between the atoms. The fluorine side of the bond picks up a partial overall negative charge (represented by the δ– in the diagram), while the hydrogen side of the bond has an overall partial positive charge (represented by the δ+ in the diagram). Such a bond is called a ***polar covalent bond***.

Electrostatic Potential Map

In larger organic molecules, the dipole moment can be observed using an electrostatic potential map, where the positive, neutral,

and negative areas of the molecule are shown in different colors. It is important to note that depending on who made the potential map, the choice of color may vary. As shown below in the electrostatic potential map of acetone, one end of acetone has a partial negative charge (red), and the other end has a partial positive charge (blue). The dipole-dipole force is an attractive force between the positive end of one molecule and the negative end of the neighboring molecule.

Figure 2.3.6: Electrostatic potential map of acetone

Hydrogen Bonds

First of all, do not let the name mislead you! Although it is called a “bond”, a hydrogen bond is not a covalent bond, it is a type of intermolecular force. Molecules with **hydrogen atoms** bonded to electronegative atoms such as **O, N, and F** tend to exhibit unusually strong intermolecular interactions due to a particularly strong type of dipole-dipole attraction called **hydrogen bonding**. The large difference in electronegativity between the H atom (2.1) and the atom to which it is bonded (4.0 for an F atom, 3.5 for an O atom, or 3.0 for a N atom), combined with the very small size of a H atom and the relatively small sizes of F, O, or N atoms, leads to ***highly concentrated partial charges*** with these atoms. Because the hydrogen atom does not have any electrons other than the ones in the covalent bond, its positively charged nucleus is almost completely exposed, allowing strong attractions to other nearby lone pairs of electrons. It can be shown in a general way as:

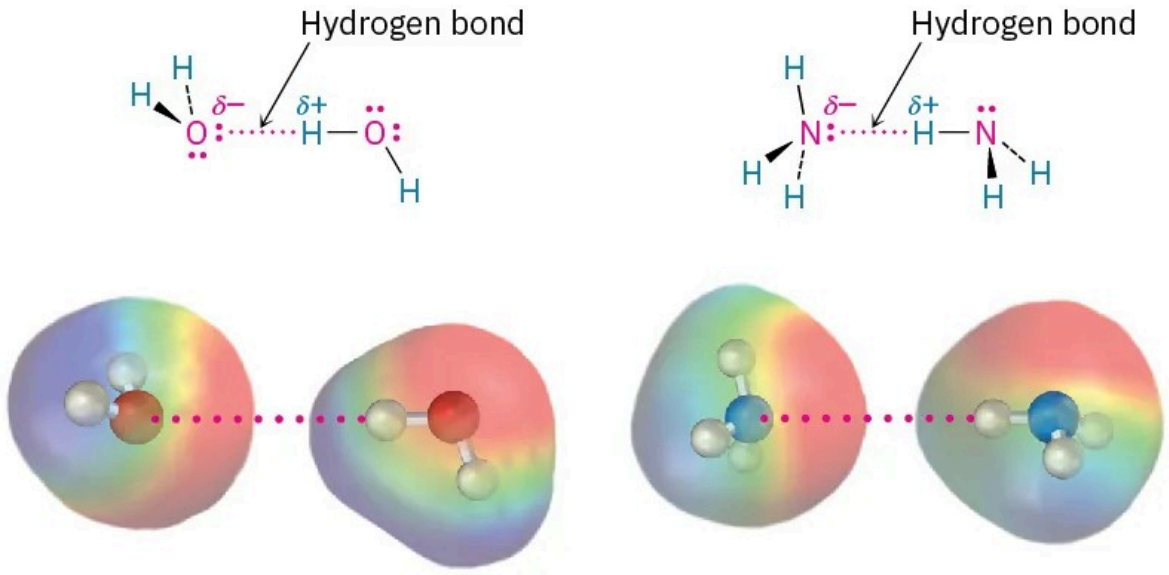


Figure 2.3.7: Hydrogen bond

The most common example of hydrogen bonding is for water molecules. Water has two O-H bonds, and both are available as hydrogen bond donors for neighboring molecules. This explains the extraordinarily high b.p. of water (100 °C), considering the rather small molar mass of 18.0 g/mol. As a comparison, the methane molecule CH_4 with a similar size has a b.p. of -167.7 °C.

Figure 2.3.8: Simplified Diagram of Hydrogen Bonds between Water Molecules.

Electrostatic potential maps of water and ammonia clearly show the positively polarized hydrogens (blue) and the negatively polarized oxygens and nitrogens (red).



For organic compounds, hydrogen bonds play important roles in determining the properties of compounds with OH or NH bonds, for example alcohol (R-OH), carboxylic acid (R-COOH), amine (R-NH_2) and amide R$CONH_2$. Figure 2.3.9 shows how methanol (CH_3OH) molecules experience hydrogen bonding. Methanol contains both a hydrogen atom attached to O; methanol can thus form hydrogen bonds by acting as either a hydrogen bond donor or a hydrogen bond acceptor (lone pair). The hydrogen-bonded structure of methanol is as follows:

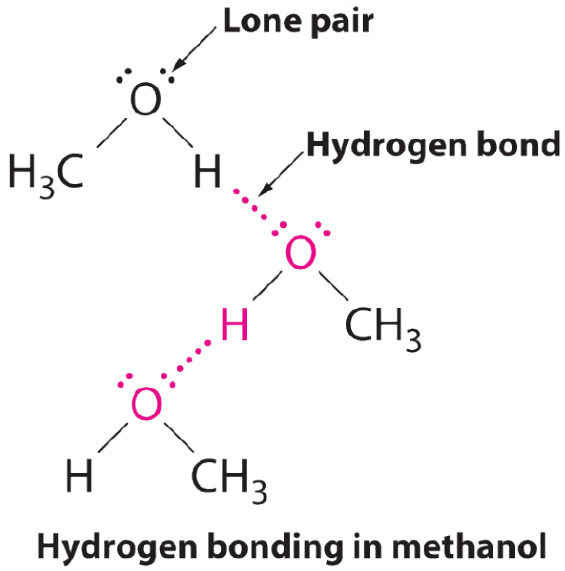


Figure 2.3.9: Methanol molecule is capable of hydrogen-bonding interactions to other methanol molecules like itself.

Polar vs Non-Polar molecules

As indicated in **Table** 2.3.1, the nature of molecular polarity determines the types of force(s) applied to a certain substance. Here, we will have discussions on how to determine whether a molecule is polar or non-polar.

Table 2.3.1 Summary of the Three Major Intermolecular Forces

Type of Force	Applied to	Strength (kJ/m
London Dispersion forces	All Molecules	0

Type of Force	Applied to	Strength (kJ/m
Dipole-Dipole	Polar Molecules	5
Hydrogen bond	Polar Molecules with N-H, O-H, or F-H bond	5

The polarity of the compound can be determined by its formula and shape.

For **diatomic molecules**, the molecular polarity is the same as the bonding polarity. That means all homonuclear molecules, like H_2, N_2, O_2, F_2, are non-polar because of their non-polar bond, while all heteronuclear molecules, like HF, HCl, are polar.

For **polyatomic molecules**, the molecular polarity depends on the shape of the molecule as well. Let's see the examples of CO_2 and H_2O.

Figure 2.3.10: Molecular polarity depends on the shape of the molecule, CO_2 is a non-polar molecule while having polar bonds and H_2O is a polar molecule with polar bonds.

Both H_2O and CO_2 have two polar bonds. H_2O is in the bent shape, so the bond polarities of the two O-H bonds add up to give the molecular polarity of the whole molecule (shown above), therefore H_2O is polar molecule. On the other hand, the shape of CO_2 is linear, and the bond polarities of the two C=O bonds cancel out, so the whole CO_2 molecule is non-polar.

There are other examples of non-polar molecules where the bond polarity cancels out, such as BF_3, CCl_4, PCl_5, XeO_4 etc.

For organic compounds, the hydrocarbons (C_xH_y) are always non-polar. This is mainly because of the small electronegativity difference between carbon atoms and hydrogen atoms, making C-H bonds technically non-polar bonds. For other organic compounds that contain functional groups with heteroatoms, like R-O-R, C=O, OH, NH, they are all polar molecules.

The following diagram provides a summary of all the discussions about molecular polarities.

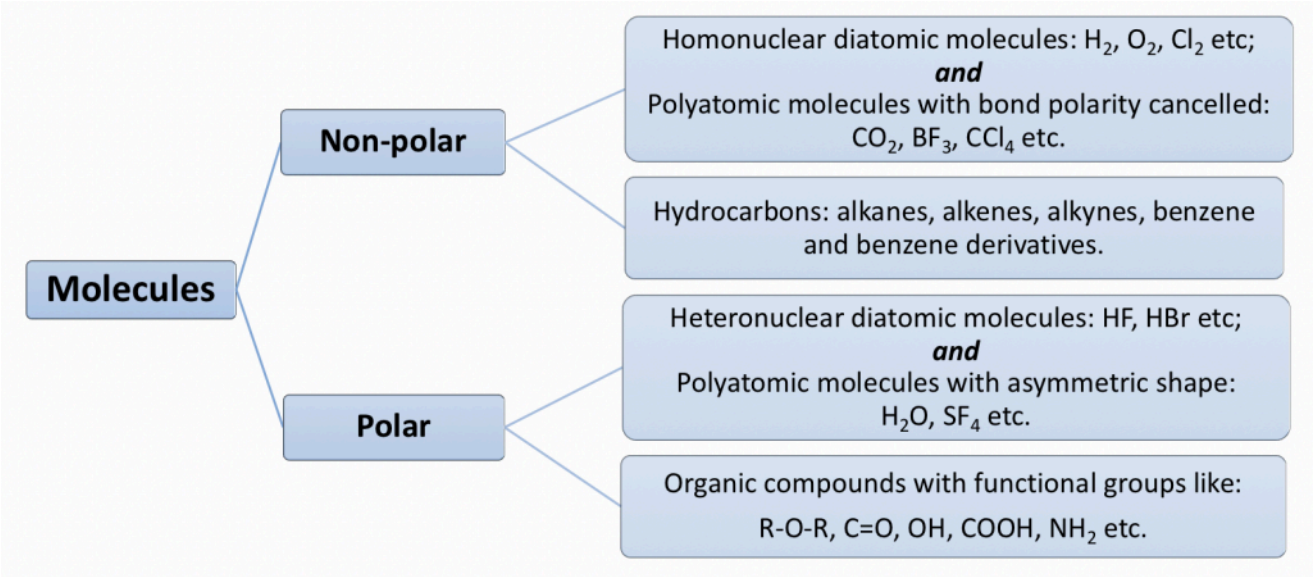


Figure 2.3.11: Summary of Molecular Polarities

Other than the three types of intermolecular forces, there is another interaction that is very important for understanding the physical property of a compound, which is the ion-dipole force.

Ion-Dipole Force

Ion-dipole force is not categorized as an intermolecular force, however it is a type of important non-covalent force that is responsible for the interaction between ions and other polar substances. A simple example is the dissolving of an ionic solid, or salt, in water. When table salt (NaCl) is dissolved in water, the interactions between the ions and water molecules are strong

enough to overcome the ionic bond that holds the ions in the crystal lattice. As a result, the cations and anions are separated apart completely, and each ion is surrounded by a cluster of water molecules. This is called a **solvation** process. The solvation occurs through the strong ion-dipole force. Lots salts, or ionic compounds, are soluble in water because of such interactions.

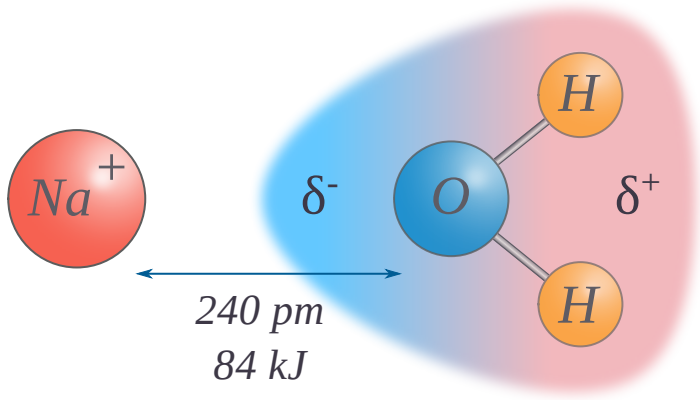


Figure 2.3.12: Ion - Dipole Interaction. (CC BY-NC; Ümit Kaya)

Ionic Bond

The strongest force between any two particles is the ionic bond, in which two ions of opposing charge are attracted to each other. Thus, ionic interactions between particles are another type of intermolecular interaction. Substances that contain ionic interactions are relatively strongly held together, so these substances typically have high melting and boiling points. Sodium chloride (Figure 2.3.13) is an example of a substance whose particles experience ionic interactions (Table 2.3.1). These attractive forces are sometimes referred to as ion-ion interactions.

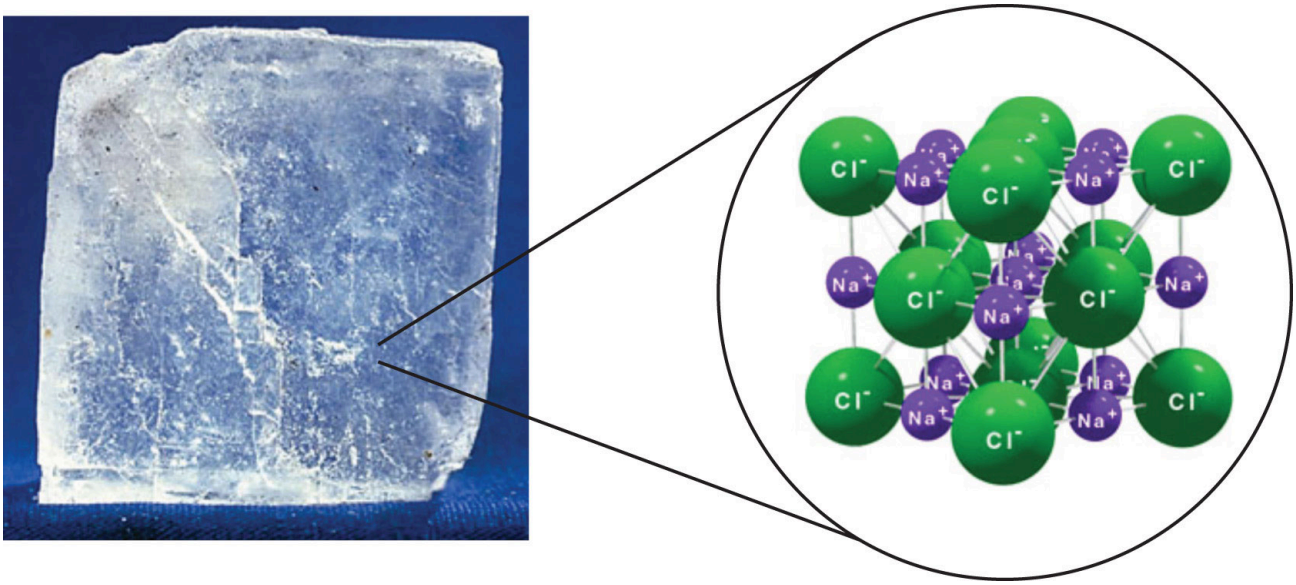


Figure 2.3.13: Solid NaCl (sodium chloride) is held together by ionic interactions. Source: Photo © Thinkstock

Applications of Intermolecular Forces in Biology

Folding Proteins

These interactions are common in proteins and contribute to the protein's folding. Ion-ion interactions are called salt bridges.

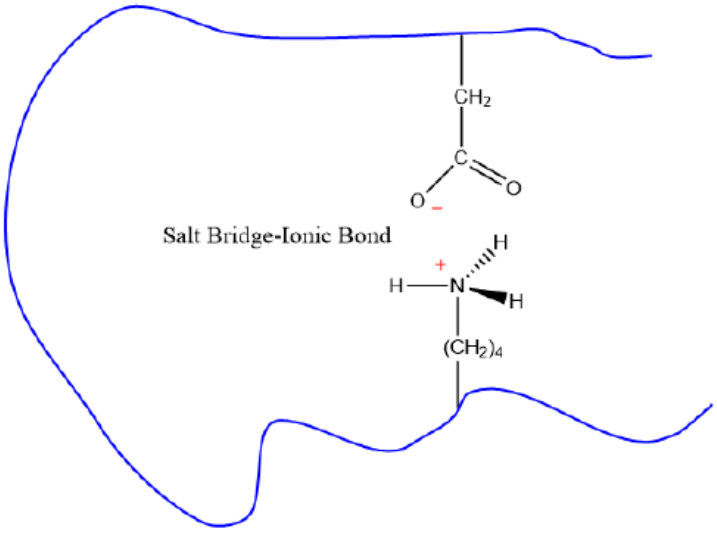
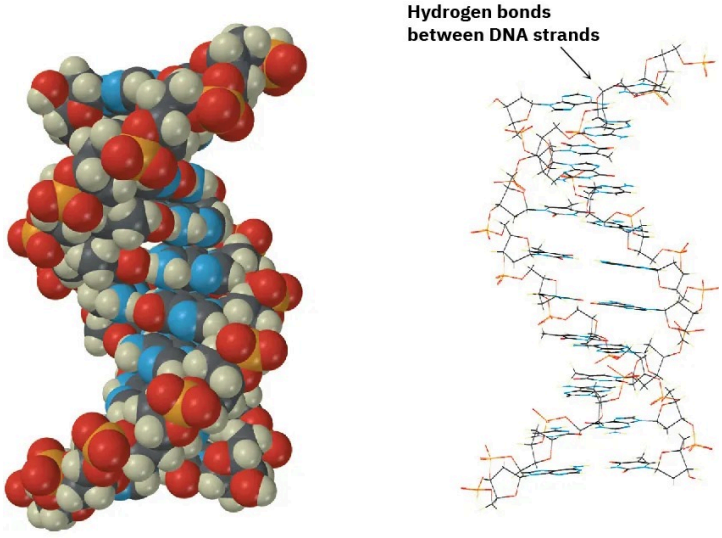


Figure 2.3.14: A protein strand in blue folds into a compact structure via ionic interactions called salt bridges.

Hydrogen Bonding and DNA

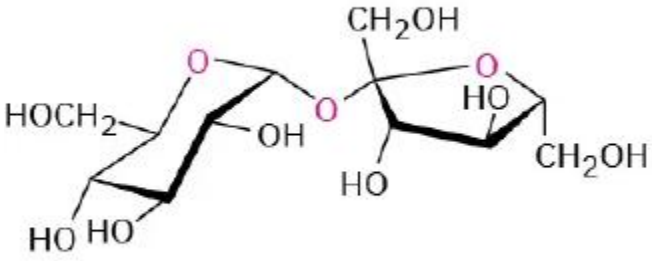
Hydrogen bonding has enormous consequences for living organisms. Hydrogen bonds cause water to be a liquid rather than a gas at ordinary temperatures, they hold enzymes in the shapes necessary for catalyzing biological reactions, and they cause strands of deoxyribonucleic acid (DNA) to pair up and coil into the double helix that stores genetic information.



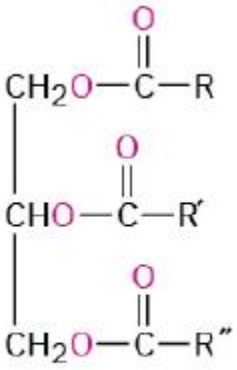
A deoxyribonucleic acid segment

One further point before leaving the subject of noncovalent interactions: biochemists frequently use the term hydrophilic, meaning “water-loving,” to describe a substance that is attracted to water and the term hydrophobic, meaning “water-fearing,” to describe a substance that is not strongly attracted to water. Hydrophilic substances, such as table sugar, often have a number of –OH groups

in their structure so they can form hydrogen bonds and dissolve in water, whereas hydrophobic substances, such as vegetable oil, do not have groups that form hydrogen bonds and do not dissolve in water.



Sucrose
(a disaccharide)



Animal fat—a triester
(R, R′, R″ = C_{11}—C_{19} chains)

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2.4: Physical Properties of Organic Compounds

Physical Properties and Intermolecular Forces

Understanding intermolecular forces helps us understand and explain the physical properties of substances, since they account for properties such as phases, melting and boiling points, viscosities, etc. For organic chemistry purposes, we will focus on boiling point (b.p.) and solubility.

Boiling point (b.p):

The boiling point trend of different substances directly correlates with the total intermolecular forces. Generally speaking, the stronger the overall intermolecular force applied to a certain substance, the higher the boiling point of the substance. The boiling point is the temperature at which the liquid phase of the substance vaporizes to become a gas. In order to vaporize a liquid, the intermolecular forces that hold the molecules together must be overcome. The stronger the forces, the more energy is needed to overcome the forces, and a higher temperature is required, thus leading to a higher boiling point.

Between the same kind of intermolecular forces, the strength of the intermolecular interactions increases as the dipole moment of the molecules increases, within a series of compounds of similar molar mass, as shown in Table 2.4.1. Using what we learned previously about predicting relative bond polarities from the electronegativities of the bonded atoms, we can make educated guesses about the relative boiling points of similar molecules.

Table 2.4.1: Relationships between the Dipole Moment and the Boiling Point for Organic Compounds of Similar Molar Mass

Compound	Molar Mass (g/mol)	IMF	Dipole Moment (D)	Boiling Point (K)
C_3H_6 (cyclopropane)	42	London Dispersion forces	0	240
CH_3OCH_3 (dimethyl ether)	46	Dipole-Dipole	1.3	248
CH_3CN (acetonitrile)	41	Dipole-Dipole	3.9	355

Within a series of compounds of similar molar mass, the dispersion forces are at a similar level. However, the three compounds have different molecular polarities. Butane is a non-polar substance that only has dispersion forces, propanal is a polar molecule with both dispersion forces and dipole-dipole forces, and propanol is a polar molecule with an OH bond, so all three types of forces apply to. Therefore, the overall amount of intermolecular forces is strongest for propanol, and weakest for butane, which is in the same order as their boiling points.

Table 2.4.2: Relationships between the intermolecular forces and the Boiling Point for Organic Compounds of Similar Molar Mass

Compound	Molar Mass (g/mol)	IMF	Boiling Point (C)
C_4H_{10} (butane)	58	London Dispersion forces	-0.5
CH_3CH_2CHO (propanal)	58	Dipole-Dipole	48
$CH_3CH_2CH_2OH$ (propanol)	60	Hydrogen bond	97

Solubility:

A general rule for solubility is summarized by the expression “like dissolves like”. This means that one substance can dissolve in another with similar polarity, and as a result, with similar intermolecular forces. More specifically:

- Nonpolar substances are usually soluble in nonpolar solvents.

- Polar and ionic substances are usually soluble in polar solvents.
- Polar and nonpolar substances are insoluble in each other.

Water, methanol, and ethanol are examples of very polar solvents that can form Hydrogen bonds. Ether, ketone, halide, and esters are polar solvents as well, but as they can form hydrogen bonds by themselves, they are not as polar as water or methanol. Non-polar molecules are considered non-polar solvents; examples include hydrocarbons like hexane, benzene, and toluene.

For some organic compounds, however, it may not be that easy to simply call it polar or non-polar, because part of the compound may be polar, and the other part may be non-polar. This is often described as hydrophilic or hydrophobic.

- **Hydrophobic** (*hydro*, water; *phobic*: fearing or avoiding) means it does not like water, or is insoluble in water;
- **Hydrophilic** (*hydro*, water; *philic*: loving or seeking) means it likes water, or is soluble in water.

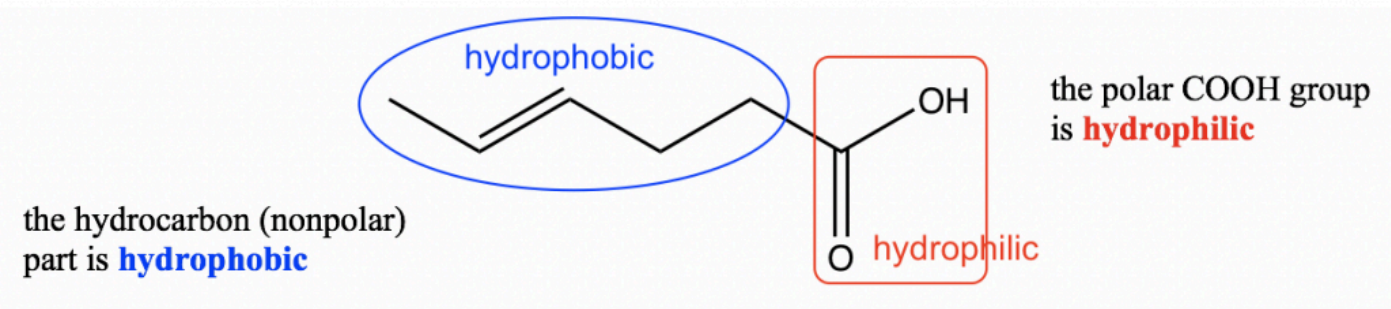


Figure 2.4.1: Hydrophobic and Hydrophilic

The hydrocarbon part of the organic compound is *hydrophobic*, because it is nonpolar and therefore does not dissolve in polar water. The functional groups OH, COOH, NH_2, are polar and are, therefore, *hydrophilic*. When both hydrophobic and hydrophilic parts are present in an organic compound, the overall polarity depends on which part is the major one. If the carbon chain is short (1~3 carbons), the hydrophilic effect of the polar group is the major one, so the whole compound is soluble in water; with carbon chains of 4~5 carbons, the hydrophobic effect begins to overcome the hydrophilic effect, and water solubility is lost.

The solubility differences of different alcohols demonstrate this trend clearly; as the length of the carbon chain increases, the solubility of alcohol in water decreases dramatically (**Table** 2.4.3):

Table 2.4.3**: Solubility of different alcohols in water**

Alcohol	Solubility in water (g/100mL)
methanol, ethanol, propanol(CH_3OH, CH_3CH_2OH, $CH_3CH_2CH_2OH$)	miscible (dissolve in all proportions)
1-butanol ($CH_3CH_2CH_2CH_2OH$)	9
1-pentanol ($CH_3CH_2CH_2CH_2CH_2OH$)	2.7
1-octanol ($CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2OH$)	0.06

For organic compounds that are water *insoluble*, they can sometimes be converted to the “salt derivative” via a proper reaction, and thus can become water soluble. This method is used commonly in labs for the separation of organic compounds.

Example:

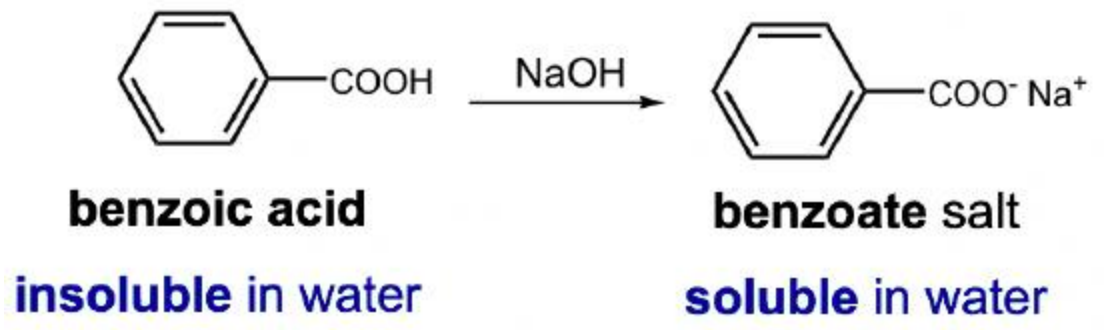
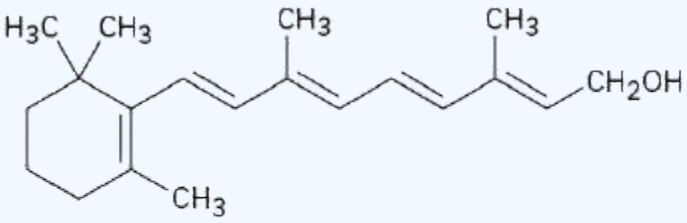


Figure 2.4.2: Convert insoluble organic compound to the soluble salt derivative.

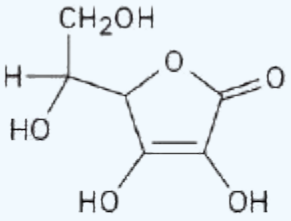
Applying acid-base reactions is the most common way to achieve such purposes. As shown in the example above, adding a strong base to benzoic acid initiates an acid-base reaction, converting benzoic acid to its salt, sodium benzoate, which is water-soluble (because of the ion-dipole forces we learned earlier). The benzoic acid can, therefore, be brought into the water (aqueous) phase and separated from other organic compounds that do not have similar properties.

Exercise 2.4.1

Of the two vitamins A and C, one is hydrophilic and water-soluble while the other is hydrophobic and fat-soluble. Which is which?



Vitamin A
(retinol)



Vitamin C
(ascorbic acid)

Answer available at the end of this section.

Answers

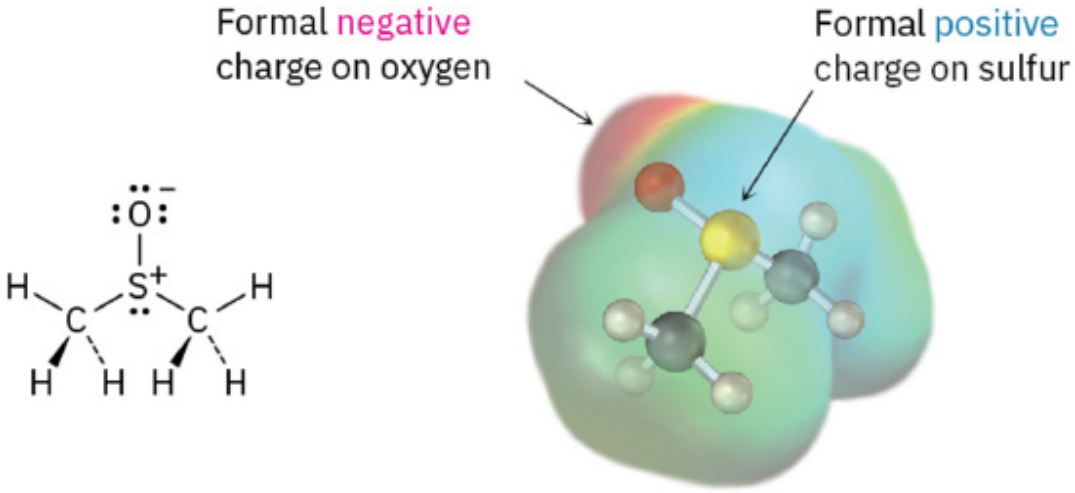
Exercise 2.4.1

Vitamin C is water-soluble (hydrophilic); vitamin A is fat-soluble (hydrophilic).

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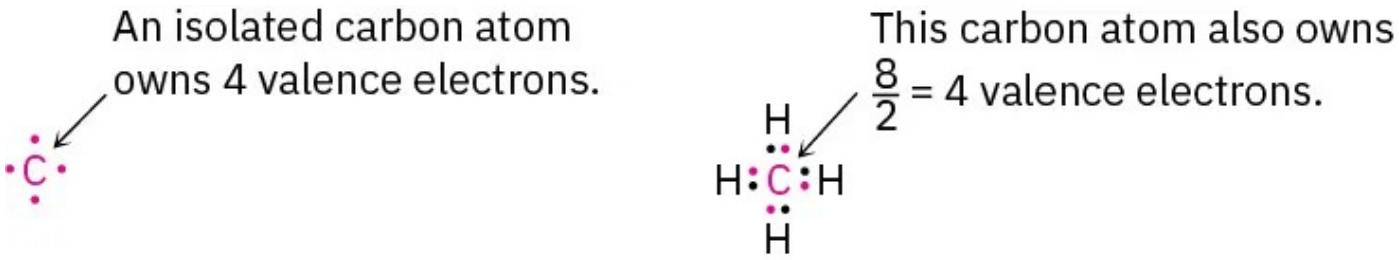
2.5: Formal Charges

Closely related to the ideas of bond polarity and dipole moment is the assignment of *formal charges* to specific atoms within a molecule, particularly atoms that have an apparently "abnormal" number of bonds. Look at dimethyl sulfoxide (CH_3SOCH_3), for instance, a solvent commonly used for preserving biological cell lines at low temperature. The sulfur atom in dimethyl sulfoxide has three bonds rather than the usual two and has a formal positive charge. The oxygen atom, by contrast, has one bond rather than the usual two and has a formal negative charge. Note that an electrostatic potential map of dimethyl sulfoxide shows the oxygen as negative (red) and the sulfur as relatively positive (blue), in accordance with the formal charges.

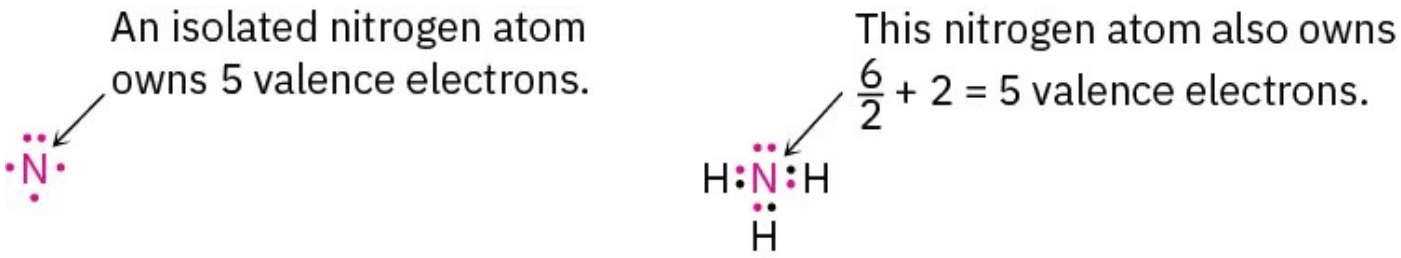


Dimethyl sulfoxide

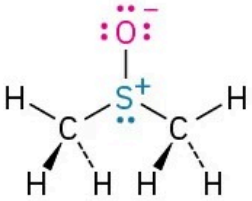
Formal charges, as the name suggests, are a formalism and don't imply the presence of actual ionic charges in a molecule. Instead, they're a device for electron "bookkeeping" and can be thought of in the following way: A typical covalent bond is formed when each atom donates one electron. Although the bonding electrons are shared by both atoms, each atom can still be considered to "own" one electron for bookkeeping purposes. In methane, for instance, the carbon atom owns one electron in each of the four C–H bonds. Because a neutral, isolated carbon atom has four valence electrons, and because the carbon atom in methane still owns four, the methane carbon atom is neutral and has no formal charge.



The same is true for the nitrogen atom in ammonia, which has three covalent N–H bonds and two nonbonding electrons (a lone pair). Atomic nitrogen has five valence electrons, and the ammonia nitrogen also has five—one in each of three shared N–H bonds plus two in the lone pair. Thus, the nitrogen atom in ammonia has no formal charge.



The situation is different in dimethyl sulfoxide. Atomic sulfur has six valence electrons, but the dimethyl sulfoxide sulfur owns only five—one in each of the two S–C single bonds, one in the S–O single bond, and two in a lone pair. Thus, the sulfur atom has formally lost an electron and therefore has a positive formal charge. A similar calculation for the oxygen atom shows that it has formally gained an electron and has a negative charge. Atomic oxygen has six valence electrons, but the oxygen in dimethyl sulfoxide has seven—one in the O–S bond and two in each of three lone pairs. Thus, the oxygen has formally gained an electron and has a negative formal charge.



For sulfur:

Sulfur valence electrons	= 6
Sulfur bonding electrons	= 6
Sulfur nonbonding electrons	= 2
Formal charge = 6 − 6/2 − 2	= +1

For oxygen:

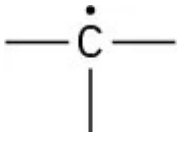
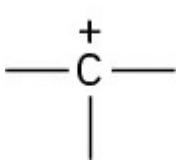
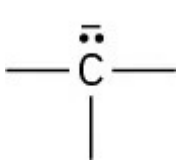
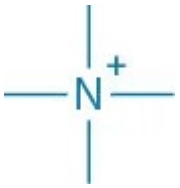
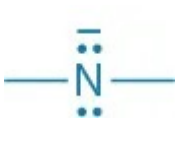
Oxygen valence electrons	= 6
Oxygen bonding electrons	= 2
Oxygen nonbonding electrons	= 6
Formal charge = 6 − 2/2 − 6	= −1

To express the calculations in a general way, the formal charge on an atom is equal to the number of valence electrons in a neutral, isolated atom minus the number of electrons owned by that bonded atom in a molecule. The number of electrons in the bonded atom, in turn, is equal to half the number of bonding electrons plus the nonbonding, lone-pair electrons.

$$\begin{aligned}\text{Formal Charge} &= (\text{Number of valence electron in free atom}) - (\text{Number of valence electrons in bonded atom}) \\ &= (\text{Number of valence electron in free atom}) - \left(\frac{\text{Number of bonding electrons}}{2} + \text{Number of nonbonding electrons}\right)\end{aligned}$$

A summary of commonly encountered formal charges and the bonding situations in which they occur is given in Table 2.5.1. Although only a bookkeeping device, formal charges often give clues about chemical reactivity, so it's helpful to be able to identify and calculate them correctly.

Table 2.5.1: A Summary of Common Formal Charges

Atom	C			N		O	
Structure							

Atom	C			N		O	
Valence electrons	4	4	4	5	5	6	6
Number of bonds	3	3	3	4	2	3	1
Number of nonbonding electrons	1	0	2	0	4	2	6
Formal charge	0	+1	–1	+1	–1	+1	–1

Exercise 2.5.1

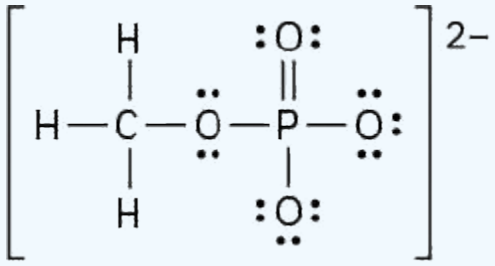
Calculate formal charges for the non-hydrogen atoms in the following molecules:

a. Diazomethane, $H_2C=N=\ddot{N}:$
b. Acetonitrile oxide, $H_3C-C\equiv N-\ddot{O}:$
c. Methyl isocyanide, $H_3C-N\equiv C:$

Answer available at the end of this section.

Exercise 2.5.2

Organic phosphate groups occur commonly in biological molecules. Calculate formal charges on the four O atoms in the methyl phosphate dianion.



Methyl phosphate dianion

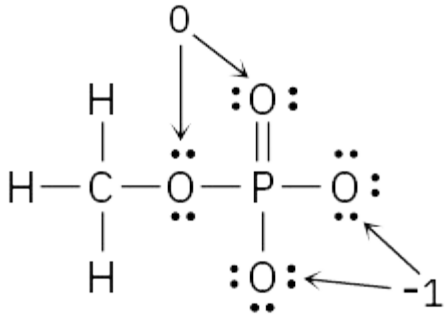
Answer available at the end of this section.

Answers

Exercise 2.5.1

a. For carbon: FC = 4 – 8/2 – 0 = 0 For the middle nitrogen: FC = 5 – 8/2 – 0 = +1 For the end nitrogen: FC = 5 – 4/2 – 4 = –1
b. For nitrogen: FC = 5 – 8/2 – 0 = +1 For oxygen: FC = 6 – 2/2 – 6 = –1
c. For nitrogen: FC = 5 – 8/2 – 0 = +1 For the triply bonded carbon: FC = 4 – 6/2 – 2 = –1

Exercise 2.5.2

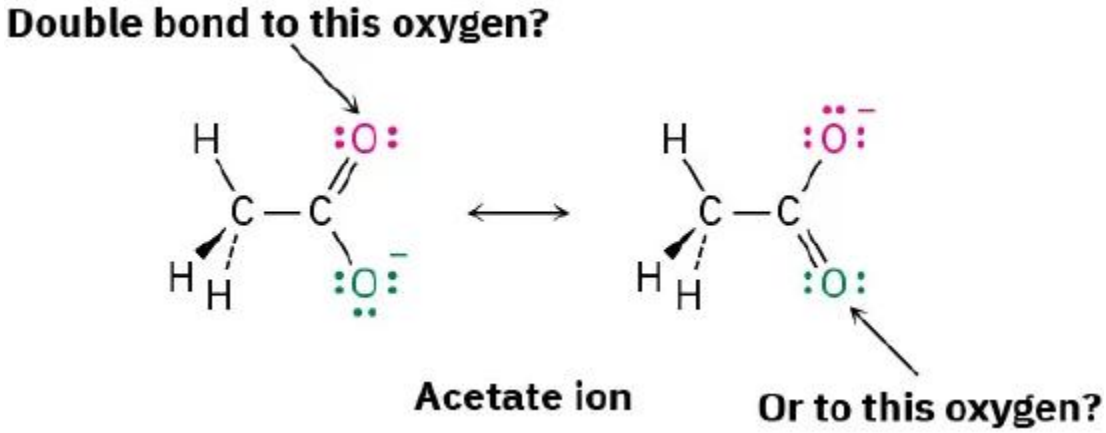


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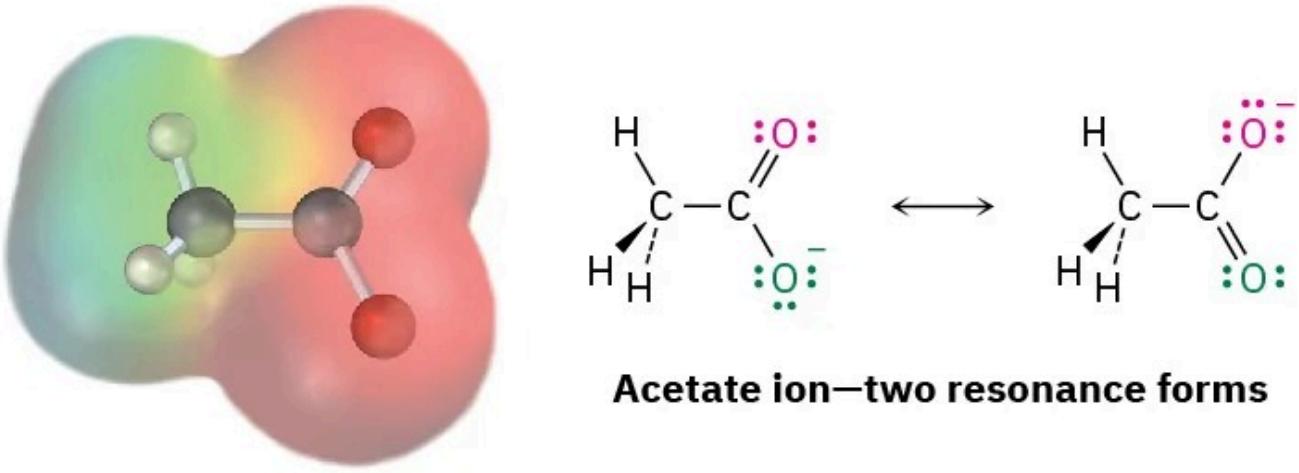
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2.6: Resonance

Most substances can be represented unambiguously by the Kekulé line-bond structures we've been using up to this point, but an interesting problem sometimes arises. Look at the acetate ion, for instance. When we draw a line-bond structure for acetate, we need to show a double bond to one oxygen and a single bond to the other. But which oxygen is which? Should we draw a double bond to the "top" oxygen and a single bond to the "bottom" oxygen, or vice versa?



Although the two oxygen atoms in the acetate ion appear different in line-bond structures, experiments show that they are equivalent. Both carbon–oxygen bonds, for instance, are 127 pm in length, midway between the length of a typical C–O single bond (135 pm) and a typical $\mathrm{C{=}O}$ double bond (120 pm). In other words, neither of the two structures for acetate is correct by itself. The true structure is intermediate between the two, and an electrostatic potential map shows that both oxygen atoms share the negative charge and have equal electron densities (red).

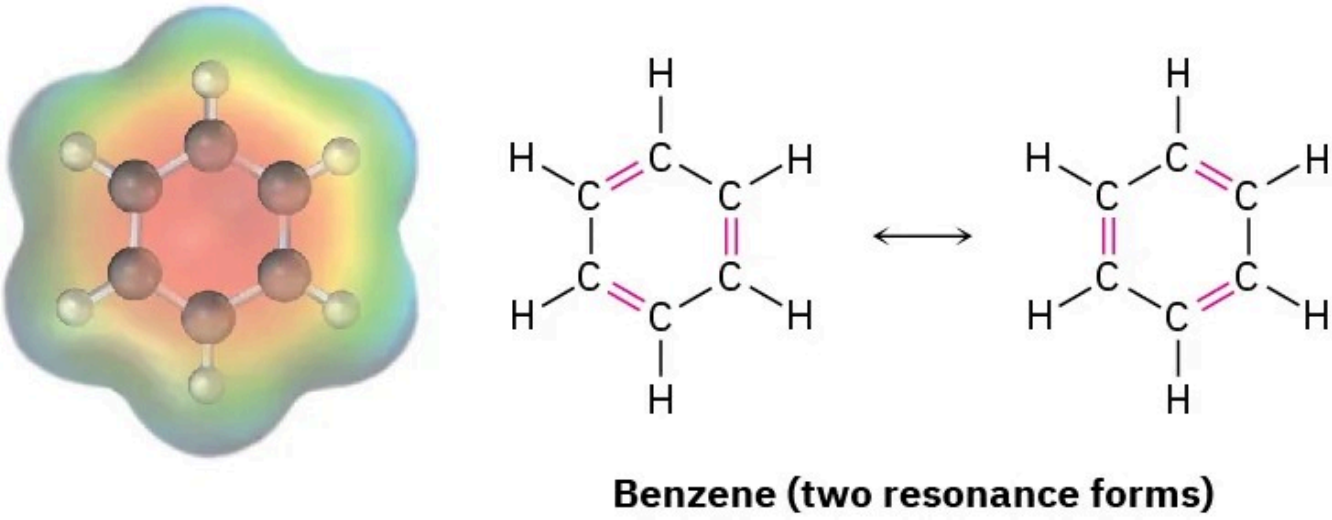


The two individual line-bond structures for the acetate ion are called resonance forms, and their special resonance relationship is indicated by the double-headed arrow between them. The only difference between the two resonance forms is the placement of the π and nonbonding valence electrons. The atoms themselves occupy exactly the same place in both resonance forms, the connections between atoms are the same, and the three-dimensional shapes of the resonance forms are the same.

A good way to think about resonance forms is to realize that a substance like the acetate ion is the same as any other. Acetate doesn't jump back and forth between two resonance forms, spending part of the time looking like one and part of the time looking like the other. Rather, acetate has a single unchanging structure that we say is a resonance hybrid of the two individual forms

and has characteristics of both. The only “problem” with acetate is that we can’t draw it accurately using a familiar line-bond structure—line-bond structures just don’t work for resonance hybrids. The difficulty, however, is with the *representation* of acetate on paper, not with acetate itself.

Resonance is a very useful concept that we’ll return to on numerous occasions throughout the rest of this book. For instance, the six carbon–carbon bonds in aromatic compounds, such as benzene, are equivalent and that benzene is best represented as a hybrid of two resonance forms. Although each individual resonance form seems to imply that benzene has alternating single and double bonds, neither form is correct by itself. The true benzene structure is a hybrid of the two individual forms, and all six carbon–carbon bonds are equivalent. This symmetrical distribution of electrons around the molecule is evident in an electrostatic potential map.



Benzene (two resonance forms)

When first dealing with resonance forms, it’s useful to have a set of guidelines that describe how to draw and interpret them. The following rules should be helpful:

Rules for Resonance Forms

RULE 1

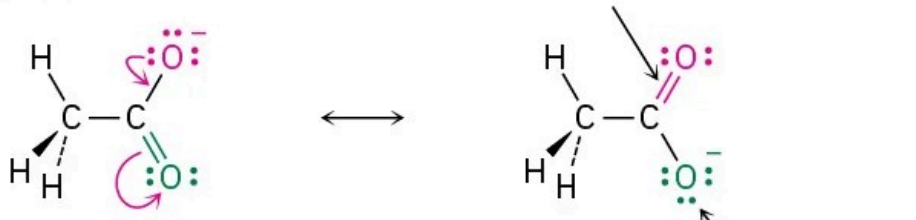
Individual resonance forms are imaginary, not real. The real structure is a composite, or resonance hybrid, of the different forms. Species such as the acetate ion and benzene are no different from any other. They have single, unchanging structures, and they don't switch back and forth between resonance forms. The only difference between these and other substances is in the way they are represented in drawings.

RULE 2

Resonance forms differ only in the placement of their π or nonbonding electrons. Neither the position nor the hybridization of any atom changes from one resonance form to another. In the acetate ion, for instance, the carbon atom is sp^2-hybridized and the oxygen atoms remain in exactly the same place in both resonance forms. Only the positions of the π electrons in the $\mathrm{C{=}O}$ bond and the lone-pair electrons on oxygen differ from one form to another. This movement of electrons from one resonance structure to another can be indicated with curved arrows. *A curved arrow always indicates the movement of electrons, not the movement of atoms.* An arrow shows that a pair of electrons moves *from* the atom or bond at the tail of the arrow *to* the atom or bond at the head of the arrow.

The red curved arrow indicates that a lone pair of electrons moves from the top oxygen atom to become part of a C=O bond.

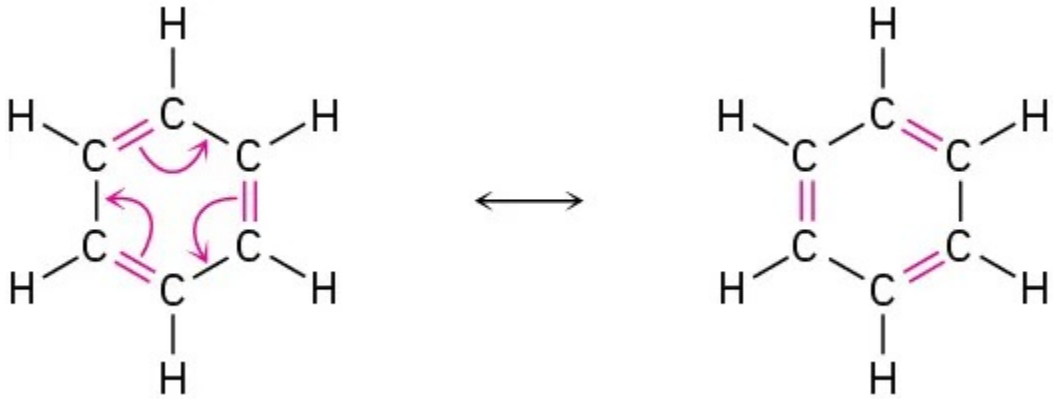
The new resonance form has a double bond here...



Simultaneously, two electrons from the C=O bond move onto the bottom oxygen atom to become a lone pair.

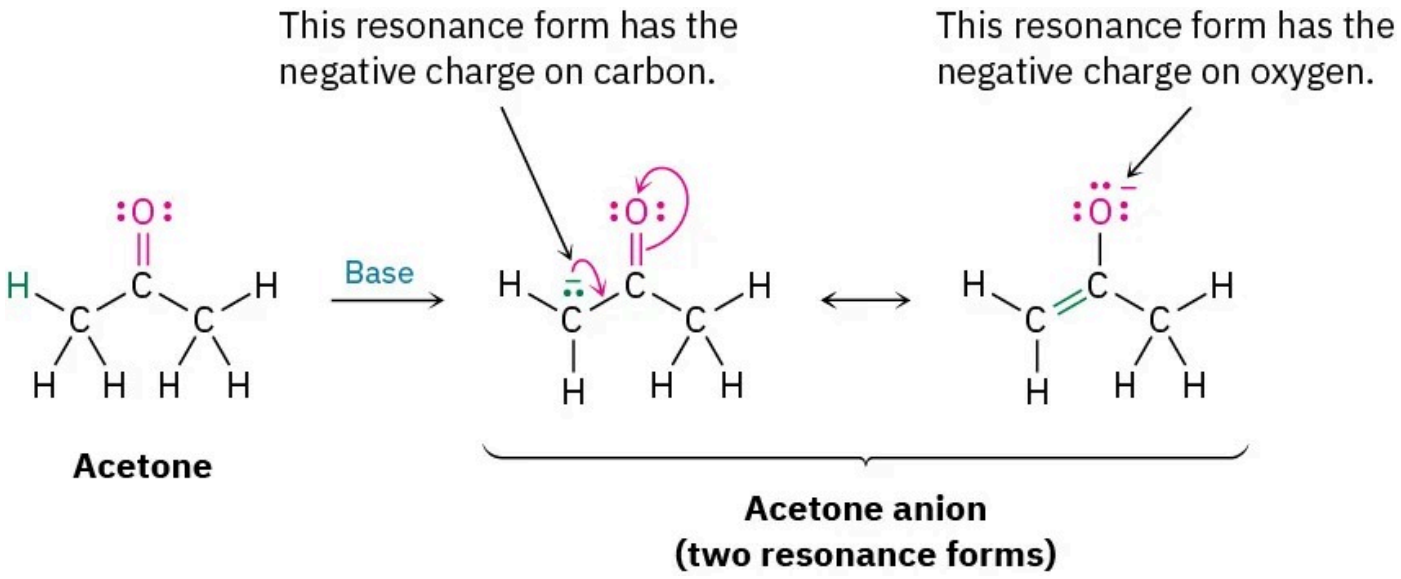
and has a lone pair of electrons here.

The situation with benzene is similar to that with acetate. The π electrons in the double bonds move, as shown with curved arrows, but the carbon and hydrogen atoms remain in place.



RULE 3

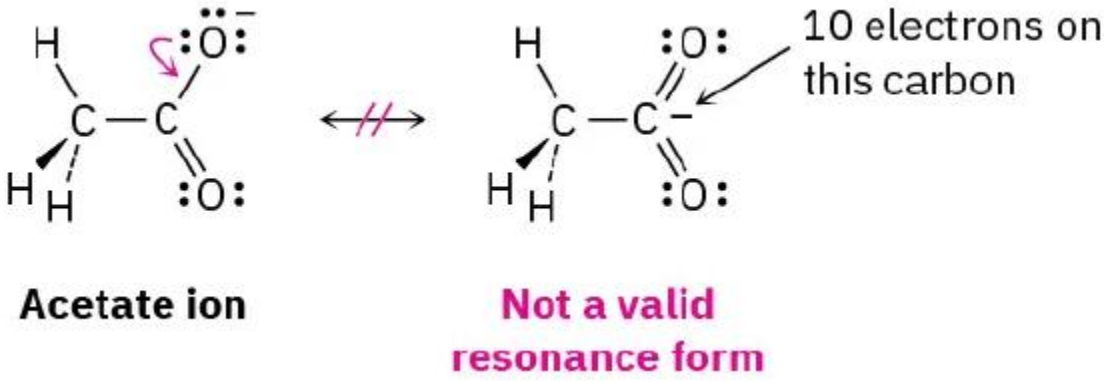
Different resonance forms of a substance don't have to be equivalent. As an example, we'll see in Chapter 22 that a compound such as acetone, which contains a $\mathrm{C{=}O}$ bond, can be converted into its anion by reaction with a strong base. The resultant anion has two resonance forms. One form contains a carbon–*oxygen* double bond and has a negative charge on *carbon;* the other contains a carbon–*carbon* double bond and has a negative charge on *oxygen*. Even though the two resonance forms aren't equivalent, both contribute to the overall resonance hybrid.



When two resonance forms are nonequivalent, the actual structure of the resonance hybrid resembles the more stable form. Thus, we might expect the true structure of the acetone anion to be more like that of the form that places the negative charge on the electronegative oxygen atom rather than on the carbon.

RULE 4

Resonance forms obey normal rules of valency. A resonance form is like any other structure: the octet rule still applies to second-row, main-group atoms. For example, one of the following structures for the acetate ion is not a valid resonance form because the carbon atom has five bonds and ten valence electrons:



RULE 5

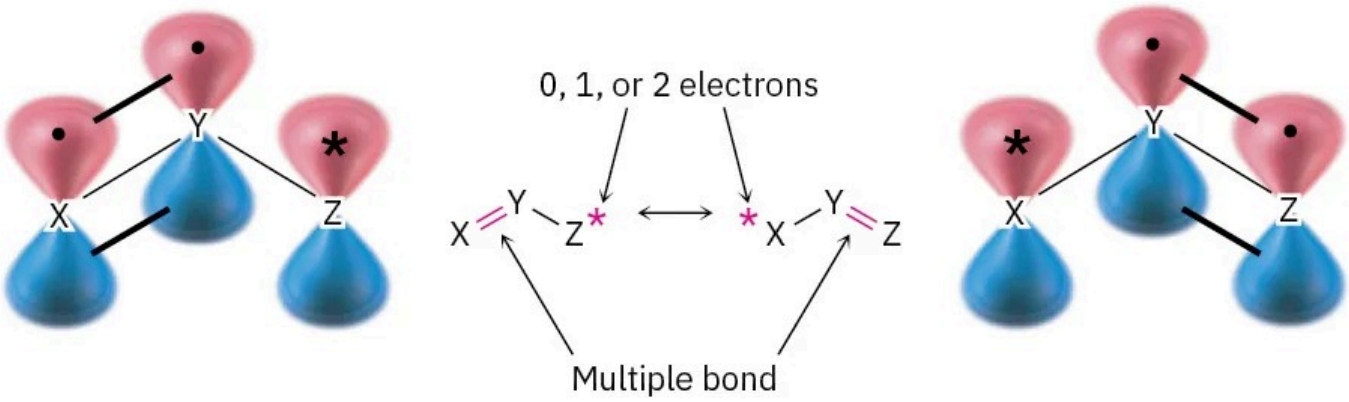
The resonance hybrid is more stable than any individual resonance form. In other words, resonance leads to stability. Generally speaking, the larger the number of resonance forms a substance has, the more stable the substance is, because its electrons are spread out over a larger part of the molecule and are closer to more nuclei. For instance, a benzene ring is more stable because of resonance than might otherwise be expected.

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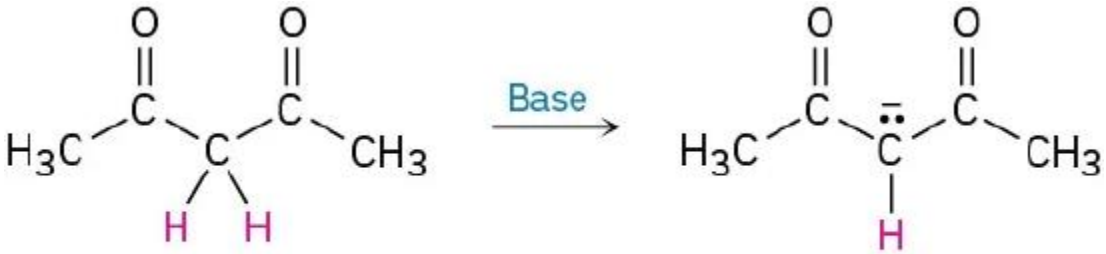
2.7: Drawing Resonance Forms

Look back at the resonance forms of the acetate ion and the acetone anion shown in the previous section. The pattern seen there is a common one that leads to a useful technique for drawing resonance forms. In general, any three-atom grouping with a *p* orbital on each atom has two resonance forms:



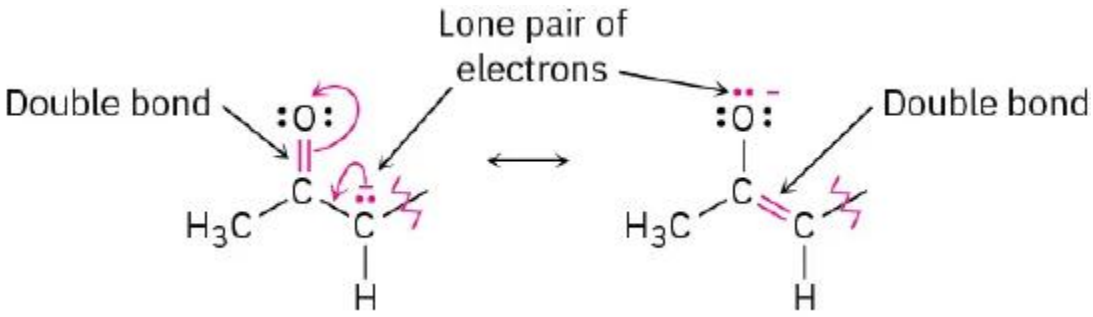
The atoms X, Y, and Z in the general structure might be C, N, O, P, S, or others, and the asterisk (*) might mean that the *p* orbital on atom Z is vacant, that it contains a single electron, or that it contains a lone pair of electrons. The two resonance forms differ simply by an exchange in the position of the multiple bond and the asterisk from one end of the three-atom grouping to the other.

By learning to recognize such three-atom groupings within larger structures, resonance forms can be systematically generated. Look, for instance, at the anion produced when H^+ is removed from 2,4-pentanedione by reaction with a base. How many resonance structures does the resultant anion have?

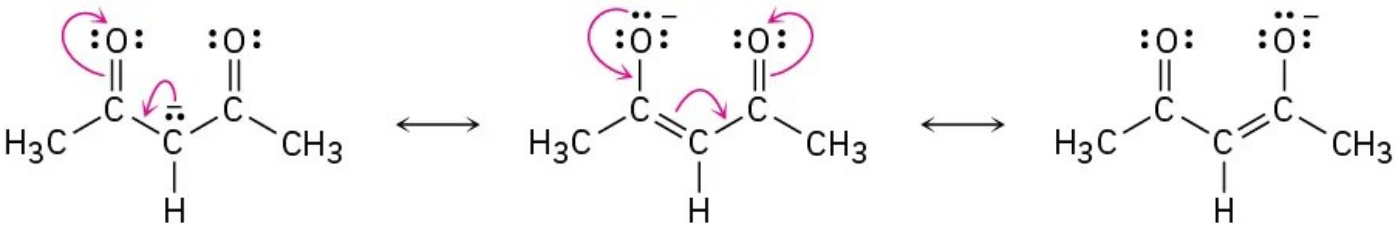


2,4-Pentanedione

The 2,4-pentanedione anion has a lone pair of electrons and a formal negative charge on the central carbon atom, next to a $C{=}O$ bond on the left. The $O{=}C{-}C{:}^-$ grouping is a typical one for which two resonance structures can be drawn.

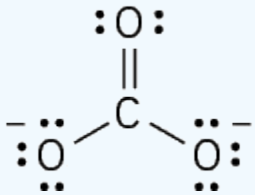


Just as there is a C=O bond to the left of the lone pair, there is a second C=O bond to the right. Thus, we can draw a total of three resonance structures for the 2,4-pentanedione anion.



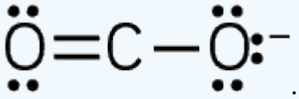
Worked Example 2.7.1: Drawing Resonance Forms for an Anion

Draw three resonance structures for the carbonate ion, CO_3^{2-}.



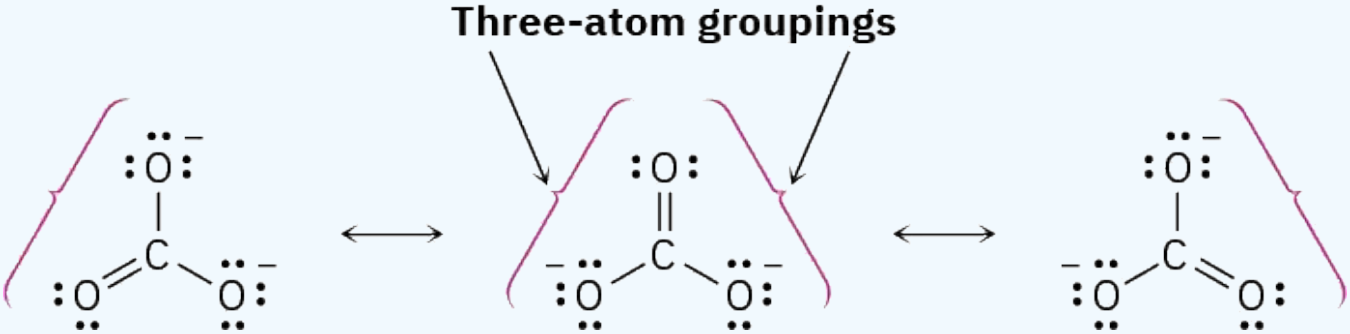
Carbonate ion

Strategy

Look for three-atom groupings that contain a multiple bond next to an atom with a *p* orbital. Then exchange the positions of the multiple bond and the electrons in the *p* orbital. In the carbonate ion, each singly bonded oxygen atom with three lone pairs and a negative charge is adjacent to the C=O double bond, giving the grouping .

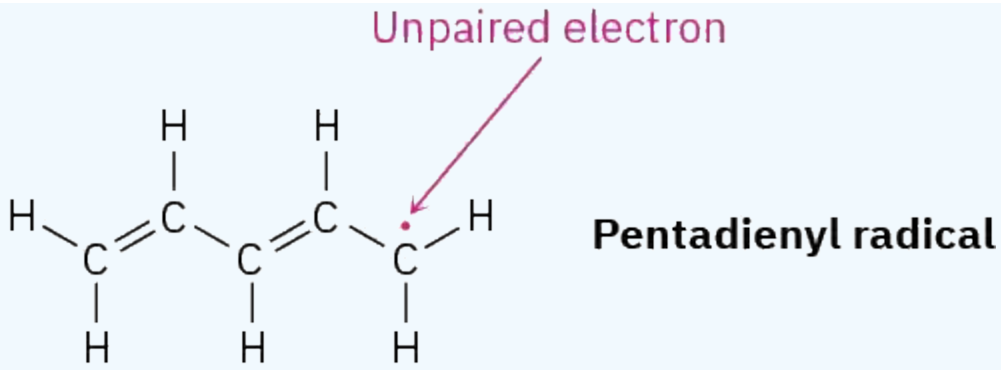
Solution

Exchanging the position of the double bond and an electron lone pair in each grouping generates three resonance structures.



Worked Example 2.7.2: Drawing Resonance Forms for a Radical

Draw three resonance forms for the pentadienyl radical, where a **radical** is a substance that contains a single, unpaired electron in one of its orbitals, denoted by a dot (•).

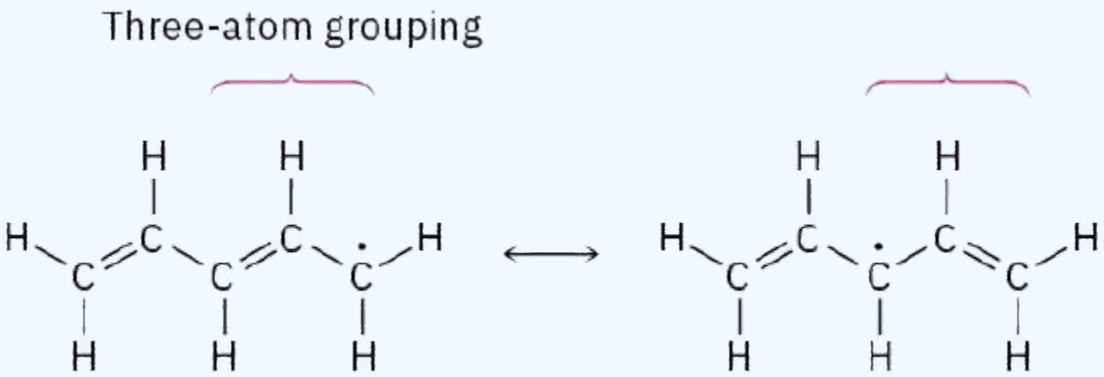


Strategy

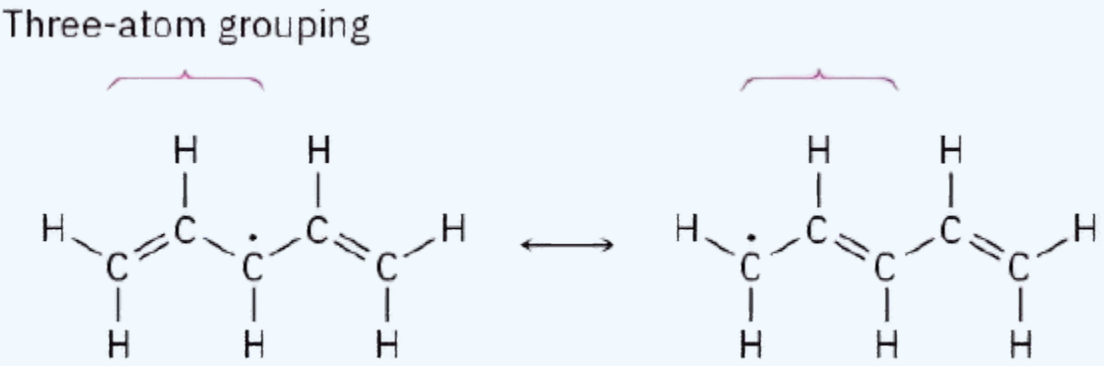
Find the three-atom groupings that contain a multiple bond next to an atom with a *p* orbital.

Solution

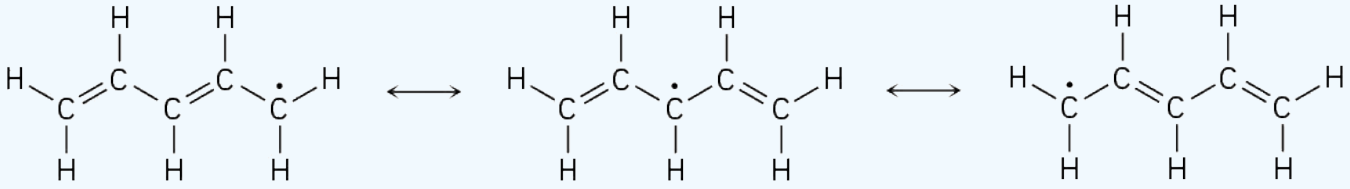
The unpaired electron is on a carbon atom next to a $\mathrm{C{=}C}$ bond, giving a typical three-atom grouping that has two resonance forms.



In the second resonance form, the unpaired electron is next to another double bond, giving another three-atom grouping and leading to another resonance form.



Thus, the three resonance forms for the pentadienyl radical are:

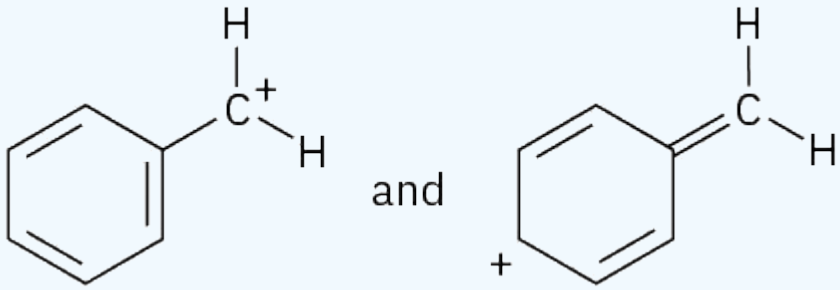


Exercises

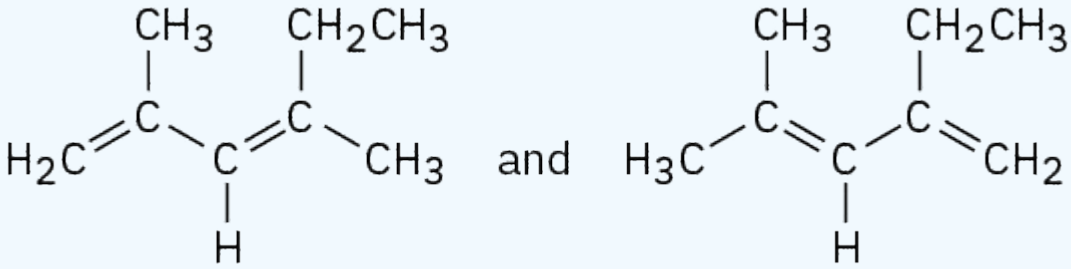
Exercise 2.7.1

Which of the following pairs of structures represent resonance forms, and which do not? Explain.

a.



b.

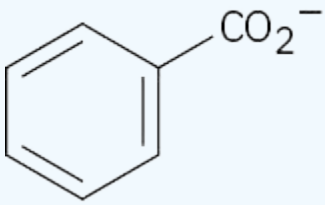


Answer available at the end of this section.

Exercise 2.7.2

Draw the indicated number of resonance forms for each of the following substances:

a. The methyl phosphate anion, $CH_3OPO_3^{2-}$ (3 resonance structures)
b. The nitrate anion, NO_3^- (3)
c. The allyl cation, $H_2C{=}CH{-}CH_2^+$ (2)
d. The benzoate anion (2)



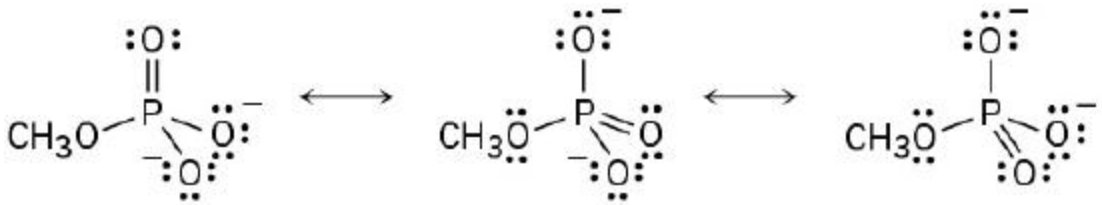
Answer available at the end of this section.

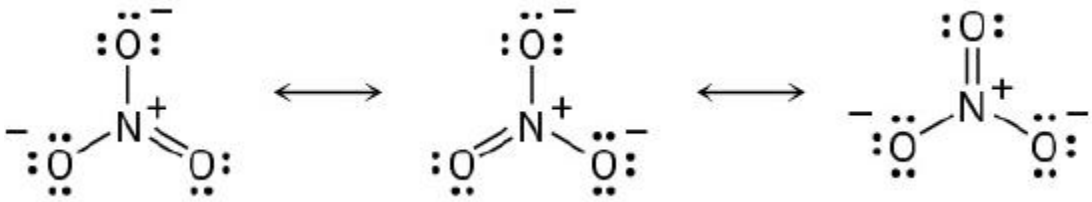
Answers

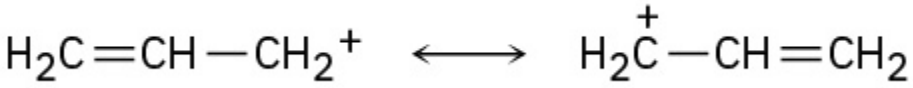
Exercise 2.7.1

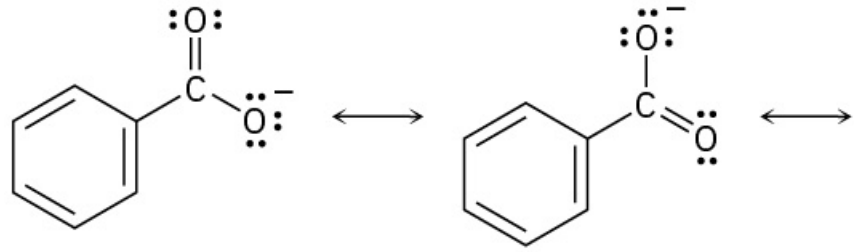
The structures in **(a)** are resonance forms.

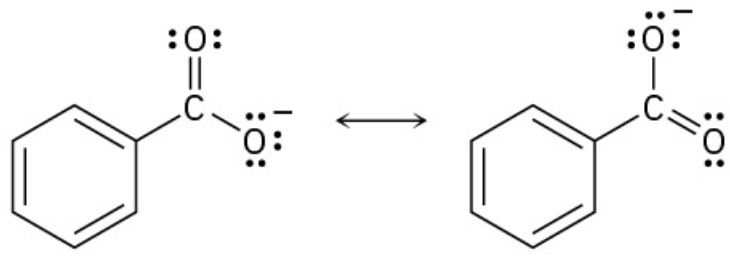
Exercise 2.7.2

a. 

b. 

c. 

d. 



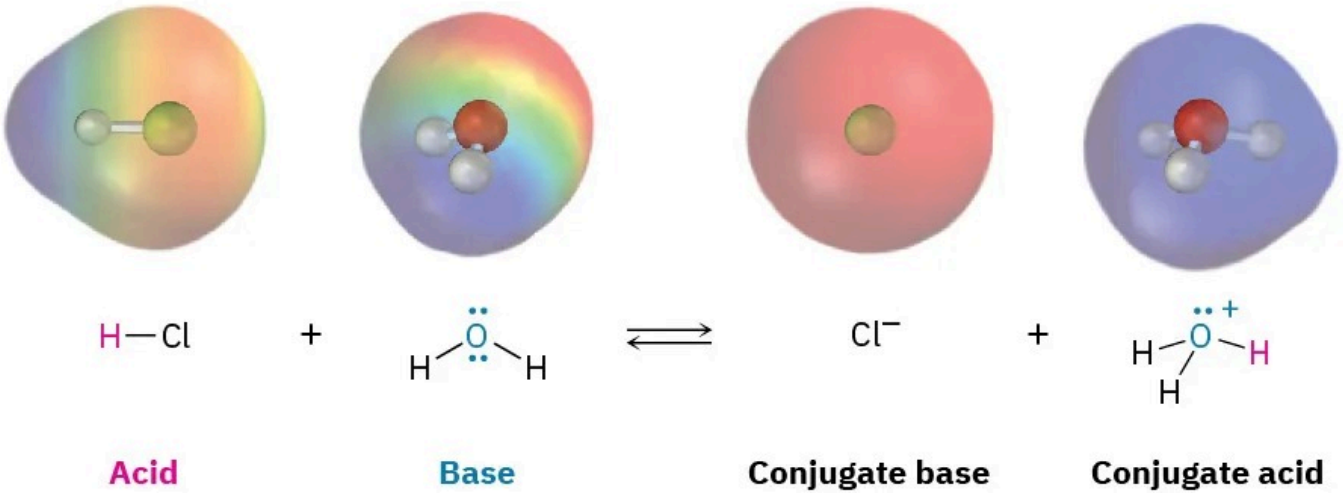
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2.8: Acids and Bases - The Brønsted-Lowry Definition

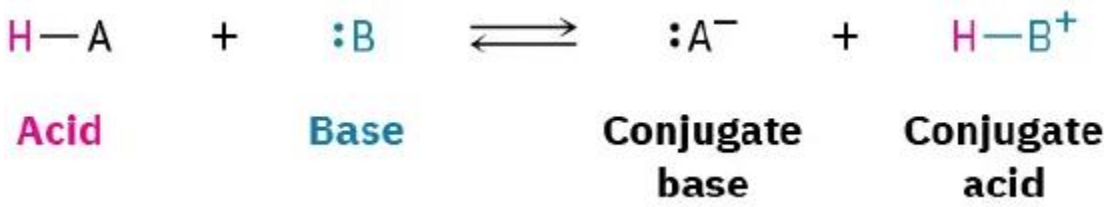
Perhaps the most important of all concepts related to electronegativity and polarity is that of *acidity* and *basicity*. We'll soon see, in fact, that the acid–base behavior of organic molecules explains much of their chemistry. You may recall from a course in general chemistry that two definitions of acidity are frequently used: the *Brønsted–Lowry definition* and the *Lewis definition*. We'll look at the Brønsted–Lowry definition in this and the following three sections and then discuss the Lewis definition in **Section 2.12**.

A Brønsted–Lowry acid is a substance that donates a hydrogen ion, H^+, and a Brønsted–Lowry base is a substance that accepts a hydrogen ion. (The name *proton* is often used as a synonym for H^+ because loss of the valence electron from a neutral hydrogen atom leaves only the hydrogen nucleus—a proton.) When gaseous hydrogen chloride dissolves in water, for example, a polar HCl molecule acts as an acid and donates a proton, while a water molecule acts as a base and accepts the proton, yielding chloride anion (Cl^-) and hydronium cation (H_3O^+). This and other acid–base reactions are reversible, so we'll write them with double, forward-and-backward arrows.

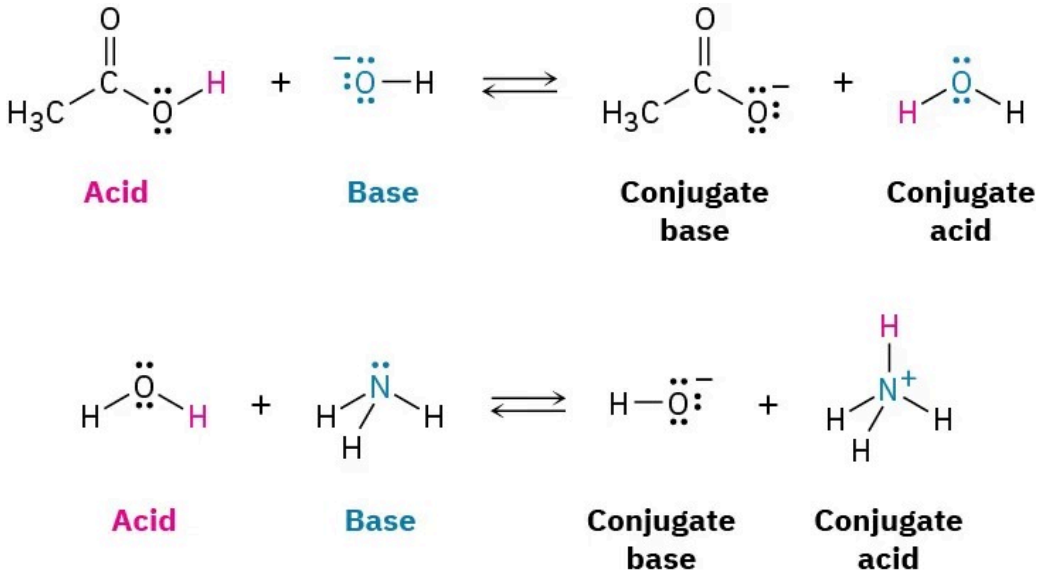


Chloride ion, the product that results when the acid HCl loses a proton, is called the conjugate base of the acid, and hydronium ion, the product that results when the base H_2O gains a proton, is called the conjugate acid of the base. Other common mineral acids such as H_2SO_4 and HNO_3 behave similarly, as do organic acids such as acetic acid, CH_3CO_2H.

In a general sense,



For example:



Notice that water can act either as an acid or as a base, depending on the circumstances. In its reaction with HCl, water is a base that accepts a proton to give the hydronium ion, H_3O^+. In its reaction with ammonia (NH_3), however, water is an acid that donates a proton to give ammonium ion (NH_4^+) and hydroxide ion, HO^-.

Exercises

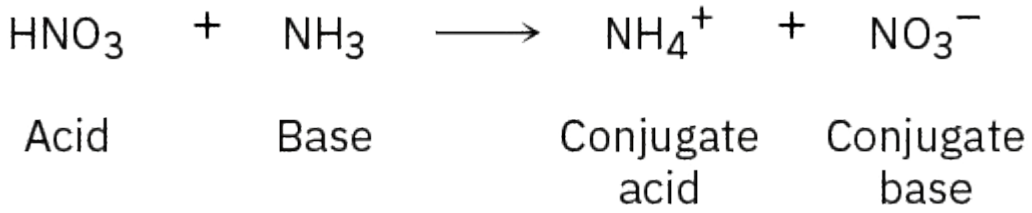
Exercise 2.8.1

Nitric acid (HNO_3) reacts with ammonia (NH_3) to yield ammonium nitrate. Write the reaction, and identify the acid, the base, the conjugate acid product, and the conjugate base product.

Answer available at the end of this section.

Answers

Exercise 2.8.1



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2.9: Acid and Base Strength

Different acids differ in their ability to donate H^+. Stronger acids, such as HCl, react almost completely with water, whereas weaker acids, such as acetic acid (CH_3CO_2H), react only slightly. The exact strength of a given acid HA in water solution is described using the **acidity constant** (K_a) for the acid-dissociation equilibrium.

$$\mathrm{HA\,(aq) + H_2O\,(l)\ \rightleftharpoons H_3O^+\,(aq) + A^-\,(aq)}$$

the acid ionization constant is written

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

Recall from general chemistry that the solvent concentration does not appear in the equilibrium expression, and that brackets [ ] around a substance refer to the concentration of the enclosed species in moles per liter (molarity).

Note

Equilibrium constant expressions are actually ratios of activities, and the value of K is determined at the limit of infinite dilution of the solutes. In these very dilute solutions, the activity of the solvent has a value of unity (1) and the activity of each solute can be approximated by its molar concentration.

Stronger acids have their equilibria toward the right and thus have larger acidity constants, whereas weaker acids have their equilibria toward the left and have smaller acidity constants. The range of K_a values for different acids is enormous, running from about 10^{15} for the strongest acids to about 10^{-60} for the weakest. Common inorganic acids such as H_2SO_4 , HNO_3 , and HCl have K_a 's in the range of 10^1 to 10^9 , while organic acids generally have K_a 's in the range of 10^{-5} to 10^{-15} . As you gain experience, you'll develop a rough feeling for which acids are "strong" and which are "weak" (always remembering that the terms are relative, not absolute).

Acid strengths are normally expressed using pK_a values rather than K_a values, where the pK_a is the negative common logarithm of the K_a:

$$\mathrm{pK_a = -\log K_a}$$

A stronger acid (larger K_a) has a smaller pK_a, and a weaker acid (smaller K_a) has a larger pK_a. Table 2.9.1 lists the pK_a's of some common acids in order of their strength, and a more comprehensive table is given in Appendix B.

Notice that the pK_a value shown in Table 2.9.1 for water is 14.00, which results from the following calculation.

$$\mathrm{H_2O\,(l) + H_2O\,(l)\ \rightleftharpoons H_3O^+\,(aq) + OH^-\,(aq)} \tag{2.9.1}$$

with

$$K_w = K_a = [\mathrm{H_3O^+}][\mathrm{OH^-}] \tag{2.9.2}$$

As explained above, because the water is the solvent and has an activity of unity (1), water is not shown explicitly in the equilibrium constant expression for K_w

Notice also in Table 2.9.1 that there is an inverse relationship between the acid strength of an acid and the base strength of its conjugate base. A strong acid has a weak conjugate base, and a weak acid has a strong conjugate base. To understand this inverse relationship, think about what is happening to the acidic hydrogen in an acid–base reaction. A strong acid is one that loses H^+ easily, meaning that its conjugate base holds the H^+ weakly and is therefore a weak base. A weak acid is one that loses H^+ with difficulty, meaning that its conjugate base holds the proton tightly and is therefore a strong base. The fact that HCl is a strong acid, for example, means that Cl^- does not hold H^+ tightly and is thus a weak base. Water, on the other hand, is a weak

acid, meaning that OH^- holds H^+ tightly and is a strong base.

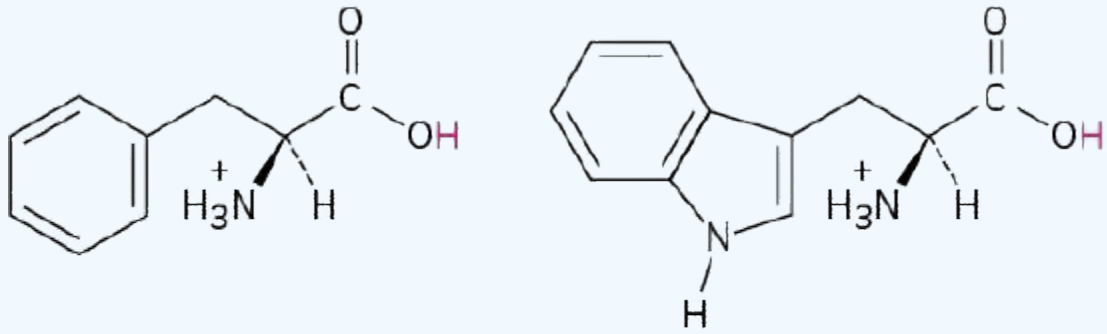
Table 2.9.1: Relative Strengths of Some Common Acids and Their Conjugate Bases

	Acid	Name	pK_a	Conjugate base	Name	
Weaker acid	CH_3CH_2OH	Ethanol	16.00	$CH_3CH_2O^-$	Ethoxide ion	Stronger base
	H_2O	Water	14.00	HO^-	Hydroxide ion	
	HCN	Hydrocyanic acid	9.31	CN^-	Cyanide ion	
	$H_2PO_4^-$	Dihydrogen phosphate ion	7.21	HPO_4^{2-}	Hydrogen phosphate ion	
	CH_3CO_2H	Acetic acid	4.76	$CH_3CO_2^-$	Acetate ion	
	H_3PO_4	Phosphoric acid	2.16	$H_2PO_4^-$	Dihydrogen phosphate ion	
	H_3O^+	Hydronium ion	0.0	H_2O	Water	
	HNO_3	Nitric acid	–1.3	NO_3^-	Nitrate ion	
Stronger acid	HCl	Hydrochloric acid	–7.0	Cl^-	Chloride ion	Weaker base

Exercises

Exercise 2.9.1

The amino acid phenylalanine has pK_a = 1.83, and tryptophan has pK_a = 2.83. Which is the stronger acid?



Phenylalanine (pK_a = 1.83)

Tryptophan (pK_a = 2.83)

Answer available at the end of this section.

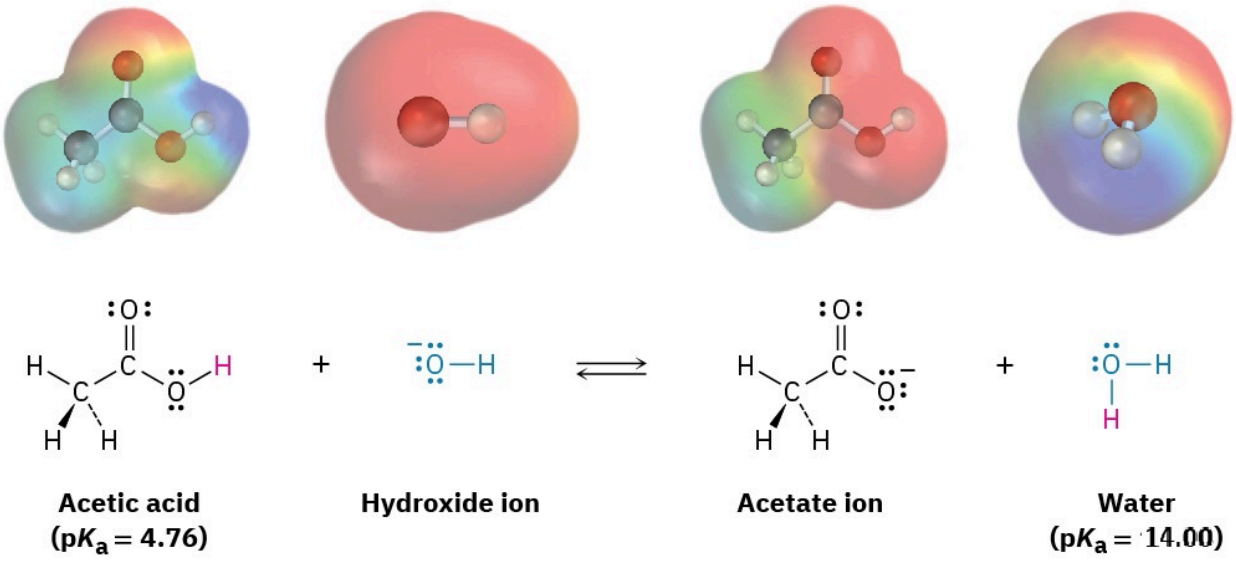
Exercise 2.9.2

Amide ion, H_2N^-, is a much stronger base than hydroxide ion, HO^-. Which is the stronger acid, NH_3 or H_2O? Explain.

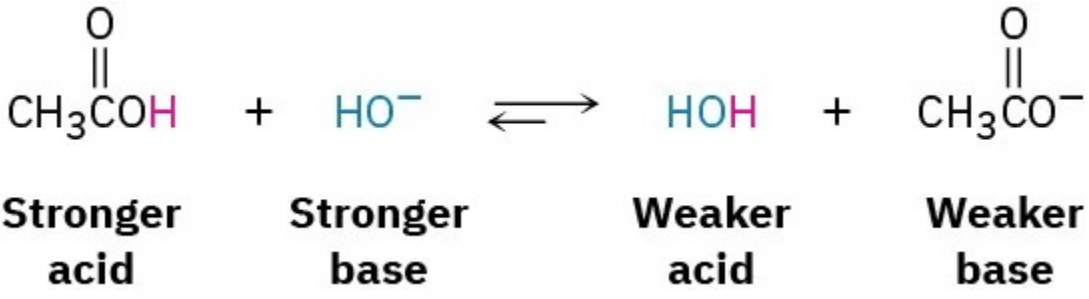
Answer available at the end of this section.

Predicting Acid-Base Reactions from pKa Values

Compilations of pK_a values like those in Table 2.9.1 and Appendix B are useful for predicting whether a given acid–base reaction will take place, because H^+ will always go *from* the stronger acid *to* the stronger base. That is, an acid will donate a proton to the conjugate base of a weaker acid, and the conjugate base of a weaker acid will remove a proton from a stronger acid. Since water (pK_a = 14.00) is a weaker acid than acetic acid (pK_a = 4.76), for example, hydroxide ion holds a proton more tightly than acetate ion does. Hydroxide ion will therefore react to a large extent with acetic acid, CH_3CO_2H, to yield acetate ion and H_2O.

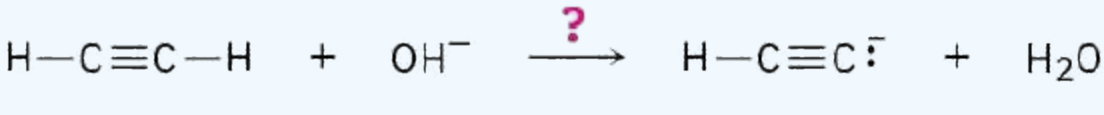


Another way to predict acid–base reactivity is to remember that the product conjugate acid in an acid–base reaction must be weaker and less reactive than the starting acid and the product conjugate base must be weaker and less reactive than the starting base. In the reaction of acetic acid with hydroxide ion, for example, the product conjugate acid (H_2O) is weaker than the starting acid (CH_3CO_2H), and the product conjugate base ($CH_3CO_2^-$) is weaker than the starting base (OH^-).



Worked Example 2.9.1: Predicting Acid Strengths from pK_a Values

Water has pK_a = 14.00, and acetylene has pK_a = 25. Which is the stronger acid? Does hydroxide ion react to a significant extent with acetylene?



Acetylene

Strategy

When comparing two acids, the one with the lower pK_a is stronger. Thus, water is a stronger acid than acetylene and gives up H^+ more easily.

Solution

Because water is a stronger acid and gives up H^+ more easily than acetylene, the HO^- ion must have less affinity for H^+ than the $HC{\equiv}C{:}^-$ ion. In other words, the anion of acetylene is a stronger base than hydroxide ion, and the reaction will not proceed significantly as written.

Worked Example 2.9.2: Calculating K_a from pK_a

According to the data in Table 2.9.1, acetic acid has pK_a = 4.76. What is its K_a?

Strategy

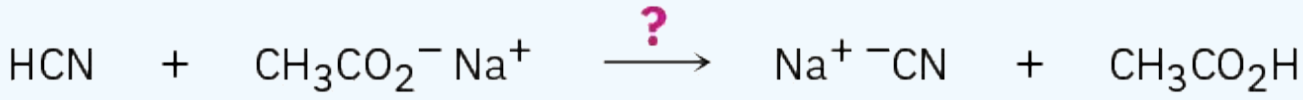
Since pK_a is the negative logarithm of K_a, it's necessary to use a calculator with an ANTILOG or INV LOG function. Enter the value of the pK_a (4.76), change the sign (–4.76), and then find the antilog (1.74×10^{-5}).

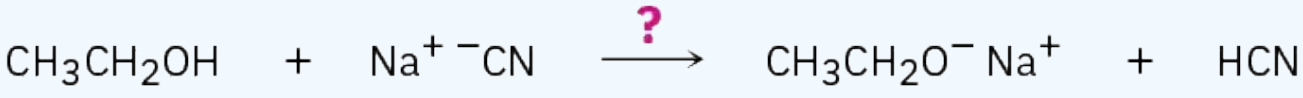
Solution

$K_a = 1.74 \times 10^{-5}$.

Exercise 2.9.3

Will either of the following reactions take place to a significant extent as written, according to the data in Table 2.9.1?

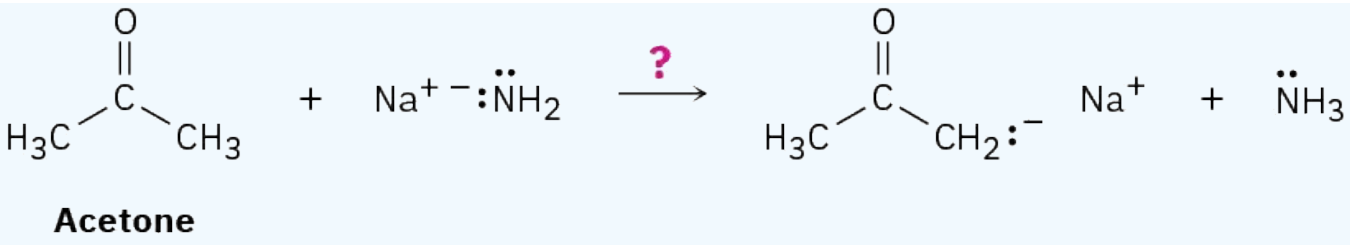
a. 

b. 

Answer available at the end of this section.

Exercise 2.9.4

Ammonia, NH_3, has p$K_a \approx 36$, and acetone has p$K_a \approx 19$. Will the following reaction take place to a significant extent?



Acetone

Answer available at the end of this section.

Exercise 2.9.5

What is the K_a of HCN if its pK_a = 9.31?

Answer available at the end of this section.

Answers

Exercise 2.9.1

Phenylalanine is stronger.

Exercise 2.9.2

Water is a stronger acid.

Exercise 2.9.3

Neither reaction will take place.

Exercise 2.9.4

The reaction will take place.

Exercise 2.9.5

$K_a = 4.9 \times 10^{-10}$

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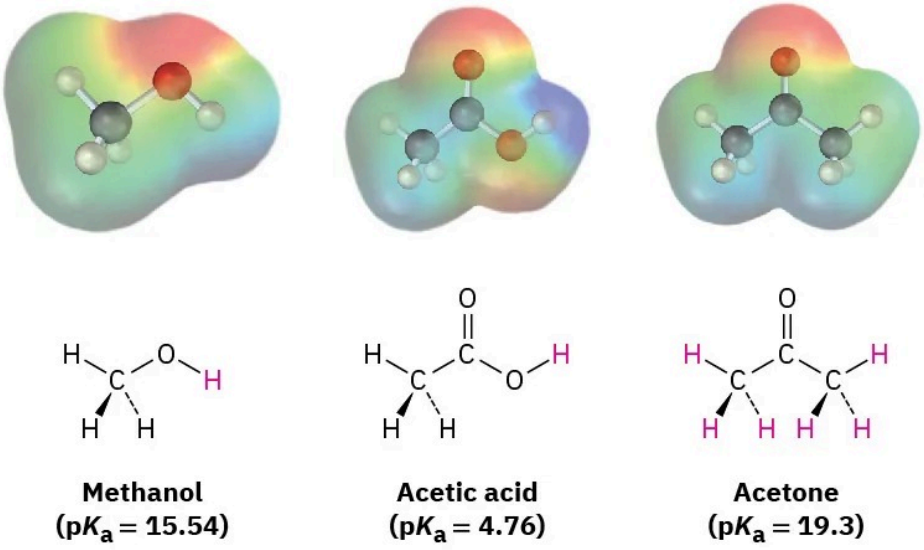
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2.10: Organic Acids and Organic Bases

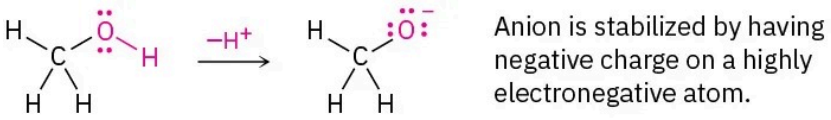
Many of the reactions we'll be seeing in future chapters, including practically all biological reactions, involve organic acids and organic bases. Although it's too early to go into the details of these processes now, you might keep the following generalities in mind:

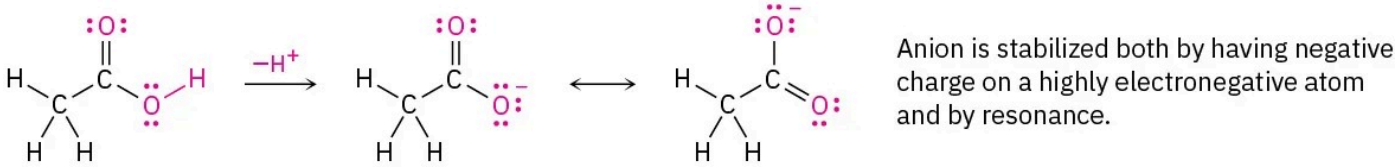
Organic Acids

Organic acids are characterized by the presence of a positively polarized hydrogen atom (blue in electrostatic potential maps) and are of two main kinds: acids such as methanol and acetic acid that contain a hydrogen atom bonded to an electronegative oxygen atom (O–H) and those such as acetone (Section 2.6) that contain a hydrogen atom bonded to a carbon atom next to a C=O bond (O=C–C–H).

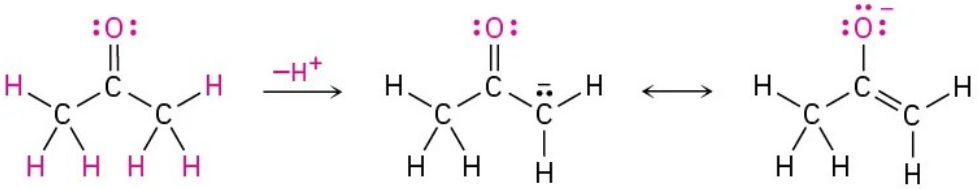


Methanol contains an O–H bond and is a weak acid, while acetic acid also contains an O–H bond and is a somewhat stronger acid. In both cases, acidity is due to the fact that the conjugate base resulting from loss of H^+ is stabilized by having its negative charge on a strongly electronegative oxygen atom. In addition, the conjugate base of acetic acid is stabilized by resonance.





The acidity of acetone and other compounds with C=O bonds is due to the fact that the conjugate base resulting from the loss of H^+ is stabilized by resonance. In addition, one of the resonance forms stabilizes the negative charge by placing it on an electronegative oxygen atom.



Anion is stabilized both by resonance and by having negative charge on a highly electronegative atom.

Electrostatic potential maps of the conjugate bases from methanol, acetic acid, and acetone are shown in Figure 2.5. As you might expect, all three show a substantial amount of negative charge (red) on oxygen.

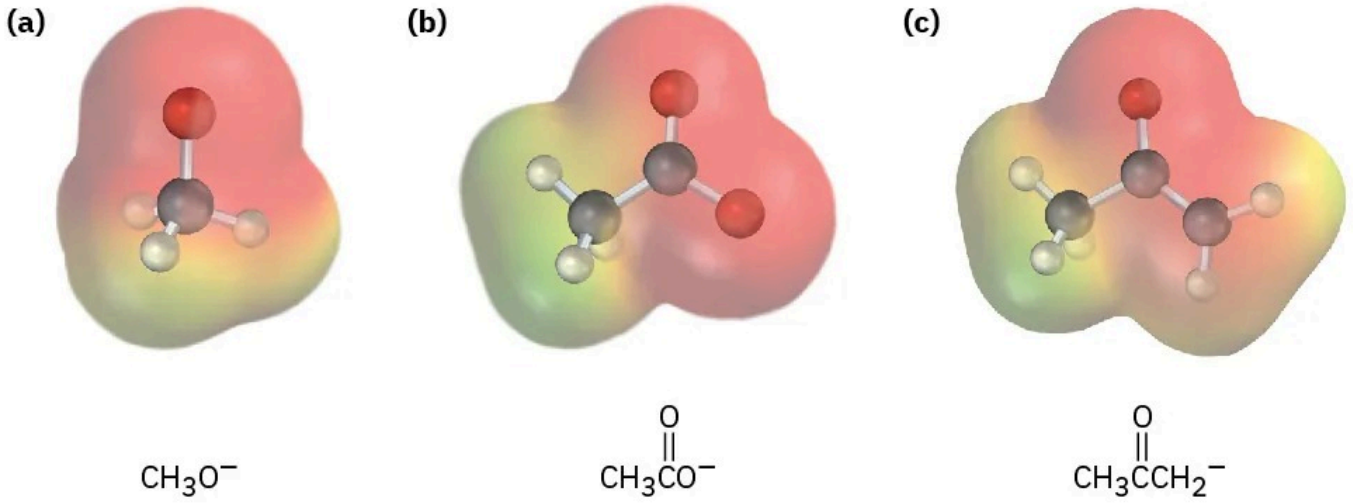
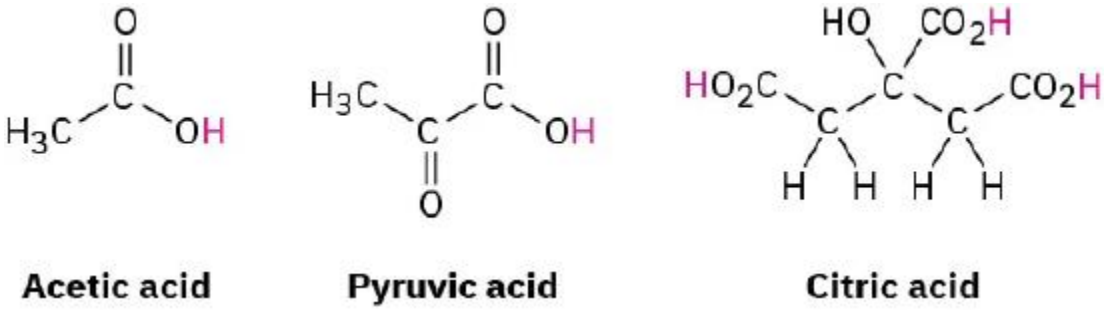


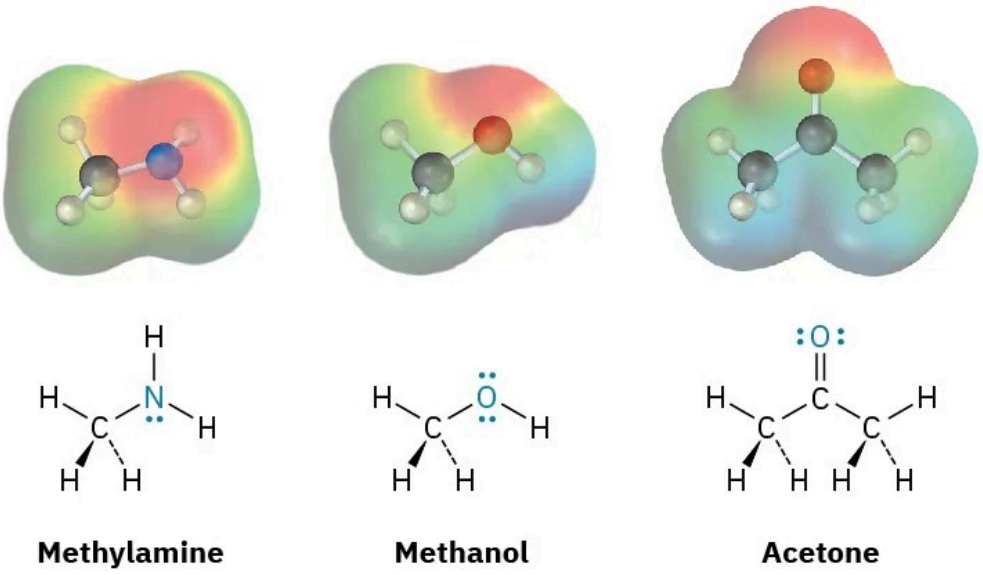
Figure 2.5 Electrostatic potential maps of the conjugate bases of **(a)** methanol, **(b)** acetic acid, and **(c)** acetone. The electronegative oxygen atoms stabilize the negative charge in all three.

Compounds called *carboxylic acids,* which contain the $-CO_2H$ grouping, occur abundantly in all living organisms and are involved in almost all metabolic pathways. Acetic acid, pyruvic acid, and citric acid are examples. You might note that at the typical pH of 7.3 found within cells, carboxylic acids are usually dissociated and exist as their carboxylate anions, $-CO_2^-$.

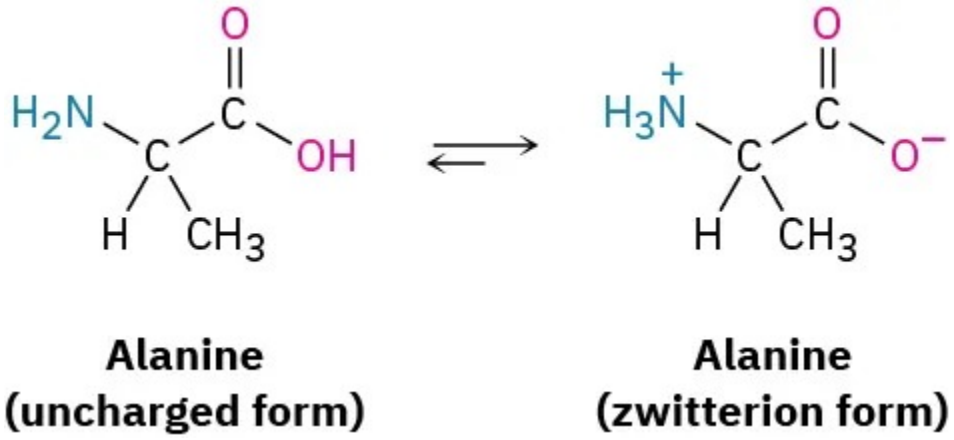


Organic Bases

Organic bases are characterized by the presence of an atom (reddish in electrostatic potential maps) with a lone pair of electrons that can bond to H^+. Nitrogen-containing compounds such as methylamine are the most common organic bases and are involved in almost all metabolic pathways, but oxygen-containing compounds can also act as bases when reacting with a sufficiently strong acid. Note that some oxygen-containing compounds can act both as acids and as bases depending on the circumstances, just as water can. Methanol and acetone, for instance, act as acids when they donate a proton but as bases when their oxygen atom accepts a proton.



Substances called amino acids, so-named because they are both amines ($-NH_2$) and carboxylic acids ($-CO_2H$), are the building blocks from which the proteins in all living organisms are made. Twenty different amino acids go into making up proteins—alanine is an example. Interestingly, alanine and other amino acids exist primarily in a doubly charged form called a *zwitterion* rather than in the uncharged form. The zwitterion form arises because amino acids have both acidic and basic sites within the same molecule and therefore undergo an internal acid–base reaction.



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2.11: Structural Effects on Acidity and Basicity

We have learned that different functional groups have different strengths in terms of acidity. In this section, we will gain an understanding of the fundamental reasons behind this, which is *why* one group is more acidic than the other one. Many of the concepts that we will learn here will continue to apply throughout this course as we tackle many other organic topics.

To determine the relative strength of two acids, without knowing their p*K*a values, we compare the **stability of their conjugate bases**.

The stronger the acid, the more stable its conjugate base!

When an acid loses a proton, it forms the conjugate base, which has a **lone pair of electrons** that resulted from the loss of H+. To determine the stability of a conjugate base, we are actually looking at the **stability of the lone pair**. The more effectively a conjugate base can stabilize its negative charge (that is lone pair), the stronger the acid.

Four main factors affect the stability of a **negative charge**:

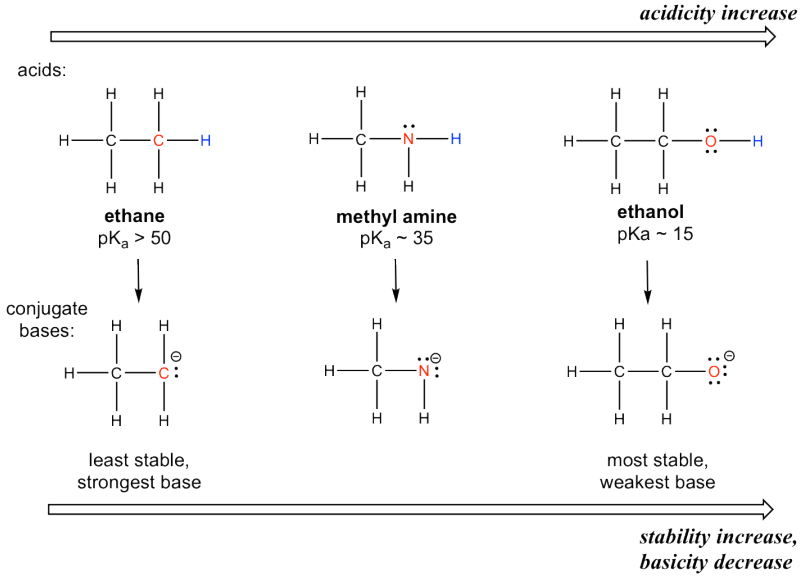
- The type of **atom** that carries the charge.
- **Resonance.**
- **Induction.**
- The type of **orbital** in which the charge resides.

These factors can be remembered with the acronym **ARIO.**

(A) Atom

A. Periodic Trend: Electronegativity

The element effect is about the ***individual atom that connects with the*** **hydrogen** (keep in mind that the acidity is about the ability to donate a certain hydrogen). Let's compare the acidity of hydrogens in ethane, methylamine and ethanol as shown below.



A clear trend in the acidity of these compounds is: the acidity increases for the elements from left to right along the second row of the periodic table, C to N, and then to O. This is consistent with the increasing trend of electronegativity along the period from left to right. The connection between electronegativity and acidity can be explained as the atom with a higher electronegativity being able to better accommodate the negative charge of the conjugate base, therefore stabilizing the conjugate base in a better

way. Therefore, ***the more stable the conjugate base, the weaker the conjugate base is, and the stronger the acid is***. For the discussions in this section, the trend in the stability (or basicity) of the conjugate bases often helps to explain the trend of the acidity.

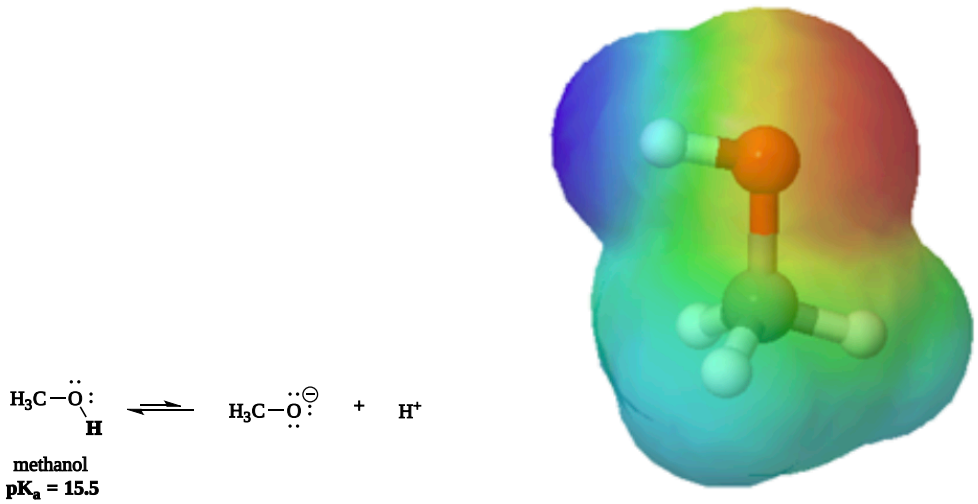
The relative acidity of elements in the same period is:

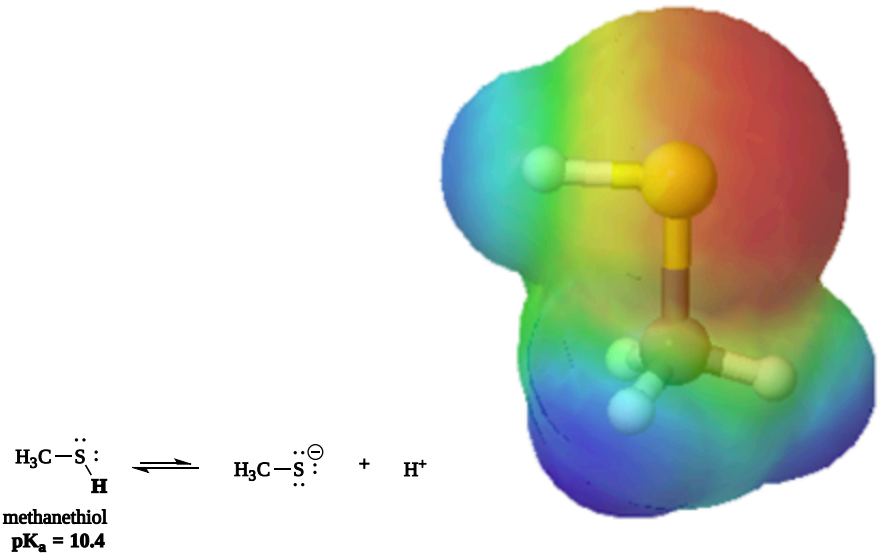
For elements in the same period, the more electronegative an atom, the stronger the acid is; the acidity increases from left to right across the period.

B. Group (vertical) Trend: Size of the atom

When moving vertically within a given group on the periodic table, the trend is that acidity increases from top to bottom.

The acidity of the H in the thiol SH group is also stronger than the corresponding alcohol OH group, following the same trend. For example, the pK_a of CH_3CH_2SH is ~10, which is much more acidic than ethanol CH_3CH_2OH with a pK_a of ~16.

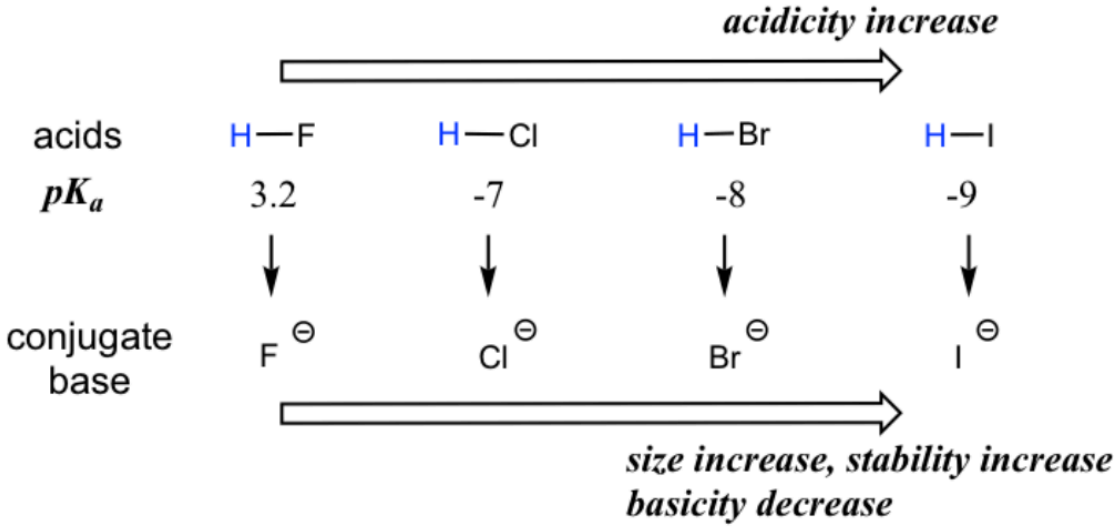




The difference in size is easily visible when comparing the electrostatic potential maps for the corresponding conjugate bases: Methoxide and methanethiolate. The sulfur atom is larger than the oxygen atom. The larger size of sulfur will be better able to

delocalize and stabilize the negative charge in its conjugate base metanethiolate.

This can explain why HF is the only haloacidic acid, HX, that is not considered a strong acid. It can be illustrated with the haloacids and halides as shown below: the acidity of HX increases from top to bottom, and the basicity of the conjugate bases X^- decreases from top to bottom.



In order to make sense of this trend, we will once again consider the stability of the conjugate bases. When moving vertically in the same group of the periodic table, the *size* of the atom overrides its electronegativity with regard to basicity. The atomic radius of iodine is approximately twice that of fluorine, so in an iodide ion, the negative charge is spread out over a significantly larger volume, so I^- is more stable and less basic, making HI more acidic.

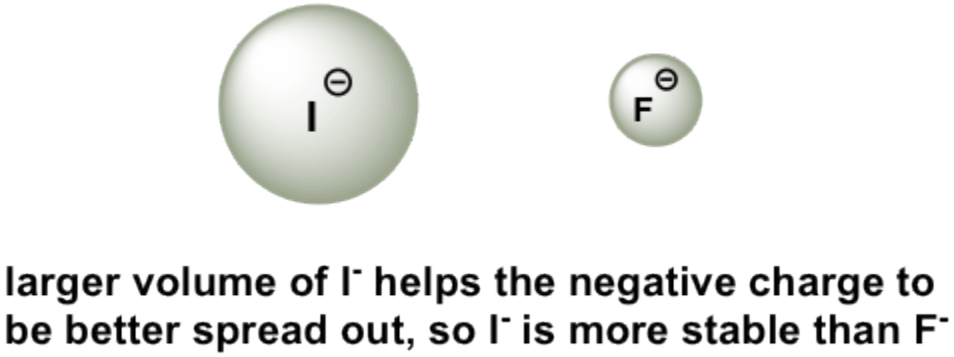
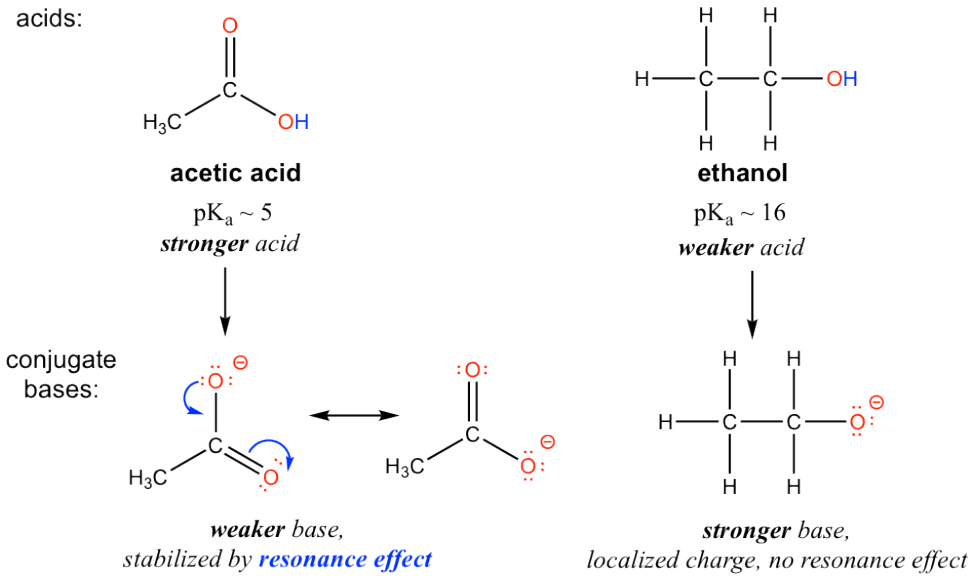


Figure 2.11.1: Representation of fluorine and iodide ions.

For elements in the same group, the larger the size of the atom, the stronger the acid is; the acidity increases from top to bottom along the group.

(R) Resonance Effect

The resonance effect accounts for the acidity difference between ethanol and acetic acid. For both ethanol and acetic acid, the hydrogen is bonded with the oxygen atom, so there is no element effect that matters. However, the pK_a values (and the acidity) of ethanol and acetic acid are very different. What makes a carboxylic acid so much more acidic than an alcohol? As stated before, we begin by considering the stability of the conjugate bases, remembering that a more stable (weaker) conjugate base corresponds to a stronger acid.

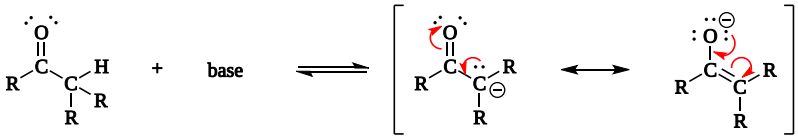


For acetate, the conjugate base of acetic acid, two resonance contributors can be drawn and therefore the negative charge can be delocalized (shared) over two oxygen atoms. However, no other resonance contributor is available in the ethoxide ion, the conjugate base of ethanol, so the negative charge is localized on the oxygen atom. As we have learned, **the conjugate base that has more resonance contributors gains stability;** therefore, acetate is more stable than ethoxide, and is weaker as a base, so acetic acid is a stronger acid than ethanol.

The charge delocalization by resonance has a very powerful effect on the reactivity of organic molecules, enough to account for the big difference of over 10 pK_a units between ethanol and acetic acid. Because pK_a = –log K_a, that means that there is a factor of about 10^{10} between the K_a values for the two molecules!

Acidity of Hydrogen α (alpha) to Carbonyl

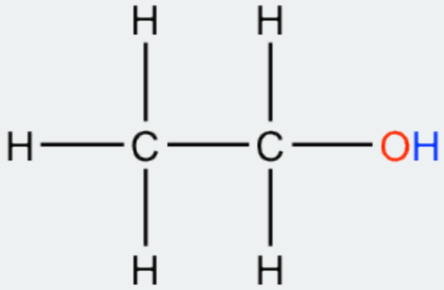
Alkyl hydrogen atoms bonded to a carbon atom in an α (alpha) position (directly adjacent) relative to a C=O group display unusual acidity. While the pKa values for alkyl C-H bonds in is typically on the order of 40-50, pKa values for these alpha hydrogens are more on the order of 19-20. This is almost exclusively due to the resonance stabilization of the product carbanion, called an enolate, as illustrated in the diagram below. The effect of the stabilizing C=O is seen when comparing the pKa for the α hydrogens of aldehydes (~16-18), ketones (~19-21), and esters (~23-25).



enolate ion

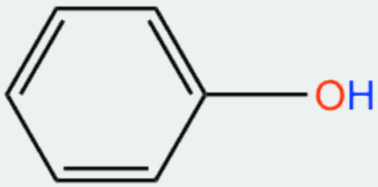
Worked Example

The pK_a of the OH group in alcohol is about 15, however OH in phenol (OH group connected on a benzene ring) has a pK_a of about 10, which is much stronger in acidity than other alcohols. Explain the difference.



ethanol

$pK_a \sim 16$

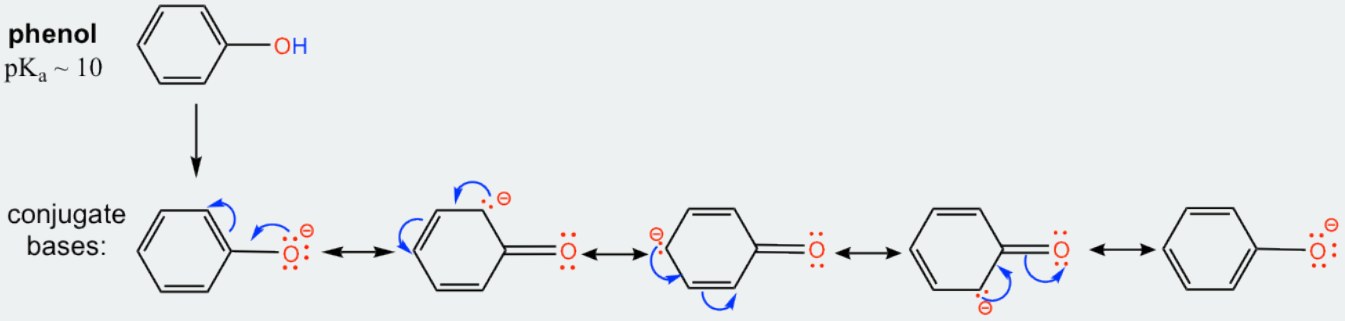


phenol

$pK_a \sim 10$

Solution:

The difference can be explained by the resonance effect. There is no resonance effect on the conjugate base of ethanol, as mentioned before. However, the conjugate base of phenol is stabilized by the resonance effect with four more resonance contributors, and the negative is delocalized on the benzene ring, so the conjugate base of phenol is much more stable and is a weaker base. Therefore phenol is much more acidic than other alcohols.



resonance contributors of conjugate base; charge deloczlized and base is stabilized by resonance effect

- Practice drawing the resonance structures of the conjugate base of phenol by yourself!
- It is because of the special acidity of phenol (and other aromatic alcohols), that NaOH can be used to deprotonate phenol effectively, but not to normal alcohols, like ethanol. Show the reaction equations of these reactions and explain the difference by applying the pK_a values.

It is because of the special acidity of phenol (and other aromatic alcohols) that NaOH can be used to deprotonate phenol effe



The equilibrium lies on the **product side**, so NaOH is able to deprotonate phenol.



Stay at **equilibrium**, so NaOH is **not** able to deprotonate ethanol effectively.

(I) Inductive Effect

The **inductive effect** is an experimentally observed phenomenon resulting from the transmission of charge through a chain of atoms in a molecule, which leads to a permanent dipole in a bond.

Withdrawing Inductive Effects

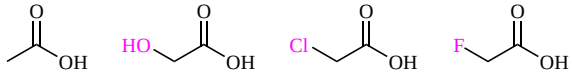
A fluorine atom is more electronegative than a carbon atom, and thus it is able to 'induce', or 'pull' the electron density of covalent bonds towards itself. In the fluoroacetate anion, the electrons in the C-F covalent bond are pulled toward the fluorine, giving the carbon a partial positive charge. The positively charged carbon, in turn, draws electron density away from the carboxylate anion, dispersing the charge and creating a stabilizing effect. Stabilizing the carboxylate anion increases the acidity of the corresponding carboxylic acid. In this context, the fluorine substituent is acting as an **electron-withdrawing group**.

The following diagram shows the inductive effect of fluoroacetate and chloroacetate as examples.



Figure 2.11.2: Fluoroacetate anion and Chloroacetate ion are stabilized by the electron-withdrawing inductive effect: Fluorine and Chlorine atoms pull electrons through sigma bonds, which helps to disperse the negative charge.

A similar effect is seen when other electron-withdrawing groups are attached to -CH_2CO_2H. As the power of the electron-withdrawing group becomes stronger, there is a corresponding drop in the pK_a of the carboxylic acid.



pK_a = 4.8 pK_a = 3.9 pK_a = 2.8 pK_a = 2.6

As the inductive effect is the charge-dispersal effect of electronegative atoms through σ bonds, it can be additive. For example, the presence of more chlorine atoms has an overall stronger effect, which explains the increasing acidity from mono, to di-, to tri-chlorinated acetic acid. Let's compare the pK_a values of acetic acid and its mono-, di-, and tri-chlorinated derivatives:

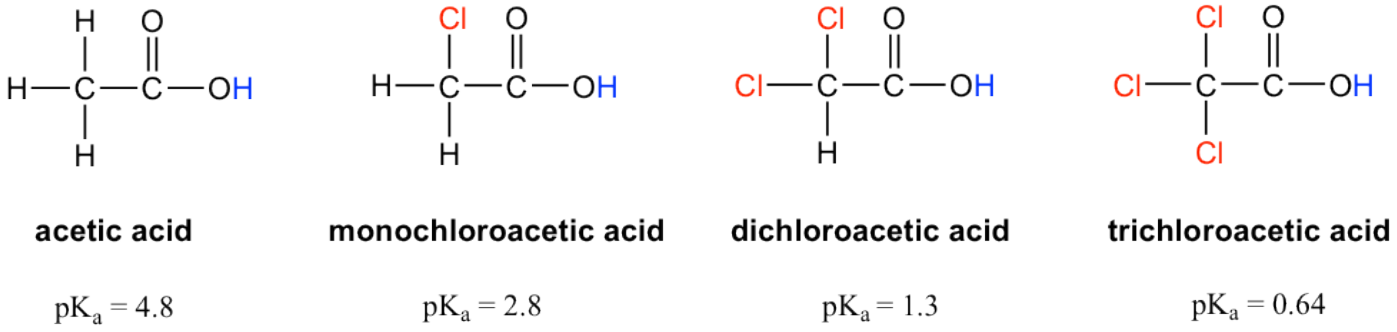


Figure 2.11.3: Acetic acid and its mono-, di-, and tri-chlorinated derivatives

Because the inductive effect depends on electronegativity, fluorine substituents have a stronger inductive effect than chlorine substituents, making trifluoroacetic acid (TFA) a very strong organic acid.

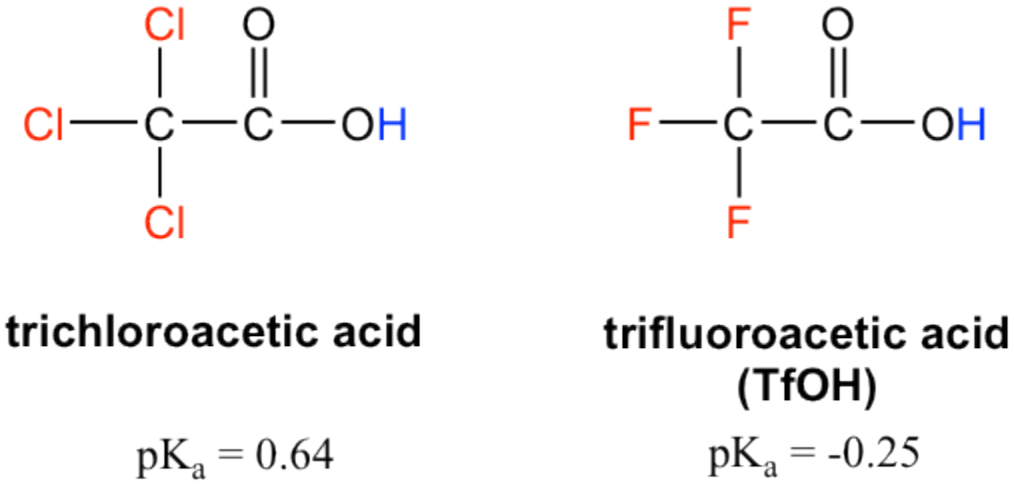


Figure 2.11.4: trichloroacetic acid (pKa = 0.64) and trifluoroacetic acid (TfOH) (pKa = -0.25)

In addition, because the inductive effect takes place through covalent bonds, its influence decreases significantly with distance — thus a chlorine that is two carbons away from a carboxylic acid group has a weaker effect compared to a chlorine just one carbon away.

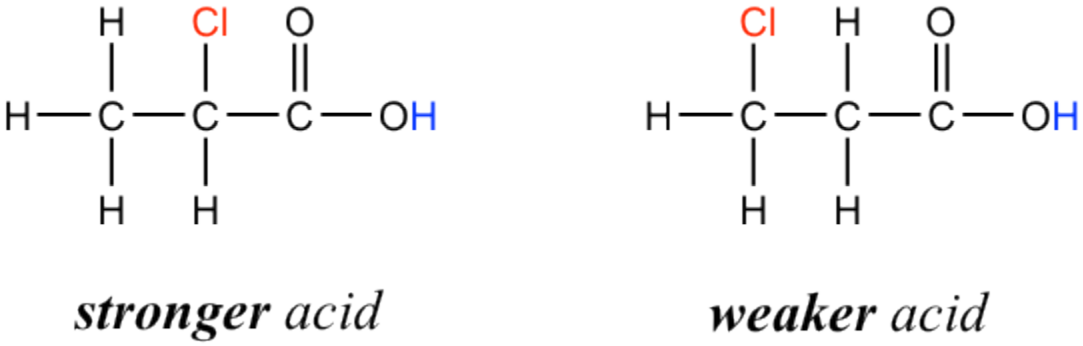
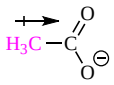


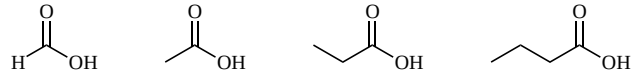
Figure 2.11.5: 2-chloropropanoic acid (pKa = 2.8) and 3-chloropropanoic acid (pKa = 4.0)

Donating Inductive Effects

Alkyl groups (hydrocarbons) are inductively electron-donating. In this case, the inductive effects pushes electron density onto the carboxylate anion, producing a destabilizing effect, decreasing the acidity of the carboxylic acid.



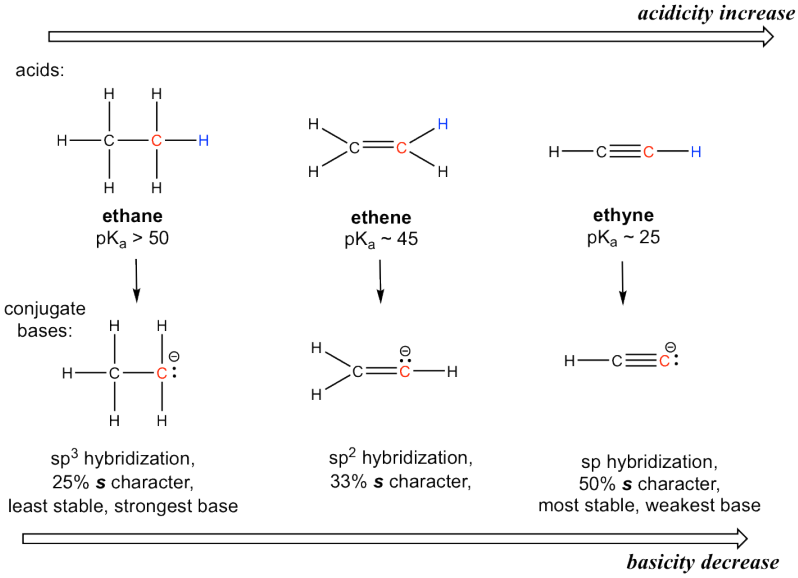
Lengthening the alkyl chain of a carboxylic acid can increase this inductive effect but it no longer decreases the acidity further after the chain is about three carbons long.



$pK_a = 3.75$ $pK_a = 4.76$ $pK_a = 4.87$ $pK_a = 4.82$

(O) Orbital Effect

To introduce the hybridization effect, we will take a look at the acidity difference between alkane, alkene and alkyne.



The hydrogen atom is bonded with a carbon atom in all the three functional groups, so the element effect does not invoke. Also, considering the conjugate base of each, there is no extra resonance contributor possible.

The key difference between the conjugate base anions is the hybridization of the carbon atom, that is sp^3, sp^2 and sp respectively for alkane, alkene, and alkyne. Different hybridizations leads to different **s character**, that is the percent of s orbitals out of the total amount of orbitals. The sp^3 hybridization means 25% *s* character (one *s* and three *p* orbitals, so *s* character is 1/4 = 25%), sp^2 hybridization has 33.3% *s* character, and the number is 50% for sp hybridization. Electrons of 2*s* orbitals are in the lower energy level than those of 2*p* orbitals because 2*s* is much closer to the nucleus. So for the anion with more *s* character, the electrons are closer to the nucleus and experience stronger attraction, therefore the anion has lower energy and is more stable.

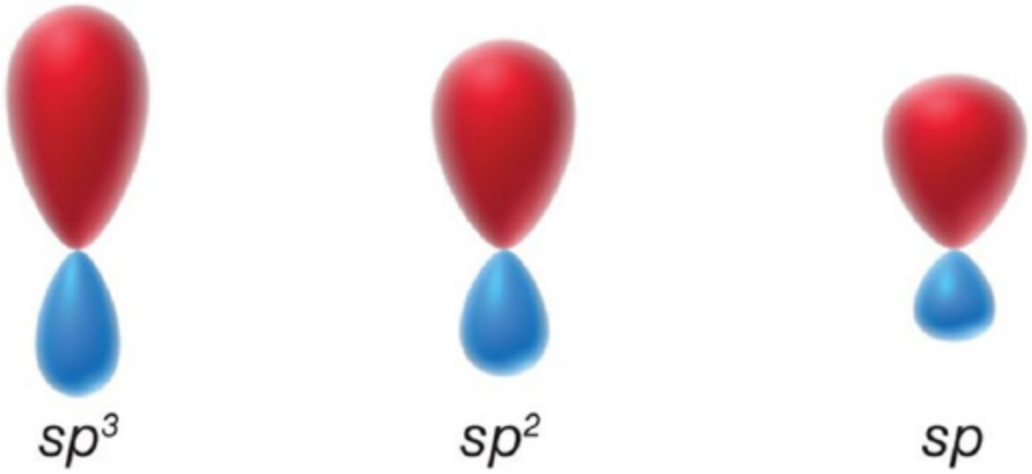


Figure 2.11.5: The type of orbital also can affect the stability of a formal negative charge. The closer electrons are held to the nucleus, the more stable they are. The shorter the atomic orbital, the closer to the nucleus.

The relative stability of three anions (conjugate bases) for alkane, alkene, and alkyne can also be illustrated by the electrostatic potential map, in which the lighter color (less red) indicates less electron density of the anion and higher stability.

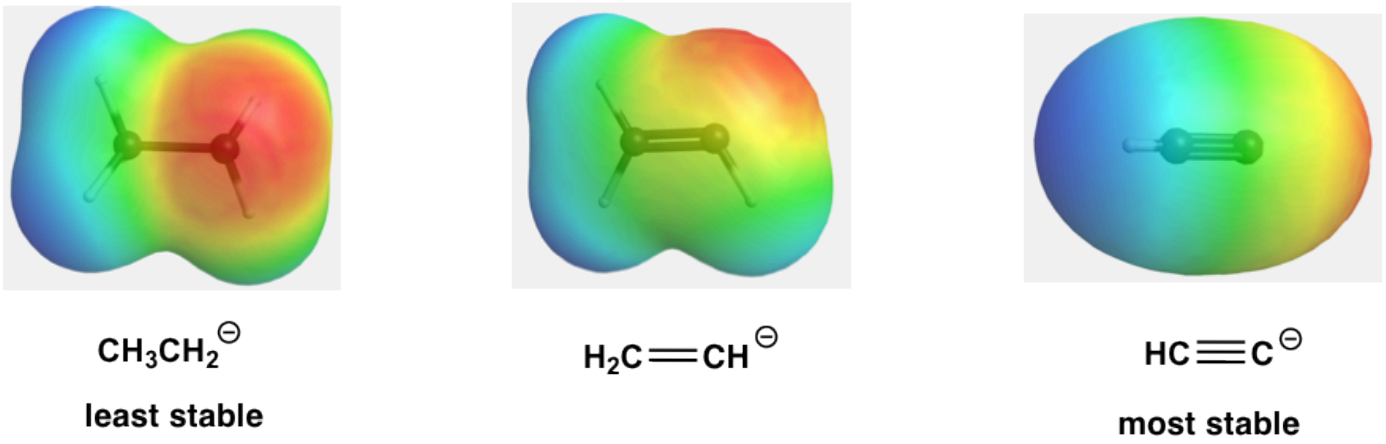
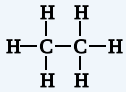
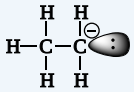
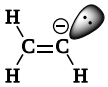
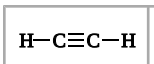
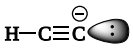


Figure 2.11.6: Electrostatic potential map of the conj. bases

This can also be stated in a more general way that the more s-character in the hybrid orbitals makes the atom more electronegative. ***For the same atom, an sp hybridized atom is more electronegative than sp^2 hybridized atom, which is more electronegative than sp^3 hybridized atom.***

The table below shows how orbital hybridization influences relative acidity.

compound	conjugate base	hybridization	s character	pK_a	Acidic Strength
		sp^3	25%	50	weakest acid
		sp^2	33%	44	↓
NH_3	$^{\ominus}NH_2$	sp^3		36 (Atom and hybridization are competing factors)	↓

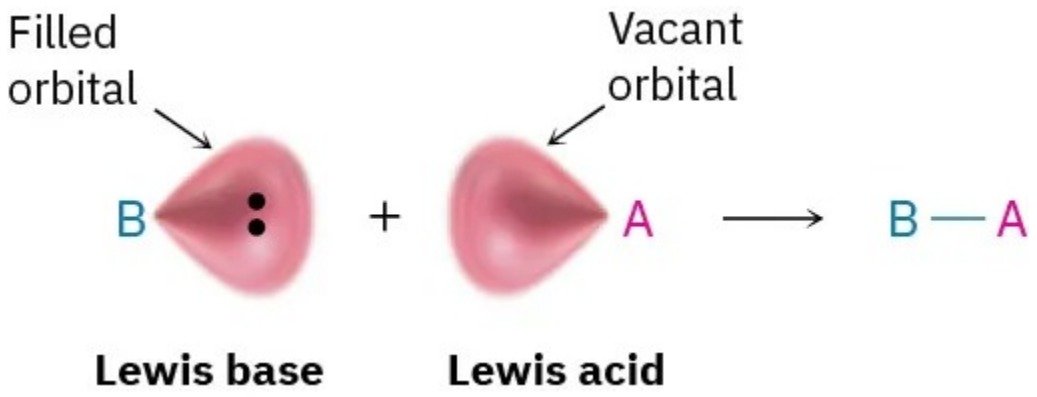
		sp	50%	25	↓
				16	strongest acid

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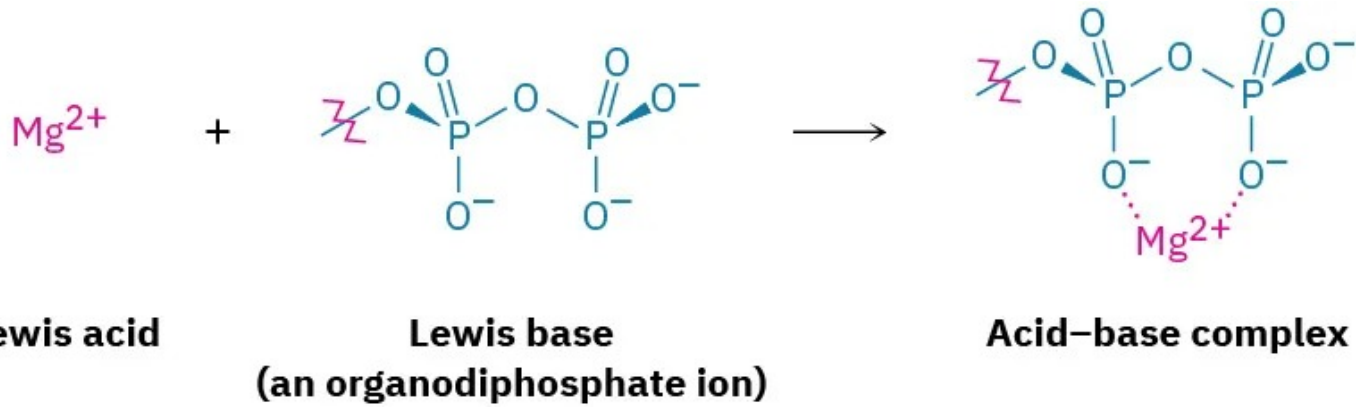
2.12: Acids and Bases - The Lewis Definition

The Lewis definition of acids and bases is more encompassing than the Brønsted–Lowry definition because it's not limited to substances that donate or accept just protons. A Lewis acid is a substance that accepts an electron pair, and a Lewis base is a substance that donates an electron pair. The donated electron pair is shared between the acid and the base in a covalent bond.



Lewis Acids and the Curved Arrow Formalism

The fact that a Lewis acid is able to accept an electron pair means that it must have either a vacant, low-energy orbital or a polar bond to hydrogen so that it can donate H^+ (which has an empty 1s orbital). Thus, the Lewis definition of acidity includes many species in addition to H^+. For example, various metal cations, such as Mg^{2+}, are Lewis acids because they accept a pair of electrons when they form a bond to a base. We'll also see in later chapters that certain metabolic reactions begin with an acid–base reaction between Mg^{2+} as a Lewis acid and an organic diphosphate or triphosphate ion as the Lewis base.



In the same way, compounds of group 3A elements, such as BF_3 and $AlCl_3$, are Lewis acids because they have unfilled valence orbitals and can accept electron pairs from Lewis bases, as shown in Figure 2.12.1. Similarly, many transition-metal compounds, such as $TiCl_4$, $FeCl_3$, $ZnCl_2$, and $SnCl_4$, are Lewis acids.

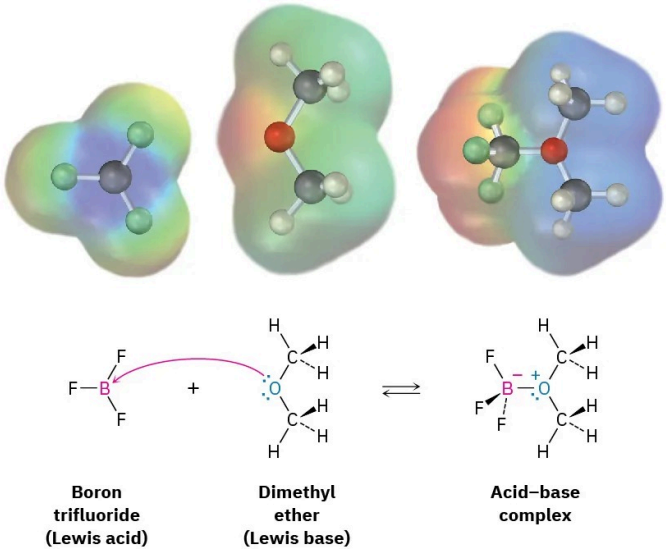
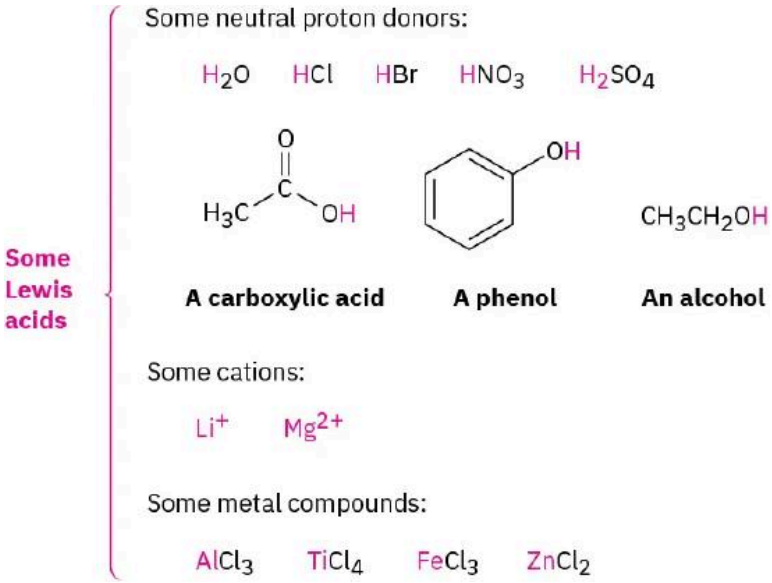


Figure 2.12.1: The reaction of boron trifluoride, a Lewis acid, with dimethyl ether, a Lewis base. The Lewis acid accepts a pair of electrons, and the Lewis base donates a pair of nonbonding electrons. Note how the movement of electrons from the Lewis base to the Lewis acid is indicated by a curved arrow. Note also how, in electrostatic potential maps, **the boron becomes more negative (red)** after reaction because it has gained electrons and **the oxygen atom becomes more positive (blue)** because it has donated electrons.

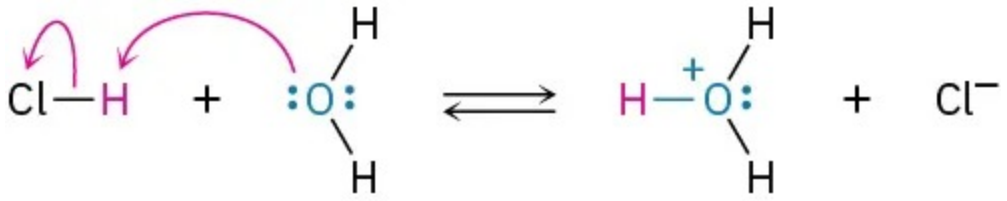
Look closely at the acid–base reaction in Figure 2.12.1, and notice how it's shown. Dimethyl ether, the Lewis base, donates an electron pair to a vacant valence orbital of the boron atom in BF_3, a Lewis acid. The direction of electron-pair flow from base to acid is shown using a curved arrow, just as the direction of electron flow from one resonance structure to another was shown using curved arrows in Section 2.6. We'll use this curved-arrow notation throughout the remainder of this text to indicate electron flow during reactions, so get used to seeing it.

Some further examples of Lewis acids follow:



Lewis Bases

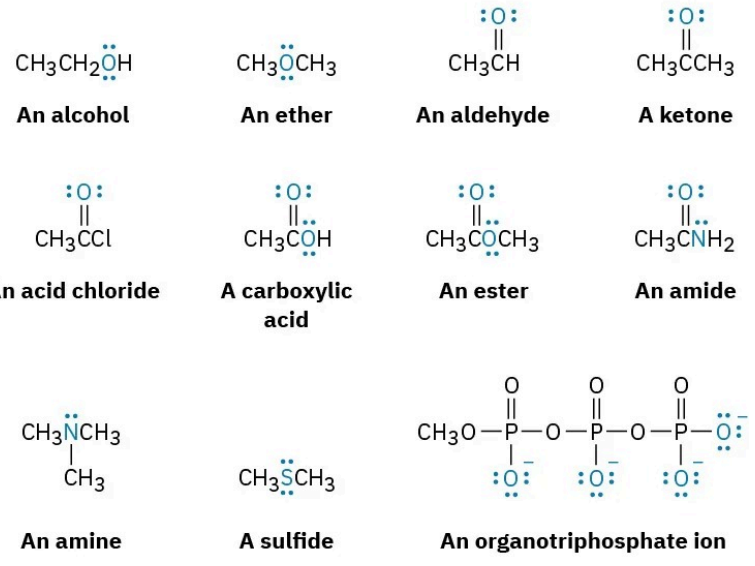
The Lewis definition of a base—a compound with a pair of nonbonding electrons that it can use to bond to a Lewis acid—is similar to the Brønsted–Lowry definition. Thus, H_2O, with its two pairs of nonbonding electrons on oxygen, acts as a Lewis base by donating an electron pair to an H^+ in forming the hydronium ion, H_3O^+.



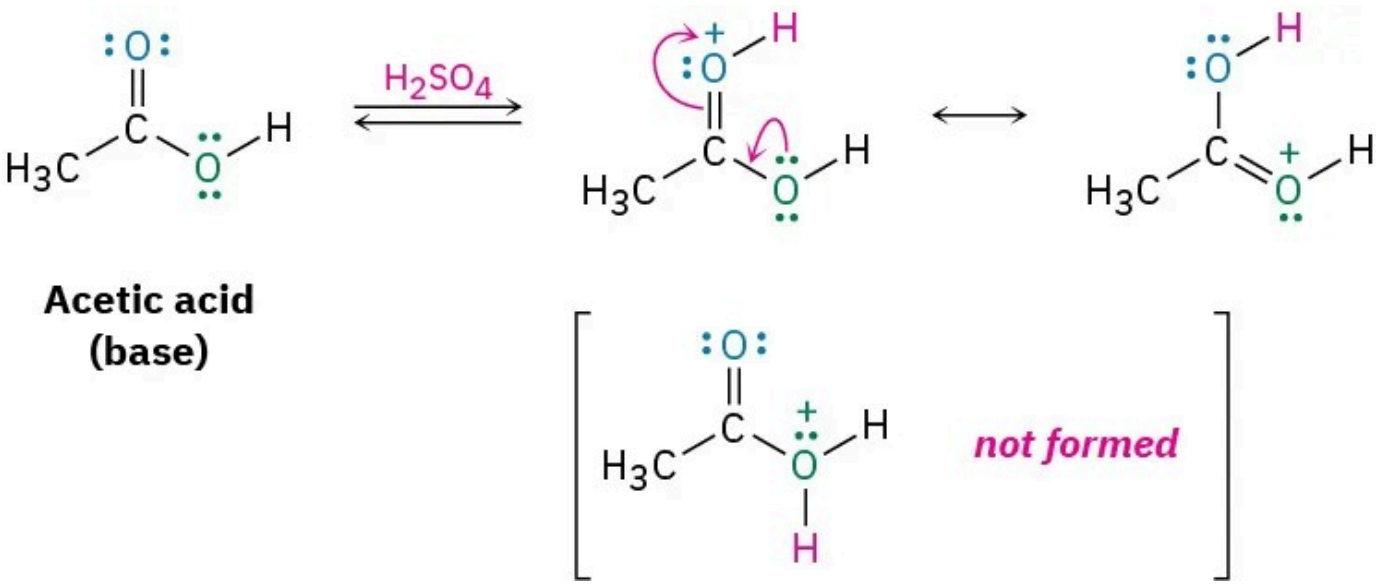
Acid **Base** **Hydronium ion**

In a more general sense, most oxygen- and nitrogen-containing organic compounds can act as Lewis bases because they have lone pairs of electrons. A divalent oxygen compound has two lone pairs of electrons, and a trivalent nitrogen compound has one lone pair. Note in the following examples that some compounds can act as both acids and bases, just as water can. Alcohols and carboxylic acids, for instance, act as acids when they donate an H^+ but as bases when their oxygen atom accepts an H^+.

Some Lewis bases



Note also that some Lewis bases, such as carboxylic acids, esters, and amides, have more than one atom with a lone pair of electrons and can therefore react at more than one site. Acetic acid, for example, can be protonated either on the doubly bonded oxygen atom or on the singly bonded oxygen atom. The reaction normally occurs only once in such instances, and the more stable of the two possible protonation products are formed. For acetic acid, protonation by reaction with sulfuric acid occurs on the doubly bonded oxygen because that product is stabilized by two resonance forms.



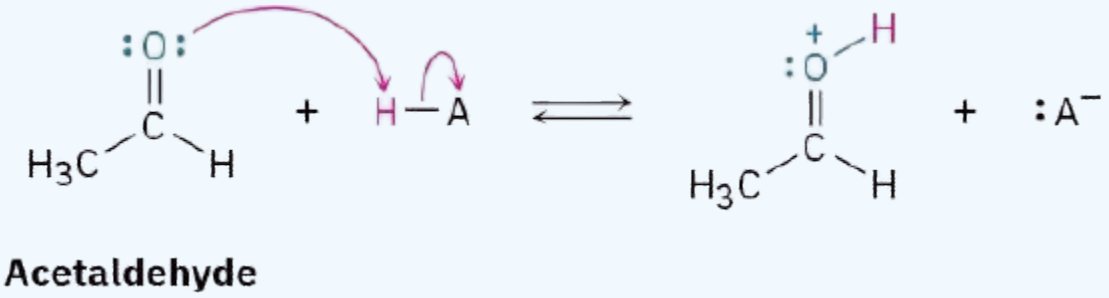
Worked Example 2.12.1: Using Curved Arrows to Show Electron Flow

Using curved arrows, show how acetaldehyde, CH_3CHO, can act as a Lewis base.

Strategy

A Lewis base donates an electron pair to a Lewis acid. We therefore need to locate the electron lone pairs on acetaldehyde and use a curved arrow to show the movement of a pair toward the H atom of the acid.

Solution



Exercise 2.12.1

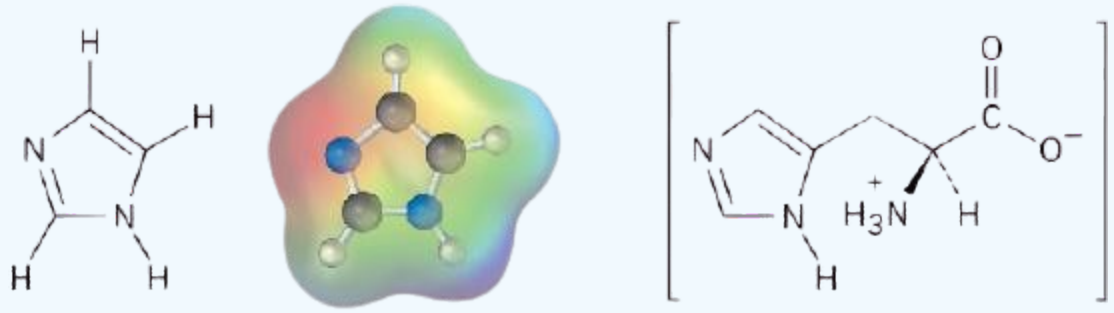
Using curved arrows, show how the species in part **(a)** can act as Lewis bases in their reactions with HCl, and show how the species in part **(b)** can act as Lewis acids in their reaction with OH^-.

a. CH_3CH_2OH, $HN(CH_3)_2$, $P(CH_3)_3$
b. H_3C^+, $B(CH_3)_3$, $MgBr_2$

Answer available at the end of this section.

Exercise 2.12.2

Imidazole, which forms part of amino acid histidine, can act as both an acid and a base.



Imidazole Histidine

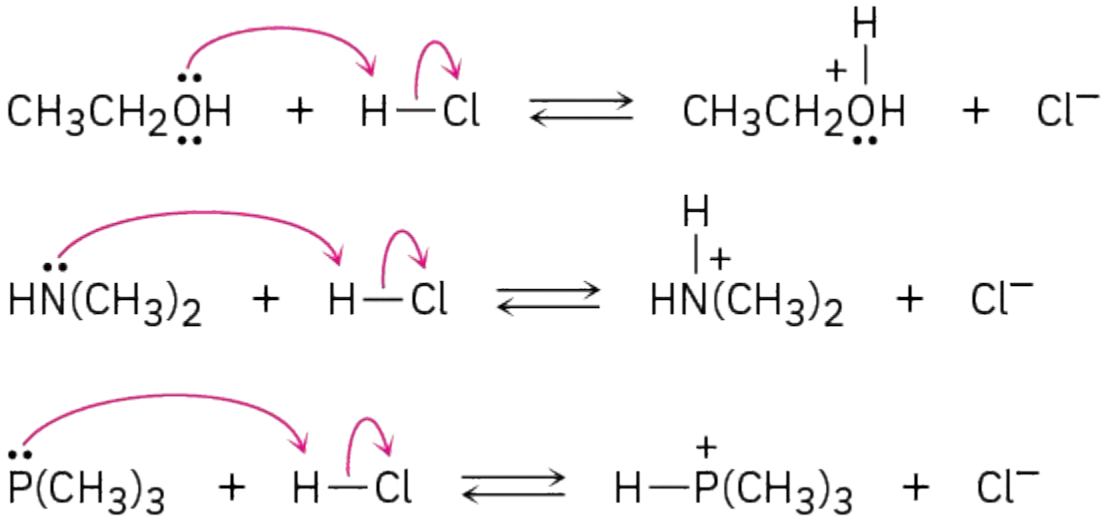
a. Look at the electrostatic potential map of imidazole, and identify the most acidic hydrogen atom and the most basic nitrogen atom.
b. Draw structures for the resonance forms of the products that result when imidazole is protonated by an acid and deprotonated by a base.

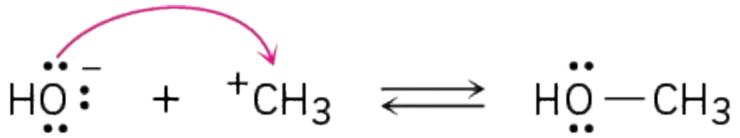
Answer available at the end of this section.

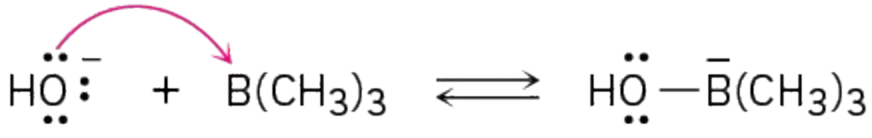
Answers

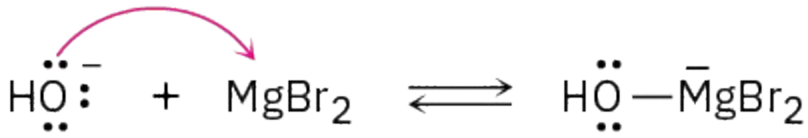
Exercise 2.12.1

a.



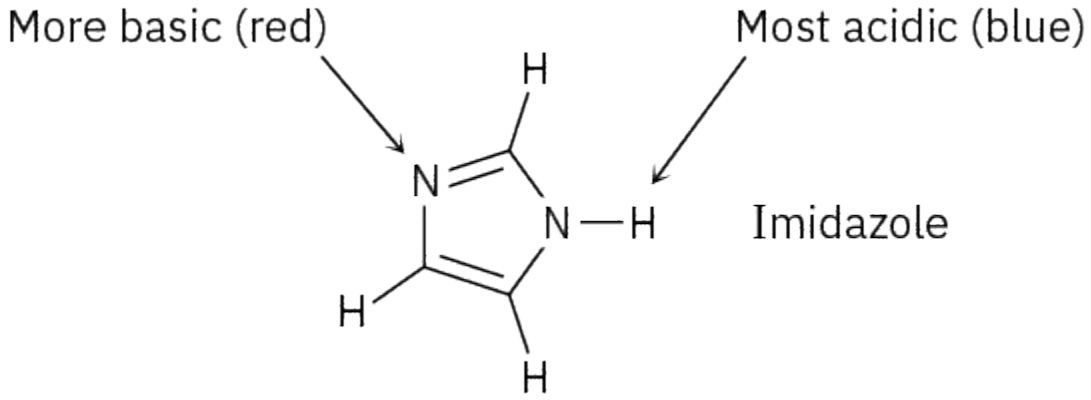




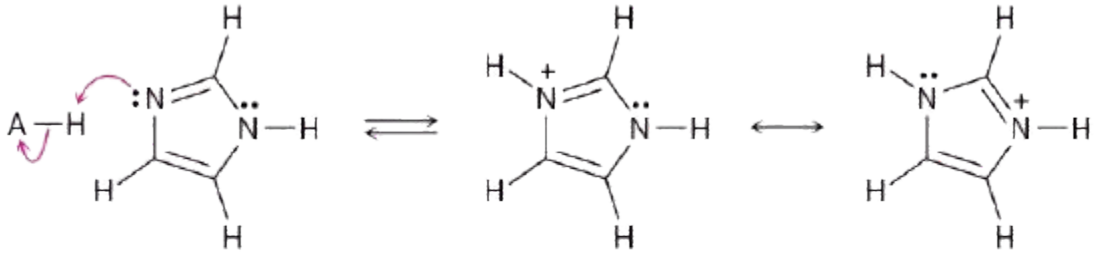


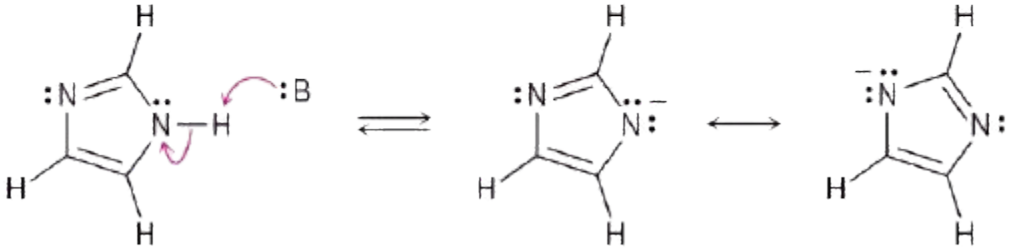
b.

Exercise 2.12.2



a.





b.

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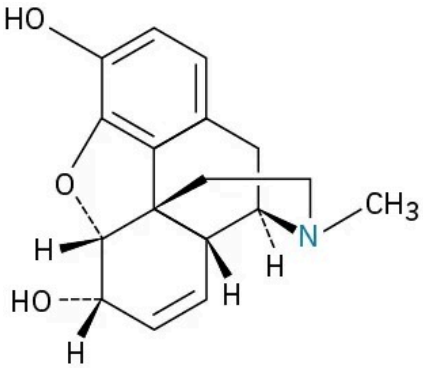
2.13: Chemistry Matters—Alkaloids- From Cocaine to Dental Anesthetics

Just as ammonia (NH_3) is a weak base, there are a large number of nitrogen-containing organic compounds called amines that are also weak bases. In the early days of organic chemistry, basic amines derived from natural sources were known as vegetable alkali, but they are now called **alkaloids**. More than 20,000 alkaloids are known. Their study provided much of the impetus for the growth of organic chemistry in the nineteenth century and remains today an active and fascinating area of research.

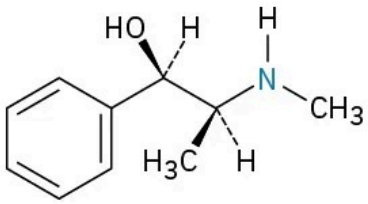


Figure 2.13.1: The coca bush *Erythroxylon coca,* native to upland rain forest areas of Colombia, Ecuador, Peru, Bolivia, and western Brazil, is the source of the alkaloid cocaine. (credit: "*Erythroxylum coca*" by Danna Guevara/Wikimedia Commons, CC BY 4.0)

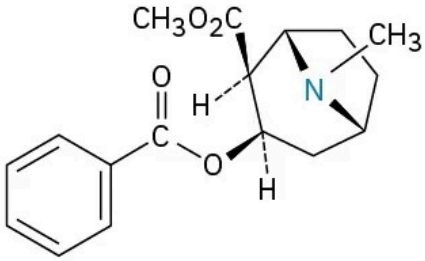
Many alkaloids have pronounced biological properties, and approximately 50% of pharmaceutical agents used today are derived from naturally occurring amines. As just three examples, morphine, an analgesic agent (painkiller), is obtained from the opium poppy *Papaver somniferum*. Ephedrine, a bronchodilator, decongestant, and appetite suppressant, is obtained from *Ephedra sinica*, an evergreen shrub native to Mongolia and northeastern China. Cocaine, both an anesthetic and a stimulant, is obtained from the coca bush *Erythroxylon coca,* endemic to the upland rain forest areas of central South America. (And yes, there really was a small amount of cocaine in the original Coca-Cola recipe, although it was removed in 1906.)



Morphine



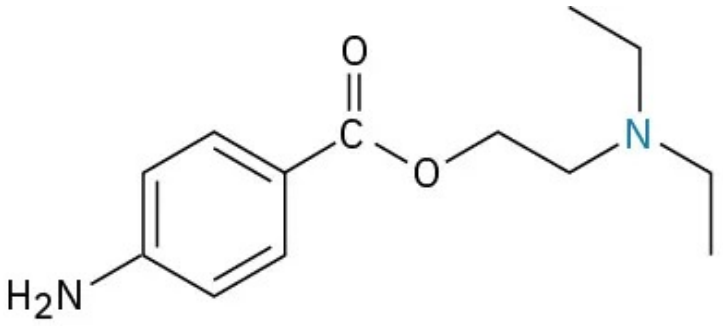
Ephedrine



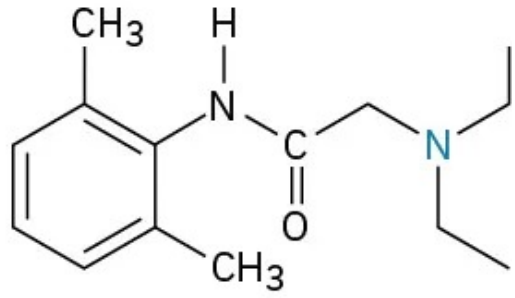
Cocaine

Cocaine itself is rarely used medically because it is too addictive, but its anesthetic properties provoked a long search for related but nonaddictive compounds. This search ultimately resulted in the synthesis of the “caine” anesthetics that are commonly used today in dental and surgical anesthesia. Procaine, the first such compound, was synthesized in 1898 and marketed under the

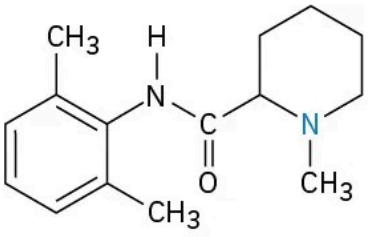
name Novocain. It was rapidly adopted and remains in use today as a topical anesthetic. Other related compounds with different activity profiles followed: Lidocaine, marketed as Xylocaine, was introduced in 1943, and mepivacaine (Carbocaine) in the early 1960s. More recently, bupivacaine (Marcaine) and prilocaine (Citanest) have gained popularity. Both are quick-acting, but the effects of bupivacaine last for 3 to 6 hours while those of prilocaine fade after 45 minutes. Notice some structural similarity of all the caines to cocaine itself.



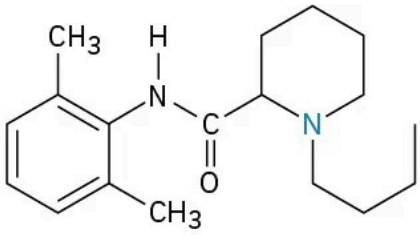
Procaine (Novocain)



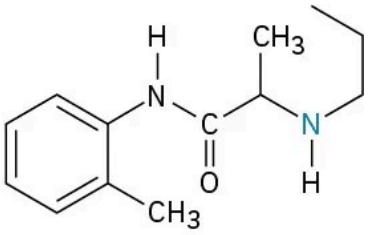
Lidocaine (Xylocaine)



Mepivacaine (Carbocaine)



Bupivacaine (Marcaine)



Prilocaine (Citanest)

An estimate from the U.S. National Academy of Sciences is that less than 1% of all living species have been characterized. Thus, alkaloid chemistry remains an active area of research, and innumerable substances with potentially useful properties have yet to be discovered. Undoubtedly even the caine anesthetics will become obsolete at some point, perhaps supplanted by newly discovered alkaloids.

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2.A: Polar Covalent Bonds; Acids and Bases (Summary)

Concepts & Vocabulary

2.1 Polar Covalent Bonds: Electronegativity

- The difference in electronegativity values of two atoms determines whether the bond between those atoms is classified as either **ionic**, **polar covalent**, or **non-polar covalent**.
- **Ionic bonds** result from large differences in electronegativity values, such as that between a metal and non-metal atom (Na and Cl).
- Covalent bonding generally results when both atoms are non-metals, like C, H, O, N and the halides.
- When both atoms the same and/or have the same electronegativity value, then the bonding electrons are shared equally and the bond is classified as **non-polar covalent**.
- **Polar covalent** bonds occur when the difference in electronegativity values is small, and the bonding electrons are not shared equally.

2.2 Polar Covalent Bonds: Dipole Moments

- The **molecular dipole moment** is the sum of all the bond dipoles within a molecule and depends on both the molecular geometry and the bond polarity.
- Molecules that contain no polar bonds, like CH_4, and/or completely symmetrical molecules, like CO_2, generally have no net dipole moment.
- Asymmetrical molecules that contain bonds of different polarities or non-bonding lone pairs typically have a molecular dipole moment.

2.3: Non-Covalent Interactions between Molecules

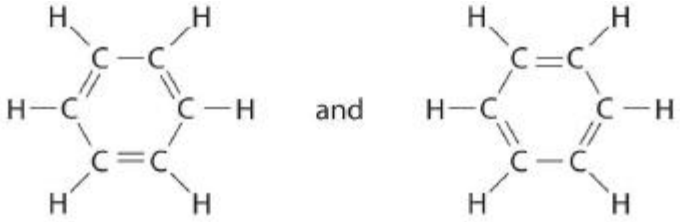
- Non-covalent Interactions, also known as Intermolecular Forces, significantly effect the physical properties of organic molecules. Hydrogen bonding is the most important of these interactions, but others include ion-dipole, dipole-dipole, and London Dispersion Forces.

2.5 Formal Charges

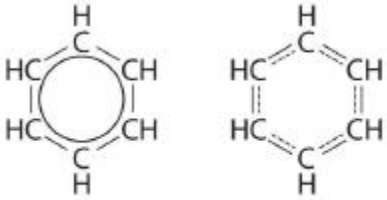
- Formal Charge compares how many valence electrons surround a free atom versus how many surround that same type of atom bonded with a molecule or ion.
- **Formal Charge = (# of valence electrons in free atom) - (# of lone-pair electrons) - (1/2 # of bond pair electrons)** *Eqn. 2.3.1*
- Formal charges of zero generally represent the most stable structures.
- These bonding patterns for the atoms commonly found in organic molecules result in a formal charge of zero
  - Carbon - 4 bonds, no lone pairs
  - Hydrogen - 1 bond, no lone pairs
  - Nitrogen - 3 bonds, 1 lone pair
  - Oxygen - 2 bonds, 2 lone pairs
  - Halogens - 1 bond, 3 lone pairs.

2.6 Resonance

- Resonance Theory is often used when the observed chemical and physical properties of a molecule or ion cannot be adequately described by a single Lewis Structure. A classic example is the benzene molecule, C_6H_6. The Lewis Structure of benzene could be drawn in two different ways. Both structures have alternating double bond and single bonds between the carbons. The only difference is the location of the pi bonds.



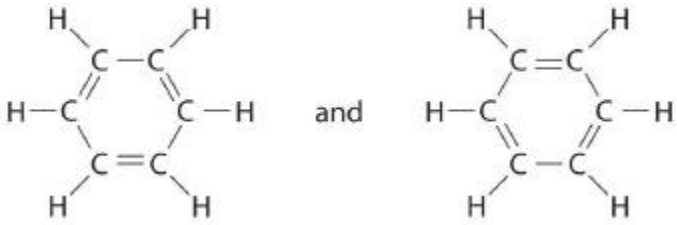
If these structures are correct, then the benzene molecule should have two different C-C bond lengths and bond energies, corresponding to a C-C single bond and to a C=C double bond. However, analysis shows that benzene contains only one type of carbon-carbon bond and it's bond length and energy are half between those of a single bond and double bond. Resonance theory states that benzene exists as the "average" of the two structures called a **resonance hybrid**, in which the six pi electrons **delocalized** over all six carbon atoms. Each C-C bond in benzene would be the average of a single bond and double bond or a "bond and a half". Dashed lines are often used to show type of "partial" bonding in a resonance hybrid of benzene



Benzene

Rules for Resonance Forms

- The rules for estimating stability of resonance structures are
  - The resonance form in which all atoms have complete valence shells is more stable.
  - The **greater the number of covalent bonds**, the greater the stability since more atoms will have complete octets
  - The structure with the **least number of formal charges** is more stable
  - The structure with the **least separation of formal charges** is more stable
  - A structure with a **negative charge on the more electronegative atom** will be more stable
  - **Positive charges on the least electronegative atom** (most electropositive) is more stable
  - **Resonance forms that are equivalent have no difference in stability and contribute equally.** (eg. benzene)
- If these rules are applied to the two Lewis Structures of benzene, the result would be that both structures will have the same relative stability and will both contribute equally to the character of the resonance hybrid.



2.7 Drawing Resonance Forms

- In resonance structures, the electrons are able to move to help stabilize the molecule. This movement of the electrons is called delocalization.
- The rules for drawing resonance structures are:
  - Resonance structures should have the same number of electrons, do not add or subtract any electrons. (You can check the number of electrons by counting them)
  - All resonance structures must follow the rules of writing Lewis Structures.
  - The hybridization of the structure must stay the same.
  - The skeleton of the structure can not be changed (only the electrons move).
  - Resonance structures must also have the same amount of lone pairs.

2.8 Acids and Bases - The Brønsted-Lowry Definition

- A Brønsted-Lowry acid is a proton (H^+) donor and a Brønsted-Lowry base is a proton acceptor.

2.9 Acid and Base Strength

- The strength of Brønsted-Lowry acids is measured indicated by its pKa value. The lower the pKa - the stronger the acid.
- A strong acid will have a weak conjugate base. A strong base will have a weak conjugate acid.

Predicting Acid-Base Reactions from pKa Values

- The equilibrium of an acid-base reaction favors the formation of weaker acids from stronger acids. To predict the direction of the equilibrium, identify Brønsted-Lowry acid on each side of the reaction. Assign/look up pKa values for each acid. The equilibrium will favor the side that has the weakest acid (the highest pKa).

2.10 Organic Acids and Organic Bases

- Organic acids are stronger when the conjugate base that is formed upon loss of a proton is more stable.
- Some factors that affect the stability of the conjugate base (often an anion) are the anionic atom's size and electronegativity, resonance effects, inductive effects, and solvation.

2.11 Structural Effects on Acidity and Basicity

2.12 Acids and Bases - The Lewis Definition

- A Lewis acid is a lone pair acceptor and a Lewis base is a lone pair donor.

Skills to Master

- Skill 2.1 Predict whether a bond is ionic, polar covalent, or non-polar covalent based on the position of the atoms in the periodic table.
- Skill 2.2 Identify the partial positive and partial negative atoms of a polar covalent bond based on relative electronegativity.
- Skill 2.3 Determine the dipole moment of a molecule based on molecular geometry and bond polarity.
- Skill 2.4 Identify the chemicals in a reaction as Brønsted-Lowry acids or bases, and conjugate acids and bases.
- Skill 2.5 Predict the products of an acid-base reaction.
- Skill 2.6 Use pKa values to predict the equilibrium direction of an acid-base reaction.
- Skill 2.7 Predict the relative strength of an organic acid by examining the stability of the conjugate base.
- Skill 2.8 Use molecular structure and analysis of intermolecular forces to rank a series of organic molecules with respect to physical properties like melting point and boiling point.
- Skill 2.9 Identify the chemicals in a reaction as Lewis acids or bases.

Memorization Tasks (MT)

MT 2.1 Memorize that the C-H bond is considered to be non-polar.

MT 2.2 Memorize the common bonding patterns for C, H, N, O and the halogens that have a zero formal charge.

MT 2.3 Memorize the factors that affect the relativity stability of conjugate bases.

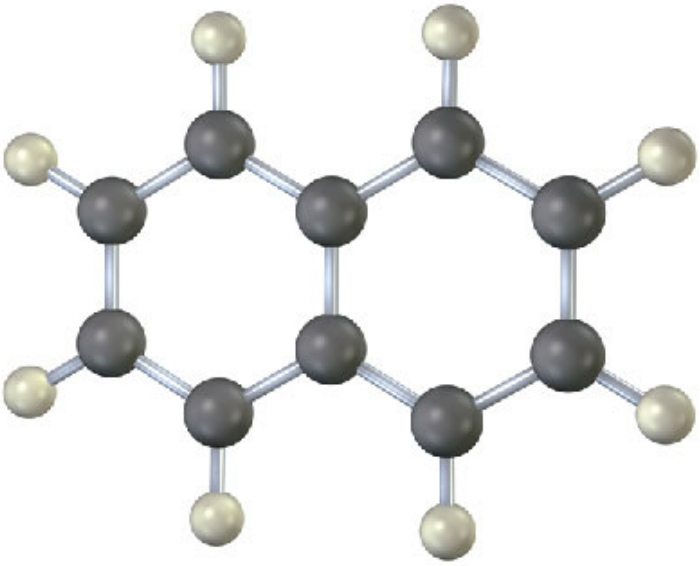
Contributors

- Dr. Kelly Matthews (Professor of Chemistry, Harrisburg Area Community College)

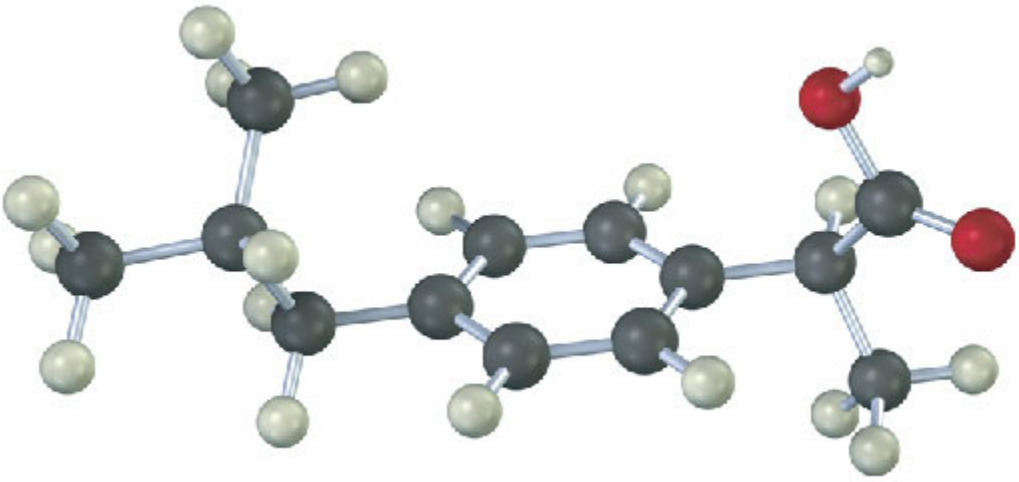
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2.B: Additional Problems

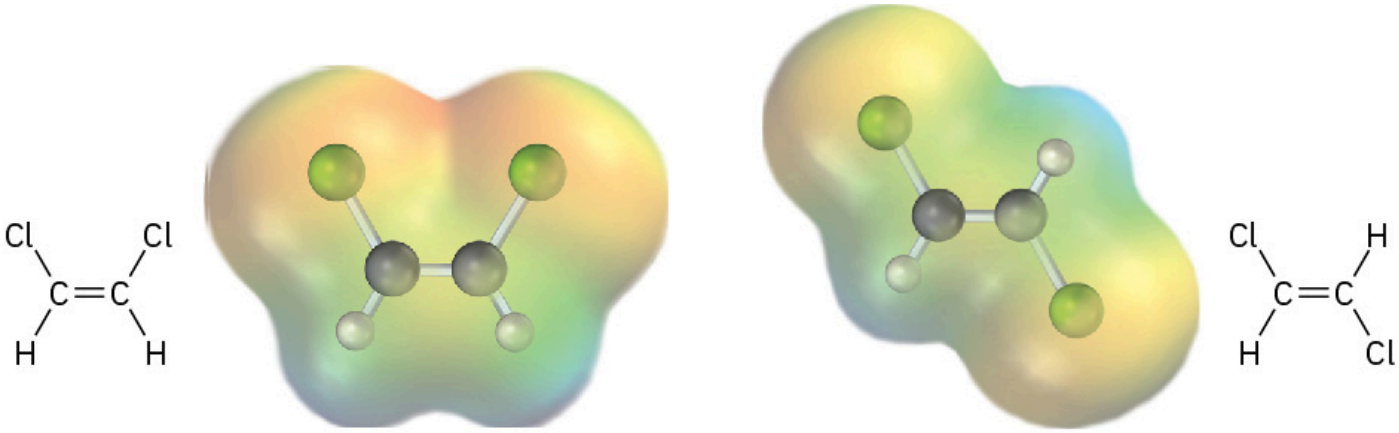
PROBLEM2-20 Fill in the multiple bonds in the following model of naphthalene, $C_{10}H_8$ (black = C, gray = H). How many resonance structures does naphthalene have? Draw them.



PROBLEM2-21 The following model is a representation of ibuprofen, a common over-the-counter pain reliever. Indicate the positions of the multiple bonds, and draw a skeletal structure (black = C, red = O, gray = H).



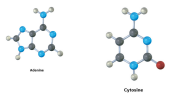
PROBLEM2-22 *cis*-1,2-Dichloroethylene and *trans*-1,2-dichloroethylene are *isomers,* compounds with the same formula but different chemical structures. Look at the following electrostatic potential maps, and tell whether either compound has a dipole moment.



***cis*-1,2-Dichloroethylene** ***trans*-1,2-Dichloroethylene**

PROBLEM2-23 The following molecular models are representations of **(a)** adenine and **(b)** cytosine, constituents of DNA (deoxyribonucleic acid). Indicate the positions of multiple bonds and lone pairs for both, and draw skeletal structures (black = C, red = O, blue = N, gray = H).

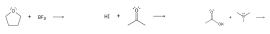
a. **b.**



Mechanism Problems

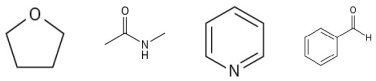
PROBLEM2-24 Predict the product(s) of the following acid/base reactions. Draw curved arrows to show the formation and breaking of bonds.

a. **b.** **c.**

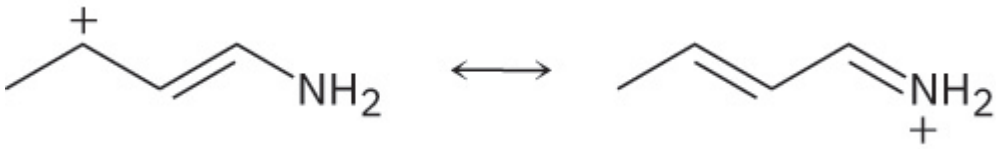


PROBLEM2-25 Use curved arrows to draw the protonated form of the following Lewis bases.

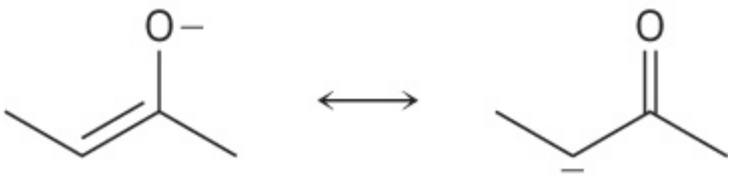
a. **b.** **c.** **d.**



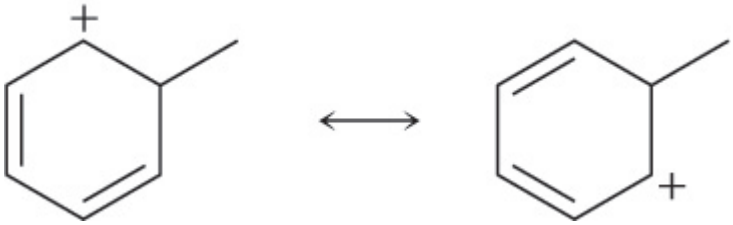
PROBLEM2-26 Use the curved-arrow formalism to show how the electrons flow in the resonance form on the left to give the one on the right.



(a)



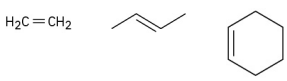
(b)



(c)

PROBLEM2-27 Double bonds can also act like Lewis bases, sharing their electrons with Lewis acids. Use curved arrows to show how each of the following double bonds will react with HCl and draw the resulting carbocation.

a. **b.** **c.**



Electronegativity and Dipole Moments

PROBLEM2-28 Identify the most electronegative element in each of the following molecules:

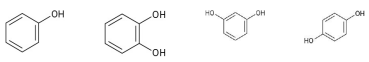
(a) CH_2FCl **(b)** $FCH_2CH_2CH_2Br$ **(c)** $HOCH_2CH_2NH_2$ **(d)** CH_3OCH_2Li

PROBLEM2-29 Use the electronegativity table given in Figure 2.3 to predict which bond in each of the following pairs is more polar, and indicate the direction of bond polarity for each compound.

(a) $H_3C–Cl$ or Cl–Cl **(b)** $H_3C–H$ or H–Cl **(c)** $HO–CH_3$ or $(CH_3)_3Si–CH_3$ **(d)** $H_3C–Li$ or Li–OH

PROBLEM2-30 Which of the following molecules has a dipole moment? Indicate the expected direction of each.

a. **b.** **c.** **d.**



PROBLEM2-31

a. The H–Cl bond length is 136 pm. What would the dipole moment of HCl be if the molecule were 100% ionic, H^+ Cl^-?
b. The actual dipole moment of HCl is 1.08 D. What is the percent ionic character of the H–Cl bond?

PROBLEM2-32 Phosgene, $Cl_2C{=}O$, has a smaller dipole moment than formaldehyde, $H_2C{=}{=}O$, even though it contains electronegative chlorine atoms in place of hydrogen. Explain.

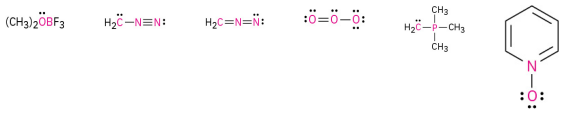
PROBLEM2-33 Fluoromethane (CH_3F, μ = 1.81 D) has a smaller dipole moment than chloromethane (CH_3Cl, μ = 1.87 D) even though fluorine is more electronegative than chlorine. Explain.

PROBLEM2-34 Methanethiol, CH_3SH, has a substantial dipole moment (μ = 1.52) even though carbon and sulfur have identical electronegativities. Explain.

Formal Charges

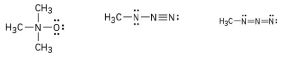
PROBLEM2-35 Calculate the formal charges on the atoms shown in red.

a. **b.** **c.** **d.** **e.** **f.**



PROBLEM2-36 Assign formal charges to the atoms in each of the following molecules:

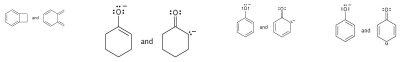
a. **b.** **c.**



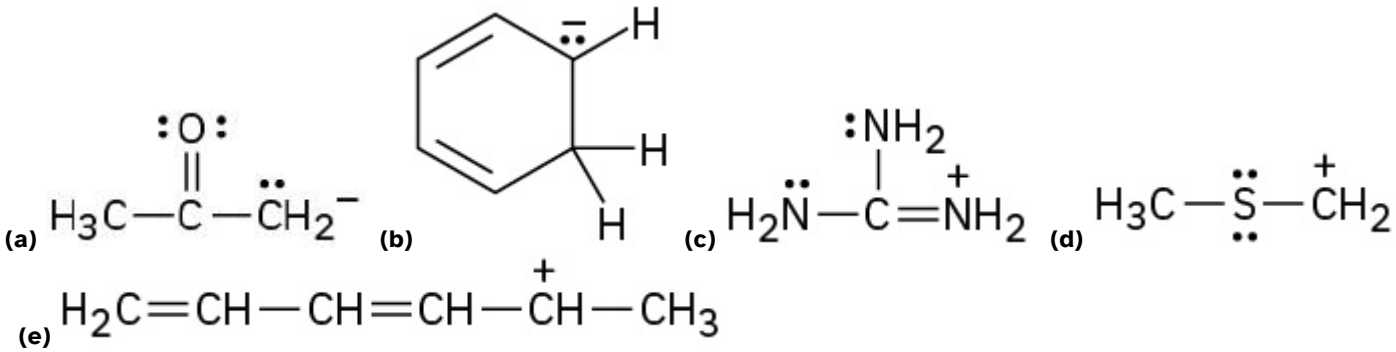
Resonance

PROBLEM2-37 Which of the following pairs of structures represent resonance forms?

a. **b.** **c.** **d.**



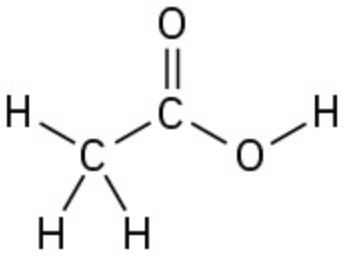
PROBLEM2-38 Draw as many resonance structures as you can for the following species:



Acids and Bases

PROBLEM2-40 Alcohols can act either as weak acids or as weak bases, just as water can. Show the reaction of methanol, CH_3OH, with a strong acid such as HCl and with a strong base such as $Na^{+-}NH_2$

PROBLEM2-41 The O–H hydrogen in acetic acid is more acidic than any of the C–H hydrogens. Explain this result using resonance structures.



Acetic acid

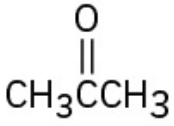
PROBLEM2-42 Draw electron-dot structures for the following molecules, indicating any unshared electron pairs. Which of the compounds are likely to act as Lewis acids and which as Lewis bases?

(a) $AlBr_3$ **(b)** $CH_3CH_2NH_2$ **(c)** BH_3 **(d)** HF **(e)** CH_3SCH_3 **(f)** $TiCl_4$

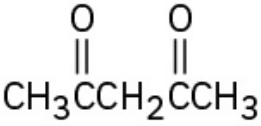
PROBLEM2-43 Write the products of the following acid–base reactions:

(a) $CH_3OH + H_2SO_4 \rightleftarrows$? **(b)** $CH_3OH + NaNH_2 \rightleftarrows$? **(c)** $CH_3NH_3^+ \ Cl^- + NaOH \rightleftarrows$?

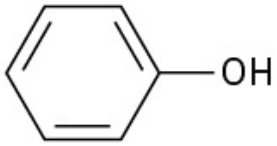
PROBLEM2-44 Rank the following substances in order of increasing acidity:



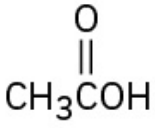
Acetone
(pK_a = 19.3)



2,4-Pentanedione
(pK_a = 9)



Phenol
(pK_a = 9.9)

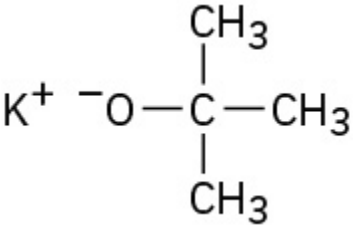


Acetic acid
(pK_a = 4.76)

PROBLEM2-45 Which, if any, of the substances in Problem 2-44 is a strong enough acid to react almost completely with NaOH? (The pK_a of H_2O is 15.74.)

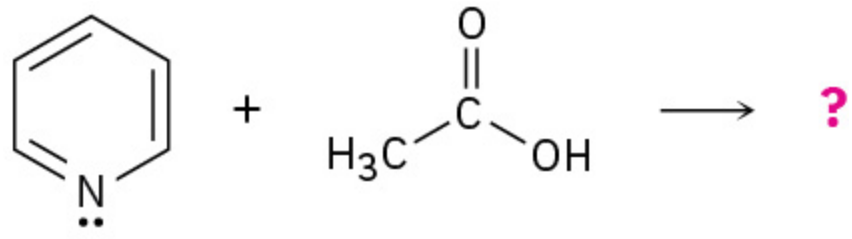
PROBLEM2-46 The ammonium ion (NH_4^+, pK_a = 9.25) has a lower pK_a than the methylammonium ion ($CH_3NH_3^+$, pK_a = 10.66). Which is the stronger base, ammonia (NH_3) or methylamine (CH_3NH_2)? Explain.

PROBLEM2-47 Is *tert*-butoxide anion a strong enough base to react significantly with water? In other words, can a solution of potassium *tert*-butoxide be prepared in water? The pK_a of *tert*-butyl alcohol is approximately 18.



Potassium *tert*-butoxide

PROBLEM2-48 Predict the structure of the product formed in the reaction of the organic base pyridine with the organic acid acetic acid, and use curved arrows to indicate the direction of electron flow.



Pyridine **Acetic acid**

PROBLEM2-49 Calculate K_a values from the following pK_a's:

(a) Acetone, pK_a = 19.3 **(b)** Formic acid, pK_a = 3.75

PROBLEM2-50 Calculate pK_a values from the following K_a's:

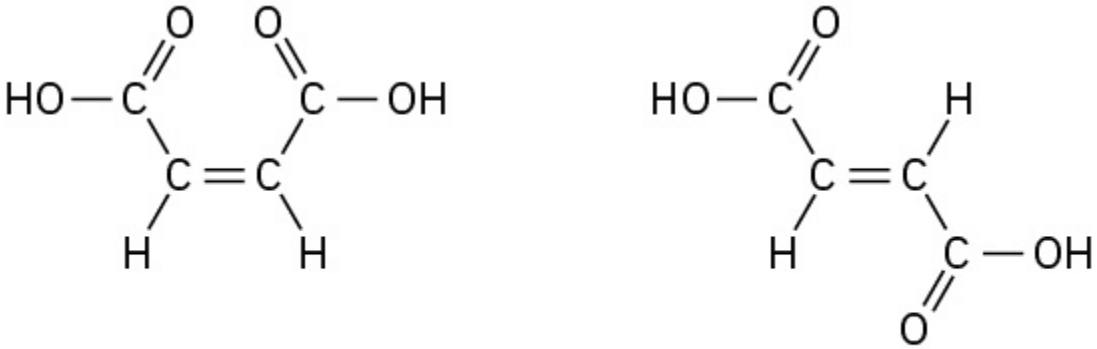
(a) Nitromethane, $K_a = 5.0 \times 10^{-11}$ **(b)** Acrylic acid, $K_a = 5.6 \times 10^{-5}$

PROBLEM2-51 What is the pH of a 0.050 M solution of formic acid, pK_a = 3.75?

PROBLEM2-52 Sodium bicarbonate, $NaHCO_3$, is the sodium salt of carbonic acid (H_2CO_3), pK_a = 6.37. Which of the substances shown in Problem 2-44 will react significantly with sodium bicarbonate?

General Problems

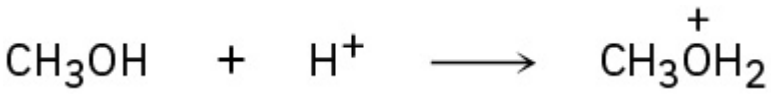
PROBLEM2-53 Maleic acid has a dipole moment, but the closely related fumaric acid, a substance involved in the citric acid cycle by which food molecules are metabolized, does not. Explain.



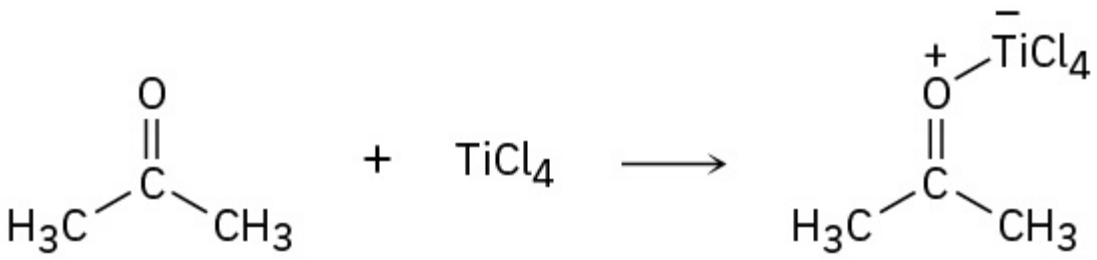
Maleic acid **Fumaric acid**

PROBLEM2-54 Assume that you have two unlabeled bottles, one of which contains phenol (pK_a = 9.9) and one of which contains acetic acid (pK_a = 4.76). In light of your answer to Problem 2-52, suggest a simple way to determine what is in each bottle.

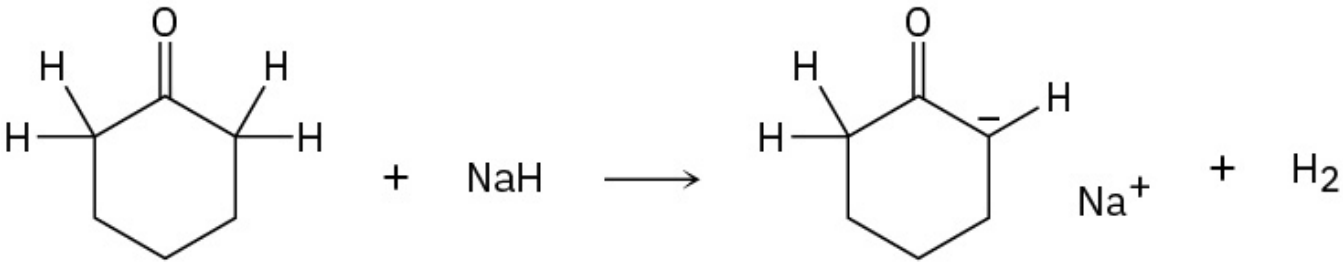
PROBLEM2-55 Identify the acids and bases in the following reactions:

a. 

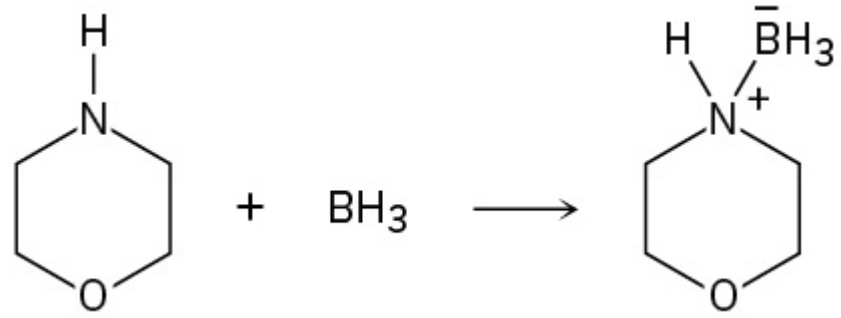
b.



c.

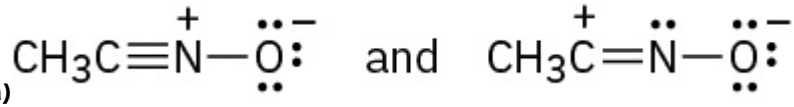


d.

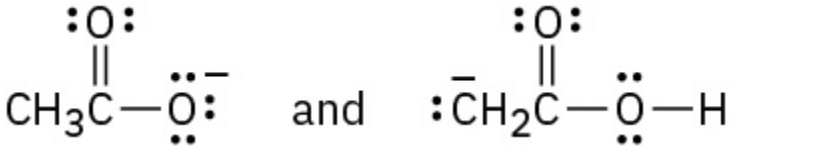


PROBLEM2-56 Which of the following pairs represent resonance structures?

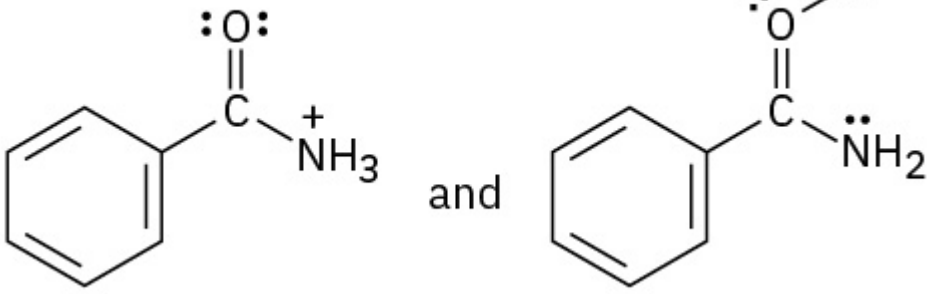
(a)



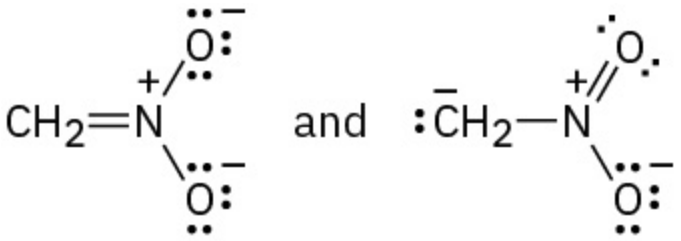
(b)



(c)

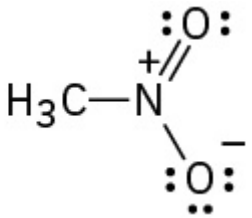


(d)



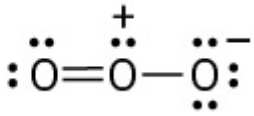
PROBLEM2-57 Draw as many resonance structures as you can for the following species, adding appropriate formal charges to each:

Nitromethane,



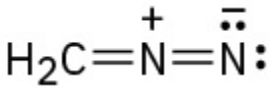
(a)

(b) Ozone,

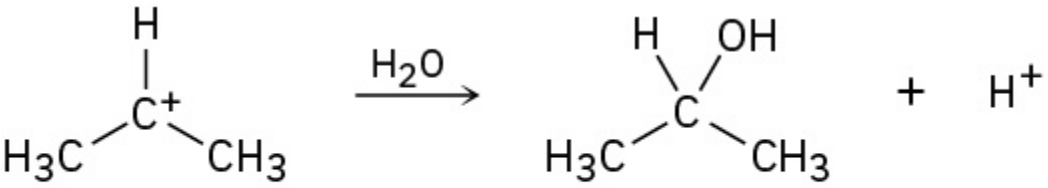


(c)

Diazomethane,

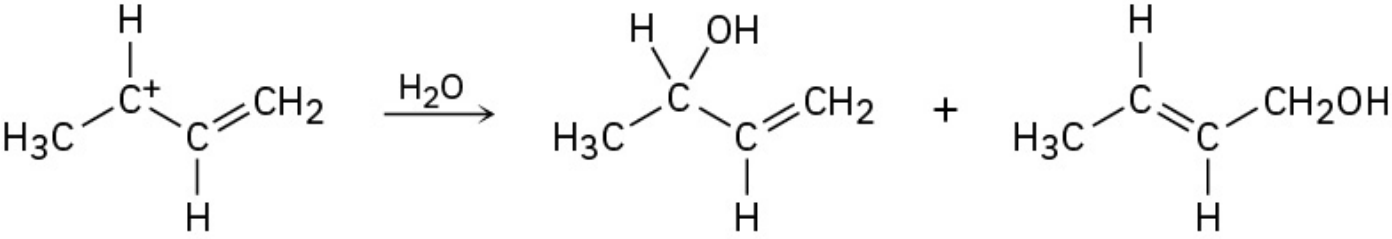


PROBLEM2-58 Carbocations, which contain a trivalent, positively charged carbon atom, react with water to give alcohols:

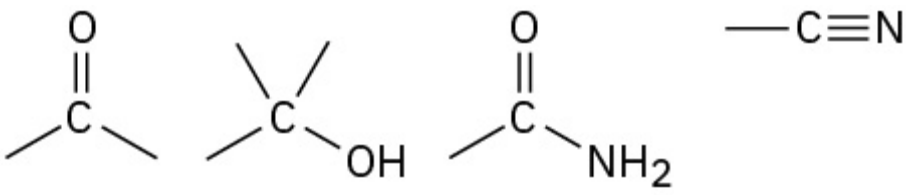


A carbocation **An alcohol**

How can you account for the fact that the following carbocation gives a mixture of *two* alcohols on reaction with water?

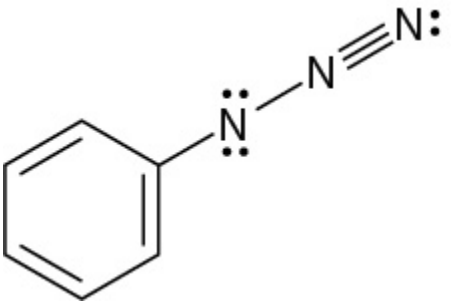


PROBLEM2-59 We'll see in the next chapter that organic molecules can be classified according to the functional groups they contain, where a functional group is a collection of atoms with a characteristic chemical reactivity. Use the electronegativity values given in Figure 2.3 to predict the direction of polarization of the following functional groups.



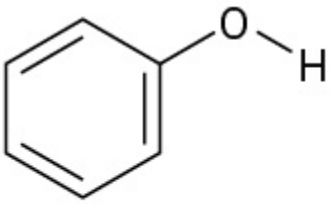
(a) Ketone (b) Alcohol (c) Amide (d) Nitrile

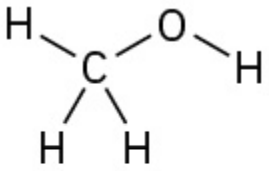
PROBLEM2-60 The *azide* functional group, which occurs in azidobenzene, contains three adjacent nitrogen atoms. One resonance structure for azidobenzene is shown. Draw three additional resonance structures, and assign appropriate formal charges to the atoms in all four.



Azidobenzene

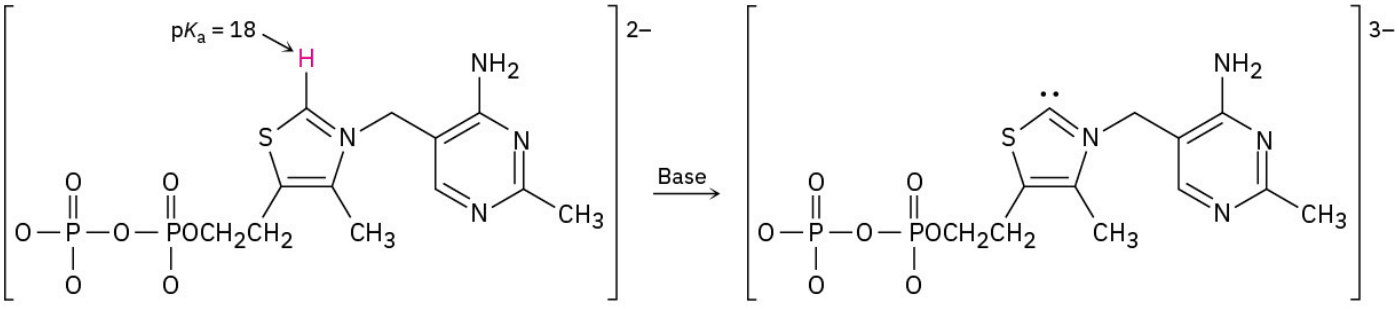
PROBLEM2-61 Phenol, C_6H_5OH, is a stronger acid than methanol, CH_3OH, even though both contain an O–H bond. Draw the structures of the anions resulting from loss of H^+ from phenol and methanol, and use resonance structures to explain the difference in acidity.





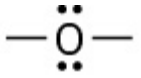
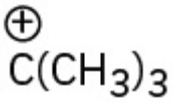
Phenol (pK_a = 9.89) **Methanol (pK_a = 15.54)**

PROBLEM2-62 Thiamin diphosphate (TPP), a derivative of vitamin B_1 required for glucose metabolism, is a weak acid that can be deprotonated by a base. Assign formal charges to the appropriate atoms in both TPP and its deprotonation product.



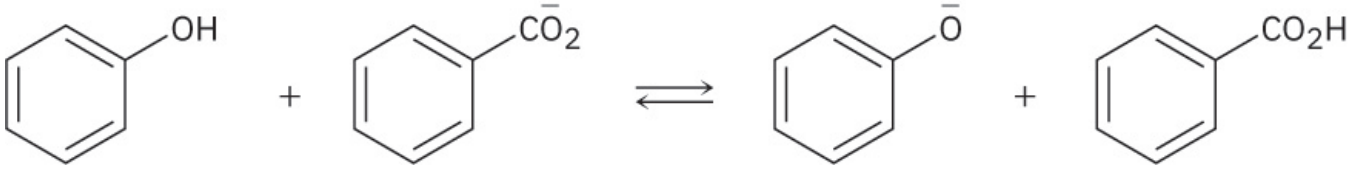
Thiamin diphosphate (TPP)

PROBLEM2-63 Which of the following compounds or ions have a dipole moment?

(a) Carbonate ion (CO_3^{2-}) **(b)**  **(c)** 

PROBLEM2-64 Use the pK_a table in Appendix B to determine in which direction the equilibrium is favored.

a.



b. $CH_3CH_2CH_2OH + \bar{N}H_2 \rightleftharpoons CH_3CH_2CH_2\bar{O} + NH_3$

c. $\bar{C}H_3 + CH_3NO_2 \rightleftharpoons CH_4 + \bar{C}H_2NO_2$

PROBLEM2-65 Which intermolecular force is predominantly responsible for each observation below?

a. $CH_3(CH_2)_{29}CH_3$, a component found in paraffin wax, is a solid at room temperature while $CH_3(CH_2)_6CH_3$ is a liquid.
b. $CH_3CH_2CH_2OH$ has a higher boiling point than CH_4.
c. CH_3CO_2H, which is found in vinegar, will dissolve in water but not in oil. Assume that oil is $CH_3(CH_2)_4CH_3$.

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3: ORGANIC COMPOUNDS- FUNCTIONAL GROUPS AND NOMENCLATURE

Learning Objectives

After you have completed Chapter 3, you should be able to

1. fulfill the detailed objectives listed under each section.
2. identify some of the commonest functional groups.
3. write the structures and names of the first ten straight-chain alkanes.
4. recognize and name the simple alkyl substituents, and give the systematic names for branched-chain alkanes.
5. write the structures and names of alkenes, alkynes, alcohols and haloalkanes.
6. briefly describe some of the processes used during the refining of petroleum.
7. briefly describe the physical properties of alkanes.
8. define, and use in context, the key terms introduced in this chapter.

This chapter begins with an introduction to the concept of the functional group, a concept that facilitates the systematic study of organic chemistry. Next, we introduce the fundamentals of organic nomenclature (i.e., the naming of organic chemicals) through examination of the alkane family of compounds. We then discuss, briefly, the occurrence and properties of alkanes.

3.0: Why This Chapter?

3.1: Functional Groups

3.2: Alkanes and Alkane Isomers

3.3: Alkyl Groups

3.4: Naming Alkanes

3.5: Naming Cycloalkanes

3.6: Naming Alkenes

3.7: Naming Alkynes

3.8: Names of Alkyl Halides

3.9: Naming Alcohols

3.10: Chemistry Matters—Gasoline

3.A: Functional Groups and Nomenclature (Summary)

3.B: Additional Problems

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3.0: Why This Chapter?

According to *Chemical Abstracts,* the publication that abstracts and indexes the chemical literature, there are more than 195 million known organic compounds. Each of these compounds has its own physical properties, such as melting point and boiling point, and each has its own chemical reactivity.

Chemists have learned through years of experience that organic compounds can be classified into families according to their structural features and that the members of a given family have similar chemical behavior. Instead of 195 million compounds with random reactivity, there are a few dozen families of organic compounds whose chemistry is reasonably predictable.

The group of organic compounds called *alkanes* is simple and relatively unreactive, but they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we'll use alkanes to introduce the basic approach to naming organic compounds and to take an initial look at some of the three-dimensional aspects of molecules, a topic of particular importance in understanding biological organic chemistry.



Figure 3.0.1: The bristlecone pine is the oldest living organism on Earth. The waxy coating on its needles contains a mixture of organic compounds called alkanes. (credit: "Gnarly Bristlecone Pine" by Rick Goldwaser/Flickr, CC BY 2.0)

The structural features that make it possible to classify compounds into families are called *functional groups*. A functional group is a group of atoms within a molecule that has a characteristic chemical behavior. Chemically, a given functional group behaves in nearly the same way in every molecule it's a part of. For example, compare ethylene, a plant hormone that causes fruit to ripen, with menthene, a much more complicated molecule found in peppermint oil. Both substances contain a carbon–carbon double-bond functional group, and both therefore react with Br_2 in the same way to give a product in which a Br atom has added to each of the double-bond carbons (Figure 3.0.2). This example is typical: *the chemistry of every organic molecule, regardless of size and complexity, is determined by the functional groups it contains.*

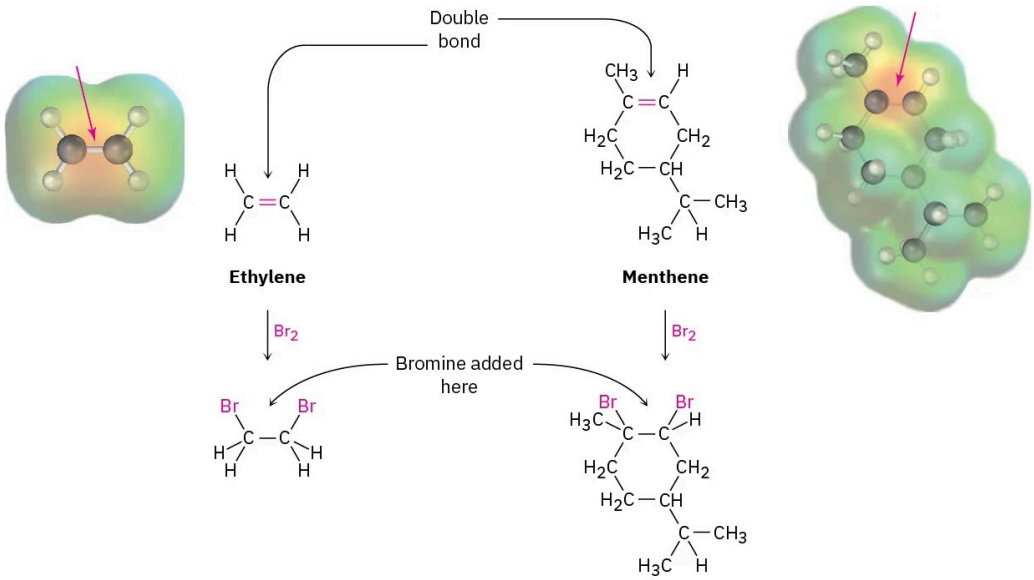


Figure 3.0.2: The reactions of ethylene and menthene with bromine. In both molecules, the carbon–carbon double-bond functional group has a similar polarity pattern, so both molecules react with Br_2 in the same way. The size and complexity of the molecules are not important.

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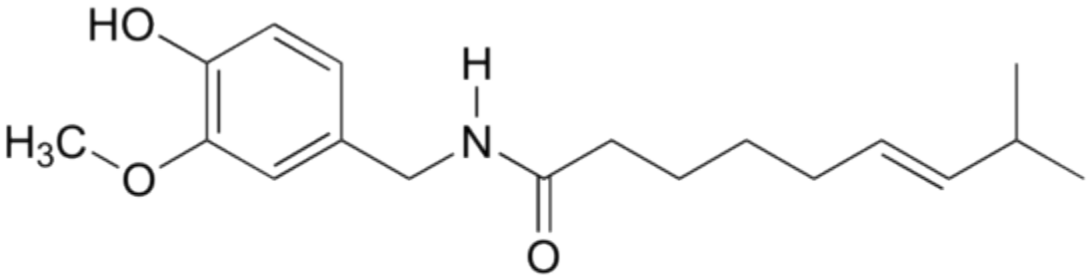
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3.1: Functional Groups

Functional groups are atoms or small groups of atoms (two to four) that exhibit a characteristic reactivity. A particular functional group will almost always display its characteristic chemical behavior when it is present in a compound. Because of their importance in understanding organic chemistry, functional groups have characteristic names that often carry over in the naming of individual compounds incorporating specific groups.

As we progress in our study of organic chemistry, it will become increasingly important to quickly recognize the most common functional groups, as they are the key structural elements that determine how organic molecules react. For now, we will focus only on drawing and recognizing each functional group, as depicted in Lewis and line structures. Much of the remainder of your study of organic chemistry will be taken up with learning about how the different functional groups tend to behave in organic reactions.

Capsaicin, the compound responsible for the heat in hot peppers, contains phenol, ether, amide, and alkene functional groups.



capsiacin

Simplest Hydrocarbons: Alkanes

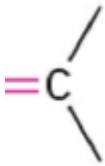
Alkanes are organic compounds that consist entirely of single-bonded carbon and hydrogen atoms and lack any other functional groups. Alkanes are described as saturated hydrocarbons and are subdivided into the following three groups: the linear straight-chain (o linear) alkanes, branched alkanes, and cycloalkanes.



Figure 3.1.1: Alkanes have all single bonds between carbons. Linear, branched and cycloalkanes.

Functional Groups with Carbon–Carbon Multiple Bonds

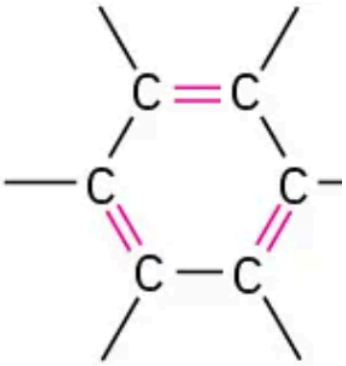
Alkenes, alkynes, and arenes (aromatic compounds) all contain carbon–carbon multiple bonds. *Alkenes* have a double bond, *alkynes* have a triple bond, and *arenes* have alternating double and single bonds in a six-membered ring of carbon atoms. They look different, but because of their structural similarities, they also have chemical similarities.



kene



Alkyne

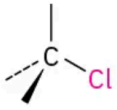


Arene
(aromatic ring

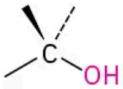
*The bonds whose connections aren't specified are assumed to be attached to carbon or hydrogen atoms in the rest of the molecule.

Functional Groups with Carbon Singly Bonded to an Electronegative Atom (N, O, S, X)

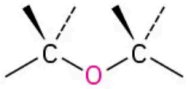
Alkyl halides (haloalkanes), alcohols, ethers, alkyl phosphates, amines, thiols, sulfides, and disulfides all have a carbon atom singly bonded to an electronegative atom—halogen, oxygen, nitrogen, or sulfur. Alkyl halides have a carbon atom bonded to halogen (–X), alcohols have a carbon atom bonded to the oxygen of a hydroxyl group (–OH), ethers have two carbon atoms bonded to the same oxygen, organophosphates have a carbon atom bonded to the oxygen of a phosphate group ($-OPO_3^{2-}$).



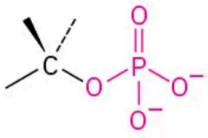
Alkyl halide (haloalkane)



Alcohol

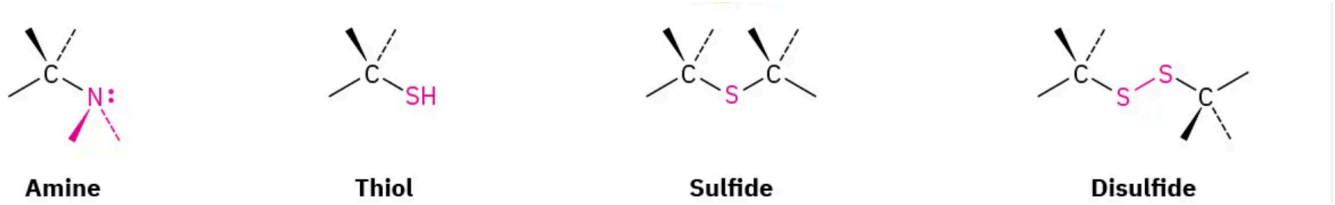


Ether



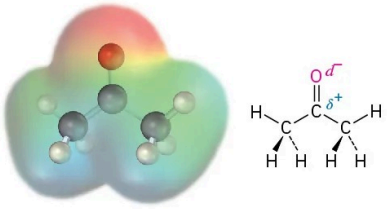
Phosphate

Amines have a carbon atom bonded to a nitrogen, thiols have a carbon atom bonded to the sulfur of an –SH group, sulfides have two carbon atoms bonded to the same sulfur, and disulfides have carbon atoms bonded to two sulfurs that are joined together. In all cases, the bonds are polar, with the carbon atom bearing a partial positive charge ($\delta+$) and the electronegative atom bearing a partial negative charge ($\delta-$).

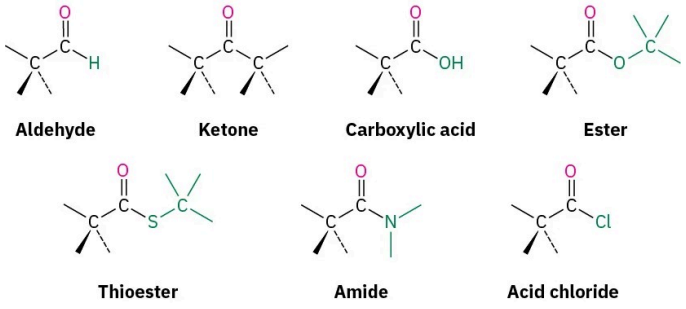


Functional Groups with a Carbon–Oxygen Double Bond (Carbonyl Groups)

The carbonyl group C=O appears in several functional groups. Aldehydes have at least one H atom bonded to the C=O, ketones have two carbon atoms bonded to the C=O, carboxylic acids have an -OH group bonded to the C=O, thioesters have a sulfide-like sulfur bonded to the C=O, amides have an amine-like nitrogen bonded to the C=O, acid chlorides have a chlorine bonded to the C=O, and so on. In all of these functional groups, the carbonyl carbon atom bears a partial positive charge (δ^+), and the oxygen atom bears a partial negative charge (δ^-).

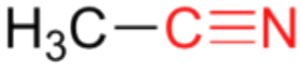


Acetone—a typical carbonyl compound



Functional Group with a Carbon–Nitrogen Triple Bond

Finally, in a **nitrile** group, a carbon is triple-bonded to a nitrogen. Nitriles are also often referred to as **cyano** groups.

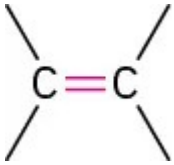
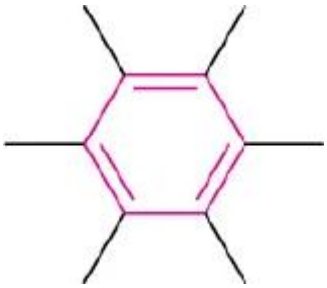
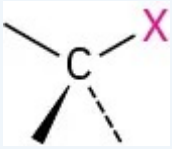
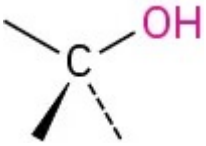
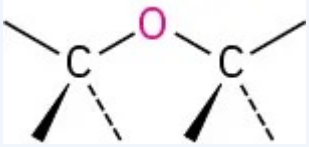
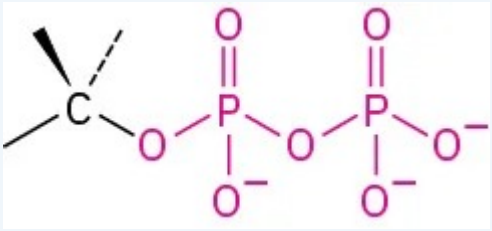


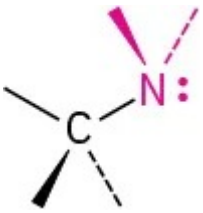
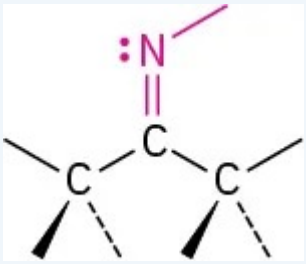
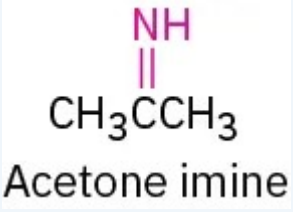
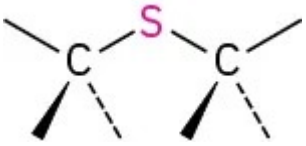
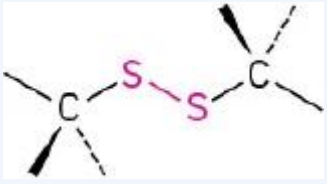
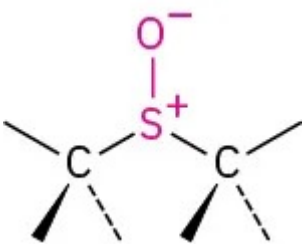
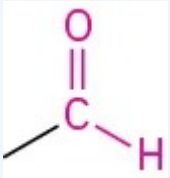
a nitrile

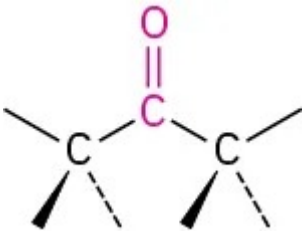
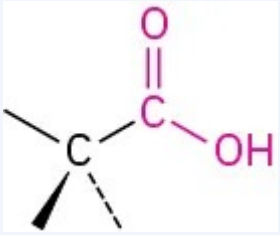
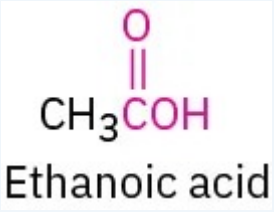
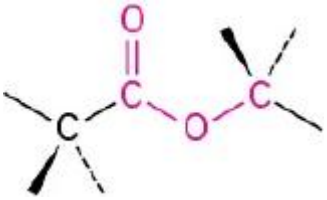
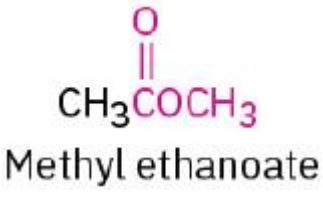
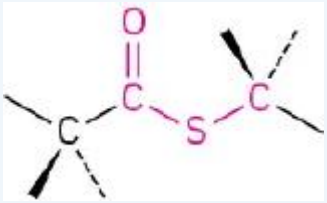
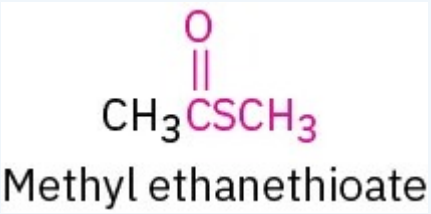
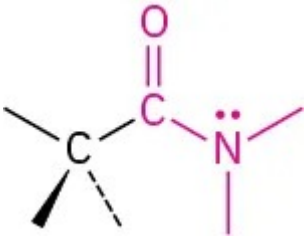
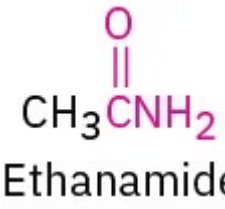
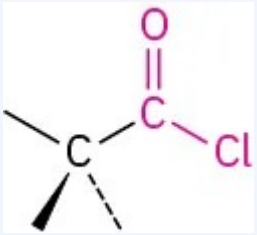
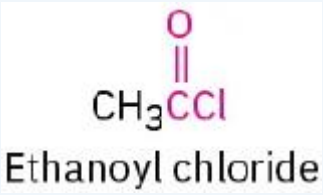
Table of Functional Groups

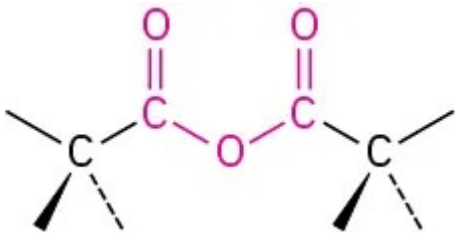
Look at Table 3.1.1, which lists many of the common functional groups and gives simple examples of their occurrence. Some functional groups have only carbon–carbon double or triple bonds; others have halogen atoms; and still others contain oxygen, nitrogen, or sulfur. Much of the chemistry you'll be studying is the chemistry of these functional groups.

Table 3.1.1 Structures of Some Common Functional Groups

Name	Structure*	Name ending	Example
Alkene (double bond)		*-ene*	$H_2C{=}CH_2$ Ethene
Alkyne (triple bond)	–C≡C–	*-yne*	HC≡CH Ethyne
Arene (aromatic ring)		None	 Benzene
Halide	 (X=F, Cl, Br, I)	None	CH_3**Cl** Chloromethane
Alcohol		*-ol*	CH_3**OH** Methanol
Ether		*ether*	CH_3**-O-**CH_3 Dimethyl ether
Monophosphate		*phosphate*	CH_3-OPO_3^{2-} Methyl phosphate
Diphosphate		*diphosphate*	CH_3-$OP_2O_6^{3-}$ Methyl diphosphate

Name	Structure*	Name ending	Example
Amine		*-amine*	CH_3-NH_2 Methylamine
Imine (Schiff base)		None	 Acetone imine
Nitrile	–C≡N	*-nitrile*	$CH_3C{\equiv}N$ Ethanenitrile
Thiol		*-thiol*	CH_3-SH Methanethiol
Sulfide		*sulfide*	CH_3-**S**-CH_3 Dimethyl sulfide
Disulfide		*disulfide*	CH_3S-SCH_3 Dimethyl disulfide
Sulfoxide		*sulfoxide*	 Dimethyl sulfoxide
Aldehyde		*-al*	 Ethanal

Name	Structure*	Name ending	Example
Ketone		*-one*	
Carboxylic acid		*-oic acid*	
Ester		*-oate*	
Thioester		*-thioate*	
Amide		*-amide*	
Acid chloride		*-oyl chloride*	

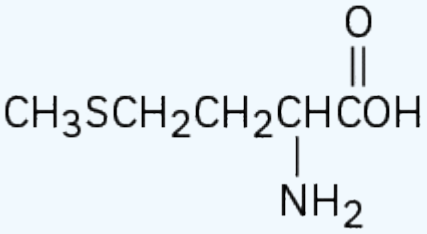
Name	Structure*	Name ending	Example
Carboxylic acid anhydride		*-oic anhydride*	 Ethanoic anhydride

Exercises

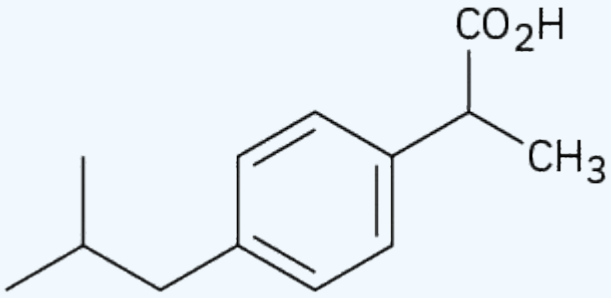
Exercise 3.1.1

Use Table 3.1.1 to identify the functional groups in each of the following molecules:

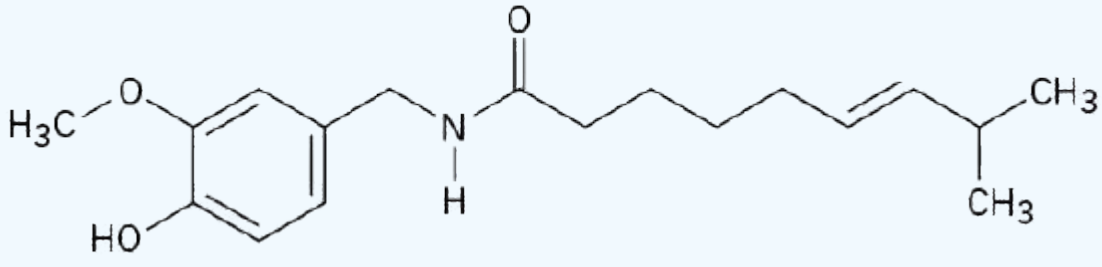
a. Methionine, an amino acid:



b. Ibuprofen, a pain reliever:



c. Capsaicin, the pungent substance in chili peppers:



Answer available at the end of this section.

Exercise 3.1.2

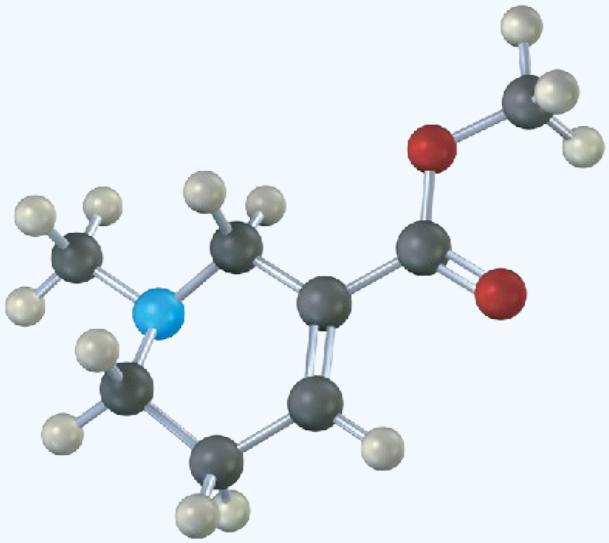
Propose structures for simple molecules that contain the following functional groups:

a. Alcohol
b. Aromatic ring
c. Carboxylic acid
d. Amine
e. Both ketone and amine
f. Two double bonds

Answer available at the end of this section.

Exercise 3.1.3

Identify the functional groups in the following model of arecoline, a veterinary drug used to control worms in animals. Convert the drawing into a line-bond structure and a molecular formula (red = O, blue = N, black = C, gray = H).



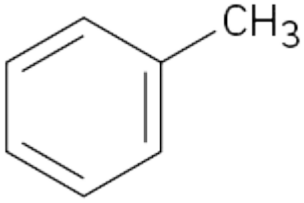
Answer available at the end of this section.

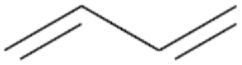
Answers

Exercise 3.1.1

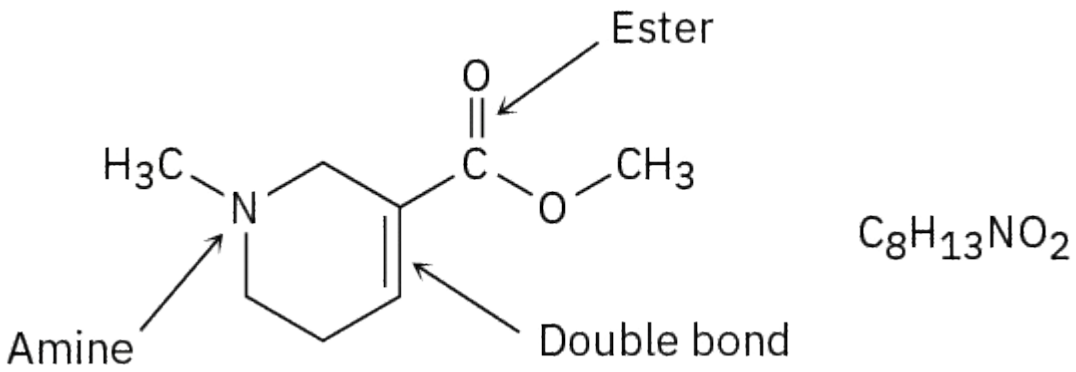
a. Sulfide, carboxylic acid, amine
b. Aromatic ring, carboxylic acid
c. Ether, alcohol, aromatic ring, amide, C=C bond

Exercise 3.1.2

(a) CH_3OH (b)  (c) CH_3COH (d) CH_3NH_2 (e) $CH_3CCH_2NH_2$ (f)



Exercise 3.1.3

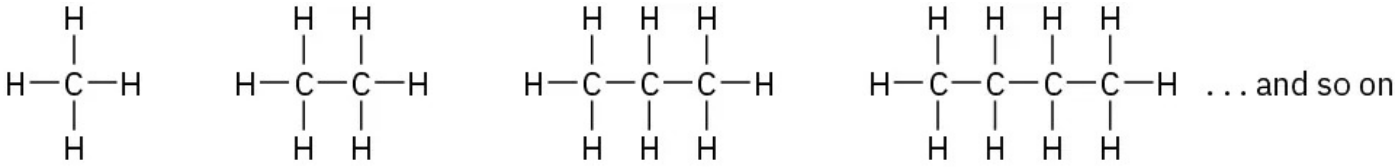


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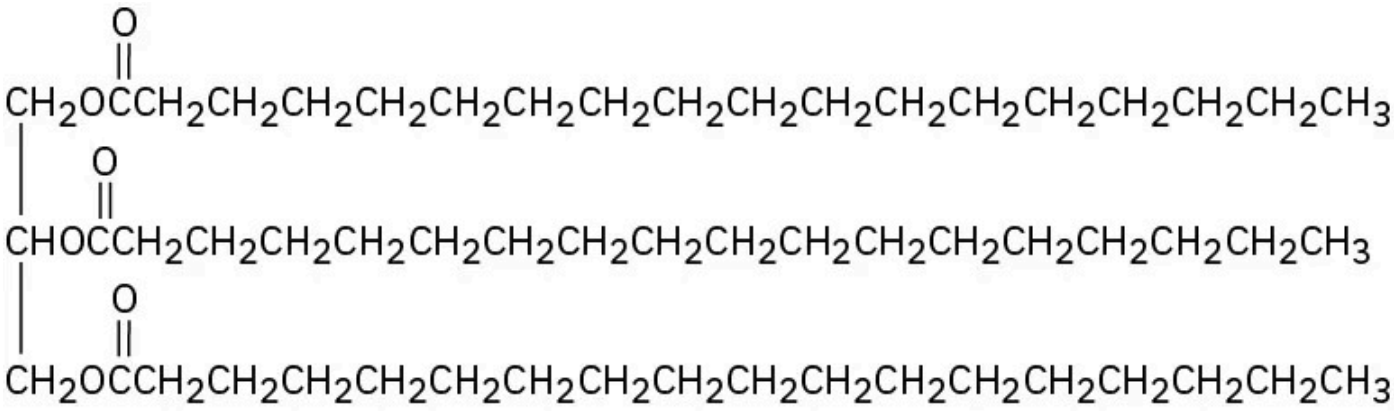
3.2: Alkanes and Alkane Isomers

Before beginning a systematic study of the different functional groups, let's first look at the simplest family of molecules to develop some general ideas that apply to all families. We saw in Section 1.8 that the carbon–carbon single bond in ethane results from σ (head-on) overlap of carbon sp^3 hybrid orbitals. If we imagine joining three, four, five, or even more carbon atoms by C–C single bonds, we can generate the large family of molecules called alkanes.



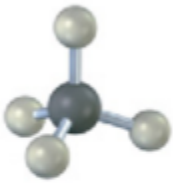
Methane **Ethane** **Propane** **Butane**

Alkanes are often described as *saturated hydrocarbons:* hydrocarbons because they contain only carbon and hydrogen; saturated because they have only C–C and C–H single bonds and thus contain the maximum possible number of hydrogens per carbon. They have the general formula C_nH_{2n+2}, where n is an integer. Alkanes are also occasionally called aliphatic compounds, a name derived from the Greek *aleiphas,* meaning "fat." Many animal fats contain long carbon chains similar to alkanes.



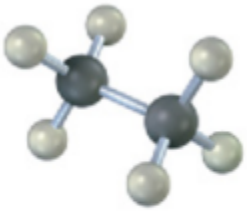
A typical animal fat

Think about the ways that carbon and hydrogen might combine to make alkanes. With one carbon and four hydrogens, only one structure is possible: methane, CH_4. Similarly, there is only one combination of two carbons with six hydrogens (ethane, CH_3CH_3) and only one combination of three carbons with eight hydrogens (propane, $CH_3CH_2CH_3$).



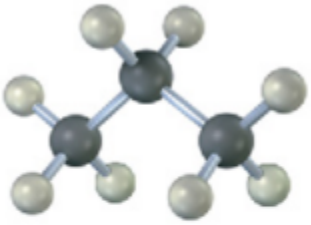
CH_4

Methane, CH_4



CH_3CH_3

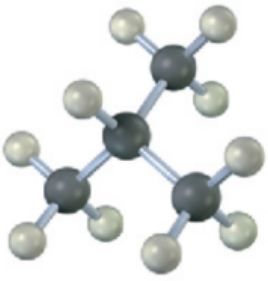
Ethane, C_2H_6



$CH_3CH_2CH_3$

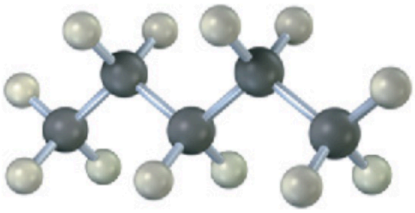
Propane, C_3H_8

When larger numbers of carbons and hydrogens combine, however, more than one structure is possible. For example, there are two substances with the formula C_4H_{10}: the four carbons can all be in a row (butane), or they can branch (isobutane). Similarly, there are three C_5H_{12} molecules, and so on for larger alkanes. Compounds like butane and pentane, whose carbons are all connected in a row, are called straight-chain alkanes, or *normal alkanes*. Compounds like 2-methylpropane (isobutane), 2-methylbutane, and 2,2-dimethylpropane, whose carbon chains branch, are called branched-chain alkanes.



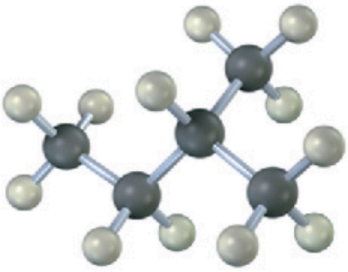
CH_3CHCH_3 (CH_3 above)

Isobutane, C_4H_{10} (2-methylpropane)



$CH_3CH_2CH_2CH_2CH_3$

Pentane, C_5H_{12}



$CH_3CH_2CHCH_3$ (CH_3 above)

2-Methylbutane, C_5H_{12}

Compounds like the two C_4H_{10} molecules and the three C_5H_{12} molecules, which have the same formula but different structures, are called Isomers, from the Greek *isos* + *meros,* meaning "made of the same parts." Isomers have the same numbers and kinds of atoms but differ in the way the atoms are arranged. Compounds like butane and isobutane, whose atoms are connected differently, are called constitutional isomers. We'll see shortly that other kinds of isomers are also possible, even among compounds whose atoms are connected in the same order. As Table 3.2.1 shows, the number of possible alkane isomers increases dramatically with the number of carbon atoms.

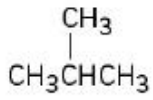
Table 3.2.1: Number of Alkane Isomers

Formula	Number of isomers	Formula	Number of isomers
C_6H_{14}	5	$C_{10}H_{22}$	75

Formula	Number of isomers	Formula	Number of isomers
C_7H_{16}	9	$C_{15}H_{32}$	4347
C_8H_{18}	18	$C_{20}H_{42}$	366,319
C_9H_{20}	35	$C_{30}H_{62}$	4,111,846,763

Constitutional isomerism is not limited to alkanes—it occurs widely throughout organic chemistry. Constitutional isomers may have different carbon skeletons (as in isobutane and butane), different functional groups (as in ethanol and dimethyl ether), or different locations of a functional group along the chain (as in isopropylamine and propylamine). Regardless of the reason for the isomerism, constitutional isomers are always different compounds with different properties but with the same formula.

Different carbon skeletons
C_4H_{10}



2-Methylpropane (isobutane)

and

$CH_3CH_2CH_2CH_3$

Butane

Different functional groups
C_2H_6O

CH_3CH_2OH

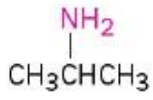
Ethanol

and

CH_3OCH_3

Dimethyl ether

Different position of functional groups
C_3H_9N



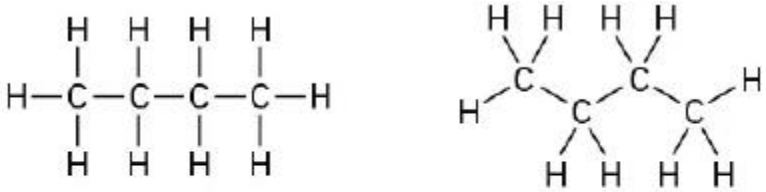
Isopropylamine

and

$CH_3CH_2CH_2NH_2$

Propylamine

A given alkane can be drawn in many ways. For example, the straight-chain, four-carbon alkane called butane can be represented by any of the structures shown in Figure 3.3. These structures don't imply any particular three-dimensional geometry for butane; they indicate only the connections among atoms. In practice, as noted in Section 1.12, chemists rarely draw all the bonds in a molecule and usually refer to butane by the condensed structure, $CH_3CH_2CH_2CH_3$ or $CH_3(CH_2)_2CH_3$. Still more simply, butane can be represented as *n*-C_4H_{10}, where *n* denotes *normal* (straight-chain) butane.



$CH_3—CH_2—CH_2—CH_3$ $CH_3CH_2CH_2CH_3$ $CH_3(CH_2)_2CH_3$

Figure 3.3: Some representations of butane, C_4H_{10}. The molecule is the same regardless of how it's drawn. These structures imply only that butane has a continuous chain of four carbon atoms; they do not imply any specific geometry.

Straight-chain alkanes are named according to the number of carbon atoms they contain, as shown in Table 3.2.2. With the exception of the first four compounds—methane, ethane, propane, and butane—whose names have historical roots, the alkanes are named based on Greek numbers. The suffix *-ane* is added to the end of each name to indicate that the molecule identified is an alkane. Thus, *pent*ane is the five-carbon alkane, *hex*ane is the six-carbon alkane, and so on. We'll soon see that these alkane names form the basis for naming all other organic compounds, so at least the first ten should be memorized.

Table 3.2.2 Names of Straight-Chain Alkanes

Number of carbons (n)	Name	Formula (C_nH_{2n+2})	Number of carbons (n)	Name	Formula (C_nH_{2n+2})
1	Methane	CH_4	9	Nonane	C_9H_{20}
2	Ethane	C_2H_6	10	Decane	$C_{10}H_{22}$
3	Propane	C_3H_8	11	Undecane	$C_{11}H_{24}$
4	Butane	C_4H_{10}	12	Dodecane	$C_{12}H_{26}$
5	Pentane	C_5H_{12}	13	Tridecane	$C_{13}H_{28}$
6	Hexane	C_6H_{14}	20	Icosane	$C_{20}H_{42}$
7	Heptane	C_7H_{16}	30	Triacontane	$C_{30}H_{62}$
8	Octane	C_8H_{18}			

Worked Example 3.2.1: Drawing the Structures of Isomers

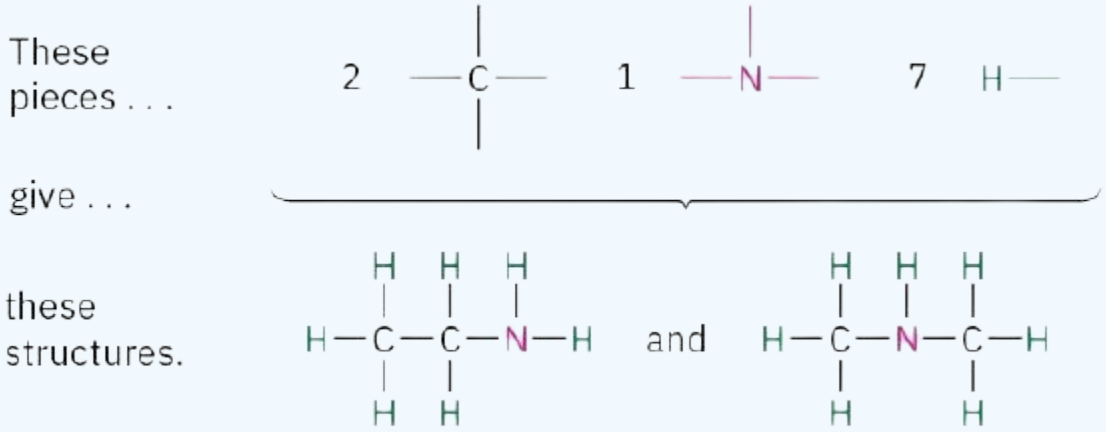
Propose structures for two isomers with the formula C_2H_7N.

Strategy

We know that carbon forms four bonds, nitrogen forms three, and hydrogen forms one. Write down the carbon atoms first, and then use trial and error plus intuition to put the pieces together.

Solution

There are two isomeric structures. One has the connection C–C–N, and the other has the connection C–N–C.



Exercises

Exercise 3.2.1

Draw structures of the five isomers of C_6H_{14}.

Answer available at the end of this section.

Exercise 3.2.2

Propose structures that meet the following descriptions:

a. Two isomeric esters with the formula $C_5H_{10}O_2$:
b. Two isomeric nitriles with the formula C_4H_7N
c. Two isomeric disulfides with the formula $C_4H_{10}S_2$

Answer available at the end of this section.

Exercise 3.2.3

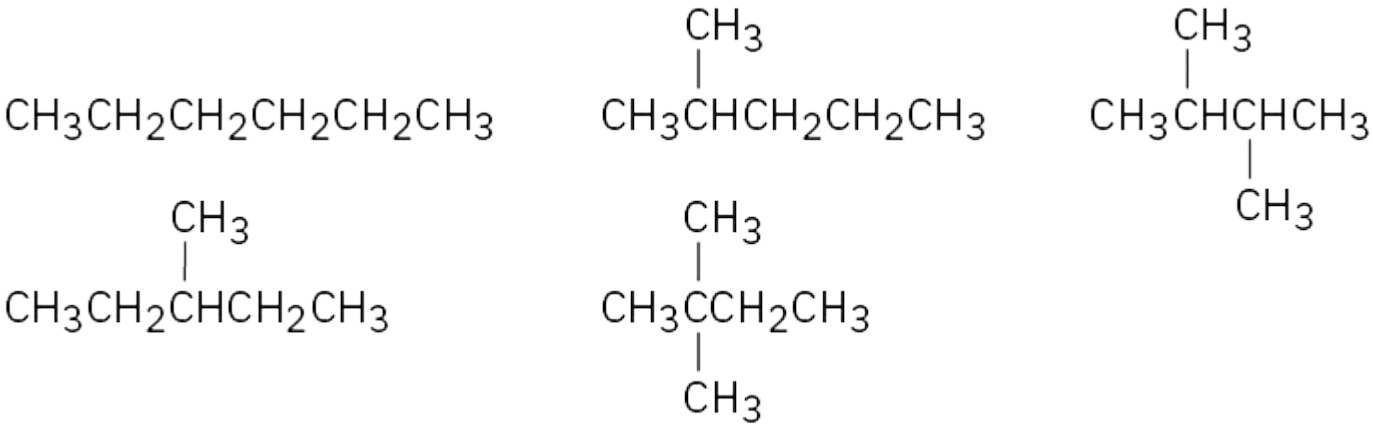
How many isomers are there with the following descriptions?

a. Alcohols with the formula C_3H_8O
b. Bromoalkanes with the formula C_4H_9Br
c. Thioesters with the formula C_4H_8OS

Answer available at the end of this section.

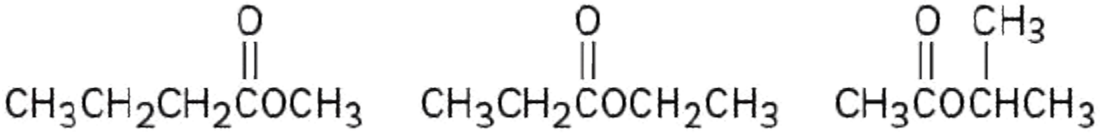
Answers

Exercise 3.2.1

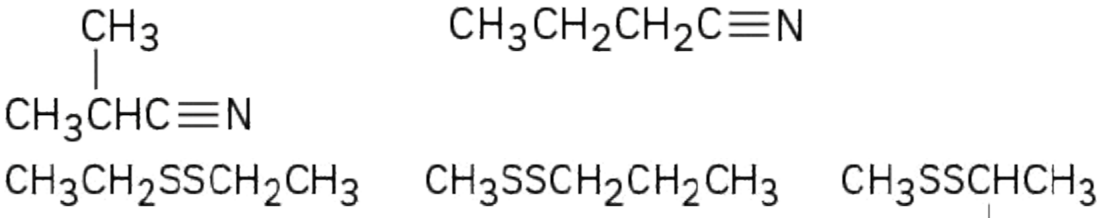


Exercise 3.2.2

a.



b.



c.



Exercise 3.2.3

a. Two
b. Four
c. Four

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3.3: Alkyl Groups

If you imagine removing a hydrogen atom from an **alkane**, the partial structure that remains is called an **alkyl group**. Alkyl groups are not stable compounds themselves, they are simply parts of larger compounds and are named by replacing the *-ane* ending of the parent alkane with an *-yl* ending. For example, removal of a hydrogen from methane, CH_4, generates a methyl group, $–CH_3$, and removal of a hydrogen from ethane, CH_3CH_3, generates an ethyl group, $–CH_2CH_3$. Similarly, removal of a hydrogen atom from the end carbon of any straight-chain alkane gives the series of straight-chain alkyl groups shown in Table 3.3.1. Combining an alkyl group with any of the functional groups listed earlier makes it possible to generate and name many thousands of compounds. For example:

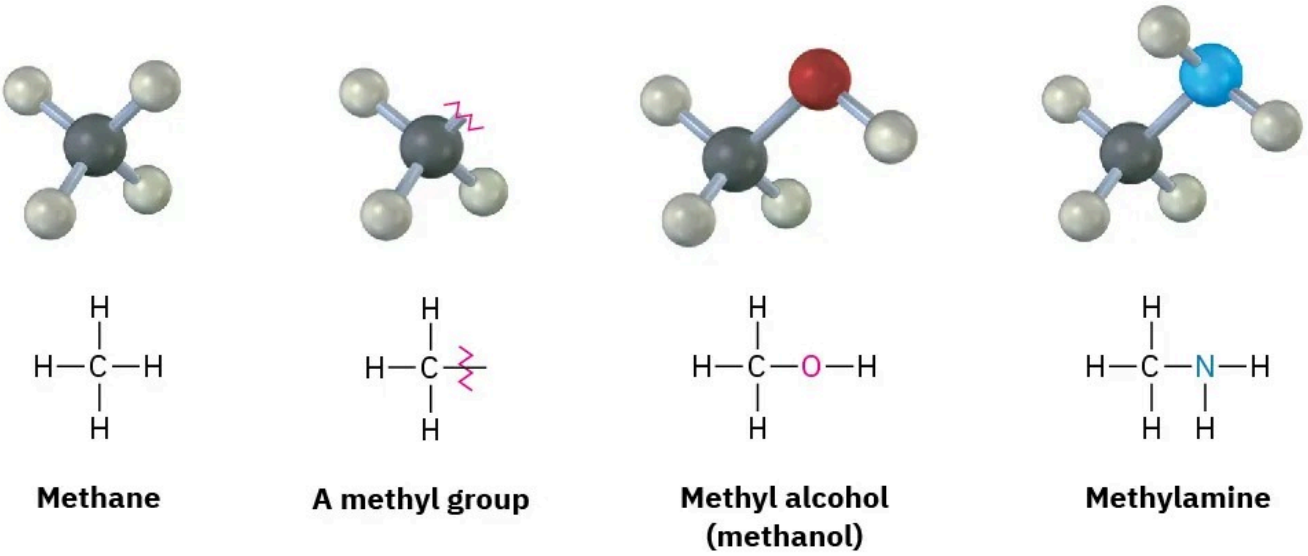


Table 3.3.1 Some Straight-Chain Alkyl Groups

Alkane	Name	Alkyl group	Name (abbreviation)
CH_4	Methane	$–CH_3$	Methyl (Me)
CH_3CH_3	Ethane	$–CH_2CH_3$	Ethyl (Et)
$CH_3CH_2CH_3$	Propane	$–CH_2CH_2CH_3$	Propyl (Pr)
$CH_3CH_2CH_2CH_3$	Butane	$–CH_2CH_2CH_2CH_3$	Butyl (Bu)
$CH_3CH_2CH_2CH_2CH_3$	Pentane	$–CH_2CH_2CH_2CH_2CH_3$	Pentyl, or amyl

Just as straight-chain alkyl groups are generated by removing a hydrogen from an end carbon, branched alkyl groups are generated by removing a hydrogen atom from an internal carbon. There are four 4-carbon alkyl groups possible (Figure 3.3.1) and two 3-carbon alkyl groups (Figure 3.3.2).

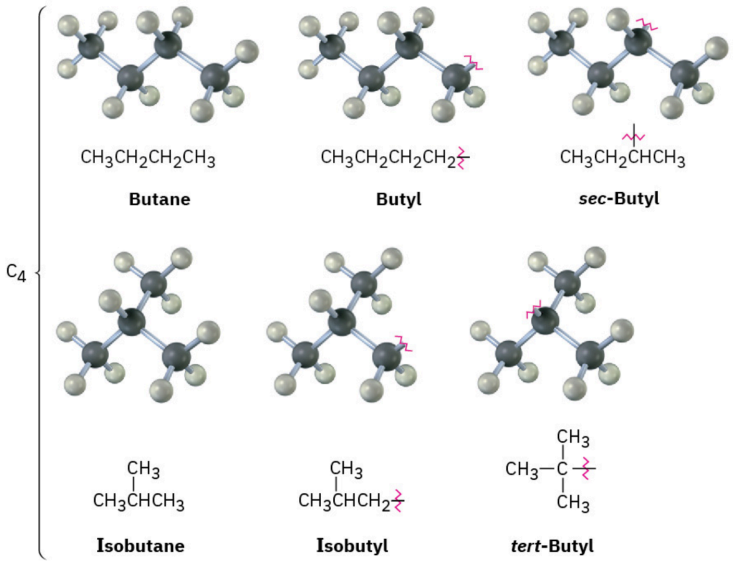


Figure 3.3.1: Alkyl groups generated from an alkane with 4 carbon atoms.

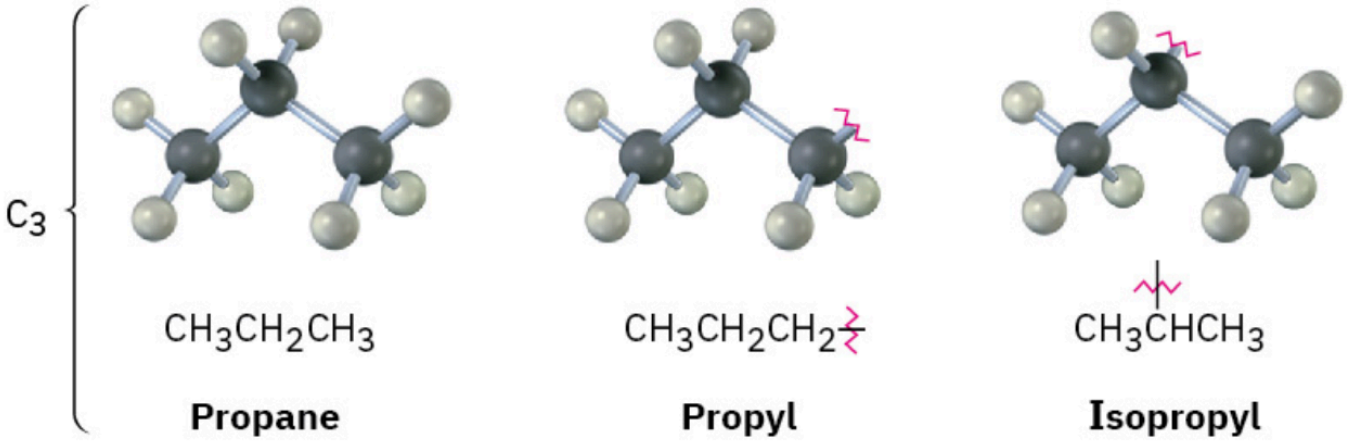
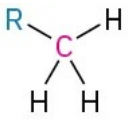


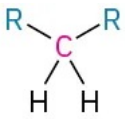
Figure 3.3.2: Alkyl groups generated from an alkane with 3 carbon atoms.

Classification of Carbon

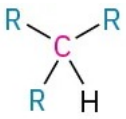
One further comment about naming alkyl groups: the prefixes *sec*- (for secondary) and *tert*- (for tertiary) used for the C_4 alkyl groups in Figure 3.3.1 refer to the number of other carbon atoms attached to the branching carbon atom. There are four possibilities: primary (1°), secondary (2°), tertiary (3°), and quaternary (4°).



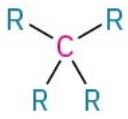
***Primary* carbon (1°) is bonded to one other carbon.**



***Secondary* carbon (2°) is bonded to two other carbons.**



***Tertiary* carbon (3°) is bonded to three other carbons.**

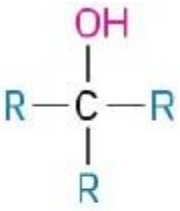


***Quaternary* carbon (4°) is bonded to four other carbons.**

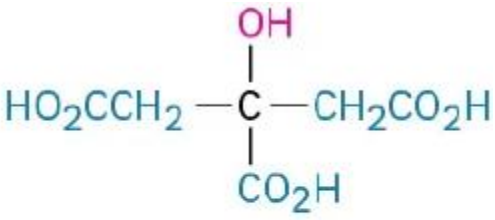
Note

The symbol R is used here and throughout organic chemistry to represent a generalized organic group. The R group can be methyl, ethyl, propyl, or any of a multitude of others. You might think of **R** as representing the **R**est of the molecule, which isn't specified.

The terms *primary, secondary, tertiary,* and *quaternary* are routinely used in organic chemistry, and their meanings need to become second nature. For example, if we were to say, "Citric acid is a tertiary alcohol," we would mean that it has an alcohol functional group (–OH) bonded to a carbon atom that is itself bonded to three other carbons.

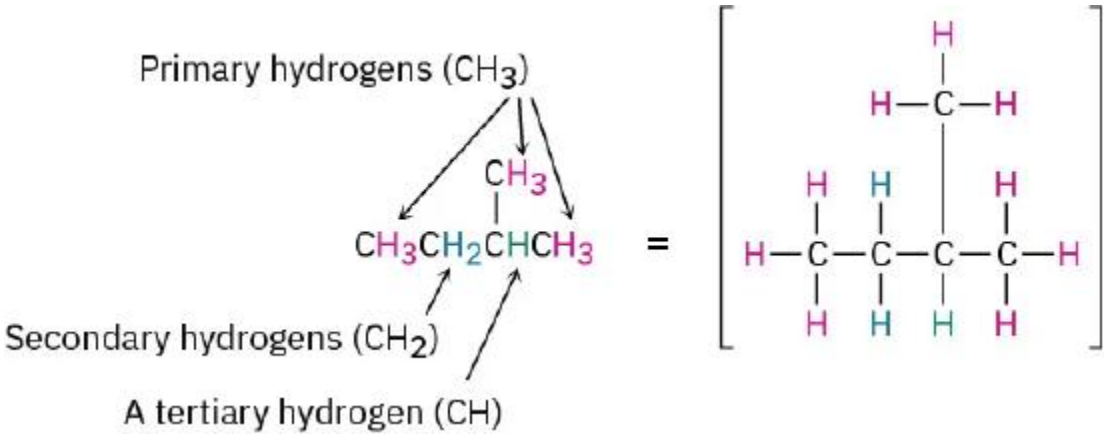


General class of tertiary alcohols, R_3COH



Citric acid—a specific tertiary alcohol

In addition to speaking of carbon atoms as being primary, secondary, or tertiary, we speak of hydrogens in the same way. Primary hydrogen atoms are attached to primary carbons (RCH_3), secondary hydrogens are attached to secondary carbons (R_2CH_2), and tertiary hydrogens are attached to tertiary carbons (R_3CH). There is, however, no such thing as a quaternary hydrogen. (Why not?)



Exercises

Exercise 3.3.1

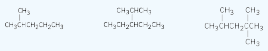
Draw the eight 5-carbon alkyl groups (pentyl isomers).

Answer available at the end of this section.

Exercise 3.3.2

Identify the carbon atoms in the following molecules as primary, secondary, tertiary, or quaternary:

a. **b.** **c.**



Answer available at the end of this section.

Exercise 3.3.3

Identify the hydrogen atoms on the compounds shown in Problem 3.3.2 as primary, secondary, or tertiary.

Answer available at the end of this section.

Exercise 3.3.4

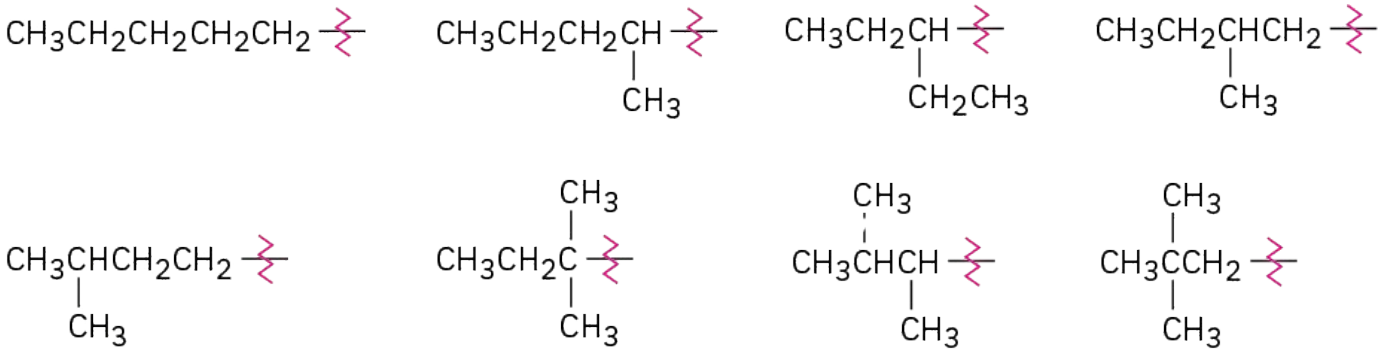
Draw structures of alkanes that meet the following descriptions:

a. An alkane with two tertiary carbons
b. An alkane that contains an isopropyl group
c. An alkane that has one quaternary and one secondary carbon

Answer available at the end of this section.

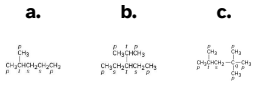
Answers

Exercise 3.3.1



Exercise 3.3.2

a. **b.** **c.**

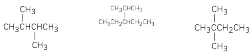


Exercise 3.3.3

Primary carbons have primary hydrogens, secondary carbons have secondary hydrogens, and tertiary carbons have tertiary hydrogens.

Exercise 3.3.4

a. **b.** **c.**



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3.4: Naming Alkanes

In earlier times, new compounds were named at the whim of their discoverer. Thus, urea (CH_4N_2O) is a crystalline substance isolated from urine; morphine ($C_{17}H_{19}NO_3$) is an analgesic (painkiller) named after Morpheus, the Greek god of dreams; and acetic acid, the primary organic constituent of vinegar, is named from the Latin word for vinegar, *acetum*.

As the science of organic chemistry slowly grew in the 19th century, so too did the number of known compounds and the need for a systematic method of naming them. The system of naming (nomenclature) we'll use in this book is that devised by the International Union of Pure and Applied Chemistry (IUPAC, usually spoken as **eye**-you-pac).

A chemical name typically has four parts in the IUPAC system: parent, prefix, locant, and suffix. The **parent** name identifies the main part of the molecule and tells how many carbon atoms are in that part. **Prefixes** identify the various substituent groups attached to the parent. **Locants** give the positions of the attached substituents. And the **suffix** identifies the primary functional group attached to the parent.

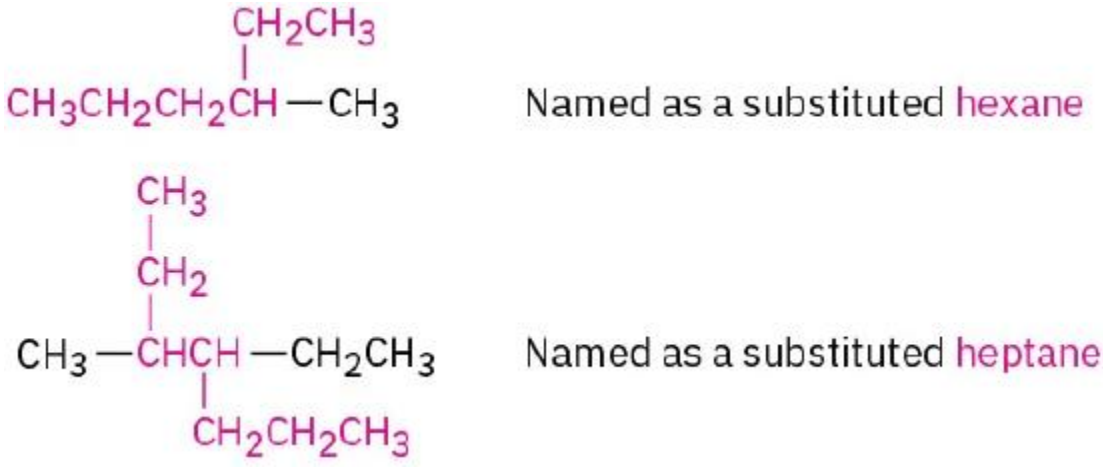


As we cover new functional groups in later chapters, the applicable IUPAC rules of nomenclature will be given. In addition, Appendix A at the back of this book gives an overall view of organic nomenclature and shows how compounds that contain more than one functional group are named. (If preferred, you can study that appendix now.) For the present, let's see how to name branched-chain alkanes and learn some general rules that are applicable to all compounds. All but the most complex branched-chain alkanes can be named by following four steps. For a very few compounds, a fifth step is needed.

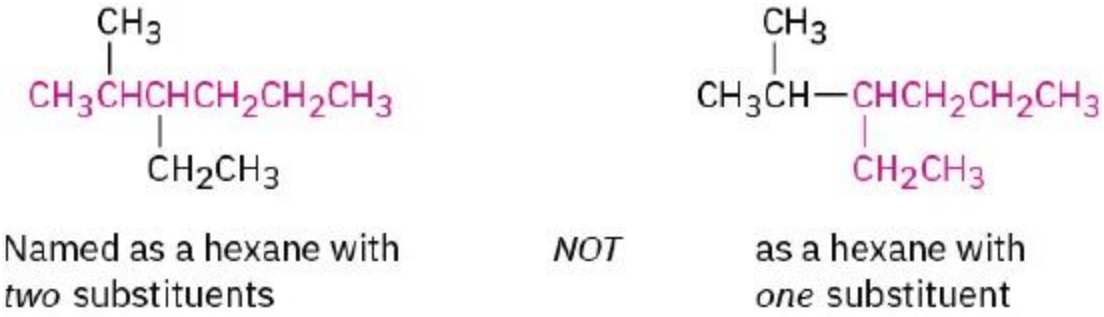
STEP 1:

Identify the parent hydrocarbon

(a) Find the longest continuous chain of carbon atoms in the molecule, and use the name of that chain as the parent name. The longest chain may not always be apparent from the manner of writing; you may have to "turn corners."



(b) If two different chains of equal length are present, choose the one with the larger number of branch points as the parent.



STEP 2:

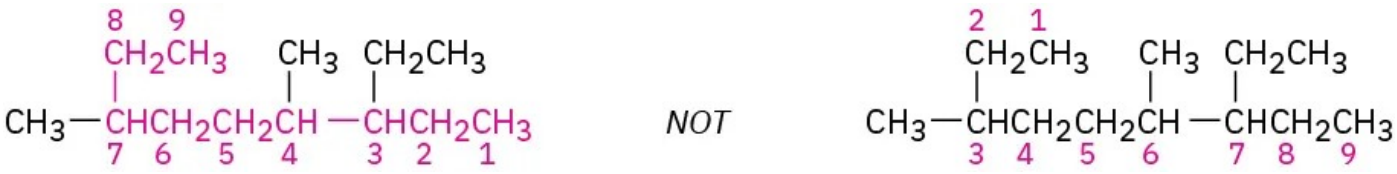
Number the atoms in the longest chain

(a) Beginning at the end nearer the first branch point, number each carbon atom in the parent chain.



The first branch occurs at C3 in the proper system of numbering, not at C4.

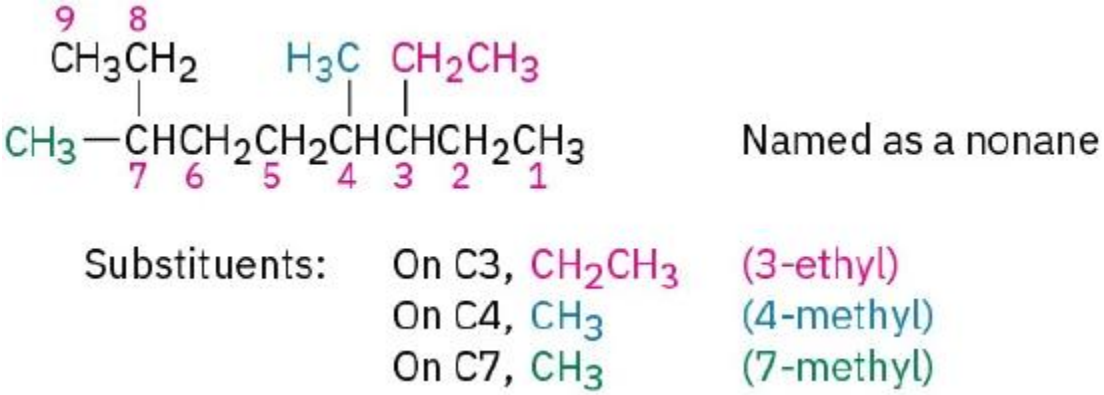
(b) If there is branching an equal distance away from both ends of the parent chain, begin numbering at the end nearer the second branch point.



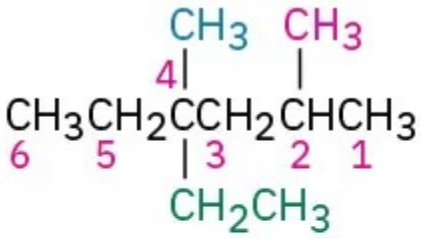
STEP 3:

Identify and number the substituents

(a) Assign a number to each substituent to locate its point of attachment to the parent chain.



(b) If there are two substituents on the same carbon, give both the same number. There must be as many numbers in the name as there are substituents.



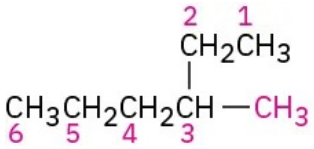
Named as a hexane

Substituents: On C2, CH_3 (2-methyl)
On C4, CH_3 (4-methyl)
On C4, CH_2CH_3 (4-ethyl)

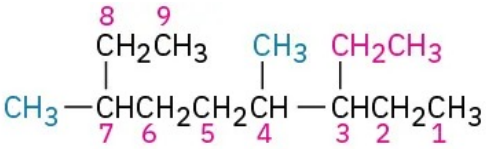
STEP 4:

Write the name as a single word

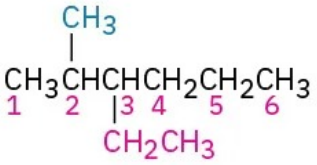
Use hyphens to separate the different prefixes, and use commas to separate numbers. If two or more different substituents are present, cite them in alphabetical order. If two or more identical substituents are present on the parent chain, use one of the multiplier prefixes *di-*, *tri-*, *tetra-*, and so forth, but don't use these prefixes for alphabetizing. Full names for some of the examples we have been using are as follows:



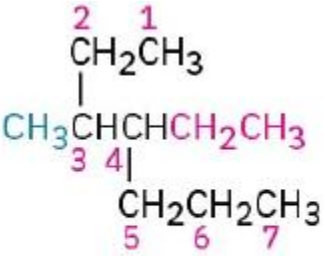
3-Methylhexane



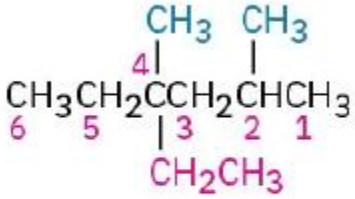
3-Ethyl-4,7-dimethylnonane



3-Ethyl-2-methylhexane



4-Ethyl-3-methylheptane

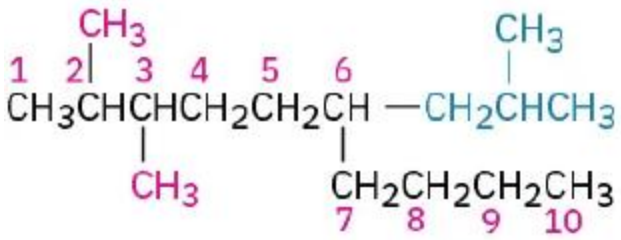


4-Ethyl-2,4-dimethylhexane

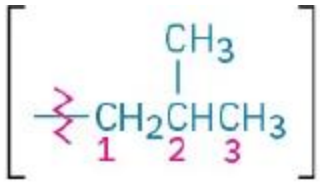
STEP 5:

Name a branched substituent as though it were itself a compound

In some particularly complex cases, a fifth step is necessary. It occasionally happens that a substituent on the main chain is itself branched. In the following case, for instance, the substituent at C6 is a three-carbon chain with a methyl group. To name the compound fully, the branched substituent must first be named.

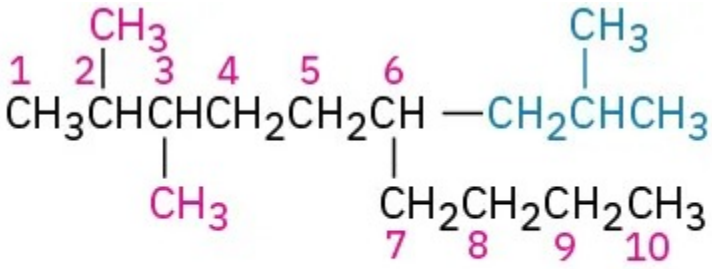


Named as a 2,3,6-trisubstituted decane



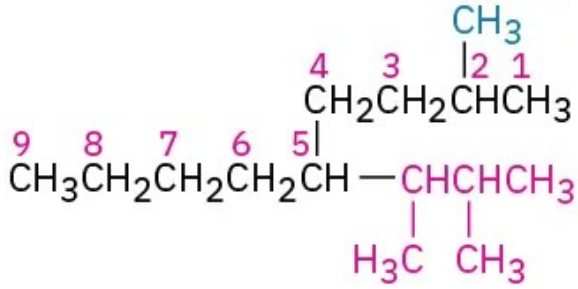
A 2-methylpropyl substituent

Number the branched substituent beginning at the point of its attachment to the main chain, and identify it—in this case, a 2-methylpropyl group. The substituent is treated as a whole and is alphabetized according to the first letter of its complete name, including any numerical prefix. It is set off in parentheses when naming the entire molecule.

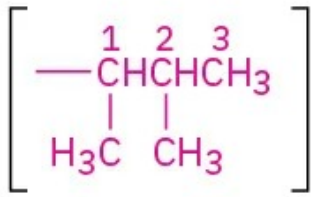


2,3-Dimethyl-6-(2-methylpropyl)decane

As a further example:



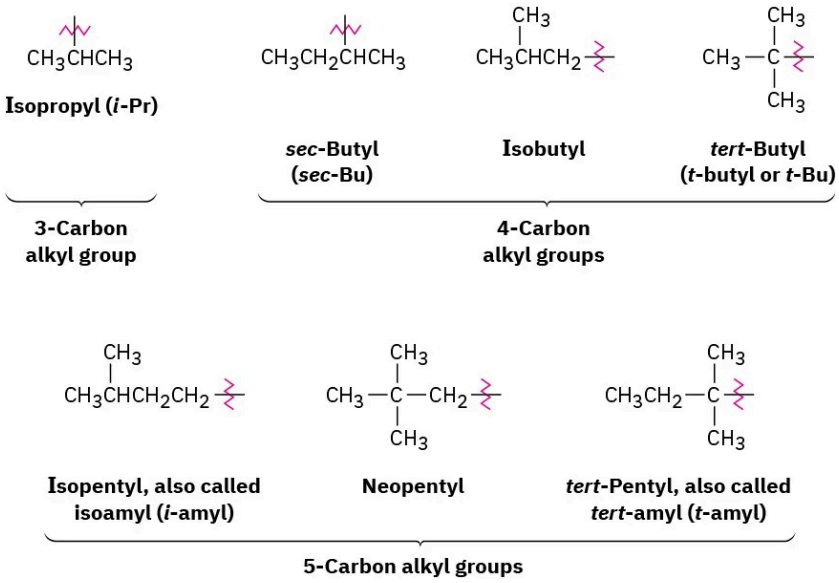
5-(1,2-Dimethylpropyl)-2-methylnonane



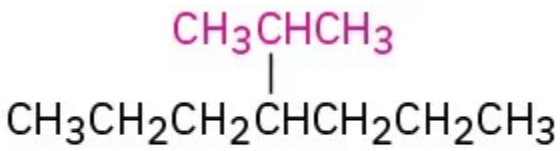
A 1,2-dimethylpropyl group

Common Names

For historical reasons, some of the simpler branched-chain alkyl groups also have nonsystematic, common names, as noted earlier.



The common names of these simple alkyl groups are so well entrenched in the chemical literature that IUPAC rules make allowance for them. Thus, the following compound is properly named either 4-(1-methylethyl)heptane or 4-isopropylheptane. There's no choice but to memorize these common names; fortunately, there are only a few of them.

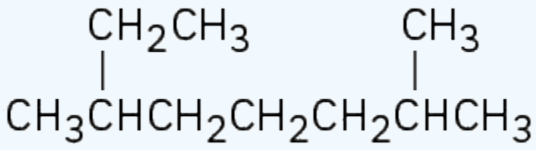


4-(1-Methylethyl)heptane or 4-Isopropylheptane

When writing an alkane name, the nonhyphenated prefix iso- is considered part of the alkyl-group name for alphabetizing purposes, but the hyphenated and italicized prefixes *sec*- and *tert*- are not. Thus, isopropyl and isobutyl are listed alphabetically under *i*, but *sec*-butyl and *tert*-butyl are listed under *b*.

Worked Example 3.4.1: Naming Alkanes

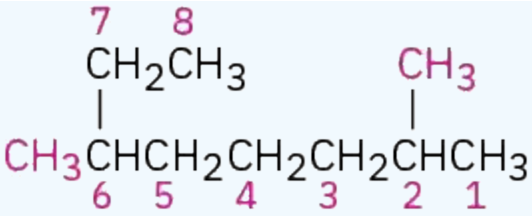
What is the IUPAC name for the following alkane?



Strategy

Find the longest continuous carbon chain in the molecule, and use that as the parent name. This molecule has an eight-carbon chain—octane—with two methyl substituents. (You have to turn corners to see it.) Numbering from the end nearer the first methyl substituent indicates that the methyls are at C2 and C6.

Solution



2,6-Dimethyloctane

Worked Example 3.4.2: Converting a Chemical Name into a Structure

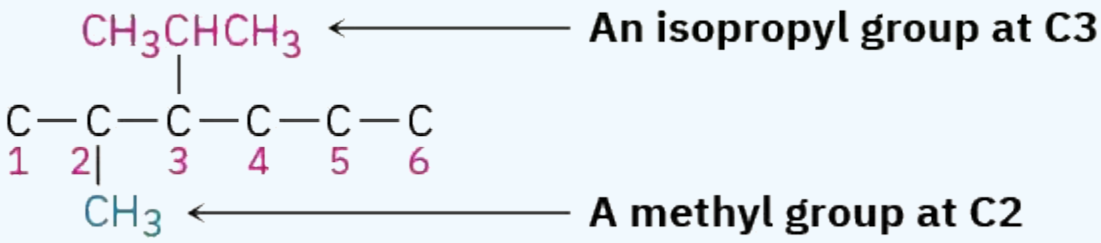
Draw the structure of 3-isopropyl-2-methylhexane.

Strategy

This is the reverse of Worked Example 3.2 and uses a reverse strategy. Look at the parent name (hexane), and draw its carbon structure.

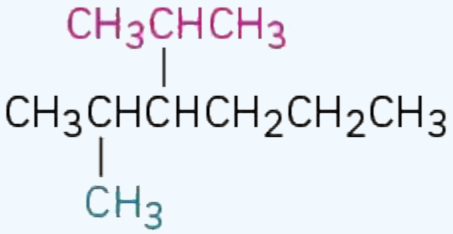
C–C–C–C–C–C Hexane

Next, find the substituents (3-isopropyl and 2-methyl), and place them on the proper carbons.



Finally, add hydrogens to complete the structure.

Solution



3-Isopropyl-2-methylhexane

Exercises

Exercise 3.4.1

Give IUPAC names for the following compounds:

a. The three isomers of C_5H_{12} **b.** **c.** **d.**



Answer available at the end of this section.

Exercise 3.4.2

Draw structures corresponding to the following IUPAC names:

a. 3,4-Dimethylnonane
b. 3-Ethyl-4,4-dimethylheptane
c. 2,2-Dimethyl-4-propyloctane
d. 2,2,4-Trimethylpentane

Answer available at the end of this section.

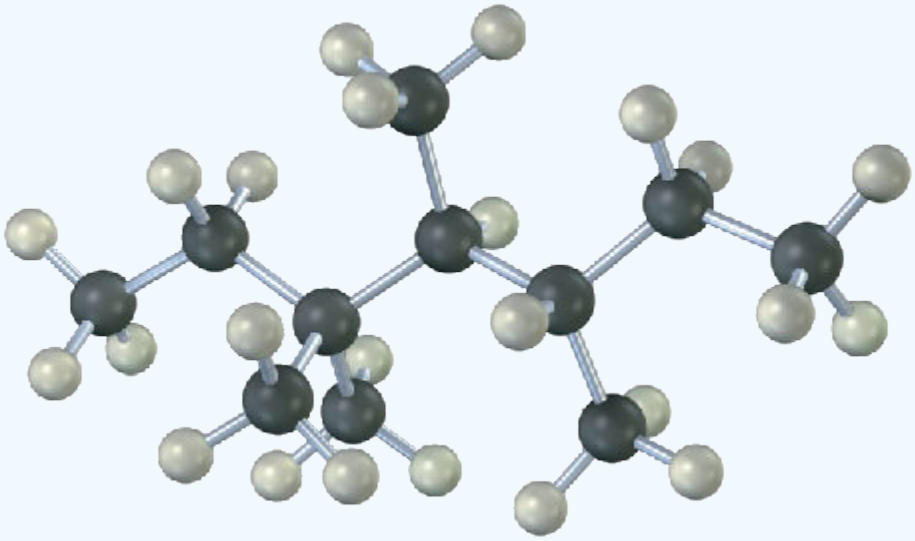
Exercise 3.4.3

Name the eight 5-carbon alkyl groups you drew in Exercise 3.3.1.

Answer available at the end of this section.

Exercise 3.4.4

Give the IUPAC name for the following hydrocarbon, and convert the drawing into a skeletal structure.

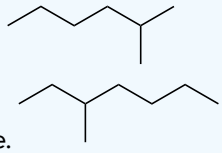


Answer available at the end of this section.

Exercise 3.4.5

Label the parent chain carbons using numbers and identify the alkyl group.

a. The name of this molecule is 2-methylhexane.

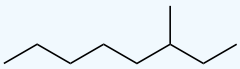


b. The name of this molecule is 3-methylheptane.

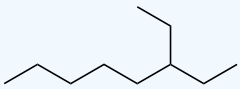
Exercise 3.4.6

Label the parent chain carbons using numbers. Identify the alkyl group in the following molecules. What is the name of these molecules?

a. Molecule A:



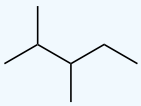
b. Molecule B:



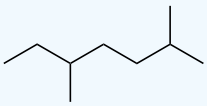
Exercise 3.4.7

a. The name of the molecule on the left is 2,3-dimethylpentane. What is the name of Molecule A?

2,3-dimethylpentane:

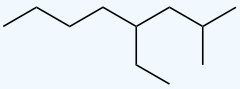


Molecule A:

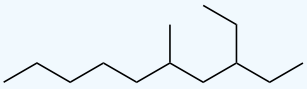


b. The name of the molecule on the left is 4-ethyl-2-methyloctane. What is the name of Molecule B?

4-ethyl-2-methyloctane:

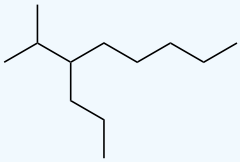


Molecule B:

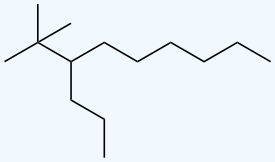


c. The name of the molecule on the left is 4-isopropylnonane. What is the name of Molecule C?

4-isopropylnonane:



Molecule C:



Answers

Exercise 3.4.1

a. Pentane, 2-methylbutane, 2,2-dimethylpropane
b. 2,3-Dimethylpentane
c. 2,4-Dimethylpentane
d. 2,2,5-Trimethylhexane

Exercise 3.4.2

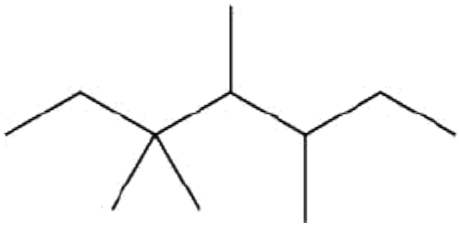
a. **b.** **c.** **d.**



Exercise 3.4.3

Pentyl, 1-methylbutyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl

Exercise 3.4.4



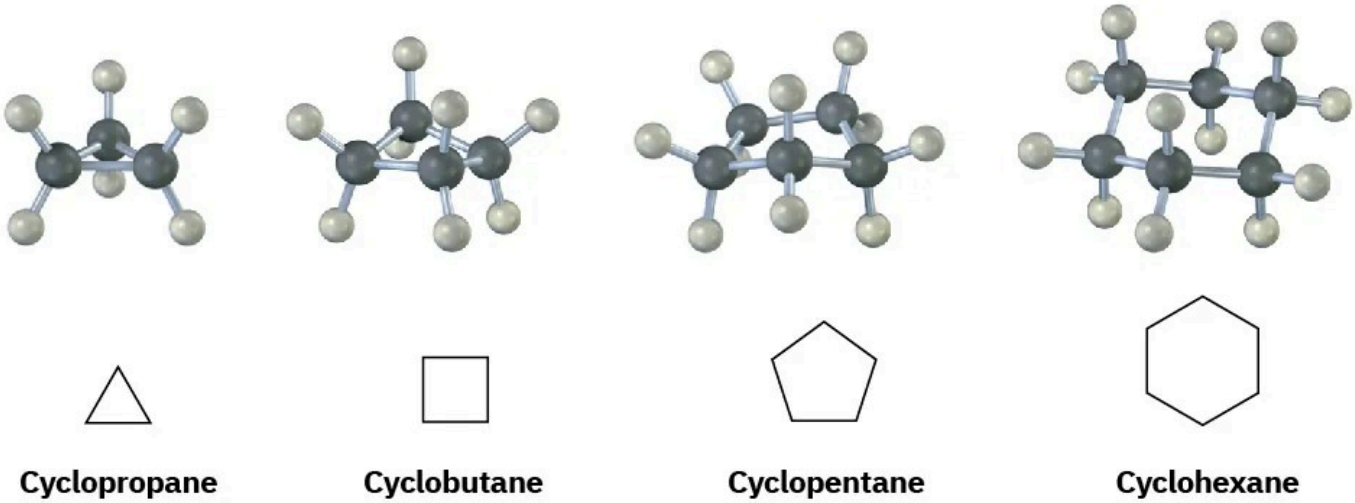
3,3,4,5-Tetramethylheptane

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3.5: Naming Cycloalkanes

Saturated cyclic hydrocarbons are called cycloalkanes, or alicyclic compounds (**ali**phatic **cyclic**). Because cycloalkanes consist of rings of $-CH_2-$units, they have the general formula $(CH_2)_n$, or C_nH_{2n}, and can be represented by polygons in skeletal drawings.

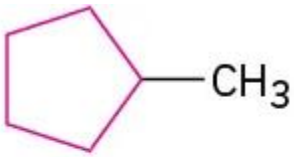


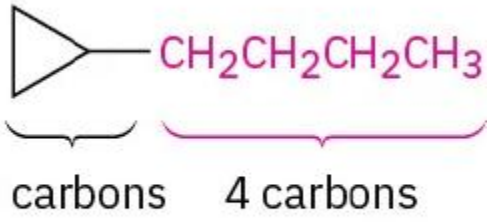
Cyclopropane **Cyclobutane** **Cyclopentane** **Cyclohexane**

Substituted cycloalkanes are named by rules similar to those we saw for open-chain alkanes. For most compounds, there are only two steps.

STEP 1: Find the parent

Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent is greater than the number in the ring, the compound is named as a cycloalkyl-substituted alkane. For example:

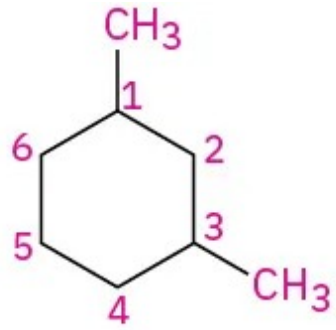




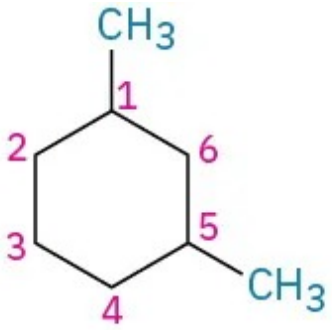
Methylcyclopentane **1-Cyclopropylbutane**

STEP 2: Number the substituents, and write the name

For an alkyl- or halo-substituted cycloalkane, choose a point of attachment as carbon 1 and number the substituents on the ring so that the *second* substituent has as low a number as possible. If ambiguity still exists, number so that the third or fourth substituent has as low a number as possible, until a point of difference is found.



NOT

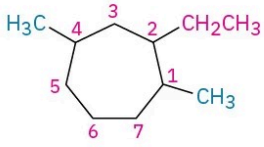


1,3-Dimethylcyclohexane

Lower

1,5-Dimethylcyclohexane

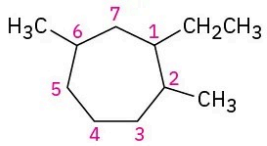
Higher



2-Ethyl-1,4-dimethylcycloheptane

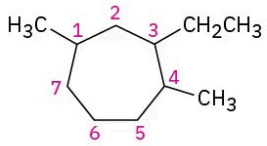
Lower Lower

NOT



1-Ethyl-2,6-dimethylcycloheptane

Higher

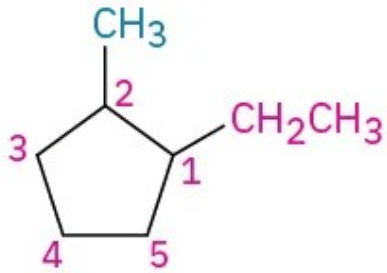


3-Ethyl-1,4-dimethylcycloheptane

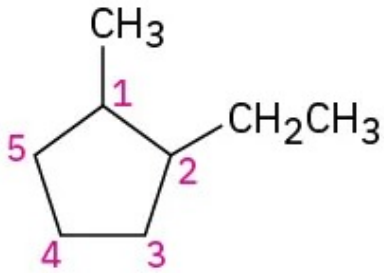
Higher

SUBSTEP 2a

When two or more different alkyl groups are present that could potentially take the same numbers, number them by alphabetical priority, ignoring numerical prefixes such as di- and tri-.



NOT

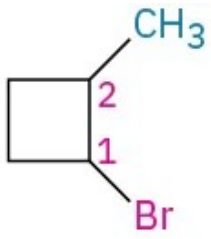


1-Ethyl-2-methylcyclopentane

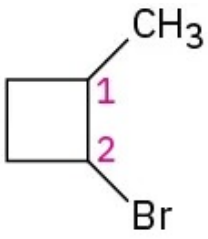
2-Ethyl-1-methylcyclopentane

SUBSTEP 2b

If halogens are present, treat them just like alkyl groups.

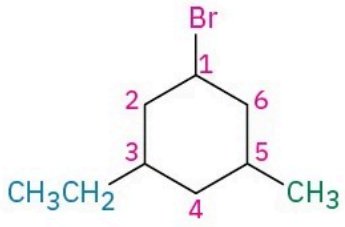


NOT

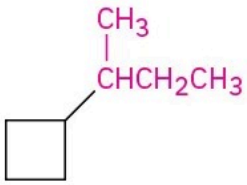


1-Bromo-2-methylcyclobutane **2-Bromo-1-methylcyclobutane**

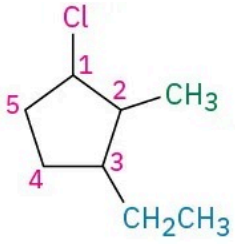
Some additional examples follow:



1-Bromo-3-ethyl-5-methyl-cyclohexane



(1-Methylpropyl)cyclobutane or *sec*-butylcyclobutane



1-Chloro-3-ethyl-2-methyl-cyclopentane

Exercises

Exercise 3.5.1

a. a. The name of this molecule is cyclobutane. What is the name of Molecule A?

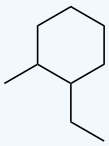
cyclobutane: 

Molecule A: 

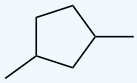
b. b. The name of this molecule is methylcyclobutane. Identify the alkyl group. Label the parent chain



c. d. The name of this molecule is 1-ethyl-2-methylcyclohexane. Identify the alkyl group. Label the parent chain



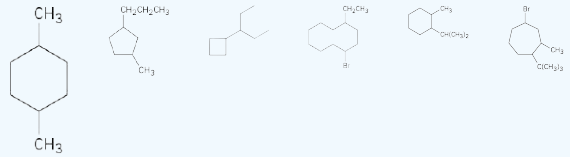
d. e. What is the name of Molecule B?

Molecule B: 

Exercise 3.5.2

Give IUPAC names for the following cycloalkanes:

a. **b.** **c.** **d.** **e.** **f.**



Answer available at the end of this section.

Exercise 3.5.3

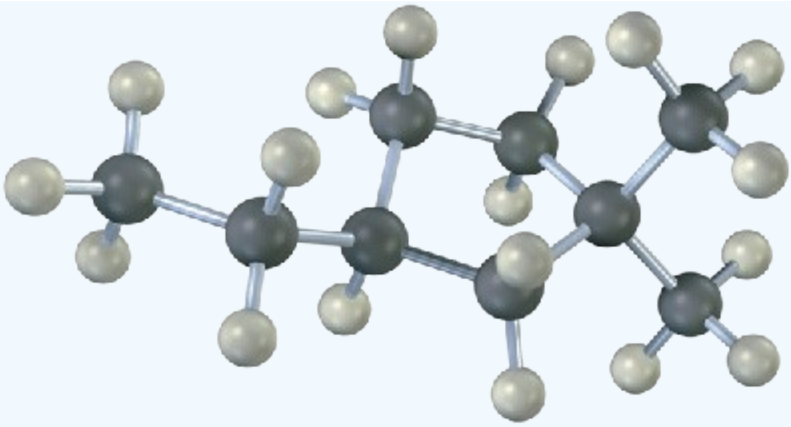
Draw structures corresponding to the following IUPAC names:

a. 1,1-Dimethylcyclooctane
b. 3-Cyclobutylhexane
c. 1,2-Dichlorocyclopentane
d. 1,3-Dibromo-5-methylcyclohexane

Answer available at the end of this section.

Exercise 3.5.4

Name the following cycloalkane:



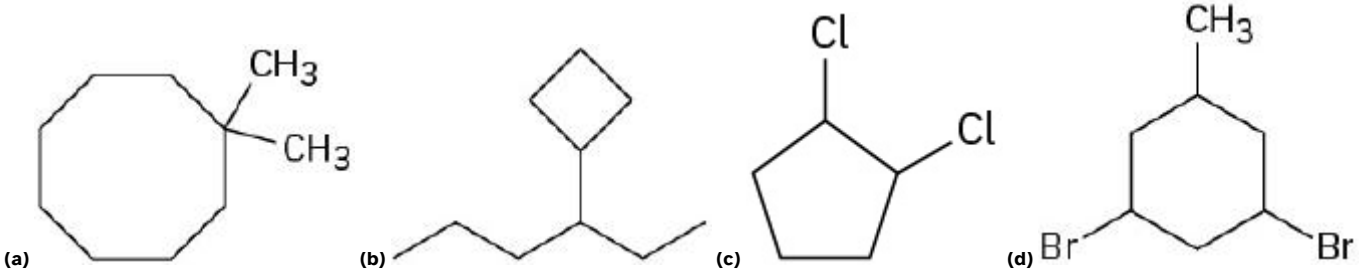
Answer available at the end of this section.

Answers

Exercise 3.5.2

- **a.** 1,4-Dimethylcyclohexane
- **b.** 1-Methyl-3-propylcyclopentane
- **c.** 3-Cyclobutylpentane
- **d.** 1-Bromo-4-ethylcyclodecane
- **e.** 1-Isopropyl-2-methylcyclohexane
- **f.** 4-Bromo-1-*tert*-butyl-2-methylcycloheptane

Exercise 3.5.3



Exercise 3.5.4

3-Ethyl-1,1-dimethylcyclopentane

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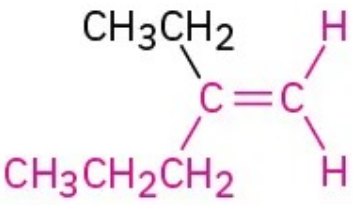
3.6: Naming Alkenes

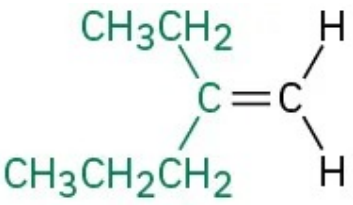
An **alkane** is a **saturated** hydrocarbon, meaning that the molecule contains all the possible hydrogen atoms because all the carbon-carbon bonds are single bonds. If one of those carbon-carbon bonds is a double bond, the resulting hydrocarbon is **unsaturated** and called an **alkene**.

Alkenes are named using a series of rules similar to those for alkanes, with the suffix *-ene* used instead of *-ane* to identify the functional group. There are three steps to this process.

STEP 1:

Name the parent hydrocarbon: Find the longest carbon chain containing the double bond, and name the compound accordingly, using the suffix *-ene:*

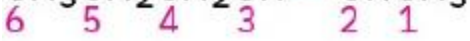


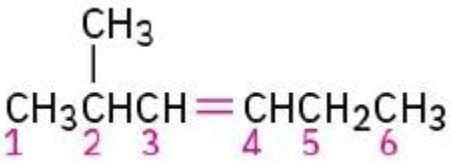


Named as a *pentene* *NOT* as a hexene, since the double bond is not contained in the six-carbon chain

STEP 2:

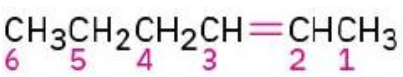
Number the carbon atoms in the chain: Begin at the end nearer the double bond or, if the double bond is equidistant from the two ends, begin at the end nearer the first branch point. This rule ensures that the double-bond carbons receive the lowest possible numbers.



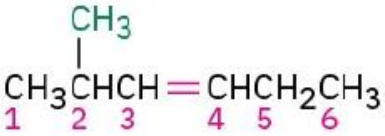


STEP 3:

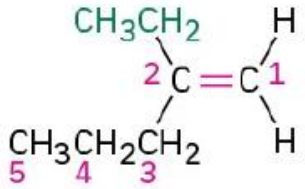
Write the full name: Number the substituents according to their positions in the chain, and list them alphabetically. Indicate the position of the double bond by giving the number of the first alkene carbon and placing that number directly before the parent name. If more than one double bond is present, indicate the position of each and use one of the suffixes *-diene, -triene,* and so on.



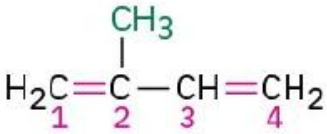
2-Hexene



2-Methyl-3-hexene

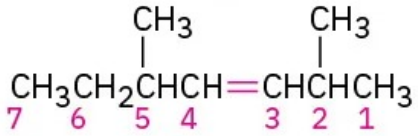


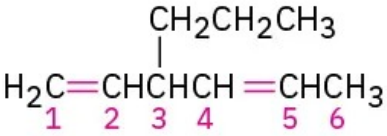
2-Ethyl-1-pentene



2-Methyl-1,3-butadiene

We should also note that IUPAC changed their naming recommendations in 1993 to place the locant indicating the position of the double bond immediately before the *-ene* suffix rather than before the parent name: but-2-ene rather than 2-butene, for instance. This change has not been widely accepted by the chemical community in the United States, however, so we'll stay with the older but more commonly used names. Be aware, though, that you may occasionally encounter the newer system.

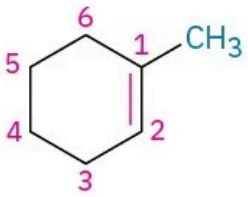


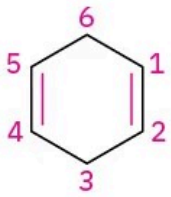


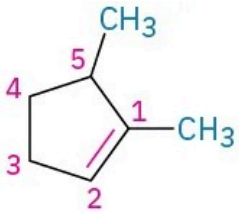
Newer naming system: 2,5-Dimethylhept-3-ene 3-Propylhexa-1,4-diene

(Older naming system: 2,5-Dimethyl-3-heptene 3-Propyl-1,4-hexadiene**)**

Cycloalkenes are named similarly, but because there is no chain end to begin from, we number the cycloalkene so that the double bond is between C1 and C2, and the first substituent has as low a number as possible. It's not necessary to indicate the position of the double bond in the name because it's always between C1 and C2. As with open-chain alkenes, the newer but not yet widely accepted naming rules place the locant immediately before the suffix in a cyclic alkene.



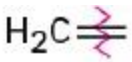




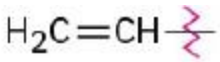
1-Methylcyclohexene 1,4-Cyclohexadiene 1,5-Dimethylcyclopentene

(New: Cyclohexa-1,4-diene)

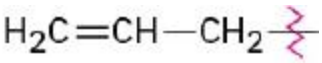
For historical reasons, there are a few alkenes whose names are firmly entrenched in common usage but don't conform to the rules. For example, the alkene derived from ethane should be called *ethene,* but the name *ethylene* has been used for so long that it is accepted by IUPAC. Table $3.6.1$ lists several other common names that are often used and are recognized by IUPAC. Note also that a $=CH_2$ substituent is called a **methylene group**, a $H_2C{=}CH^-$ substituent is called a **vinyl group**, and a $H_2C{=}CHCH_2{}^-$ substituent is called an **allyl group**.



A methylene group

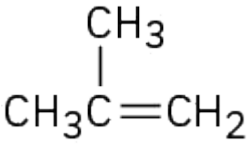
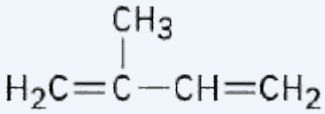


A vinyl group



An allyl group

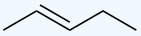
Table 3.6.1: Common Names of Some Alkenes

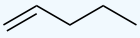
Compound	Systematic name	Common name
$H_2C{=}CH_2$	Ethene	Ethylene
$CH_3CH{=}CH_2$	Propene	Propylene
	2-Methylpropene	Isobutylene
	2-Methyl-1,3-butadiene	Isoprene

Exercises

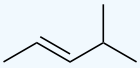
Exercise 3.6.1

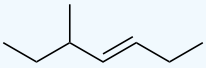
a. The name of the molecule on the left is 2-pentene. What is the name of the molecule in the right: Molecule A?

2-pentene: 

Molecule A: 

b. The name of the molecule on the left is 4-methyl-2-pentene. What is the name of the molecule in the right: Molecule B?

4-methyl-2-pentene: 

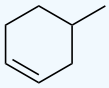
Molecule B: 

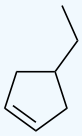
c. The name of the molecule on the left is cyclohexene. What is the name of the molecule in the right: Molecule C?

Cyclohexene: 

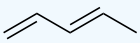
Molecule C: 

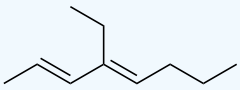
d. The name of the molecule on the left is 4-methylcyclohexene. What is the name of the molecule in the right: Molecule D?

4-methylcyclohexene: 

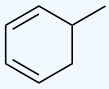
Molecule D: 

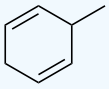
e. The name of the molecule on the left is 1,3-pentadiene. What is the name of the molecule in the right: Molecule E?

1,3-pentadiene: 

Molecule E: 

f. The location of substituents relative to the double bonds can lead to a type of constitutional isomer known as a **positional isomer**. The name of the molecule on the left is 5-methyl-1,3-cyclohexadiene. What is the name of Molecule F?

5-methyl-1,3-cyclohexadiene: 

Molecule F: 

Exercise 3.6.2

Give IUPAC names for the following compounds:

a. **b.** **c.** **d.**

Answer available at the end of this section.

Exercise 3.6.3

Draw structures corresponding to the following IUPAC names:

a. 2-Methyl-1,5-hexadiene
b. 3-Ethyl-2,2-dimethyl-3-heptene
c. 2,3,3-Trimethyl-1,4,6-octatriene
d. 3,4-Diisopropyl-2,5-dimethyl-3-hexene

Answer available at the end of this section.

Exercise 3.6.4

Name the following cycloalkenes:

a. **b.** **c.**

Answer available at the end of this section.

Answers

Exercise 3.6.2

a. 3,4,4-Trimethyl-1-pentene
b. 3-Methyl-3-hexene
c. 4,7-Dimethyl-2,5-octadiene
d. 6-Ethyl-7-methyl-4-nonene

Exercise 3.6.3

a. **b.** **c.** **d.**



Exercise 3.6.4

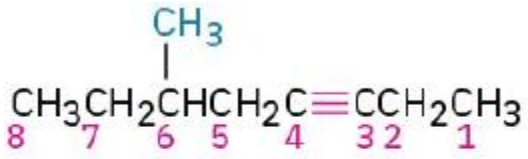
a.1,2-Dimethylcyclohexene **b.**4,4-Dimethylcycloheptene **c.**3-Isopropylcyclopentene

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3.7: Naming Alkynes

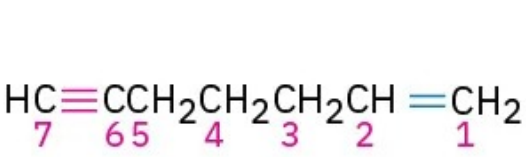
Alkyne nomenclature follows the general rules for hydrocarbons. The suffix *-yne* is used, and the position of the triple bond is indicated by giving the number of the first alkyne carbon in the chain. Numbering the main chain begins at the end nearer the triple bond so that the triple bond receives as low a number as possible.



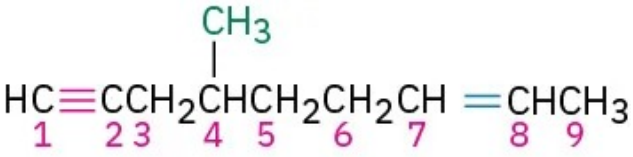
Begin numbering at the end nearer the triple bond.

6-Methyl-3-octyne
(New: 6-Methyloct-3-yne)

Compounds with more than one triple bond are called diynes, triynes, and so forth; compounds containing both double and triple bonds are called **enynes** (not ynenes). Numbering of an enyne chain starts from the end nearer the first multiple bond, whether double or triple. When there is a choice in numbering, double bonds receive lower numbers than triple bonds. For example:

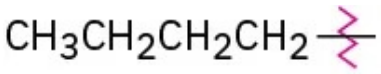


1-Hepten-6-yne
(New: Hept-1-en-6-yne)

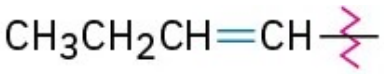


4-Methyl-7-nonen-1-yne
(New: 4-Methylnon-7-en-1-yne)

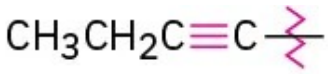
As with alkyl and alkenyl substituents derived from alkanes and alkenes, respectively, alkynyl groups are also possible.



Butyl
(an alkyl group)



1-Butenyl
(a vinylic group)
(New: But-1-enyl)

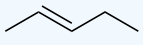


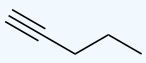
1-Butynyl
(an alkynyl group)
(New: But-1-ynyl)

Exercises

Exercise 3.7.1

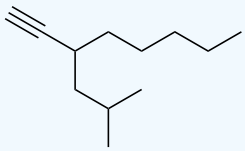
a. The name of the molecule on the left is 2-pentene. What is the name of the molecule in the right: Molecule A?

2-pentene: 

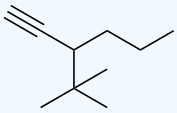
Molecule A: 

b. The name of the molecule on the left is 3-isobutyl-1-octyne. What is the name of the molecule in the right: Molecule B?

3-isobutyl-1-octyne:



Molecule B:



Exercise 3.7.2

Name the following alkynes:

a. **b.** **c.** **d.** **e.**

Answer available at the end of this section.

Exercise 3.7.3

There are seven isomeric alkynes with the formula C_6H_{10}. Draw and name them.

Answer available at the end of this section.

Answers

Exercise 3.7.2

a. 2,5-Dimethyl-3-hexyne
b. 3,3-Dimethyl-1-butyne
c. 3,3-Dimethyl-4-octyne
d. 2,5,5-Trimethyl-3-heptyne
e. 2,4-Octadiene-6-yne

Exercise 3.7.3

1-Hexyne, 2-hexyne, 3-hexyne, 3-methyl-1-pentyne, 4-methyl-1-pentyne, 4-methyl-2-pentyne, 3,3-dimethyl-1-butyne

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3.8: Names of Alkyl Halides

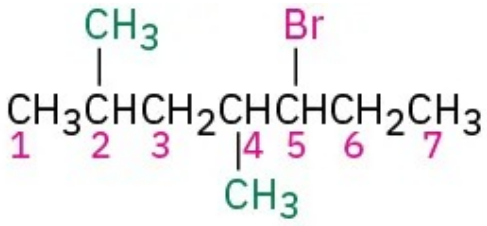
Although commonly called *alkyl halides*, halogen-substituted alkanes are named systematically as *haloalkanes*, treating the halogen as a substituent on a parent alkane chain. There are three steps:

STEP 1

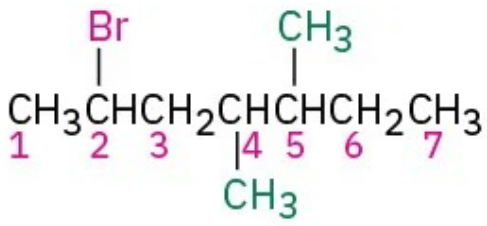
Find the longest chain, and name it as the parent. If a double or triple bond is present, the parent chain must contain it.

STEP 2

Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo. Assign each substituent a number according to its position on the chain.

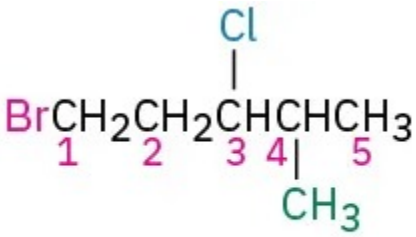


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

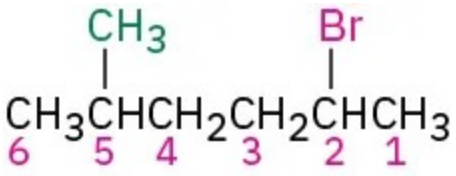
If different halogens are present, number each one and list them in alphabetical order when writing the name.



1-Bromo-3-chloro-4-methylpentane

STEP 3

If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.

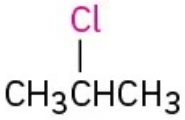


2-Bromo-5-methylhexane
(*Not* 5-bromo-2-methylhexane)

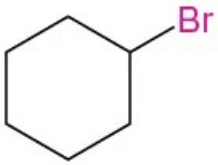
In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.



Iodomethane
(or methyl iodide)



2-Chloropropane
(or isopropyl chloride)

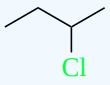


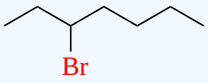
Bromocyclohexane
(or cyclohexyl bromide)

Exercises

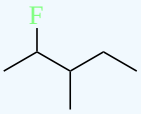
Exercise 3.8.1

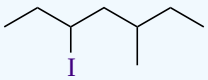
a. The name of the molecule on the left is 2-chlorobutane. What is the name of Molecule A?

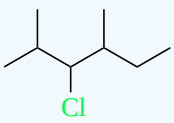
2-chlorobutane: 

olecule A: 

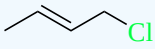
b. The name of the molecule on the left is 2-fluoro-3-methylpentane. What are the names of Molecule B and C?

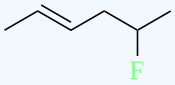
2-fluoro-3-methylpentane: 

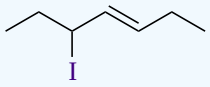
Molecule B: 

Molecule C: 

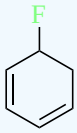
c. The name of the molecule on the left is 1-chloro-2-butene. What is the name of Molecule D?

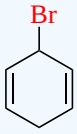
1-chloro-2-butene: 

5-fluoro-2-hexadiene: 

Molecule D: 

d. The name of the molecule on the left is 5-fluoro-1,3-cyclohexadiene. What is the name of the molecule in the right: Molecule E?

5-fluoro-1,3-cyclohexadiene: 

Molecule E: 

Exercise 3.8.2

Give IUPAC names for the following alkyl halides:

a. **b.** **c.**

d. **e.** **f.**

Answer available at the end of this section.

Exercise 3.8.3

Draw structures corresponding to the following IUPAC names:

a.2-Chloro-3,3-dimethylhexane **b.**3,3-Dichloro-2-methylhexane **c.**3-Bromo-3-ethylpentane

d.1,1-Dibromo-4-isopropylcyclohexane **e.**4-*sec*-Butyl-2-chlorononane **f.**1,1-Dibromo-4-*tert*-butylcyclohexane

Answer available at the end of this section.

Answers

Exercise 3.8.2

a.1-Iodobutane **b.**1-Chloro-3-methylbutane **c.**1,5-Dibromo-2,2-dimethylpentane

d.1,3-Dichloro-3-methylbutane **e.**1-Chloro-3-ethyl-4-iodopentane **f.**2-Bromo-5-chlorohexane

Exercise 3.8.3

a. **b.** **c.**

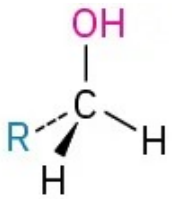
d. **e.** **f.**

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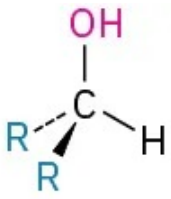
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3.9: Naming Alcohols

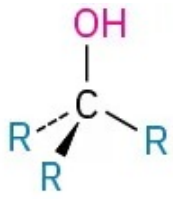
Alcohols are classified as primary (1°), secondary (2°), or tertiary (3°), depending on the number of organic groups bonded to the hydroxyl-bearing carbon.



A primary (1°) alcohol



A secondary (2°) alcohol



A tertiary (3°) alcohol

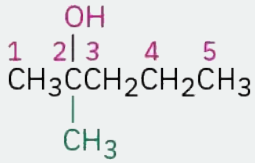
Simple alcohols are named in the IUPAC system as derivatives of the parent alkane, using the suffix *-ol*.

Alcohol Nomenclature

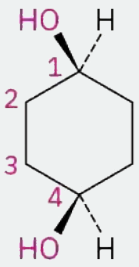
RULE 1: Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the *-e* ending of the corresponding alkane with *-ol*. The *-e* is deleted to prevent the occurrence of two adjacent vowels: propanol rather than propaneol, for example.

RULE 2: Number the alkane chain beginning at the end nearer the hydroxyl group.

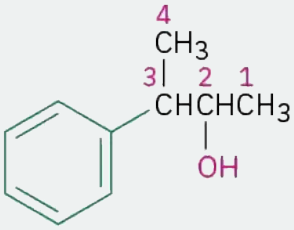
RULE 3: Number the substituents according to their position on the chain, and write the name, listing the substituents in alphabetical order and identifying the position to which the –OH is bonded. Note that in naming *cis*-1,4-cyclohexanediol, the final *-e* of cyclohexane is not deleted because the next letter, *d,* is not a vowel; that is, cyclohexanediol rather than cyclohexandiol. Also, as with alkenes (Section 7.3), newer IUPAC naming recommendations place the locant immediately before the suffix rather than before the parent.



2-Methyl-2-pentanol
(New: 2-Methylpentan-2-ol)

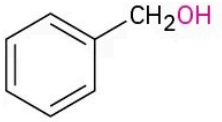


***cis*-1,4-Cyclohexanediol**
(New: *cis*-Cyclohexane-1,4-diol)

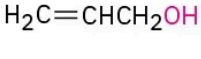


3-Phenyl-2-butanol
(New: 3-Phenylbutan-2-ol)

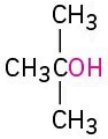
Some simple and widely occurring alcohols have common names that are accepted by IUPAC. For example:



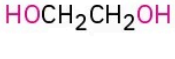
Benzyl alcohol
(phenylmethanol)



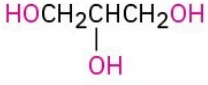
Allyl alcohol
(2-propen-1-ol)



***tert*-Butyl alcohol**
(2-methyl-2-propanol)



Ethylene glycol
(1,2-ethanediol)

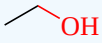


Glycerol
(1,2,3-propanetriol)

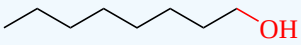
Exercises

Exercise 3.9.1

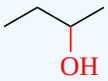
a. The name of the molecule on the left is ethanol. What are the names of the molecules A and B?

Ethanol: 

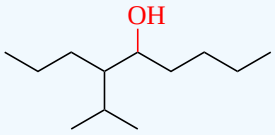
Molecule A:



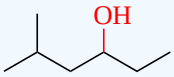
Molecule B:



b. The name of the molecule on the left is 6-isopropyl-5-nonanol. What is the name of Molecule C?

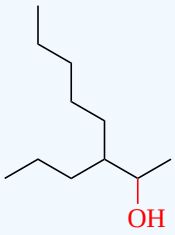


6-isopropyl-5-nonanol:

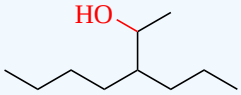


Molecule C:

c. The name of the molecule on the left is 3-propyl-2-octanol. What is the name of Molecule D?

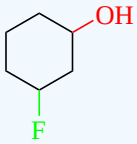


3-propyl-2-octanol:

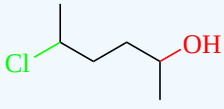


Molecule D:

d. The name of the molecule on the left is 3-fluorocyclohexanol. What is the name of Molecule E?

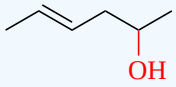


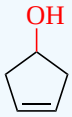
3-fluorocyclohexanol:



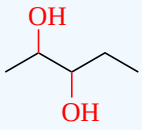
Molecule E:

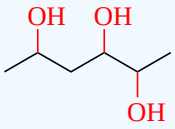
e. The name of the molecule on the left is 4-hexen-2-ol. What is the name of Molecule F?

4-hexen-2-ol: 

Molecule F: 

f. The name of the molecule on the left is 2,3-pentanediol. What is the name of Molecule G?

2,3-pentanediol: 

Molecule G: 

Exercise 3.9.2

Give IUPAC names for the following compounds:

a.  **b.**  **c.**  **d.** 

Answer available at the end of this section.

Exercise 3.9.3

Draw structures corresponding to the following IUPAC names:

a. 2-Ethyl-2-buten-1-ol
b. 3-Cyclohexen-1-ol
c. 3-Chlorocycloheptanol
d. 1,4-Pentanediol

Answer available at the end of this section.

Answers

Exercise 3.9.2

a. 5-Methyl-2,4-hexanediol
b. 4,4-Dimethylcyclohexanol
c. *trans*-2-Bromocyclopentanol
d. 2-Cyclopenten-1-ol

Exercise 3.9.3

a.  **b.**  **c.**  **d.** 

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- 1.3: Alkyl Substituents by Rebekah O'Donnell is licensed CC BY 4.0.

3.10: Chemistry Matters—Gasoline

British Foreign Minister Ernest Bevin once said that “The Kingdom of Heaven runs on righteousness, but the Kingdom of Earth runs on alkanes.” (Actually, he said “runs on oil” not “runs on alkanes,” but they’re essentially the same.) By far, the major sources of alkanes are the world’s natural gas and petroleum deposits. Laid down eons ago, these deposits are thought to be derived primarily from the decomposition of tiny single-celled marine organisms called foraminifera. Natural gas consists chiefly of methane but also contains ethane, propane, and butane. Petroleum is a complex mixture of hydrocarbons that must be separated into fractions and then further refined before it can be used.

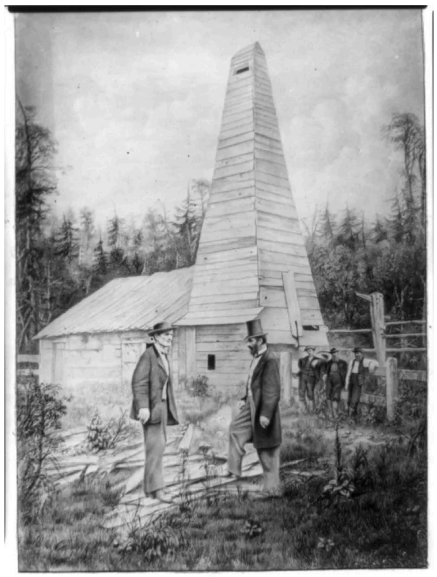
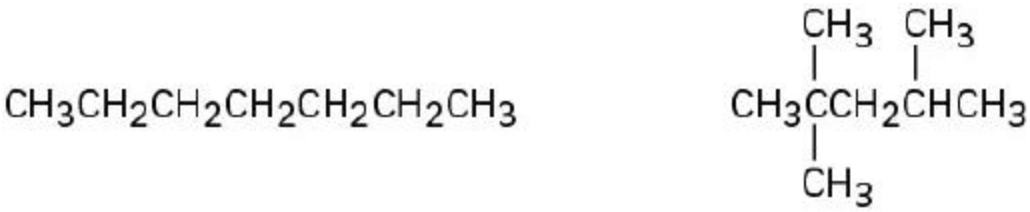


Figure 3.10.1: Gasoline is a finite resource. It won’t be around forever. (credit: “The first oil well” by Unknown/Library of Congress)

The petroleum era began in August 1859, when the world’s first oil well was drilled by Edwin Drake near Titusville, Pennsylvania. The petroleum was distilled into fractions according to boiling point, but it was high-boiling kerosene, or lamp oil, rather than gasoline that was primarily sought. Literacy was becoming widespread at the time, and people wanted better light for reading than was available from candles. Gasoline was too volatile for use in lamps and was initially considered a waste by-product. The world has changed greatly since those early days, however, and it is now gasoline rather than lamp oil that is prized.

Petroleum refining begins by fractional distillation of crude oil into three principal cuts according to boiling point (bp): straight-run gasoline (bp 30–200 °C), kerosene (bp 175–300 °C), and heating oil, or diesel fuel (bp 275–400 °C). Further distillation under reduced pressure then yields lubricating oils and waxes and leaves a tarry residue of asphalt. The distillation of crude oil is only the first step in gasoline production, however. Straight-run gasoline turns out to be a poor fuel in automobiles because of engine knock, an uncontrolled combustion that can occur in a hot engine causing potentially serious damage.

The *octane number* of a fuel is the measure by which its antiknock properties are judged. It was recognized long ago that straight-chain hydrocarbons are far more prone to inducing engine knock than highly branched compounds. Heptane, a particularly bad fuel, is assigned a base value of 0 octane number, and 2,2,4-trimethylpentane, commonly known as isooctane, has a rating of 100.



Heptane
(octane number = 0)

2,2,4-Trimethylpentane
(octane number = 100)

Because straight-run gasoline burns so poorly in engines, petroleum chemists have devised numerous methods for producing higher-quality fuels. One of these methods, *catalytic cracking*, involves taking the high-boiling kerosene cut (C_{11}–C_{14}) and "cracking" it into smaller branched molecules suitable for use in gasoline. Another process, called *reforming*, is used to convert C_6–C_8 alkanes to aromatic compounds such as benzene and toluene, which have substantially higher octane numbers than alkanes. The final product that goes in your tank has an approximate composition of 15% C_4–C_8 straight-chain alkanes, 25% to 40% C_4–C_{10} branched-chain alkanes, 10% cyclic alkanes, 10% straight-chain and cyclic alkenes, and 25% arenes (aromatics).

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3.A: Functional Groups and Nomenclature (Summary)

Concepts & Vocabulary

3.1: Functional Groups

- **Functional groups** are atoms or small groups of atoms (two to four) that exhibit a characteristic reactivity.
- Functional groups have characteristic names that often carry over into the naming of compounds.
- The most common organic functional groups that will be encountered is this course are: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, nitro compounds, sulfides and sulfoxides.

3.2: Alkanes and Alkane Isomers

- Hydrocarbons are a common class of organic molecules that contain only carbon and hydrogen atoms.
- Alkanes are one type of hydrocarbon that contains only carbon-carbon and carbon hydrogen single bonds.
- Straight chain and branched alkanes have the generic formula C_nH_{2n+2}, where *n* is equal to the number of carbons. Cycloalkanes have the generic formula C_nH_{2n}.
- Structural isomers are molecules with the same molecular formula, but different structures.

3.3: Alkyl Groups

- Alkyl groups are small hydrocarbon chains attached to the parent alkane chain. The names of alkyl groups use the same prefixes to indicate the number of carbons (meth-, eth-, etc.), but use "-yl" as the ending, instead of "-ane".

3.4: Naming Alkanes

- The IUPAC System of nomenclature provides a set of rules for assigning every molecule a unique name.

3.5: Naming Cycloalkanes

- Cycloalkanes are saturated hydrocarbons that have the generic formula $\mathbf{C_nH_{2n}}$, where **n** is the number of carbons in the ring.
- The IUPAC rules for naming cycloalkanes are very similar to the rules used for naming alkanes.

3.6 Naming Alkenes

- Follow IUPAC rules in naming alkenes.

3.7 Naming Alkynes

- Follow IUPAC rules in naming alkynes.

3.8 Names and Properties of Alkyl Halides

- Follow IUPAC rules in naming alkyl Halides.
- Alkyl halides are categorized by the number of bonds to other alkyl groups (**primary**, **secondary**, and **tertiary**).

3.9 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary, or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

Skills to Master

- Skill 3.1 Identify the following functional groups that are present in a given organic molecule: alkanes, alkenes, alkynes, arenes, (alkyl and aryl) halides, alcohols, ethers, aldehydes, ketones, esters, carboxylic acids, acid chlorides, amides, amines, nitriles, and nitro compounds.
- Skill 3.2 Name and draw structures of straight chain alkanes up to ten carbons in length.
- Skill 3.3 Name and draw structures for all the structural isomers of a given molecular formula.
- Skill 3.4 Identify methyl, primary, secondary, tertiary, and quaternary carbons in organic structures.
- Skill 3.5 Provide the IUPAC name of any given alkane or cycloalkane structure.
- Skill 3.6 Draw the structure of an alkane or cycloalkane given its IUPAC name.
- Skill 3.7 Be able to name and draw alkenes and alkynes
- Skill 3.8 Be able to name and draw alkyl halides.
- Skill 3.9 Be able to name and draw alcohols.

Memorization Tasks (MT)

- MT 3.1 Memorize the name and structure of each of the common functional groups listed in Skill 3.1.
- MT 3.2 Memorize the names and be able to draw the first ten straight chain alkanes.
- MT 3.3 Memorize the structures and common names of the alkyl substitutent groups - isopropyl, *sec*-butyl, isobutyl,, and *tert*-butyl.

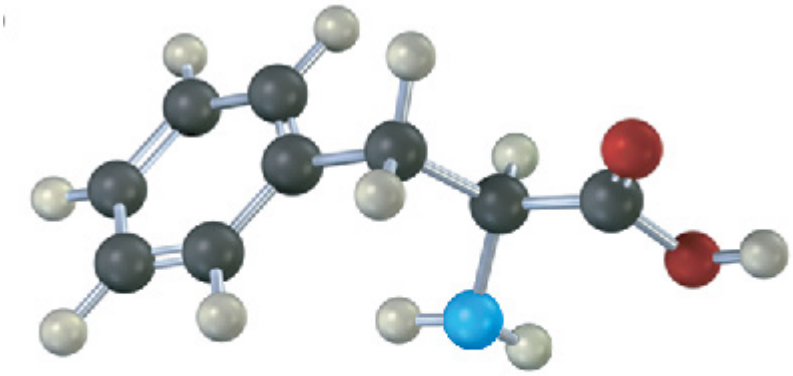
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3.B: Additional Problems

Visualizing Chemistry

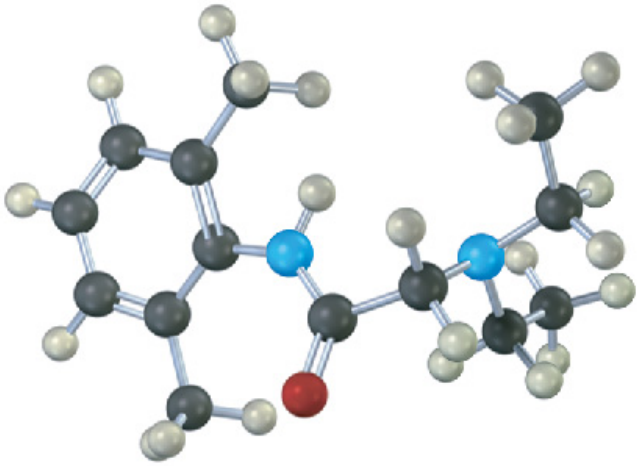
PROBLEM 3-19 Identify the functional groups in the following substances, and convert each drawing into a molecular formula (red = O, blue = N).



Phenylalanine

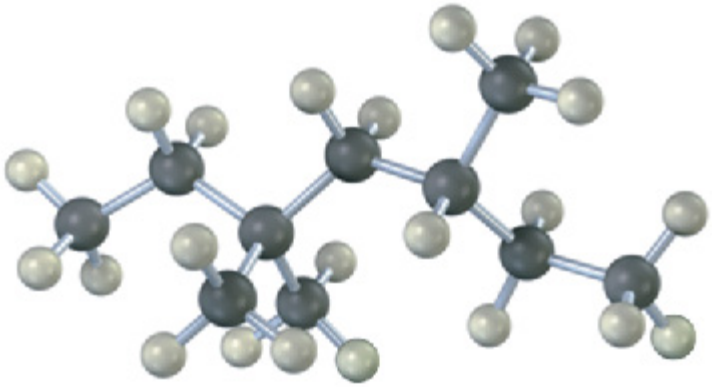
(a)

(b)

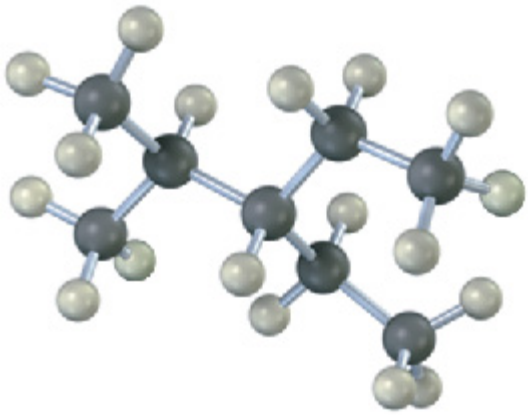


Lidocaine

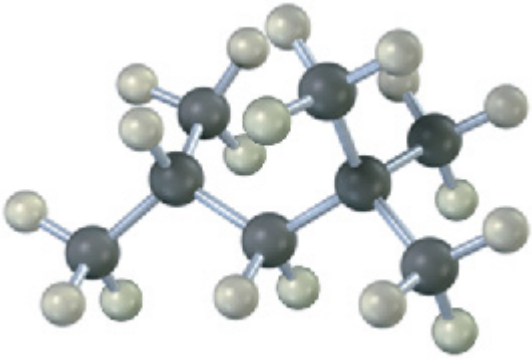
PROBLEM 3-20 Give IUPAC names for the following alkanes, and convert each drawing into a skeletal structure.



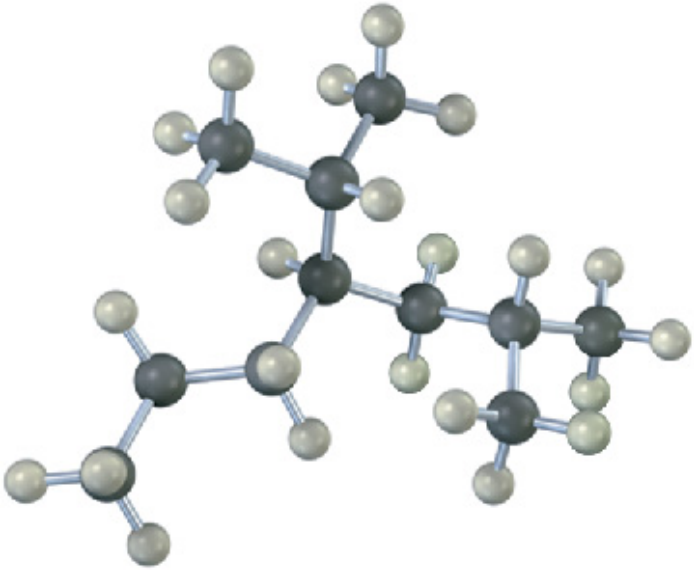
(a)



(b)

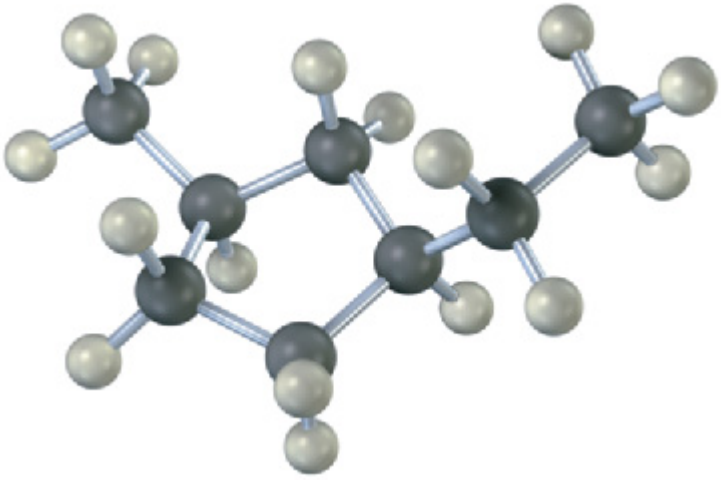


(c)



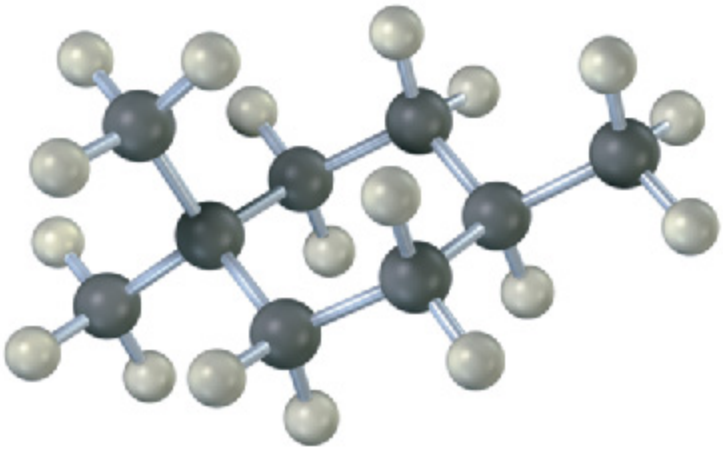
(d)

PROBLEM 3-21 Name the following cycloalkanes:



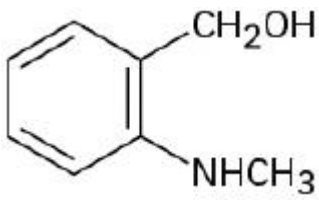
(a)

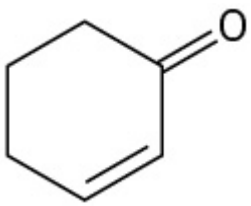
(b)

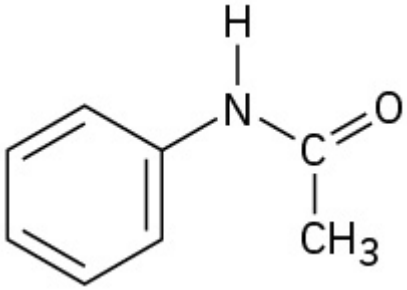


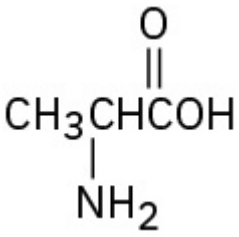
Functional Groups

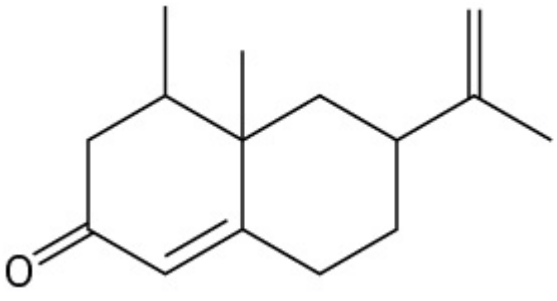
PROBLEM 3-22 Locate and identify the functional groups in the following molecules.

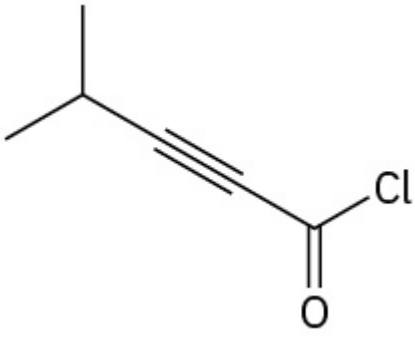
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM 3-23 Propose structures that meet the following descriptions:

(a) A ketone with five carbons (b) A four-carbon amide (c) A five-carbon ester
(d) An aromatic aldehyde (e) A keto ester (f)An amino alcohol

PROBLEM 3-24 Propose structures for the following:

(a) A ketone, C_4H_8O (b) A nitrile, C_5H_9N (c) A dialdehyde, $C_4H_6O_2$ (d) A bromoalkene, $C_6H_{11}Br$
(e) An alkane, C_6H_{14} (f) *cyclic* saturated hydrocarbon, C_6H_{12} (g) A diene (dialkene), C_5H_8 (h) A keto alkene, C_5H_8O

PROBLEM 3-25 Predict the hybridization of the carbon atom in each of the following functional groups:

(a) Ketone (b) Nitrile (c) Carboxylic acid

PROBLEM 3-26 Draw the structures of the following molecules:

(a) Biacetyl, $C_4H_6O_2$, a substance with the aroma of butter; it contains no rings or carbon–carbon multiple bonds.
(b) Ethylenimine, C_2H_5N, a substance used in the synthesis of melamine polymers; it contains no multiple bonds.
(c) Glycerol, $C_3H_8O_3$, a substance isolated from fat and used in cosmetics; it has an –OH group on each carbon.

Isomers

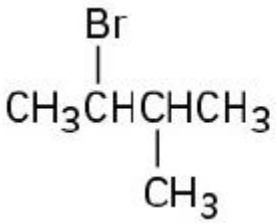
PROBLEM 3-27 Draw structures that meet the following descriptions (there are many possibilities):

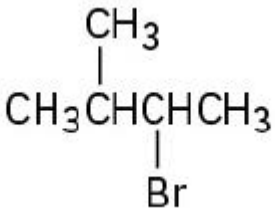
(a) Three isomers with the formula C_8H_{18}
(b) Two isomers with the formula $C_4H_8O_2$

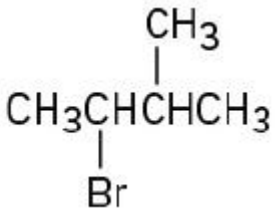
PROBLEM 3-28 Draw structures of the nine isomers of C_7H_{16}.

PROBLEM 3-29 In each of the following sets, which structures represent the same compound and which represent different compounds?

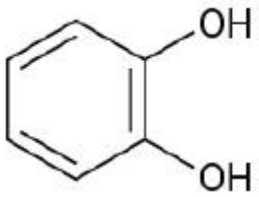
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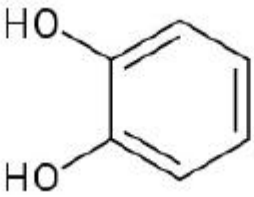


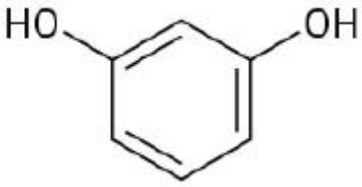




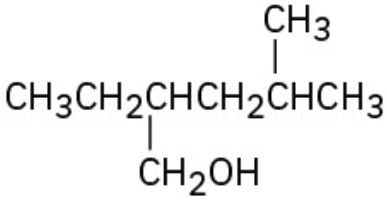
(b)

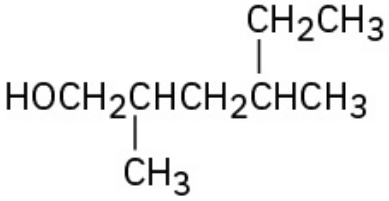


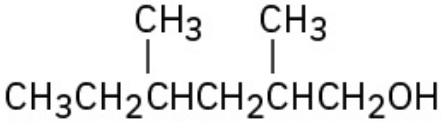




(c)







PROBLEM 3-30 Seven constitutional isomers have the formula $C_4H_{10}O$. Draw as many as you can.

PROBLEM 3-31 Draw as many compounds as you can that fit the following descriptions:

(a) Alcohols with formula $C_4H_{10}O$ (b) Amines with formula $C_5H_{13}N$
(c) Ketones with formula $C_5H_{10}O$ (d) Aldehydes with formula $C_5H_{10}O$
(e) Esters with formula $C_4H_8O_2$ (f) Ethers with formula $C_4H_{10}O$

PROBLEM 3-32 Draw compounds that contain the following:

(a) A primary alcohol (b) A tertiary nitrile (c) A secondary thiol
(d) Both primary and secondary alcohols (e) An isopropyl group (f) A quaternary carbon

Naming Compounds

PROBLEM 3-33 Draw and name all monobromo derivatives of pentane, $C_5H_{11}Br$.

PROBLEM 3-34 Draw and name all monochloro derivatives of 2,5-dimethylhexane, $C_8H_{17}Cl$.

PROBLEM 3-35 Draw structures for the following:

(a) 2-Methylheptane (b) 4-Ethyl-2,2-dimethylhexane (c) 4-Ethyl-3,4-dimethyloctane
(d) 2,4,4-Trimethylheptane (e) 3,3-Diethyl-2,5-dimethylnonane (f) 4-Isopropyl-3-methylheptane

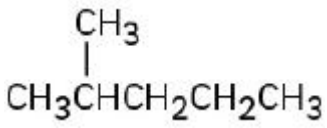
PROBLEM 3-36 Draw a compound that:

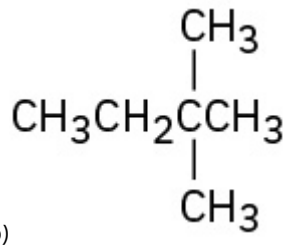
(a)Has only primary and tertiary carbons
(b) Has no secondary or tertiary carbons
(c) Has no secondary or tertiary carbons

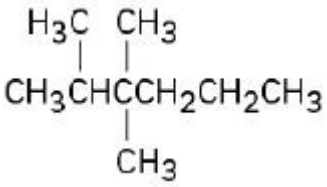
PROBLEM 3-37 Draw a compound that:

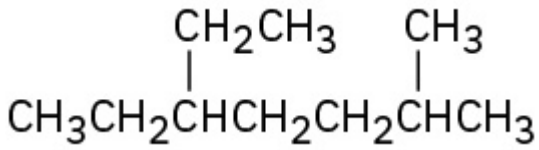
(a) Has nine primary hydrogens (b) Has only primary hydrogens

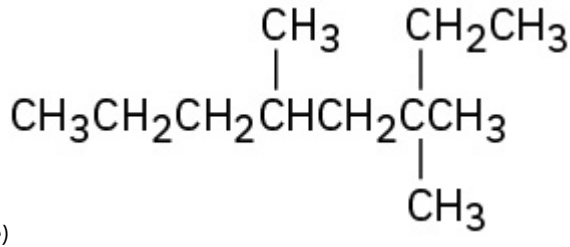
PROBLEM 3-38 Give IUPAC names for the following compounds:

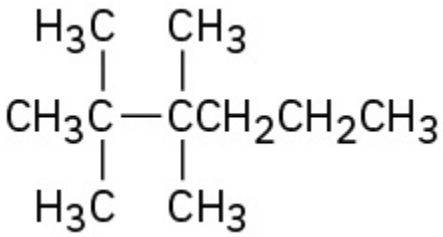
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM 3-39 Name the five isomers of C_6H_{14}.

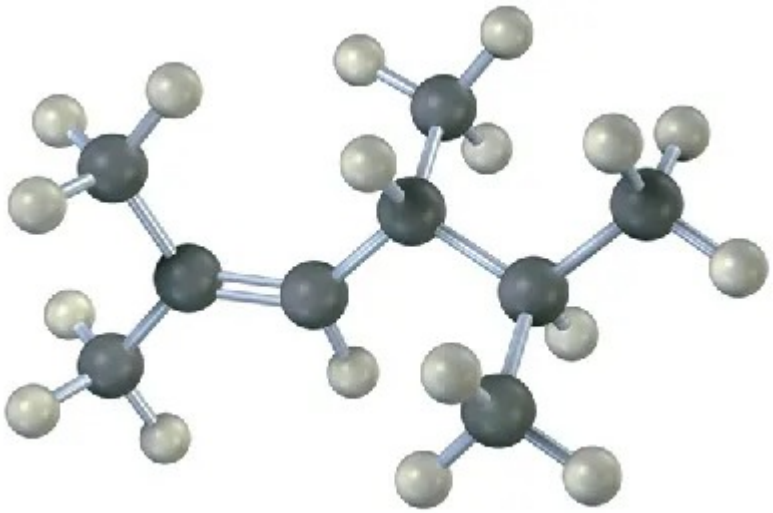
PROBLEM 3-40 Explain why each of the following names is incorrect:

(a) 2,2-Dimethyl-6-ethylheptane (b) 4-Ethyl-5,5-dimethylpentane
(c) 3-Ethyl-4,4-dimethylhexane (d) 5,5,6-Trimethyloctane (e) 2-Isopropyl-4-methylheptane

PROBLEM 3-41 Propose structures and give IUPAC names for the following:

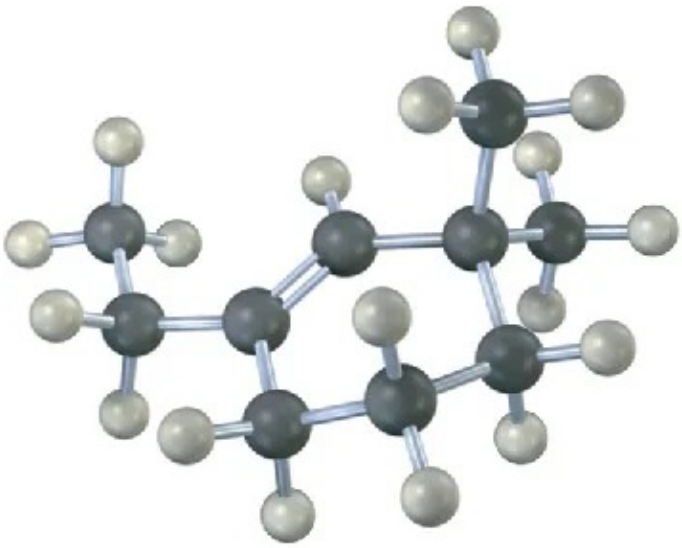
(a) A diethyldimethylhexane (b) A (3-methylbutyl)-substituted alkane

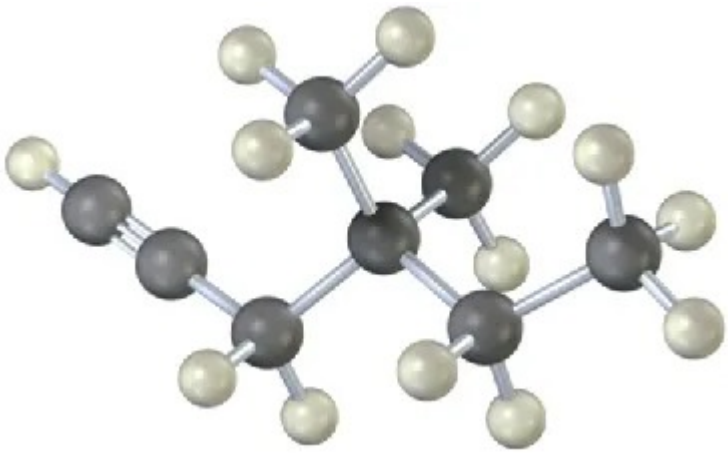
PROBLEM 3-42 Name the following alkenes, and convert each drawing into a skeletal structure:



(a)

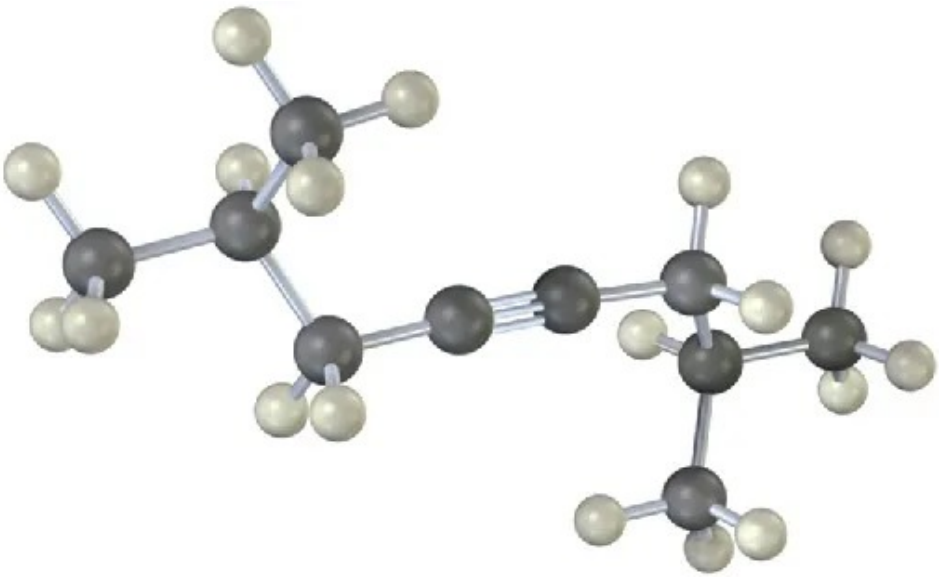
(b)

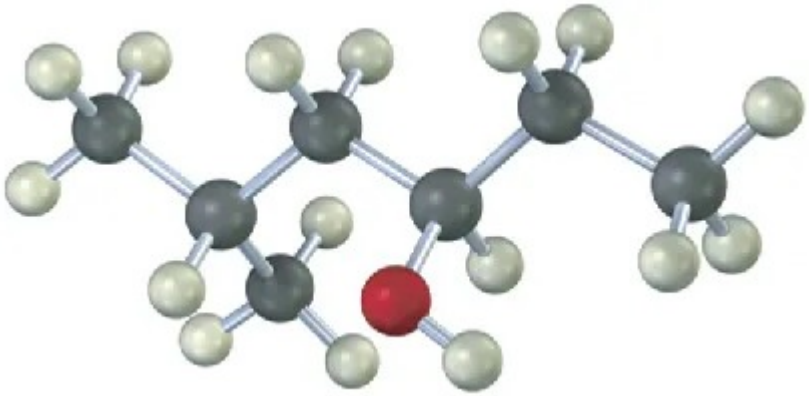




(c)

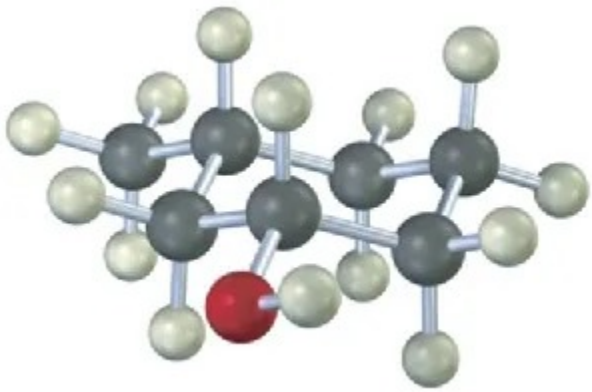
(d)



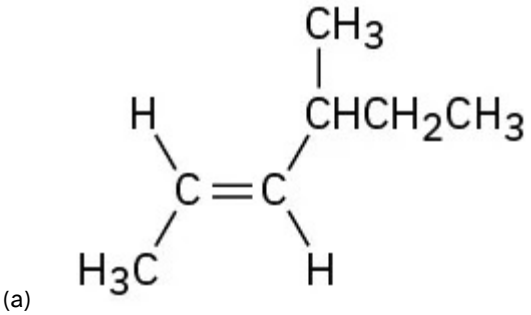


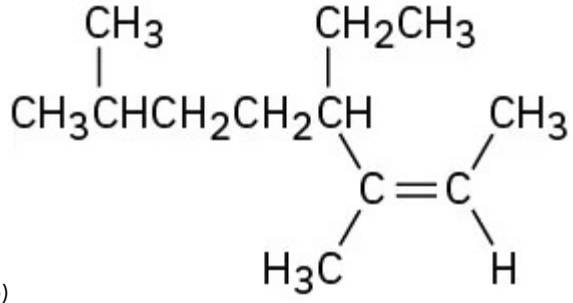
(e)

(f)

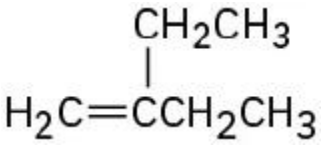


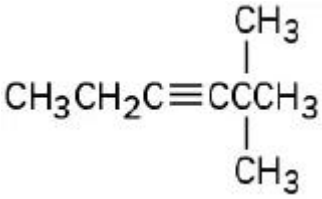
PROBLEM 3-43 Name the following alkenes and alkynes:

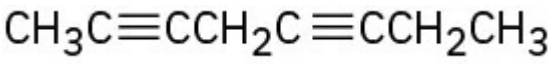

(a)

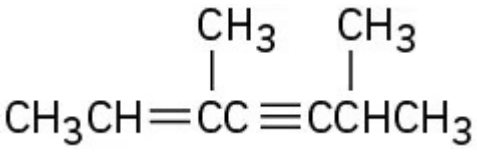

(b)

(c)

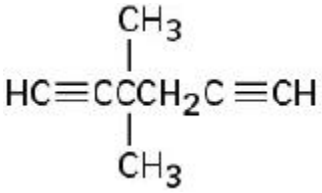

(d)

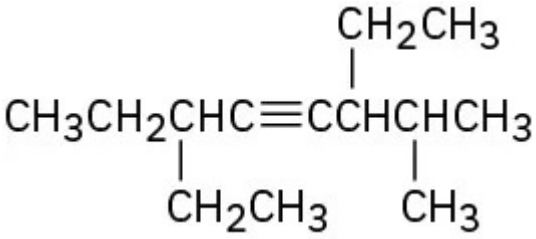


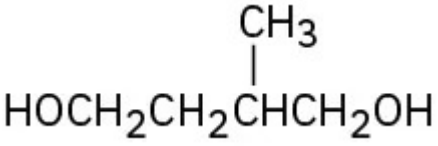

(e)

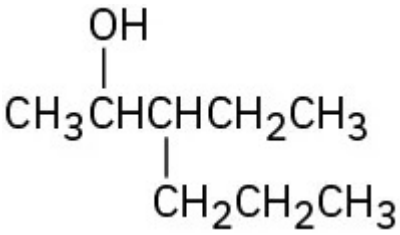

(f)

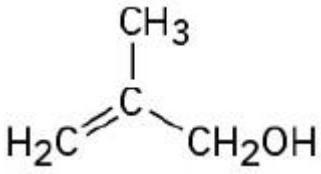
(g)


(h)




(i)


(j)

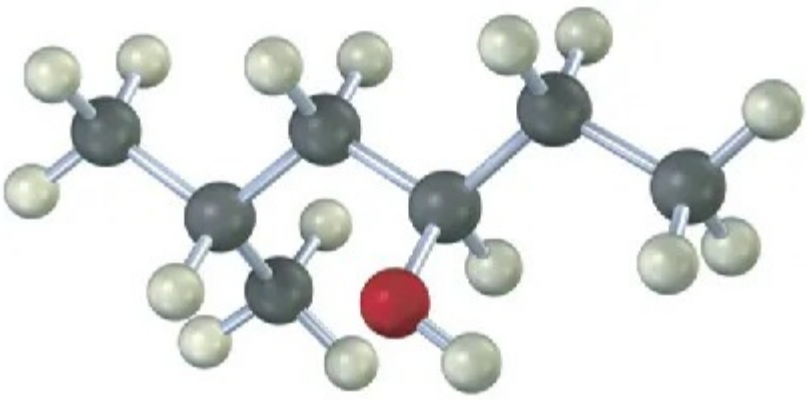

(k)

PROBLEM 3-44 Draw structures corresponding to the following systematic names:

(a) 2,4-Dimethyl-1,4-hexadiene **(b)** 4-Methyl-1,2-pentadiene **(c)** 3-Butyl-2-heptene **(d)** 2,2,5,5-Tetramethyl-3-hexyne

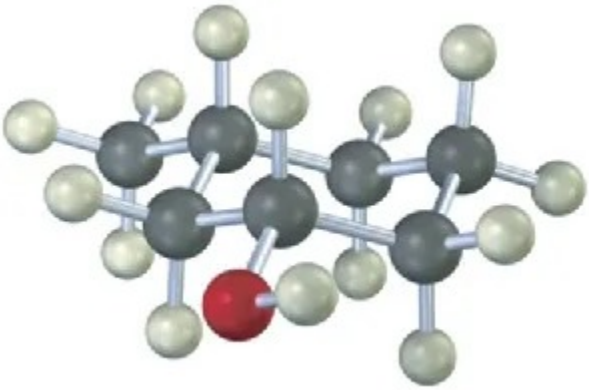
(e) 3,4-Dimethylcyclodecyne **(f)** 3,5-Heptadien-1-yne **(g)** 3-Chloro-4,4-dimethyl-1-nonen-6-yne

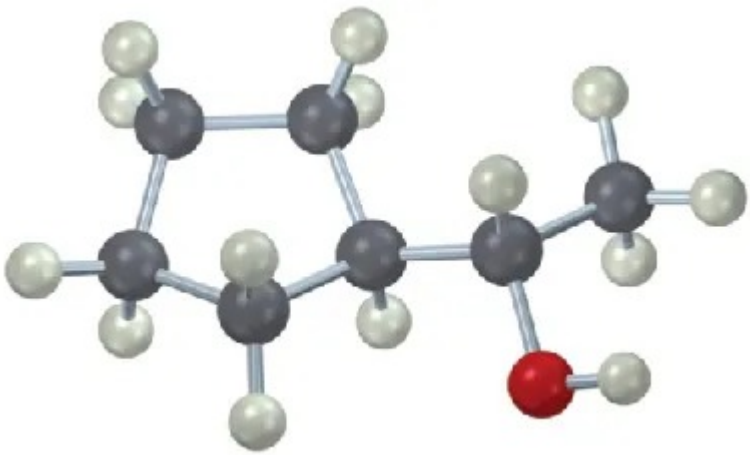
PROBLEM 12-20 Give IUPAC names for the following alcohols:



(a)

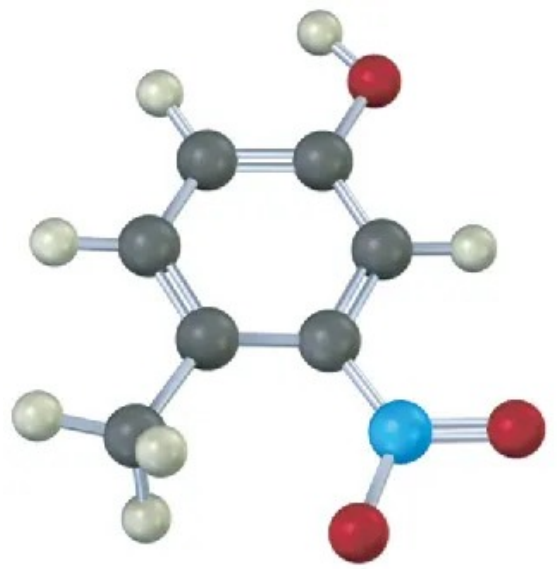
(b)





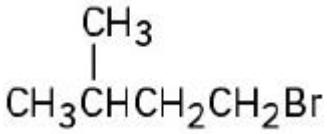
(c)

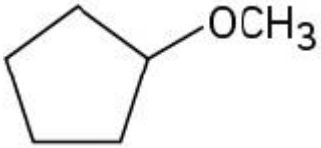
(d)

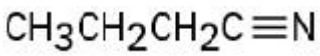


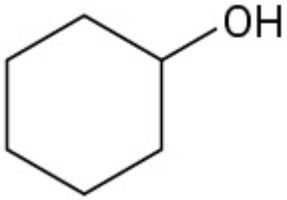
General Problems

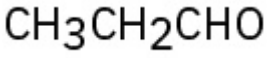
PROBLEM 3-48 For each of the following compounds, draw an isomer that has the same functional groups.

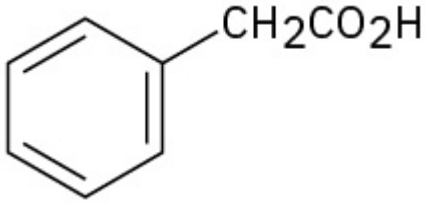
(a) 

(b) 

(c) 

(d) 

(e) 

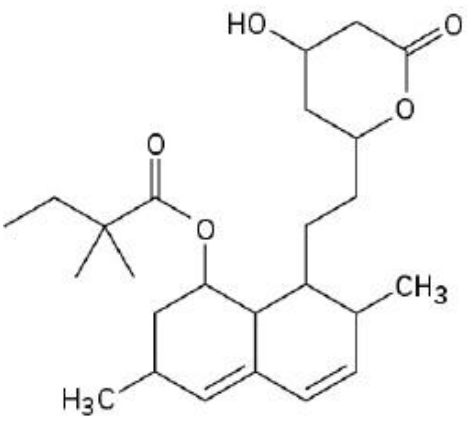
(f) 

PROBLEM 3-49 Malic acid, $C_4H_6O_5$, has been isolated from apples. Because this compound reacts with 2 molar equivalents of base, it is a dicarboxylic acid.

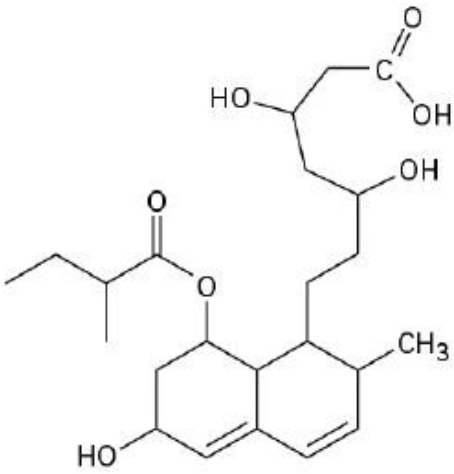
(a) Draw at least five possible structures.
(b) If malic acid is a secondary alcohol, what is its structure?

PROBLEM 3-50 Formaldehyde, $H_2C{=}O$, is known to all biologists because of its usefulness as a tissue preservative. When pure, formaldehyde trimerizes to give trioxane, $C_3H_6O_3$, which, surprisingly enough, has no carbonyl groups. Only one monobromo derivative ($C_3H_5BrO_3$) of trioxane is possible. Propose a structure for trioxane.

PROBLEM 3-53 The cholesterol-lowering agents called *statins*, such as simvastatin (Zocor) and pravastatin (Pravachol), are among the most widely prescribed drugs in the world, with annual sales estimated at approximately $25 billion. Identify the functional groups in both, and tell how the two substances differ.



Simvastatin (Zocor)



Pravastatin (Pravachol)

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4: ORGANIC COMPOUNDS - CONFORMATION OF ALKANES AND CYCLOALKANES

Learning Objectives

After you have completed Chapter 4, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw a number of possible conformations of some simple alkanes and alkane-like compounds, and represent the energies of such conformations on energy versus rotation diagrams.
3. draw the *cis-trans* isomers of some simple disubstituted cycloalkanes.
4. define, and use in context, the key terms introduced in this chapter.

This chapter deals with the concept of stereochemistry and conformational analysis in linear and cyclic compounds, a description of *cis-trans* isomerism in cycloalkanes, the causes of various ring strains and their effects on the overall energy level of a cycloalkane are discussed.

4.0: Why This Chapter?

4.1: Conformations of Ethane

4.2: Conformations of Other Alkanes

4.3: Cis-Trans Isomerism in Cycloalkanes

4.4: Stability of Cycloalkanes - Ring Strain

4.5: Conformations of Cycloalkanes

4.6: Conformations of Cyclohexane

4.7: Axial and Equatorial Bonds in Cyclohexane

4.8: Conformations of Monosubstituted Cyclohexanes

4.9: Conformations of Disubstituted Cyclohexanes

4.10: Conformations of Polycyclic Molecules

4.11: Chemistry Matters—Molecular Mechanics

4.A: Conformation of Alkanes and Cycloalkanes (Summary)

4.B: Additional Problems

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- 4: Organic Compounds - Cycloalkanes and their Stereochemistry by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

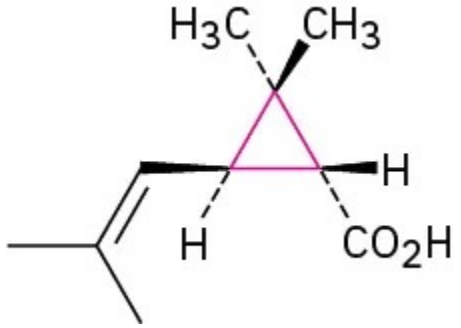
4.0: Why This Chapter?

We'll see numerous instances in future chapters where the chemistry of a given functional group is affected by being in a ring rather than an open chain. Because cyclic molecules are encountered in most pharmaceuticals and in all classes of biomolecules, including proteins, lipids, carbohydrates, and nucleic acids, it's important to understand the behavior of cyclic structures.



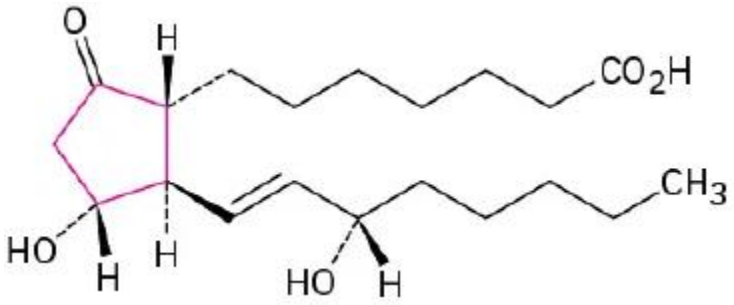
Figure 4.0.1: The musk gland of the male Himalayan musk deer secretes a substance once used in perfumery that contains cycloalkanes of 14 to 18 carbons. (credit: modification of work "Siberian musk deer in the tiaga" by ErikAdamsson/Wikimedia Commons, CC0 1.0)

Although we've only discussed open-chain compounds up to now, most organic compounds contain *rings* of carbon atoms. Chrysanthemic acid, for instance, whose esters occur naturally as the active insecticidal constituents of chrysanthemum flowers, contains a three-membered (cyclopropane) ring.



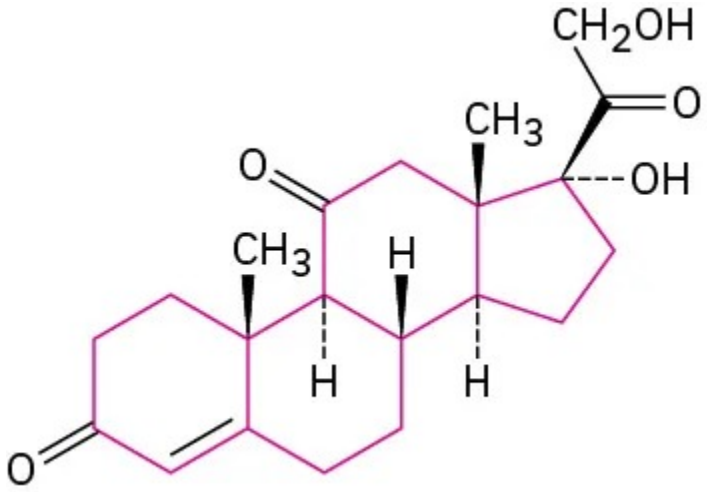
Chrysanthemic acid

Prostaglandins, potent hormones that control an extraordinary variety of physiological functions in humans, contain a five-membered (cyclopentane) ring.



Prostaglandin E_1

Steroids, such as cortisone, contain four rings joined together—three six-membered (cyclohexane) and one five-membered. We'll discuss steroids and their properties in more detail in **Sections 27.6** and **27.7**.



Cortisone

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4.1: Conformations of Ethane

Up until now, we've viewed molecules primarily in a two-dimensional way and have given little thought to any consequences that might arise from the spatial arrangement of atoms in molecules. Now it's time to add a third dimension to our study. Stereochemistry is the branch of chemistry concerned with the three-dimensional aspects of molecules. We'll see on many occasions in future chapters that the exact three-dimensional structure of a molecule is often crucial to determining its properties and biological behavior.

We know from Section 1.6 that σ bonds are cylindrically symmetrical. In other words, the intersection of a plane cutting through a carbon–carbon single-bond orbital looks like a circle. Because of this cylindrical symmetry, rotation is possible around carbon–carbon bonds in open-chain molecules. In ethane, for instance, rotation around the C–C bond occurs freely, constantly changing the spatial relationships between the hydrogens on one carbon and those on the other (Figure 4.1.1).

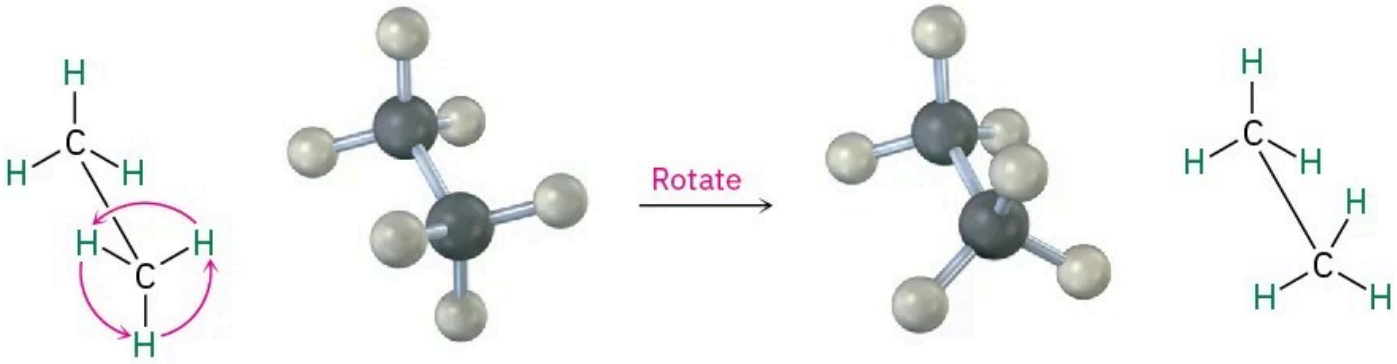


Figure 4.1.1: Rotation occurs around the carbon–carbon single bond in ethane because of σ bond cylindrical symmetry.

The different arrangements of atoms that result from bond rotation are called conformations, and molecules that have different arrangements are called conformational isomers, or conformers. Unlike constitutional isomers, however, different conformers often can't be isolated because they interconvert too rapidly.

Conformational isomers are represented in two ways, as shown in Figure 4.1.2. A sawhorse representation views the carbon–carbon bond from an oblique angle and indicates spatial orientation by showing all C–H bonds. A Newman projection views the carbon–carbon bond directly end-on and represents the two carbon atoms by a circle. Bonds attached to the front carbon are represented by lines to the center of the circle, and bonds attached to the rear carbon are represented by lines to the edge of the circle.

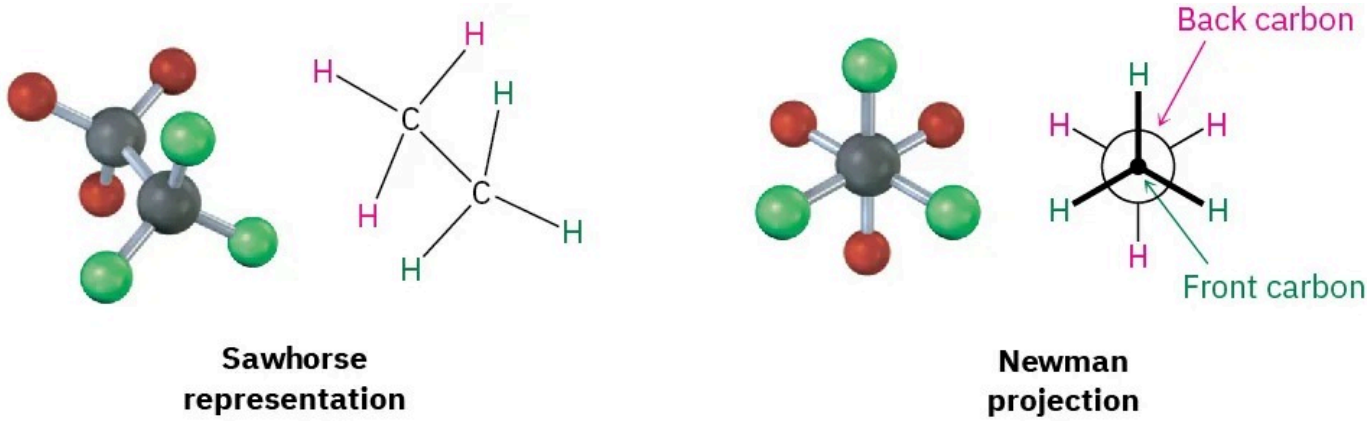
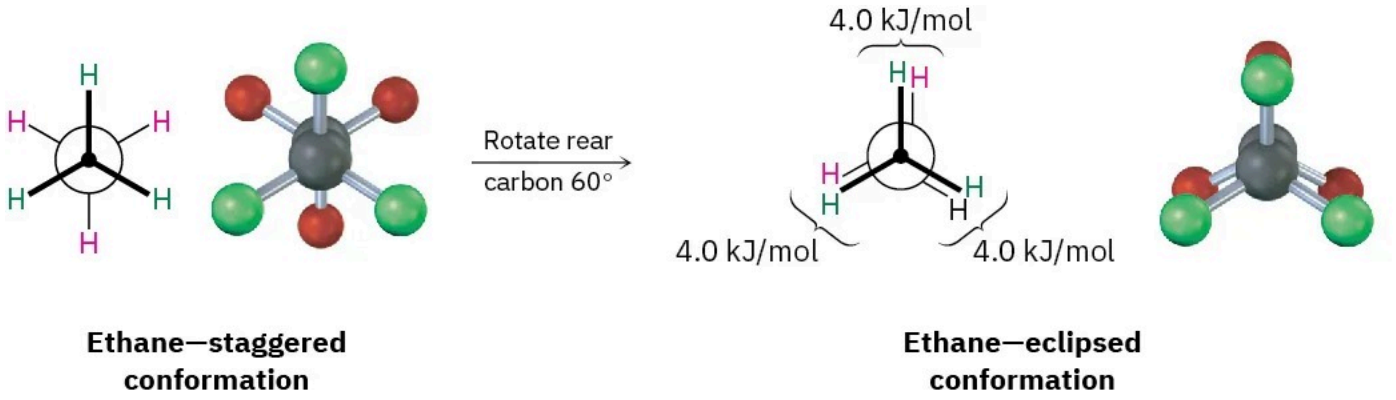


Figure 4.1.2: A sawhorse representation and a Newman projection of ethane. The sawhorse representation views the molecule from an oblique angle, while the Newman projection views the molecule end-on. Note that the molecular model of the Newman projection appears at first to have six atoms attached to a single carbon. Actually, the front carbon, with three attached **green atoms**, is directly in front of the rear carbon, with three attached **red atoms**.

Despite what we've just said, we actually don't observe perfectly free rotation in ethane. Experiments show that there is a small (12 kJ/mol; 2.9 kcal/mol) barrier to rotation and that some conformations are more stable than others. The lowest-energy, most stable conformation is the one in which all six C–H bonds are as far away from one another as possible—*staggered* when viewed end-on in a Newman projection. The highest-energy, least stable conformation is the one in which the six C–H bonds are as close as possible—*eclipsed* in a Newman projection. At any given instant, about 99% of ethane molecules have an approximately staggered conformation and only about 1% are near the eclipsed conformation.



Ethane—staggered conformation **Ethane—eclipsed conformation**

The extra 12 kJ/mol of energy present in the eclipsed conformation of ethane is called torsional strain. Its cause has been the subject of controversy, but the major factor is an interaction between C–H bonding orbitals on one carbon and antibonding orbitals on the adjacent carbon, which stabilizes the staggered conformation relative to the eclipsed one. Because a total strain of 12 kJ/mol arises from three equal hydrogen–hydrogen eclipsing interactions, we can assign a value of approximately 4.0 kJ/mol (1.0 kcal/mol) to each single interaction. The barrier to rotation that results can be represented on a graph of potential energy versus degree of rotation, in which the angle between C–H bonds on the front and back carbons as viewed end-on (the *dihedral angle*) goes full circle from 0 to 360°. Energy minima occur at staggered conformations, and energy maxima occur at eclipsed conformations, as shown in Figure 4.1.3.

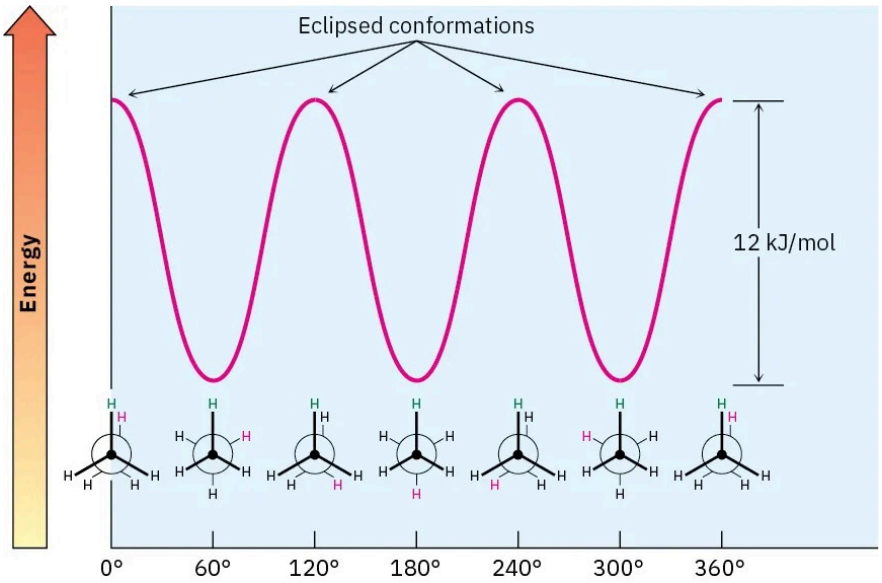


Figure 4.1.3: A graph of potential energy versus bond rotation in ethane. The staggered conformations are 12 kJ/mol lower in energy than the eclipsed conformations.

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4.2: Conformations of Other Alkanes

Propane, the next-higher member in the alkane series, also has a torsional barrier that results in hindered rotation around the carbon–carbon bonds. The barrier is slightly higher in propane than in ethane—a total of 14 kJ/mol (3.4 kcal/mol) versus 12 kJ/mol.

The eclipsed conformation of propane has three interactions—two ethane-type hydrogen–hydrogen interactions and one additional hydrogen–methyl interaction. Since each eclipsing H ⋄ H interaction is the same as that in ethane and thus has an energy "cost" of 4.0 kJ/mol, we can assign a value of 14 – (2 × 4.0) = 6.0 kJ/mol (1.4 kcal/mol) to the eclipsing H ⋄ CH_3 interaction (Figure 4.2.1).

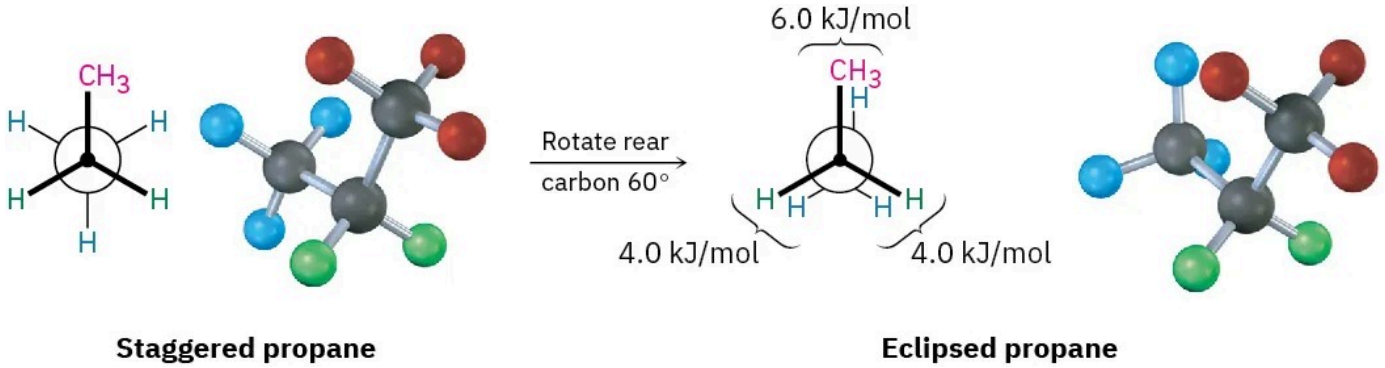
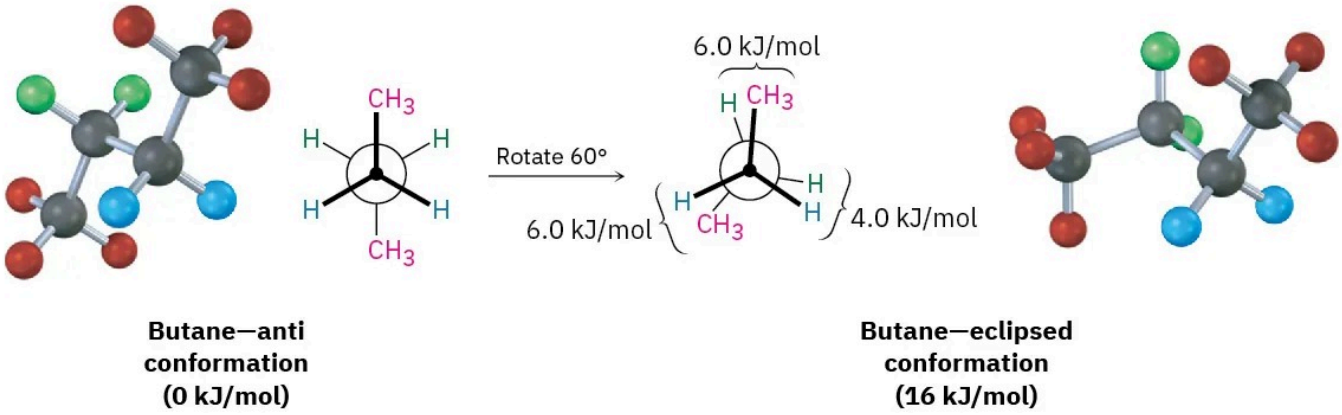
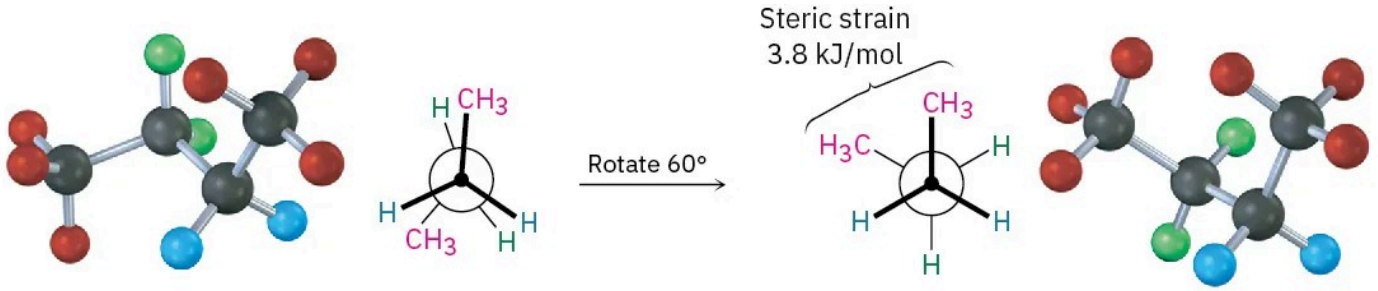


Figure 4.2.1: Newman projections of propane showing staggered and eclipsed conformations. The staggered conformer is lower in energy by 14 kJ/mol.

The conformational situation becomes more complex for larger alkanes because not all staggered conformations have the same energy and not all eclipsed conformations have the same energy. In butane, for instance, the lowest-energy arrangement, called the anti conformation, is the one in which the two methyl groups are as far apart as possible—180° away from each other. As rotation around the C2–C3 bond occurs, an eclipsed conformation is reached where there are two CH_3 ⋄ H interactions and one H ⋄ H interaction. Using the energy values derived previously from ethane and propane, this eclipsed conformation is more strained than the anti conformation by 2 × 6.0 kJ/mol + 4.0 kJ/mol (two CH_3 ⋄ H interactions plus one H ⋄ H interaction), for a total of 16 kJ/mol (3.8 kcal/mol).



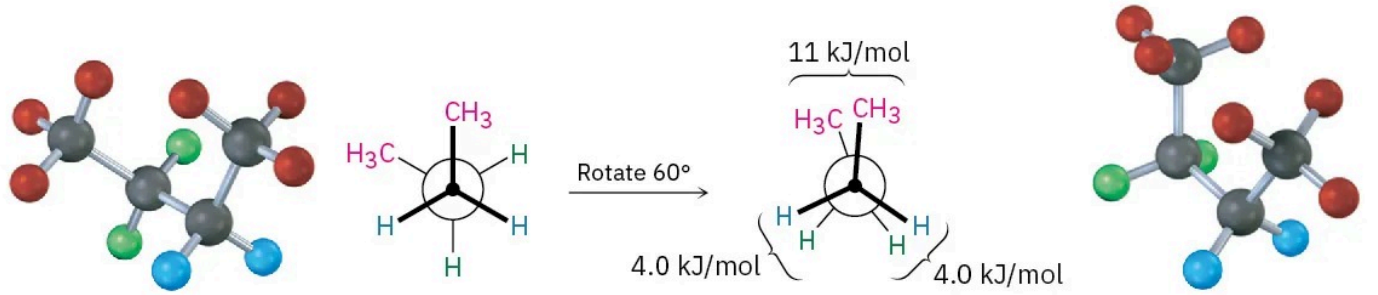
As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are 60° apart. Called the gauche conformation, it lies 3.8 kJ/mol (0.9 kcal/mol) higher in energy than the anti conformation even though it has no eclipsing interactions. This energy difference occurs because the hydrogen atoms of the methyl groups are near one another in the gauche conformation, resulting in what is called **steric strain**. Steric strain is the repulsive interaction that occurs when atoms are forced closer together than their atomic radii allow. It's the result of trying to force two atoms to occupy the same space.



Butane—eclipsed conformation (16 kJ/mol)

Butane—gauche conformation (3.8 kJ/mol)

As the dihedral angle between the methyl groups approaches zero, an energy maximum is reached at a second eclipsed conformation. Because the methyl groups are forced even closer together than in the gauche conformation, both torsional strain and steric strain are present. A total strain energy of 19 kJ/mol (4.5 kcal/mol) has been estimated for this conformation, making it possible to calculate a value of 11 kJ/mol (2.6 kcal/mol) for the CH_3 ⦰ CH_3 eclipsing interaction: total strain of 19 kJ/mol minus the strain of two H ⦰ H eclipsing interactions (2 × 4.0 kcal/mol) equals 11 kJ/mol.



Butane—gauche conformation (3.8 kJ/mol)

Butane—eclipsed conformation (19 kJ/mol)

After 0°, the rotation becomes a mirror image of what we've already seen: another gauche conformation is reached, another eclipsed conformation, and finally a return to the anti conformation. A plot of potential energy versus rotation about the C2–C3 bond is shown in Figure 4.2.2.

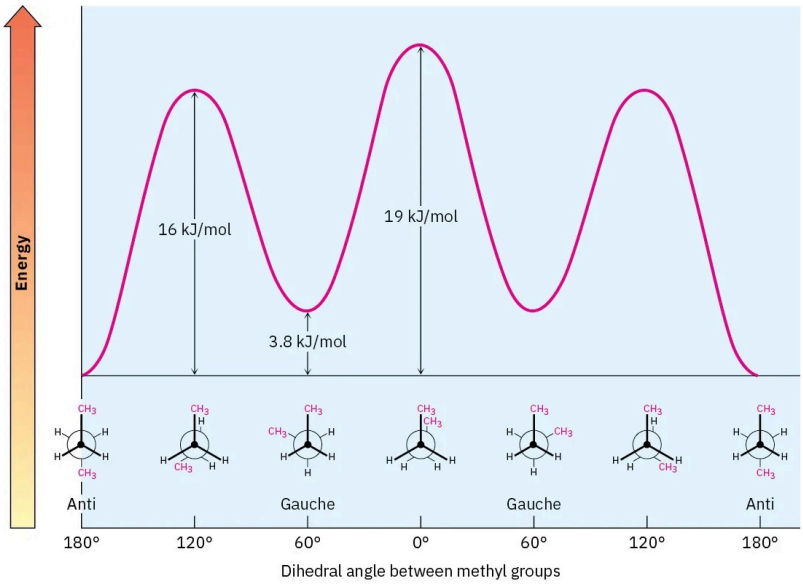


Figure 4.2.2: A plot of potential energy versus rotation for the C2–C3 bond in butane. The energy maximum occurs when the two methyl groups eclipse each other, and the energy minimum occurs when the two methyl groups are 180° apart (anti).

The notion of assigning definite energy values to specific interactions within a molecule is very useful, and we'll return to it in the next chapter. A summary of what we've seen thus far is given in Table 4.2.1.

Table 4.2.1: Energy Costs for Interactions in Alkane Conformers

Interaction	Cause	Energy cost	
		(kJ/mol)	(kcal/mol)
H ⋯ H eclipsed	Torsional strain	4.0	1.0
H ⋯ CH_3 eclipsed	Mostly torsional strain	6.0	1.4
CH_3 ⋯ CH_3 eclipsed	Torsional and steric strain	11.0	2.6
CH_3 ⋯ CH_3 gauche	Steric strain	3.8	0.9

The same principles just developed for butane apply to pentane, hexane, and all higher alkanes. The most favorable conformation for any alkane has the carbon–carbon bonds in staggered arrangements, with large substituents arranged anti to one another. A generalized alkane structure is shown in Figure 4.2.3.

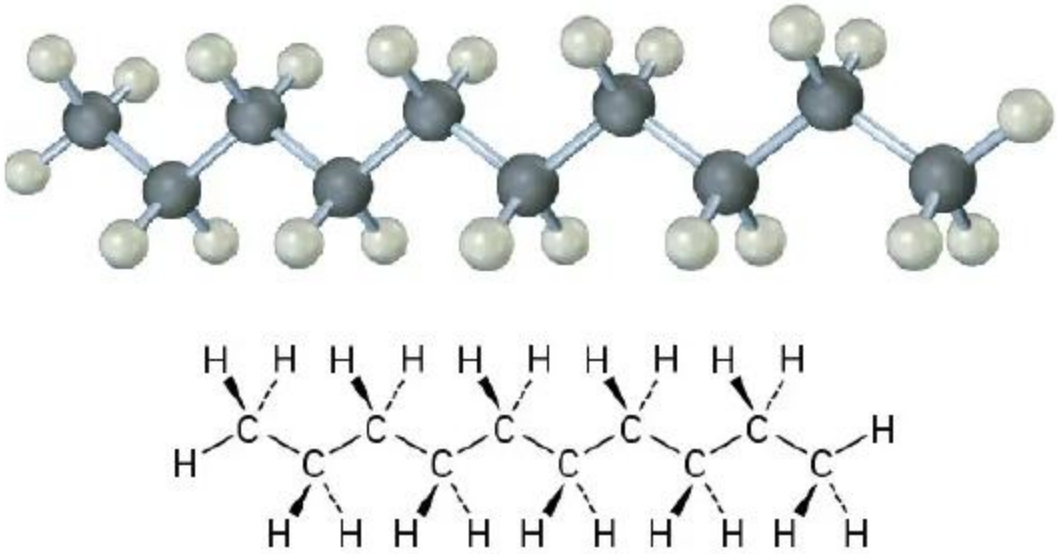


Figure 4.2.3: The most stable alkane conformation is the one in which all substituents are staggered and the carbon–carbon bonds are arranged anti, as shown in this model of decane.

One final point: saying that one particular conformer is “more stable” than another doesn’t mean the molecule adopts and maintains only the more stable conformation. At room temperature, rotations around σ bonds occur so rapidly that all conformers are in equilibrium. At any given instant, however, a larger percentage of molecules will be found in a more stable conformation than in a less stable one.

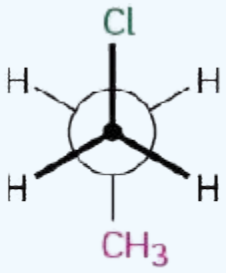
Worked Example 4.2.1: Newman Projections

Sight along the C1–C2 bond of 1-chloropropane, and draw Newman projections of the most stable and least stable conformations.

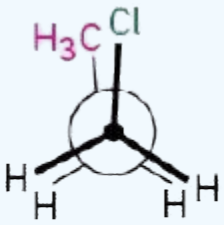
Strategy

The most stable conformation of a substituted alkane is generally a staggered one in which large groups have an anti relationship. The least stable conformation is generally an eclipsed one in which large groups are as close as possible.

Solution



Most stable (staggered)



Least stable (eclipsed)

Exercise 4.2.1

Make a graph of potential energy versus angle of bond rotation for propane, and assign values to the energy maxima.

Answer available at the end of this section.

Exercise 4.2.2

a. Draw a Newman projection of the most stable conformation.
b. Draw a Newman projection of the least stable conformation.
c. Make a graph of energy versus angle of rotation around the C2–C1 bond.
d. Assign relative values to the maxima and minima in your graph, given that an H ⧫ H eclipsing interaction costs 4.0 kJ/mol and an H ⧫ CH_3 eclipsing interaction costs 6.0 kJ/mol.

Answer available at the end of this section.

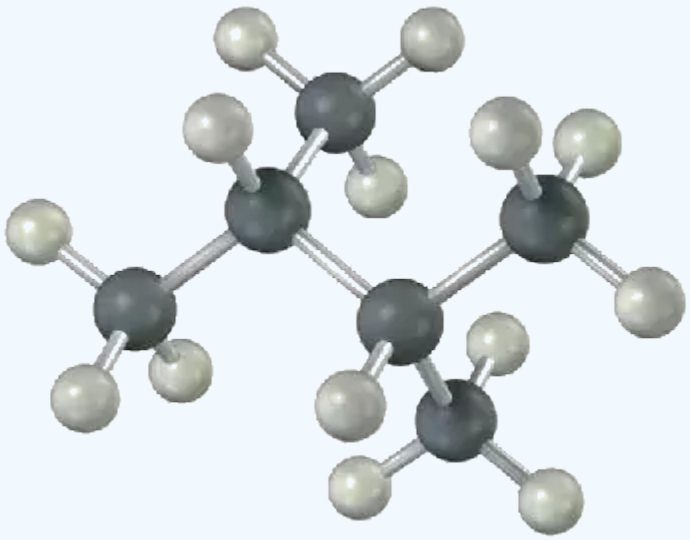
Exercise 4.2.3

Sight along the C2–C3 bond of 2,3-dimethylbutane, and draw a Newman projection of the most stable conformation.

Answer available at the end of this section.

Exercise 4.2.4

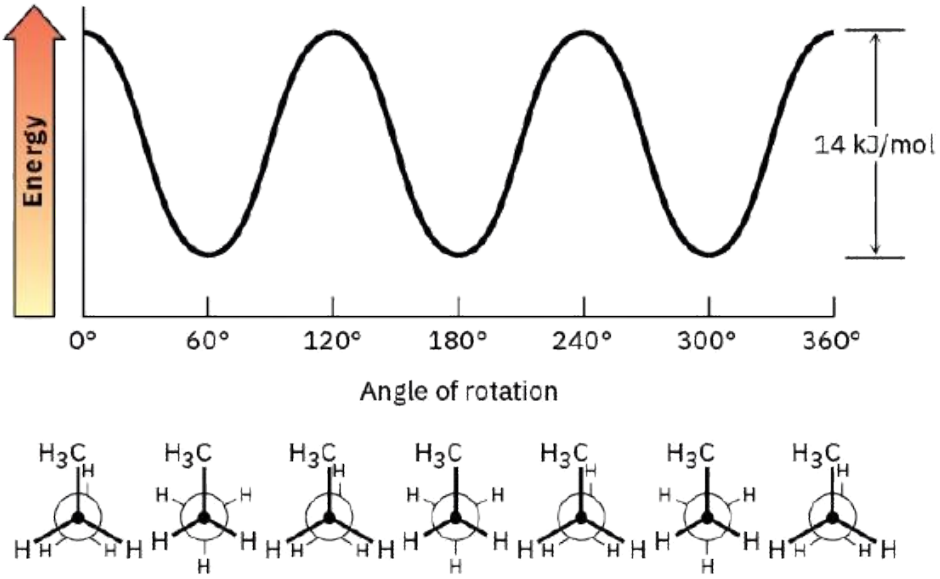
Draw a Newman projection along the C2–C3 bond of the following conformation of 2,3-dimethylbutane, and calculate a total strain energy:



Answer available at the end of this section.

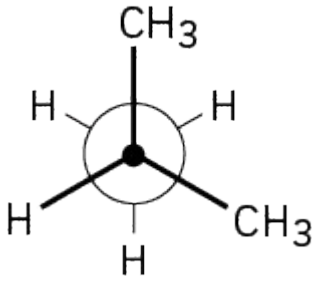
Answers

Exercise 4.2.1

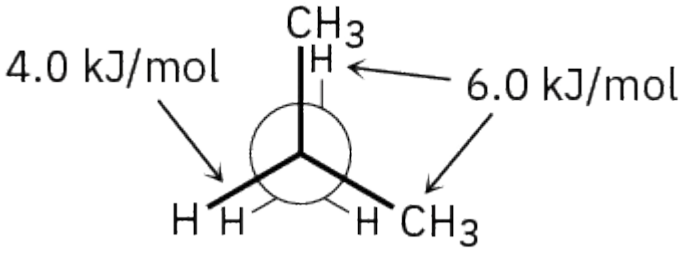


Exercise 4.2.2

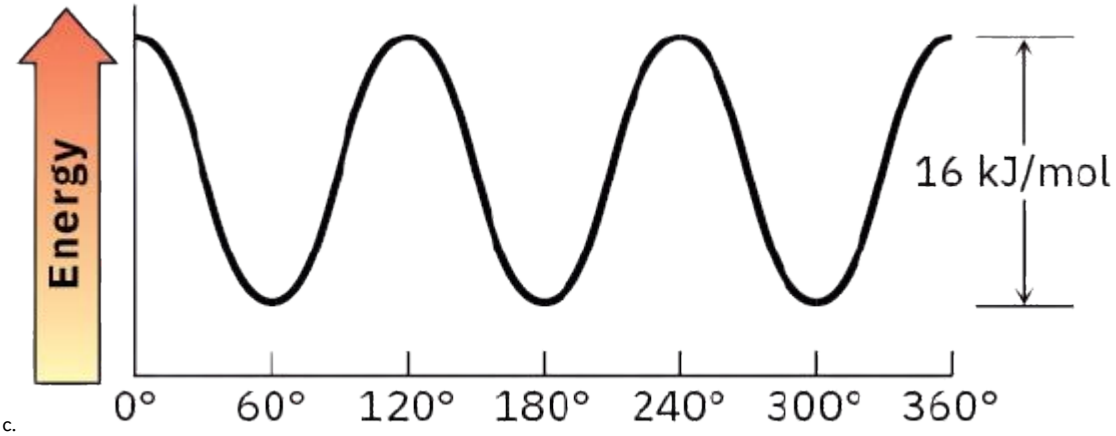
a.



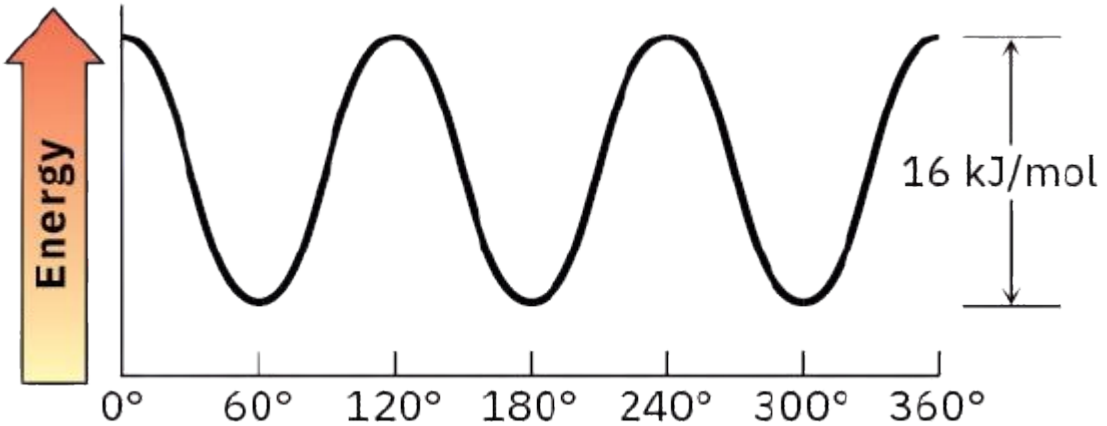
b.



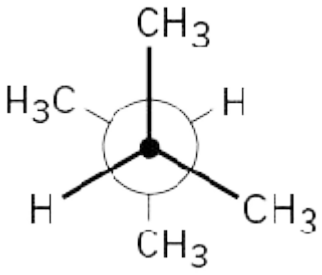
c.



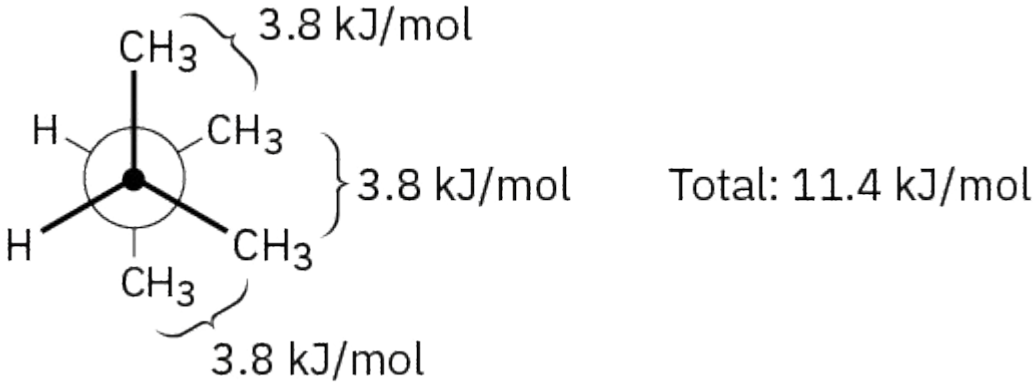
d.



Exercise 4.2.3



Exercise 4.2.4



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4.3: Cis-Trans Isomerism in Cycloalkanes

In many respects, the chemistry of cycloalkanes is like that of open-chain alkanes: both are nonpolar and fairly inert. There are, however, some important differences. One difference is that cycloalkanes are less flexible than open-chain alkanes. In contrast with the relatively free rotation around single bonds in open-chain alkanes, there is much less freedom in cycloalkanes. Cyclopropane, for example, must be a rigid, planar molecule because three points (the carbon atoms) define a plane. No bond rotation can take place around a cyclopropane carbon–carbon bond without breaking open the ring (Figure 4.3.1).

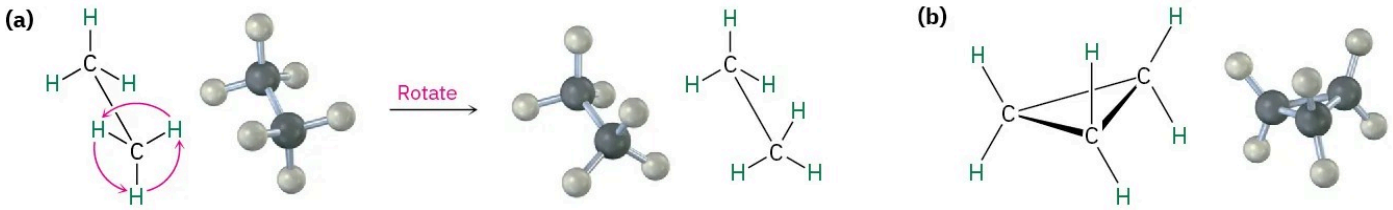
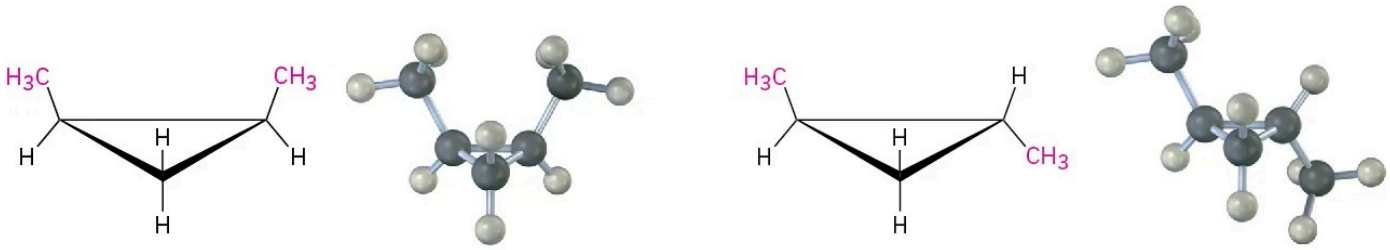


Figure 4.3.1: Bond rotation in ethane and cyclopropane. (a) Rotation occurs around the carbon–carbon bond in ethane, but **(b)** no rotation is possible around the carbon–carbon bonds in cyclopropane without breaking open the ring.

Larger cycloalkanes have increasing rotational freedom, and very large rings (C_{25} and up) are so floppy that they are nearly indistinguishable from open-chain alkanes. The common ring sizes (C_3–C_7), however, are severely restricted in their molecular motions.

Because of their cyclic structures, cycloalkanes have two faces when viewed edge-on, a “top” face and a “bottom” face. As a result, isomerism is possible in substituted cycloalkanes. For example, there are two different 1,2-dimethylcyclopropane isomers, one with the two methyl groups on the same face of the ring and one with the methyl groups on opposite faces (Figure 4.3.2). Both isomers are stable compounds, and neither can be converted into the other without breaking and reforming chemical bonds.

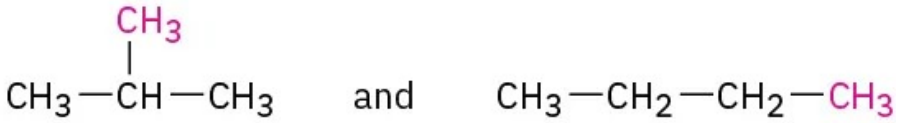


***cis*-1,2-Dimethylcyclopropane** ***trans*-1,2-Dimethylcyclopropane**

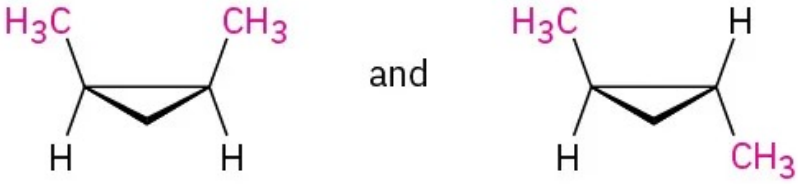
Figure 4.3.2: There are two different 1,2-dimethylcyclopropane isomers, one with the methyl groups on the same face of the ring (cis) and the other with the methyl groups on opposite faces of the ring (trans). The two isomers do not interconvert.

Unlike the constitutional isomers butane and isobutane, which have their atoms connected in a different order (Section 3.3), the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, with atoms connected in the same order but differing in three-dimensional orientation, are called stereochemical isomers, or stereoisomers. As we saw in Section 3.6, the term stereochemistry is used generally to refer to the three-dimensional aspects of structure and reactivity.

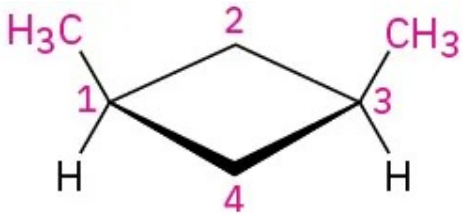
Constitutional isomers (different connections between atoms)

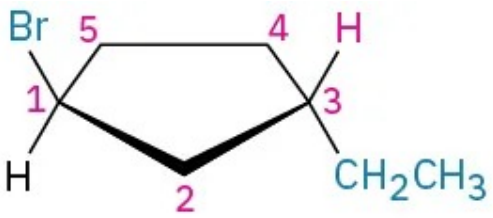


Stereoisomers (same connections but different three-dimensional geometry)



The 1,2-dimethylcyclopropanes are members of a subclass of stereoisomers called cis–trans isomers. The prefixes *cis*- (Latin "on the same side") and *trans*- (Latin "across") are used to distinguish between them. Cis–trans isomerism is a common occurrence in substituted cycloalkanes and in many cyclic biological molecules.

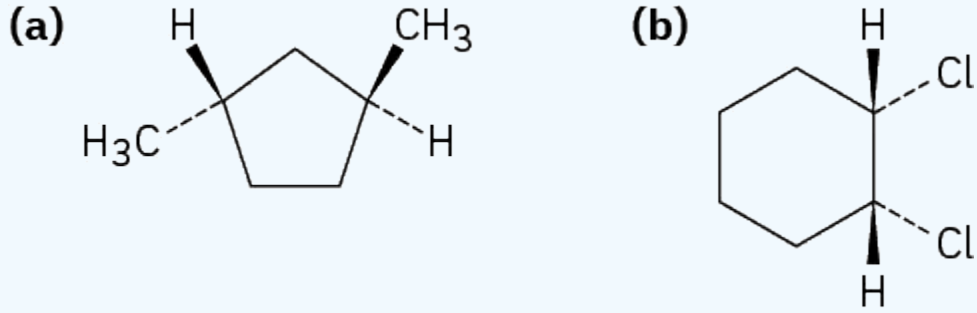




***cis*-1,3-Dimethylcyclobutane** ***trans*-1-Bromo-3-ethylcyclopentane**

Worked Example 4.3.1: Naming Cycloalkanes

Name the following substances, including the *cis*- or *trans*- prefix:



Strategy

In these views, the ring is roughly in the plane of the page, a wedged bond protrudes out of the page, and a dashed bond recedes into the page. Two substituents are cis if they are both out of or both into the page, and they are trans if one is out of and one is into the page.

Solution

a.*trans*-1,3-Dimethylcyclopentane **b.***cis*-1,2-Dichlorocyclohexane

Exercises

Exercise 4.3.1

Name the following substances, including the *cis*- or *trans*- prefix:

a. **b.**

Answer available at the end of this section.

Exercise 4.3.2

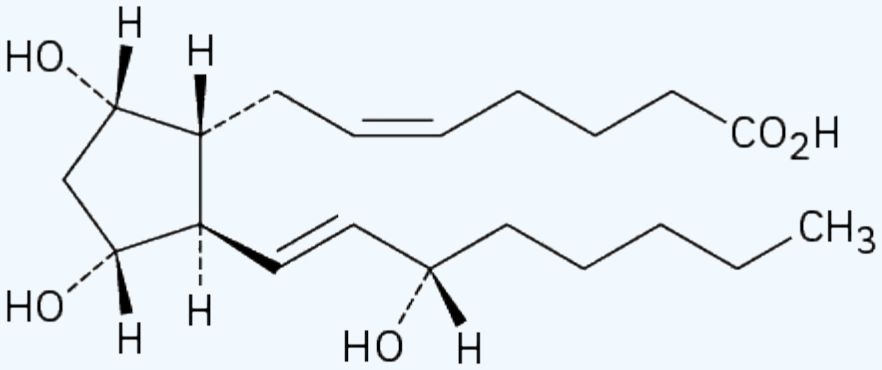
Draw the structures of the following molecules:

a. *trans*-1-Bromo-3-methylcyclohexane
b. *cis*-1,2-Dimethylcyclobutane
c. *trans*-1-*tert*-Butyl-2-ethylcyclohexane

Answer available at the end of this section.

Exercise 4.3.3

Prostaglandin $F_{2\alpha}$, a hormone that causes uterine contraction during childbirth, has the following structure. Are the two hydroxyl groups (–OH) on the cyclopentane ring cis or trans to each other? What about the two carbon chains attached to the ring



Prostaglandin $F_{2\alpha}$

Answer available at the end of this section.

Exercise 4.3.4

Name the following substances, including the *cis*- or *trans*- prefix (red-brown = Br):

a. **b.**

Answer available at the end of this section.

Answers

Exercise 4.3.1

a.*trans*-1-Chloro-4-methylcyclohexane **b.***cis*-1-Ethyl-3-methylcycloheptane

Exercise 4.3.2

a. **b.** **c.**



Exercise 4.3.3

The two hydroxyl groups are cis. The two side chains are trans.

Exercise 4.3.4

a.*cis*-1,2-Dimethylcyclopentane **b.***cis*-1-Bromo-3-methylcyclobutane

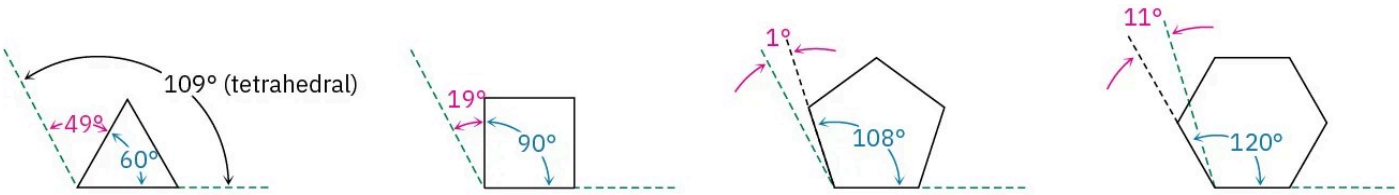
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4.4: Stability of Cycloalkanes - Ring Strain

Chemists in the late 1800s knew that cyclic molecules existed, but the limitations on ring size were unclear. Although numerous compounds containing five-membered and six-membered rings were known, smaller and larger ring sizes had not been prepared, despite many attempts.

A theoretical interpretation of this observation was proposed in 1885 by Adolf von Baeyer, who suggested that small and large rings might be unstable due to angle strain—the strain induced in a molecule when bond angles are forced to deviate from the ideal 109° tetrahedral value. Baeyer based his suggestion on the simple geometric notion that a three-membered ring (cyclopropane) should be an equilateral triangle with bond angles of 60° rather than 109°, a four-membered ring (cyclobutane) should be a square with bond angles of 90°, a five-membered ring should be a regular pentagon with bond angles of 108°, and so on. Continuing this argument, large rings should be strained by having bond angles that are much greater than 109°.



Cyclopropane **Cyclobutane** **Cyclopentane** **Cyclohexane**

What are the facts? To measure the amount of strain in a compound, we have to measure the total energy of the compound and then subtract the energy of a strain-free reference compound. The difference between the two values should represent the amount of extra energy in the molecule due to strain. The simplest experimental way to do this for a cycloalkane is to measure its *heat of combustion,* the amount of heat released when the compound burns completely with oxygen. The more energy (strain) the compound contains, the more energy (heat) is released by combustion.

$$(CH_2)_n + \frac{3n}{2}\ O_2 \longrightarrow n\,CO_2 + n\,H_2O + \text{Heat (add)}$$

Because the heat of combustion of a cycloalkane depends on size, we need to look at heats of combustion per CH_2 unit. Subtracting a reference value derived from a strain-free acyclic alkane and then multiplying by the number of CH_2 units in the ring gives the overall strain energy. Figure $4.4.1$ shows the results.

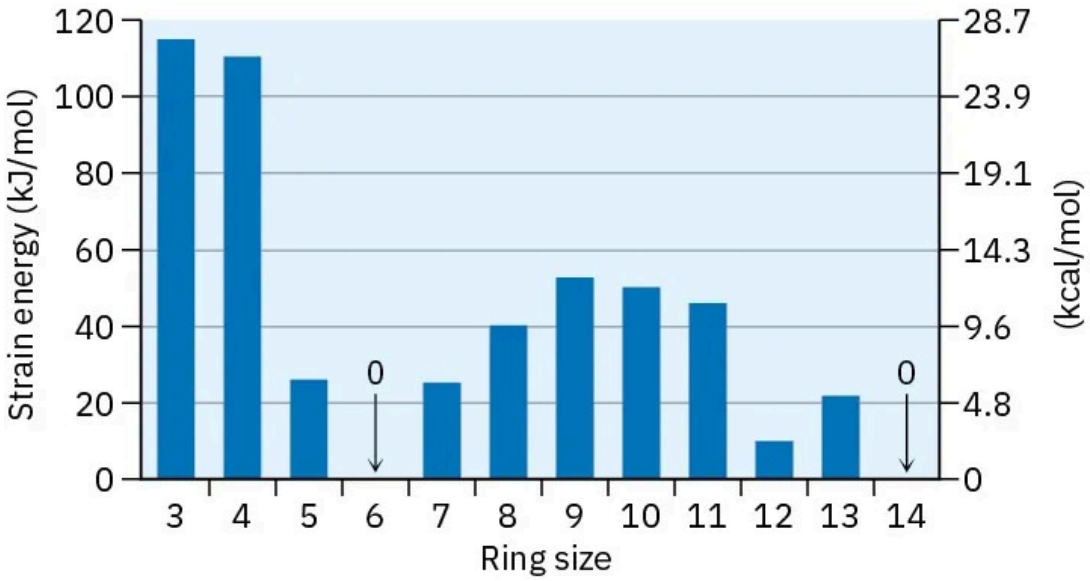


Figure 4.4.1: Cycloalkane strain energies, as calculated by taking the difference between cycloalkane heat of combustion per CH_2 and acyclic alkane heat of combustion per CH_2, and multiplying by the number of CH_2 units in a ring. Small and medium rings are strained, but cyclohexane rings and very large rings are strain-free.

The data in Figure 4.4.1 show that Baeyer's theory is only partially correct. Cyclopropane and cyclobutane are indeed strained, just as predicted, but cyclopentane is more strained than predicted, and cyclohexane is strain-free. Cycloalkanes of intermediate size have only modest strain, and rings of 14 carbons or more are strain-free. Why is Baeyer's theory wrong?

Baeyer's theory is wrong for the simple reason that he assumed all cycloalkanes to be flat. In fact, as we'll see in the next section, most cycloalkanes are not flat; instead, they adopt puckered three-dimensional conformations that allow bond angles to be nearly tetrahedral. As a result, angle strain occurs only in three- and four-membered rings, which have little flexibility. For most ring sizes, particularly the medium-ring (C_7–C_{11}) cycloalkanes, torsional strain caused by H ⇳ H eclipsing interactions at adjacent carbons and steric strain caused by the repulsion between nonbonded atoms that approach too closely (Section 3.8) are the most important factors. Thus, three kinds of strain contribute to the overall energy of a cycloalkane.

- **Angle strain**—the strain due to expansion or compression of bond angles
- **Torsional strain**—the strain due to eclipsing of bonds between neighboring atoms
- **Steric strain**—the strain due to repulsive interactions when atoms approach each other too closely

Exercise 4.4.1

Each H ⇳ H eclipsing interaction in ethane costs about 4.0 kJ/mol. How many such interactions are present in cyclopropane? What fraction of the overall 115 kJ/mol (27.5 kcal/mol) strain energy of cyclopropane is due to torsional strain?

Answer available at the end of this section.

Exercise 4.4.2

cis-1,2-Dimethylcyclopropane has more strain than *trans*-1,2-dimethylcyclopropane. How can you account for this difference? Which of the two compounds is more stable?

Answer available at the end of this section.

Answers

Exercise 4.4.1

Six interactions; 21% of strain

Exercise 4.4.2

The cis isomer is less stable because the methyl groups nearly eclipse each other.

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4.5: Conformations of Cycloalkanes

Cyclopropane

Cyclopropane is the most strained of all rings, primarily due to the angle strain caused by its 60° C–C–C bond angles. In addition, cyclopropane has considerable torsional strain because the C–H bonds on neighboring carbon atoms are eclipsed (Figure 4.5.1).

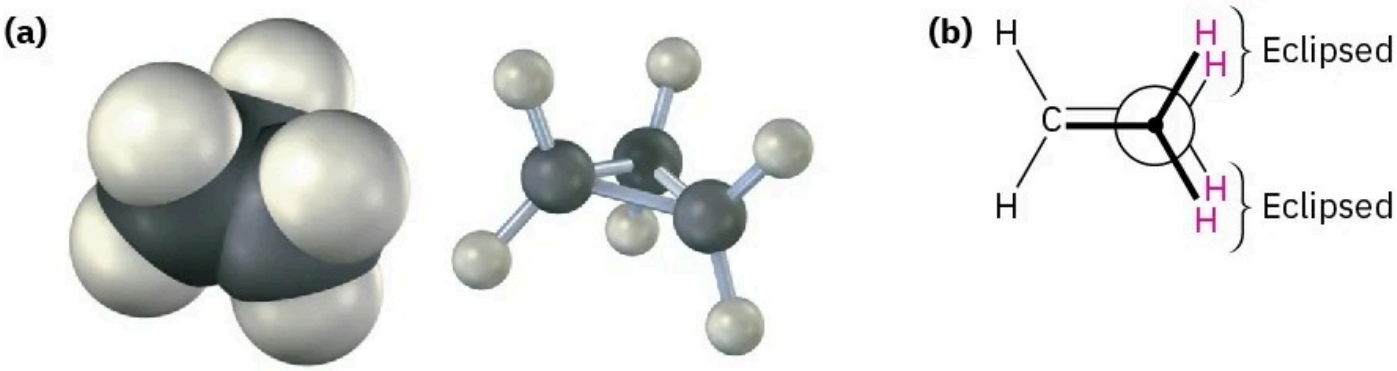
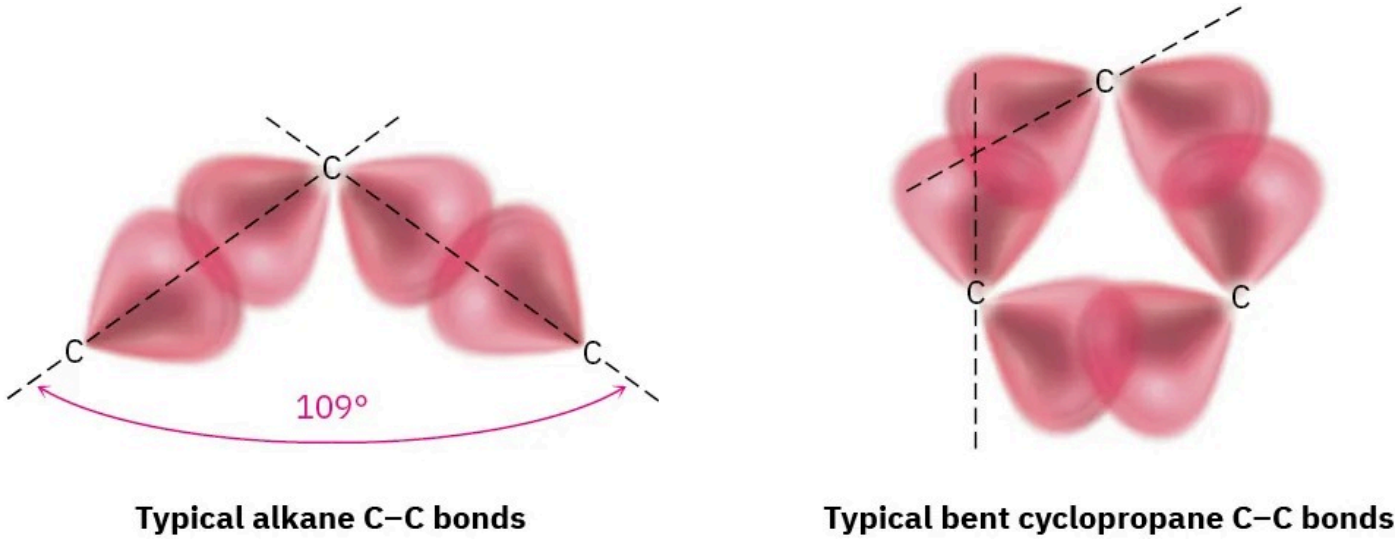


Figure 4.5.1: The structure of cyclopropane, showing the eclipsing of neighboring C–H bonds that gives rise to torsional strain. Part **(b)** is a Newman projection along a C–C bond.

How can the hybrid-orbital model of bonding account for the large distortion of bond angles from the normal 109° tetrahedral value to 60° in cyclopropane? The answer is that cyclopropane has *bent bonds*. In an unstrained alkane, maximum bonding is achieved when two atoms have their overlapping orbitals pointing directly toward each other. In cyclopropane, though, the orbitals can't point directly toward each other; instead, they overlap at a slight angle. The result is that cyclopropane bonds are weaker and more reactive than typical alkane bonds—255 kJ/mol (61 kcal/mol) for a C–C bond in cyclopropane versus 370 kJ/mol (88 kcal/mol) for a C–C bond in open-chain propane.



Typical alkane C–C bonds **Typical bent cyclopropane C–C bonds**

Cyclobutane

Cyclobutane has less angle strain than cyclopropane but has more torsional strain because of its larger number of ring hydrogens. As a result, the total strain for the two compounds is nearly the same—110 kJ/mol (26.4 kcal/mol) for cyclobutane versus 115 kJ/mol (27.5 kcal/mol) for cyclopropane. Cyclobutane is not quite flat but is slightly bent so that one carbon atom lies about 25°

above the plane of the other three (Figure 4.5.2). The effect of this slight bend is to increase angle strain but to decrease torsional strain, until a minimum-energy balance between the two opposing effects is achieved.

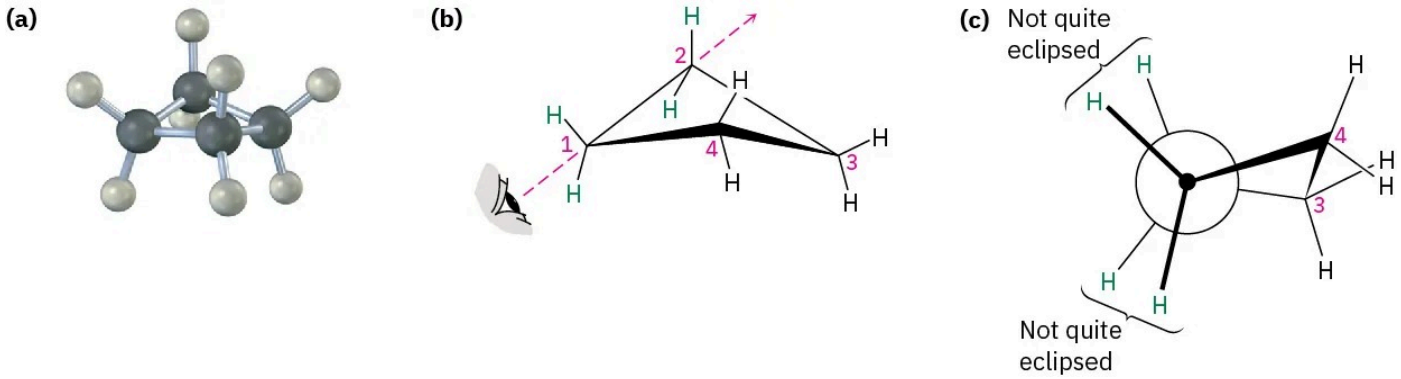


Figure 4.5.2: The conformation of cyclobutane. Part **(c)** is a Newman projection along a C–C bond, showing that neighboring C–H bonds are not quite eclipsed.

Cyclopentane

Cyclopentane was predicted by Baeyer to be nearly strain-free, but it actually has a total strain energy of 26 kJ/mol (6.2 kcal/mol). Although planar cyclopentane has practically no angle strain, it has a large torsional strain. Cyclopentane therefore twists to adopt a puckered, nonplanar conformation that strikes a balance between increased angle strain and decreased torsional strain. Four of the cyclopentane carbon atoms are in approximately the same plane, with the fifth carbon atom bent out of the plane. Most of the hydrogens are nearly staggered with respect to their neighbors (Figure 4.5.3).

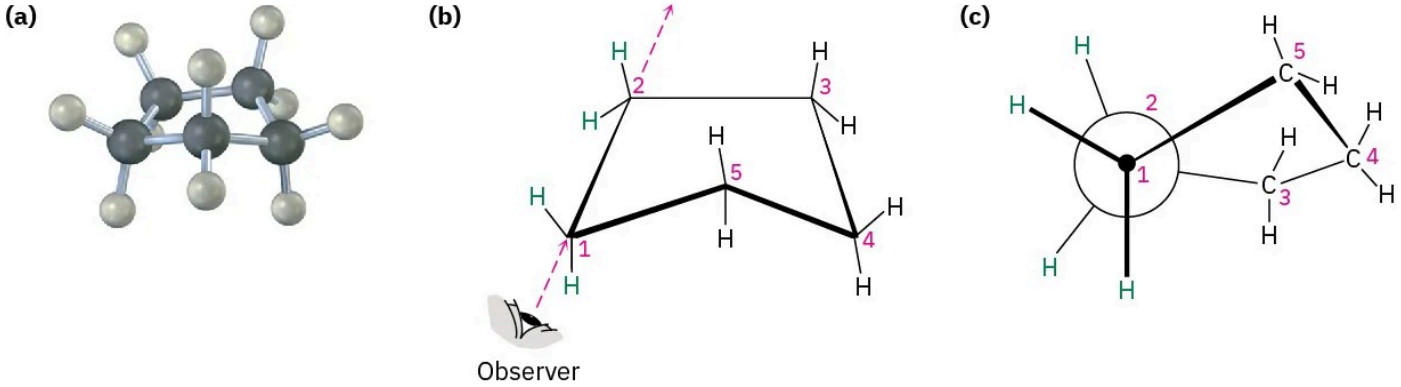


Figure 4.5.3: The conformation of cyclopentane. Carbons 1, 2, 3, and 4 are nearly coplanar, but carbon 5 is out of the plane. Part **(c)** is a Newman projection along the C1–C2 bond, showing that neighboring C–H bonds are nearly staggered.

Exercise 4.5.1

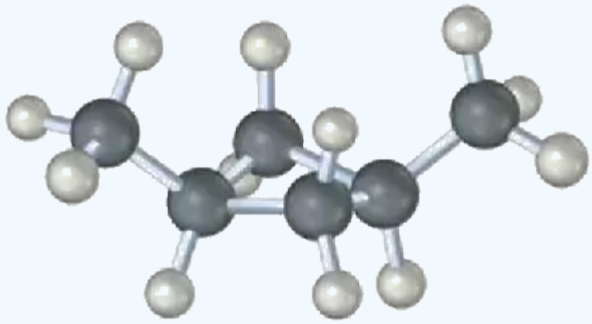
How many H ⋄ H eclipsing interactions would be present if cyclopentane were planar? Assuming an energy cost of 4.0 kJ/mol for each eclipsing interaction, how much torsional strain would planar cyclopentane have? Since the measured total strain of cyclopentane is 26 kJ/mol, how much of the torsional strain is relieved by puckering?

Answer available at the end of this section.

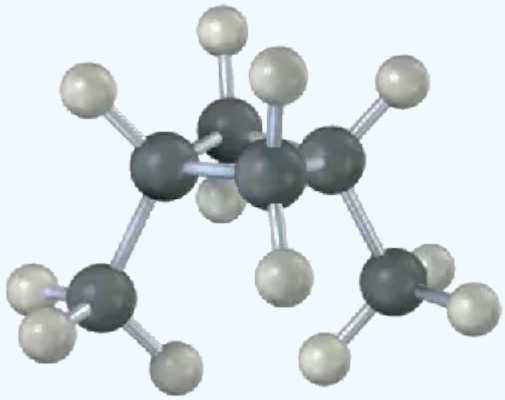
Exercise 4.5.1

Two conformations of *cis*-1,3-dimethylcyclobutane are shown. What is the difference between them, and which do you think is likely to be more stable?

a.



b.



Answer available at the end of this section.

Answers

Exercise 4.5.1

Ten eclipsing interactions; 40 kJ/mol; 35% is relieved.

Exercise 4.5.1

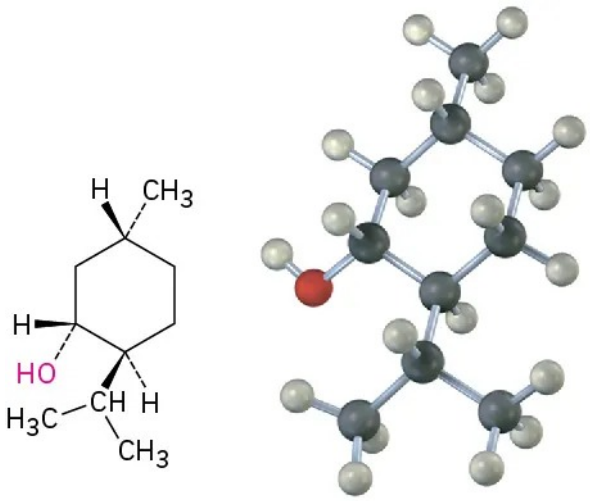
Conformation **(a)** is more stable because the methyl groups are farther apart.

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4.6: Conformations of Cyclohexane

Substituted cyclohexanes are the most common cycloalkanes and occur widely in nature. A large number of compounds, including steroids and many pharmaceutical agents, have cyclohexane rings. The flavoring agent menthol, for instance, has three substituents on a six-membered ring.



Menthol

Cyclohexane adopts a strain-free, three-dimensional shape that is called a chair conformation because of its similarity to a lounge chair, with a back, seat, and footrest (Figure 4.6.1). Chair cyclohexane has neither angle strain nor torsional strain—all C–C–C bond angles are near the 109° tetrahedral value, and all neighboring C–H bonds are staggered.

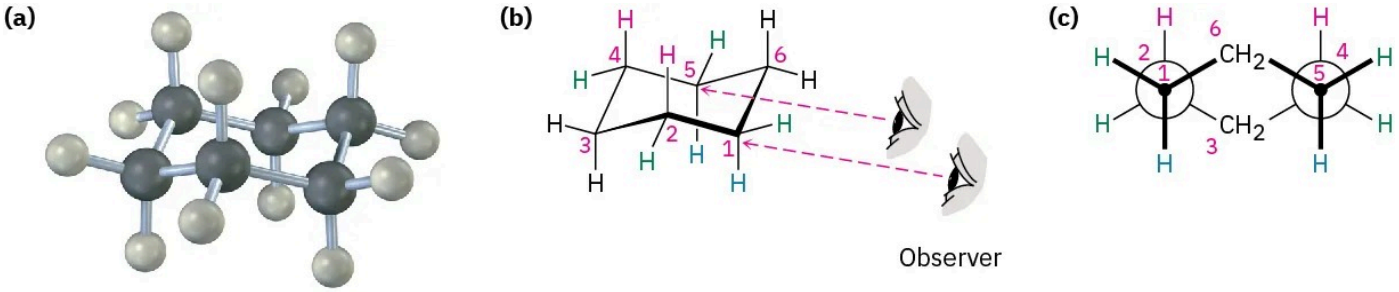
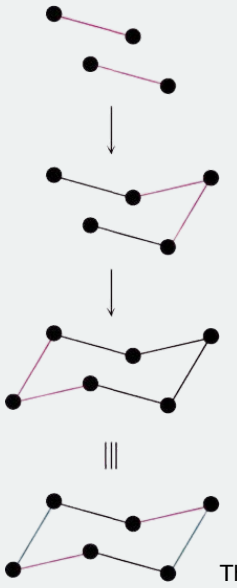


Figure 4.6.1: The strain-free chair conformation of cyclohexane. All C–C–C bond angles are 111.5°, close to the ideal 109° tetrahedral angle, and all neighboring C–H bonds are staggered.

The easiest way to visualize chair cyclohexane is to build a molecular model if you have access to a model kit, or alternatively to explore with one of the many computer-based modeling programs you may have access to.

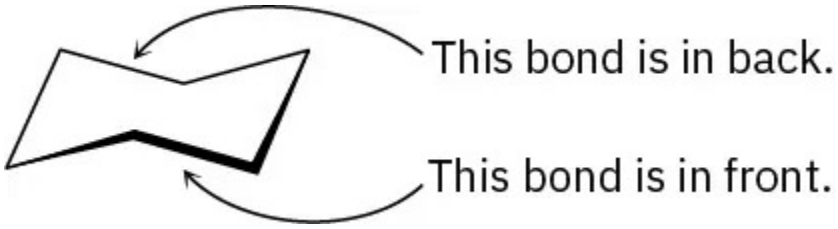
Chair Conformation of Cyclohexane



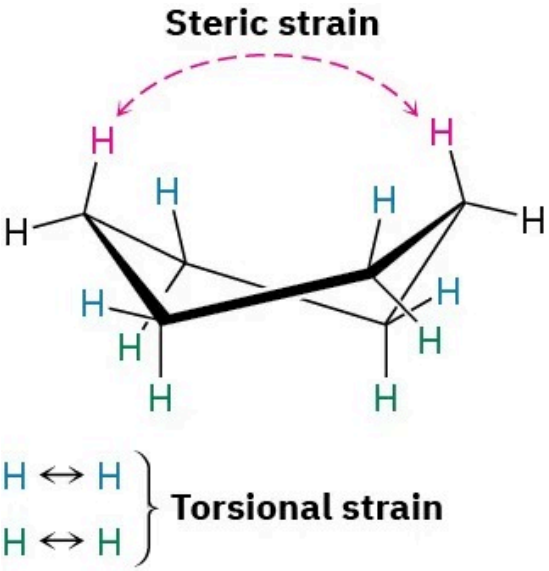
The chair conformation of cyclohexane can be drawn in three steps.

- **STEP 1:** Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.
- **STEP 2:** Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.
- **STEP 3:** Place the bottommost carbon atom below and to the left of the plane of the middle four, and connect the bonds. Note that the bonds to the bottommost carbon atom are parallel to the bonds to the topmost carbon.

When viewing cyclohexane, it's helpful to remember that the lower bond is in front and the upper bond is in back. If this convention isn't defined, it can appear that the reverse is true. For clarity, all cyclohexane rings drawn in this book will have the front (lower) bond heavily shaded to indicate nearness to the viewer.



In addition to the chair conformation of cyclohexane, there is an alternative conformation of cyclohexane that bears a slight resemblance to a twisted boat. Called the twist-boat conformation, it is nearly free of angle strain. It does, however, have both steric strain and torsional strain and is about 23 kJ/mol (5.5 kcal/mol) higher in energy than the chair conformation. As a result, molecules adopt the twist-boat geometry only rarely.



Torsional strain



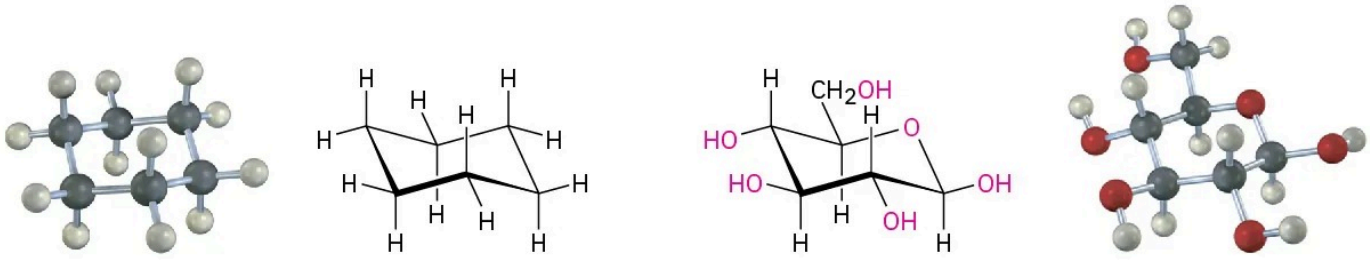
Twist-boat cyclohexane
(23 kJ/mol strain)

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4.7: Axial and Equatorial Bonds in Cyclohexane

The chair conformation of cyclohexane has many consequences. We'll see, that the chemical behavior of many substituted cyclohexanes is influenced by their conformation. In addition, we'll see in **CHEM 232** that simple carbohydrates, such as glucose, adopt a conformation based on the cyclohexane chair and that their chemistry is directly affected as a result.



Cyclohexane (chair conformation) **Glucose (chair conformation)**

Another trait of the chair conformation is that there are two kinds of positions for substituents on the cyclohexane ring: *axial* positions and *equatorial* positions (as shown in Figure 4.7.1). The six axial positions are parallel to the ring **axis**, while the six equatorial positions are in the rough plane of the ring, around the ring **equator**.

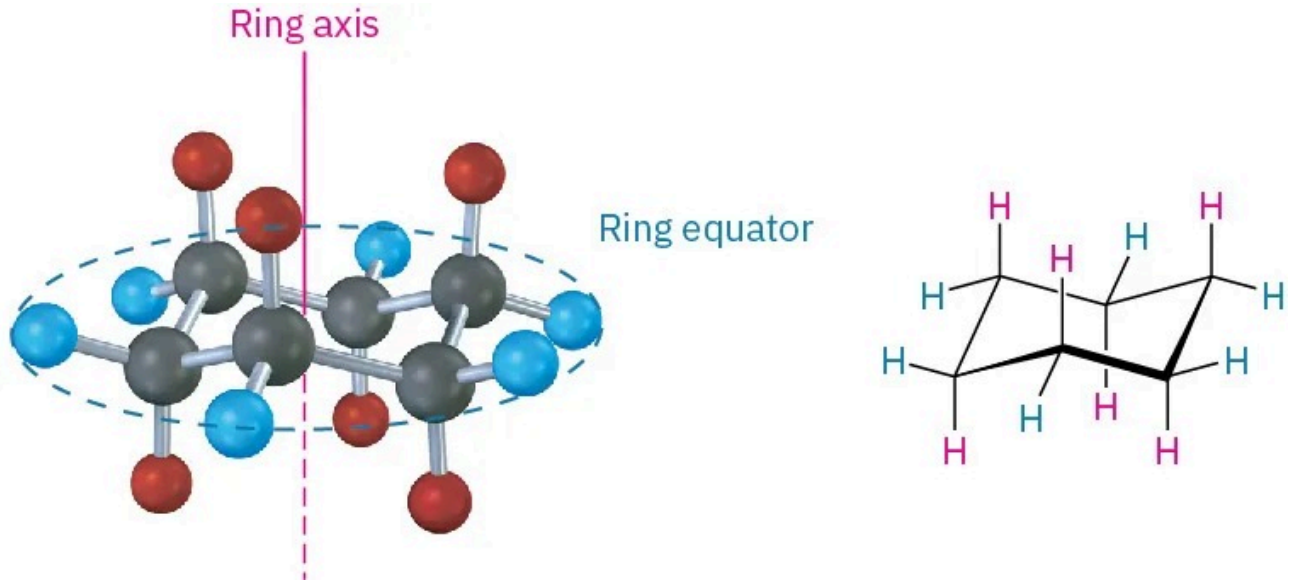


Figure 4.7.1: Axial and equatorial positions in chair cyclohexane. The six axial hydrogens are parallel to the ring axis, and the six equatorial hydrogens are in a band around the ring equator.

As shown in Figure 4.7.1, each carbon atom in chair cyclohexane has one axial and one equatorial hydrogen. Furthermore, each side of the ring has three axial and three equatorial hydrogens in an alternating arrangement. For example, if the top side of the ring has axial hydrogens on carbons 1, 3, and 5, then it has equatorial hydrogens on carbons 2, 4, and 6. The reverse is true for the bottom side: carbons 1, 3, and 5 have equatorial hydrogens, but carbons 2, 4, and 6 have axial hydrogens (Figure 4.7.2).

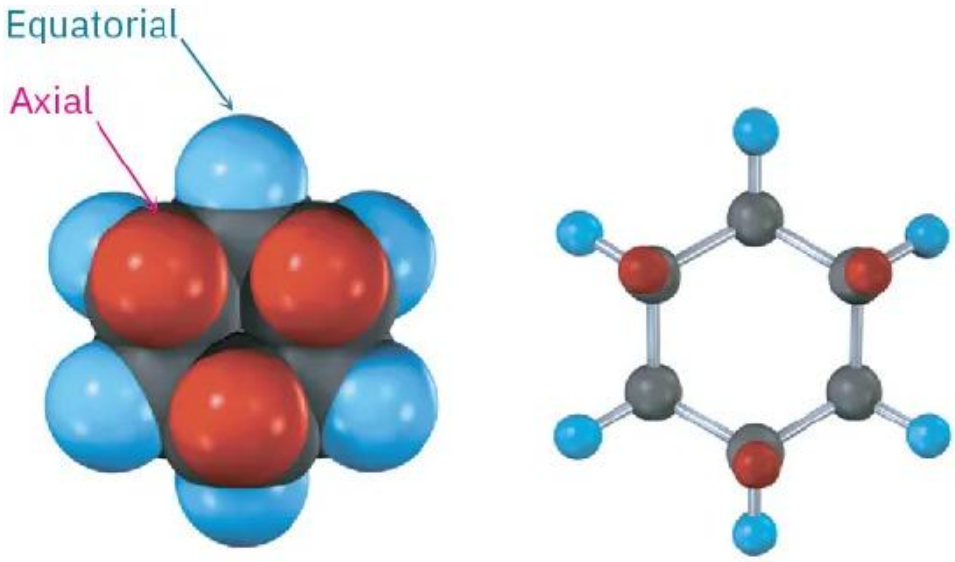
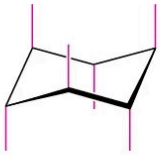


Figure 4.7.2: Alternating axial and equatorial positions in chair cyclohexane, looking directly down the ring axis. Each carbon atom has one axial and one equatorial position, and each face has alternating axial and equatorial positions.

Note that we haven't used the words *cis* and *trans* in this discussion of cyclohexane conformation. Two hydrogens on the same side of the ring are always cis, regardless of whether they're axial or equatorial and regardless of whether they're adjacent. Similarly, two hydrogens on opposite sides of the ring are always trans.

Axial and equatorial bonds can be drawn following the procedure shown in Figure 4.7.3. If possible, look at a molecular model as you practice.

Axial bonds: The six axial bonds, one on each carbon, are parallel and alternate up–down.



Equatorial bonds: The six equatorial bonds, one on each carbon, come in three sets of two parallel lines. Each set is also parallel to two ring bonds. Equatorial bonds alternate between sides around the ring.



Completed cyclohexane

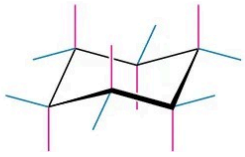


Figure 4.7.3: A procedure for drawing axial and equatorial bonds in chair cyclohexane.

Because chair cyclohexane has two kinds of positions—axial and equatorial—we might expect to find two isomeric forms of a monosubstituted cyclohexane. In fact, we don't. There is only one methylcyclohexane, one bromocyclohexane, one cyclohexanol (hydroxycyclohexane), and so on, because cyclohexane rings are conformationally mobile at room temperature. Different chair conformations readily interconvert, exchanging axial and equatorial positions. This interconversion, called a ring-flip, is shown in Figure 4.7.4.

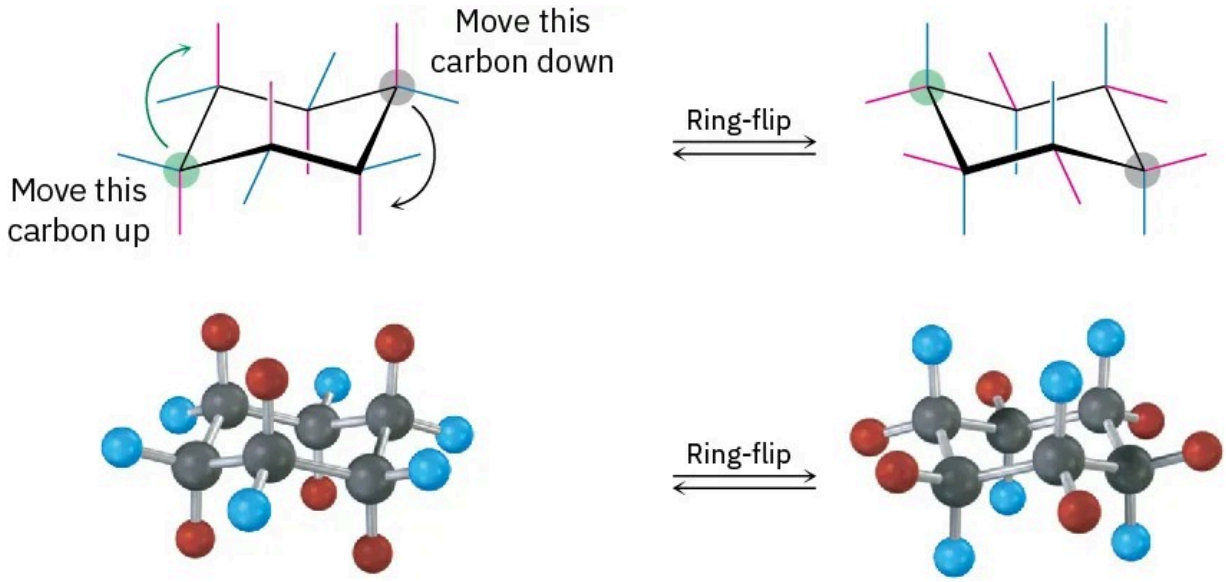
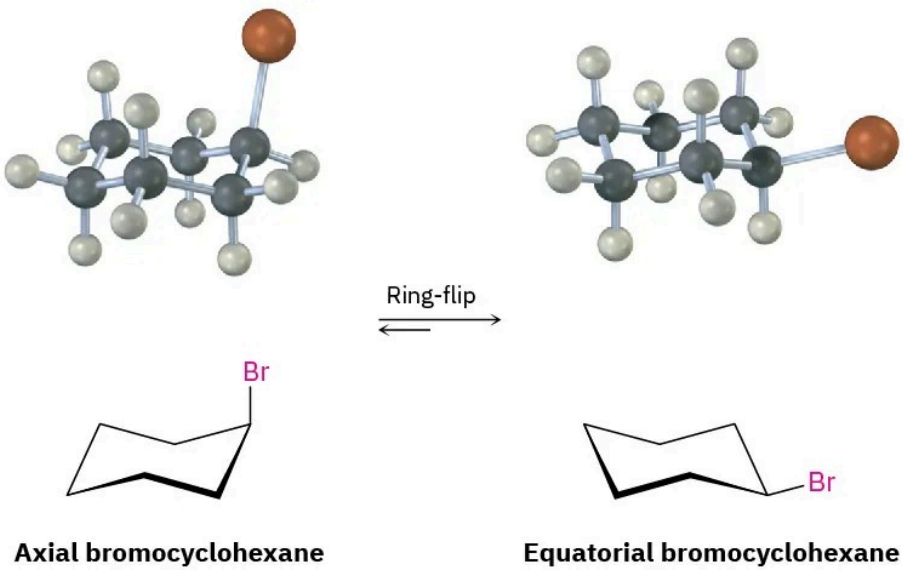


Figure 4.7.4: A ring-flip in chair cyclohexane interconverts axial and equatorial positions. What is **axial** in the starting structure becomes **equatorial** in the ring-flipped structure, and what is **equatorial** in the starting structure is **axial** after ring-flip.

As shown in Figure 4.7.4, a chair cyclohexane can be ring-flipped by keeping the middle four carbon atoms in place while folding the two end carbons in opposite directions. In so doing, an axial substituent in one chair form becomes an equatorial substituent in the ring-flipped chair form and vice versa. For example, axial bromocyclohexane becomes equatorial bromocyclohexane after a ring-flip. Since the energy barrier to chair–chair interconversion is only about 45 kJ/mol (10.8 kcal/mol), the process is rapid at room temperature and we see what appears to be a single structure rather than distinct axial and equatorial isomers.



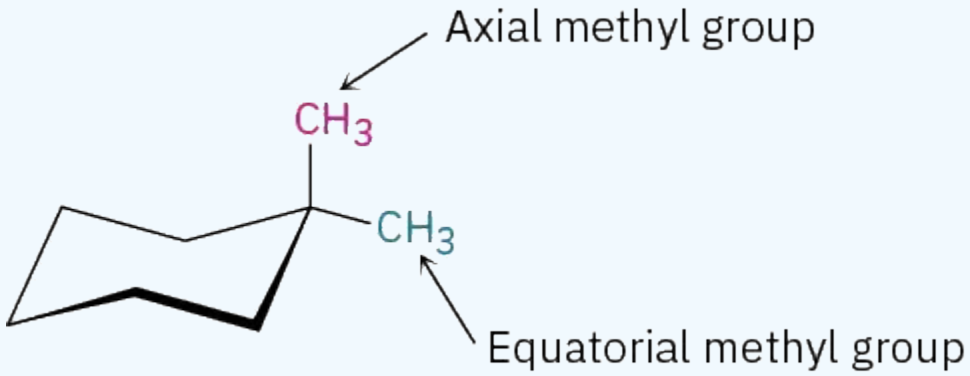
Worked Example 4.7.1: Drawing the Chair Conformation of a Substituted Cyclohexane

Draw 1,1-dimethylcyclohexane in a chair conformation, indicating which methyl group in your drawing is axial and which is equatorial.

Strategy

Draw a chair cyclohexane ring using the procedure in Figure 4.7.3, and then put two methyl groups on the same carbon. The methyl group in the rough plane of the ring is equatorial, and the one directly above or below the ring is axial.

Solution



Exercise

Exercise 4.7.1

Draw two different chair conformations of cyclohexanol (hydroxycyclohexane), showing all hydrogen atoms. Identify each position as axial or equatorial.

Answer available at the end of this section.

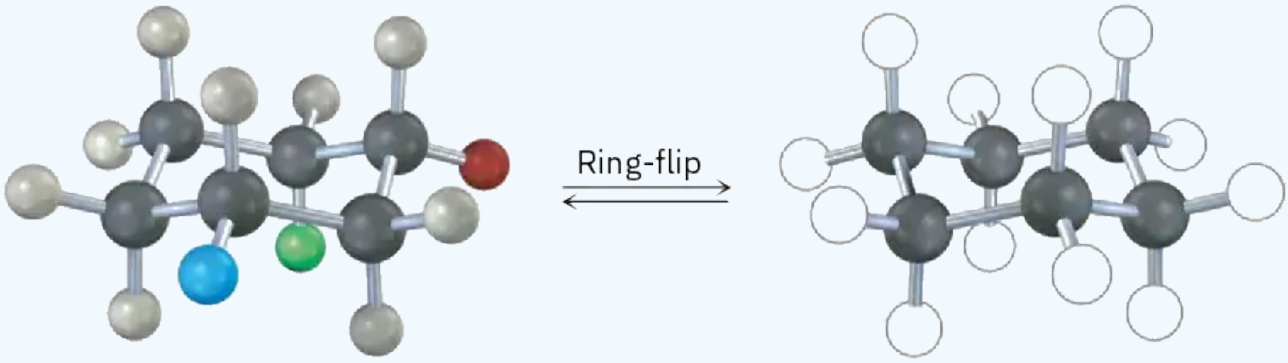
Exercise 4.7.2

Draw two different chair conformations of *trans*-1,4-dimethylcyclohexane, and label all positions as axial or equatorial.

Answer available at the end of this section.

Exercise 4.7.3

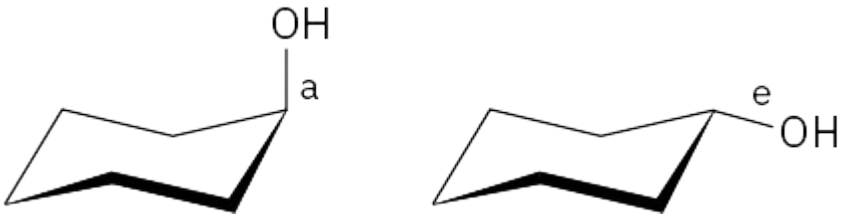
Identify each of the colored positions—red, blue, and green—as axial or equatorial. Then carry out a ring-flip, and show the new positions occupied by each color.



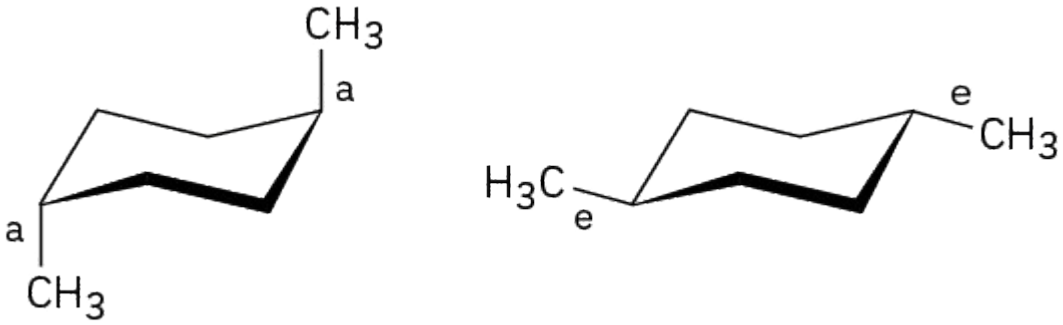
Answer available at the end of this section.

Answers

Exercise 4.7.1



Exercise 4.7.2



Exercise 4.7.3

Before the ring-flip, red and blue are equatorial and green is axial. After the ring-flip, red and blue are axial and green is equatorial.

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4.8: Conformations of Monosubstituted Cyclohexanes

Even though cyclohexane rings flip rapidly between chair conformations at room temperature, the two conformations of a monosubstituted cyclohexane aren't equally stable. In methylcyclohexane, for instance, the equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol (1.8 kcal/mol). The same is true of other monosubstituted cyclohexanes: a substituent is almost always more stable in an equatorial position than in an axial position.

You might recall from your general chemistry course that it's possible to calculate the percentages of two isomers at equilibrium using the equation $\Delta E = -RT \ln K$, where ΔE is the energy difference between isomers, R is the gas constant [8.315 J/(K·mol)], T is the Kelvin temperature, and K is the equilibrium constant between isomers. For example, an energy difference of 7.6 kJ/mol means that about 95% of methylcyclohexane molecules have an equatorial methyl group at any given instant while only 5% have an axial methyl group. Figure 4.8.1 plots the relationship between energy and isomer percentages.

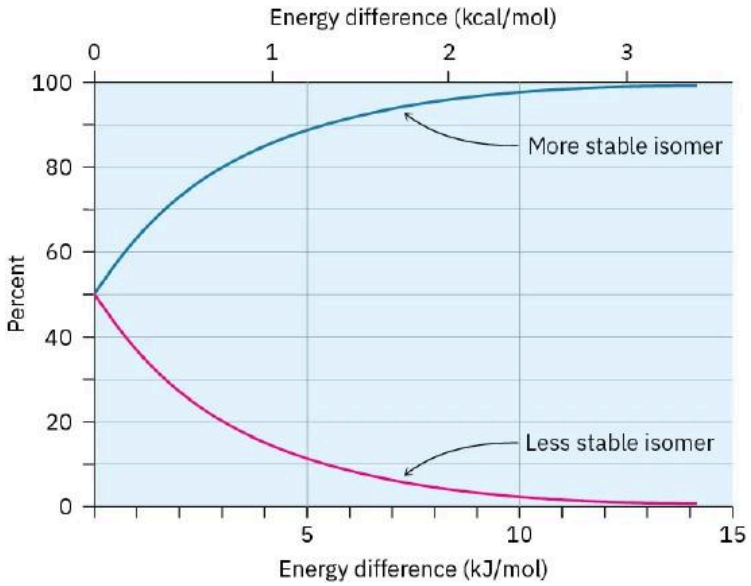


Figure 4.8.1: A plot of the percentages of two isomers at equilibrium versus the energy difference between them. The curves are calculated using the equation $\Delta E = -RT \ln K$.

The energy difference between axial and equatorial conformations is due to steric strain caused by 1,3-diaxial interactions. The axial methyl group on C1 is too close to the axial hydrogens three carbons away on C3 and C5, resulting in 7.6 kJ/mol of steric strain (Figure 4.8.2).

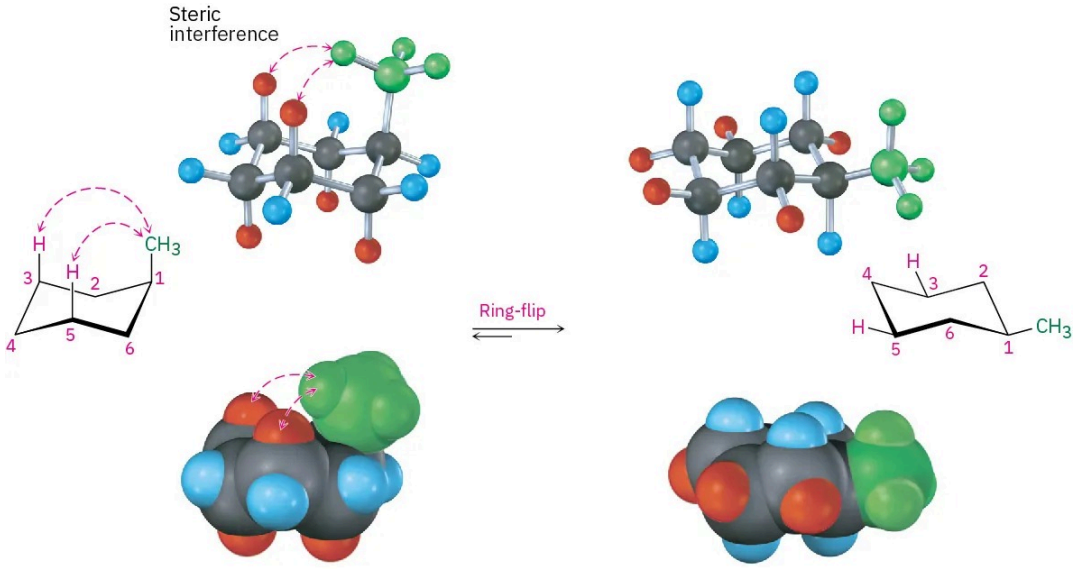


Figure 4.8.2: Interconversion of axial and equatorial methylcyclohexane, represented in several formats. The equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol.

The 1,3-diaxial steric strain in substituted methylcyclohexane is already familiar—we saw it previously as the steric strain between methyl groups in gauche in Section 3.8). Gauche butane is less stable than anti butane by 3.8 kJ/mol (0.9 kcal/mol) because of steric interference between hydrogen atoms on the two methyl groups. Comparing a four-carbon fragment of axial methylcyclohexane with gauche butane shows that the steric interaction is the same in both (Figure 4.8.3). Because axial methylcyclohexane has two such interactions, it has 2 × 3.8 = 7.6 kJ/mol of steric strain. Equatorial methylcyclohexane has no such interactions and is therefore more stable.

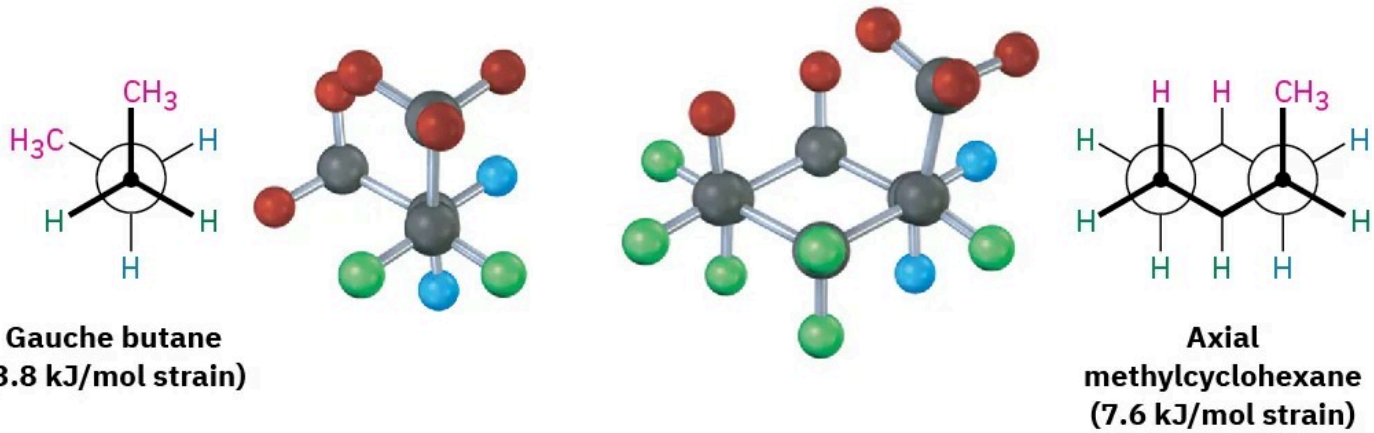
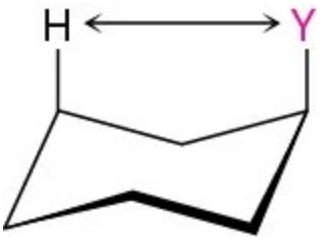


Figure 4.8.3: The origin of 1,3-diaxial interactions in methylcyclohexane. The steric strain between **an axial methyl group** and **an axial hydrogen atom** three carbons away is identical to the steric strain in gauche butane. (To display clearly the diaxial interactions in methylcyclohexane, two of the equatorial hydrogens are not shown.)

The exact amount of 1,3-diaxial steric strain in a given substituted cyclohexane depends on the nature and size of the substituent, as indicated in Table 4.8.1. Not surprisingly, the amount of steric strain increases through the series $H_3C^- < CH_3CH_2^- < (CH_3)_2CH^- \ll (CH_3)_3C^-$, paralleling the increasing size of the alkyl groups.



Note that the values given in Table 4.8.4 refer to 1,3-diaxial interactions of the substituent with a single hydrogen atom. These values must be doubled to arrive at the amount of strain in a monosubstituted cyclohexane.

Table 4.8.1: Steric Strain in Monosubstituted Cyclohexanes

Substitution (Y)	1,3-Diaxial strain (kJ/mol)	1,3-Diaxial strain (kcal/mol)
F	0.5	0.12
Cl, Br	1.0	0.25
OH	2.1	0.5
CH_3	3.8	0.9
CH_2CH_3	4.0	0.95
$CH(CH_3)_2$	4.6	1.1
$C(CH_3)_3$	11.4	2.7
C_6H_5	6.3	1.5
CO_2H	2.9	0.7
CN	0.4	0.1

Exercise 4.8.1

What is the energy difference between the axial and equatorial conformations of cyclohexanol (hydroxycyclohexane)?

Answer available at the end of this section.

Exercise 4.8.2

Why do you suppose an axial cyano (–CN) substituent causes practically no 1,3-diaxial steric strain (0.4 kJ/mol)?

Answer available at the end of this section.

Exercise 4.8.3

Look back at Figure 4.8.1 and estimate the percentages of axial and equatorial conformations present at equilibrium in bromocyclohexane.

Answer available at the end of this section.

Answers

Exercise 4.8.1

4.2 kJ/mol

Exercise 4.8.2

Cyano group points straight up.

Exercise 4.8.3

Equatorial = 70%; axial = 30%

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4.9: Conformations of Disubstituted Cyclohexanes

Monosubstituted cyclohexanes are always more stable with their substituent in an equatorial position, but the situation with disubstituted cyclohexanes is more complex because the steric effects of both substituents must be taken into account. All steric interactions for both possible chair conformations must be analyzed before deciding which conformation is favored.

Let's look at 1,2-dimethylcyclohexane as an example. There are two isomers, *cis*-1,2-dimethylcyclohexane and *trans*-1,2-dimethylcyclohexane, which must be considered separately. In the cis isomer, both methyl groups are on the same face of the ring and the compound can exist in either of the two chair conformations shown in Figure 4.9.1. (It may be easier for you to see whether a compound is cis- or trans-disubstituted by first drawing the ring as a flat representation and then converting it to a chair conformation.)

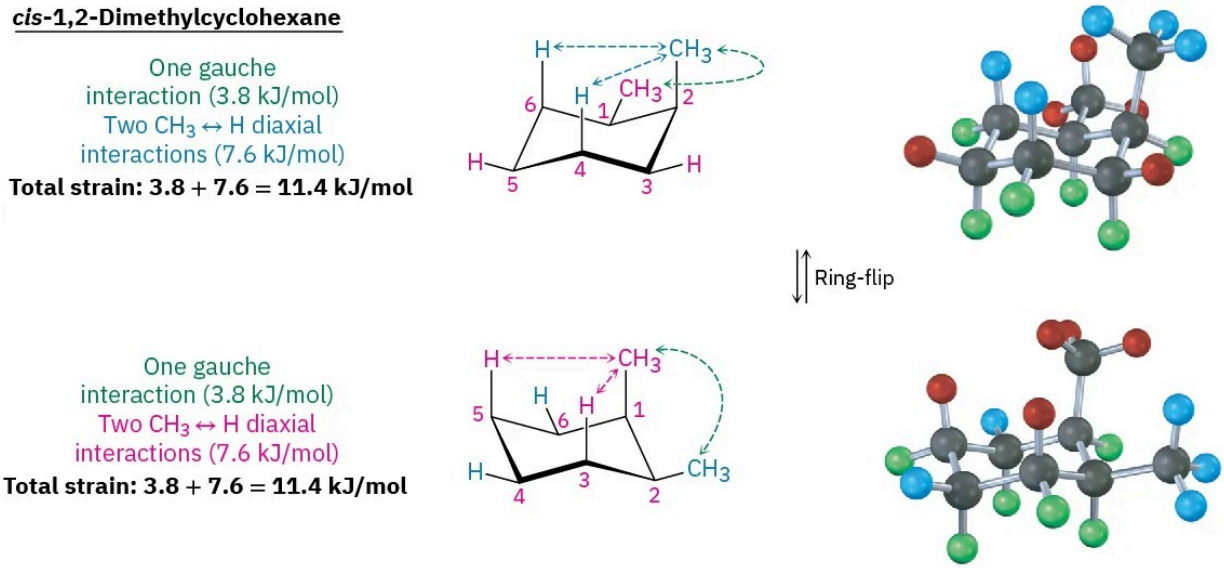


Figure 4.9.1: Conformations of *cis*-1,2-dimethylcyclohexane. The two chair conformations are equal in energy because each has one axial methyl group and one equatorial methyl group.

Both chair conformations of *cis*-1,2-dimethylcyclohexane have one axial methyl group and one equatorial methyl group. The top conformation in Figure 4.9.1 has an axial methyl group at C2, which has 1,3-diaxial interactions with hydrogens on C4 and C6. The ring-flipped conformation has an axial methyl group at C1, which has 1,3-diaxial interactions with hydrogens on C3 and C5. In addition, both conformations have gauche butane interactions between the two methyl groups. The two conformations are equal in energy, with a total steric strain of 3 × 3.8 kJ/mol = 11.4 kJ/mol (2.7 kcal/mol).

In *trans*-1,2-dimethylcyclohexane, the two methyl groups are on opposite sides of the ring and the compound can exist in either of the two chair conformations shown in Figure 4.9.2. The situation here is quite different from that of the cis isomer. The top conformation in Figure 4.9.2 has both methyl groups equatorial with only a gauche butane interaction between them (3.8 kJ/mol) but no 1,3-diaxial interactions. The ring-flipped conformation, however, has both methyl groups axial. The axial methyl group at C1 interacts with axial hydrogens at C3 and C5, and the axial methyl group at C2 interacts with axial hydrogens at C4 and C6. These four 1,3-diaxial interactions produce a steric strain of 4 × 3.8 kJ/mol = 15.2 kJ/mol and make the diaxial conformation 15.2 – 3.8 = 11.4 kJ/mol less favorable than the diequatorial conformation. We therefore predict that *trans*-1,2-dimethylcyclohexane will exist almost exclusively in the diequatorial conformation.

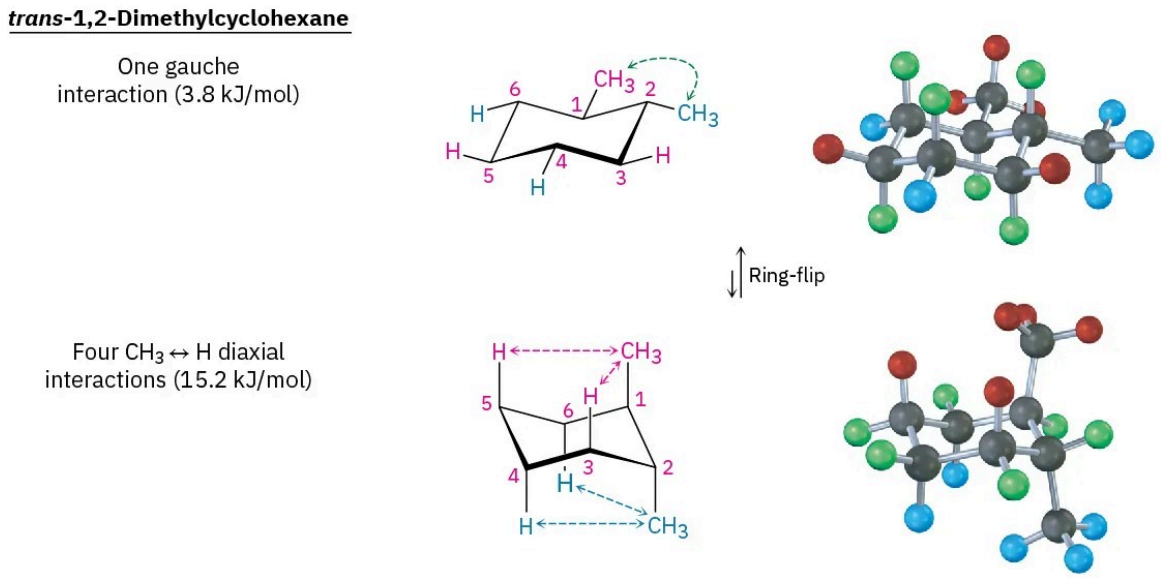
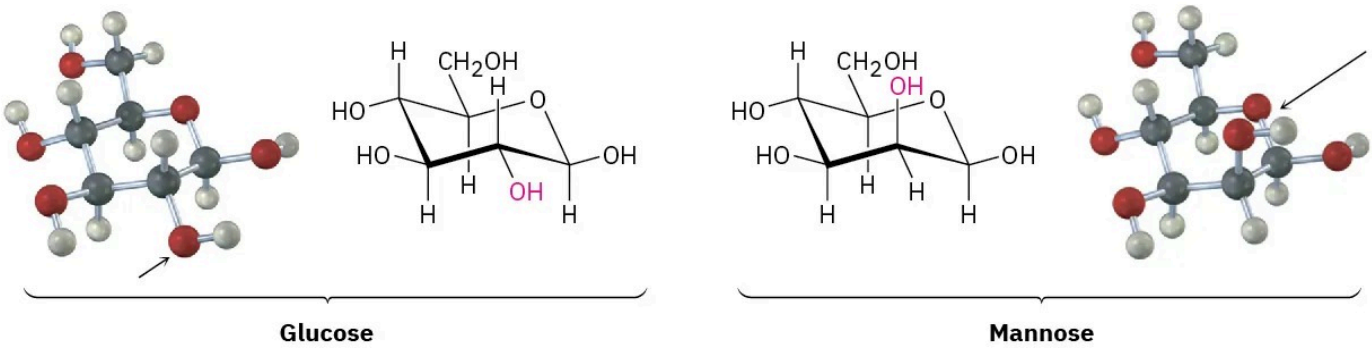


Figure 4.9.2: Conformations of *trans*-1,2-dimethylcyclohexane. The conformation with both methyl groups equatorial (top) is favored by 11.4 kJ/mol (2.7 kcal/mol) over the conformation with both methyl groups axial (bottom).

The same kind of conformational analysis just carried out for *cis*- and *trans*-1,2-dimethylcyclohexane can be done for any substituted cyclohexane, such as *cis*-1-*tert*-butyl-4-chlorocyclohexane (see Worked Example 4.3). As you might imagine, though, the situation becomes more complex as the number of substituents increases. For instance, compare glucose with mannose, a carbohydrate present in seaweed. Which do you think is more strained? In glucose, all substituents on the six-membered ring are equatorial, while in mannose, one of the –OH groups is axial, making it more strained.



A summary of the various axial and equatorial relationships among substituent groups in the different possible cis and trans substitution patterns for disubstituted cyclohexanes is given in Table 4.9.1.

Table 4.9.1: Axial and Equatorial Relationships in Cis- and Trans-Disubstituted Cyclohexanes

Cis/trans substitution pattern	Axial/equatorial relationships
1,2-Cis disubstituted	a,e or e,a
1,2-Trans disubstituted	a,a or e,e
1,3-Cis disubstituted	a,a or e,e
1,3-Trans disubstituted	a,e or e,a
1,4-Cis disubstituted	a,e or e,a
1,4-Trans disubstituted	a,a or e,e

Worked Example 4.9.1: Drawing the Most Stable Conformation of a Substituted Cyclohexane

Draw the more stable chair conformation of *cis*-1-*tert*-butyl-4-chlorocyclohexane. By how much is it favored?

Strategy

Draw the two possible chair conformations, and calculate the strain energy in each. Remember that equatorial substituents cause less strain than axial substituents.

Solution

First draw the two chair conformations of the molecule:



2 × 1.0 = 2.0 kJ/mol steric strain

2 × 11.4 = 22.8 kJ/mol steric strain

In the conformation on the left, the *tert*-butyl group is equatorial and the chlorine is axial. In the conformation on the right, the *tert*-butyl group is axial and the chlorine is equatorial. These conformations aren't of equal energy because an axial *tert*-butyl substituent and an axial chloro substituent produce different amounts of steric strain. Table 4.1 shows that the 1,3-diaxial interaction between a hydrogen and a *tert*-butyl group costs 11.4 kJ/mol (2.7 kcal/mol), whereas the interaction between a hydrogen and a chlorine costs only 1.0 kJ/mol (0.25 kcal/mol). An axial *tert*-butyl group therefore produces (2 × 11.4 kJ/mol) – (2 × 1.0 kJ/mol) = 20.8 kJ/mol (4.9 kcal/mol) more steric strain than an axial chlorine, and the compound preferentially adopts the conformation with the chlorine axial and the *tert*-butyl equatorial.

Exercise 4.9.1

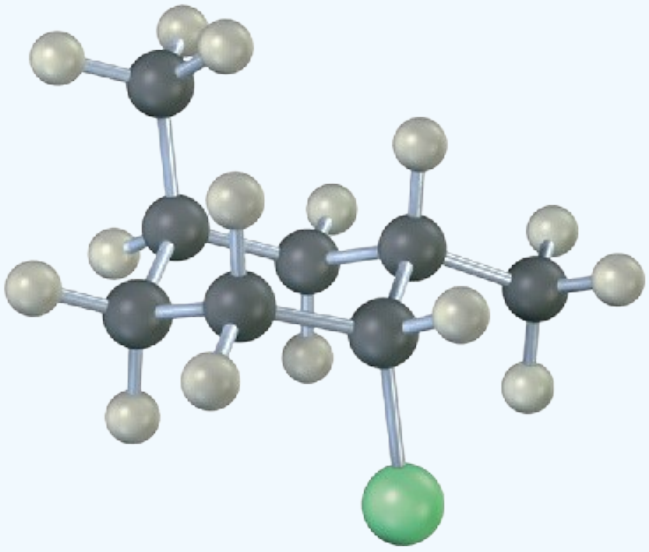
Draw the more stable chair conformation of the following molecules, and estimate the amount of strain in each:

a. *trans*-1-Chloro-3-methylcyclohexane
b. *cis*-1-Ethyl-2-methylcyclohexane
c. *cis*-1-Bromo-4-ethylcyclohexane
d. *cis*-1-*tert*-Butyl-4-ethylcyclohexane

Answer available at the end of this section.

Exercise 4.9.2

Identify each substituent in the following compound as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



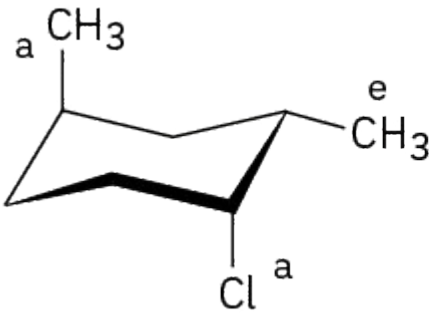
Answer available at the end of this section.

Answers

Exercise 4.9.1

a. 2.0 kJ/mol (axial Cl)
b. 11.4 kJ/mol (axial CH_3)
c. 2.0 kJ/mol (axial Br)
d. 8.0 kJ/mol (axial CH_2CH_3)

Exercise 4.9.2



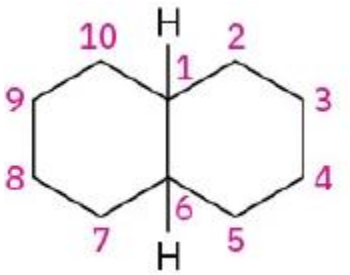
1-Chloro-2,4-dimethyl-cyclohexane
(less stable chair form)

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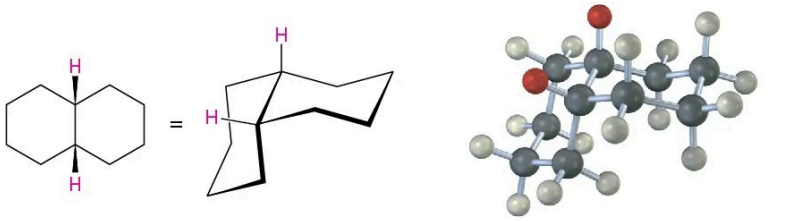
4.10: Conformations of Polycyclic Molecules

The final point we'll consider about cycloalkane stereochemistry is to see what happens when two or more cycloalkane rings are fused together along a common bond to construct a polycyclic molecule—for example, decalin.

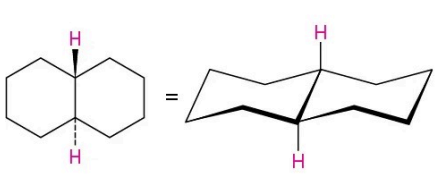


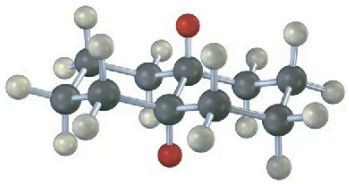
Decalin—two fused cyclohexane rings

Decalin consists of two cyclohexane rings joined to share two carbon atoms (the *bridgehead* carbons, C1 and C6) and a common bond. Decalin can exist in either of two isomeric forms, depending on whether the rings are trans fused or cis fused. In *cis*-decalin, the hydrogen atoms at the bridgehead carbons are on the same side of the rings; in *trans*-decalin, the bridgehead hydrogens are on opposite sides. Figure 4.10.1 shows how both compounds can be represented using chair cyclohexane conformations. Note that the two decalin isomers are not interconvertible by ring-flips or other rotations. They are cis–trans stereoisomers and have the same relationship to each other that *cis*- and *trans*-1,2-dimethylcyclohexane have.



***cis*-Decalin**

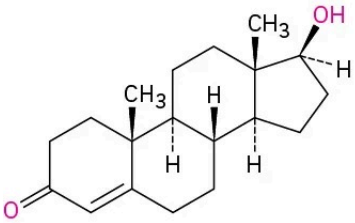


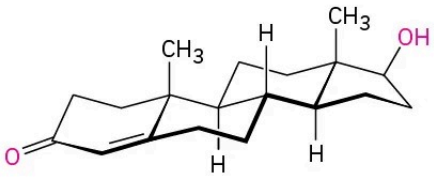


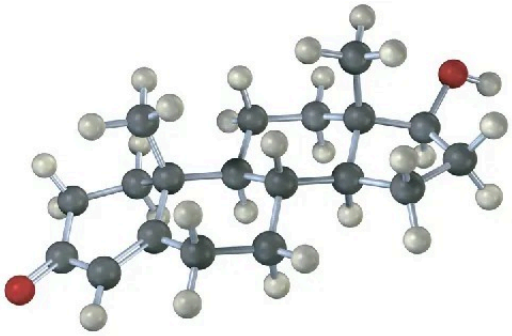
***trans*-Decalin**

Figure 4.10.1: Representations of *cis*- and *trans*-decalin. **Hydrogen atoms** at the bridgehead carbons are on the same face of the rings in the cis isomer but on opposite faces in the trans isomer.

Polycyclic compounds are common in nature, and many valuable substances have fused-ring structures. For example, steroids, such as testosterone, the primary sex hormone in males, have three six-membered rings and one five-membered ring fused together. Although steroids look complicated compared with cyclohexane or decalin, the same principles that apply to the conformational analysis of simple cyclohexane rings apply equally well (and often better) to steroids.

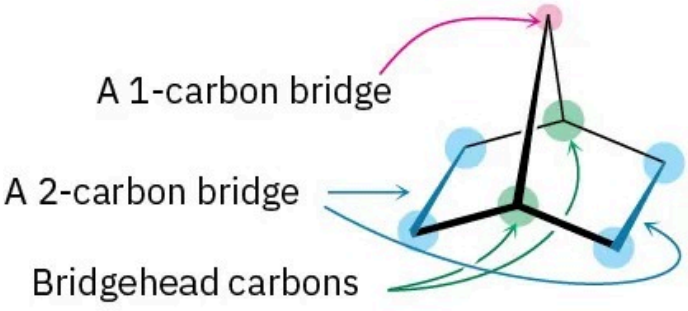


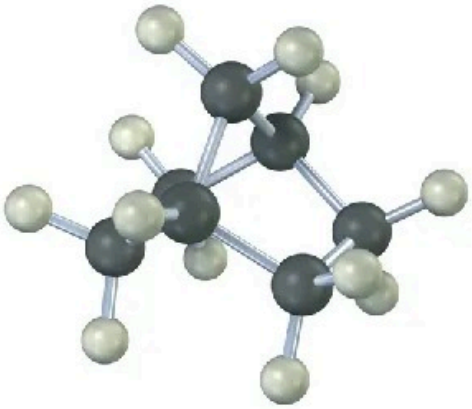




Testosterone (a steroid)

Another common ring system is the norbornane, or bicyclo[2.2.1]heptane, structure. Like decalin, norbornane is a bicycloalkane, so called because two rings would have to be broken open to generate an acyclic structure. Its systematic name, bicyclo[2.2.1]heptane, reflects the fact that the molecule has seven carbons, is bicyclic, and has three "bridges" of 2, 2, and 1 carbon atoms connecting the two bridgehead carbons.

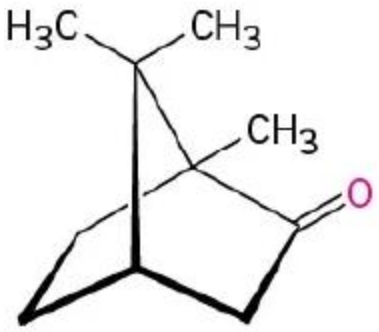


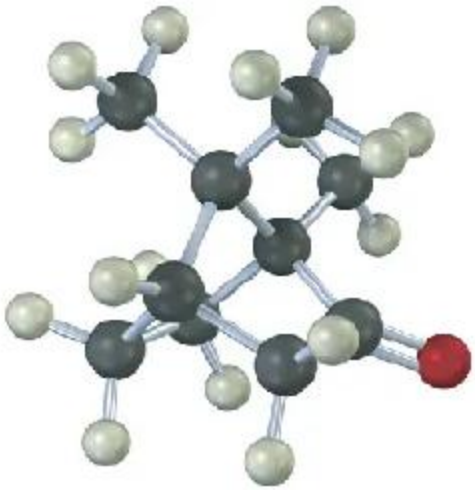


Norbornane
(bicyclo[2.2.1]heptane)

Norbornane has a conformationally locked boat cyclohexane ring (Section 4.5) in which carbons 1 and 4 are joined by an additional CH_2 group. In drawing this structure, a break in the rear bond indicates that the vertical bond crosses in front of it. Making a molecular model is particularly helpful when trying to see the three-dimensionality of norbornane.

Substituted norbornanes, such as camphor, are found widely in nature, and many have been important historically in developing organic structural theories.





Camphor

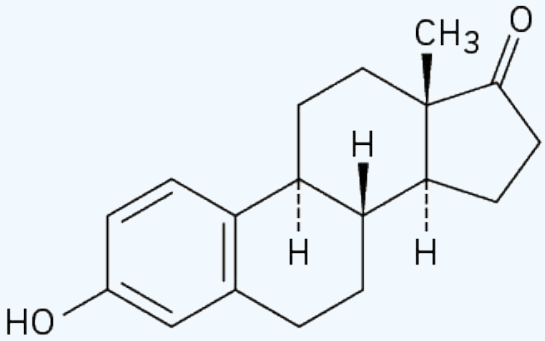
Exercise 4.10.1

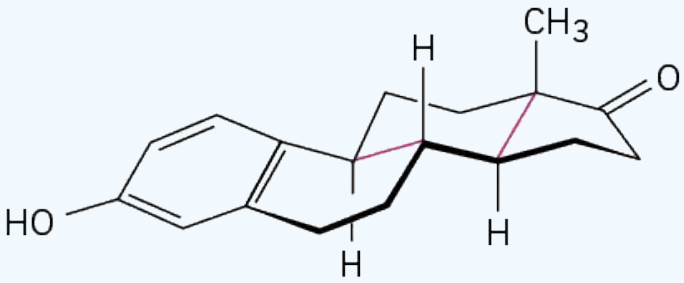
Which isomer is more stable, *cis*-decalin or *trans*-decalin (Figure 4.10.1)? Explain.

Answer available at the end of this section.

Exercise 4.10.2

Look at the following structure of estrone, the primary sex hormone in females, and tell whether each of the two indicated (red) ring-fusions is cis or trans.





Estrone

Answer available at the end of this section.

Answers

Exercise 4.10.1

trans-Decalin is more stable because it has no 1,3-diaxial interactions.

Exercise 4.10.2

Both ring-fusions are trans.

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4.11: Chemistry Matters—Molecular Mechanics

All the structural models in this book are computer-drawn. To make sure they accurately represent bond angles, bond lengths, torsional interactions, and steric interactions, the most stable geometry of each molecule has been calculated on a desktop computer using a commercially available *molecular mechanics* program based on work by Norman Allinger at the University of Georgia.

The idea behind molecular mechanics is to begin with a rough geometry for a molecule and then calculate a total strain energy for that starting geometry, using mathematical equations that assign values to specific kinds of molecular interactions. Bond angles that are too large or too small cause angle strain; bond lengths that are too short or too long cause stretching or compressing strain; unfavorable eclipsing interactions around single bonds cause torsional strain; and nonbonded atoms that approach each other too closely cause steric, or *van der Waals,* strain.

$$E_{\text{total}} = E_{\text{bond stretching}} + E_{\text{angle strain}} + E_{\text{torsional strain}} + E_{\text{van der Waals}}$$

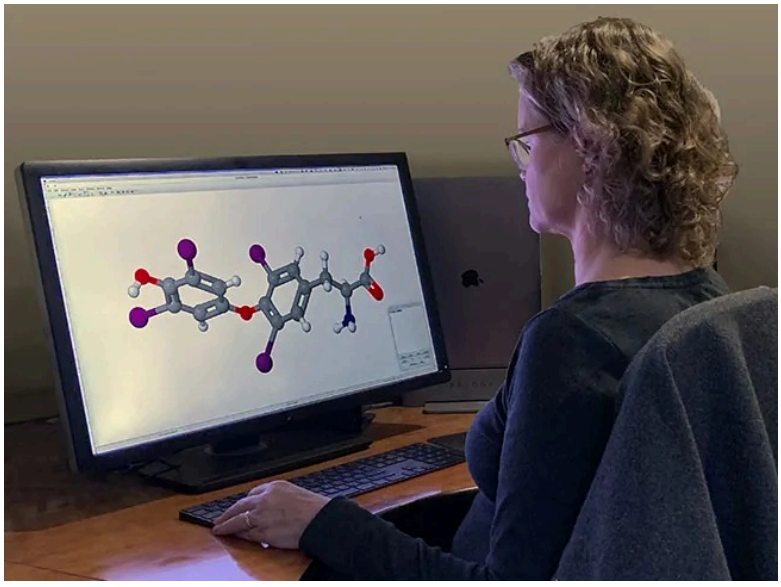


Figure 4.11.1: Computer programs make it possible to accurately represent molecular geometry. (credit: “Molecular geometry” by Jane Whitney/Flickr, CC BY 4.0)

After calculating a total strain energy for the starting geometry, the program automatically changes the geometry slightly in an attempt to lower strain—perhaps by lengthening a bond that is too short or decreasing an angle that is too large. Strain is recalculated for the new geometry, more changes are made, and more calculations are done. After dozens or hundreds of iterations, the calculation ultimately converges on a minimum energy that corresponds to the most favorable, least strained conformation of the molecule.

Similar calculations have proven to be particularly useful in pharmaceutical research, where a complementary fit between a drug molecule and a receptor molecule in the body is often the key to designing new pharmaceutical agents (Figure 4.11.2).

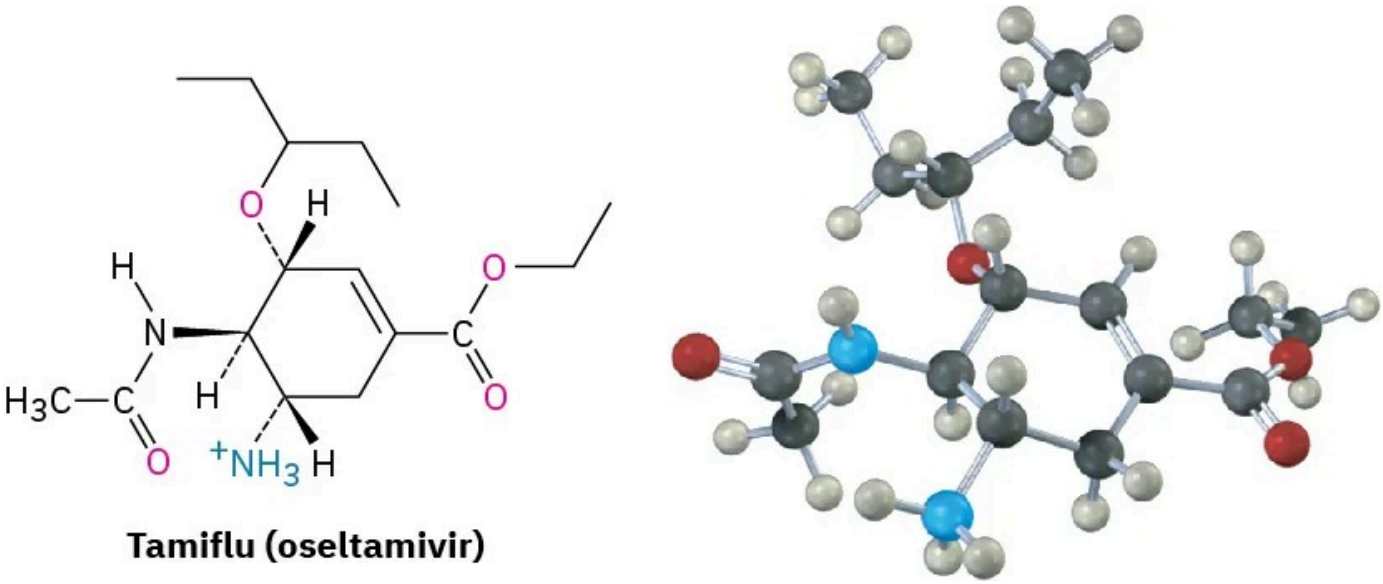


Figure 4.11.2: The structure of Tamiflu (oseltamivir), an antiviral agent active against type A influenza, along with a molecular model of its minimum-energy conformation as calculated by molecular mechanics.

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4.A: Conformation of Alkanes and Cycloalkanes (Summary)

Concepts & Vocabulary

4.2: Conformations of Ethane

- Rotation about the carbon-carbon sigma bonds in ethane results in different **rotational isomers** (also known as **conformational isomers** or **conformers**). **Newman projections** are a very common way of depicting conformers.
- The two most common conformers of ethane are called **staggered** and **eclipsed**. The staggered conformer is lower in energy (more stable) than the eclipsed conformer, because it has less **torsional strain**.

4.3: Conformations of Other Alkanes

- Alkanes more complex than ethane, will have a greater variety of possible conformers. The **anti** and **gauche** conformers of butane are specific types of staggered conformations.

4.4: Cis-Trans Isomerism in Cycloalkanes

- **Stereoisomers** are molecules that have the same molecular formula, the same atom connectivity, but they differ in the relative spatial orientation of the atoms.
- Di-substituted cycloalkanes exhibit ***cis-*** / ***trans-*** stereoisomerism. The ***cis-*** isomer has both substituents on the same face of the ring, while the **trans-** isomer has groups on opposite faces of the ring.

4.5: Stability of Cycloalkanes - Ring Strain

- **Ring strain** is the total strain in a ring due to **torsional strain**, **steric strain** and **angle strain**.
- Angle strain is when the C-C-C bond angles in rings are different than 109.5^{o}, the optimal bond angle for sp^3 hybridized carbons.
- Ring strain causes small cycloalkanes, like cyclopropane and cyclobutane, to be much less stable than other cycloalkanes.

4.6: Conformations of Cycloalkanes

- Cyclopentane has less ring strain than cyclopropane and cyclobutane, because its ring carbons have more flexibility to rotate away from planarity, resulting in lower angle and torsional strains.

4.7: Conformations of Cyclohexane

- Cyclohexane has significantly lower ring strain than smaller cycloalkanes, because cyclohexane can adopt non-planar structures, which minimize angle strain and torsional strain.
- The common non-planar structures of cyclohexane are the boat, twist-boat, and chair conformations. The most stable, and hence, the most common, is the chair conformation.

4.8: Axial and Equatorial Bonds in Cyclohexane

- The two chair conformations of cyclohexane interconvert rapidly at room temperature in a process called **chair flip** or **ring flip**.
- In the chair conformation of cyclohexane, of the two groups attached to each ring carbon, one of the groups occupies the **axial** position, while the other group occupies the **equatorial** position.
- A group that was axial will switch to the equatorial position during a ring flip, and vice versa.

4.9: Conformations of Monosubstituted Cyclohexanes

- To minimize the steric effects of **1,3-diaxial interactions**, the single group on a monosubstituted cyclohexane ring will prefer to be in the equatorial position over the axial position. The larger the group, the greater is the preference shifts.

4.10: Conformations of Disubstituted Cyclohexanes

- The preference for large groups to be in the equatorial position affects the relative stability of the *cis* and *trans* isomers of disubstituted cyclohexanes. **Conformational analysis** is the process used to determine which isomer, *cis* or *trans*, is most stable.

4.11: Conformations of Polycyclic Molecules

Skills to Master

- Skill 4.1 Be able to draw Newman Projections of different conformers of alkanes.
- Skill 4.2 Be able to evaluate a conformer in terms of torsional and steric strain.
- Skill 4.3 Be able to identify the staggered, eclipsed, anti, and gauche conformers of alkanes and to order them with respect to relative energy.
- Skill 4.4 Identify and draw the *cis*- and *trans*- stereoisomers of disubstituted cycloalkanes.
- Skill 4.5 Determine the effects of torsional strain, steric strain, and angle strain on the overall ring strain of a cycloalkane.
- Skill 4.6 Draw the chair conformers of cyclohexane.
- Skill 4.7 Draw and identify the axial and equatorial positions in a chair conformer of cyclohexane and its ring-flip conformer.
- Skill 4.8 Use conformational analysis to determine the most stable stereoisomer in disubstituted and polysubstituted cyclohexanes.

Contributors

- Dr. Kelly Matthews, Harrisburg Area Community College

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4.B: Additional Problems

Conformations

PROBLEM 3-42 Consider 2-methylbutane (isopentane). Sighting along the C2–C3 bond:

(a) Draw a Newman projection of the most stable conformation.
(b) Draw a Newman projection of the least stable conformation.
(c) If a CH_3 ⧫ CH_3 eclipsing interaction costs 11 kJ/mol (2.5 kcal/mol) and a CH_3 ⧫ CH_3 gauche interaction costs 3.8 kJ/mol (0.9 kcal/mol), make a quantitative plot of energy versus rotation about the C2–C3 bond.

PROBLEM 3-43 What are the relative energies of the three possible staggered conformations around the C2–C3 bond in 2,3-dimethylbutane? (See Problem 3-42.)

PROBLEM 3-44 Construct a qualitative potential-energy diagram for rotation about the C–C bond of 1,2-dibromoethane. Which conformation would you expect to be most stable? Label the anti and gauche conformations of 1,2-dibromoethane.

PROBLEM 3-45Which conformation of 1,2-dibromoethane (Problem 3-44) would you expect to have the largest dipole moment? The observed dipole moment of 1,2-dibromoethane is μ = 1.0 D. What does this tell you about the actual conformation of the molecule?

PROBLEM 3-46 Draw the most stable conformation of pentane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

PROBLEM 3-47 Draw the most stable conformation of 1,4-dichlorobutane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

PROBLEM 3-51 The barrier to rotation about the C–C bond in bromoethane is 15 kJ/mol (3.6 kcal/mol).

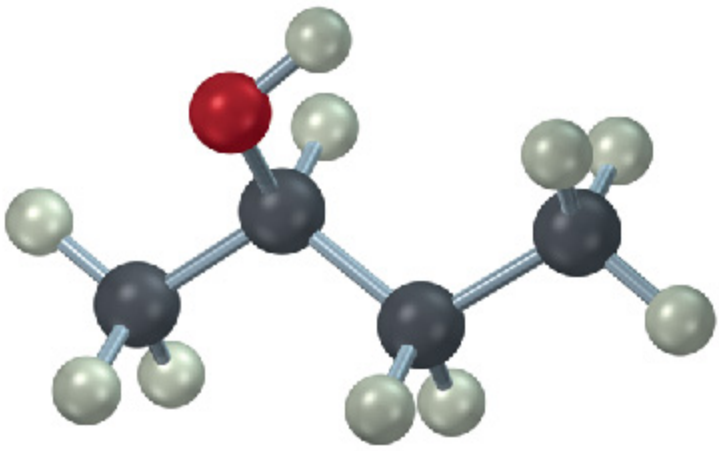
(a) What energy value can you assign to an H ↔ Br eclipsing interaction?
(b) Construct a quantitative diagram of potential energy versus bond rotation for bromoethane.

PROBLEM 3-52 Increased substitution around a bond leads to increased strain. Take the four substituted butanes listed below, for example. For each compound, sight along the C2–C3 bond and draw Newman projections of the most stable and least stable conformations. Use the data in Table 3.5 to assign strain-energy values to each conformation. Which of the eight conformations is most strained? Which is least strained?

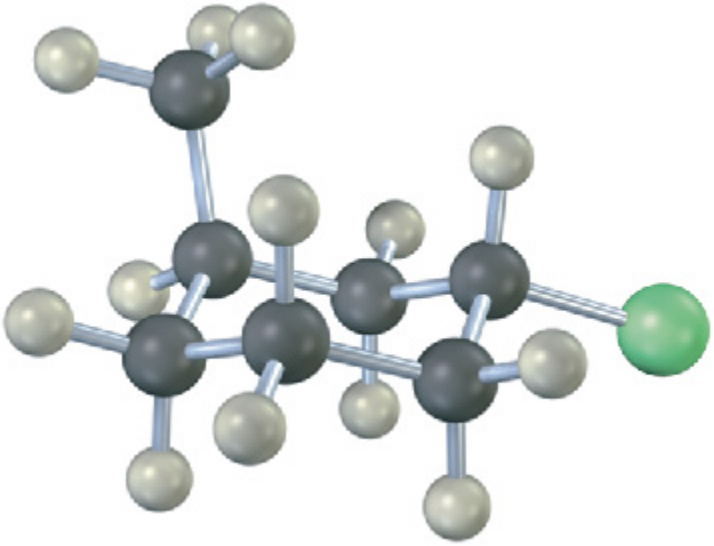
(a) 2-Methylbutane (b) 2,2-Dimethylbutane (c) 2,3-Dimethylbutane (d) 2,2,3-Trimethylbutane

Visualizing Chemistry

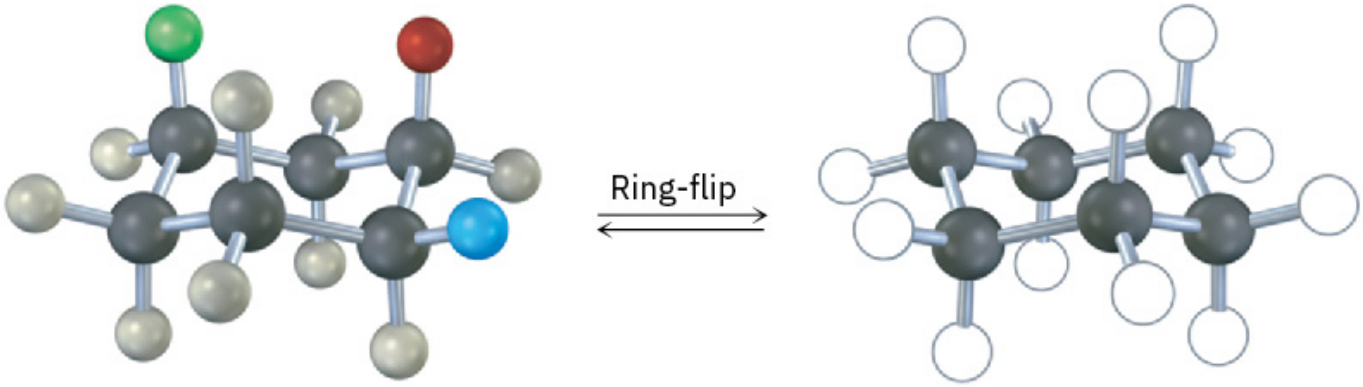
PROBLEM 4-22 Draw a Newman projection along the C2–C3 bond of the following conformation of 2-butanol.



PROBLEM 4-23 Name the following compound, identify each substituent as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):

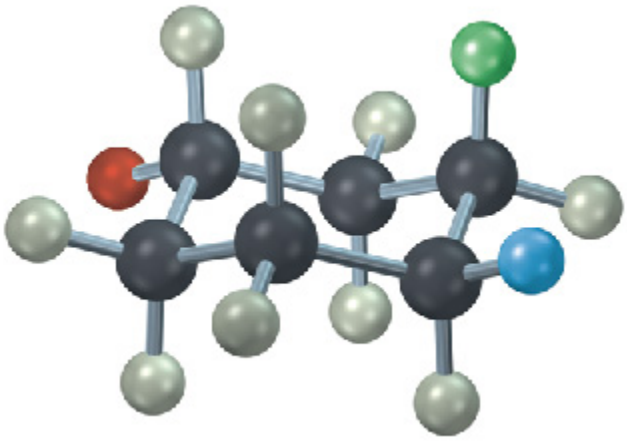


PROBLEM 4-24 A trisubstituted cyclohexane with three substituents—red, green, and blue—undergoes a ring-flip to its alternate chair conformation. Identify each substituent as axial or equatorial, and show the positions occupied by the three substituents in the ring-flipped form.

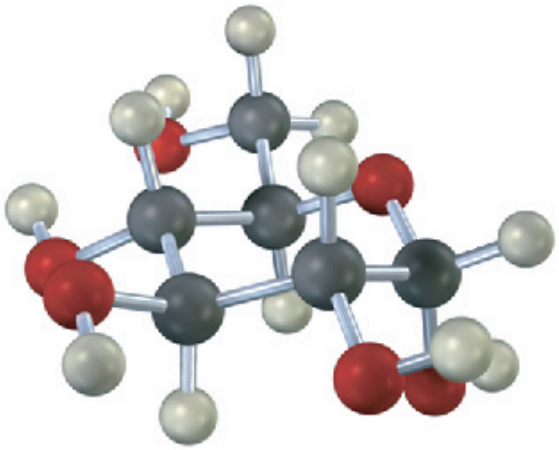


PROBLEM 4-25 The following cyclohexane derivative has three substituents—red, green, and blue. Identify each substituent as

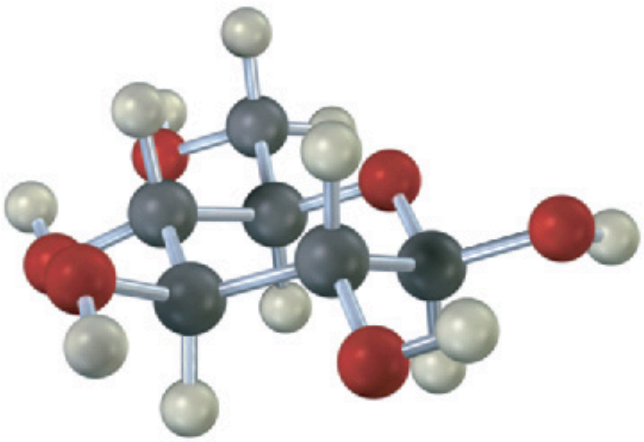
axial or equatorial, and identify each pair of relationships (red–blue, red–green, and blue–green) as cis or trans.



PROBLEM 4-26 Glucose exists in two forms having a 36:64 ratio at equilibrium. Draw a skeletal structure of each, describe the difference between them, and tell which of the two you think is more stable (red = O).



α-Glucose



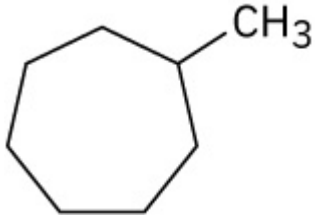
β-Glucose

Cycloalkane Isomers

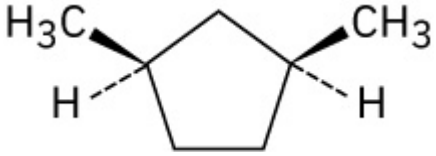
PROBLEM 4-27 Draw the five cycloalkanes with the formula C_5H_{10}.

PROBLEM 4-28 Give IUPAC names for the following compounds.

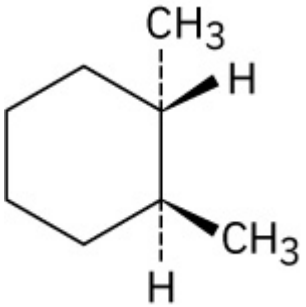
(a)



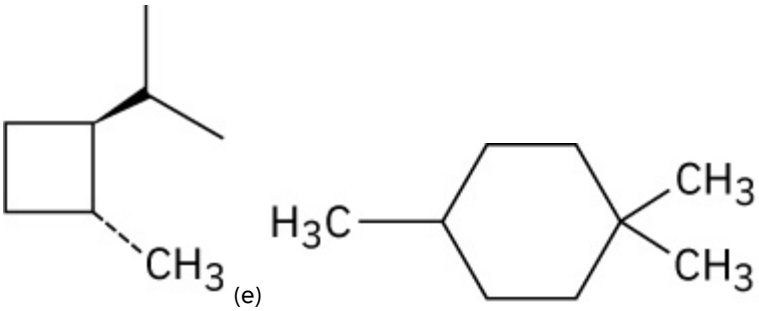
(b)



(c)



(d)



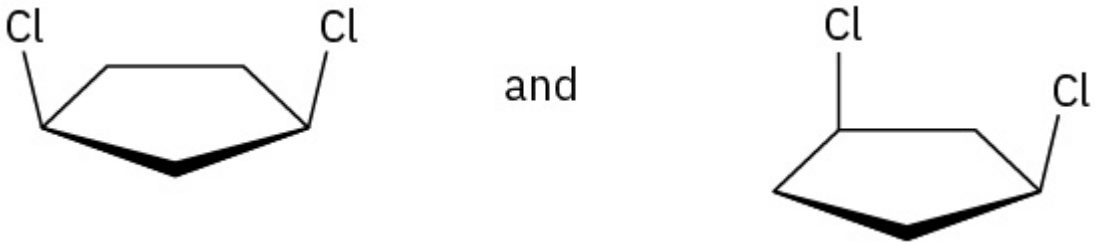
(e)

PROBLEM 4-29 Draw a stereoisomer of *trans*-1,3-dimethylcyclobutane.

PROBLEM 4-30 Tell whether the following pairs of compounds are identical, constitutional isomers, stereoisomers, or unrelated.

(a) *cis*-1,3-Dibromocyclohexane and *trans*-1,4-dibromocyclohexane

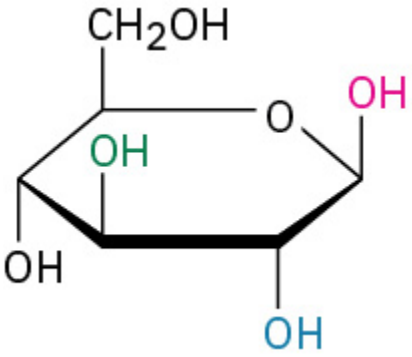
(b) 2,3-Dimethylhexane and 2,3,3-trimethylpentane



(c)

PROBLEM 4-31 Draw three isomers of *trans*-1,2-dichlorocyclobutane, and label them as either constitutional isomers or stereoisomers.

PROBLEM 4-32 Identify each pair of relationships among the –OH groups in glucose (red–blue, red–green, red–black, blue–green, blue–black, green–black) as cis or trans.

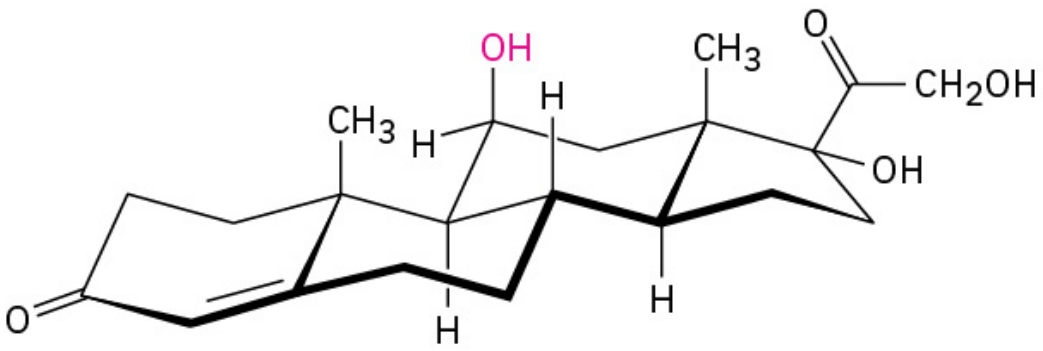


Glucose

PROBLEM 4-33 Draw 1,3,5-trimethylcyclohexane using a hexagon to represent the ring. How many cis–trans stereoisomers are possible?

Cycloalkane Conformation and Stability

PROBLEM 4-34 Hydrocortisone, a naturally occurring hormone produced in the adrenal glands, is often used to treat inflammation, severe allergies, and numerous other conditions. Is the indicated –OH group axial or equatorial?



Hydrocortisone

PROBLEM 4-35 A 1,2-cis disubstituted cyclohexane, such as *cis*-1,2-dichlorocyclohexane, must have one group axial and one group equatorial. Explain.

PROBLEM 4-36 A 1,2-trans disubstituted cyclohexane must have either both groups axial or both groups equatorial. Explain.

PROBLEM 4-37 Why is a 1,3-cis disubstituted cyclohexane more stable than its trans isomer?

PROBLEM 4-38 Which is more stable, a 1,4-trans disubstituted cyclohexane or its cis isomer?

PROBLEM 4-39 *cis*-1,2-Dimethylcyclobutane is less stable than its trans isomer, but *cis*-1,3-dimethylcyclobutane is more stable than its trans isomer. Draw the most stable conformations of both, and explain.

PROBLEM 4-40 From the data in Figure 4.13 and Table 4.1, estimate the percentages of molecules that have their substituents in an axial orientation for the following compounds:

(a) Isopropylcyclohexane

(b) Fluorocyclohexane

(c) Cyclohexanecarbonitrile, $C_6H_{11}CN$

PROBLEM 4-41 Assume that you have a variety of cyclohexanes substituted in the positions indicated. Identify the substituents as either axial or equatorial. For example, a 1,2-cis relationship means that one substituent must be axial and one equatorial, whereas a 1,2-trans relationship means that both substituents are axial or both are equatorial.

(a) 1,3-Trans disubstituted (b) 1,4-Cis disubstituted (c) 1,3-Cis disubstituted

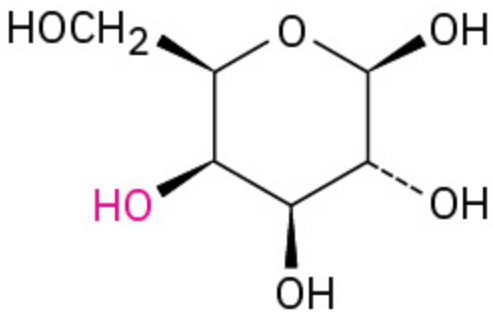
(d) 1,5-Trans disubstituted (e) 1,5-Cis disubstituted (f) 1,6-Trans disubstituted

Cyclohexane Conformational Analysis

PROBLEM 4-42 Draw the two chair conformations of *cis*-1-chloro-2-methylcyclohexane. Which is more stable, and by how much?

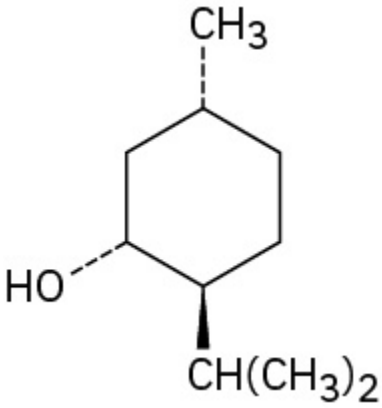
PROBLEM 4-43 Draw the two chair conformations of *trans*-1-chloro-2-methylcyclohexane. Which is more stable?

PROBLEM 4-44 Galactose, a sugar related to glucose, contains a six-membered ring in which all the substituents except the –OH group, indicated below in red, are equatorial. Draw galactose in its more stable chair conformation.



Galactose

PROBLEM 4-45 Draw the two chair conformations of menthol, and tell which is more stable.



Menthol

PROBLEM 4-46 There are four cis–trans isomers of menthol (Problem 4-45), including the one shown. Draw the other three.

PROBLEM 4-47 The diaxial conformation of *cis*-1,3-dimethylcyclohexane is approximately 23 kJ/mol (5.4 kcal/mol) less stable than the diequatorial conformation. Draw the two possible chair conformations, and suggest a reason for the large energy difference.

PROBLEM 4-48 Approximately how much steric strain does the 1,3-diaxial interaction between the two methyl groups introduce into the diaxial conformation of *cis*-1,3-dimethylcyclohexane? (See Problem 4-47.)

PROBLEM 4-49 In light of your answer to Problem 4-48, draw the two chair conformations of 1,1,3-trimethylcyclohexane and estimate the amount of strain energy in each. Which conformation is favored?

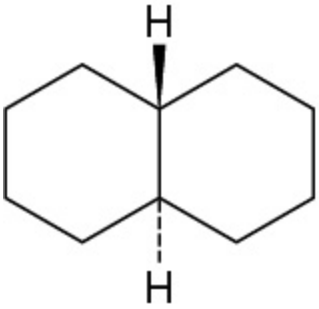
PROBLEM 4-50 One of the two chair structures of *cis*-1-chloro-3-methylcyclohexane is more stable than the other by 15.5 kJ/mol (3.7 kcal/mol). Which is it? What is the energy cost of a 1,3-diaxial interaction between a chlorine and a methyl group?

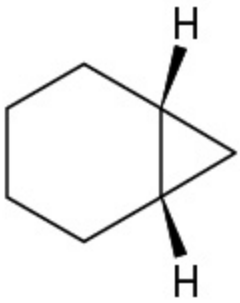
General Problems

PROBLEM 4-51 We saw in Problem 4.10.1 that *cis*-decalin is less stable than *trans*-decalin. Assume that the 1,3-diaxial interactions in *cis*-decalin are similar to those in axial methylcyclohexane [that is, one CH2↔H interaction costs 3.8 kJ/mol (0.9 kcal/mol)], and calculate the magnitude of the energy difference between *cis*- and *trans*-decalin.

PROBLEM 4-52 Using molecular models as well as structural drawings, explain why *trans*-decalin is rigid and cannot ring-flip whereas *cis*-decalin can easily ring-flip.

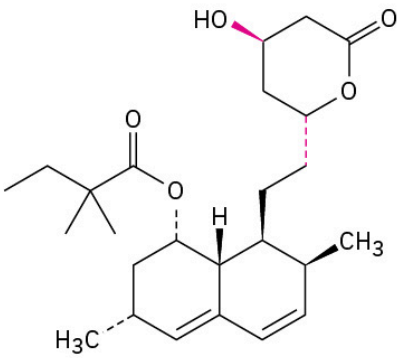
PROBLEM 4-53 *trans*-Decalin is more stable than its cis isomer, but *cis*-bicyclo[4.1.0]heptane is more stable than its trans isomer. Explain.



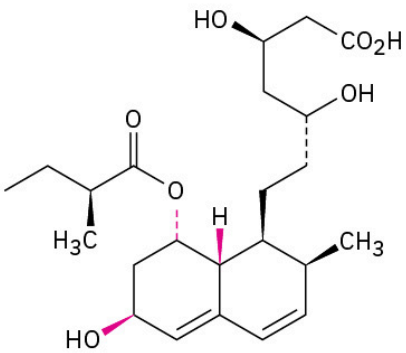


***trans*-Decalin** ***cis*-Bicyclo[4.1.0]heptane**

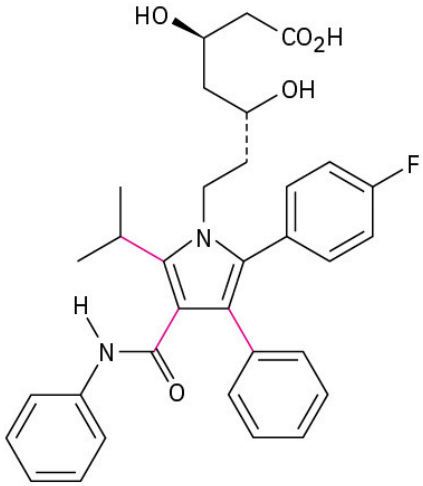
PROBLEM 4-54 As mentioned before, statin drugs, such as simvastatin (Zocor), pravastatin (Pravachol), and atorvastatin (Lipitor), are the most widely prescribed drugs in the world.



Simvastatin (Zocor)



Pravastatin (Pravachol)



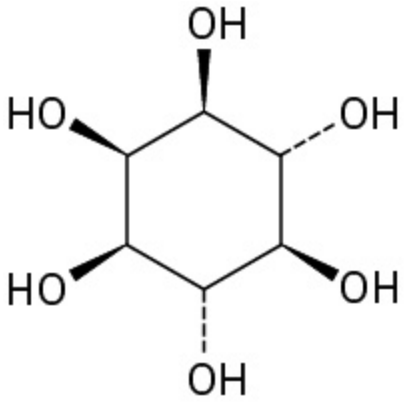
Atorvastatin (Lipitor)

(a) Are the two indicated bonds on simvastatin cis or trans?

(b) What are the cis/trans relationships among the three indicated bonds on pravastatin?

(c) Why can't the three indicated bonds on atorvastatin be identified as cis or trans?

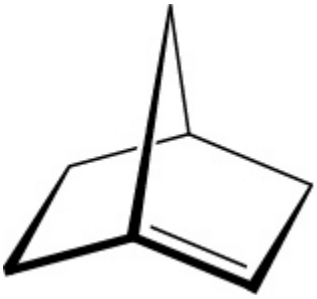
PROBLEM 4-55 *myo*-Inositol, one of the isomers of 1,2,3,4,5,6-hexahydroxycyclohexane, acts as a growth factor in both animals and microorganisms. Draw the most stable chair conformation of *myo*-inositol.



***myo*-Inositol**

PROBLEM 4-56 How many cis–trans stereoisomers of *myo*-inositol (Problem 4-55) are there? Draw the structure of the most stable isomer.

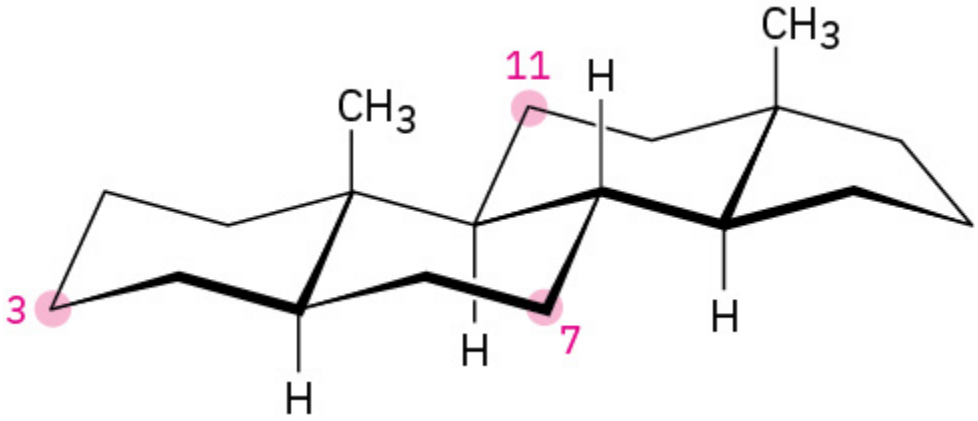
PROBLEM 4-57 Julius Bredt, discoverer of the structure of camphor, proposed in 1935 that bicycloalkenes such as 1-norbornene, which have a double bond to a bridgehead carbon, are too strained to exist. Explain. (Making a molecular model will be helpful.



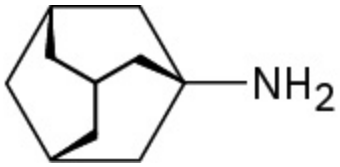
1-Norbornene

PROBLEM 4-58 Tell whether each of the following substituents on a steroid is axial or equatorial. (A substituent that is "up" is on the top side of the molecule as drawn, and a substituent that is "down" is on the bottom side.

(a) Substituent up at C3 (b) Substituent down at C7 (c) Substituent down at C11

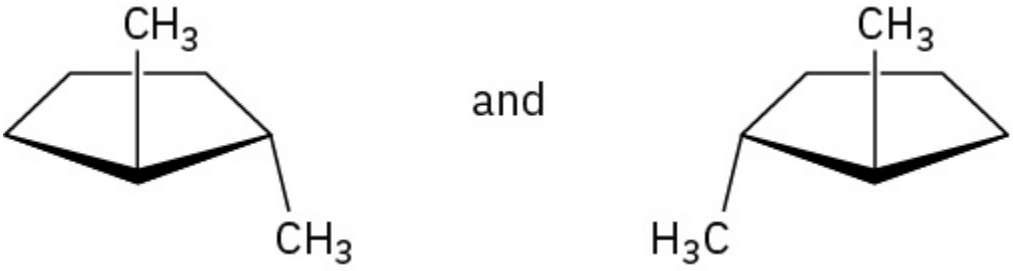


PROBLEM 4-59 Amantadine is an antiviral agent that is active against influenza type A infection. Draw a three-dimensional representation of amantadine, showing the chair cyclohexane rings.

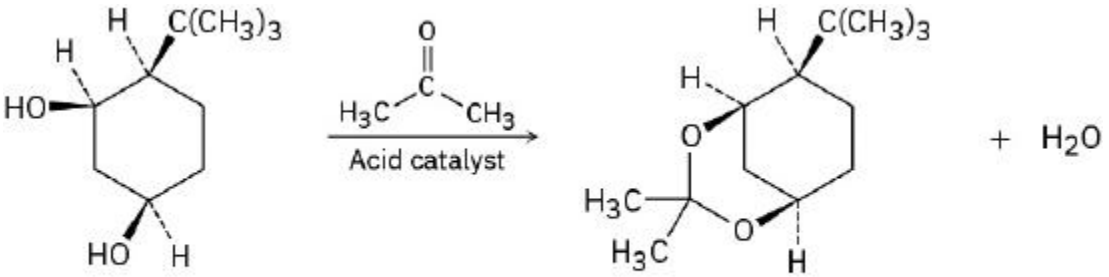


Amantadine

PROBLEM 4-60 There are two different isomers named *trans*-1,2-dimethylcyclopentane. Similarly, you have two different appendages called hands. What is the relationship between them? (We'll explore this kind of isomerism in the next chapter.)

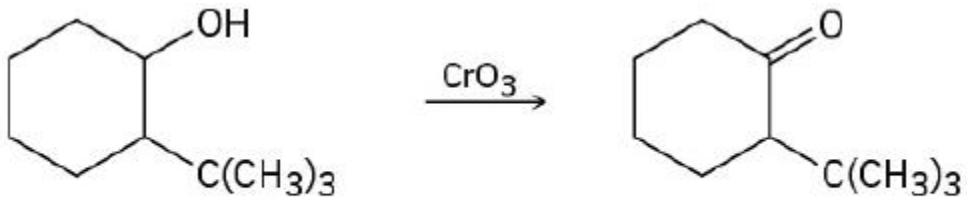


PROBLEM 4-61 Ketones react with alcohols to yield products called *ketals*. Why does the all-cis isomer of 4-*tert*-butyl-1,3-cyclohexanediol react readily with acetone and an acid catalyst to form a ketal, but other stereoisomers do not react? In formulating your answer, draw the more stable chair conformations of all four stereoisomers and the product ketal for each one.



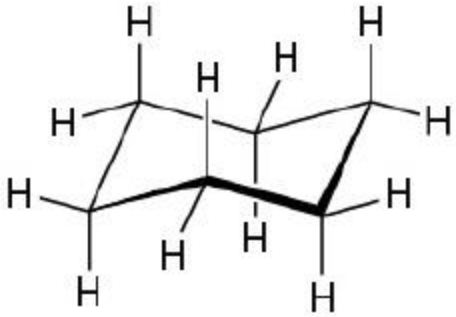
A ketal

PROBLEM 4-62 Alcohols undergo an *oxidation* reaction to yield carbonyl compounds when treatment with CrO_3. For example, 2-*tert*-butylcyclohexanol gives 2-*tert*-butylcyclohexanone. If axial –OH groups are generally more reactive than their equatorial isomers, which do you think reacts faster, the cis isomer of 2-*tert*-butylcyclohexanol or the trans isomer? Explain.

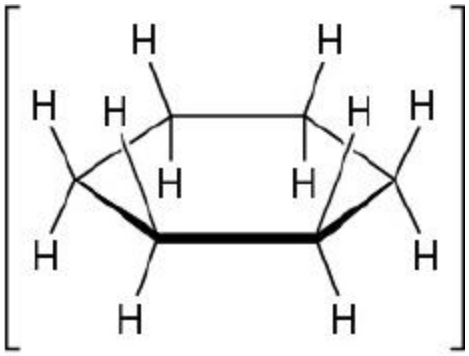


2-*tert*-Butylcyclohexanol **2-*tert*-Butylcyclohexanone**

PROBLEM 4-63 C*ycloalkanes*—saturated cyclic hydrocarbons—generally adopt puckered, nonplanar conformations. Cyclohexane, for instance, has a puckered shape like a lounge chair rather than a flat shape. Why?

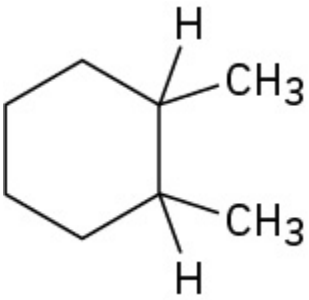


Nonplanar cyclohexane



Planar cyclohexane

PROBLEM 4-64 There are two isomeric substances, both named 1,2-dimethylcyclohexane. Explain.



1,2-Dimethylcyclohexane

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5: STEREOCHEMISTRY AT TETRAHEDRAL CENTERS

Learning Objectives

After you have completed Chapter 5, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use molecular models in solving problems on stereochemistry.
- solve road-map problems that include stereochemical information.
- define, and use in context, the new key terms.

This chapter introduces the concept of chirality, and discusses the structure of compounds containing one or two chiral centers. A convenient method of representing the three-dimensional arrangement of the atoms in chiral compounds is explained; furthermore, throughout the chapter , considerable emphasis is placed on the use of molecular models to assist in the understanding of the phenomenon of chirality. The chapter continues with an examination of stereochemistry—the three-dimensional nature of molecules. The subject is introduced using the experimental observation that certain substances have the ability to rotate plane-polarized light. Finally, certain reactions of alkenes are re-examined in the light of the new material encountered in this chapter.

5.0: Why This Chapter?

5.1: Enantiomers and the Tetrahedral Carbon

5.2: The Reason for Handedness in Molecules - Chirality

5.3: Optical Activity

5.4: Pasteur's Discovery of Enantiomers

5.5: Sequence Rules for Specifying Configuration

5.6: Diastereomers

5.7: Meso Compounds

5.8: Racemic Mixtures and the Resolution of Enantiomers

5.9: A Review of Isomerism

5.10: Chirality at Nitrogen, Phosphorus, and Sulfur

5.11: Prochirality

5.12: Chirality in Nature and Chiral Environments

5.13: Chemistry Matters—Chiral Drugs

5.A: Stereochemistry at Tetrahedral Centers (Summary)

5.B: Additional Problems

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5.0: Why This Chapter?

Understanding the causes and consequences of molecular handedness is crucial to understanding organic and biological chemistry. The subject can be a bit complex at first, but the material covered in this chapter nevertheless forms the basis for much of the remainder of the book.

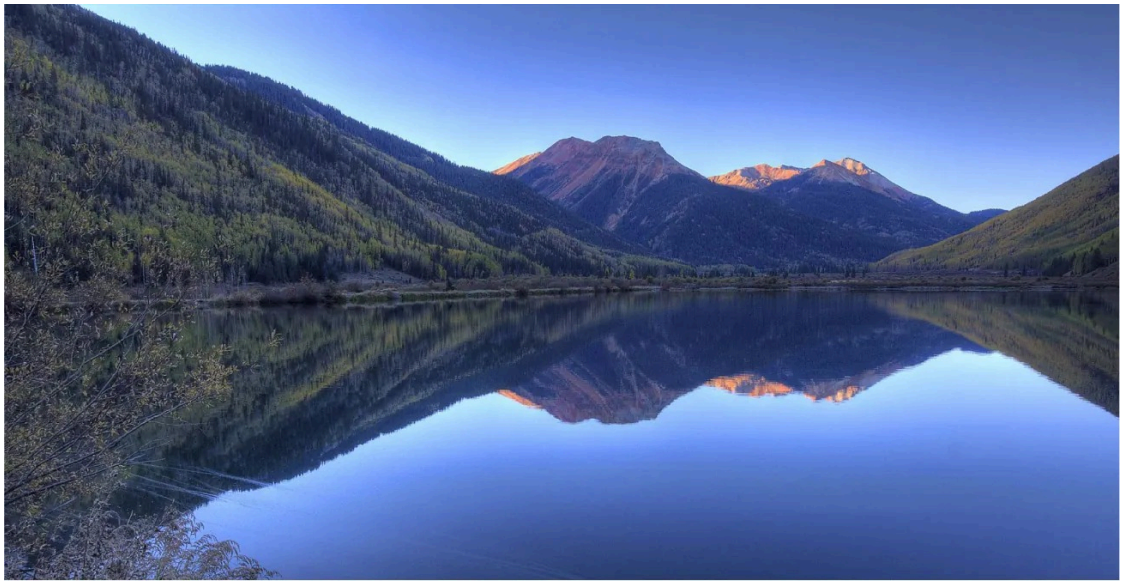


Figure 5.0.1: Like the mountain whose image is reflected in a lake, many organic molecules also have mirror-image counterparts. (credit: modification of work “Crystal Lake sunrise reflection” by Sandy Horvath-Dori/Wikimedia Commons, CC BY 2.0)

Are you right-handed or left-handed? You may not spend much time thinking about it, but handedness plays a surprisingly large role in your daily activities. Many musical instruments, such as oboes and clarinets, have a handedness to them; the last available softball glove always fits the wrong hand. The reason for these difficulties is that our hands aren’t identical; rather, they’re *mirror images*. When you hold a left hand up to a mirror, the image you see looks like a right hand. Try it.



Handedness is also important in organic and biological chemistry, where it arises primarily as a consequence of the tetrahedral stereochemistry of sp^3-hybridized carbon atoms. Many drugs and almost all the molecules in our bodies—amino acids, carbohydrates, nucleic acids, and many more—have a handedness. Furthermore, molecular handedness enables the precise

interactions between enzymes and their substrates that are involved in the hundreds of thousands of chemical reactions on which life is based.

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5.1: Enantiomers and the Tetrahedral Carbon

What causes molecular handedness? Look at generalized molecules of the type CH_3X, CH_2XY, and CHXYZ shown in Figure 5.1.1 . On the left are three molecules, and on the right are their images reflected in a mirror. The CH_3X and CH_2XY molecules are identical to their mirror images and thus are not handed. If you make a molecular model of each molecule and its mirror image, you find that you can superimpose one on the other so that all atoms coincide. The CHXYZ molecule, by contrast, is not identical to its mirror image. You can't superimpose a model of this molecule on a model of its mirror image for the same reason that you can't superimpose a left hand on a right hand: they simply aren't the same.

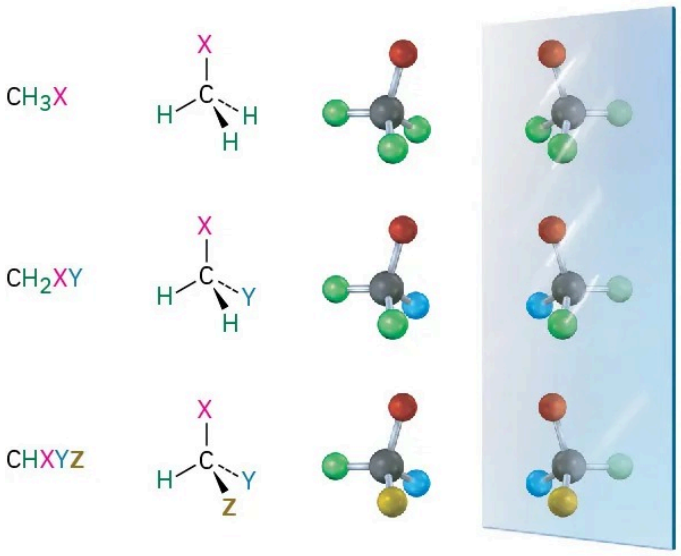
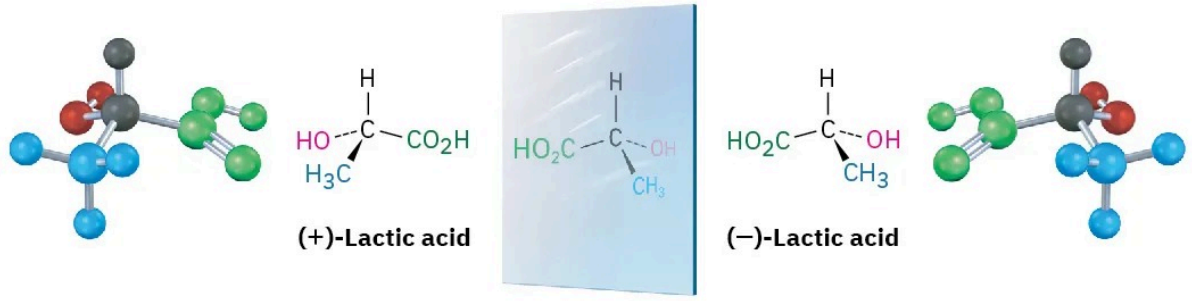


Figure 5.1.1: Tetrahedral carbon atoms and their mirror images. Molecules of the type CH_3X and CH_2XY are identical to their mirror images, but a molecule of the type CHXYZ is not. A CHXYZ molecule is related to its mirror image in the same way a right hand is related to a left hand.

A molecule that is not identical to its mirror image is a kind of stereoisomer (Section 4.4) called an **enantiomer** (e-**nan**-tee-oh-mer, from the Greek enantio, meaning "opposite"). Enantiomers are related to each other as a right hand is related to a left hand, and result whenever a tetrahedral carbon is bonded to four different substituents (one need not be H). For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups (–H, –OH, $–CH_3$, $–CO_2H$) bonded to the central carbon atom. The enantiomers are called (+)-lactic acid and (–)-lactic acid. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.



Lactic acid: a molecule of the general formula CHXYZ



No matter how hard you try, you can't superimpose a molecule of (+)-lactic acid on a molecule of (−)-lactic acid. If any two groups match up, say –H and $-CO_2H$, the remaining two groups don't match (Figure 5.1.2).

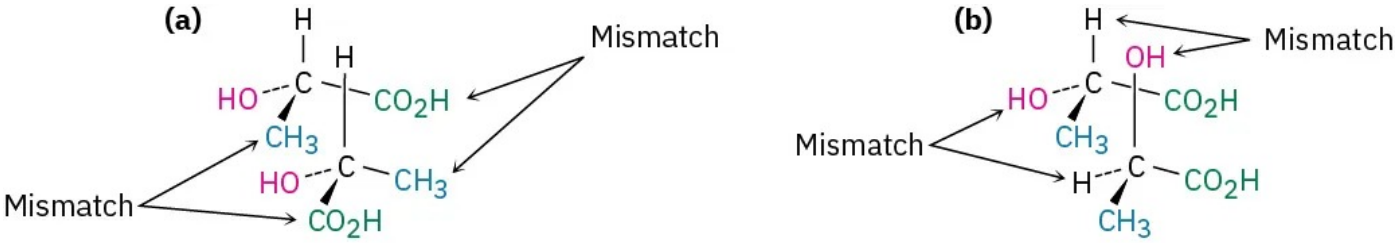


Figure 5.1.2: Attempts at superimposing the mirror-image forms of lactic acid. **(a)** When the –H and –OH substituents match up, the $-CO_2H$ and $-CH_3$ substituents don't; **(b)** when $-CO_2H$ and $-CH_3$ match up, –H and –OH don't. Regardless of how the molecules are oriented, they aren't identical.

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5.2: The Reason for Handedness in Molecules - Chirality

A molecule that is not identical to its mirror image is said to be chiral (**ky**-ral, from the Greek *cheir,* meaning “hand”). You can’t take a chiral molecule and its enantiomer and place one on the other so that all atoms coincide.

How can you predict whether a given molecule is or is not chiral? A molecule is not chiral if it has a plane of symmetry. A plane of symmetry is a plane that cuts through the middle of a molecule (or any object) in such a way that one half of the molecule or object is a mirror image of the other half. A coffee mug, for example, has a plane of symmetry. If you were to cut the coffee mug in half from top to bottom, one half would be a mirror image of the other half. A hand, however, does not have a plane of symmetry. One “half” of a hand is not a mirror image of the other half (Figure 5.2.1).

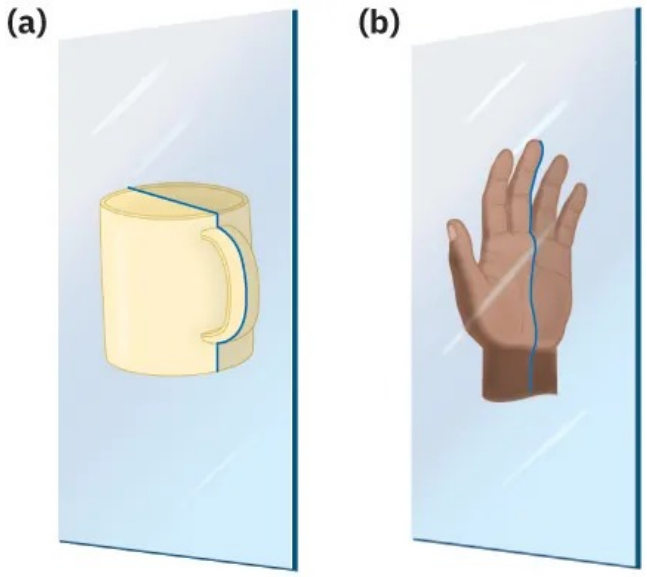


Figure 5.2.1: The meaning of symmetry plane. **(a)** An object like the coffee mug has a symmetry plane cutting through it so that right and left halves are mirror images. **(b)** An object like a hand has no symmetry plane; the right “half” of a hand is not a mirror image of the left half.

A molecule that has a plane of symmetry in any conformation must be identical to its mirror image and must be nonchiral, or achiral. Thus, propanoic acid, $CH_3CH_2CO_2H$, has a plane of symmetry when lined up as shown in Figure 5.2.2 and is achiral, while lactic acid, $CH_3CH(OH)CO_2H$, has no plane of symmetry in any conformation and is chiral.

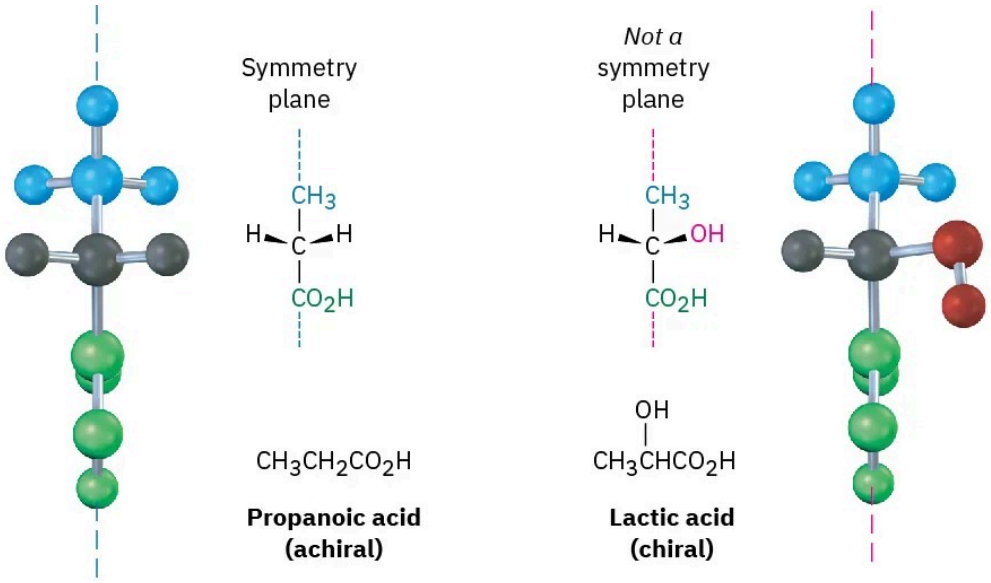
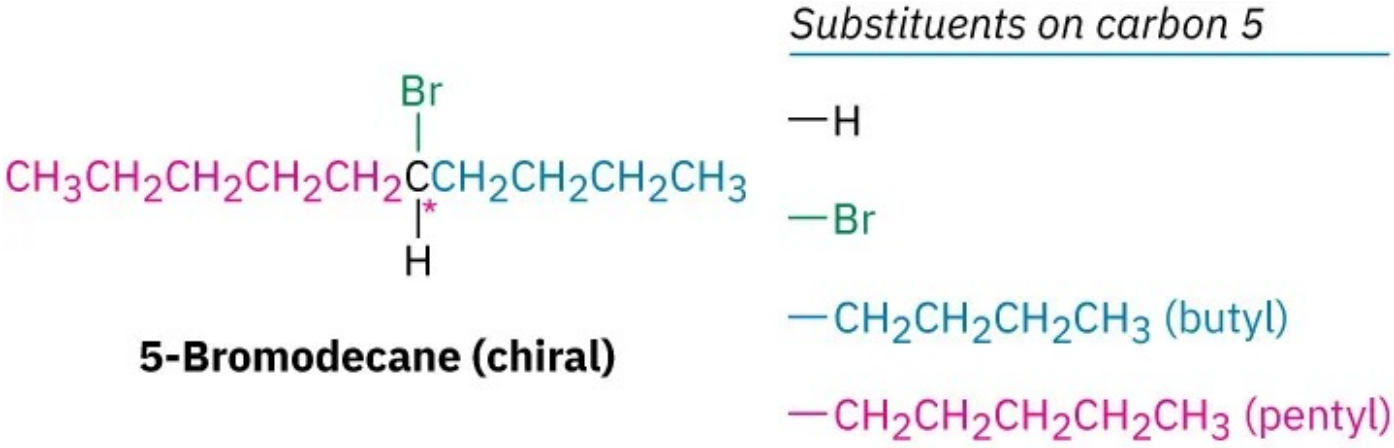


Figure 5.2.2: The achiral propanoic acid molecule versus the chiral lactic acid molecule. Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other. Lactic acid has no such symmetry plane.

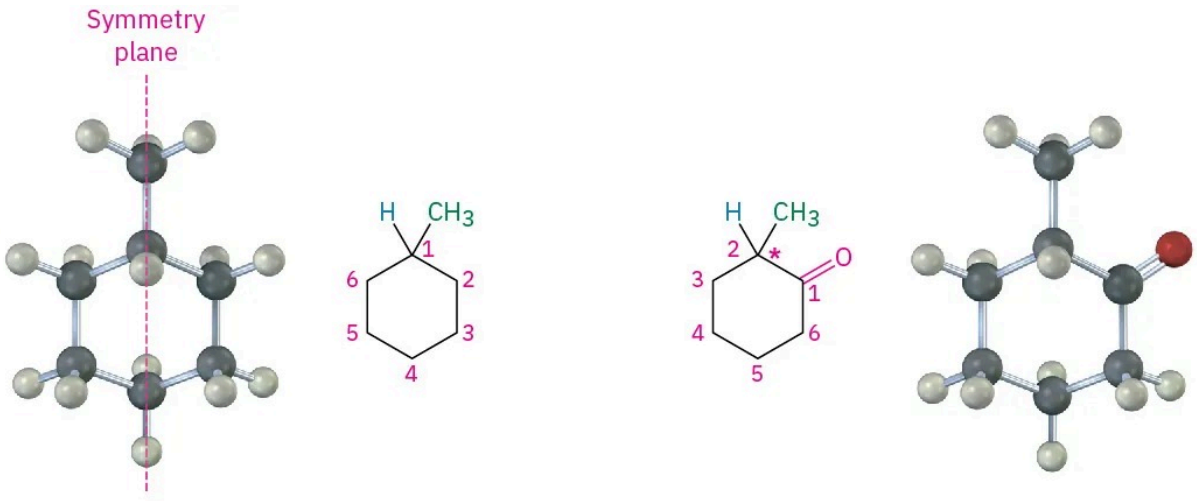
The most common, although not the only, cause of chirality in organic molecules is the presence of a tetrahedral carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are referred to as chirality centers, although other terms such as stereocenter, asymmetric center, and stereogenic center have also been used. Note that *chirality* is a property of the entire molecule, whereas a chirality *center* is the *cause* of chirality.

Detecting a chirality center in a complex molecule takes practice because it's not always immediately apparent whether four different groups are bonded to a given carbon. The differences don't necessarily appear right next to the chirality center. For example, 5-bromodecane is a chiral molecule because four different groups are bonded to C5, the chirality center (marked with an asterisk). A butyl substituent is similar to a pentyl substituent, but it isn't identical. The difference isn't apparent until looking four carbon atoms away from the chirality center, but there's still a difference.



As other possible examples, look at methylcyclohexane and 2-methylcyclohexanone. Methylcyclohexane is achiral because no carbon atom in the molecule is bonded to four different groups. You can immediately eliminate all $-CH_2-$ carbons and the $-CH_3$ carbon from consideration, but what about C1 on the ring? The C1 carbon atom is bonded to a $-CH_3$ group, to an –H atom, and to C2 and C6 of the ring. Carbons 2 and 6 are equivalent, however, as are carbons 3 and 5. Thus, the C6–C5–C4 "substituent" is equivalent to the C2–C3–C4 substituent, and methylcyclohexane is achiral. Another way of reaching the same conclusion is to realize that methylcyclohexane has a symmetry plane, which passes through the methyl group and through C1 and C4 of the ring.

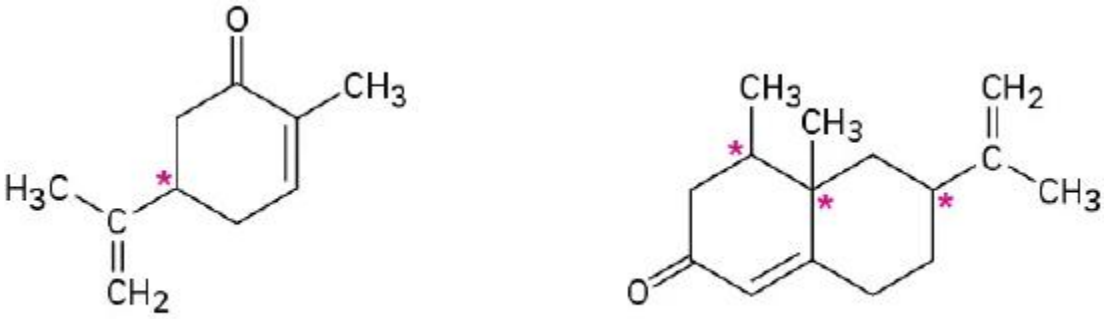
The situation is different for 2-methylcyclohexanone. 2-Methylcyclohexanone has no symmetry plane and is chiral because its C2 is bonded to four different groups: a $-CH_3$ group, an –H atom, a $-COCH_2-$ ring bond (C1), and a $-CH_2CH_2-$ ring bond (C3).



Methylcyclohexane (achiral)

2-Methylcyclohexanone (chiral)

Several more examples of chiral molecules are shown below. Check for yourself that the labeled carbons are chirality centers. You might note that carbons in $-CH_2-$, $-CH_3$, C=O, C=C, and C≡C groups can't be chirality centers. (Why not?)



Carvone (spearmint oil)

Nootkatone (grapefruit oil)

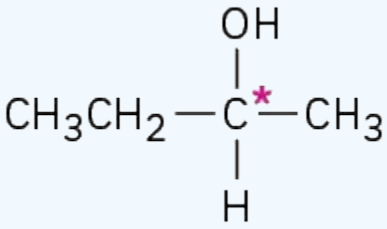
Worked Example 5.2.1: Drawing the Three-Dimensional Structure of a Chiral Molecule

Draw the structure of a chiral alcohol.

Strategy

An alcohol is a compound that contains the –OH functional group. To make an alcohol chiral, we need to have four different groups bonded to a single carbon atom, say –H, –OH, $-CH_3$, and $-CH_2CH_3$.

Solution



2-Butanol (chiral)

Exercises

Exercise 5.2.1

Which of the following objects are chiral?

a.Soda can **b.**Screwdriver **c.**Screw **d.**Shoe

Answer available at the end of this section.

Exercise 5.2.2

Which of the following molecules are chiral? Identify the chirality center(s) in each.

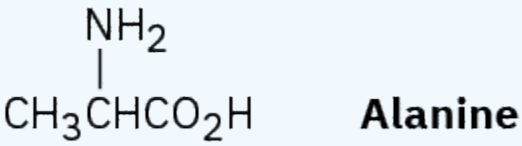
a. **b.** **c.**



Answer available at the end of this section.

Exercise 5.2.3

Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.



Alanine

Answer available at the end of this section.

Exercise 5.2.4

Identify the chirality centers in the following molecules (gray = H, black = C, red = O, green = Cl, yellow-green = F):

a. **b.**

Answer available at the end of this section.

Answers

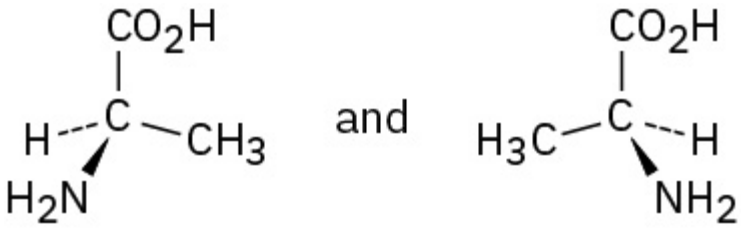
Exercise 5.2.1

Chiral: screw, shoe

Exercise 5.2.2

a. **b.** **c.**

Exercise 5.2.3



Exercise 5.2.4

a. **b.**

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5.3: Optical Activity

The study of chirality originated in the early 19th century during investigations by the French physicist Jean-Baptiste Biot into the nature of *plane-polarized light*. A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to its direction of travel. When a beam of ordinary light passes through a device called a polarizer, however, only the light waves oscillating in a single plane pass through and the light is said to be plane-polarized. Light waves in all other planes are blocked out.

Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or camphor, the plane of polarization is rotated through an angle, α. Not all organic substances exhibit this property, but those that do are said to be optically active.

The angle of rotation can be measured with an instrument called a polarimeter, represented in Figure 5.6. A solution of optically active organic molecules is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the polarization plane occurs. The light then goes through a second polarizer called the analyzer. By rotating the analyzer until the light passes through *it*, we can find the new plane of polarization and can tell to what extent rotation has occurred.

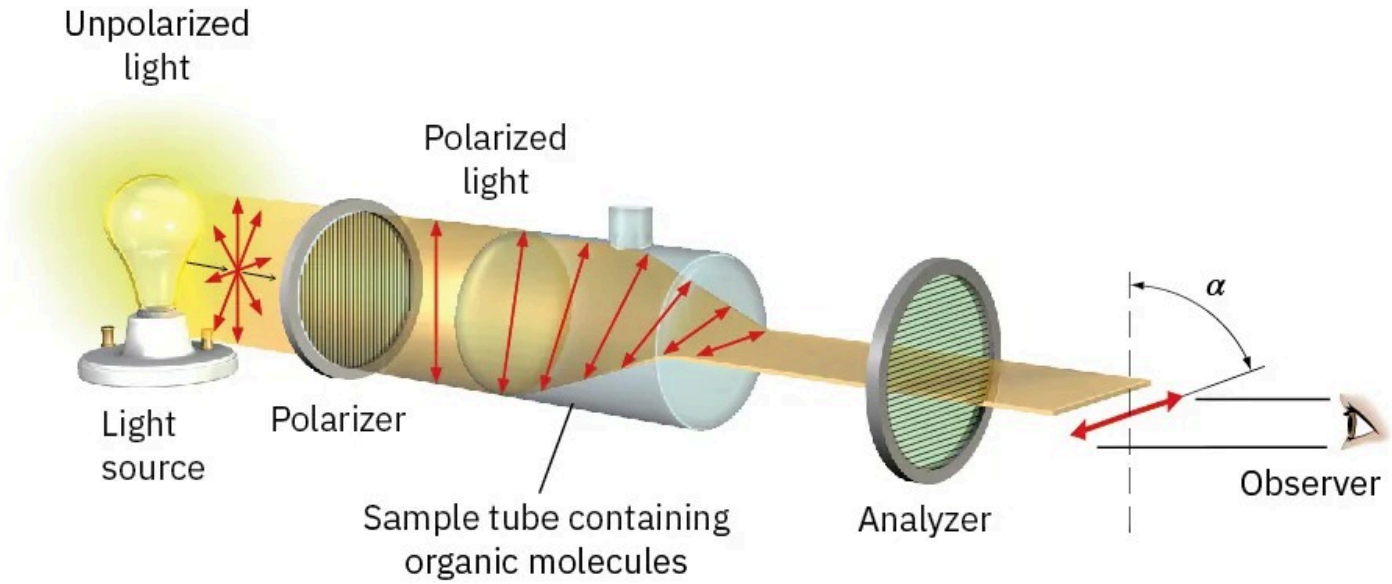


Figure 5.3.1: Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.

In addition to determining the extent of rotation, we can also find the direction. From the vantage point of the observer looking directly at the analyzer, some optically active molecules rotate polarized light to the left (counterclockwise) and are said to be levorotatory, whereas others rotate polarized light to the right (clockwise) and are said to be dextrorotatory. By convention, rotation to the left is given a minus sign (−) and rotation to the right is given a plus sign (+). (−)-Morphine, for example, is levorotatory, and (+)-sucrose is dextrorotatory.

The extent of rotation observed in a polarimetry experiment depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample pathlength. If the concentration of the sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation doubles. It also happens that the angle of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The specific rotation, $[\alpha]_D$, of a compound is defined as the observed rotation when light of 589.6 nanometer (nm; 1 nm = 10^{-9} m) wavelength is used with a sample pathlength l of 1 decimeter (dm; 1 dm = 10 cm) and a sample concentration c of 1 g/cm^3. (Light of 589.6 nm, the so-called sodium D line, is the yellow light emitted from common sodium street lamps.)

$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlengt, } l \text{ (dm)} \times \text{Concentration, } c \text{ (}}$$

When optical rotations are expressed in this standard way, the specific rotation, $[\alpha]_D$, is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has $[\alpha]_D = +3.82$, and (−)-lactic acid has $[\alpha]_D = -3.82$. That is, the two enantiomers rotate plane-polarized light to exactly the same extent but in opposite directions. Note that the units of specific rotation are [(deg • cm^2)/g] but the values are usually expressed without units. Some additional examples are listed in Table 5.1.

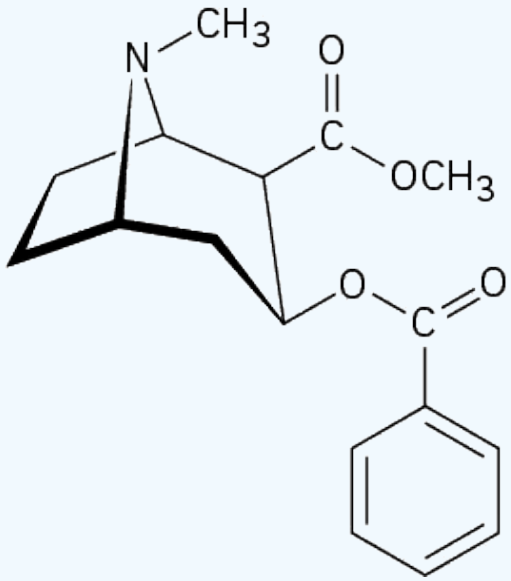
Table 5.1 Specific Rotations of Some Organic Molecules

Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	+233	Cholesterol	−31.5
Sucrose	+66.47	Morphine	−132
Camphor	+44.26	Cocaine	−16
Chloroform	0	Acetic acid	0

Worked Example 5.1

Calculating an Optical Rotation

A 1.200 g sample of cocaine, $[\alpha]_D = -16$, was dissolved in 7.500 mL of chloroform and placed in a sample tube having a pathlength of 5.000 cm. What was the observed rotation?



Cocaine

Strategy

Since $[\alpha]_D = \frac{\alpha}{l \times c}$

Then $\alpha = l \times c \times [\alpha]_D$
where $[\alpha]_D = -16; l = 5.00 \text{ cm} = 0.500 \text{dm}; c = 1.20 \text{ g}/7.50 \text{ cm}^3 = 0.160 \text{ g/cm}^3$

Solution

$$\alpha = (-16)(0.500)(0.160) = -1.3^\circ. \tag{5.3.1}$$

Exercise 5.3.1

Is cocaine (Worked Example 5.2) dextrorotatory or levorotatory?

Answer available at the end of this section.

Exercise 5.3.2

A 1.50 g sample of coniine, the toxic extract of poison hemlock, was dissolved in 10.0 mL of ethanol and placed in a sample cell with a 5.00 cm pathlength. The observed rotation at the sodium D line was +1.21°. Calculate $[\alpha]_D$ for coniine.

Answer available at the end of this section.

Optical Activity of Mixtures

When a sample under measurement contains only one enantiomer, it is considered **enantiomerically pure**, meaning it contains only one enantiomer.

The sample may also consist of a mixture of a pair of enantiomers. For such a mixture sample, the observed rotation value of the mixture, together with the information of the specific rotation of one of the enantiomers, allows us to calculate the percentage (%) of each enantiomer in the mixture. To do such calculation, the concept of enantiomer excess (**ee**) will be needed. The enantiomeric excess (ee) tells how much an excess of one enantiomer is in the mixture, and it can be calculated as:

$$\text{ee} = \frac{observed\ rotation}{specific\ rotation\ of\ pure\ enantiomer}$$

We will use a series of hypothetical examples in the next table for detailed explanation.

If the specific rotation of a (+)-enantiomer is +100°, then the observed rotation of the following samples are (assume the sample tube has the length of 1 dm, and the concentration for each sample is 1.0 g/mL):		
Sample Number	Sample	Observed rotation (°)
1	pure (+) enantiomer	+100
2	Pure (-)-enantiomer	-100
3	Racemic mixture of 50% (+)-enantiomer and 50% (-)-enantiomer	0
4	Mixture of 75% (+)-enantiomer and 25% (-)-enantiomer	+50
4	Mixture of 20% (+)-enantiomer and 80% (-)-enantiomer	-60

Sample #1 and **#2** are straightforward.

Sample #3 is for a mixture with an equal amount of two enantiomers, and such a mixture is called a **racemic mixture** or

racemate. Racemic mixtures do not rotate the plane of polarization of plane-polarized light, which means **racemic mixtures are optically inactive and have an observed rotation of zero!** This is because for every molecule in the mixture that rotates the plane of polarization in one direction, there is an enantiomer molecule that rotates the plane of polarization in the *opposite* direction with the same angle, and the rotation gets cancelled out. As a net result, no rotation is observed for the overall racemic mixture. The symbol **(±)** sometimes is used to indicate a mixture is racemic mixture.

Sample #4, the (+)-enantiomer is in excess. Since there are 75% (+)-enantiomer and 25%(-)-enantiomer, the enantiomeric excess (ee) value of (+)-enantiomer is 75% – 25% = **50%.** The formula can also calculate this:

$$\text{ee} = \frac{\textit{observed rotation}}{\textit{specific rotation of pure enantiomer}} = \frac{50}{100} = 0.5 = 50\%$$

In this sample of mixture, the rotation of the (-)-enantiomer is *cancelled* by the rotation caused by part of the (+)-enantiomer, so the overall net observed rotation depends on how much "net amount" of (+)-enantiomer is present. This can be shown by the diagram below, which helps to illustrate the concept.

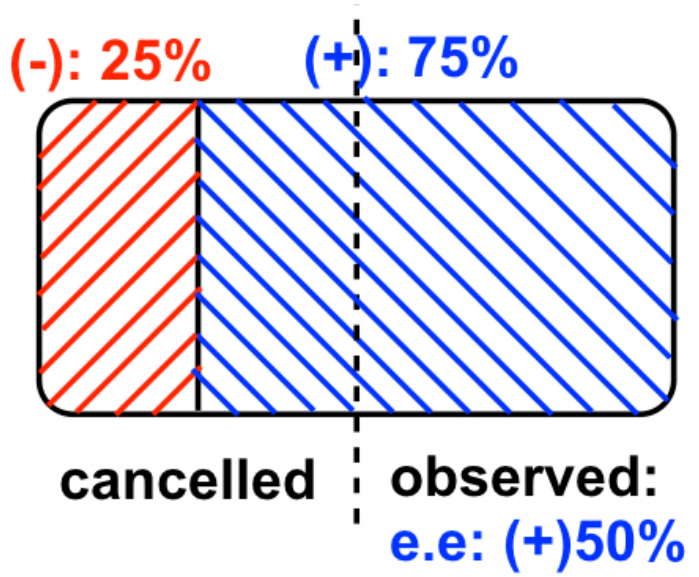


Figure 5.3.2: Cancelled & observed

Sample #5, the (-)-enantiomer is in excess, and because there is 80% (-)-enantiomer and 20% (+)-enantiomer, the enantiomeric excess (ee) value of (-)-enantiomer is 80% – 20% = **60%**, this can also be calculated by the formula:

$$\text{ee} = \frac{\textit{observed rotation}}{\textit{specific rotation of pure enantiomer}} = \frac{60}{100} = 0.6 = 60\%$$

Please note: to calculate the e.e value, it is not necessary to include the sign of the rotation angle, as long as ***you keep in mind*** that the sign (**+** or **–**) of the observed rotation indicates which enantiomer is in excess.

Worked Example 5.2

Calculating an Optical Rotation

The (+)-enantiomer of a compound has specific rotation ($[\alpha]^{20}_{D}$) of +100°. For a sample (1 g/ml in 1 dm cell) that is a mixture of (+) and (-) enantiomers, the observed rotation α is -45°. What is the percentage of (+) enantiomer present in this sample?

Solution

The observed rotation is in "-", so (-)-enantiomer is in excess.

ee of (-)-enantiomer is:

$$\text{e.e} = \frac{\textit{observed rotation}}{\textit{specific rotation of pure enantiomer}} = \frac{45}{100} = 0.45 = 45\%$$

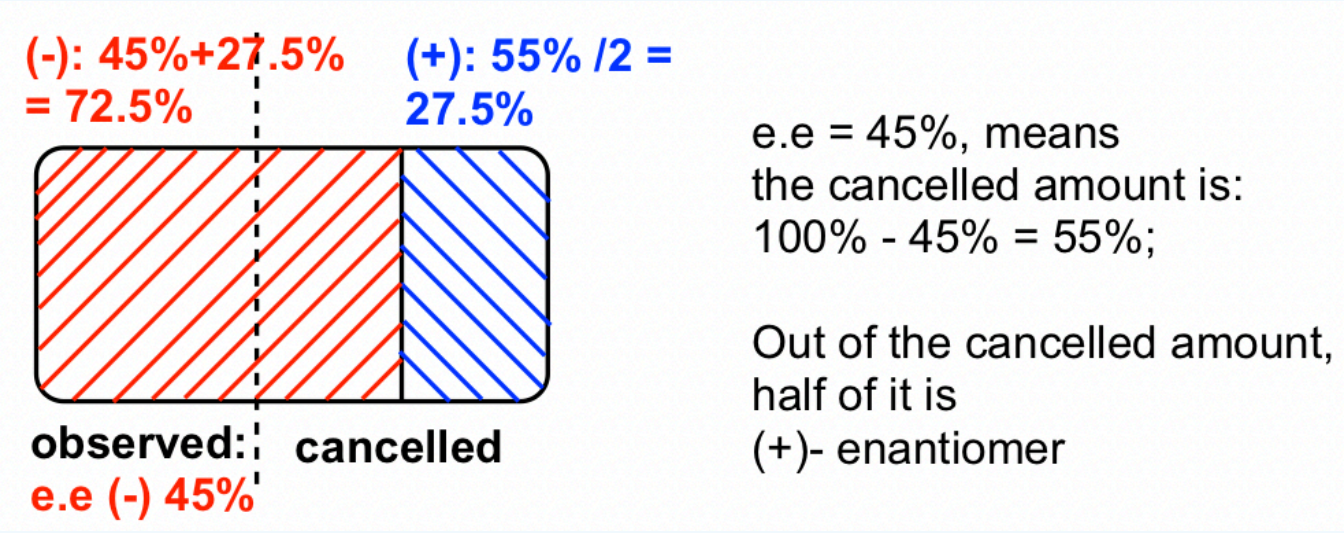
From here, we will see two ways of solving this type of question:

Method I:

- solving algebra, % of (-)-enantiomer is set as "x"; % of (+)-enantiomer is set as "y"
- x + y = 100%
- x – y = 45%
- Solve x = 72.5%; y = 27.5%;
- So there is 72.5% (-)-enantiomer and 27.5% of (+)-enantiomer in the sample.

Method II:

using diagram, the answer is in blue color, there is 27.5% of (+)-enantiomer.



Exercise 5.3.3

Calculating an Optical Rotation

Draw the diagram for ***Sample #5*** *by referring to the diagram for* ***Sample #4*** *.*

Answers

Exercise 5.3.1

Levorotatory

Exercise 5.3.2

+16.1°

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5.4: Pasteur's Discovery of Enantiomers

Little was done to build on Biot's discovery of optical activity until 1848, when Louis Pasteur began work on a study of crystalline tartaric acid salts derived from wine. On crystallizing a concentrated solution of sodium ammonium tartrate below 28 °C, Pasteur made the surprising observation that two distinct kinds of crystals were obtained. Furthermore, the two kinds of crystals were nonsuperimposable mirror images and were related in the same way that a right hand is related to a left hand.

Working carefully with tweezers, Pasteur was able to separate the crystals into two piles, one of "right-handed" crystals and one of "left-handed" crystals, like those shown in Figure 5.4.1. Although the original sample, a 50:50 mixture of right and left, was optically inactive, solutions of the crystals from each of the sorted piles were optically active and their specific rotations were equal in magnitude but opposite in sign.

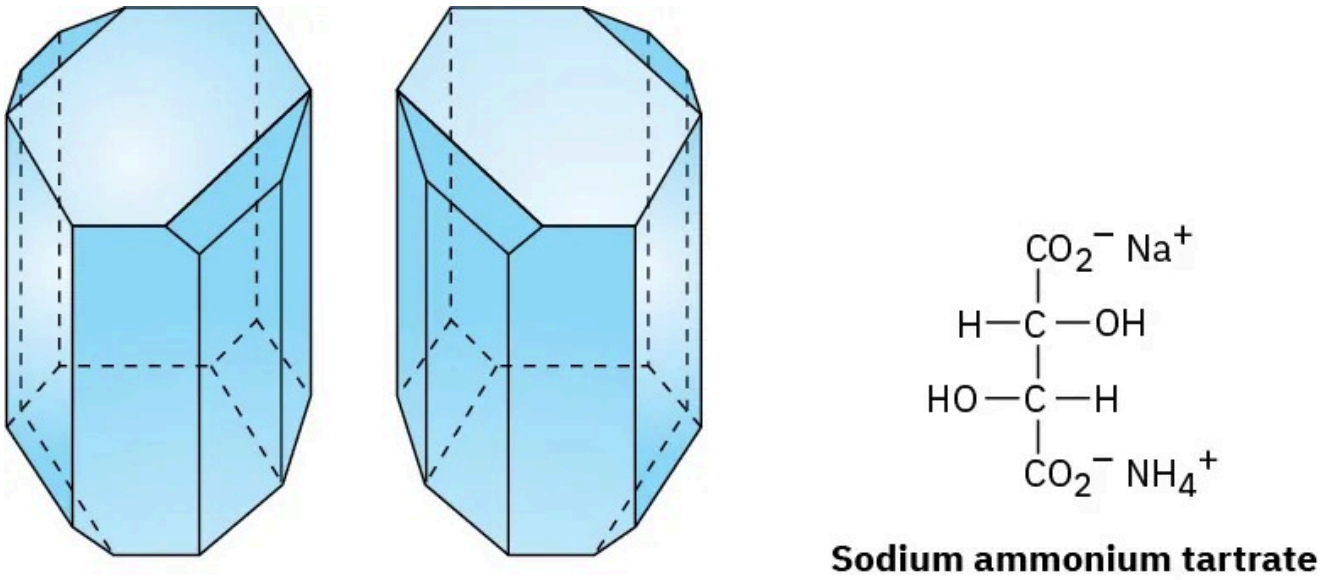


Figure 5.4.1: Drawings of sodium ammonium tartrate crystals taken from Pasteur's original sketches. One of the crystals is dextrorotatory in solution, and the other is levorotatory.

Pasteur was far ahead of his time. Although the structural theory of Kekulé had not yet been proposed, Pasteur explained his results by speaking of the molecules themselves, saying, "There is no doubt that [in the *dextro* tartaric acid] there exists an asymmetric arrangement having a nonsuperimposable image. It is no less certain that the atoms of the *levo* acid have precisely the inverse asymmetric arrangement." Pasteur's vision was extraordinary, for it was not until 25 years later that his ideas regarding asymmetric carbon atoms were confirmed.

Today, we would describe Pasteur's work by saying that he had discovered enantiomers. **Enantiomers**, also called **optical isomers**, have identical physical properties, such as melting point and boiling point, but differ in the direction in which their solutions rotate plane-polarized light.

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5.5: Sequence Rules for Specifying Configuration

Structural drawings provide a visual representation of stereochemistry, but a written method for indicating the three-dimensional arrangement, or configuration, of substituents at a chirality center is also needed. The method used a set of **sequence rules** to rank the four groups attached to the chirality center and then looks at the handedness with which those groups are attached. Called the **Cahn–Ingold–Prelog rules** after the chemists who proposed them, the sequence rules are as follows:

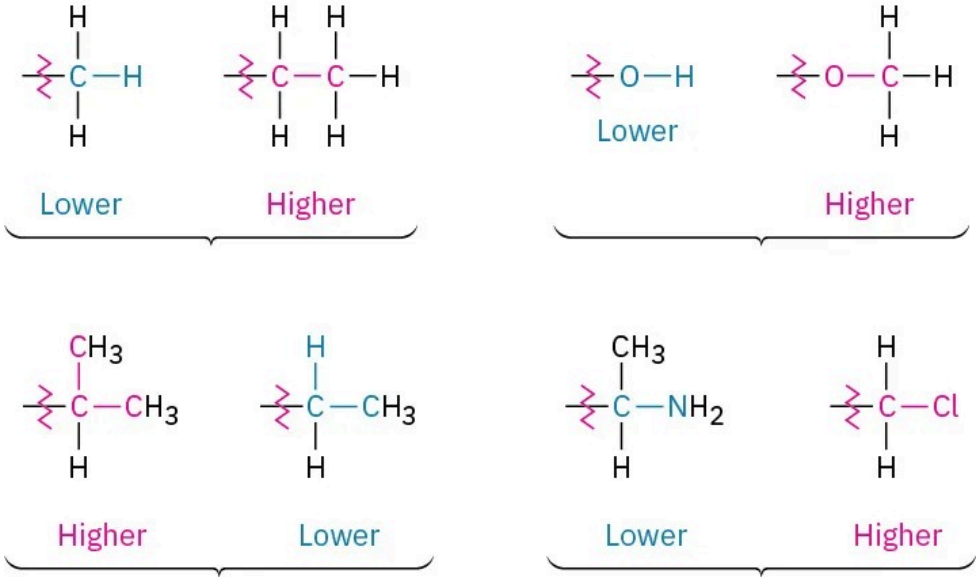
RULE 1

Look at the four atoms directly attached to the chirality center, and rank them according to atomic number. The atom with the highest atomic number has the highest ranking (first), and the atom with the lowest atomic number (usually hydrogen) has the lowest ranking (fourth). When different isotopes of the same element are compared, such as deuterium (^2H) and protium (^1H), the heavier isotope ranks higher than the lighter isotope. Thus, atoms commonly found in organic compounds have the following order.

Atomic number	35	17	16	15	8	7	6	(2)	(1)	
Higher rank	Br	> Cl	> S	> P	> O	> N	> C	> ^2H	> ^1H	Lower rank

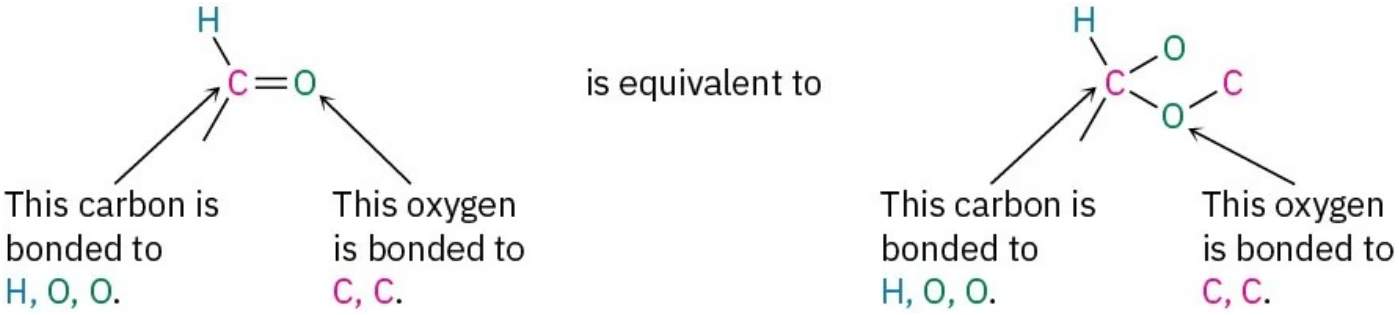
RULE 2

If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the chirality center until the first difference is found. A $-CH_2CH_3$ substituent and a $-CH_3$ substituent are equivalent by rule 1 because both have carbon as the first atom. By rule 2, however, ethyl ranks higher than methyl because ethyl has a carbon as its highest second atom, while methyl has only hydrogen as its second atom. Look at the following pairs of examples to see how the rule works:

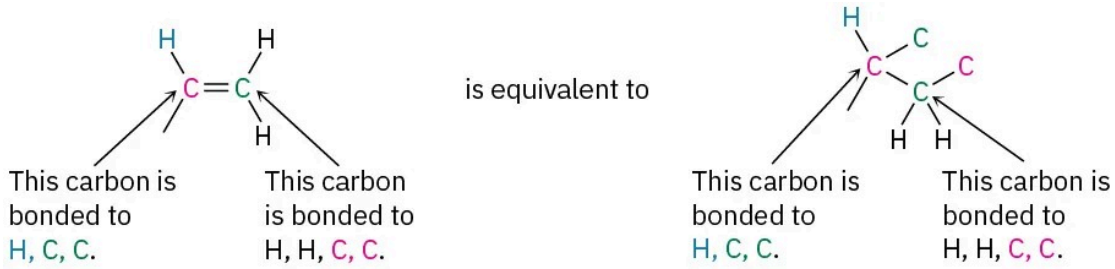


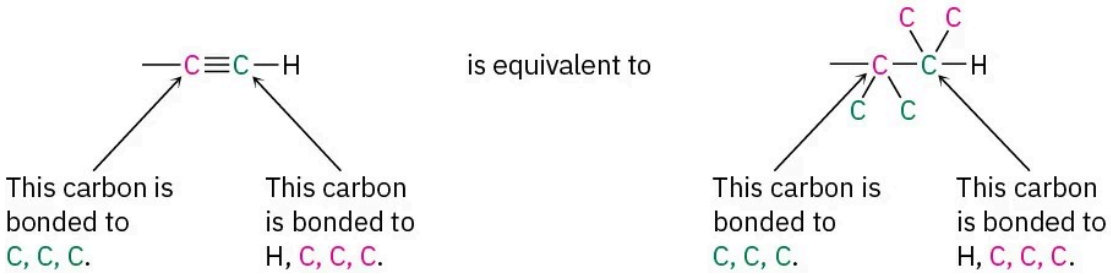
RULE 3

Multiple-bonded atoms are equivalent to the same number of single-bonded atoms. For example, an aldehyde substituent ($-CH{=}O$), which has a carbon atom *doubly* bonded to *one* oxygen, is equivalent to a substituent having a carbon atom *singly* bonded to *two* oxygens:



As further examples, the following pairs are equivalent:





Having ranked the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group with the lowest ranking (4) points directly away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel (Figure 5.5.1). If a curved arrow drawn from the highest to second-highest to third-highest ranked substituent (1 → 2 → 3) is clockwise, we say that the chirality center has the *R* configuration (S for the Latin *rectus,* meaning “right”). If an arrow from 1 → 2 → 3 is counterclockwise, the chirality center has the *S* configuration (Latin *sinister*, meaning “left”). To remember these assignments, think of a car’s steering wheel when making a *R*ight (clockwise) turn.

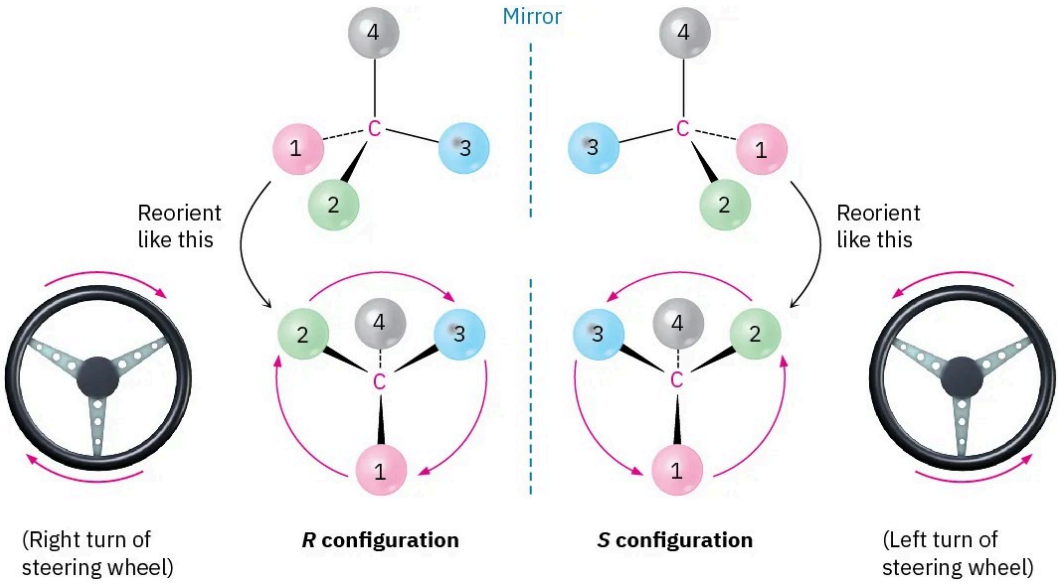


Figure 5.5.1: Assigning *R* and S configurations to chirality centers. When the molecule is oriented so that the lowest-ranked group (**4**) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel 1 → 2 → 3 is clockwise (right turn), the center has the *R* configuration. If the direction of travel 1 → 2 → 3 is counterclockwise (left turn), the center is S.

Look at (–)-lactic acid in Figure 5.5.2 for an example of how to assign configuration. Sequence rule 1 says that –OH is ranked 1 and –H is ranked 4, but it doesn't allow us to distinguish between $-CH_3$ and $-CO_2H$ because both groups have carbon as their first atom. Sequence rule 2, however, says that $-CO_2H$ ranks higher than $-CH_3$ because O (the highest second atom in $-CO_2H$) outranks H (the highest second atom in $-CH_3$). Now, turn the molecule so that the fourth-ranked group (–H) is oriented toward the rear, away from the observer. Since a curved arrow from 1 (–OH) to 2 ($-CO_2H$) to 3 ($-CH_3$) is clockwise (right turn of the steering wheel), (–)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.

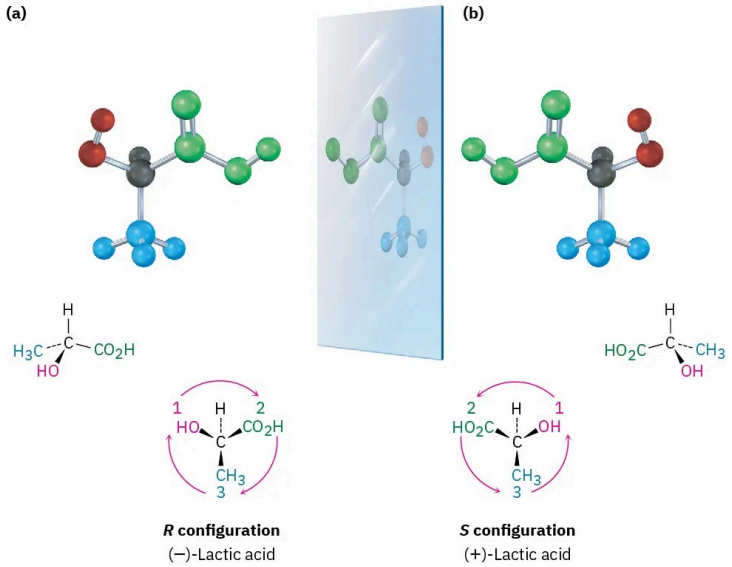


Figure 5.5.2: Assigning configuration to **(a)** (*R*)-(–)-lactic acid and **(b)** (S)-(+)-lactic acid.

Further examples are provided by naturally occurring (–)-glyceraldehyde and (+)-alanine, which both have the *S* configuration as shown in Figure 5.5.3. Note that the sign of optical rotation, (+) or (–), is not related to the *R,S* designation. (*S*)-Glyceraldehyde happens to be levorotatory (–), and (*S*)-alanine happens to be dextrorotatory (+). There is no simple correlation between *R,S* configuration and direction or magnitude of optical rotation.

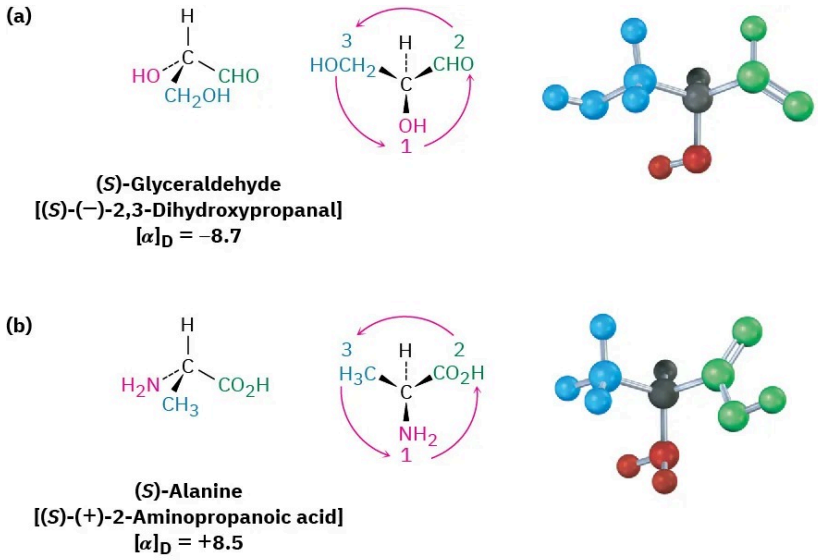
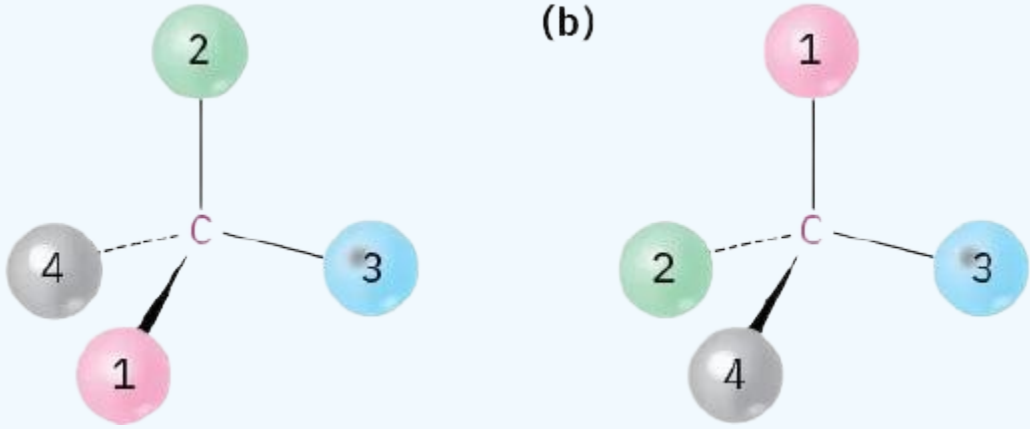


Figure 5.5.3: Assigning configuration to **(a)** (−)-glyceraldehyde. **(b)** (+)-alanine. Both happen to have the S configuration, although one is levorotatory and the other is dextrorotatory.

One additional point needs to be mentioned—the matter of absolute configuration. How do we know that the assignments of *R* and S configuration are correct in an absolute sense, rather than a relative, sense? Since there is no correlation between the *R,S* configuration and the direction or magnitude of optical rotation, how do we know that the *R* configuration belongs to the levorotatory enantiomer of lactic acid? This difficult question was finally solved in 1951, when an X-ray diffraction method was found for determining the absolute spatial arrangement of atoms in a molecule. Based on those results, we can say with certainty that the *R,S* conventions are correct.

Worked Example 5.5.1: Assigning Configuration to Chirality Centers

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or S configuration to each:

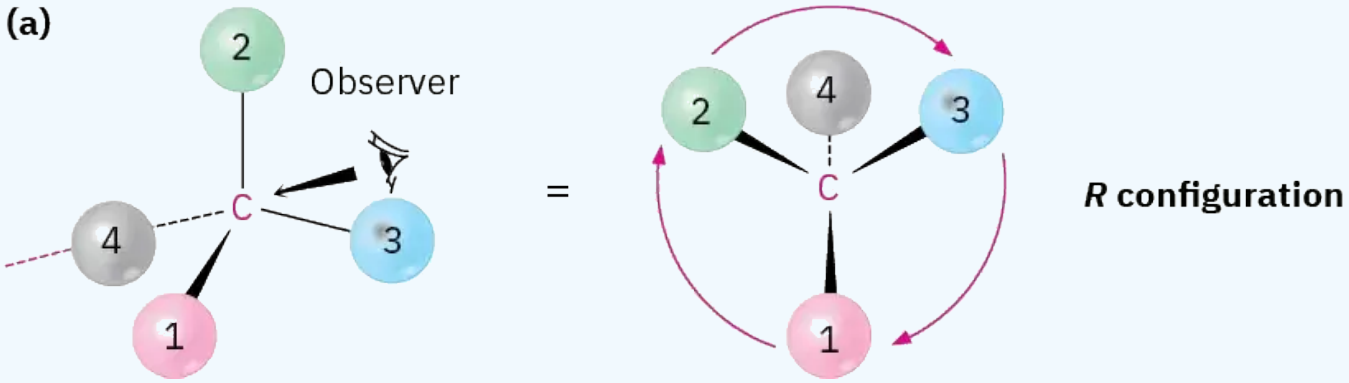


Strategy

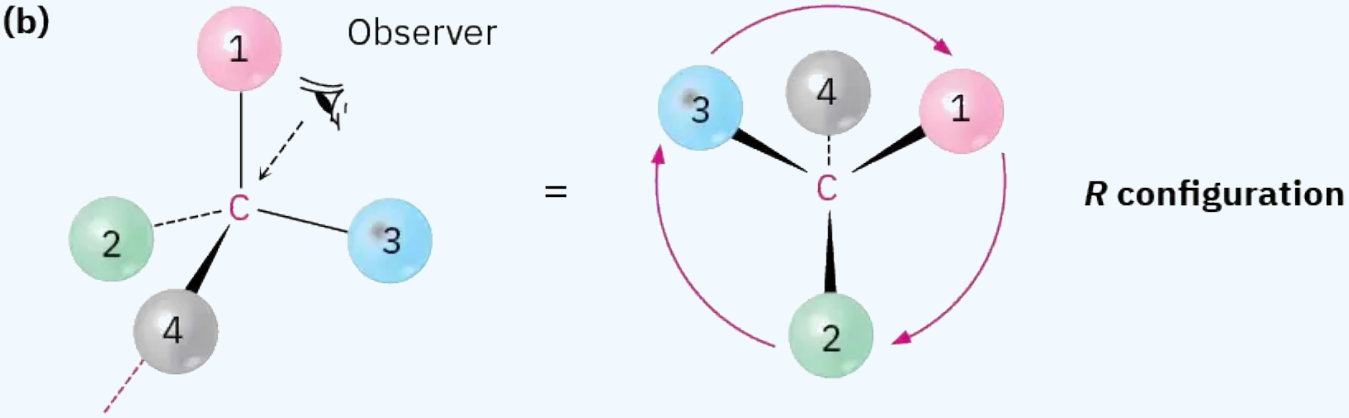
It takes practice to be able to visualize and orient a chirality center in three dimensions. You might start by indicating where the observer must be located—180° opposite the lowest-ranked group. Then imagine yourself in the position of the observer, and redraw what you would see.

Solution

In **(a)**, you would be located in front of the page toward the top right of the molecule, and you would see group 2 to your left, group 3 to your right, and group 1 below you. This corresponds to an *R* configuration.



In **(b)**, you would be located behind the page toward the top left of the molecule from your point of view, and you would see group 3 to your left, group 1 to your right, and group 2 below you. This also corresponds to an *R* configuration.



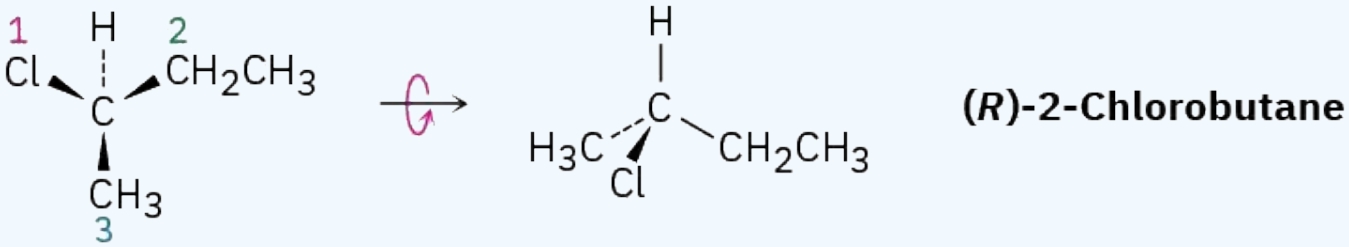
Worked Example 5.5.2: Drawing the Three-Dimensional Structure of a Specific Enantiomer

Draw a tetrahedral representation of (*R*)-2-chlorobutane.

Strategy

Begin by ranking the four substituents bonded to the chirality center: (1) –Cl, (2) $–CH_2CH_3$, (3) $–CH_3$, (4) –H. To draw a tetrahedral representation of the molecule, orient the lowest-ranked group (–H) away from you and imagine that the other three groups are coming out of the page toward you. Then, place the remaining three substituents such that the direction of travel 1 → 2 → 3 is clockwise (right turn), and tilt the molecule toward you to bring the rear hydrogen into view. Using molecular models is a real help in working problems of this sort.

Solution



Exercises

Exercise 5.5.1

Which member in each of the following sets ranks higher?

a. –H or –Br
b. –Cl or –Br
c. $-CH_3$ or $-CH_2CH_3$
d. $-NH_2$ or –OH
e. $-CH_2OH$ or $-CH_3$
f. $-CH_2OH$ or –CH=O

Answer available at the end of this section.

Exercise 5.5.2

Rank each of the following sets of substituents:

a. –H, –OH, $-CH_2CH_3$, $-CH_2CH_2OH$
b. $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, –OH
c. –CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-NH_2$
d. –SH, $-CH_2SCH_3$, $-CH_3$, $-SSCH_3$

Answer available at the end of this section.

Exercise 5.5.3

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or S configuration:

a. **b.** **c.**



Answer available at the end of this section.

Exercise 5.5.4

Assign *R* or S configuration to the chirality center in each of the following molecules:

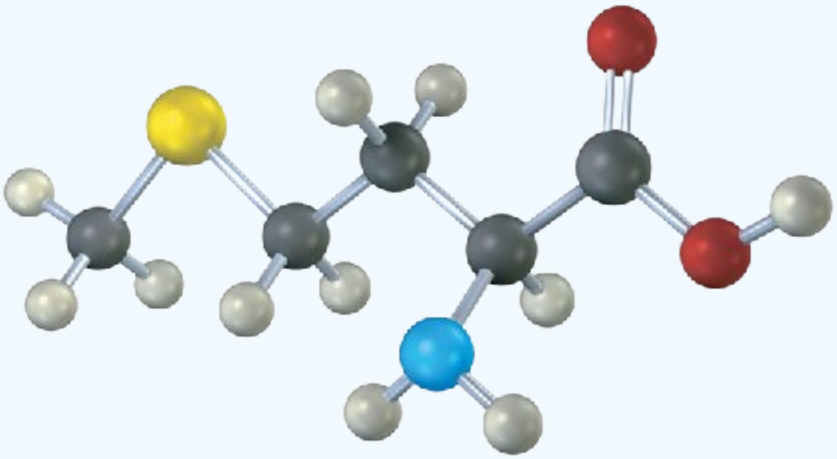
a. **b.** **c.**



Answer available at the end of this section.

Exercise 5.5.5

Assign *R* or S configuration to the chirality center in the following molecular model of the amino acid methionine (blue = N, yellow = S):



Answer available at the end of this section.

Answers

Exercise 5.5.1

a. –Br **b.** –Br **c.** $–CH_2CH_3$ **d.** –OH **e.** $–CH_2OH$ **f.** –CH=O

Exercise 5.5.2

a. –OH, $–CH_2CH_2OH$, $–CH_2CH_3$, –H
b. –OH, $–CO_2CH_3$, $–CO_2H$, $–CH_2OH$
c. $–NH_2$, –CN, $–CH_2NHCH_3$, $–CH_2NH_2$
d. $–SSCH_3$, –SH, $–CH_2SCH_3$, $–CH_3$

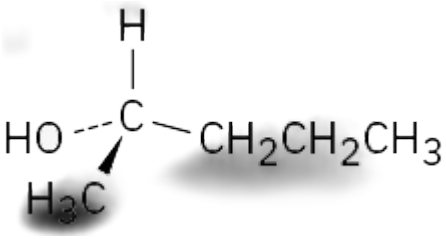
Exercise 5.5.3

a. S **b.** *R* **c.** S

Exercise 5.5.4

a. S **b.** S **c.** *R*

Exercise 5.5.5



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5.6: Diastereomers

Molecules like lactic acid, alanine, and glyceraldehyde are relatively simple because each has only one chirality center and thus only two stereoisomers. The situation becomes more complex, however, with molecules that have more than one chirality center. As a general rule, a molecule with *n* chirality centers can have up to 2^n stereoisomers (although it may have fewer, as we'll see below). Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for example. Since threonine has two chirality centers (C2 and C3), there are four possible stereoisomers, as shown in Figure 5.6.1. Check for yourself that the *R*,S configurations of all stereoisomers are correct.

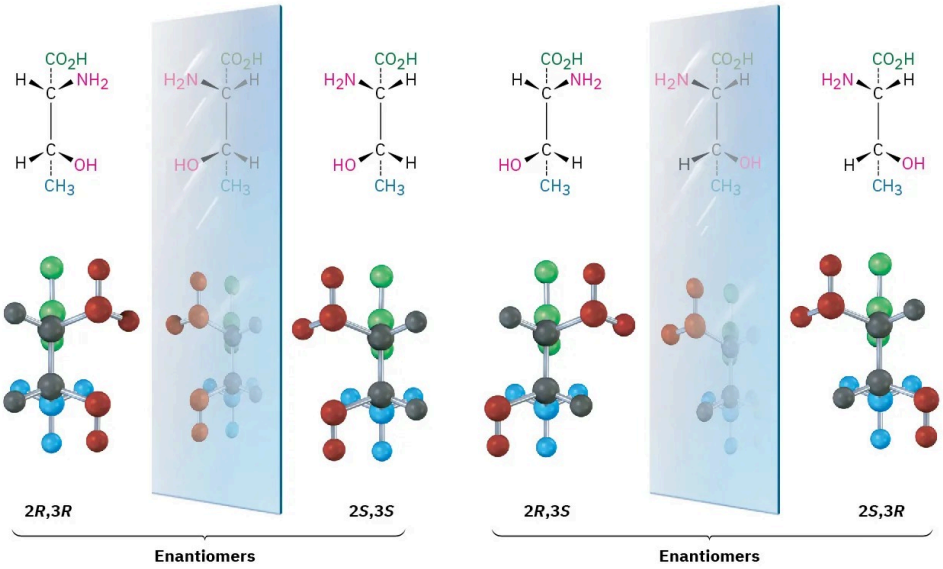


Figure 5.6.1: The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The 2*R*,3*R* stereoisomer is the mirror image of 2*S*,3*S*, and the 2*R*,3*S* stereoisomer is the mirror image of 2*S*,3*R*. But what is the relationship between any two molecules that are not mirror images? What, for instance, is the relationship between the 2*R*,3*R* isomer and the 2*R*,3*S* isomer? They are stereoisomers, yet they aren't enantiomers. To describe such a relationship, we need a new term: *diastereomer*.

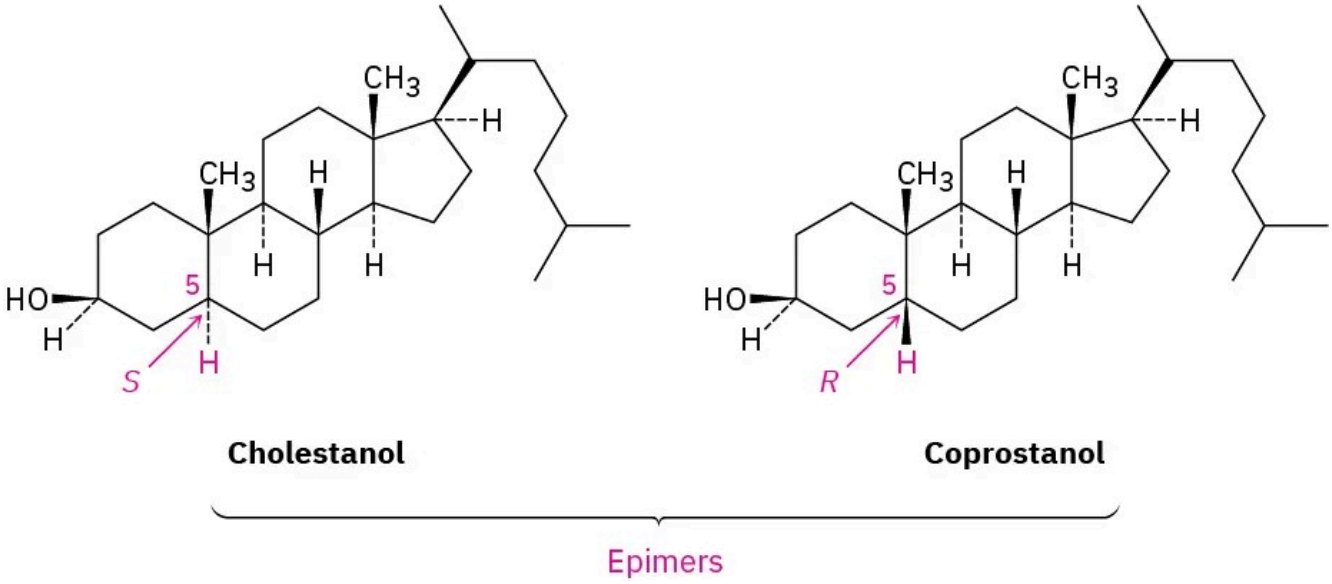
Diastereomers are stereoisomers that are not mirror images. Since we used the right-hand/left-hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and your friend's hand look similar, but they aren't identical, and they aren't mirror images. The same is true of diastereomers: they're similar, but they aren't identical, and they aren't mirror images.

Note carefully the difference between enantiomers and diastereomers: enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. A full description of the four stereoisomers of threonine is given in Table 5.6.1. Of the four, only the 2*S*,3*R* isomer, $[\alpha]_D = -28.3$, occurs naturally in plants and animals and is an essential nutrient for humans. This result is typical: most biological molecules are chiral, and usually only one stereoisomer is found in nature.

Table 5.6.1 Relationships among the Four Stereoisomers of Threonine

Stereoisomer	Enantiomer	Diastereomer
2*R*,3*R*	2*S*,3*S*	2*R*,3*S* and 2*S*,3*R*
2*S*,3*S*	2*R*,3*R*	2*R*,3*S* and 2*S*,3*R*
2*R*,3*S*	2*S*,3*R*	2*R*,3*R* and 2*S*,3*S*
2*S*,3*R*	2*R*,3*S*	2*R*,3*R* and 2*S*,3*S*

In the special case where two diastereomers differ at only one chirality center but are the same at all others, we say that the compounds are **epimers**. Cholestanol and coprostanol, for instance, are both found in human feces, and both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric* at C5.



Exercise 5.6.1

One of the following molecules **(a)**–**(d)** is D-erythrose 4-phosphate, an intermediate in the Calvin photosynthetic cycle by which plants incorporate CO_2 into carbohydrates. If D-erythrose 4-phosphate has *R* stereochemistry at both chirality centers, which of the structures is it? Which of the remaining three structures is the enantiomer of D-erythrose 4-phosphate, and which are diastereomers?

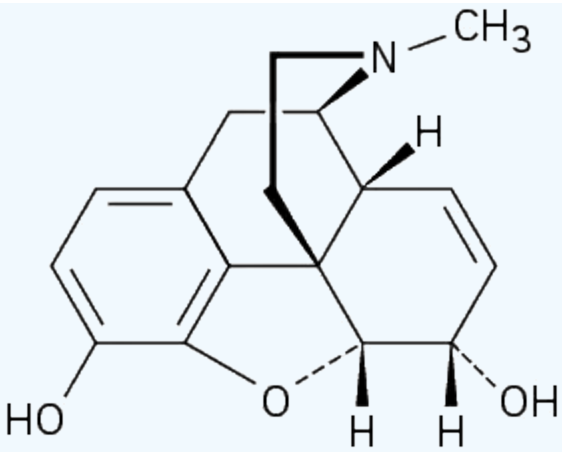
a. **b.** **c.** **d.**



Answer available at the end of this section.

Exercise 5.6.2

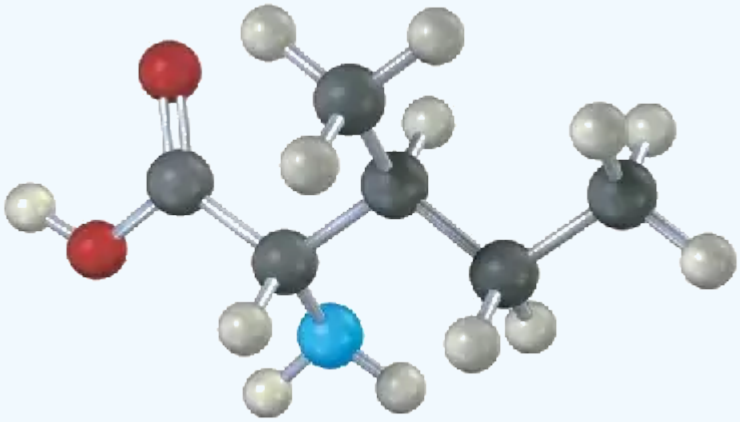
How many chirality centers does morphine have? How many stereoisomers of morphine are possible in principle?



Morphine

Answer available at the end of this section.

Exercise 5.6.3



Assign *R* or *S* configuration t o each chirality center in the following molecular model of the amino acid isoleucine (blue = N):

Answer available at the end of this section.

Answers

Exercise 5.6.1

Compound **(a)** is D-erythrose 4-phosphate, **(d)** is its enantiomer, and **(b)** and **(c)** are diastereomers.

Exercise 5.6.2

Five chirality centers and 2^5 = 32 stereoisomers

Exercise 5.6.3

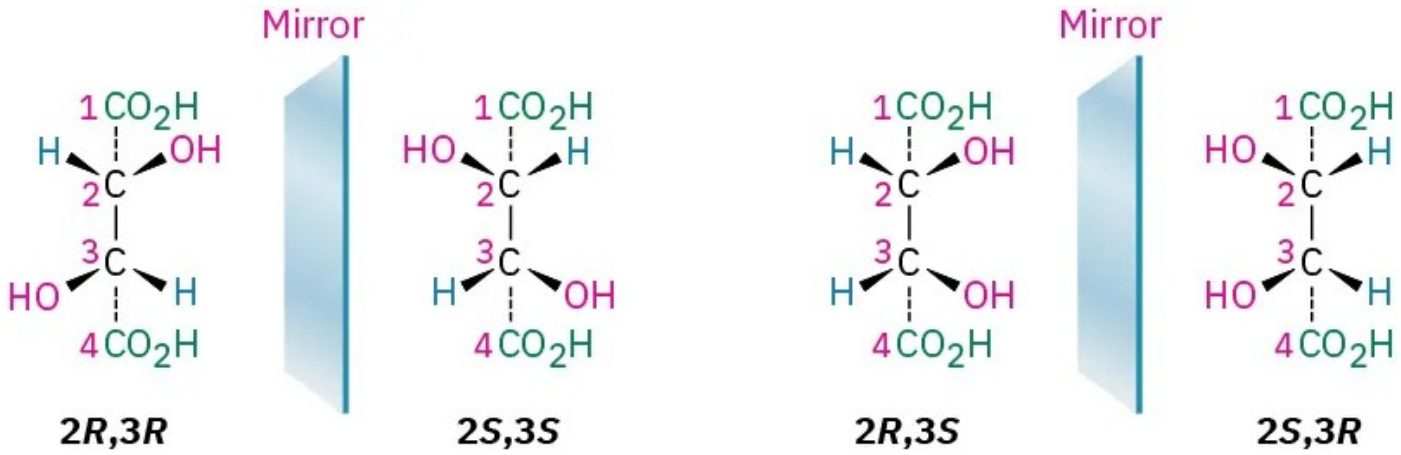
S,S

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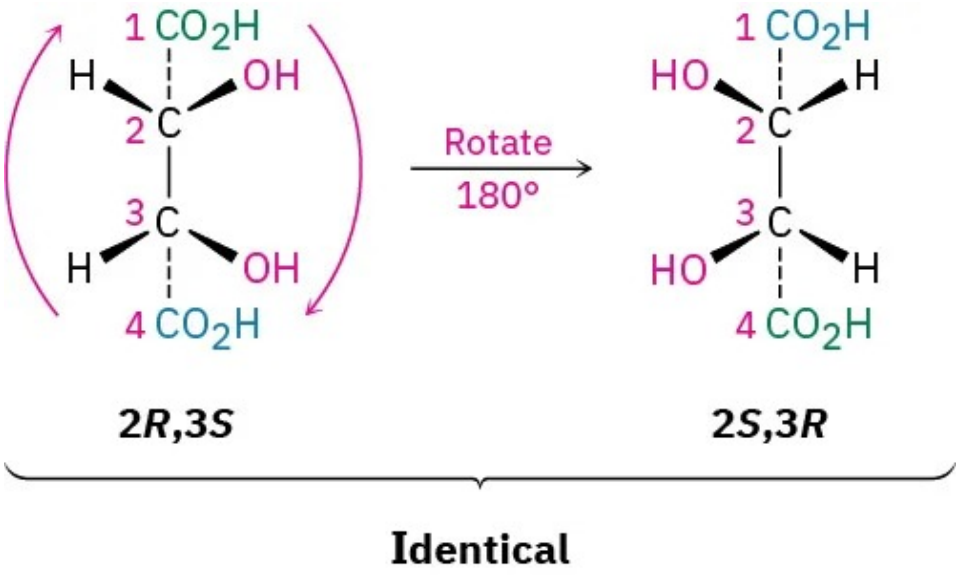
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5.7: Meso Compounds

Let's look at another example of a compound with more than one chirality center: the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The 2*R*,3*R* and 2S,3S structures are nonsuperimposable mirror images and therefore represent a pair of enantiomers. A close look at the 2*R*,3S and 2*S*,3*R* structures, however, shows that they *are* superimposable, and thus identical, as can be seen by rotating one structure 180°.



The 2*R*,3*S* and 2*S*,3*R* structures are identical because the molecule has a plane of symmetry and is therefore achiral. The symmetry plane cuts through the C2–C3 bond, making one half of the molecule a mirror image of the other half (Figure 5.7.1). Because of the plane of symmetry, the molecule is achiral, despite the fact that it has two chirality centers. Such compounds, which are achiral, yet contain chirality centers, are called **meso compounds (me-zo)**. Thus, tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

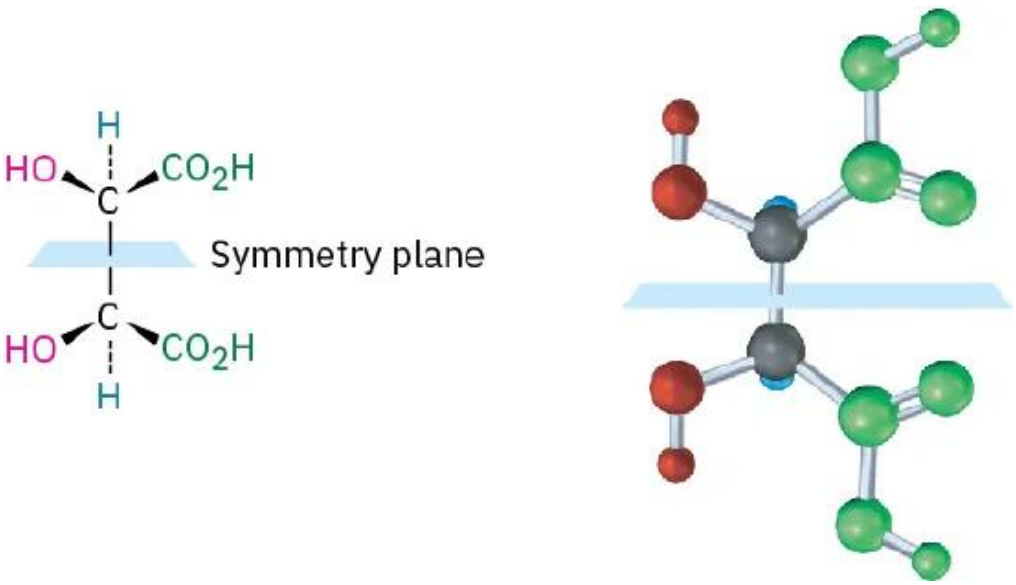


Figure 5.7.1: A symmetry plane through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral.

Some physical properties of the three stereoisomers are listed in Table 5.7.1. The (+)- and (–)-tartaric acids have identical melting points, solubilities, and densities, but they differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (–) forms. It has no mirror-image relationship to (+)- and (–)-tartaric acids, is a different compound altogether, and thus has different physical properties.

Table 5.7.1 Some Properties of the Stereoisomers of Tartaric Acid Some Properties of the Stereoisomers of Tartaric Acid

Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm^3)	Solubility at 20 °C (g/100 mL H_2O)
(+)	168–170	+12	1.7598	139.0
(–)	168–170	–12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

Worked Example 5.7.1: Distinguishing Chiral Compounds from Meso Compounds

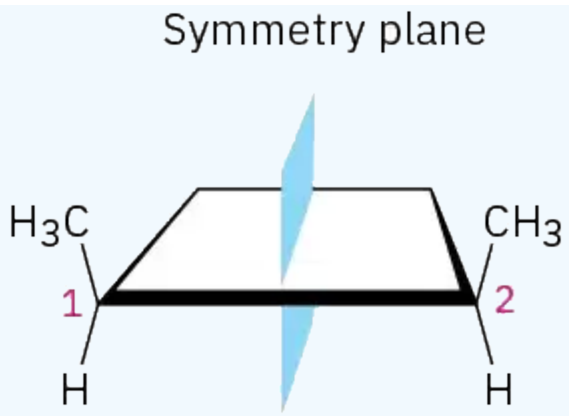
Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

Strategy

To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for the presence or absence of a symmetry plane. Not all molecules with chirality centers are chiral overall—meso compounds are an exception.

Solution

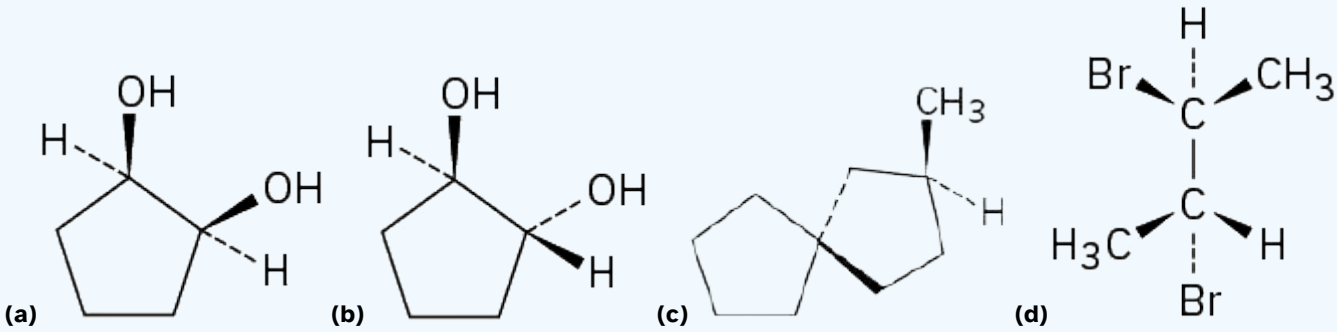
A look at the structure of *cis*-1,2-dimethylcyclobutane shows that both methyl-bearing ring carbons (C1 and C2) are chirality centers. Overall, though, the compound is achiral because there is a symmetry plane bisecting the ring between C1 and C2. Thus, the molecule is a meso compound.



Exercises

Exercise 5.7.1

Which of the following structures represents meso compounds?



Answer available at the end of this section.

Exercise 5.7.2

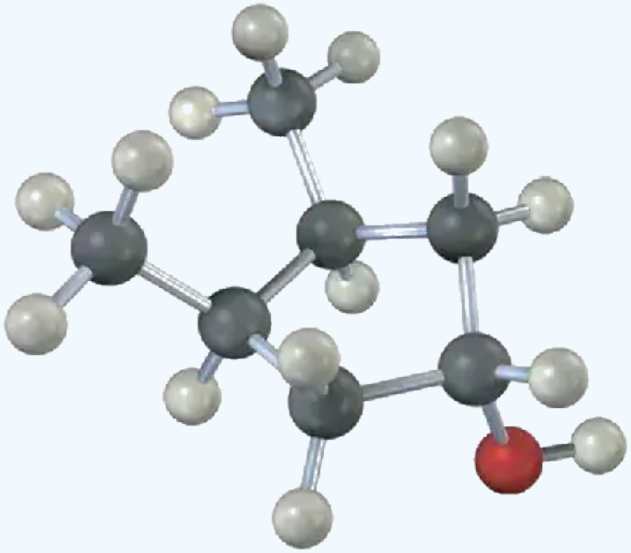
Which of the following molecules has a meso form? (Recall that the *-ol* suffix refers to an alcohol, ROH.)

a.2,3-Butanediol **b.**2,3-Pentanediol **c.**2,4-Pentanediol

Answer available at the end of this section.

Exercise 5.7.3

Does the following structure represent a meso compound? If so, indicate the symmetry plane.



Answer available at the end of this section.

Answers

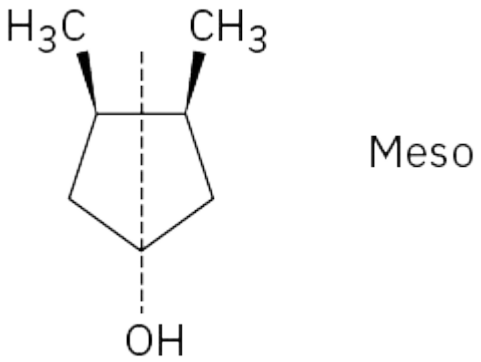
Exercise 5.7.1

Compounds **(a)** and **(d)** are meso.

Exercise 5.7.2

Compounds **(a)** and **(c)** have meso forms.

Exercise 5.7.3



Meso

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5.8: Racemic Mixtures and the Resolution of Enantiomers

To end this discussion of stereoisomerism, let's return for a last look at Pasteur's pioneering work, described in Section 5.5. Pasteur took an optically inactive tartaric acid salt and found that he could crystallize from it two optically active forms having what we would now call 2*R*,3*R* and 2*S*,3*S* configurations. But what was the optically inactive form he started with? It couldn't have been *meso*-tartaric acid, because *meso*-tartaric acid is a different chemical compound and can't interconvert with the two chiral enantiomers without breaking and re-forming chemical bonds.

The answer is that Pasteur started with a 50 : 50 mixture of the two chiral tartaric acid enantiomers. Such a mixture is called a racemate (**rass**-uh-mate), or **racemic mixture,** and is denoted by either the symbol (±) or the prefix *d,l* to indicate an equal mixture of dextrorotatory and levorotatory forms. Racemates show no optical rotation because the (+) rotation from one enantiomer exactly cancels the (–) rotation from the other. Through good luck, Pasteur was able to separate, or resolve, racemic tartaric acid into its (+) and (–) enantiomers. Unfortunately, the fractional crystallization technique he used doesn't work for most racemates, so other methods are needed.

The most common method for resolving the racemate of a chiral carboxylic acid (RCO_2H) is to carry out an acid-base reaction between the acid and an amine base (RNH_2) to yield an ammonium salt:



To understand how this method of resolution works, let's see what happens when a racemic mixture of chiral acids, such as (+)- and (–)-lactic acids, reacts with an achiral amine base, such as methylamine, CH_3NH_2. The situation is analogous to what happens when left and right hands (chiral) pick up a ball (achiral). Both left and right hands pick up the ball equally well, and the products—ball in right hand versus ball in left hand—are mirror images. In the same way, both (+)- and (–)-lactic acid react with methylamine equally well, and the product is a racemic mixture of the two enantiomers methylammonium (+)-lactate and methylammonium (–)-lactate (Figure 5.8.1).

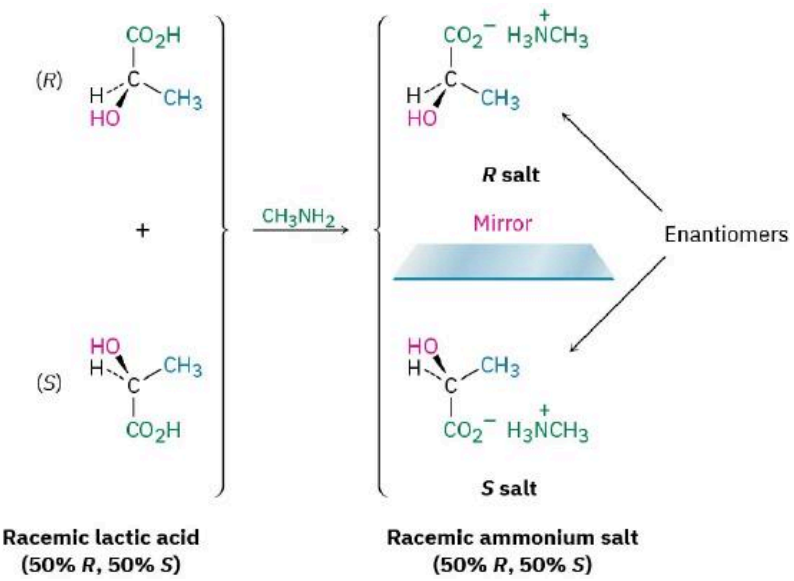


Figure 5.8.1: Reaction of racemic lactic acid with achiral methylamine gives a racemic mixture of ammonium salts.

Now let's see what happens when the racemic mixture of (+)- and (−)-lactic acids reacts with a single enantiomer of a chiral amine base, such as (*R*)-1-phenylethylamine. The situation is analogous to what happens when left and right hands (chiral) put on a right-handed glove (*also chiral*). Left and right hands don't put on the right-handed glove in the same way, so the products—right hand in right glove versus left hand in right glove—are not mirror images; they're similar but different.

In the same way, (+)- and (−)-lactic acids react with (*R*)-1-phenylethylamine to give two different products (Figure 5.8.2). (*R*)-Lactic acid reacts with (*R*)-1-phenylethylamine to give the *R,R* salt, and (*S*)-lactic acid reacts with the *R* amine to give the *S,R* salt. The two salts are diastereomers, not enantiomers. They have different chemical and physical properties, and it may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with a strong acid makes it possible to isolate the two pure enantiomers of lactic acid and to recover the chiral amine for reuse.

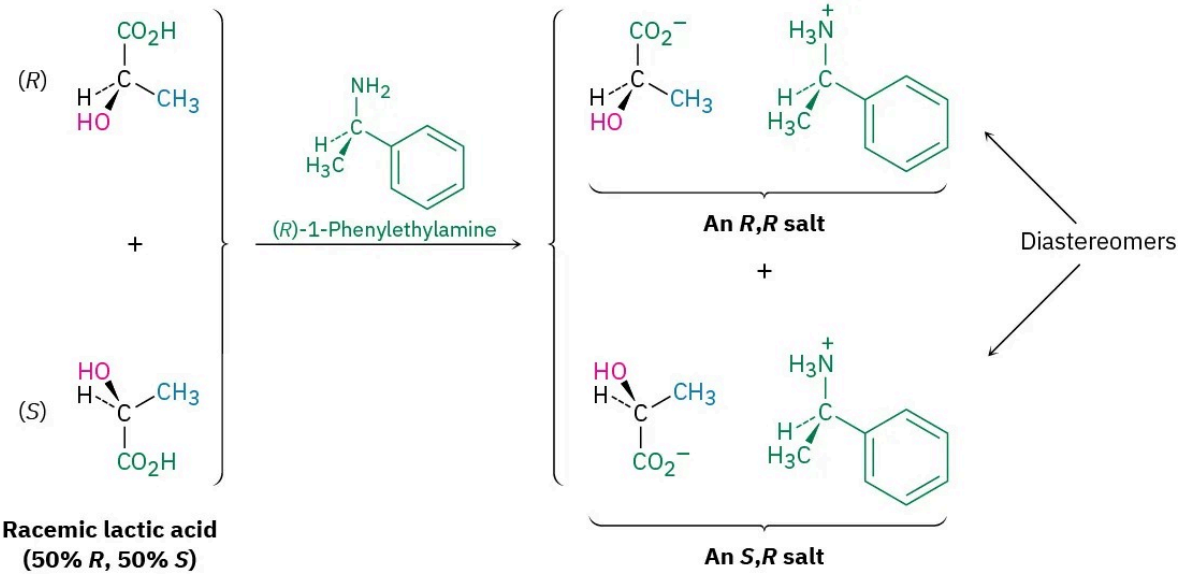
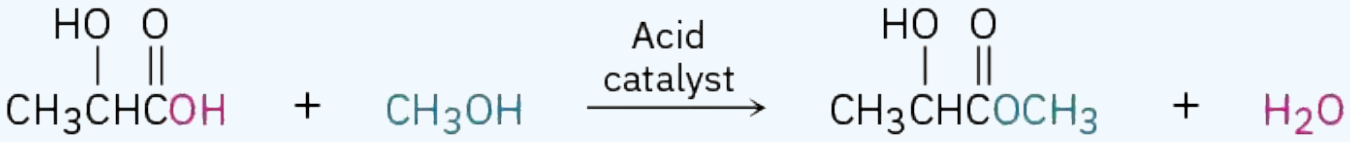


Figure 5.8.2: Reaction of racemic lactic acid with (*R*)-1-phenylethylamine yields a mixture of diastereomeric ammonium salts, which have different properties and can be separated.

Worked Example 5.8.1: Predicting the Chirality of a Reaction Product

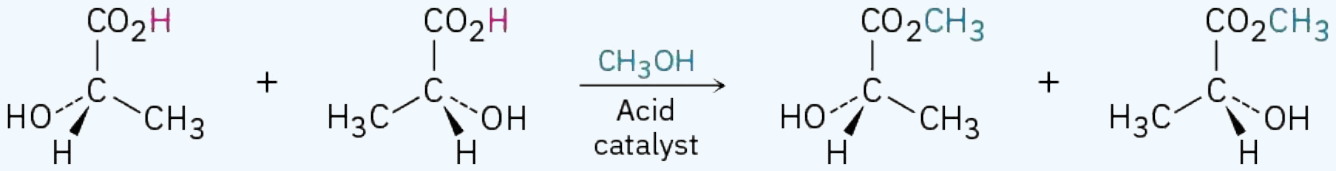
We'll see in **Section 21.4** that carboxylic acids (RCO_2H) react with alcohols ($R'OH$) to form esters (RCO_2R'). Suppose that (±)-lactic acid reacts with CH_3OH to form the ester, methyl lactate. What stereochemistry would you expect the product(s) to have? What is the relationship of the products?



Lactic acid **Methanol** **Methyl lactate**

Solution

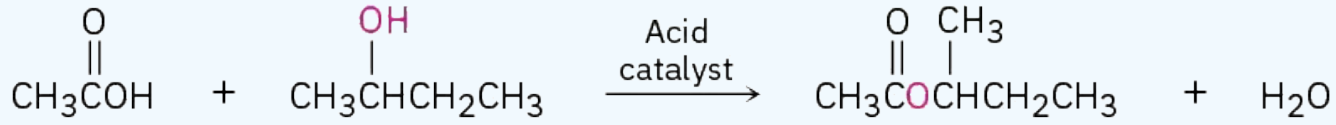
Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products.



(*S*)-Lactic acid **(*R*)-Lactic acid** **Methyl (*S*)-lactate** **Methyl (*R*)-lactate**

Exercise 5.8.1

Suppose that acetic acid (CH_3CO_2H) reacts with (S)-2-butanol to form an ester (see Worked Example 5.6). What stereochemistry would you expect the product(s) to have? What is the relationship of the products?



Acetic acid **2-Butanol** ***sec*-Butyl acetate**

Exercise 5.8.2

What stereoisomers would result from reaction of (±)-lactic acid with (S)-1-phenylethylamine, and what is the relationship between them?

Answer available at the end of this section.

Answers

Exercise 5.8.2

Two diastereomeric salts: (*R*)-lactic acid plus (S)-1-phenylethylamine and (S)-lactic acid plus (S)-1-phenylethylamine

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5.9: A Review of Isomerism

As noted on several previous occasions, isomers are compounds with the same chemical formula but different structures. We've seen several kinds of isomers in the past few chapters, and it's a good idea at this point to see how they relate to one another (Figure 5.9.1).

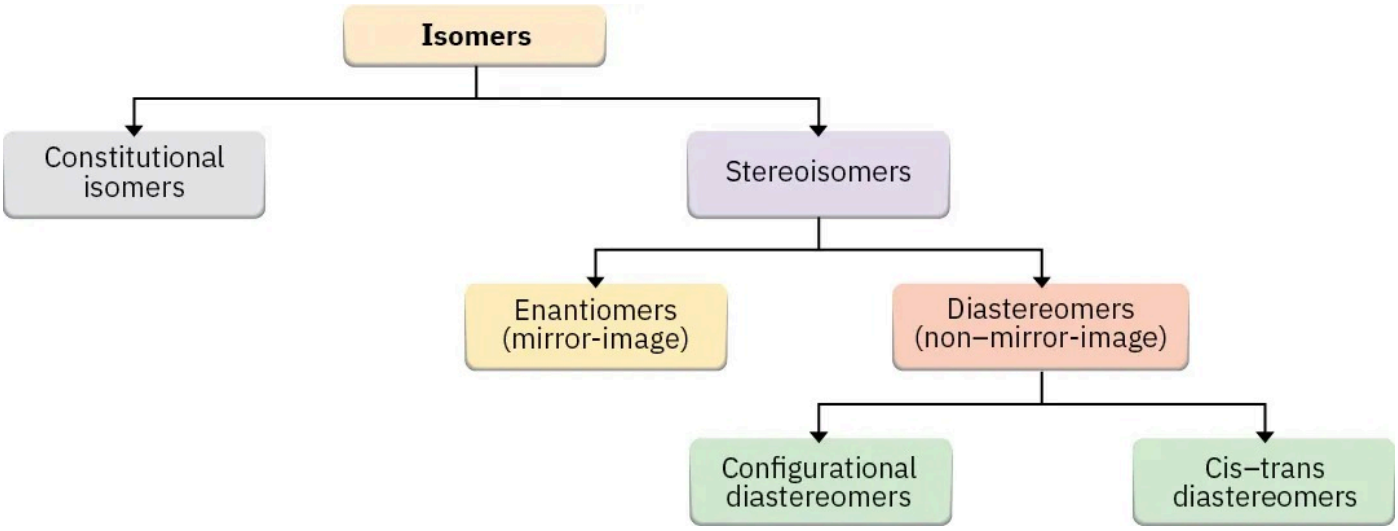
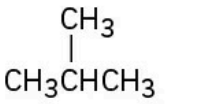


Figure 5.9.1: A summary of the different kinds of isomers.

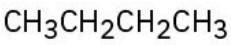
There are two fundamental types of isomers, both of which we've now encountered: constitutional isomers and stereoisomers.

Constitutional isomers (Section 3.3) are compounds whose atoms are connected differently. Among the kinds of constitutional isomers we've seen are skeletal, functional, and positional isomers.

Different carbon skeletons

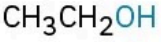


and



2-Methylpropane and **Butane**

Different functional groups

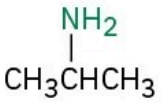


and

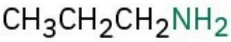


Ethyl alcohol and **Dimethyl ether**

Different position of functional groups



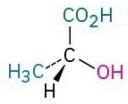
and



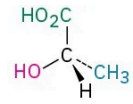
Isopropylamine and **Propylamine**

Stereoisomers (Section 4.3) are compounds whose atoms are connected in the same order but with a different spatial arrangement. Among the kinds of stereoisomers we've seen are enantiomers, diastereomers, and cis–trans isomers of cycloalkanes. Actually, cis–trans isomers are just a subclass of diastereomers because they are non–mirror-image stereoisomers:

Enantiomers
(nonsuperimposable mirror-image stereoisomers)



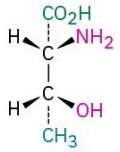
(*R*)-Lactic acid



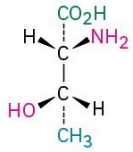
(*S*)-Lactic acid

Diastereomers
(nonsuperimposable non–mirror-image stereoisomers)

Configurational diastereomers

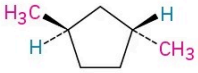


(2*R*,3*R*)-2-Amino-3-hydroxybutanoic acid



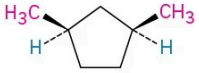
(2*R*,3*S*)-2-Amino-3-hydroxybutanoic acid

Cis–trans diastereomers
(substituents on same side or opposite side of double bond or ring)



***trans*-1,3-Dimethylcyclopentane**

and



***cis*-1,3-Dimethylcyclopentane**

Exercise 5.9.1

What kinds of isomers are the following pairs?

a. (S)-5-Chloro-2-hexene and chlorocyclohexane
b. (2*R*,3*R*)-Dibromopentane and (2S,3*R*)-dibromopentane

Answer available at the end of this section.

Answers

Exercise 5.9.1

a. Constitutional isomers
b. Diastereomers

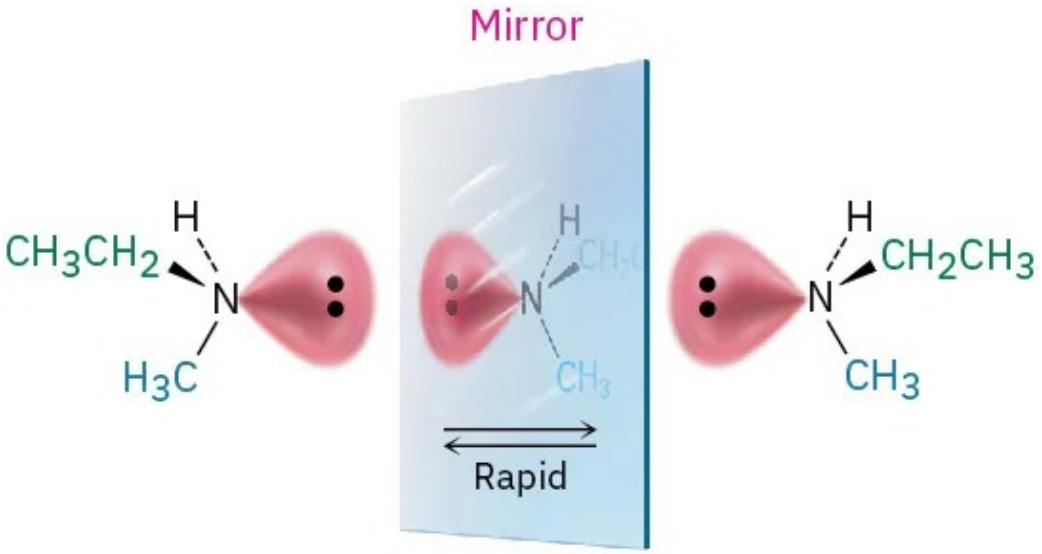
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5.10: Chirality at Nitrogen, Phosphorus, and Sulfur

As noted previously, the most common cause of chirality in a molecule is the presence of four different substituents bonded to a tetrahedral atom. Although that atom is usually carbon, it doesn't necessarily have to be. Nitrogen, phosphorus, and sulfur atoms are all commonly encountered in organic molecules, and can all be chirality centers. We know, for instance, that trivalent nitrogen is tetrahedral, with its lone pair of electrons acting as the fourth "substituent" (Section 1.11). Is trivalent nitrogen chiral? Does a compound such as ethylmethylamine exist as a pair of enantiomers?

The answer is both yes and no. Yes in principle, but no in practice. It turns out that most trivalent nitrogen compounds undergo a rapid umbrella-like inversion that interconverts enantiomers, so we can't isolate individual enantiomers except in special cases.

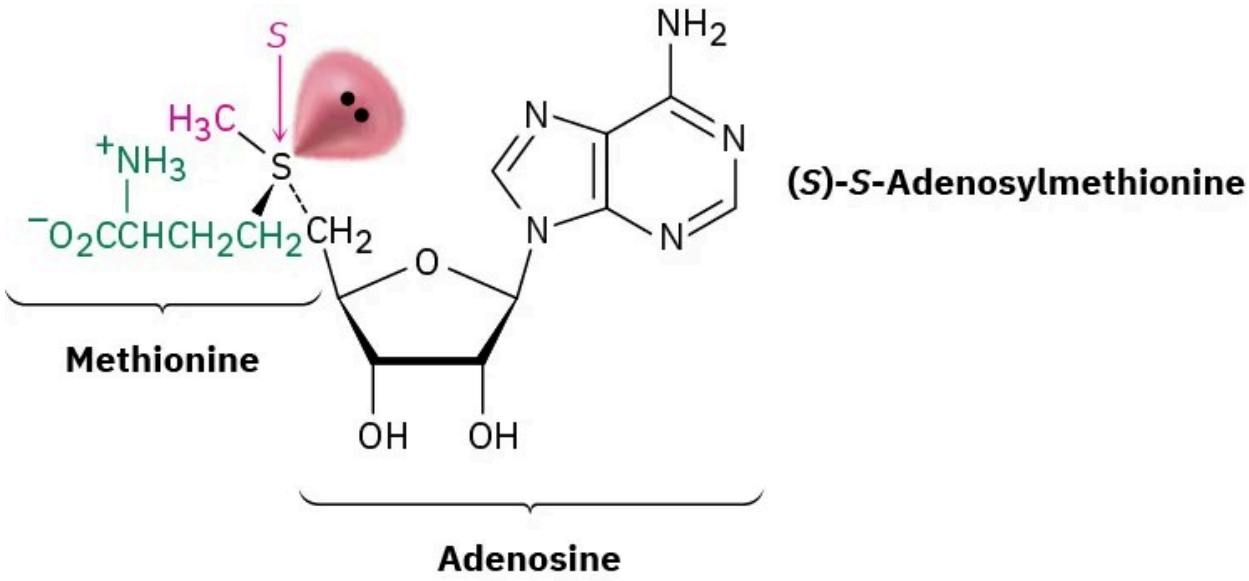


A similar situation occurs in trivalent phosphorus compounds, called phosphines, but the inversion at phosphorus is substantially slower than inversion at nitrogen, so stable chiral phosphines can be isolated. (*R*)- and (*S*)-methylpropylphenylphosphine, for instance, are configurationally stable for several hours at 100 °C. We'll see the importance of phosphine chirality in **Section 26.8** in connection with the synthesis of chiral amino acids.



Divalent sulfur compounds are achiral, but trivalent sulfur compounds called *sulfonium salts* (R_3S^+) can be chiral. Like phosphines, sulfonium salts undergo relatively slow inversion, so chiral sulfonium salts are configurationally stable and can be isolated. Perhaps the best known example is the coenzyme *S*-adenosylmethionine, the so-called biological methyl donor, which is involved in many metabolic pathways as a source of CH_3 groups. (The "S" in the name *S*-adenosylmethionine stands for *sulfur* and means that the adenosyl group is attached to the sulfur atom of the amino acid methionine.) The molecule has *S* stereochemistry at sulfur and is configurationally stable for several days at room temperature. Its *R* enantiomer is also known but is not biologically

active.

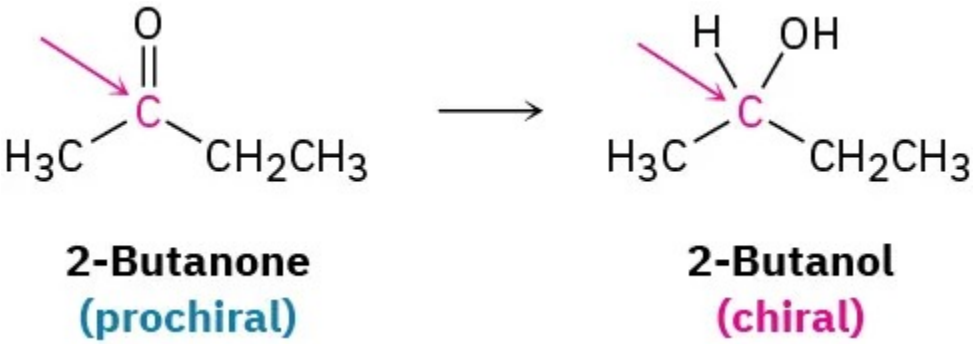


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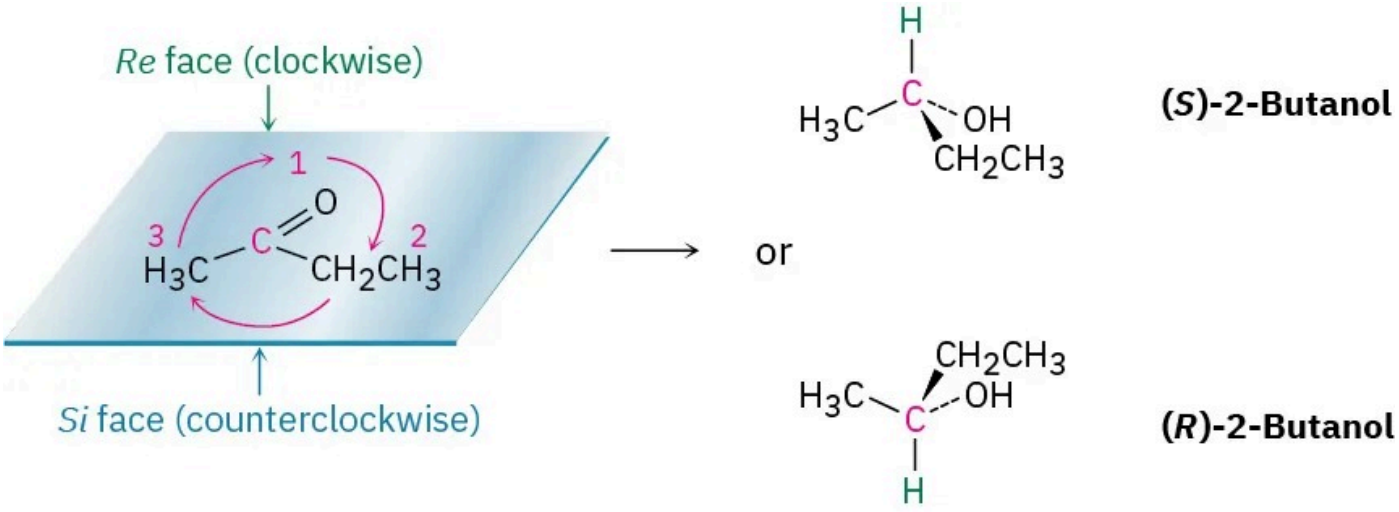
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5.11: Prochirality

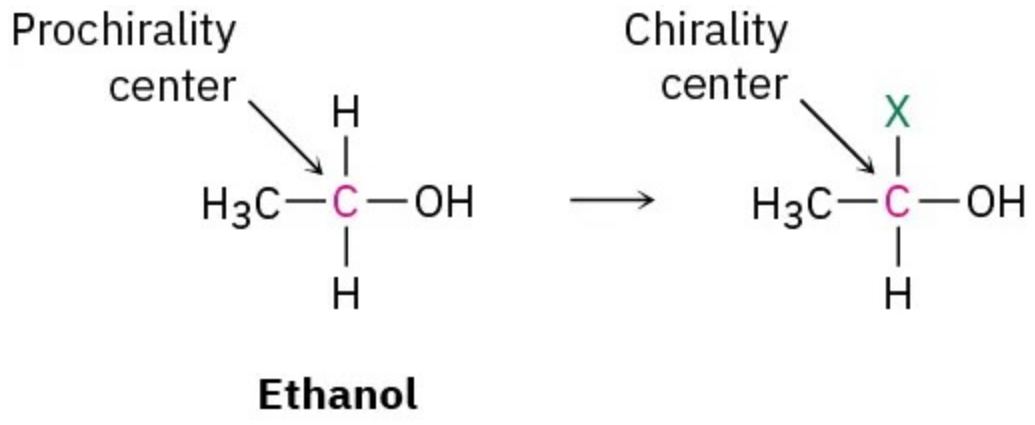
Closely related to the concept of chirality, and particularly important in biological chemistry, is the notion of *prochirality*. A molecule is said to be prochiral if it can be converted from achiral to chiral in a single chemical step. For instance, an unsymmetrical ketone like 2-butanone is prochiral because it can be converted to the chiral alcohol 2-butanol by the addition of hydrogen, as we'll see next semester.



Which enantiomer of 2-butanol is produced depends on which face of the planar carbonyl group undergoes reaction. To distinguish between the possibilities, we use the stereochemical descriptors Re and Si. Rank the three groups attached to the trigonal, sp^2-hybridized carbon, and imagine curved arrows from the highest to second-highest to third-highest ranked substituents. The face on which the arrows curve clockwise is designated the Re face (similar to *R*), and the face on which the arrows curve counterclockwise is designated the Si face (similar to *S*). In this example, addition of hydrogen from the Re face gives (S)-2-butane, and addition from the Si face gives (*R*)-2-butane.

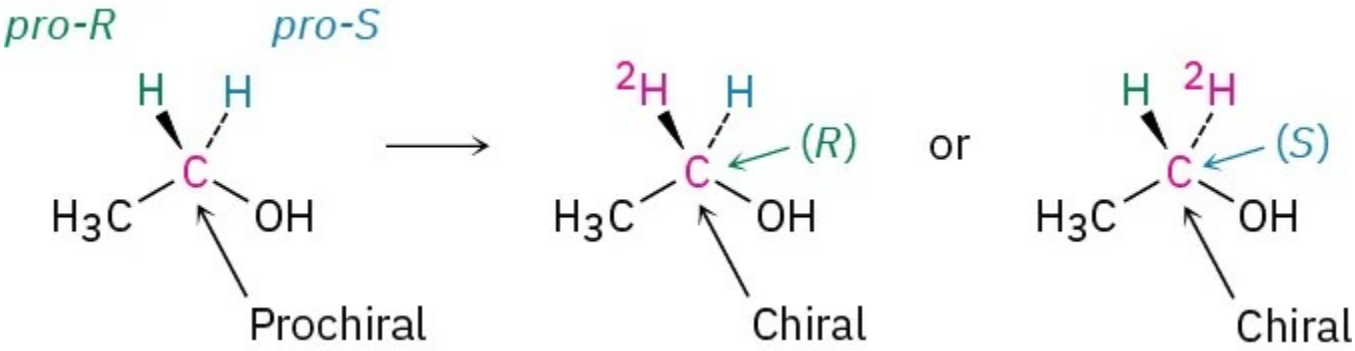


In addition to compounds with planar, sp^2-hybridized atoms, compounds with tetrahedral, sp^3-hybridized atoms can also be prochiral. An sp^3-hybridized atom is said to be a prochirality center if, by changing one of its attached groups, it becomes a chirality center. The $-CH_2OH$ carbon atom of ethanol, for instance, is a prochirality center because changing one of its attached –H atoms converts it into a chirality center.

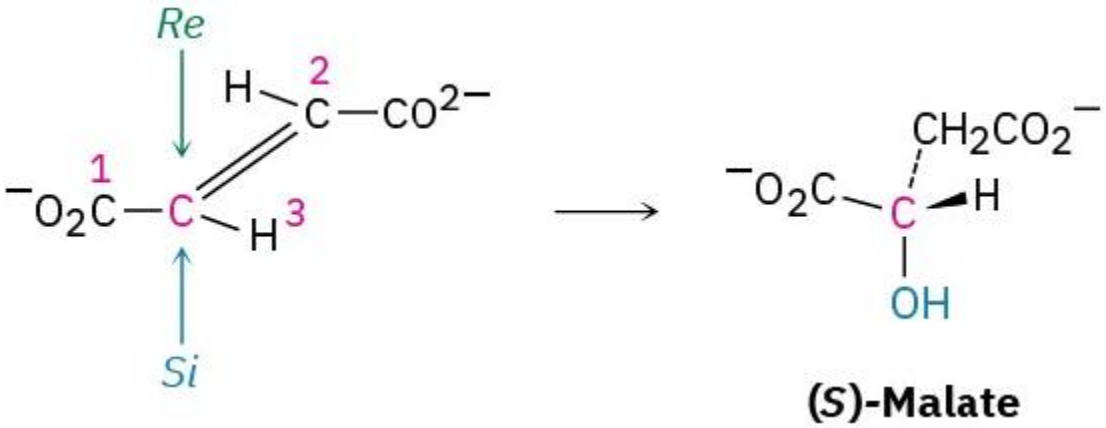


Ethanol

To distinguish between the two identical atoms (or groups of atoms) on a prochirality center, we imagine a change that will raise the ranking of one atom over the other without affecting its rank with respect to other attached groups. On the $-CH_2OH$ carbon of ethanol, for instance, we might imagine replacing one of the ^1H atoms (protium) by ^2H (deuterium). The newly introduced ^2H atom ranks higher than the remaining ^1H atom, but it remains lower than other groups attached to the carbon. Of the two identical atoms in the original compound, the atom whose replacement leads to an *R* chirality center is said to be pro-*R* and the atom whose replacement leads to an *S* chirality center is pro-S.

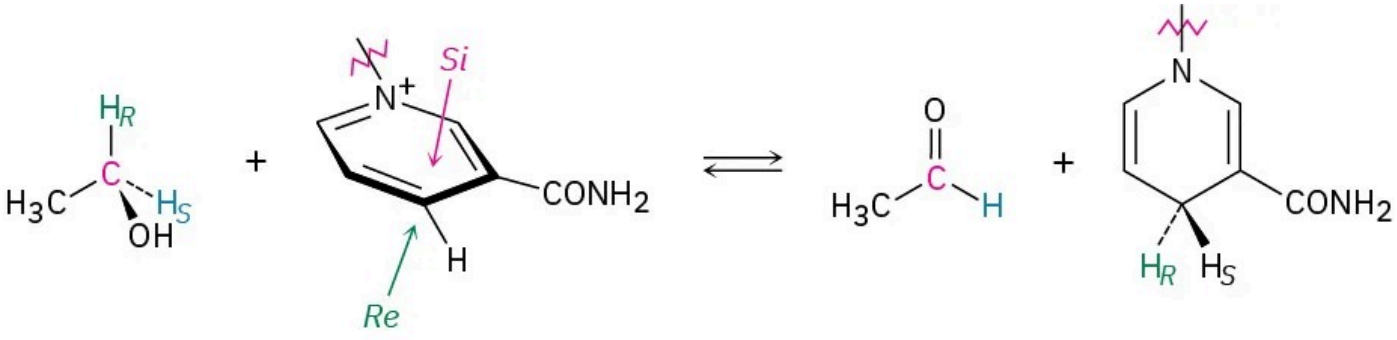


A large number of biological reactions involve prochiral compounds. One of the steps in the citric acid cycle by which food is metabolized, for instance, is the addition of H_2O to fumarate to give malate. Addition of –OH occurs on the Si face of a fumarate carbon and gives (*S*)-malate as product.



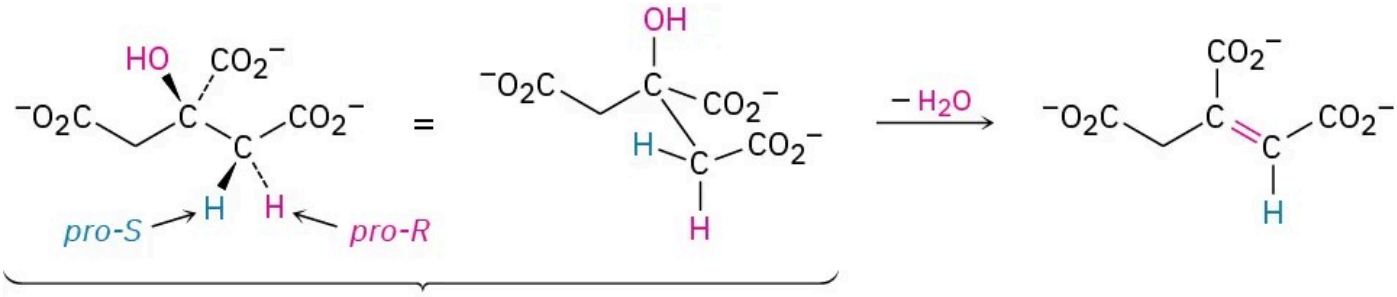
(*S*)-Malate

As another example, studies with deuterium-labeled substrates have shown that the reaction of ethanol with the coenzyme nicotinamide adenine dinucleotide (NAD^+), catalyzed by yeast alcohol dehydrogenase, occurs with exclusive removal of the pro-*R* hydrogen from ethanol and with addition only to the Re face of NAD^+.



Ethanol **NAD$^+$** **Acetaldehyde** **NADH**

Determining the stereochemistry of reactions at prochirality centers is a powerful method for studying detailed mechanisms in biochemical reactions. As just one example, the conversion of citrate to *cis*-aconitate in the citric acid cycle has been shown to occur with loss of a pro-*R* hydrogen, implying that the OH and H groups leave from opposite sides of the molecule.



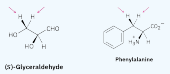
Citrate ***cis*-Aconitate**

Exercises

Exercise 5.11.1

Identify the indicated hydrogens in the following molecules as pro-*R* or pro-*S*:

a. **b.**

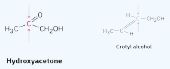


Answer available at the end of this section.

Exercise 5.11.2

Identify the indicated faces of carbon atoms in the following molecules as Re or Si:

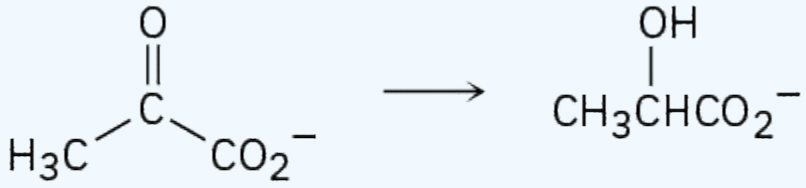
a. **b.**



Answer available at the end of this section.

Exercise 5.11.3

The lactic acid that builds up in tired muscles is formed from pyruvate. If the reaction occurs with the addition of hydrogen to the Re face of pyruvate, what is the stereochemistry of the product?

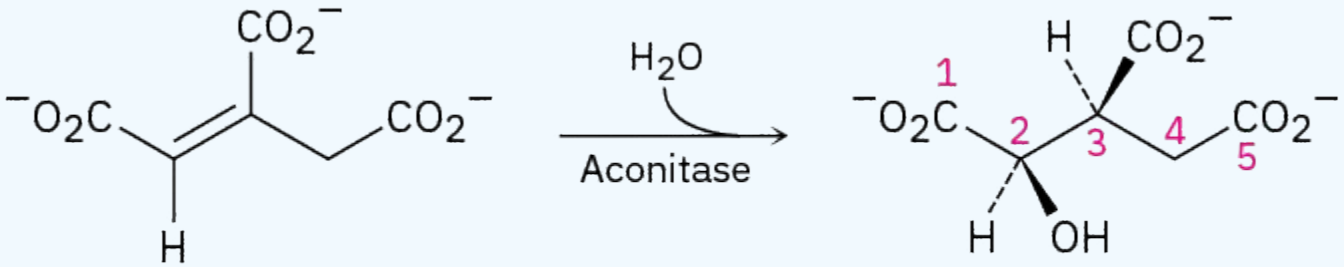


Pyruvate **Lactate**

Answer available at the end of this section.

Exercise 5.11.4

The aconitase-catalyzed addition of water to *cis*-aconitate in the citric acid cycle occurs with the following stereochemistry. Does the addition of the OH group occur on the Re or Si face of the substrate? What about the addition of the H? Do the H and OH groups add from the same side of the double bond or from opposite sides?



***cis*-Aconitate** **(2*R*,3*S*)-Isocitrate**

Answer available at the end of this section.

Answers

Exercise 5.11.1

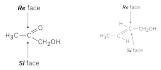
a. **b.**



Note: In the place of H_3C should read Ph=Phenyl group

Exercise 5.11.2

a. **b.**



Exercise 5.11.3

(*S*)-Lactate

Exercise 5.11.4

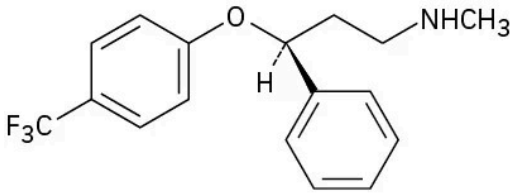
The –OH adds to the Re face of C2, and –H adds to the Re face of C3. The overall addition has anti-stereochemistry.

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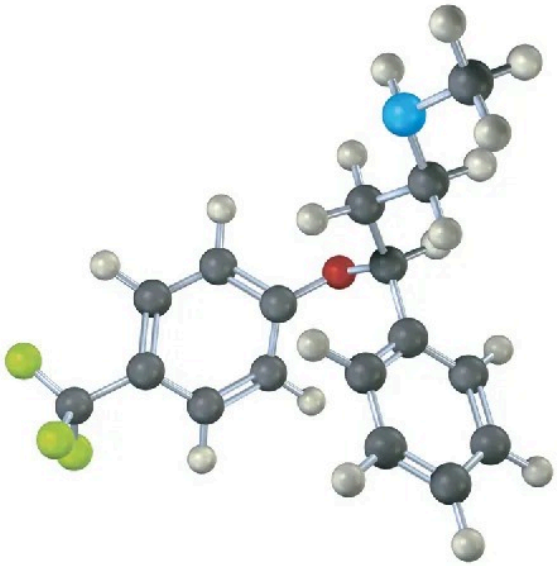
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5.12: Chirality in Nature and Chiral Environments

Although the different enantiomers of a chiral molecule have the same physical properties, they usually have different biological properties. For example, a change in chirality can affect the biological properties of many drugs, such as fluoxetine, a heavily prescribed medication sold under the trade name Prozac. Racemic fluoxetine is an effective antidepressant but has no activity against migraine. The pure S enantiomer, however, works remarkably well in preventing migraine. Other examples of how chirality affects biological properties are given in the Chapter 5 *Chemistry Matters* at the end of this chapter.



(*S*)-Fluoxetine
(prevents migraine)



Why do different enantiomers have different biological properties? To have a biological effect, a substance typically must fit into an appropriate receptor that has a complementary shape. But because biological receptors are chiral, only one enantiomer of a chiral substrate can fit, just as only a right hand can fit into a right-handed glove. The mirror-image enantiomer will be a misfit, like a left hand in a right-handed glove. A representation of the interaction between a chiral molecule and a chiral biological receptor is shown in Figure 5.12.1: one enantiomer fits the receptor perfectly, but the other does not.

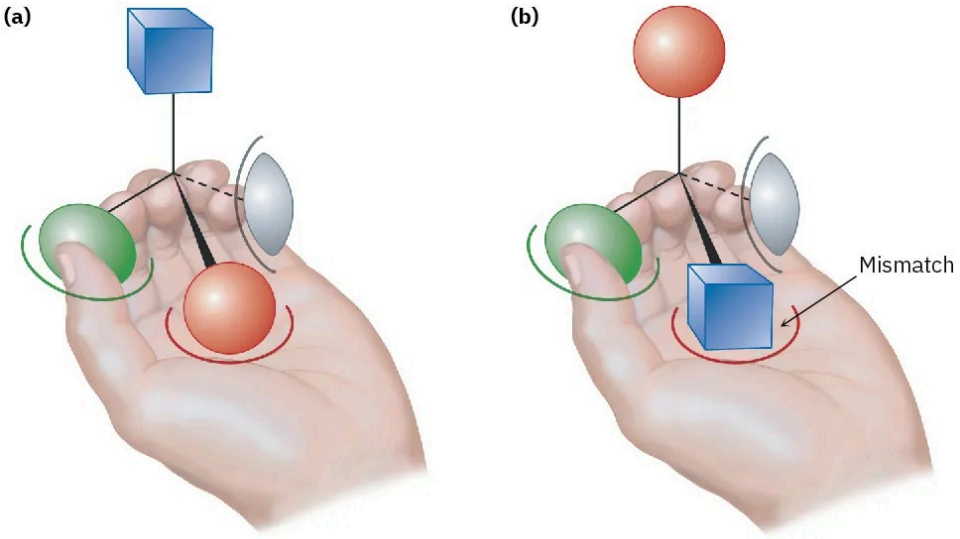
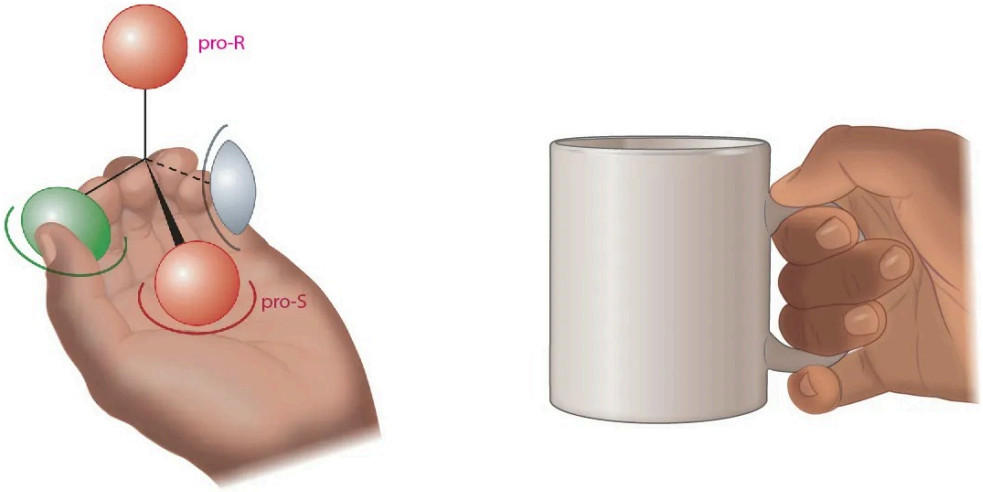


Figure 5.12.1: Interaction of a chiral object with a chiral receptor. A left hand interacts with a chiral object, much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: **green thumb**, **red palm**, and **gray pinkie finger**, with the **blue substituent exposed**. **(b)** The other enantiomer, however, can't fit into the hand. When the green thumb and gray pinkie finger interact appropriately, the palm holds a blue substituent rather than a red one, with the **red substituent exposed**.

The hand-in-glove fit of a chiral substrate into a chiral receptor is relatively straightforward, but it's less obvious how a prochiral substrate can undergo a selective reaction. Take the reaction of ethanol with NAD^+ catalyzed by yeast alcohol dehydrogenase. As we saw at the end of Section 5.12, this reaction occurs with exclusive removal of the pro-*R* hydrogen from ethanol and with addition only to the Re face of the NAD^+ carbon.

We can understand this result by imagining that the chiral enzyme receptor again has three binding sites, as in Figure 5.12.1. When green and gray substituents of a prochiral substrate are held appropriately, however, only one of the two red substituents—say, the pro-S one—is also held while the other, pro-*R,* substituent is exposed for reaction.

We describe the situation by saying that the receptor provides a chiral environment for the substrate. In the absence of a **chiral environment**, the two red substituents are chemically identical, but in the presence of a chiral environment, they are chemically distinctive (Figure 5.12.2*a*). The situation is similar to what happens when you pick up a coffee mug. By itself, the mug has a plane of symmetry and is achiral. When you pick up the mug, however, your hand provides a chiral environment so that one side becomes much more accessible and easier to drink from than the other (Figure 5.12.2*b*).



(a) (b)

Figure 5.12.2: (a) When a prochiral molecule is held in a chiral environment, the **two seemingly identical substituents** are **distinguishable.** **(b)** Similarly, when an achiral coffee mug is held in the chiral environment of your hand, it's much easier to drink from one side than the other because the two sides of the mug are now distinguishable.

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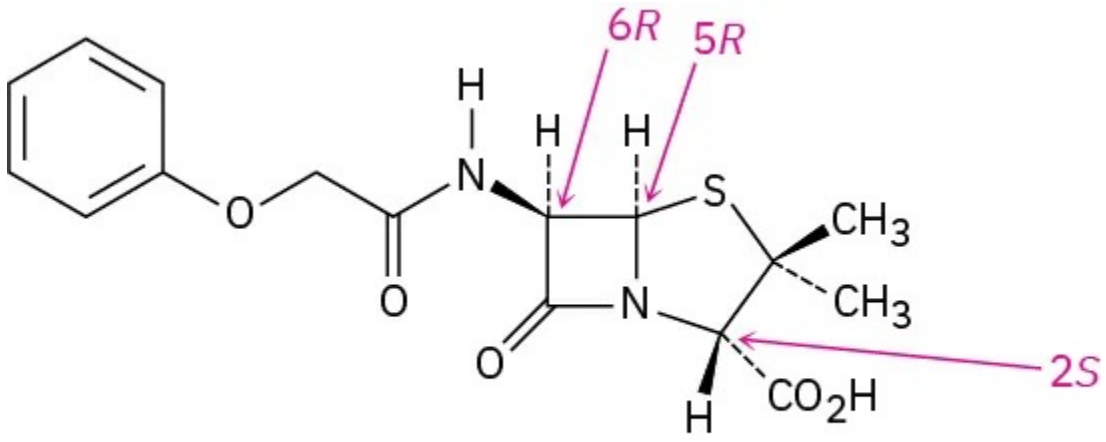
5.13: Chemistry Matters—Chiral Drugs

The many hundreds of different pharmaceutical agents approved for use by the U.S. Food and Drug Administration come from many sources. Many drugs are isolated directly from plants or bacteria, and others are made by chemical modification of naturally occurring compounds. An estimated 33%, however, are made entirely in the laboratory and have no relatives in nature.



Figure 5.13.1: The S enantiomer of ibuprofen soothes the aches and pains of athletic injuries much more effectively than the *R* enantiomer. (credit: "World Athletic Championships 2007 in Osaka" by Eckhard Pecher/Wikimedia Commons, CC BY 2.5)

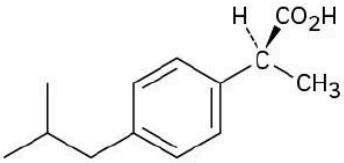
Those drugs that come from natural sources, either directly or after laboratory modification, are usually chiral and are generally found only as a single enantiomer rather than as a racemate. Penicillin V, for example, an antibiotic isolated from the *Penicillium* mold, has the 2*S*,5*R*,6*R* configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.



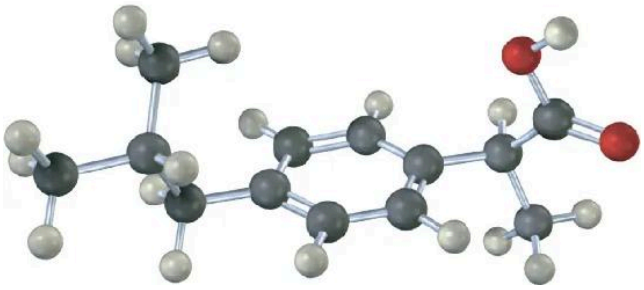
Penicillin V (2*S*,5*R*,6*R* configuration)

In contrast to drugs from natural sources, drugs that are made entirely in the laboratory are either achiral or, if chiral, are often produced and sold as racemates. Ibuprofen, for example, has one chirality center and is sold commercially under such trade names as Advil, Nuprin, and Motrin as a 50 : 50 mixture of *R* and S. It turns out, however, that only the S enantiomer is active as an analgesic and anti-inflammatory agent. The *R* enantiomer of ibuprofen is inactive, although it is slowly converted in the body

to the active S form.



(*S*)-Ibuprofen
(an active analgesic agent)



Not only is it chemically wasteful to synthesize and administer an enantiomer that does not serve the intended purpose, many instances are now known where the presence of the "wrong" enantiomer in a racemic mixture either affects the body's ability to utilize the "right" enantiomer or has unintended pharmacological effects of its own. The presence of (*R*)-ibuprofen in the racemic mixture, for instance, slows the rate at which the S enantiomer takes effect in the body, from 12 minutes to 38 minutes.

To get around this problem, pharmaceutical companies attempt to devise methods of *enantioselective* synthesis, which allow them to prepare only a single enantiomer rather than a racemic mixture. Viable methods have been developed for the preparation of (S)-ibuprofen, which is marketed in Europe. We'll look further into enantioselective synthesis in the Chapter 19 *Chemistry Matters*.

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5.A: Stereochemistry at Tetrahedral Centers (Summary)

Concepts & Vocabulary

5.1: Enantiomers and the Tetrahedral Carbon

- Every molecule is either **chiral** (not superimposable on its mirror image) or **achiral** (superimposable on its mirror image).
- **Chiral** molecules do not have a plane of symmetry, while **achiral** molecules have one or more **planes of symmetry**.
- **Stereoisomers** vary by spatial arrangement of atoms but have the same atom connectivity.
- **Stereoisomers** that are mirror images of one another but are not superimposable are called **enantiomers**.

5.2: The Reason for Handedness in Molecules - Chirality

- A Tetrahedral carbon atom bonded to four different substituents is an **asymetric** carbon (also called a **stereocenter** or **chiral** carbon), which typically leads to a **chiral** molecule (meso compounds are the exception in section 5.7).

5.3: Optical Activity

- **Enantiomers** cause rotation of plane-polarized light in equal amounts in opposite directions. This is called **optical activity.** Clockwise rotation is called d**extrorotatory** (+) and counter-clockwise is called **levorotatory** (-).
- **Specific rotation** is the amount that a sample of a chemical rotates planne-polarized light. It can be used to calculate the purity of a mixture of **enantiomers** called the **enantiomeric excess**.
- **Resolution** is the separation of a mixture of **enatiomers**.
- **Racemates** are defined as a 50:50 mixture of **enantiomers**, resulting in a sample that is not **optically active**. The process of forming a **racemic** mixture is called **racemization**.

5.5: Sequence Rules for Specifying Configuration

- Use the CIP rules to determine the priority of each substituent attached to a **chiral** carbon to determine whether configuration is **R** or **S**. With the lowest priority group facing away from you, draw an arc connecting groups 1-2-3. If that arc is clockwise, the configuration is **R**. If counterclockwise, the configuration is **S**.

5.6: Diastereomers

- **Stereoisomers** that are not mirror images of one another are called **diastereomers**.
- **Diastereomers** have two or more **stereocenters**. The configurations of the **stereocenters** cannot be inverse of each other (example R,R and S,S) because that defines a pair of **enantiomers**.

5.7: Meso Compounds

- **Meso** compounds are **achiral** but have **chiral** centers. This is caused by having an internal **plane of symmetry** that allows the two molecules to be superimposable on one another and be **optically inactive**.

5.8: Racemic Mixtures and the Resolution of Enantiomers

- Each component of a **racemic** mixture rotates plane-polarized light an equal amount in opposite directions, so there is no **optical activity**.
- **Racemic** mixtures can be separated into the component **enantiomers** by reaction with a **chiral** reagent, which will form **diastereomer** intermediates of the molecules which can then be separated. Following separation, the **chiral** reagent is removed to yield the two pure **enantiomers**.

5.9: A Review of Isomerism

- There are several categories of **isomers** with the largest distinction between:
  - constitutional (structural) isomers that contain the same number of each atom but differ in connectivity
  - **stereoisomers** that have all the same atoms with the same connectivity, but only differ in how the atoms are arranged

three dimensionally
- In addition to the **diastereomers** and **enantiomers** that have been discussed at length in this chapter, **stereoisomers** can also be:
  - cis/trans or E/Z isomers which differ by spatial arrangement around a double bond
  - conformational **isomers** (conformers) which occur due to free rotation of sigma bonds

5.10: Chirality at Nitrogen, Phosphorus, and Sulfur

- Nitrogen when bonded to three different atoms is **chiral**, however the lone pair of electrons moves freely between positions on the Nitrogen causing these molecules to become a **racemic** mixture.
- When bonded to four different atoms in quaternary ammonium salts, nitrogen atoms lead to **chiral** molecules.
- Organic phosphates with four different groups can also be **chiral**.

5.11: Prochirality

- When a carbon can be converted to a **chiral** center by changing only one of its attached groups, it is called **prochiral**.
- If a molecule has two hydrogens on the same atom and replacement of either one with deuterium would lead to **enantiomers**, the hydrogens are **enantiotopic**.
- Similarly if this replacement would lead to **diastereomer** molecules, the hydrogens are **diastereotopic**.
- If replacement of a hydrogen would not lead to a chiral center being created, they are termed **homotopic**.

Skills to Master

- Skill 5.1 Identify stereocenters in molecular structures.
- Skill 5.2 Identify whether two structures are identical (not meso), constitutional isomers, enantiomers, diastereomers or meso and identical.
- Skill 5.3 Explain how plane-polarized light is used to show optical activity.
- Skill 5.4 Calculate specific rotation from experimental data.
- Skill 5.5 Calculate optical purity and enantiomeric excess from experimental data.
- Skill 5.6 Determine configuration of stereocenters as R or S.
- Skill 5.7 Draw the enantiomer and diastereomers of a given compound with one or more stereocenters.
- Skill 5.8 Identify planes of symmetry in meso compounds.
- Skill 5.9 Describe a process for separating a mixture of enantiomers.
- Skill 5.10 Explain why racemic mixtures are optically inactive.
- Skill 5.11 Explain the difference between constitutional and stereoisomers.
- Skill 5.12 Give an example of a chiral center that is not carbon.

Memorization Tasks

MT 5.1 Memorize the rules for determining R and S configuration.

MT 5.2 Memorize the types of isomers and how to identify them.

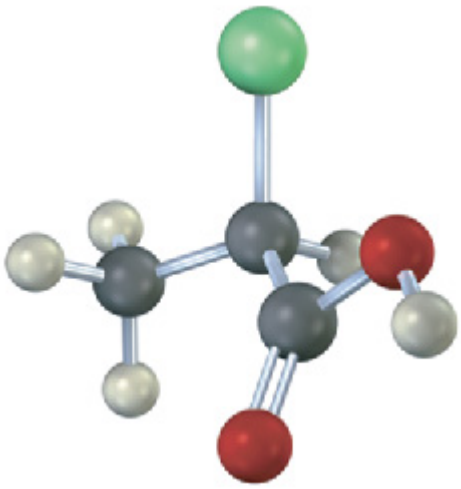
Contributors

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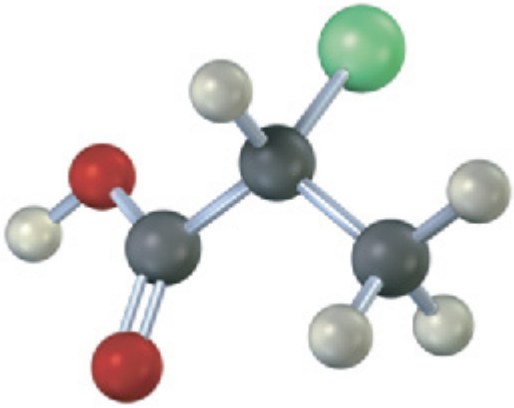
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5.B: Additional Problems

PROBLEM 5-26 Which of the following structures are identical? (Green = Cl.)

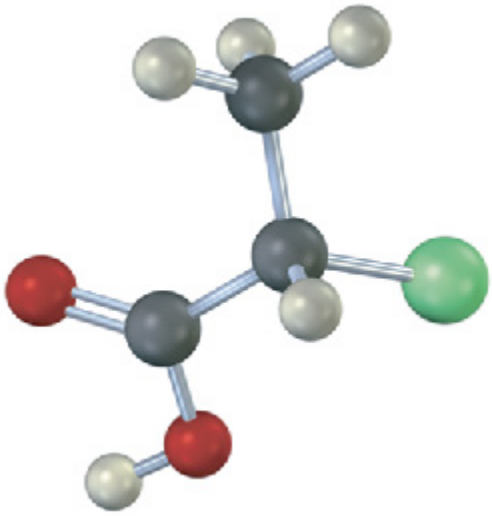


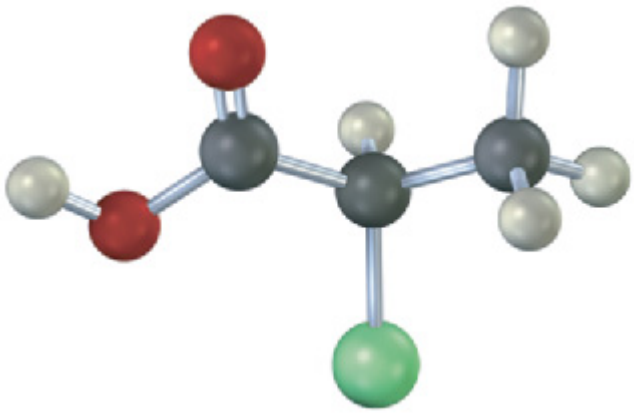
(a)



(b)

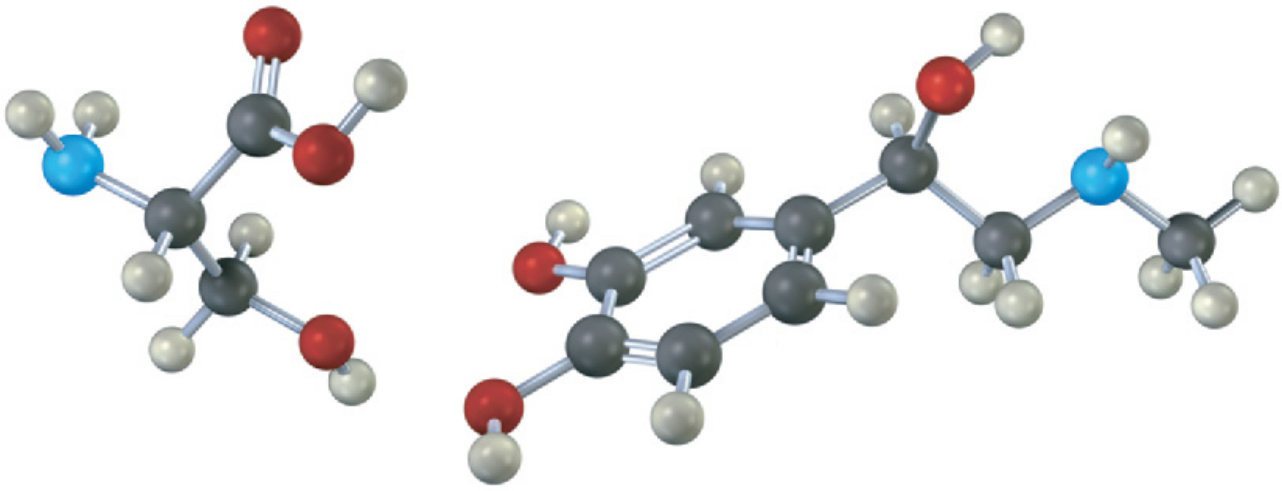
(c)





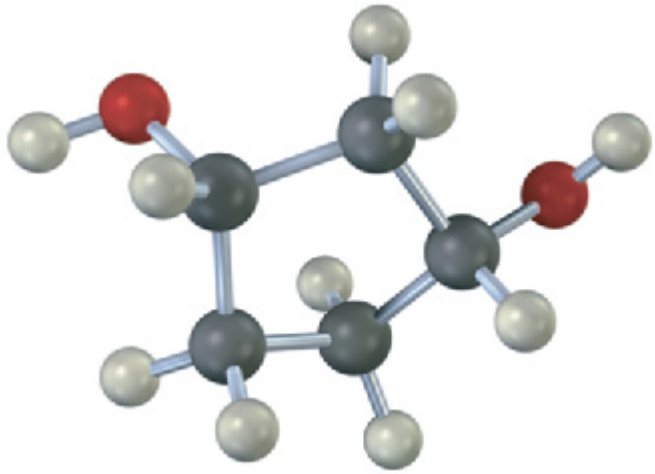
(d)

PROBLEM 5-27 Assign *R* or S configurations to the chirality centers in the following molecules (blue = N):

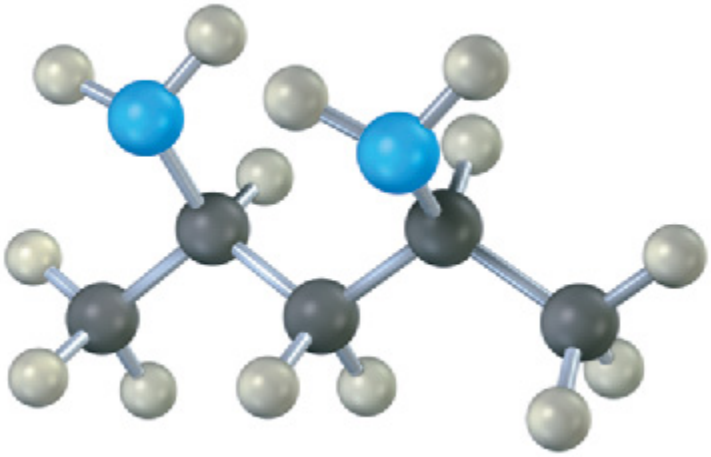


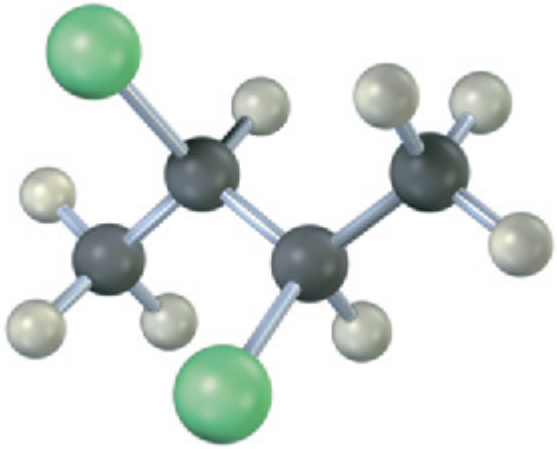
(a) Serine (b) Adrenaline

PROBLEM 5-28 Which, if any, of the following structures represent meso compounds? (Blue = N, green = Cl.)



(a)

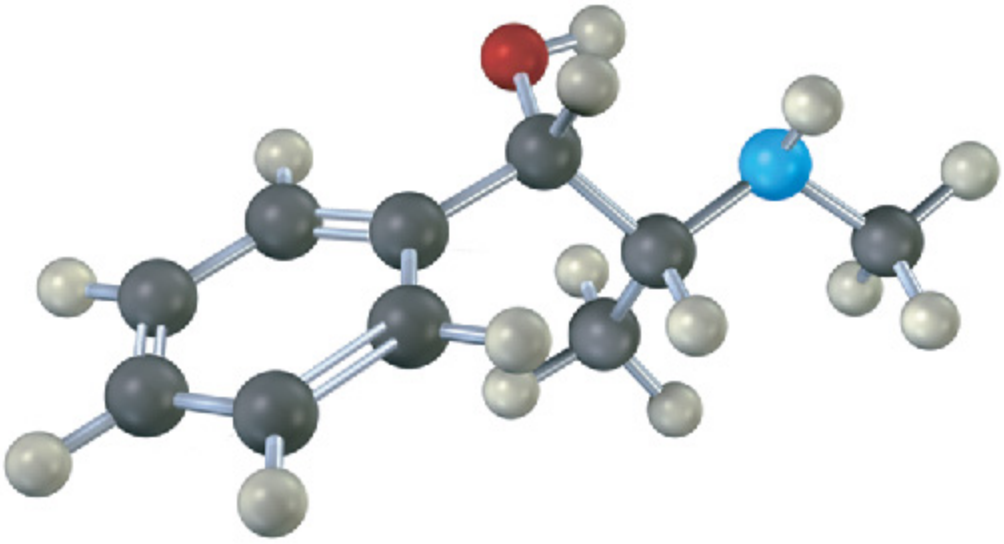




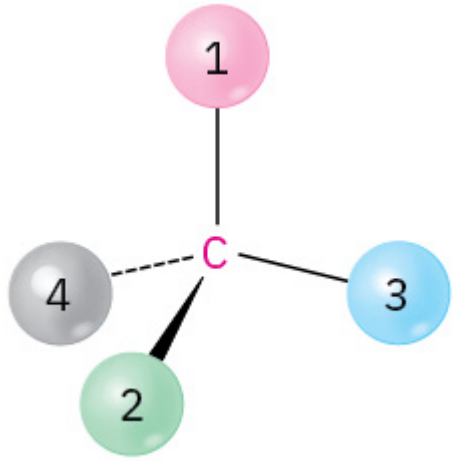
(b)

(c)

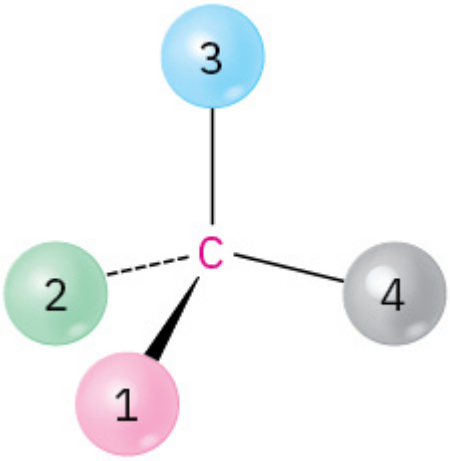
PROBLEM 5-29 Assign *R* or *S* configuration to each chirality center in pseudoephedrine, an over-the-counter decongestant found in cold remedies (blue = N).



PROBLEM 5-30 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

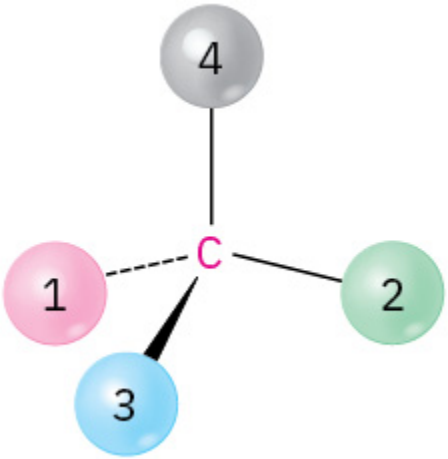


(a)



(b)

(c)



Chirality and Optical Activity

PROBLEM 5-31

Which of the following objects are chiral?

(a) A basketball **(b)** A fork **(c)** A wine glass **(d)** A golf club **(e)** A spiral staircase **(f)** A snowflake

PROBLEM 5-32

Which of the following compounds are chiral? Draw them, and label the chirality centers.

(a) 2,4-Dimethylheptane **(b)** 5-Ethyl-3,3-dimethylheptane **(c)** *cis*-1,4-Dichlorocyclohexane

PROBLEM 5-33

Draw chiral molecules that meet the following descriptions:

(a) A chloroalkane, $C_5H_{11}Cl$ **(b)** An alcohol, $C_6H_{14}O$ **(c)** An alkene, C_6H_{12} **(d)** An alkane, C_8H_{18}

PROBLEM 5-34

Eight alcohols have the formula $C_5H_{12}O$. Draw them. Which are chiral?

PROBLEM 5-35

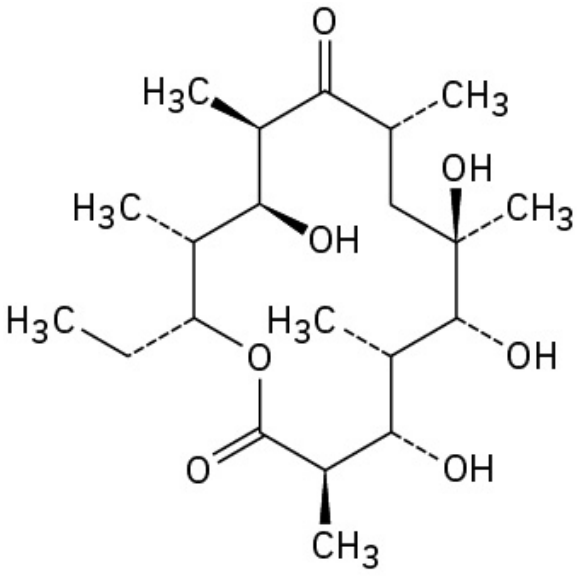
Draw compounds that fit the following descriptions:

(a) A chiral alcohol with four carbons **(b)** A chiral carboxylic acid with the formula $C_5H_{10}O_2$

(c) A compound with two chirality centers **(d)** A chiral aldehyde with the formula C_3H_5BrO

PROBLEM 5-36

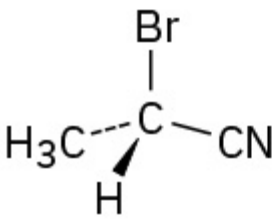
Erythronolide B is the biological precursor of erythromycin, a broad-spectrum antibiotic. How many chirality centers does erythronolide B have? Identify them.



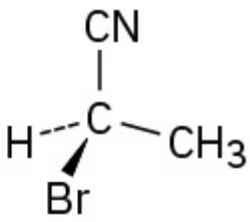
Erythronolide B

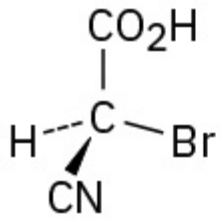
Assigning Configuration to Chirality Centers

PROBLEM 5-37 Which of the following pairs of structures represent the same enantiomer, and which represent different enantiomers?

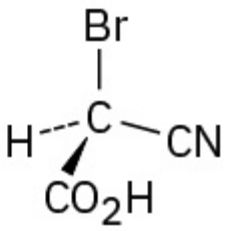


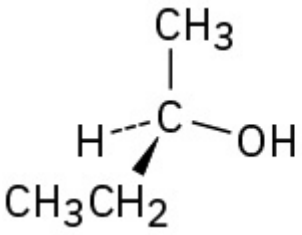
(a)



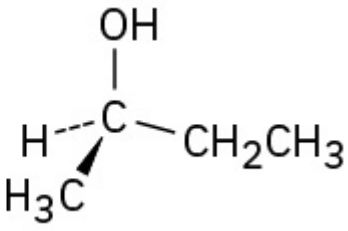


(b)

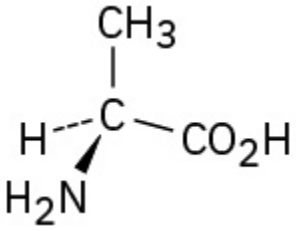


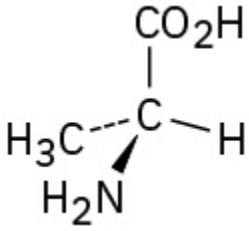


(c)



(d)





PROBLEM 5-38

What is the relationship between the specific rotations of (2*R*,3*R*)-dichloropentane and (2*S*,3*S*)-dichloropentane? Between (2*R*,3*S*)-dichloropentane and (2*R*,3*R*)-dichloropentane?

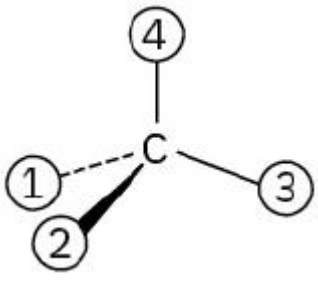
PROBLEM 5-39 What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-2,4-octanediol?

PROBLEM 5-40

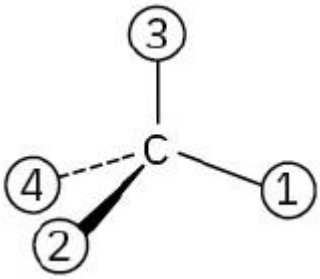
What are the stereochemical configurations of the two diastereomers of (2*S*,4*R*)-2,4-octanediol? (A diol is a compound with two –OH groups.)

PROBLEM 5-41

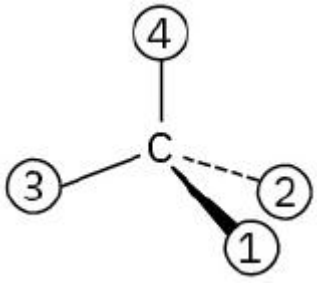
Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



(a)



(b)

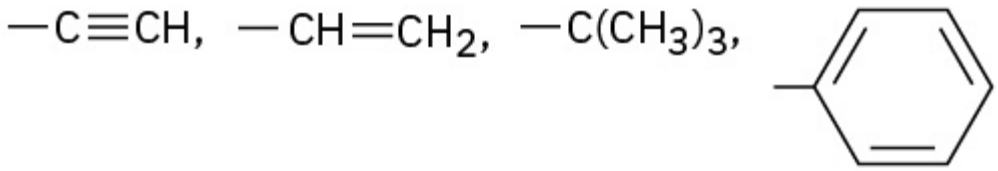


(c)

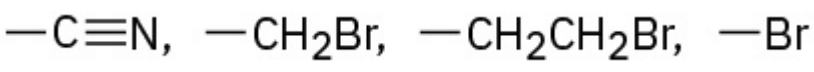
PROBLEM 5-42

Assign Cahn–Ingold–Prelog rankings to the following sets of substituents:

(a) $-CH{=}CH_2,\ -CH(CH_3)_2,\ -C(CH_3)_3,\ -CH_2CH_3$

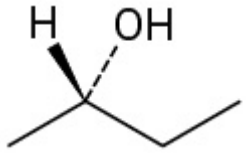
(b) 

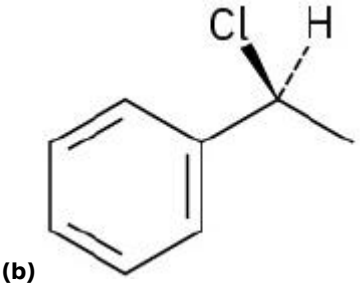
(c) 

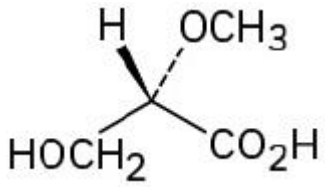
(d) 

PROBLEM 5-43

Assign *R* or *S* configurations to each chirality center in the following molecules:

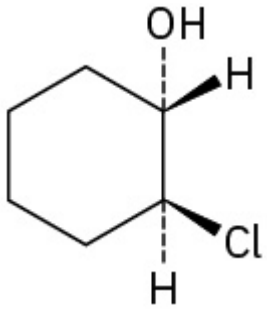
(a) 

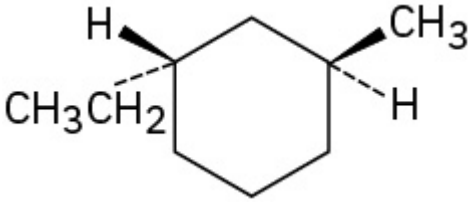
(b) 

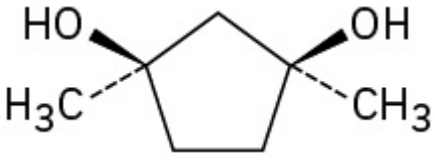
(c) 

PROBLEM 5-44

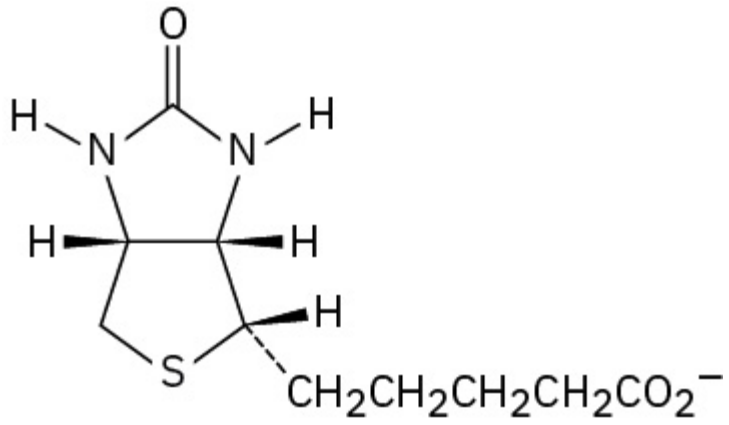
Assign *R* or *S* configuration to each chirality center in the following molecules:

(a) 

(b) 

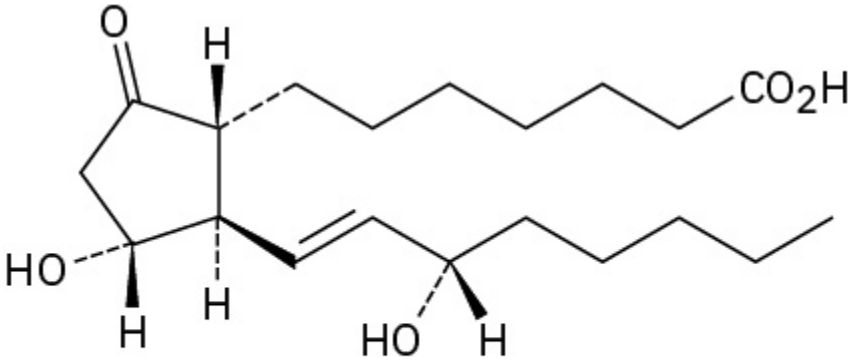
(c) 

PROBLEM 5-45 Assign *R* or *S* configuration to each chirality center in the following biological molecules:



Biotin

(a)



Prostaglandin E_1

(b)

PROBLEM 5-46

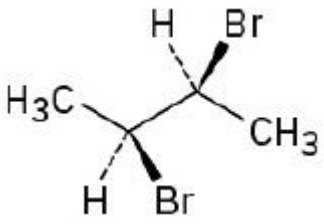
Draw tetrahedral representations of the following molecules:

(a) (*S*)-2-Chlorobutane

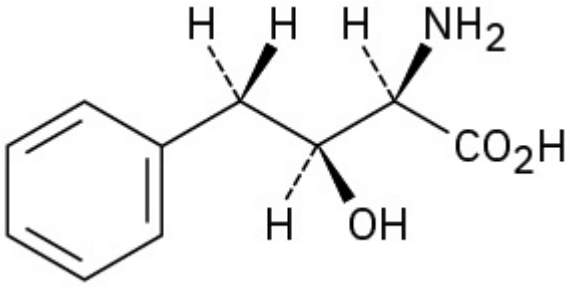
(b) (*R*)-3-Chloro-1-pentene [$H_2C{=}CHCH(Cl)CH_2CH_3$]

PROBLEM 5-47 Assign *R* or *S* configuration to each chirality center in the following molecules:

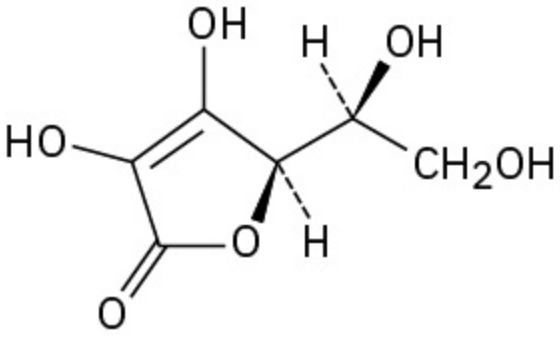
(a)



(b)

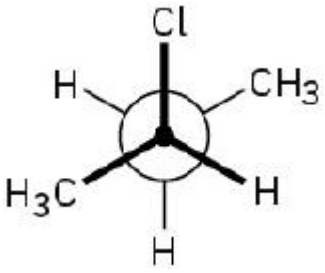


PROBLEM 5-48 Assign *R* or *S* configurations to the chirality centers in ascorbic acid (vitamin C).

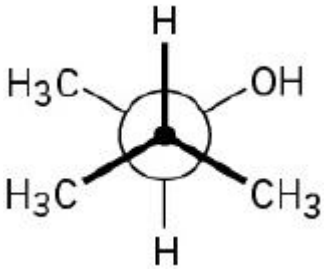


Ascorbic acid

PROBLEM 5-49 Assign *R* or *S* stereochemistry to the chirality centers in the following Newman projections:

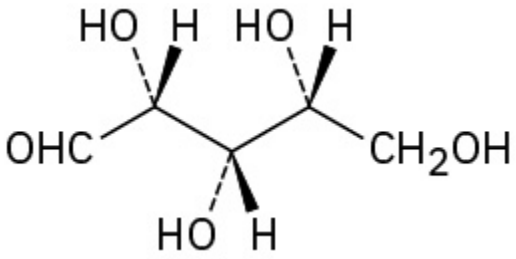


(a)



(b)

PROBLEM 5-50 Xylose is a common sugar found in many types of wood, including maple and cherry. Because it is much less prone to cause tooth decay than sucrose, xylose has been used in candy and chewing gum. Assign *R* or *S* configurations to the chirality centers in xylose.



(+)-Xylose

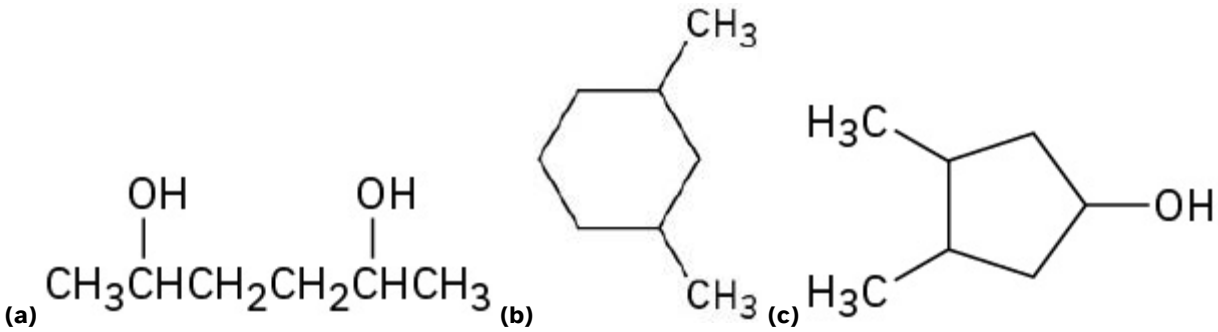
Meso Compounds

PROBLEM 5-51 Draw examples of the following:

(a) A meso compound with the formula C_8H_{18} **(b)** A meso compound with the formula C_9H_{20}

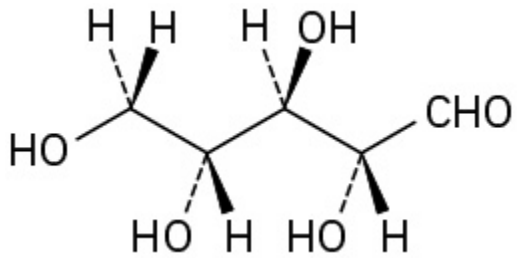
(c) A compound with two chirality centers, one *R* and the other *S*

PROBLEM 5-52 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:



PROBLEM 5-53 Draw the structure of a meso compound that has five carbons and three chirality centers.

PROBLEM 5-54 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:

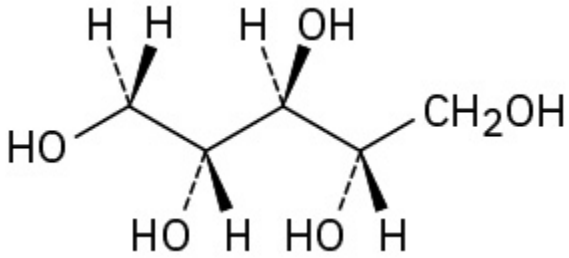


Ribose

(a) How many chirality centers does ribose have? Identify them. **(b)** How many stereoisomers of ribose are there?

(c) Draw the structure of the enantiomer of ribose. **(d)** Draw the structure of a diastereomer of ribose.

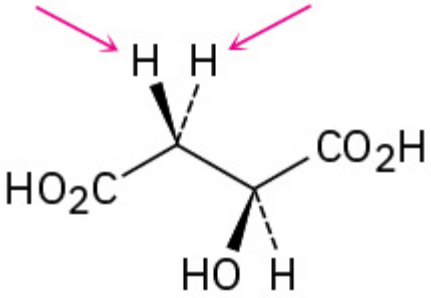
PROBLEM 5-55 On reaction with hydrogen gas in the presence of a platinum catalyst, ribose (Problem 5-54) is converted into ribitol. Is ribitol optically active or inactive? Explain.



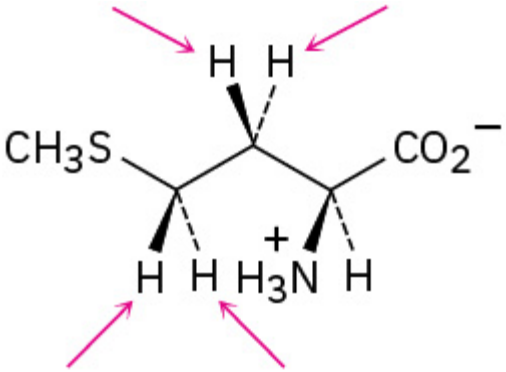
Ribitol

Prochirality

PROBLEM 5-56 Identify the indicated hydrogens in the following molecules as pro-*R* or pro-*S*:

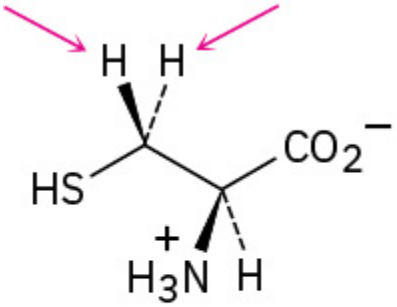


(a) **Malic acid**



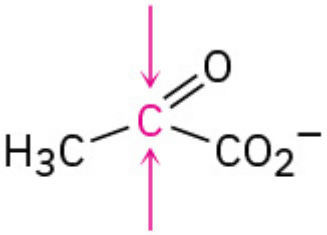
(b) **Methionine**

(c)

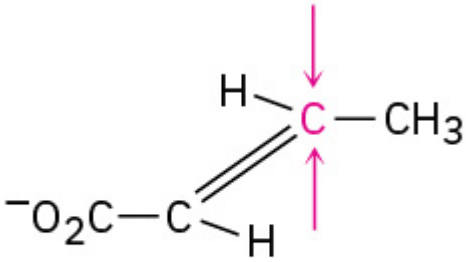


Cysteine

PROBLEM 5-57 Identify the indicated faces in the following molecules as Re or Si:

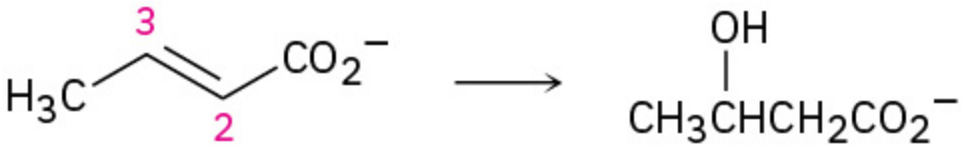


(a) **Pyruvate**



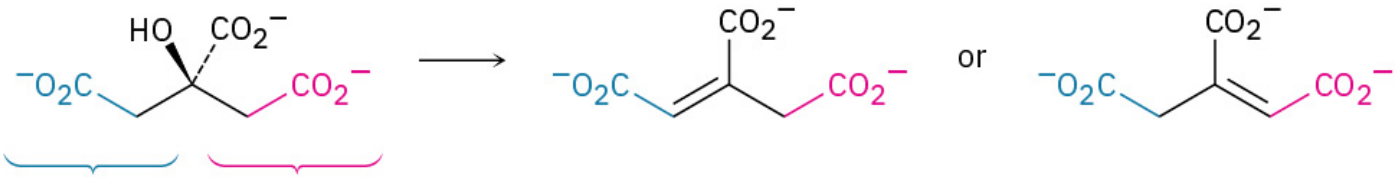
(b) **Crotonate**

PROBLEM 5-58 One of the steps in fat metabolism is the hydration of crotonate to yield 3-hydroxybutyrate. The reaction occurs by addition of –OH to the Si face at C3, followed by protonation at C2, also from the Si face. Draw the product of the reaction, showing the stereochemistry of each step.



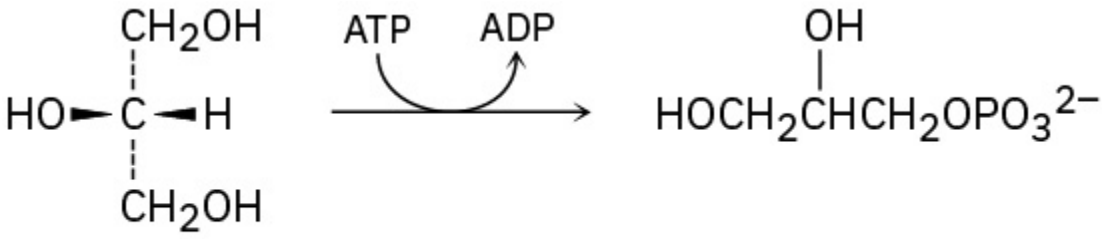
Crotonate **3-Hydroxybutyrate**

PROBLEM 5-59 The dehydration of citrate to yield *cis*-aconitate, a step in the citric acid cycle, involves the pro-*R* "arm" of citrate rather than the pro-S arm. Which of the following two products is formed?



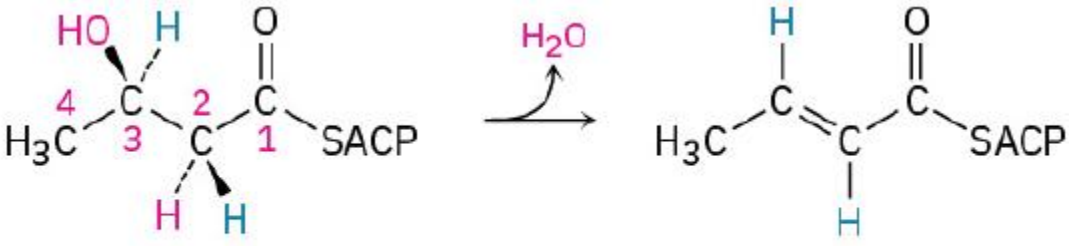
Citrate ***cis*-Aconitate**

PROBLEM 5-60 The first step in the metabolism of glycerol, formed by digestion of fats, is phosphorylation of the pro-*R* $-CH_2OH$ group by reaction with adenosine triphosphate (ATP) to give the corresponding glycerol phosphate plus adenosine diphosphate (ADP). Show the stereochemistry of the product.



Glycerol **Glycerol phosphate**

PROBLEM 5-61 One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotonyl ACP. Does the reaction remove the pro-*R* or the pro-S hydrogen from C2?



(*R*)-3-Hydroxybutyryl ACP ***trans*-Crotonyl ACP**

General Problems

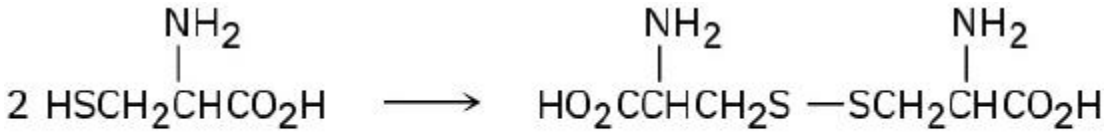
PROBLEM 5-62 Draw all possible stereoisomers of 1,2-cyclobutanedicarboxylic acid, and indicate the interrelationships. Which, if any, are optically active? Do the same for 1,3-cyclobutanedicarboxylic acid.

PROBLEM 5-63

Draw tetrahedral representations of the two enantiomers of the amino acid cysteine, $HSCH_2CH(NH_2)CO_2H$, and identify each as *R* or *S*.

PROBLEM 5-64

The naturally occurring form of the amino acid cysteine (Problem 5-63) has the *R* configuration at its chirality center. On treatment with a mild oxidizing agent, two cysteines join to give cystine, a disulfide. Assuming that the chirality center is not affected by the reaction, is cystine optically active? Explain.

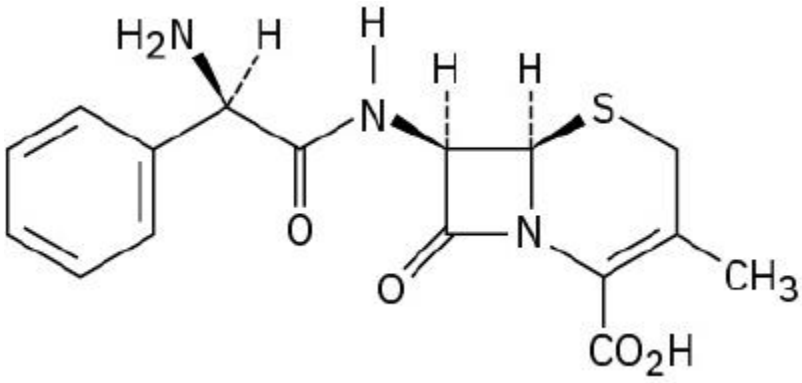


Cysteine **Cystine**

PROBLEM 5-65 Draw tetrahedral representations of the following molecules:

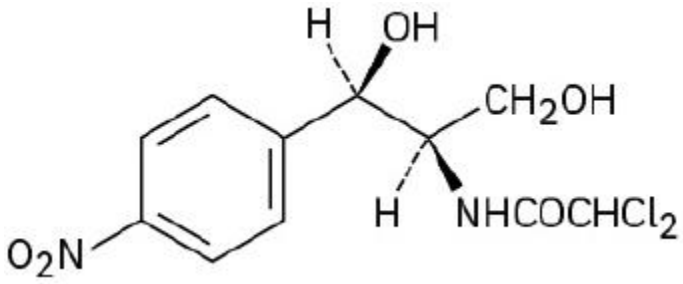
(a) The 2*S*,3*R* enantiomer of 2,3-dibromopentane **(b)** The meso form of 3,5-heptanediol

PROBLEM 5-66 Assign *R* or *S* configurations to the chiral centers in cephalexin, trade-named Keflex, the most widely prescribed antibiotic in the United States.



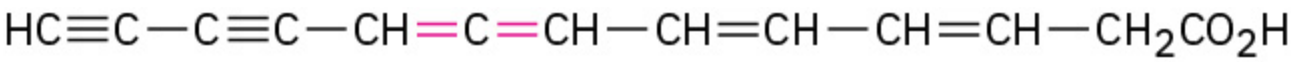
Cephalexin

PROBLEM 5-67 Chloramphenicol, a powerful antibiotic isolated in 1947 from the *Streptomyces venezuelae* bacterium, is active against a broad spectrum of bacterial infections and is particularly valuable against typhoid fever. Assign *R* or *S* configurations to the chirality centers in chloramphenicol.



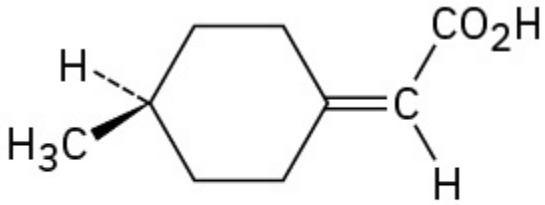
Chloramphenicol

PROBLEM 5-68 *Allenes* are compounds with adjacent carbon–carbon double bonds. Many allenes are chiral, even though they don't contain chirality centers. Mycomycin, for example, a naturally occurring antibiotic isolated from the bacterium *Nocardia acidophilus,* is chiral and has $[\alpha]_D = -130$. Explain why mycomycin is chiral.



Mycomycin

PROBLEM 5-69 Long before chiral allenes were known (Problem 5-68), the resolution of 4-methylcyclohexylideneacetic acid into two enantiomers had been carried out. Why is it chiral? What geometric similarity does it have to allenes?



4-Methylcyclohexylideneacetic acid

PROBLEM 5-70 (S)-1-Chloro-2-methylbutane undergoes light-induced reaction with Cl_2 to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane.

(a) Write the reaction, showing the correct stereochemistry of the reactant.

(b) One of the two products is optically active, but the other is optically inactive. Which is which?

PROBLEM 5-71

How many stereoisomers of 2,4-dibromo-3-chloropentane are there? Draw them, and indicate which are optically active.

PROBLEM 5-72

Draw both *cis*- and *trans*-1,4-dimethylcyclohexane in their more stable chair conformations.

(a) How many stereoisomers are there of *cis*-1,4-dimethylcyclohexane, and how many of *trans*-1,4-dimethylcyclohexane?

(b) Are any of the structures chiral?

(c) What are the stereochemical relationships among the various stereoisomers of 1,4-dimethylcyclohexane?

PROBLEM 5-73

Draw both *cis*- and *trans*-1,3-dimethylcyclohexane in their more stable chair conformations.

(a) How many stereoisomers are there of *cis*-1,3-dimethylcyclohexane, and how many of *trans*-1,3-dimethylcyclohexane?

(b) Are any of the structures chiral?

(c) What are the stereochemical relationships among the various stereoisomers of 1,3-dimethylcyclohexane?

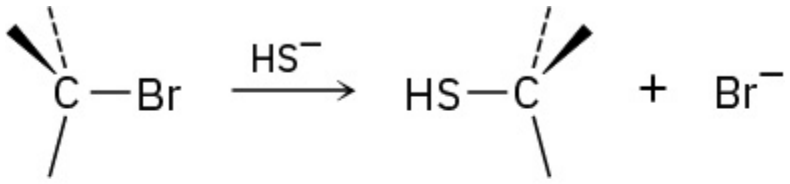
PROBLEM 5-74

cis-1,2-Dimethylcyclohexane is optically inactive even though it has two chirality centers. Explain.

PROBLEM 5-75

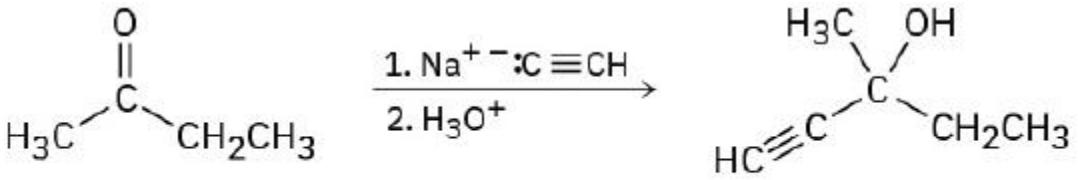
Alkyl halides react with hydrosulfide ion (HS^-) to give a product whose stereochemistry is inverted from that of the reactant. Draw the reaction of (S)-2-bromobutane with HS^- ion to yield 2-butanethiol, $CH_3CH_2CH(SH)CH_3$. Is the stereochemistry of the product

R or *S*?



An alkyl bromide

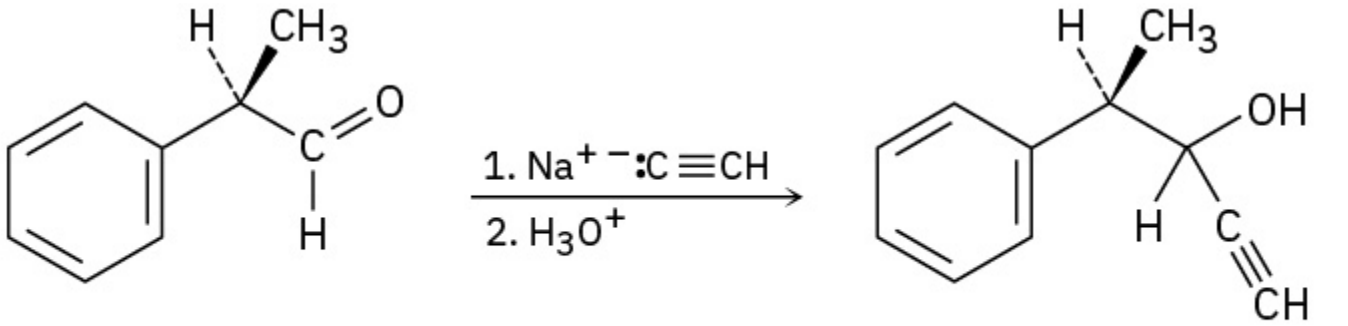
PROBLEM 5-76 Ketones react with sodium acetylide (the sodium salt of acetylene, Na^{+-} : C≡CH) to give alcohols. For example, the reaction of sodium acetylide with 2-butanone yields 3-methyl-1-pentyn-3-ol:



2-Butanone **3-Methyl-1-pentyn-3-ol**

(a) Is the product chiral? **(b)** Assuming that the reaction takes place with equal likelihood from both Re and Si faces of the carbonyl group, is the product optically active? Explain.

PROBLEM 5-77 Imagine that a reaction similar to that in Problem 5-76 is carried out between sodium acetylide and (*R*)-2-phenylpropanal to yield 4-phenyl-1-pentyn-3-ol:



(*R*)-2-Phenylpropanal **4-Phenyl-1-pentyn-3-ol**

(a) Is the product chiral?

(b) Draw both major and minor reaction products, assuming that the reaction takes place preferentially from the Re face of the carbonyl group. Is the product mixture optically active? Explain.

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6: AN OVERVIEW OF ORGANIC REACTIONS

Learning Objectives

After you have completed Chapter 6, you should be able to

1. fulfill the detailed objectives listed under each individual section.
2. identify the polarity pattern in the common functional groups, and explain the importance of being able to do so.
3. describe the essential differences between polar and radical reactions, and assign a given reaction to one of these two categories.
4. discuss how kinetic and thermodynamic factors determine the rate and extent of a chemical reaction.
5. use bond dissociation energies to calculate the $\Delta H°$ of simple reactions, and *vice versa*.
6. draw and interpret reaction energy diagrams.
7. define, and use in context, the new key terms.

This chapter is designed to provide a gentle introduction to the subject of reaction mechanisms. Two types of reactions are introduced—polar reactions and radical reactions. The chapter briefly reviews a number of topics you should be familiar with, including rates and equilibria, elementary thermodynamics and bond dissociation energies. You must have a working knowledge of these topics to obtain a thorough understanding of organic reaction mechanisms. Reaction energy diagrams are used to illustrate the energy changes that take place during chemical reactions, and to emphasize the difference between a reaction intermediate and a transition state.

6.0: Why This Chapter?

6.1: Kinds of Organic Reactions

6.2: How Organic Reactions Occur - Mechanisms

6.3: Radical Reactions

6.4: Polar Reactions

6.5: An Example of a Polar Reaction - Addition of HBr to Ethylene

6.6: Using Curved Arrows in Polar Reaction Mechanisms

6.7: Describing a Reaction - Equilibria, Rates, and Energy Changes

6.8: Describing a Reaction - Bond Dissociation Energies

6.9: Describing a Reaction - Energy Diagrams and Transition States

6.10: Describing a Reaction- Intermediates

6.11: A Comparison between Biological Reactions and Laboratory Reactions

6.12: Chemistry Matters—Where Do Drugs Come From?

6.A: An Overview of Organic Reactions (Summary)

6.B: Additional Problems

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6.0: Why This Chapter?

All chemical reactions, whether they take place in the laboratory or in living organisms, follow the same “rules.” Reactions in living organisms often look more complex than laboratory reactions because of the size of the biomolecules and the involvement of biological catalysts called enzymes, but the principles governing all chemical reactions are the same.



Figure 6.1: Many chemical reactions are like pole vaulters going over the bar. They need a big, initial push of activation energy. (credit: “UChicago Pole Vault” by Eric Guo/Flickr, CC BY 2.0)

To understand both organic and biological chemistry, it’s necessary to know not just *what* occurs but also *why* and *how* chemical reactions take place. In this chapter, we’ll start with an overview of the fundamental kinds of organic reactions, we’ll see why reactions occur, and we’ll see how reactions can be described. Once this background is out of the way, we’ll then be ready to begin studying the details of organic chemistry in future chapters.

When first approached, organic chemistry might seem overwhelming. It’s not so much that any one part is difficult to understand, it’s that there are so many parts: tens of millions of compounds, dozens of functional groups, and an apparently endless number of reactions. With study, though, it becomes evident that there are only a few fundamental ideas that underlie all organic reactions. Far from being a collection of isolated facts, organic chemistry is a beautifully logical subject that is unified by a few broad themes. When these themes are understood, learning organic chemistry becomes much easier and memorization is minimized. The aim of this book is to describe the themes and clarify the patterns that unify organic chemistry in future chapters.

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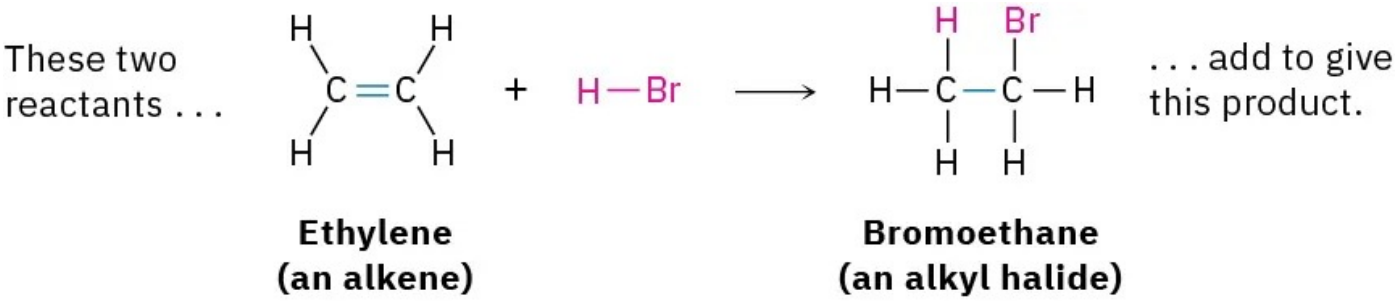
6.1: Kinds of Organic Reactions

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.

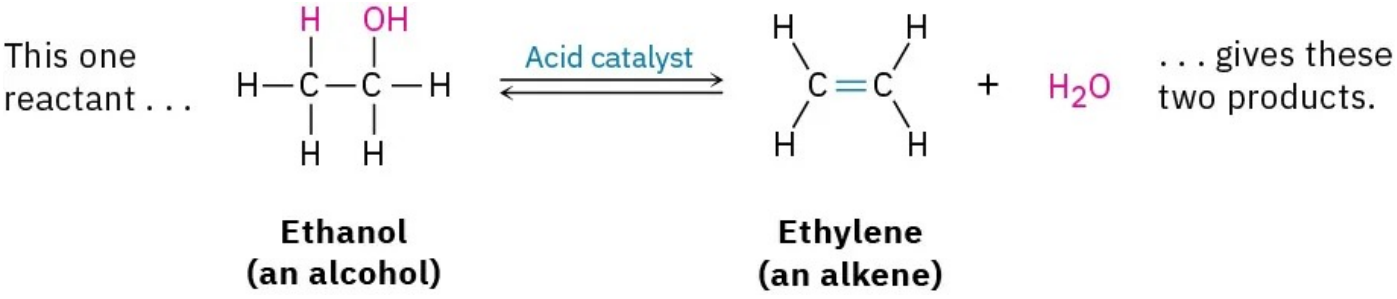
> Ultimately, the best way to achieve proficiency in organic chemistry is to understand how reactions take place, and to recognize the various factors that influence their course.

Organic chemical reactions can be organized broadly in two ways—by what kinds of reactions occur and by how those reactions occur. Let's look first at the kinds of reactions that take place. There are four general types of organic reactions: *additions, eliminations, substitutions,* and *rearrangements*.

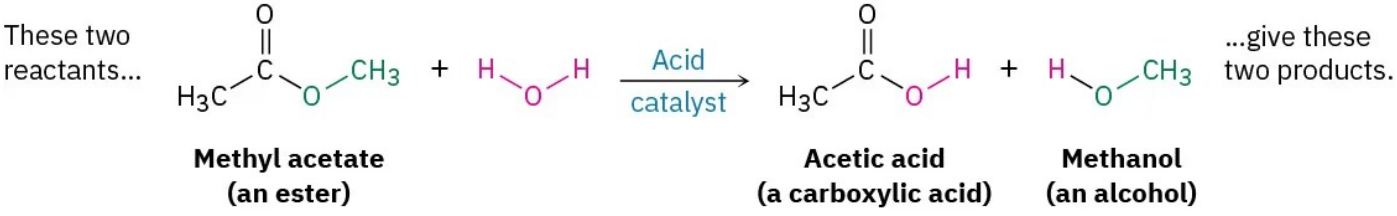
- **Addition reactions** occur when two reactants add together to form a single product with no atoms "left over." The addition of atoms or groups happened to multiple bonds (such as double or triple bonds). Examples include hydration (addition of water), hydrogenation (addition of hydrogen), and halogenation (addition of halogens). An example that we'll be studying soon is the reaction of an alkene, such as ethylene, with HBr to yield an alkyl bromide.



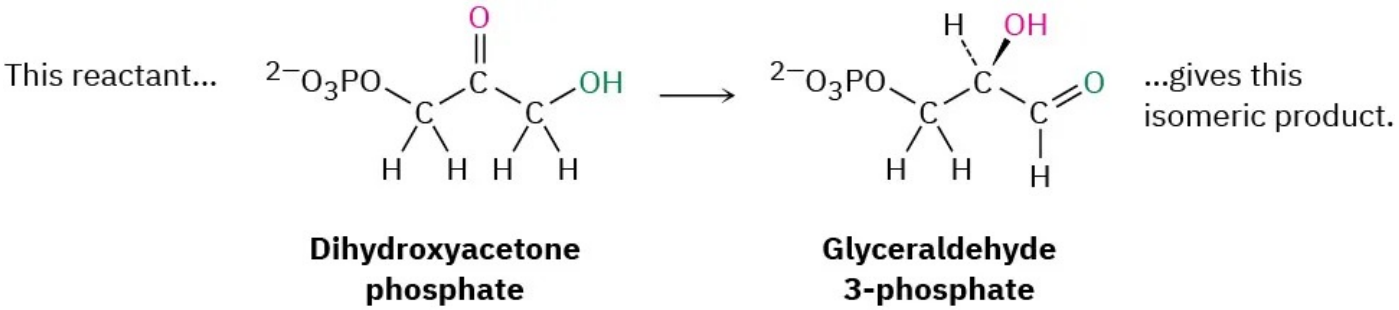
- **Elimination reactions** are, in a sense, the opposite of addition reactions. They occur when a single reactant splits into two products, often with the formation of a small molecule such as water or HBr. An example is the acid-catalyzed reaction of an alcohol to yield water and an alkene.



- **Substitution reactions** occur when two reactants exchange parts to give two new products. An example is the reaction of an ester such as methyl acetate with water to yield a carboxylic acid plus an alcohol. Similar reactions occur in many biological pathways, including the metabolism of dietary fats.



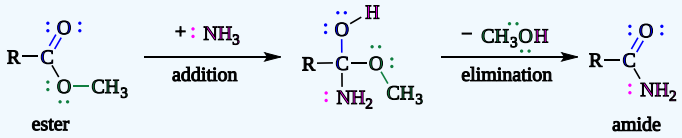
- **Rearrangement reactions** occur when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product. An example is the conversion of dihydroxyacetone phosphate into its constitutional isomer glyceraldehyde 3-phosphate, a step in the glycolysis pathway by which carbohydrates are metabolized.



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 the 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 usually does not change.

Example 6.1.1: Reaction of an Ester with Ammonia

The reaction of an ester with ammonia to give an amide, as shown below, appears to be a substitution reaction (Y = CH_3O & Z = NH_2); however, it is actually two reactions, an addition followed by an elimination.



Example 6.1.2: The Addition of Water to a Nitrile

The addition of water to a nitrile does not seem to fit any of the above reaction types, but it is simply a slow addition reaction followed by a rapid rearrangement, as shown in the following equation. Rapid rearrangements of this kind are called **tautomerizations**.



Exercises

Exercise 6.1.1

Classify each of the following reactions as an addition, elimination, substitution, or rearrangement:

a. \(\ce{CH3Br + KOH → CH3OH + KBr}\)
b. \(\ce{CH3CH2Br → H2C=CH2 + HBr}\)
c. \(\ce{H2C=CH2 + H2 → CH3CH3}\)

Answer available at the end of this section.

Answers

Exercise 6.1.1

a. Substitution
b. Elimination
c. Addition

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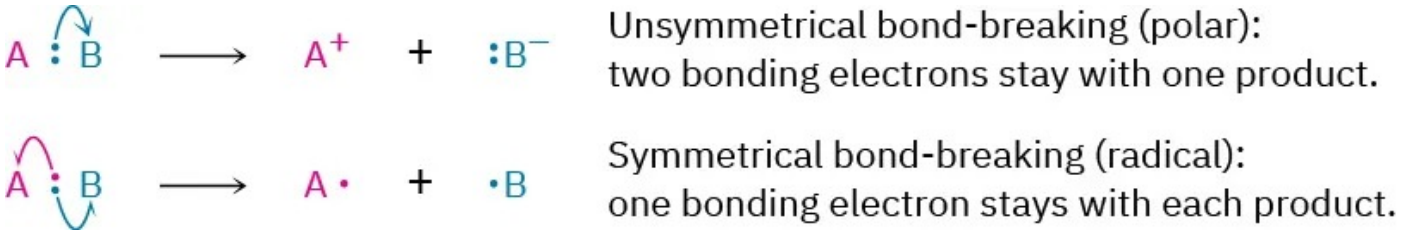
6.2: How Organic Reactions Occur - Mechanisms

Having looked at the kinds of reactions that take place, let's now see how they occur. An overall description of how a reaction occurs is called a reaction mechanism. A mechanism describes in detail exactly what takes place at each stage of a chemical transformation—which bonds are broken and in what order, which bonds are formed and in what order, and what the relative rates are for each step. A complete mechanism must also account for all reactants used and all products formed.

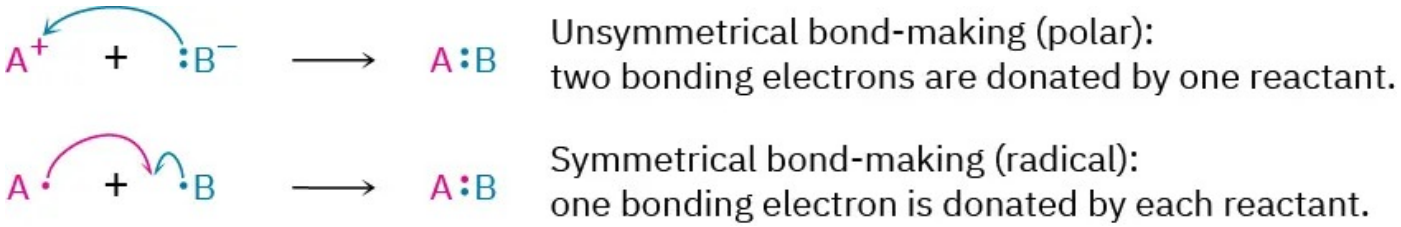
All chemical reactions involve bond-breaking and bond-making. When two molecules come together, react, and yield products, specific bonds in the reactant molecules are broken and specific bonds in the product molecules are formed. Fundamentally, there are two ways in which a covalent two-electron bond can break. A bond can break in an electronically unsymmetrical way so that both bonding electrons remain with one product fragment, leaving the other with a vacant orbital, or a bond can break in an electronically symmetrical way so that one electron remains with each product fragment.

The unsymmetrical cleavage is said to be ***Heterolytic* cleavage**, and the symmetrical cleavage is said to be ***Homolytic* cleavage**.

The movement of *two* electrons in the unsymmetrical process is indicated using a full-headed curved arrow (↷), whereas the movement of *one* electron in the symmetrical process is indicated using a half-headed, or "fishhook," arrow (↶).



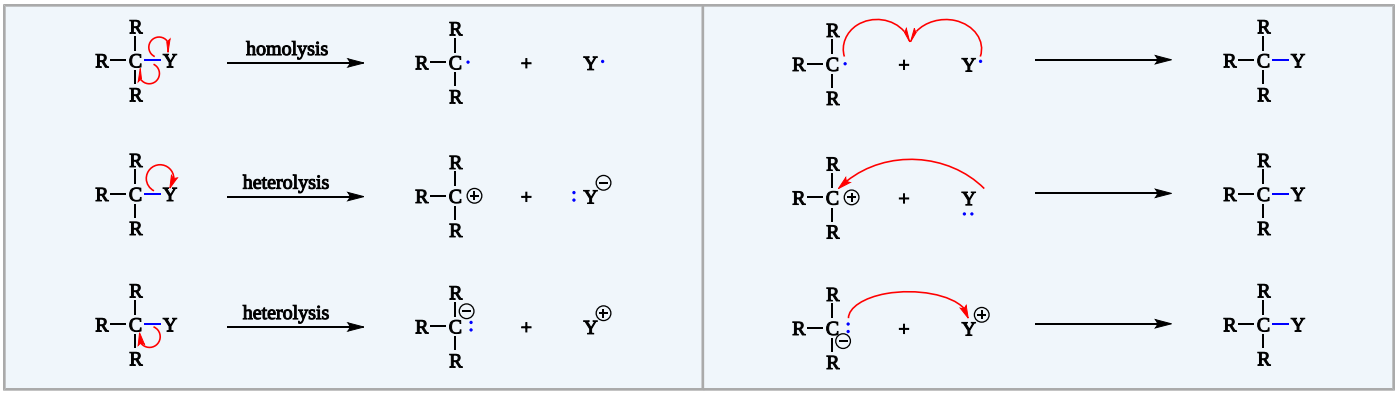
Just as there are two ways in which a bond can break, there are two ways in which a covalent two-electron bond can form. A bond can form in an electronically unsymmetrical way if both bonding electrons are donated to the new bond by one reactant, or in a symmetrical way if one electron is donated by each reactant.



Processes that involve unsymmetrical bond-breaking and bond-making are called **polar reactions**. Polar reactions involve species that have an even number of electrons and thus have only electron pairs in their orbitals. Polar processes are by far the more common reaction type in both organic and biological chemistry, and a large part of this book is devoted to their description.

Processes that involve symmetrical bond-breaking and bond-making are called **radical reactions**. A radical, often called a **free radical**, is a neutral chemical species that contains an odd number of electrons and thus has a single, unpaired electron in one of its orbitals.

Bond-Breaking	Bond-Making



In addition to polar and radical reactions, there is a third, less commonly encountered process called a *pericyclic reaction*. Rather than explain pericyclic reactions now, though, we'll look at them more carefully next semester.

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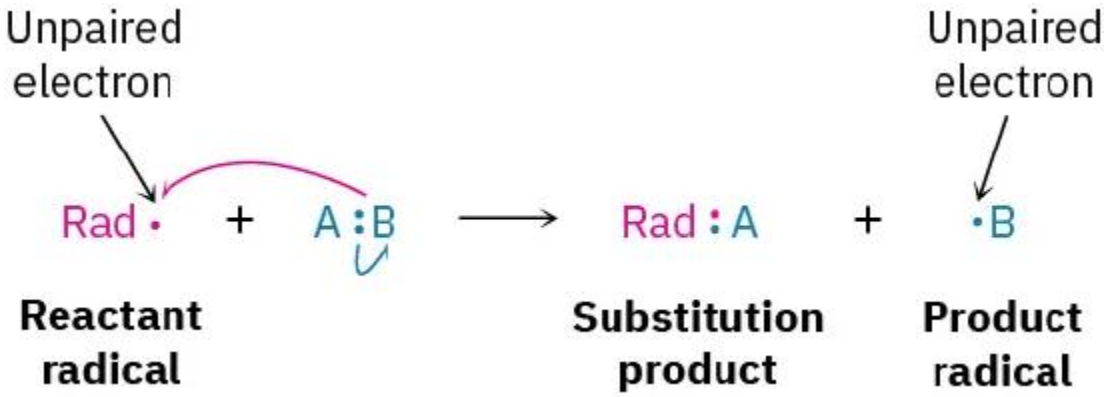
6.3: Radical Reactions

Objectives

After completing this section, you should be able to

1. give an example of a radical substitution reaction.
2. Identify the three steps (initiation, propagation, and termination) that occur in a typical radical substitution reaction.
3. Write out the steps involved in a simple radical substitution reaction, such as the chlorination of methane.
4. Explain why the halogenation of an alkane is not a particularly useful method of preparing specific alkyl halides.

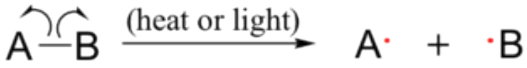
A radical is highly reactive because it contains an atom with an odd number of electrons (usually seven) in its valence shell, rather than a noble-gas octet. The radical can achieve a valence-shell octet in several ways, however. For instance, it might abstract an atom and one bonding electron from another reactant, leaving behind a new radical. The net result is a radical substitution reaction.



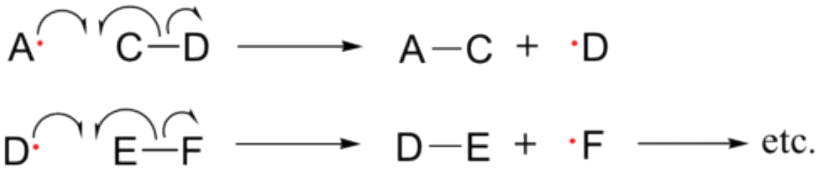
The Three Phases of Radical Chain Reactions

Because of their high reactivity, free radicals have the potential to be both extremely powerful chemical tools and extremely harmful contaminants. Much of the power of free radical species stems from the natural tendency of radical processes to occur in a chain reaction fashion. **Radical chain reactions** have three distinct phases: initiation, propagation, and termination.

initiation



propagation



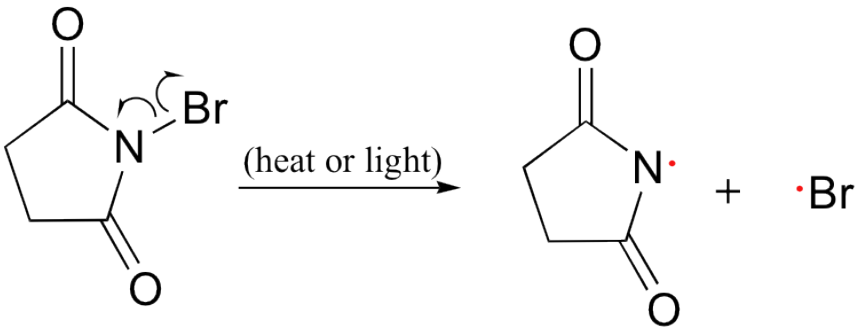
termination



The **initiation phase** describes the step that initially creates a radical species. In most cases, this is a homolytic cleavage, and takes place very rarely due to the high energy barriers involved. Often, the influence of heat, UV radiation, or a metal-containing catalyst is necessary to overcome the energy barrier.

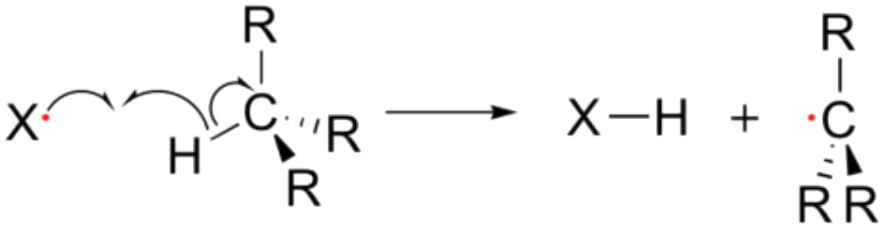
Molecular chlorine and bromine will both undergo homolytic cleavage to form radicals when subjected to heat or light. Other functional groups that also tend to form radicals when exposed to heat or light are chlorofluorocarbons, peroxides, and the halogenated amide N-bromosuccinimide (NBS).

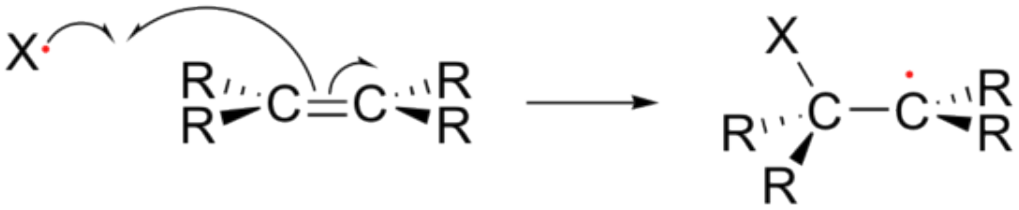




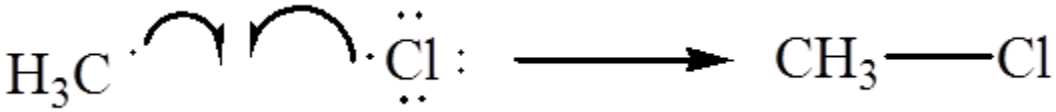
NBS

The **propagation phase** describes the 'chain' part of chain reactions. Once a reactive free radical is generated, it can react with stable molecules to form new free radicals. These new free radicals go on to generate yet more free radicals, and so on. Propagation steps often involve hydrogen abstraction or the addition of the radical to double bonds.





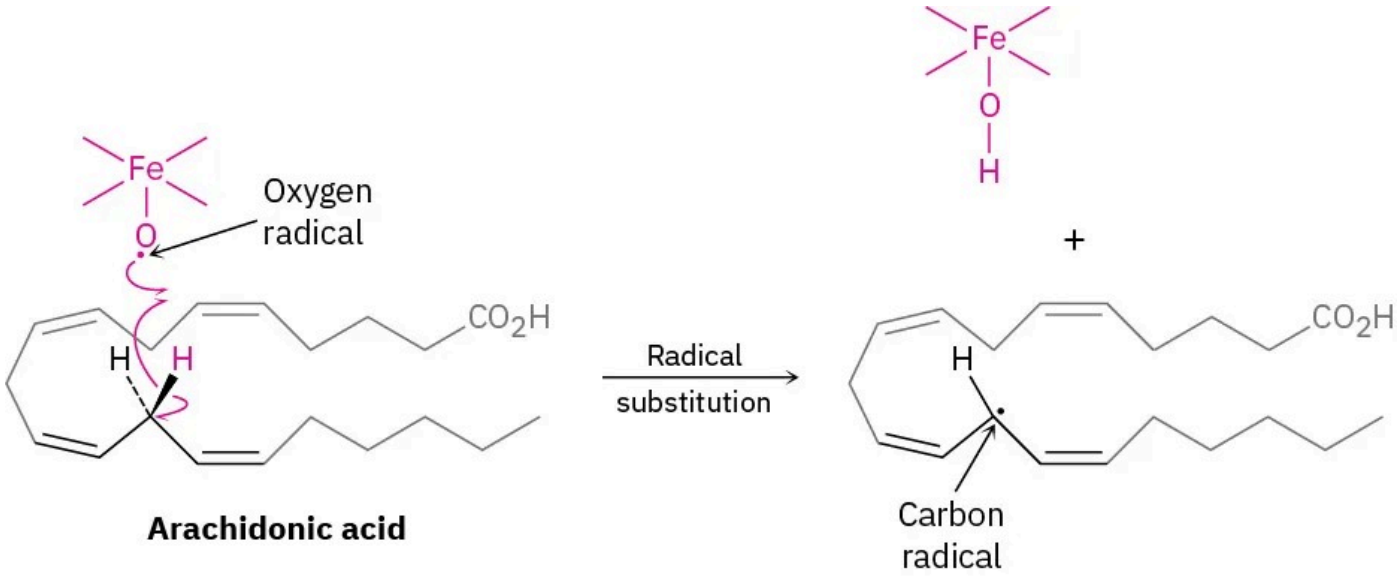
Chain termination occurs when two free radical species react with each other to form a stable, non-radical adduct. Although this is a very thermodynamically downhill event, it is also very rare due to the low concentration of radical species and the small likelihood of two radicals colliding with one another. In other words, the Gibbs free energy barrier is very high for this reaction, mostly due to entropic rather than enthalpic considerations. The active sites of enzymes, of course, can evolve to overcome this entropic barrier by positioning two radical intermediates adjacent to one another.



Application in Biology

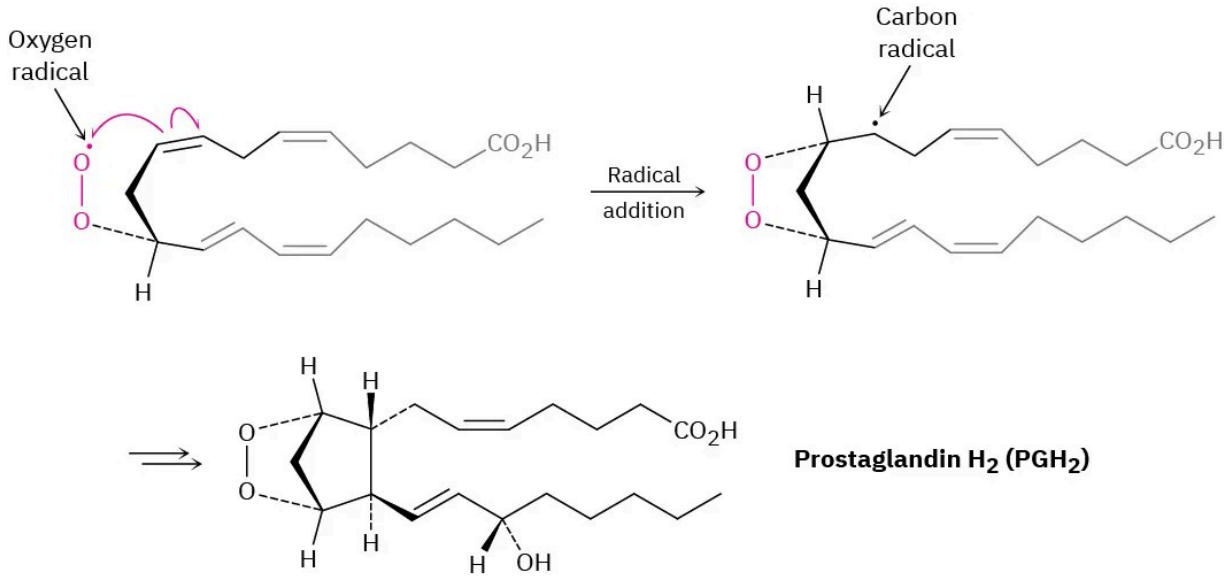
As a biological example of a radical reaction, look at the synthesis of *prostaglandins*, a large class of molecules found in virtually all body tissues and fluids. A number of pharmaceuticals are based on or derived from prostaglandins, including medicines that induce labor during childbirth, reduce intraocular pressure in glaucoma, control bronchial asthma, and help treat congenital heart defects.

Prostaglandin biosynthesis is initiated by the abstraction of a hydrogen atom from arachidonic acid by an iron–oxygen radical, thereby generating a carbon radical in a substitution reaction. Don't be intimidated by the size of the molecules; focus on the changes that occur in each step. (To help you do that, the unchanged part of the molecule is "ghosted," with only the reactive part clearly visible.)



Arachidonic acid

Following the initial abstraction of a hydrogen atom, the carbon radical then reacts with O_2 to give an oxygen radical, which reacts with a $C{=}C$ bond within the same molecule in an addition reaction. Several further transformations ultimately yield prostaglandin H_2.

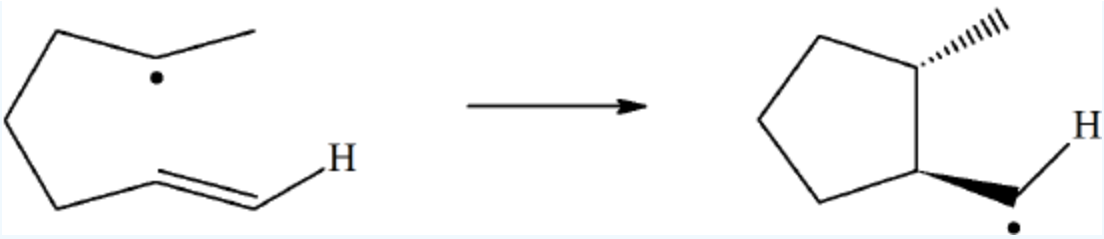


Prostaglandin H_2 (PGH_2)

Exercises

Exercise 6.3.3

Propose a radical mechanism for the following reaction; to do so, you need to add the proper mechanism arrows.



Answer available at the end of this section.

Key Terms

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

- chain reaction
- initiation step
- propagation step
- radical substitution
- termination step

Study Notes

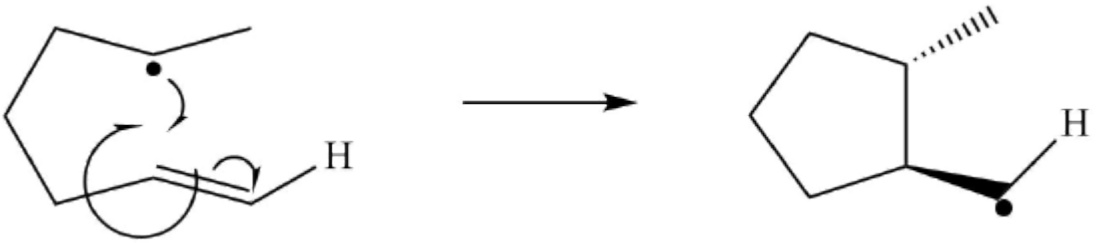
A *radical substitution reaction* is a reaction which occurs by a free radical mechanism and results in the substitution of one or more of the atoms or groups present in the substrate by different atoms or groups.

The *initiation step* in a radical chain reaction is the step in which a free radical is first produced. A *termination step* of a radical chain reaction is one in which two radicals react together in some way so that the chain can no longer be propagated.

While radical halogenation of very simple alkanes can be an effective synthetic strategy, it cannot be employed for larger more complex alkanes to yield specific alkyl halides, since the reactive nature of radicals always leads to mixtures of single- and multiple-halogenated products.

Answers

Exercise 6.3.3



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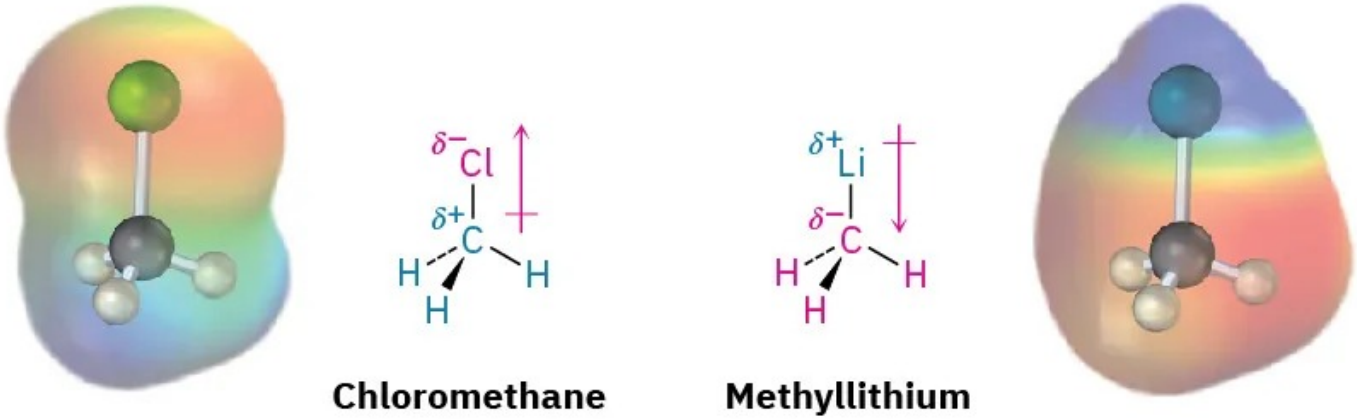
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6.4: Polar Reactions

Polar reactions occur because of the electrical attraction between positively polarized and negatively polarized centers on functional groups in molecules. To see how these reactions take place, let's first recall the discussion of polar covalent bonds in Section 2.1 and then look more deeply into the effects of bond polarity on organic molecules.

Most organic compounds are electrically neutral; they have no net charge, either positive or negative. We saw in Section 2.1, however, that certain bonds within a molecule, particularly the bonds in functional groups, are polar. Bond polarity is a consequence of an unsymmetrical electron distribution in a bond and is due to the difference in electronegativity of the bonded atoms.

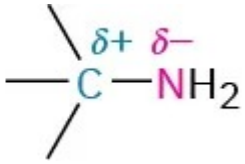
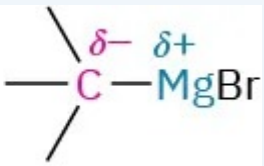
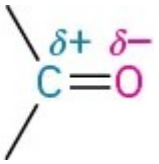
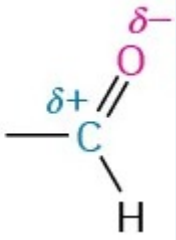
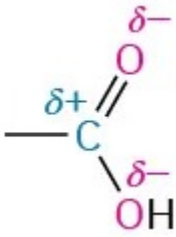
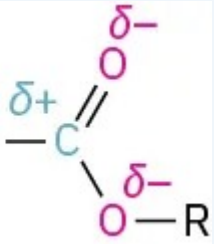
Elements such as oxygen, nitrogen, fluorine, and chlorine are more electronegative than carbon, so a carbon atom bonded to one of these atoms has a partial positive charge ($\delta+$). Metals are less electronegative than carbon, so a carbon atom bonded to a metal has a partial negative charge ($\delta-$). Electrostatic potential maps of chloromethane and methyllithium illustrate these charge distributions, showing that the carbon atom in chloromethane is electron-poor (blue) while the carbon in methyllithium is electron-rich (red).



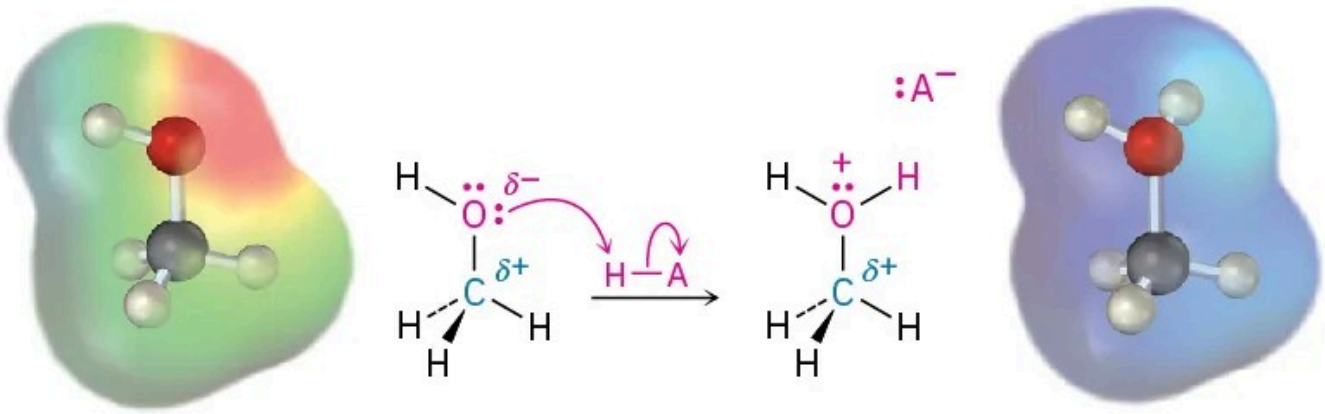
The polarity patterns of some common functional groups are shown in Table 6.4.1. Note that carbon is always positively polarized except when bonded to a metal.

Table 6.4.1: Polarity Patterns in Some Common Functional Groups

Compound type	Functional group	Compound type	Functional group
Alcohol	δ+ δ− C—OH	Alkyl halide	— C
Alkene	C=C Symmetrical, nonpolar	Ether	δ+ δ — C — (

Compound type	Functional group	Compound type	Functional group
Amine		Thiol	
Grignard reagent		Alkyllithium	
Carbonyl		Nitrile	
Aldehyde		Ketone	
Carboxylic acid		Carboxylic acid chloride	
Ester		Thioester	

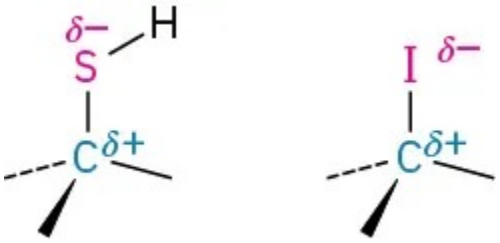
This discussion of bond polarity is oversimplified in that we've considered only bonds that are inherently polar due to differences in electronegativity. Polar bonds can also result from the interaction of functional groups with acids or bases. Take an alcohol such as methanol, for example. In neutral methanol, the carbon atom is somewhat electron-poor because the electronegative oxygen attracts the electrons in the C–O bond. On protonation of the methanol oxygen by an acid, however, a full positive charge on oxygen attracts the electrons in the C–O bond much more strongly and makes the carbon much more electron-poor. We'll see numerous examples throughout this book of reactions that are catalyzed by acids because of the resultant increase in bond polarity upon protonation.



Methanol—weakly electron-poor carbon

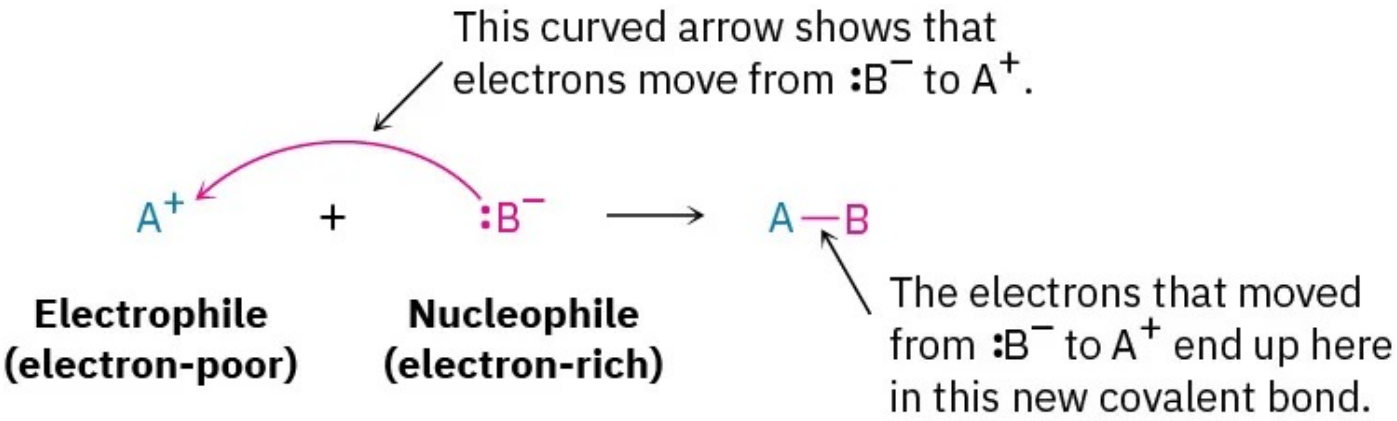
Protonated methanol—strongly electron-poor carbon

Yet a further consideration is the polarizability (as opposed to polarity) of atoms in a molecule. As the electric field around a given atom changes because of changing interactions with solvent or other polar molecules nearby, the electron distribution around that atom also changes. The measure of this response to an external electrical influence is called the polarizability of the atom. Larger atoms with more loosely held electrons are more polarizable, and smaller atoms with fewer, tightly held electrons are less polarizable. Thus, sulfur is more polarizable than oxygen, and iodine is more polarizable than chlorine. The effect of this higher polarizability of sulfur and iodine is that carbon–sulfur and carbon–iodine bonds, although nonpolar according to electronegativity values (Figure 2.3), nevertheless usually react as if they were polar.



What does functional-group polarity mean with respect to chemical reactivity? Because unlike charges attract, the fundamental characteristic of all polar organic reactions is that electron-rich sites react with electron-poor sites. Bonds are made when an electron-rich atom donates a pair of electrons to an electron-poor atom, and bonds are broken when one atom leaves with both electrons from the former bond.

As we saw in Section 2.12, the movement of an electron pair during a polar reaction is indicated using a curved, full-headed arrow to show where electrons move when reactant bonds are broken and product bonds are formed during the reaction.



In referring to the electron-rich and electron-poor species involved in polar reactions, chemists use the words *nucleophile* and *electrophile*. A nucleophile is a substance that is "nucleus-loving." (Remember that a nucleus is positively charged.) A nucleophile has a negatively polarized, electron-rich atom and can form a bond by donating a pair of electrons to a positively polarized, electron-poor atom. Nucleophiles can be either neutral or negatively charged; ammonia, water, hydroxide ion, and chloride ion are examples. An electrophile, by contrast, is "electron-loving." An electrophile has a positively polarized, electron-poor atom and can form a bond by accepting a pair of electrons from a nucleophile. Electrophiles can be either neutral or positively charged. Acids (H^+ donors), alkyl halides, and carbonyl compounds are examples (Figure 6.4.2).

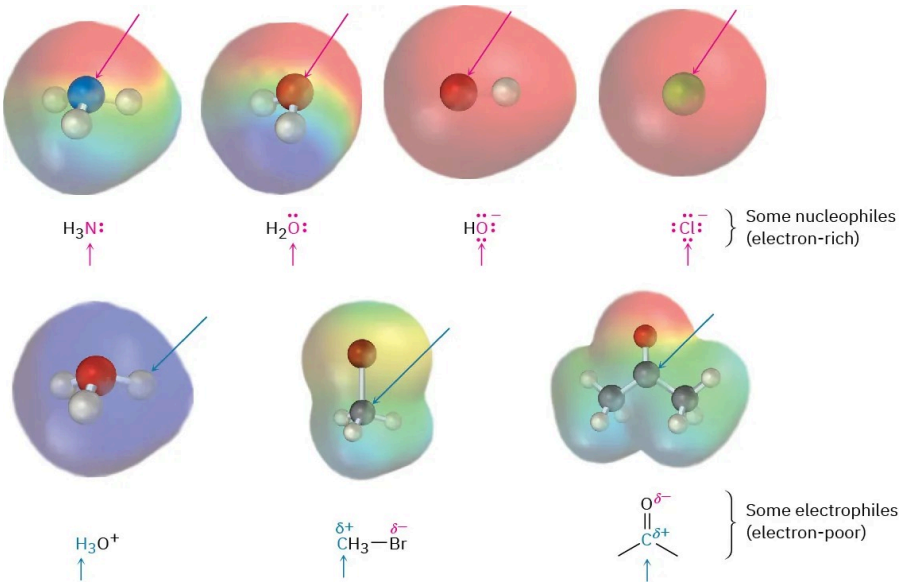


Figure 6.4.2: Some nucleophiles and electrophiles. Electrostatic potential maps identify the nucleophilic **(negative)** and electrophilic **(positive)** atoms.

Note that neutral compounds can often react either as nucleophiles or as electrophiles, depending on the circumstances. After all, if a compound is neutral yet has an electron-*rich* nucleophilic site, it must also have a corresponding electron-*poor* electrophilic site. Water, for instance, acts as an electrophile when it donates H^+ but acts as a nucleophile when it donates a nonbonding pair of electrons. Similarly, a carbonyl compound acts as an electrophile when it reacts at its positively polarized carbon atom, yet acts as a nucleophile when it reacts at its negatively polarized oxygen atom.

If the definitions of nucleophiles and electrophiles sound similar to those given in Section 2.12 for Lewis acids and Lewis bases, that's because there is indeed a correlation. Lewis bases are electron donors and behave as nucleophiles, whereas Lewis acids are electron acceptors and behave as electrophiles. Thus, much of organic chemistry is explainable in terms of acid–base reactions. The main difference is that the words *acid* and *base* are used broadly in all fields of chemistry, while the words *nucleophile* and *electrophile* are used primarily in organic chemistry when carbon bonding is involved.

Worked Example 6.4.1: Identifying Electrophiles and Nucleophiles

Which of the following species is likely to behave as a nucleophile and which as an electrophile?

a. NO_2^+ **b.** CN^- **c.** CH_3NH_2 **d.** $(CH_3)_3S^+$

Strategy

A nucleophile has an electron-rich site, either because it is negatively charged or because it has a functional group containing an atom that has a lone pair of electrons. An electrophile has an electron-poor site, either because it is positively charged or because it has a functional group containing an atom that is positively polarized.

Solution

a. NO_2^+ (nitronium ion) is likely to be an electrophile because it is positively charged.
b. $:C{\equiv}N^-$ (cyanide ion) is likely to be a nucleophile because it is negatively charged.
c. CH_3NH_2 (methylamine) might be either a nucleophile or an electrophile, depending on the circumstances. The lone pair of electrons on the nitrogen atom makes methylamine a potential nucleophile, while positively polarized N–H hydrogens make methylamine a potential acid (electrophile).
d. $(CH_3)_3S^+$ (trimethylsulfonium ion) is likely to be an electrophile because it is positively charged.

Exercises

Exercise 6.4.1

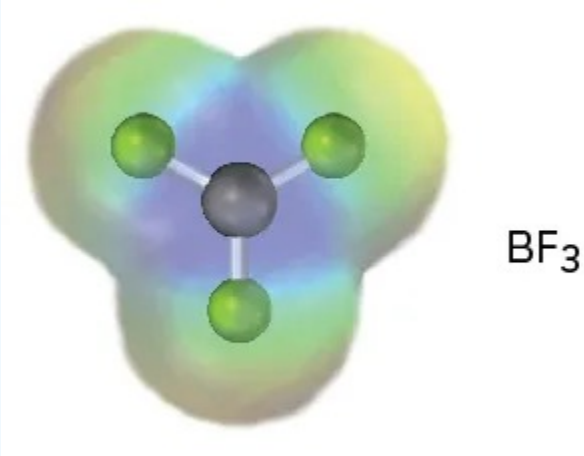
Which of the following species are likely to be nucleophiles and which electrophiles? Which might be both?

a. CH_3Cl **b.** CH_3S^- **c.**  **d.** 

Answer available at the end of this section.

Exercise 6.4.2

An electrostatic potential map of boron trifluoride is shown. Is BF_3 likely to be a nucleophile or an electrophile? Draw a Lewis structure for BF_3, and explain your answer.



Answer available at the end of this section.

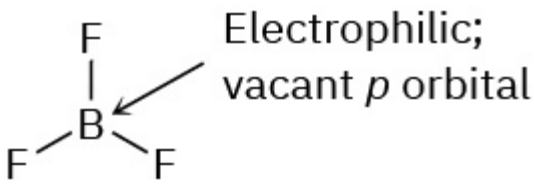
Answers

Exercise 6.4.1

a. Carbon is electrophilic.
b. Sulfur is nucleophilic.
c. Nitrogens are nucleophilic (Lewis base).
d. Oxygen is nucleophilic; carbon is electrophilic.

Exercise 6.4.2

Electrophile; Boron has a vacant *p* orbital.

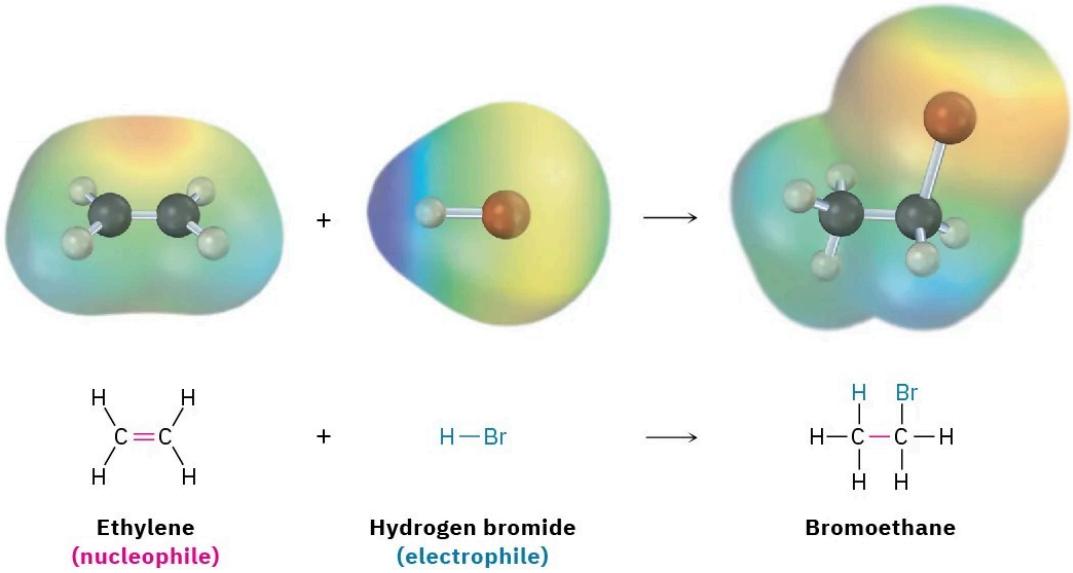


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6.5: An Example of a Polar Reaction - Addition of HBr to Ethylene

Let's look at a typical polar process—the addition reaction of an alkene, such as ethylene, with hydrogen bromide. When ethylene is treated with HBr at room temperature, bromoethane is produced. Overall, the reaction can be formulated as



The reaction is an example of a polar reaction type known as an *electrophilic addition reaction* and can be understood using the general ideas discussed in the previous section. Let's begin by looking at the two reactants.

What do we know about ethylene? We know from Section 1.9 that a carbon–carbon double bond results from the orbital overlap of two sp^2-hybridized carbon atoms. The σ part of the double bond results from sp^2–sp^2 overlap, and the π part results from p–p overlap.

What kind of chemical reactivity might we expect from a $\mathrm{C{=}C}$ bond? We know that alkanes, such as ethane, are relatively inert because all valence electrons are tied up in strong, nonpolar, C–C and C–H bonds. Furthermore, the bonding electrons in alkanes are relatively inaccessible to approaching reactants because they are sheltered in σ bonds between nuclei. The electronic situation in alkenes is quite different, however. For one thing, double bonds have a greater electron density than single bonds—four electrons in a double bond versus only two in a single bond. In addition, the electrons in the π bond are accessible to approaching reactants because they are located above and below the plane of the double bond rather than being sheltered between the nuclei (Figure $6.5.1$). As a result, the double bond is nucleophilic and the chemistry of alkenes is dominated by reactions with electrophiles.

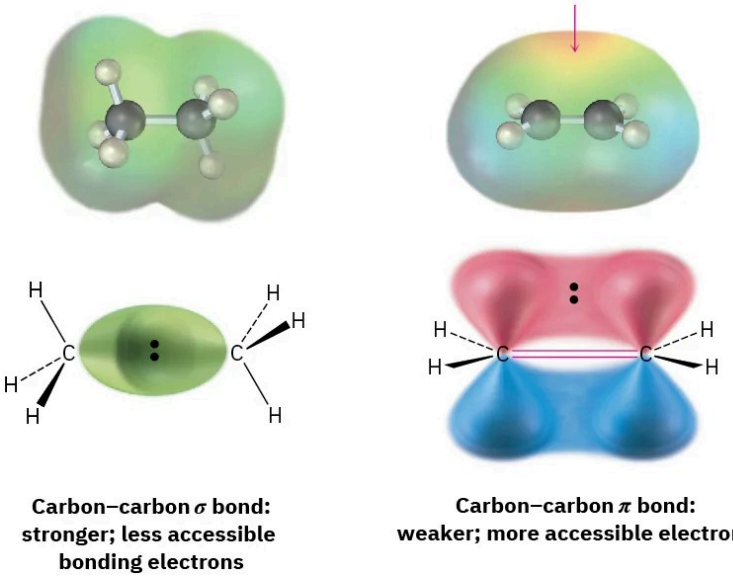


Figure 6.5.1: A comparison of carbon–carbon single and double bonds. A double bond is both more accessible to approaching reactants than a single bond and more electron-rich (more nucleophilic). An electrostatic potential map of ethylene indicates that the double bond is the region of **highest negative charge.**

What about the second reactant, HBr? As a strong acid, HBr is a powerful proton (H^+) donor and electrophile. Thus, the reaction between HBr and ethylene is a typical electrophile–nucleophile combination, characteristic of all polar reactions.

We'll see more details about alkene electrophilic addition reactions shortly, but for the present we can imagine the reaction as taking place by the pathway shown in Figure 6.5.2. The reaction begins when the alkene nucleophile donates a pair of electrons from its C=C bond to HBr to form a new C–H bond plus Br^-, as indicated by the path of the curved arrows in the first step of Figure 6.5.2. One curved arrow begins at the middle of the double bond (the source of the electron pair) and points to the hydrogen atom in HBr (the atom to which a bond will form). This arrow indicates that a new C–H bond forms using electrons from the former C=C bond. Simultaneously, a second curved arrow begins in the middle of the H–Br bond and points to the Br, indicating that the H–Br bond breaks and the electrons remain with the Br atom, giving Br^-.

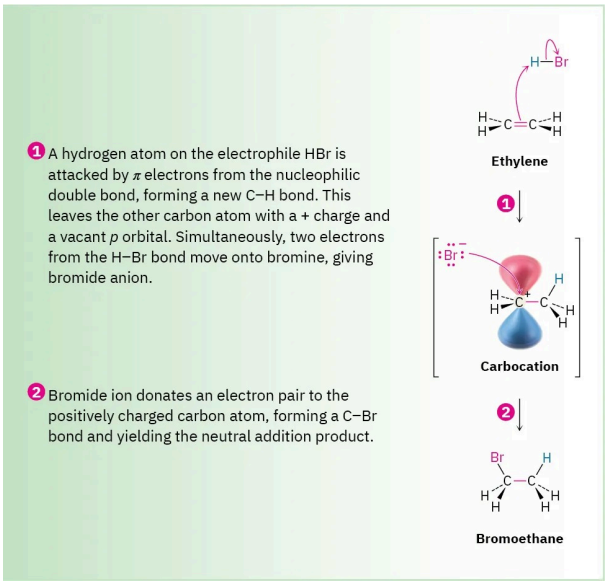


Figure 6.5.2: The electrophilic addition reaction of ethylene and HBr. The reaction takes place in two steps, both of which involve electrophile–nucleophile interactions.

When one of the alkene carbon atoms bonds to the incoming hydrogen, the other carbon atom, having lost its share of the double-bond electrons, now has only six valence electrons and is left with a positive charge. This positively charged species—a carbon-

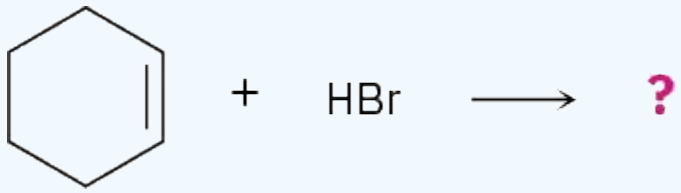
cation, or carbocation—is itself an electrophile that can accept an electron pair from nucleophilic Br^- anion in a second step, forming a C–Br bond and yielding the observed addition product. Once again, a curved arrow in Figure 6.5.2 shows the electron-pair movement from Br^- to the positively charged carbon.

The electrophilic addition of HBr to ethylene is only one example of a polar process; there are many others that we'll study in depth in later chapters. But regardless of the details of individual reactions, all polar reactions take place between an electron-poor site and an electron-rich site and involve the donation of an electron pair from a nucleophile to an electrophile.

Exercises

Exercise 6.5.1

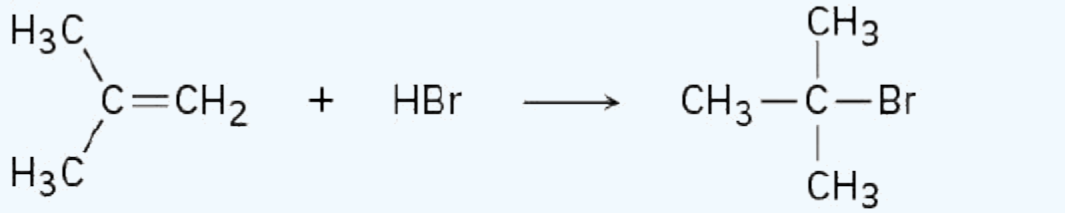
What product would you expect from the reaction of cyclohexene with HBr? With HCl?



Answer available at the end of this section.

Exercise 6.5.2

Reaction of HBr with 2-methylpropene yields 2-bromo-2-methylpropane. What is the structure of the carbocation formed during the reaction? Show the mechanism of the reaction.



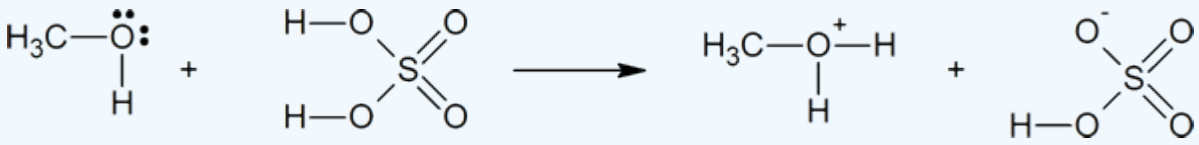
2-Methylpropene **2-Bromo-2-methylpropane**

Answer available at the end of this section.

Exercise 6.5.3

Supply the missing curved arrows in the equations given below.

a-



b-



c-



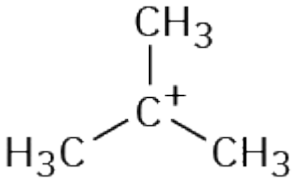
Answer available at the end of this section.

Answers

Exercise 6.5.1

Bromocyclohexane; chlorocyclohexane.

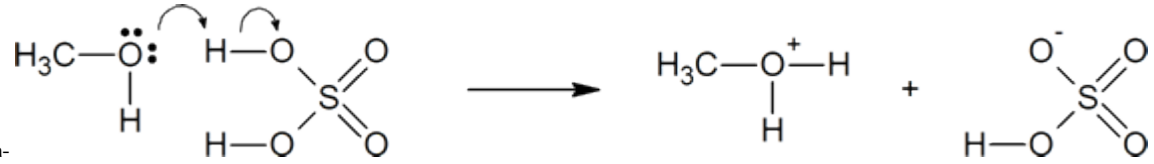
Exercise 6.5.2



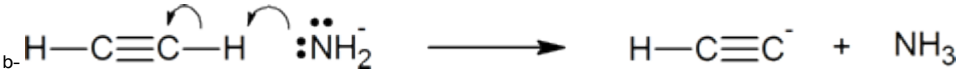
The mechanism is shown in Figure 6.5.2.

Exercise 6.5.3

a-



b-



c-



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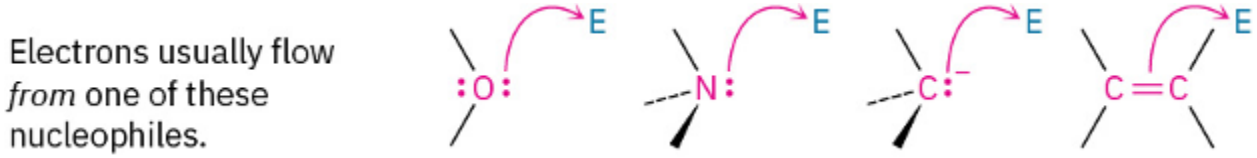
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6.6: Using Curved Arrows in Polar Reaction Mechanisms

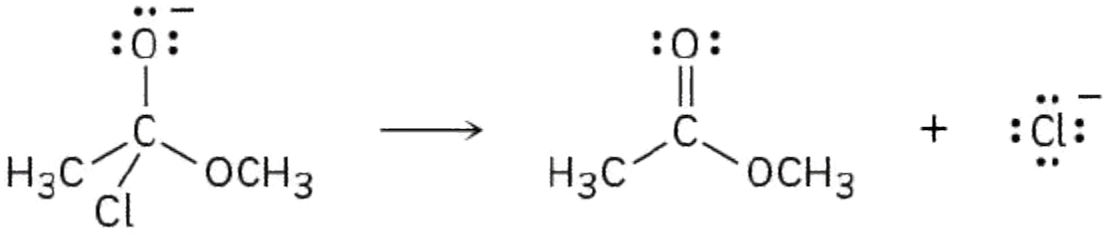
It takes practice to use curved arrows properly in reaction mechanisms, but there are a few rules and a few common patterns you should look for that will help you become more proficient:

RULE 1

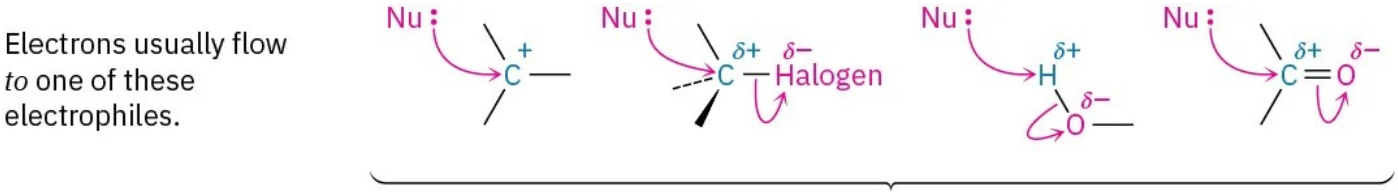
Electrons move *from* a nucleophilic source (Nu: or Nu:$^-$) *to* an electrophilic sink (E or E$^+$). The nucleophilic source must have an electron pair available, usually either as a lone pair or in a multiple bond.



For example:

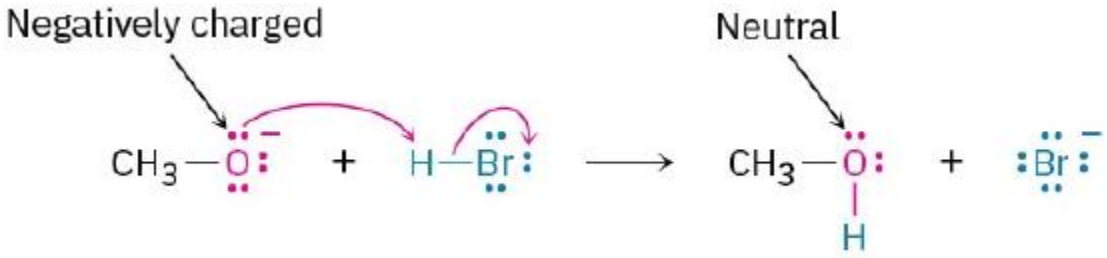


The electrophilic sink must be able to accept an electron pair, usually because it has either a positively charged atom or a positively polarized atom in a functional group. For example:

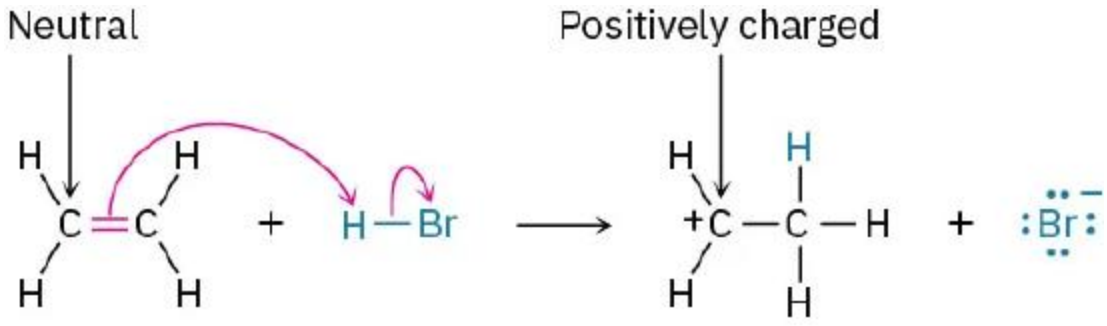


RULE 2

The nucleophile can be either negatively charged or neutral. If the nucleophile is negatively charged, the atom that donates an electron pair becomes neutral. For example:

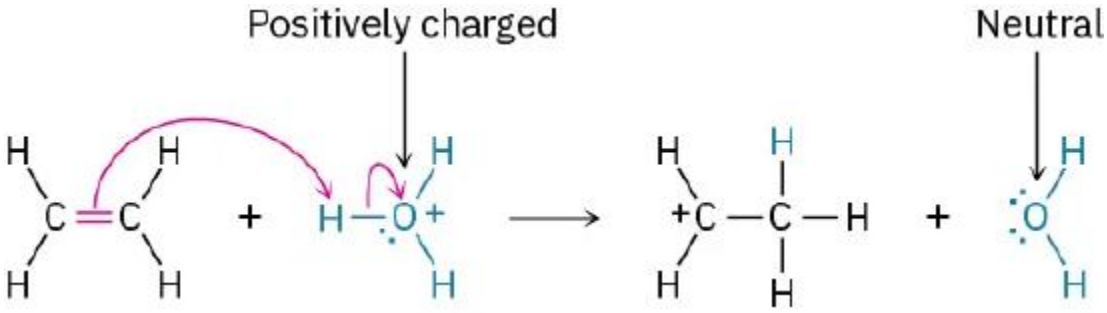


If the nucleophile is neutral, the atom that donates the electron pair acquires a positive charge. For example:

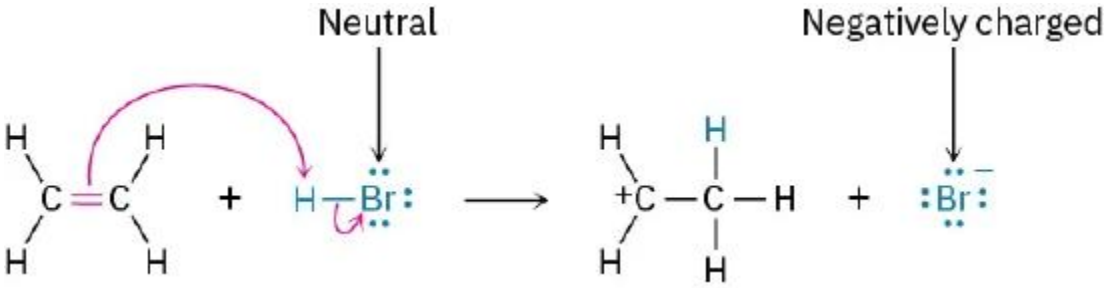


RULE 3

The electrophile can be either positively charged or neutral. If the electrophile is positively charged, the atom bearing that charge becomes neutral after accepting an electron pair. For example:



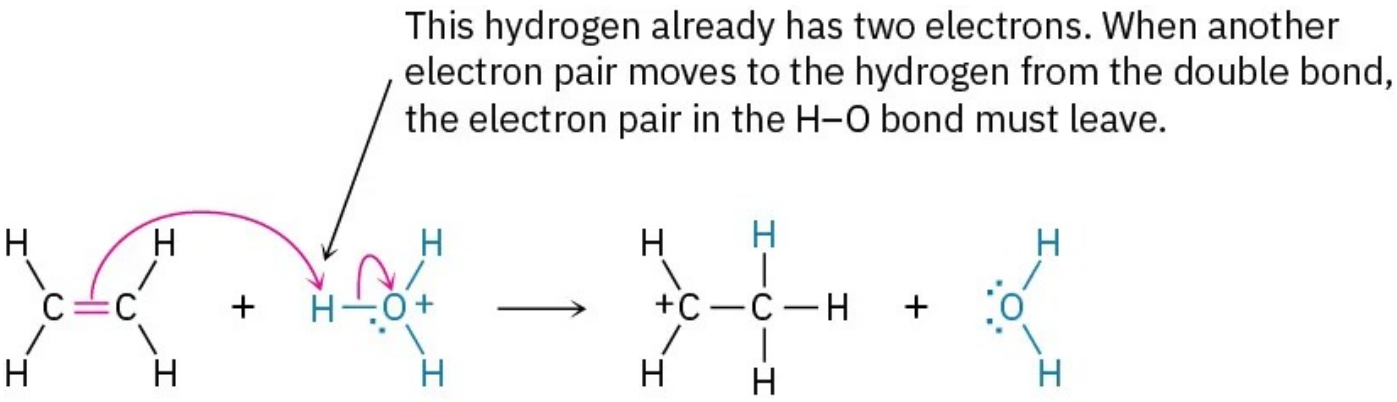
If the electrophile is neutral, the atom that ultimately accepts the electron pair acquires a negative charge. For this to happen, however, the negative charge must be stabilized by being on an electronegative atom such as oxygen, nitrogen, or a halogen. Carbon and hydrogen do not typically stabilize a negative charge. For example:



The result of Rules 2 and 3 together is that charge is conserved during the reaction. A negative charge in one of the reactants gives a negative charge in one of the products, and a positive charge in one of the reactants gives a positive charge in one of the products.

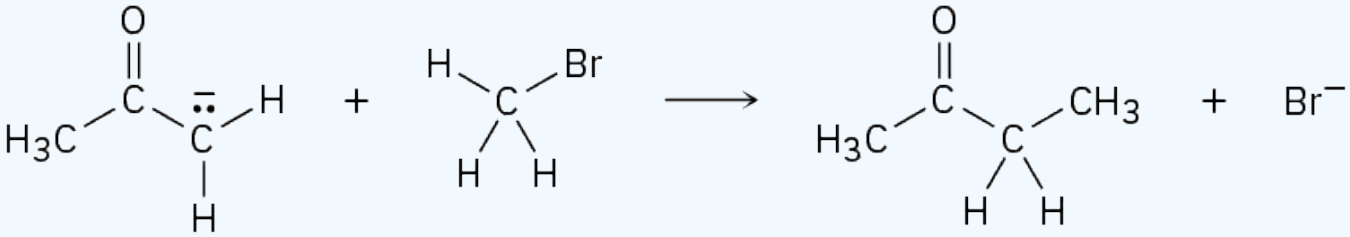
RULE 4

The octet rule must be followed. That is, no second-row atom can be left with ten electrons (or four for hydrogen). If an electron pair moves *to* an atom that already has an octet (or two electrons for hydrogen), another electron pair must simultaneously move from that atom to maintain the octet. When two electrons move from the C=C bond of ethylene to the hydrogen atom of H_3O^+, for instance, two electrons must leave that hydrogen. This means that the H–O bond must break and the electrons must stay with the oxygen, giving neutral water.



Worked Example 6.6.1: Using Curved Arrows in Reaction Mechanisms

Add curved arrows to the following polar reaction to show the flow of electrons:



Strategy

Look at the reaction, and identify the bonding changes that have occurred. In this case, a C–Br bond has broken and a C–C bond has formed. The formation of the C–C bond involves donation of an electron pair from the nucleophilic carbon atom of the reactant on the left to the electrophilic carbon atom of CH_3Br, so we draw a curved arrow originating from the lone pair on the negatively charged C atom and pointing to the C atom of CH_3Br. At the same time that the C–C bond forms, the C–Br bond must break so that the octet rule is not violated. We therefore draw a second curved arrow from the C–Br bond to Br. The bromine is now a stable Br^- ion.

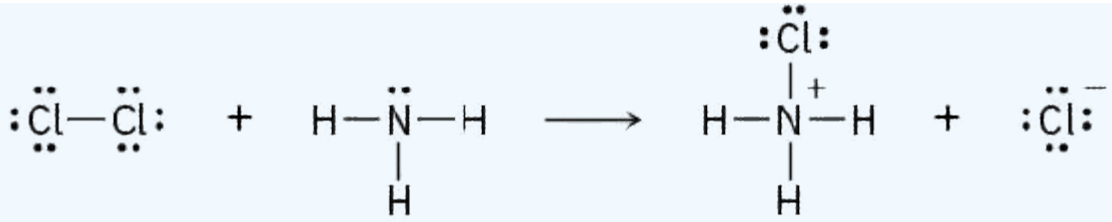
Solution



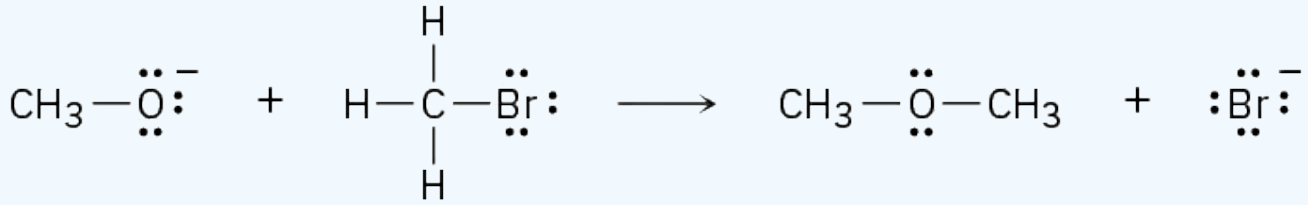
Exercise 6.6.1

Add curved arrows to the following polar reactions to indicate the flow of electrons in each:

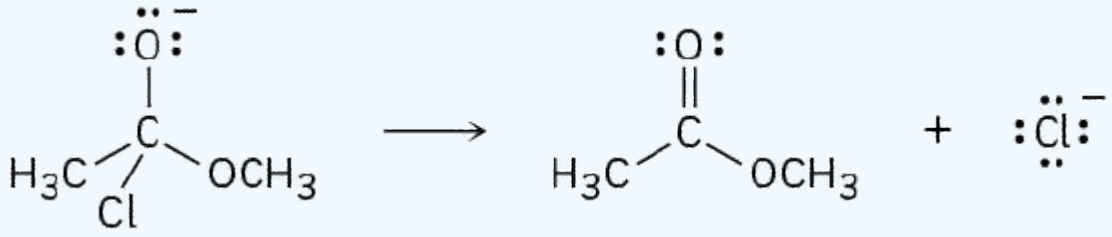
a.



b.



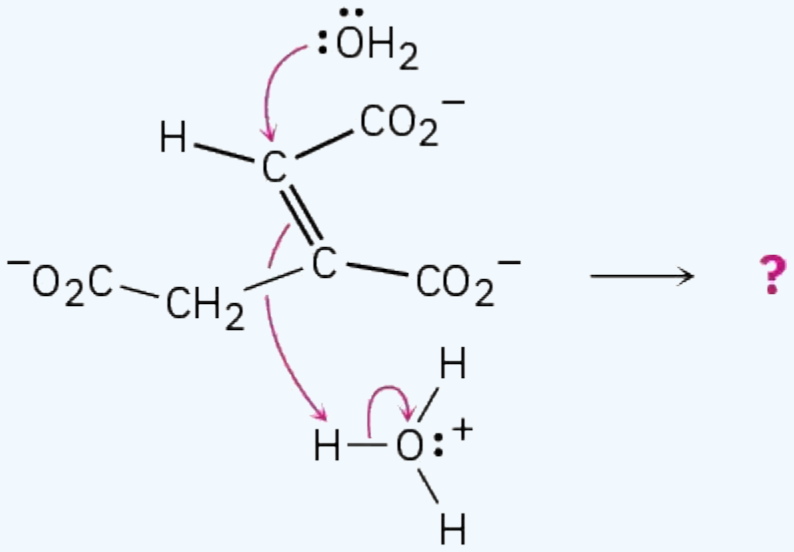
c.



Answer available at the end of this section.

Exercise 6.6.2

Predict the products of the following polar reaction, a step in the citric acid cycle for food metabolism, by interpreting the flow of electrons indicated by the curved arrows:

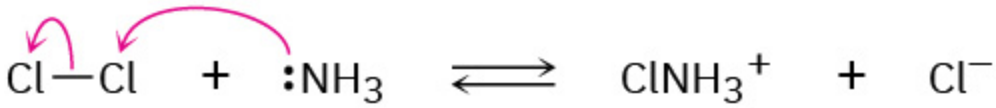


Answer available at the end of this section.

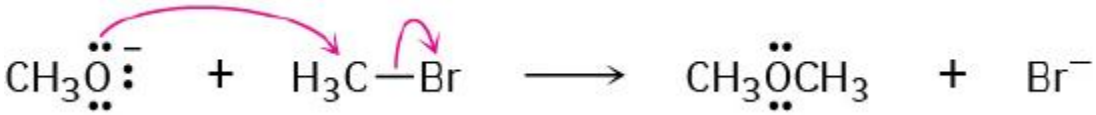
Answers

Exercise 6.6.1

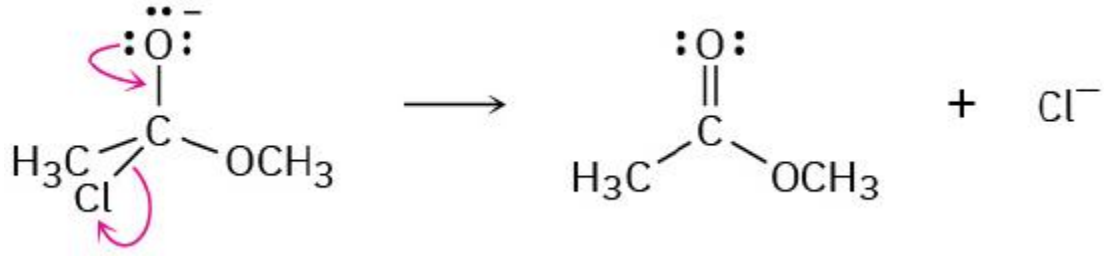
a.



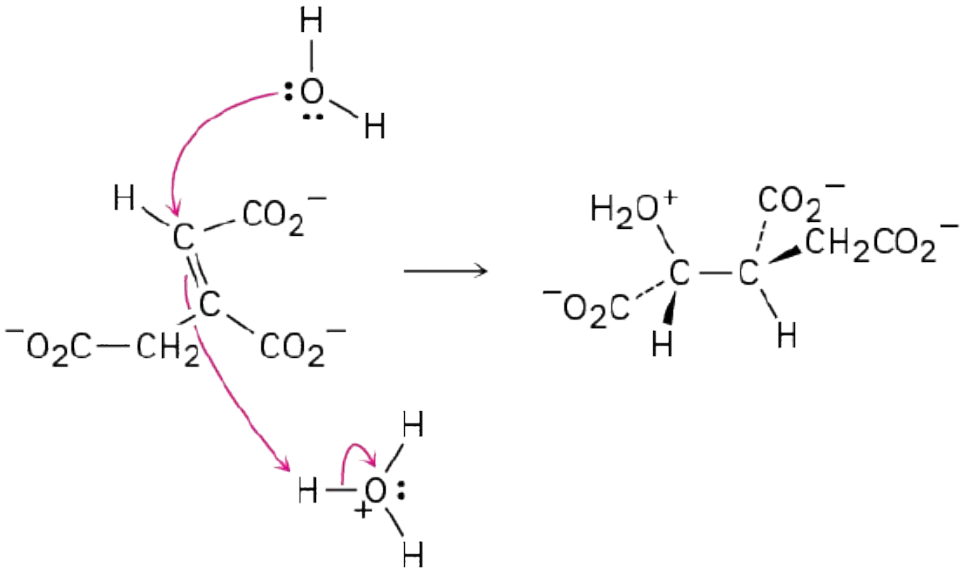
b.



c.



Exercise 6.6.2



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6.7: Describing a Reaction - Equilibria, Rates, and Energy Changes

Every chemical reaction can go in either a forward or reverse direction. Reactants can go forward to products, and products can revert to reactants. As you may remember from your general chemistry course, the position of the resulting chemical equilibrium is expressed by an equation in which K_{eq}, the equilibrium constant, is equal to the product concentrations multiplied together, divided by the reactant concentrations multiplied together, with each concentration raised to the power of its coefficient in the balanced equation. For the generalized reaction

$$a\ \mathrm{A} + b\ \mathrm{B} \rightleftharpoons c\mathrm{C} + d\mathrm{D}$$

we have

$$K_{\mathrm{eq}} = \frac{[\mathrm{C}]^c[\mathrm{D}]^d}{[\ \mathrm{A}]^a[\ \mathrm{B}]^b}$$

The value of the equilibrium constant tells which side of the reaction arrow is energetically favored. If K_{eq} is much larger than 1, then the product concentration term $[C]^c[D]^d$ is much larger than the reactant concentration term $[\ A]^a[\ B]^b$, and the reaction proceeds as written from left to right. If K_{eq} is near 1, appreciable amounts of both reactant and product are present at equilibrium. And if K_{eq} is much smaller than 1, the reaction does not take place as written but instead goes in the reverse direction, from right to left.

For example, consider the reaction of ethylene with HBr:

$$\mathrm{H_2C{=}CH_2} + \mathrm{HBr} \rightleftharpoons \mathrm{CH_3CH_2Br}$$

We can write the following equilibrium expression and determine experimentally that the equilibrium constant at room temperature is approximately 7.1×10^7:

$$K_{\mathrm{eq}} = \frac{[\mathrm{CH_3CH_2Br}]}{[\mathrm{H_2C{=}CH_2}][\mathrm{HBr}]} = 7.1 \times 10^7 \tag{6.7.1}$$

Because K_{eq} is relatively large, the reaction proceeds as written and more than 99.99999% of the ethylene is converted into bromoethane. For practical purposes, an equilibrium constant greater than about 10^3 means that the amount of reactant left over will be barely detectable (less than 0.1%).

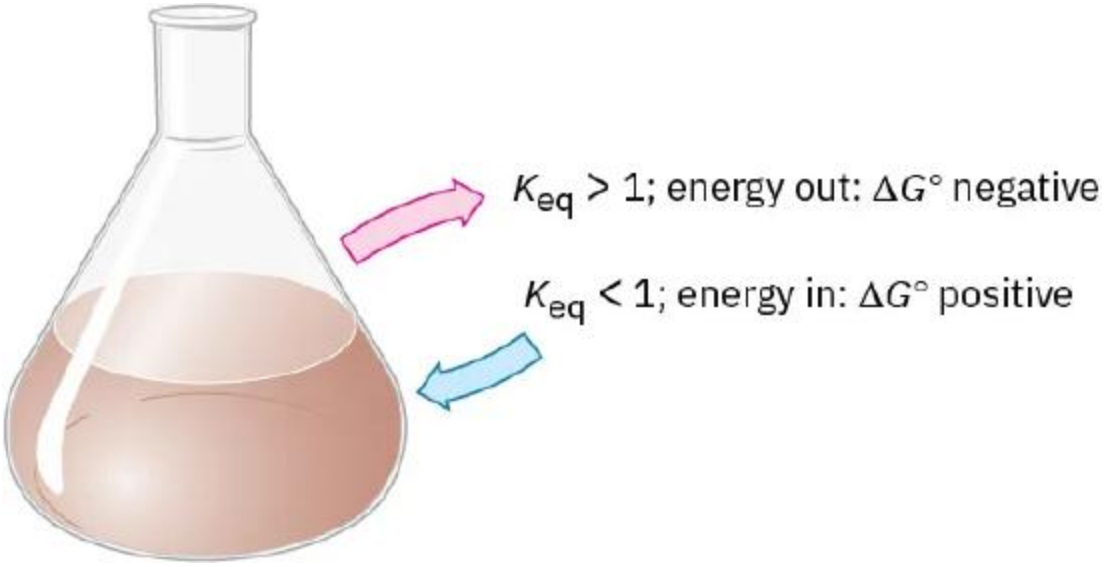
What determines the magnitude of the equilibrium constant? For a reaction to have a favorable equilibrium constant and proceed as written, the energy of the products must be lower than the energy of the reactants. In other words, energy must be released. This situation is analogous to that of a rock poised precariously in a high-energy position near the top of a hill. When it rolls downhill, the rock releases energy until it reaches a more stable, low-energy position at the bottom.

The energy change that occurs during a chemical reaction is called the **Gibbs free-energy change** (ΔG), which is equal to the free energy of the products minus the free energy of the reactants:

$$\Delta G = G_{products} - G_{reactants}. \tag{6.7.2}$$

For a favorable reaction, ΔG has a negative value, meaning that energy is lost by the chemical system and released *to* the surroundings, usually as heat. Such reactions are said to be exergonic. For an unfavorable reaction, ΔG has a positive value, meaning that energy is absorbed by the chemical system *from* the surroundings. Such reactions are said to be endergonic.

You might also recall from general chemistry that the *standard* free-energy change for a reaction is denoted as ΔG°, where the superscript ° means that the reaction is carried out under standard conditions, with pure substances in their most stable form at 1 atm pressure and a specified temperature, usually 298 K. For biological reactions, the standard free-energy change is denoted as $\Delta G^{\circ\prime}$ and refers to a reaction carried out at pH = 7.0 with solute concentrations of 1.0 M.



Because the equilibrium constant, K_{eq}, and the standard free-energy change, $\Delta G°$, both measure whether a reaction is favorable, they are mathematically related by the equation

$$\Delta G^\circ = -RT \ln K_{\text{eq}} \tag{6.7.3}$$

or

$$K_{\text{eq}} = e^{-\Delta G^\circ / RT} \tag{6.7.4}$$

where

$$\begin{aligned} &R = 8.314 \text{ J/(K} \cdot \text{mol)} = 1.987 \text{cal/(K} \cdot \text{mol)} \\ &T = \text{ Kelvin temperature} \\ &e = 2.718 \\ &\ln K_{\text{eq}} = \text{ natural logarithm of } K_{\text{eq}} \end{aligned} \tag{6.7.5}$$

For example, the reaction of ethylene with HBr (Equation 6.7.2) has $K_{eq} = 7.1 \times 10^7$, so $\Delta G° = -44.8$ kJ/mol (−10.7 kcal/mol) at 298 K:

$$\begin{aligned} &K_{\text{eq}} = 7.1 \times 10^7 \text{ and } \ln K_{\text{eq}} = 18.08 \\ &\Delta G^\circ = -RT \ln K_{\text{eq}} = -[8.314 \text{ J/(K} \cdot \text{mol)}](298 \text{ K})(18.08) \\ &= -44,800 \text{ J/mol} = -44.8 \text{ kJ/mol} \end{aligned} \tag{6.7.6}$$

The free-energy change ΔG is made up of two terms, an *enthalpy* term, ΔH, and a temperature-dependent *entropy* term, $T\Delta S$. Of the two terms, the enthalpy term is often larger and more dominant.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{6.7.7}$$

For the reaction of ethylene with HBr at room temperature (298 K), the approximate values are



The enthalpy change (ΔH), also called the **heat of reaction**, is a measure of the change in total bonding energy during a reaction. If ΔH is negative, as in the reaction of HBr with ethylene, the products have less energy than the reactants. Thus, the products are more stable and have stronger bonds than the reactants, heat is released, and the reaction is said to be exothermic. If ΔH is positive, the products are less stable and have weaker bonds than the reactants, heat is absorbed, and the reaction is said to be endothermic. For example, if a reaction breaks reactant bonds with a total strength of 380 kJ/mol and forms product bonds with a total strength of 400 kJ/mol, then ΔH for the reaction is 400 kJ/mol – 380 kJ/mol = –20 kJ/mol and the reaction is exothermic. The entropy change (ΔS) is a measure of the change in the amount of molecular randomness, or freedom of motion, that accompanies a reaction. For example, in an elimination reaction of the type

$$\mathrm{A} \longrightarrow \mathrm{B} + \mathrm{C}$$

there is more freedom of movement and molecular randomness in the products than in the reactant because one molecule has split into two. Thus, there is a net increase in entropy during the reaction and ΔS has a positive value.

On the other hand, for an addition reaction of the type

$$\mathrm{A} + \mathrm{B} \longrightarrow \mathrm{C}$$

the opposite is true. Because such reactions restrict the freedom of movement of two molecules by joining them together, the product has less randomness than the reactants and ΔS has a negative value. The reaction of ethylene and HBr to yield bromoethane, which has $\Delta S° = -0.132$ kJ/(K · mol), is an example. Table 6.7.1 describes the thermodynamic terms more fully.

Table 6.7.1: Explanation of Thermodynamic Quantities: $\Delta G° = \Delta H° - T\Delta S°$

Term	Name	Explanation
$\Delta G°$	**Gibbs free-energy change**	The energy difference between reactants and products. When $\Delta G°$ is negative, the reaction is **exergonic**, has a favorable equilibrium constant, and can occur spontaneously. When $\Delta G°$ is positive, the reaction is **endergonic**, has an unfavorable equilibrium constant, and cannot occur spontaneously.
$\Delta H°$	**Enthalpy change**	The heat of reaction, or difference in strength between the bonds broken in a reaction and the bonds formed. When $\Delta H°$ is negative, the reaction releases heat and is **exothermic**. When $\Delta H°$ is positive, the reaction absorbs heat and is **endothermic**.
$\Delta S°$	**Entropy change**	The change in molecular randomness during a reaction. When $\Delta S°$ is negative, randomness decreases. When $\Delta S°$ is positive, randomness increases.

Knowing the value of K_{eq} for a reaction is useful, but it's important to realize its limitations. An equilibrium constant tells only the position of the equilibrium, or how much product is theoretically possible. It doesn't tell the rate of reaction, or how fast the equilibrium is established. Some reactions are extremely slow even though they have favorable equilibrium constants. Gasoline is stable at room temperature, for instance, because the rate of its reaction with oxygen is slow at 298 K. Only at higher temperatures, such as contact with a lighted match, does gasoline react rapidly with oxygen and undergo complete conversion to the equilibrium products water and carbon dioxide. Rates (how fast a reaction occurs) and equilibria (how much a reaction occurs) are entirely different.

- **Rate** → Is the reaction fast or slow?
- **Equilibrium** → In what direction does the reaction proceed?

Exercises

Exercise 6.7.1

Which reaction is more energetically favored, one with $\Delta G° = -44$ kJ/mol or one with $\Delta G° = +44$ kJ/mol?

Answer available at the end of this section.

Exercise 6.7.2

Which reaction is more exergonic, one with K_{eq}=1000 or one with K_{eq}=0.001?

Answer available at the end of this section.

Answers

Exercise 6.7.1

Negative $\Delta G°$ is favored.

Exercise 6.7.2

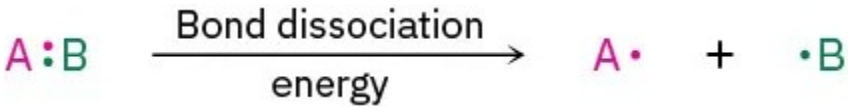
Larger K_{eq} is more exergonic.

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6.8: Describing a Reaction - Bond Dissociation Energies

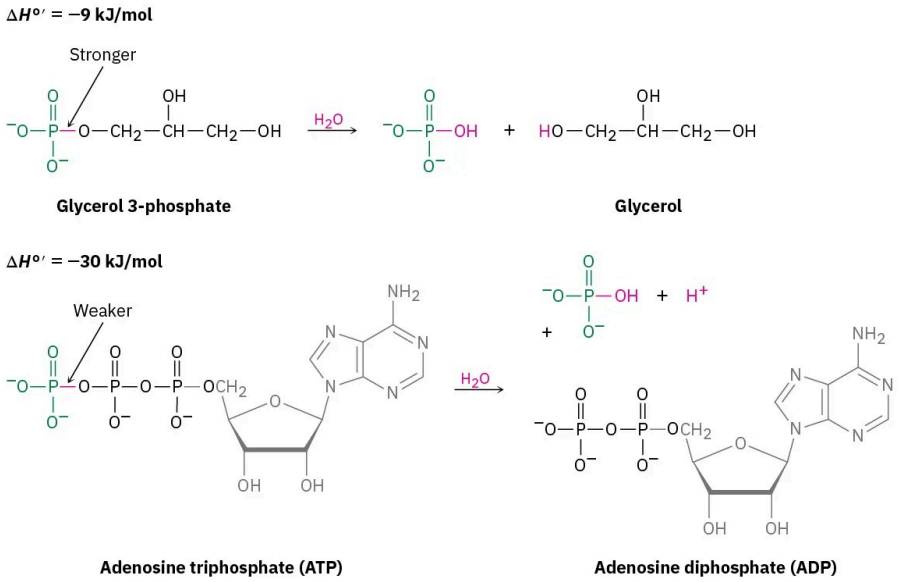
We've just seen that heat is released (negative ΔH) when a bond is formed because the products are more stable and have stronger bonds than the reactants. Conversely, heat is absorbed (positive ΔH) when a bond is broken because the products are less stable and have weaker bonds than the reactants. The amount of energy needed to break a given bond to produce two radical fragments when the molecule is in the gas phase at 25 °C is a quantity called the **bond strength**, or **bond dissociation energy** (D).



Each specific bond has its own characteristic strength, and extensive tables of such data are available. For example, a C–H bond in methane has a bond dissociation energy D = 439.3 kJ/mol (105.0 kcal/mol), meaning that 439.3 kJ/mol must be added to break a C–H bond of methane to give the two radical fragments $\cdot CH_3$ and ·H. Conversely, 439.3 kJ/mol of energy is released when a methyl radical and a hydrogen atom combine to form methane. Table 6.8.1 lists some other bond strengths.

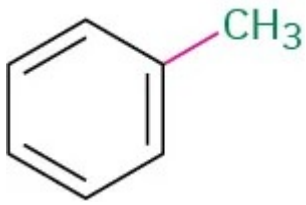
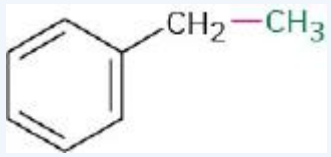
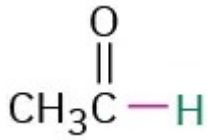
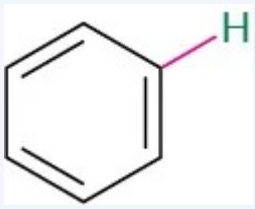
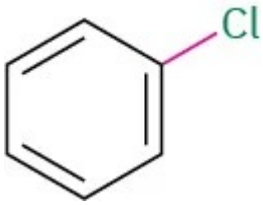
ATP: High Energy Compound

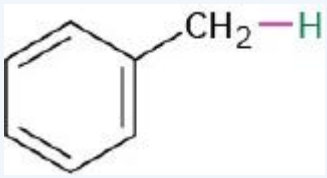
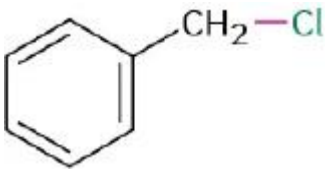
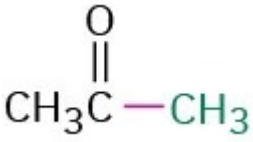
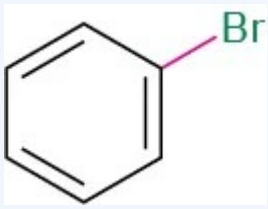
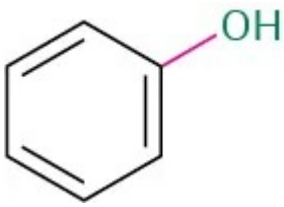
Sometimes, particularly in biochemistry, reactive substances that undergo highly exothermic reactions, such as ATP (adenosine triphosphate), are referred to as "energy-rich" or "high-energy" compounds. Such a label doesn't mean that ATP is special or different from other compounds, it only means that ATP has relatively weak bonds that require a relatively small amount of heat to break, thus leading to a larger release of heat when a strong new bond forms in a reaction. When a typical organic phosphate such as glycerol 3-phosphate reacts with water, for instance, only 9 kJ/mol of heat is released ($\Delta H°' = -9$ kJ/mol), but when ATP reacts with water, 30 kJ/mol of heat is released ($\Delta H°' = -30$ kJ/mol). The difference between the two reactions is due to the fact that the bond broken in ATP is substantially weaker than the bond broken in glycerol 3-phosphate. We'll see the metabolic importance of this reaction in later chapters.



Bond Dissociation Energies

Table 6.8.1: *Some Bond Dissociation Energies, D*

Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)
H—H	436	$(CH_3)_2CH$—H	410	C_2H_5—CH_3	370
H—F	570	$(CH_3)_2CH$—Cl	354	$(CH_3)_2CH$—CH_3	369
H—Cl	431	$(CH_3)_2CH$—Br	299	$(CH_3)_3C$—CH_3	363
H—Br	366	$(CH_3)_3C$—H	400	H_2C=CH—CH_3	426
H—I	298	$(CH_3)_3C$—Cl	352	H_2C=$CHCH_2$—CH_3	318
Cl—Cl	242	$(CH_3)_3C$—Br	293	H_2C=CH_2	728
Br—Br	194	$(CH_3)_3C$—I	227		427
I—I	152	H_2C=CH—H	464		325
CH_3—H	439	H_2C=CH—Cl	396		374
CH_3—Cl	350	H_2C=$CHCH_2$—H	369	HO—H	497
CH_3—Br	294	H_2C=$CHCH_2$—Cl	298	HO—OH	211
CH_3—I	239		472	CH_3O—H	440
CH_3—OH	385		400	CH_3S—H	366

Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)
CH_3—NH_2	386		375	C_2H_5O—H	441
C_2H_5—H	421		300		352
C_2H_5—CI	352		336	CH_3CH_2O—CH_3	355
C_2H_5—Br	293		464	NH_2—H	450
C_2H_5—I	233	HC≡CHC≡CC—H	558	H—CN	528
C_2H_5—OH	391	CH_3—CH_3	377		

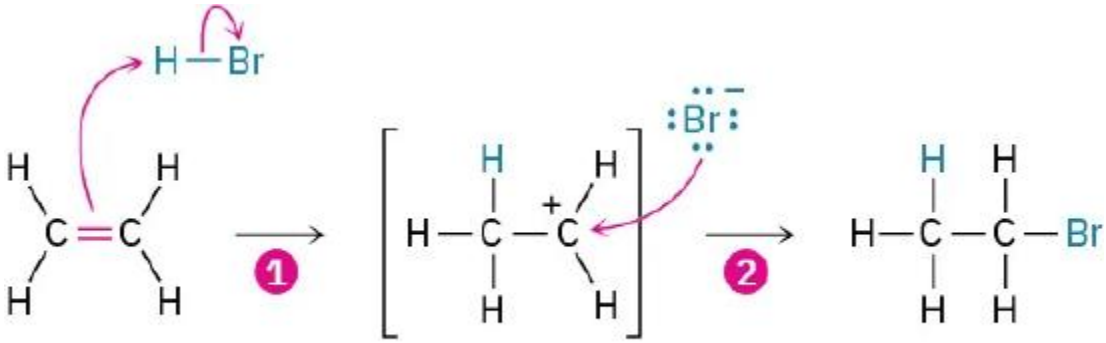
Think again about the connection between bond strengths and chemical reactivity. In an exothermic reaction, more heat is released than is absorbed. But because making bonds in the products releases heat and breaking bonds in the reactants absorbs heat, the bonds in the products must be stronger than the bonds in the reactants. In other words, exothermic reactions are favored by products with strong bonds and by reactants with weak, easily broken bonds.

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6.9: Describing a Reaction - Energy Diagrams and Transition States

For a reaction to take place, reactant molecules must collide and reorganization of atoms and bonds must occur. Let's again look at the addition reaction of HBr and ethylene.



As the reaction proceeds, ethylene and HBr approach each other, the ethylene π bond and the H–Br bond break, a new C–H bond forms in step **1** and a new C–Br bond forms in step **2**.

To depict graphically the energy changes that occur during a reaction, chemists use energy diagrams, such as that in Figure 6.9.1. The vertical axis of the diagram represents the total energy of all reactants, and the horizontal axis, called the reaction coordinate, represents the progress of the reaction from beginning to end. Let's see how the addition of HBr to ethylene can be described in an energy diagram.

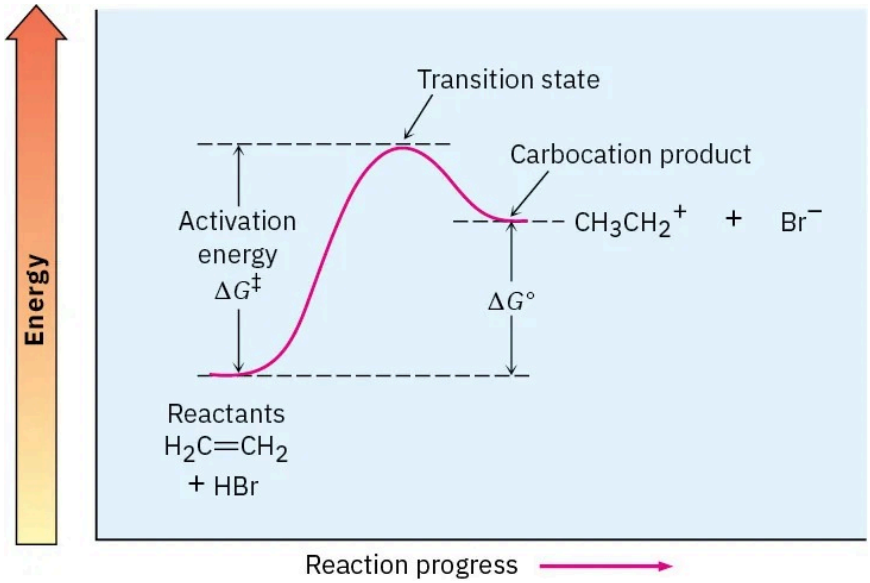


Figure 6.9.1: An energy diagram for the first step in the reaction of ethylene with HBr. The energy difference between reactants and the transition state, $\Delta G^{\ddagger}$, defines the reaction rate. The energy difference between reactants and carbocation product, $\Delta G°$, defines the position of the equilibrium.

At the beginning of the reaction, ethylene and HBr have the total amount of energy indicated by the reactant level on the left side of the diagram in Figure 6.9.1. As the two reactants collide and reaction commences, their electron clouds repel each other, causing the energy level to rise. If the collision has occurred with enough force and proper orientation, however, the reactants

continue to approach each other despite the rising repulsion until the new C–H bond starts to form. At some point, a structure of maximum energy is reached, a structure called the transition state.

The transition state represents the highest-energy structure involved in this step of the reaction. It is unstable and can't be isolated, but we can imagine it to be an activated complex of the two reactants in which both the C=C π bond and H–Br bond are partially broken and the new C-H bond is partially formed (Figure 6.9.2).

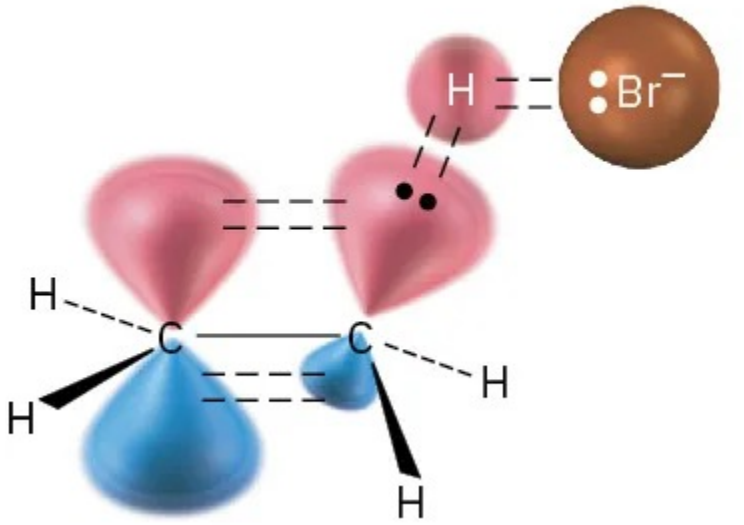


Figure 6.9.2: A hypothetical transition-state structure for the first step of the reaction of ethylene with HBr. The C=C π bond and H–Br bond are just beginning to break, and the C–H bond is just beginning to form.

The energy difference between reactants and the transition state is called the activation energy, $\Delta G^{\ddagger}$, and determines how rapidly the reaction occurs at a given temperature. (The double-dagger superscript, ‡, always refers to the transition state.) A high activation energy results in a slow reaction because few collisions occur with enough energy for the reactants to reach the transition state. A low activation energy results in a rapid reaction because almost all collisions occur with enough energy for the reactants to reach the transition state.

As an analogy, you might think of reactants that need enough energy to climb the activation barrier to the transition state as hikers who need enough energy to climb to the top of a mountain pass. If the pass is a high one, the hikers need a lot of energy and surmount the barrier with difficulty. If the pass is low, the hikers need less energy and reach the top easily.

As a rough generalization, many organic reactions have activation energies in the range 40 to 150 kJ/mol (10–35 kcal/mol). The reaction of ethylene with HBr, for example, has an activation energy of approximately 140 kJ/mol (34 kcal/mol). Reactions with activation energies less than 80 kJ/mol take place at or below room temperature, while reactions with higher activation energies normally require a higher temperature to give the reactants enough energy to climb the activation barrier.

Once the transition state is reached, the reaction can either continue on to give the carbocation product or revert back to reactants. When reversion to reactants occurs, the transition-state structure comes apart and an amount of free energy corresponding to $-\Delta G^{\ddagger}$ is released. When the reaction continues on to give the carbocation, the new C–H bond forms fully and an amount of energy is released corresponding to the difference between the transition state and carbocation product. The net energy change for the step, $\Delta G°$, is represented in the diagram as the difference in level between reactant and product. Since the carbocation is higher in energy than the starting alkene, the step is endergonic, has a positive value of $\Delta G°$, and absorbs energy.

Not all energy diagrams are like that shown for the reaction of ethylene and HBr. Each reaction has its own energy profile. Some reactions are fast (small $\Delta G^{\ddagger}$) and some are slow (large $\Delta G^{\ddagger}$); some have a negative $\Delta G°$, and some have a positive $\Delta G°$. Figure 6.9.3 illustrates some different possibilities.

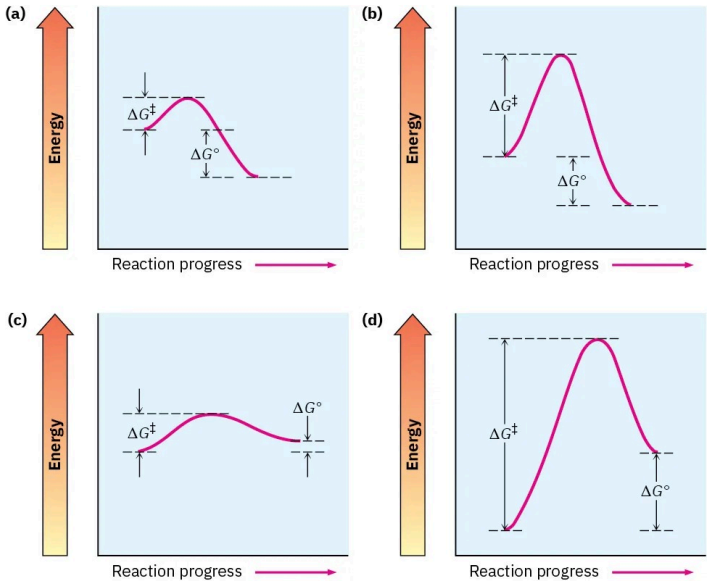


Figure 6.9.3: Some hypothetical energy diagrams: **(a)** a fast exergonic reaction (low $\Delta G^{\ddagger}$, negative $\Delta G°$); **(b)** a slow exergonic reaction (high $\Delta G^{\ddagger}$, negative $\Delta G°$); **(c)** a fast endergonic reaction (small $\Delta G^{\ddagger}$, small positive $\Delta G°$); **(d)** a slow endergonic reaction (high $\Delta G^{\ddagger}$, positive $\Delta G°$).

Exercise 6.9.1

Which reaction is faster, one with $\Delta G‡$ = +45 kJ/mol or one with $\Delta G‡$ = +70 kJ/mol?

Answer available at the end of this section.

Answers

Exercise 6.9.1

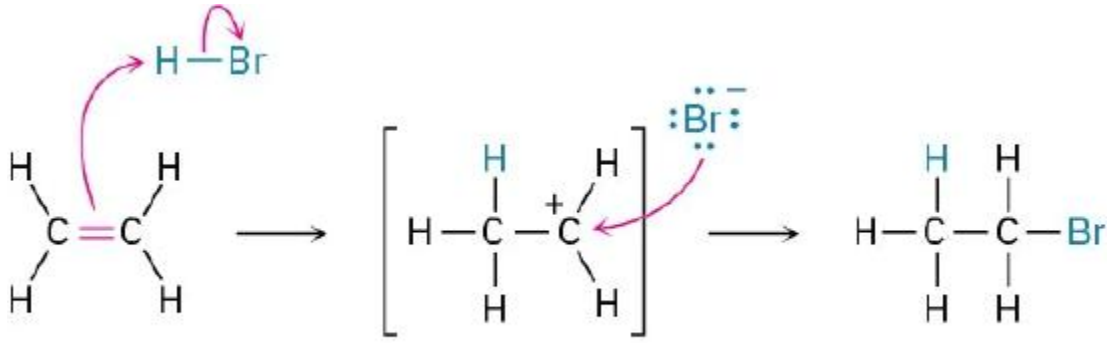
Lower $\Delta G^{\ddagger}$ is faster.

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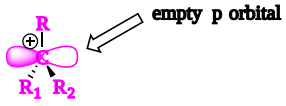
6.10: Describing a Reaction- Intermediates

How can we describe the carbocation formed in the first step of the reaction of ethylene with HBr? The carbocation is clearly different from the reactants, yet it isn't a transition state and it isn't a final product. We call the carbocation, which exists only transiently during the course of the multistep reaction, a reaction intermediate.



Reaction intermediate

This results in the formation of a carbocation: because the central carbon has only three bonds, it bears a formal charge of +1. Recall that a carbocation should be pictured as sp^2 hybridized, with trigonal planar geometry. Perpendicular to the plane formed by the three sp^2 hybrid orbitals is an empty, unhybridized *p* orbital.



As soon as the intermediate is formed in the first step by reaction of ethylene with H^+, it reacts further with Br^- in a second step to give the final product, bromoethane. This second step has its own activation energy ($\Delta G^{\ddagger}$), its own transition state, and its own energy change ($\Delta G°$). We can picture the second transition state as an activated complex between the electrophilic carbocation intermediate and the nucleophilic bromide anion, in which Br^- donates a pair of electrons to the positively charged carbon atom as the new C–Br bond just starts to form.

A complete energy diagram for the overall reaction of ethylene with HBr is shown in Figure 6.10.1. In essence, we draw a diagram for each of the individual steps and then join them so that the carbocation product of step 1 is the reactant for step 2. As indicated in Figure 6.10.1, the reaction intermediate lies at an energy minimum between steps. Because the energy level of the intermediate is higher than the level of either the reactant that formed it or the product it yields, the intermediate can't normally be isolated. It is, however, more stable than its two neighboring transition states.

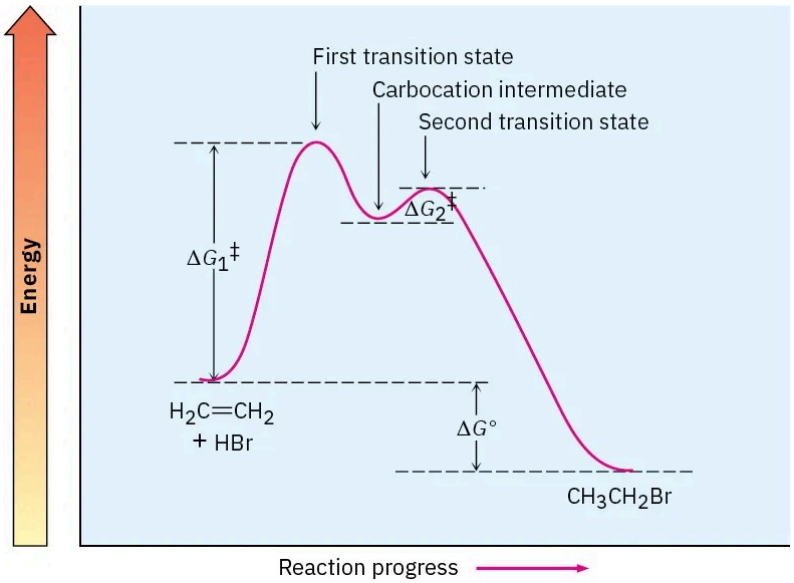


Figure 6.10.1: **An energy diagram for the reaction of ethylene with HBr.** Two separate steps are involved, each with its own activation energy ($\Delta G^{\ddagger}$) and free-energy change ($\Delta G°$). The overall $\Delta G^{\ddagger}$ for the complete reaction is the energy difference between reactants and the highest transition state (which corresponds to $\Delta G1^{\ddagger}$ in this case), and the overall $\Delta G°$ for the reaction is the energy difference between reactants and final products.

Each step in a multistep process can always be considered separately. Each step has its own $\Delta G^{\ddagger}$ and its own $\Delta G°$. The overall activation energy that controls the rate of the reaction, however, is the energy difference between the initial reactants and the highest transition state, regardless of which step it occurs in. The overall $\Delta G°$ of the reaction is the energy difference between reactants and final products.

The biological reactions that take place in living organisms have the same energy requirements as reactions that take place in the laboratory and can be described in similar ways. They are, however, constrained by the fact that they must have low enough activation energies to occur at moderate temperatures, and they must release energy in relatively small amounts to avoid overheating the organism. These constraints can be met through the use of large, structurally complex, enzyme catalysts that alter the mechanism of a reaction to a pathway that can proceed through a series of small steps rather than one or two large steps. Thus, an energy diagram for a biological reaction might look like that in Figure 6.10.2.

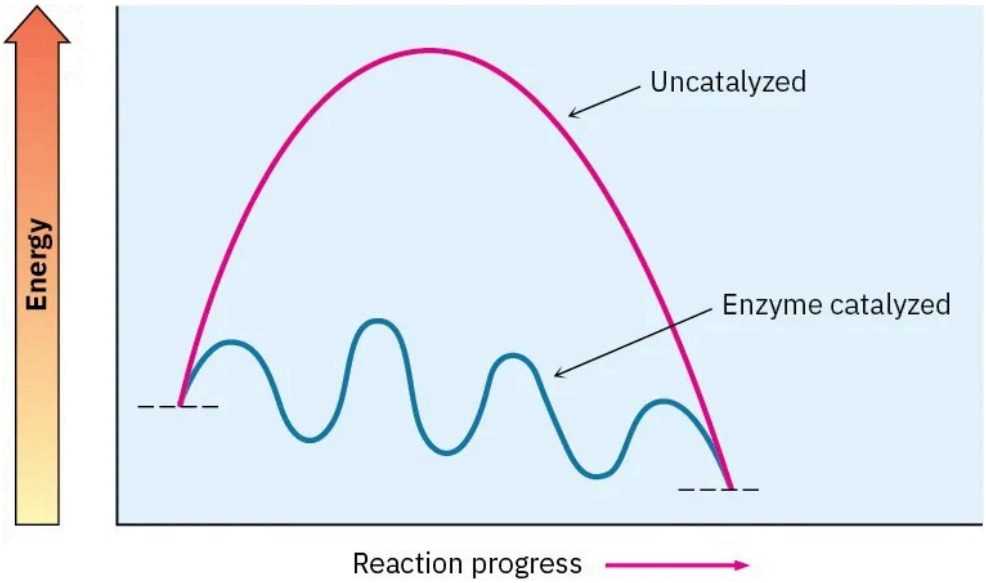


Figure 6.10.2: Energy diagrams for a typical, enzyme-catalyzed biological reaction and an **uncatalyzed laboratory reaction**. The biological reaction involves many steps, each of which has a relatively small activation energy and small energy change. The end result is the same, however.

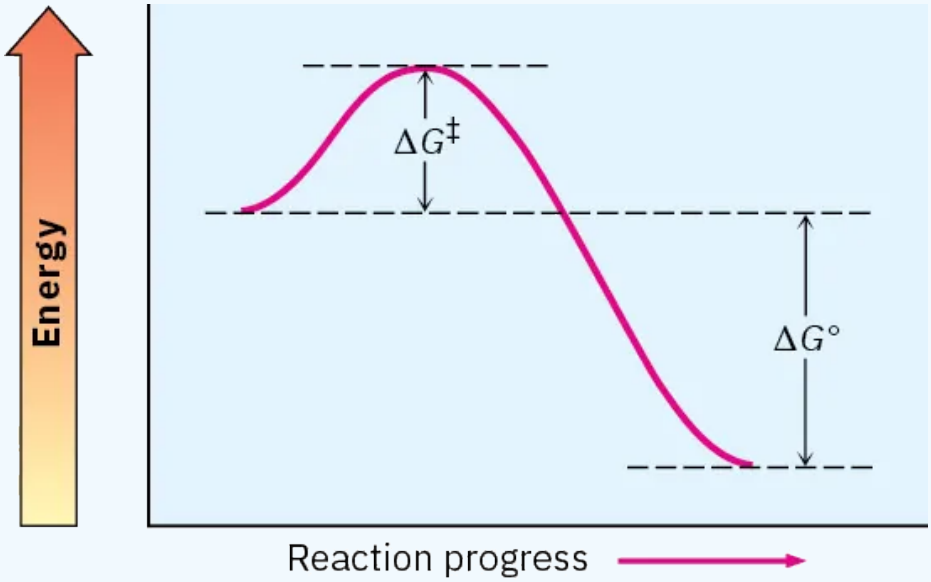
Worked Example 6.10.1: Drawing a Reaction Energy Diagram

Sketch an energy diagram for a one-step reaction that is fast and highly exergonic.

Strategy

A fast reaction has a small $\Delta G^{\ddagger}$, and a highly exergonic reaction has a large negative $\Delta G°$.

Solution



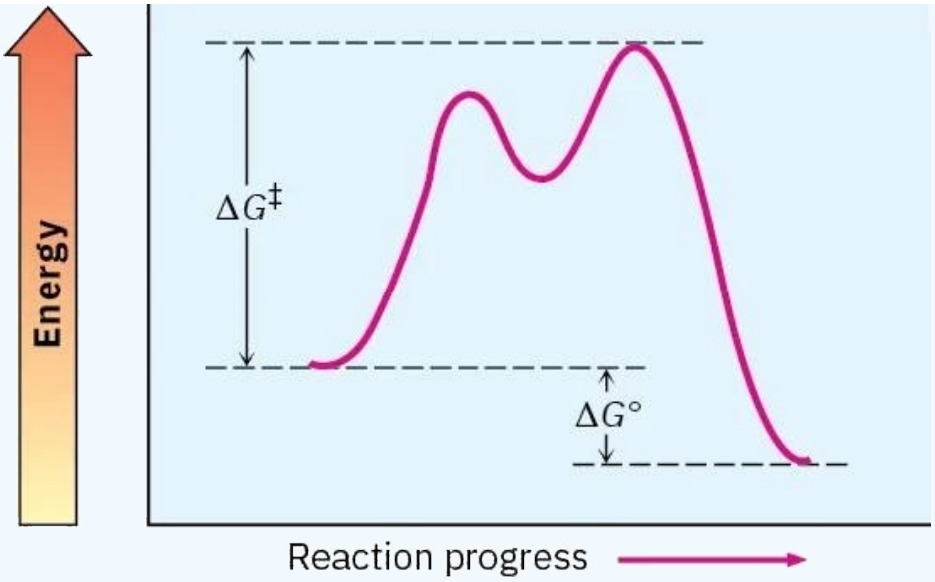
Worked Example 6.10.2: Drawing a Reaction Energy Diagram

Sketch an energy diagram for a two-step exergonic reaction whose second step has a higher-energy transition state than its first step. Show $\Delta G^{\ddagger}$ and $\Delta G°$ for the overall reaction.

Strategy

A two-step reaction has two transition states and an intermediate between them. The $\Delta G^{\ddagger}$ for the overall reaction is the energy change between reactants and the highest-energy transition state—the second one in this case. An exergonic reaction has a negative overall $\Delta G°$.

Solution



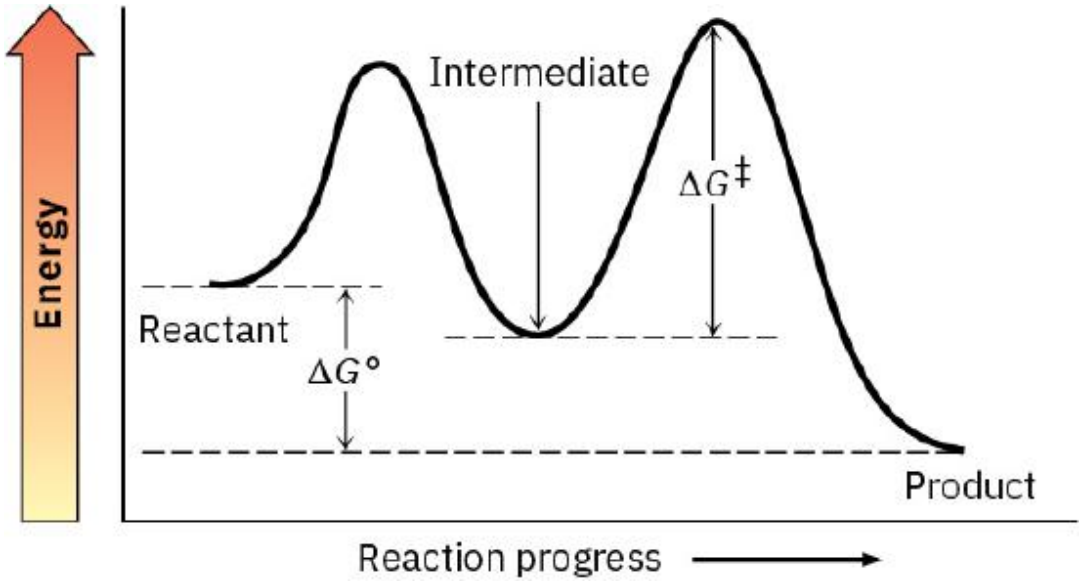
Exercise 6.10.1

Sketch an energy diagram for a two-step reaction in which both steps are exergonic and in which the second step has a higher-energy transition state than the first. Label the parts of the diagram corresponding to reactant, product, intermediate, overall $\Delta G^{\ddagger}$, and overall $\Delta G°$..

Answer available at the end of this section.

Answers

Exercise 6.10.1



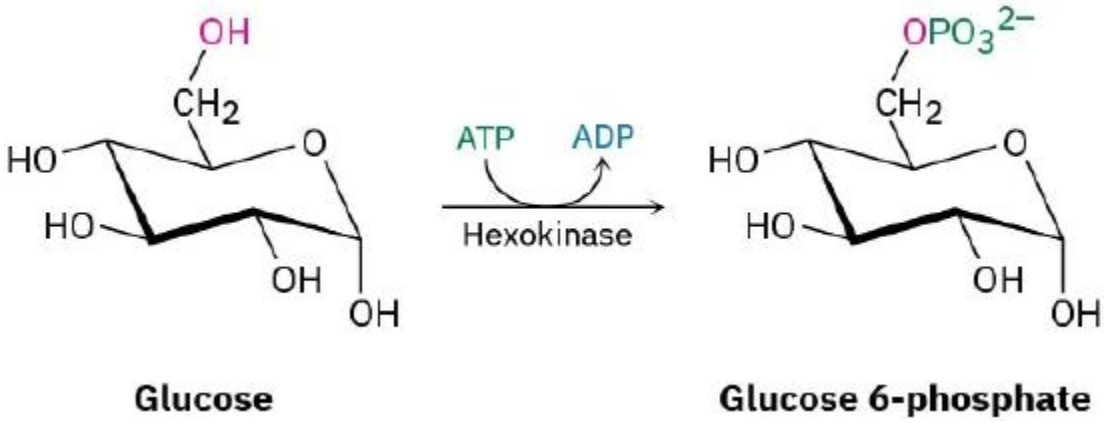
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6.11: A Comparison between Biological Reactions and Laboratory Reactions

Beginning in the next chapter, we'll be seeing a lot of reactions, some that are important in laboratory chemistry yet don't occur in nature, and others that have counterparts in biological pathways. In comparing laboratory reactions with biological reactions, several differences are apparent. For one, laboratory reactions are usually carried out in an organic solvent such as diethyl ether or dichloromethane to dissolve the reactants and bring them into contact, whereas biological reactions occur in the aqueous medium within cells. For another, laboratory reactions often take place over a wide range of temperatures without catalysts, while biological reactions take place at the temperature of the organism and are catalyzed by enzymes.

We'll look at enzymes in more detail in the second semester, but you may already be aware that an enzyme is a large, globular, protein molecule that contains in its structure a protected pocket called its active site. The active site is lined by acidic or basic groups as needed for catalysis and has precisely the right shape to bind and hold a substrate molecule in the orientation necessary for reaction. Figure 6.11.1 shows a molecular model of hexokinase, along with an X-ray crystal structure of the glucose substrate and adenosine diphosphate (ADP) bound in the active site. Hexokinase is an enzyme that catalyzes the initial step of glucose metabolism—the transfer of a phosphate group from ATP to glucose, giving glucose 6-phosphate and ADP. The structures of ATP and ADP were shown at the end of Section 6.8.



Glucose **Glucose 6-phosphate**

Note how the hexokinase-catalyzed phosphorylation reaction of glucose is written. It's common when writing biological equations to show only the structures of the primary reactant and product, while abbreviating the structures of various biological "reagents" and by-products such as ATP and ADP. A curved arrow intersecting the straight reaction arrow indicates that ATP is also a reactant and ADP also a product.

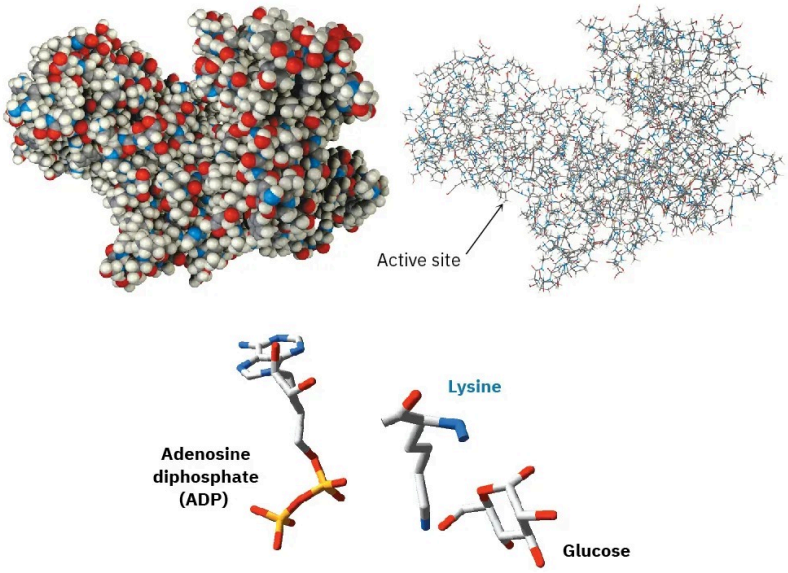
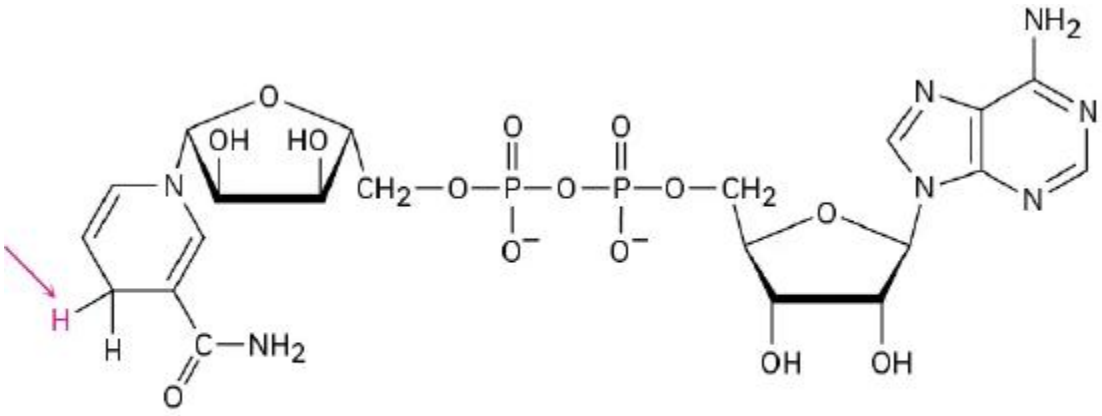


Figure 6.11.1: Models of hexokinase in space-filling and wire-frame formats, showing the cleft that contains the active site where substrate binding and reaction catalysis occur. At the bottom is an X-ray crystal structure of the enzyme active site, showing the positions of both glucose and ADP as well as a lysine amino acid that acts as a base to deprotonate glucose.

Yet a third difference between laboratory and biological reactions is that laboratory reactions are often done using relatively small, simple reagents such as Br_2, HCl, $NaBH_4$, CrO_3, and so forth, while biological reactions usually involve relatively complex "reagents" called *coenzymes*. In the hexokinase-catalyzed phosphorylation of glucose just shown, ATP is the coenzyme. As another example, compare the H_2 molecule, a laboratory reagent that adds to a carbon–carbon double bond to yield an alkane, with the reduced nicotinamide adenine dinucleotide (NADH) molecule, a coenzyme that effects an analogous addition of hydrogen to a double bond in many biological pathways. Of all the atoms in the coenzyme, only the one hydrogen atom shown in red is transferred to the double-bond substrate.



Reduced nicotinamide adenine dinucleotide, NADH (a coenzyme)

Don't be intimidated by the size of the ATP or NADH molecule; most of the structure is there to provide an overall shape for binding to the enzyme and to provide appropriate solubility behavior. When looking at biological molecules, focus on the small part of the molecule where the chemical change takes place.

One final difference between laboratory and biological reactions is in their specificity. A catalyst might be used in the laboratory to catalyze the reaction of thousands of different substances, but an enzyme, because it can only bind a specific substrate molecule having a specific shape, will usually catalyze only a specific reaction. It's this exquisite specificity that makes biological chemistry so remarkable, and that makes life possible. Table 6.11.1 summarizes some of the differences between laboratory and biological reactions.

Table 6.11.1: A Comparison of Typical Laboratory and Biological Reactions A Comparison of Typical Laboratory and Biological Reactions

	Laboratory reaction	Biological reaction
Solvent	Organic liquid, such as ether	Aqueous environment in cells
Temperature	Wide range; −80 to 150 °C	Temperature of the organism
Catalyst	Either none, or very simple	Large, complex enzymes needed
Reagent size	Usually small and simple	Relatively complex coenzymes
Specificity	Little specificity for substrate	Very high specificity for substrate

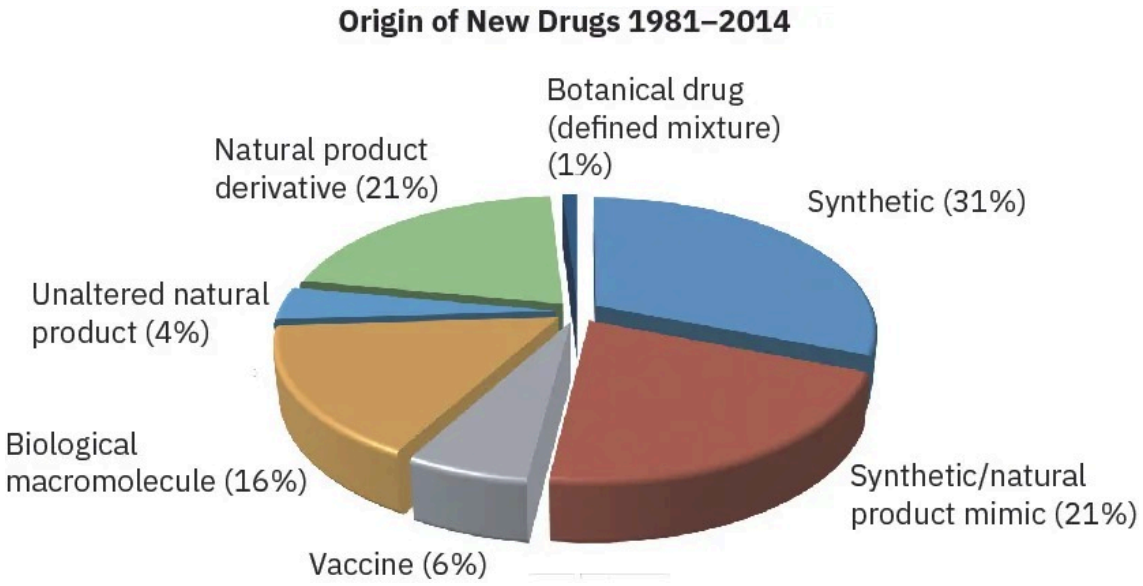
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6.12: Chemistry Matters—Where Do Drugs Come From?

It has been estimated that major pharmaceutical companies in the United States spent some $200 billion on drug research and development in 2020, while government agencies and private foundations spent another $28 billion. What does this money buy? From 1983 to 2022, the money resulted in a total of 1237 new molecular entities (NMEs)—new biologically active chemical substances approved for sale as drugs by the U.S. Food and Drug Administration (FDA).

Where do the new drugs come from? According to a study carried out several years ago at the U.S. National Cancer Institute, only about 33% of new drugs are entirely synthetic and completely unrelated to any naturally occurring substance. The remaining 67% take their lead, to a greater or lesser extent, from nature. Vaccines and genetically engineered proteins of biological origin account for 15% of NMEs, but most new drugs come from *natural products*, a catchall term generally taken to mean small molecules found in bacteria, plants, algae, and other living organisms. Unmodified natural products isolated directly from the producing organism account for 24% of NMEs, while natural products that have been chemically modified in the laboratory account for the remaining 28%.

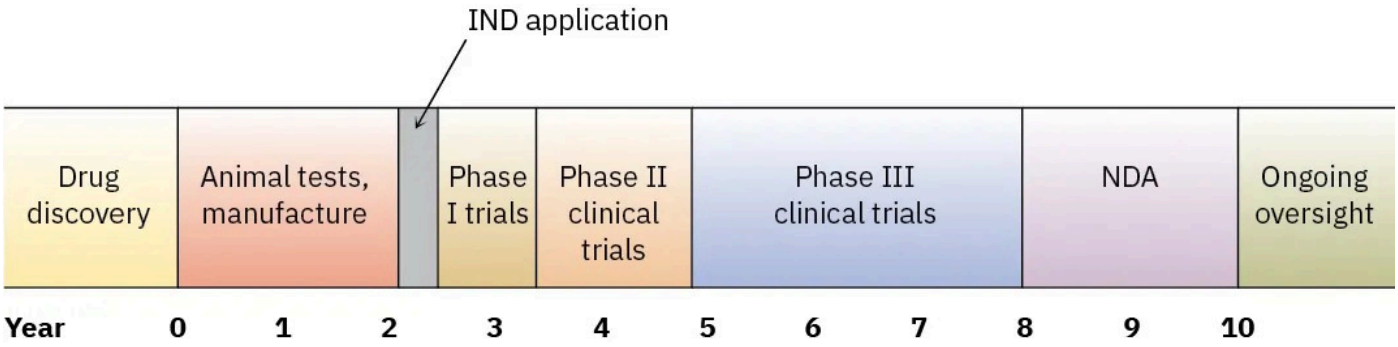


Many years of work go into screening many thousands of substances to identify a single compound that might ultimately gain approval as an NME. But after that single compound has been identified, the work has just begun because it takes an average of 9 to 10 years for a drug to make it through the approval process. First, the safety of the drug in animals must be demonstrated and an economical method of manufacture must be devised. With these preliminaries out of the way, an Investigational New Drug (IND) application is submitted to the FDA for permission to begin testing in humans.



Figure 6.12.1: Introduced in June, 2006, Gardasil is the first vaccine ever approved for the prevention of cancer. Where do new drugs like this come from? (credit: "COVIran Barekat vaccine production" by Sadegh Nikgostar/Wikimedia Commons, CC BY 4.0)

Human testing takes, or should take, 5 to 7 years and is divided into three phases. Phase I clinical trials are carried out on a small group of healthy volunteers to establish safety and look for side effects. Several months to a year are needed, and only about 70% of drugs pass at this point. Phase II clinical trials next test the drug for 1 to 2 years in several hundred patients with the target disease or condition, looking both for safety and efficacy, and only about 33% of the original group pass. Finally, phase III trials are undertaken on a large sample of patients to document definitively the drug's safety, dosage, and efficacy. If the drug is one of the 25% of the original group that make it to the end of phase III, all the data are then gathered into a New Drug Application (NDA) and sent to the FDA for review and approval, which can take another 2 years. Ten years have elapsed, and at least $500 million has been spent, with only a 20% success rate for the drugs that began testing. Finally, though, the drug will begin to appear in medicine cabinets. The following timeline shows the process.



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6.A: An Overview of Organic Reactions (Summary)

Concepts & Vocabulary

6.1: Kinds of Organic Reactions

- **Addition** reactions increase the number of sigma bonds in a molecule.
- **Elimination** reactions reduce the number of sigma bonds in a molecule.
- **Substitution** reactions incorporate the replacement of an atom or group with another.
- **Rearrangement** reactions cause a molecule to be converted to a constitutional isomer without gaining or losing any atoms.

6.2: How Organic Reactions Occur: Mechanisms

- A reaction **mechanism** describes movement of electrons by using curved arrows to show bonds that are breaking and forming.
- **Homolysis** occurs when a bond breaks with each atom keeping one electron.
- **Heterolysis** occurs when a bond breaks and both electrons remain with one of the atoms.
- Some reactions occur in more than one step with a **reactive intermediate** formed briefly on the way to the new product.
- **Reactive intermediates** can be charged species, such as carbocations and carbanions, or uncharged species, such as **radicals**.
- In organic chemistry Lewis acids are more often referred to as **electrophiles**, having an affinity for an electron pair.
- In organic chemistry Lewis bases are more often referred to as **nucleophiles**, having an electron pair that is available to bond to an **electrophile**.
- **Ionic** reactions involve charged species.
- **Polar** reactions involve bonds with unequally shared electrons.

6.3: Radical Reactions

- **Radical chain reactions** have three distinct phases: initiation, propagation and termination.
  - Initiation causes radicals to be created from non-radical species.
  - During the Propagation phase, radicals react with stable molecules to form new radicals.
  - Termination occurs when two radicals react together to form a stable molecule.

6.4: Polar Reactions

- Carbon when bonded to a halogen, oxygen, nitrogen, sulfur, or metal has a partial positive charge. This allows these carbons to react with many **nucleophiles**.
- For carbonyl groups, bond polarity is reinforced by resonance, making the carbon even more positive than in other molecules. This makes carbonyl groups prone to addition and substitution reactions with **nucleophiles**.
- **Nucleophiles** have electron-rich atoms that are able to donate a pair of electrons.
- In nucleophilic substitution reactions, the **electrophile** is typically carbon bonded to a more electronegative atom.

6.5: An Example of a Polar Reaction: Addition of HBr to Ethylene

- Alkene addition reaction with HBr occurs through the pi bond, reacting as a nucleophile and abstracting a proton from the acid. This creates a carbocation intermediate which reacts with the bromide ion to form the final product.
- Reaction rates for this alkene addition reaction increase with larger halogens and more substituted alkenes.
- Markovnikov's Rule states that addition reactions of unsymmetrical alkenes yield the more substituted product.

6.6: Using Curved Arrows in Polar Reaction Mechanisms

- Curved arrows in mechanism drawings always represent electrons moving, starting at either a bond or lone pair of electrons.
- Electrons flow from electron-rich to electron-poor.

6.7: Describing a Reaction: Equilibria, Rates, and Energy Changes

- **Exergonic reactions** have a negative free energy meaning they are thermodynamically favorable and give off energy.
- **Endergonic reactions** have a positive free energy and require energy from the surroundings to occur.

6.8: Describing a Reaction: Bond Dissociation Energies

- **Bond dissociation energy** for a molecule is the difference in enthalpy of formation (**homolytic**) for the products and reactants.
- **Bond dissociation energies** are independent of the path of reaction, so they do not give direct information on mechanisms. However, they can be used to evaluate the results of individual steps of a mechanism.
- **Bond dissociation energies** show that sigma bonds formed with sp-hybridized carbon are stronger than those formed with sp2, which are stronger than bonds formed with sp3 carbons.
- **Bond dissociation energies** show that carbon-hydrogen bonds on primary carbons are stronger than secondary, which are stronger than tertiary.

6.9: Describing a Reaction: Energy Diagrams and Transition States

- **Reaction coordinate** diagrams are a special type of energy diagram that has the reaction coordinate (or reaction progress) on the x-axis.
- **Thermodynamics** of a reaction is conveyed on a reaction coordinate diagram by the difference in energy between the reactants and products.
- **Activation energy** is the energy barrier to a reaction occurring.
- A **transition state** is the highest energy point during the process of bonds forming and breaking in a reaction step.
- **Kinetics** of a reaction is conveyed on a **reaction coordinate** diagram by the difference in energy between the reactants and transition state.
- A **rate expression** relates the rate to the **rate constant** and concentration of reactants.

6.10: Describing a Reaction: Intermediates

- A **reaction intermediate** is a short-lived species that goes on to react in a subsequent reaction step.
- **Reaction intermediates** appear as a local minimum (or valley) on a reaction coordinate diagram.
- **Catalysts** cause reaction rates to increase by lowering activation energy.

6.11: A Comparison between Biological Reactions and Laboratory Reactions

- An enzyme's **active site** is the location where the enzyme interacts with its **substrate** and where **catalysis** occurs.
- **Substrates** are reactant molecules in enzymatic reactions.

Skills to Master

- Skill 6.1 Identify organic reactions by type (addition, elimination, substitution, rearrangement).
- SKill 6.2 Draw homolytic and heterolytic bond breaking as part of reaction mechanisms.
- Skill 6.3 Identify radical and ionic reactions.
- Skill 6.4 Identify and write out steps in a typical radical substitution reaction (initiation, propagation, termination).
- Skill 6.5 Identify the polarity of bonds in organic molecules.
- Skill 6.6 Use curved arrows to indicate movement of electrons in resonance and reaction mechanisms.
- Skill 6.7 Predict whether a chemical species will act as an electrophile or nucleophile.
- Skill 6.8 Write an equilibrium expression for a reaction.
- Skill 6.9 Determine the direction of a reaction based on the equilibrium constant.
- Skill 6.10 Explain how rate and equilibrium are related to $\Delta G°$ and K_{eq}.
- Skill 6.11 Calculate bond dissociation energy given enthalpies of formation for reactants and products.
- Skill 6.12 Describe the order of bond strength based on bond dissociation energy.
- Skill 6.13 Explain activation energy, kinetics, thermodynamics, and transition states based on energy diagrams (reaction coordinate diagrams).

- Skill 6.14 Predict possible transition state structures for single reaction steps.
- Skill 6.15 Differentiate between transition states and intermediates.
- Skill 6.16 Draw a reaction coordinate diagram for a given multi-step process.
- Skill 6.17 Interpret a reaction coordinate diagram for a multi-step process.
- Skill 6.18 Briefly explain how enzymes catalyze reactions.

Memorization Tasks

MT 6.1 Memorize that arrows in reaction mechanisms always define the movement of electrons.

MT 6.2 Memorize the relative electronegativities of common atoms (necessary for determining the polarity of bonds).

MT 6.3 Memorize the equations that relate equilibrium, free energy, enthalpy, and entropy.

$\Delta G^\circ = -RT\ln K$

$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$

Contributors

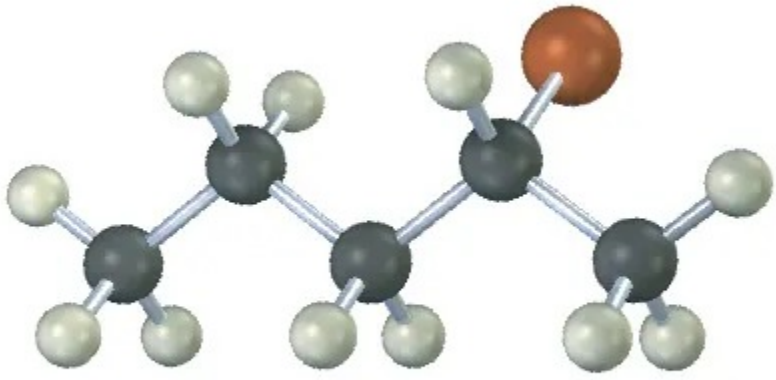
- Layne Morsch (University of Illinois Springfield)

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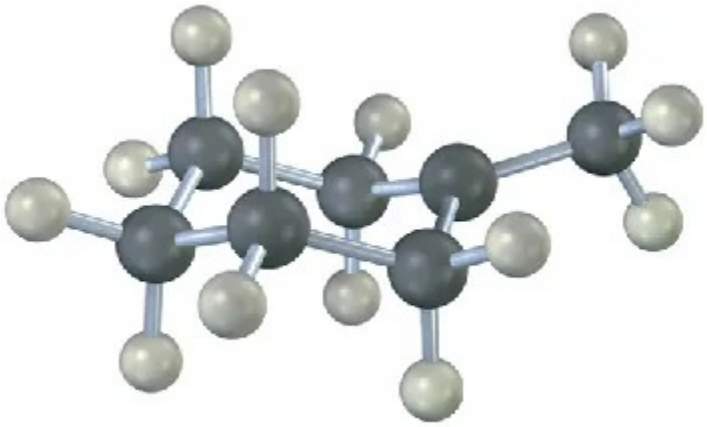
6.B: Additional Problems

Visualizing Chemistry

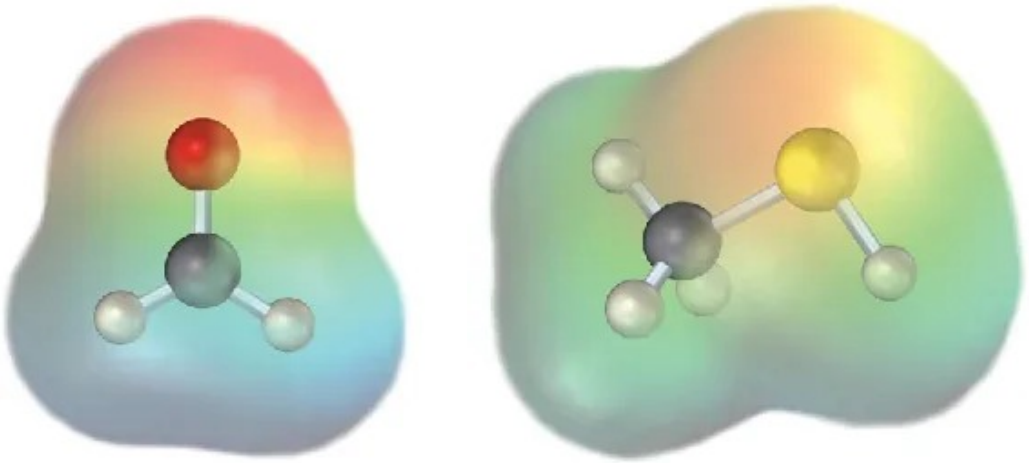
PROBLEM 6-14 The following alkyl halide can be prepared by the addition of HBr to two different alkenes. Draw the structures of both (reddish-brown = Br).



PROBLEM 6-15 The following structure represents the carbocation intermediate formed in the addition reaction of HBr to two different alkenes. Draw the structures of both.

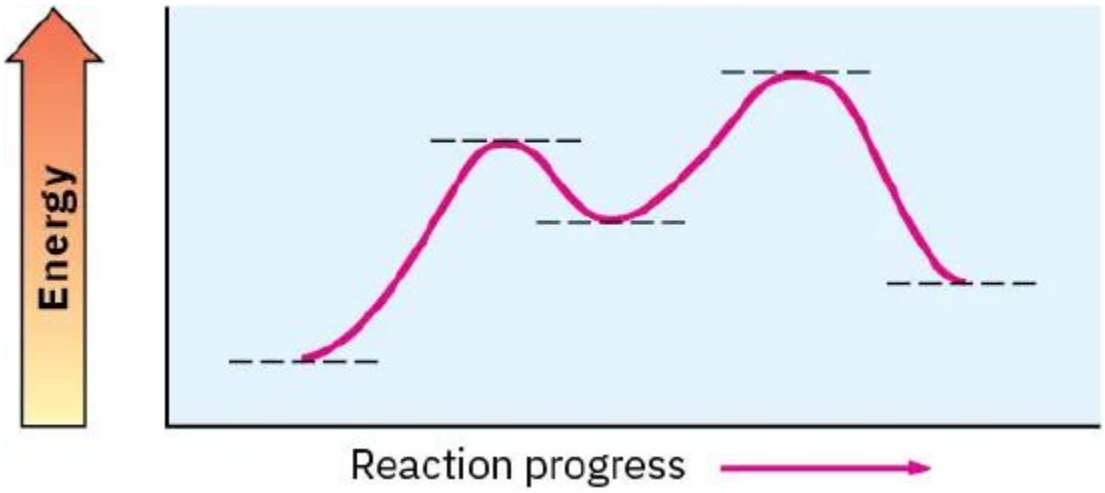


PROBLEM 6-16 Electrostatic potential maps of **(a)** formaldehyde (CH_2O) and **(b)** methanethiol (CH_3SH) are shown. Is the formaldehyde carbon atom likely to be electrophilic or nucleophilic? What about the methanethiol sulfur atom? Explain.



(a) Formaldehyde (b) Methanethiol

PROBLEM 6-17 Look at the following energy diagram:

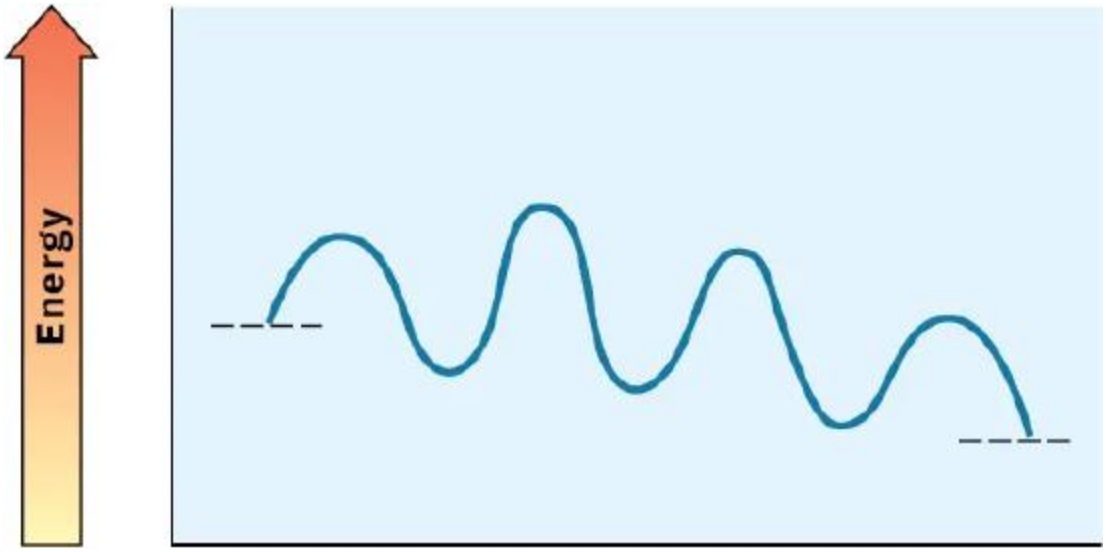


(a) Is $\Delta G°$ for the reaction positive or negative? Label it on the diagram.

(b) How many steps are involved in the reaction?

(c) How many transition states are there? Label them on the diagram.

PROBLEM 6-18 Look at the following energy diagram for an enzyme-catalyzed reaction:



(a) How many steps are involved?

(b) Which step is most exergonic?

(c) Which step is the slowest?

Energy Diagrams and Reaction Mechanisms

PROBLEM 6-19 What is the difference between a transition state and an intermediate?

PROBLEM 6-20 Draw an energy diagram for a one-step reaction with $K_{eq} < 1$. Label the parts of the diagram corresponding to reactants, products, transition state, $\Delta G°$, and $\Delta G^{‡}$. Is $\Delta G°$ positive or negative?

PROBLEM 6-21 Draw an energy diagram for a two-step reaction with $K_{eq} > 1$. Label the overall $\Delta G°$, transition states, and intermediate. Is $\Delta G°$ positive or negative?

PROBLEM 6-22 Draw an energy diagram for a two-step exergonic reaction whose second step is faster than its first step.

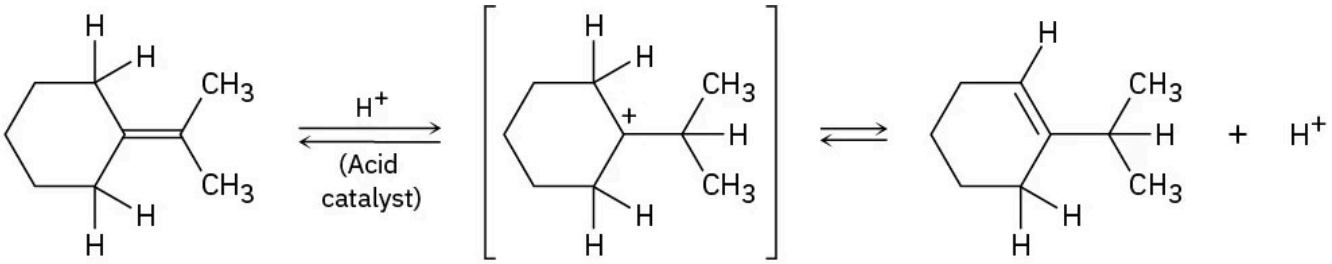
PROBLEM 6-23 Draw an energy diagram for a reaction with $K_{eq} = 1$. What is the value of $\Delta G°$ in this reaction?

PROBLEM 6-24 The addition of water to ethylene to yield ethanol has the following thermodynamic parameters:

$$H_2C{=}CH_2 \quad + \quad H_2O \quad \rightleftharpoons \quad CH_3CH_2OH \qquad \begin{cases} \Delta H° = -44\ \text{kJ/mol} \\ \Delta S° = -0.12\ \text{kJ/(K} \cdot \text{mol)} \\ K_{eq} = 24 \end{cases}$$

- (a) Is the reaction exothermic or endothermic?
- (b) Is the reaction favorable (spontaneous) or unfavorable (nonspontaneous) at room temperature (298 K)?

PROBLEM 6-25 When isopropylidenecyclohexane is treated with strong acid at room temperature, isomerization occurs by the mechanism shown below to yield 1-isopropylcyclohexene:



Isopropylidenecyclohexane **1-Isopropylcyclohexene**

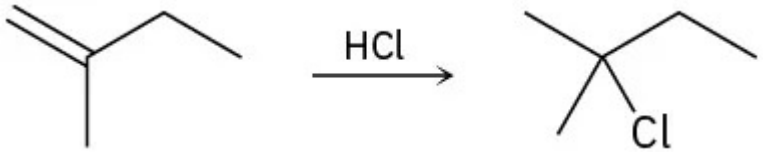
At equilibrium, the product mixture contains about 30% isopropylidenecyclohexane and about 70% 1-isopropylcyclohexene.

- (a) What is an approximate value of K_{eq} for the reaction?
- (b) Since the reaction occurs slowly at room temperature, what is its approximate $\Delta G^{\ddagger}$?
- (c) Draw an energy diagram for the reaction.

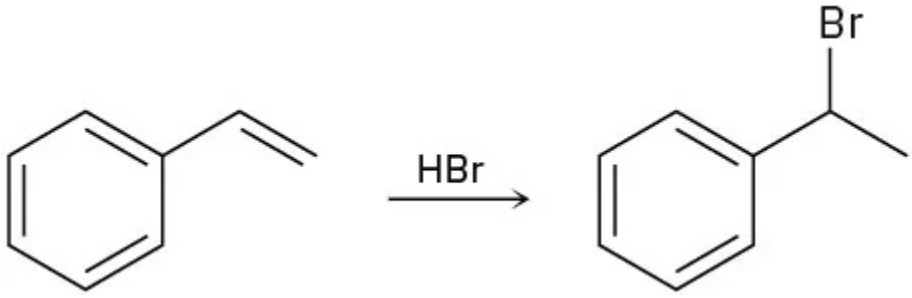
PROBLEM 6-26 Add curved arrows to the mechanism shown in Problem 6-25 to indicate the electron movement in each step.

PROBLEM 6-27 Draw the complete mechanism for each of the following polar reactions.

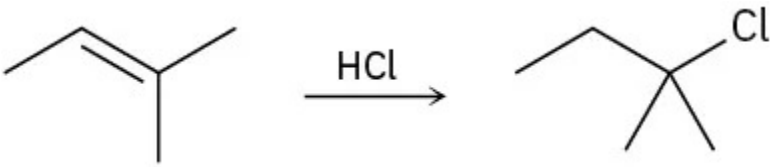
(a)



(b)

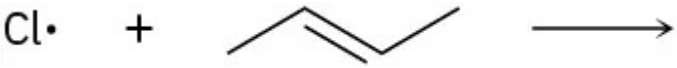


(c)

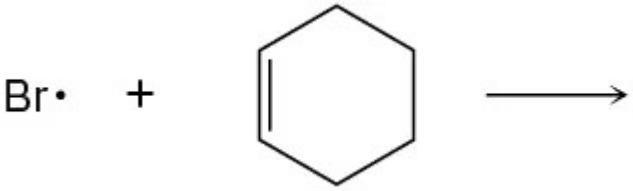


PROBLEM 6-28 Use curved arrows to show the flow of electrons, and draw the carbon radical that is formed when the halogen radicals below add to the corresponding alkenes.

(a)



(b)



(c)

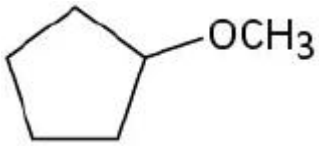


Polar Reactions

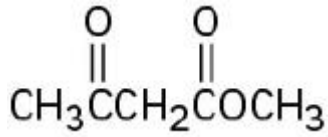
PROBLEM 6-29 Identify the functional groups in the following molecules, and show the polarity of each:

(a) $CH_3CH_2C{\equiv}N$

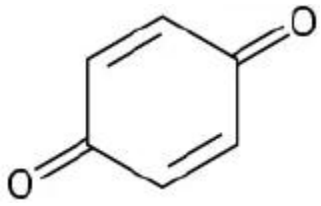
(b)



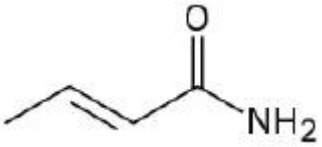
(c)



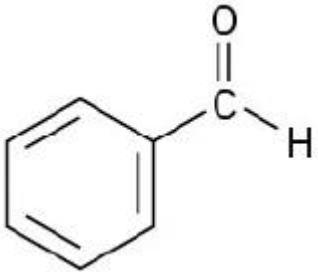
(d)



(e)



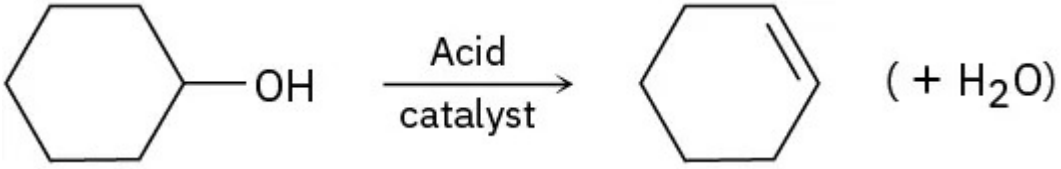
(f)



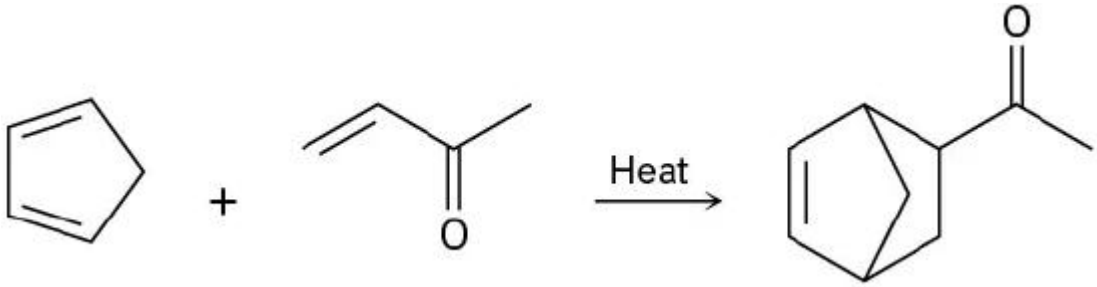
PROBLEM 6-30 Identify the following reactions as additions, eliminations, substitutions, or rearrangements:

(a) $CH_3CH_2Br + NaCN \longrightarrow CH_3CH_2CN\ (+ NaBr)$

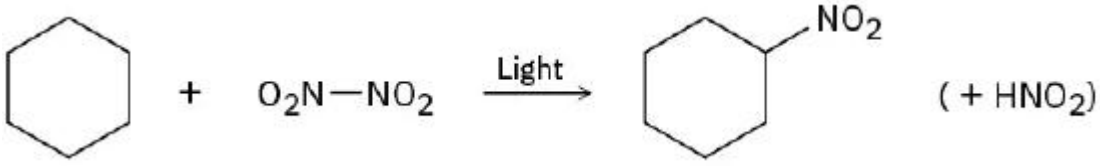
(b)



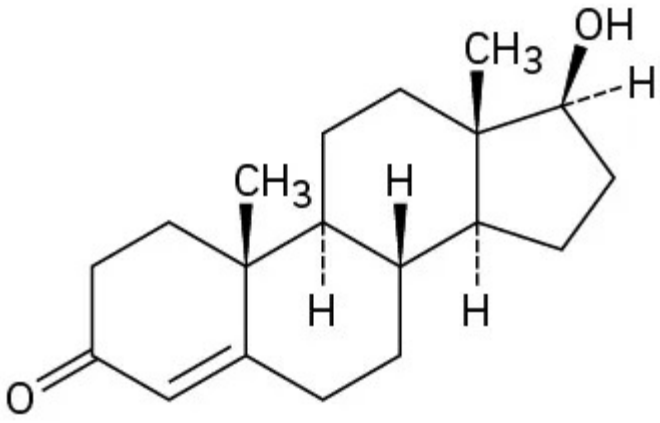
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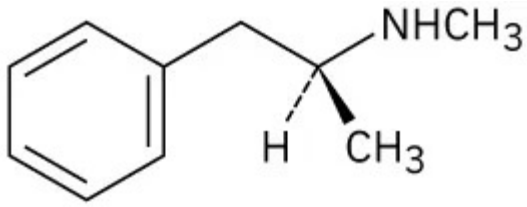
(d)



PROBLEM 6-31 Identify the likely electrophilic and nucleophilic sites in each of the following molecules:



(a) **Testosterone**



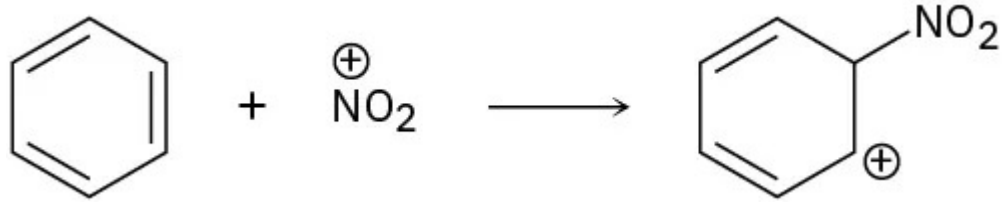
(b) **Methamphetamine**

PROBLEM 6-32 Identify the electrophile and the nucleophile.

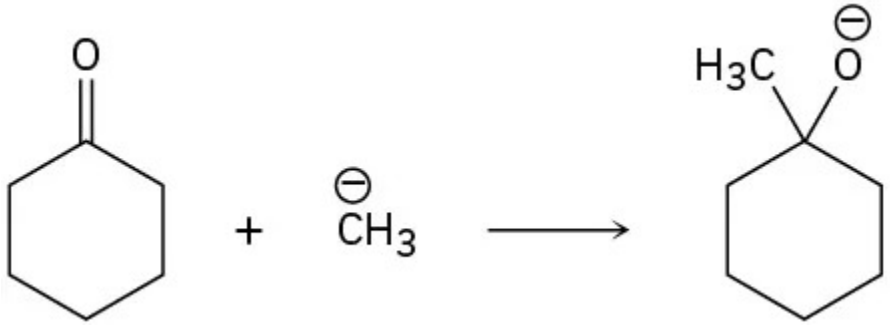
(a)



(b)

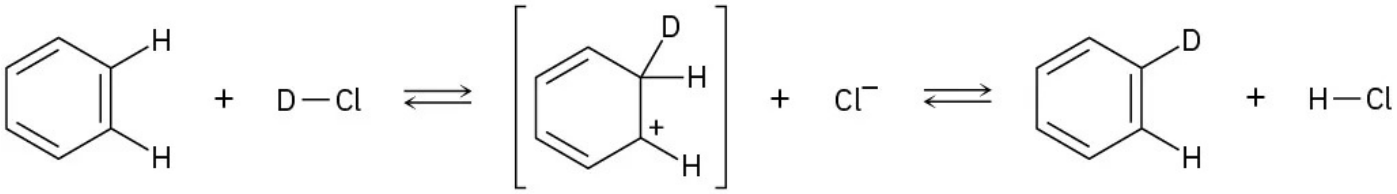


(c)

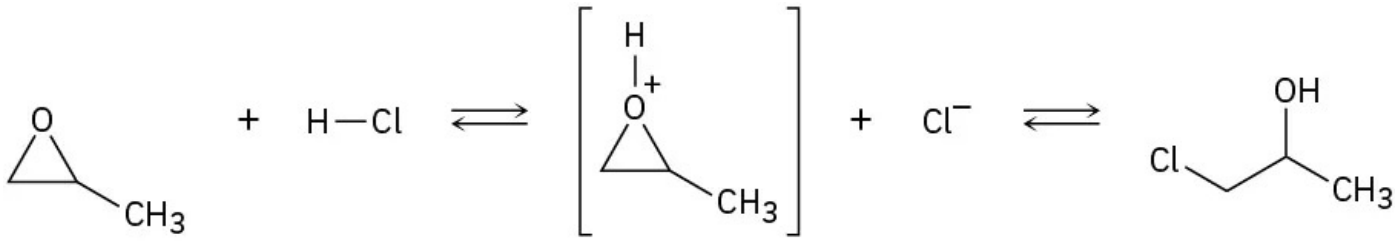


PROBLEM 6-33 Add curved arrows to the following polar reactions to indicate the flow of electrons in each:

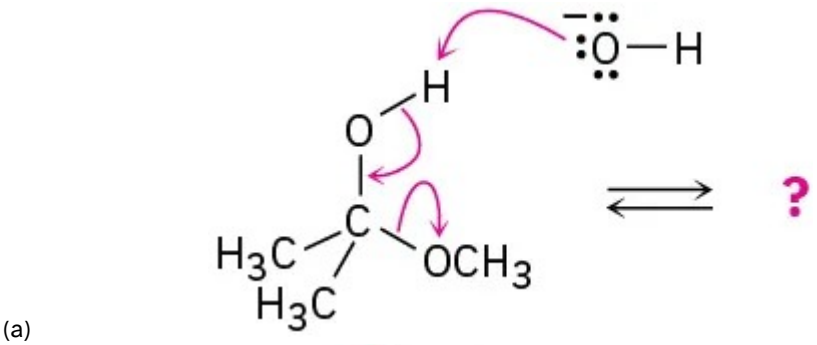
(a)



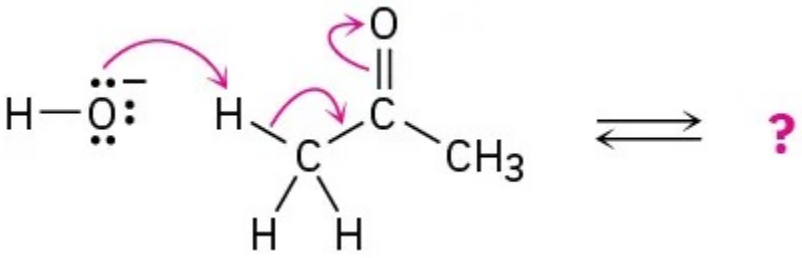
(b)



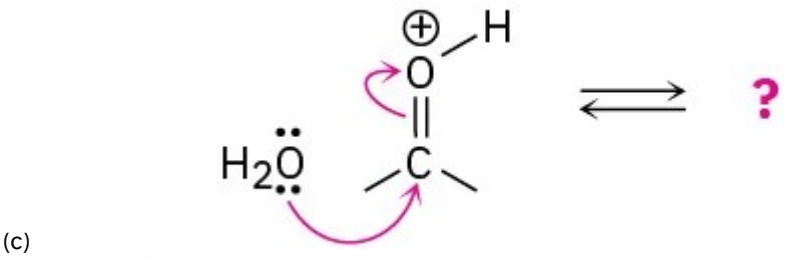
PROBLEM 6-34 Follow the flow of electrons indicated by the curved arrows in each of the following polar reactions, and predict the products that result:



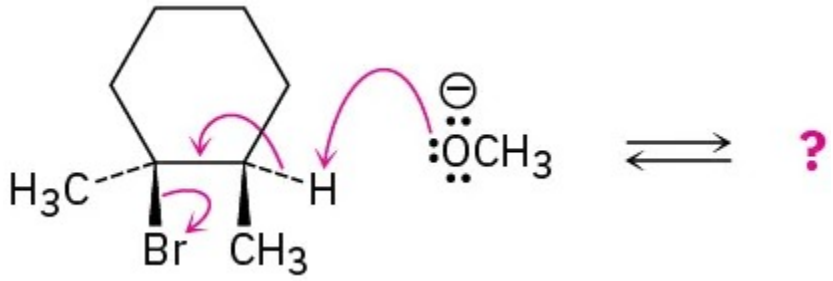
(a)



(b)



(c)



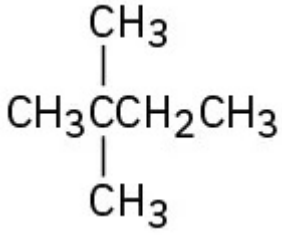
(d)

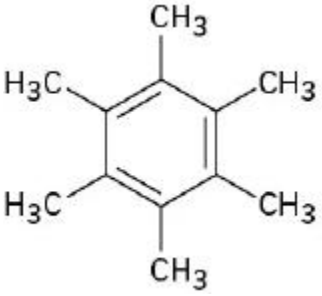
Radical Reactions

PROBLEM 6-35 Radical chlorination of pentane is a poor way to prepare 1-chloropentane, but radical chlorination of neopentane, $(CH_3)_4C$, is a good way to prepare neopentyl chloride, $(CH_3)_3CCH_2Cl$. Explain.

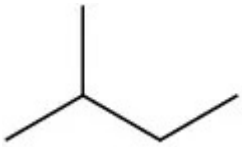
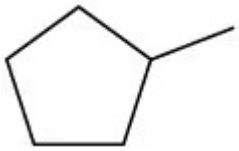
PROBLEM 6-36 Despite the limitations of radical chlorination of alkanes, the reaction is still useful for synthesizing certain

halogenated compounds. For which of the following compounds does radical chlorination give a single monochloro product?

(a) CH_3CH_3 **(b)** $CH_3CH_2CH_3$ **(c)**  **(d)**  **(e)** $CH_3C{\equiv}CCH_3$ **(f)**

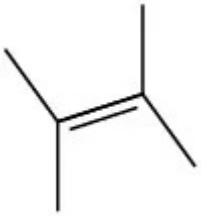


PROBLEM 6-37 Draw the different monochlorinated constitutional isomers you would obtain by the radical chlorination of the following compounds.

(a)  (b)  (c) 

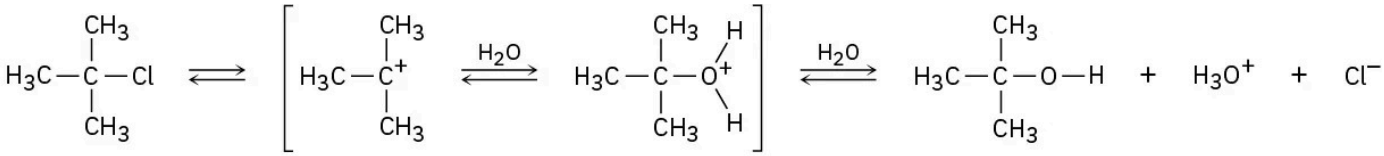
PROBLEM 6-38 Answer question 37, taking all stereoisomers into account.

PROBLEM 6-39 Show the structure of the carbocation that would result when each of the following alkenes reacts with an acid, H<sup">+.</sup">

(a)  (b)  (c) 

General Problems

PROBLEM 6-40 2-Chloro-2-methylpropane reacts with water in three steps to yield 2-methyl-2-propanol. The first step is slower than the second, which in turn is much slower than the third. The reaction takes place slowly at room temperature, and the equilibrium constant is approximately 1.



2-Chloro-2-methylpropane **2-Methyl-2-propanol**

- (a) Give approximate values for $\Delta G^{\ddagger}$ and $\Delta G°$ that are consistent with the above information.
- (b) Draw an energy diagram for the reaction, labeling all points of interest and placing relative energy levels on the diagram consistent with the information given.

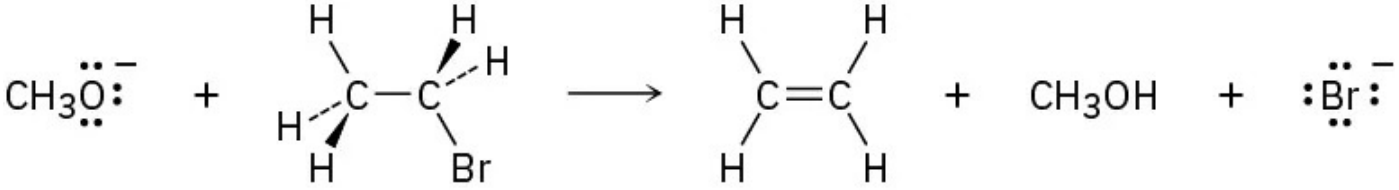
PROBLEM 6-41 Add curved arrows to the mechanism shown in Problem 6-40 to indicate the electron movement in each step.

PROBLEM 6-42 The reaction of hydroxide ion with chloromethane to yield methanol and chloride ion is an example of a general reaction type called a nucleophilic substitution reaction:

$$HO^- + CH_3Cl \rightleftarrows CH_3OH + Cl^-$$

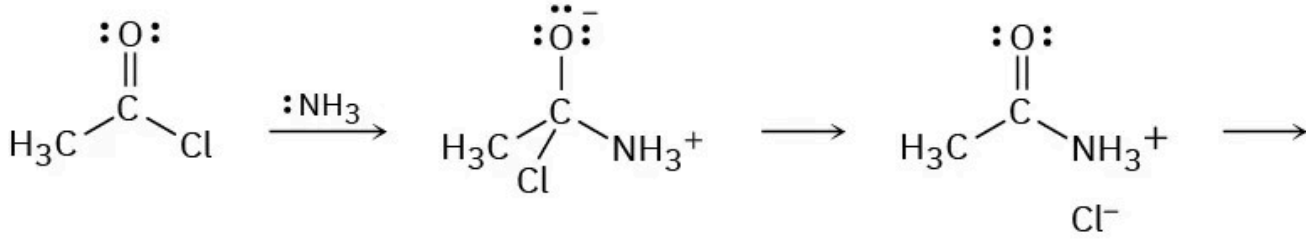
The value of $\Delta H°$ for the reaction is –75 kJ/mol, and the value of $\Delta S°$ is +54 J/(K·mol). What is the value of $\Delta G°$ (in kJ/mol) at 298 K? Is the reaction exothermic or endothermic? Is it exergonic or endergonic?

PROBLEM 6-43 Methoxide ion (CH_3O^-) reacts with bromoethane in a single step according to the following equation:

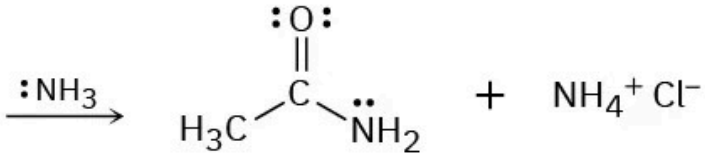


Identify the bonds broken and formed, and draw curved arrows to represent the flow of electrons during the reaction.

PROBLEM 6-44 Ammonia reacts with acetyl chloride (CH_3COCl) to give acetamide (CH_3CONH_2). Identify the bonds broken and formed in each step of the reaction, and draw curved arrows to represent the flow of electrons in each step.



Acetyl chloride



Acetamide

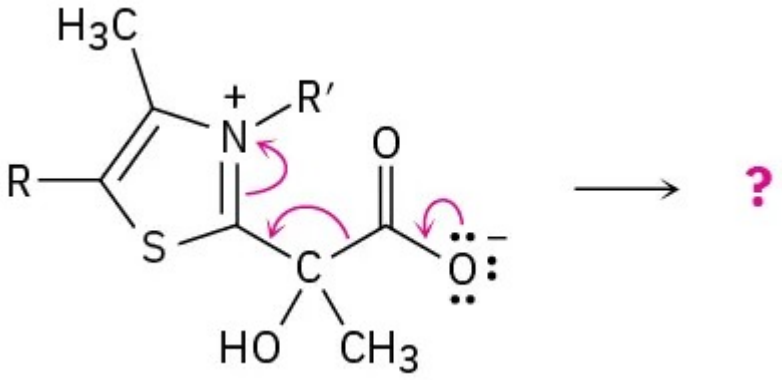
PROBLEM 6-45 The naturally occurring molecule *α*-terpineol is biosynthesized by a route that includes the following step:



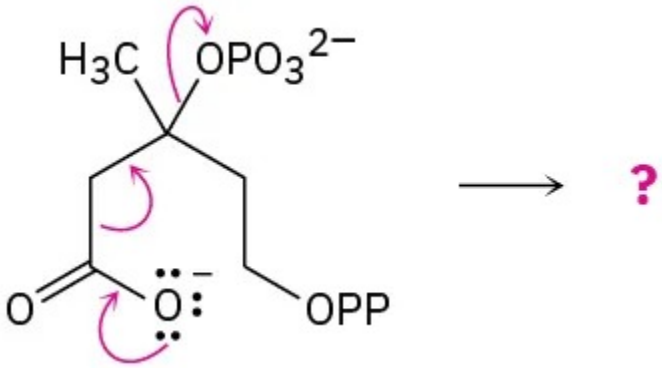
Carbocation **α-Terpineol**

- (a) Propose a likely structure for the isomeric carbocation intermediate.
- (b) Show the mechanism of each step in the biosynthetic pathway, using curved arrows to indicate electron flow.

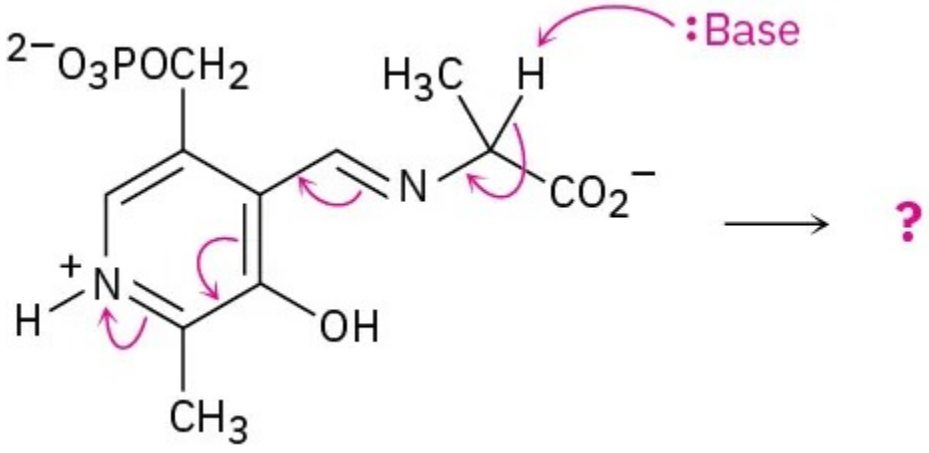
PROBLEM 6-46 Predict the product(s) of each of the following biological reactions by interpreting the flow of electrons as indicated by the curved arrows:



(a) (b)



(c)

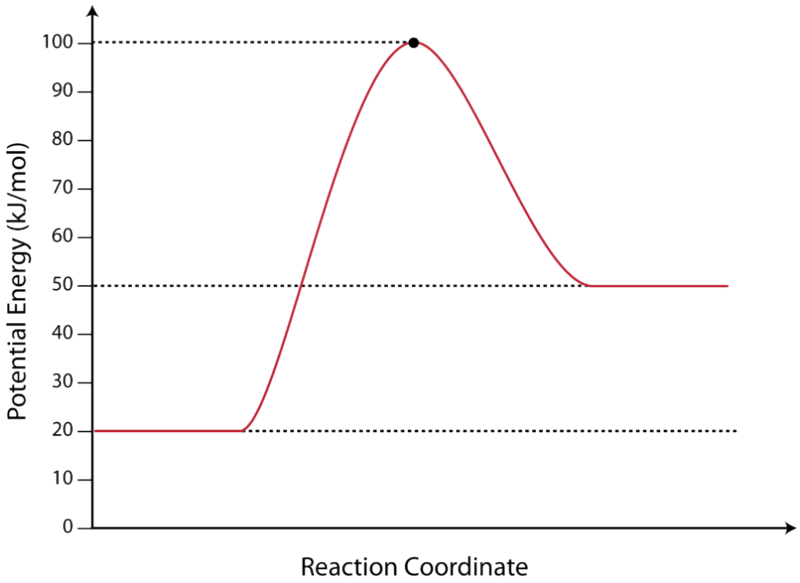


PROBLEM 6-47 Reaction of 2-methylpropene with HBr might, in principle, lead to a mixture of two alkyl bromide addition products. Name them, and draw their structures.

PROBLEM 6-48 Draw the structures of the two carbocation intermediates that might form during the reaction of 2-methylpropene with HBr (Problem 47). We'll see in the next chapter that the stability of carbocations depends on the number of alkyl substituents attached to the positively charged carbon—the more alkyl substituents there are, the more stable the cation. Which of the two carbocation intermediates you drew is more stable?

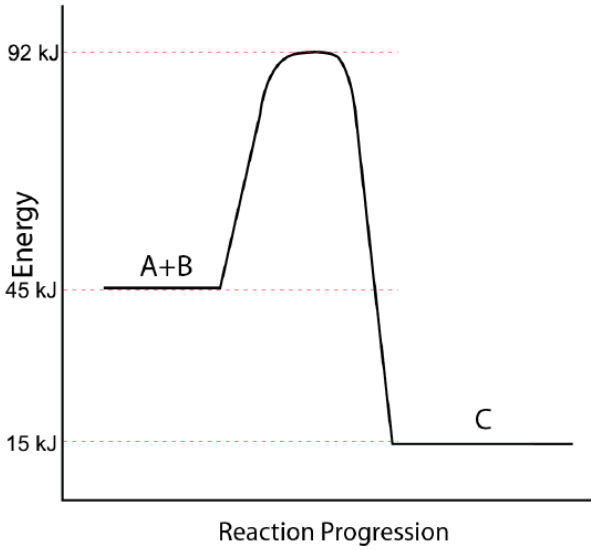
Additional Problems

PROBLEM 6-49 Use the potential energy diagram below to answer the following questions.



a. What is the potential energy of the reactants?
b. What is the potential energy of the products?
c. What is the heat of reaction ($\Delta H = E_{products} - E_{reactants}$)?
d. What is the potential energy of the activated complex?
e. What is the activation energy for the reaction?
f. Is the reaction endothermic or exothermic?
g. Which of the values in a-e above would be changed by the use of a catalyst in the reaction?
h. What is the activation energy of the reverse reaction?
i. What is the heat of reaction ($\Delta H = E_{products} - E_{reactants}$) of the reverse reaction?

PROBLEM 6-50 Use the potential energy diagram below to answer the following questions.



a. What is the potential energy of the reactants?
b. What is the potential energy of the products?
c. What is the heat of reaction ($\Delta H = E_{products} - E_{reactants}$)?
d. What is the potential energy of the activated complex?
e. What is the activation energy for the reaction?
f. Is the reaction endothermic or exothermic?
g. Which of the values in a-e above would be changed by the use of a catalyst in the reaction?
h. What is the activation energy of the reverse reaction?
i. What is the heat of reaction ($\Delta H = E_{products} - E_{reactants}$) of the reverse reaction?

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7: ALKENES- STRUCTURE AND REACTIVITY

Learning Objectives

After you have completed Chapter 7, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. describe the importance of alkenes to the chemical industry.
3. use the concept of “degree of unsaturation” in determining chemical structures.
4. describe the electronic structure and geometry of alkenes.
5. describe the factors that influence alkene stability, and determine the relative stability of a number of given alkenes.
6. write the IUPAC name of a given alkene, and draw the structure of any alkene, given its IUPAC name.
7. determine whether a given alkene has an *E* configuration or a *Z* configuration.
8. explain why alkenes are more reactive than alkanes.
9. describe the reaction between an alkene and a hydrogen halide, and explain why one product is formed rather than another. Base your explanation on the concepts of carbocation stability and the Hammond postulate.
10. define, and use in context, the key terms introduced in this chapter.

This, the first of two chapters devoted to the chemistry of alkenes, describes how certain alkenes occur naturally, then shows the industrial importance of ethylene and propylene (the simplest members of the alkene family). The electronic structure of alkenes is reviewed, and their nomenclature discussed in detail. After dealing with the question of cis-trans isomerism in alkenes, Chapter 7 introduces the reactivity of the carbon-carbon double bond. The chapter then focuses on one specific reaction—the addition of hydrogen halides to alkenes—to raise a number of important concepts, including carbocation stability and the Hammond postulate.

7.0: Why This Chapter?

7.1: Industrial Preparation and Use of Alkenes

7.2: Calculating Degree of Unsaturation

7.3: Cis-Trans Isomerism in Alkenes

7.4: Alkene Stereochemistry and the E,Z Designation

7.5: Stability of Alkenes

7.6: Electrophilic Addition Reactions of Alkenes

7.7: Orientation of Electrophilic Additions - Markovnikov's Rule

7.8: Carbocation Structure and Stability

7.9: The Hammond Postulate

7.10: Evidence for the Mechanism of Electrophilic Additions - Carbocation Rearrangements

7.11: Chemistry Matters—Bioprospecting- Hunting for Natural Products

7.A: Alkenes - Structure and Reactivity (Summary)

7.B: Additional Problems

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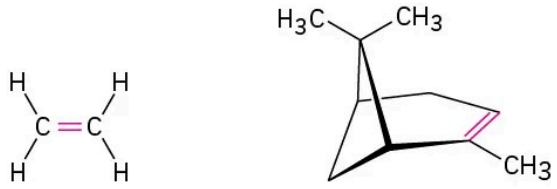
7.0: Why This Chapter?

Carbon–carbon double bonds are present in most organic and biological molecules, so a good understanding of their behavior is needed. In this chapter, we'll look at some consequences of alkene stereoisomerism and then focus on the broadest and most general class of alkene reactions, the electrophilic addition reaction. Carbon-carbon triple bonds, by contrast, occur much less commonly, so we'll not spend much time on their chemistry.



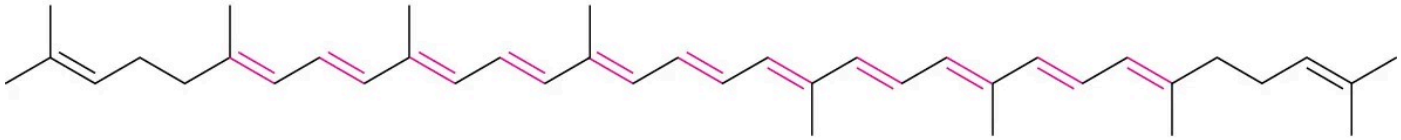
Figure 7.0.1: Tomatoes are good for you. Their red color is due to lycopene, which has 13 double bonds. (credit: "Tomatoes" by Jeremy Keith/ Flickr, CC BY 2.0)

An alkene, sometimes called an *olefin* from the German term for oil forming, is a hydrocarbon that contains a carbon–carbon double bond, while an **alkyne** is a hydrocarbon that contains a carbon-carbon triple bond. Alkenes occur abundantly in nature. Ethylene, for instance, is a plant hormone that induces ripening in fruit, and α-pinene is the major component of turpentine. Lycopene, found in fruits such as watermelon and papaya as well as tomatoes, is an antioxidant with numerous health benefits such as sun protection and cardiovascular protection.



Ethylene

α-Pinene



Lycopene, a conjugated polyene

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7.1: Industrial Preparation and Use of Alkenes

Ethylene and propylene, the simplest alkenes, are the two most important organic chemicals produced industrially. Approximately 220 million tons of ethylene and 138 million tons of propylene are produced worldwide each year for use in the synthesis of polyethylene, polypropylene, ethylene glycol, acetic acid, acetaldehyde, and a host of other substances (Figure 7.1.1).

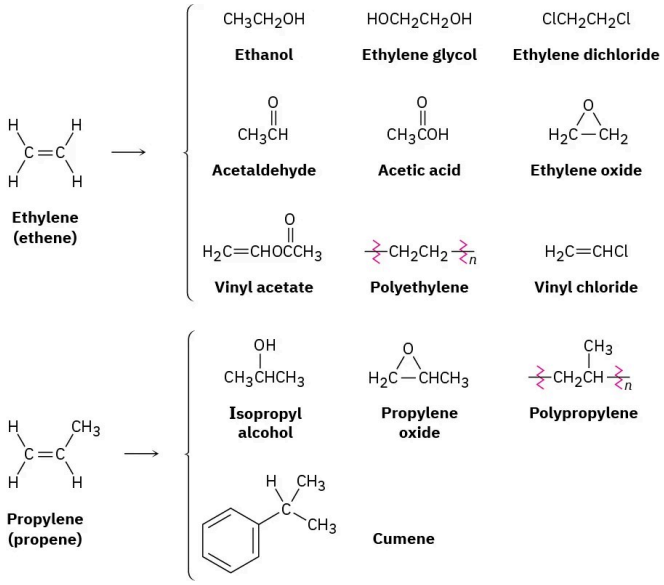
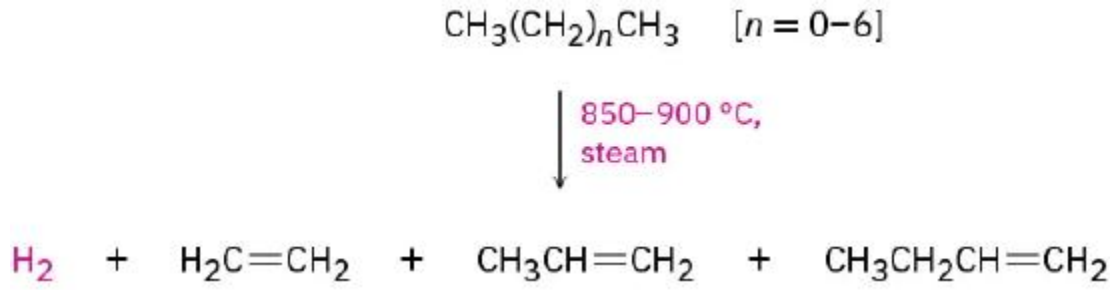
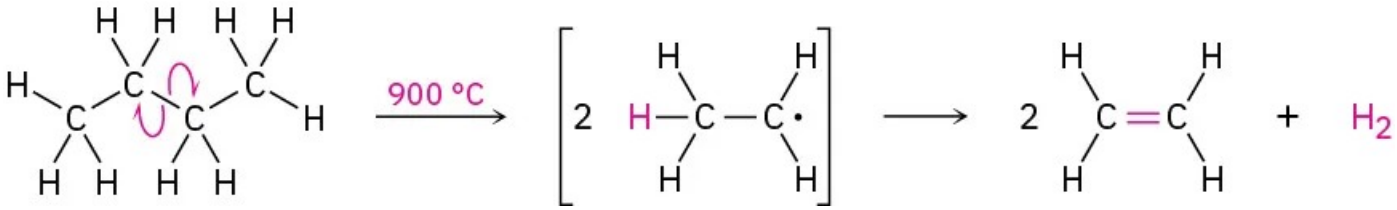


Figure 7.1.1: Compounds derived industrially from ethylene and propylene.

Ethylene, propylene, and butene are synthesized from (C_2–C_8) alkanes by a process called *steam cracking* at temperatures up to 900 °C.



The cracking process is complex, although it undoubtedly involves radical reactions. The high-temperature reaction conditions cause spontaneous breaking of C–C and C–H bonds, with the resultant formation of smaller fragments. We might imagine, for instance, that a molecule of butane splits into two ethyl radicals, each of which then loses a hydrogen atom to generate two molecules of ethylene.



Steam cracking is an example of a reaction whose energetics are dominated by entropy ($\Delta S°$) rather than by enthalpy ($\Delta H°$) in the free-energy equation $\Delta G° = \Delta H° - T\Delta S°$ discussed in Section 6.7. Although the bond dissociation energy D for a carbon–carbon single bond is relatively high (about 370 kJ/mol) and cracking is endothermic, the large positive entropy change resulting from

the fragmentation of one large molecule into several smaller pieces, together with the high temperature, makes the $T\Delta S°$ term larger than the $\Delta H°$ term, thereby favoring the cracking reaction.

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7.2: Calculating Degree of Unsaturation

Learning Objectives

After completing this section, you should be able to

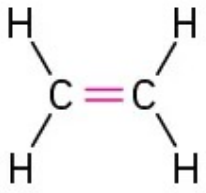
- determine the degree of unsaturation of an organic compound, given its molecular formula, and hence determine the number of double bonds, triple bonds, and rings present in the compound.
- draw all the possible isomers corresponding to a given molecular formula containing only carbon (up to a maximum of six atoms) and hydrogen.
- draw a specified number of isomers corresponding to a given molecular formula containing carbon, hydrogen, and possibly other elements, such as oxygen, nitrogen and the halogens.

Saturated and Unsaturated Molecules

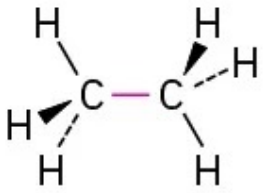
A C-H molecule only containing single bonds with no rings is considered saturated, as no additional atoms can be added without removing any.

$CH_3CH_2CH_3$	chewiki_sat.bmp	chewiki_sat2 (3).bmp	1-methyoxypentane

Unlike saturated molecules, unsaturated molecules contain double bond(s), triple bond(s) and/or ring(s). Because its double bond, an alkene has fewer hydrogens than an alkane with the same number of carbons—C_nH_{2n} for an alkene versus C_nH_{2n+2} for an alkane—and is therefore referred to as unsaturated. Ethylene, for example, has the formula C_2H_4, whereas ethane has the formula C_2H_6.



Ethylene: C_2H_4
(Fewer hydrogens—*Unsaturated*)



Ethane: C_2H_6
(More hydrogens—*Saturated*)

Calculating The Degree of Unsaturation (DoU) or Index of Hydrogen Deficiency (IHD)

For organic compounds containing only C and H atoms

- 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.
- if H = 2C + 2 the molecule is considered saturated, DoU is equal to 0.

Combining these mathematical concepts, the degree of unsaturation can be defined in the following equation:

$$DoU = [2C + 2 - H] / 2$$

C represents the total amount of carbons, and H represents the total amount of hydrogens.

Worked Example 7.2.1

Example: Calculate the degree of unsaturation in $CH_3CH_2CH_3$, the molecular formula is C_3H_8

Solution

Applying the simplified equation: DoU = [2C + 2 – H] / 2

$$DoU = (2*3 + 2 - 8) / 2$$

$$DoU = 0$$

DoU = 0 means that no unsaturation is observed in this molecule.

In general, each ring or double bond in a molecule corresponds to a loss of two hydrogens from the alkane formula C_nH_{2n+2}. Knowing this relationship, it's possible to work backward from a molecular formula to calculate a molecule's degree of unsaturation—the number of rings and/or multiple bonds present in the molecule.

As an example, for the molecular formula C_3H_4. The number of actual hydrogens needed for a compound with 3 carbon atoms to be saturated is 8. Calculated as 2C + 2 = (2*3) + 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 half the number of hydrogens the molecule needs to be classified as saturated (4 /2). Hence, the DoU is 2.

Worked Example 7.2.2

Now let's assume that we want to find the structure of an unknown hydrocarbon. A molecular weight determination yields a value of 82 amu, which corresponds to a molecular formula of C_6H_{10}.

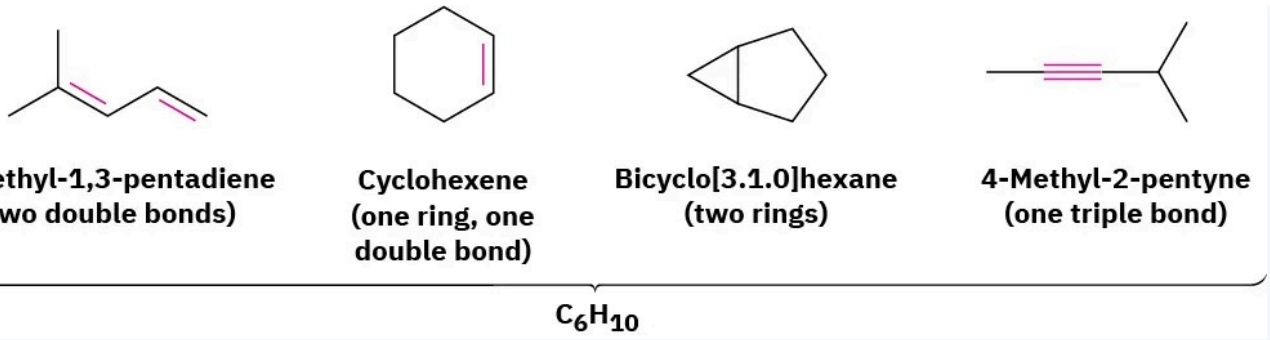
Solution

Since the saturated C_6 alkane (hexane) has the formula C_6H_{14}, the unknown compound has two fewer pairs of hydrogens ($H_{14} - H_{10} = H_4 = 2\ H_2$) so its degree of unsaturation is 2. The unknown therefore contains either two double bonds, one ring and one double bond, two rings, or one triple bond. There's still a long way to go to establish its structure, but the simple calculation has told us a lot about the molecule.

$$DoU = [2C + 2 - H] / 2$$

$$DoU = (2*6 + 2 - 10) / 2$$

$$DoU= 4 / 2 = 2$$



Similar calculations can be carried out for compounds containing elements other than just carbon and hydrogen.

For Organic Compounds Containing Oxygen

- **Organooxygen compounds (C, H, O)**
  - Oxygen forms two bonds. When an oxygen atom is inserted into an alkane bond: C–C becomes C–O–C or C–H becomes C–O–H, and there is no change in the number of hydrogen atoms, so it doesn't affect the formula of an equivalent hydrocarbon and can be ignored when calculating the degree of unsaturation.

Worked Example 7.2.3

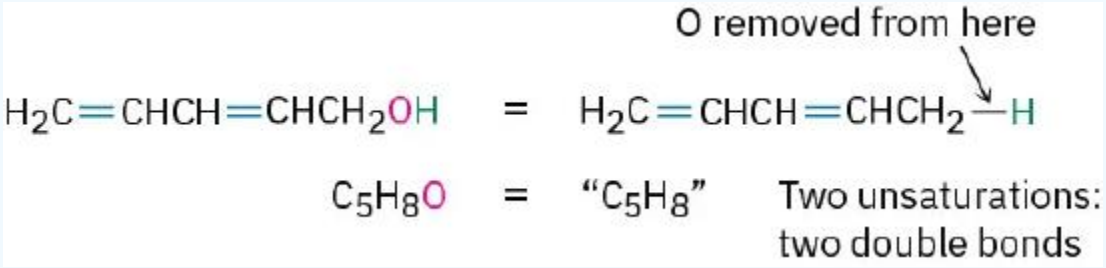
Calculate the degree of unsaturation for the formula C_5H_8O.

Solution

C_5H_8O is equivalent to the hydrocarbon formula C_5H_8 and thus corresponds to two degrees of unsaturation. Using the equation: DoU = [2C + 2 – H] / 2

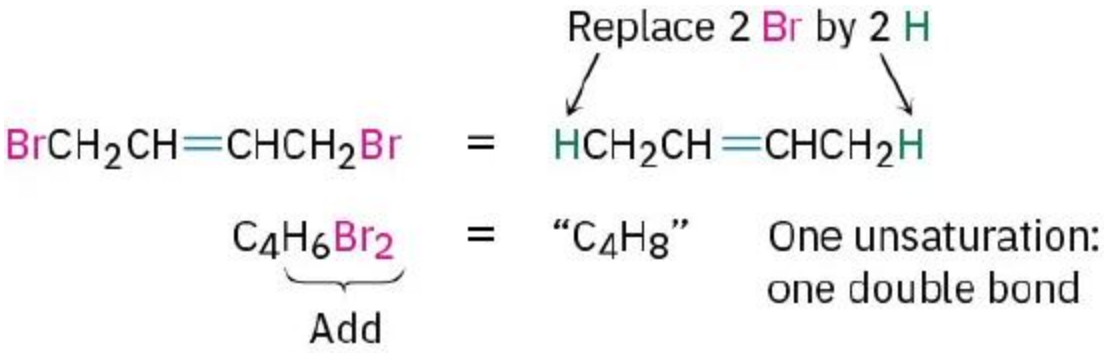
$$DoU = (2*5 + 2 - 8) / 2$$

$$DoU = 4 / 2 = 2$$



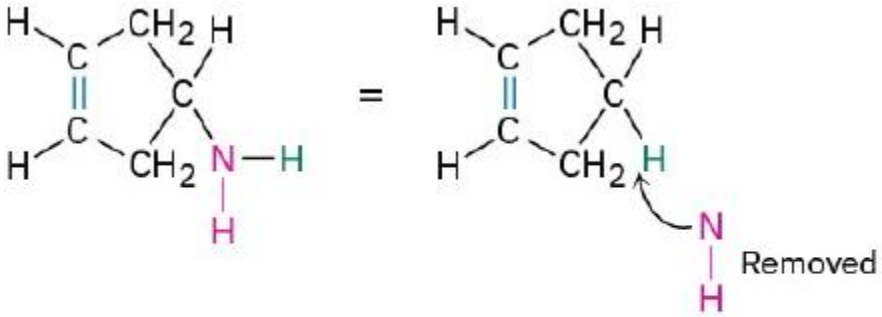
For Organic Compounds Containing Halogens

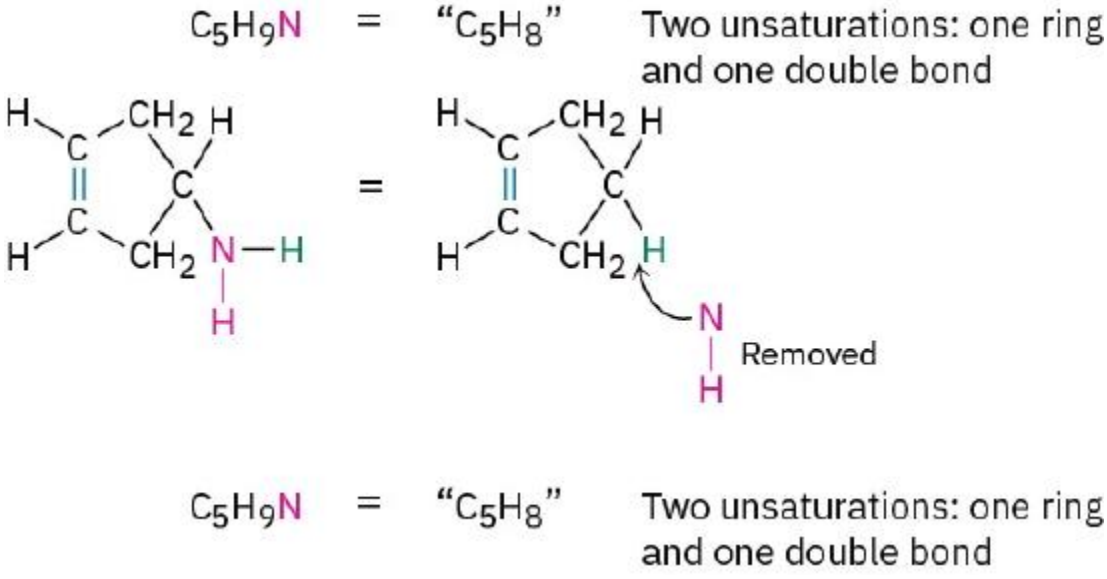
- **Organohalogen compounds (C, H, X, where X = F, Cl, Br, or I)**
  - A halogen substituent acts as a replacement for hydrogen in an organic molecule, so we can add the number of halogens and hydrogens to arrive at an equivalent hydrocarbon formula from which the degree of unsaturation can be found.
  - For example, the formula $C_4H_6Br_2$ is equivalent to the hydrocarbon formula C_4H_8 and thus corresponds to one degree of unsaturation.



For Organic Compounds Containing Nitrogens

- **Organonitrogen compounds (C, H, N)**
  - Nitrogen forms three bonds, so an organonitrogen compound has one more hydrogen than a related hydrocarbon. We therefore subtract the number of nitrogens from the number of hydrogens to arrive at the equivalent hydrocarbon formula. Again, you can convince yourself of this by seeing what happens when a nitrogen atom is inserted into an alkane bond: C–C becomes C–NH–C or C–H becomes C–NH_2, meaning that one additional hydrogen atom has been added. We must, therefore, subtract one from the number of hydrogen atoms per each nitrogen present in the molecule to arrive at the equivalent hydrocarbon formula.
  - For example, the formula C_5H_9N is equivalent to C_5H_8 and thus has two degrees of unsaturation.





As a Summary

- **Ignore** the number of oxygens.
- **Add** the number of halogens to the number of hydrogens.
- **Subtract** the number of nitrogens from the number of hydrogens.

Combined Equation: **DoU = [2C + 2 – (H + X - N)] / 2**

- 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

Exercise 7.2.1

Calculate the degree of unsaturation in each of the following formulas, and then draw as many structures as you can for each:

a. C_4H_8 **b.** C_4H_6 **c.** C_3H_4

Answer available at the end of this section.

Exercise 7.2.2

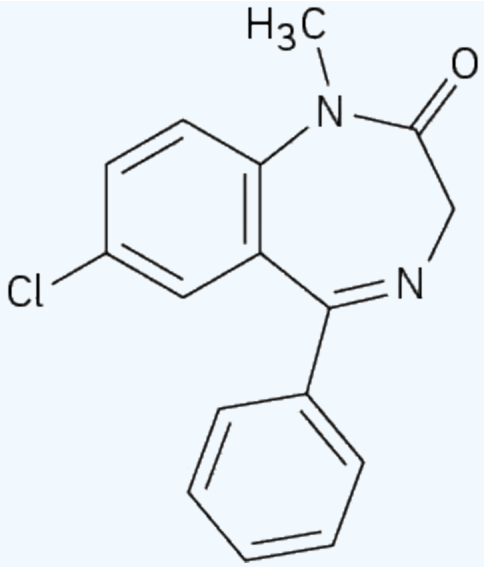
Calculate the degree of unsaturation in each of the following formulas:

a. C_6H_5N **b.** $C_6H_5NO_2$ **c.** $C_8H_9Cl_3$ **d.** $C_9H_{16}Br_2$ **e.** $C_{10}H_{12}N_2O_3$ **f.** $C_{20}H_{32}ClN$

Answer available at the end of this section.

Exercise 7.2.3

Diazepam, marketed as an antianxiety medication under the name Valium, has three rings, eight double bonds, and the formula $C_{16}H_?ClN_2O$. How many hydrogens does diazepam have? (Calculate the answer; don't count hydrogens in the structure.)

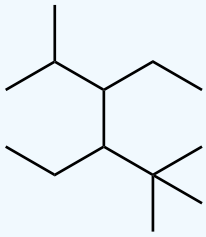


Diazepam

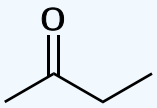
Answer available at the end of this section.

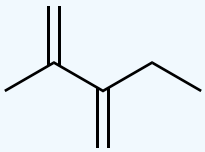
Exercise 7.2.4

How many degrees of unsaturation do the following compounds have?

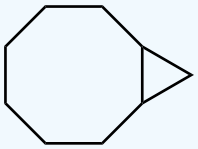
a) 

b) $CH_3CH_2CH{=}CHCF_3$

c) 

d) 

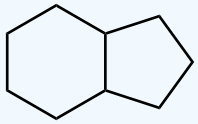
e) 3-chloro-5-octyne

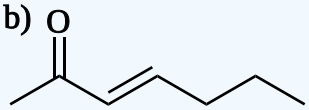
f) 

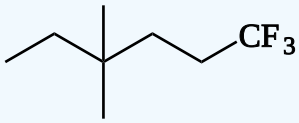
Answer available at the end of this section.

Exercise 7.2.5

Determine whether the following molecules are saturated or unsaturated.
Then, determine the degrees of unsaturation for each of the following compounds.

a) 

b) 

c) 

d) $C_{10}H_6N_4$

e) $C_5H_{10}O$

f) $C_6H_{12}F_2$

Answer available at the end of this section.

Exercise 7.2.6

Calculate the degrees of unsaturation for the following molecular formulas:

a) C_9H_{20} b) C_7H_8 c) C_5H_7Cl d) $C_9H_9NO_4$

Answer available at the end of this section.

Answers

Exercise 7.2.1

a. 1 b. 2 c. 2

Exercise 7.2.2

a) 5 b) 5 c) 3 d) 1 e) 6 F) 5

Exercise 7.2.3

$C_{16}H_{13}ClN_2O$

Exercise 7.2.4

a) 0 b) 1 c) 1 d) 2 e) 2 F) 2

Exercise 7.2.5

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 c) 0 d) 10 e) 1 F) 0

Exercise 7.2.6

a) 0 b) 4 c) 2 d) 6

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7.3: Cis-Trans Isomerism in Alkenes

We saw in the chapter on Structure and Bonding that the carbon–carbon double bond can be described in two ways. In valence bond language (Section 1.9), the carbons are sp^2-hybridized and have three equivalent hybrid orbitals that lie in a plane at angles of 120° to one another. The carbons form a σ bond by a head-on overlap of sp^2 orbitals and form a π bond by sideways overlap of unhybridized p orbitals oriented perpendicular to the sp^2 plane.

In molecular orbital language (Section 1.12), interaction between the p orbitals leads to one bonding and one antibonding π molecular orbital. The π bonding MO has no node between nuclei and results from a combination of p orbital lobes with the same algebraic sign. The π antibonding MO has a node between nuclei and results from a combination of lobes with different algebraic signs.

Although essentially free rotation around single bonds is possible (Section 4.2), the same is not true of double bonds. For rotation to occur around a double bond, the π bond must break and re-form (Figure 7.3.1). Thus, the barrier to double-bond rotation must be at least as great as the strength of the π bond itself, an estimated 350 kJ/mol (84 kcal/mol). Recall that the barrier to bond rotation in ethane is only 12 kJ/mol.

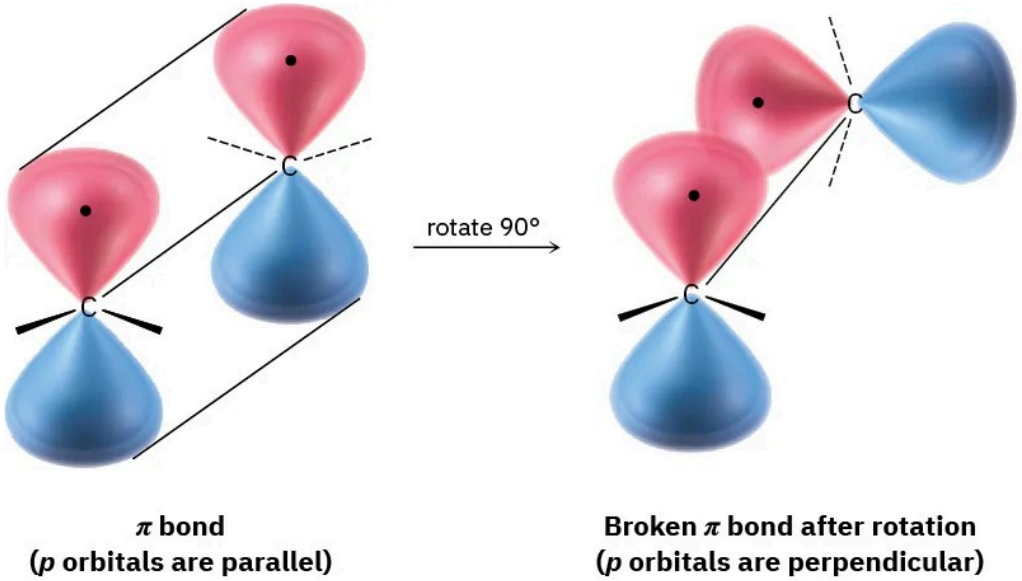
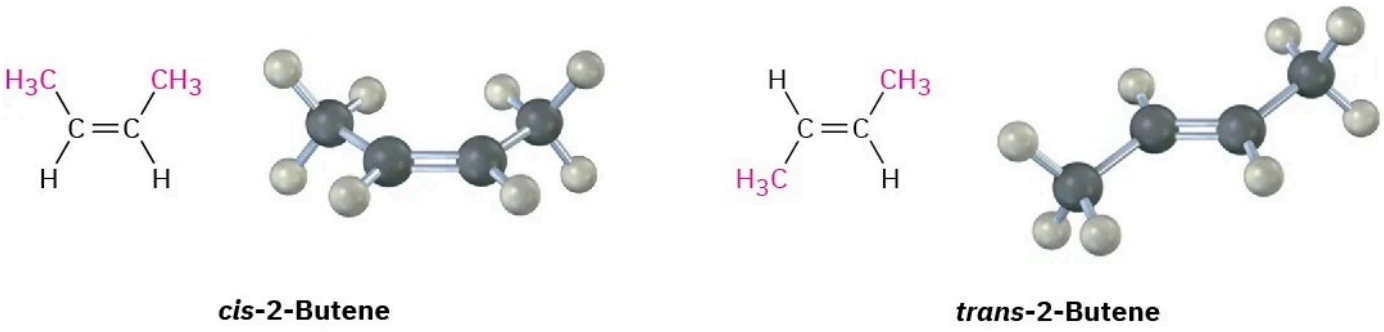


Figure 7.3.1: The π bond must break for rotation to take place around a carbon–carbon double bond.

The lack of rotation around carbon–carbon double bonds is of more than just theoretical interest; it also has chemical consequences. Imagine the situation for a disubstituted alkene such as 2-butene. (Disubstituted means that two substituents other than hydrogen are bonded to the double-bond carbons.) The two methyl groups in 2-butene can either be on the same side of the double bond or on opposite sides, a situation similar to that in disubstituted cycloalkanes (Section 4.3).

Since bond rotation can't occur, the two 2-butenes can't spontaneously interconvert; they are different, isolable compounds. As with disubstituted cycloalkanes, we call such compounds cis–trans stereoisomers. The compound with substituents on the same side of the double bond is called *cis*-2-butene, and the isomer with substituents on opposite sides is *trans*-2-butene (Figure 7.3.2).



***cis*-2-Butene** ***trans*-2-Butene**

Figure 7.3.2: Cis and trans isomers of 2-butene. The cis isomer has the two methyl groups on the same side of the double bond, and the trans isomer has methyl groups on opposite sides.

Cis–trans isomerism is not limited to disubstituted alkenes. It can occur whenever both double-bond carbons are attached to two different groups. If one of the double-bond carbons is attached to two identical groups, however, cis–trans isomerism is not possible (Figure 7.3.3).

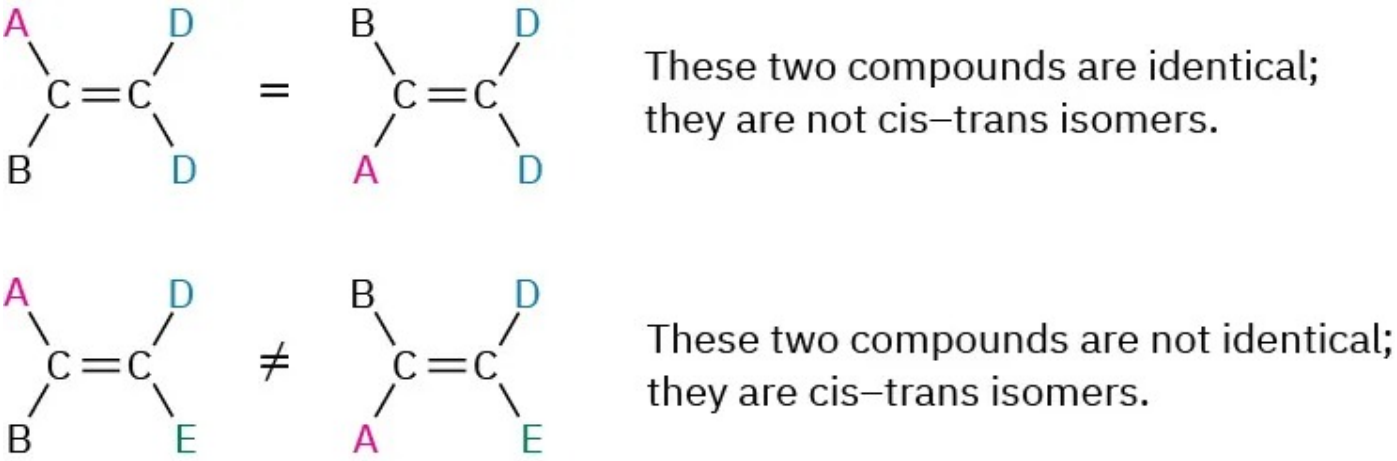
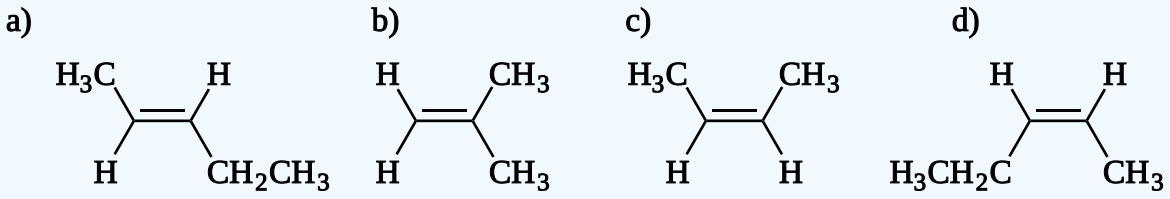


Figure 7.3.3: The requirement for cis–trans isomerism in alkenes. Compounds that have one of their carbons bonded to two identical groups can't exist as cis–trans isomers. Only when both carbons are bonded to two different groups is cis–trans isomerism possible.

Exercises

Exercise 7.3.1

Classify each compound as a *cis* isomer, a *trans* isomer, or neither.



Answer available at the end of this section.

Exercise 7.3.2

The sex attractant of the common housefly is an alkene named *cis*-9-tricosene. Draw its structure. (Tricosane is the straight-chain alkane $C_{23}H_{48}$.)

Answer available at the end of this section.

Exercise 7.3.3

Which of the following compounds can exist as pairs of cis–trans isomers? Draw each pair, and indicate the geometry of each isomer.

a) $CH_3CH{=}CH_2$ **b)** $(CH_3)_2C{=}CHCH_3$ **c)** $CH_3CH_2CH{=}CHCH_3$

d) $(CH_3)_2C{=}C(CH_3)CH_2CH_3$ **e)** $ClCH{=}CHCl$ **f)** $BrCH{=}CH$

Answer available at the end of this section.

Exercise 7.3.4

Which of the following compounds can exist as pairs of cis–trans isomers? Draw each pair, and indicate the geometry of each isomer.

a) 3-hexene. **b)** 1-hexene

c) 4-methylpent-2-ene (4-methyl-2-pentene)

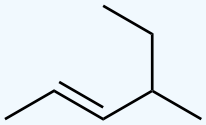
d) 1,1-dibromobut-2-ene (1,1-dibromo-2-butene)

Answer available at the end of this section.

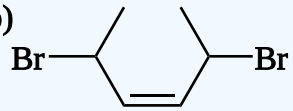
Exercise 7.3.5

Name the following alkenes, including a cis or trans designation:

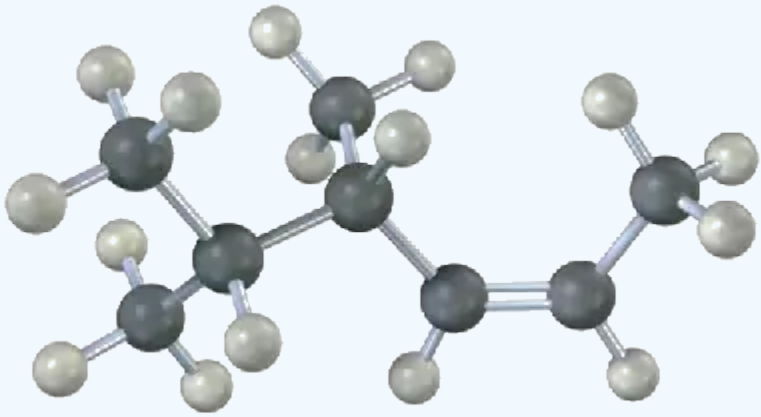
a)



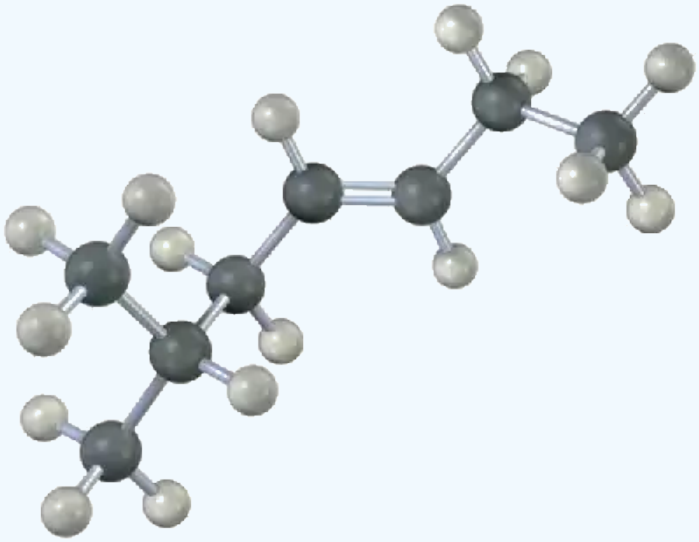
b)



c)



d)



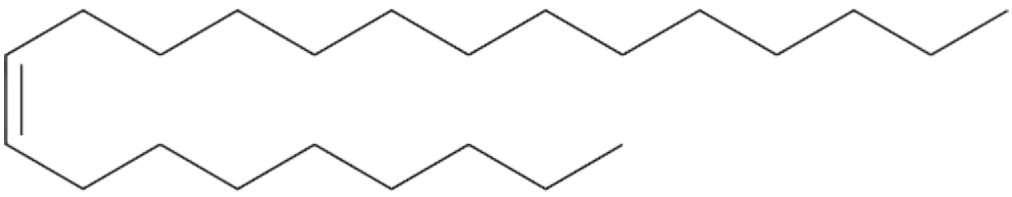
Answer available at the end of this section.

Answers

Exercise 7.3.1

a) trans isomer. b) neither. c) cis isomer. d) cis isomer.

Exercise 7.3.2

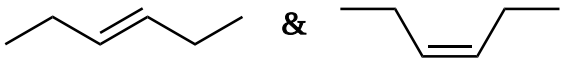


Exercise 7.3.3

Compounds (c), (e), and (f) have cis–trans isomers.

Exercise 7.3.4

a)



trans isomer

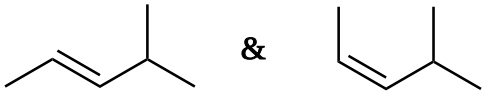
cis isomer

b)



no cis/trans isomers

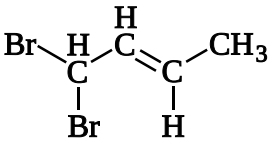
c)

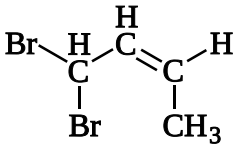


trans isomer

cis isomer

d)





trans isomer

cis isomer

Exercise 7.3.5

a. *trans*-4-methylhex-2-ene (*trans*-4-methyl-2-hexene)
b. *cis*-2,5-dibromohex-3-ene (*cis*-2,5-dibromo-3-hexene)
c. *cis*-4,5-Dimethyl-2-hexene
d. *trans*-6-Methyl-3-heptene

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7.4: Alkene Stereochemistry and the E,Z Designation

The cis–trans naming system used in the previous section works only with disubstituted alkenes—compounds that have two substituents other than hydrogen on the double bond. With trisubstituted and tetrasubstituted double bonds, a more general method is needed for describing double-bond geometry. (*Trisubstituted* means three substituents other than hydrogen on the double bond; *tetrasubstituted* means four substituents other than hydrogen.)

The method used for describing alkene stereochemistry is called the ***E,Z* system** and employs the same Cahn–Ingold–Prelog sequence rules given in Section 5.6 for specifying the configuration of a chirality center. Let's briefly review the sequence rules and then see how they're used to specify double-bond geometry. For a more thorough review, reread Section 5.6.

RULE 1

Considering each of the double-bond carbons separately, look at the two substituents attached and rank them according to the atomic number of the first atom in each (8 for oxygen, 6 for carbon, 1 for hydrogen, and so forth). An atom with higher atomic number ranks higher than an atom with lower atomic number.

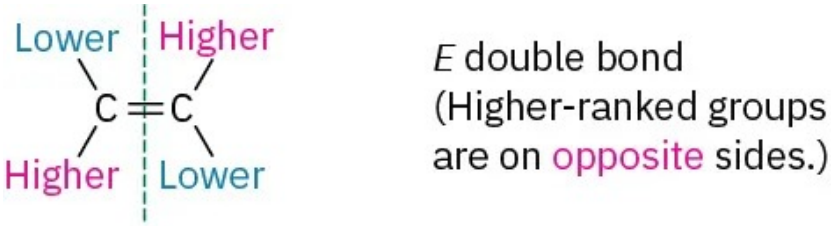
RULE 2

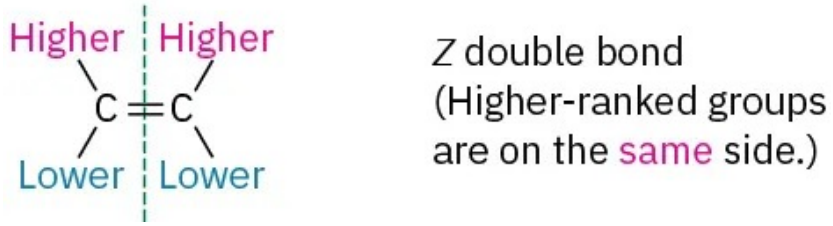
If a decision can't be reached by ranking the first atoms in the two substituents, look at the second, third, or fourth atoms away from the double-bond until the first difference is found.

RULE 3

Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.

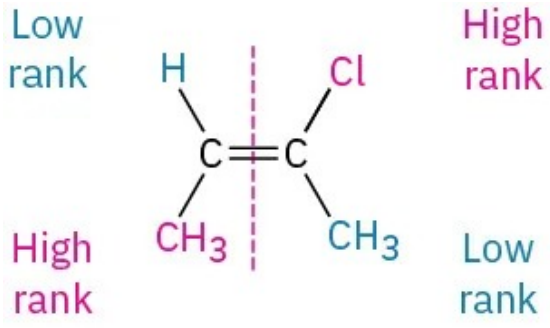
Once the two groups attached to each double-bonded carbon have been ranked as either higher or lower, look at the entire molecule. If the higher-ranked groups on each carbon are on the same side of the double bond, the alkene is said to have a *Z* configuration, for the German *zusammen,* meaning "together." If the higher-ranked groups are on opposite sides, the alkene has an *E* configuration, for the German *entgegen,* meaning "opposite." (For a simple way to remember which is which, note that the groups are on "ze zame zide" in the *Z* isomer.)



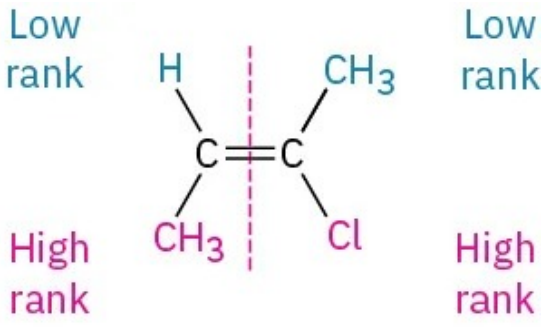


As an example, look at the following two isomers of 2-chloro-2-butene. Because chlorine has a higher atomic number than carbon, a –Cl substituent is ranked higher than a $-CH_3$ group. Methyl is ranked higher than hydrogen, so isomer **(a)** is designated *E*

because the higher-ranked groups are on opposite sides of the double bond. Isomer **(b)** has a *Z* configuration because its higher-ranked groups are on the same side of the double bond.

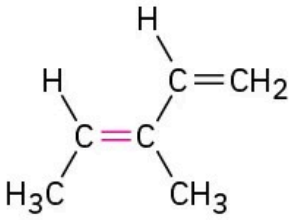


(a) (*E*)-2-Chloro-2-butene

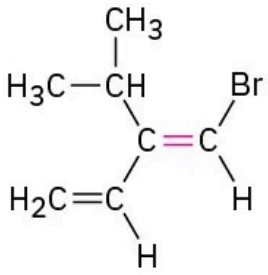


(b) (*Z*)-2-Chloro-2-butene

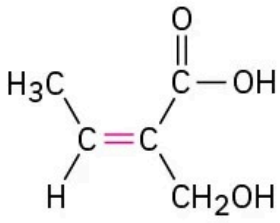
In the following examples, observe the configuration and identify the high-rank groups that make the assignment correct:



(*E*)-3-Methyl-1,3-pentadiene



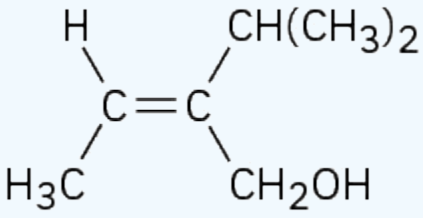
(*E*)-1-Bromo-2-isopropyl-1,3-butadiene



(*Z*)-2-Hydroxymethyl-2-butenoic acid

Worked Example 7.4.1: Assigning E and Z Configurations to Alkenes

Assign *E* or *Z* configuration to the double bond in the following compound:

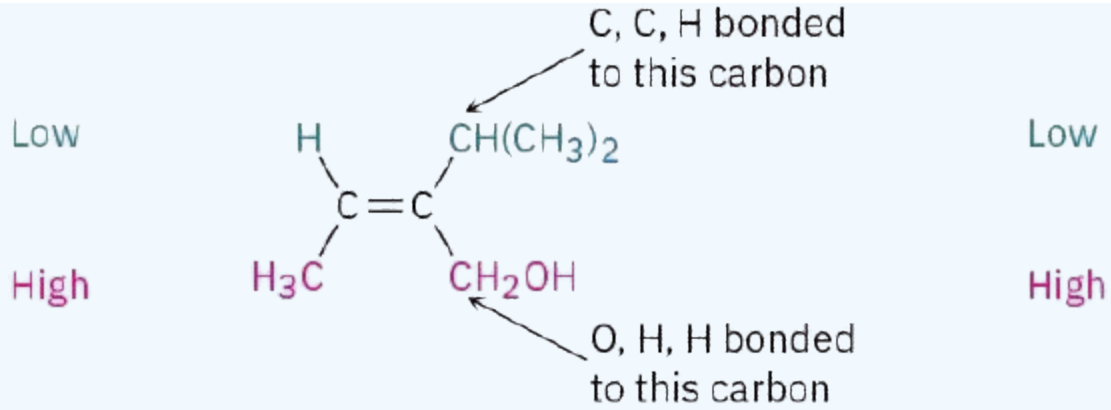


Strategy

Look at the two substituents connected to each double-bonded carbon, and determine their ranking using the Cahn–Ingold–Prelog rules. Then, check whether the two higher-ranked groups are on the same or opposite sides of the double bond.

Solution

The left-hand carbon has –H and $-CH_3$ substituents, of which $-CH_3$ ranks higher by sequence rule 1. The right-hand carbon has $-CH(CH_3)_2$ and $-CH_2OH$ substituents, which are equivalent by rule 1. By rule 2, however, $-CH_2OH$ ranks higher than $-CH(CH_3)_2$ because the substituent $-CH_2OH$ has an oxygen as its highest second atom, but $-CH(CH_3)_2$ has a carbon as its highest second atom. The two higher-ranked groups are on the same side of the double bond, so we assign a *Z* configuration.



***Z* configuration**

Exercise 7.4.2

Which member in each of the following sets ranks higher?

a. –H or $-CH_3$
b. –Cl or $-CH_2Cl$
c. $-CH_2CH_2Br$ or $-CH=CH_2$
d. $-NHCH_3$ or $-OCH_3$
e. $-CH_2OH$ or –CH=O
f. $-CH_2OCH_3$ or –CH=O

Answer available at the end of this section.

Exercise 7.4.3

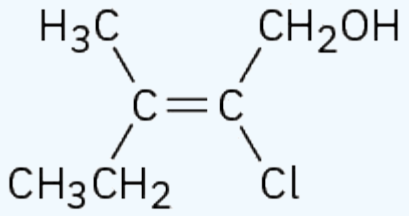
Rank the substituents in each of the following sets according to the sequence rules:

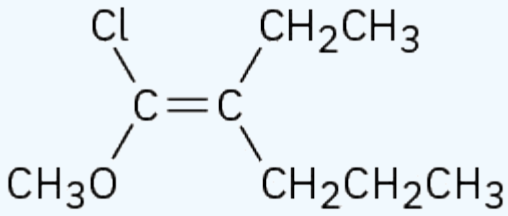
a. $-CH_3$, –OH, –H, –Cl
b. $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CH_2OH$
c. $-CO_2H$, $-CH_2OH$, –C≡N, $-CH_2NH_2$
d. $-CH_2CH_3$, –C≡CH, –C≡N, $-CH_2OCH_3$

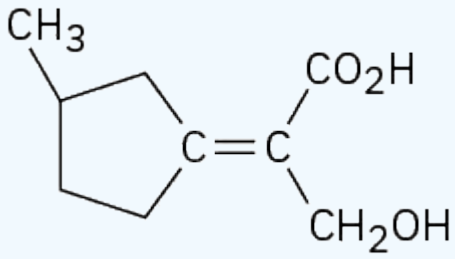
Answer available at the end of this section.

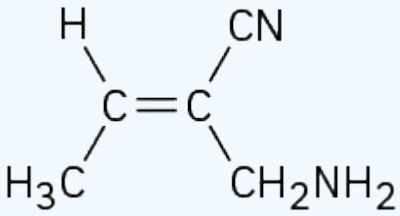
Exercise 7.4.4

Assign *E* or *Z* configuration to the following alkenes:

a. 

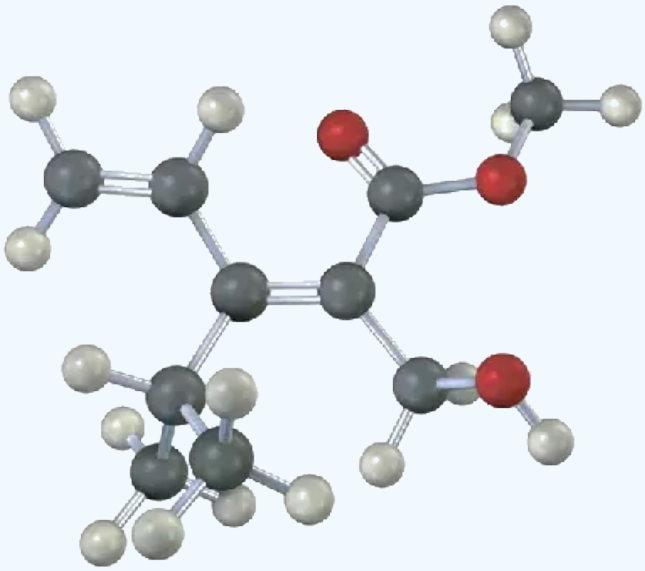
b. 

c. 

d. 

Answer available at the end of this section.

Exercise 7.4.5

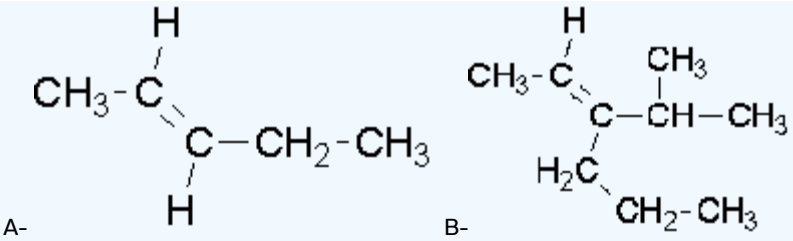


Assign stereochemistry (*E* or *Z*) to the double bond in the following compound, and convert the drawing into a skeletal structure (red = O):

Answer available at the end of this section.

Exercise 7.4.6

Aname the following compounds using both conventions:



Answer available at the end of this section.

Answers

Exercise 7.4.2

a. $-CH_3$ b. $-Cl$ c. $-CH=CH_2$ d. $-OCH_3$ e. $-CH=O$ f. $-CH=O$

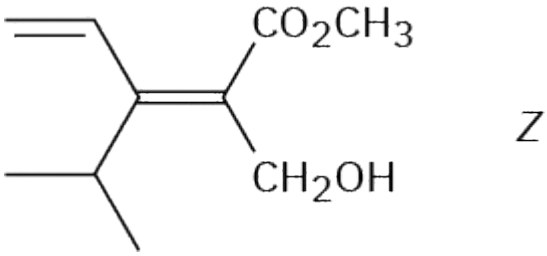
Exercise 7.4.3

a. $-Cl$, $-OH$, $-CH_3$, $-H$
b. $-CH_2OH$, $-CH=CH_2$, $-CH_2CH_3$, $-CH_3$
c. $-CO_2H$, $-CH_2OH$, $-C \equiv N$, $-CH_2NH_2$
d. $-CH_2OCH_3$, $-C\equiv N$, $-C\equiv CH$, $-CH_2CH_3$

Exercise 7.4.4

a. Z b. E c. Z d. E

Exercise 7.4.5



Z

Exercise 7.4.6

Structure A: (*trans)* 2-pentene or (*E*) 2-pentene

Structure B: cis and trans convention cannot be used there are more than two non hydrogen attachments to the alkene

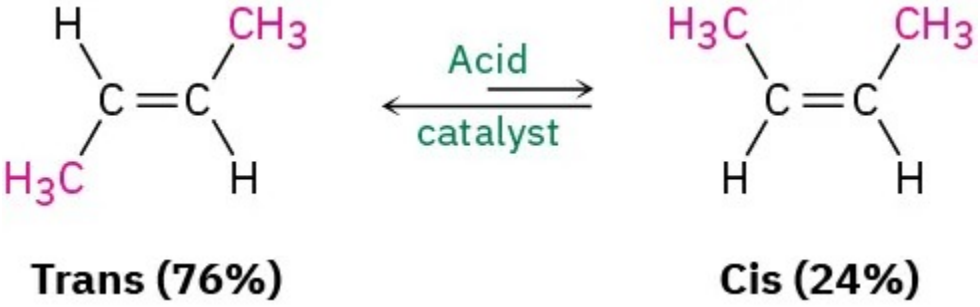
(*E*) 3-isopropyl-2-hexene or (*E*) 3-(1-methylethyl)-2-hexene

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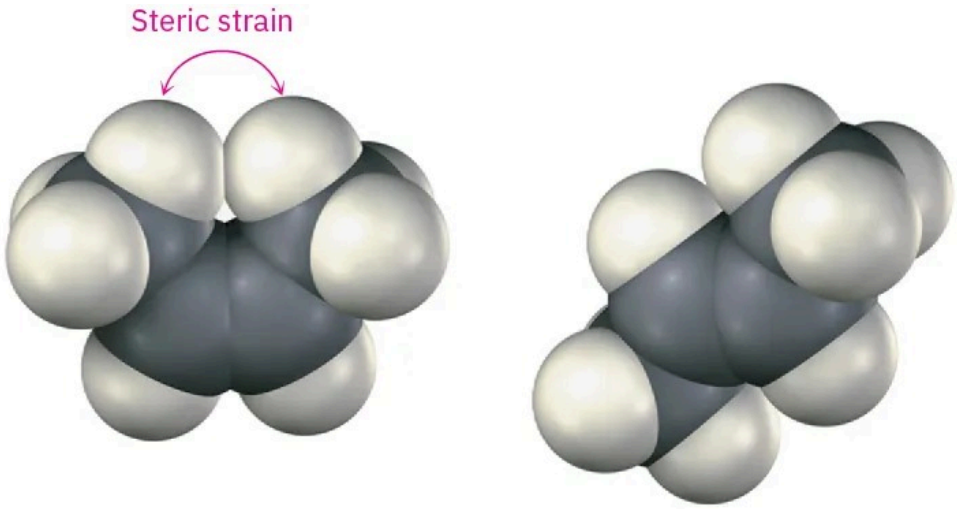
7.5: Stability of Alkenes

Although the cis–trans interconversion of alkene isomers does not occur spontaneously, it can often be made to happen by treating the alkene with a strong acid catalyst. If we interconvert *cis*-2-butene with *trans*-2-butene and allow them to reach equilibrium, we find that they aren't of equal stability. The trans isomer is more stable than the cis isomer by 2.8 kJ/mol (0.66 kcal/mol) at room temperature, corresponding to a 76 : 24 ratio.



Trans (76%) **Cis (24%)**

Cis alkenes are less stable than their trans isomers because of steric strain between the two larger substituents on the same side of the double bond. This is the same kind of steric interference that we saw previously in the axial conformation of methylcyclohexane (Section 4.7).

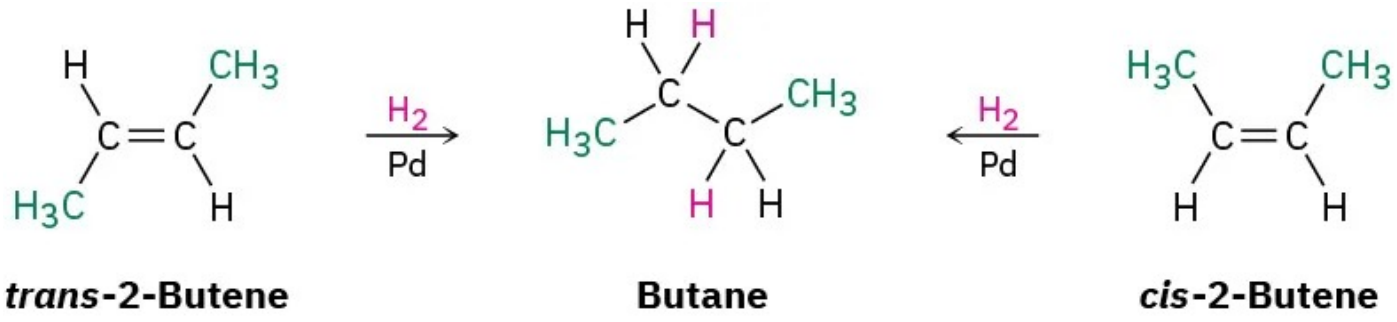


***cis*-2-Butene** ***trans*-2-Butene**

Hydrogenation Reaction

Although it's sometimes possible to find relative stabilities of alkene isomers by establishing a cis–trans equilibrium through treatment with strong acid, a more general method is to take advantage of the fact that alkenes undergo a *hydrogenation* reaction to give the corresponding alkane when treated with H_2 gas in the presence of a catalyst such as palladium or platinum.

Alkene hydrogenation is the syn-addition of hydrogen to an alkene, saturating the bond. The alkene reacts with hydrogen gas in the presence of a metal catalyst which allows the reaction to occur quickly. The energy released in this process, called the heat of hydrogenation, indicates the relative stability of the double bond in the molecule.



***trans*-2-Butene** **Butane** ***cis*-2-Butene**

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. With this catalyst present, the sigma bond of H_2 breaks, and the two hydrogen atoms bind to the metal (see #2 in the figure below). The π bond of the alkene weakens as it also interacts with the metal (see #3 below).

Since both reactants are bound to the metal catalyst, the hydrogen atoms can easily add, one at a time, to the previously double-bonded carbons (see #4 and #5 below). The position of both reactants bound to the catalyst makes it so the hydrogen atoms are only exposed to one side of the alkene. This explains why the hydrogen atoms add to same side of the molecule, called syn-addition.

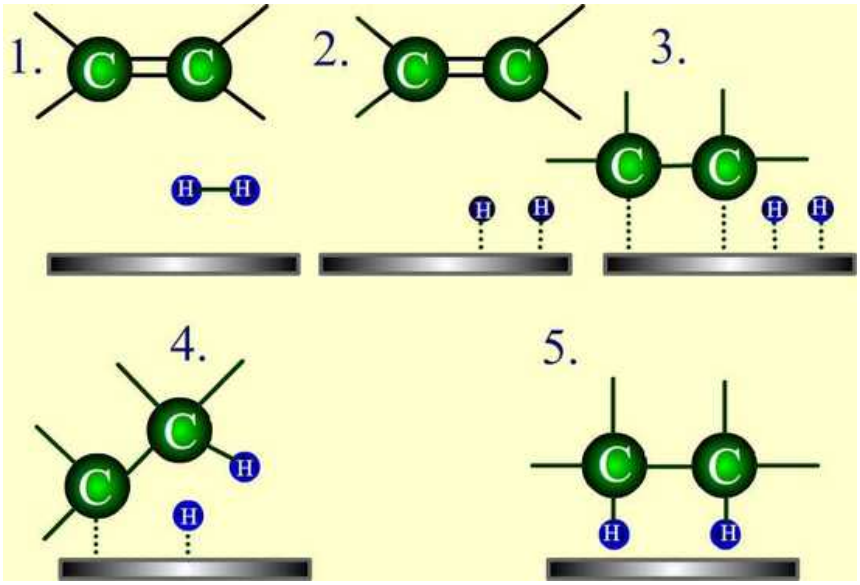


Figure 7.5.1: Hydrogenation takes place in the presence of a metal catalyst.

Energy diagrams for the hydrogenation reactions of *cis*- and *trans*-2-butene are shown in Figure 7.5.1. Because *cis*-2-butene is less stable than *trans*-2-butene by 2.8 kJ/mol, the energy diagram shows the cis alkene at a higher energy level. After reaction, however, both curves are at the same energy level (butane). It therefore follows that $\Delta G°$ for reaction of the cis isomer must be larger than $\Delta G°$ for reaction of the trans isomer by 2.8 kJ/mol. In other words, more energy is released in the hydrogenation of the cis isomer than the trans isomer because the cis isomer has more energy to begin with.

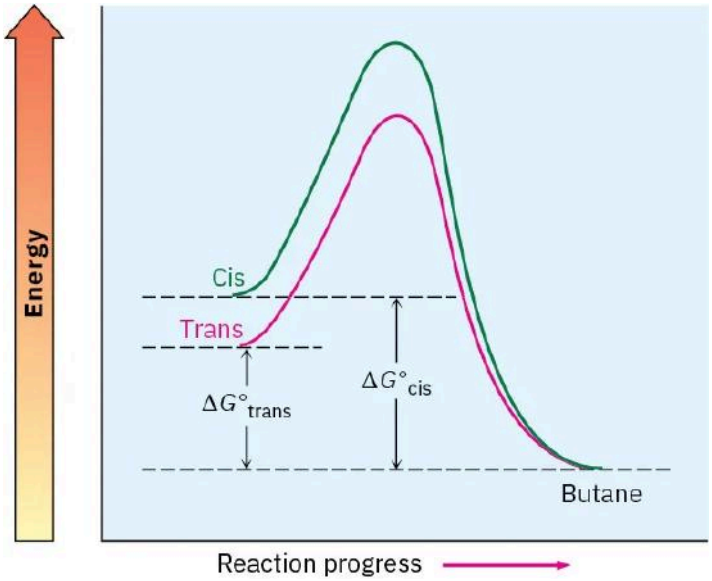


Figure 7.5.2: Energy diagrams for hydrogenation of *cis*- and *trans*-2-butene. The cis isomer is higher in energy than the trans isomer by about 2.8 kJ/mol and therefore releases more energy when hydrogenated.

Alkene stability 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 ($\Delta H°_{hydrog}$) can be measured very accurately.

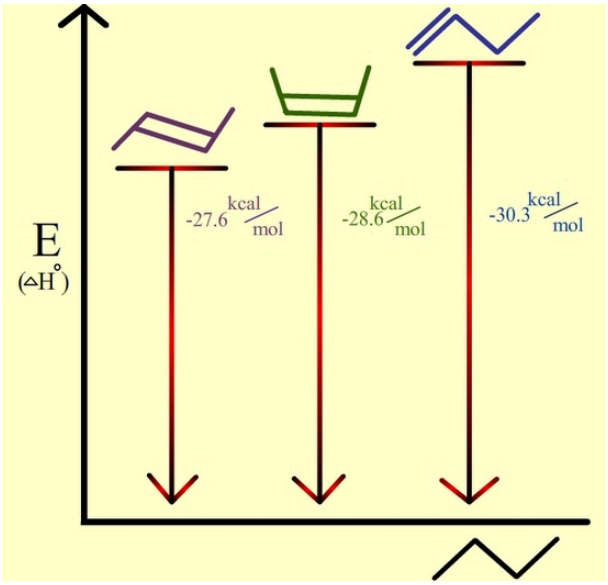
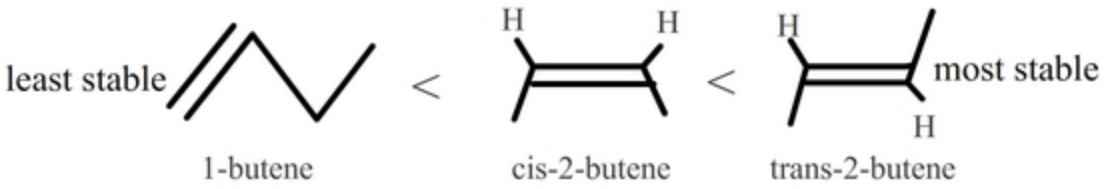


Figure 7.5.3: *Trans-2-butene is the most stable because it has the lowest heat of hydrogenation.*

The ($\Delta H°_{hydrog}$) 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.

Example: cis-2-Butene, for instance, has $\Delta H°_{hydrog}$ = −28.6 kcal/mol, while trans-2-butene has $\Delta H°_{hydrog}$ = −27.6 kcal/mol —a difference of 4 kJ/mol. While 1-butene, the terminal alkene has $\Delta H°_{hydrog}$ = −30.3 kcal/mol, closer to the expected value.

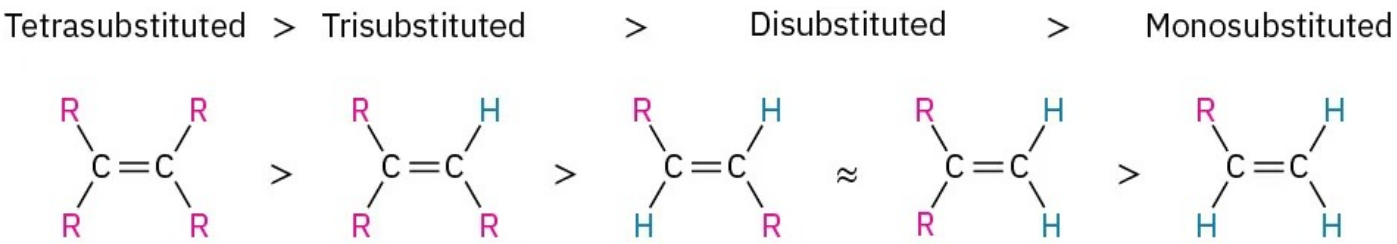


The 4 kJ/mol energy difference between the 2-butene isomers calculated from heats of hydrogenation agrees reasonably well with the 2.8 kJ/mol energy difference calculated from equilibrium data, but the values aren't exactly the same for two reasons. First, there is probably some experimental error, because heats of hydrogenation are difficult to measure accurately. Second, heats of reaction and equilibrium constants don't measure exactly the same thing. Heats of reaction measure enthalpy changes, $\Delta H°$, whereas equilibrium constants measure free-energy changes, $\Delta G°$, so we might expect a slight difference between the two.

Table 7.5.1: Heats of Hydrogenation of Some Alkenes

Substitution	Alkene	$\Delta H°_{hydrog}$ (kJ/mol)	$\Delta H°_{hydrog}$ (kcal/mol)
Ethylene	$H_2C{=}CH_2$	–136	–32.6
Monosubstituted	$CH_3CH{=}CH_2$	–125	–29.9
Disubstituted	$CH_3CH{=}CHCH_3$ (cis) $CH_3CH{=}CHCH_3$ (trans) $(CH_3)_2C{=}CH_2$	–119 –115 –118	–28.3 –27.4 –28.2
Trisubstituted	$(CH_3)_2C{=}CHCH_3$	–112	–26.7
Tetrasubstituted	$(CH_3)_2C{=}C(CH_3)_2$	–110	–26.4

Table 7.5.1 lists some representative data for the hydrogenation of different alkenes and shows that alkenes become more stable with increasing substitution. That is, alkenes follow the stability order:



The stability order of substituted alkenes is due to a combination of two factors. One is a stabilizing interaction between the $C{=}C$ π orbital and adjacent C–H σ bonds on substituents. In valence-bond language, the interaction is called **hyperconjugation**. In a molecular orbital description, there is a bonding MO that extends over the four-atom $C{=}C{-}C{-}H$ grouping, as shown in Figure 7.5.2. The more substituents present on the double bond, the more hyperconjugation occurs and the more stable the alkene.

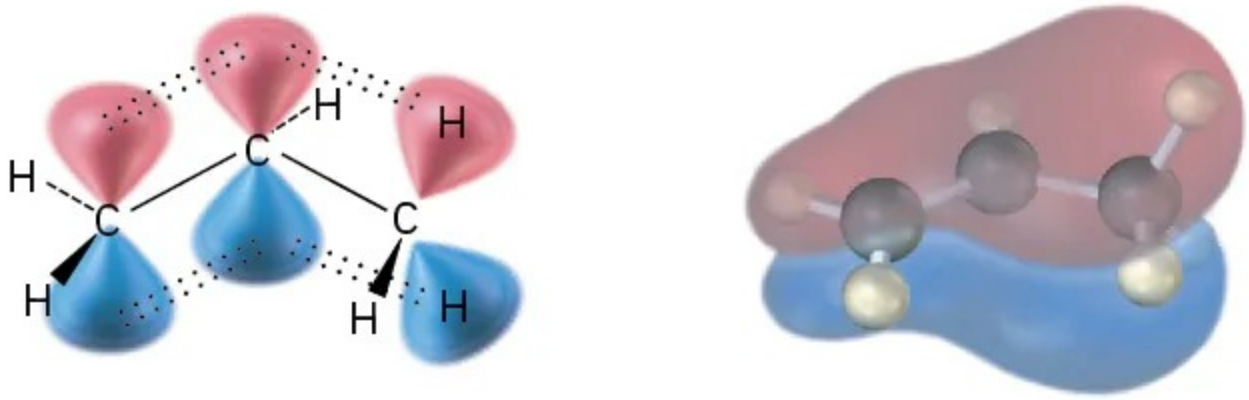
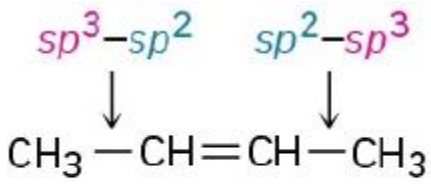
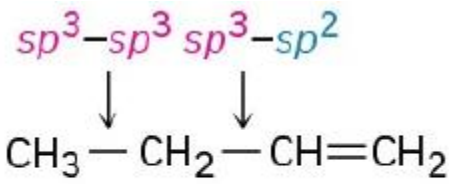


Figure 7.5.4: Hyperconjugation is a stabilizing interaction between the C=C π orbital and adjacent C–H σ bonds on substituents. The more substituents there are, the greater the stabilization of the alkene.

A second factor that contributes to alkene stability involves bond strengths. A bond between a sp^2 carbon and a sp^3 carbon is somewhat stronger than a bond between two sp^3 carbons. Thus, in comparing 1-butene and 2-butene, the monosubstituted isomer has one sp^3–sp^3 bond and one sp^3–sp^2 bond, while the disubstituted isomer has two sp^3–sp^2 bonds. More highly substituted alkenes always have a higher ratio of sp^3–sp^2 bonds to sp^3–sp^3 bonds than less highly substituted alkenes and are therefore more stable.



2-Butene
(more stable)

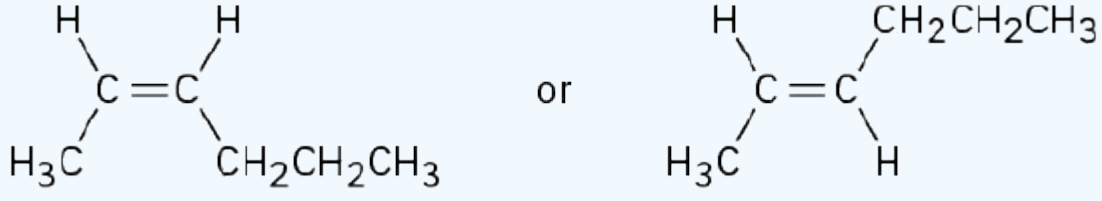


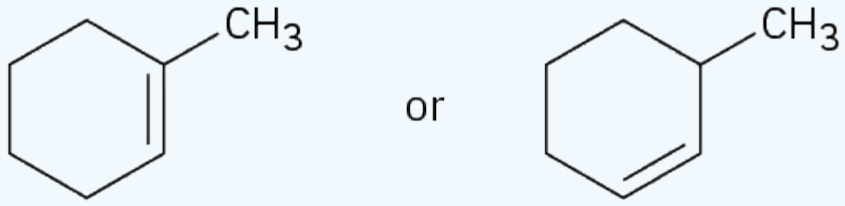
1-Butene
(less stable)

Exercise 7.5.1

Name the following alkenes, and tell which compound in each pair is more stable:

a. $H_2C{=}CHCH_2CH_3$ or $H_2C{=}C(CH_3)CH_3$

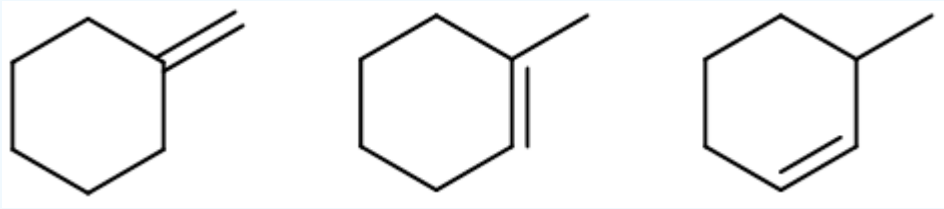
b. 

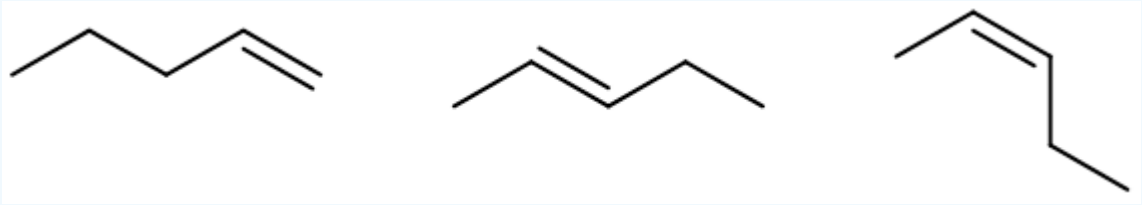
c. 

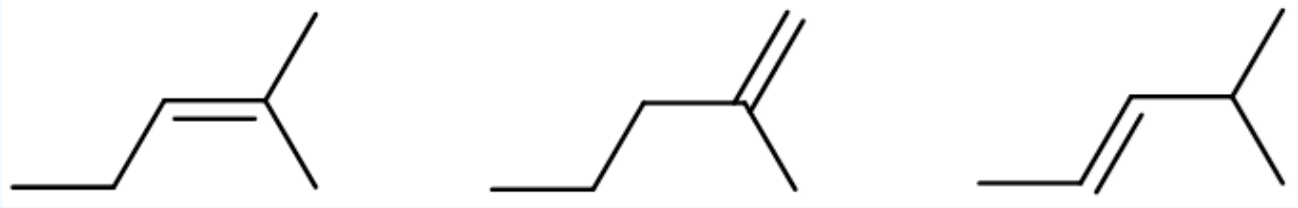
Answer available at the end of this section.

Exercise 7.5.2

Name the following alkenes, and indicate the order of stability, from the most stable to the least stable:

a. 

b. 

c. 

Answer available at the end of this section.

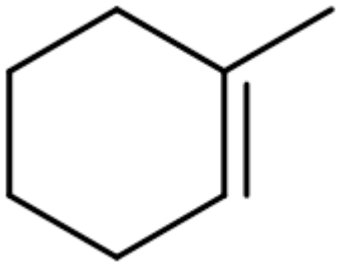
Answers

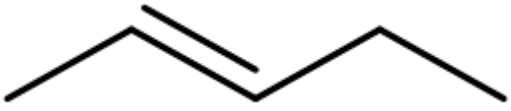
Exercise 7.5.1

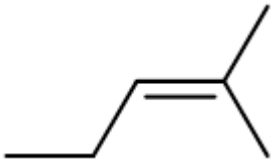
a. 2-Methylpropene is more stable than 1-butene
b. trans-2-Hexene is more stable than cis-2-hexene
c. 1-Methylcyclohexene is more stable than 3-methylcyclohexene

Exercise 7.5.2

Most stables:

a. 

b. 

c. 

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7.6: Electrophilic Addition Reactions of Alkenes

Before beginning a detailed discussion of alkene reactions, let's review briefly some conclusions from the previous chapter. We said in Section 6.6 that alkenes behave as nucleophiles (Lewis bases) in polar reactions, donating a pair of electrons from their electron-rich C=C bond to an electrophile (Lewis acid). For example, reaction of 2-methylpropene with HBr yields 2-bromo-2-methylpropane. A careful study of this and similar reactions by the British chemist Christopher Ingold and others in the 1930s led to the generally accepted mechanism shown in Figure 7.6.1 for an electrophilic addition reaction.

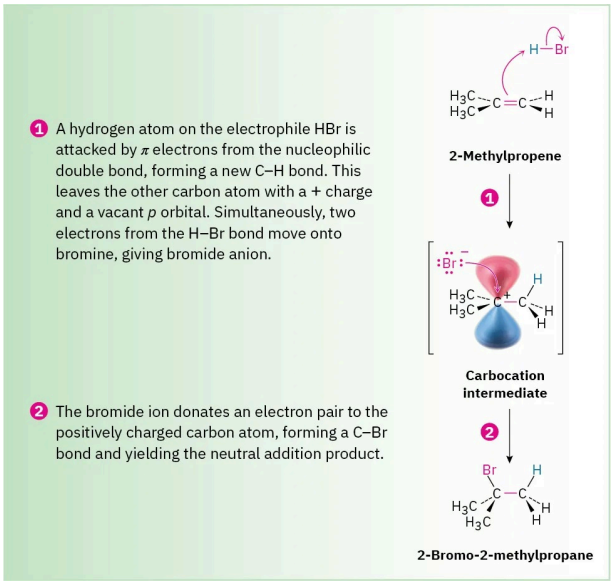


Figure 7.6.1: Mechanism of the electrophilic addition of HBr to 2-methylpropene. The reaction occurs in two steps, protonation and bromide addition, and involves a carbocation intermediate.

The reaction begins with an attack on the hydrogen of the electrophile HBr by the electrons of the nucleophilic π bond. Two electrons from the π bond form a new σ bond between the entering hydrogen and an alkene carbon, as shown by the curved arrow at the top of Figure 7.6.1. The resulting carbocation intermediate is itself an electrophile, which can accept an electron pair from nucleophilic Br^- ion to form a C–Br bond and yield a neutral addition product.

An energy diagram for the overall electrophilic addition reaction (Figure 7.6.2) has two peaks (transition states) separated by a valley (carbocation intermediate). The energy level of the intermediate is higher than that of the starting alkene, but the reaction as a whole is exergonic (negative $\Delta G°$). The first step, protonation of the alkene to yield the intermediate cation, is relatively slow. But once the cation intermediate is formed, it rapidly reacts to yield the final alkyl bromide product. The relative rates of the two steps are indicated in Figure 7.6.2 by the fact that $\Delta G_1^{\ddagger}$ is larger than $\Delta G_2^{\ddagger}$.

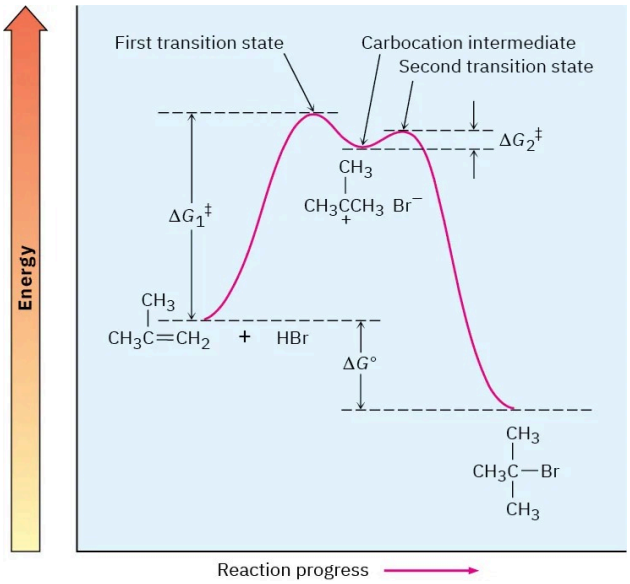
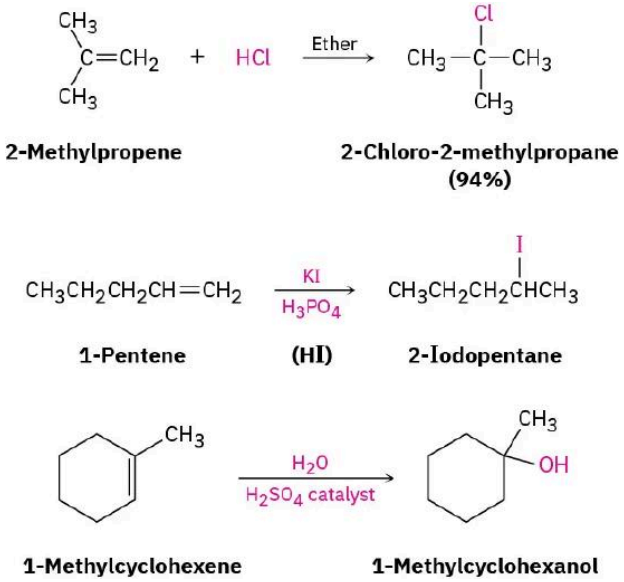


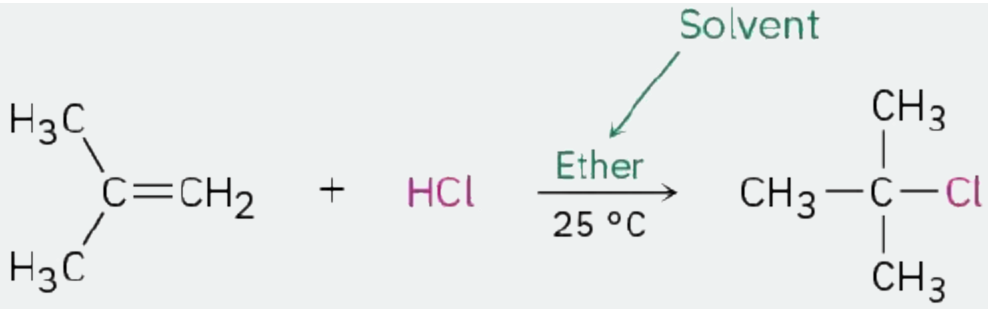
Figure 7.6.2: Energy diagram for the two-step electrophilic addition of HBr to 2-methylpropene. The first step is slower than the second step.

Electrophilic addition to alkenes is successful not only with HBr but with HCl, HI, and H_2O as well. Note that HI is usually generated in the reaction mixture by treating potassium iodide with phosphoric acid and that a strong acid catalyst is needed for the addition of water.

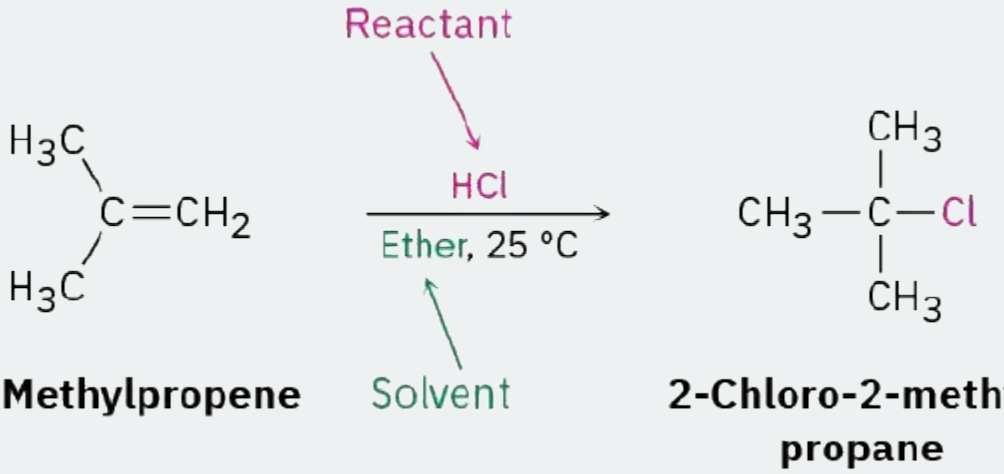


Writing Organic Reactions

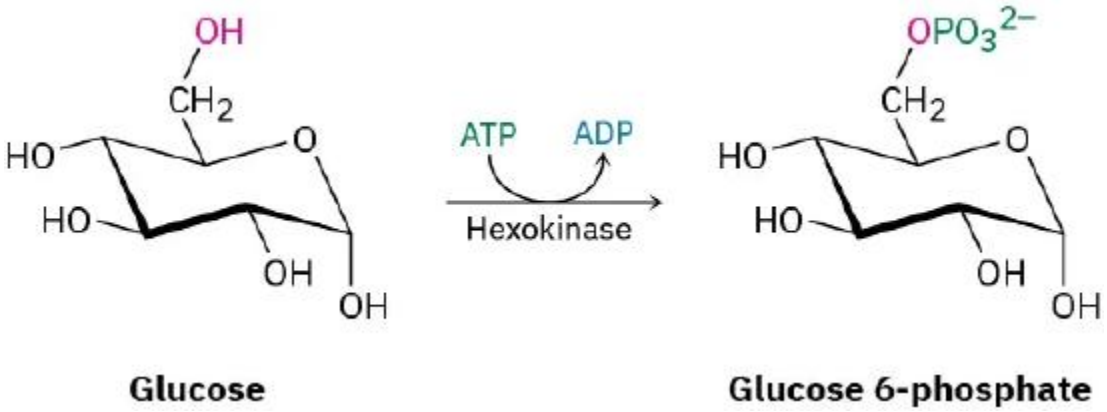
This is a good place to mention that the equations for organic reactions are sometimes written in different ways to emphasize different points. In describing a laboratory process, for instance, the reaction of 2-methylpropene with HCl might be written in the format A + B ⟶ C to emphasize that both reactants are equally important for the purposes of the discussion. The solvent and notes about other reaction conditions such as temperature are written either above or below the reaction arrow.



Alternatively, we might write the same reaction in a format to emphasize that 2-methylpropene is the reactant whose chemistry is of greater interest. The second reactant, HCl, is placed above the reaction arrow together with notes about solvent and reaction conditions.



In describing a biological process, the reaction is almost always written to show only the structures of the primary reactant and product, while abbreviating the structures of various biological "reagents" and by-products with a curved arrow that intersects the straight reaction arrow. As discussed in Section 6.12, the reaction of glucose with ATP to give glucose 6-phosphate plus ADP would then be written as

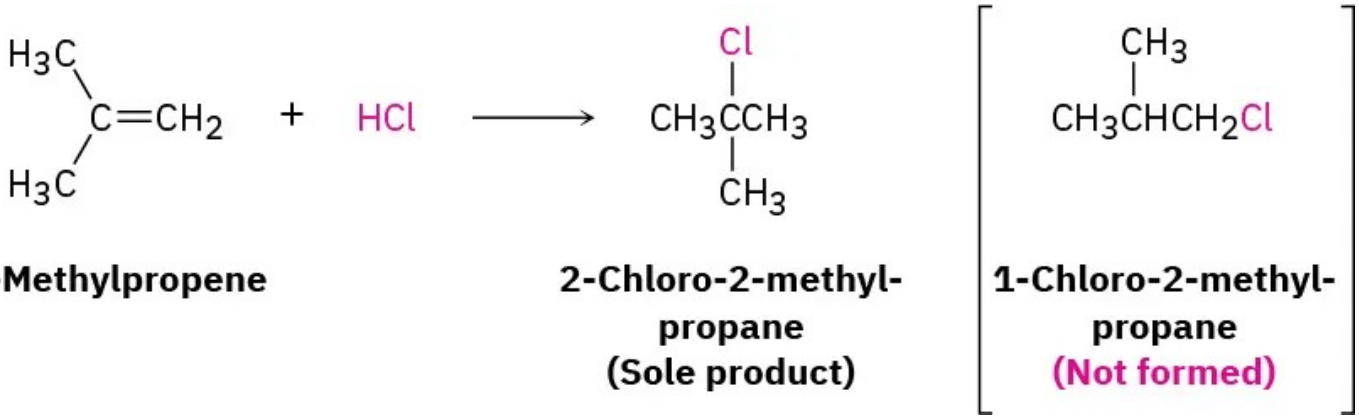


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7.7: Orientation of Electrophilic Additions - Markovnikov's Rule

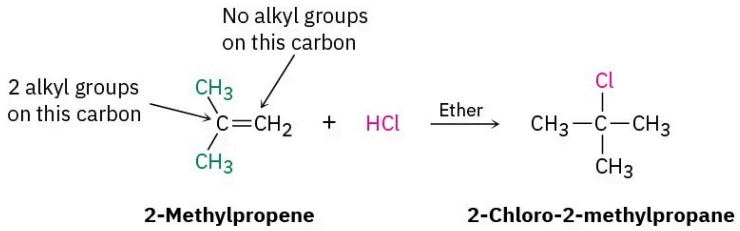
Look carefully at the electrophilic addition reactions shown in the previous section. In each case, an unsymmetrically substituted alkene has given a single addition product rather than the mixture that might be expected. For example, 2-methylpropene might react with HCl to give both 2-chloro-2-methylpropane and 1-chloro-2-methylpropane, but it doesn't. It gives only 2-chloro-2-methylpropane as the sole product. Similarly, it's invariably the case in biological alkene addition reactions that only a single product is formed. We say that such reactions are regiospecific (**ree**-jee-oh-specific) when only one of two possible orientations of an addition occurs.

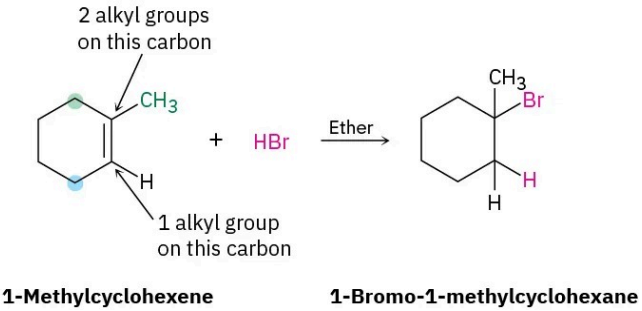


After looking at the results of many such reactions, the Russian chemist Vladimir Markovnikov proposed in 1869 what has become known as Markovnikov's rule.

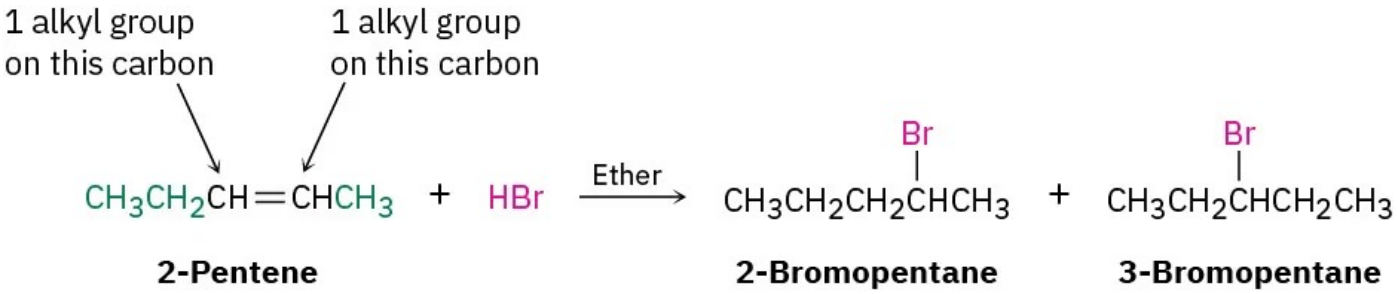
Markovnikov's Rule

In the addition of HX to an alkene, the H attaches to the carbon with fewer alkyl substituents and the X attaches to the carbon with more alkyl substituents.





When both double-bonded carbon atoms have the same degree of substitution, a mixture of addition products results.

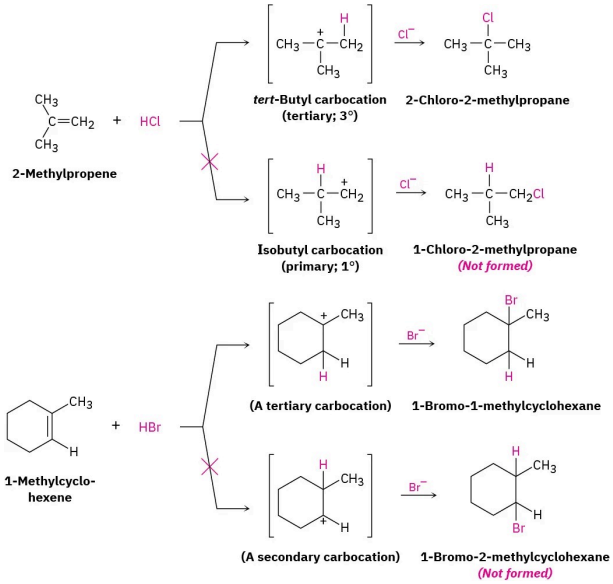


Because carbocations are involved as intermediates in these electrophilic addition reactions, Markovnikov's rule can be restated in the following way:

Markovnikov's Rule Restated

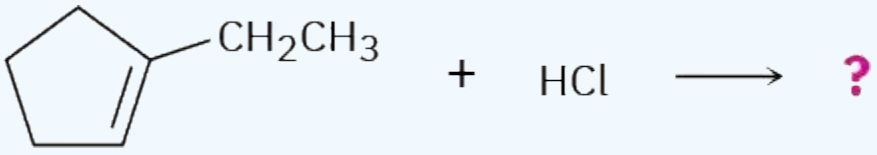
In the addition of HX to an alkene, the more highly substituted carbocation is formed as the intermediate rather than the less highly substituted one.

For example, addition of H^+ to 2-methylpropene yields the intermediate *tertiary* carbocation rather than the alternative primary carbocation, and addition to 1-methylcyclohexene yields a tertiary cation rather than a secondary one. Why should this be?



Worked Example 7.7.1: Predicting the Product of an Electrophilic Addition Reaction

What product would you expect from reaction of HCl with 1-ethylcyclopentene?



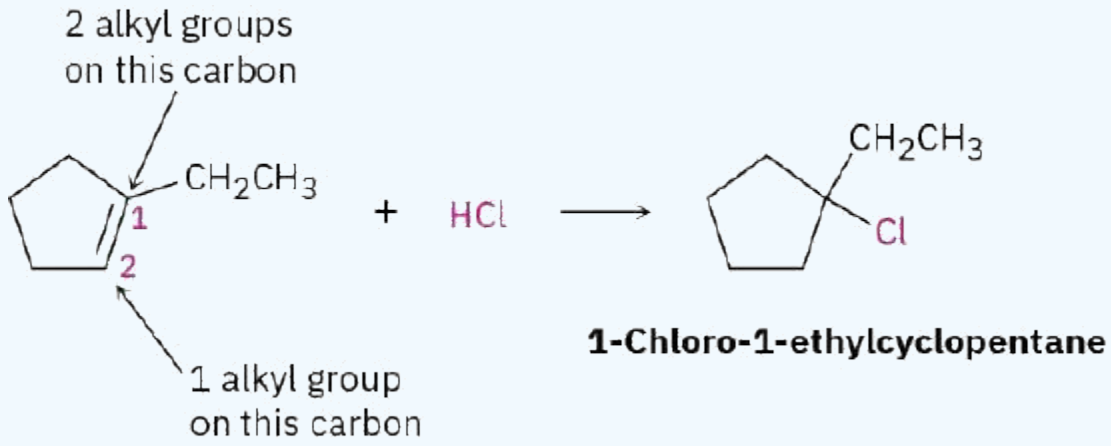
Strategy

When solving a problem that asks you to predict a reaction product, begin by looking at the functional group(s) in the reactants and deciding what kind of reaction is likely to occur. In the present instance, the reactant is an alkene that will probably undergo an electrophilic addition reaction with HCl. Next, recall what you know about electrophilic addition

reactions to predict the product. You know that electrophilic addition reactions follow Markovnikov's rule, so H^+ will add to the double-bond carbon that has one alkyl group (C2 on the ring) and the Cl will add to the double-bond carbon that has two alkyl groups (C1 on the ring).

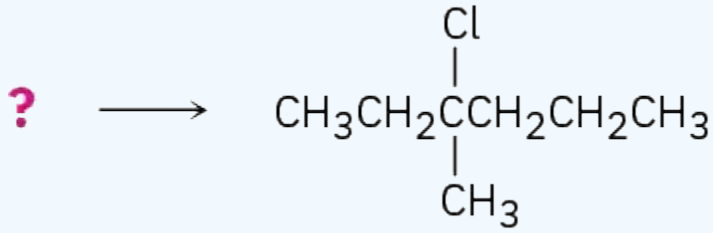
Solution

The expected product is 1-chloro-1-ethylcyclopentane.



Worked Example 7.7.1: Synthesizing a Specific Compound

What alkene would you start with to prepare the following alkyl halide? There may be more than one possibility.

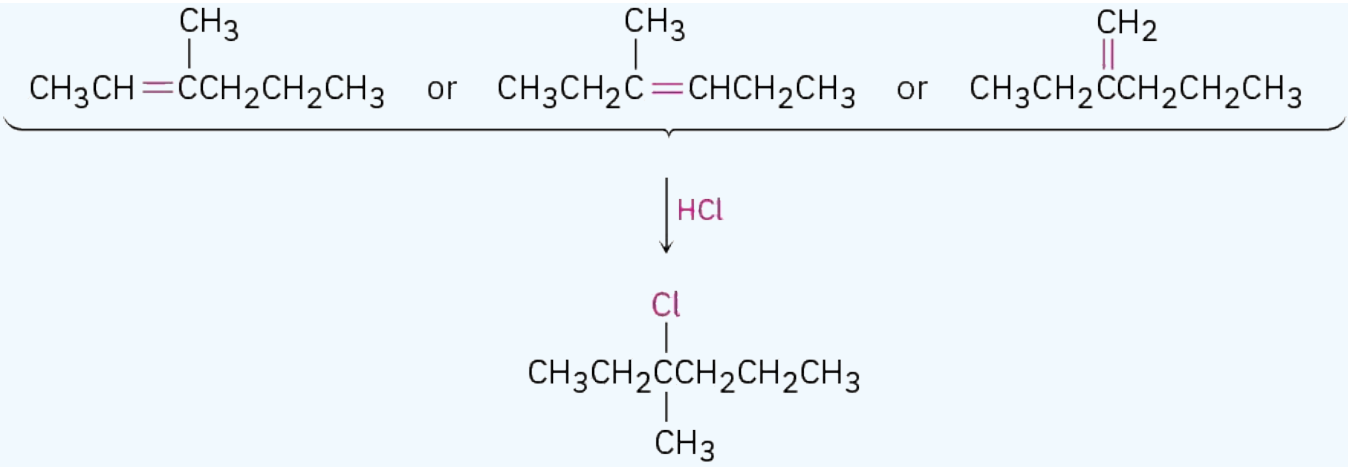


Strategy

When solving a problem that asks how to prepare a given product, always work backward. Look at the product, identify the functional group(s) it contains, and ask yourself, "How can I prepare that functional group?" In the present instance, the product is a tertiary alkyl chloride, which can be prepared by reaction of an alkene with HCl. The carbon atom bearing the –Cl atom in the product must be one of the double-bond carbons in the reactant. Draw and evaluate all possibilities.

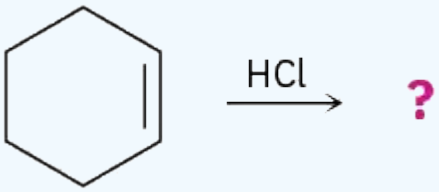
Solution

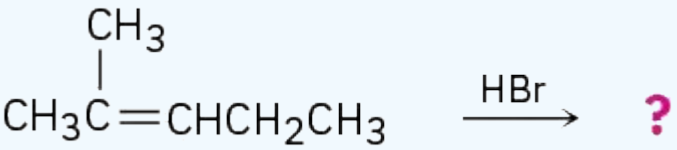
There are three possibilities, all of which could give the desired product according to Markovnikov's rule.

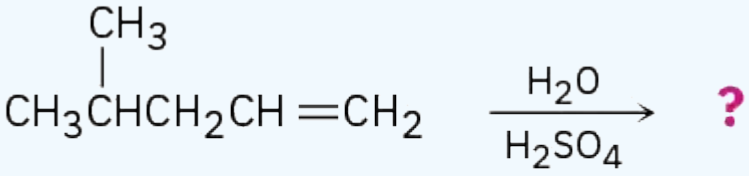


Exercise 7.7.1

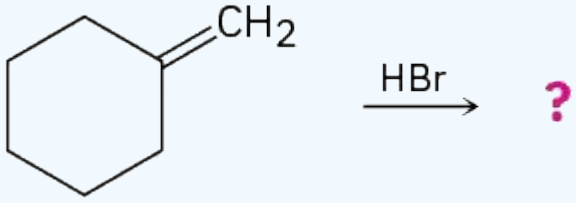
Predict the products of the following reactions:

a. 

b. 



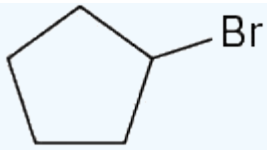
c. (Addition of H_2O occurs.)

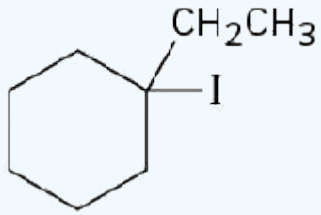
d. 

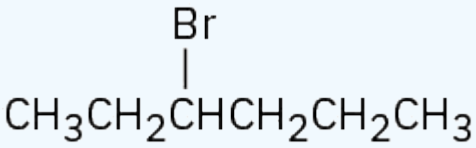
Answer available at the end of this section.

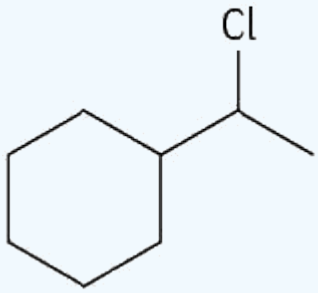
Exercise 7.7.2

What alkenes would you start with to prepare the following products? (a)

a. 

b. 

c. 

d. 

Answer available at the end of this section.

Answers

Exercise 7.7.1

a. Chlorocyclohexane
b. 2-Bromo-2-methylpentane
c. 4-Methyl-2-pentanol
d. 1-Bromo-1-methylcyclohexane

Exercise 7.7.2

a. Cyclopentene
b. 1-Ethylcyclohexene or ethylidenecyclohexane
c. 3-Hexene
d. Vinylcyclohexane (cyclohexylethylene)

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7.8: Carbocation Structure and Stability

To understand why Markovnikov's rule works, we need to learn more about the structure and stability of carbocations and about the general nature of reactions and transition states. The first point to explore involves structure.

A great deal of experimental evidence has shown that carbocations are planar. The trivalent carbon is sp^2-hybridized, and the three substituents are oriented toward the corners of an equilateral triangle, as indicated in Figure 7.8.1. Because there are only six valence electrons on carbon and all six are used in the three σ bonds, the p orbital extending above and below the plane is unoccupied.

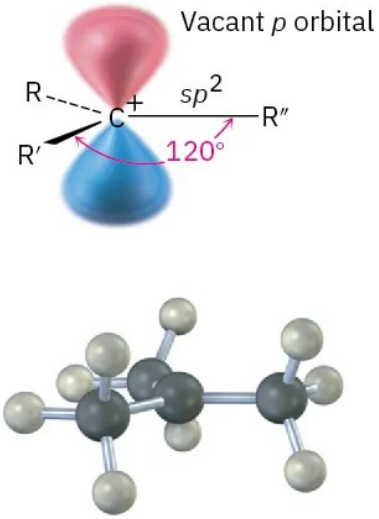
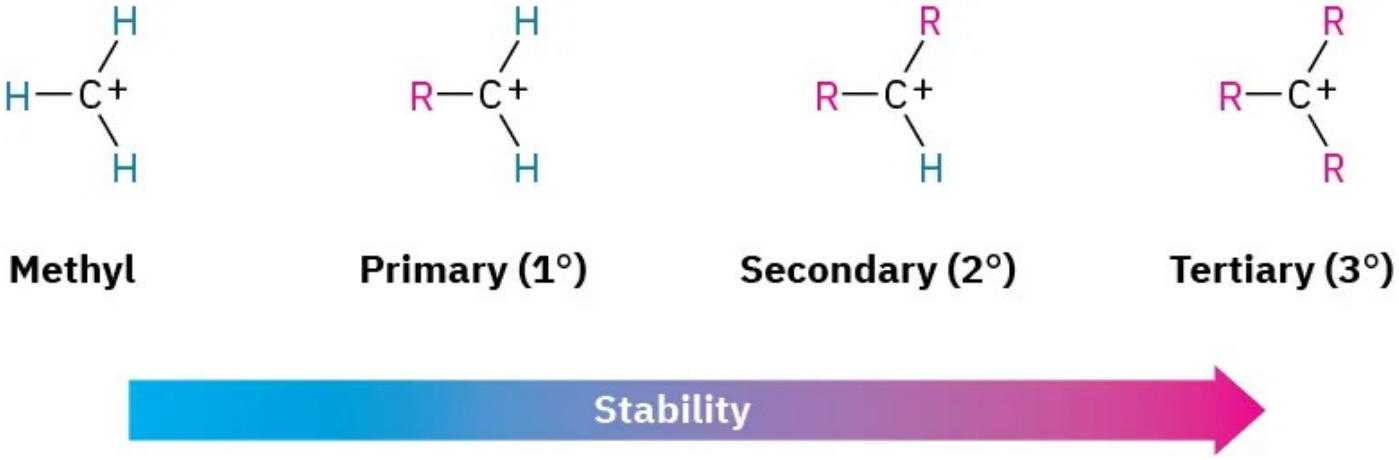


Figure 7.8.1: The structure of a carbocation. The trivalent carbon is sp^2-hybridized and has a vacant p orbital perpendicular to the plane of the carbon and three attached groups.

The second point to explore involves carbocation stability. 2-Methylpropene might react with H^+ to form a carbocation having three alkyl substituents (a tertiary ion, 3°), or it might react to form a carbocation having one alkyl substituent (a primary ion, 1°). Since the tertiary alkyl chloride, 2-chloro-2-methylpropane, is the only product observed, formation of the tertiary cation is evidently favored over formation of the primary cation. Thermodynamic measurements show that, indeed, the stability of carbocations increases with increasing substitution so that the stability order is tertiary > secondary > primary > methyl.



One way of determining carbocation stabilities is to measure the amount of energy required to form a carbocation by dissociation

of the corresponding alkyl halide, $R - X \rightarrow R^+ + :X^-$. As shown in Figure 7.8.2, tertiary alkyl halides dissociate to give carbocations more easily than secondary or primary ones. Thus, trisubstituted carbocations are more stable than disubstituted ones, which are more stable than monosubstituted ones. The data in Figure 7.8.2 are taken from measurements made in the gas phase, but a similar stability order is found for carbocations in solution. The dissociation enthalpies are much lower in solution because polar solvents can stabilize the ions, but the order of carbocation stability remains the same.

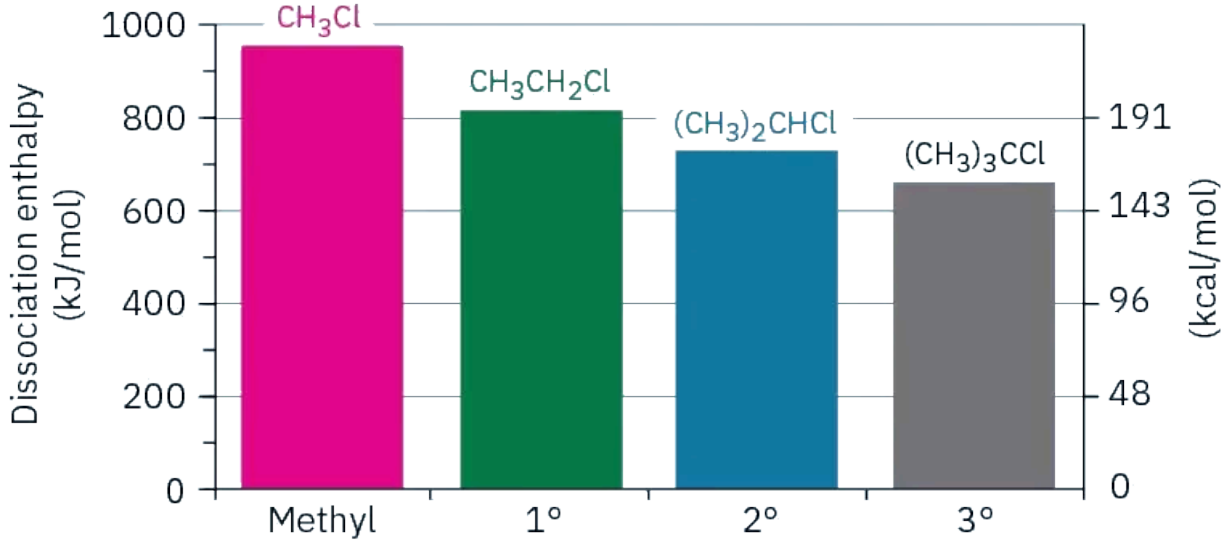


Figure 7.8.2: A plot of dissociation enthalpy versus substitution pattern for the gas-phase dissociation of alkyl chlorides to yield carbocations. More highly substituted alkyl halides dissociate more easily than less highly substituted ones.

Why are more highly substituted carbocations more stable than less highly substituted ones? There are at least two reasons. Part of the answer has to do with inductive effects, and part has to do with hyperconjugation. Inductive effects, discussed in Section 2.2 in connection with polar covalent bonds, result from the shifting of electrons in a σ bond in response to the electronegativity of nearby atoms. In the present instance, electrons from a relatively larger and more polarizable alkyl group can shift toward a neighboring positive charge more easily than the electron from a hydrogen. Thus, the more alkyl groups attached to the positively charged carbon, the more electron density shifts toward the charge and the more inductive stabilization of the cation occurs (Figure 7.8.3).

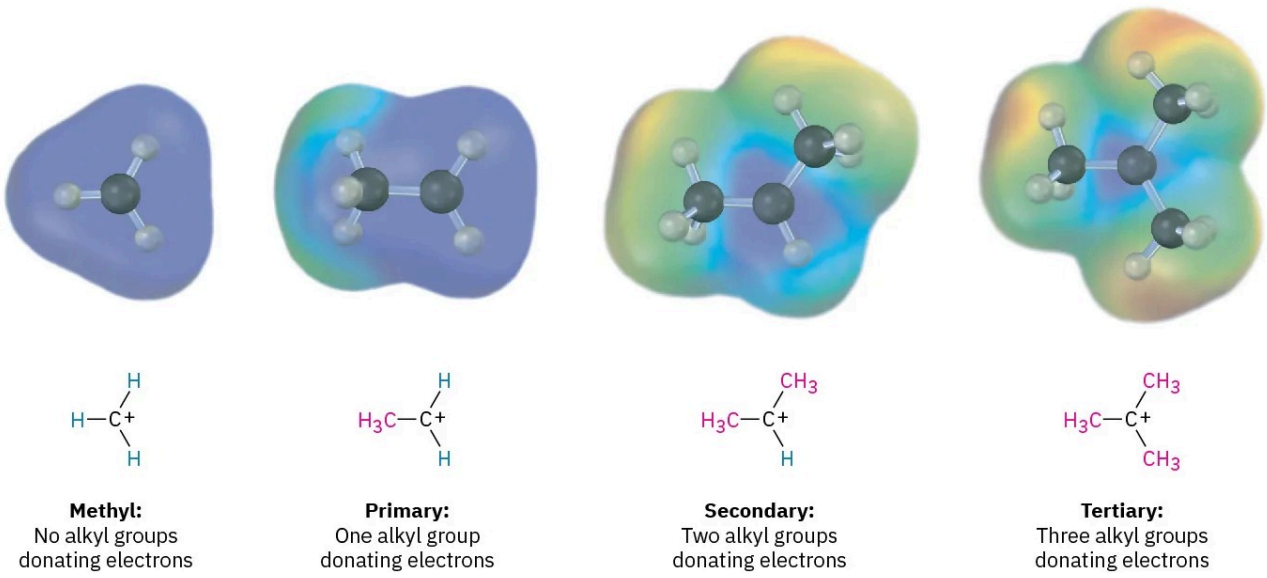


Figure 7.8.3: A comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups that are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron-poor (blue in electrostatic potential maps).

Hyperconjugation, discussed in Section 7.7 in connection with the stabilities of substituted alkenes, is the stabilizing interaction between a *p* orbital and properly oriented C–H *σ* bonds on neighboring carbons that are roughly parallel to the *p* orbital. The more alkyl groups there are on the carbocation, the more possibilities there are for hyperconjugation and the more stable the carbocation. Figure 7.8.4 shows the molecular orbital for the ethyl carbocation, $CH_3CH_2^+$, and indicates the difference between the C–H bond perpendicular to the cation *p* orbital and the two C–H bonds more parallel to the cation *p* orbital. Only these roughly parallel C–H bonds are oriented properly to take part in hyperconjugation.

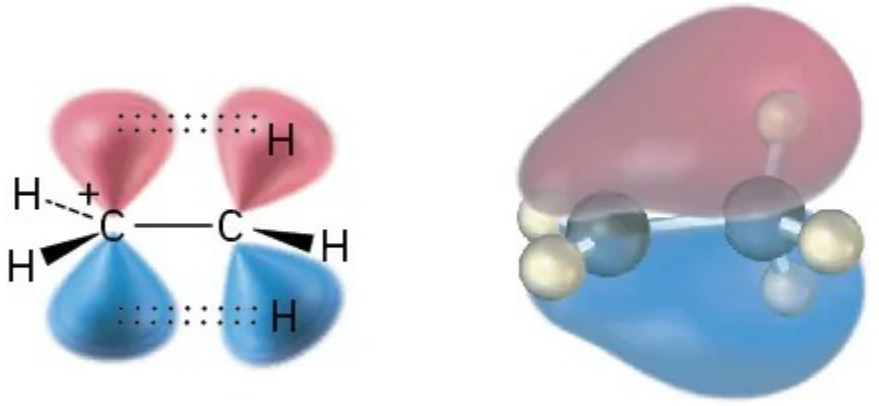
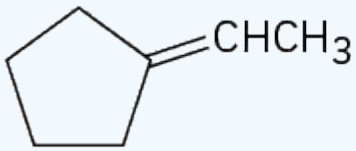


Figure 7.8.4: Stabilization of the ethyl carbocation, $CH_3CH_2^+$, through hyperconjugation. Interaction of neighboring C–H *σ* bonds with the vacant *p* orbital stabilizes the cation and lowers its energy. The molecular orbital shows that only the two C–H bonds more parallel to the cation *p* orbital are oriented properly. The C–H bond perpendicular to the cation *p* orbital can't take part properly.

Exercise 7.8.1

Show the structures of the carbocation intermediates you would expect in the following reactions:

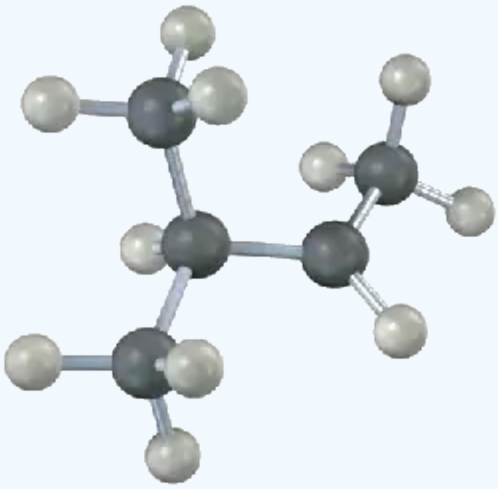
a. $CH_3CH_2C(CH_3)=CHCH(CH_3)CH_3 \xrightarrow{HBr}$?

b.  $\xrightarrow{HI}$?

Answer available at the end of this section.

Exercise 7.8.2

Draw a skeletal structure of the following carbocation. Identify it as primary, secondary, or tertiary, and identify the hydrogen atoms that have the proper orientation for hyperconjugation in the conformation shown.

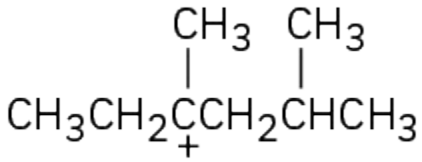


Answer available at the end of this section.

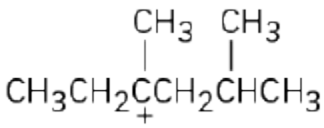
Answers

Exercise 7.8.1

a.



b.



Exercise 7.8.2

In the conformation shown, only the methyl- group C–H that is parallel to the carbocation *p* orbital can show hyperconjugation.

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7.9: The Hammond Postulate

Let's summarize what we've learned of electrophilic addition reactions to this point:

- **Electrophilic addition to an unsymmetrically substituted alkene gives the more substituted carbocation intermediate.** A more substituted carbocation forms faster than a less substituted one and, once formed, rapidly goes on to give the final product.
- **A more substituted carbocation is more stable than a less substituted one.** That is, the stability order of carbocations is tertiary > secondary > primary > methyl.

What we have not yet seen is how these two points are related. Why does the stability of the carbocation intermediate affect the rate at which it's formed and thereby determine the structure of the final product? After all, carbocation stability is determined by the free-energy change $\Delta G°$, but reaction rate is determined by the activation energy $\Delta G^{‡}$. The two quantities aren't directly related.

Although there is no simple quantitative relationship between the stability of a carbocation intermediate and the rate of its formation, there *is* an intuitive relationship. It's generally true when comparing two similar reactions that the more stable intermediate forms faster than the less stable one. The situation is shown graphically in Figure 7.9.1, where the energy profile in part **(a)** represents the typical situation, as opposed to the profile in part **(b)**. That is, the curves for two similar reactions don't cross one another.

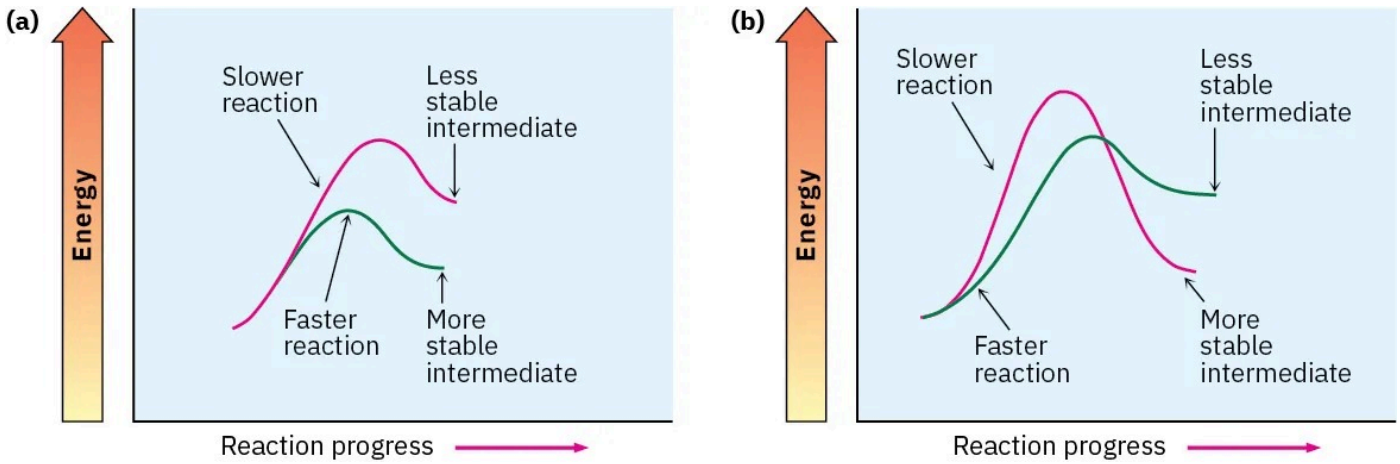


Figure 7.9.1: Energy diagrams for two similar competing reactions. In **(a)**, the faster reaction yields the more stable intermediate. In **(b)**, the slower reaction yields the more stable intermediate. The curves shown in **(a)** represent the typical situation.

Called the Hammond postulate, the explanation of the relationship between reaction rate and intermediate stability goes like this: Transition states represent energy maxima. They are high-energy activated complexes that occur transiently during the course of a reaction and immediately go on to a more stable species. Although we can't actually observe transition states because they have no finite lifetime, the Hammond postulate says that we can get an idea of a particular transition state's structure by looking at the structure of the nearest stable species. Imagine the two cases shown in Figure 7.9.2, for example. The reaction profile in part **(a)** shows the energy curve for an endergonic reaction step, and the profile in part **(b)** shows the curve for an exergonic step.

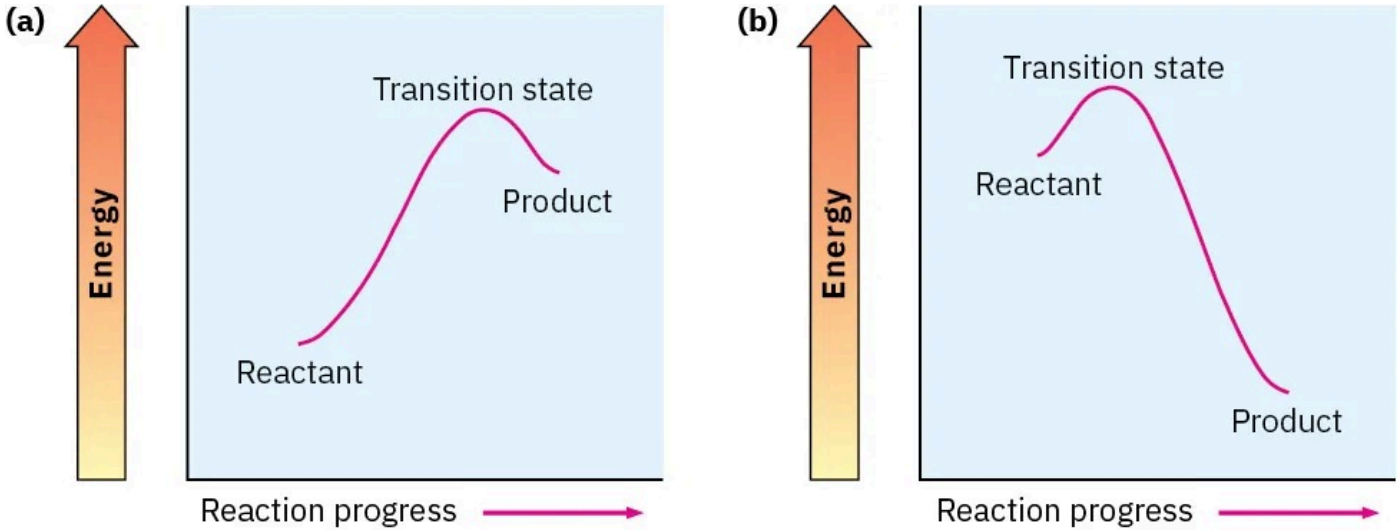


Figure 7.9.2: Energy diagrams for endergonic and exergonic steps. **(a)** In an endergonic step, the energy levels of transition state and *product* are closer. **(b)** In an exergonic step, the energy levels of transition state and *reactant* are closer.

In an endergonic reaction (Figure 7.9.2a), the energy level of the transition state is closer to that of the product than that of the reactant. Since the transition state is closer energetically to the product, we make the natural assumption that it's also closer structurally. In other words, the transition state for an endergonic reaction step structurally resembles the product of that step. Conversely, the transition state for an exergonic reaction (Figure 7.9.2b), is closer energetically, and thus structurally, to the reactant than to the product. We therefore say that the transition state for an exergonic reaction step structurally resembles the reactant for that step.

Hammond Postulate

The structure of a transition state resembles the structure of the nearest stable species. Transition states for endergonic steps structurally resemble products, and transition states for exergonic steps structurally resemble reactants.

How does the Hammond postulate apply to electrophilic addition reactions? The formation of a carbocation by protonation of an alkene is an endergonic step. Thus, the transition state for alkene protonation structurally resembles the carbocation intermediate, and any factor that stabilizes the carbocation will also stabilize the nearby transition state. Since increasing alkyl substitution stabilizes carbocations, it also stabilizes the transition states leading to those ions, thus resulting in a faster reaction. In other words, more stable carbocations form faster because their greater stability is reflected in the lower-energy transition state leading to them (Figure 7.9.3).

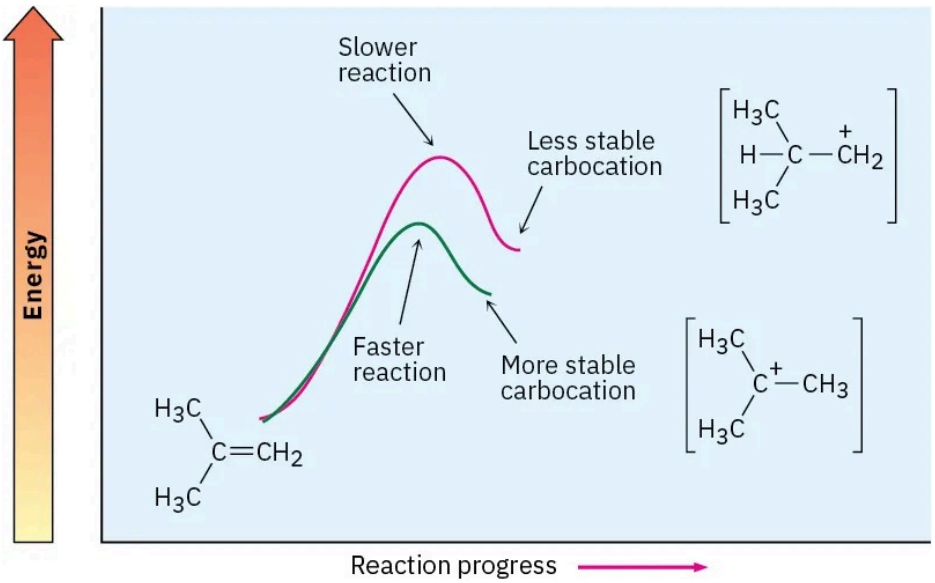


Figure 7.9.3: Energy diagrams for carbocation formation. The more stable tertiary carbocation is formed faster **(green curve)** because its increased stability lowers the energy of the transition state leading to it.

We can imagine the transition state for alkene protonation to be a structure in which one of the alkene carbon atoms has almost completely rehybridized from sp^2 to sp^3 and the remaining alkene carbon bears much of the positive charge (Figure 7.9.4). This transition state is stabilized by hyperconjugation and inductive effects in the same way as the product carbocation. The more alkyl groups that are present, the greater the extent of stabilization and the faster the transition state forms.

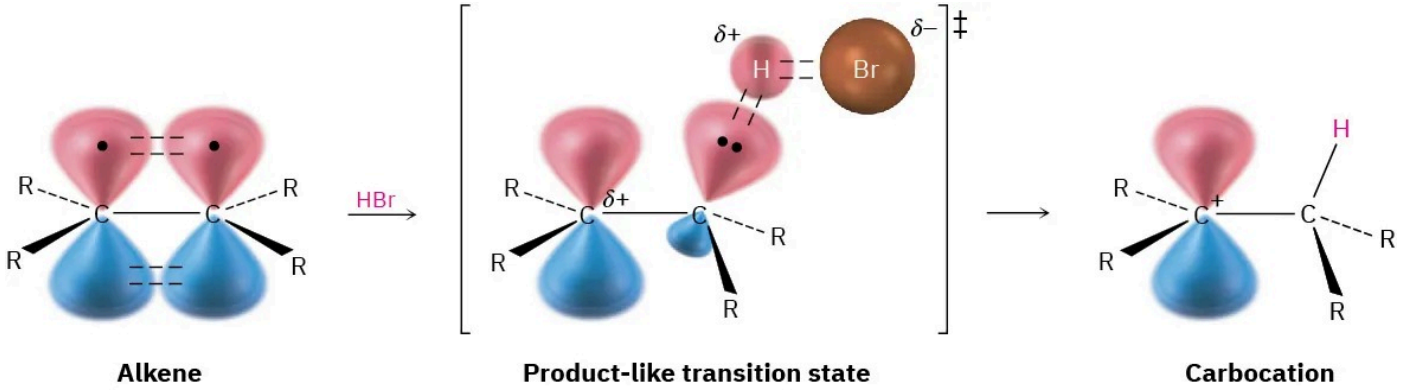


Figure 7.9.4: The hypothetical structure of a transition state for alkene protonation. The transition state is closer in both energy and structure to the carbocation than to the alkene. Thus, an increase in carbocation stability (lower $\Delta G°$) also causes an increase in transition-state stability (lower $\Delta G^{‡}$), thereby increasing the rate of its formation.

Exercise 7.9.1

What about the second step in the electrophilic addition of HCl to an alkene—the reaction of chloride ion with the carbocation intermediate? Is this step exergonic or endergonic? Does the transition state for this second step resemble the reactant (carbocation) or product (alkyl chloride)? Make a rough drawing of what the transition-state structure might look like.

Answer available at the end of this section.

Answers

Exercise 7.9.1

The second step is exergonic; the transition state resembles the carbocation.

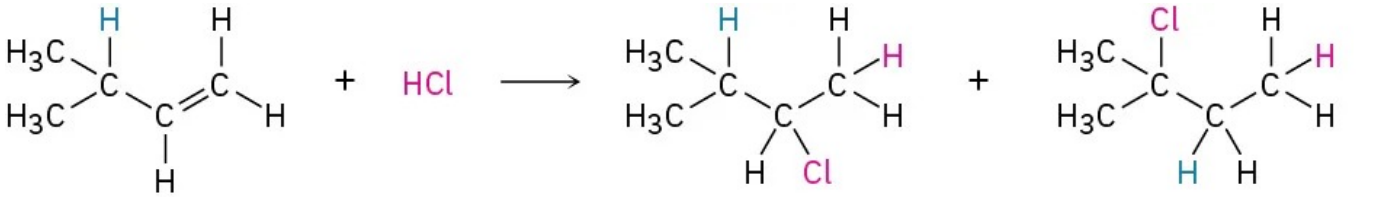
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7.10: Evidence for the Mechanism of Electrophilic Additions - Carbocation Rearrangements

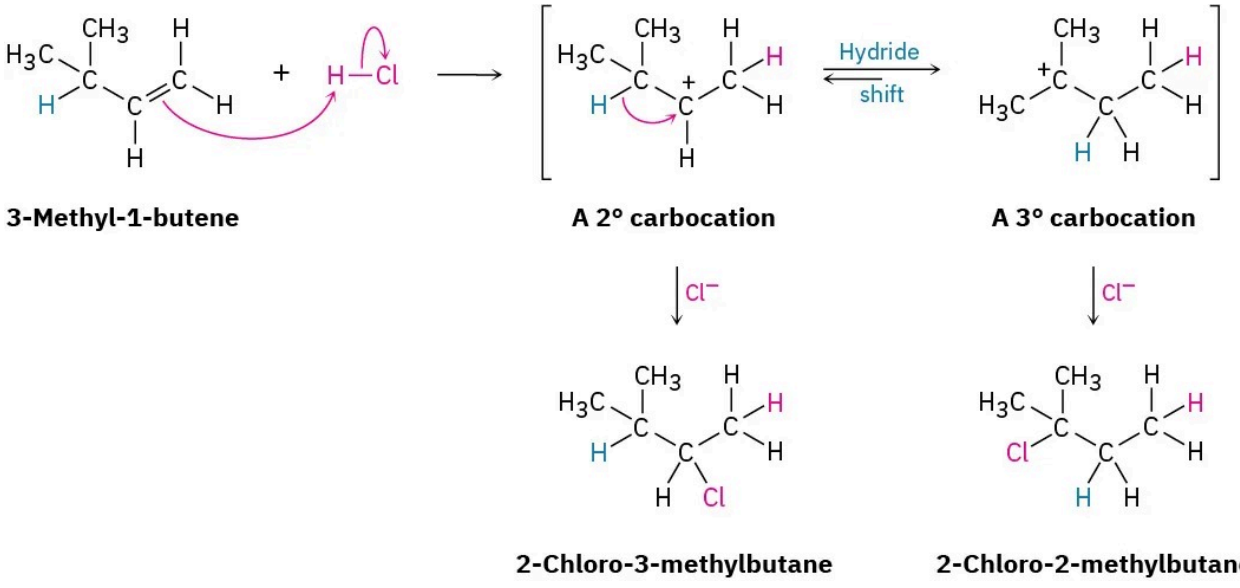
How do we know that the carbocation mechanism for electrophilic addition reactions of alkenes is correct? The answer is that we *don't* know it's correct; at least we don't know with complete certainty. Although an incorrect reaction mechanism can be disproved by demonstrating that it doesn't account for observed data, a correct reaction mechanism can never be entirely proven. The best we can do is to show that a proposed mechanism is consistent with all known facts. If enough facts are accounted for, the mechanism is probably correct.

One of the best pieces of evidence supporting the carbocation mechanism for the electrophilic addition reaction was discovered during the 1930s by F. C. Whitmore of Pennsylvania State University, who found that structural rearrangements often occur during the reaction of HX with an alkene. For example, reaction of HCl with 3-methyl-1-butene yields a substantial amount of 2-chloro-2-methylbutane in addition to the "expected" product, 2-chloro-3-methylbutane.



3-Methyl-1-butene | **2-Chloro-3-methylbutane (approx. 50%)** | **2-Chloro-2-methylbutane (approx. 50%)**

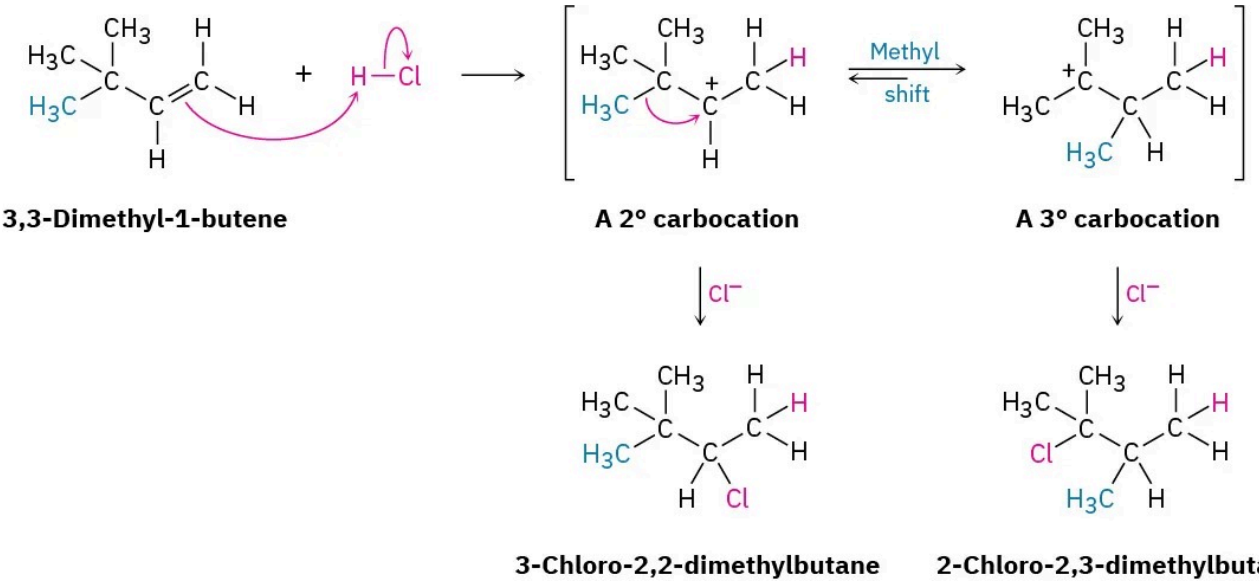
If the reaction takes place in a single step, it would be difficult to account for rearrangement, but if the reaction takes place in several steps, rearrangement is more easily explained. Whitmore suggested that it is a carbocation intermediate that undergoes rearrangement. The secondary carbocation intermediate formed by protonation of 3-methyl-1-butene rearranges to a more stable tertiary carbocation by a hydride shift—the shift of a hydrogen atom and its electron pair (a hydride ion, $:H^-$) between neighboring carbons.



3-Methyl-1-butene | **A 2° carbocation** | **A 3° carbocation**

2-Chloro-3-methylbutane | **2-Chloro-2-methylbutane**

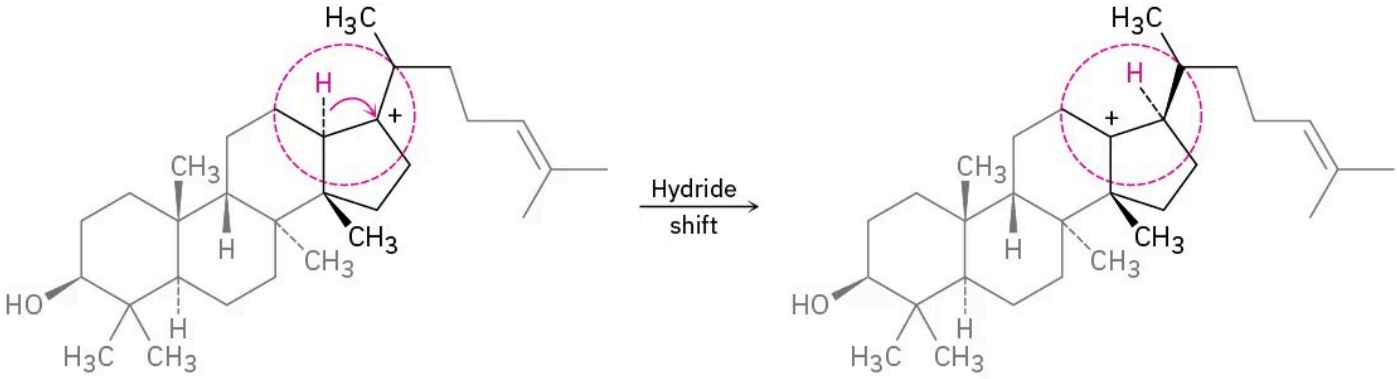
Carbocation rearrangements can also occur by the shift of an alkyl group with its electron pair. For example, reaction of 3,3-dimethyl-1-butene with HCl leads to an equal mixture of unrearranged 3-chloro-2,2-dimethylbutane and rearranged 2-chloro-2,3-dimethylbutane. In this instance, a secondary carbocation rearranges to a more stable tertiary carbocation by the shift of a methyl group.



3,3-Dimethyl-1-butene | **A 2° carbocation** | **A 3° carbocation**

3-Chloro-2,2-dimethylbutane | **2-Chloro-2,3-dimethylbutane**

Note the similarities between the two carbocation rearrangements: in both cases, a group ($:H^-$ or $:CH_3^-$) moves to an adjacent positively charged carbon, taking its bonding electron pair with it. Also in both cases, a less stable carbocation rearranges to a more stable ion. Rearrangements of this kind are a common feature of carbocation chemistry and are particularly important in the biological pathways by which steroids and related substances are synthesized. An example is the following hydride shift that occurs during the biosynthesis of cholesterol.

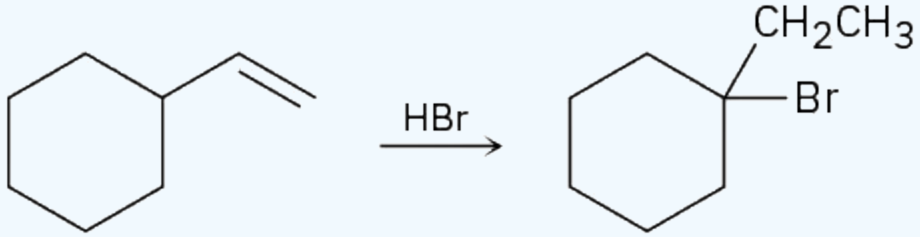


A tertiary carbocation | **An isomeric tertiary carbocation**

As always, when looking at any complex chemical transformation, whether biochemical or not, focus on the part of the molecule where the change is occurring and don't worry about the rest. The tertiary carbocation just pictured looks complicated, but all the chemistry is taking place in the small part of the molecule inside the red circle.

Exercise 7.10.1

On treatment with HBr, vinylcyclohexane undergoes addition and rearrangement to yield 1-bromo-1-ethylcyclohexane. Using curved arrows, propose a mechanism to account for this result.

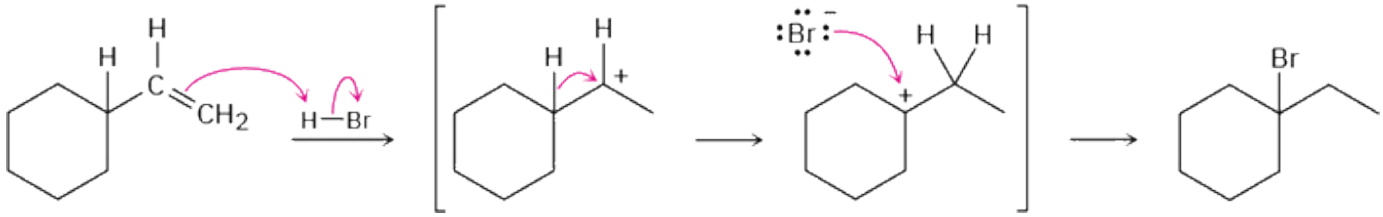


Vinylcyclohexane **1-Bromo-1-ethylcyclohexane**

Answer available at the end of this section.

Answers

Exercise 7.10.1



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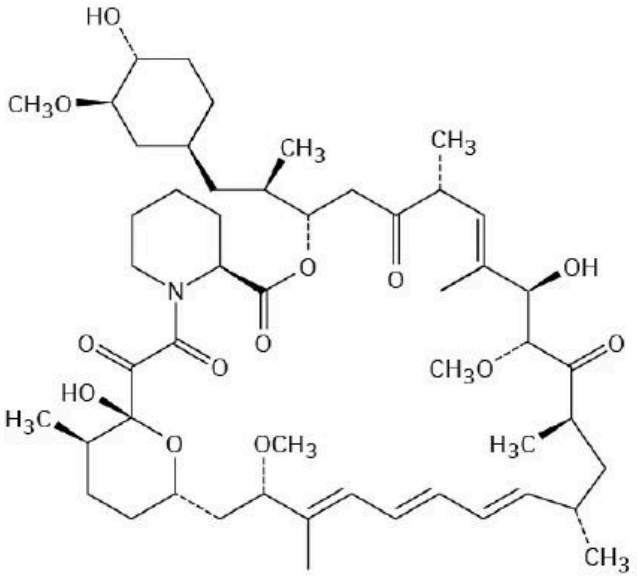
7.11: Chemistry Matters—Bioprospecting- Hunting for Natural Products

Most people know the names of the common classes of biomolecules—proteins, carbohydrates, lipids, and nucleic acids—but there are many more kinds of compounds in living organisms than just those four. All living organisms also contain a vast diversity of substances usually grouped under the heading *natural products*. The term **natural product** really refers to any naturally occurring substance but is generally taken to mean a so-called secondary metabolite—a small molecule that is not essential to the growth and development of the producing organism and is not classified by structure.



Figure 7.11.1: Rapamycin, an immunosuppressant natural product used during organ transplants, was originally isolated from a soil sample found on Rapa Nui (Easter Island), an island 2200 miles off the coast of Chile known for its giant Moai statues. (credit: modification of work "Moai facing inland at Ahu Tongariki" by Ian Sewell/Wikimedia Commons, CC BY 2.5)

It has been estimated that well over 300,000 secondary metabolites exist, and it's thought that their primary function is to increase the likelihood of an organism's survival by repelling or attracting other organisms. Alkaloids, such as morphine; antibiotics, such as erythromycin and the penicillins; and immunosuppressive agents, such as rapamycin (sirolimus) prescribed for liver transplant recipients, are examples.



Rapamycin (Sirolimus)

Where do these natural products come from, and how are they found? Although most chemists and biologists spend their working time in the laboratory, a few spend their days scuba diving on South Pacific islands or trekking through the rainforests of South America and Southeast Asia at work as bioprospectors. Their job is to hunt for new and unusual natural products that might be useful as drugs.

As noted in the Chapter 6 *Chemistry Matters*, more than half of all new drug candidates come either directly or indirectly from natural products. Morphine from the opium poppy, prostaglandin E_1 from sheep prostate glands, erythromycin A from a *Streptomyces erythreus* bacterium cultured from a Philippine soil sample, and benzylpenicillin from the mold *Penicillium notatum* are examples. The immunosuppressive agent rapamycin, whose structure is shown previously, was first isolated from a *Streptomyces hygroscopicus* bacterium found in a soil sample from Rapa Nui (Easter Island), located 2200 miles off the coast of Chile.

With less than 1% of living organisms yet investigated, bioprospectors have a lot of work to do. But there is a race going on. Rainforests throughout the world are being destroyed at an alarming rate, causing many species of both plants and animals to become extinct before they can even be examined. The governments in many countries seem aware of the problem, but there is as yet no international treaty on biodiversity that could help preserve vanishing species.

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7.A: Alkenes - Structure and Reactivity (Summary)

Concepts & Vocabulary

7.1 Industrial Preparation and Use of Alkenes

- Breaking up large hydrocarbon molecules into smaller, useful molecules is called cracking.

7.2 Calculating Degree of Unsaturation

- Saturated molecules contain only single bonds and no rings.
- Saturated hydrocarbons have the formula C_nH_{2n+2}, where n can be any integer.
- Degrees of unsaturation account for the total number of rings and pi bonds in a molecule.
- Each degree of unsaturation reduces the number of hydrogens in the molecule by 2.

7.4 Cis-Trans Isomerism in Alkenes

7.5 Alkene Stereochemistry and the E, Z Designation

- *E* and *Z* are less limited than cis and trans in naming.
- *E* and *Z* configurations use the same priority rules as R and S (CIP rules).

7.6 Stability of Alkenes

- Relative stability of alkenes can be measured by using heats of hydrogenation upon reduction to the related alkane.
- More substituted alkenes are more stable than less substituted.
- Alkenes with the largest groups trans are more stable than cis.

7.7 Electrophilic Addition Reactions of Alkenes

- In electrophilic addition reactions, the pi bond of the alkene acts as the nucleophile.
- Electrophilic addition reactions occur faster with larger hydrogen halides as well as more substituted alkenes.

7.8 Orientation of Electrophilic Additions: Markovnikov's Rule

- The more substituted carbocation intermediate forms during electrophilic addition reactions, since more substituted carbocations are more stable. This is known as Markovnikov's rule.

7.9 Carbocation Structure and Stability

- Molecules or ions that can disperse (delocalize) charge are more stable than structures with charge localized on a single atom.
- Due to inductive stabilization, carbocation stability follows the order:

tertiary > secondary > primary > methyl

- Electron donating groups stabilize carbocations.
- Electron withdrawing groups destabilize carbocations.
- Resonance effects can stabilize a carbocation (some examples include benzylic and allylic carbocations).
- Vinylic carbocations are unstable and are unlikely to form.

7.10 The Hammond Postulate

- The Hammond Postulate states that transition state structure most resembles the nearest stable species.
- Based on the Hammond Postulate, transition states for exothermic reaction steps resemble reactants, while endergonic step transition states resemble products.

7.11 Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements

- Carbocations will rearrange from less stable to more stable isomers through hydride shifts or alkyl shifts.

Skills to Master

- Skill 7.1 Calculate the degree of unsaturation for organic molecular formulae.
- Skill 7.2 Draw isomers from a molecular formula.
- Skill 7.3 Name alkenes following IUPAC rules, including configuration (*E*, *Z*).
- Skill 7.4 Draw structures from IUPAC name.
- Skill 7.5 Describe bonding in alkenes, including bond length, strength, angle, and restricted rotation.
- Skill 7.6 Explain the stability of alkenes.
- Skill 7.7 Rank alkenes in order of stability.
- Skill 7.8 Draw the mechanism for electrophilic addition of HX to alkenes, including regiochemistry.
- Skill 7.9 Explain the stability of carbocations.
- Skill 7.10 Explain transition states related to the Hammond Postulate.
- Skill 7.11 Explain products formed by carbocation rearrangements.

Memorization Tasks

MT 7.1 Memorize formula for saturated hydrocarbons C_nH_{2n+2}.

MT 7.2 Memorize basic IUPAC naming rules.

MT 7.3 Memorize relative stability of alkenes.

MT 7.4 Memorize relative stability of carbocations.

Contributors

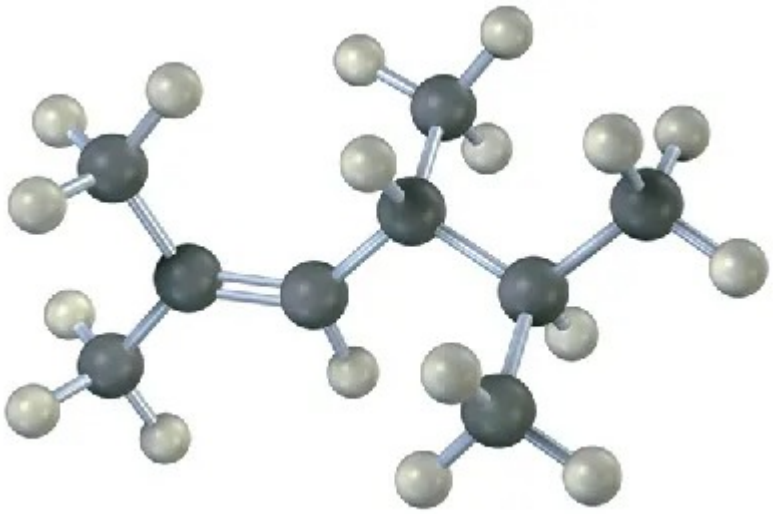
- Layne Morsch (University of Illinois Springfield)

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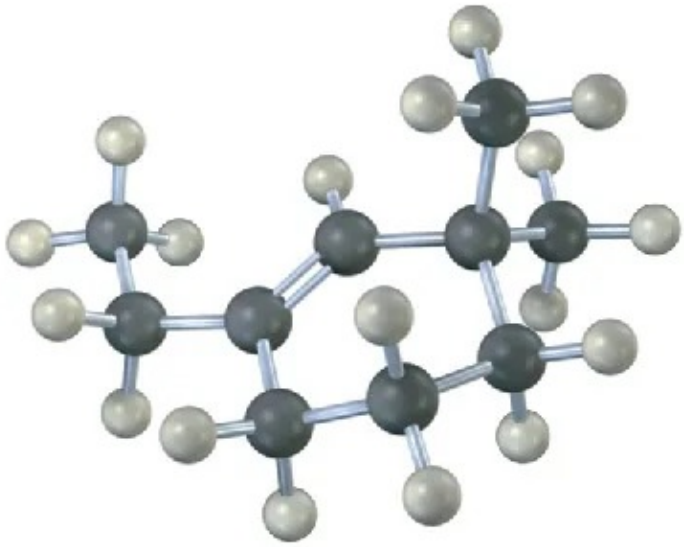
7.B: Additional Problems

Visualizing Chemistry

PROBLEM 7-22 Name the following alkenes, and convert each drawing into a skeletal structure:

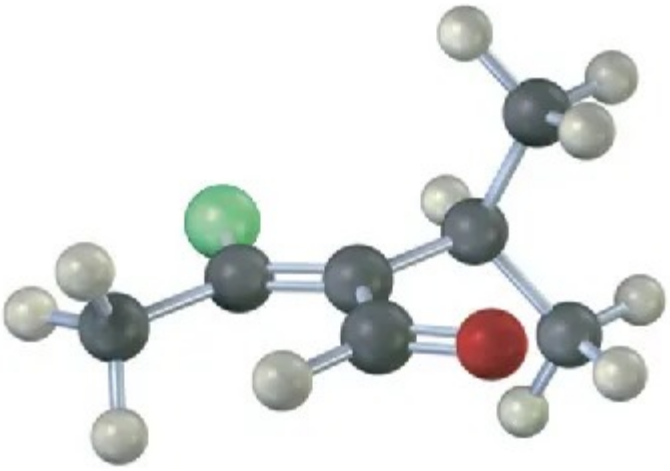


(a)

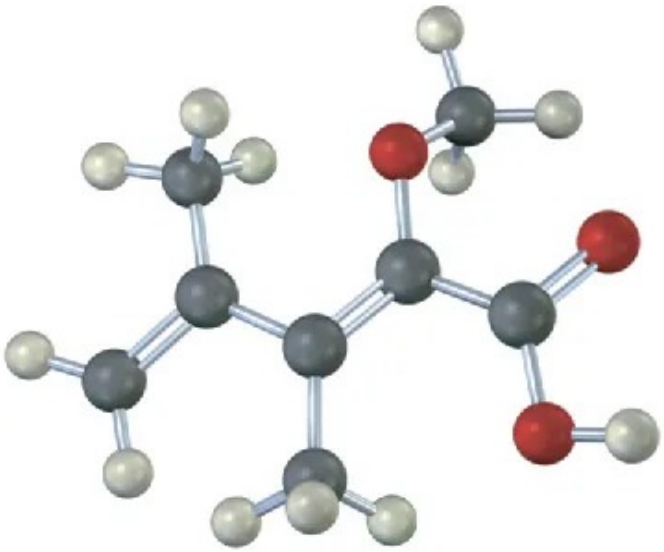


(b)

PROBLEM 7-23 Assign E or *Z* stereochemistry to the double bonds in each of the following alkenes, and convert each drawing into a skeletal structure (red = O, green = Cl):

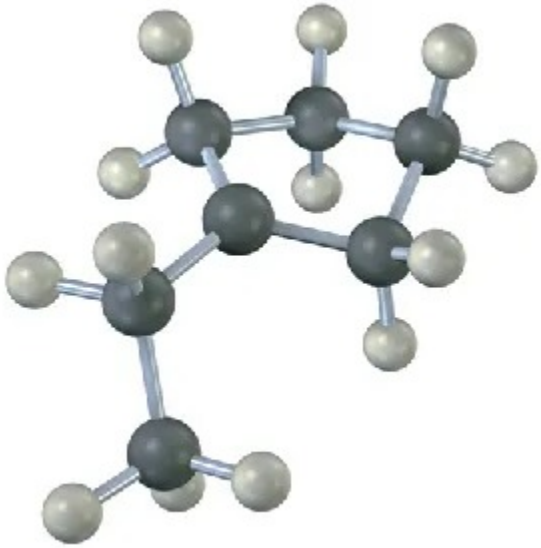


(a)

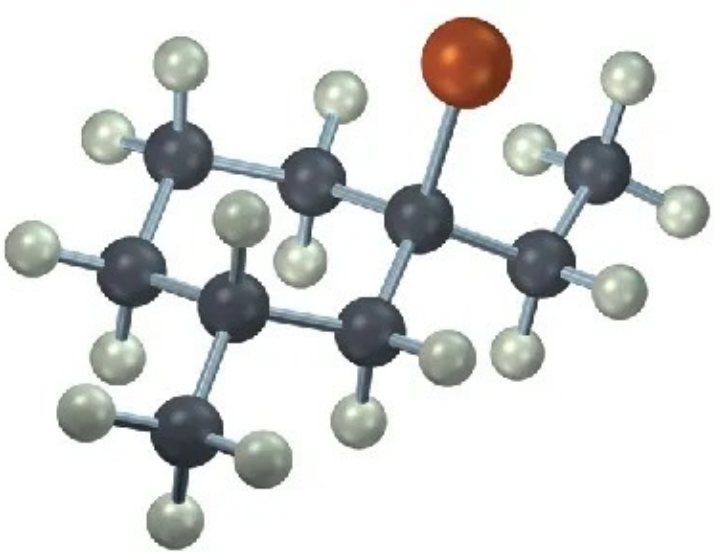


(b)

PROBLEM 7-24 The following carbocation is an intermediate in the electrophilic addition reaction of HCl with two different alkenes. Identify both, and tell which C–H bonds in the carbocation are aligned for hyperconjugation with the vacant *p* orbital on the positively charged carbon.



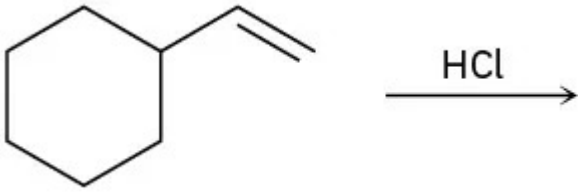
PROBLEM 7-25 The following alkyl bromide can be made by HBr addition to three different alkenes. Show their structures.



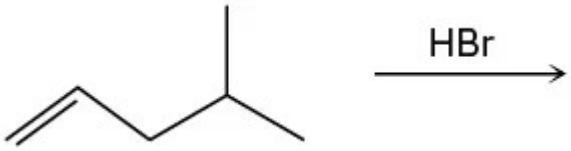
Mechanism Problems

PROBLEM 7-26 Predict the major product and show the complete mechanism for each of the following electrophilic addition reactions.

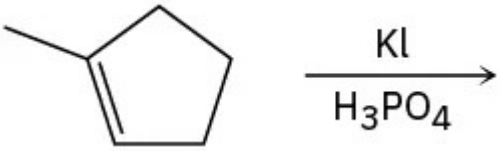
(a)



(b)

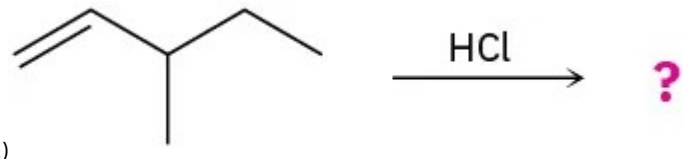


(c)

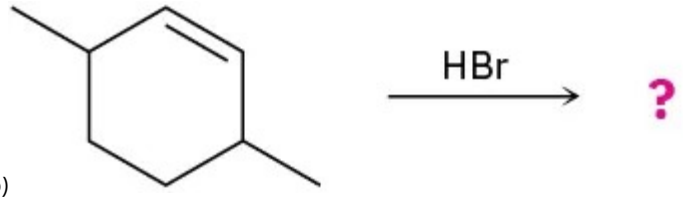


PROBLEM 7-27 Each of the following electrophilic addition reactions involves a carbocation rearrangement. Predict the product and draw the complete mechanism of each using curved arrows.

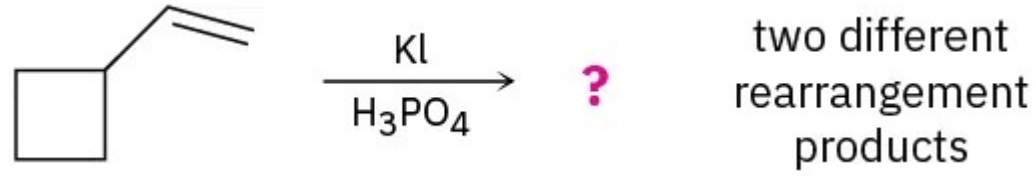
(a)



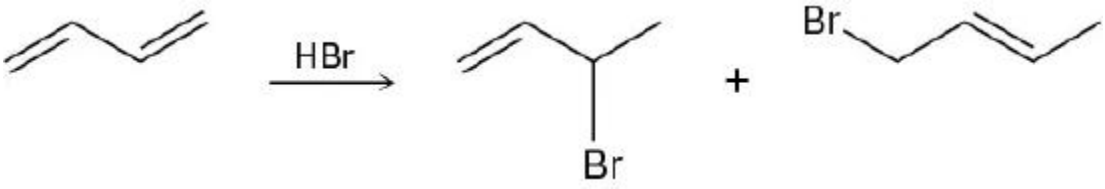
(b)



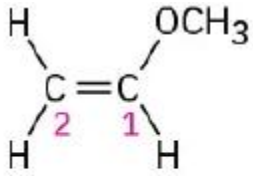
(c)



PROBLEM 7-28 When 1,3-butadiene reacts with 1 mol of HBr, two isolable products result. Propose mechanisms for both.

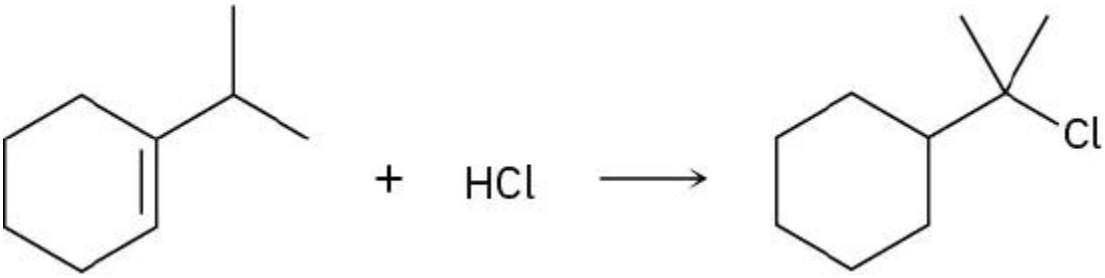


PROBLEM 7-29 When methyl vinyl ether reacts with a strong acid, H^+ adds to C2 instead of C1 or the oxygen atom. Explain.

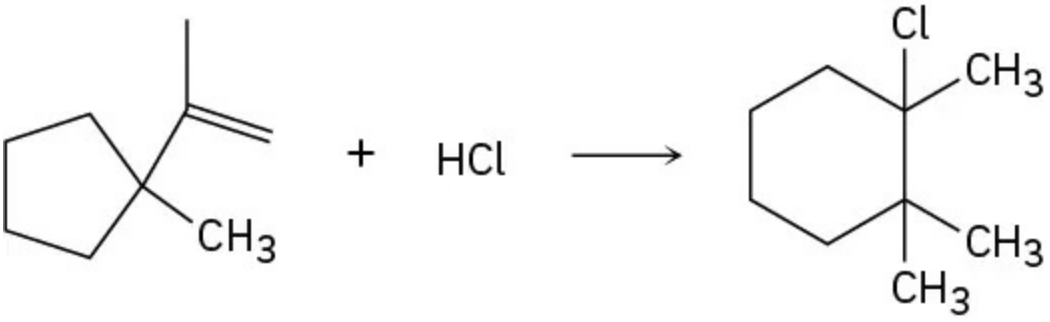


Methyl vinyl ether

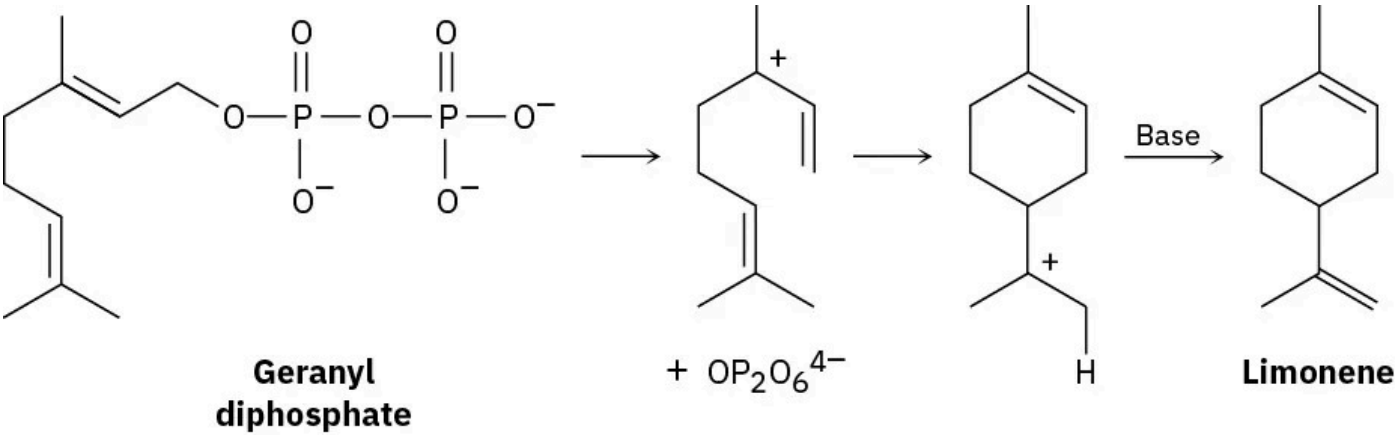
PROBLEM 7-30 Addition of HCl to 1-isopropylcyclohexene yields a rearranged product. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.



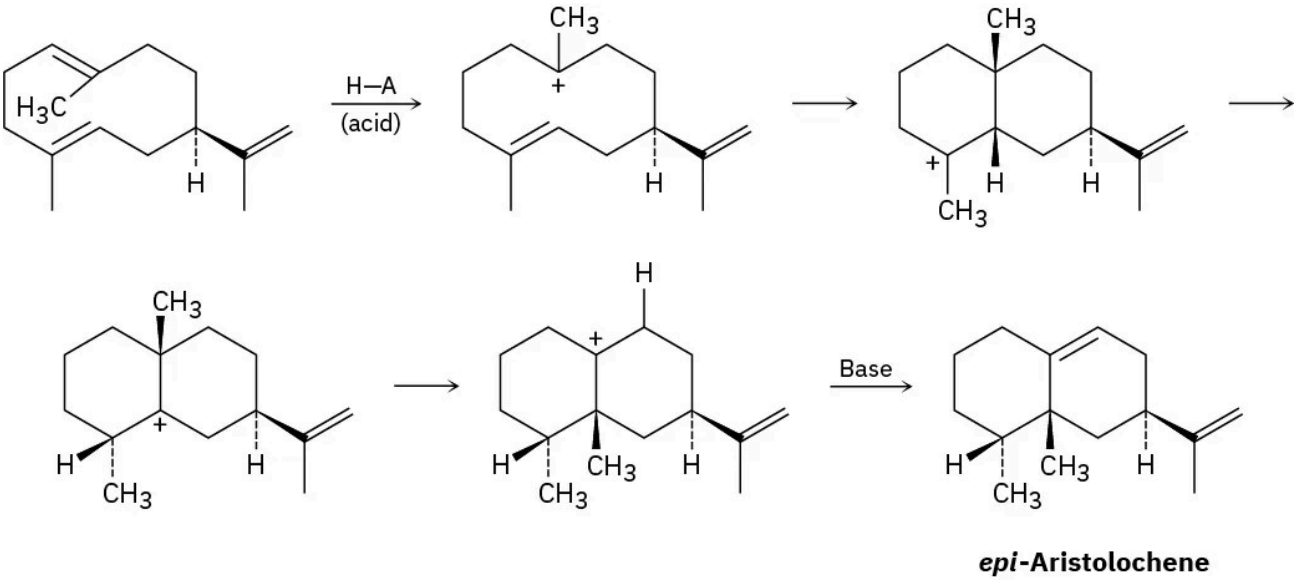
PROBLEM 7-31 Addition of HCl to 1-isopropenyl-1-methylcyclopentane yields 1-chloro-1,2,2-trimethylcyclohexane. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.



PROBLEM 7-32 Limonene, a fragrant hydrocarbon found in lemons and oranges, is biosynthesized from geranyl diphosphate by the following pathway. Add curved arrows to show the mechanism of each step. Which step involves an alkene electrophilic addition? (The ion $OP_2O_6^{4-}$ is the diphosphate ion, and "Base" is an unspecified base in the enzyme that catalyzes the reaction.)



PROBLEM 7-33 *epi*-Aristolochene, a hydrocarbon found in both pepper and tobacco, is biosynthesized by the following pathway. Add curved arrows to show the mechanism of each step. Which steps involve alkene electrophilic addition(s), and which involve carbocation rearrangement(s)? (The abbreviation H—A stands for an unspecified acid, and "Base" is an unspecified base in the enzyme.)



Calculating Degree of Unsaturation

PROBLEM 7-34 Calculate the degree of unsaturation in the following formulas, and draw five possible structures for each:

(a) $C_{10}H_{16}$ (b) C_8H_8O (c) $C_7H_{10}Cl_2$ (d) $C_{10}H_{16}O_2$ (e) $C_5H_9NO_2$ (f) $C_8H_{10}ClNO$

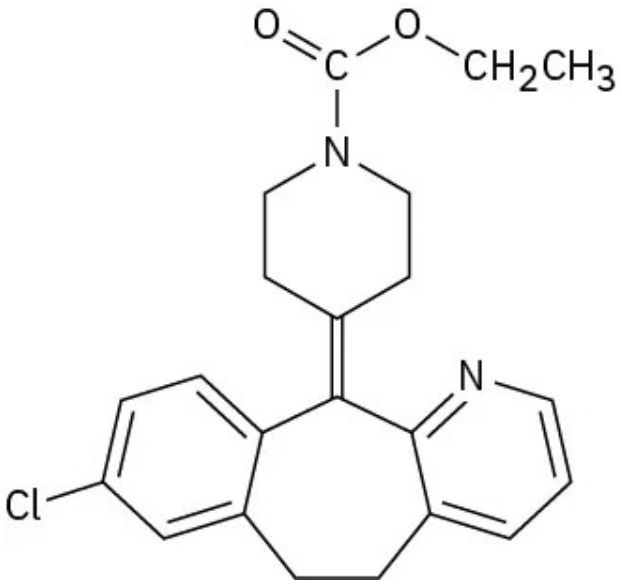
PROBLEM 7-35 How many hydrogens does each of the following compounds have?

(a) $C_8H_?O_2$, has two rings and one double bond.

(b) $C_7H_?N$, has two double bonds.

(c) $C_9H_?NO$, has one ring and three double bonds.

PROBLEM 7-36 Loratadine, marketed as an antiallergy medication under the brand name Claritin, has four rings, eight double bonds, and the formula $C_{22}H_?ClN2O2$. How many hydrogens does loratadine have? (Calculate your answer; don't count hydrogens in the structure.)

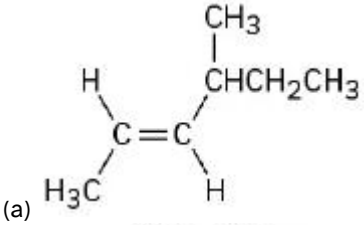


Loratadine

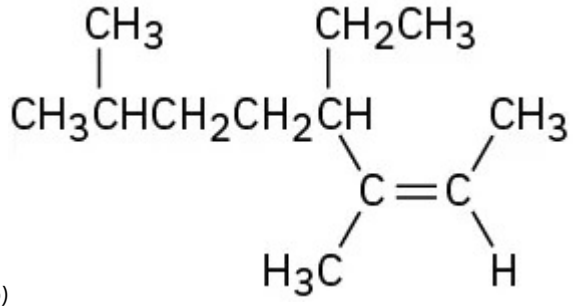
Naming Alkenes

PROBLEM 7-37 Name the following alkenes:

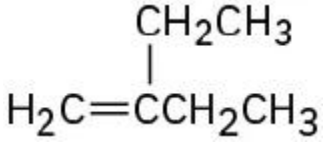
(a)



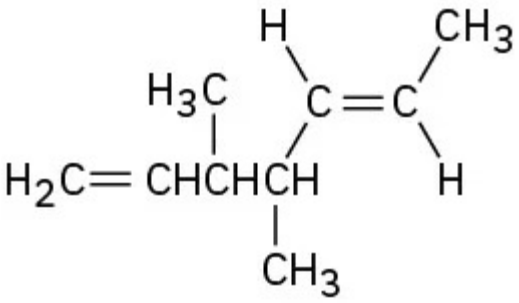
(b)



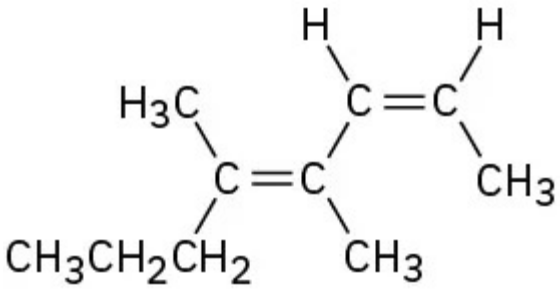
(c)



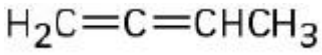
(d)



(e)



(f)



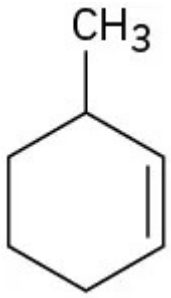
PROBLEM 7-38 Draw structures corresponding to the following systematic names:

(a) (4*E*)-2,4-Dimethyl-1,4-hexadiene **(b)** *cis*-3,3-Dimethyl-4-propyl-1,5-octadiene **(c)** 4-Methyl-1,2-pentadiene

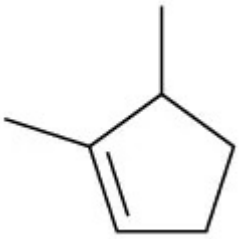
(d) (3*E*,5*Z*)-2,6-Dimethyl-1,3,5,7-octatetraene **(e)** 3-Butyl-2-heptene **(f)** *trans*-2,2,5,5-Tetramethyl-3-hexene

PROBLEM 7-39 Name the following cycloalkenes:

(a)



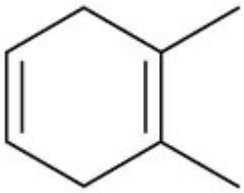
(b)



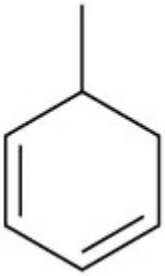
(c)



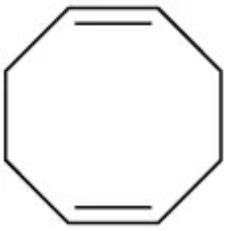
(d)



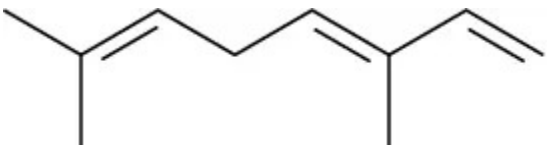
(e)



(f)

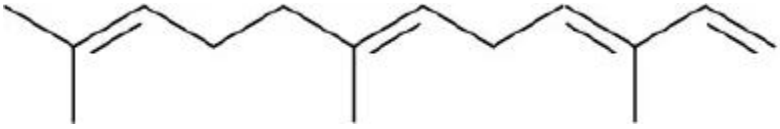


PROBLEM 7-40 Ocimene is a triene found in the essential oils of many plants. What is its IUPAC name, including stereochemistry?



Ocimene

PROBLEM 7-41 α-Farnesene is a constituent of the natural wax found on apples. What is its IUPAC name, including stereochemistry?



α-Farnesene

PROBLEM 7-42 Menthene, a hydrocarbon found in mint plants, has the systematic name 1-isopropyl-4-methylcyclohexene. Draw its structure.

PROBLEM 7-43 Draw and name the six alkene isomers, C_5H_{10}, including *E,Z* isomers.

PROBLEM 7-44 Draw and name the 17 alkene isomers, C_6H_{12}, including *E,Z* isomers.

Alkene Isomers and Their Stability

PROBLEM 7-45 Rank the following sets of substituents according to the Cahn–Ingold–Prelog sequence rules:

(a) $-CH_3, -Br, -H, -I$

(b) $-OH, -OCH_3, -H, -CO_2H$

(c) $-CO_2H, -CO_2CH_3, -CH_2OH, -CH_3$

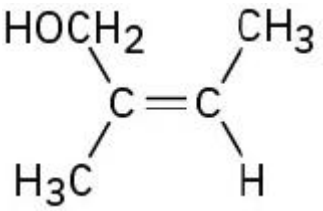
(d) $-CH_3, -CH_2CH_3, -CH_2CH_2OH, -CCH_3$ (O)

(e) $-CH{=}CH_2, -CN, -CH_2NH_2, -CH_2Br$

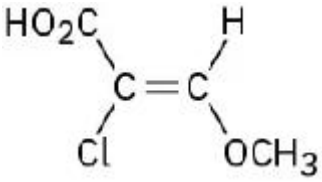
(f) $-CH{=}CH_2, -CH_2CH_3, -CH_2OCH_3, -CH_2OH$

Problem 7-46 Assign *E* or *Z* configuration to each of the following compounds:

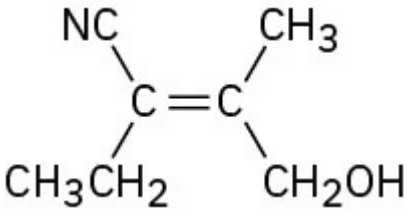
(a)



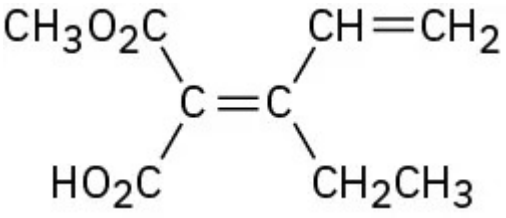
(b)



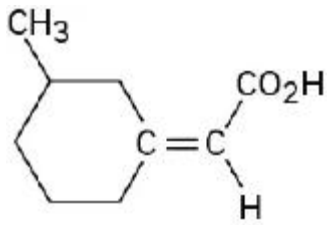
(c)



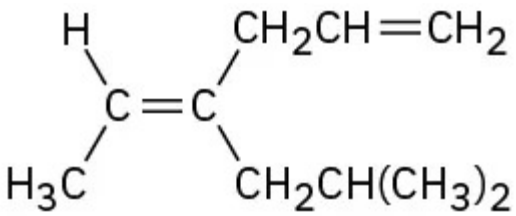
(d)



Problem 7-47 Which of the following *E, Z* designations are correct, and which are incorrect?

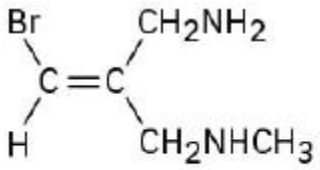


(a) *Z*

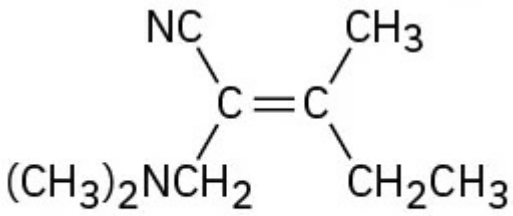


(b) *E*

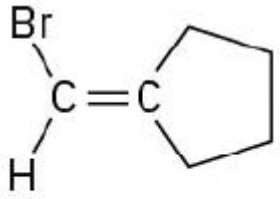
(c)



Z

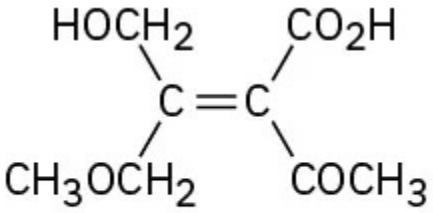


(d) *E*



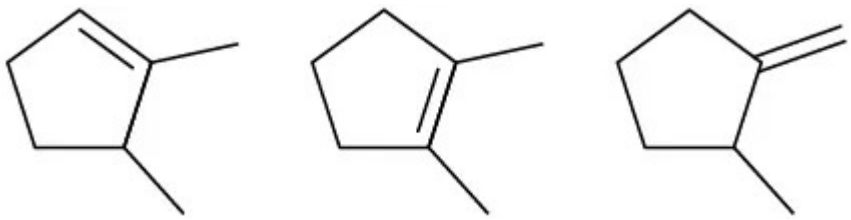
(e) *Z*

(f)



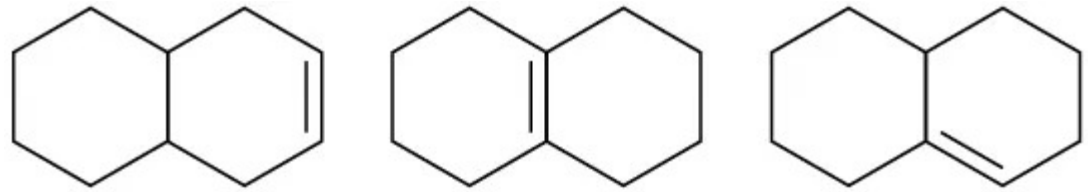
E

Problem 7-48 Rank the double bonds according to their increasing stability.

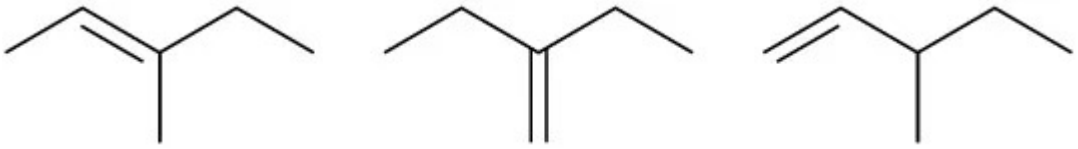


(a)

(b)



(c)



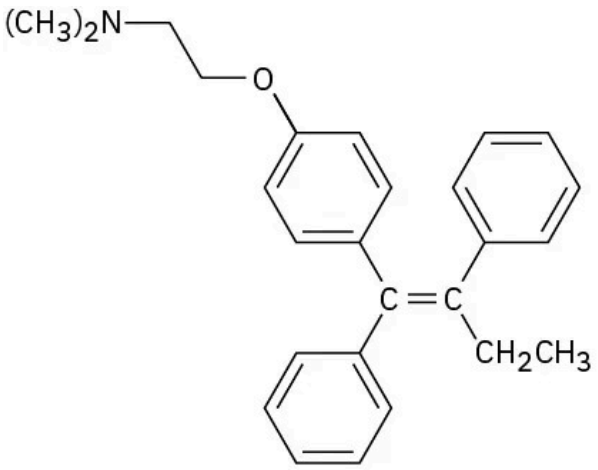
Problem 7-49 *trans*-2-Butene is more stable than *cis*-2-butene by only 4 kJ/mol, but *trans*-2,2,5,5-tetramethyl-3-hexene is more stable than its cis isomer by 39 kJ/mol. Explain.

Problem 7-50 Cyclodecene can exist in both cis and trans forms, but cyclohexene cannot. Explain.

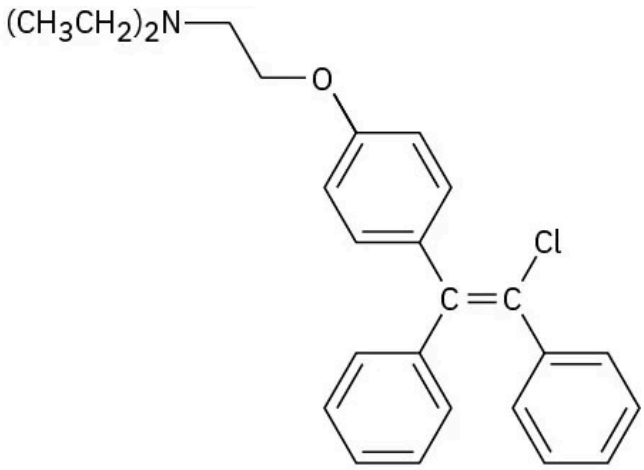
Problem 7-51 Normally, a trans alkene is more stable than its cis isomer. *trans*-Cyclooctene, however, is less stable than *cis*-cyclooctene by 38.5 kJ/mol. Explain.

Problem 7-52 *trans*-Cyclooctene is less stable than *cis*-cyclooctene by 38.5 kJ/mol, but *trans*-cyclononene is less stable than *cis*-cyclononene by only 12.2 kJ/mol. Explain.

Problem 7-53 Tamoxifen, a drug used in the treatment of breast cancer, and clomiphene, a drug used in fertility treatment, have similar structures but very different effects. Assign *E* or *Z* configuration to the double bonds in both compounds.



Tamoxifen
(anticancer)

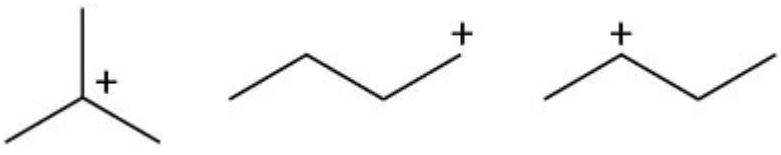


Clomiphene
(fertility treatment)

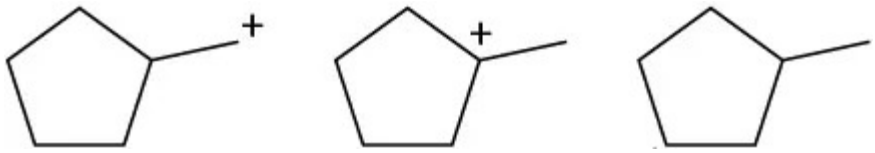
Carbocations and Electrophilic Addition Reactions

Problem 7-54 Rank the following carbocations according to their increasing stability.

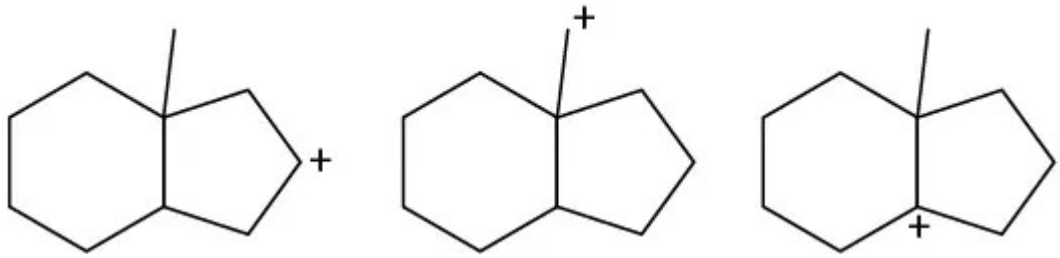
(a)



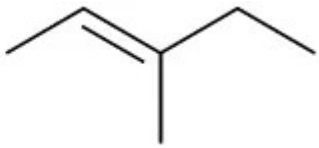
(b)

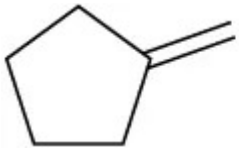
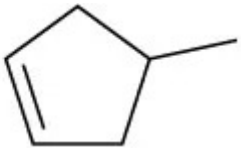


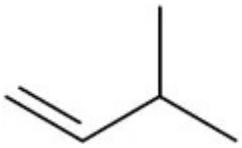
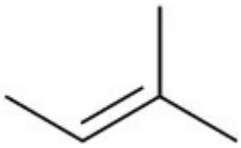
(c)



Problem 7-55 Use the Hammond Postulate to determine which alkene in each pair would be expected to form a carbocation faster in an electrophilic addition reaction.

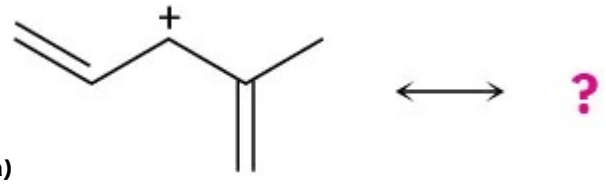
(a) _____  *vs.*  _____

(b) _____  *vs.*  _____

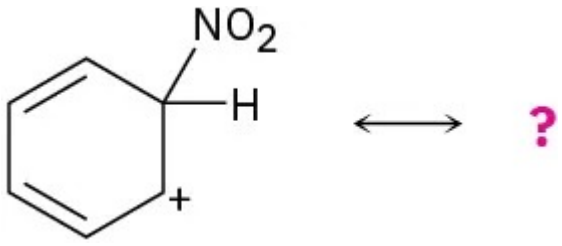
(c) _____  *vs.*  _____

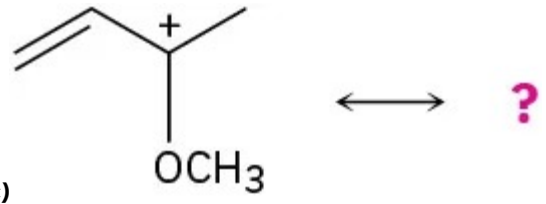
Problem 7-56 The following carbocations can be stabilized by resonance. Draw all the resonance forms that would stabilize each carbocation.

(a)



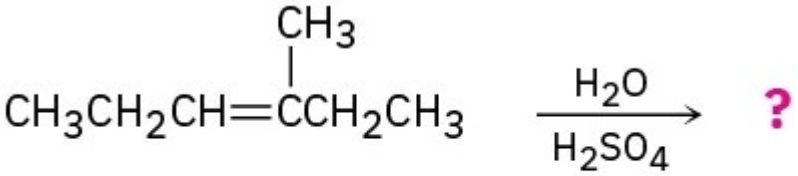
(b)





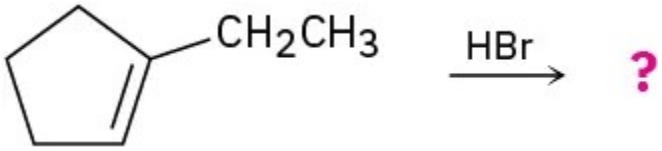
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Problem 7-57 Predict the major product in each of the following reactions:

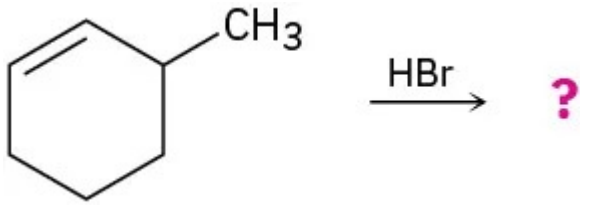


(Addition of H_2O occurs.)

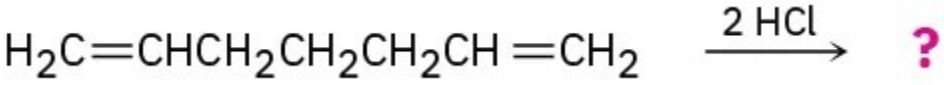
(a)



(b)



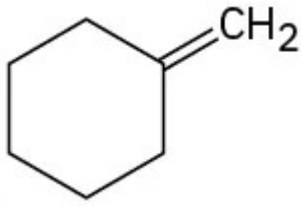
(c)



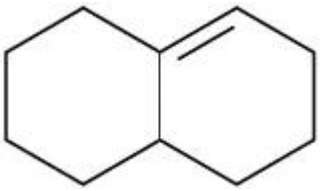
(d)

Problem 7-58 Predict the major product from the addition of HBr to each of the following alkenes:

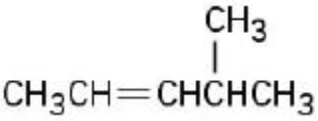
(a)



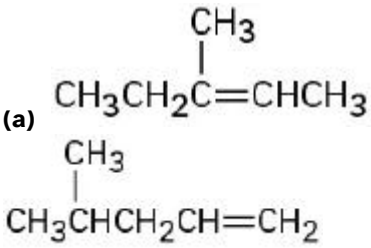
(b)

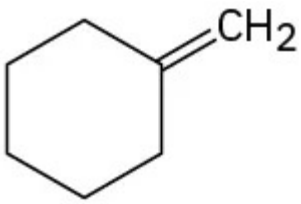


(c)



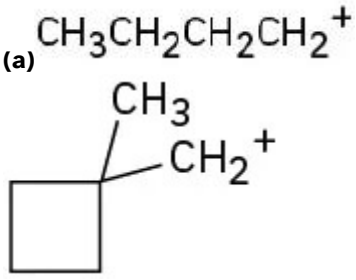
Problem 7-59 Alkenes can be converted into alcohols by acid-catalyzed addition of water. Assuming that Markovnikov's rule is valid, predict the major alcohol product from each of the following alkenes.

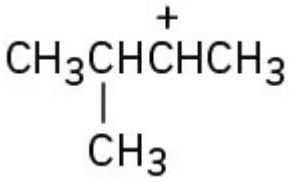
(a) 

(b) 

(c)

Problem 7-60 Each of the following carbocations can rearrange to a more stable ion. Propose structures for the likely rearrangement products.

(a) 

(b) 

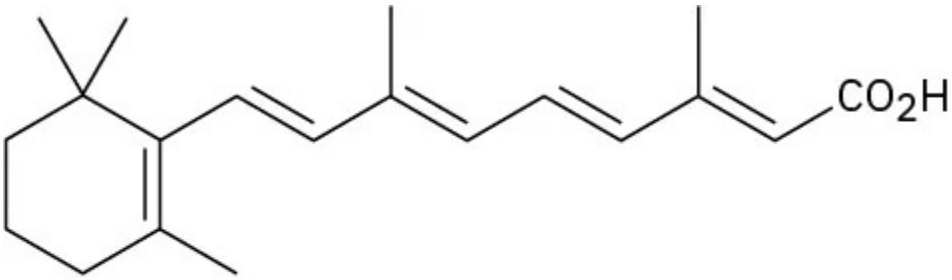
(c)

General Problems

Problem 7-61 Allene (1,2-propadiene), $H_2C{=}C{=}CH_2$, has two adjacent double bonds. What kind of hybridization must the central carbon have? Sketch the bonding π orbitals in allene. What shape do you predict for allene?

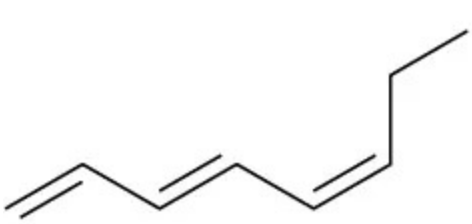
Problem 7-62 The heat of hydrogenation for allene (Problem 7-61) to yield propane is –295 kJ/mol, and the heat of hydrogenation for a typical monosubstituted alkene, such as propene, is –125 kJ/mol. Is allene more stable or less stable than you might expect for a diene? Explain.

Problem 7-63 Retin A, or retinoic acid, is a medication commonly used to reduce wrinkles and treat severe acne. How many different isomers arising from *E,Z* double-bond isomerizations are possible?

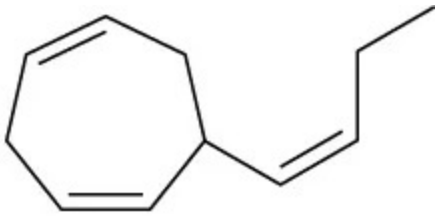


Retin A (retinoic acid)

Problem 7-64 Fucoserratene and ectocarpene are sex pheromones produced by marine brown algae. What are their systematic names? (Ectocarpene is difficult; make your best guess, and then check your answer in the *Student Solutions Manual*.)

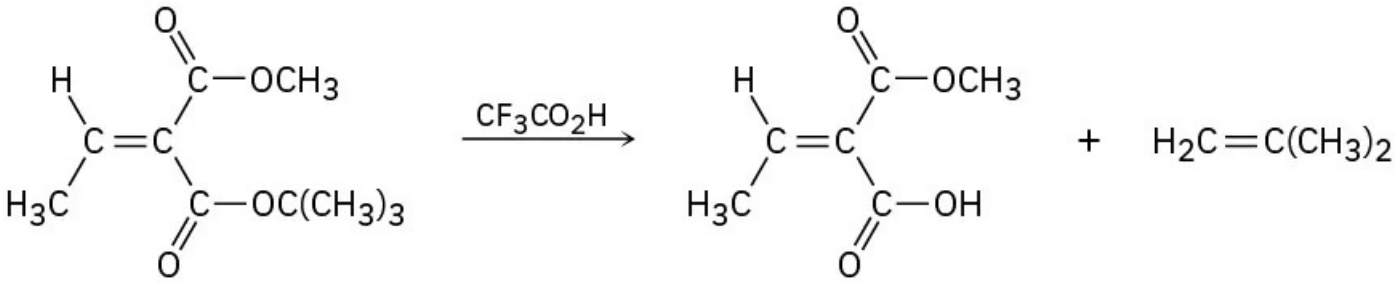


Fucoserratene

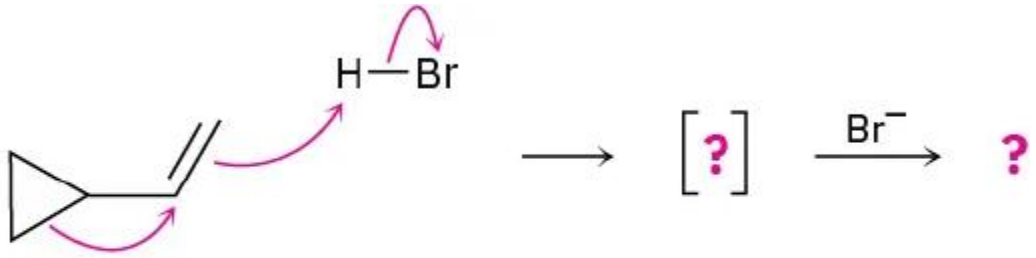


Ectocarpene

Problem 7-65 *tert*-Butyl esters [$RCO_2C(CH_3)_3$] are converted into carboxylic acids (RCO_2H) by reaction with trifluoroacetic acid, a reaction useful in protein synthesis (Section 26.7). Assign *E,Z* designation to the double bonds of both reactant and product in the following scheme, and explain why there is an apparent change in double-bond stereochemistry:



Problem 7-66 Vinylcyclopropane reacts with HBr to yield a rearranged alkyl bromide. Follow the flow of electrons as represented by the curved arrows, show the structure of the carbocation intermediate in brackets, and show the structure of the final product.



Vinylcyclopropane

Problem 7-67 Calculate the degree of unsaturation in each of the following formulas:

(a) Cholesterol, $C_{27}H_{46}O$ **(b)** DDT, $C_{14}H_9Cl_5$ **(c)** Prostaglandin E_1, $C_{20}H_{34}O_5$

(d) Caffeine, $C_8H_{10}N_4O_2$ **(e)** Cortisone, $C_{21}H_{28}O_5$ **(f)** Atropine, $C_{17}H_{23}NO_3$

Problem 7-68 The isobutyl cation spontaneously rearranges to the *tert*-butyl cation by a hydride shift. Is the rearrangement exergonic or endergonic? Draw what you think the transition state for the hydride shift might look like according to the Hammond postulate.

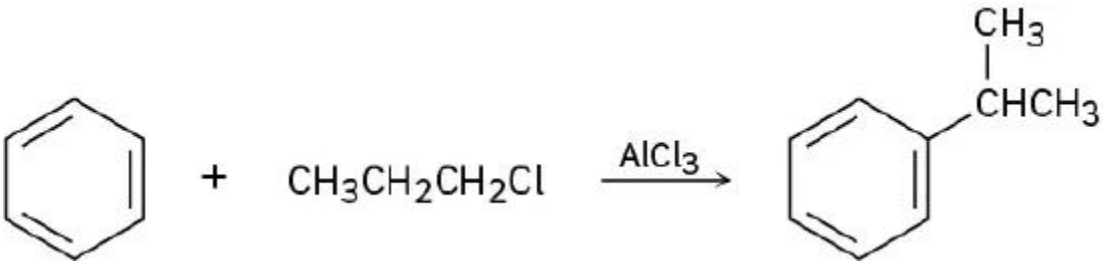


Isobutyl cation ***tert*-Butyl cation**

Problem 7-69 Draw an energy diagram for the addition of HBr to 1-pentene. Let one curve on your diagram show the formation of 1-bromopentane product and another curve on the same diagram show the formation of 2-bromopentane product. Label the positions for all reactants, intermediates, and products. Which curve has the higher-energy carbocation intermediate? Which curve has the higher-energy first transition state?

Problem 7-70 Sketch the transition-state structures involved in the reaction of HBr with 1-pentene (Problem 7-69). Tell whether each structure resembles reactant or product.

Problem 7-71 Aromatic compounds such as benzene react with alkyl chlorides in the presence of $AlCl_3$ catalyst to yield alkylbenzenes. This reaction occurs through a carbocation intermediate, formed by reaction of the alkyl chloride with $AlCl_3$ ($R–Cl + AlCl_3 \diamond R^+ + AlCl_4^-$). How can you explain the observation that the reaction of benzene with 1-chloropropane yields isopropylbenzene as the major product?



Problem 7-72 Reaction of 2,3-dimethyl-1-butene with HBr leads to an alkyl bromide, $C_6H_{13}Br$. On treatment of this alkyl bromide with KOH in methanol, elimination of HBr occurs, and a hydrocarbon that is isomeric with the starting alkene is formed. What is the structure of this hydrocarbon, and how do you think it is formed from the alkyl bromide?

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8: ALKENES- REACTIONS AND SYNTHESIS

As you have seen, addition reactions dominate the chemistry of alkenes. This chapter shows how a variety of reagents can add to alkenes; how hydrogen bromide can be made to add to alkenes in a non-Markovnikov manner; and how alkene molecules can be cleaved into easily identifiable parts. First, you will examine the preparation of alkenes by elimination reactions.

8.0: Why This Chapter?

8.1: Preparation of Alkenes - A Preview of Elimination Reactions

8.2: Halogenation of Alkenes - Addition of X_2

8.3: Halohydrins from Alkenes - Addition of HO-X

8.4: Hydration of Alkenes- Acid-Catalyzed Hydration

8.5: Stereochemistry of Reactions

8.6: Hydration of Alkenes - Addition of H_2O by Oxymercuration

8.7: Hydration of Alkenes - Addition of H_2O by Hydroboration

8.8: Reduction of Alkenes - Hydrogenation

8.9: Oxidation of Alkenes - Epoxidation and Hydroxylation

8.10: Oxidation of Alkenes - Cleavage to Carbonyl Compounds

8.11: Addition of Carbenes to Alkenes - Cyclopropane Synthesis

8.12: Radical Additions to Alkenes - Chain-Growth Polymers

8.13: Biological Additions of Radicals to Alkenes

8.14: Chemistry Matters—Terpenes- Naturally Occurring Alkenes

8.A: Alkenes - Reactions and Synthesis (Summary)

8.B: Additional Problems

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8.0: Why This Chapter?

Much of the background needed to understand organic reactions has now been covered, and it's time to begin a systematic description of the major functional groups. In this chapter on alkenes, and in future chapters on other functional groups, we'll discuss a variety of reactions, but try to focus on the general principles and patterns of reactivity that tie organic chemistry together. There are no shortcuts; you have to know the reactions to understand organic and biological chemistry.



Figure 8.0.1: The Spectra fiber used to make the bulletproof vests used by police and military is made of ultra-high-molecular-weight polyethylene, a simple alkene polymer. (credit: modification of work "US Navy 081028-N-3857R-007 Seabees participate in a chemical, biological and radiological warfare drill" by U.S. Navy photo by Mass Communication Specialist 1st Class Chad Runge/Wikimedia Commons, Public Domain)

Alkene addition reactions occur widely, both in the laboratory and in living organisms. Although we've studied only the addition of HX thus far, many closely related reactions also take place. In this chapter, we'll see briefly how alkenes are prepared and we'll discuss further examples of alkene addition reactions. Particularly important are the addition of a halogen (X_2) to give a 1,2-dihalide, addition of a hypohalous acid (HOX) to give a halohydrin, addition of water to give an alcohol, addition of hydrogen to give an alkane, addition of a single oxygen to give a three-membered cyclic ether called an **epoxide**, and addition of two hydroxyl groups to give a 1,2-diol.

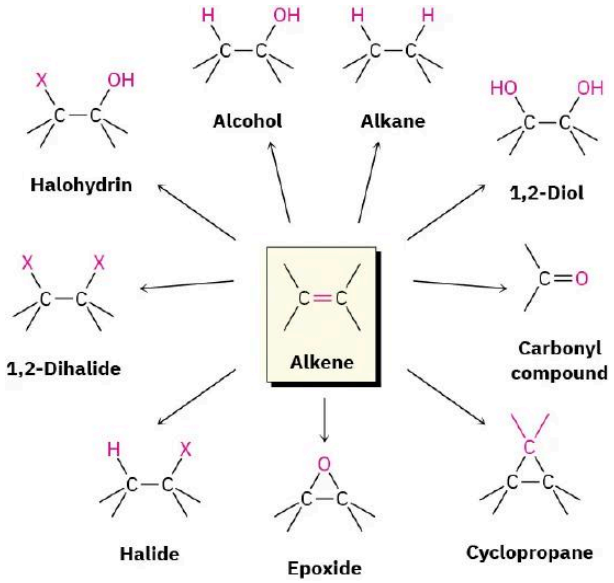


Figure 8.0.2: Some useful alkene reactions.

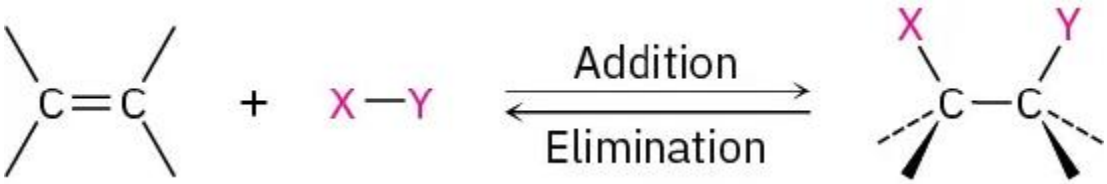
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8.1: Preparation of Alkenes - A Preview of Elimination Reactions

Before getting to the main subject of this chapter—the reactions of alkenes—let's take a brief look at how alkenes are prepared. The subject is a bit complex, though, so we'll return to it later for a more detailed study. For the present, it's enough to realize that alkenes are readily available from simple precursors—usually alcohols in biological systems and either alcohols or alkyl halides in the laboratory.

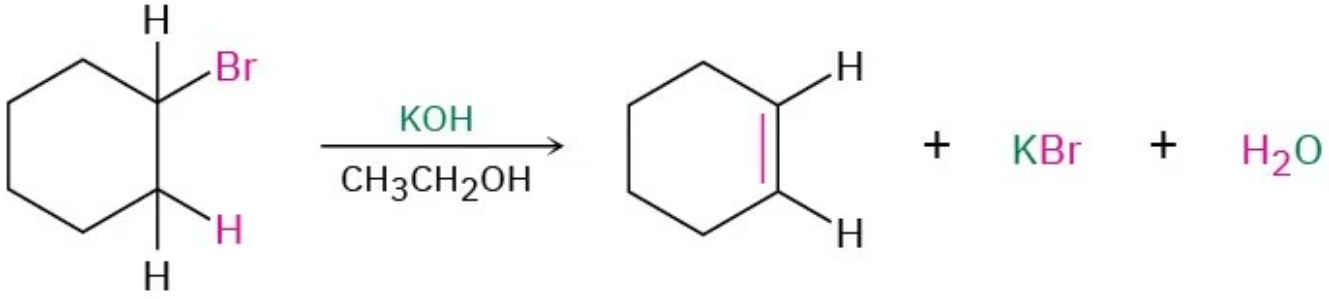
Just as the chemistry of alkenes is dominated by addition reactions, the preparation of alkenes is dominated by elimination reactions. Additions and eliminations are, in many respects, two sides of the same coin. That is, an addition reaction might involve the addition of HBr or H_2O to an alkene to form an alkyl halide or alcohol, whereas an elimination reaction might involve the loss of HBr or H_2O from an alkyl halide or alcohol to form an alkene.



The two most common elimination reactions are dehydrohalogenation—the loss of HX from an alkyl halide—and dehydration—the loss of water from an alcohol.

Dehydrohalogenation

Dehydrohalogenation usually occurs by reaction of an alkyl halide with strong base such as potassium hydroxide. For example, bromocyclohexane yields cyclohexene when treated with KOH in ethanol solution.

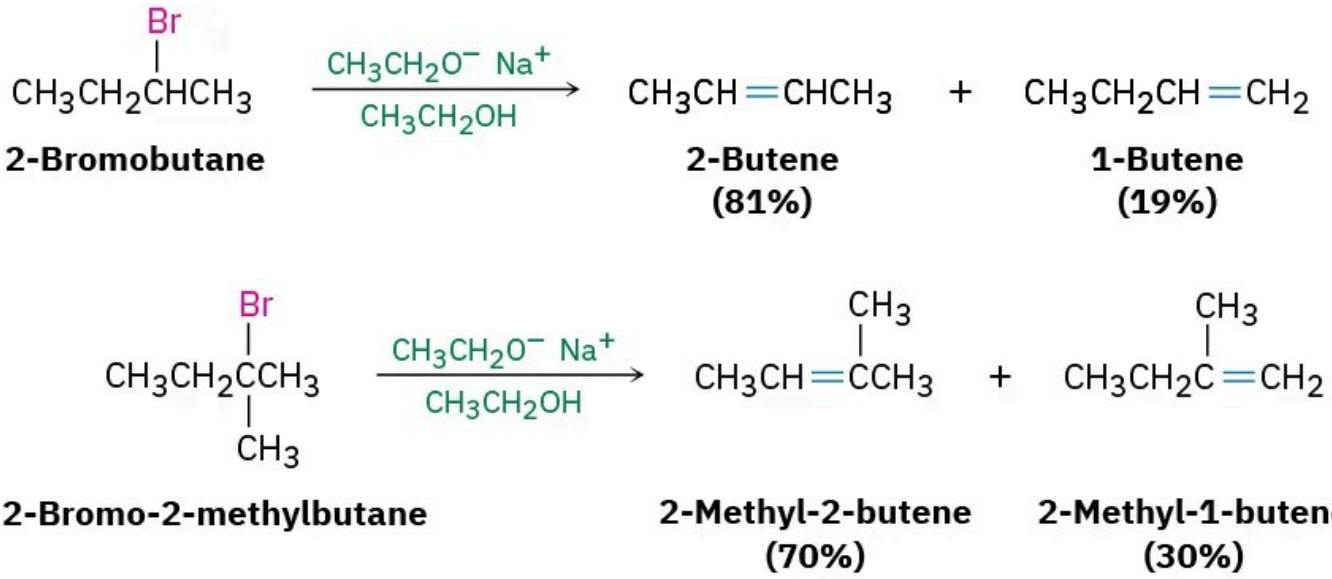


Bromocyclohexane **Cyclohexene (81%)**

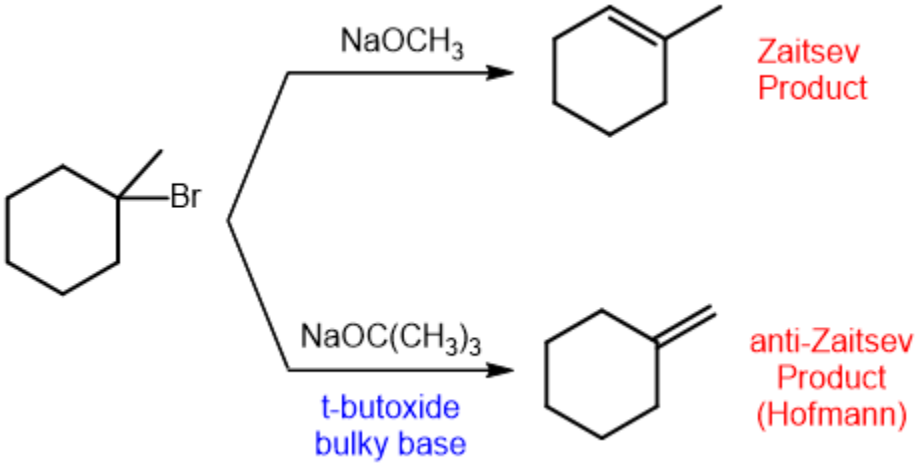
According to Zaitsev's rule, formulated in 1875 by the Russian chemist Alexander Zaitsev, **small base-induced elimination** reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.

ZAITSEV'S RULE

In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

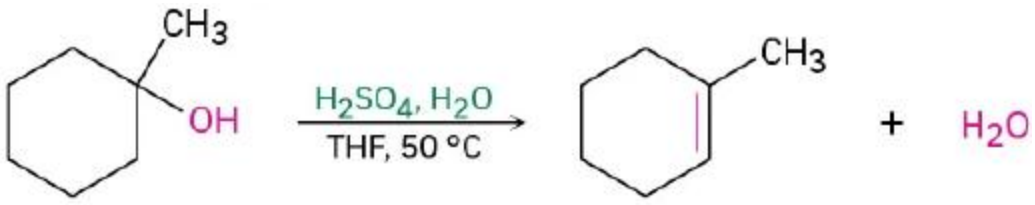


The Zaitsev Rule is a good predictor for simple elimination reactions of alkyl chlorides, bromides and iodides as long as relatively small strong bases are used. Thus hydroxide, methoxide and ethoxide bases give comparable results. Bulky bases such as tert-butoxide tend to give higher yields of the less substituted double bond isomers, a characteristic that has been attributed to steric hindrance. In the case of 2-bromo-2,3-dimethylbutane, described above, tert-butoxide gave a 4:1 ratio of 2,3-dimethyl-1-butene to 2,3-dimethyl-2-butene (essentially the opposite result to that obtained with hydroxide or methoxide).



Dehydration

Dehydration is often carried out in the laboratory by treatment of an alcohol with a strong acid. For example, when 1-methylcyclohexanol is warmed with aqueous sulfuric acid in tetrahydrofuran (THF) solvent, loss of water occurs and 1-methylcyclohexene is formed.

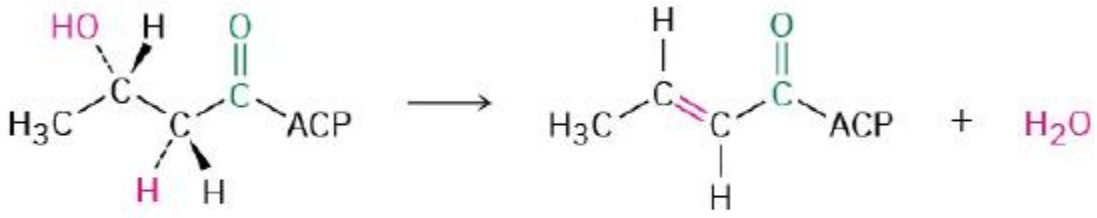


1-Methylcyclohexanol **1-Methylcyclohexene (91%)**



Tetrahydrofuran (THF)—a common solvent

In biological pathways, dehydrations rarely occur with isolated alcohols. Instead, they normally take place on substrates in which the –OH is positioned two carbons away from a C=O group. In the biosynthesis of fats, for instance, *β*-hydroxybutyryl ACP is converted by dehydration to *trans*-crotonyl ACP, where ACP is an abbreviation for *acyl carrier protein*. We'll see the reason for this requirement in **Section 11.11**.



***β*-Hydroxybutyryl ACP** ***trans*-Crotonyl ACP**

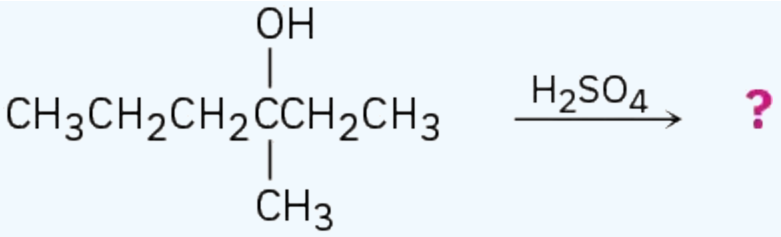
Exercise 8.1.1

One problem with elimination reactions is that mixtures of products are often formed. For example, treatment of 2-bromo-2-methylbutane with KOH in ethanol yields a mixture of two alkene products. What are their likely structures?

Answer available at the end of this section.

Exercise 8.1.2

How many alkene products, including *E*,*Z* isomers, might be obtained by dehydration of 3-methyl-3-hexanol with aqueous sulfuric acid?



3-Methyl-3-hexanol

Answer available at the end of this section.

Answers

Exercise 8.1.1

2-Methyl-2-butene and 2-methyl-1-butene.

Exercise 8.1.2

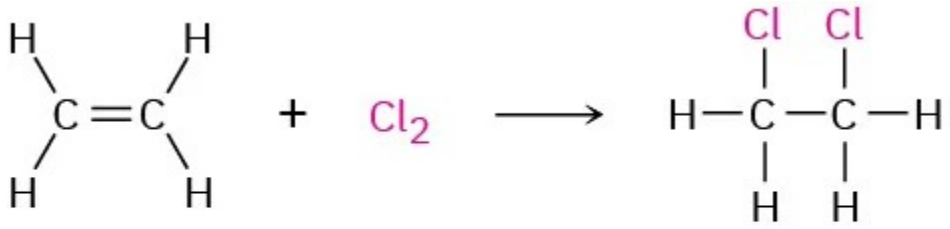
Five.

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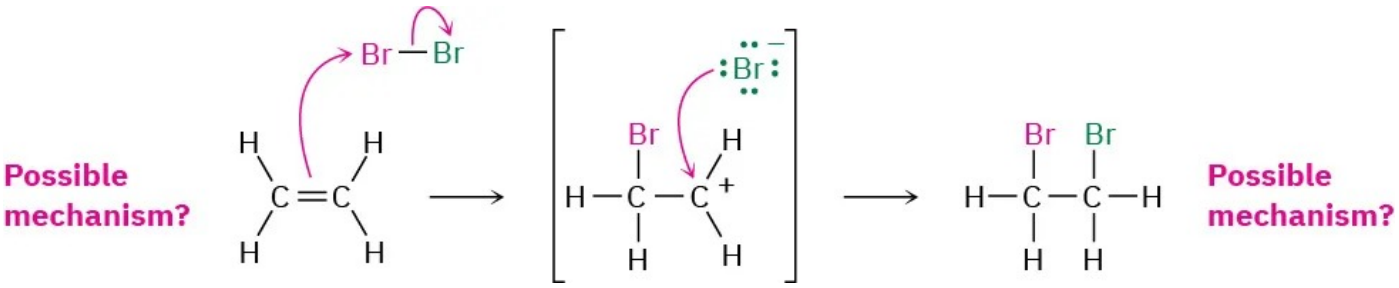
8.2: Halogenation of Alkenes - Addition of X_2

Bromine and chlorine add rapidly to alkenes to yield 1,2-dihalides, a process called *halogenation*. For example, nearly 50 million tons of 1,2-dichloroethane (ethylene dichloride) are synthesized worldwide each year, much of it by addition of Cl_2 to ethylene. The product is used both as a solvent and as starting material for the manufacture of poly(vinyl chloride), PVC, the third most widely synthesized polymer in the world afterpolyethelyne and polypropolyne. Fluorine is too reactive and difficult to control for most laboratory applications, and iodine does not react with most alkenes.



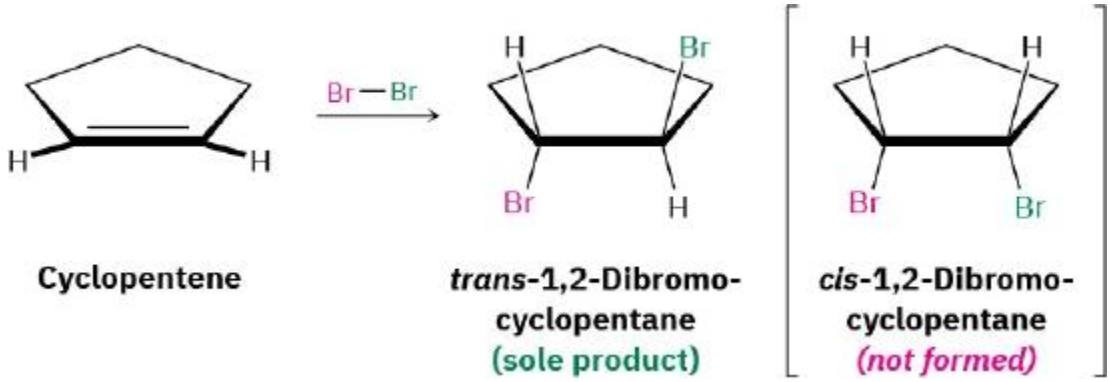
Ethylene **1,2-Dichloroethane (ethylene dichloride)**

Based on what we've seen thus far, a possible mechanism for the reaction of bromine with alkenes might involve electrophilic addition of Br^+ to the alkene, giving a carbocation intermediate that could undergo further reaction with Br^- to yield the dibromo addition product.



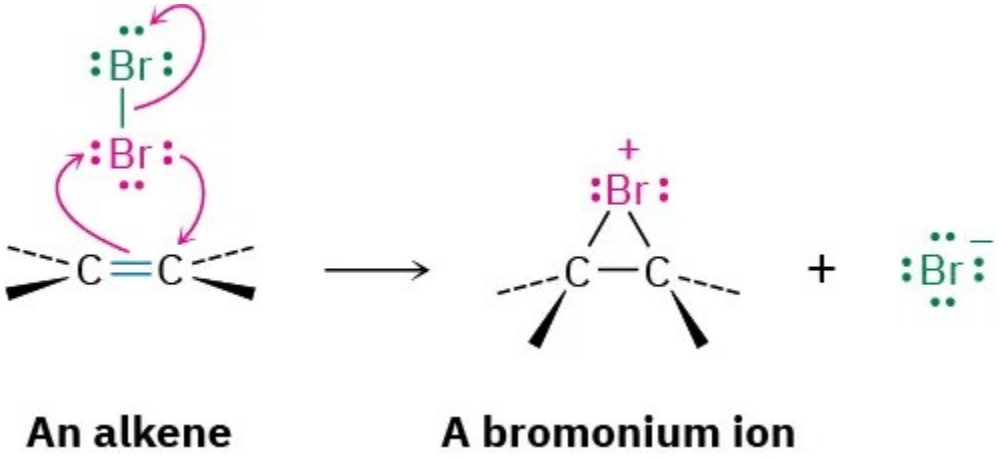
Although this mechanism seems plausible, it's not fully consistent with known facts. In particular, it doesn't explain the stereochemistry of the addition reaction. That is, the mechanism doesn't account for which product stereoisomer is formed.

When the halogenation reaction is carried out on a cycloalkene, such as cyclopentene, only the *trans* stereoisomer of the dihalide addition product is formed, rather than the mixture of cis and trans isomers that might have been expected if a planar carbocation intermediate were involved. We say that the reaction occurs with anti stereochemistry, meaning that the two bromine atoms come from opposite faces of the double bond—one from the top face and one from the bottom face.

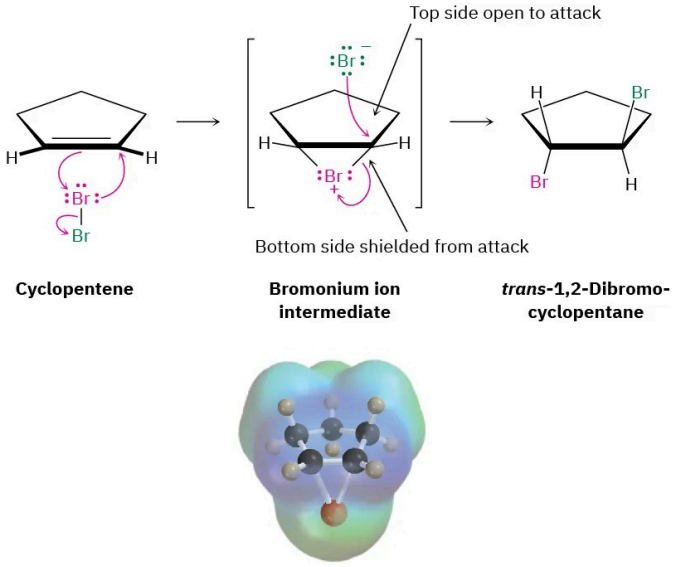


Cyclopentene ***trans*-1,2-Dibromo-cyclopentane (sole product)** ***cis*-1,2-Dibromo-cyclopentane *(not formed)***

An explanation for the observed stereochemistry of addition was suggested in 1937 by George Kimball and Irving Roberts, who proposed that the reaction intermediate is not a carbocation but is instead a bromonium ion, \(\ce{R2Br^{+}}\), formed by electrophilic addition of Br^+ to the alkene. (Similarly, a chloronium ion contains a positively charged, divalent chlorine, R_2Cl^+.) The bromonium ion is formed in a single step by interaction of the alkene with Br_2 and the simultaneous loss of Br^-.

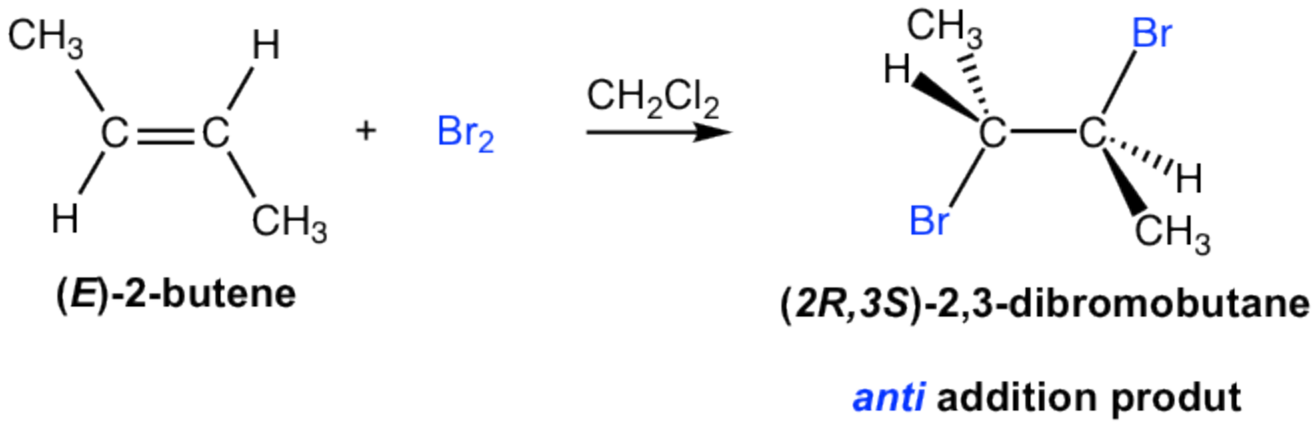


How does the formation of a bromonium ion account for the observed anti-stereochemistry of addition to cyclopentene? If a bromonium ion is formed as an intermediate, we can imagine that the large bromine atom might "shield" one side of the molecule. Reaction with Br^- ion in the second step could then occur only from the opposite, unshielded side to give the trans product.

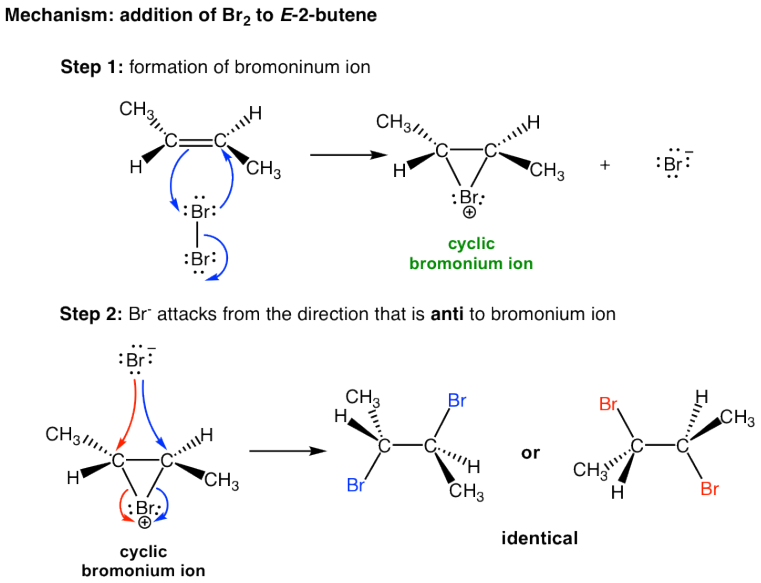


Mechanism for the Addition of Halogen to E or Z Alkenes

The products for the addition of halogen to alkenes seem straightforward, with each halogen added to each double bond carbon. However, the addition proceeds with a unique stereochemistry feature that needs special attention. It turns out that the halogen atoms are added via ***anti* addition** to the double bond, as shown here:



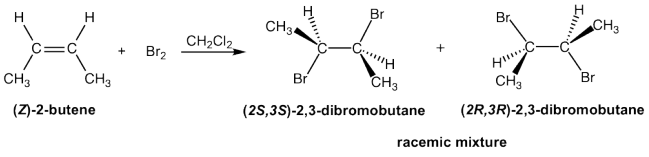
The mechanism that accounts for the anti addition of halogen involves the electron pairs transferred in a way that is different to what we are familiar with, and the formation of the cyclic halonium ion intermediate. We will take the addition of bromine to (*E*)-2-butene as example to explain the mechanism.



When Br_2 molecule approaching alkene in the first step, the electron density of the π bond in alkene repels electron density in the bromine, polarizing the bromine molecule and make the bromine atom that is closer to the double bond electrophilic. The alkene donate a pair of π electrons to the closer bromine, causing the displacement of the bromine atom that is further away. The lone pair on the closer bromine atom then acts as nucleophile to attack the other sp^2 carbon. Thus, the same bromine atom is both electrophile and the nucleophile, and two single bonds are formed between the two sp^2 carbons and the closer bromine that gives the cyclic bromonium ion intermediate.

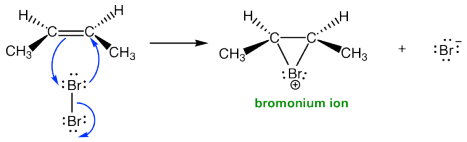
In the second step, the nucleophilic bromide, Br– (generated in step 1), attacks the carbon of the cyclic intermediate. Since the bottom side of the intermediate is blocked by the ring, the Br– can only attack from the top side, that results in the anti position of the two Br in the product. The attack is similar to SN2 reaction and cause the ring to open and the formation of vicinal dibromide. For the above example, the two carbons in the bromonium ion intermediate are in same chemical environment, so they both have the same chance to be attacked by Br–, as shown in blue and red arrows. The two attacks result in the same product, the meso compound (2R,3S)-2,3-dibromobutane, in this reaction.

Next, let's exam the addition of bromine to (Z)-2-butene. As you may expect, the reaction goes through the same mechanism that involves the cyclic bromonium ion intermediate, however the products have different stereochemistry features.

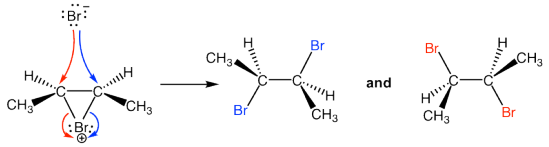


Mechanism: addition of Br_2 to *(Z)*-2-butene

Step 1: formation of bromoninum ion



Step 2: attack of Br^- to bromonium ion from anti direction

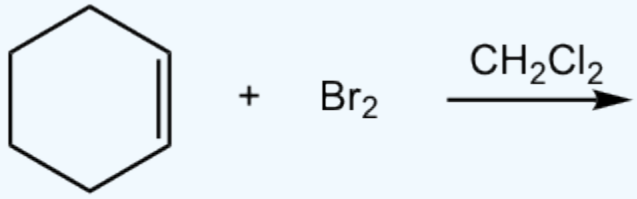


In the addition of Br_2 to (Z)-2-butene, the attack of Br-to either carbon in bromonium ion by following blue or red arrow results in different enantiomer (step 2 in above mechanism). Since both carbons have the same chance to be attacked, so the product is the 50:50 racemic mixture of the two enantiomer.

Starting from the two different diastereomers, (E)-2-butene and (Z)-2-butene,the addition reaction produces different stereoisomers. The addition of (E)-2-butene gives one product, the meso compound (2R,3S)-2,3-dibromobutane, while the addition of (Z)-2-butene produces the racemic mixture of two enantiomers, (2S,3S)-2,3-dibromobutane and (2R,3R)-2,3-dibromobutane. Such reaction, the one where a particular stereoisomer of the starting material yields a specific stereoisomer of the product is called stereospecific reaction. The anti-addition of a halogen to an alkene is an example of a stereospecific reaction.

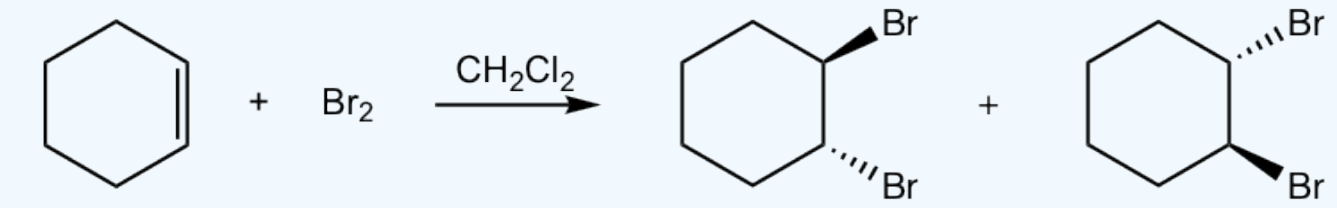
Worked Example 8.2.1

Show the product of the following addition.



cyclohexene

Solution



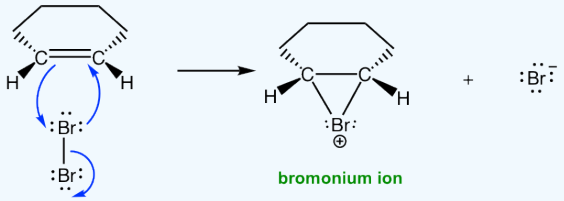
cyclohexene

racemic mixture: two enantiomers of *trans*-1,2-dibromocyclohexane

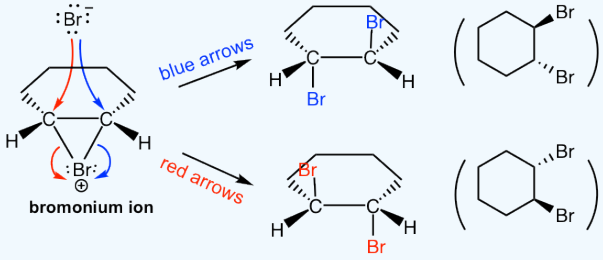
The formation of the racemic mixture product can be explained by the mechanism:

Mechanism

Step 1:



Step 2:



Exercise 8.2.1

What product would you expect to obtain from the addition of Cl_2 to 1,2-dimethylcyclohexene? Show the stereochemistry of the product.

Answer available at the end of this section.

Exercise 8.2.2

The addition of HCl to 1,2-dimethylcyclohexene yields a mixture of two products. Show the stereochemistry of each, and explain why a mixture is formed.

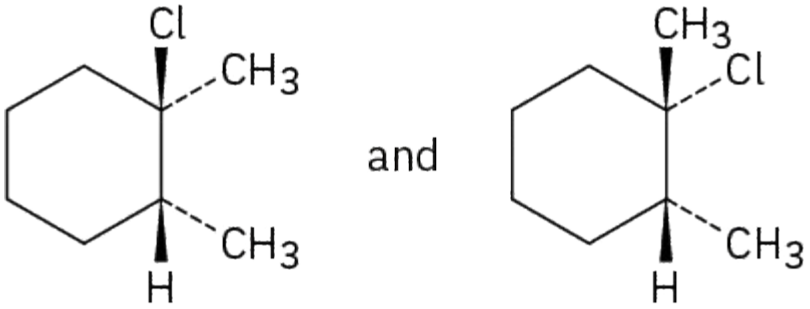
Answer available at the end of this section.

Answers

Exercise 8.2.1

trans-1,2-Dichloro-1,2-dimethylcyclohexane.

Exercise 8.2.2

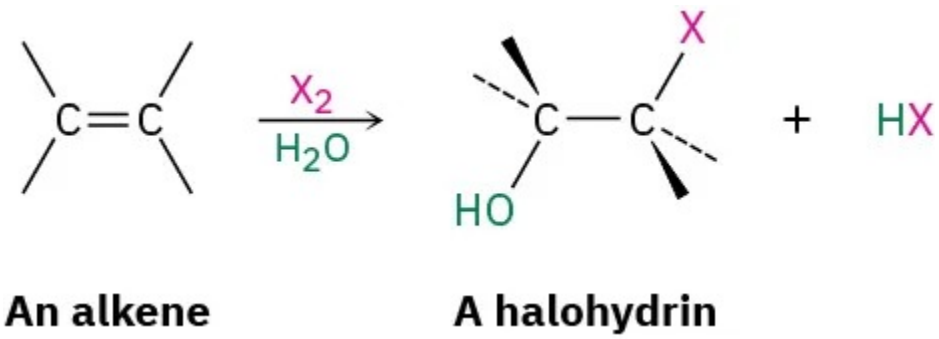


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8.3: Halohydrins from Alkenes - Addition of HO-X

Another example of an electrophilic addition is the reaction of an alkene with either Br2 or Cl2 in the presence of water to yield a 1,2-halo alcohol, called a halohydrin.



We saw in the previous section that when Br_2 reacts with an alkene, the cyclic bromonium ion intermediate reacts with the only nucleophile present, Br^- ion. If the reaction is carried out in the presence of an additional nucleophile, however, the intermediate bromonium ion can be intercepted by the added nucleophile and diverted to a different product. In the presence of a high concentration of water, for instance, water competes with Br^- ion as a nucleophile and reacts with the bromonium ion intermediate to yield a *bromohydrin*. The net effect is the addition of HO–Br to the alkene by the pathway shown in Figure $8.3.1$.

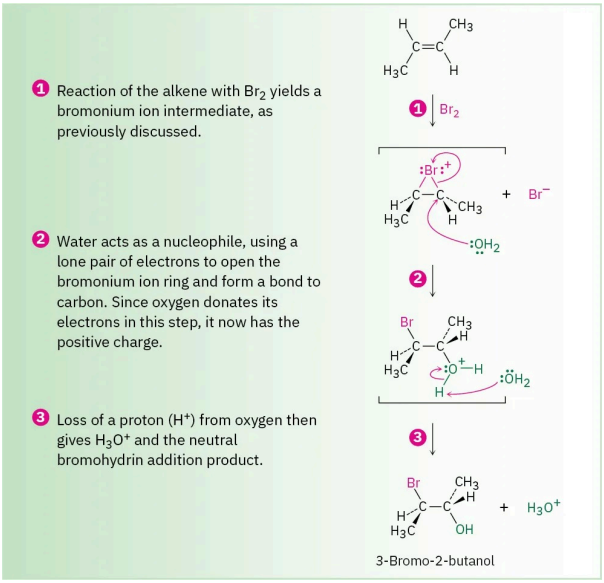
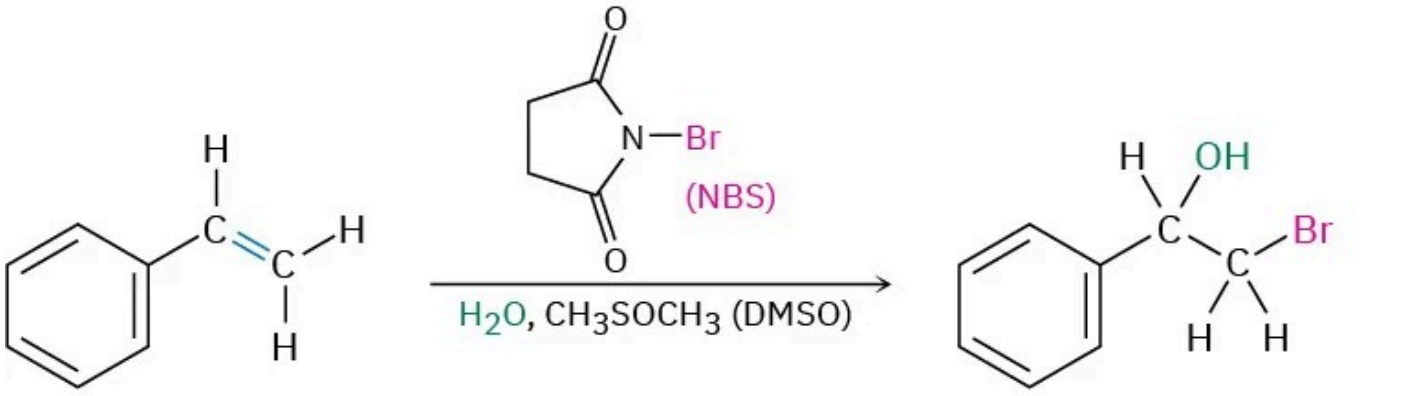


Figure $8.3.1$: Bromohydrin formation by reaction of an alkene with $\mathrm{Br_2}$ in the presence of water. Water acts as a nucleophile in step 2 to react with the intermediate bromonium ion.

In practice, few alkenes are soluble in water, and bromohydrin formation is often carried out in a solvent such as aqueous dimethyl sulfoxide, CH_3SOCH_3 (DMSO), using a reagent called *N*-bromosuccinimide (NBS) as a source of Br_2. NBS is a stable, easily handled compound that slowly decomposes in water to yield Br_2 at a controlled rate. Bromine itself can also be used in the addition reaction, but it is more dangerous and more difficult to handle than NBS.

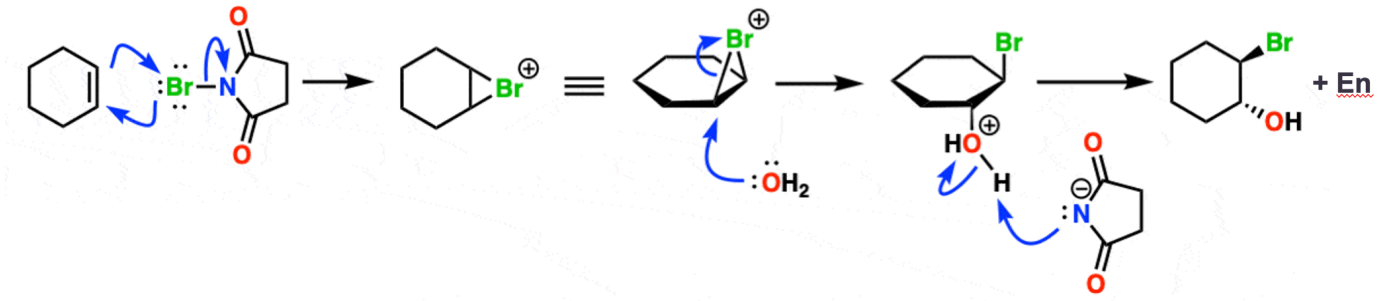


Styrene **2-Bromo-1-phenylethanol (70%)**

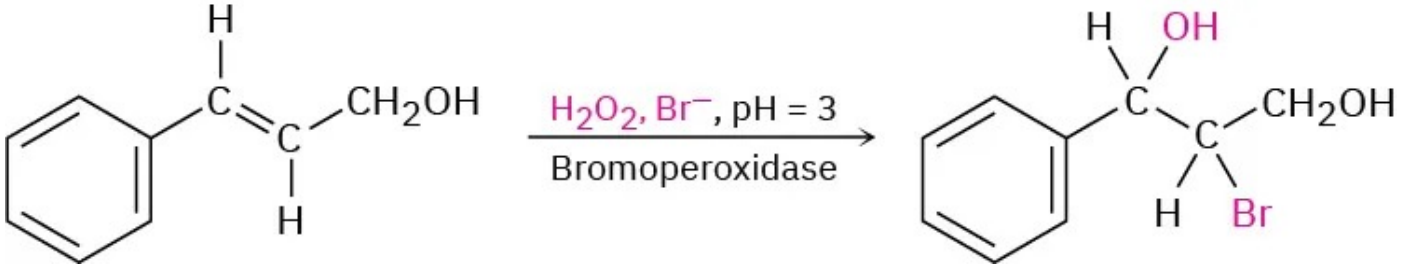
Notice that the aromatic ring in the above example does not react with Br_2, even though it appears to have three carbon–carbon double bonds. As we'll see in Section 15.3, aromatic rings are a good deal more stable and less reactive than might be expected.

Mechanism:

NBS will react with alkenes to form bromonium ions with alkenes. When water (or an alcohol) is used as a solvent, it will attack the bromonium ion, resulting in formation of the halohydrin. Note that the stereochemistry is always "anti".

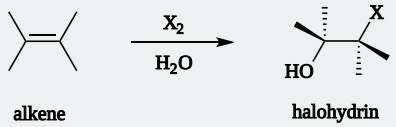


There are a number of biological examples of halohydrin formation, particularly in marine organisms. As with halogenation, halohydrin formation is carried out by *haloperoxidases*. For example:



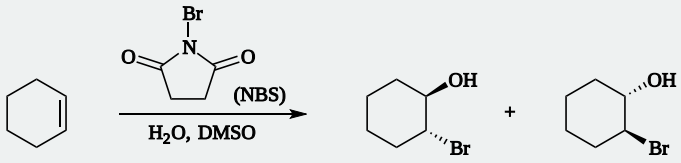
Study Note

Bromohydrin and chlorohydrin are examples of halohydrins (where X = Br or Cl).



Chemists often abbreviate the names of frequently used chemicals: DMSO for dimethyl sulfoxide, NBS for N-bromosuccinimide, etc. You should already be familiar with some similar examples from everyday life: DDT for dichlorodiphenyltrichloroethane, PCB for polychlorinated biphenyl, and ASA for acetylsalicylic acid (aspirin). You can see how someone with a limited knowledge of chemistry could misinterpret the abbreviation NBS—it is not a compound containing nitrogen, boron and sulfur!

NBS can serve as a less dangerous and easier to handle replacement for Br_2 in the formation of bromohydrins.



Exercise 8.3.1

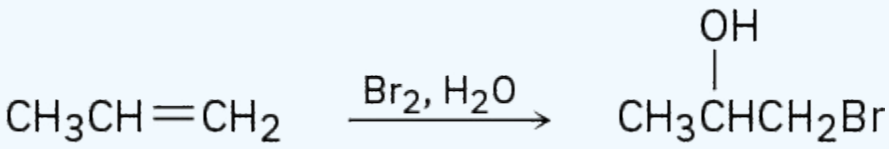
What product would you expect from the reaction of cyclopentene with NBS and water? Show the stereochemistry.

Answer available at the end of this section.

Answer available at the end of this section.

Exercise 8.3.2

When an unsymmetrical alkene such as propene is treated with *N*-bromosuccinimide in aqueous dimethyl sulfoxide, the major product has the bromine atom bonded to the less highly substituted carbon atom. Is this Markovnikov or non-Markovnikov orientation? Explain.



Answer available at the end of this section.

Answers

Exercise 8.3.1

Exercise 8.3.1

trans-2-Bromocyclopentanol

Exercise 8.3.2

Markovnikov

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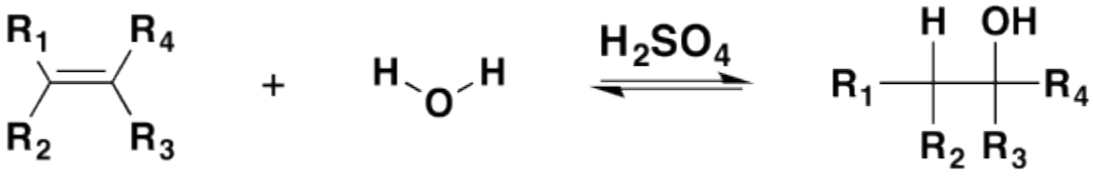
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8.4: Hydration of Alkenes- Acid-Catalyzed Hydration

Electrophilic hydration is the act of adding electrophilic hydrogen from a non-nucleophilic strong acid (a reusable catalyst, examples of which include sulfuric and phosphoric acid) and applying appropriate temperatures to break the alkene's double bond. After a carbocation is formed, water bonds with the carbocation to form a 1°, 2°, or 3° alcohol on the alkane.

What Is Electrophilic Hydration?

Electrophilic hydration is the reverse dehydration of alcohols and has practical application in making alcohols for fuels and reagents for other reactions. The basic reaction under certain temperatures (given below) is the following:



The phrase "electrophilic" literally means "electron-loving" (whereas "nucleophilic" means "nucleus-loving"). 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 (see S_N2 for more details).

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 formed product.*

- Primary Alcohol: Less than 170°C
- Secondary Alcohol: Less than 100°C
- Tertiary Alcohol: Less than 25°C

How Does Electrophilic Hydration Work?

Mechanism for 3° Alcohol (1° and 2° mechanisms are similar):

The reaction takes place through the treatment of the alkene with water and a strong acid catalyst, such as H_2SO_4, by a mechanism similar to that of HX addition. Thus, as shown in Figure $8.4.1$, protonation of an alkene double bond yields a carbocation intermediate, which reacts with water to yield a protonated alcohol product, ROH_2^+. Loss of H^+ from this protonated alcohol gives the neutral alcohol and regenerates the acid catalyst.

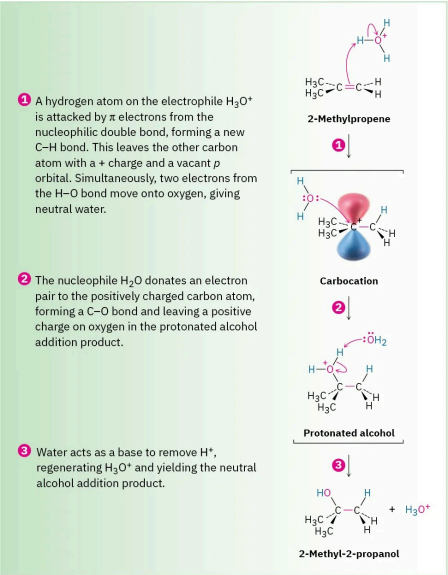


Figure 8.4.1: Mechanism of the acid-catalyzed hydration of an alkene to yield an alcohol. Protonation of the alkene gives a carbocation intermediate, which reacts with water. The initial product is then deprotonated.

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.

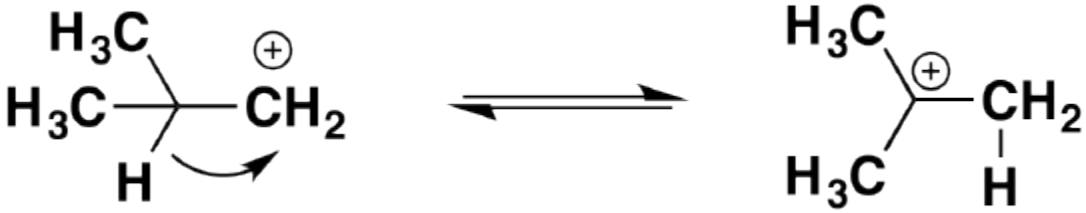
What is Regiochemistry and How Does It Apply?

In the case of electrophilic hydration, Markovnikov's rule is the only rule that *directly* applies.

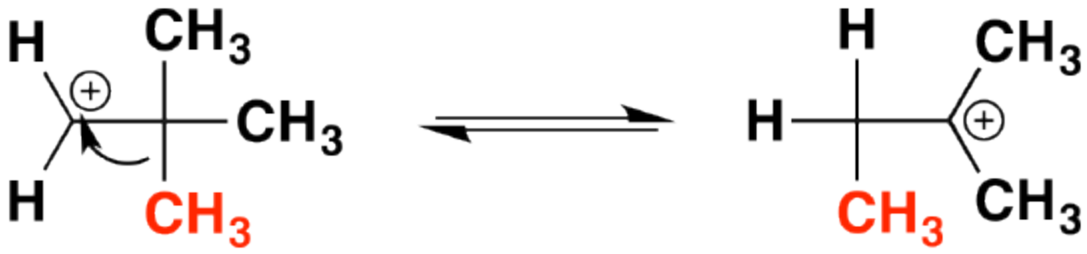
In the mechanism for a 3° alcohol shown above, the green H is added to the least-substituted carbon connected to the nucleophilic double bonds (it has less carbons attached to it). This means that the carbocation forms on the 3° carbon, causing it to be highly stabilized by *hyperconjugation*—electrons 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:

- **Hydride shifts:** a hydrogen atom bonded to a carbon atom next to the carbocation leaves that carbon to bond with the carbocation (after the hydrogen has taken both electrons from the single bond, it is known as a hydride). This changes the once neighboring carbon to a carbocation, and the former carbocation becomes a neighboring carbon atom.



- **Alkyl shifts:** if no hydrogen atoms are available for a hydride shift, an entire methyl group performs the same shift



The nucleophile attacks the positive charge formed on the most substituted carbon connected to the double bond, because the nucleophile is seeking that positive charge. In the mechanism for a 3° 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.**

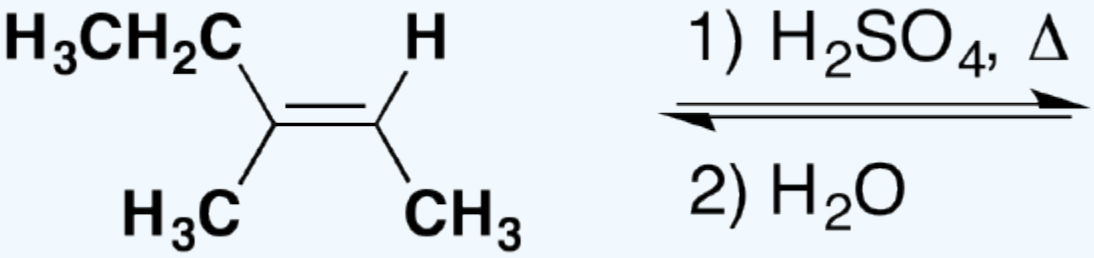
Is this a Reversible Synthesis?

Electrophilic hydration is reversible because an alkene in water is in equilibrium with the alcohol product. To shift the equilibrium one way or the other, the temperature or the concentration of the non-nucleophilic strong acid can be adjusted. For example:

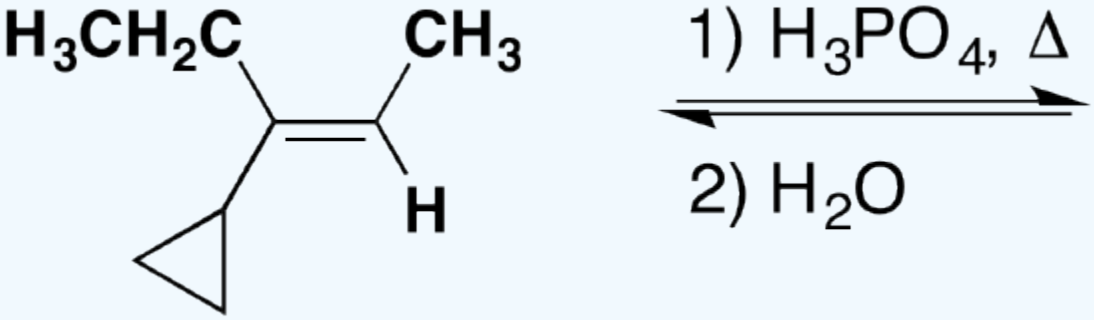
- Less sulfuric or phosphoric acid and excess water facilitate the synthesis of more alcohol products.
- Lower temperatures facilitate the synthesis of more alcohol products.

Exercises

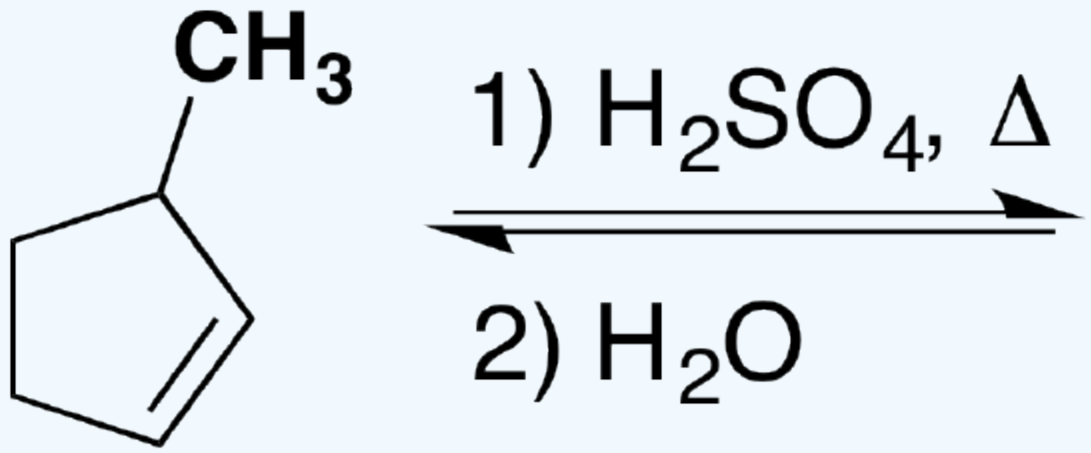
1) Predict the product of each reaction.



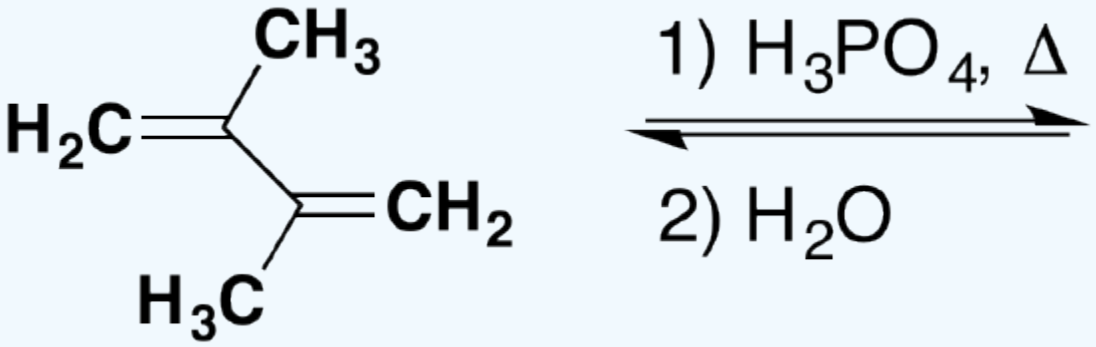
2) Predict the product of each reaction. How does the cyclopropane group affect the reaction?



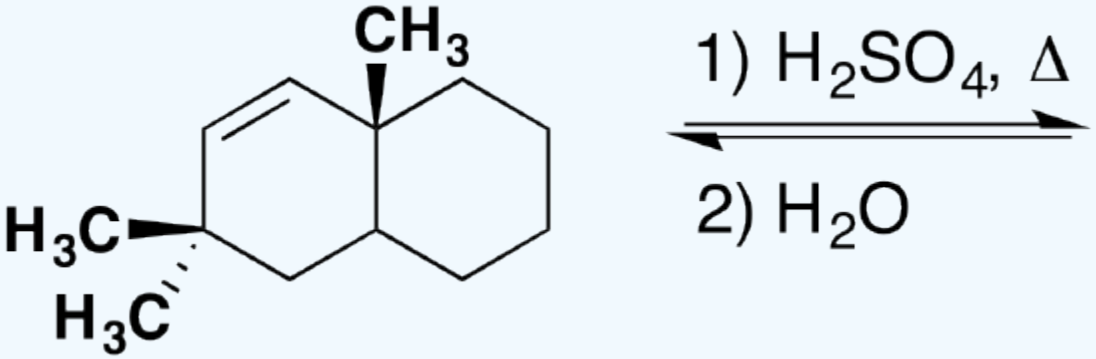
3) Predict the product of each reaction. What is different about this problem?



4) Predict the product of each reaction. Consider stereochemistry.



5) Indicate any shifts as well as the major product:



Answer available at the end of this section.

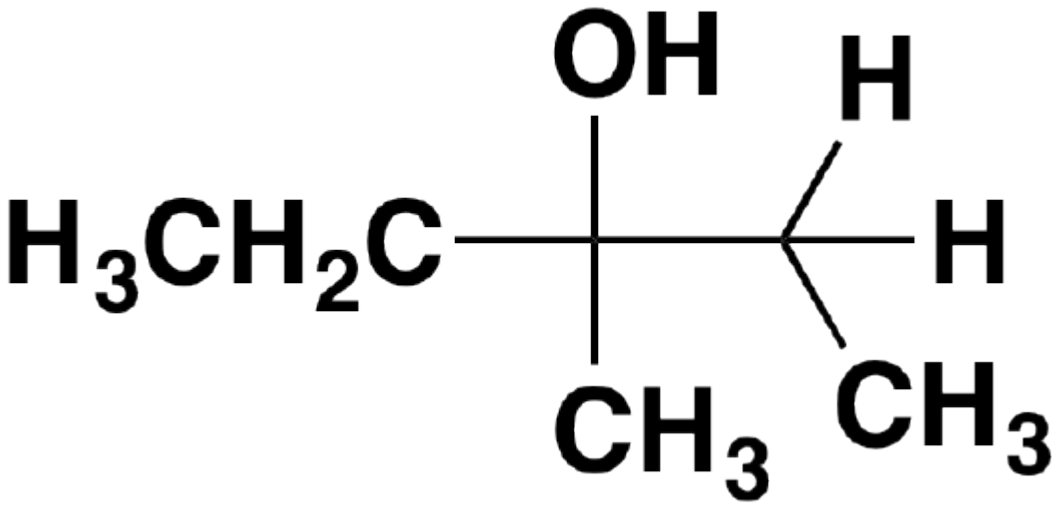
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2. Krow, Grant. "Sulfuric Acid." Encyclopedia of Reagents for Organic Synthesis. Philadelphia, Pennsylvania: John Wiley & Sons, 2001.

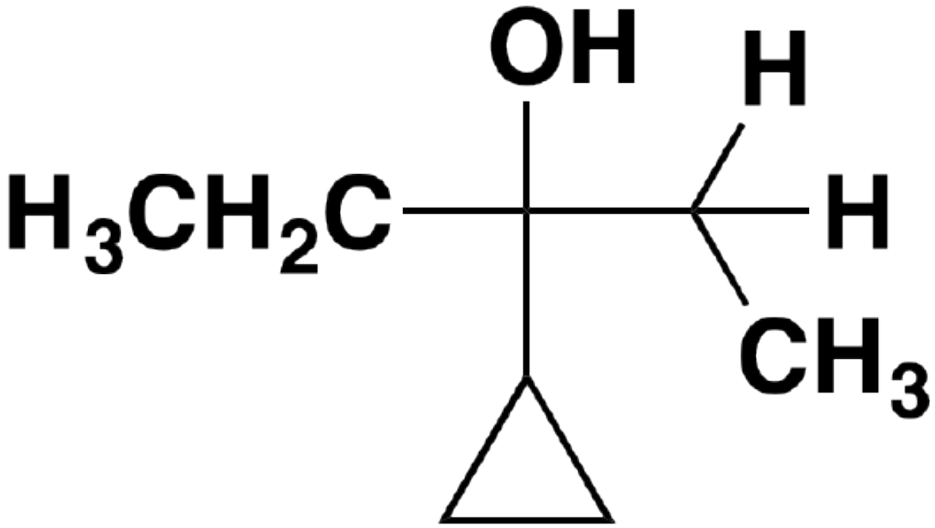
Answers

Exercises

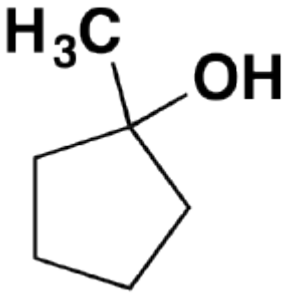
1) This is a basic electrophilic hydration.



2) The answer is additional side products, but **the major product formed is still the same** (the product shown). Depending on the temperatures used, the cyclopropane may open up into a straight chain, which makes it unlikely that the major product will form (after the reaction, it is unlikely that the 3° carbon will remain as such).

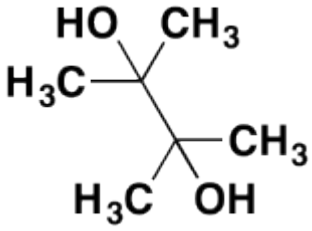


3) A hydride shift actually occurs from the top of the 1-methylcyclopentane to where the carbocation had formed.

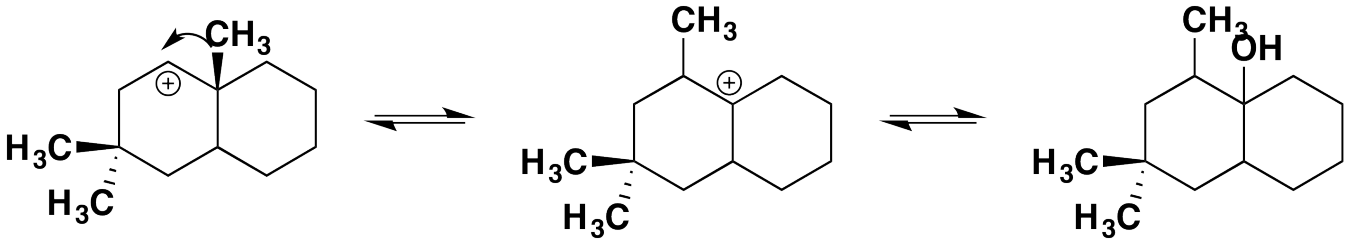


4) **This reaction will have poor yields due to a very unstable intermediate**. For a brief moment, carbocations can form on the two center carbons, which are more stable than the outer two carbons. The carbocations have an sp^2 hybridization, and when the water is added on, the carbons change their hybridization to

sp^3. This makes the methyl and alcohol groups equally likely to be found going into or out of the plane of the paper- the product is racemic.



5) In the first picture shown below, an alkyl shift occurs but a hydride shift (which occurs faster) is possible. Why doesn't a hydride shift occur? The answer is because **the alkyl shift leads to a more stable product**. There is a noticeable amount of side product that forms where the two methyl groups are, but the major product shown below is still the most significant due to the hyperconjugation that occurs by being in between the two cyclohexanes.



major product

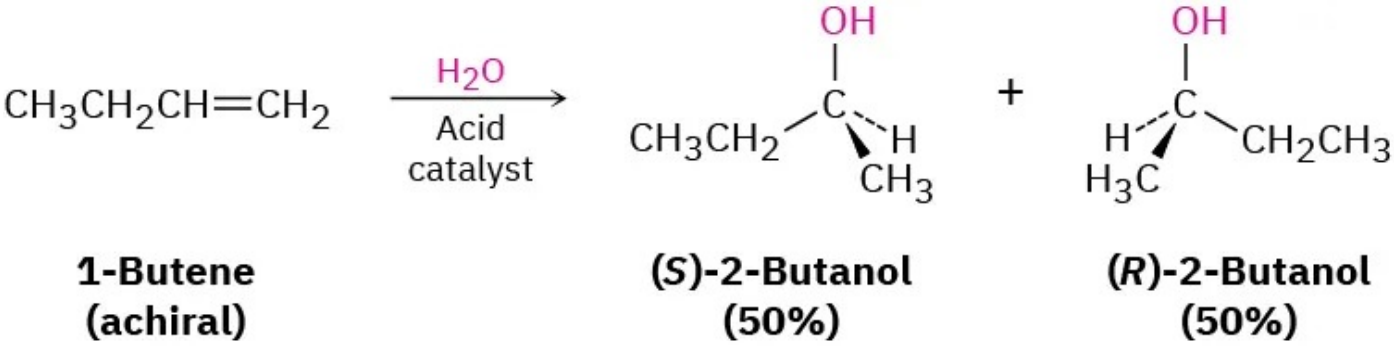
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8.5: Stereochemistry of Reactions

Addition of H_2O to an Achiral Alkene

Most biochemical reactions that occur in the body, as well as many organic reactions in the laboratory, yield products with chiral centers. For example, acid-catalyzed addition of H_2O to 1-butene in the laboratory yields 2-butanol, a chiral alcohol. What is the stereochemistry of this chiral product? If a single enantiomer is formed, is it *R* or *S*? If a mixture of enantiomers is formed, how much of each? In fact, the 2-butanol produced is a racemic mixture of *R* and *S* enantiomers. Let's see why.



To understand why a racemic product results from the reaction of H_2O with 1-butene, think about the reaction mechanism. 1-Butene is first protonated to yield an intermediate secondary carbocation. Because the trivalent carbon is sp^2-hybridized and planar, the cation has a plane of symmetry and is achiral. As a result, it can react with H_2O equally well from either the top or the bottom. Reaction from the top leads to (*S*)-2-butanol through transition state 1 (TS 1) in Figure 8.5.1, and reaction from the bottom leads to (*R*)-2-butanol through TS 2. But the two transition states are mirror images, so they have identical energies, form at identical rates, and are equally likely to occur.

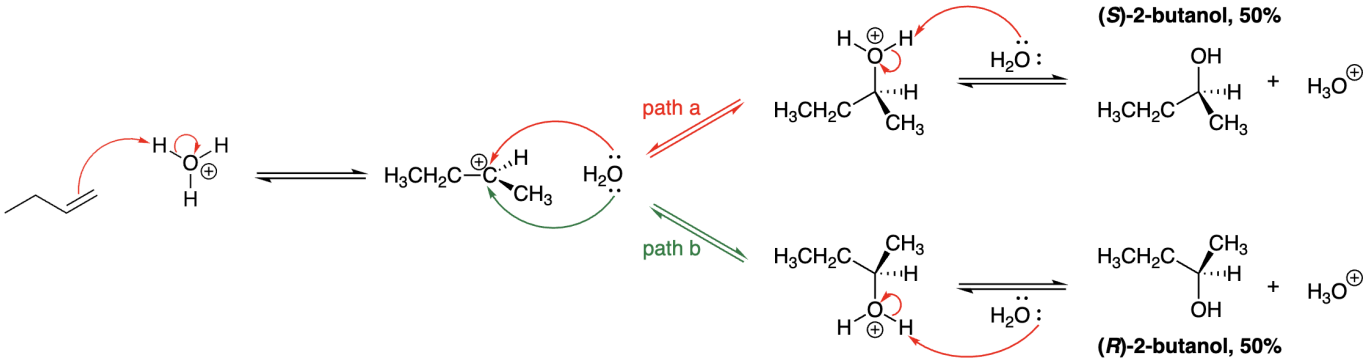
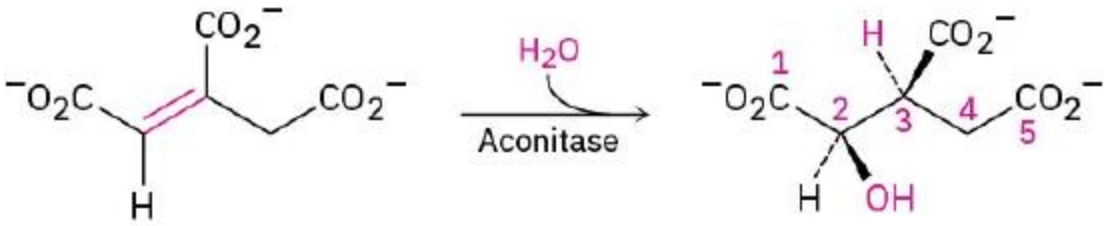


Figure 8.5.1: Reaction of H_2O with the carbocation resulting from protonation of 1-butene. Reaction from the top leads to *the S product, and it is the mirror image of the reaction from the bottom, which leads to the R* product. Because they are energetically identical, they lead to a racemic mixture of products.

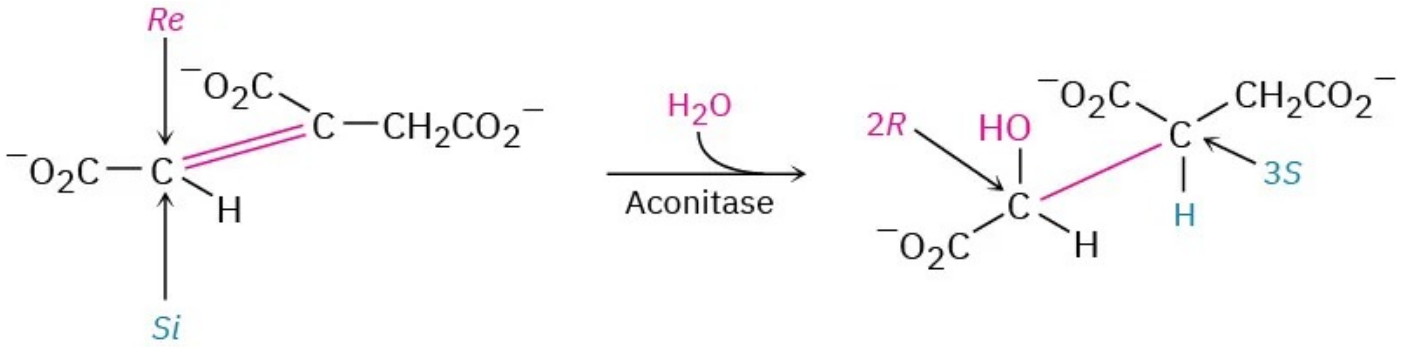
As a general rule, the formation of a new chirality center by achiral reactants always leads to a racemic mixture of enantiomeric products. Put another way, optical activity can't appear from nowhere; an optically active product can only result from starting with an optically active reactant or chiral environment (Section 5.12).

In contrast to laboratory reactions, enzyme-catalyzed biological reactions often give a single enantiomer of a chiral product, even when the substrate is achiral. One step in the citric acid cycle of food metabolism, for instance, is the aconitase-catalyzed addition of water to (*Z*)-aconitate (also known as *cis*-aconitate) to form isocitrate.



***cis*-Aconitate (achiral)** **(2*R*,3*S*)-Isocitrate**

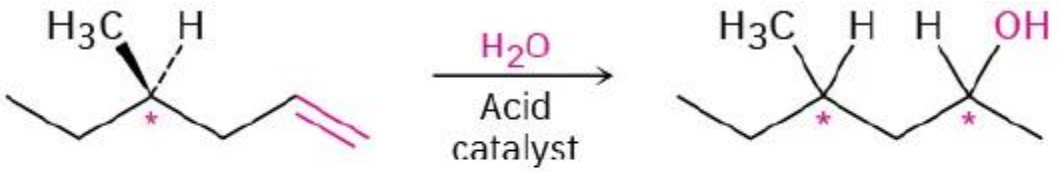
Even though *cis*-aconitate is achiral, only the (2*R*,3S) enantiomer of the product is formed. As discussed in Chapter 5, *cis*-aconitate is a prochiral molecule, which is held in a chiral environment by the aconitase enzyme during the reaction. In this environment, the two faces of the double bond are chemically distinct, and addition occurs on only the Re face at C2.



***cis*-Aconitate** **(2*R*,3*S*)-Isocitrate**

Addition of H_2O to a Chiral Alkene

The reaction discussed previously involves the addition to an achiral reactant and forms an optically inactive, racemic mixture of two enantiomeric products. What would happen, though, if we were to carry out the reaction on a single enantiomer of a chiral reactant? For example, what stereochemical result would be obtained from the addition of H_2O to a chiral alkene, such as (*R*)-4-methyl-1-hexene? The product of the reaction, 4-methyl-2-hexanol, has two chiral centers and four possible stereoisomers.



(*R*)-4-Methyl-1-hexene (chiral) **4-Methyl-2-hexanol (chiral)**

Let's think about the two chirality centers separately. What about the configuration at C4, the methyl-bearing carbon atom? Since C4 has the *R* configuration in the starting material, and this chirality center is unaffected by the reaction, its configuration is unchanged. Thus, the configuration at C4 in the product remains *R* (assuming that the relative rankings of the four attached groups are not changed by the reaction).

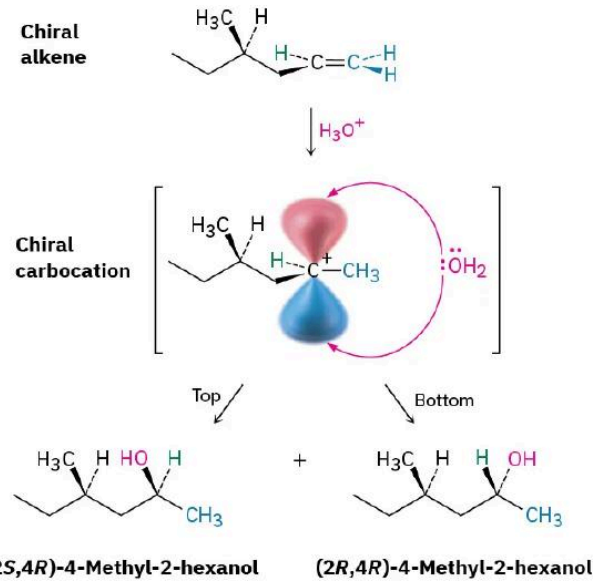


Figure 8.5.1: Stereochemistry of the acid-catalyzed addition of H_2O to the chiral alkene, (*R*)-4-methyl-1-hexene. A mixture of diastereomeric 2*R*,4*R* and 2S,4*R* products is formed in unequal amounts because the reaction of the chiral carbocation intermediate is not equally likely from top and bottom. The product mixture is optically active.

What about the configuration at C2, the newly formed chirality center? As shown in Figure 8.5.1, the stereochemistry at C2 is established by reaction of H_2O with a carbocation intermediate in the usual manner. But this carbocation doesn't have a plane of symmetry; it is chiral because of the chirality center at C4. Because the carbocation is chiral and has no plane of symmetry, it doesn't react equally well from the top and bottom faces. One of the two faces is likely, for steric reasons, to be a bit more accessible than the other, leading to a mixture of *R* and *S* products in some ratio other than 50:50. Thus, two diastereomeric products, (2*R*,4*R*)-4-methyl-2-hexanol and (2S,4*R*)-4-methyl-2-hexanol, are formed in unequal amounts, and the mixture is optically active.

As a general rule, the formation of a new chirality center by a chiral reactant leads to unequal amounts of diastereomeric products. If the chiral reactant is optically active because only one enantiomer is used rather than a racemic mixture, then the products are also optically active.

Exercises

Exercise 8.5.1

What products are formed from acid-catalyzed hydration of racemic (±)-4-methyl-1-hexene? What can you say about the relative amounts of the products? Is the product mixture optically active?

Answer available at the end of this section.

Exercise 8.5.2

What products are formed from the hydration of 4-methylcyclopentene? What can you say about the relative amounts of the products?

Answer available at the end of this section.

Answers

Exercise 8.5.1

An optically inactive, non-50 : 50 mixture of two racemic pairs: (2*R*,4*R*) + (2S,4S) and (2*R*,4S) + (2S,4*R*)

Exercise 8.5.2

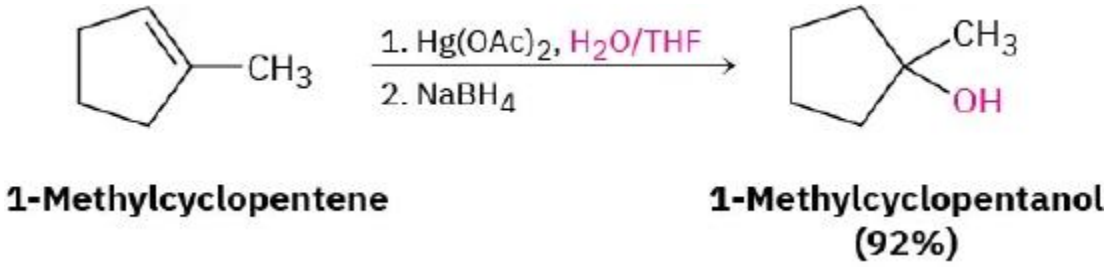
Non-50:50 mixture of two racemic pairs: (1S,3*R*) + (1*R*,3S) and (1S,3S) + (1*R*,3*R*)

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8.6: Hydration of Alkenes - Addition of H_2O by Oxymercuration

In the laboratory, alkenes are often hydrated by the oxymercuration–demercuration procedure, which involves electrophilic addition of Hg^{2+} to the alkene on reaction with mercury(II) acetate [$(CH_3CO_2)_2Hg$]. The intermediate organomercury compound is then treated with sodium borohydride, $NaBH_4$, and demercuration occurs to produce an alcohol. For example:



Alkene oxymercuration is closely analogous to halohydrin formation. The reaction is initiated by electrophilic addition of Hg^{2+} (mercuric) ion to the alkene to give an intermediate *mercurinium ion*, whose structure resembles that of a bromonium ion (Figure 8.6.1). Nucleophilic addition of water as in halohydrin formation, followed by the loss of a proton, then yields a stable organomercury product. The final step, demercuration of the organomercury compound by reaction with sodium borohydride, is complex and involves radicals. Note that the regiochemistry of the reaction corresponds to Markovnikov addition of water; that is, the –OH group attaches to the more highly substituted carbon atom, and the –H attaches to the less highly substituted carbon. The hydrogen that replaces mercury in the demercuration step can attach from either side of the molecule depending on the exact circumstances.

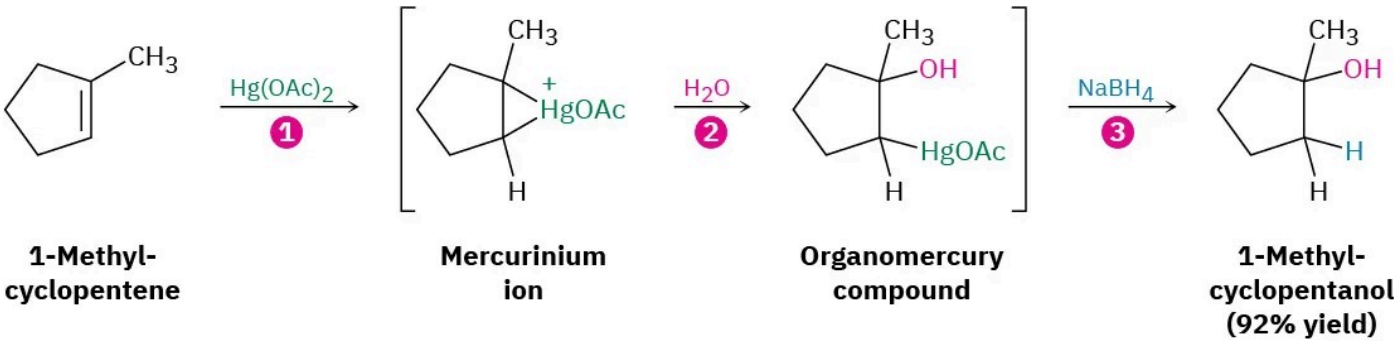


Figure 8.6.1: Mechanism of the oxymercuration of an alkene to yield an alcohol. (**1**) Electrophilic addition of Hg^{2+} gives a mercurinium ion, which (**2**) reacts with water as in halohydrin formation. Loss of a proton gives an organomercury product, and (**3**) reaction with $NaBH_4$ removes the mercury. The product of the reaction is a more highly substituted alcohol, corresponding to Markovnikov regiochemistry.

Exercise 8.6.1

What products would you expect from oxymercuration–demercuration of the following alkenes?

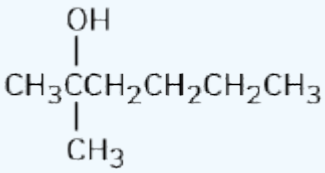
a. $CH_3CH_2CH_2CH{=}CH_2$

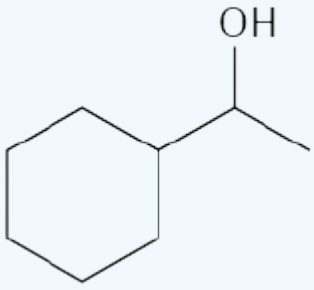
b. $CH_3C(CH_3){=}CHCH_2CH_3$

Answer available at the end of this section.

Exercise 8.6.2

From what alkenes might the following alcohols have been prepared?

a. 

b. 

Answer available at the end of this section.

Answers

Exercise 8.6.1

a. 2-Pentanol
b. 2-Methyl-2-pentanol

Exercise 8.6.2

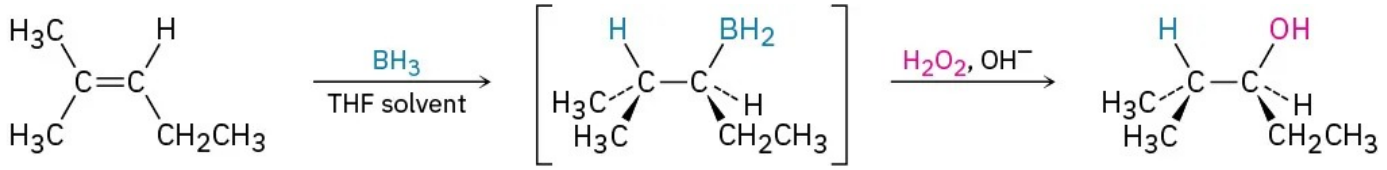
a. Oxymercuration of 2-methyl-1-hexene or 2-methyl-2-hexene
b. Oxymercuration of cyclohexylethylene or hydroboration of ethylidenecyclohexane

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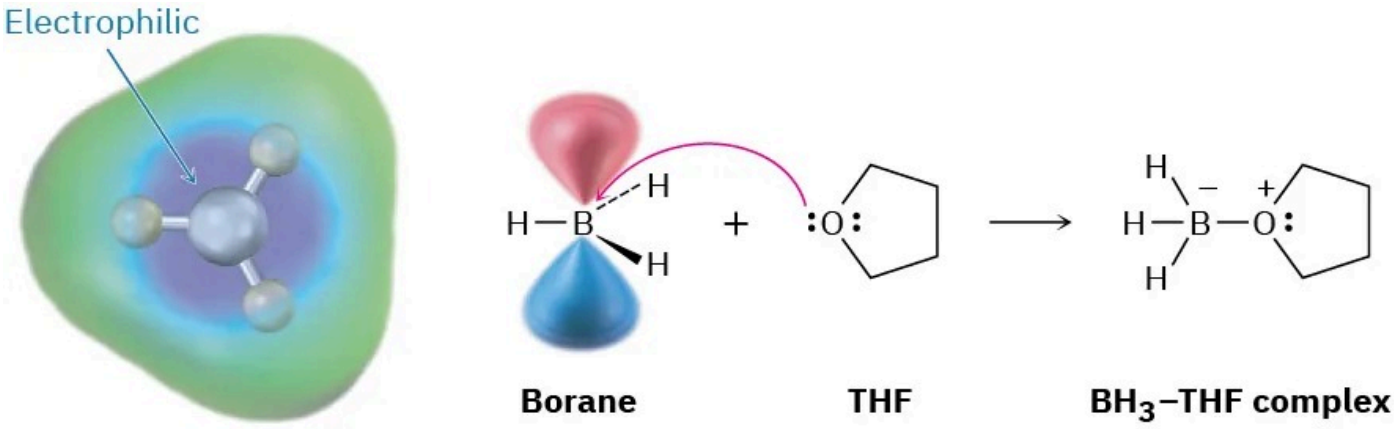
8.7: Hydration of Alkenes - Addition of H_2O by Hydroboration

In addition to the oxymercuration–demercuration method, which yields the Markovnikov product, a complementary method that yields the non-Markovnikov product is also useful. Discovered in 1959 by H.C. Brown at Purdue University and called hydroboration, the reaction involves addition of a B–H bond of borane, BH_3, to an alkene to yield an organoborane intermediate, RBH_2. Oxidation of the organoborane by reaction with basic hydrogen peroxide, H_2O_2, then gives an alcohol. For example:



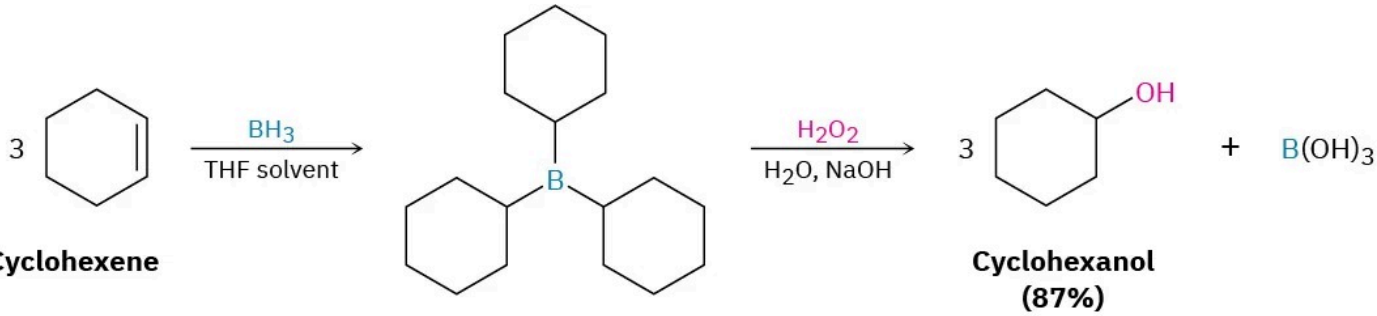
2-Methyl-2-pentene | **Organoborane intermediate** | **2-Methyl-3-pentanol**

Borane is very reactive as a Lewis acid because the boron atom has only six electrons in its valence shell rather than an octet. In tetrahydrofuran solution, BH_3 accepts an electron pair from a solvent molecule in a Lewis acid–base reaction to complete its octet and form a stable BH_3–THF complex.



Borane | **THF** | **BH_3–THF complex**

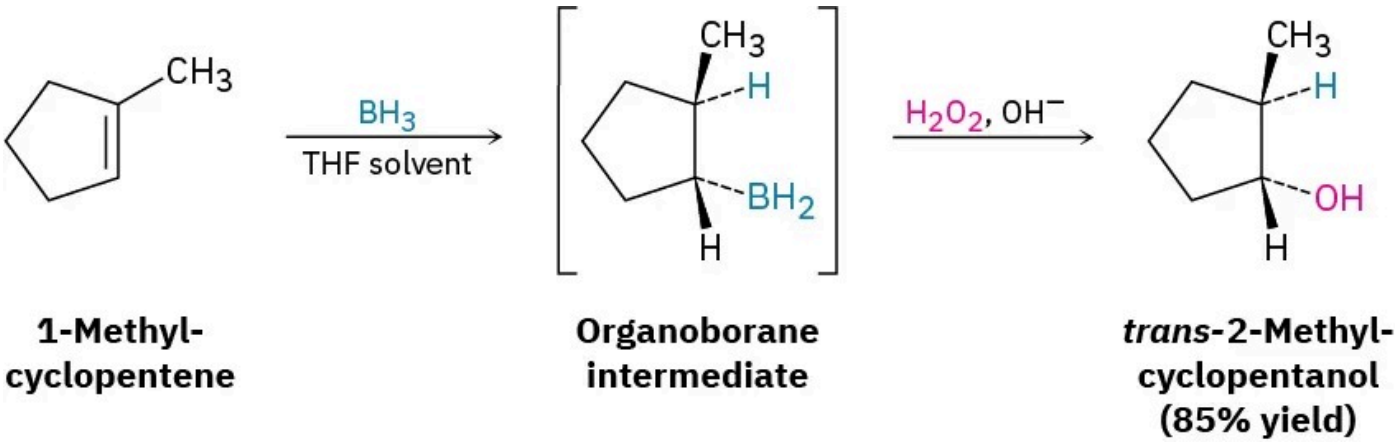
When an alkene reacts with BH_3 in THF solution, rapid addition to the double bond occurs three times and a trialkylborane, R_3B, is formed. For example, 1 molar equivalent of BH_3 adds to 3 molar equivalents of cyclohexene to yield tricyclohexylborane. When tricyclohexylborane is then treated with aqueous hydrogen H_2O_2 in basic solution, an oxidation takes place. The three C–B bonds are broken, –OH groups bond to the three carbons, and 3 equivalents of cyclohexanol are produced. The net effect of the two-step hydroboration–oxidation sequence is hydration of the alkene double bond.



Cyclohexene | **Tricyclohexylborane** | **Cyclohexanol (87%)**

One of the features that makes the hydroboration reaction so useful is the regiochemistry that results when an unsymmetrical

alkene is hydroborated. For example, hydroboration–oxidation of 1-methylcyclopentene yields *trans*-2-methylcyclopentanol. In this process, boron and hydrogen add to the alkene from the same face of the double bond—that is, with syn stereochemistry, the opposite of anti—with boron attaching to the less highly substituted carbon. During the oxidation step, the boron is replaced by an –OH with the same stereochemistry, resulting in an overall syn non-Markovnikov addition of water. This stereochemical result is particularly useful because it is complementary to the Markovnikov regiochemistry observed for oxymercuration–demercuration.



Why does alkene hydroboration take place with syn, non-Markovnikov regiochemistry to yield the less highly substituted alcohol? Hydroboration differs from many other alkene addition reactions in that it occurs in a single step without a carbocation intermediate (Figure 8.7.1). Because the C–H and C–B bonds form at the same time and from the same face of the alkene, syn stereochemistry results. Non-Markovnikov regiochemistry occurs because attachment of boron is favored at the less sterically crowded carbon atom of the alkene.

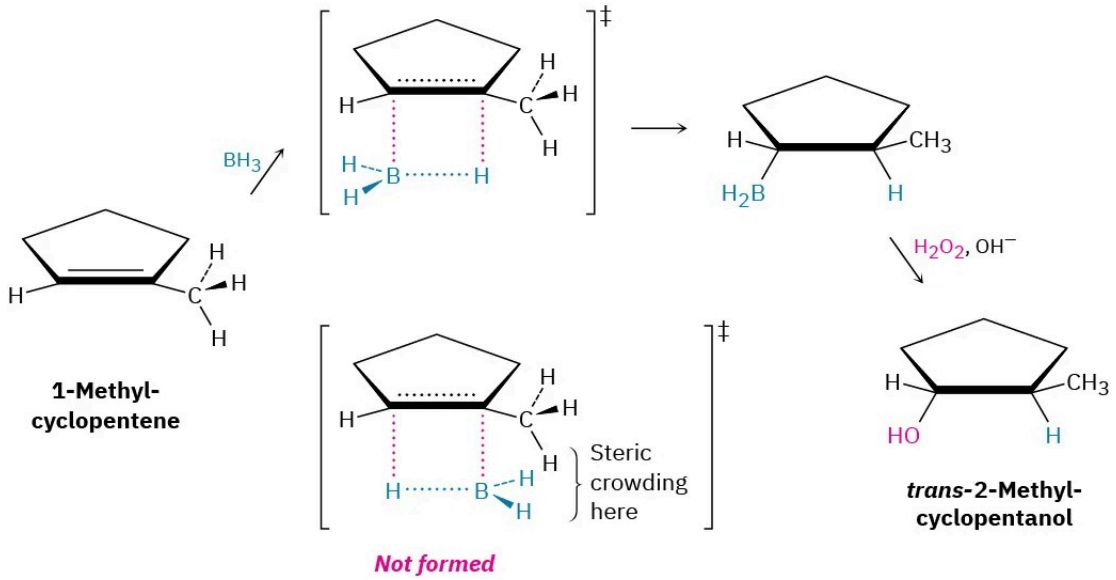


Figure 8.7.1: Mechanism of alkene hydroboration. The reaction occurs in a single step in which the C–H and C–B bonds form at the same time and on the same face of the double bond. The lower energy, more rapidly formed transition state is the one with less steric crowding, leading to non-Markovnikov regiochemistry.

Solved Examples

Worked Example 8.1: Predicting the Products of a Hydration Reaction

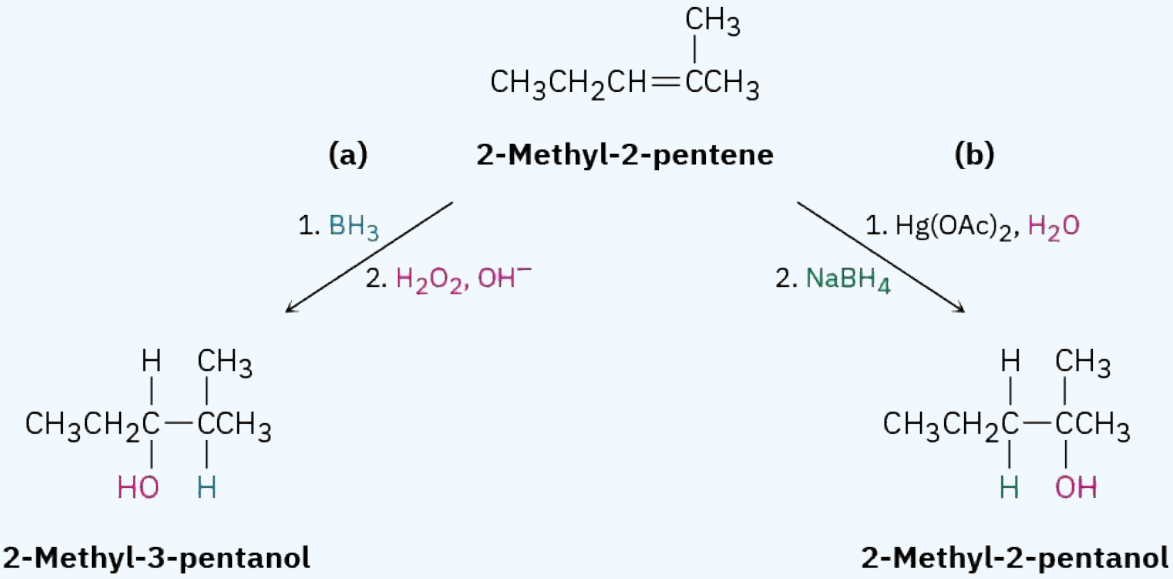
What products would you obtain from reaction of 2-methyl-2-pentene with:

a. BH_3, followed by H_2O_2, OH^-
b. $Hg(OAc)_2$, followed by $NaBH_4$

Strategy

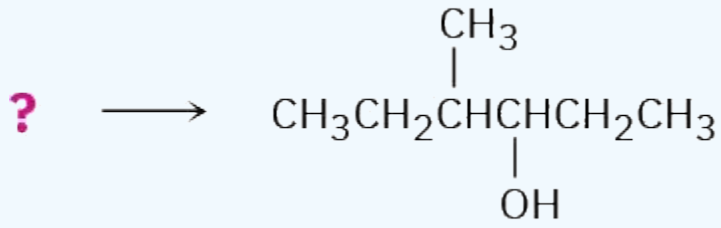
When predicting the product of a reaction, you have to recall what you know about the kind of reaction being carried out and apply that knowledge to the specific case you're dealing with. In the present instance, recall that the two methods of hydration—hydroboration–oxidation and oxymercuration–demercuration—give complementary products. Hydroboration–oxidation occurs with syn stereochemistry and gives the non-Markovnikov addition product; oxymercuration–demercuration gives the Markovnikov product.

Solution



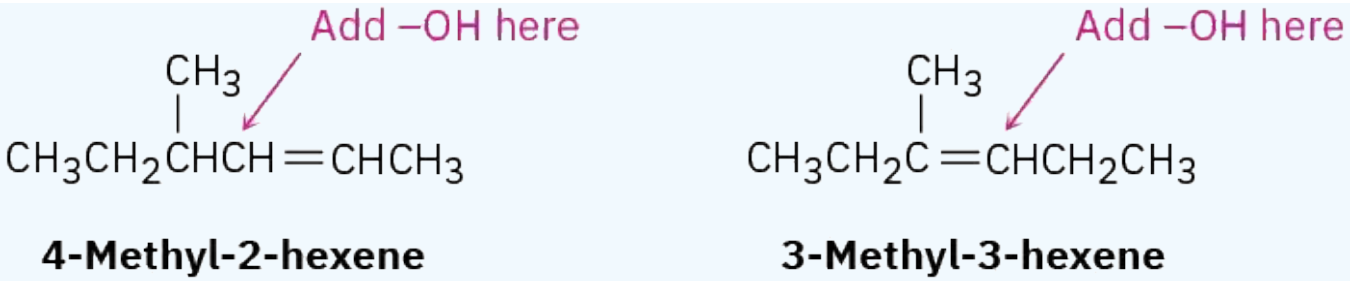
Worked Example 8.2: Synthesizing an Alcohol

How might you prepare the following alcohol?



Strategy

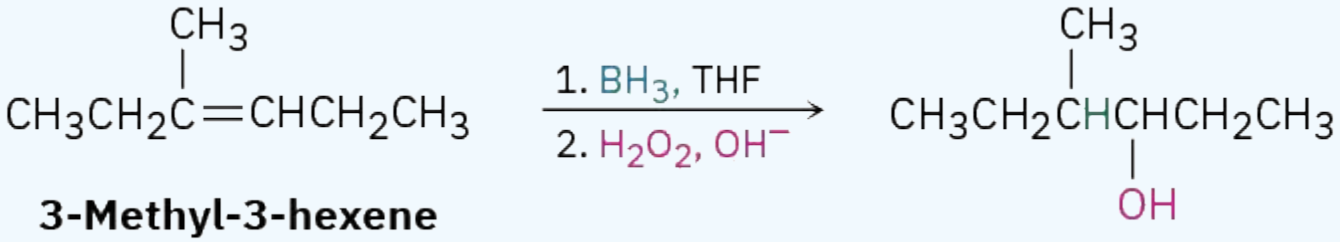
Problems that require the synthesis of a specific target molecule should always be worked backward. Look at the target, identify its functional group(s), and ask yourself, "What are the methods for preparing that functional group?" In the present instance, the target molecule is a secondary alcohol (R_2CHOH), and we've seen that alcohols can be prepared from alkenes by either hydroboration–oxidation or oxymercuration–demercuration. The –OH-bearing carbon in the product must have been a double-bond carbon in the alkene reactant, so there are two possibilities here: 4-methyl-2-hexene and 3-methyl-3-hexene.



4-Methyl-2-hexene **3-Methyl-3-hexene**

4-Methyl-2-hexene has a disubstituted double bond, $\mathrm{RCH{=}CHR'}$, and will probably give a mixture of two alcohols with either hydration method since Markovnikov's rule does not apply to symmetrically substituted alkenes. 3-Methyl-3-hexene, however, has a trisubstituted double bond, and should give only the desired product on non-Markovnikov hydration using the hydroboration–oxidation method.

Solution

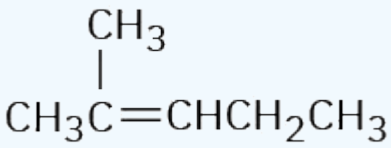


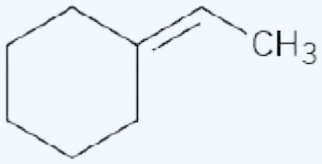
3-Methyl-3-hexene

Exercises

Exercise 8.7.1

Show the structures of the products you would obtain by hydroboration–oxidation of the following alkenes:

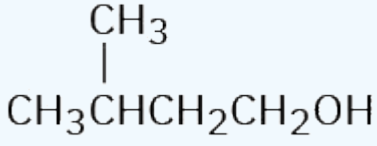
a. 

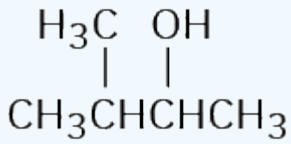
b. 

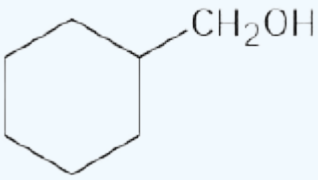
Answer available at the end of this section.

Exercise 8.7.2

What alkenes might be used to prepare the following alcohols by hydroboration–oxidation?

a. 

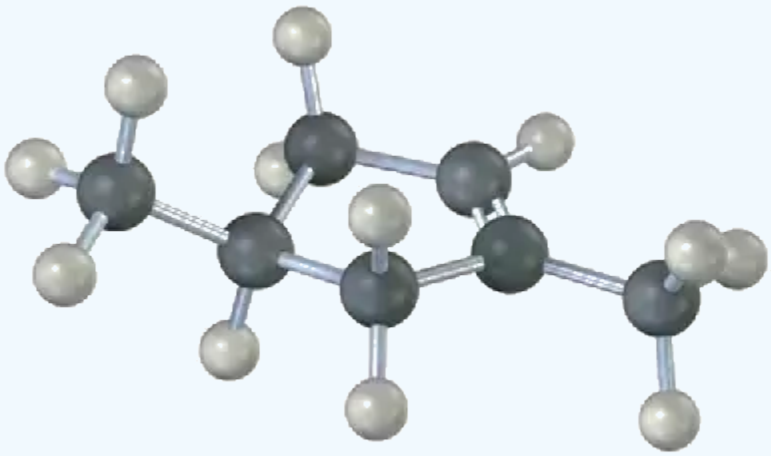
b. 

c. 

Answer available at the end of this section.

Exercise 8.7.3

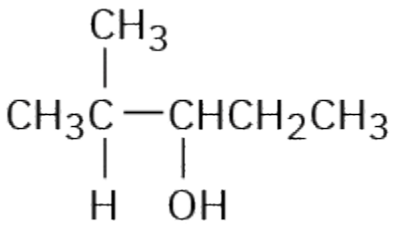
The following cycloalkene gives a mixture of two alcohols on hydroboration followed by oxidation. Draw the structures of both, and explain the result.



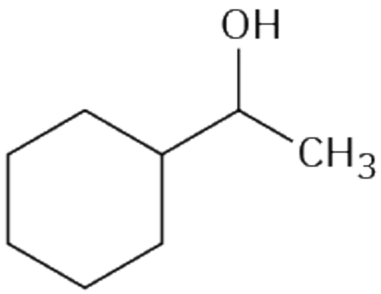
Answer available at the end of this section.

Answers

Exercise 8.7.1

a. 

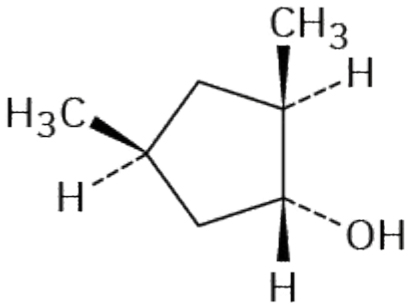
b.



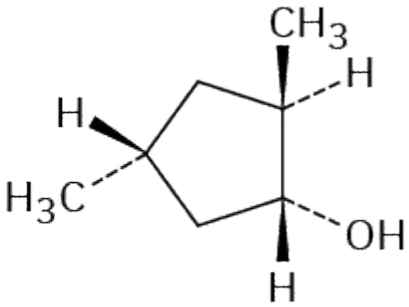
Exercise 8.7.2

a. 3-Methyl-1-butene
b. 2-Methyl-2-butene
c. Methylenecyclohexane

Exercise 8.7.3



and



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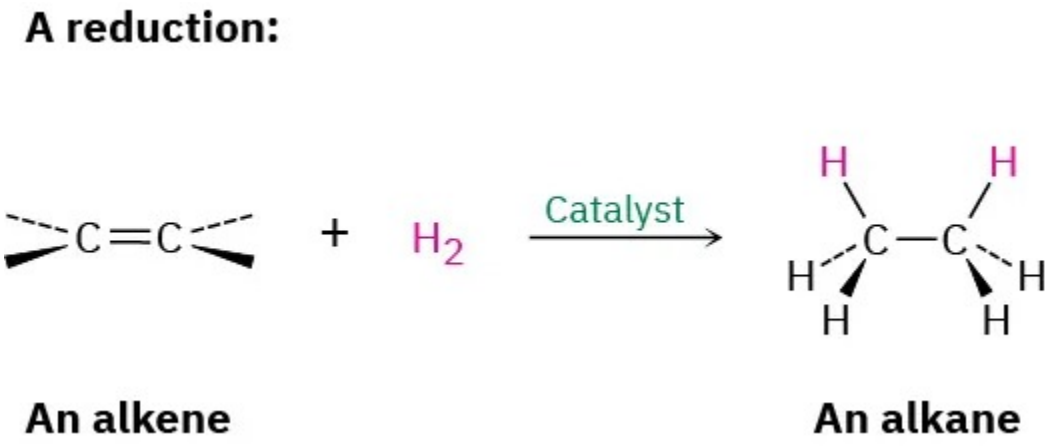
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8.8: Reduction of Alkenes - Hydrogenation

Alkenes react with H_2 in the presence of a metal catalyst such as palladium or platinum to yield the corresponding saturated alkanes. We describe the result by saying that the double bond has been hydrogenated, or *reduced*. Note that the word *reduction* is used somewhat differently in organic chemistry from what you might have learned previously. In general chemistry, a reduction is defined as the gain of one or more electrons by an atom. In organic chemistry, however, a reduction is a reaction that results in a gain of electron density for carbon, caused either by bond formation between carbon and a less electronegative atom—usually hydrogen—or by bond-breaking between carbon and a more electronegative atom—usually oxygen, nitrogen, or a halogen. We'll explore this topic in more detail in **Section 10.9**.

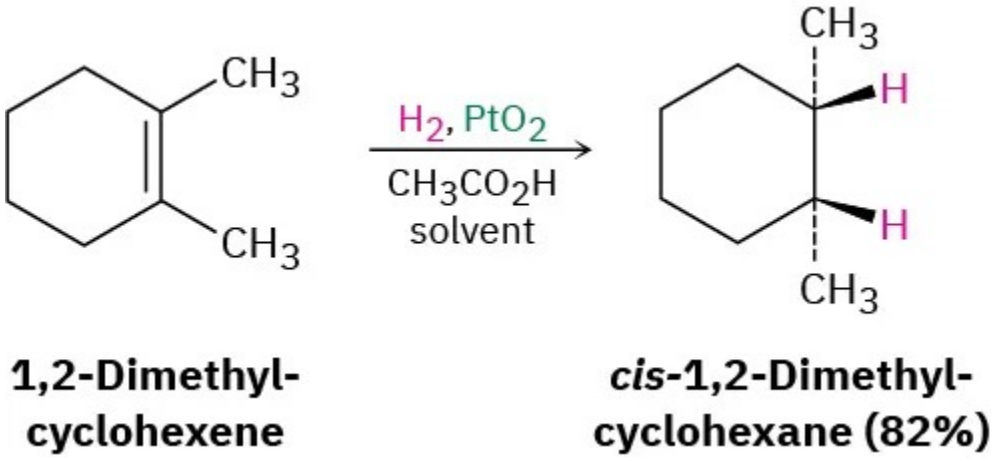
Reduction

Reduces the oxidation state on the carbon by forming this: $\mathrm{C{-}H}$ or breaking one of these: $\mathrm{C{-}O}$, $\mathrm{C{-}N}$, $\mathrm{C{-}X}$



Platinum and palladium are the most common laboratory catalysts for alkene hydrogenations. Palladium is normally used as a very fine powder "supported" on an inert material such as charcoal (Pd/C) to maximize surface area. Platinum is normally used as PtO_2.

Catalytic hydrogenation, unlike most other organic reactions, is a *heterogeneous* process rather than a homogeneous one. That is, the hydrogenation reaction does not occur in a homogeneous solution but instead takes place on the surface of solid catalyst particles. Hydrogenation usually occurs with syn stereochemistry: both hydrogens add to the double bond from the same face.



As shown in Figure $8.8.1$, hydrogenation begins with adsorption of H_2 onto the catalyst surface. Complexation between catalyst

and alkene then occurs as a vacant orbital on the metal interacts with the filled alkene π orbital on the alkene. In the final steps, hydrogen is inserted into the double bond and the saturated product diffuses away from the catalyst. The stereochemistry of hydrogenation is syn because both hydrogens add to the double bond from the same catalyst surface.

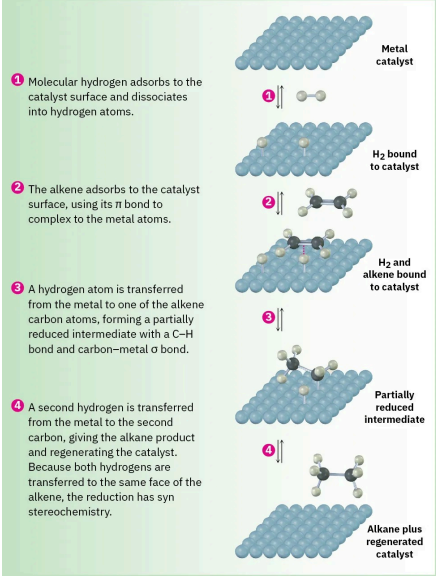
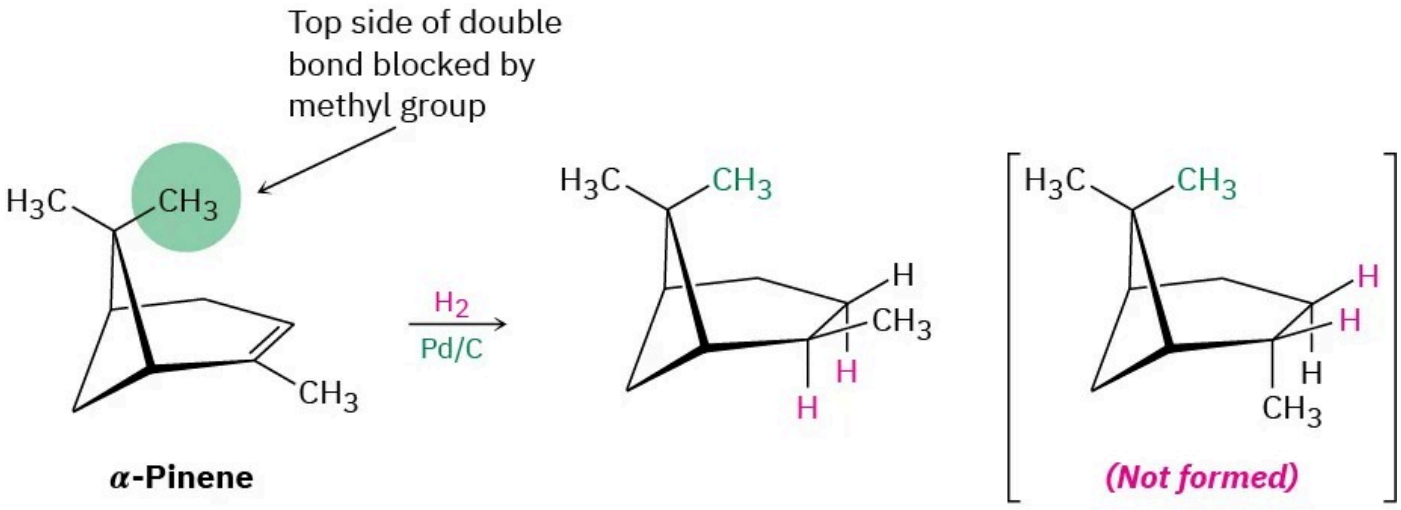
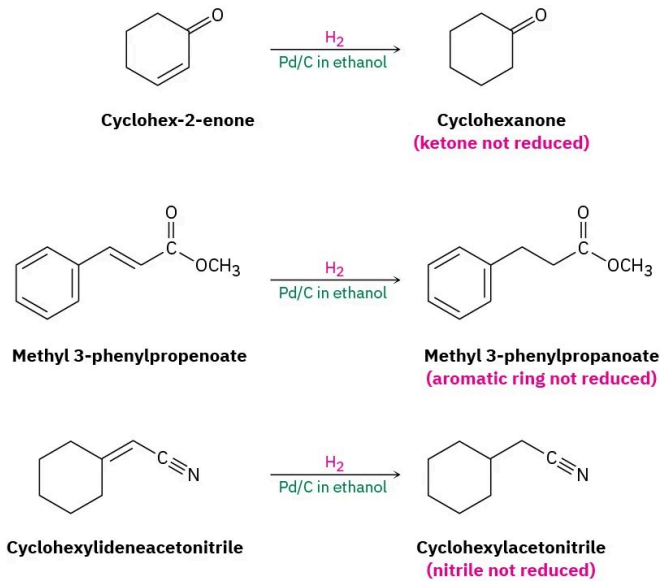


Figure 8.8.1: Mechanism of alkene hydrogenation. The reaction takes place with syn stereochemistry on the surface of insoluble catalyst particles.

A notable feature of catalytic hydrogenation is that the reaction is highly sensitive to the steric environment surrounding the double bond. As a result, the catalyst usually approaches the more accessible face of an alkene, giving rise to a single product. In α-pinene, for example, one of the methyl groups attached to the four-membered ring hangs over the top face of the double bond and blocks approach of the hydrogenation catalyst from that side. Reduction therefore occurs exclusively from the bottom face to yield the product shown.



Alkenes are much more reactive toward catalytic hydrogenation than most other unsaturated functional groups, and the reaction is therefore quite selective. Other functional groups, such as aldehydes, ketones, esters, and nitriles, often survive alkene hydrogenation conditions unchanged, although reaction with these groups does occur under more vigorous conditions. Note that, particularly in the hydrogenation of methyl 3-phenylpropenoate shown below, the aromatic ring is not reduced by hydrogen and palladium even though it contains apparent double bonds.



In addition to its usefulness in the laboratory, catalytic hydrogenation is also important in the food industry, where unsaturated vegetable oils are reduced on a large scale to produce the saturated fats used in margarine and cooking products (Figure 8.8.2). As we'll see next semester, vegetable oils are triesters of glycerol, $HOCH_2CH(OH)CH_2OH$, with three long-chain carboxylic acids, known as *fatty acids*. The fatty acids are generally polyunsaturated, and their double bonds have cis stereochemistry. Complete hydrogenation yields the corresponding saturated fatty acids, but incomplete hydrogenation often results in partial cis–trans isomerization of a remaining double bond. When consumed and digested, the free trans fatty acids are released, which raises blood cholesterol levels and may contribute to coronary problems.

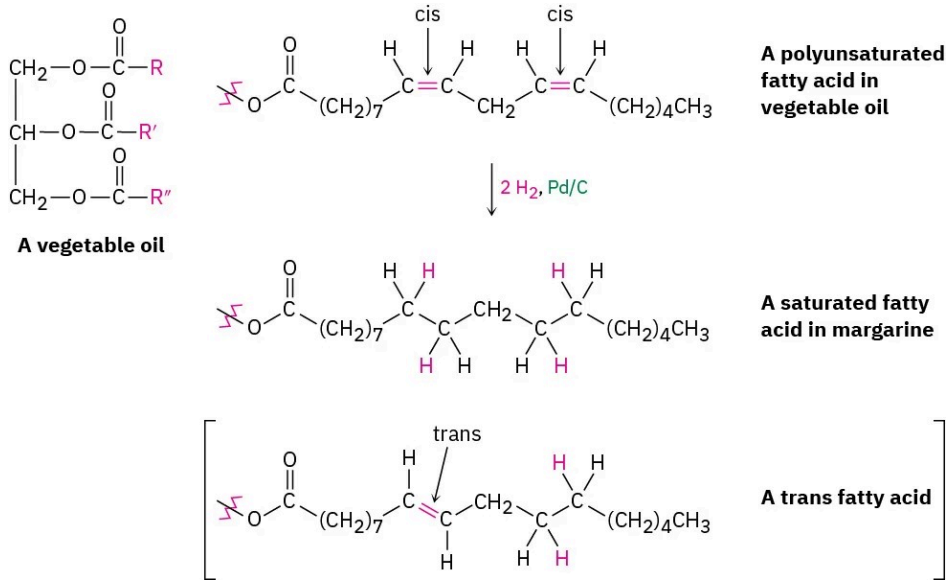


Figure 8.8.2: Catalytic hydrogenation of polyunsaturated fats leads primarily to saturated products, along with a small amount of isomerized trans fats.

Double-bond reductions are very common in biological pathways, although the mechanism is completely different from that of laboratory catalytic hydrogenation over palladium. As with biological hydrations (Section 8.5), biological reductions usually occur in two steps and require that the double bond be adjacent to a carbonyl group. In the first step, the biological reducing agent NADPH (reduced nicotinamide adenine dinucleotide phosphate), adds a hydride ion ($H:^-$) to the double bond to give an anion. In the second, the anion is protonated by acid HA, leading to overall addition of H_2. An example is the reduction of *trans*-crotonyl ACP to yield butyryl ACP, a step involved in the biosynthesis of fatty acids (Figure 8.8.3).

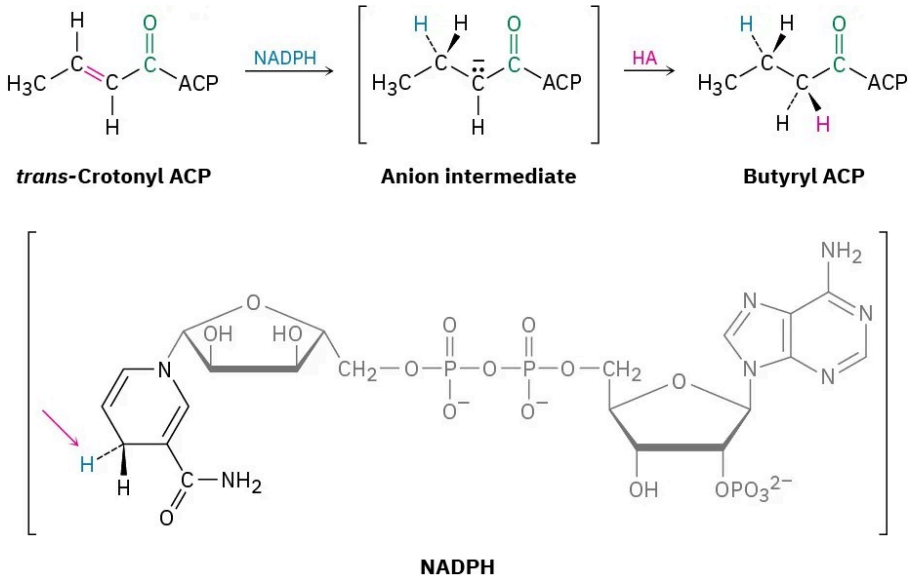


Figure 8.8.3: Reduction of the carbon–carbon double bond in *trans*-crotonyl ACP, a step in the biosynthesis of fatty acids. **One hydrogen** is delivered from NADPH as a hydride ion, H:⁻; the **other hydrogen** is delivered by protonation of the anion intermediate with an acid, HA.

exercise

Exercise 8.8.1

What product would you obtain from catalytic hydrogenation of the following alkenes?

a. **b.** **c.**

Answer available at the end of this section.

Answers

Exercise 8.8.1

a. 2-Methylpentane
b. 1,1-Dimethylcyclopentane
c. *tert*-Butylcyclohexane

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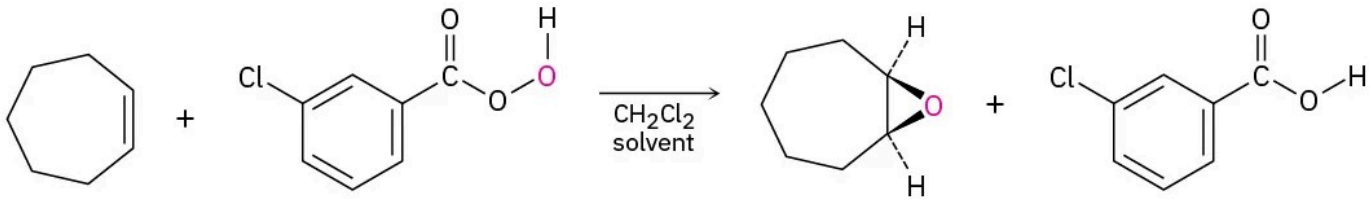
8.9: Oxidation of Alkenes - Epoxidation and Hydroxylation

Like the word *reduction* used in the previous section for the addition of hydrogen to a double bond, the word *oxidation* has a slightly different meaning in organic chemistry than what you might have previously learned. In general chemistry, an oxidation is defined as the loss of one or more electrons by an atom. In organic chemistry, however, an oxidation is a reaction that results in a loss of electron density on carbon, caused either by bond formation between carbon and a more electronegative atom—usually oxygen, nitrogen, or a halogen—or by bond-breaking between carbon and a less electronegative atom—usually hydrogen. Note that *oxidation* often involves the addition of oxygen, while *reduction* often involves the addition of hydrogen.

Oxidation

Increases the oxidation number of the carbon by forming one of these: $\mathrm{C{-}O}$, $\mathrm{C{-}N}$, $\mathrm{C{-}X}$ or breaking this: $\mathrm{C{-}H}$.

In the laboratory, alkenes are oxidized to give *epoxides* on treatment with a *peroxyacid*, RCO_3H, such as *meta*-chloroperoxybenzoic acid. An epoxide, also called an oxirane, is a cyclic ether with an oxygen atom in a three-membered ring. For example:



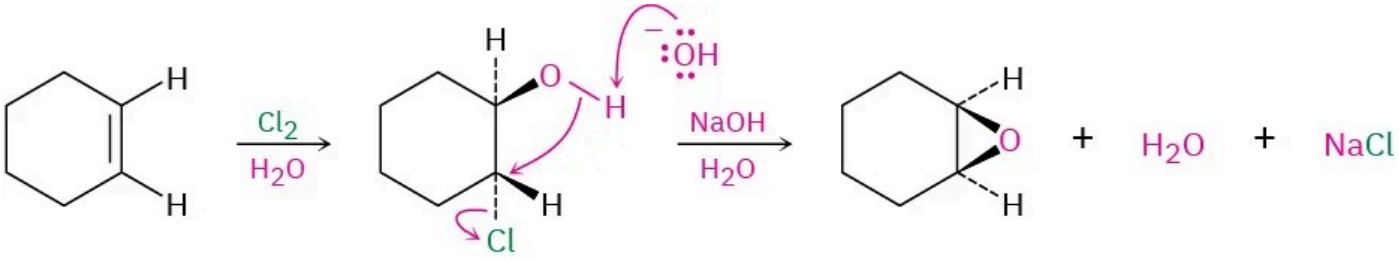
Cycloheptene | ***meta*-Chloroperoxy-benzoic acid** | **1,2-Epoxy-cycloheptane** | ***meta*-Chloro-benzoic acid**

Peroxyacids transfer an oxygen atom to the alkene with syn stereochemistry—both $\mathrm{C{-}O}$ bonds form on the same face of the double bond—through a one-step mechanism without intermediates. The oxygen atom farthest from the carbonyl group is the one transferred.

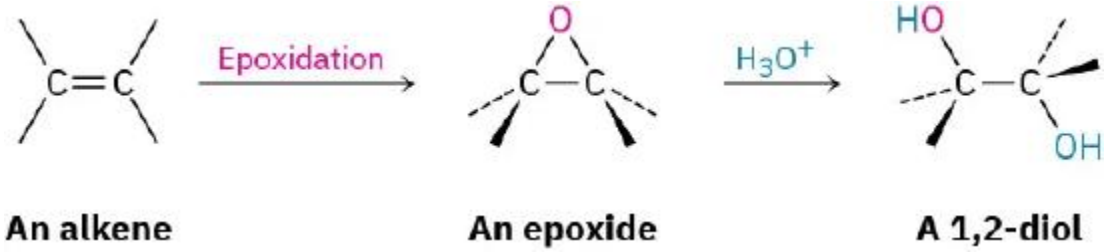


Alkene | **Peroxyacid** | **Epoxide** | **Acid**

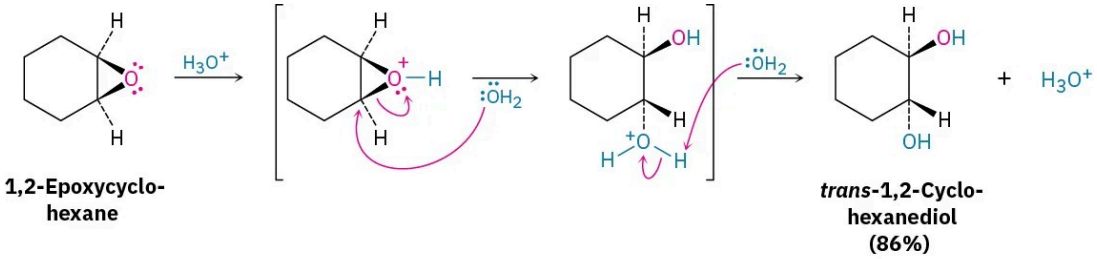
Another method for synthesizing epoxides involves the use of halohydrins, which are prepared by the electrophilic addition of HO–X to alkenes (Section 8.4). When a halohydrin is treated with base, HX is eliminated and an epoxide is produced.

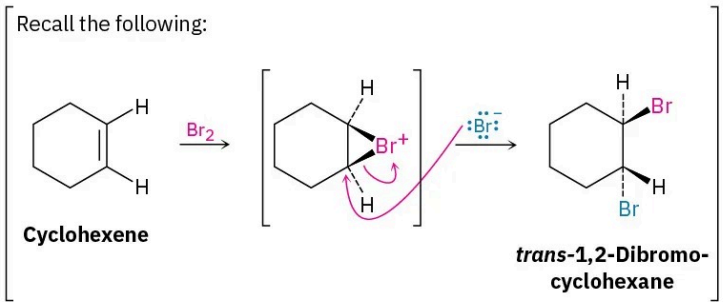


Epoxides undergo an acid-catalyzed ring-opening reaction with water (a hydrolysis) to give the corresponding 1,2-dialcohol, or *diol*, also called a glycol. Thus, the net result of the two-step alkene epoxidation/hydrolysis is hydroxylation—the addition of an –OH group to each of the two double-bond carbons. In fact, approximately 20 million tons of ethylene glycol, $HOCH_2CH_2OH$, most of it used for automobile antifreeze, are produced worldwide each year by the epoxidation of ethylene and subsequent hydrolysis.

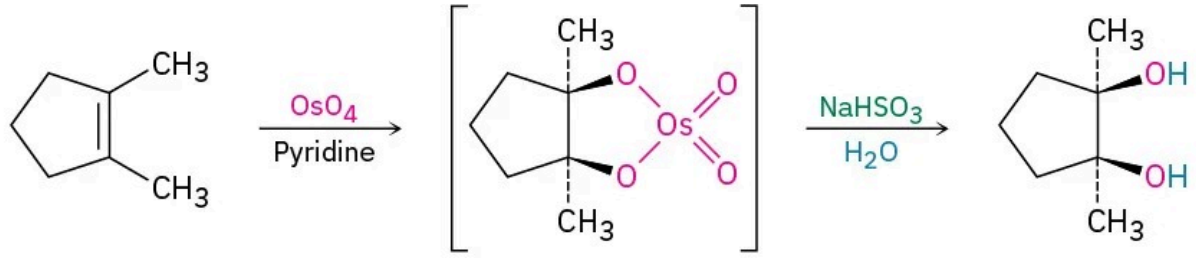


Acid-catalyzed epoxide opening begins with protonation of the epoxide to increase its reactivity, followed by nucleophilic addition of water. This nucleophilic addition is analogous to the final step of alkene bromination, in which a cyclic bromonium ion is opened by a nucleophile (Section 8.3). That is, a *trans*-1,2-diol results when an epoxycycloalkane is opened by aqueous acid, just as a *trans*-1,2-dibromide results when a cycloalkene is brominated.



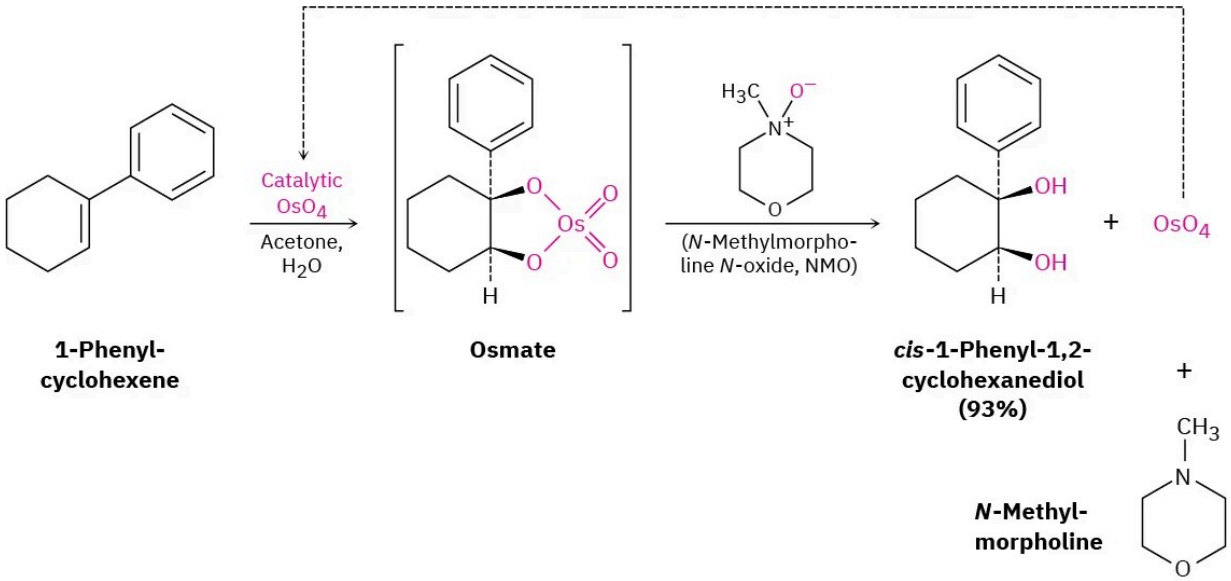


Hydroxylation can also be carried out directly (without going through an intermediate epoxide) by treating an alkene with osmium tetroxide, OsO_4. The reaction occurs with syn stereochemistry and does not involve a carbocation intermediate. Instead, it takes place through an intermediate cyclic *osmate*, which is formed in a single step by addition of OsO_4 to the alkene. This cyclic osmate is then cleaved using aqueous sodium bisulfite, $NaHSO_3$.



1,2-Dimethylcyclopentene | **A cyclic osmate intermediate** | ***cis*-1,2-Dimethyl-1,2-cyclopentanediol (87%)**

Because OsO_4 is both very expensive and *very* toxic, the reaction is usually carried out using only a small, catalytic amount of OsO_4 in the presence of a stoichiometric amount of a safe and inexpensive co-oxidant such as *N*-methylmorpholine *N*-oxide, abbreviated NMO. The initially formed osmate intermediate reacts rapidly with NMO to yield the product diol, plus *N*-methylmorpholine, and reoxidized OsO4, which then reacts with another alkene in a catalytic cycle.



1-Phenylcyclohexene | **Osmate** | ***cis*-1-Phenyl-1,2-cyclohexanediol (93%)** + ***N*-Methylmorpholine**

Exercise 8.9.1

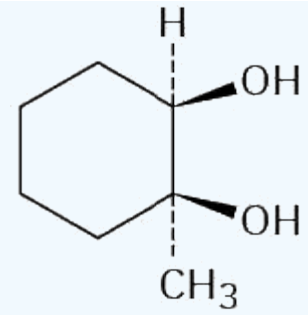
What product would you expect from the reaction of *cis*-2-butene with *meta*-chloroperoxybenzoic acid? Show the stereochemistry.

Answer available at the end of this section.

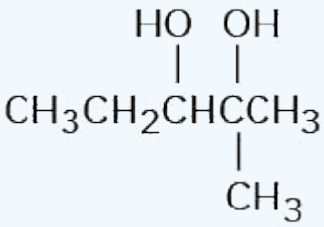
Exercise 8.9.2

Starting with an alkene, how would you prepare each of the following compounds?

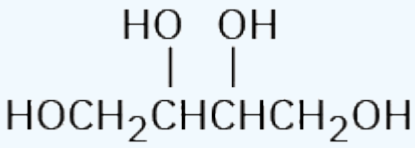
a.



b.



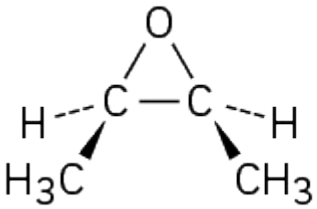
c.



Answer available at the end of this section.

Answers

Exercise 8.9.1



cis-2,3-Epoxybutane

Exercise 8.9.2

a. 1-Methylcyclohexene
b. 2-Methyl-2-pentene
c. 1,3-Butadiene

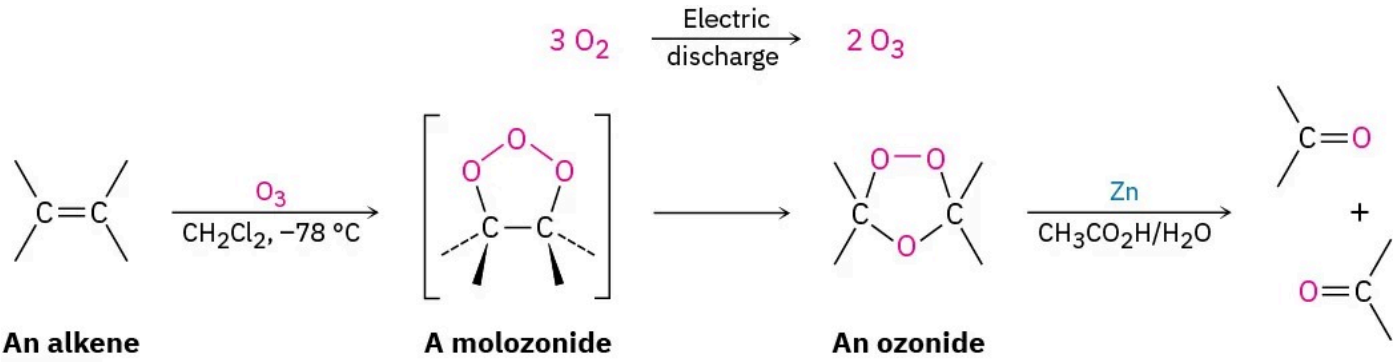
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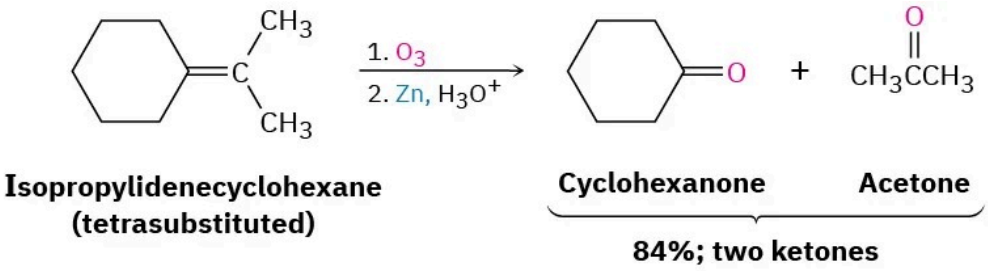
8.10: Oxidation of Alkenes - Cleavage to Carbonyl Compounds

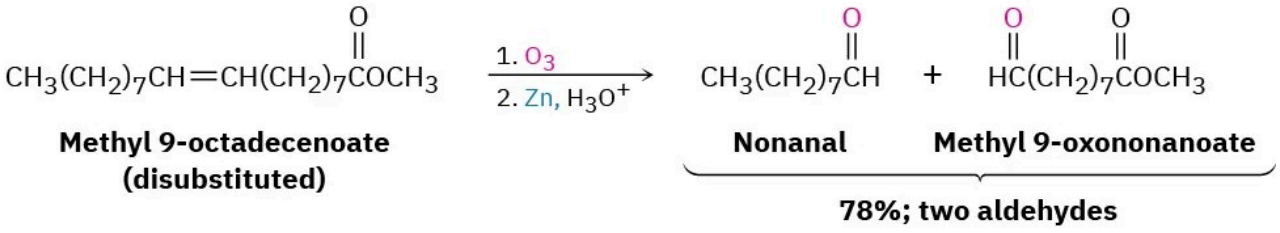
In all the alkene addition reactions we've seen thus far, the carbon–carbon double bond has been converted into a single bond but the carbon skeleton has been unchanged. There are, however, powerful oxidizing reagents that will cleave C=C bonds and produce two carbonyl-containing fragments.

Ozone (O_3) is perhaps the most useful double-bond cleavage reagent. Prepared by passing a stream of oxygen through a high-voltage electrical discharge, ozone adds rapidly to a C=C bond at low temperature to give a cyclic intermediate called a **molozonide**. Once formed, the molozonide spontaneously rearranges to form an ozonide. Although we won't study the mechanism of this rearrangement in detail, it involves the molozonide coming apart into two fragments that then recombine in a different way.



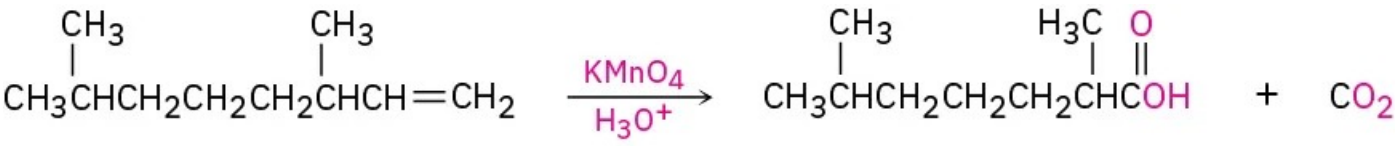
Low-molecular-weight ozonides are explosive and therefore not isolated. Instead, the ozonide is immediately treated with a reducing agent, such as zinc metal in acetic acid, to produce carbonyl compounds. The net result of the ozonolysis/reduction sequence is that the C=C bond is cleaved and an oxygen atom becomes doubly bonded to each of the original alkene carbons. If an alkene with a tetrasubstituted double bond is ozonized, two ketone fragments result; if an alkene with a trisubstituted double bond is ozonized, one ketone and one aldehyde result; and so on.





Several oxidizing reagents other than ozone also cause double-bond cleavage, although such reactions are not often used. For example, potassium permanganate ($KMnO_4$) in neutral or acidic solution cleaves alkenes to give carbonyl-containing products. If hydrogens are present on the double bond, carboxylic acids are produced; if two hydrogens are present on one carbon, CO_2 is

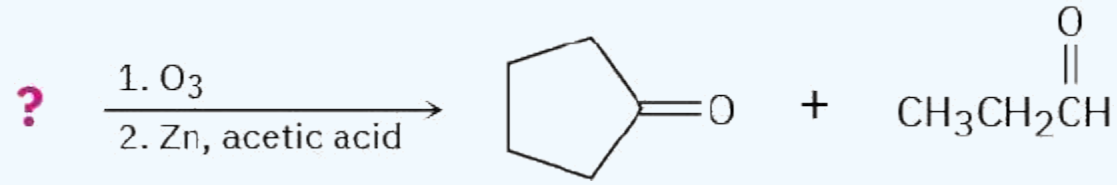
formed.



3,7-Dimethyl-1-octene **2,6-Dimethylheptanoic acid (45%)**

Worked Example 8.10.1: Predicting the Reactant in an Ozonolysis Reaction

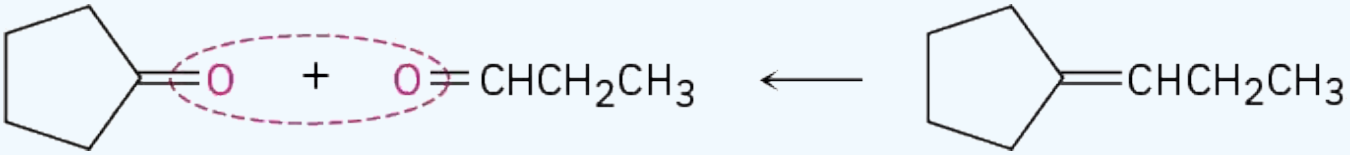
What alkene would yield a mixture of cyclopentanone and propanal on treatment with ozone followed by reduction with zinc?



Strategy

Reaction of an alkene with ozone, followed by reduction with zinc, cleaves the C=C bond and becomes two C=O bonds. Working backward from the carbonyl-containing products, the alkene precursor can be found by removing the oxygen from each product and joining the two carbon atoms.

Solution



Exercise 8.10.1

What products would you expect from the reaction of 1-methylcyclohexene with the following reagents?

a. Aqueous acidic $KMnO_4$
b. O_3, followed by Zn, CH_3CO_2H

Answer available at the end of this section.

Exercise 8.10.2

Propose the structures for alkenes that yield the following products in the reaction with ozone, followed by treatment with Zn.

a. $(CH_3)_2C{=}O + H_2C{=}O$
b. 2 equiv $CH_3CH_2CH{=}O$

Answer available at the end of this section.

Answers

Exercise 8.10.1

a. $CH_3COCH_2CH_2CH_2CH_2CO_2H$
b. $CH_3COCH_2CH_2CH_2CH_2CHO$

Exercise 8.10.2

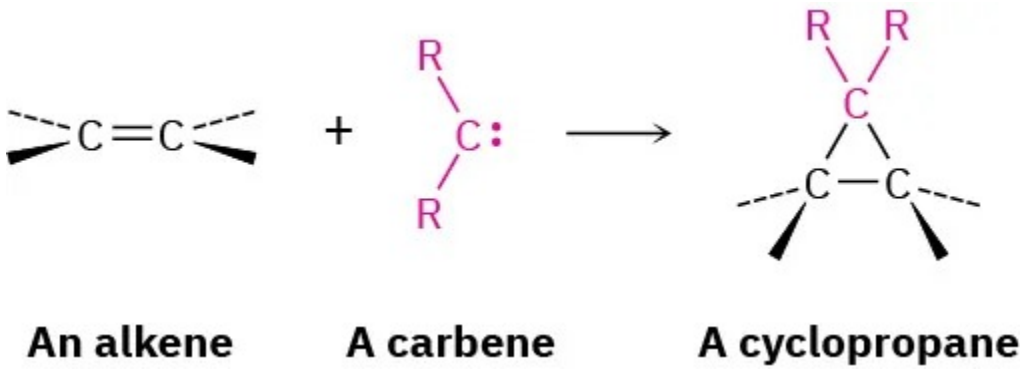
a. 2-Methylpropene
b. 3-Hexene

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8.11: Addition of Carbenes to Alkenes - Cyclopropane Synthesis

Yet another kind of alkene addition is the reaction with a *carbene* to yield a cyclopropane. A carbene, R_2C:, is a neutral molecule containing a divalent carbon with only six electrons in its valence shell. It is therefore highly reactive and generated only as a reaction intermediate, rather than as an isolable molecule. Because they're electron-deficient, carbenes behave as electrophiles and react with nucleophilic $C{=}C$ bonds. The reaction occurs in a single step without intermediates.



One of the simplest methods for generating a substituted carbene is by treatment of chloroform, $CHCl_3$, with a strong base such as KOH. As shown in Figure $8.11.1$, the loss of a proton from $CHCl_3$ gives trichloromethanide anion, $^{-}{:}CCl_2$, which spontaneously expels a Cl^{-} ion to yield dichlorocarbene, $:CCl_2$.

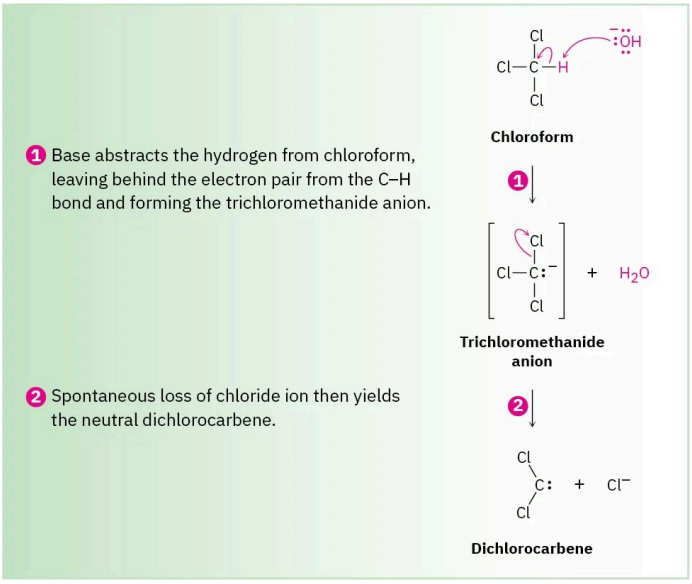


Figure $8.11.1$: Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base. Deprotonation of CHCl3 gives the trichloromethanide anion, $^{-}:CCl_2$, which spontaneously expels a Cl^{-} ion.

The carbon atom in dichlorocarbene is sp^2-hybridized, with a vacant *p* orbital extending above and below the plane of the three atoms and with an unshared pair of electrons occupying the third sp^2 lobe. Note that this electronic description of dichlorocarbene is similar to that of a carbocation (Section 7.10) with respect to both the sp^2 hybridization of carbon and the vacant *p* orbital. Electrostatic potential maps further illustrate the similarity (Figure $8.11.2$).

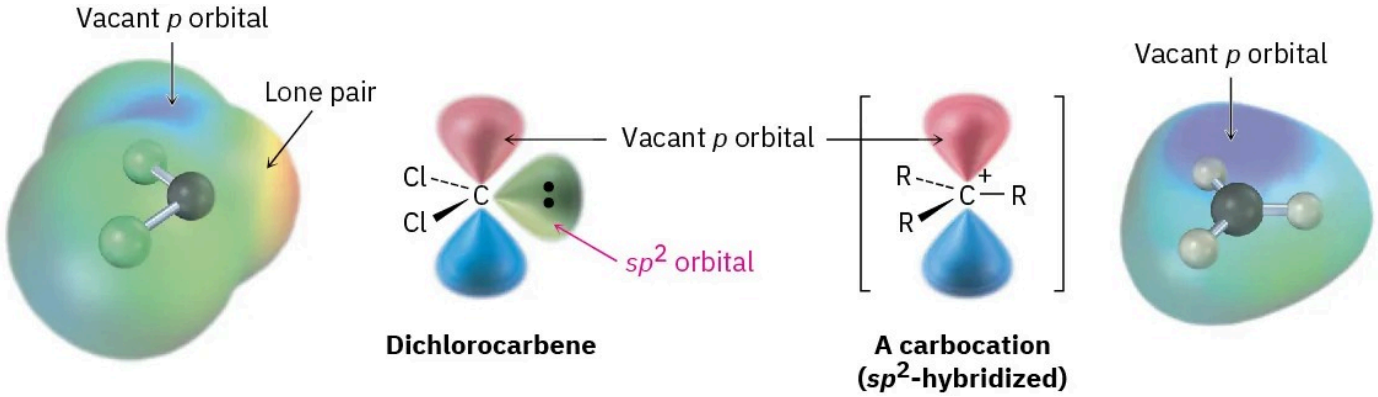
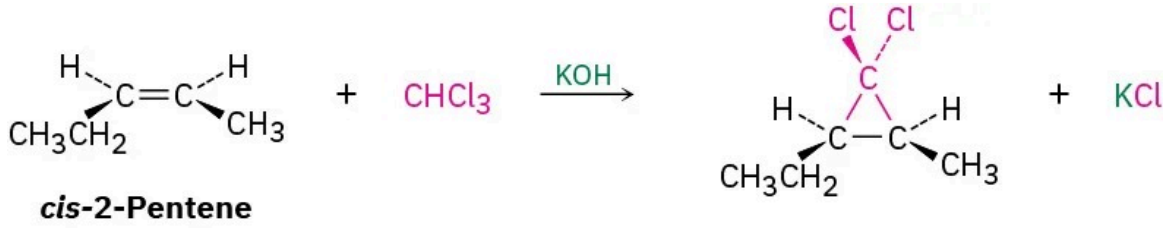
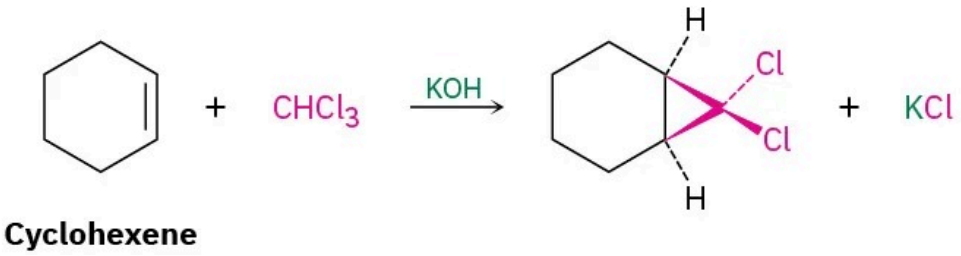


Figure 8.11.2: The structure of dichlorocarbene. Electrostatic potential maps show how **the positive region** coincides with the empty *p* orbital in both dichlorocarbene and a carbocation (CH_3^+). The **negative region** in the dichlorocarbene map coincides with the lone-pair electrons.

If dichlorocarbene is generated in the presence of an alkene, addition to the double bond occurs and a dichlorocyclopropane is formed. As the reaction of dichlorocarbene with *cis*-2-pentene demonstrates, the addition is stereospecific, meaning that only a single stereoisomer is formed as product. Starting from a cis alkene, for instance, only cis-disubstituted cyclopropane is produced; starting from a trans alkene, only trans-disubstituted cyclopropane is produced.

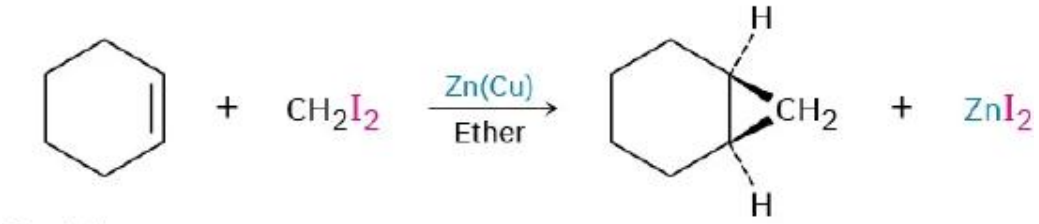




The best method for preparing nonhalogenated cyclopropanes is by a process called the Simmons–Smith reaction. First investigated at the DuPont company, this reaction does not involve a free carbene. Rather, it utilizes a *carbenoid*—a metal-complexed reagent with carbene-like reactivity. When diiodomethane is treated with a specially prepared zinc–copper mix, (iodomethyl)zinc iodide, ICH_2ZnI, is formed. In the presence of an alkene, ICH_2ZnI transfers a CH_2 group to the double bond to yield cyclopropane. For example, cyclohexene reacts cleanly and with good yield to give the corresponding cyclopropane. Although we won't discuss the mechanistic details, carbene addition to an alkene is one of a general class of reactions called *cycloadditions,* which we'll study more carefully in Chapter 30.



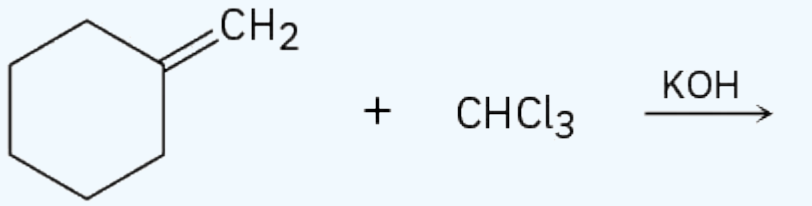
Diiodomethane — **(Iodomethyl)zinc iodide (a carbenoid)**

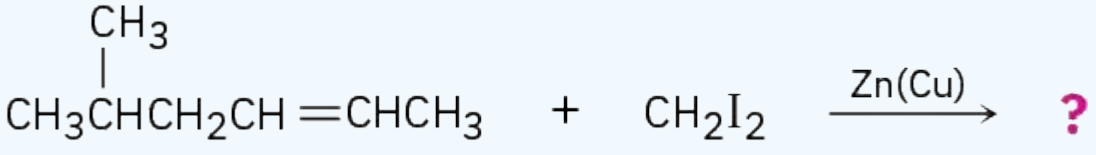


Cyclohexene — **Bicyclo[4.1.0]heptane (92%)**

Exercise 8.11.1

What products would you expect from the following reactions?

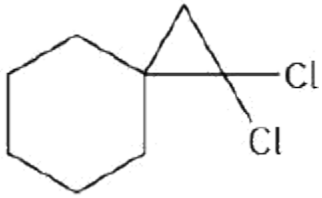
a. 

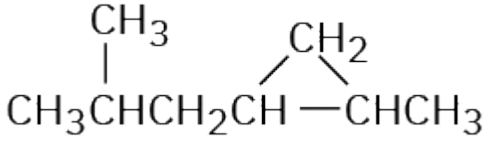
b. 

Answer available at the end of this section.

Answers

Exercise 8.11.1

a. 

b. 

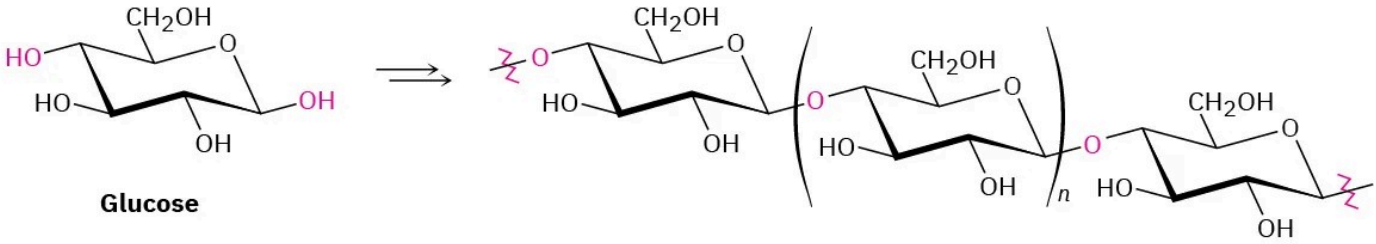
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8.12: Radical Additions to Alkenes - Chain-Growth Polymers

In our brief introduction to radical reactions in Section 6.7, we said that radicals can add to C=C bonds, taking one electron from the double bond and leaving one behind to yield a new radical. Let's now look at the process in more detail, focusing on the industrial synthesis of alkene polymers. A polymer is a large—sometimes *very* large—molecule, built up by repetitive joining together of many smaller molecules, called monomers.

Cellulose—a glucose polymer

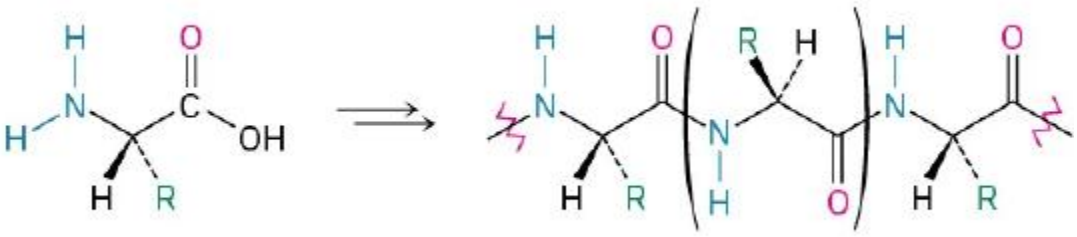


Glucose

Cellulose

Nature makes wide use of biological polymers. Cellulose, for instance, is a polymer built of repeating glucose monomer units; proteins are polymers built of repeating amino acid monomers; and nucleic acids are polymers built of repeating nucleotide monomers.

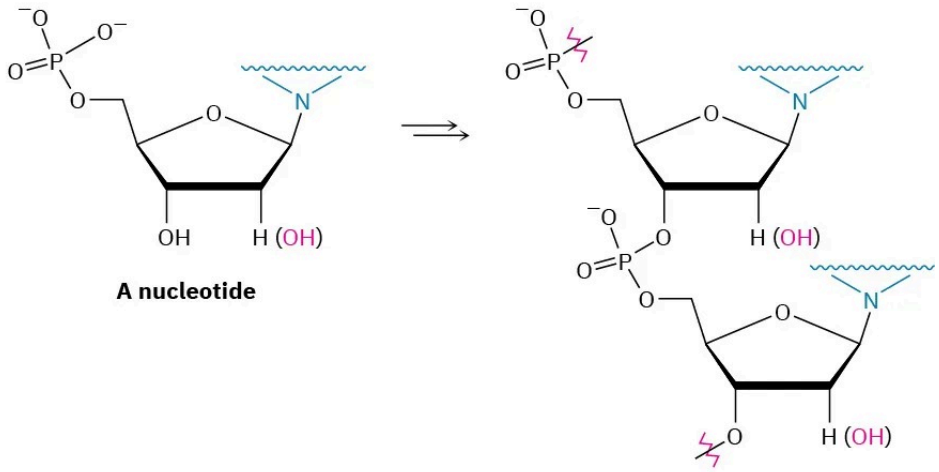
Protein—an amino acid polymer



An amino acid

A protein

Nucleic acid—a nucleotide polymer



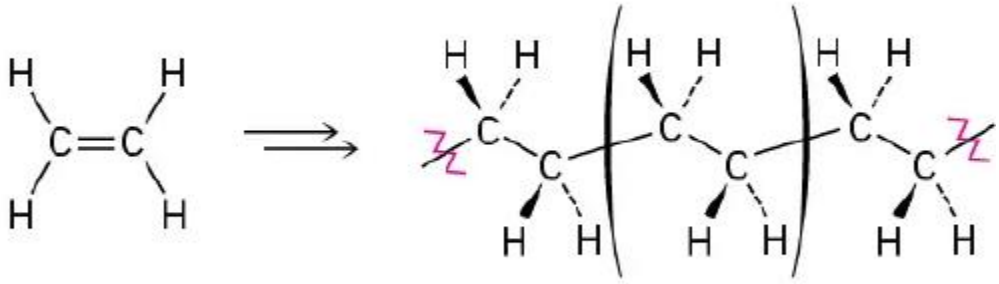
A nucleotide

A nucleic acid

Synthetic polymers, such as polyethylene, are much simpler chemically than biopolymers, but there is still a great diversity to their

structures and properties, depending on the identity of the monomers and on the reaction conditions used for polymerization. The simplest synthetic polymers are those that result when an alkene is treated with a small amount of a suitable catalyst. Ethylene, for example, yields polyethylene, an enormous alkane that may have a molecular weight up to *6 million* u and may contain as many as 200,000 monomer units. Worldwide production of polyethylene is approximately 88 million tons per year.

Polyethylene—a synthetic alkene polymer

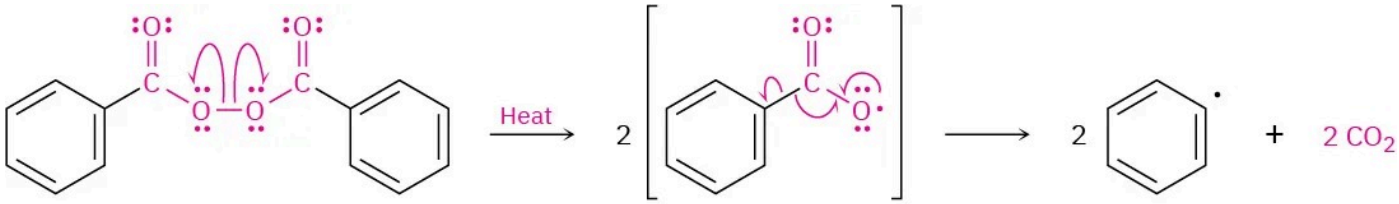


Ethylene **Polyethylene**

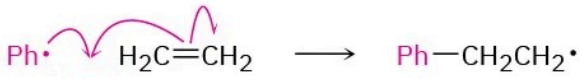
Polyethylene and other simple alkene polymers are called chain-growth polymers because they are formed in a chain-reaction process in which an initiator adds to a carbon–carbon double bond to yield a reactive intermediate. The intermediate then reacts with a second molecule of monomer to yield a new intermediate, which reacts with a third monomer unit, and so on.

Historically, ethylene polymerization was carried out at high pressure (1000–3000 atm) and high temperature (100–250 °C) in the presence of a radical initiator such as benzoyl peroxide. Like many radical reactions, the mechanism of ethylene polymerization occurs in three steps: initiation, propagation, and termination:

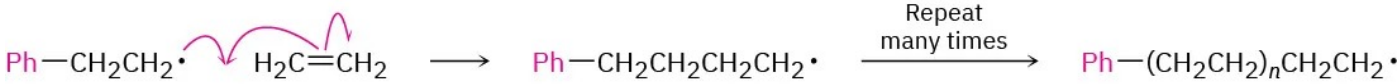
- **Initiation:** The polymerization reaction is initiated when a few radicals are generated on heating a small amount of benzoyl peroxide catalyst to break the weak O–O bond. The initially formed benzoyloxy radical loses CO_2 and gives a phenyl radical (Ph·), which adds to the $C{=}C$ bond of ethylene to start the polymerization process. One electron from the ethylene double bond pairs up with the odd electron on the phenyl radical to form a new C–C bond, and the other electron remains on carbon.



Benzoyl peroxide **Benzoyloxy radical** **Phenyl radical (Ph·)**



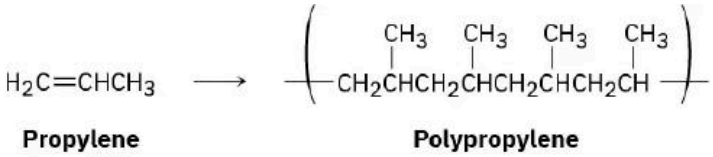
- **Propagation:** Polymerization occurs when the carbon radical formed in the initiation step adds to another ethylene molecule to yield another radical. Repetition of the process for hundreds or thousands of times builds the polymer chain.



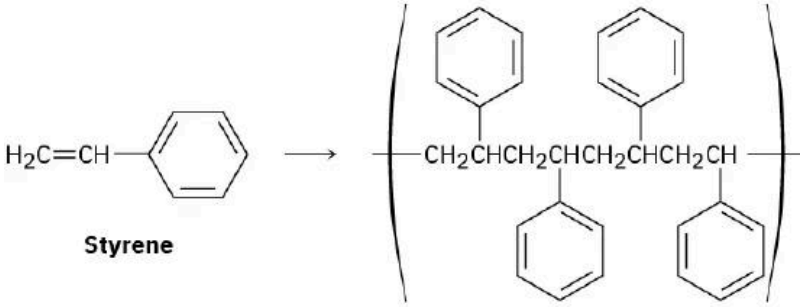
- **Termination:** The chain process is eventually ended by a reaction that consumes the radical. The combination of two growing chains is one possible chain-terminating reaction.

$$2\mathrm{R-CH_2CH_2\cdot \longrightarrow R-CH_2CH_2CH_2CH_2-R}$$

Ethylene is not unique in its ability to form a polymer. Many substituted ethylenes, called vinyl monomers, also undergo polymerization to yield polymers with substituent groups regularly spaced on alternating carbon atoms along the chain. Propylene, for example, yields polypropylene, and styrene yields polystyrene.



Propylene **Polypropylene**



Styrene **Polystyrene**

When an unsymmetrically substituted vinyl monomer such as propylene or styrene is polymerized, the radical addition steps can take place at either end of the double bond to yield either a primary radical intermediate (RCH_2•) or a secondary radical (R_2CH•). Just as in electrophilic addition reactions, however, we find that only the more highly substituted, secondary radical is formed.

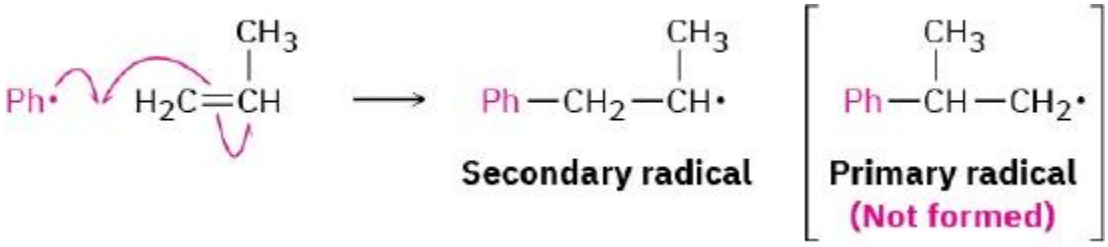
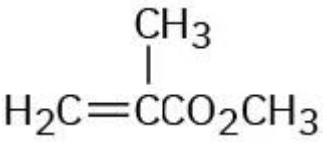


Figure 8.12.1 shows some commercially important alkene polymers, their uses, and the monomers from which they are made.

Figure 8.12.1*: Some Alkene Polymers and Their Uses*

Monomer	Formula	Trade or common name of polymer	Uses
Ethylene	$H_2C{=}CH_2$	Polyethylene	Packaging, bottles
Propene (propylene)	$H_2C{=}CHCH_3$	Polypropylene	Moldings, rope, carpets
Chloroethylene (vinyl chloride)	$H_2C{=}CHCl$	Poly(vinyl chloride)	Insulation, films, pipes
Styrene	$H_2C{=}CHC_6H_5$	Polystyrene	Foam, moldings
Tetrafluoroethylene	$F_2C{=}CF_2$	Teflon	Gaskets, nonstick coatings
Acrylonitrile	$H_2C{=}CHCN$	Orlon, Acrilan	Fibers

Monomer	Formula	Trade or common name of polymer	Uses
Methyl methacrylate		Plexiglas, Lucite	Paint, sheets, moldings
Vinyl acetate	$H_2C{=}CHOCOCH_3$	Poly(vinyl acetate)	Paint, adhesives, foams

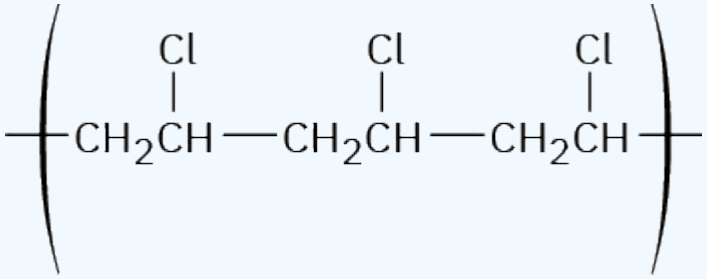
Worked Example 8.12.1: Predicting the Structure of a Polymer

Show the structure of poly(vinyl chloride), a polymer made from $H_2C{=}CHCl$, by drawing several repeating units.

Strategy

Break the carbon–carbon double bond in the monomer unit, and form single bonds by connecting several units together.

Solution

The general structure of poly(vinyl chloride) is 

Exercise 8.12.1

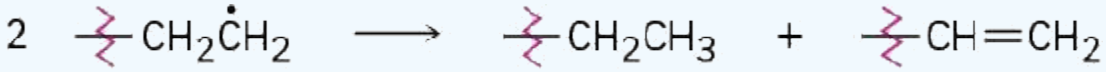
Show the monomer units you would use to prepare the following polymers:

a. **b.**

Answer available at the end of this section.

Exercise 8.12.2

One of the chain-termination steps that sometimes occurs to interrupt polymerization is the following reaction between two radicals. Propose a mechanism for the reaction, using fishhook arrows to indicate electron flow.



Answer available at the end of this section.

Answers

Exercise 8.12.1

a. $H_2C{=}CHOCH_3$ **b.** $ClCH{=}CHCl$

Exercise 8.12.2



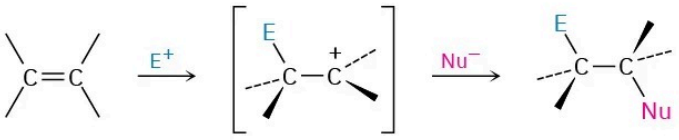
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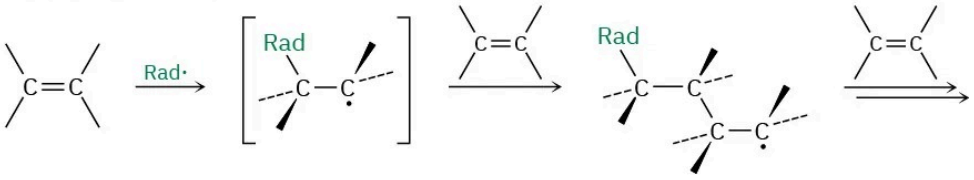
8.13: Biological Additions of Radicals to Alkenes

The same high reactivity of radicals that enables the alkene polymerization we saw in the previous section also makes it difficult to carry out controlled radical reactions on complex molecules. As a result, there are severe limitations on the usefulness of radical addition reactions in the laboratory. In contrast to an electrophilic addition, where reaction occurs once and the reactive cation intermediate is rapidly quenched by a nucleophile, the reactive intermediate in a radical reaction is not usually quenched. Instead, it reacts again and again in a largely uncontrollable way.

Electrophilic addition
(Intermediate is quenched,
so reaction stops.)



Radical addition
(Intermediate is not quenched,
so reaction does not stop.)



In biological reactions, the situation is different from that in the laboratory. Only one substrate molecule at a time is present in the active site of an enzyme, and that molecule is held in a precise position, with other necessary reacting groups nearby. As a result, biological radical reactions are more controlled and more common than laboratory or industrial radical reactions. A particularly impressive example occurs in the biosynthesis of prostaglandins from arachidonic acid, where a sequence of four radical additions take place. Its reaction mechanism was discussed briefly in Section 6.7.

As shown in Figure $8.13.1$, prostaglandin biosynthesis begins with abstraction of a hydrogen atom from C13 of arachidonic acid by an iron–oxy radical to give a carbon radical that reacts with O_2 at C11 through a resonance form. The oxygen radical that results adds to the C8–C9 double bond to give a carbon radical at C8, which adds to the C12–C13 double bond and gives a carbon radical at C13. A resonance form of this carbon radical adds at C15 to a second O_2 molecule, completing the prostaglandin skeleton. Reduction of the O–O bond then gives prostaglandin H_2, called PGH_2. The pathway looks complicated, but the entire process is catalyzed with exquisite control by a single enzyme.

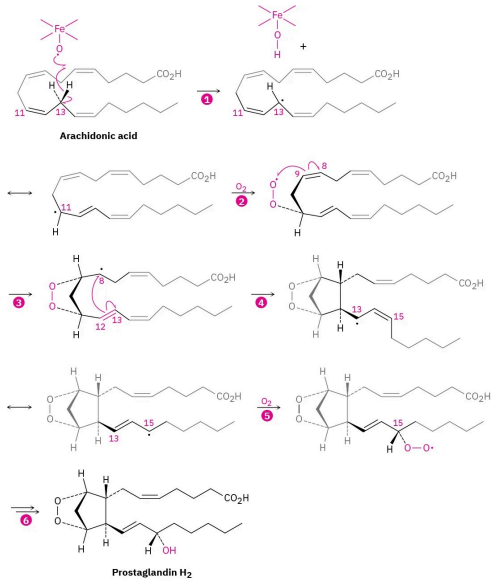


Figure 8.13.1: Pathway for the biosynthesis of prostaglandins from arachidonic acid. Steps **2** and **5** are radical addition reactions to O_2; steps **3** and **4** are radical additions to carbon–carbon double bonds.

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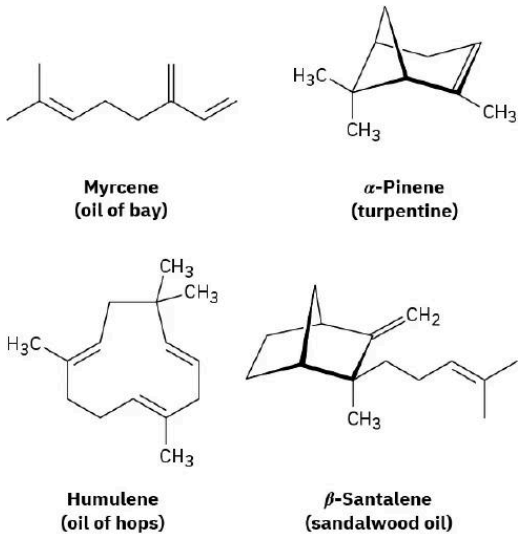
8.14: Chemistry Matters—Terpenes- Naturally Occurring Alkenes

Ever since its discovery in Persia around 1000 A.D., it has been known that *steam distillation*, the distillation of plant materials together with water, produces a fragrant mixture of liquids called essential oils. The resulting oils have long been used as medicines, spices, and perfumes, and their investigation played a major role in the emergence of organic chemistry as a science during the 19th century.



Figure 8.14.1: The wonderful fragrance of leaves from the California bay laurel is due primarily to myrcene, a simple terpene. (credit: "California Bay Umbellularia californica" by Don Loaire/Flickr, CC BY 2.0)

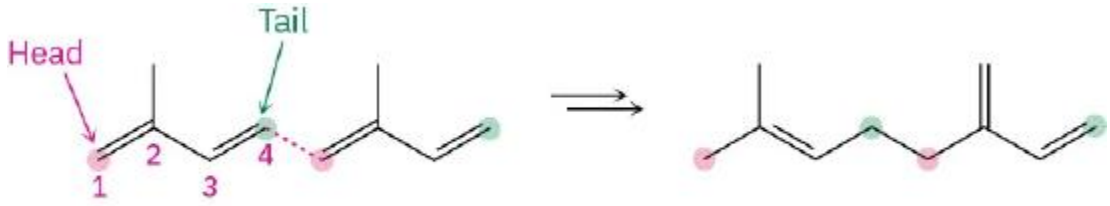
Chemically, plant essential oils consist largely of mixtures of compounds called terpenoids—small organic molecules with an immense diversity of structure. More than 60,000 different terpenoids are known. Some are open-chain molecules, and others contain rings; some are hydrocarbons, and others contain oxygen. Hydrocarbon terpenoids, in particular, are known as terpenes, and all contain double bonds. For example:



Myrcene (oil of bay) | ***α*-Pinene (turpentine)**

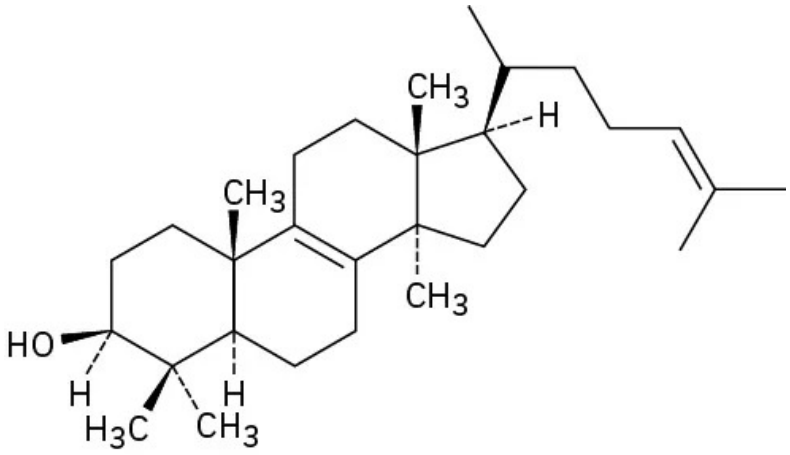
Humulene (oil of hops) | ***β*-Santalene (sandalwood oil)**

Regardless of their apparent structural differences, all terpenoids are related. According to a formalism called the isoprene rule, they can be thought of as arising from head-to-tail joining of 5-carbon isoprene units (2-methyl-1,3-butadiene). Carbon 1 is the head of the isoprene unit, and carbon 4 is the tail. For example, myrcene contains two isoprene units joined head to tail, forming an 8-carbon chain with two 1-carbon branches. α-Pinene similarly contains two isoprene units assembled into a more complex cyclic structure, and humulene contains three isoprene units. See if you can identify the isoprene units in α-pinene, humulene, and β-santalene.



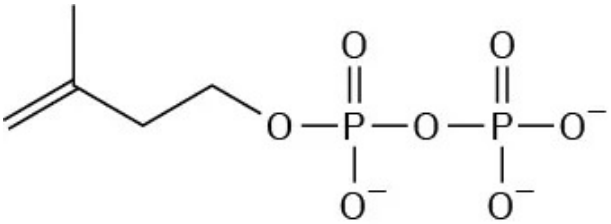
Two isoprene units **Myrcene**

Terpenes (and terpenoids) are further classified according to the number of 5-carbon units they contain. Thus, monoterpenes are 10-carbon substances derived from two isoprene units, sesquiterpenes are 15-carbon molecules derived from three isoprene units, diterpenes are 20-carbon substances derived from four isoprene units, and so on. Monoterpenes and sesquiterpenes are found primarily in plants, but the higher terpenoids occur in both plants and animals, and many have important biological roles. The triterpenoid lanosterol, for instance, is the biological precursor from which all steroid hormones are made.

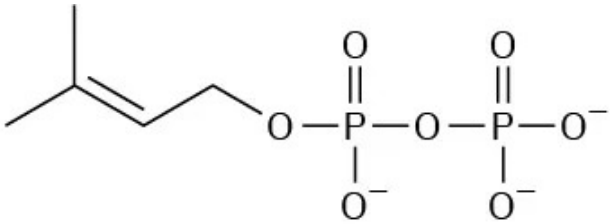


Lanosterol
(a triterpene, C_{30})

Isoprene itself is not the true biological precursor of terpenoids. Nature instead uses two “isoprene equivalents”—isopentenyl diphosphate and dimethylallyl diphosphate—which are themselves made by two different routes depending on the organism. Lanosterol, in particular, is biosynthesized from acetic acid by a complex pathway that has been worked out in great detail. We’ll look at the subject more closely in **Sections 27.6** and **27.8**.



Isopentenyl diphosphate



Dimethylallyl diphosphate

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8.A: Alkenes - Reactions and Synthesis (Summary)

Concepts & Vocabulary

8.1 Preparing Alkenes: A Preview of Elimination Reactions

- Alkenes can be prepared by either E1 or E2 elimination reactions of alkyl halides.

8.2 Halogenation of Alkenes: Addition of X_2

- Halogen molecules can react as **electrophiles** due to polarization of the halogen-halogen bond.
- During **electrophilic addition** of halogens to pi bonds, an intermediate halonium ion is formed.
- During electrophilic halogenation, ring opening of the halonium intermediate causes **anti** stereochemistry of the halogen atoms in the dihalide product.

8.3 Halohydrins from Alkenes: Addition of HOX

- **Halohydrins** have a halogen and a hydroxide on adjacent carbon atoms. Bromohydrin and chlorohydrin are the specific types of halohydrins where the halogen is bromine or chlorine respectively.
- In **halohydrin** formation a carbocation intermediate is formed on the more substituted carbon (when available). This causes the hydroxide to be added to the more substituted carbon of the original alkene and the halogen to add to the less substituted carbon.

8.4 Hydration of Alkenes: Acid-Catalyzed Hydration

- Electrophilic hydration is the addition of water to an alkene with one carbon adding a hydrogen and the other carbon a hydroxide.
- The mechanism begins with addition of a proton, yielding the more substituted **carbocation**.
- Carbocations can undergo **hydride shifts** and **alkyl shifts** to form a more stable **carbocation** when possible.

8.5 Reaction Stereochemistry: Addition of H_2O to an Achiral Alkene

- Since the addition of water to an alkene proceeds through a planar carbocation intermediate, achiral alkenes lead to a racemic mixture of alcohol products.

Reaction Stereochemistry: Additon of H_2O to a Chiral Alkene

- Addition of water to alkenes which also contain a stereocenter does not lead to a 50:50 mixture of R and S products as the chiral center can reduce reactivity from one side of the carbocation. The products of this type of reaction will be diastereomers, since the original stereocenter will not change and the product will have an additional stereocenter.

8.6 Hydration of Alkenes: Addition of H_2O by Oxymercuration

- **Markovnikov** addition through acid and water or oxymercuration-demercuration yields the more substituted alcohol product (when the two sides of the alkene are not equally substituted).
- Oxymercuration-demercuration avoids carbocation rearrangements through mercurinium ion bridge.

8.7 Hydration of Alkenes: Addition of H_2O by Hydroboration

- Hydroboration-oxidation proceeds through anti-**Markovnikov** addition of water to an alkene, yielding the less substituted alcohol.

8.8 Reduction of Alkenes: Hydrogenation

- Hydrogenation reactions increase the number of carbon-hydrogen bonds, therefore are reduction reactions.
- The addition of hydrogen to carbon-carbon pi bonds is called hydrogenation.

- Hydrogenation requires a catalyst to lower the activation energy allowing the reaction to proceed (commonly nickel, palladium or platinum).
- Hydrogenation reactions occur primarily with syn addition of the two hydrogen atoms, though potential for isomerization makes this uncertain.

8.9 Oxidation of Alkenes: Epoxidation and Hydroxylation

- **Epoxidation** can be carried out by reacting an alkene with a peroxy acid such as MCPBA.
- Anti **dihydroxylation** is achieved by ring opening an epoxide with water under acidic or basic conditions.
- Vicinal diols have hydroxy groups on adjacent carbon atoms.
- Syn dihydroxylation occurs through reaction with osmium tetraoxide, followed by reduction of the intermediate with sulfur compounds.

8.10 Oxidation of Alkenes: Cleavage to Carbonyl Compounds

- Ozonolysis is the cleavage of an alkene, resulting in carbonyls at each carbon of the alkene.
- Alkenes can be cleaved by potassium permanganate, which also results in carbonyls at each alkene carbon, though potassium permanganate will oxidize every carbon-hydrogen bond on the alkene to a carbon-oxygen bond.

8.11 Addition of Carbenes to Alkenes: Cyclopropane Synthesis

- Organic molecules that have a carbon with only two bonds and a lone pair of electrons are called carbenes.
- Most carbenes are highly reactive and short-lived and are often created *in situ*.
- Carbenes can be formed from diazo compounds by reacting wtih a copper catalyst.
- Carbenes will react with alkenes to form cyclopropane rings.

8.12 Radical Addition to Alkenes: Chain-Growth Polymers

- Monomers are units that repeat to form a polymer.
- In radical polymerization, the polymer chain reaction is initiated by a radical.
- Polymer chain reactions occur through a series of steps beginning with **initiation**, continuing through **propagation**, and ending in **termination**.

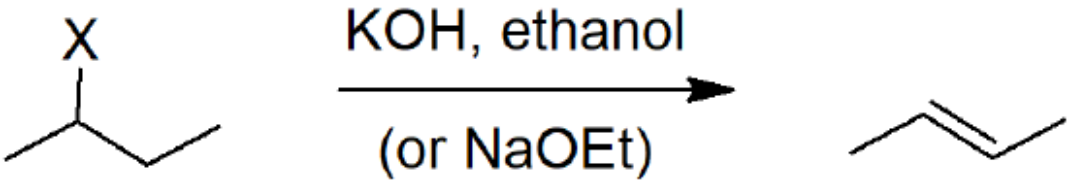
Skills to Master

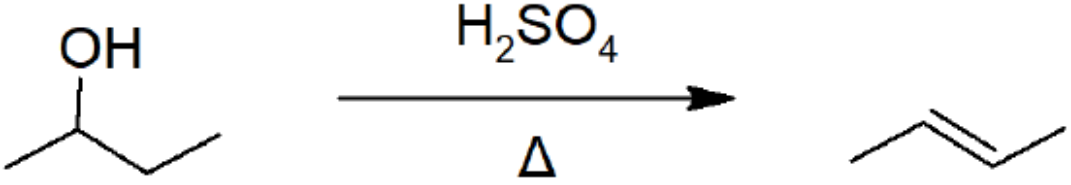
- Skill 8.1 Draw accurate Electrophilic Addition Mechanisms incorporating halonium intermediates.
- Skill 8.2 Draw accurate Electrophilic Addition Mechanisms incorporating carbocation intermediates.
- Skill 8.3 Draw Markovnikov products of alkene additions based on the most substituted carbocation intermediate.
- Skill 8.4 Draw hydrogenation products of alkenes.
- Skill 8.5 Draw appropriate epoxidation products including sterechemistry.
- Skill 8.6 Describe how to prepare syn and anti diols from alkenes.
- Skill 8.7 Draw products of oxidative cleavage reactions.
- Skill 8.8 Describe radical chain reactions to form polymers.

Summary of Reactions

No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.

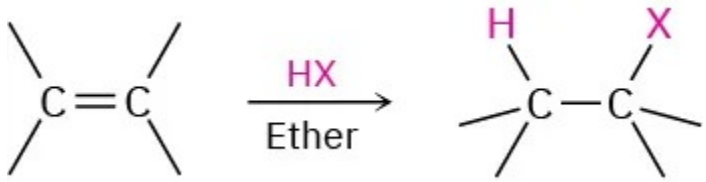
Preparation of Alkenes - Elimination Reaction



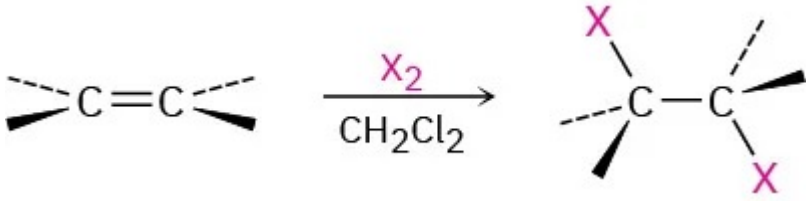


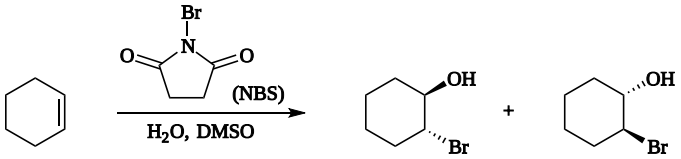
Addition Reactions

- **Addition of HCl, HBr, and HI (Chapter 7)**
  - Markovnikov regiochemistry occurs, with H adding to the less highly substituted alkene carbon and halogen adding to the more highly substituted carbon.

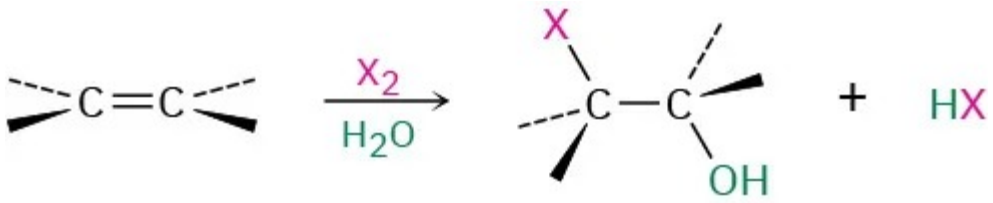


- **Addition of halogens Cl_2 and Br_2**
  Anti addition is observed through a halonium ion intermediate.



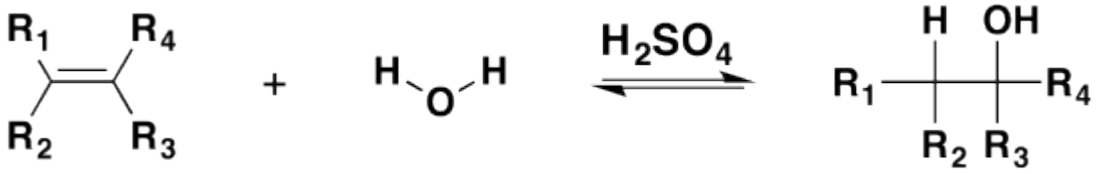


- **Halohydrin formation**
  Markovnikov regiochemistry and anti stereochemistry occur.

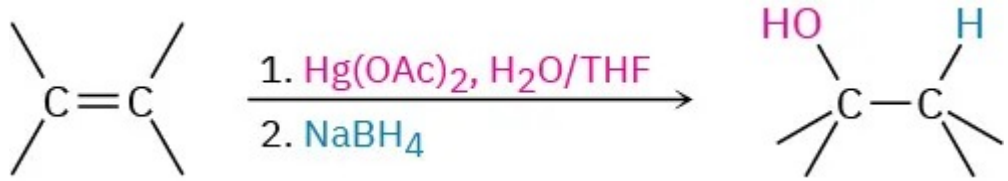


Hydration of Alkenes

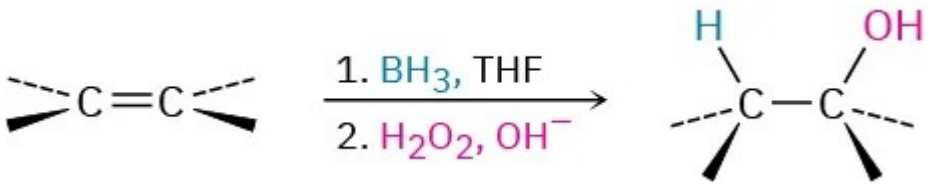
- Addition of water by Acid-Catalyzed Hydration
  Markovnikov regiochemistry and rearrangements occur.



- Addition of water by oxymercuration–demercuration
  Markovnikov regiochemistry occurs.

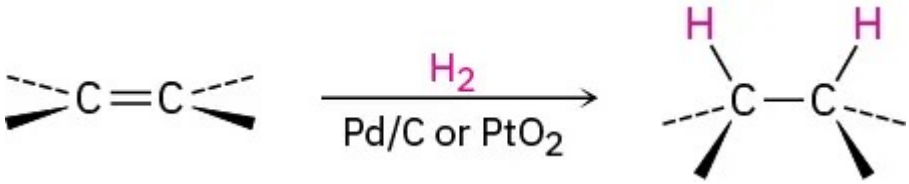


- Addition of water by hydroboration–oxidation
  Non-Markovnikov syn addition occurs.



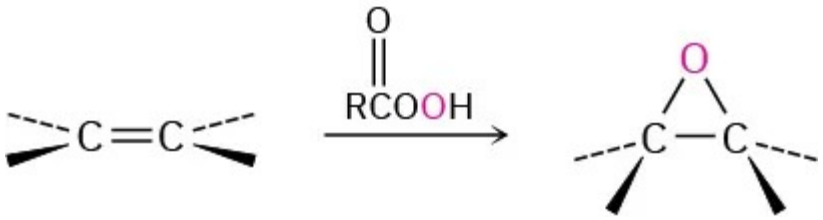
Reduction of Alkenes

- Catalytic hydrogenation
  Syn addition occurs.

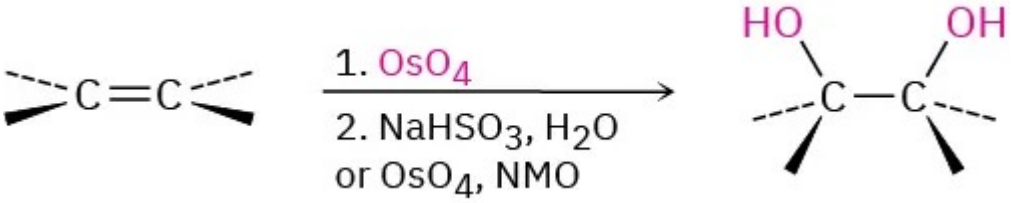


Oxidation of Alkenes

- Epoxidation with a peroxyacid
  Syn addition occurs. (Example of peroxyacid: MCPBA)

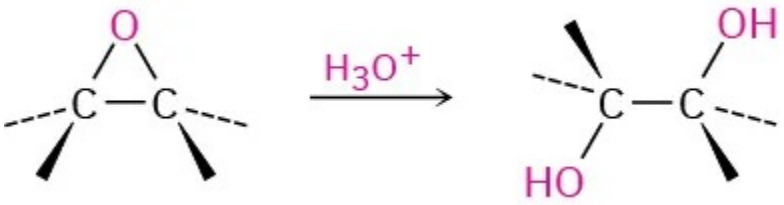


- Hydroxylation with OsO_4
  Syn addition occurs.



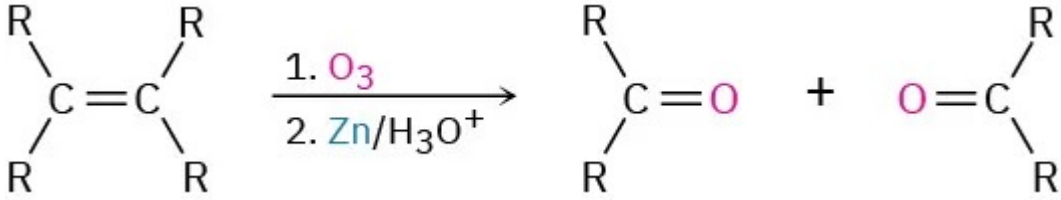
Hydroxylation by acid-catalyzed epoxide hydrolysis

Anti-stereospecificity occurs.

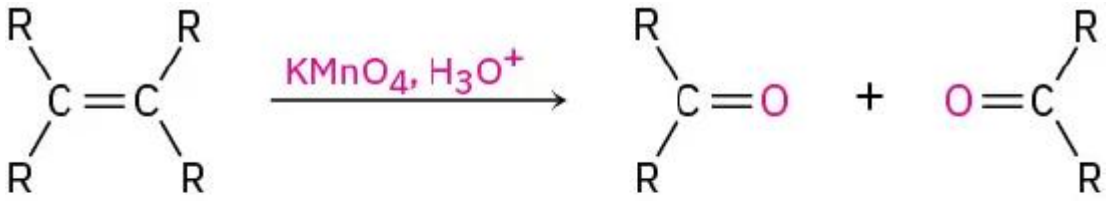


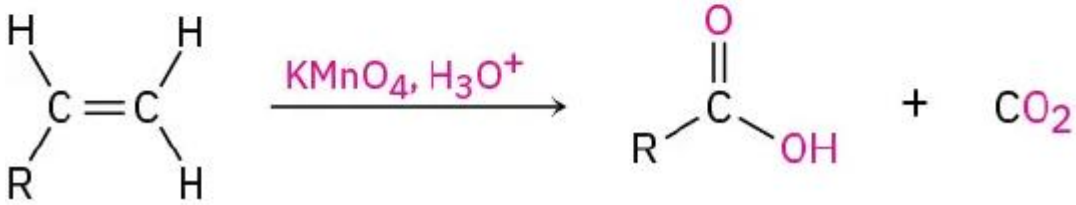
Oxidative cleavage of alkenes

a. Reaction with ozone followed by zinc in acetic acid

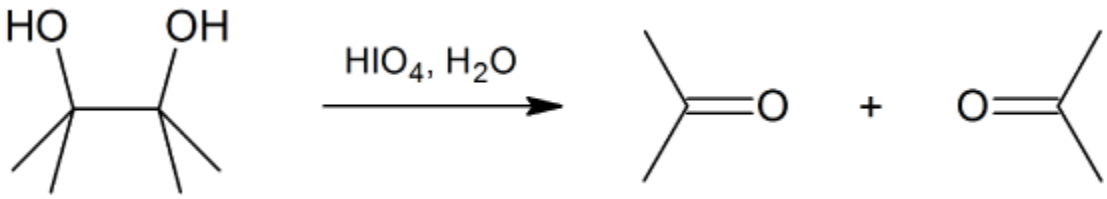


b. Reaction with $KMnO_4$ in acidic conditions





Cleavage of 1,2-diols

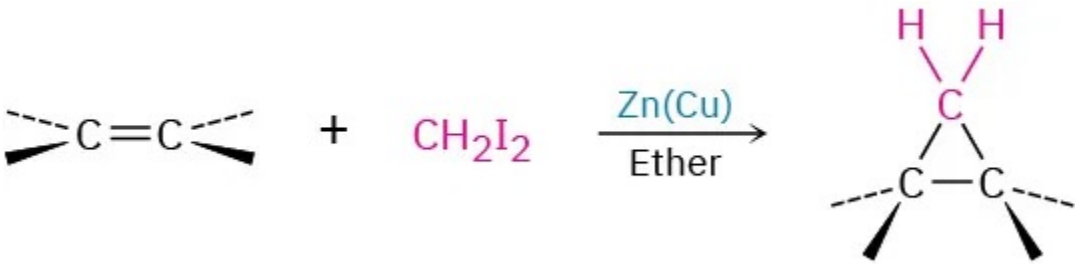


Addition of carbenes to yield cyclopropanes

(1) Dichlorocarbene addition



(2) Simmons–Smith reaction



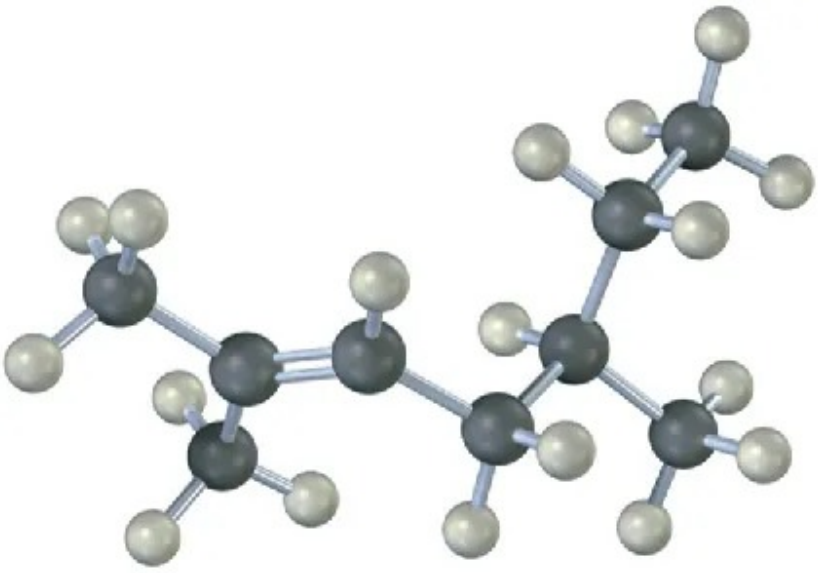
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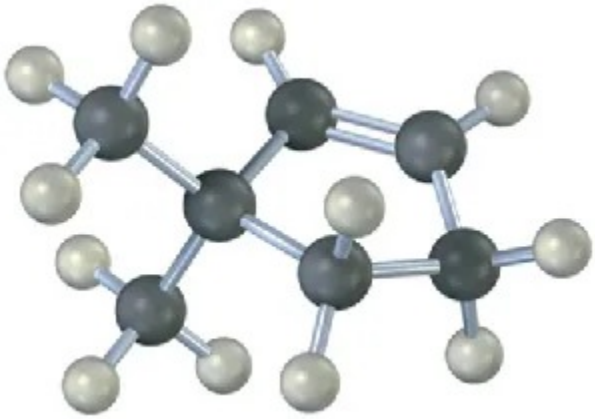
8.B: Additional Problems

Visualizing Chemistry

Problem 8-22 Name the following alkenes, and predict the products of their reaction with (1) *meta*-chloroperoxybenzoic acid, (2) $KMnO_4$ in aqueous acid, (3) O_3, followed by Zn in acetic acid:

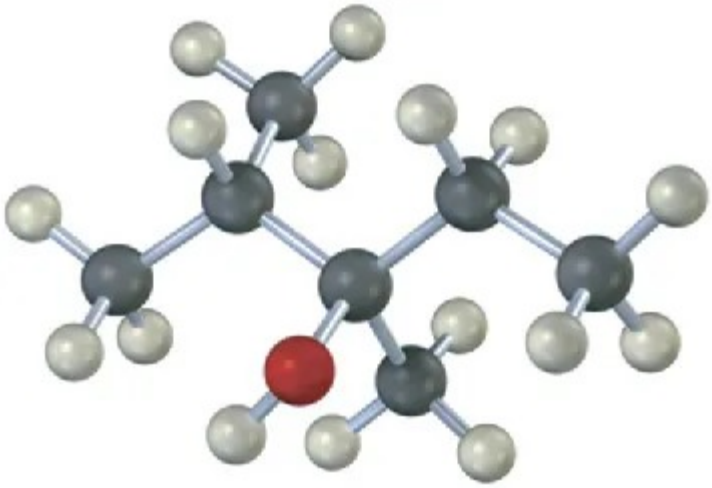


(a)

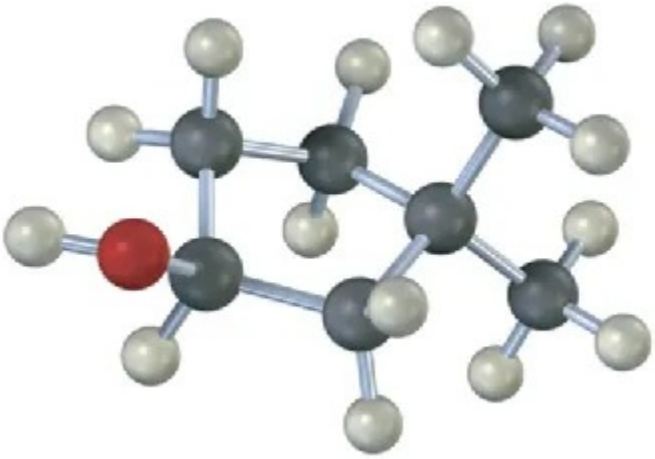


(b)

Problem 8-23 Draw the structures of alkenes that would yield the following alcohols on hydration (red = O). Tell in each case whether you would use hydroboration–oxidation or oxymercuration–demercuration.

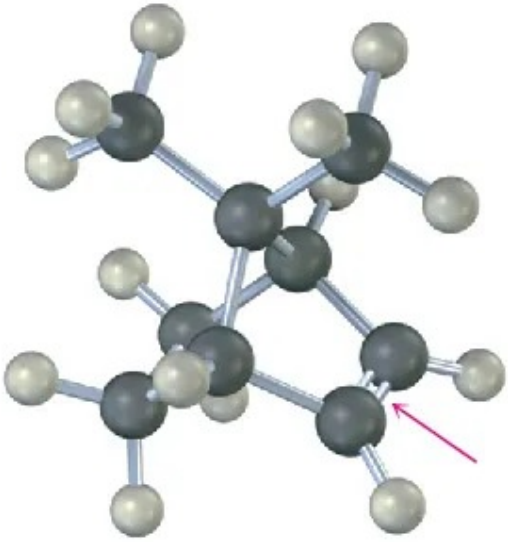


(a)

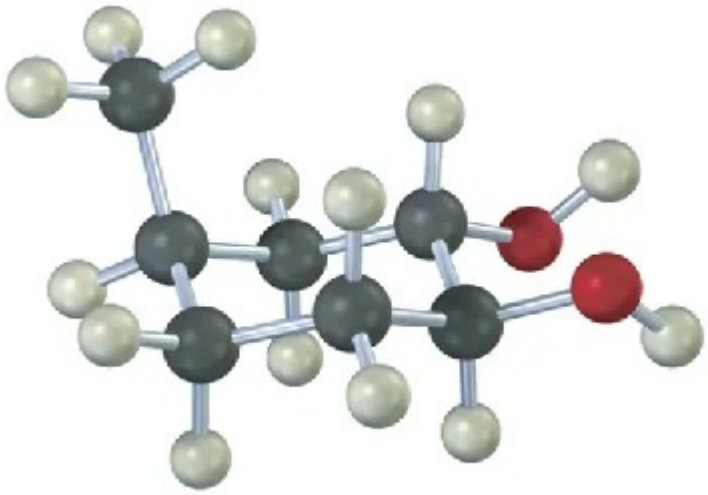


(b)

Problem 8-24 The following alkene undergoes hydroboration–oxidation to yield a single product rather than a mixture. Explain the result, and draw the product showing its stereochemistry.

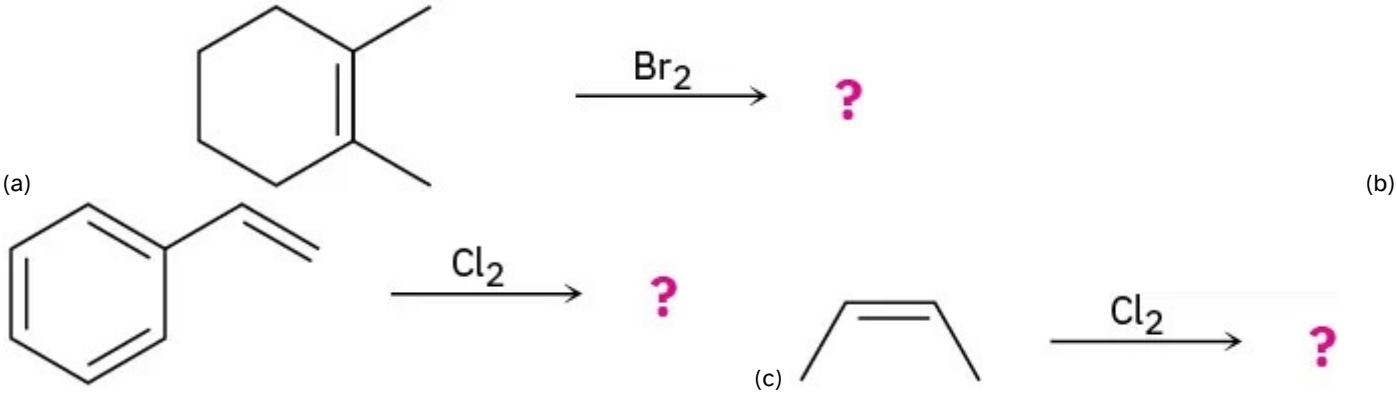


Problem 8-25 From what alkene was the following 1,2-diol made, and what method was used, epoxide hydrolysis or OsO_4?

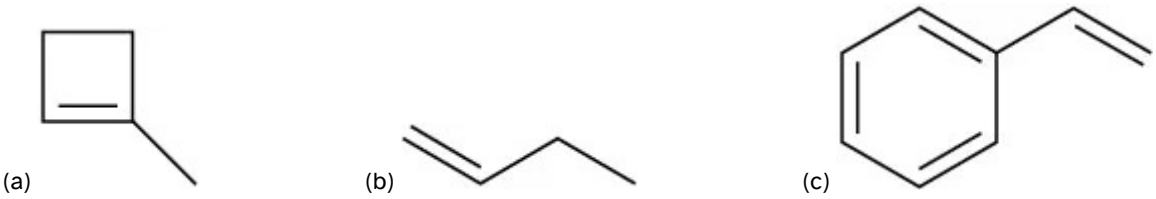


Mechanism Problems

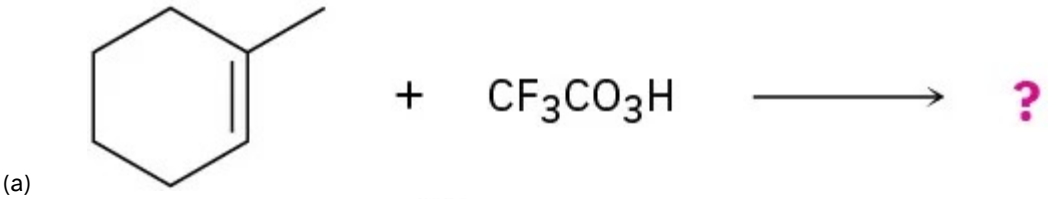
Problem 8-26 Predict the products for the following reactions, showing the complete mechanism and appropriate stereochemistry:



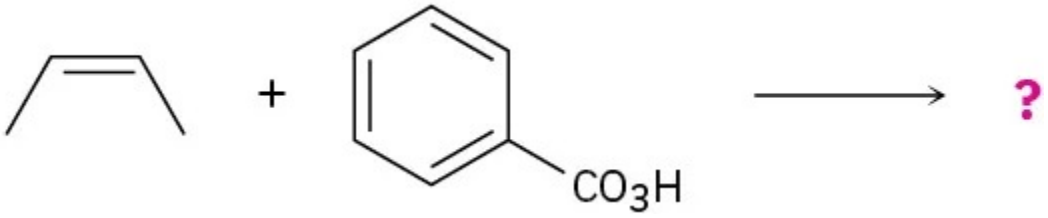
Problem 8-27 Draw the structures of the organoboranes formed when borane reacts with the following alkenes, including the regiochemistry and stereochemistry as appropriate. Propose a mechanism for each reaction.



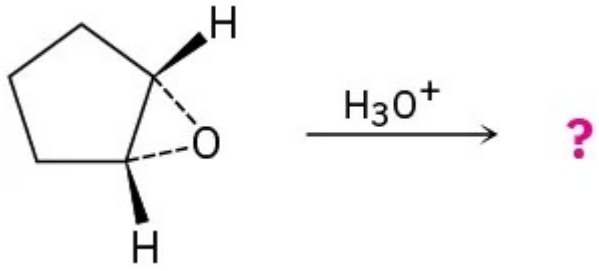
Problem 8-28 *meta*-Chlorobenzoic acid is not the only peroxyacid capable of epoxide formation. For each reaction below, predict the products and show the mechanism.



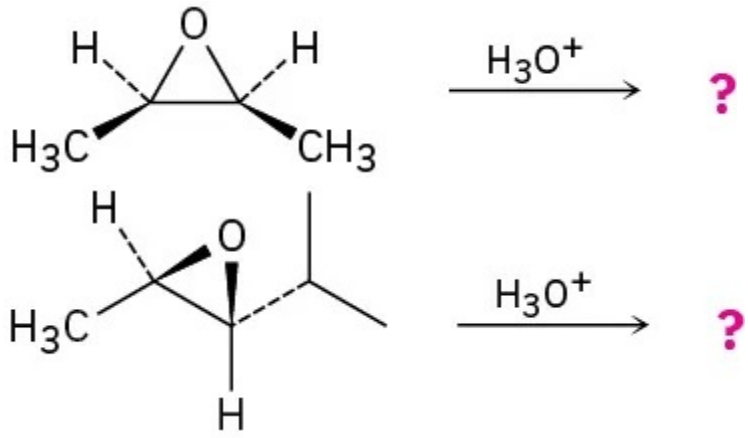
(a) (b)



Problem 8-29 Give the mechanism and products for the following acid-catalyzed epoxide-opening reactions, including appropriate stereochemistry.

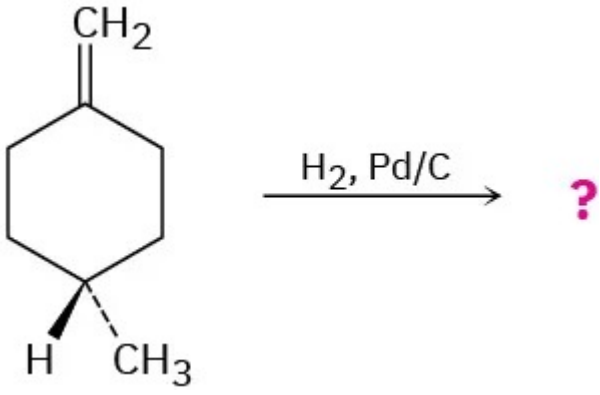


(a) (b)

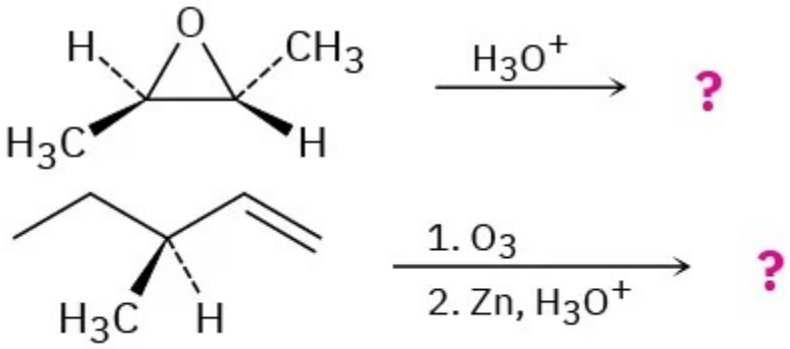


(c)

Problem 8-30 Which of the reactions below would result in a product mixture that would rotate plane-polarized light?



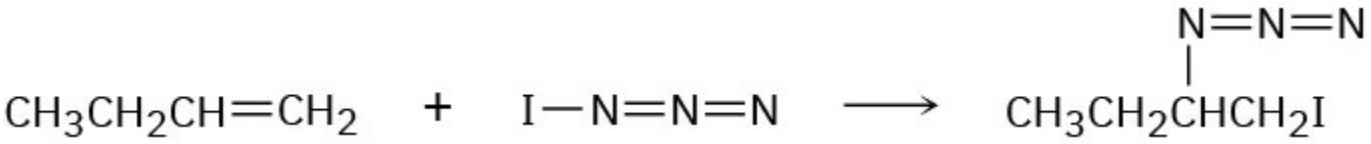
(a) (b)



(c)

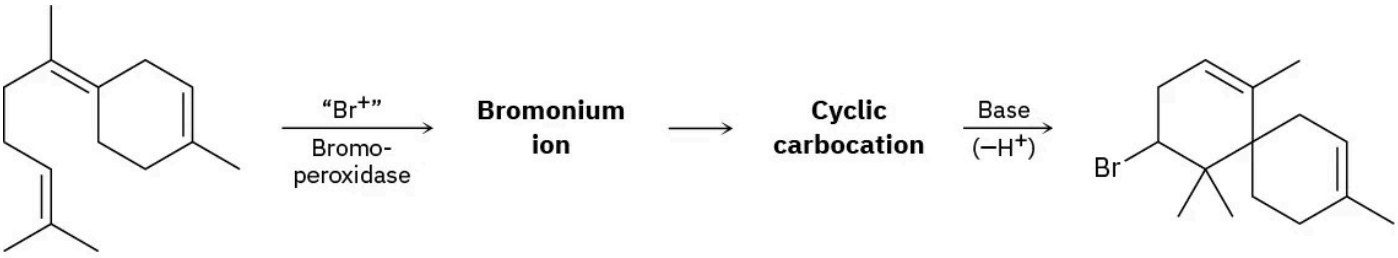
Problem 8-31 Reaction of 2-methylpropene with CH_3OH in the presence of H_2SO_4 catalyst yields methyl *tert*-butyl ether, $CH_3OC(CH_3)_3$, by a mechanism analogous to that of acid-catalyzed alkene hydration. Write the mechanism, using curved arrows for each step.

Problem 8-32 Iodine azide, IN_3, adds to alkenes by an electrophilic mechanism similar to that of bromine. If a monosubstituted alkene such as 1-butene is used, only one product results:



- (a) Add lone-pair electrons to the structure shown for IN_3, and draw a second resonance form for the molecule.
- (b) Calculate formal charges for the atoms in both resonance structures you drew for IN_3 in part **(a)**.
- (c) In light of the result observed when IN_3 adds to 1-butene, what is the polarity of the $I-N_3$ bond? Propose a mechanism for the reaction using curved arrows to show the electron flow in each step.

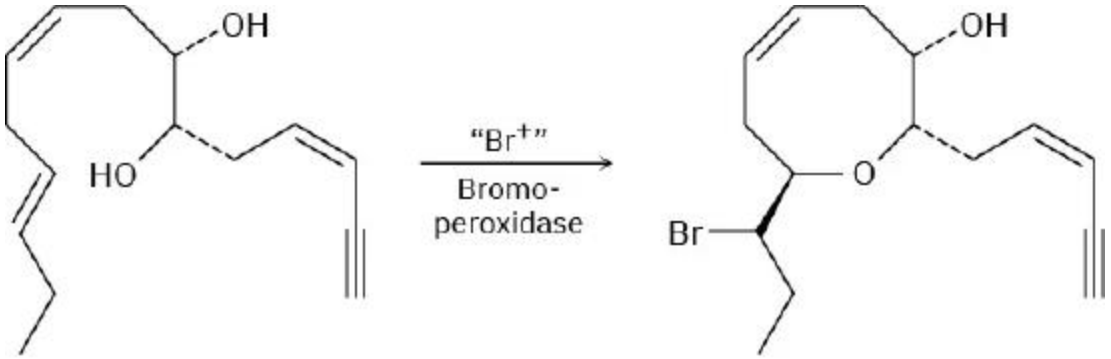
Problem 8-33 10-Bromo-α-chamigrene, a compound isolated from marine algae, is thought to be biosynthesized from γ-bisabolene by the following route. Draw the structures of the intermediate bromonium and cyclic carbocation, and propose mechanisms for all three steps.



γ-Bisabolene

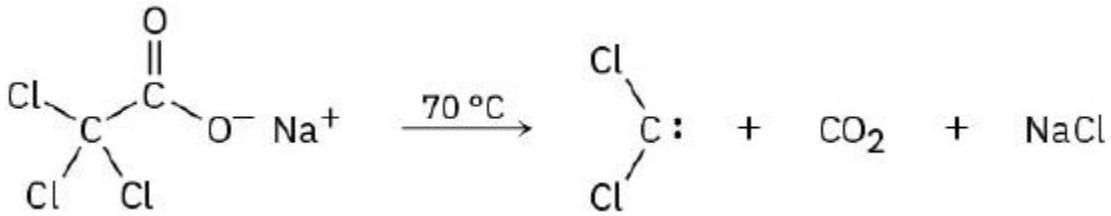
10-Bromo-α-chamigrene

Problem 8-34 Isolated from marine algae, prelaureatin is thought to be biosynthesized from laurediol by the following route. Propose a mechanism.

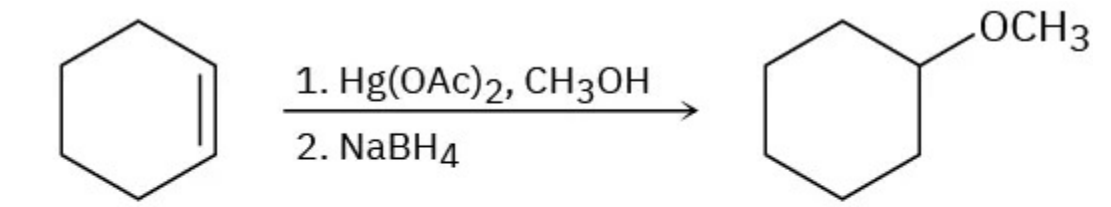


Laurediol **Prelaureatin**

Problem 8-35 Dichlorocarbene can be generated by heating sodium trichloroacetate. Propose a mechanism for the reaction, and use curved arrows to indicate the movement of electrons in each step. What relationship does your mechanism bear to the base-induced elimination of HCl from chloroform?

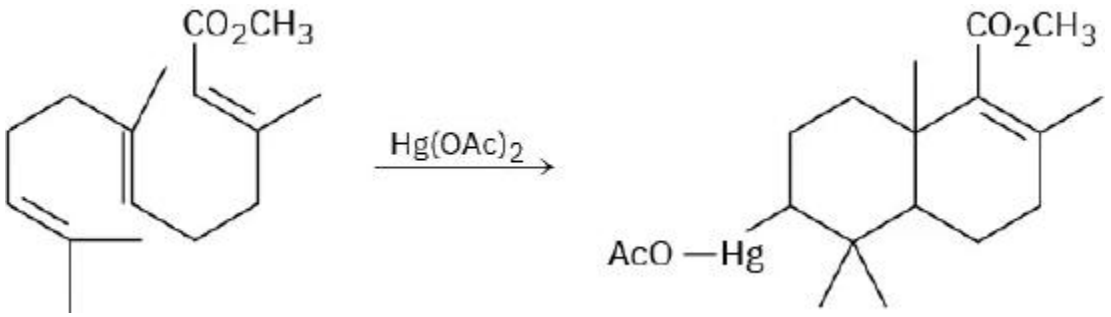


Problem 8-36 Reaction of cyclohexene with mercury(II) acetate in CH_3OH rather than H_2O, followed by treatment with $NaBH_4$, yields cyclohexyl methyl ether rather than cyclohexanol. Suggest a mechanism.



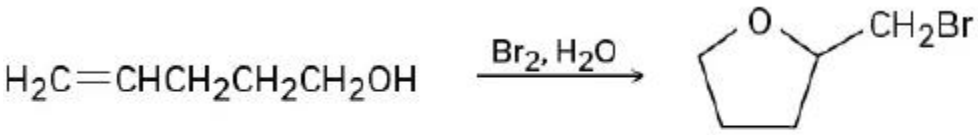
Cyclohexene **Cyclohexyl methyl ether**

Problem 8-37 Use your general knowledge of alkene chemistry to suggest a mechanism for the following reaction.



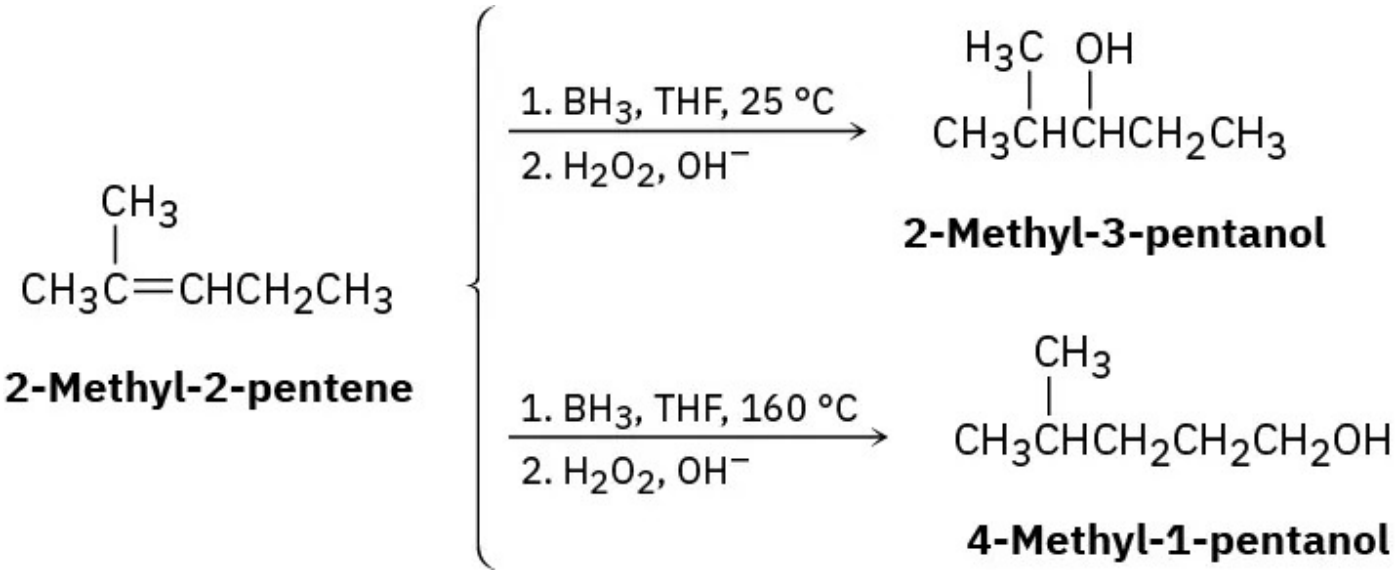
Problem 8-38 Treatment of 4-penten-1-ol with aqueous Br_2 yields a cyclic bromo ether rather than the expected bromohydrin.

Suggest a mechanism, using curved arrows to show electron movement.



4-Penten-1-ol **2-(Bromomethyl)tetrahydrofuran**

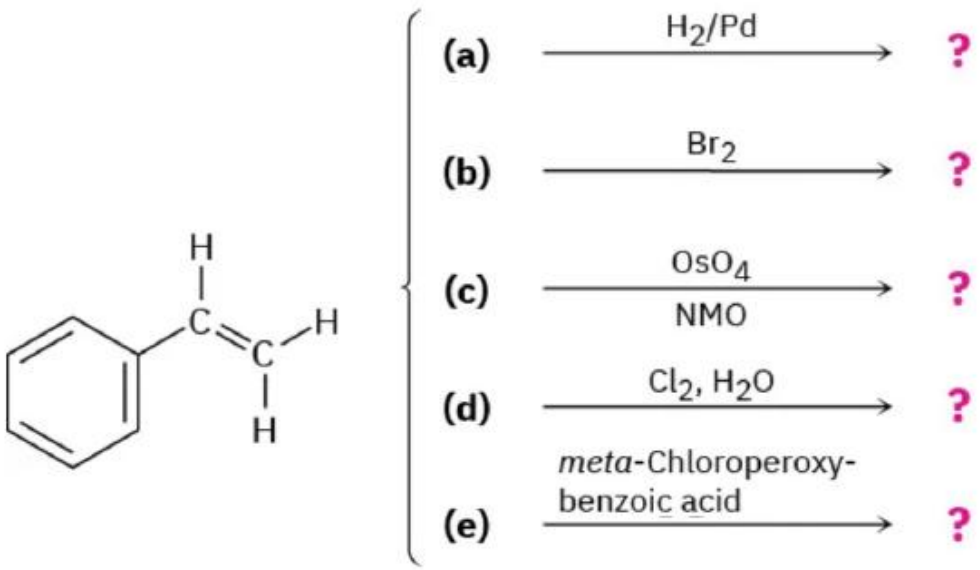
Problem 8-39 Hydroboration of 2-methyl-2-pentene at 25 °C, followed by oxidation with alkaline H_2O_2, yields 2-methyl-3-pentanol, but hydroboration at 160 °C followed by oxidation yields 4-methyl-1-pentanol. Suggest a mechanism.



2-Methyl-2-pentene **2-Methyl-3-pentanol** **4-Methyl-1-pentanol**

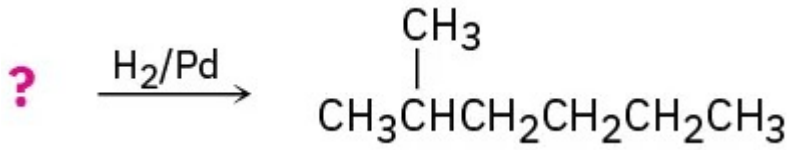
Reactions of Alkenes

Problem 8-40 Predict the products of the following reactions (the aromatic ring is unreactive in all cases). Indicate regiochemistry when relevant.

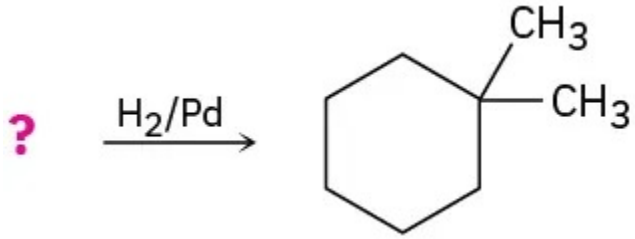


Problem 8-41 Suggest structures for alkenes that give the following reaction products. There may be more than one answer for some cases.

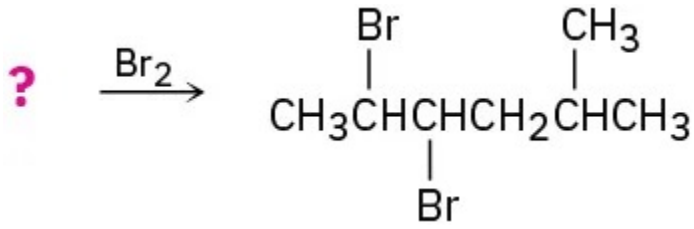
(a)



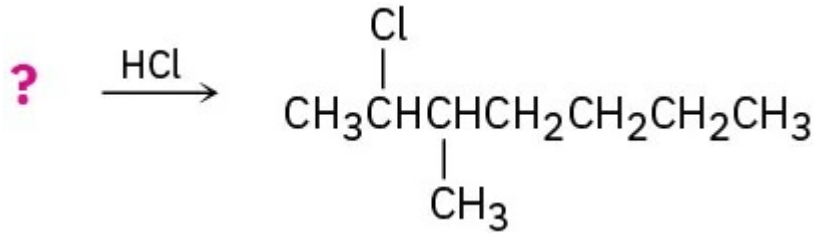
(b)



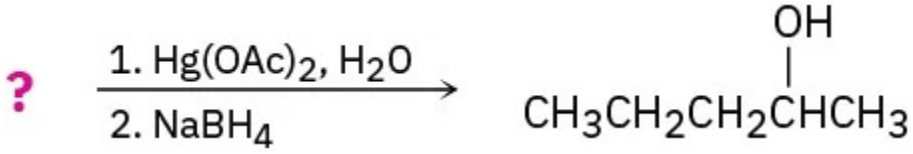
(c)



(d)

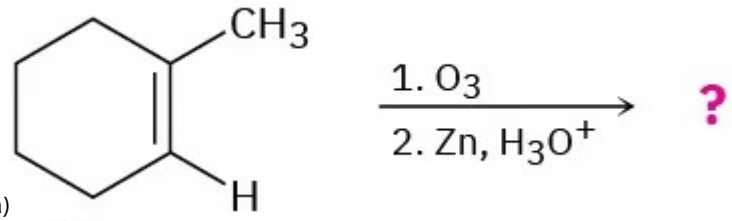


(e)

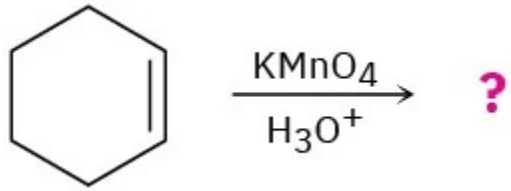


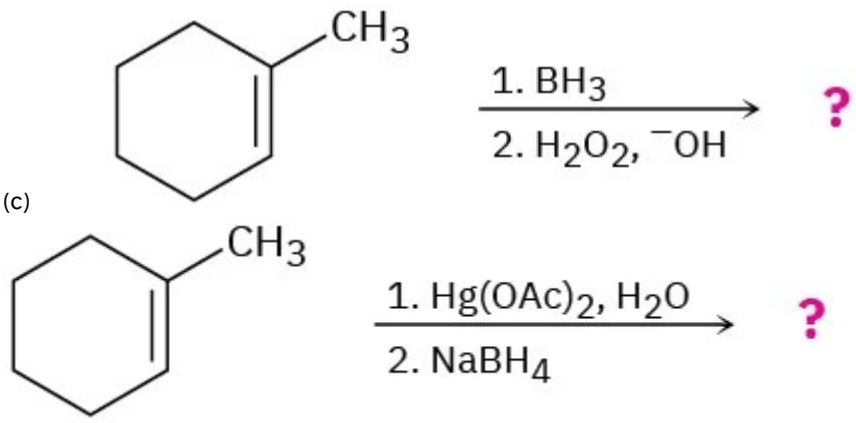
Problem 8-42 Predict the products of the following reactions, showing both regiochemistry and stereochemistry where appropriate:

(a)



(b)





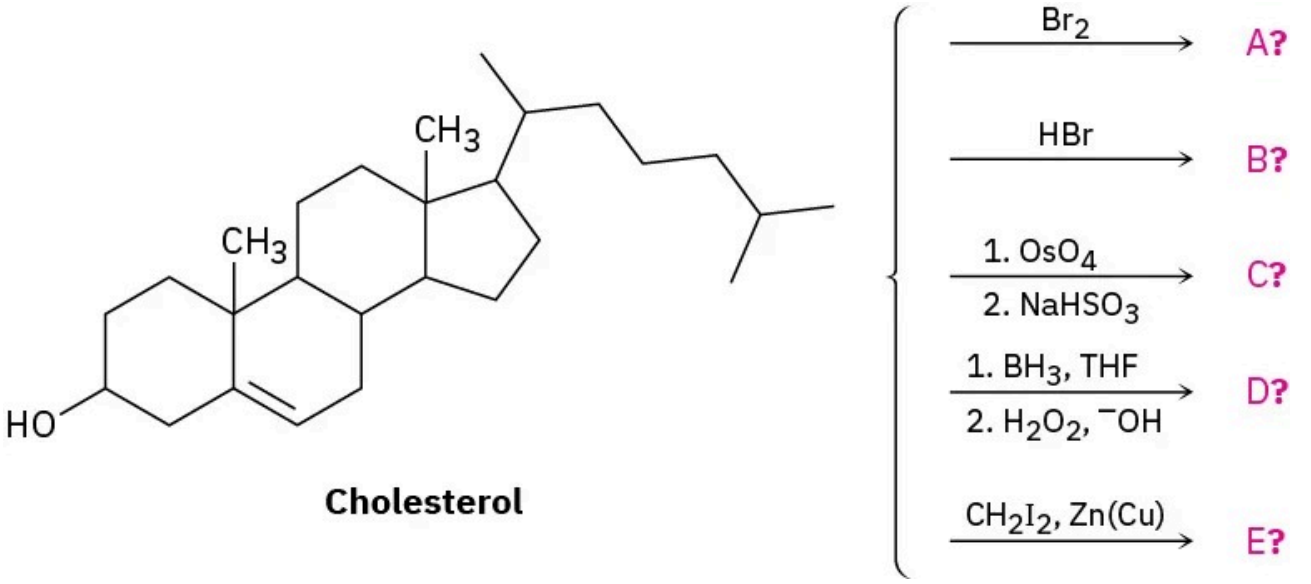
(c) (d)

Problem 8-43 Which reaction would you expect to be faster, the addition of HBr to cyclohexene or to 1-methylcyclohexene? Explain.

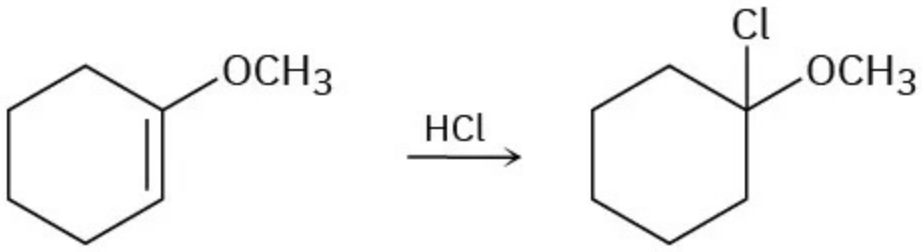
Problem 8-44 What product will result from hydroboration–oxidation of 1-methylcyclopentene with deuterated borane, BD_3? Show both the stereochemistry (spatial arrangement) and the regiochemistry (orientation) of the product.

Problem 8-45 Removed.

Problem 8-46 Predict the products of the following reactions. Don't worry about the size of the molecule; concentrate on the functional groups. No need to answer E.



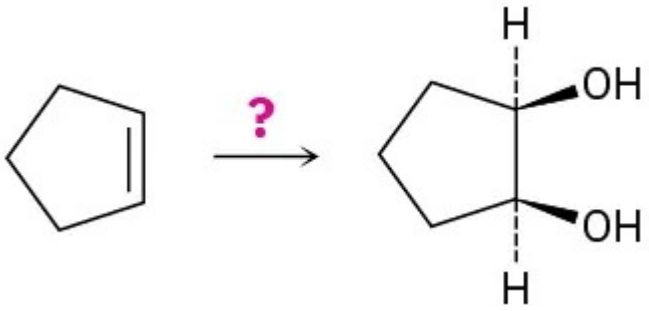
Problem 8-47 Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as a sole product. Use resonance structures of the carbocation intermediate to explain why none of the alternate regioisomer is formed.



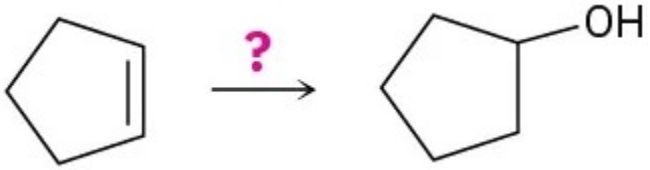
1-Methoxycyclohexene **1-Chloro-1-methoxy-cyclohexane**

Synthesis Using Alkenes

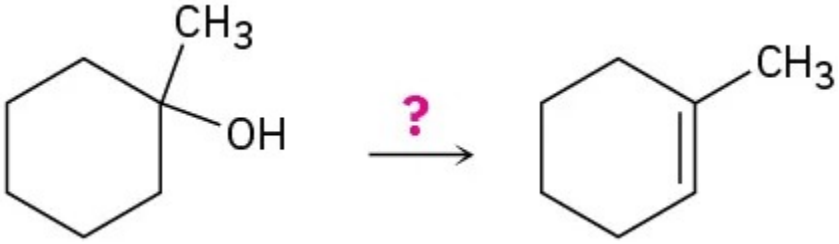
Problem 8-48 How would you carry out the following transformations? What reagents would you use in each case?



(a) (b)



(c)



(e)



(f)



Problem 8-49 Draw the structure of an alkene that yields only acetone, $(CH_3)_2C{=}O$, on ozonolysis followed by treatment with Zn.

Problem 8-50 Show the structures of alkenes that give the following products on oxidative cleavage with $KMnO_4$

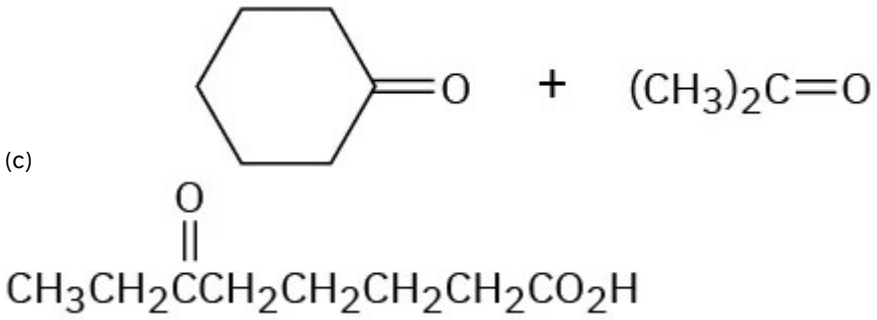
(a)

$$CH_3CH_2CO_2H \quad + \quad CO_2$$

$$(CH_3)_2C{=}O \quad + \quad CH_3CH_2CH_2CO_2H$$

(b)

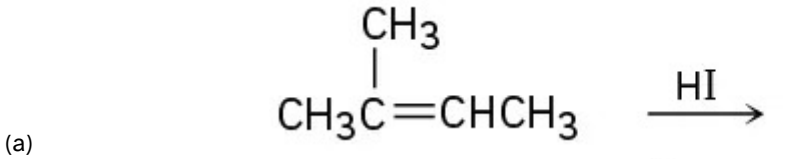
(c)



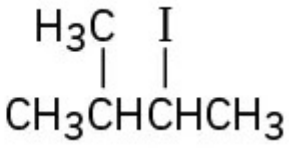
(d)

Problem 8-51 In planning the synthesis of one compound from another, it's just as important to know what not to do as to know what to do. The following reactions all have serious drawbacks. Explain the potential problems of each.

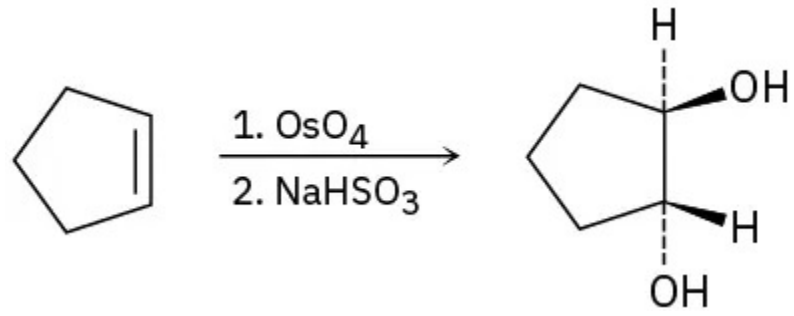
(a)



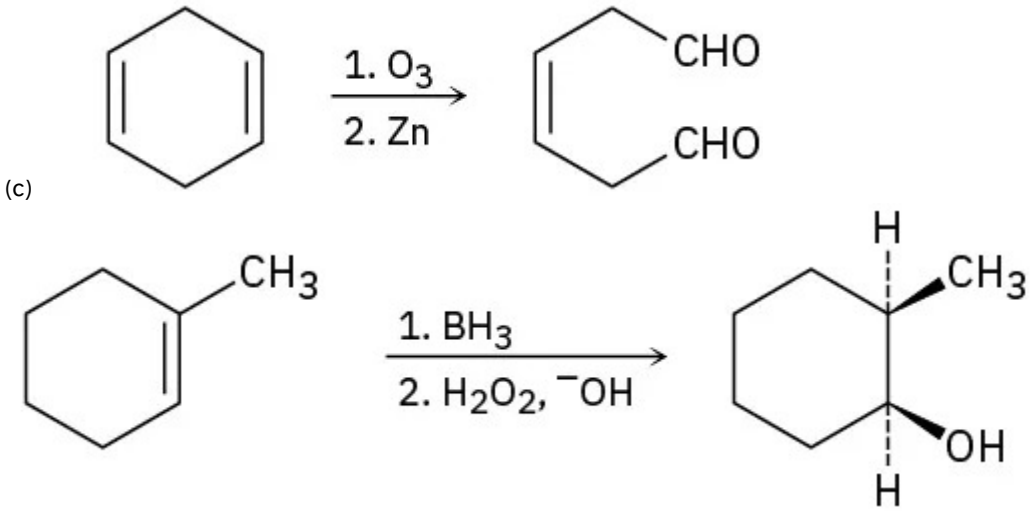
(b)



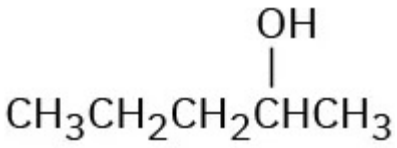
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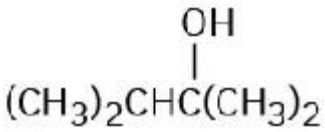


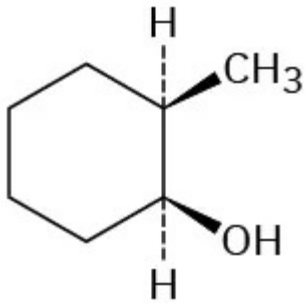
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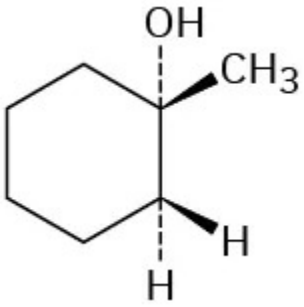


Problem 8-52 Which of the following alcohols could not be made selectively by hydroboration–oxidation of an alkene? Explain.

(a) 

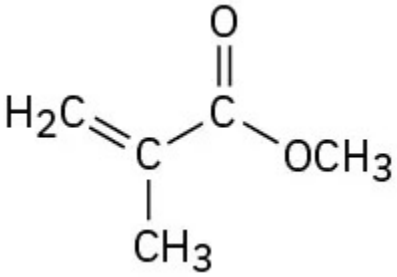
(b) 

(c) 

(d) 

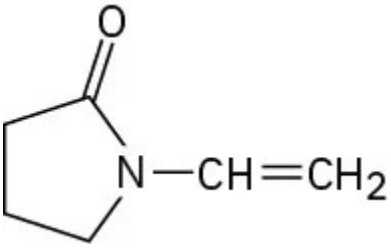
Polymers

Problem 8-53 Plexiglas, a clear plastic used to make many molded articles, is made by polymerization of methyl methacrylate. Draw a representative segment of Plexiglas.



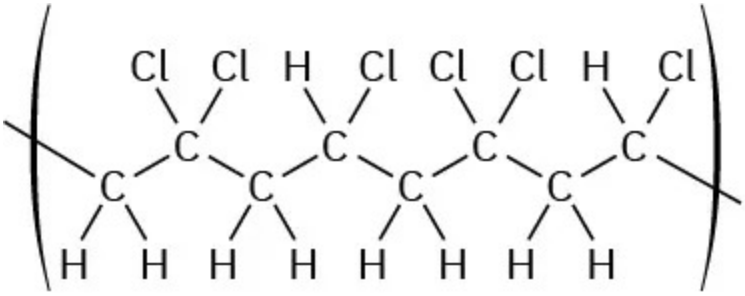
Methyl methacrylate

Problem 8-54 Poly(vinyl pyrrolidone), prepared from *N*-vinylpyrrolidone, is used both in cosmetics and as a component of a synthetic substitute for blood. Draw a representative segment of the polymer.



***N*-Vinylpyrrolidone**

Problem 8-55 When a single alkene monomer, such as ethylene, is polymerized, the product is a *homopolymer*. If a mixture of two alkene monomers is polymerized, however, a *copolymer* often results. The following structure represents a segment of a copolymer called *Saran*. What two monomers were copolymerized to make Saran?



Saran

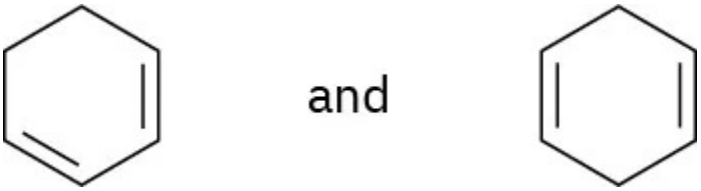
General Problems

Problem 8-56 Compound A has the formula C<sub">10H$_{16}$. On catalytic hydrogenation over palladium, it reacts with only 1 molar equivalent of H_2. Compound **A** also undergoes reaction with ozone, followed by zinc treatment, to yield a symmetrical diketone, **B** ($C_{10}H_{16}O_2$).</sub">

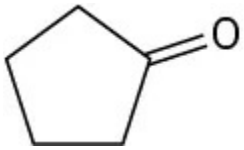
- (a) How many rings does **A** have?
- (b) What are the structures of **A** and **B**?
- (c) Write the reactions.

Problem 8-57 An unknown hydrocarbon **A** with the formula C_6H_{12} reacts with 1 molar equivalent of H_2 over a palladium catalyst. Hydrocarbon **A** also reacts with OsO_4 to give diol **B**. When oxidized with $KMnO_4$ in acidic solution, **A** gives two fragments. One fragment is propanoic acid, $CH_3CH_2CO_2H$, and the other fragment is ketone **C**. What are the structures of **A**, **B**, and **C**? Write all reactions.

Problem 8-58 Using an oxidative cleavage reaction, explain how you would distinguish between the following two isomeric dienes:

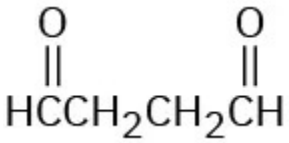


Problem 8-59 Compound **A**, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 50 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Identify **A** and **B**, and write the reactions.



Cyclopentanone

Problem 8-60 Draw the structure of a hydrocarbon that absorbs 2 molar equivalents of H_2 on catalytic hydrogenation and gives only butanedial on ozonolysis.



Butanedial

Problem 8-61 The sex attractant of the common housefly is a hydrocarbon with the formula $C_{23}H_{46}$. On treatment with aqueous acidic $KMnO_4$, two products are obtained, $CH_3(CH_2)_{12}CO_2H$ and $CH_3(CH_2)_7CO_2H$. Propose a structure.

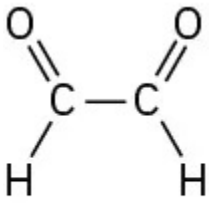
Problem 8-62 Compound **A** has the formula C_8H_8. It reacts rapidly with $KMnO_4$ to give CO_2 and a carboxylic acid, **B** ($C_7H_6O_2$), but reacts with only 1 molar equivalent of H_2 on catalytic hydrogenation over a palladium catalyst. On hydrogenation under conditions that reduce aromatic rings, 4 equivalents of H_2 are taken up and hydrocarbon **C** (C_8H_{16}) is produced. What are the structures of **A**, **B**, and **C**? Write the reactions.

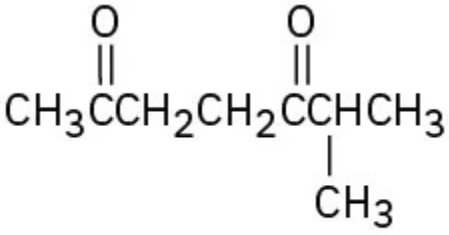
Problem 8-63 How would you distinguish between the following pairs of compounds using simple chemical tests? Tell what you would do and what you would see.

(a) Cyclopentene and cyclopentane

(b) 2-Hexene and benzene

Problem 8-64 α-Terpinene, $C_{10}H_{16}$, is a pleasant-smelling hydrocarbon that has been isolated from oil of marjoram. On hydrogenation over a palladium catalyst, α-terpinene reacts with 2 molar equivalents of H_2 to yield a hydrocarbon, $C_{10}H_{20}$. On ozonolysis, followed by reduction with zinc and acetic acid, α-terpinene yields two products, glyoxal and 6-methyl-2,5-heptanedione.

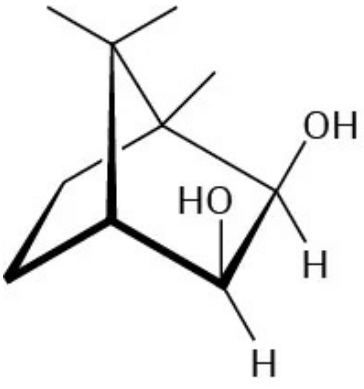


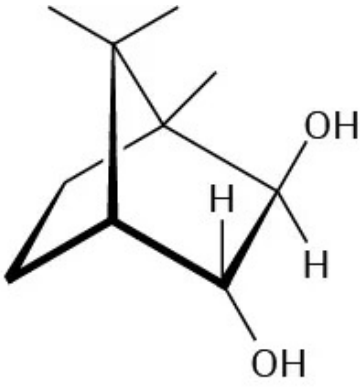


Glyoxal **6-Methyl-2,5-heptanedione**

- (a) How many degrees of unsaturation does α-terpinene have?
- (b) How many double bonds and how many rings does it have?
- (c) Propose a structure for α-terpinene.

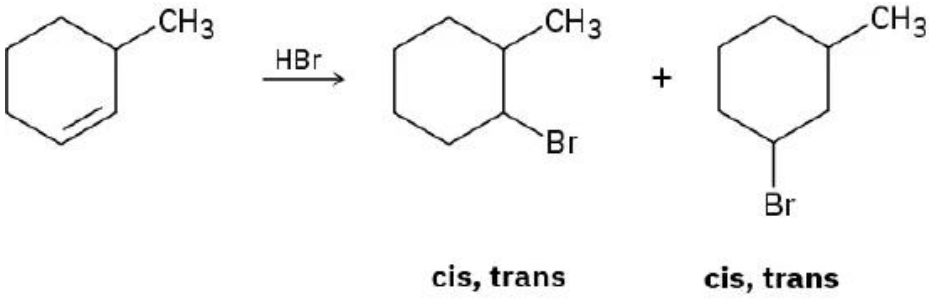
Problem 8-65 Evidence that cleavage of 1,2-diols by HIO_4 occurs through a five-membered cyclic periodate intermediate is based on the measurement of reaction rates. When diols **A** and **B** were prepared and the rates of their reaction with HIO_4 were measured, it was found that diol **A** cleaved approximately 1 million times faster than diol **B**. Make molecular models of **A** and **B** and of potential cyclic periodate intermediates, and then explain the results.

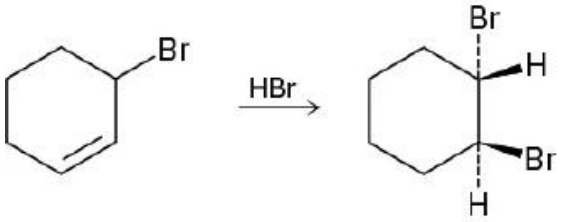




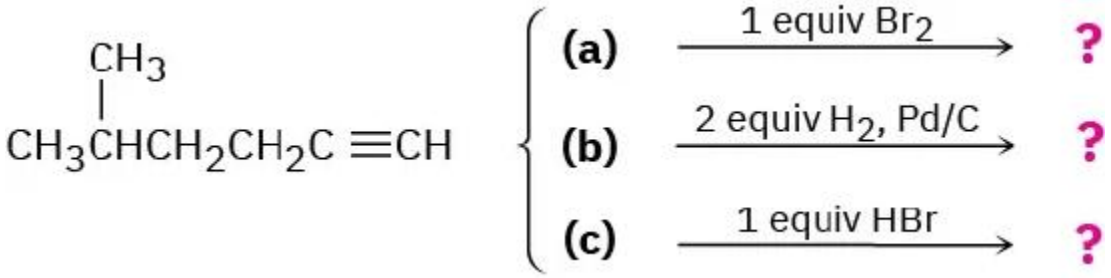
A **B**
(*cis* diol) **(*trans* diol)**

Problem 8-66 Reaction of HBr with 3-methylcyclohexene yields a mixture of four products: *cis*- and *trans*-1-bromo-3-methylcyclohexane and *cis*- and *trans*-1-bromo-2-methylcyclohexane. The analogous reaction of HBr with 3-bromocyclohexene yields *trans*-1,2-dibromocyclohexane as the sole product. Draw structures of the possible intermediates, and then explain why only a single product is formed in this reaction.





Problem 8-67 We'll see in the next chapter that alkynes undergo many of the same reactions that alkenes do. What product might you expect from each of the following reactions?



Problem 8-68 Hydroxylation of *cis*-2-butene with OsO_4 yields a different product than hydroxylation of *trans*-2-butene. Draw the structure, show the stereochemistry of each product, and explain the difference between them.

Problem 8-69 Compound A, $C_{11}H_{16}O$, was found to be an optically active alcohol. Despite its apparent unsaturation, no hydrogen was absorbed on catalytic reduction over a palladium catalyst. On treatment of A with dilute sulfuric acid, dehydration occurred and an optically inactive alkene B, $C_{11}H_{14}$, was the major product. Alkene B, on ozonolysis, gave two products. One product was identified as propanal, CH_3CH_2CHO. Compound C, the other product, was shown to be a ketone, C_8H_8O. How many degrees of unsaturation does A have? Write the reactions, and identify A, B, and C.

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9: ALKYNES - AN INTRODUCTION TO ORGANIC SYNTHESIS

Learning Objectives

After you have completed Chapter 9, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems involving any of the reactions introduced to this point.
3. design multistep syntheses using any of the reactions introduced to this point, and determine the viability of a given synthesis.
4. define, and use in context, the key terms introduced.

Addition reactions not only dominate the chemistry of alkenes, they are also the major class of reaction you will encounter. This chapter discusses an important difference between (terminal) alkynes and alkenes, that is, the acidity of the former; it also addresses the problem of devising organic syntheses. Once you have completed this chapter you will have increased the number of organic reactions in your repertoire, and should be able to design much more elaborate multistep syntheses. As you work through Chapter 9, you should notice the many similarities among the reactions described here and those in Chapters 7 and 8.

9.0: Why This Chapter?

9.1: Preparation of Alkynes - Elimination Reactions of Dihalides

9.2: Reactions of Alkynes - Addition of HX and X_2

9.3: Hydration of Alkynes

9.4: Reduction and Oxidation of Alkynes

9.5: Alkyne Acidity - Formation of Acetylide Anions

9.6: Alkylation of Acetylide Anions

9.7: An Introduction to Organic Synthesis

9.8: Chemistry Matters—The Art of Organic Synthesis

9.A: Alkynes - An Introduction to Organic Synthesis (Summary)

9.B: Additional Problems

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9.0: Why This Chapter?

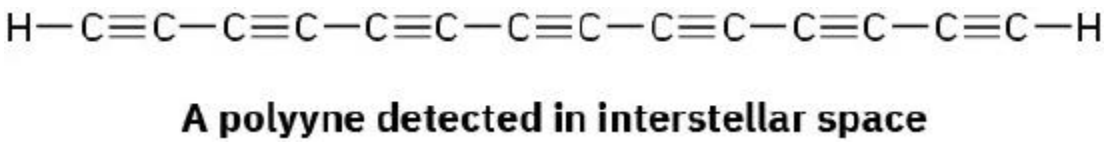
Alkynes are less common than alkenes, both in the laboratory and in living organisms, so we won't cover them in great detail. The real importance of this chapter is that we'll use alkyne chemistry as a vehicle to begin looking at some of the general strategies used in organic synthesis—the construction of complex molecules in the laboratory. Without the ability to design and synthesize new molecules in the laboratory, many of the medicines we take for granted would not exist, and few new ones would be made.



Figure 9.0.1: Synthesizing organic compounds is like conducting a musical group. When in tune, chemists can create highly complex organic compounds. (credit: modification of work "Jazz great visits Navy" by U.S. Navy, Michael Worner/Wikimedia Commons, Public Domain)

An alkyne is a hydrocarbon that contains a carbon–carbon triple bond. Acetylene, $\mathrm{H{-}C{\equiv}C{-}H}$, the simplest alkyne, was once widely used in industry as a starting material for the preparation of acetaldehyde, acetic acid, vinyl chloride, and other high-volume chemicals, but more efficient routes to these substances using ethylene as starting material are now available. Acetylene is still used in the preparation of acrylic polymers, such as Plexiglas and Lucite, but is probably best known as the gas burned in high-temperature oxy–acetylene welding torches.

In addition to simple alkynes with one triple bond, research is also being carried out on polyynes—linear carbon chains of alternating single and triple bonds. Polyynes with up to eight triple bonds are thought to be present in interstellar space, and evidence has been presented for the existence of *carbyne*, an allotrope of carbon consisting of alternating single and triple bonds in long chains of indefinite length. The electronic properties of polyynes are being explored for potential use in nanotechnology applications.



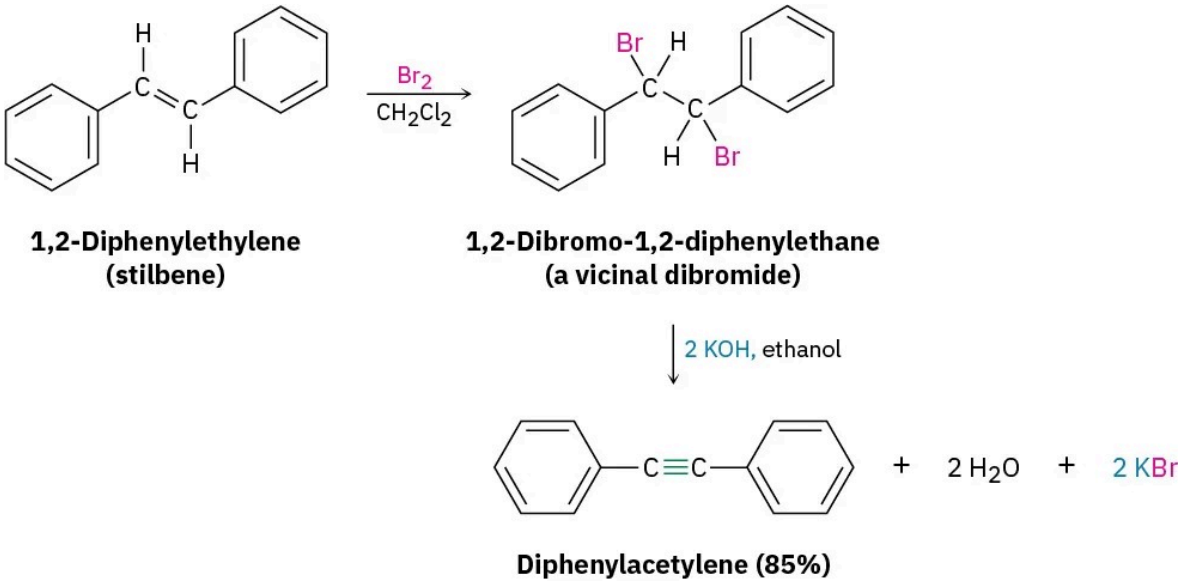
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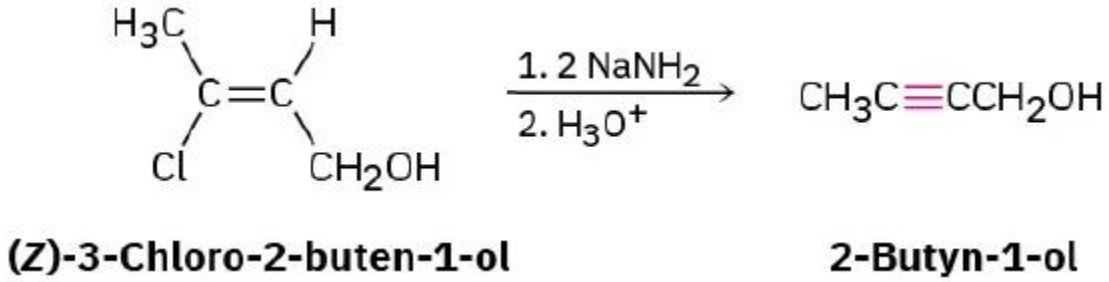
9.1: Preparation of Alkynes - Elimination Reactions of Dihalides

Alkynes can be prepared by the elimination of HX from alkyl halides in a similar manner as alkenes (Section 8.1). Treatment of a 1,2-dihaloalkane (called a *vicinal* dihalide) with an excess amount of a strong base such as KOH or $NaNH_2$ results in a twofold elimination of HX and formation of an alkyne. As with the elimination of HX to form an alkene, we'll defer a full discussion of this topic and the relevant reaction mechanisms to Chapter 11.

The starting vicinal dihalides are themselves readily available by addition of Br_2 or Cl_2 to alkenes. Thus, the overall halogenation/dehydrohalogenation sequence makes it possible to go from an alkene to an alkyne. For example, diphenylethylene is converted into diphenylacetylene by reaction with Br_2 and subsequent base treatment.



The twofold dehydrohalogenation takes place through a vinylic halide intermediate, which suggests that vinylic halides themselves should give alkynes when treated with strong base. (A vinylic substituent is one that is attached to a double-bond.) This is indeed the case. For example:



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9.2: Reactions of Alkynes - Addition of HX and X_2

You might recall from Section 1.9 that a carbon–carbon triple bond results from the interaction of two *sp*-hybridized carbon atoms. The two *sp* hybrid orbitals of carbon lie at an angle of 180° to each other along an axis perpendicular to the axes of the two unhybridized $2p_y$ and $2p_z$ orbitals. When two *sp*-hybridized carbons approach each other, one *sp*–*sp* σ bond and two *p*–*p* π bonds are formed. The two remaining *sp* orbitals form bonds to other atoms at an angle of 180° from the carbon–carbon bond. Thus, acetylene is a linear molecule with $\mathrm{H{-}C{\equiv}C}$ bond angles of 180° (Figure $9.2.1$). The length of the $\mathrm{C{\equiv}C}$ bond is 120 pm, and its strength is approximately 965 kJ/mol (231 kcal/mol), making it the shortest and strongest known carbon–carbon bond.

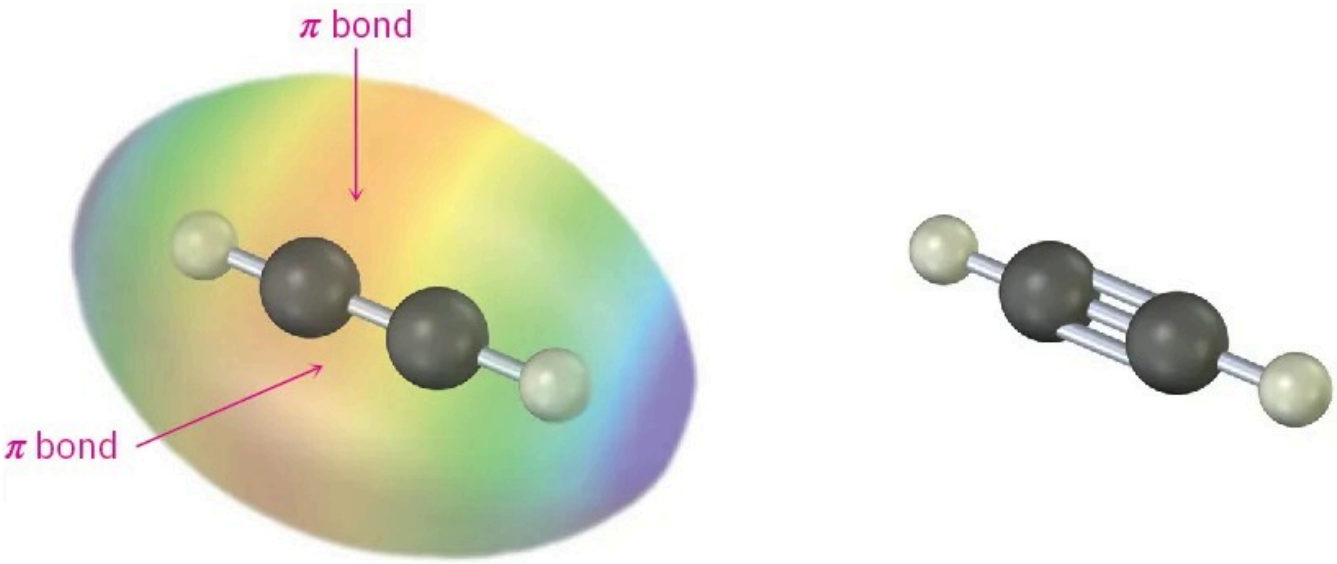


Figure $9.2.1$: The structure of acetylene, $\mathrm{H{-}C{\equiv}C{-}H}$. The $\mathrm{H{-}C{\equiv}C}$ bond angles are 180°, and the $\mathrm{C{\equiv}C}$ bond length is 120 pm. The electrostatic potential map shows that the π bonds create a negative belt around the molecule.

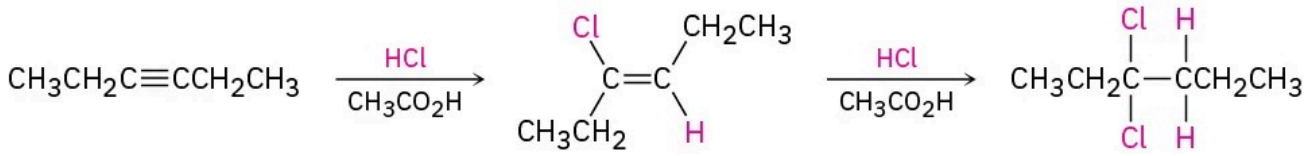
As a general rule, electrophiles undergo addition reactions with alkynes much as they do with alkenes. Take the reaction of alkynes with HX, for instance. The reaction often can be stopped with the addition of 1 equivalent of HX, but reaction with an excess of HX leads to a dihalide product. For example, reaction of 1-hexyne with 2 equivalents of HBr yields 2,2-dibromohexane. As the following examples indicate, the regiochemistry of addition follows Markovnikov's rule, with halogen adding to the more highly substituted side of the alkyne bond and hydrogen adding to the less highly substituted side. Trans stereochemistry of H and X normally, although not always, occurs in the product.

HBr addition



1-Hexyne **2-Bromo-1-hexene** **2,2-Dibromohexane**

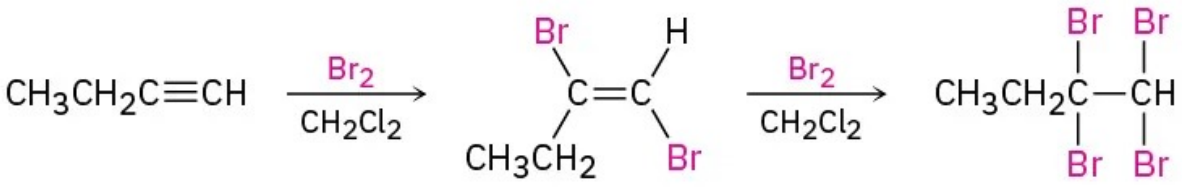
HCl addition



3-Hexyne **(*Z*)-3-Chloro-3-hexene** **3,3-Dichlorohexane**

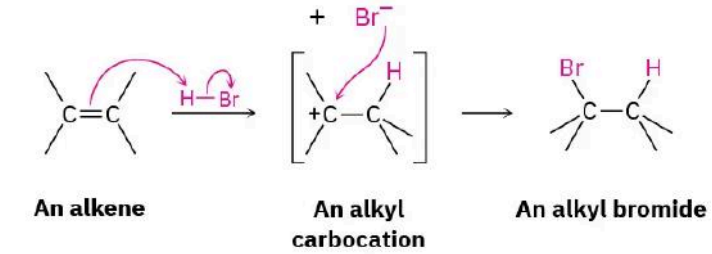
Bromine and chlorine also add to alkynes to give addition products, and trans stereochemistry again results.

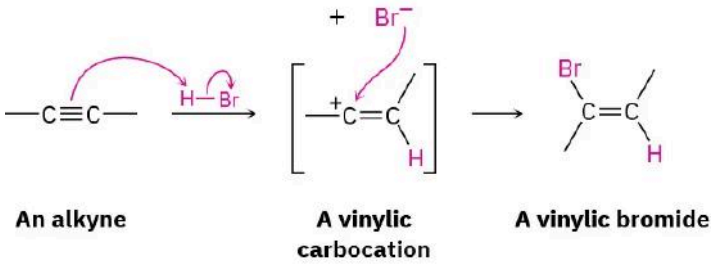
Br_2 addition



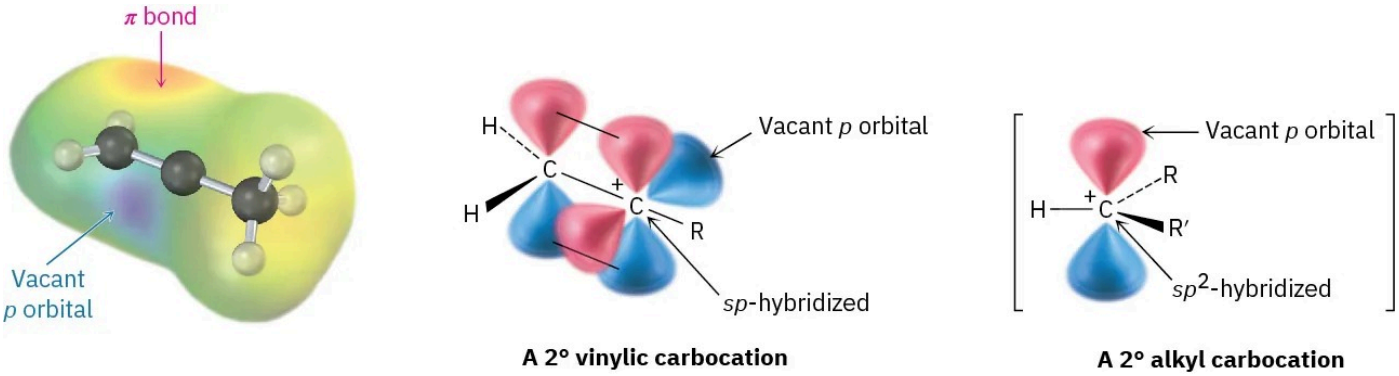
1-Butyne **(*E*)-1,2-Dibromo-1-butene** **1,1,2,2-Tetrabromobutane**

The mechanism of alkyne addition is similar but not identical to that of alkene addition. When an electrophile such as HBr adds to an alkene, the reaction takes place in two steps and involves an alkyl carbocation intermediate (Section 7.7 and Section 7.8). If HBr were to add by the same mechanism to an alkyne, an analogous vinylic carbocation would be formed as the intermediate.





A vinylic carbocation has an *sp*-hybridized carbon and generally forms less readily than an alkyl carbocation (Figure 9.2.2). As a rule, a secondary vinylic carbocation forms about as readily as a primary alkyl carbocation, but a primary vinylic carbocation is so difficult to form that there is no clear evidence it even exists. Thus, many alkyne additions occur through more complex mechanistic pathways.



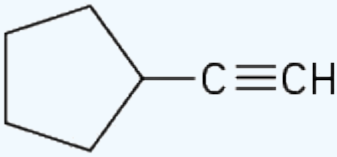
A 2° vinylic carbocation **A 2° alkyl carbocation**

Figure 9.2.2: The structure of a secondary vinylic carbocation. The cationic carbon atom is *sp*-hybridized and has a vacant *p* orbital perpendicular to the plane of the π bond orbitals. Only one R group is attached to the positively charged carbon rather than two, as in a secondary alkyl carbocation. The electrostatic potential map shows that the **most positive regions** coincide with lobes of the vacant *p* orbital and are perpendicular to the **most negative regions** associated with the π bond.

Exercise 9.2.1

What products would you expect from the following reactions?

a. $CH_3CH_2CH_2C{\equiv}CH + 2\,Cl_2 \longrightarrow ?$

b.  $+ 1\,HBr \longrightarrow ?$

c. $CH_3CH_2CH_2CH_2C{\equiv}CCH_3 + 1\,HBr \longrightarrow ?$

Answer available at the end of this section.

Answers

Exercise 9.2.1

a. 1,1,2,2-Tetrachloropentane
b. 1-Bromo-1-cyclopentylethylene
c. 2-Bromo-2-heptene and 3-bromo-2-heptene

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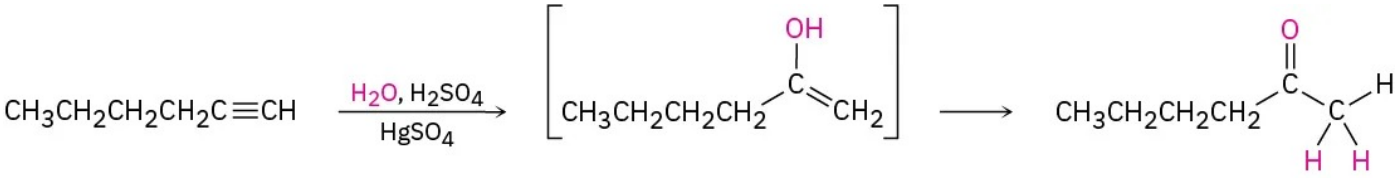
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9.3: Hydration of Alkynes

Like alkenes (Section 8.4 and Section 8.5), alkynes can be hydrated by either of two methods. Direct addition of water catalyzed by mercury(II) ion yields the Markovnikov product, and indirect addition of water by a hydroboration–oxidation sequence yields the non-Markovnikov product.

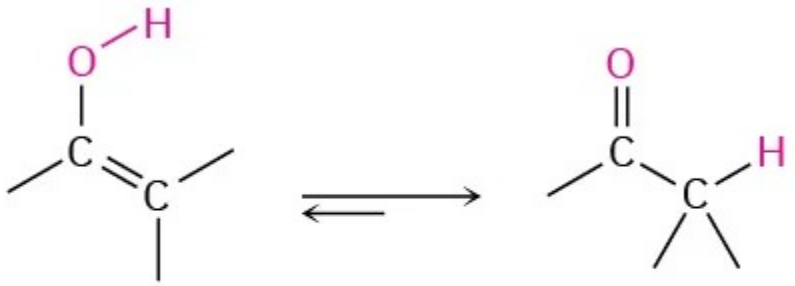
Mercury(II)-Catalyzed Hydration of Alkynes

Alkynes don't react directly with aqueous acid but will undergo hydration readily in the presence of mercury(II) sulfate as a Lewis acid catalyst. The reaction occurs with Markovnikov regiochemistry, so the –OH group adds to the more highly substituted carbon and the –H attaches to the less highly substituted one.



1-Hexyne **An enol** **2-Hexanone (78%)**

Interestingly, the actual product isolated from alkyne hydration is not a vinylic alcohol, or enol (*ene* + *ol*), but is instead a ketone. Although the enol is an intermediate in the reaction, it immediately rearranges into a ketone by a process called *keto–enol tautomerism*. The individual keto and enol forms are said to be tautomers, a word used to describe two isomers that undergo spontaneous interconversion accompanied by the change in position of a hydrogen. With few exceptions, the keto–enol tautomeric equilibrium lies on the side of the ketone; enols are almost never isolated. We'll look more closely at this equilibrium in **Section 22.1**.



Enol tautomer (less favored) **Keto tautomer (more favored)**

As shown in Figure 9.3.1, the mechanism of the mercury(II)-catalyzed alkyne hydration reaction is analogous to the oxymercuration reaction of alkenes (Section 8.4). Electrophilic addition of mercury(II) ion to the alkyne gives a vinylic cation, which reacts with water and loses a proton to yield a mercury-containing enol intermediate. In contrast with alkene oxymercuration, however, no treatment with $NaBH_4$ is necessary to remove the mercury. The acidic reaction conditions alone are sufficient to effect replacement of mercury by hydrogen. Tautomerization then gives the ketone.

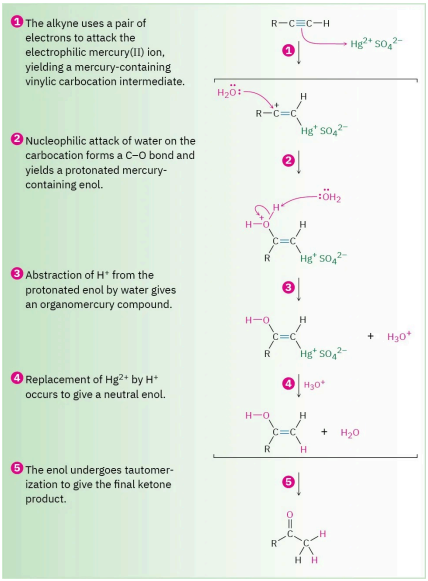
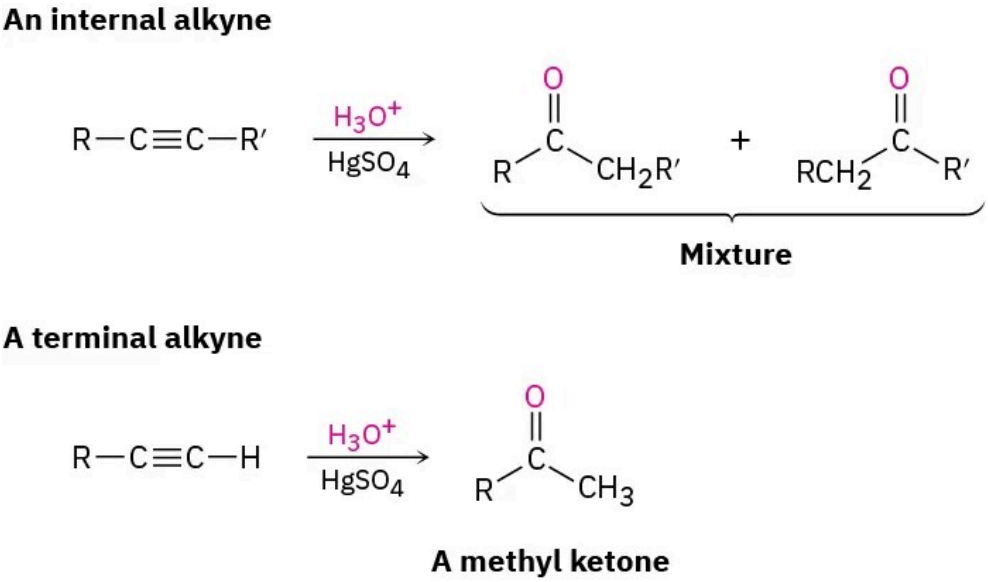


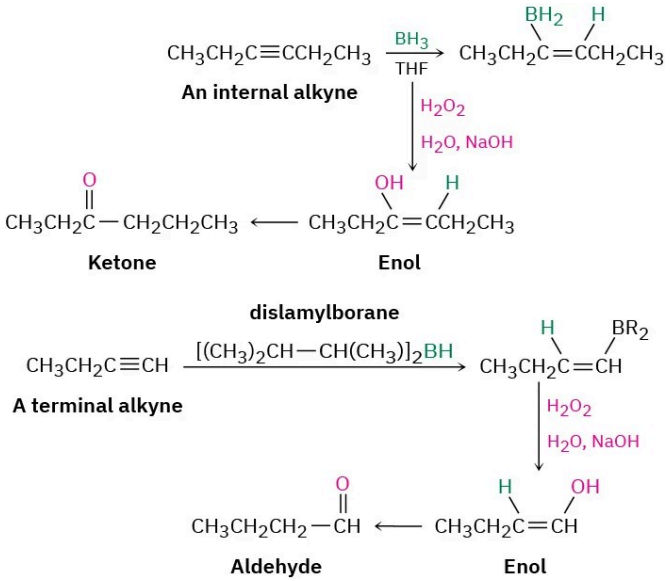
Figure 9.3.1: Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone. The reaction occurs through initial formation of an intermediate enol, which tautomerizes to the ketone.

A mixture of both possible ketones results when an unsymmetrically substituted internal alkyne ($RC{\equiv}CR'$ is hydrated. The reaction is therefore most useful when applied to a terminal alkyne ($RC{\equiv}CH$) because only a methyl ketone is formed.

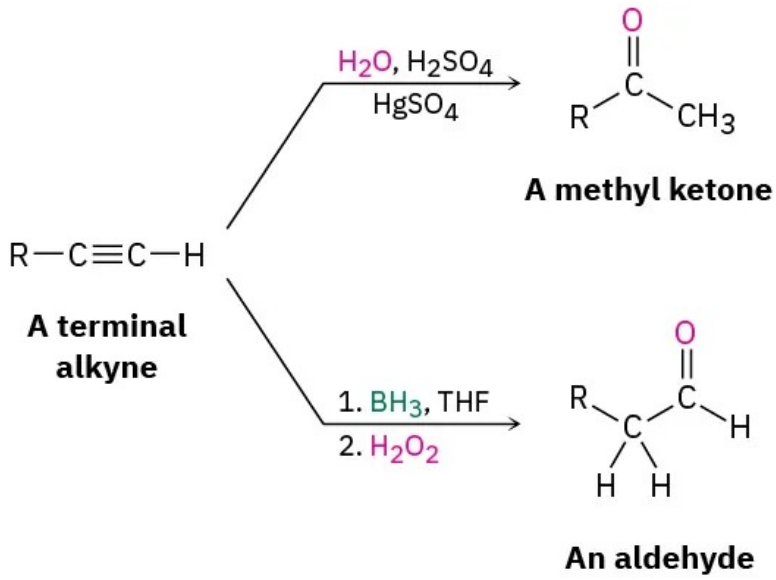


Hydroboration–Oxidation of Alkynes

Borane adds rapidly to an alkyne just as it does to an alkene, and the resulting vinylic borane can be oxidized by H_2O_2 to give an enol, which tautomerizes to either a ketone or an aldehyde, depending on the alkyne. Hydroboration–oxidation of an internal alkyne such as 3-hexyne is straightforward and gives a ketone, but hydroboration–oxidation of a terminal alkyne is more complex because two molecules of borane often add to the triple bond, complicating the situation. To prevent this double addition, a bulky, sterically encumbered borane such as bis(1,2-dimethylpropyl)borane, known commonly as disiamylborane is used in place of BH_3. When a terminal alkyne such as 1-butene reacts with disiamylborane, addition to the triple bond occurs normally, but a second addition is hindered by the bulk of the dialkylborane. Oxidation with H_2O_2 then gives an enol, which tautomerizes to the aldehyde.



The hydroboration–oxidation sequence is complementary to the direct, mercury(II)-catalyzed hydration reaction of a terminal alkyne because different products result. Direct hydration with aqueous acid and mercury(II) sulfate leads to a methyl ketone, whereas hydroboration–oxidation of the same terminal alkyne leads to an aldehyde.



Exercises

Exercise 9.3.1

What products would you obtain by mercury-catalyzed hydration of the following alkynes?

a. **b.**

Answer available at the end of this section.

Exercise 9.3.2

What alkynes would you start with to prepare the following ketones?

a. **b.**

Answer available at the end of this section.

Exercise 9.3.3

What alkyne would you start with to prepare each of the following compounds by a hydroboration–oxidation reaction?

a. **b.**

Answer available at the end of this section.

Exercise 9.3.4

How would you prepare the following carbonyl compounds starting from an alkyne (reddish brown = Br)?

a. **b.**



Answer available at the end of this section.

Answers

Exercise 9.3.1

a.4-Octanone **b.**2-Methyl-4-octanone and 7-methyl-4-octanone

Exercise 9.3.2

a.1-Pentyne **b.**2-Pentyne

Exercise 9.3.3

a. **b.**2,5-Dimethyl-3-hexyne

Exercise 9.3.4

a.Mercuric sulfate–catalyzed hydration of phenylacetylene **b.**Hydroboration/oxidation of cyclopentylacetylene

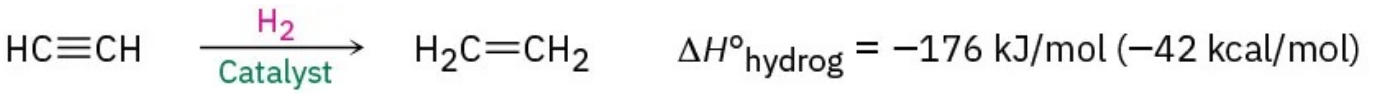
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9.4: Reduction and Oxidation of Alkynes

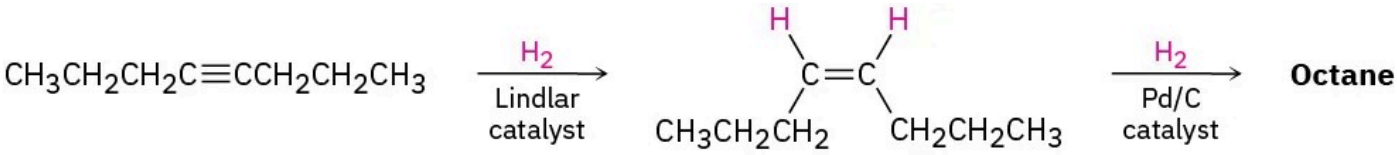
Reduction of Alkynes

Alkynes are reduced to alkanes by addition of H_2 over a metal catalyst. The reaction occurs in two steps through an alkene intermediate, and measurements show that the first step in the reaction is more exothermic than the second.





Complete reduction to the alkane occurs when palladium on carbon (Pd/C) is used as catalyst, but hydrogenation can be stopped at the alkene stage if the less active ***Lindlar catalyst*** is used. The Lindlar catalyst is a finely divided palladium metal that has been precipitated onto a calcium carbonate support and then deactivated by treatment with lead acetate and quinoline, an aromatic amine. The hydrogenation occurs with syn stereochemistry (Section 8.5), giving a cis alkene product.

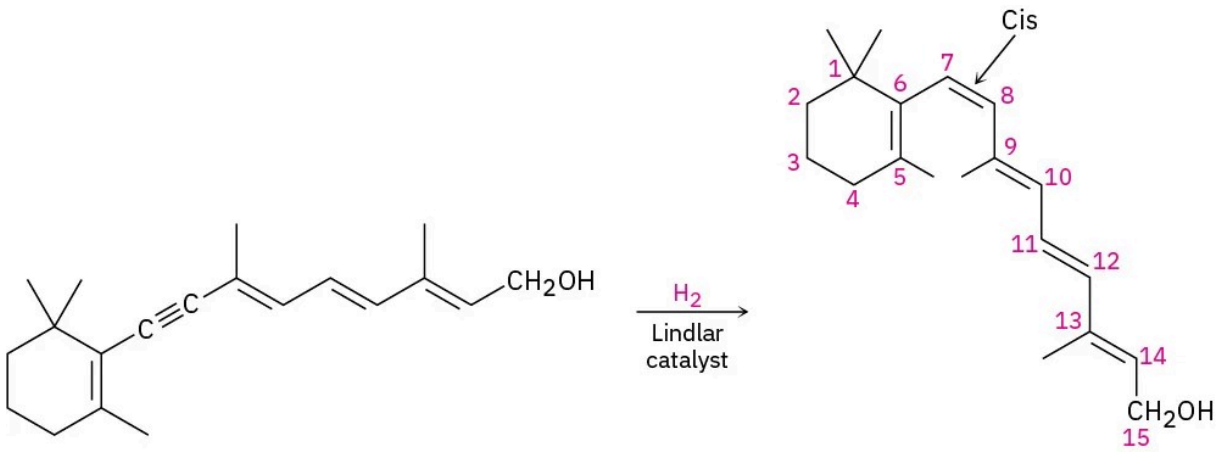


4-Octyne **cis-4-Octene**



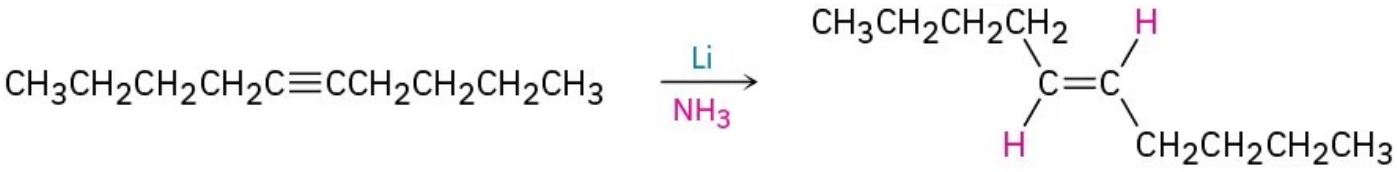
Quinoline

The alkyne hydrogenation reaction has been explored extensively by the Hoffmann–LaRoche pharmaceutical company, where it is used in the commercial synthesis of vitamin A. The cis isomer of vitamin A produced initially on hydrogenation is converted to the trans isomer by heating.



7-*cis*-Retinol
(7-*cis*-vitamin A; vitamin A has a trans double bond at C7)

An alternative method for the conversion of an alkyne to an alkene uses sodium or lithium metal as the reducing agent in liquid ammonia as solvent. This method is complementary to the Lindlar reduction because it produces trans rather than cis alkenes. For example, 5-decyne gives *trans*-5-decene on treatment with lithium in liquid ammonia. The mechanism is explained below.



5-Decyne **_trans_-5-Decene (78%)**

Alkali metals dissolve in liquid ammonia at –33 °C to produce a deep blue solution containing the metal cation and ammonia-solvated electrons. When an alkyne is then added to the solution, reduction occurs by the mechanism shown in Figure 9.4.1. An electron first adds to the triple bond to yield an intermediate anion radical—a species that is both an anion (has a negative charge) and a radical (has an odd number of electrons). This anion radical is a strong base, able to remove H^+ from ammonia to give a vinylic radical. Addition of a second electron to the vinylic radical gives a vinylic anion, which abstracts a second H^+ from ammonia to give trans alkene product.

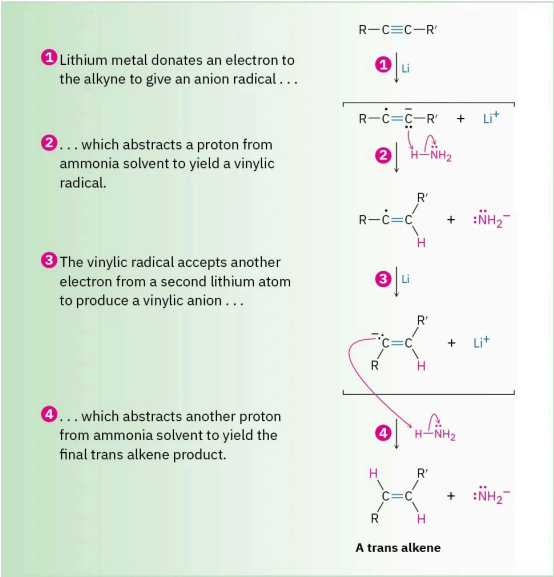


Figure 9.4.1: Mechanism of the lithium/ammonia reduction of an alkyne to produce a trans alkene.

Trans stereochemistry of the alkene product is established during the second reduction step (**3**) when the less-hindered trans vinylic anion is formed from the vinylic radical. Vinylic radicals undergo rapid cis–trans equilibration, but vinylic anions equilibrate much less rapidly. Thus, the more stable trans vinylic anion is formed rather than the less stable cis anion and is then protonated without equilibration.

Exercise 9.4.1

Using any alkyne needed, how would you prepare the following alkenes?

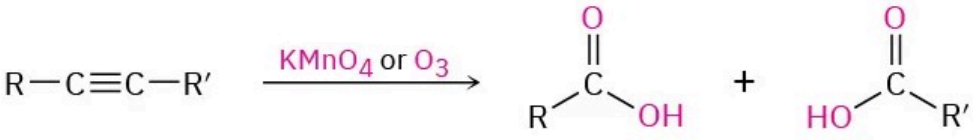
a. *trans*-2-Octene
b. *cis*-3-Heptene
c. 3-Methyl-1-pentene

Answer available at the end of this section.

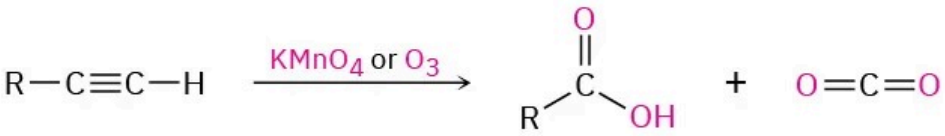
Oxidative Cleavage of Alkynes

Alkynes, like alkenes, can be cleaved by reaction with powerful oxidizing agents such as ozone or $KMnO_4$, although the reaction is of little value and it is mentioned only for completeness. A triple bond is generally less reactive than a double bond, and yields of cleavage products can be low. The products obtained from cleavage of an internal alkyne are carboxylic acids; from a terminal alkyne, CO_2 is formed as one product.

An internal alkyne



A terminal alkyne



Answers

Exercise 9.4.1

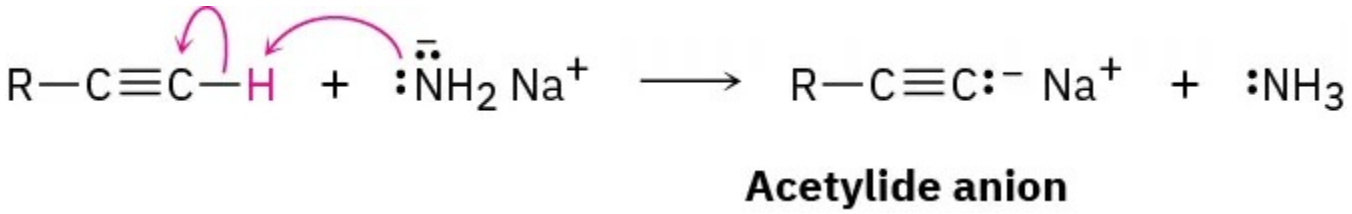
a. Reduce 2-octyne with $\mathrm{Li/NH_3}$.
b. Reduce 3-heptyne with $\mathrm{H_2}$/Lindlar catalyst.
c. Reduce 3-methyl-1-pentyne.

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9.5: Alkyne Acidity - Formation of Acetylide Anions

The most striking difference between alkenes and alkynes is that terminal alkynes are relatively acidic. When a terminal alkyne is treated with a strong base, such as sodium amide, $Na^+ \ ^-NH_2$, the terminal hydrogen is removed and the corresponding acetylide anion is formed.



According to the Brønsted–Lowry definition (Section 2.7), an acid is a substance that donates H^+. Although we usually think of oxyacids (H_2SO_4, HNO_3) or halogen acids (HCl, HBr) in this context, any compound containing a hydrogen atom can be an acid under the right circumstances. By measuring dissociation constants of different acids and expressing the results as pK_a values, an acidity order can be established. Recall from Section 2.8 that a lower pK_a corresponds to a stronger acid and a higher pK_a corresponds to a weaker one.

Where do hydrocarbons lie on the acidity scale? As the data in Table 9.5.1 show, both methane (p$K_a \approx 60$) and ethylene (pK_a = 44) are very weak acids and thus do not react with any of the common bases. Acetylene, however, has pK_a = 25 and can be deprotonated by the conjugate base of any acid whose pK_a is greater than 25. Amide ion (NH_2^-), for example, the conjugate base of ammonia (pK_a = 35), is often used to deprotonate terminal alkynes.

Table 9.5.1: Acidity of Simple Hydrocarbons

Family	Example	K_a	pK_a	
Alkyne		10^{-25}	25	Stronger acid
Alkene		10^{-44}	44	
Alkane	CH_4	10^{-60}	60	Weaker acid

Why are terminal alkynes more acidic than alkenes or alkanes? In other words, why are acetylide anions more stable than vinylic or alkyl anions? The simplest explanation involves the hybridization of the negatively charged carbon atom. An acetylide anion has an *sp*-hybridized carbon, so the negative charge resides in an orbital that has 50% "*s* character." A vinylic anion has a sp^2-hybridized carbon with 33% *s* character, and an alkyl anion (sp^3) has only 25% *s* character. Because *s* orbitals are nearer the positive nucleus and lower in energy than *p* orbitals, the negative charge is stabilized to a greater extent in an orbital with higher *s* character (Figure 9.5.1).

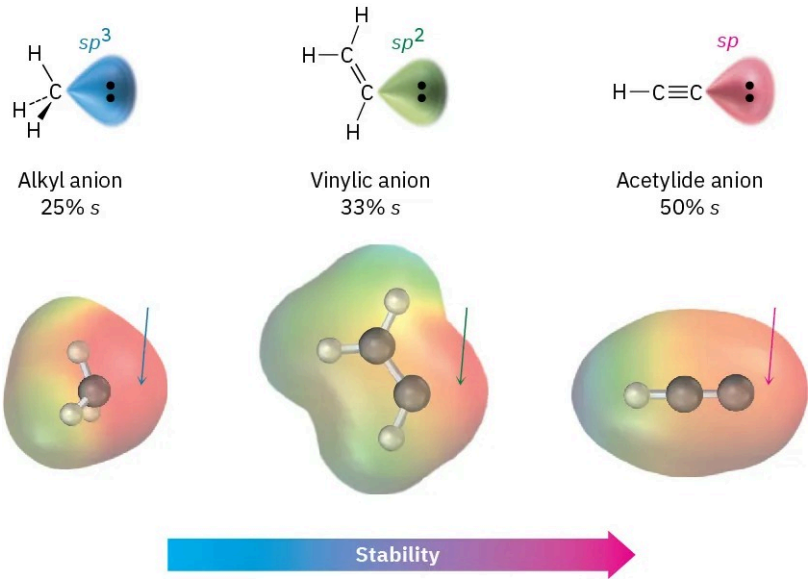


Figure 9.5.1: A comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with *sp* hybridization, has more s character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear less negative (red).

Exercise 9.5.1

The pK_a of acetone, CH_3COCH_3, is 19.3. Which of the following bases is strong enough to deprotonate acetone?

a. KOH (pK_a of H_2O = 15.7)
b. $Na^+ {}^-C{\equiv}CH$ (pK_a of C_2H_2 = 25)
c. $NaHCO_3$ (pK_a of H_2CO_3 = 6.4)
d. $NaOCH_3$ (pK_a of CH_3OH = 15.6)

Answer available at the end of this section.

Answers

Exercise 9.5.1

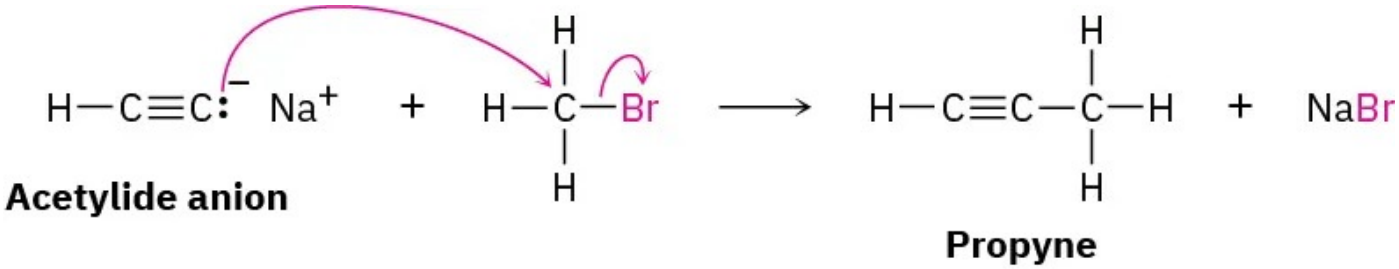
No: (a), (c), (d); yes: (b)

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9.6: Alkylation of Acetylide Anions

The negative charge and unshared electron pair on carbon make an acetylide anion strongly nucleophilic. As a result, an acetylide anion can react with electrophiles, such as alkyl halides, in a process that replaces the halide and yields a new alkyne product.



We won't study the details of this substitution reaction until Chapter 11, but for now you can picture it as happening by the pathway shown in Figure 9.6.1. The nucleophilic acetylide ion uses an electron pair to form a bond to the positively polarized, electrophilic carbon atom of bromomethane. As the new C–C bond forms, Br^- departs, taking with it the electron pair from the former C–Br bond and yielding propyne as product. We call such a reaction an alkylation because a new alkyl group has become attached to the starting alkyne.

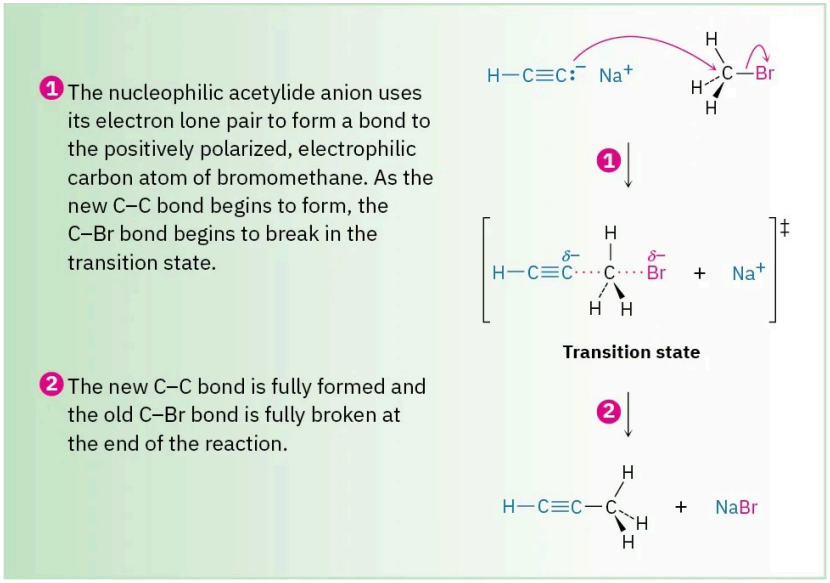
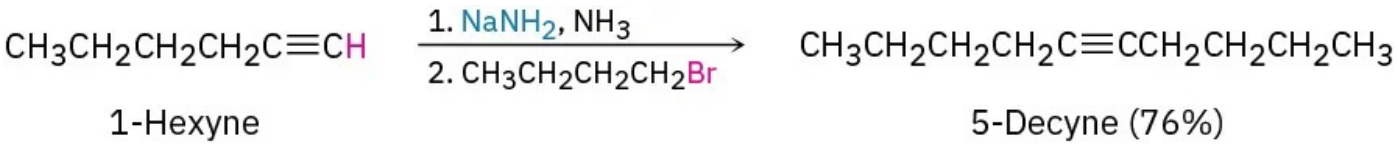
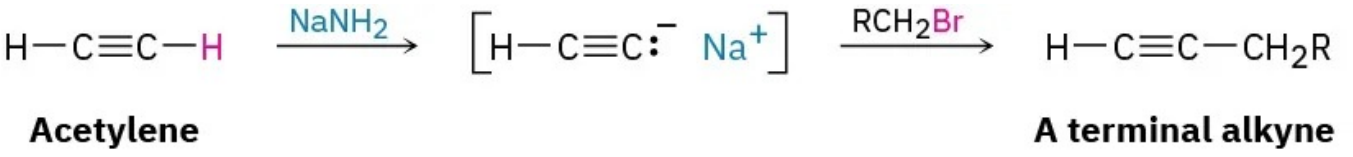


Figure 9.6.1: A mechanism for the alkylation reaction of acetylide anion with bromomethane to give propyne.

Alkyne alkylation is not limited to acetylene itself. Any terminal alkyne can be converted into its corresponding anion and then allowed to react with an alkyl halide to give an internal alkyne product. Hex-1-yne, for instance, gives dec-5-yne when treated first with $NaNH_2$ and then with 1-bromobutane.



Because of its generality, acetylide alkylation is a good method for preparing substituted alkynes from simpler precursors. A terminal alkyne can be prepared by alkylation of acetylene itself, and an internal alkyne can be prepared by further alkylation of a terminal alkyne.

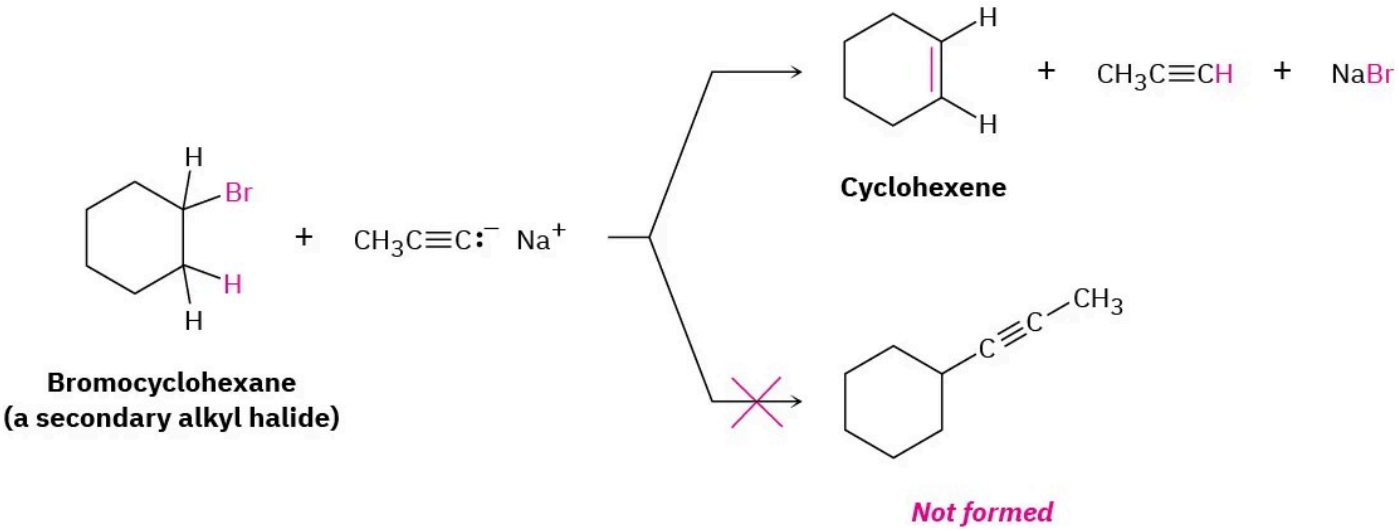


Acetylene **A terminal alkyne**



A terminal alkyne **An internal alkyne**

The only limit to the alkylation reaction is that it can only use primary alkyl bromides and alkyl iodides because acetylide ions are sufficiently strong bases to cause elimination instead of substitution when they react with secondary and tertiary alkyl halides. For example, reaction of bromocyclohexane with propyne anion yields the elimination product cyclohexene rather than the substitution product 1-propynylcyclohexane.



Bromocyclohexane (a secondary alkyl halide)

Exercise 9.6.1

Show the terminal alkyne and alkyl halide from which the following products can be obtained. If two routes look feasible, list both.

a. **b.** **c.**

Answer available at the end of this section.

Exercise 9.6.2

How would you prepare *cis*-2-butene starting from propyne, an alkyl halide, and any other reagents needed? This problem can't be worked in a single step. You'll have to carry out more than one reaction.

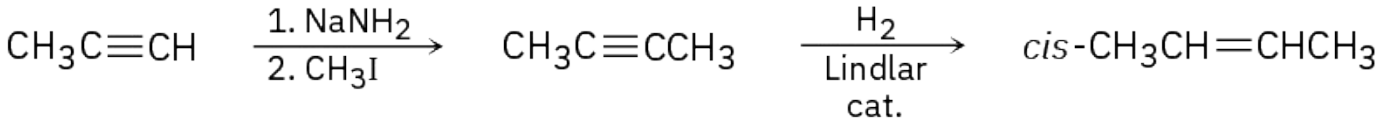
Answer available at the end of this section.

Answers

Exercise 9.6.1

a. 1-Pentyne + CH_3I or propyne + $CH_3CH_2CH_2I$
b. 3-Methyl-1-butyne + CH_3CH_2I
c. Cyclohexylacetylene + CH_3I

Exercise 9.6.2



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9.7: An Introduction to Organic Synthesis

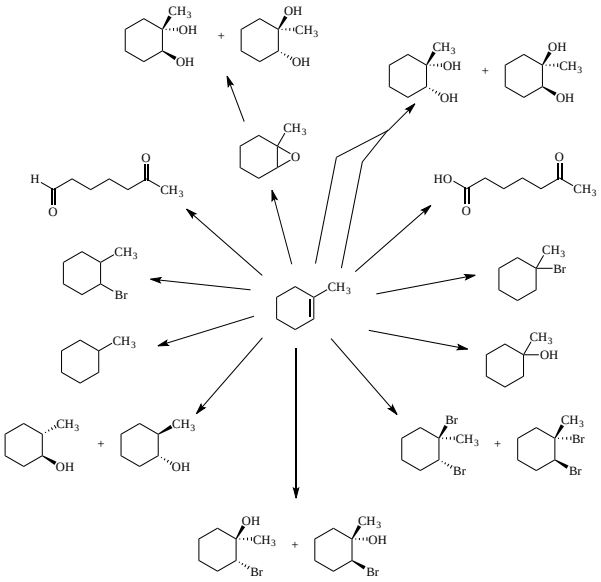
Objective

Design a multistep synthesis to prepare a given product from a given starting material, using any of the reactions introduced up to this point.

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.

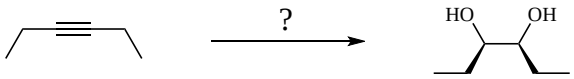


You may have noticed that some of the assigned problems require you to string together a number of organic reactions to convert one organic compound to another when there is no single reaction to achieve this goal. Such a string of reactions is called an “organic synthesis.” One of the major objectives of this course is to assist you in designing such syntheses. To achieve this objective, you will need to have all of the reactions described in the course available in your memory. You will need to recall some reactions much more frequently than others, and the only way to master this objective is to practise. The examples given in this section will be relatively simple, but soon you will design some sophisticated syntheses using a limited number of basic reactions.

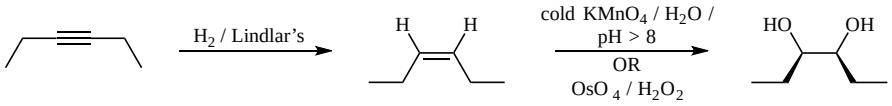
Simple Multi-Step Syntheses

A one or two-step sequence of simple reactions is not that difficult to deduce. For example, the synthesis of meso-3,4-hexanediol

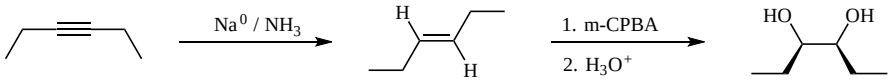
from 3-hexyne can occur by more than one multi-step pathway.



One approach would be to reduce the alkyne to cis or trans-3-hexene before undertaking glycol formation. Permanaganate or osmium tetroxide hydroxylation of cis-3-hexene would form the desired meso isomer.



From trans-3-hexene, it would be necessary to first epoxidize the alkene with a peracid, followed by ring opening with acidic or basic hydrolysis.

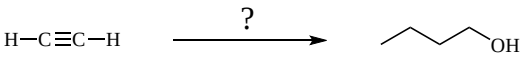


Longer multi-step syntheses require careful analysis and thought, since many options need to be considered. Like an expert chess player evaluating the long range pros and cons of potential moves, the chemist must appraise the potential success of various possible reaction paths, focusing on the scope and limitations constraining each of the individual reactions being employed. The skill is acquired by practice, experience, and often trial and error.

Thinking it Through with 3 Examples

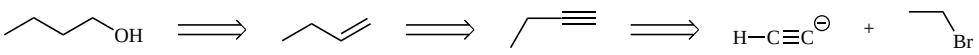
The following three examples illustrate strategies for developing multi-step syntheses from the reactions studied in the first ten chapters of this text. It is helpful to systematically look for structural changes beginning with the carbon chain and brainstorm relevant functional group conversion reactions. Retro-synthesis is the approach of working backwards from the product to the starting material.

In the first example, we are asked to synthesize 1-butanol from acetylene.

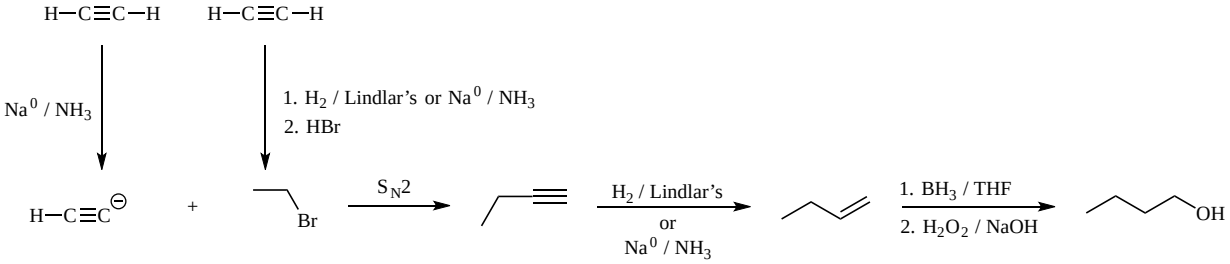


The carbon chain doubles in size indicating an acetylide S_N2 reaction with an alkyl halide. Primary alcohol formation from an anti-Markovnikov alkene hydration reaction (hydroboration-oxidation) is more likely than a substitution reaction. Applying retro-synthesis, we work backwards from the alcohol to the alkene to the alkyne from an acetylide reaction that initially builds the carbon chain.

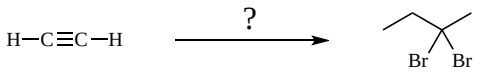
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation identified from the retro-synthesis. The ethylbromide must also be derived from acetylene so multiple reaction pathways are combined as shown below.

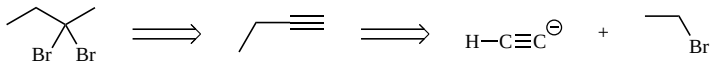


In the second example, we are asked to synthesize 1,2-dibromobutane from acetylene.

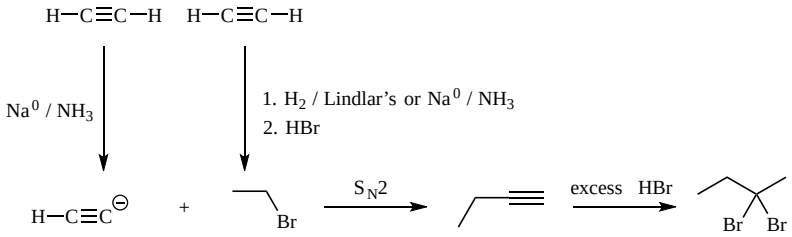


Once again, there is an increase in the carbon chain length, indicating an acetylide SN2 reaction with an alkyl halide similar to the first example. The hydrohalogenation can be subtle to discern because the hydrogen atoms are not shown in bond-line structures. Comparing the chemical formulas of 1-butyne with 1,2-dibromobutane, there is a difference of two H atoms and two Br atoms, indicating hydrohalogenation and not halogenation. The addition of both bromine atoms to the same carbon atom also supports the idea that hydrohalogenation occurs on an alkyne and not an alkene. The formation of the geminal dihalide also indicates hydrohalogenation instead of halogenation because halogenation produces vicinal dihalides. With this insight, the retro-synthesis indicates the following series of chemical transformations.

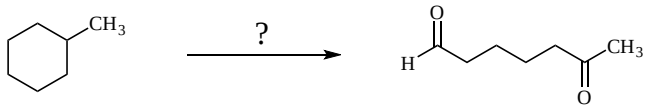
Retro-Synthesis



Working forwards, we specify the reagents needed for each transformation.

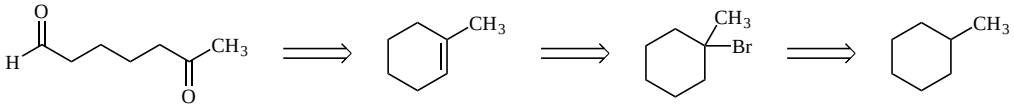


In the third example, we are asked to produce 6-oxoheptanal from methylcyclohexane.

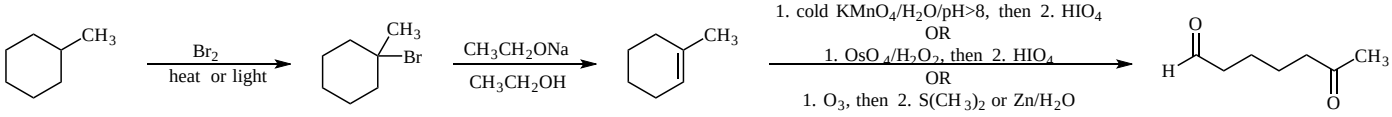


Counting the carbons, the starting material and product both contain seven carbon atoms and there is a cleavage reaction of an alkene under reductive conditions. One important missing aspect of this reaction is a good leaving group (LG). Alkanes are chemically quite boring. We can burn them as fuel or perform free-radical halogenation to create alkyl halides with excellent leaving groups. With these observations, the following retro-synthesis is reasonable.

Retro-Synthesis



Working forwards, we specify the reagents needed for each reaction. For the initial free-radical halogenation of the alkane, we have the option of chlorine (Cl_2) or bromine (Br_2). Because methylcyclohexane has several different classifications of carbons, the selectivity of Br_2 is more important than the faster reactivity of Cl_2. A strong base with heat can be used for the second step to follow an E2 mechanism and form 1-methylcyclohexene. The aldehyde group on the final product indicates gentle oxidative cleavage by any of several reaction pathways. These reactions can be combined in to the following multi-step synthesis.



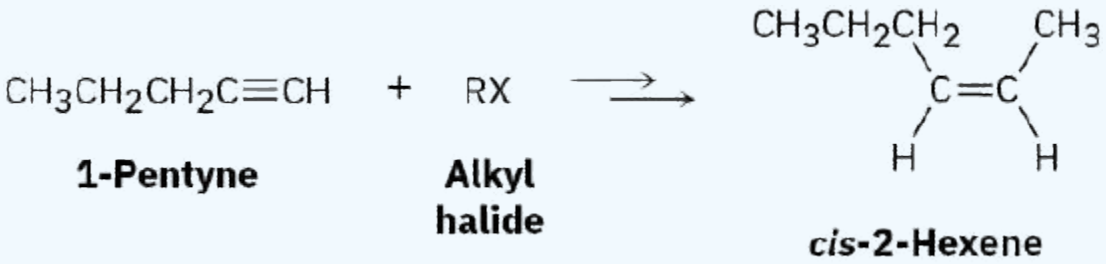
Synthesis Design and Retrosynthesis

There's no secret to planning an organic synthesis: all it takes is a knowledge of the different reactions and some practice. The only real trick is to work backward in what is often called a **retrosynthetic direction**. Don't look at a potential starting material and ask yourself what reactions it might undergo. Instead, look at the final product and ask, "What was the immediate precursor of that product?" For example, if the final product is an alkyl halide, the immediate precursor might be an alkene, to which you could add HX. If the final product is a cis alkene, the immediate precursor might be an alkyne, which you could hydrogenate using the Lindlar catalyst. Having found an immediate precursor, work backward again, one step at a time, until you get back to the starting material. You have to keep the starting material in mind, of course, so that you can work back to it, but you don't want that starting material to be your main focus.

Let's work through several examples of increasing complexity.

Worked Example 9.7.1: Devising a Synthesis Route

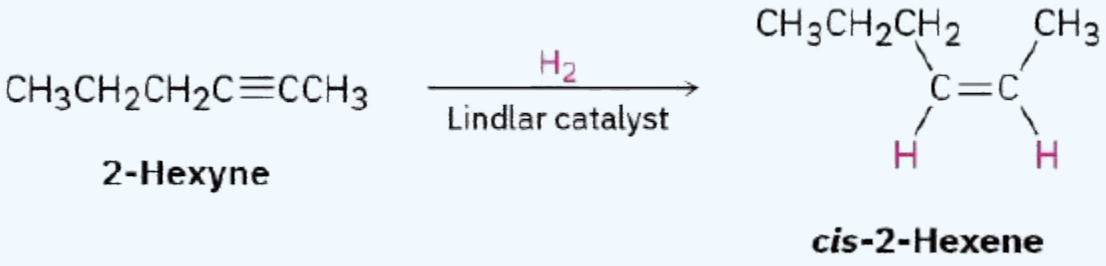
How would you synthesize *cis*-2-hexene from 1-pentyne and an alkyl halide? More than one step is needed.



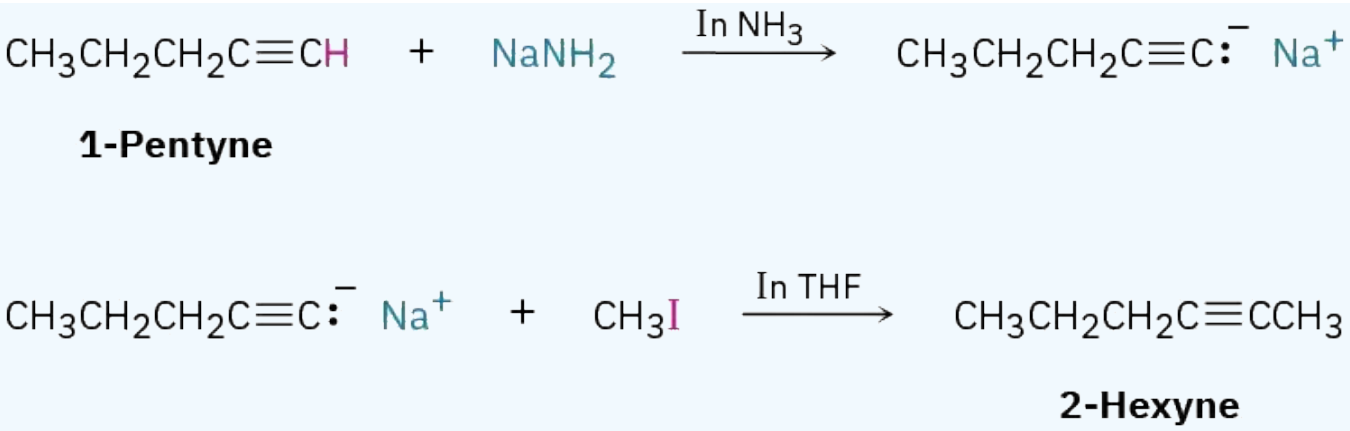
Strategy

When undertaking any synthesis problem, you should look at the product, identify the functional groups it contains, and then ask yourself how those functional groups can be prepared. Always work retrosynthetically, one step at a time.

The product in this case is a cis-disubstituted alkene, so the first question is, "What is an immediate precursor of a cis-disubstituted alkene?" We know that an alkene can be prepared from an alkyne by reduction and that the right choice of experimental conditions will allow us to prepare either a trans-disubstituted alkene (using lithium in liquid ammonia) or a cis-disubstituted alkene (using catalytic hydrogenation over the Lindlar catalyst). Thus, reduction of 2-hexyne by catalytic hydrogenation using the Lindlar catalyst should yield *cis*-2-hexene.

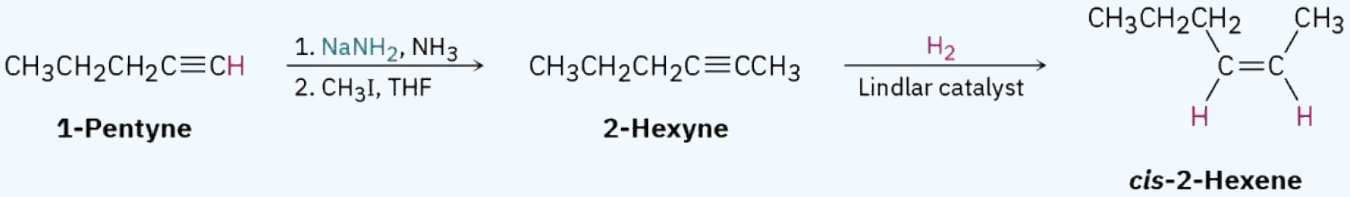


Next ask, "What is an immediate precursor of 2-hexyne?" We've seen that an internal alkyne can be prepared by alkylation of a terminal alkyne anion. In the present instance, we're told to start with 1-pentyne and an alkyl halide. Thus, alkylation of the anion of 1-pentyne with iodomethane should yield 2-hexyne.



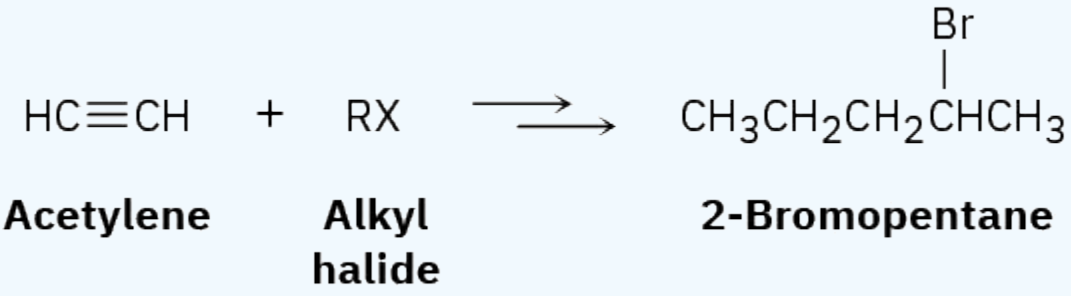
Solution

cis-2-Hexene can be synthesized from the given starting materials in three steps.



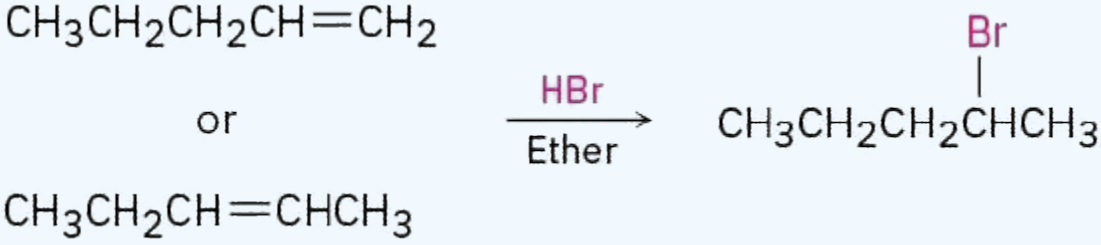
Worked Example 9.7.2: Devising a Synthesis Route

How would you synthesize 2-bromopentane from acetylene and an alkyl halide? More than one step is needed.

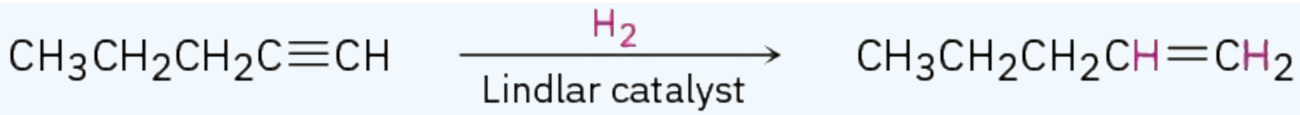


Strategy

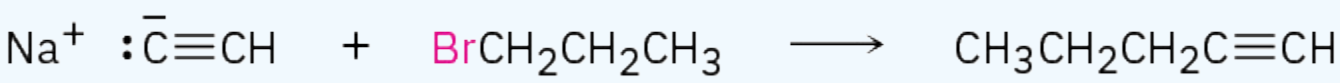
Identify the functional group in the product (an alkyl bromide) and work the problem retrosynthetically. What is an immediate precursor of an alkyl bromide? Perhaps an alkene plus HBr. Of the two possibilities, Markovnikov addition of HBr to 1-pentene looks like a better choice than addition to 2-pentene because the latter reaction would give a mixture of isomers.



What is an immediate precursor of an alkene? Perhaps an alkyne, which could be reduced.

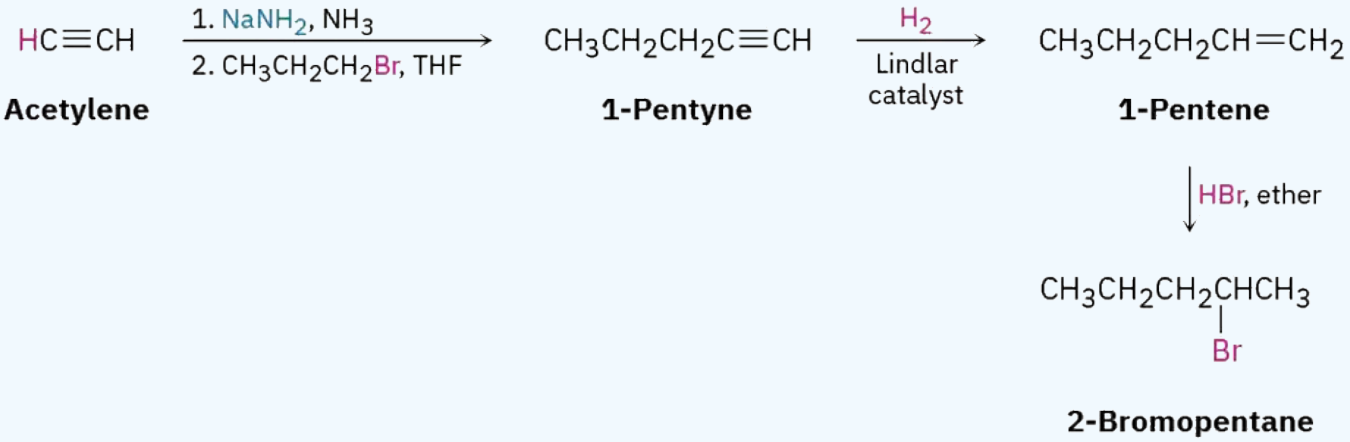


What is an immediate precursor of a terminal alkyne? Perhaps sodium acetylide and an alkyl halide.



Solution

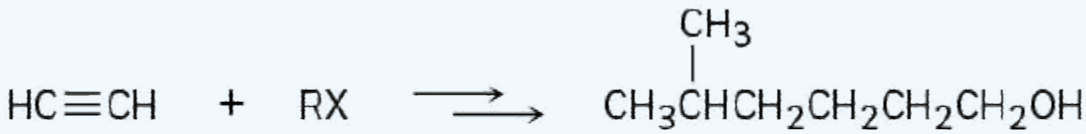
The desired product can be synthesized in four steps from acetylene and 1-bromopropane.



Acetylene **1-Pentyne** **1-Pentene** **2-Bromopentane**

Worked Example 9.7.3: Devising a Synthesis Route

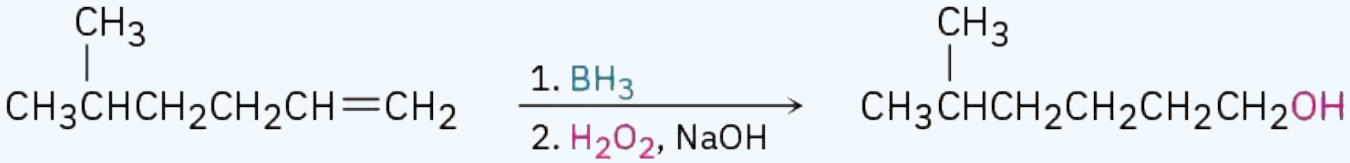
How would you synthesize 5-methyl-1-hexanol (5-methyl-1-hydroxyhexane) from acetylene and an alkyl halide?



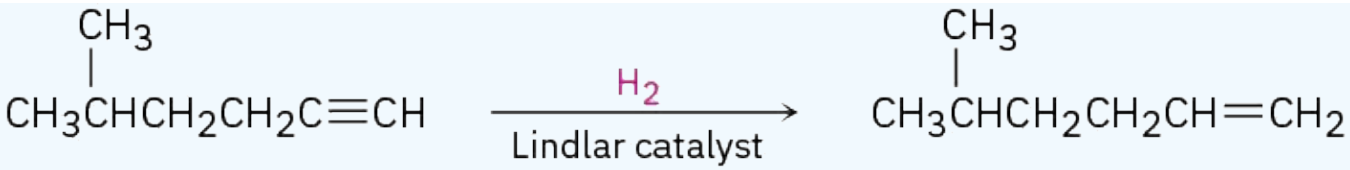
Acetylene **Alkyl halide** **5-Methyl-1-hexanol**

Strategy

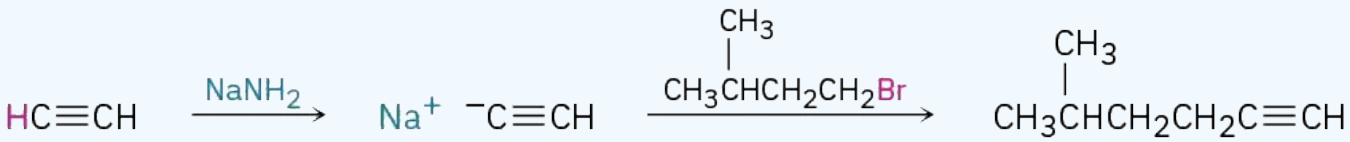
What is an immediate precursor of a primary alcohol? Perhaps a terminal alkene, which could be hydrated with non-Markovnikov regiochemistry by reaction with borane followed by oxidation with H_2O_2.



What is an immediate precursor of a terminal alkene? Perhaps a terminal alkyne, which could be reduced.

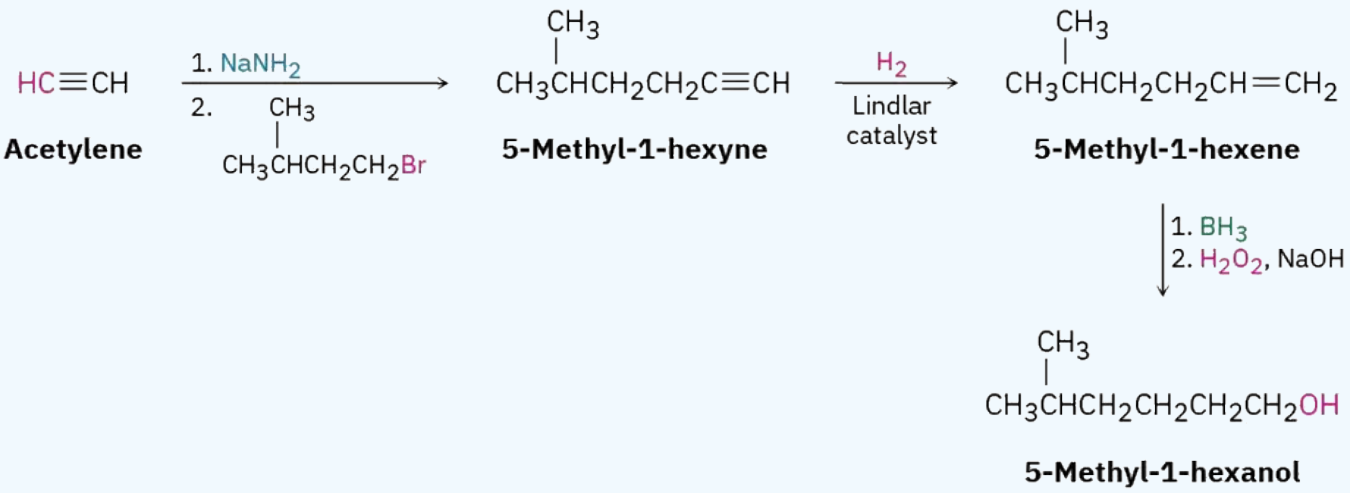


What is an immediate precursor of 5-methyl-1-hexyne? Perhaps acetylene and 1-bromo-3-methylbutane.



Solution

The synthesis can be completed in four steps from acetylene and 1-bromo-3-methylbutane:

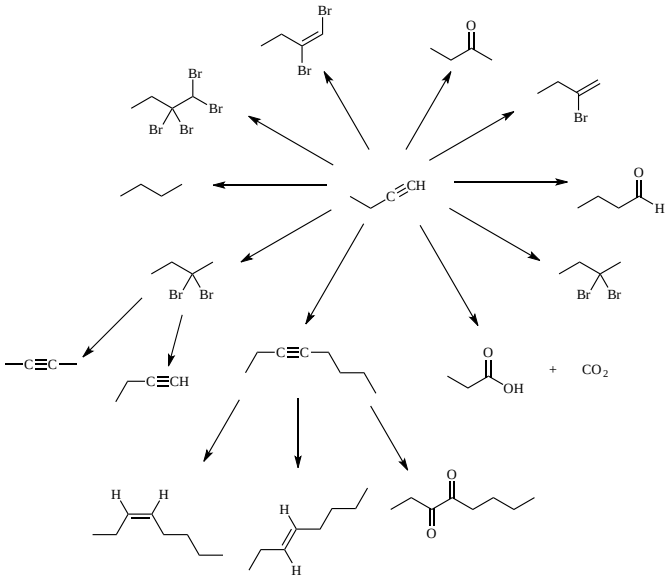


Reaction Maps to Build Functional Group Conversion Mastery

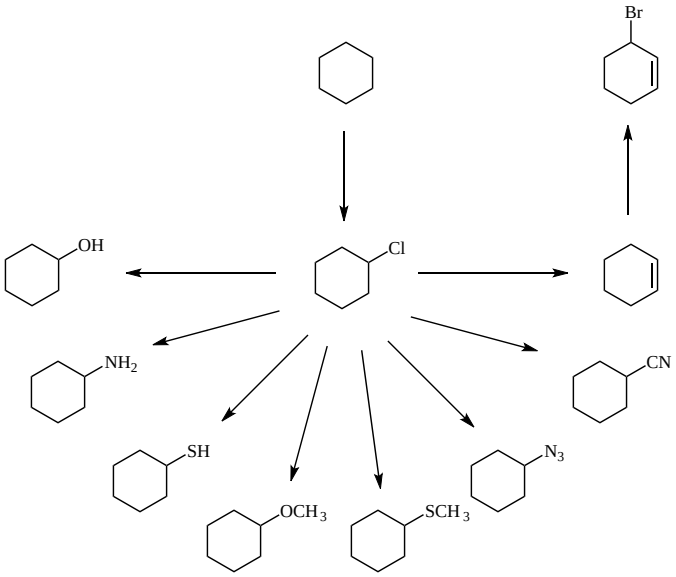
After working through the examples above, we can see how important it is to memorize all of the functional group reactions studied in the first ten chapters. We can apply the knowledge of these reactions to the wisdom of multi-step syntheses.

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.

Alkyne Reaction Map



Alkane and Alkyl Halide Reaction Map



Exercises

Example 9.7.1

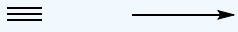
Starting at 3-hexyne predict synthetic routes to achieve:

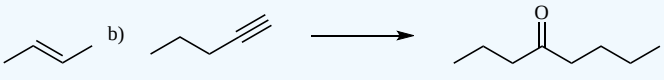
a. *trans*-3-hexene **b.** 3,4-dibromohexane **c.** 3-hexanol

Answer available at the end of this section.

Exercise 9.7.2

Show how you would accomplish the following synthetic transformations.

a) 

b) 

Answer available at the end of this section.

Exercise 9.7.3

Starting with acetylene and any alkyl halides, propose a synthesis to make:

a.pentanal **b.**hexane

Answer available at the end of this section.

Exercise 9.7.4

Beginning with 4-octyne as your only source of carbon, and using any inorganic reagents necessary, how would you synthesize the following compounds?

a. *cis*-4-Octene
b. Butanal
c. 4-Bromooctane
d. 4-Octanol
e. 4,5-Dichlorooctane
f. Butanoic acid

Answer available at the end of this section.

Exercise 9.7.5

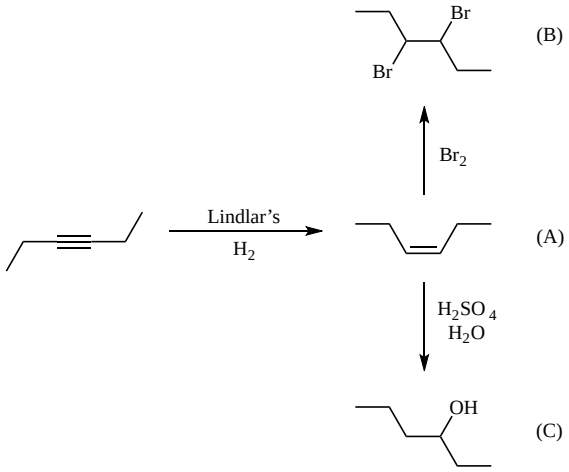
Beginning with acetylene and any alkyl halide needed, how would you synthesize the following compounds?

a.Decane **b.**2,2-Dimethylhexane **c.**Hexanal **d.**2-Heptanone

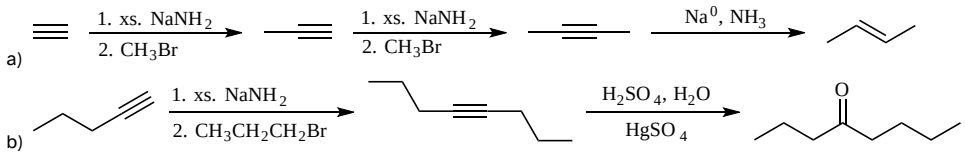
Answer available at the end of this section.

Answers

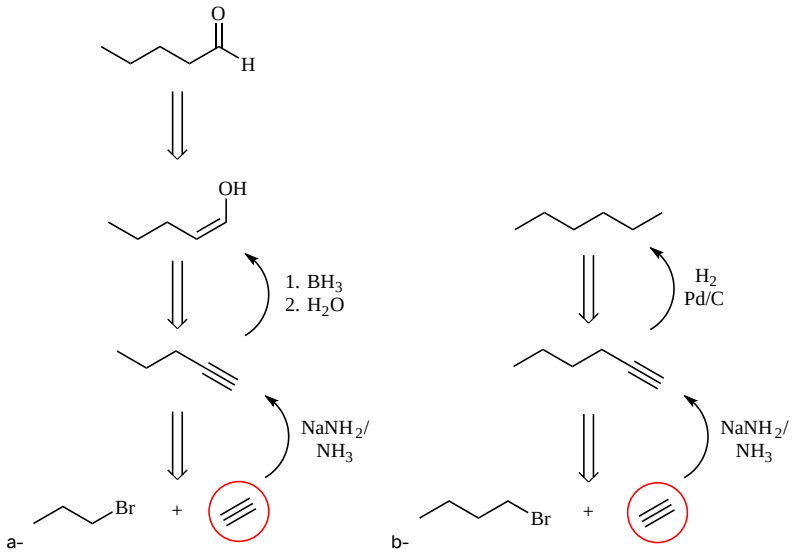
Example 9.7.1



Exercise 9.7.2



Exercise 9.7.3



Exercise 9.7.4

a. H_2, Lindlar catalyst
b. 1. H_2, Lindlar catalyst; 2. O_3; 3. Zn CH_3CO_2H
c. 1. H_2/Lindlar; 2. HBr
d. 1. H_2/Lindlar; 2. BH_3; 3. NaOH, H_2O_2
e. 1. H_2/Lindlar; 2. Cl_2
f. $KMnO_4$, H_3O^+

Exercise 9.7.5

a. 1. $HC{\equiv}CH + NaNH_2$; 2. $CH_3(CH_2)_6CH_2Br$; 3. H_2/Pd
b. 1. $HC{\equiv}CH + NaNH_2$; 2. $(CH_3)_3CCH_2CH_2I$; 3. H_2/Pd
c. 1. $HC{\equiv}CH + NaNH_2$; 2. $CH_3CH_2CH_2CH_2I$; 3. BH_3; 4. H_2O_2
d. 1. $HC{\equiv}CH + NaNH_2$; 2. $CH_3CH_2CH_2CH_2CH_2I$; 3. $HgSO_4$, H_3O^+

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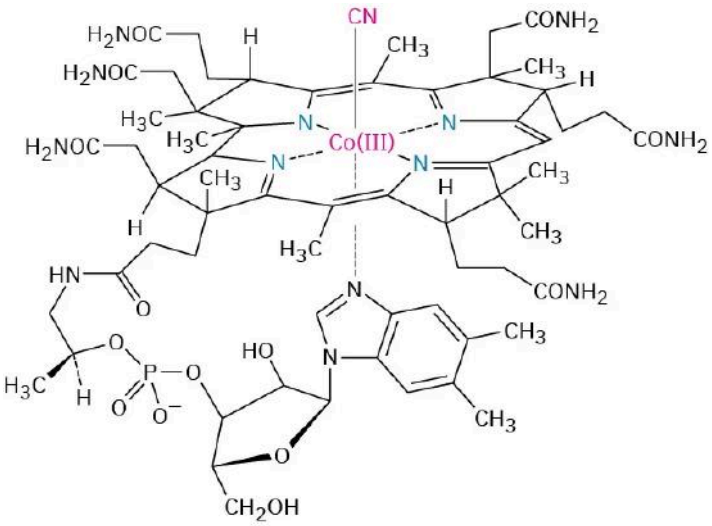
9.8: Chemistry Matters—The Art of Organic Synthesis

If you think some of the synthesis problems at the end of this chapter are difficult, try devising a synthesis of vitamin B_{12} starting only from simple substances you can buy in a chemical catalog. This extraordinary achievement was reported in 1973 as the culmination of a collaborative effort headed by Robert B. Woodward of Harvard University and Albert Eschenmoser of the Swiss Federal Institute of Technology in Zürich. More than 100 graduate students and postdoctoral associates contributed to the work, which took more than a decade to complete.



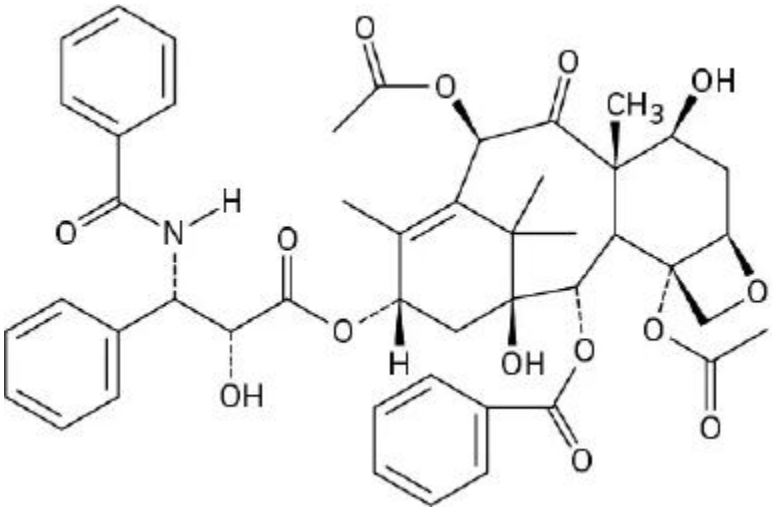
Figure 9.8.1: Vitamin B_{12} has been synthesized from scratch in the laboratory, but the bacteria growing on sludge from municipal sewage plants do a much better job. (credit: "Aeration and sludge-wasting" by U.S. Department of Agriculture/Flickr, Public Domain)

Why put such extraordinary effort into the laboratory synthesis of a molecule so easily obtained from natural sources? There are many reasons. On a basic human level, a chemist might be motivated primarily by the challenge, much as a climber might be challenged by the ascent of a difficult peak. Beyond the pure challenge, the completion of a difficult synthesis is also valuable in that it establishes new standards and raises the field to a new level. If vitamin B_{12} can be made, then why can't any molecule found in nature be made? Indeed, the decades that have passed since the work of Woodward and Eschenmoser have seen the laboratory synthesis of many enormously complex and valuable substances. Sometimes these substances—for instance, the anticancer compound paclitaxel, trade named Taxol—are not easily available in nature, so laboratory synthesis is the only method for obtaining larger quantities.



Vitamin B_{12}

But perhaps the most important reason for undertaking a complex synthesis is that, in so doing, new reactions and new chemistry are discovered. It invariably happens in a complex synthesis that a point is reached at which the planned route fails. At such a time, the only alternatives are either to quit or to devise a way around the difficulty. New reactions and new principles come from such situations, and it is in this way that the science of organic chemistry grows richer. In the synthesis of vitamin B_{12}, for example, unexpected findings emerged that led to the understanding of an entire new class of reactions—the *pericyclic* reactions that are the subject of Chapter 30 in this book. From synthesizing vitamin B_{12} to understanding pericyclic reactions—no one could have possibly predicted such a link at the beginning of the synthesis, but that is the way of science.



Paclitaxel (Taxol)

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9.A: Alkynes - An Introduction to Organic Synthesis (Summary)

Concepts & Vocabulary

Naming Alkynes

- Follow IUPAC rules in naming alkynes.

9.1 Preparation of Alkynes - Elimination Reactions of Dihalides

- **Vicinal** describes two groups on adjacent carbon atoms.
- **Geminal** describes two groups on the same carbon atom.
- Alkynes can be prepared by two successive eliminations of HX from either **vicinal** or **geminal** dihalides.

9.2 Reactions of Alkynes - Addition of HX and X_2

- **Alkynes** undergo addition reactions similarly to alkenes yielding Markovnikov products.

9.3 Hydration of Alkynes

- Enols have a hydroxyl group bonded to a sp^2 hybrid carbon (double-bonded carbon).
- Enols are usually not stable and undergo **keto-enol tautomerization** to form a ketone or aldehyde.
- Hydration of alkynes leads to an enol product which then rapidly tautomerizes into a ketone or aldehyde.

9.4 Reduction and Oxidation of Alkynes

- Alkynes can be hydrogenated with hydrogen gas and strong catalysts to yield alkanes.
- Alkynes can be hydrogenated with hydrogen gas and Lindlar's catalyst to yield Z alkenes.
- Alkynes can be hydrogenated with sodium metal and liquid ammonia to yield E alkenes.
- Oxidative cleavage of internal alkynes forms two molecules of carboxylic acids.
- Oxidative cleavage of terminal alkynes forms one molecule of carbon dioxide and one carboxylic acid.

9.5 Alkyne Acidity - Formation of Acetylide Anions

- Terminal alkynes are relatively acidic compared to alkene and alkane carbon-hydrogen bonds.
- Deprotonation of a terminal alkyne forms an acetylide ion, which is a good nucleophile.

9.6 Alkylation of Acetylide Anions

- Acetylide ions can be alkylated by adding to alkyl halides and carbonyl compounds.

9.7 An Introduction to Organic Synthesis

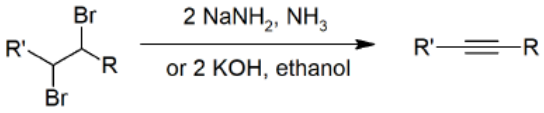
- Desired products cannot always be made from available starting materials through one reaction. Formation of these materials may require multiple reactions completed in sequence. This type of reaction sequence is termed synthesis.

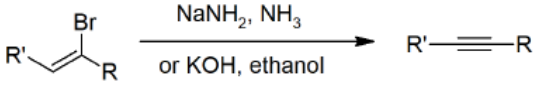
Skills to Master

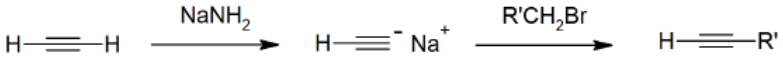
- Skill 9.1 Use IUPAC rules to accurately name alkynes.
- Skill 9.2 Draw elimination mechanisms to form alkynes.
- Skill 9.3 Draw addition mechanisms to alkynes incorporating carbocation intermediates.
- Skill 9.4 Draw addition mechanisms to alkynes incorporating halonium intermediates.
- Skill 9.5 Describe relative stability of enols to ketones and aldehydes.
- Skill 9.6 Draw keto-enol tautomerism mechanism.
- Skill 9.7 Draw products that differentiate between multiple reduction reactions of alkynes.
- Skill 9.8 Draw products of oxidative cleavage of alkynes.
- Skill 9.9 Draw mechanism for deprotonation of terminal alkynes.
- Skill 9.10 Compare acidity of terminal alkynes with other organic compounds.
- Skill 9.11 Draw reaction mechanisms using acetylide ions as nucleophiles.
- Skill 9.12 Describe schemes to accomplish synthesis of organic products given a starting material.

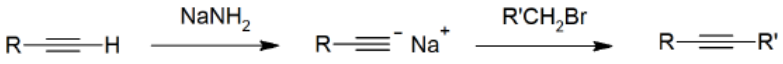
Summary of Reactions

Preparation of Alkynes

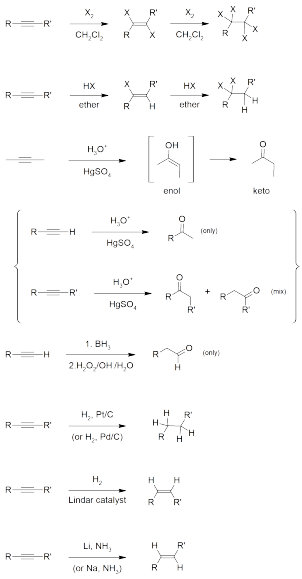








Reactions of Alkynes



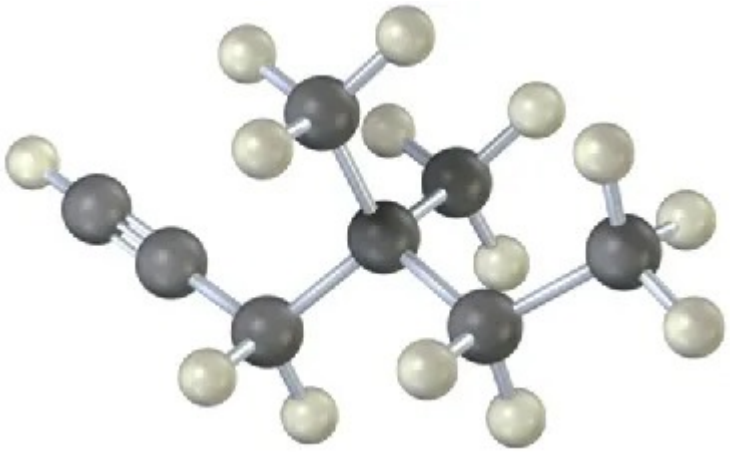
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9.B: Additional Problems

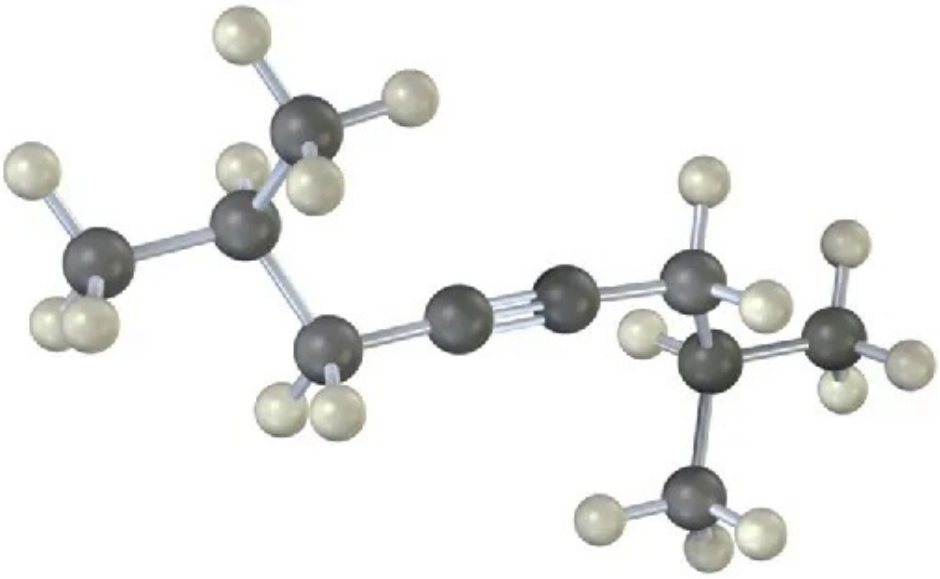
Visualizing Chemistry

PROBLEM 9.14 Name the following alkynes, and predict the products of their reaction with **(1)** H_2 in the presence of a Lindlar catalyst and **(2)** H_3O^+ in the presence of $HgSO_4$:

(a)



(b)



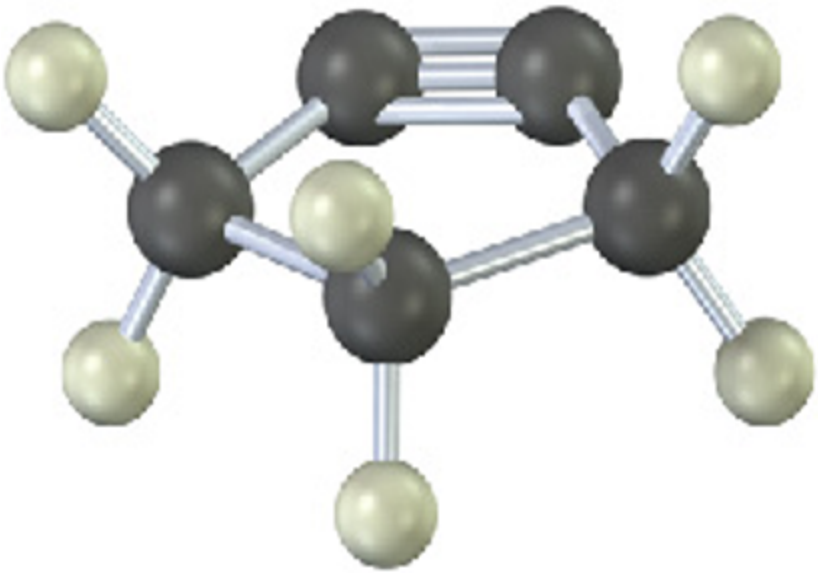
PROBLEM 9.15 From what alkyne might each of the following substances have been made? (Green = Cl.)

a. **b.**

PROBLEM 9.16 How would you prepare the following substances, starting from any compounds having four carbons or fewer?

a. **b.**

PROBLEM 9.17 The following cycloalkyne is too unstable to exist. Explain.

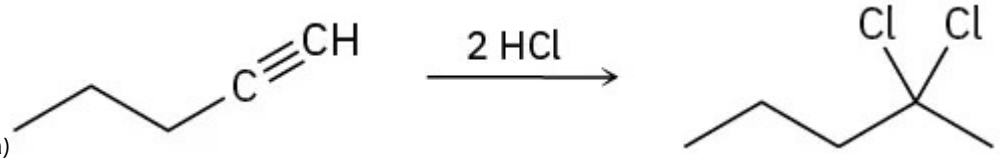


Mechanism Problems

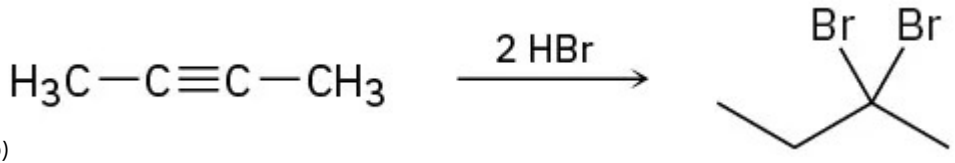
PROBLEM 9.18 Assuming that halogens add to alkynes in the same manner as they add to alkenes, propose a mechanism for and predict the product(s) of the reaction of phenylpropyne with Br_2.

PROBLEM 9.19 Assuming that strong acids add to alkynes in the same manner as they add to alkenes, propose a mechanism for each of the following reactions.

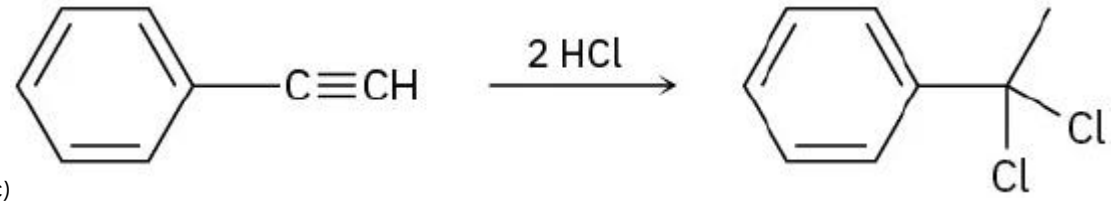
(a)



(b)

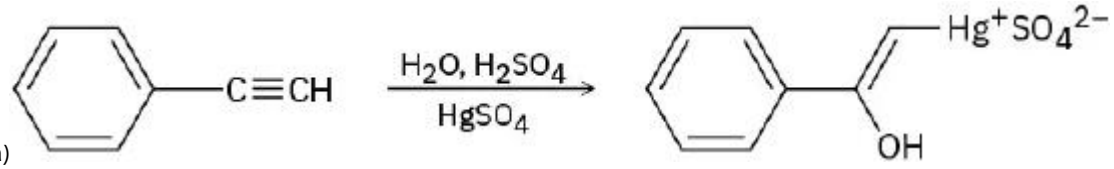


(c)

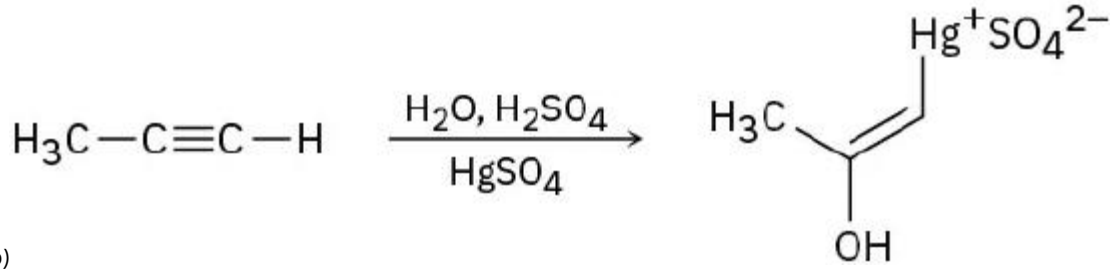


PROBLEM 9.20 The mercury-catalyzed hydration of alkynes involves the formation of an organomercury enol intermediate. Draw the electron-pushing mechanism to show how each of the following intermediates is formed.

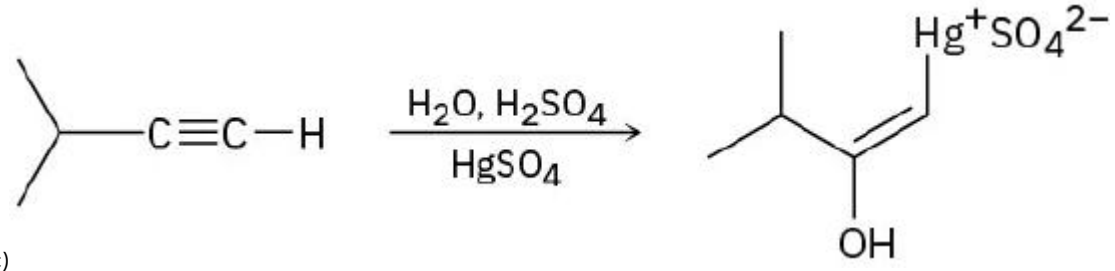
(a)



(b)

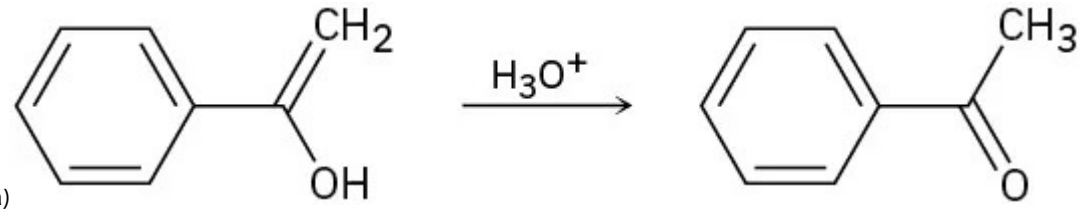


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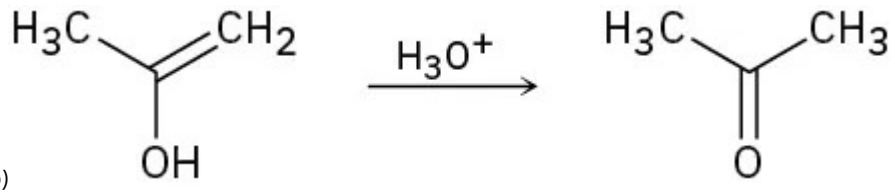


PROBLEM 9.21 The final step in the hydration of an alkyne under acidic conditions is the tautomerization of an enol intermediate to give the corresponding ketone. The mechanism involves a protonation followed by a deprotonation. Show the mechanism for each of the following tautomerizations.

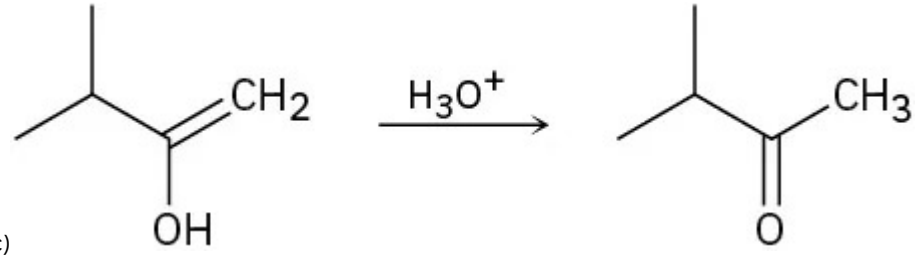
(a)



(b)

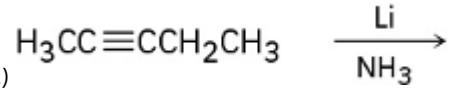


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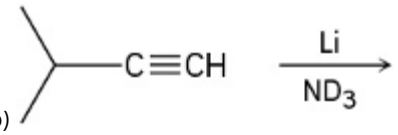


PROBLEM 9.22 Predict the product(s) and show the complete electron-pushing mechanism for each of the following dissolving metal reductions.

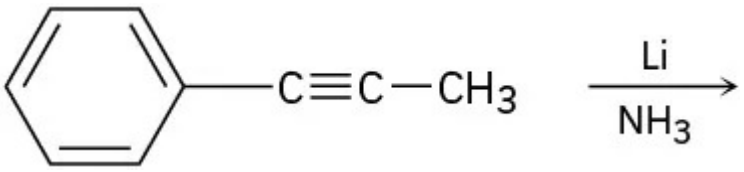
(a)



(b)

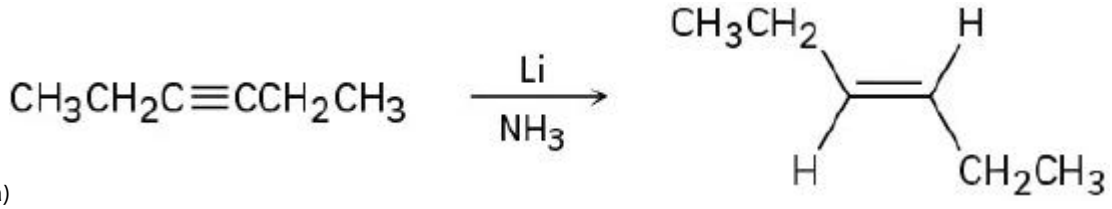


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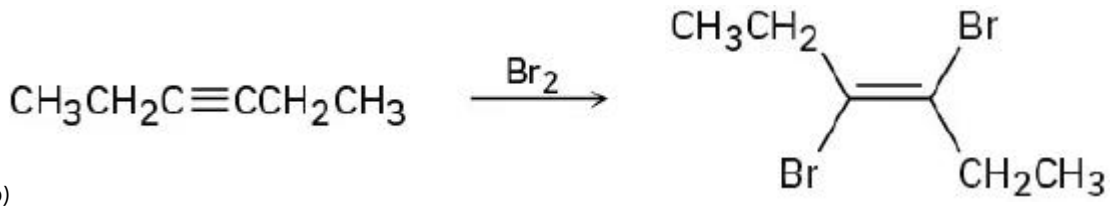


PROBLEM 9.23 Identify the mechanisms for the following reactions as *polar, radical,* or *both*.

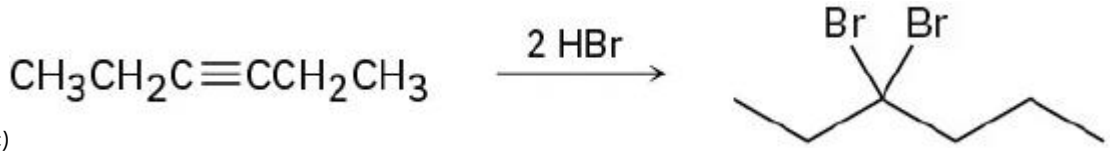
(a)



(b)

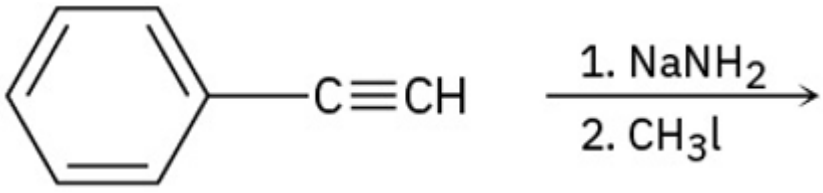


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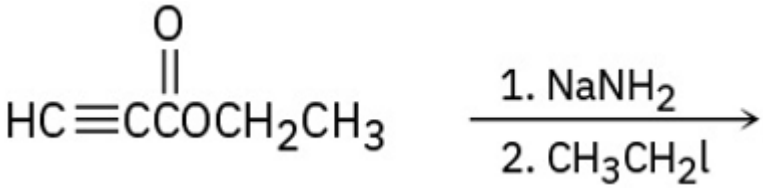


PROBLEM 9.24 Predict the product and provide the complete electron-pushing mechanism for the following two-step synthetic processes.

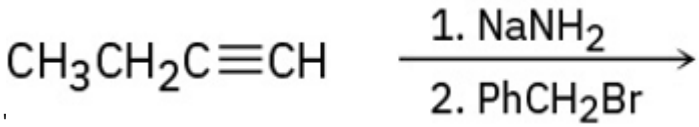
(a)



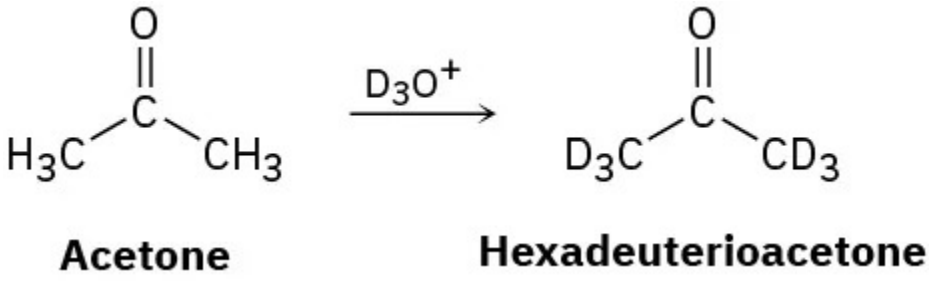
(b)



(c) '



PROBLEM 9.25 Reaction of acetone with D_3O^+ yields hexadeuterioacetone. That is, all the hydrogens in acetone are exchanged for deuterium. Review the mechanism of mercuric-ion-catalyzed alkyne hydration, and then propose a mechanism for this deuterium incorporation.

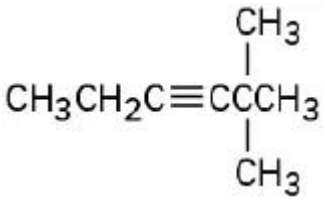


Acetone **Hexadeuterioacetone**

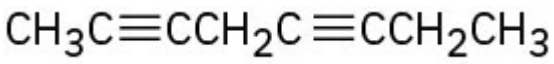
Naming Alkynes

PROBLEM 9.26 Give IUPAC names for the following compounds:

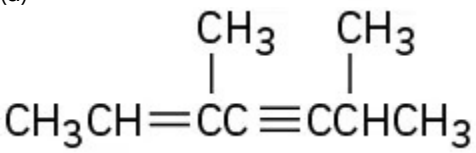
(a)



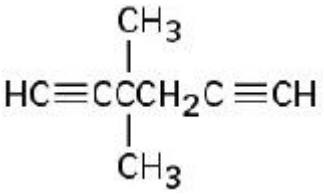
(b)



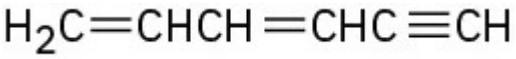
(c)



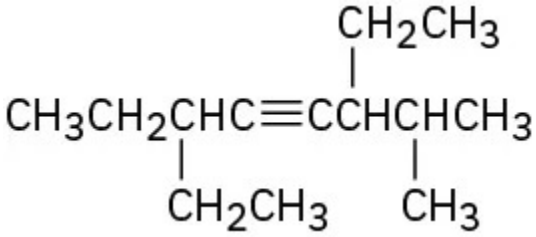
(d)



(e)



(f)



PROBLEM 9.27 Draw structures corresponding to the following names:

(a) 3,3-Dimethyl-4-octyne (b) 3-Ethyl-5-methyl-1,6,8-decatriyne

(c) 2,2,5,5-Tetramethyl-3-hexyne (d) 3,4-Dimethylcyclodecyne

(e) 3,5-Heptadien-1-yne (f) 3-Chloro-4,4-dimethyl-1-nonen-6-yne

(g) 3-*sec*-Butyl-1-heptyne (h) 5-*tert*-Butyl-2-methyl-3-octyne

PROBLEM 9.28 The following two hydrocarbons have been isolated from various plants in the sunflower family. Name them

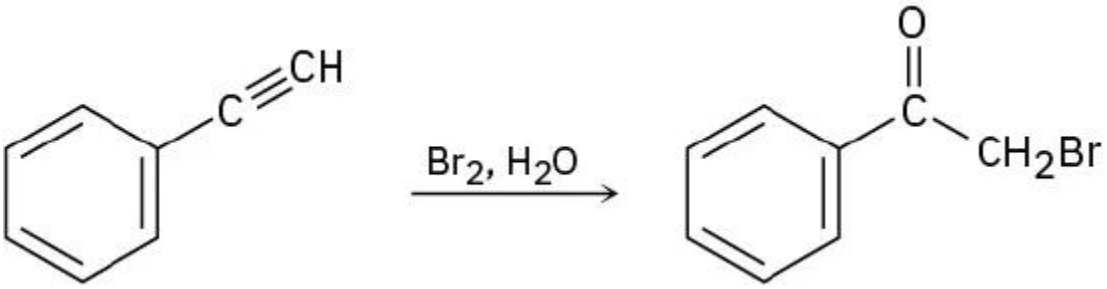
according to IUPAC rules.

(a) $CH_3CH{=}CHC{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}CHCH{=}CHCH{=}CH_2$ (all trans)

(b) $CH_3C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}CH_2$

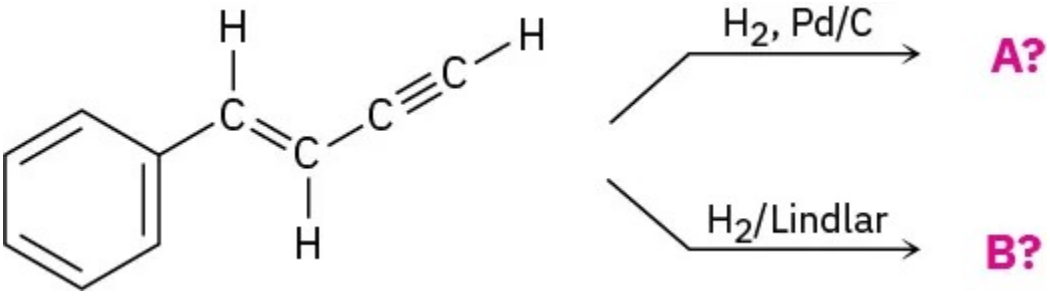
Reactions of Alkynes

PROBLEM 9.29 Terminal alkynes react with Br_2 and water to yield bromo ketones. For example:



Propose a mechanism for the reaction. To what reaction of alkenes is the process analogous?

PROBLEM 9.30 Predict the products of the following reactions:



PROBLEM 9.31 Predict the products from reaction of 1-hexyne with the following reagents:

(a) 1 equiv HBr. (b) 1 equiv Cl_2 (c) H_2, Lindlar catalyst

(d) $NaNH_2$ in NH_3, then CH_3Br (e) H_2O, H_2SO_4, $HgSO_4$ (f) 2 equiv HCl

PROBLEM 9.32 Predict the products from reaction of 5-decyne with the following reagents:

(a) H_2, Lindlar catalyst (b) Li in NH_3 (c) 1 equiv Br_2

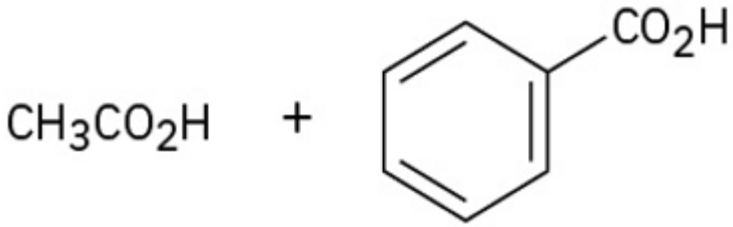
(d) BH_3 in THF, then H_2O_2, OH^- (e) H_2O, H_2SO_4, $HgSO_4$ (f) Excess H_2, Pd/C catalyst

PROBLEM 9.33 Predict the products from reaction of 2-hexyne with the following reagents:

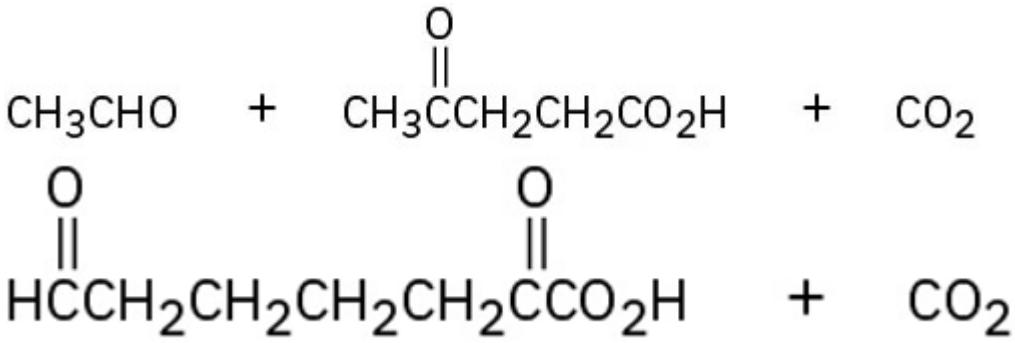
(a) 2 equiv Br_2 (b) 1 equiv HBr (c) Excess HBr (d) Li in NH_3 (e) H_2O, H_2SO_4, $HgSO_4$

PROBLEM 9.34 Propose structures for hydrocarbons that give the following products on oxidative cleavage by $KMnO_4$ or O_3:

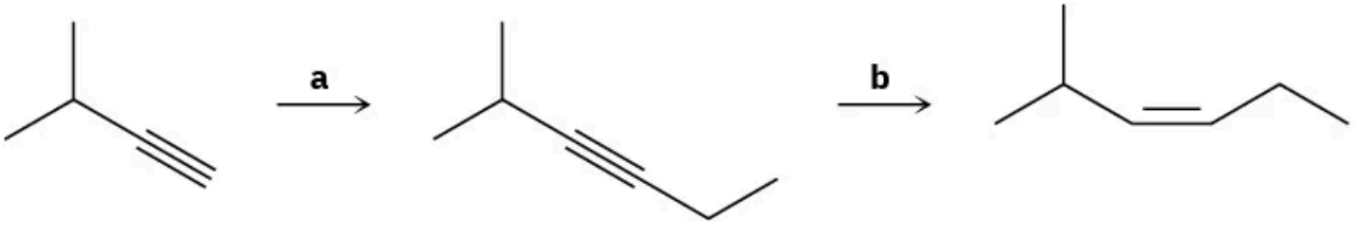
, $CO_2 + CH_3(CH_2)_5CO_2H$



- $HO_2C(CH_2)_8CO_2H$

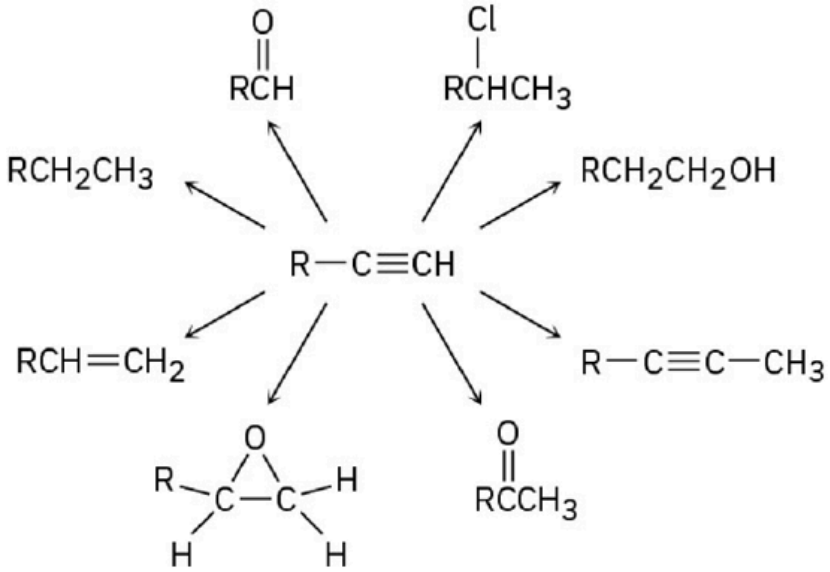


PROBLEM 9.35 Identify the reagents **a–c** in the following scheme:

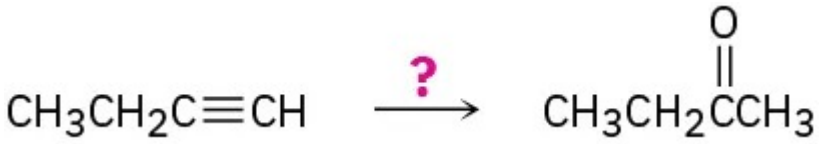


Organic Synthesis

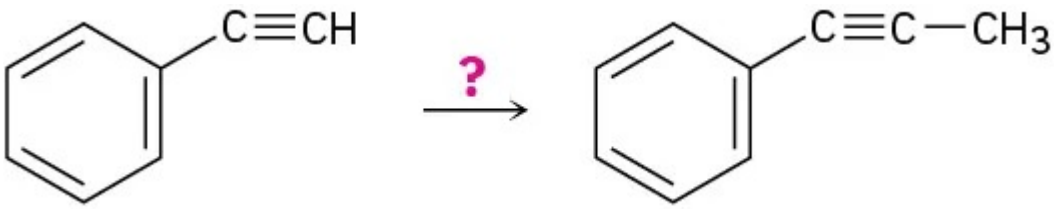
PROBLEM 9.36 How would you carry out the following multistep conversions? More than one step may be needed in some instances.

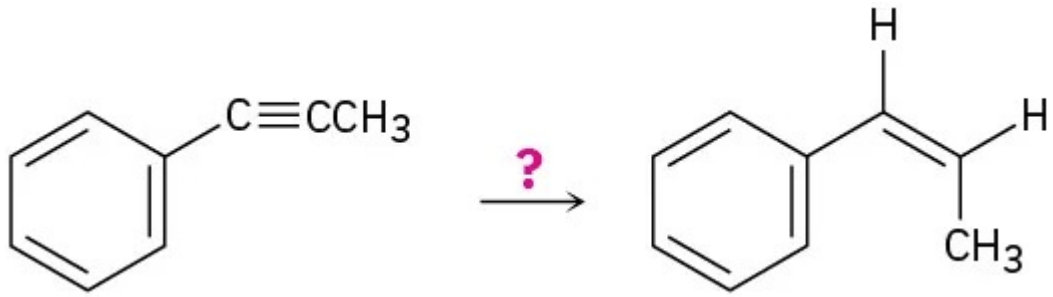


PROBLEM 9.37 How would you carry out the following reactions?

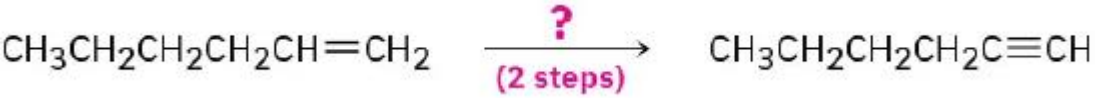
(a) 

(b) 

(c) 

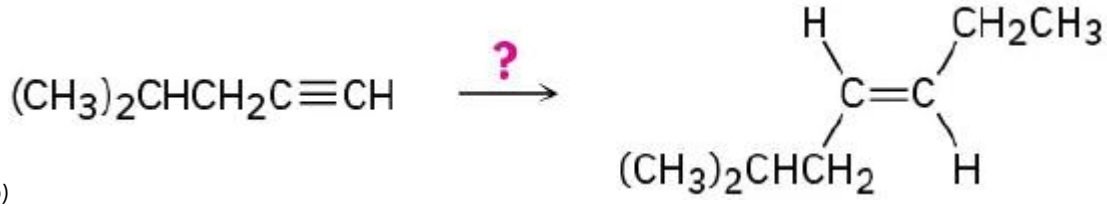
(d) 

(e) 

(f) 

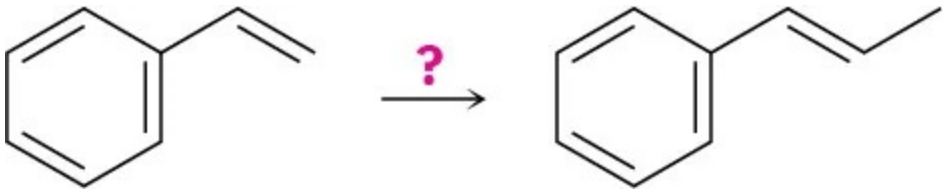
PROBLEM 9.38 Each of the following syntheses requires more than one step. How would you carry them out?

(a) 

(b) 

PROBLEM 9.39 Removed

PROBLEM 9.40 How would you carry out the following multistep conversions?



PROBLEM 9.41 Synthesize the following compound using 1-butyne as the only source of carbon, along with any inorganic reagents you need. More than one step may be needed.

(a) 1,1,2,2-Tetrachlorobutane

PROBLEM 9.42 How would you synthesize the following compounds from acetylene and any alkyl halides with four or fewer carbons? More than one step may be needed.

(a) $CH_3CH_2CH_2C{\equiv}CH$

(b) $CH_3CH_2C{\equiv}CCH_2CH_3$

(c)

$$CH_3CHCH_2CH{=}CH_2$$
$$|$$
$$CH_3$$

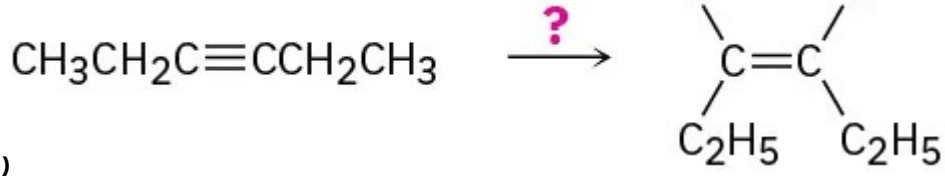
(d)

$$CH_3CH_2CH_2C(=O)CH_2CH_2CH_2CH_3$$

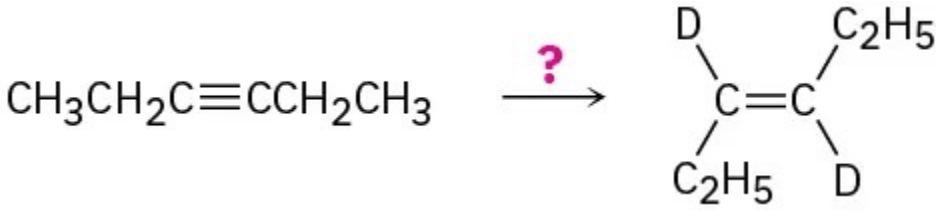
(e) $CH_3CH_2CH_2CH_2CH_2CHO$

PROBLEM 9.43 How would you carry out the following reactions to introduce deuterium into organic molecules?

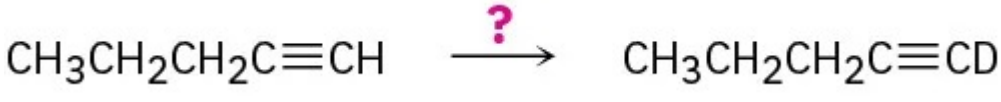
(a)



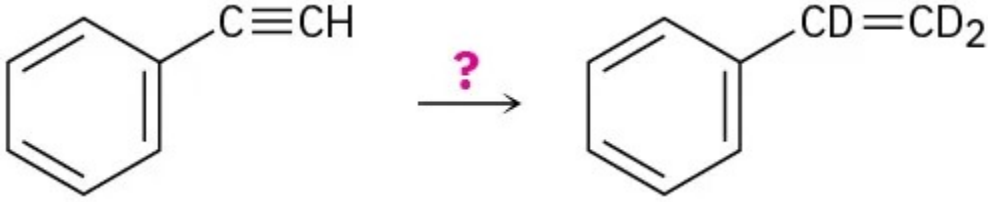
(b)



(c)

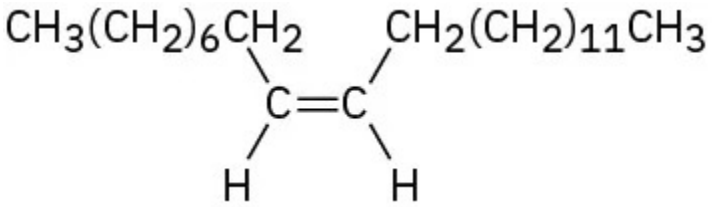


(d)



PROBLEM 9.44 How would you prepare cyclodecyne starting from acetylene and any required alkyl halide?

PROBLEM 9.45 The sex attractant given off by the common housefly is an alkene named *muscalure*. Propose a synthesis of muscalure starting from acetylene and any alkyl halides needed. What is the IUPAC name for muscalure?



Muscalure

General Problems

PROBLEM 9.46 A hydrocarbon of unknown structure has the formula C_8H_{10}. On catalytic hydrogenation over the Lindlar catalyst, 1 equivalent of H_2 is absorbed. On hydrogenation over a palladium catalyst, 3 equivalents of H_2 are absorbed.

(a) How many degrees of unsaturation are present in the unknown structure?

(b) How many triple bonds are present? **(c)** How many double bonds are present?

(d) How many rings are present? **(e)** Draw a structure that fits the data.

PROBLEM 9.47 Compound **A** (C_9H_{12}) absorbed 3 equivalents of H_2 on catalytic reduction over a palladium catalyst to give **B** (C_9H_{18}). On ozonolysis, compound **A** gave, among other things, a ketone that was identified as cyclohexanone. On treatment with $NaNH_2$ in NH_3, followed by addition of iodomethane, compound **A** gave a new hydrocarbon, **C** ($C_{10}H_{14}$). What are the structures of **A**, **B**, and **C**?

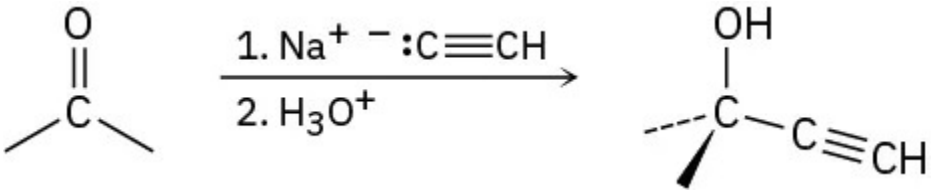
PROBLEM 9.48 Hydrocarbon **A** has the formula $C_{12}H_8$. It absorbs 8 equivalents of H_2 on catalytic reduction over a palladium catalyst. On ozonolysis, only two products are formed: oxalic acid (HO_2CCO_2H) and succinic acid ($HO_2CCH_2CH_2CO_2H$). Write the reactions, and propose a structure for **A**.

PROBLEM 9.49 Occasionally, a chemist might need to *invert* the stereochemistry of an alkene—that is, to convert a cis alkene to a trans alkene, or vice versa. There is no one-step method for doing an alkene inversion, but the transformation can be carried out by combining several reactions in the proper sequence. How would you carry out the following reactions?

(a) *trans*-5-Decene -- ? --> *cis*-5-Decene

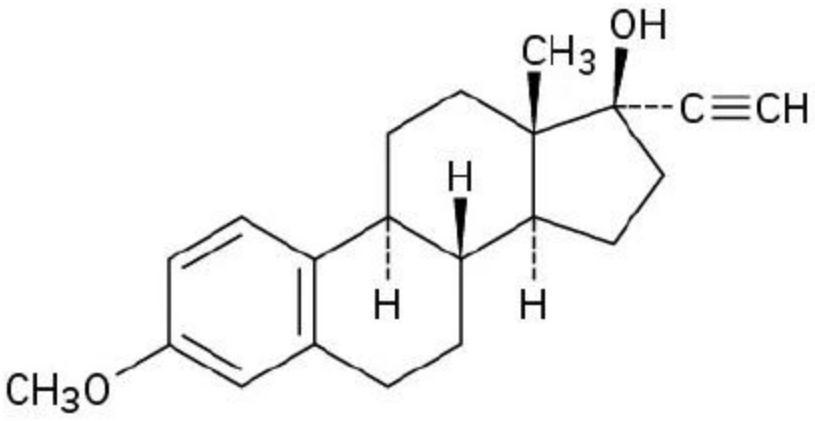
(b) *cis*-5-Decene -- ? --> *trans*-5-Decene

PROBLEM 9.50 Organometallic reagents such as sodium acetylide undergo an addition reaction with ketones, giving alcohols:



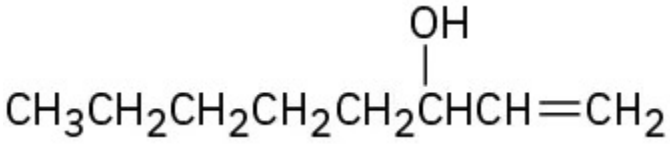
How might you use this reaction to prepare 2-methyl-1,3-butadiene, the starting material used in the manufacture of synthetic rubber?

PROBLEM 9.51 The oral contraceptive agent Mestranol is synthesized using a carbonyl addition reaction like that shown in Problem 9-50. Draw the structure of the ketone needed.



Mestranol

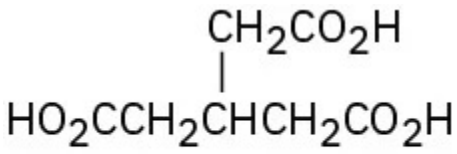
PROBLEM 9.52 1-Octen-3-ol, a potent mosquito attractant commonly used in mosquito traps, can be prepared in two steps from hexanal, $CH_3CH_2CH_2CH_2CH_2CHO$. The first step is an acetylide-addition reaction like that described in Problem 9-50. What is the structure of the product from the first step, and how can it be converted into 1-octen-3-ol?



1-Octen-3-ol

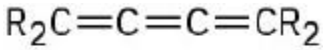
PROBLEM 9.53 Erythrogenic acid, $C_{18}H_{26}O_2$, is an acetylenic fatty acid that turns a vivid red on exposure to light. On catalytic hydrogenation over a palladium catalyst, 5 equivalents of H_2 are absorbed, and stearic acid, $CH_3(CH_2)_{16}CO_2H$, is produced. Ozonolysis of erythrogenic acid gives four products: formaldehyde, CH_2O; oxalic acid, HO_2CCO_2H; azelaic acid, $HO_2C(CH_2)_7CO_2H$; and the aldehyde acid $OHC(CH_2)_4CO_2H$. Draw two possible structures for erythrogenic acid, and suggest a way to tell them apart by carrying out some simple reactions.

PROBLEM 9.54 Hydrocarbon **A** has the formula C_9H_{12} and absorbs 3 equivalents of H_2 to yield **B**, C_9H_{18}, when hydrogenated over a Pd/C catalyst. On treatment of **A** with aqueous H_2SO_4 in the presence of mercury(II), two isomeric ketones, **C** and **D**, are produced. Oxidation of **A** with $KMnO_4$ gives a mixture of acetic acid (CH_3CO_2H) and the tricarboxylic acid **E**. Propose structures for compounds **A**–**D**, and write the reactions.



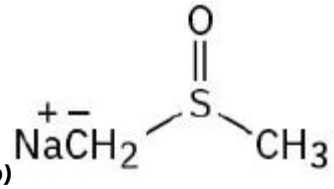
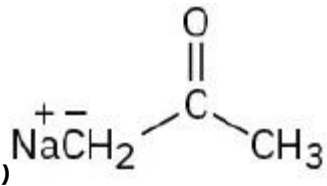
E

PROBLEM 9.55 A *cumulene* is a compound with three adjacent double bonds. Draw an orbital picture of a cumulene. What kind of hybridization do the two central carbon atoms have? What is the geometric relationship of the substituents on one end to the substituents on the other end? What kind of isomerism is possible? Make a model to help see the answer.

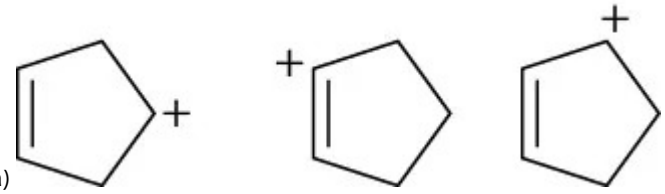


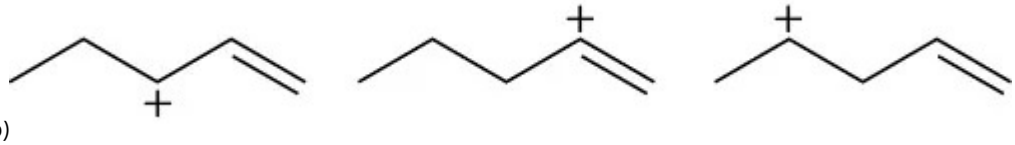
A cumulene

PROBLEM 9.56 Which of the following bases could be used to deprotonate 1-butyne?

(a) KOH (b)  (c) $CH_3CH_2CH_2CH_2Li$ (d) 

PROBLEM 9.57 Arrange the following carbocations in order of increasing stability.

(a) 

(b) 

(c) 

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10: ORGANOHALIDES

Learning Objectives

After you have completed Chapter 10, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design a multistep synthesis to prepare a given compound from a given starting material using any of the reactions studied up to this point in the course, including those which involve alkyl halides.
- solve road-map problems requiring a knowledge of any of the reactions or concepts studied up to this point, including those introduced in this chapter.
- define, and use in context, the key terms introduced.

10.0: Why This Chapter?

10.1: Names and Properties of Alkyl Halides

10.2: Preparing Alkyl Halides from Alkanes - Radical Halogenation

10.3: Radical Hydrobromination of Alkenes - HBr with peroxides

10.4: Preparing Alkyl Halides from Alkenes - Allylic Bromination

10.5: Stability of the Allyl Radical - Resonance Revisited

10.6: Preparing Alkyl Halides from Alcohols

10.7: Reactions of Alkyl Halides - Grignard Reagents

10.8: Organometallic Coupling Reactions

10.9: Oxidation and Reduction in Organic Chemistry

10.10: Chemistry Matters—Naturally Occurring Organohalides

10.A: Organohalides (Summary)

10.B: Additional Problems

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10.0: Why This Chapter?

Alkyl halides are encountered less frequently than their oxygen-containing relatives and are not often involved in the biochemical pathways of terrestrial organisms, but some of the kinds of reactions they undergo—nucleophilic substitutions and eliminations—are encountered frequently. Thus, alkyl halide chemistry is a relatively simple model for many mechanistically similar but structurally more complex reactions found in biomolecules. We'll begin this chapter with a look at how to name and prepare alkyl halides, and we'll see several of their reactions. Then, in the next chapter, we'll make a detailed study of the substitution and elimination reactions of alkyl halides—two of the most important and well-studied reaction types in organic chemistry.



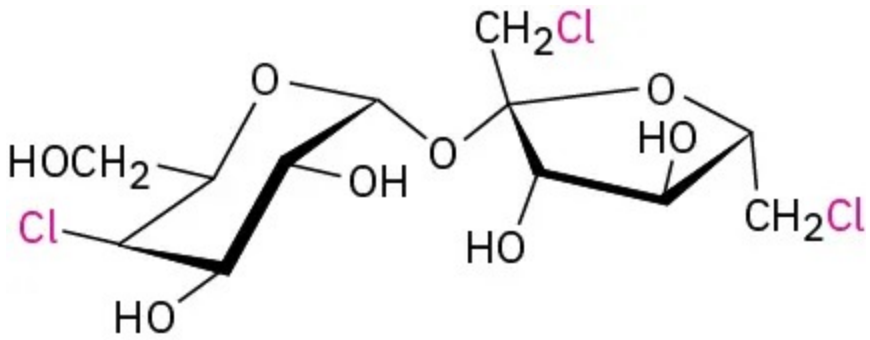
Figure 10.0.1: The gases released during volcanic eruptions contain large amounts of organohalides, including chloromethane, chloroform, dichlorodifluoromethane, and many others. (credit: "Tavurvur volcano" by Taro Taylor, Richard Bartz/Wikimedia Commons, CC BY 2.0)

Now that we've covered the chemistry of hydrocarbons, it's time to start looking at more complex substances that contain elements in addition to C and H. We'll begin by discussing the chemistry of organohalides, compounds that contain one or more halogen atoms.

Halogen-substituted organic compounds are widespread in nature, and more than 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for instance, is released in large amounts by ocean kelp, as well as by forest fires and volcanoes. Halogen-containing compounds also have an array of industrial applications, including their use as solvents, inhaled anesthetics in medicine, refrigerants, and pesticides.



Still other halo-substituted compounds are used as medicines and food additives. The nonnutritive sweetener sucralose, marketed as Splenda, contains three chlorine atoms, for instance. Sucralose is about 600 times as sweet as sucrose, so only 1 mg is equivalent to an entire teaspoon of table sugar.



Sucralose

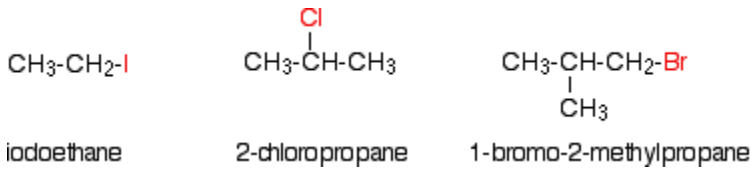
A large variety of organohalides are known. The halogen might be bonded to an alkynyl group ($\mathrm{C{\equiv}C{-}X}$), a vinylic group ($\mathrm{C{=}C{-}X}$), an aromatic ring (Ar–X), or an alkyl group. In this chapter, however, we'll be primarily concerned with alkyl halides, compounds with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

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10.1: Names and Properties of Alkyl Halides

Alkyl halides are also known as haloalkanes. This page explains what they are and discusses their physical properties. Alkyl halides are compounds in which one or more hydrogen atoms in an alkane have been replaced by halogen atoms (fluorine, chlorine, bromine, or iodine). For example:

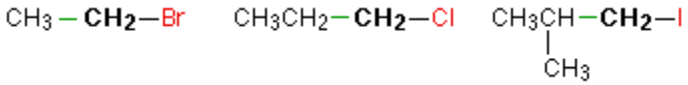


Halide Designations

Alkyl halides fall into different classes depending on how many alkyl groups are attached to the carbon that holds the halogen. There are some chemical differences between the various types. When there are **no** alkyl groups attached to the carbon holding the halogen, these are considered methyl halides (CH_3X).

Primary alkyl halides

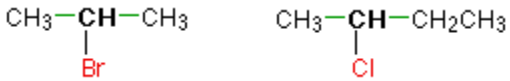
In a primary (1°) haloalkane, the carbon that carries the halogen atom is only attached to one other alkyl group. Some examples of primary alkyl halides include:



Notice that it doesn't matter how complicated the attached alkyl group is. In each case, there is only one linkage to an alkyl group from the CH_2 group holding the halogen. There is an exception to this: CH_3Br and the other methyl halides are often counted as primary alkyl halides even though there are **no** alkyl groups attached to the carbon with the halogen on it.

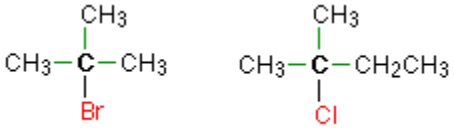
Secondary alkyl halides

In a secondary (2°) haloalkane, the carbon with the halogen attached is joined directly to two other alkyl groups, which may be the same or different. Examples:



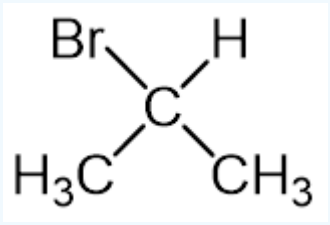
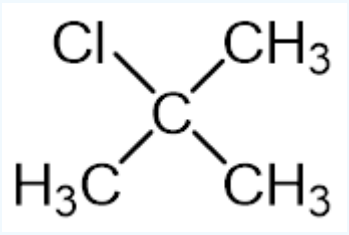
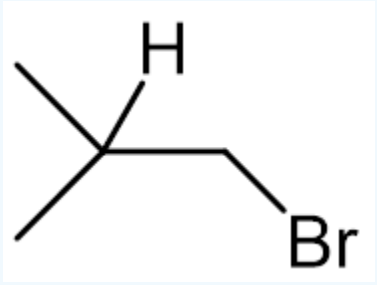
Tertiary alkyl halides

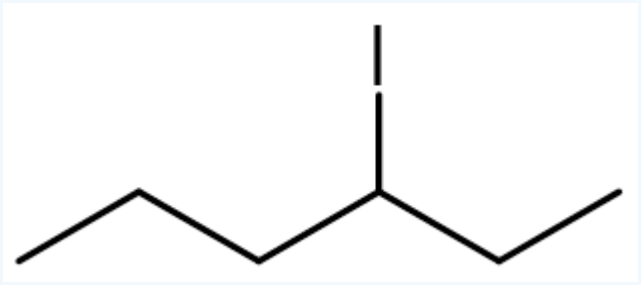
In a tertiary (3°) haloalkane, the carbon atom holding the halogen is attached directly to three alkyl groups, which may be any combination of the same or different. Examples:



Example 10.1.1

Please indicate if the following haloalkanes are methyl, 1^o, 2^o, or 3^o:

a) CH_3I b) CH_3CH_2Br c)  d)  e) 

f) 

Solution

a) methyl. b) 1^o c) 2^o d) 3^o e) 1^o f) 2^o

Nomenclature of Alkyl Halides

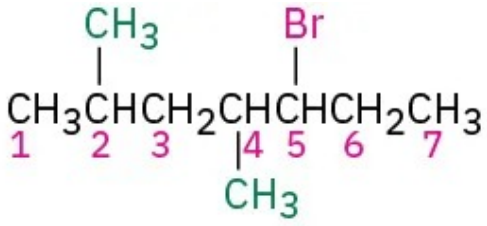
Although commonly called *alkyl halides*, halogen-substituted alkanes are named systematically as *haloalkanes* (Section 3.5), treating the halogen as a substituent on a parent alkane chain. There are three steps:

STEP 1

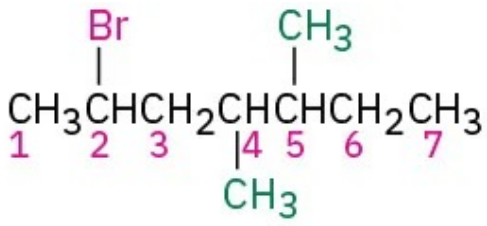
Find the longest chain, and name it as the parent. If a double or triple bond or alcohol group is present, the parent chain must contain it.

STEP 2

Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo. Assign each substituent a number according to its position on the chain. Number the parent chain consecutively, starting at the end nearest a substituent group. Then assign each substituent a number. Remember the IUPAC system uses a prefix to indicate the halogen followed by the suffix -ide. The prefixes are *fluoro-* for fluorine, *chloro-* for chlorine, *bromo-* from bromine, and *iodo-* for iodine. The name of a halogen is preceded by a number indicating the substituent's location on the parent chain.

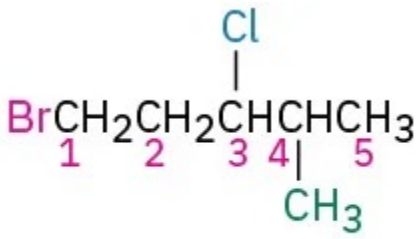


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

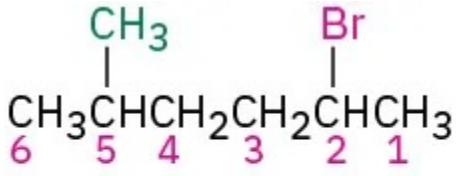
If different halogens are present, number each one and list them in alphabetical order when writing the name.



1-Bromo-3-chloro-4-methylpentane

STEP 3

If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.



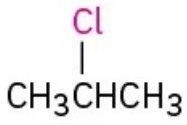
2-Bromo-5-methylhexane
(*Not* 5-bromo-2-methylhexane)

Common Names of Alkyl Halides

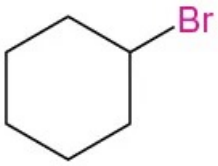
In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. Alkyl halides with simple alkyl groups are often called by common names. Those with a larger number of carbon atoms are usually given IUPAC names. The *common names* of alkyl halides consist of two parts: the name of the alkyl group plus the first syllable of the name of the halogen, with the ending *-ide*. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.



Iodomethane
(or methyl iodide)



2-Chloropropane
(or isopropyl chloride)



Bromocyclohexane
(or cyclohexyl bromide)

Halogens and the Character of the Carbon-Halogen Bond

There is a fairly large distinction between the structural and physical properties of haloalkanes and the structural and physical properties of alkanes. As mentioned above, the structural differences are due to the replacement of one or more hydrogens with a

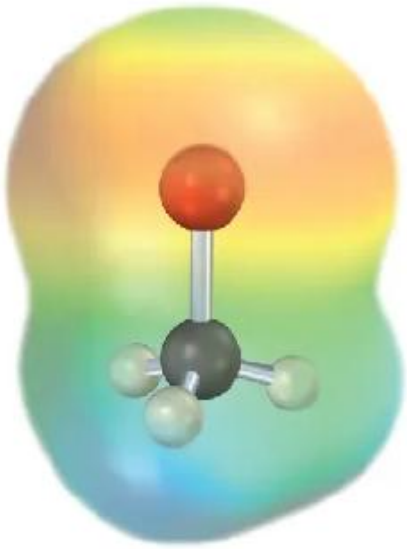
halogen atom. The differences in physical properties are a result of factors such as electronegativity, bond length, bond strength, and molecular size.

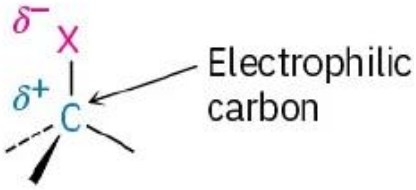
Halogens increase in size going down the periodic table, so the lengths of the corresponding carbon–halogen bonds increase accordingly (Table 10.1.1). In addition, C–X bond strengths decrease going down the periodic table. As we've been doing thus far, we'll continue using an X to represent any of the halogens F, Cl, Br, or I.

Table 10.1.1: A Comparison of the Halomethanes

Halomethane	Bond length (pm)	Bond strength		Dipole moment (*D*)
		(kJ/mol)	(kcal/mol)	
CH_3F	139	460	110	1.85
CH_3Cl	178	350	84	1.87
CH_3Br	193	294	70	1.81
CH_3I	214	239	57	1.62

In our discussion of bond polarity in functional groups in Section 6.4, we noted that halogens are more electronegative than carbon. The C–X bond is therefore polar, with the carbon atom bearing a slight positive charge ($\delta+$) and the halogen a slight negative charge ($\delta-$). This polarity results in a dipole moment for all the halomethanes (Table 10.1) and implies that the alkyl halide C–X carbon atom should behave as an electrophile in polar reactions. We'll soon see that this is indeed the case.





The following image shows the relationship between the halogens and electronegativity. Notice, as we move up the periodic table from iodine to fluorine, electronegativity increases.

Electronegativity increases from left to right starting from iodine then bromine to chlorine and finally fluorine.

The following image shows the relationships between bond length, bond strength, and molecular size. As we progress down the periodic table from fluorine to iodine, molecular size increases. As a result, we also see an increase in bond length. Conversely, as molecular size increases, the bonds get longer, and the strength of those bonds decreases.

Bond length increases from left to right starting from C-F then C-Cl to C-Br and finall C-I. Bond strength increases from left to right starting with C-I then C-Br to C-Cl and finall C-F. Molecular size increases from right to left starting with fluorine then chlorine to bromine and finally iodine.

Chemical Reactivity

The pattern in chemical reactivity lies in the strength of the bond between the carbon atom and the halogen atom. Previously in this section, it was noted that the trend for bond strength increases from C-I to C-Br to C-Cl with C-F bonds being the strongest. To react with the alkyl halides, the carbon-halogen bond has got to be broken. Because that gets easier as you go from fluoride to chloride to bromide to iodide, the compounds get more reactive in that order. Iodoalkanes are the most reactive, and fluoroalkanes are the least. In fact, fluoroalkanes are so unreactive that we will ignore them completely from now on in this section!

Haloalkanes Have Higher Boiling Points than Alkanes

When comparing alkanes and haloalkanes, we will see that haloalkanes have higher boiling points than alkanes containing the same number of carbons. London dispersion forces are the first of two types of forces that contribute to this physical property. You might recall from general chemistry that London dispersion forces increase with molecular surface area. In comparing haloalkanes with alkanes, haloalkanes exhibit an increase in surface area due to the substitution of a halogen for hydrogen. The increase in surface area leads to an increase in London dispersion forces, which then results in a higher boiling point.

Dipole-dipole interaction is the second type of force that contributes to a higher boiling point. As you may recall, this type of interaction is a coulombic attraction between the partial positive and partial negative charges that exist between carbon-halogen bonds on separate haloalkane molecules. Similar to London dispersion forces, dipole-dipole interactions establish a higher boiling point for haloalkanes in comparison to alkanes with the same number of carbons.

Dipole-Dipole interaction between two carbon-halogens. The partially positive carbon attracts the partially negative halogen of a different molecule.

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 increases with both the size of the halogen and the length of the carbon chain.

The boiling points of haloalkanes

Solubility

Solubility in water

The alkyl halides are at best only slightly soluble in water. For a haloalkane to dissolve in water the attractions between the haloalkane molecules (van der Waals dispersion and dipole-dipole interactions) and hydrogen bonds between water molecules must be broken. Both of these cost energy. Energy is released when new intermolecular forces are generated between the haloalkane molecules and water molecules. These will only be dispersion forces and dipole-dipole interactions. These are not as strong as the original hydrogen bonds in the water, and so not as much energy is released as was used to separate the water molecules. The energetics of the changes are sufficiently "unprofitable" such that very little dissolves.

Solubility in organic solvents

Alkyl halides tend to dissolve in organic solvents because the new intermolecular attractions have roughly the same strength as the ones being broken in the separate haloalkane and solvent.

Exercises

Exercise 10.1.1

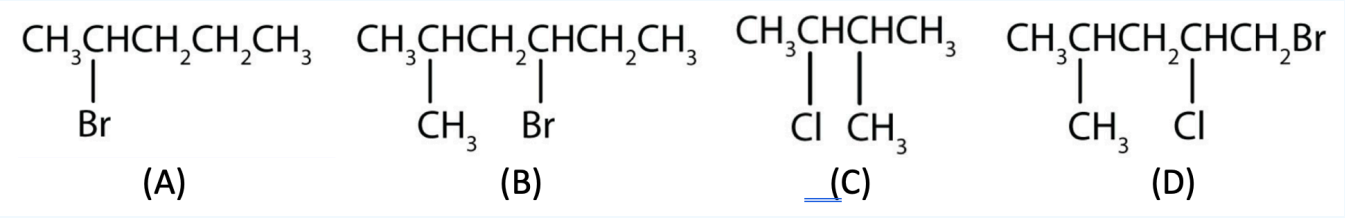
Give the common and IUPAC names for each compound.

a- $CH_3CH_2CH_2Br$ b- $(CH_3)_2CHCl$ c- CH_3CH_2I d- $CH_3CH_2CH_2CH_2F$

Answer available at the end of this section.

Exercise 10.1.2

Give the IUPAC name for each compound.



Answer available at the end of this section.

Exercise 10.1.3

Give IUPAC names for the following alkyl halides:

a. $CH_3CH_2CH_2CH_2I$

b. $CH_3CHCH_2CH_2Cl$ (with CH_3 substituent)

c. $CH_3CHCHCH_2CH_3$ (with I and CH_2CH_2Cl substituents)

d. $CH_3CCH_2CH_2Cl$ (with CH_3 and Cl substituents)

e. $BrCH_2CH_2CH_2CCH_2Br$ (with CH_3 substituent)

f. $CH_3CHCH_2CH_2CHCH_3$ (with Br and Cl substituents)

Answer available at the end of this section.

Exercise 10.1.4

Draw structures corresponding to the following IUPAC names:

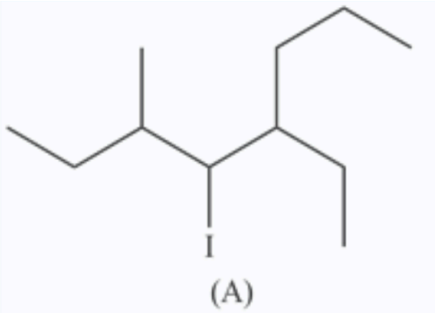
a- 2-Chloro-3,3-dimethylhexane b- 3,3-Dichloro-2-methylhexane c- 3-Bromo-3-ethylpentane

d- 1,1-Dibromo-4-isopropylcyclohexane e- 4-*sec*-Butyl-2-chlorononane f- 1,1-Dibromo-4-*tert*-butylcyclohexane

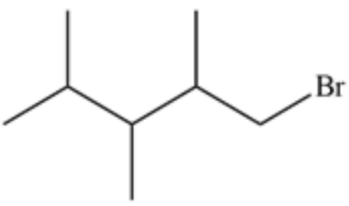
Answer available at the end of this section.

Exercise 10.1.5

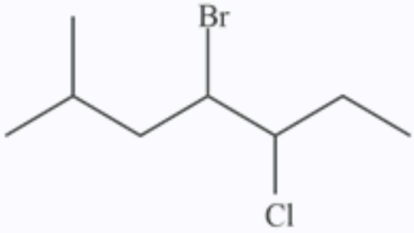
Give the names of the following organohalides:



(A)



(B)



(C)

Answer available at the end of this section.

Exercise 10.1.6

Draw the structures of the following compounds:

a) 2-Chloro-3,3-dimethylpentane b) 1,1-Dichloro-4-isopropylcyclohexane c) 3-bromo-3-ethylhexane

Answer available at the end of this section.

Answers

Exercise 10.1.1

a) The alkyl group ($CH_3CH_2CH_2$–) is a propyl group, and the halogen is bromine (Br). The common name is therefore propyl bromide. For the IUPAC name, the prefix for bromine (bromo) is combined with the name for a three-carbon chain (propane), preceded by a number identifying the carbon atom to which the Br atom is attached, so the IUPAC name is 1-bromopropane.

b) The alkyl group [$(CH_3)_2CH$–] has three carbon atoms, with a chlorine (Cl) atom attached to the middle carbon atom. The alkyl group is therefore isopropyl, and the common name of the compound is isopropyl chloride. For the IUPAC name, the Cl atom (prefix *chloro*-) attached to the middle (second) carbon atom of a propane chain results in 2-chloropropane.

c) The alkyl group (CH_3CH_2–) is an ethyl group, and the halogen is iodine (I). The common name is therefore ethyl iodide. For the IUPAC name, the prefix for iodine (iodo) is combined with the name for a two-carbon chain (ethane), preceded by a number identifying the carbon atom to which the I atom is attached, so the IUPAC name is 1-iodoethane.

d) The alkyl group ($CH_3CH_2CH_2CH_2$–) is a butyl group, and the halogen is fluorine (F). The common name is therefore butyl fluoride. For the IUPAC name, the prefix for fluorine (Fluoro) is combined with the name for a four-carbon chain (butane), preceded by a number identifying the carbon atom to which the F atom is attached, so the IUPAC name is 1-fluorobutane.

Exercise 10.1.2

a) The parent alkane has five carbon atoms in the longest continuous chain; it is pentane. A bromo (Br) group is attached to the second carbon atom of the chain. The IUPAC name is 2-bromopentane.

b) The parent alkane is hexane. Methyl (CH_3) and bromo (Br) groups are attached to the second and fourth carbon atoms, respectively. Listing the substituents in alphabetical order gives the name 4-bromo-2-methylhexane.

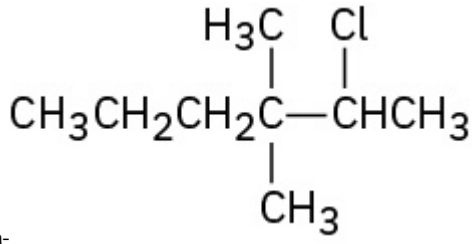
c) 2-Chloro-3-methylbutane. d) 1-Bromo-2-chloro-4-methylpentane.

Exercise 10.1.3

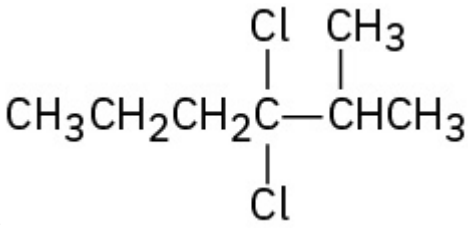
a. 1-Iodobutane. b. 1-Chloro-3-methylbutane. c. 1-Chloro-3-ethyl-4-iodopentane.

d. 1,3-Dichloro-3-methylbutane. e. 1,5-Dibromo-2,2-dimethylpentane. f. 2-Bromo-5-chlorohexane.

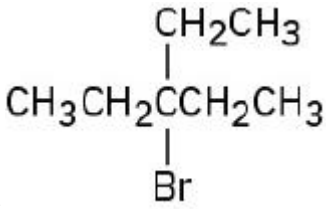
Exercise 10.1.4



a-

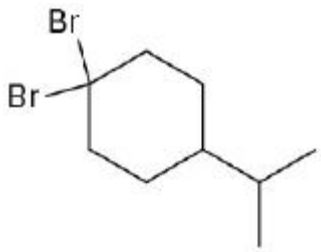


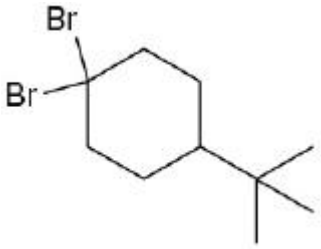
b-



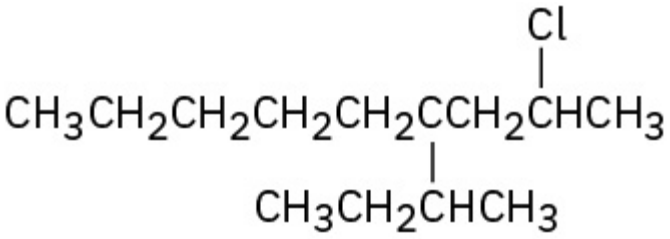
c-

d-





e-



f-

Exercise 10.1.5

a) 5-ethyl-4-iodo-3-methyloctane b) 1-bromo-2,3,4-trimethylpentane c) 4-bromo-5-chloro-2-methylheptane

Exercise 10.1.6

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10.2: Preparing Alkyl Halides from Alkanes - Radical Halogenation

Objectives

After completing this section, you should be able to

1. explain why the radical halogenation of alkanes is not usually a particularly good method of preparing pure samples of alkyl halides.
2. use C — H bond energies to account for the fact that in radical chlorinations, the reactivity of hydrogen atoms decreases in the order

$$\text{tertiary} > \text{secondary} > \text{primary}.$$

3. predict the approximate ratio of the expected products from the monochlorination of a given alkane.

Radical Halogenation

Alkanes (the simplest of all organic compounds) undergo very few reactions. One of these reactions is halogenation, or the substitution of a single hydrogen on the alkane for a single halogen (Cl_2 or Br_2) to form a haloalkane. This reaction is very important in organic chemistry because it functionalizes alkanes which opens a gateway to further chemical reactions.

General Reaction

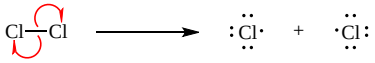
$$CH_4 + Cl_2 + energy \rightarrow CH_3Cl + HCl$$

Radical Chain Mechanism

The reaction proceeds through the radical chain mechanism which is characterized by three steps: **initiation**, **propagation,** and **termination**. Initiation requires an input of energy but after that the reaction is self-sustaining.

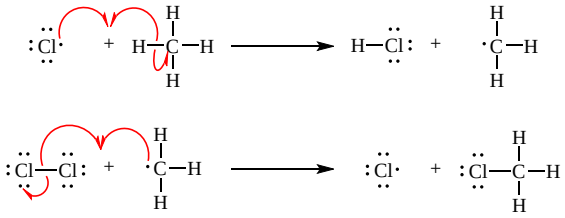
Step 1: Initiation

During the initiation step free radicals are created when ultraviolet light or heat causes the X-X halogen bond to undergo homolytic to create two halogen free radicals. It is important to note that this step is not energetically favorable and cannot occur without some external energy input. After this step, the reaction can occur continuously (as long as reactants provide) without input of more energy.



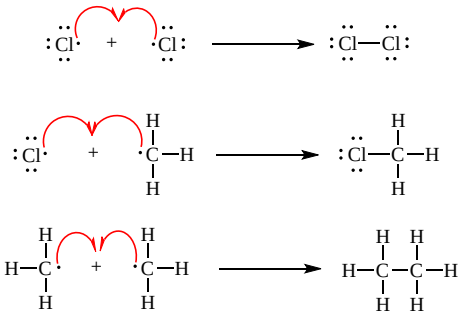
Step 2: Propagation

The next two steps in the mechanism are called propagation steps. In the first propagation step, a chlorine radical abstracts hydrogen atom from methane. This gives hydrochloric acid (HCl, the inorganic product of this reaction) and the methyl radical. In the second propagation step, the methyl radical reacts with more of the chlorine starting material (Cl_2). One of the chlorine atoms becomes a radical and the other combines with the methyl radical to form the alkyl halide product.

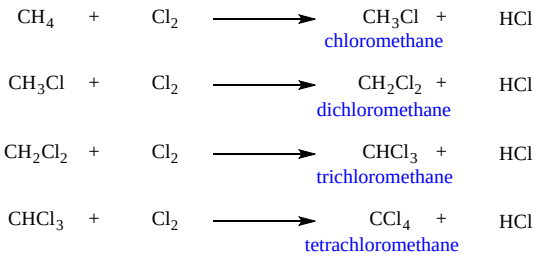


Step 3: Termination

In the three termination steps of this mechanism, radicals produced in the mechanism an undergo radical coupling to form a sigma bond. These are called termination steps because a free radical is not produced as a product, which prevents the reaction from continuing. Combining the two types of radicals produced can be combined to from three possible products. Two chlorine radicals and couple to form more halogen reactant (Cl_2). A chlorine radical and a methyl radical can couple to form more product (CH_3Cl). And finally, two methyl radicals can couple to form a side product of ethane (CH_3CH_3).



This reaction is a poor synthetic method due to the formation of polyhalogenated side products. The desired product occurs when one of the hydrogen atoms in the methane has been replaced by a chlorine atom. However, the reaction doesn't stop there, and all the hydrogens in the methane can in turn be replaced by chlorine atoms to produce a mixture of chloromethane, dichloromethane, trichloromethane and tetrachloromethane.

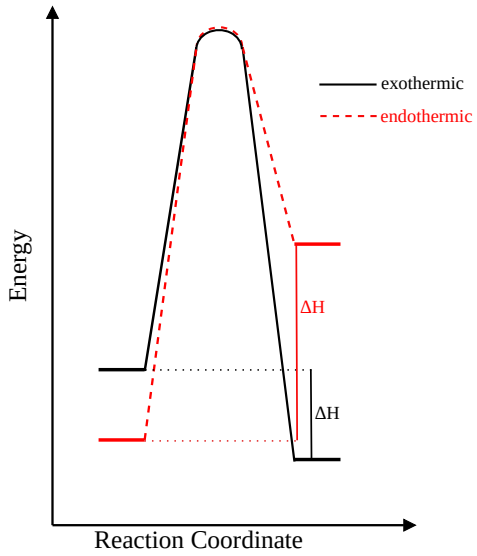


Energetics

Why do these reactions occur? Is the reaction favorable? A way to answer these questions is to look at the change in enthalpy ΔH that occurs when the reaction takes place.

$$\Delta H = (\text{Energy put into reaction}) - (\text{Energy given off from reaction})$$

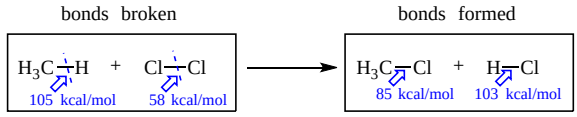
If more energy is put into a reaction than is given off, the ΔH is positive, the reaction is endothermic and not energetically favorable. If more energy is given off in the reaction than was put in, the ΔH is negative, the reaction is said to be exothermic and is considered favorable. The figure below illustrates the difference between endothermic and exothermic reactions.



ΔH can also be calculated using bond dissociation energies (ΔH°):

$$\Delta H = \sum \Delta H^\circ \text{ of bonds broken} - \sum \Delta H^\circ \text{ of bonds formed}$$

Let's look at our specific example of the chlorination of methane to determine if it is endothermic or exothermic:

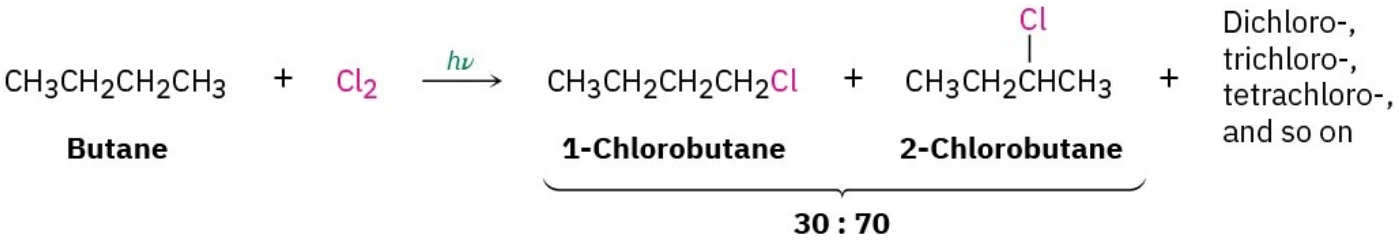


change in enthalpy = (105 kcal/mol + 58 kcal/mol) − (85 kcal/mol + 103 kcal/mol)
= −25 kcal/mol

Since the ΔH for the chlorination of methane is negative, the reaction is exothermic. Energetically, this reaction is favorable. In order to better understand this reaction, we need to look at the mechanism (a detailed step-by-step look at the reaction showing how it occurs) by which the reaction occurs.

Chlorination of Other Alkanes

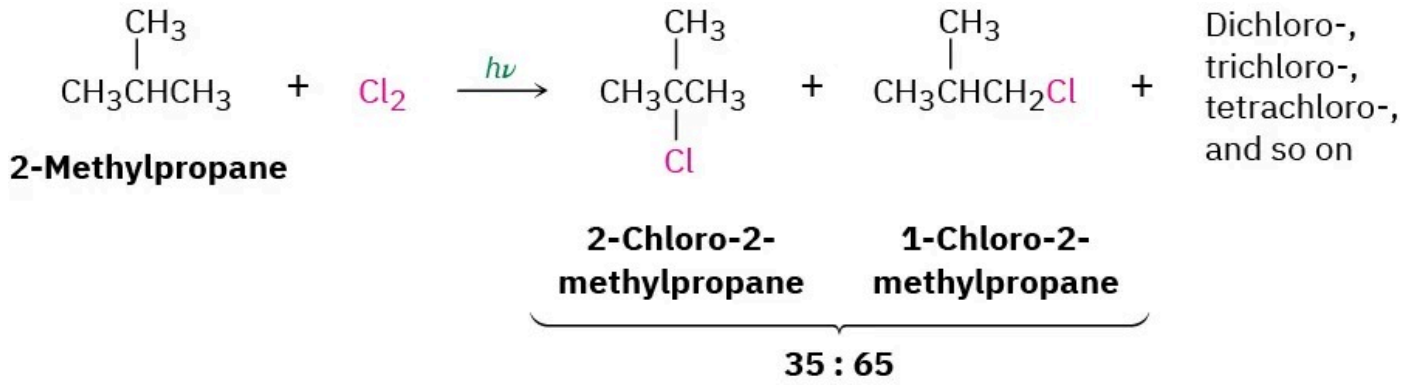
When alkanes larger than ethane are halogenated, isomeric products are formed. The halogenation of larger alkanes discloses an interesting feature of these reactions. **All the hydrogens in a complex alkane do not exhibit equal reactivity**. Chlorination of butane, for instance, gives two monochlorinated products in a 30 : 70 ratio in addition to multiply chlorinated products such as dichlorobutane, trichlorobutane, and so on.



As a second example, propane has eight hydrogens, six of them being structurally equivalent **primary**, and the other two being **secondary**. If all these hydrogen atoms were equally reactive, halogenation should give a 3:1 ratio of 1-halopropane to 2-halopropane mono-halogenated products, reflecting the primary/secondary numbers. This is not what we observe. Light-induced gas phase chlorination at 25 °C gives 45% 1-chloropropane and 55% 2-chloropropane.

$$CH_3\text{-}CH_2\text{-}CH_3 + Cl_2 \rightarrow CH_3\text{-}CH_2\text{-}CH_2Cl\ (45\%) + CH_3\text{-}CHCl\text{-}CH_3\ (55\%)$$

As another example, 2-methylpropane yields 2-chloro-2-methylpropane and 1-chloro-2-methylpropane in a 35 : 65 ratio, along with more highly chlorinated products.

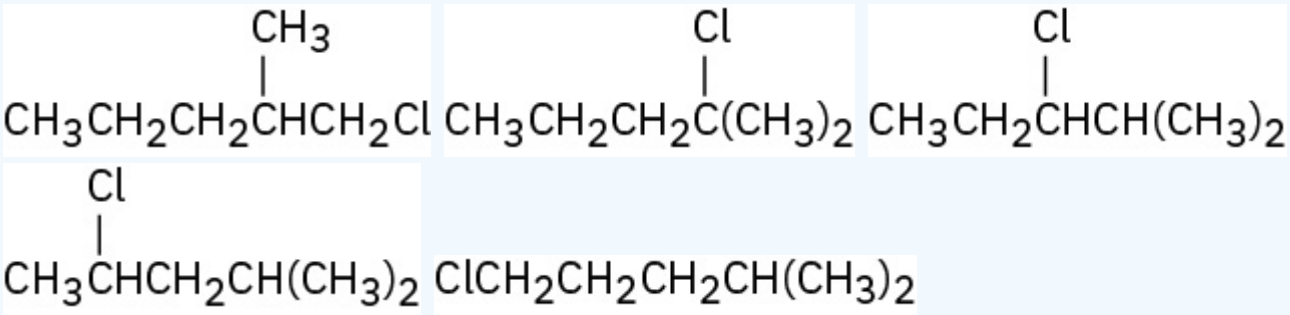


Example 10.2.1

Draw and name all monochloro products you would expect to obtain from radical chlorination of 2-methylpentane. Which, if any, are chiral?

Solution

Chiral: 1-chloro-2-methylpentane, 3-chloro-2-methylpentane, 2-chloro-4-methylpentane **Achiral:** 2-chloro-2-methylpentane, 1-chloro-4-methylpentane

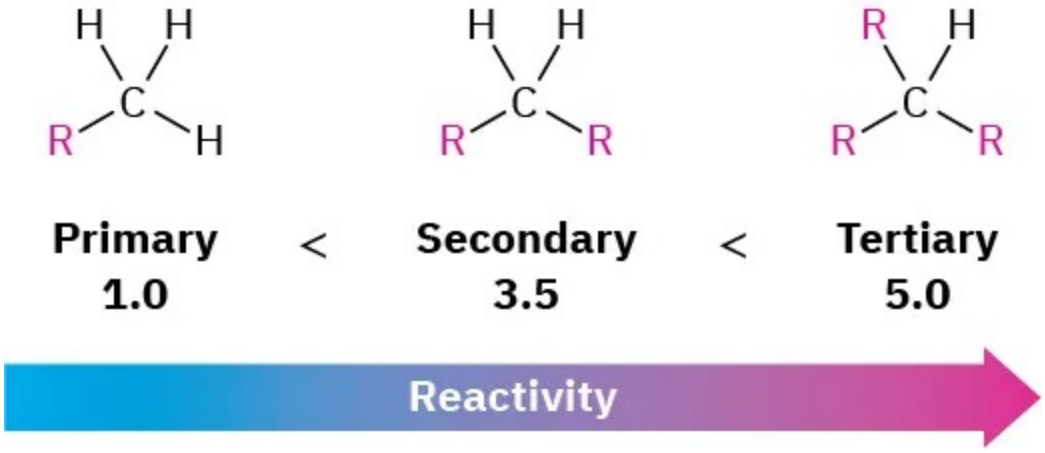


Reactivity

From these and similar reactions, it's possible to calculate a reactivity order toward chlorination for different kinds of hydrogen atoms in a molecule.

Take the butane chlorination, for instance. Butane has six equivalent primary hydrogens ($-CH_3$) and four equivalent secondary hydrogens ($-CH_2-$). The fact that butane yields 30% of 1-chlorobutane product means that each one of the six primary hydrogens is responsible for 30% ÷ 6 = 5% of the product. Similarly, the fact that 70% of 2-chlorobutane is formed means that each of the four secondary hydrogens is responsible for 70% ÷ 4 = 17.5% of the product. Thus, a secondary hydrogen reacts 17.5% ÷ 5% = 3.5 times as often as a primary hydrogen.

A similar calculation for the chlorination of 2-methylpropane indicates that each of the nine primary hydrogens accounts for 65% ÷ 9 = 7.2% of the product, while the single tertiary hydrogen (R_3CH) accounts for 35% of the product. Thus, a tertiary hydrogen is 35% ÷ 7.2% = 5 times as reactive as a primary hydrogen toward chlorination.

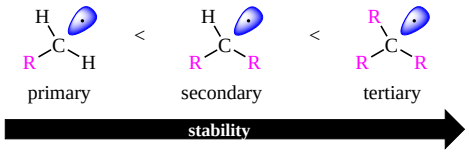


The Relative Reactivity of Hydrogens to Radical Chlorination

This difference in reactivity can only be attributed to differences in C-H bond dissociation energies. In our previous discussion of bond energy we assumed average values for all bonds of a given kind, but now we see that this is not strictly true. In the case of carbon-hydrogen bonds, there are significant differences, and the specific dissociation energies (energy required to break a bond homolytically) for various kinds of C-H bonds have been measured. These values are given in the following table.

R (in R–H)	methyl	ethyl	i-propyl	t-butyl
Bond Dissociation Energy (kcal/mole)	103	98	95	93

This data shows that a tertiary C-H bond (93 kcal/mole) is easier to break than a secondary (95 kcal/mole) and primary (98 kcal/mole) C-H bond. These bond dissociation energies can be used to estimate the relative stability of the radicals formed after homolytic cleavage. Because a tertiary C-H bond requires less energy to undergo homolytic cleavage than a secondary or primary C-H bond, it can be inferred that a tertiary radical is more stable than secondary or primary.



Relative Stability of Free Radicals

Exercises

Exercise 10.2.1

Write out the complete mechanism for the chlorination of methane.

Answer available at the end of this section.

Exercise 10.2.2

Explain, in your own words, how the first propagation step can occur without input of energy if it is energetically unfavorable.

Answer available at the end of this section.

Exercise 10.2.3

Which step of the radical chain mechanism requires outside energy? What can be used as this energy?

Answer available at the end of this section.

Exercise 10.2.4

Having learned how to calculate the change in enthalpy for the chlorination of methane apply your knowledge and using the table provided below calculate the change in enthalpy for the bromination of ethane.

Compound	Bond Dissociation Energy (kcal/mol)
CH_3CH_2-H	101
CH_3CH_2-Br	70
H-Br	87
Br_2	46

Answer available at the end of this section.

Exercise 10.2.5

Radical chlorination of alkanes is not useful due to uncontrolled substitution. Draw the mono-substituted products of Cl_2 reacting with 2-methylbutane.

Answer available at the end of this section.

Exercise 10.2.6

Taking the relative reactivities of primary, secondary, and tertiary hydrogen atoms into account:

a. What product/s would you expect to obtain from monochlorination of 3-ethylpentane?
b. What would the approximate percentage of each product be? (don't forget to take into account the number of each kind of hydrogen)

Answer available at the end of this section.

Exercise 10.2.7

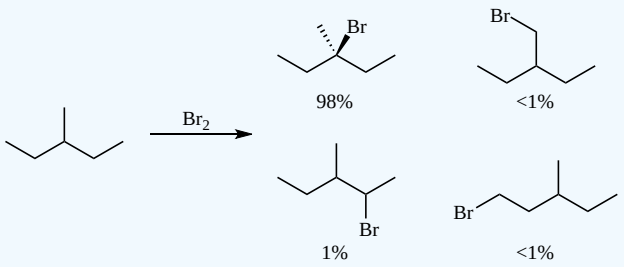
Predict the mono-substituted halogenated product(s) of chlorine gas reacting with 2-methylbutane.

Answer available at the end of this section.

Example 10.2.8

Predict the relative amount of each mono-brominated product when 3-methylpentane is reacted with Br_2. Consider 1°, 2°, 3° hydrogen.

Solution



Exercise 10.2.9

For the following compounds, give all possible monochlorinated derivatives.

a) 

b) 

c) 

d) 

e) 

f) 

Answer available at the end of this section.

Answers

Exercise 10.2.1

The answer to this problem is actually above in the initiation, propagation, and termination descriptions.

Exercise 10.2.2

Since the second step in propagation is energetically favorable and fast, it drives the equilibrium toward products, even though the first step is not favorable.

Exercise 10.2.3

The initiation step requires energy, which can be in the form of light or heat.

Exercise 10.2.4

To calculate the enthalpy of reaction, you subtract the BDE of the bonds formed from the BDE of the bonds broken.

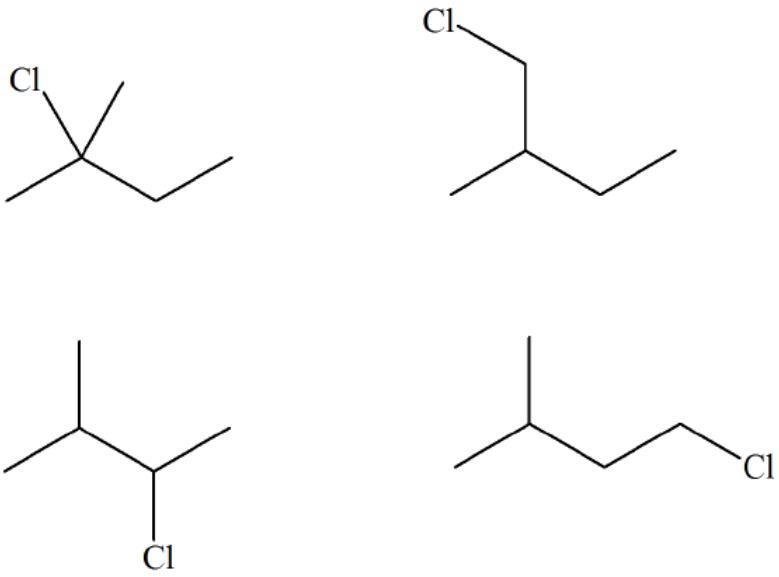
Bonds broken - bonds formed = change in enthalpy

Bonds broken are C-H and Br-Br - Bonds formed are H-Br and C-Br.

(101 kcal/mol + 46 kcal/mol) - (87 kcal/mol + 70 kcal/mol) = change in enthalpy

-10 kcal/mol = change in enthalpy for bromination of ethane.

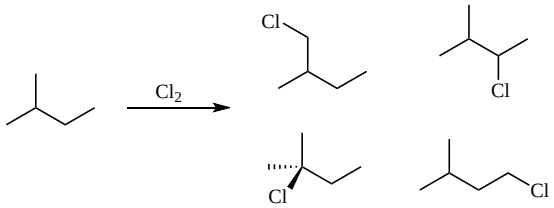
Exercise 10.2.5



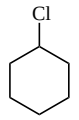
Exercise 10.2.6

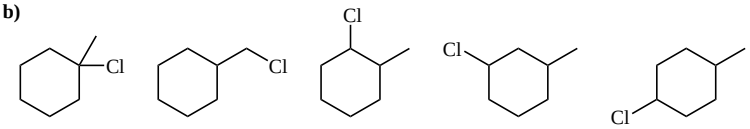
1-chloro-3-ethylpentane (24%), 2-chloro-3-ethylpentane (63%), 3-chloro-3-ethylpentane (13%)

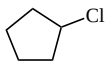
Exercise 10.2.7

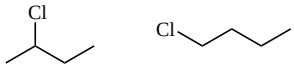


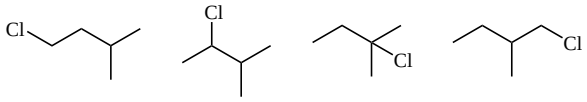
Exercise 10.2.9

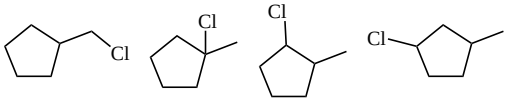
a) 

b) 

c) 

d) 

e) 

f) 

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10.3: Radical Hydrobromination of Alkenes - HBr with peroxides

Objectives

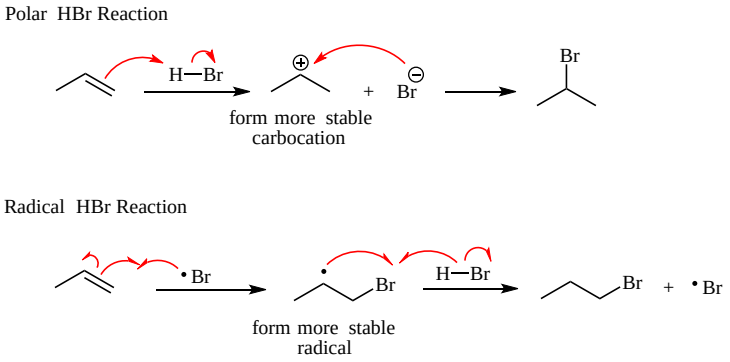
After completing this section, you should be able to

1. write the reaction for the bromination of an alkene using HBr in the presence of peroxides.
2. Predict the product formed when a given alkene is treated with HBr and peroxides.
3. Identify the starting alkene needed to produce a given bromide by radical alkene bromination.

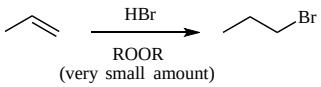
In Chapter 8, we learned about the electrophilic (polar) addition of HX to alkenes. The mechanism for these reactions proceeds via the most stable carbocation and results in X^- adding to the more substituted side of the starting alkene. In this section, we will see that it is possible to reverse that regiochemistry and directly synthesize the less substituted bromide by using peroxide in a radical mechanism.

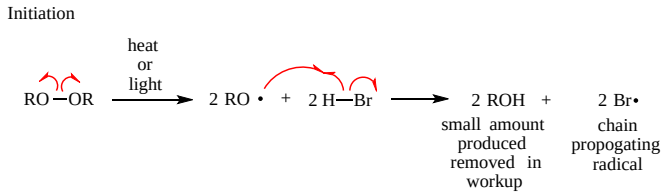
Radical Alkene Bromination

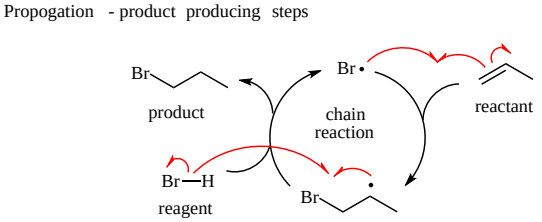
Due to HBr's unique reactivity, it can participate in a radical reaction, yielding the opposite regiochemistry. In this reaction, the Br radical adds to the alkene to generate the most stable radical (most highly substituted). The final product is synthesized upon reaction with HBr, which also regenerates the chain-propagating Br radical.



The complete mechanism with HBr is shown below. The key difference in conditions between this reaction and the polar HBr reaction is the presence of peroxides that initiate the radical chain process. The peroxide is often written as ROOR to indicate that any peroxide can serve as the initiator. So, you might see MeOOMe, $(tBuO)_2$, MeOOtBu, or another similar reagent when doing these types of problems. As always, the initiator is present at very low levels, typically around 1 mol%.







This radical reaction is only possible with HBr. HCl and HI have different bond energies that are not able to support the reaction rates required for a radical chain process.

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10.4: Preparing Alkyl Halides from Alkenes - Allylic Bromination

Objectives

After completing this section, you should be able to

1. write the equation for the bromination of a symmetrical alkene using N-bromosuccinimide.
2. predict the product formed when a given symmetrical alkene is treated with N-bromosuccinimide.
3. identify the reagent, the symmetrical alkene, or both, needed to produce a given allyl halide by allylic bromination.
4. list the following radicals in order of increasing or decreasing stability: allyl, vinyl, primary alkyl, secondary alkyl, tertiary alkyl, methyl.
5. explain the ease of forming an allyl radical, and the difficulty of forming a vinyl radical, in terms of relative $\ce{\sf{C–H}}$ bond dissociation energies.

Key Terms

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

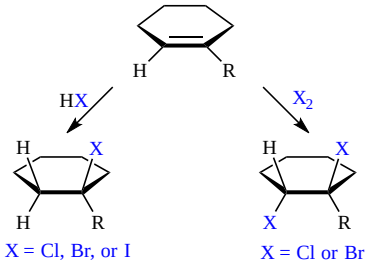
- allylic carbon

Study Notes

We have discussed the electrophilic addition of X_2 and HX to alkenes as a route to forming alkyl halides (Sections 7.8 and 8.2). In this section we introduce bromination at the allyic position with N-bromosuccinimide (NBS). Notice that at the moment we are restricting our studies to the allylic bromination of symmetrical alkenes, such as cyclohexene. When we introduce an element of asymmetry, we find that more than one allyl radical can be formed; therefore, we must assess the relative stability of each radical when trying to predict which product will predominate. The method of doing this assessment is described in the next section.

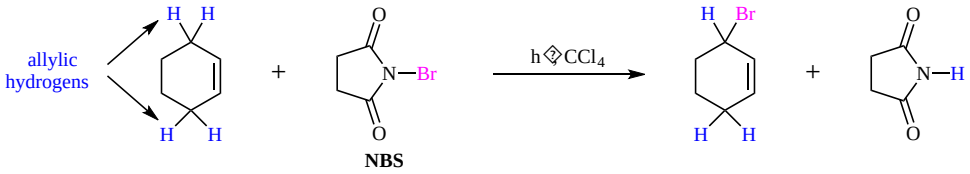
Allylic Bromination

Previously, alkyl halides have been produced though reactions with alkenes. Hydrogen halides (HCl, HBr, and HI) react with alkenes in an electrophilic addition reaction discussed in **Section 7-8** to yield alkyl halides as products. Also, Bromine (Br_2) and chlorine (Cl_2) can react with alkenes to provide dihalogenated products as discussed in **Section 8-2**.



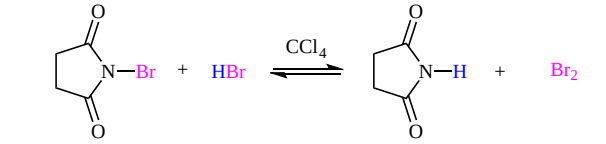
Another method for preparing alkyl halides from alkenes is with **N-bromosuccinimide (NBS)** in carbon tetrachloride (CCl_4) solution with the presence of light. The reaction specifically causes the substitution of bromine with a hydrogen attached to a carbon adjacent to the double bond - the allylic position.

General Reaction

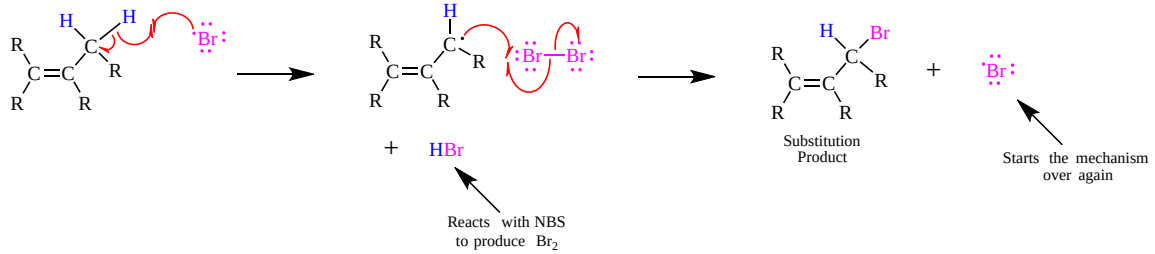


Mechanism

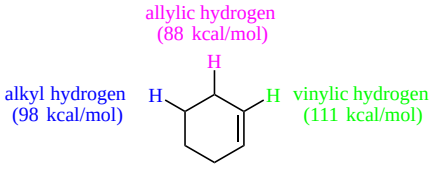
The allylic bromination with NBS is analagous to the alkane halogenation reaction (Section 10.2) since it also occurs as a radical chain reaction. NBS is the most commonly used reagent to produce low concentrations of bromine. When suspended in tetrachloride (CCl_4), NBS reacts very rapidly with the HBr formed during the reaction mechanism to provide bromine (Br_2) which is required for the reaction to continue. Under the correct conditions, NBS provides a constant but very low concentration of Br_2 in the reaction mixture. The low concentration of Br_2 helps to prevent the formation of unwanted side-products.



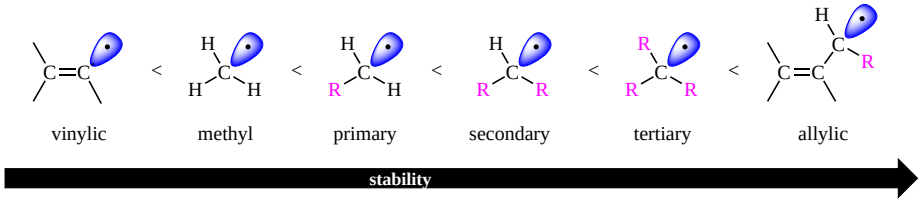
The mechanism starts with the formation of a small amount of bromine radical which then abstracts an allylic hydrogen to form an allylic radical and HBr. The HBr can then react with NBS to form the Br_2 required for the reaction. The allylic radical then abstracts a bromine atom from Br_2 to form the allyl halide product and a bromine radical. The bromine radical produced allows the reaction to continue.



The predominance of allylic substitution over other positions is based on bond dissociation energies. An allylic C-H bond has a strength of about 88 kcal/mol which is much weaker than a typical alkyl C-H bond (98 kcal/mol) or vinylic C-H bond (111 kcal/mol). Therefore, an allylic C-H bond is most likely to form a free radical and react.



Because a allylic C-H bond requires less energy to undergo homolytic cleavage than even a tertiary C-H bond, it can be inferred that a allylic radical is more stable than a tertiary radical. The ordering of stability in radicals can be expanded to include vinylic and allylic radicals. The enhanced stability of allyl radicals can be attributed to resonance stabilization which will be discussed in the next section.



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- 16.9: Oxidation of Aromatic Compounds by Dietmar Kennepohl, James Kabrhel, Steven Farmer, William Reusch is licensed CC BY-SA 4.0.

10.5: Stability of the Allyl Radical - Resonance Revisited

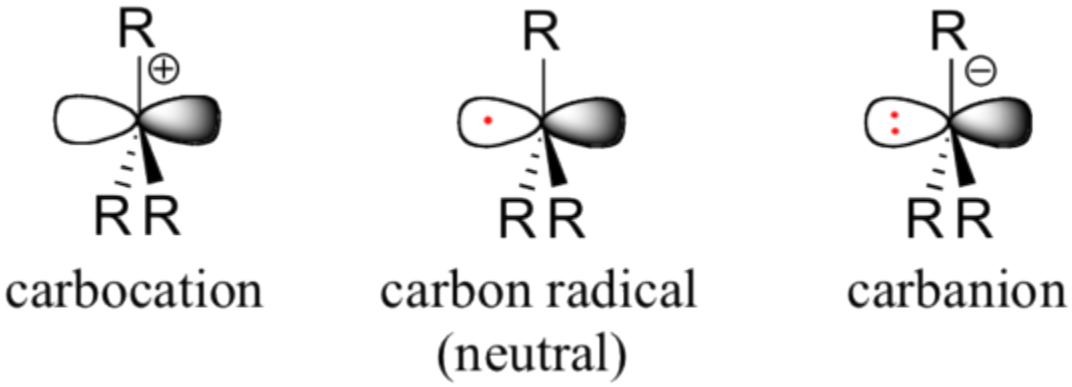
Objectives

After completing this section, you should be able to

1. explain the stability of the allyl radical in terms of resonance.
2. explain the difference between resonance and tautomerism.
3. write an equation for the reaction of an unsymmetrical alkene with N-bromosuccinimide.
4. draw the structure of each of the possible products that could be obtained from the reaction of a given unsymmetrical alkene with N-bromosuccinimide, and predict which product will predominate.
5. explain the formation of more than one product from the reaction of N-bromosuccinimide with a given unsymmetrical alkene.
6. explain the observed product ratio when a given unsymmetrical alkene is treated with N-bromosuccinimide.

The geometry and relative stability of carbon radicals

As organic chemists, we are particularly interested in radical intermediates in which the unpaired electron resides on a carbon atom. Experimental evidence indicates that the three bonds in a carbon radical have trigonal planar geometry, and therefore the carbon is considered to be sp^2-hybridized with the unpaired electron occupying the perpendicular, unhybridized $2p_z$orbital. Contrast this picture with carbocation and carbanion intermediates, which are both also trigonal planar but whose $2p_z$ orbitals contain zero or two electrons, respectively.



The trend in the stability of carbon radicals parallels that of carbocations (section 8.4): 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. To see why an allylic radical is so stable, look at the orbital picture in Figure $10.5.1$. The radical carbon atom with an unpaired electron can adopt sp^2 hybridization, placing the unpaired electron in a *p* orbital and giving a structure that is electronically symmetrical. The *p* orbital on the central carbon can therefore overlap equally well with a *p* orbital on either of the two neighboring carbons. With two resonance forms, the allylic radical is electronically symmetrical. Due to resonance hybrid theory, neither structure is correct, but instead the structure lies somewhere between the two resonance forms. Another way to phrase this is that the unpaired electron is delocalized across all the carbon atoms through the pi system and not localized on one site. The more resonance structures, the more stable the molecule. This is why the allylic radical is more stable than the alkyl radical.

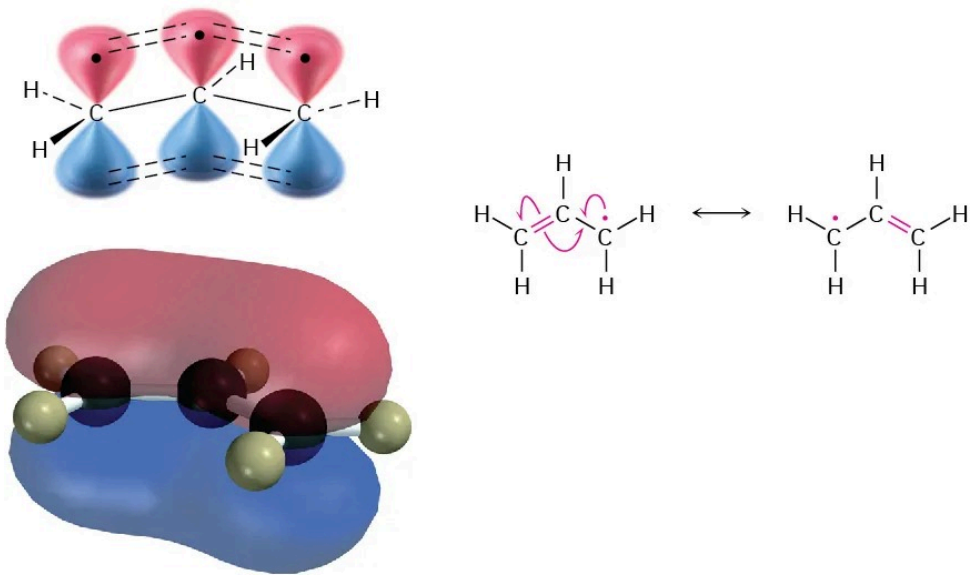
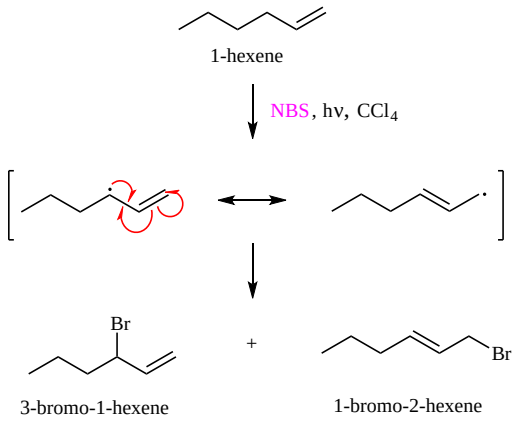


Figure 10.5.1: An orbital view of the allyl radical. The *p* orbital on the central carbon can overlap equally well with a *p* orbital on either neighboring carbon, giving rise to two equivalent resonance structures.

Because the allylic radical is symmetrical, a reaction can occur on either side. Therefore if reacting with bromine, the bromination could occur on either end of the allylic radical. When the allyl radical is symmetrical, this yields the same product. However, if you have an unsymmetrical allyl radical, it would lead to a mixture of products and not necessarily in equal amounts. This is because the intermediate radical is unsymmetrical. The reaction will occur at the less hindered site. An example would be 1-octene as a starting material in a bromination. The products the reaction would yield would be 3-bromo-1-octene and 1-bromo-2-octene.



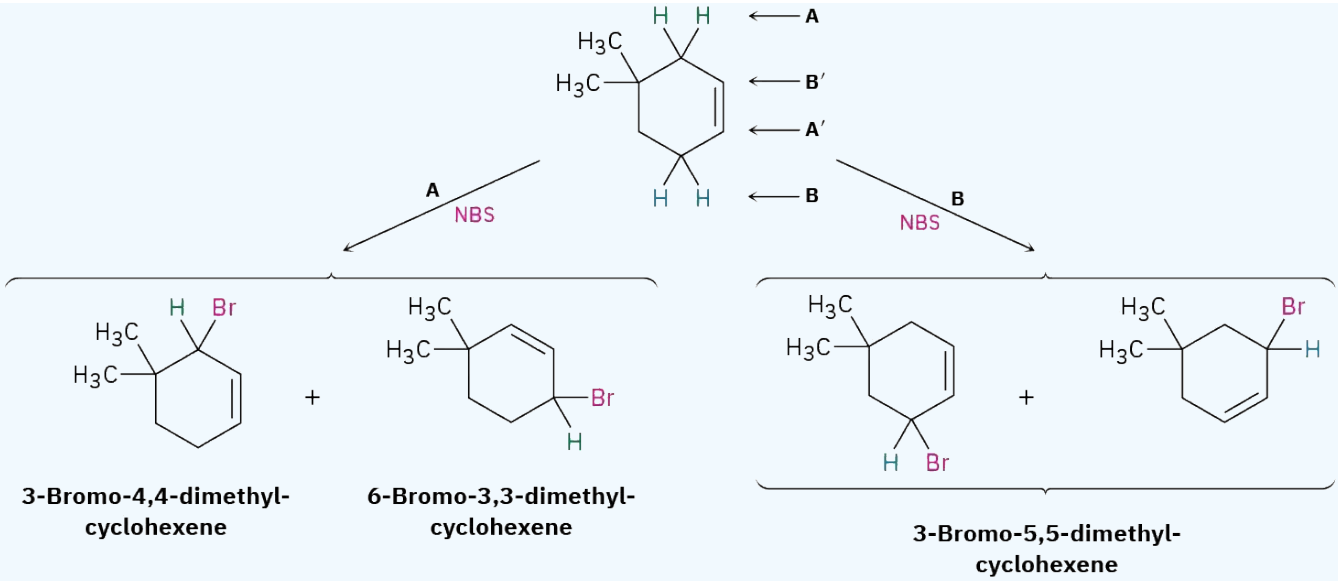
Worked Example 10.5.1: Predicting the Product of an Allylic Bromination Reaction

What products would you expect from the reaction of 4,4-dimethylcyclohexene with NBS?

Strategy

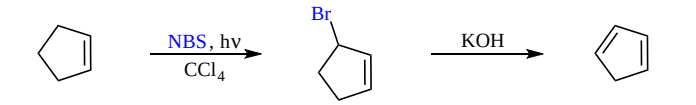
Draw the alkene reactant, and identify the allylic positions. In this case, there are two different allylic positions; we'll label them A and B. Now abstract an allylic hydrogen from each position to generate the two corresponding allylic radicals. Each of the two allylic radicals can add a Br atom at either end (A or A′; B or B′), to give a mixture of up to four products. Draw and name the products. In the present instance, the "two" products from reaction at position B are identical, so only three products are formed in this reaction.

Solution



Further Reactions

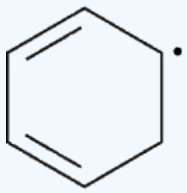
The products from allylic bromination reactions can easily be converted into dienes by elimination using a base. If the alkyl chain is long enough, alkenes can be converted to dienes through a two-step process: allylic bromination followed by elimination.



Exercises

Exercise 10.5.1

Draw three resonance forms for the cyclohexadienyl radical.

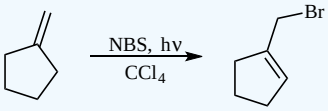


Cyclohexadienyl radical

Answer available at the end of this section.

Exercise 10.5.2

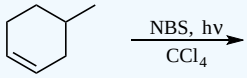
The major product of the reaction of methylenecyclopentane with *N*-bromosuccinimide is 1-(bromomethyl)cyclopentene. Explain why this would be the final product and why the 2° bromo product is not the major product.

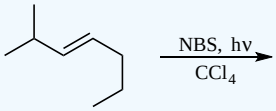


Answer available at the end of this section.

Exercise 10.5.3

Predict the products of the following reactions:

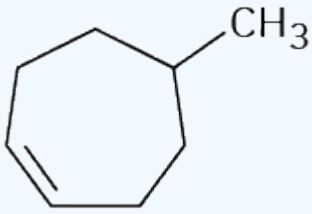


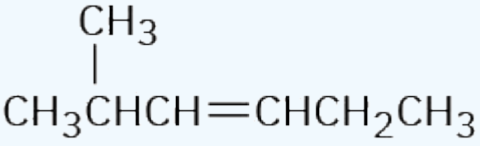


Answer available at the end of this section.

Exercise 10.5.4

What products would you expect from the reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

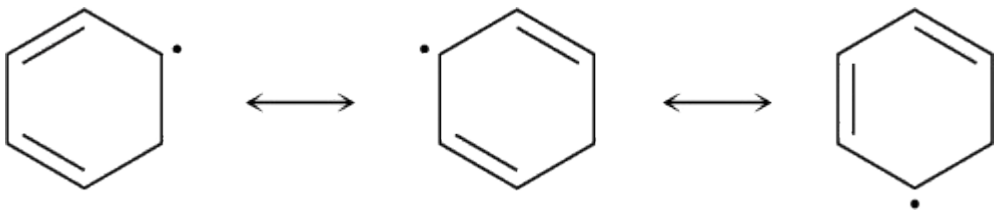
a. 

b. 

Answer available at the end of this section.

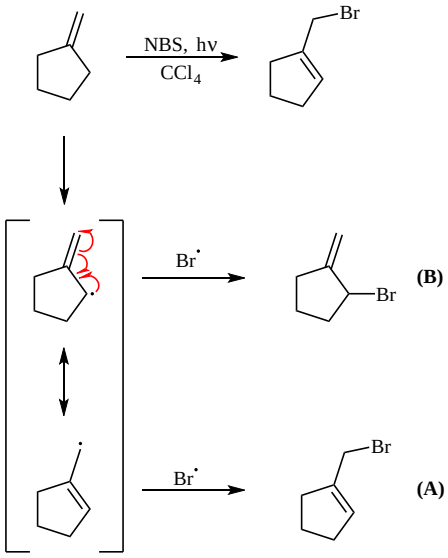
Answers

Exercise 10.5.1

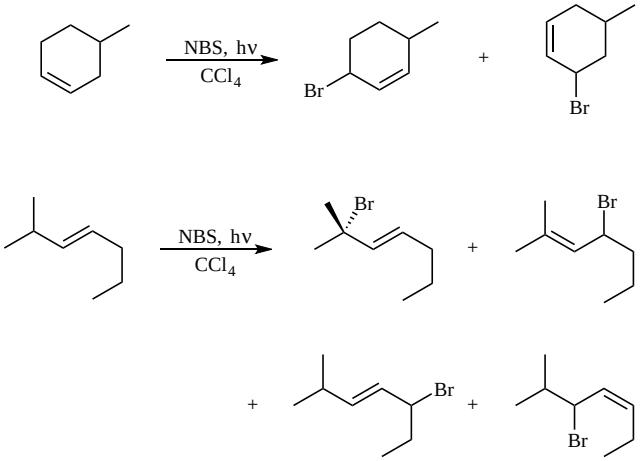


Exercise 10.5.2

The product (A) is a 1° halogen, which is the more predominant product, even though (B) had a better transition state with a 2° radical. The 1° radical intermediate is not as sterically hindered. The intermediate allylic radical reacts at the more accessible site and gives the more highly substituted double bond.



Exercise 10.5.3



Exercise 10.5.4

a. 3-Bromo-5-methylcycloheptene and 3-bromo-6-methylcycloheptene
b. Four products

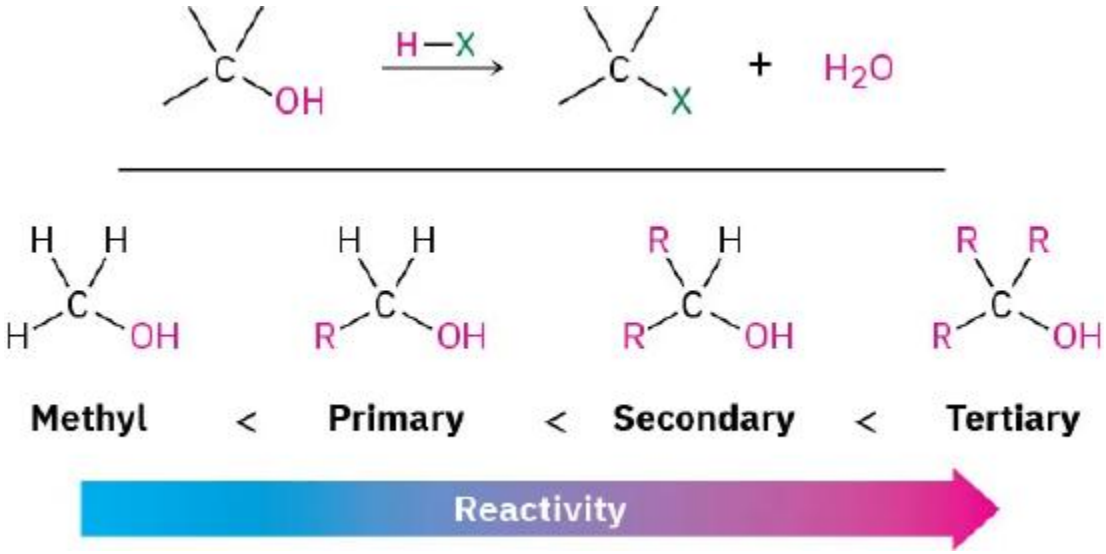
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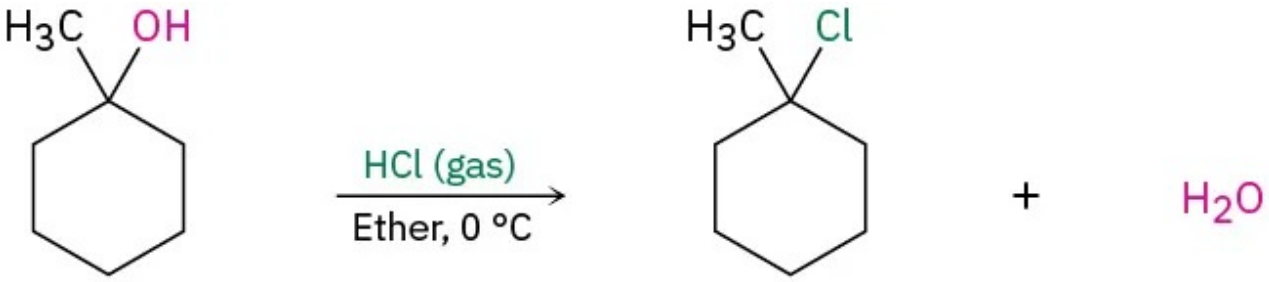
10.6: Preparing Alkyl Halides from Alcohols

Synthesis of Alkyl Halides in Acidic Conditions

The most generally useful method for preparing alkyl halides is to make them from alcohols. Because of the importance of this process, many different methods have been developed to transform alcohols into alkyl halides. The simplest method is to treat the alcohol with HCl, HBr, or HI. This reaction works best with tertiary alcohols, R_3COH. Primary and secondary alcohols react much more slowly and at higher temperatures.



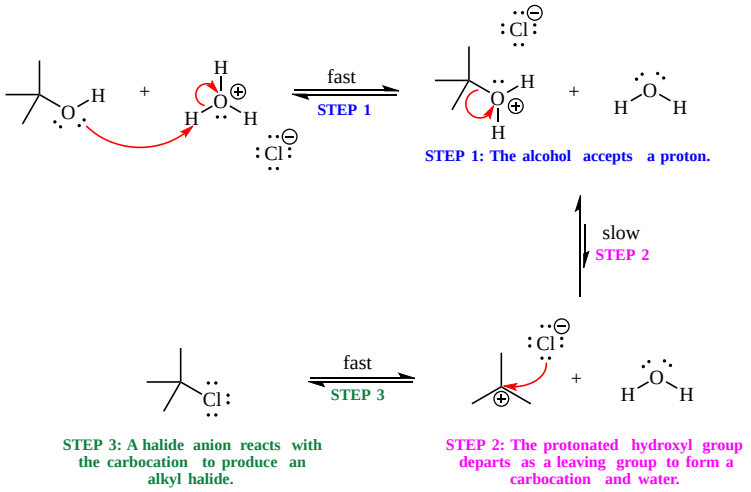
The reaction of HX with a tertiary alcohol is so rapid that it's often carried out simply by bubbling pure HCl or HBr gas into a cold ether solution of the alcohol. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treatment with HCl.



1-Methylcyclohexanol **1-Chloro-1-methylcyclohexane (90%)**

Mechanism

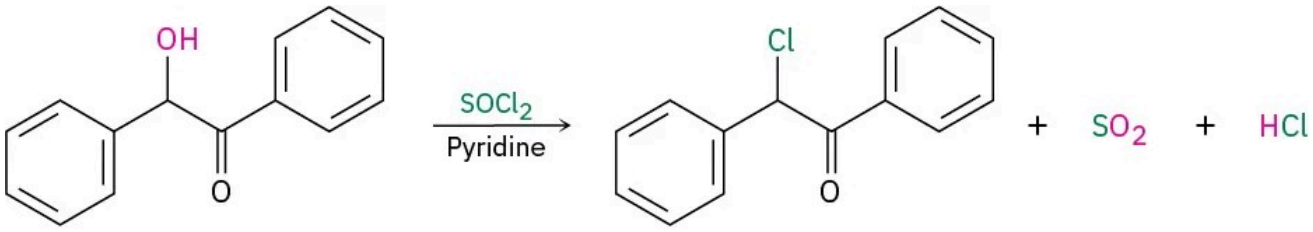
The first step in this substitution mechanism is the protonation of the alcohol to form an oxonium ion. Protonation of the alcohol converts a poor leaving group (OH^-) to a good leaving group H_2O which makes the dissociation, step 2, more favorable. In step 3, the carbocation reacts with a nucleophile (a halide ion) to complete the substitution.



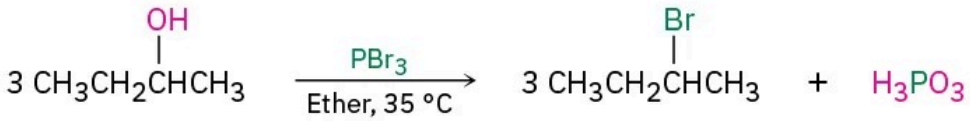
Carbocation rearrangements are extremely common in organic chemistry reactions, and are defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule. Once the carbocation has shifted over to a different carbon, we can say that there is a structural isomer of the initial molecule.

Synthesis of Alkyl Halides in Mild Conditions Using $SOCl_2$ or PBr_3

Primary and secondary alcohols are best converted into alkyl halides by treatment with either thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3). These reactions, which normally take place readily under mild conditions, are less acidic and less likely to cause acid-catalyzed rearrangements than the HX method.



Benzoin **(86%)**

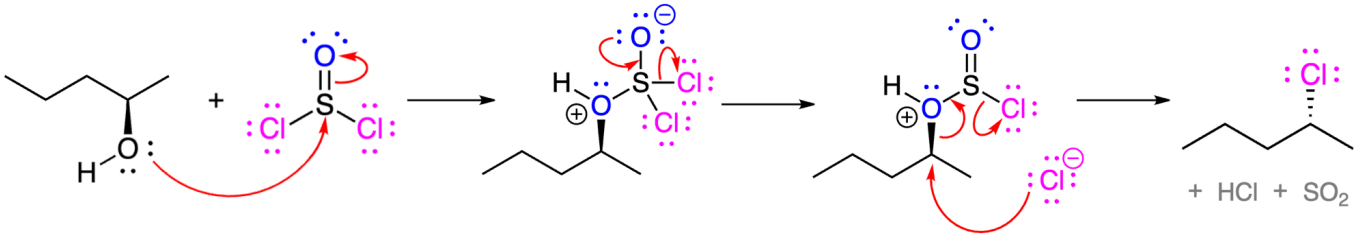


2-Butanol **2-Bromobutane (86%)**

As the preceding examples indicate, the yields of these $SOCl_2$ and PBr_3 reactions are generally high, and other functional groups such as ethers, carbonyls, and aromatic rings don't usually interfere.

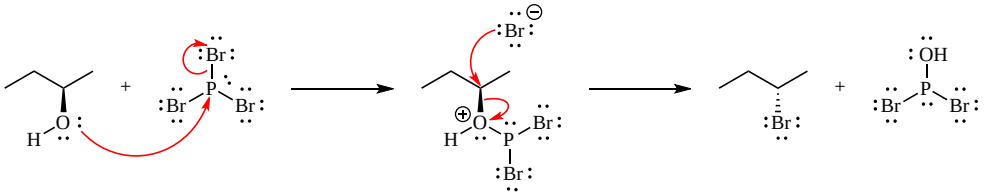
Mechanism with Thionyl chloride

Notice that during the reaction with thionyl chloride, hydrochloric acid (HCl), and sulfur dioxide (SO2) are produced as byproducts.



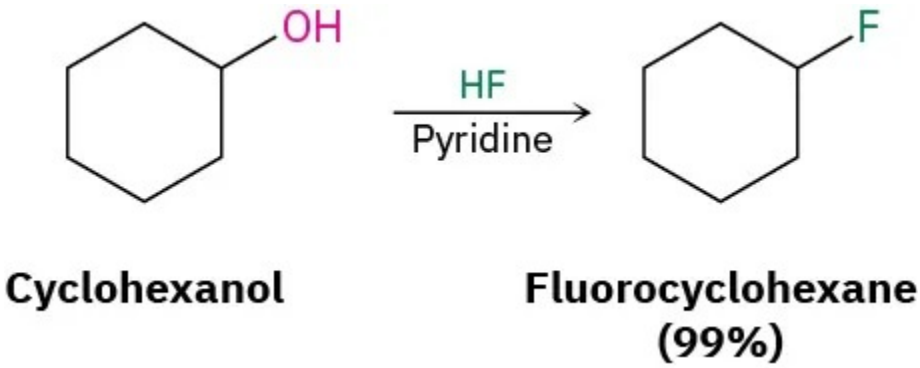
Mechanism with Phosphorus tribromide

During this reaction, $HOPBr_2$ is made as a byproduct.



Alkyl fluorides

Alkyl fluorides can also be prepared from alcohols. Numerous alternative reagents are used for such reactions, including diethylaminosulfur trifluoride $[(CH_3CH_2)_2NSF_3]$ and HF in pyridine solvent.



Exercises

Exercise 10.6.1

How would you prepare the following alkyl halides? Identify the alcohol and the reagent for each alkyl halide.

a. **b.** **c.** **d.**



Answer available at the end of this section.

Answers

Exercise 10.6.1

a. 2-Methyl-2-propanol + HCl
b. 4-Methyl-2-pentanol + PBr_3
c. 5-Methyl-1-pentanol + PBr_3
d. 3,3-Dimethyl-cyclopentanol + HF, pyridine

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10.7: Reactions of Alkyl Halides - Grignard Reagents

Objectives

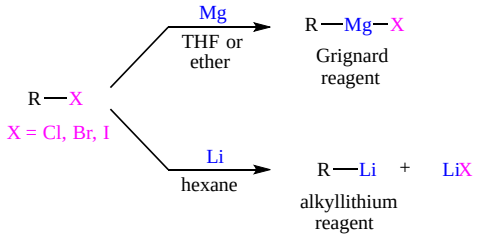
After completing this section, you should be able to

- write an equation to describe the formation of a Grignard reagent.
- Give examples of Grignard reagents formed from aryl and vinyl halides as well as from alkyl halides.
- Explain the reactivity of Grignard reagents in terms of the polarity of the carbon-magnesium bond.
- Predict the product formed from the reaction of a given organohalide with magnesium, followed by a proton donor.
- Identify the organohalide, the reagents, or both, needed to prepare a given alkane.
- Describe how a deuterium atom can be introduced into an organic molecule through the use of a Grignard reagent.
- Describe at least one limitation on the use of Grignard reagents in organic synthesis.
- Write an equation for the direct conversion of an alkyl halide to an alkane using a hydride donor, such as lithium aluminum hydride.

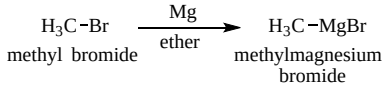
Formation of Organometallic Reagents

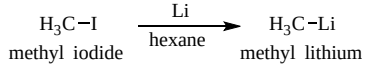
The alkali metals (Li, Na, K, etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, of which the alkali metals are stronger. These same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to a halide anion, and the carbon bonds to the metal, which has characteristics similar to a **carbanion** (R:-). Most alkyl halides can undergo this reaction, including: 1^o, 2^o, 3^o, vinyl, and aryl. Halide reactivity in these reactions increases in the order: Cl < Br < I, and Fluorides are usually not used.

Many organometallic reagents are commercially available; however, it is often necessary to make them. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination). The alkyl magnesium halides described in the first reaction are called **Grignard Reagents** after the French chemist, Victor Grignard, who discovered them and received the Nobel prize in 1912 for this work. The products of the second reaction are called **Alkyllithium Reagents.**



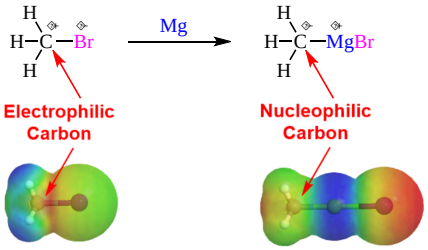
The other metals mentioned above react in a similar manner, but Grignard and Alkylithium Reagents are most widely used. Although the formulae drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

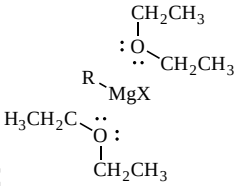




These reactions are substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is

inverted (an originally electrophilic carbon becomes nucleophilic). The Polarity change is evident when looking at the electrostatic maps of the alkyl halide and the Grignard reagent. In the alkyl halide, the electronegative halogen atom holds much of the electron density, which gives the carbon a slight positive charge (shown in blue in the electrostatic potential map below), making it electrophilic. In the Grignard reagent, the carbon has a slight negative charge, making it nucleophilic (shown in yellow & red).

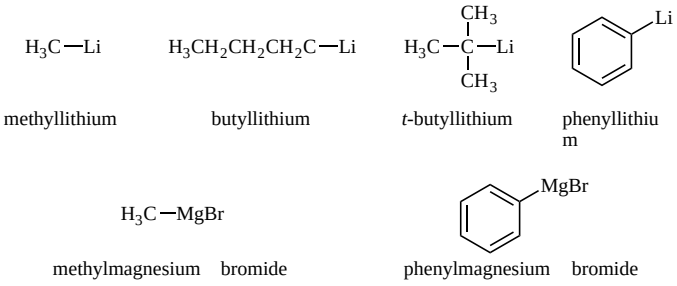




Solvent

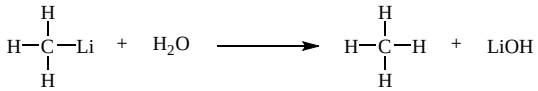
A suitable solvent must be used for reactions that form organometallic molecules. For alkyl lithium formation, pentane or hexane is usually used. Diethyl ether can also be used, but the subsequent alkyl lithium reagent must be used immediately after preparation due to an interaction with the solvent. Diethyl ether or tetrahydrofuran (THF) is essential for Grignard reagent formation. Lone pair electrons from two ether molecules form a complex with the magnesium in the Grignard reagent (as pictured in the right). This complex helps stabilize the organometallic and increases its ability to react.

Common Organometallic Reagents

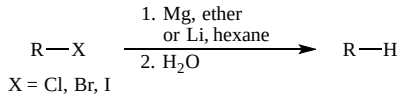


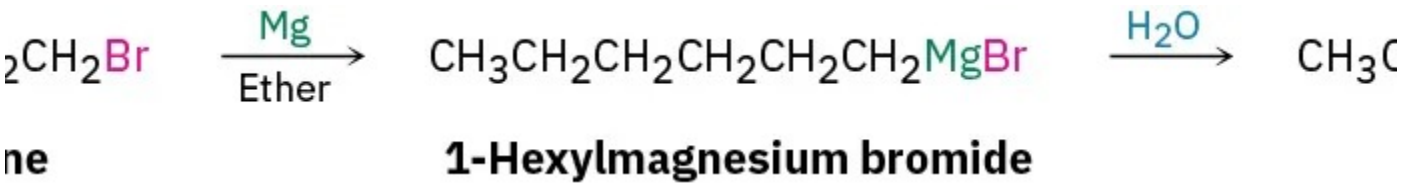
Organometallic Reagents as Bases

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 form an alkane.





A Grignard reagent is formally the magnesium salt, $R_3C^-\ ^+MgX$, of a carbon acid, $R_3C–H$, and is thus a carbon anion, or carbanion. But because hydrocarbons are such weak acids, with **p*K*$_a$**'s in the range 44 to 60 (Section 9.8), carbon anions are very strong bases. Grignard reagents must therefore be protected from atmospheric moisture to prevent their being protonated and destroyed in acid–base reactions: R–Mg–X + H_2O → R–H + HO–Mg–X.

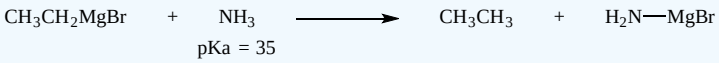
Grignard reagents themselves don't occur in living organisms, but they serve as useful carbon-based nucleophiles in several important laboratory reactions, which we'll look at in detail in CHEM 232 Section 5.7. In addition, they act as a simple model for other, more complex carbon-based nucleophiles that *are* important in biological chemistry. There are many examples of these in Metabolic Pathways.

Exercises

Exercise 10.7.1

How strong of a base would you expect ethyl Grignard to be? Would the following reactions be able to take place?

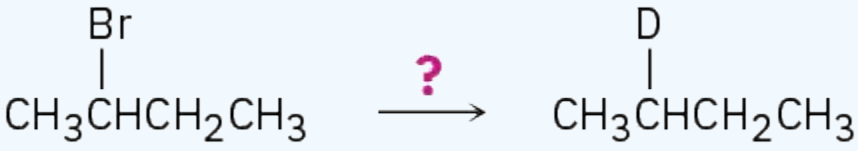




Answer available at the end of this section.

Exercise 10.7.2

How would you make a deuterated compound from an alkyl halide?



Answer available at the end of this section.

Key Terms

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

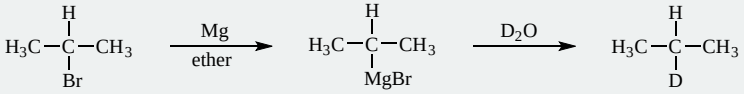
- carbanion
- Grignard reagent

Study Notes

The organomagnesium compounds formed by the reaction of an alkyl or aryl halide with magnesium are called *Grignard reagents*. As you will see throughout the remainder of this course, Grignard reagents can be used to synthesize a wide range of organic compounds and are extremely useful to the organic chemist.

In the introductory section, we tried to stress that the chemistry of alkyl halides is quite different from that of aryl (or vinyl) halides. However, both alkyl and aryl halides react with magnesium to form Grignard reagents.

The reaction of a Grignard reagent with D_2O ("heavy water") provides a convenient method for introducing a deuterium atom (remember D is equivalent to ^2H) into a molecule at a specific location. For example:



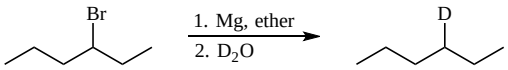
Answers

Exercise 10.7.1

Because hydrocarbons like ethane are very weak acids (pKa = 50), then the corresponding carbanion ($CH_3CH_2^-$) is expected to be a strong base. Both reactions will occur.

Exercise 10.7.2

By first making a Grignard and then exposing it to heavy water.

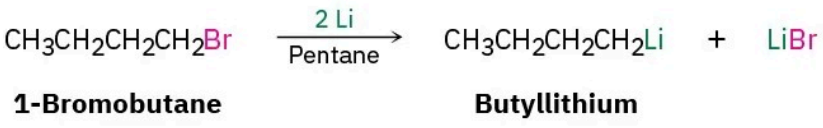


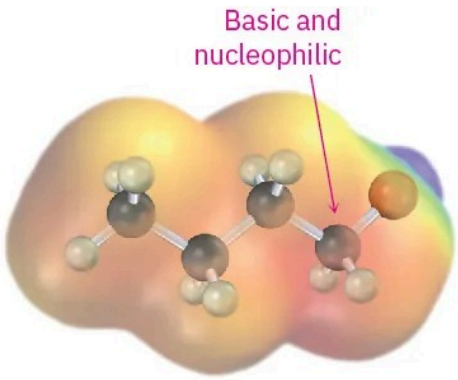
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10.8: Organometallic Coupling Reactions

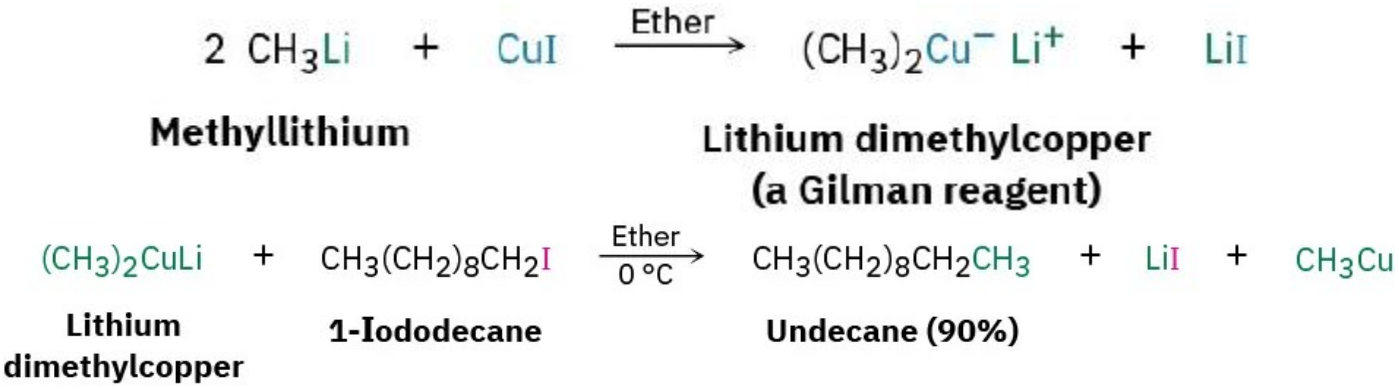
Many other kinds of organometallic compounds can be prepared in a manner similar to that of Grignard reagents. For instance, alkyllithium reagents, RLi, can be prepared by the reaction of an alkyl halide with lithium metal. Alkyllithiums are both nucleophiles and strong bases, and their chemistry is similar in many respects to that of alkylmagnesium halides.





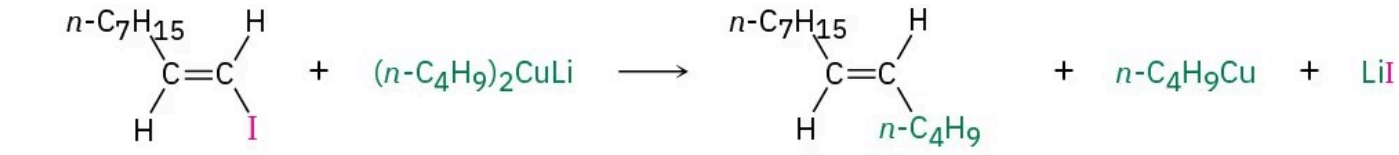
Gilman Reagents

One particularly valuable reaction of alkyllithiums occurs when making lithium diorganocopper compounds, R_2CuLi, by reaction with copper(I) iodide in diethyl ether as solvent. Often called Gilman reagents (LiR_2Cu), lithium diorganocopper compounds are useful because they undergo a *coupling* reaction with organochlorides, bromides, and iodides (but not fluorides). One of the alkyl groups from the lithium diorganocopper reagent replaces the halogen of the organohalide, forming a new carbon–carbon bond and yielding a hydrocarbon product. Lithium dimethylcopper, for instance, reacts with 1-iododecane to give undecane in a 90% yield.

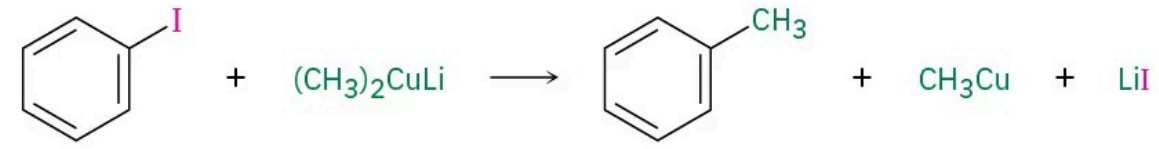


Example

This organometallic coupling reaction is useful in organic synthesis because it forms carbon–carbon bonds, thereby allowing the preparation of larger molecules from smaller ones. As the following examples indicate, the coupling reaction can be carried out on aryl and vinylic halides as well as on alkyl halides.

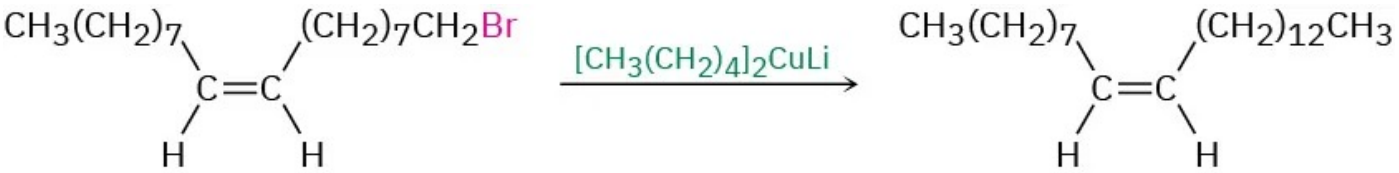


***trans*-1-Iodo-1-nonene** ***trans*-5-Tridecene (71%)**



Iodobenzene **Toluene (91%)**

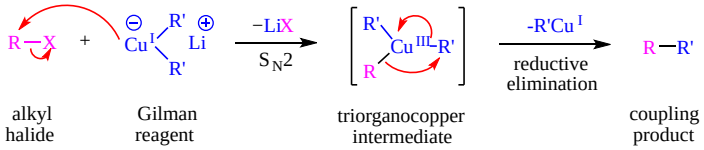
An organocopper coupling reaction is carried out commercially to synthesize muscalure, (9*Z*)-tricosene, the sex attractant secreted by the common housefly. Minute amounts of muscalure greatly increase the lure of insecticide-treated fly bait and provide an effective and species-specific means of insect control.



***cis*-1-Bromo-9-octadecene** **Muscalure (9*Z*-tricosene)**

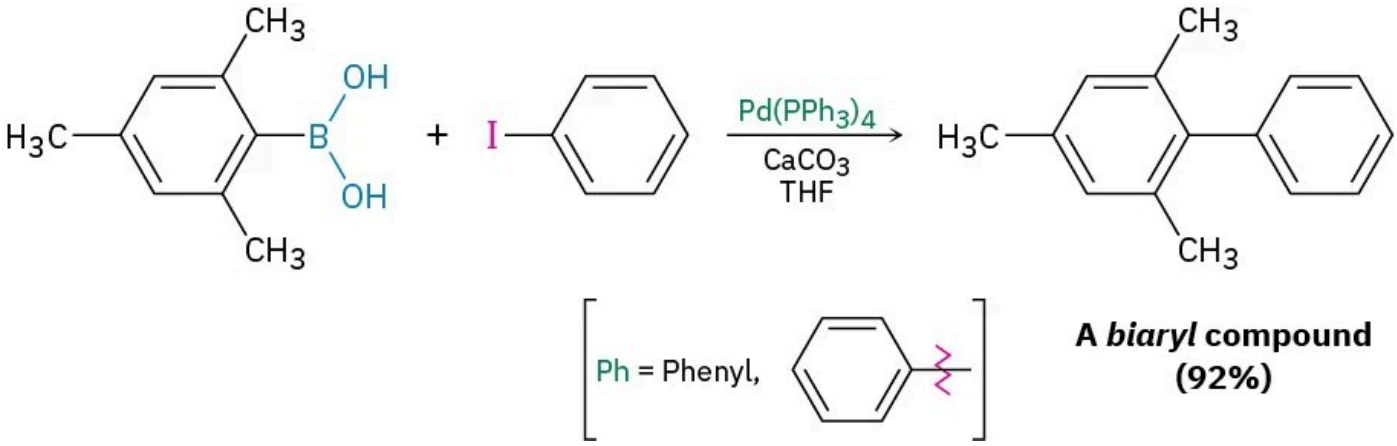
Mechanism

The mechanism of the coupling reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of a mono-organocopper, RCu. The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the next chapter.



The Suzuki-Miyaura Reaction

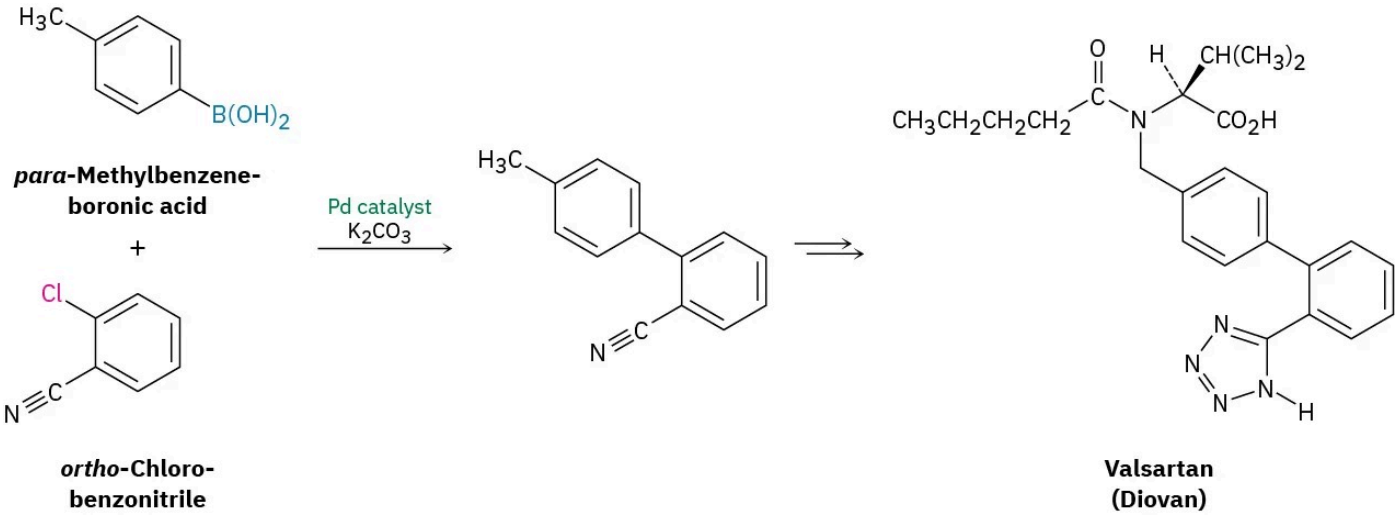
In addition to the coupling reaction of diorganocopper reagents with organohalides, related processes also occur with other organometallic reagents, particularly organopalladium compounds. One of the most commonly used procedures is the coupling reaction of an aromatic or vinyl substituted boronic acid [R—B(OH)$_2$] with an aromatic or vinyl substituted organohalide in the presence of a base and a palladium catalyst. This reaction is less general than the diorganocopper reaction because it doesn't work with alkyl substrates, but it is preferred when possible because it uses only a catalytic amount of metal rather than a full equivalent and because palladium compounds are less toxic than copper compounds. For example:



Called the **Suzuki–Miyaura reaction**, this process is particularly useful for preparing so-called biaryl compounds, which have two linked aromatic rings. A large number of commonly used drugs fit this description, so the Suzuki–Miyaura reaction is much-used in the pharmaceutical industry.

Example

As an example, valsartan, marketed as Diovan, is widely prescribed to treat high blood pressure, heart failure, and diabetic kidney disease. Its synthesis begins with a **Suzuki–Miyaura coupling** of *ortho*-chlorobenzonitrile with *para*-methylbenzeneboronic acid.



Mechanism

Shown in a simplified form in Figure 10.8.1, the mechanism of the Suzuki–Miyaura reaction involves initial reaction of the aromatic halide with the palladium catalyst to form an organopalladium intermediate, followed by reaction of that intermediate with the aromatic boronic acid. The resultant diorganopalladium complex then decomposes to the coupled biaryl product plus regenerated catalyst.

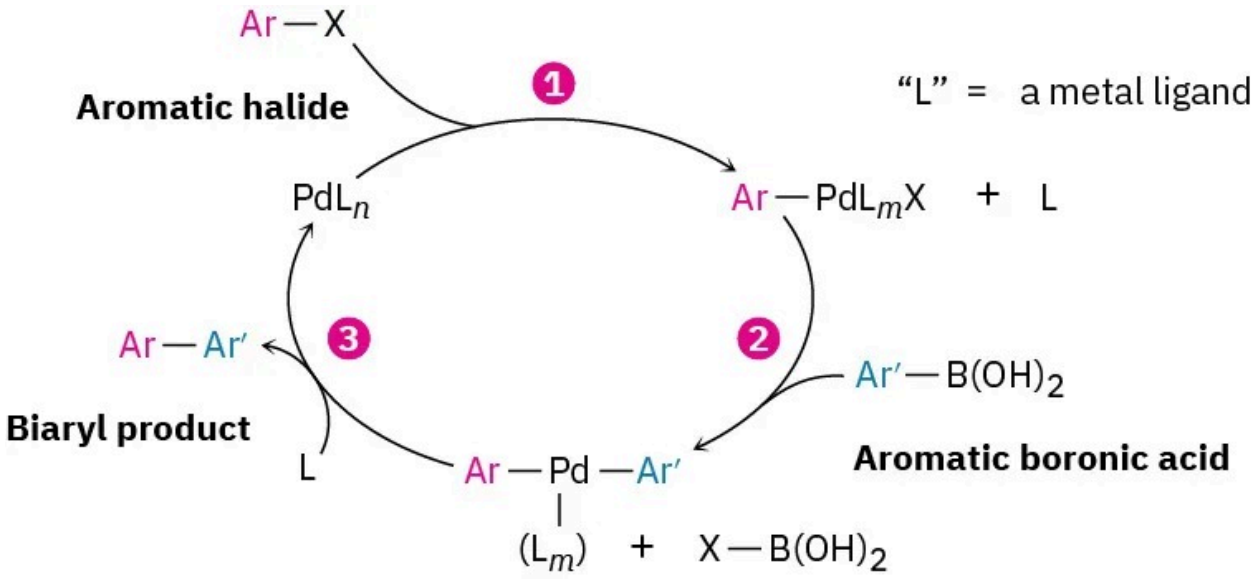


Figure 10.8.1: Mechanism of the Suzuki–Miyaura coupling reaction of an aromatic boronic acid with an aromatic halide to give a biaryl. The reaction takes place by (**1**) reaction of the aromatic halide, ArX, with the catalyst to form an organopalladium intermediate, followed by (**2**) reaction with the aromatic boronic acid. (**3**) Subsequent decomposition of the diarylpalladium intermediate gives the biaryl product.

Exercise 10.8.1

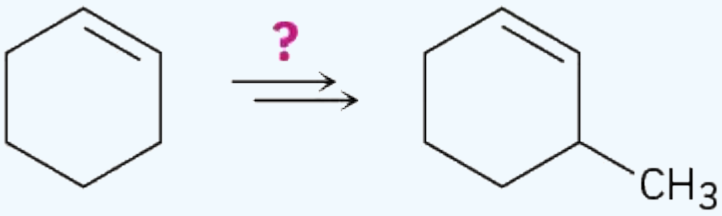
Starting with alkyl halides containing no more than four carbon atoms, how would you synthesize each of the following alkanes?

a. 2,5-dimethylhexane
b. 2-methylhexane

Answer available at the end of this section.

Exercise 10.8.2

How would you carry out the following transformations using an organocopper coupling reaction? More than one step is required in each case.

a. 

b. $CH_3CH_2CH_2CH_2Br \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

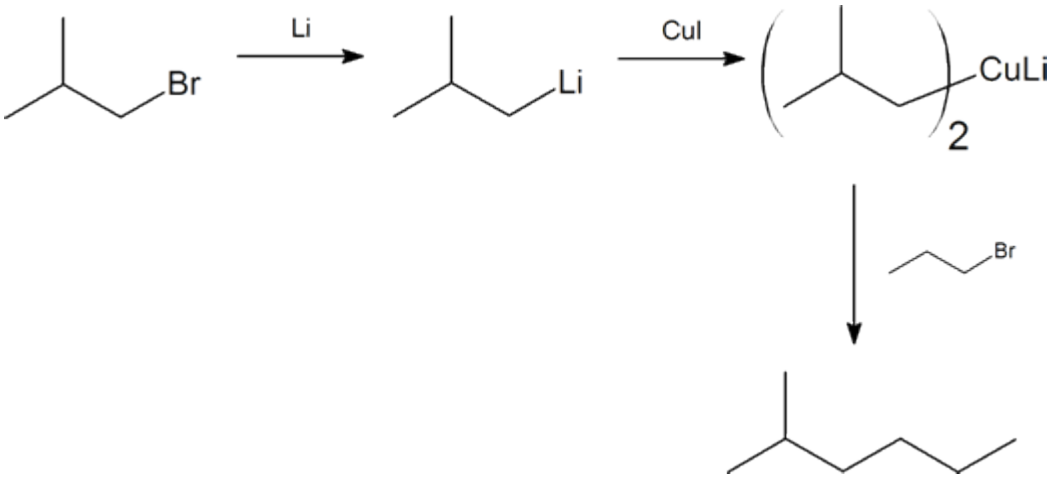
c. $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

Answer available at the end of this section.

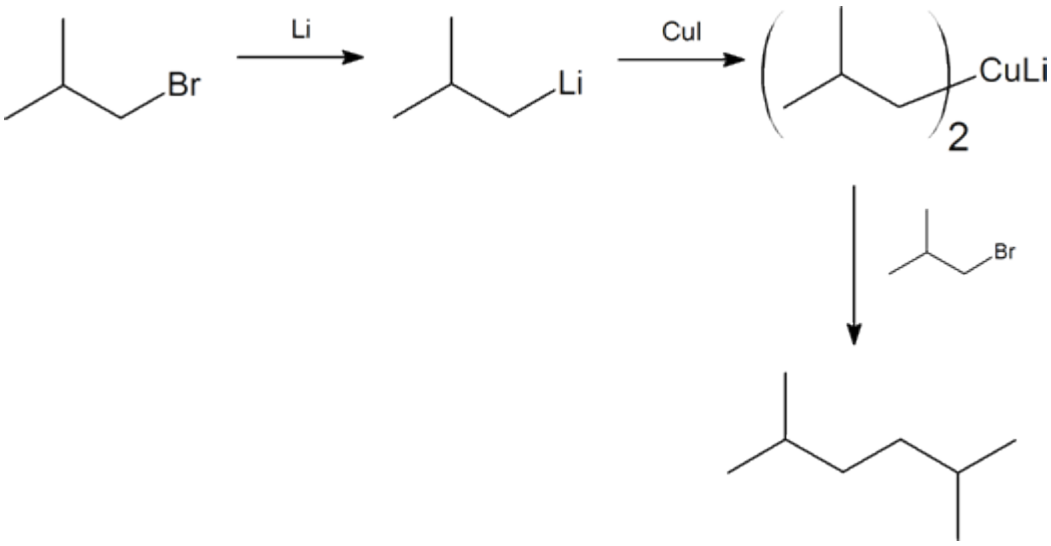
Answers

Exercise 10.8.1

Notice that in (*a*), both the alkyl halides are primary. This fact should ensure a good yield of product.



In (*b*) we have the choice of using 2-bromopropane and 1-bromobutane, or 1-bromo-2-methylpropane and 1-bromopropane. We chose the latter as it enables us to use two primary alkyl halides, and hence a simpler procedure.



Exercise 10.8.2

a. 1. NBS; 2. $(CH_3)_2CuLi$
b. 1. Li; 2. CuI; 3. $CH_3CH_2CH_2CH_2Br$
c. 1. BH_3; 2. H_2O_2, NaOH; 3. PBr_3; 4. Li, then CuI; 5. $CH_3(CH_2)_4Br$

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10.9: Oxidation and Reduction in Organic Chemistry

Objectives

After completing this section, you should be able to

- identify organic reactions as being oxidations, reductions, or neither.
- Rank the given compounds in order of their oxidation level.

We've pointed out on several occasions that some of the reactions discussed in this and earlier chapters are either oxidations or reductions. As noted in Section 8.8, an organic oxidation results in a loss of electron density by carbon, caused either by bond formation between carbon and a more electronegative atom (usually O, N, or a halogen) or by bond-breaking between carbon and a less electronegative atom (usually H). Conversely, an organic reduction results in a gain of electron density by carbon, caused either by bond formation between carbon and a less electronegative atom or by bond-breaking between carbon and a more electronegative atom (Section 8.7).

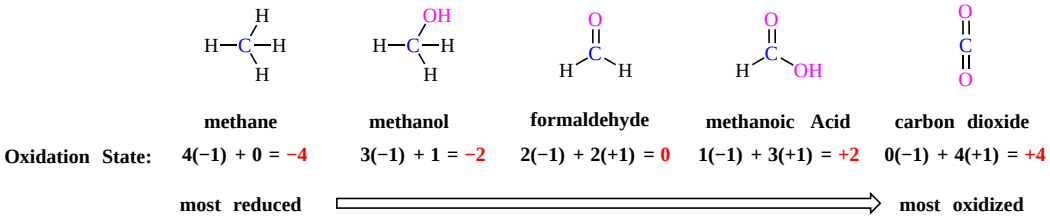
Oxidation: Decreases electron density on carbon by:

- forming one of these: C–O C–N C–X
- or breaking this:C–H

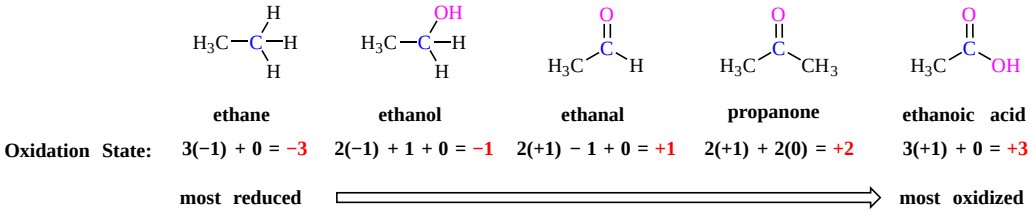
Reduction: Increases electron density on carbon by:

- forming this: C–H
- or breaking one of these: C–O C–N C–X

When looking at the oxidation states of carbon in the common functional groups shown below, it can be said that carbon loses electron density as it becomes more oxidized. We'll take a series of single-carbon compounds as an example. Methane (CH_4) is at the lowest oxidation level of carbon because it has the maximum possible number of bonds to hydrogen. Carbon dioxide (CO_2) is at the highest oxidation level because it has the maximum number of bonds to an electronegative atom.



This pattern holds true for the relevant functional groups on organic molecules with two or more carbon atoms:



A list of compounds of increasing oxidation level is shown in Figure 10.9.1. Alkanes are at the lowest oxidation level because they have the maximum possible number of C–H bonds per carbon, and CO_2 is at the highest level because it has the maximum possible number of C–O bonds per carbon. Any reaction that converts a compound from a lower level to a higher level is an oxidation, any reaction that converts a compound from a higher level to a lower level is a reduction, and any reaction that doesn't change the level is neither an oxidation nor a reduction.

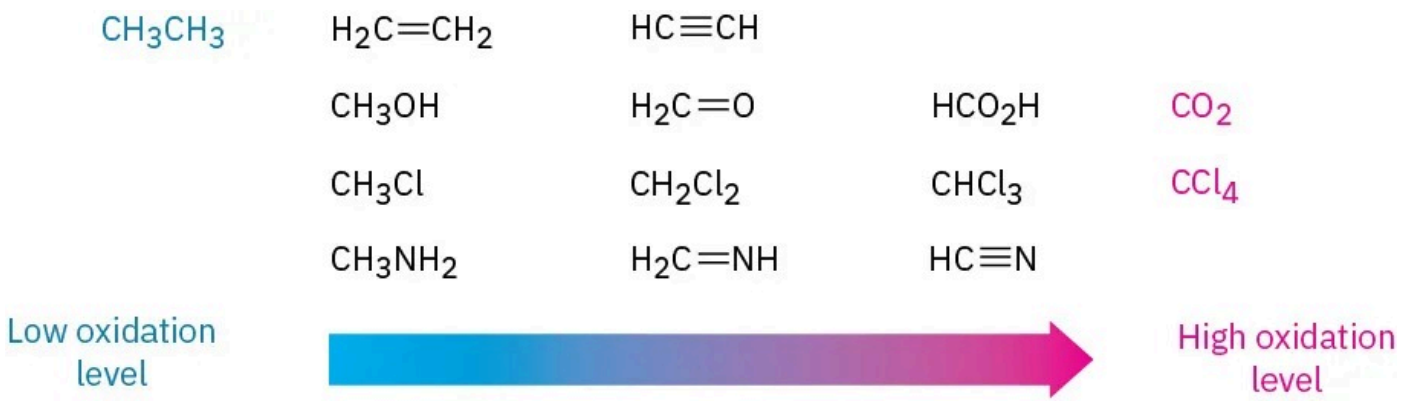
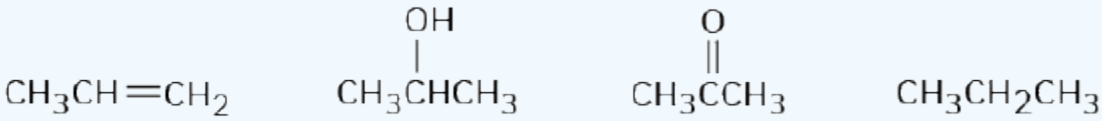


Figure 10.9.1: Oxidation levels of some common compounds.

Worked Example 10.9.1 shows how to compare the oxidation levels of different compounds with the same number of carbon atoms.

Worked Example 10.9.1: Comparing Oxidation Levels

Rank the following compounds in order of increasing oxidation level:

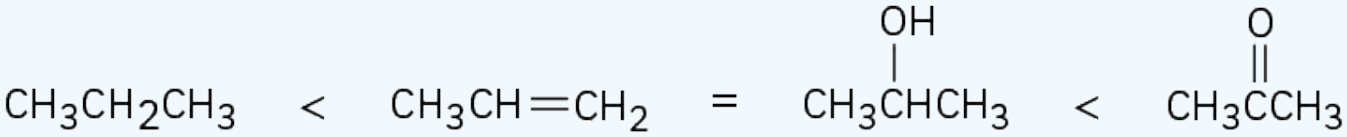


Strategy

Compounds that have the same number of carbon atoms can be compared by adding the number of C–O, C–N, and C–X bonds in each and then subtracting the number of C–H bonds. The larger the resultant value, the higher the oxidation level.

Solution

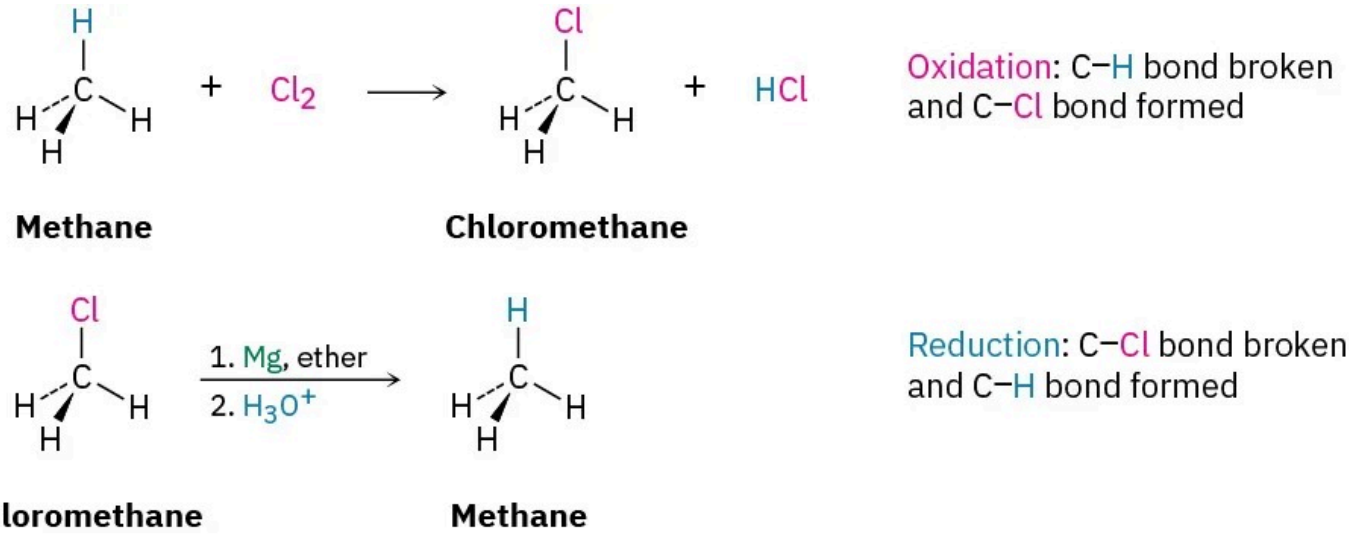
The first compound (propene) has six C–H bonds, giving an oxidation level of –6; the second (2-propanol) has one C–O bond and seven C–H bonds, giving an oxidation level of –6; the third (acetone) has two C–O bonds and six C–H bonds, giving an oxidation level of –4; and the fourth (propane) has eight C–H bonds, giving an oxidation level of –8. Thus, the order of increasing oxidation level is



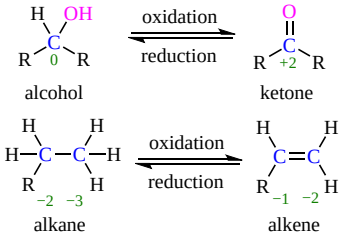
Organic Redox Reactions

It is important to be able to recognize when an organic molecule is being oxidized or reduced, because this information tells you to look for the participation of a corresponding redox agent that is being reduced or oxidized. If a reaction converts a compound to a higher oxidation level, that is an oxidation. If it converts a compound to a lower oxidation level, it is a reduction. If the oxidation level of the reactant does not change, it is not a redox reaction.

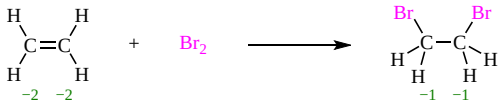
Based on these definitions, the chlorination reaction of methane to yield chloromethane is an oxidation because a C–H bond is broken and a C–Cl bond is formed. The conversion of an alkyl chloride to an alkane via a Grignard reagent followed by protonation is a reduction, however, because a C–Cl bond is broken and a C–H bond is formed.



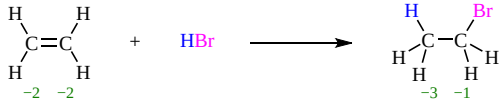
Two examples of organic redox reactions are shown below. The conversion of an alcohol to a ketone is considered an oxidation because the oxidation level of the carbon increases from 0 to +2. This implies that the reaction would require an oxidizing agent. Likewise, the conversion of a ketone to an alcohol is a reduction and would require a reducing agent. The conversion of an alkane to an alkene is an oxidation because the oxidation state on both carbons is increasing, while the reverse reaction would be a reduction.



As other examples: The electrophilic addition of Br_2 to an alkene to provide a 1,2-dibromide is an oxidation because both carbons increase their oxidation level from -2 to -1. However, the electrophilic addition of HBr to an alkene to provide an alkyl halide is not a redox reaction because the overall oxidation state of carbons involved is not changed. One carbon has its oxidation level decreased from -2 to -3, while the other carbon's oxidation level is increased from -2 to -1. Overall, the change in oxidation level cancels out to leave an overall change of oxidation level in the compound of 0.



electrophilic addition of Br_2: **oxidation**



electrophilic addition of HBr: **not redox**

Exercises

Exercise 10.9.1

Rank the following compounds in order of increasing oxidation level:

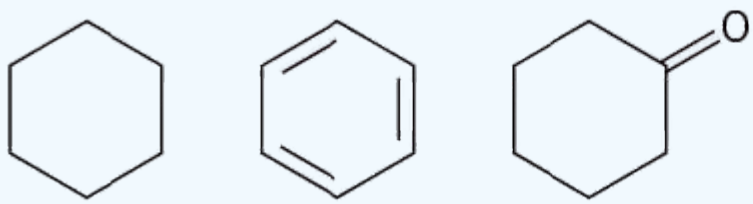


Answer available at the end of this section.

Exercise 10.9.2

Rank both sets of compounds in order of increasing oxidation level:

a.



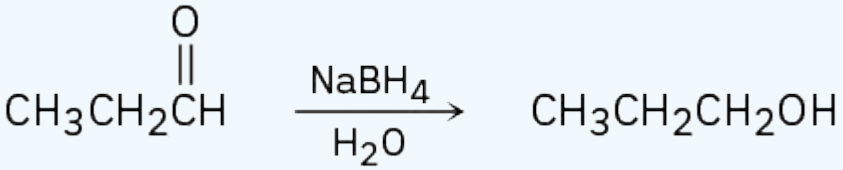
b.

Answer available at the end of this section.

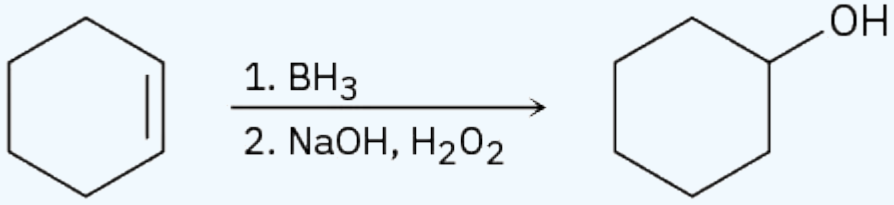
Exercise 10.9.3

Tell whether each of the following reactions is an oxidation, a reduction, or neither.

a.



b.



Answer available at the end of this section.

Answers

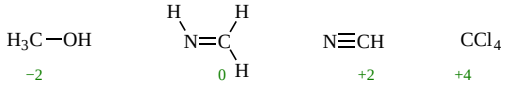
Exercise 10.9.1

The easiest way to solve this problem is to calculate the oxidation level of the carbon in each compound. Remembering that hydrogen decreases the oxidation level by one, electronegative elements increase the oxidation level by one, and carbons do not change the oxidation level, the oxidation level of each carbon can be calculated.

- The carbon in CH_3OH has three bonds to hydrogens and one bond to oxygen so it oxidation level is 3(-1) + 1(+1) = -2.

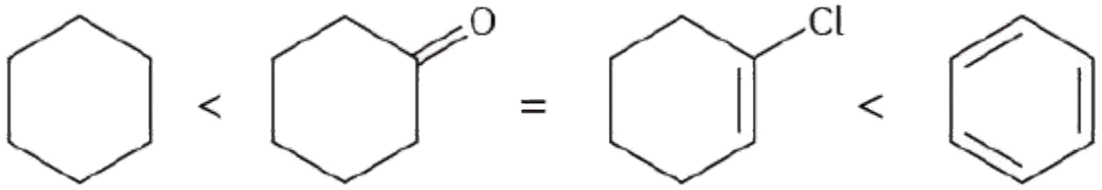
- The carbon in HCN has one bond to hydrogens and three bonds to nitrogen so it oxidation level is 1(-1) + 3(+1) = +2.
- The carbon in CH_2NH has two bonds to hydrogens and two bond to nitrogen so it oxidation level is 2(-1) + 2(+1) = 0.
- The carbon in CCl_4 has zero bonds to hydrogens and four bonds to chlorine so it oxidation level is o(-1) + 4(+1) = +4.

The compounds can now be listed in the following order of increasing oxidation level.



Exercise 10.9.2

a.



b. $CH_3CH_2NH_2 < H_2NCH_2CH_2NH_2 < CH_3C{\equiv}N$

Exercise 10.9.3

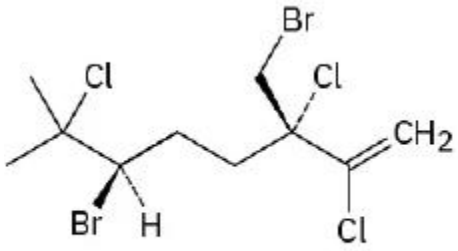
1. Reduction
2. Neither

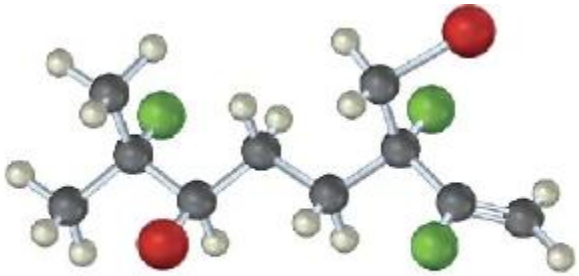
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10.10: Chemistry Matters—Naturally Occurring Organohalides

Just forty years ago in 1980, only about 30 naturally occurring organohalides were known. It was simply assumed that chloroform, halogenated phenols, chlorinated aromatic compounds called PCBs, and other such substances found in the environment were industrial pollutants. Now, less than half a century later, the situation is quite different. More than 5000 organohalides have been found to occur naturally, and tens of thousands more surely exist. From a simple compound like chloromethane to an extremely complex one like the antibiotic vancomycin, a remarkably diverse range of organohalides exists in plants, bacteria, and animals. Many even have valuable physiological activity. The pentahalogenated alkene halomon, for instance, has been isolated from the red alga *Portieria hornemannii* and found to have anticancer activity against several human tumor cell lines.





Halomon

Some naturally occurring organohalides are produced in massive quantities. Forest fires, volcanic eruptions, and marine kelp release up to 5 million tons of CH_3Cl per year, for example, while annual industrial emissions total about 26,000 tons. Termites are thought to release as much as 10^8 kg of chloroform per year. A detailed examination of the Okinawan acorn worm *Ptychodera flava* found that the 64 million worms living in a 1 km^2 study area excreted nearly 8000 pounds per year of bromophenols and bromoindoles, compounds previously thought to be non-natural pollutants.

Why do organisms produce organohalides, many of which are undoubtedly toxic? The answer seems to be that many organisms use organohalogen compounds for self-defense, either as feeding deterrents, irritants to predators, or natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalides that deter fish, starfish, and other predators. Even humans appear to produce halogenated compounds as part of their defense against infection. The human immune system contains a peroxidase enzyme capable of carrying out halogenation reactions on fungi and bacteria, thereby killing the pathogen. And most remarkable of all, even free chlorine—Cl_2—has been found to be present in humans.



Figure 10.10.1: Marine corals secrete organohalogen compounds that act as a feeding deterrent to fish. (credit: “Coral reef” by Qui Nguyen, United Nations Environment Programme/Flickr, Public Domain)

Much remains to be learned—only a few hundred of the more than 500,000 known species of marine organisms have been examined—but it’s clear that organohalides are an integral part of the world around us.

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10.A: Organohalides (Summary)

Concepts & Vocabulary

10.1 Introduction to Organohalides

- Alkyl halides (and allyl and benzyl halides) are more reactive than vinyl and aryl halides.

10.2 Names and Properties of Alkyl Halides

- Reactivity of alkyl halides is often related to the substitution of the carbon atom the halogen is attached to.
- Alkyl halides are categorized by the number of bonds to other alkyl groups (**primary**, **secondary**, and **tertiary**).
- Carbon-halogen bonds are polarized with partial positive charges on carbon and partial negative charges on the halogen.
- Fluorine is the most electronegative of the halogens while iodine is the least electronegative.
- Iodine is the largest of the halogens yielding the longest/weakest bonds to carbon of the halogens.
- Since haloalkanes have dipole-dipole interactions, they have greater intermolecular forces than similar sized alkanes and therefore higher boiling points.
- Alkyl halides are either slightly soluble or insoluble in water, but are soluble in organic solvents.

10.3 Preparing Alkyl Halides from Alkanes - Radical Halogenation

- Halogenation of alkanes is exothermic, so it is energetically favorable.
- Radical chain mechanisms consist of three steps: **initiation**, **propagation** and **termination**.
- Hydrogens on more substituted carbon atoms are more reactive to radical halogenation.

10.4 Preparing Alkyl Halides from Alkenes - Allylic Bromination

- More substituted radicals and radicals with resonance structures are more stable than other radicals.
- Radical substitution can be carried out at the allylic or benzylic carbon by reacting with NBS.

10.5 Stability of the Allyl Radical - Resonance Revisited

- Allyl cations, anions and radicals have resonance structures. To draw these resonance structures non-bonded and pi-bond electrons can be moved.
- Resonance hybrids are used to show the combination of all resonance structures for a molecule or ion.

10.6 Preparing Alkyl Halides form Alcohols

- Alcohols can be reacted with hydrohalogen acids or a mixture of halogen salts and a stronger acid (to form hydrohalogen acids *in situ*).
- Alcohols will also react with thionyl chloride or with phosphorus halides to from haloalkanes.

10.7 Reactions of Alkyl Halides - Grignard Reactions

- Organometallic reagents can be formed from alkyl halides and reactive metals (such as lithium and magnesium).
- Alkyl magnesium halide compounds are callled Grignard reagents.
- Grignard reagents react as bases where the alkyl group gets protonated and the metal complexes to the conjugate base of the reacting acid.

10.8 Organometallic Coupling Reactions

- Lithium dialkyl copper compounds are called Gilman reagents.
- Gilman reagents have different reactivity from the other organometallics (lithium and Grignard reagents).
- Organometallics can be reacted with alkyl halides to join to alkyl groups (coupling reactions).

10.9 Oxidation and Reduction in Organic Chemistry

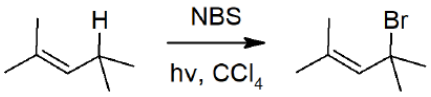
- Gaining bonds to hydrogen for organic molecules is reduction.
- Losing bonds to hydrogen for organic molecules is oxidation.

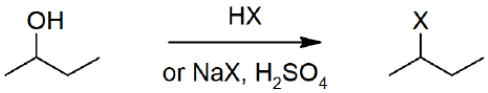
Skills to Master

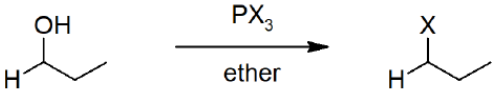
- Skill 10.1 Differentiate between types of halides (alkyl, allyl, aryl, benzyl, and vinyl).
- Skill 10.2 Differentiate between substitution of alkyl halides (primary, secondary, and tertiary).
- Skill 10.3 Identify relative reactivity of carbon-hydrogen bonds to radical halogenation.
- Skill 10.4 Draw resonance structures for radical compounds.
- Skill 10.5 Draw mechanisms for radical halogenation of alkanes (initiation, propagation and termination).
- Skill 10.6 Calculate the enthalpy change of a reaction using bond dissociation energies of reactants and products.
- Skill 10.7 Determine products for allylic bromination reactions.
- Skill 10.8 Draw resonance structures for allylic and other similar compounds and ions.
- Skill 10.9 Draw products of reactions of alcohols to form alkyl halides.
- Skill 10.10 Write equations to form Grignard reagents from alkyl halides.
- Skill 10.11 Draw reaction products for Grignard reagents acting as bases.
- Skill 10.12 Write equations for the formation of Gilman reagents.
- Skill 10.13 Draw reaction products of organometallic coupling reactions.
- Skill 10.14 Explain oxidation and reduction in organic molecules.

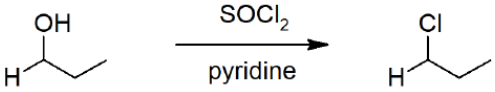
Summary of Reactions

Preparation of Alkyl Halides



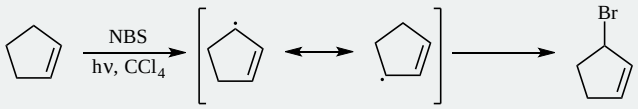




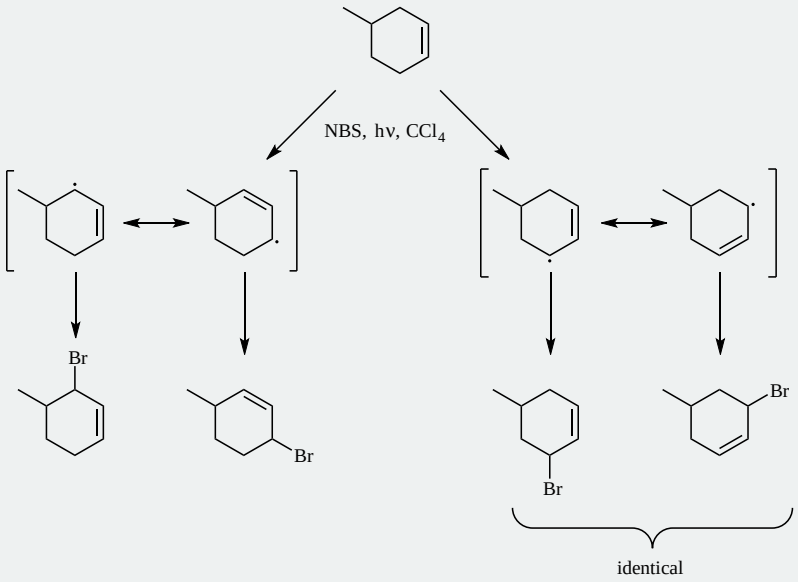


Study Notes

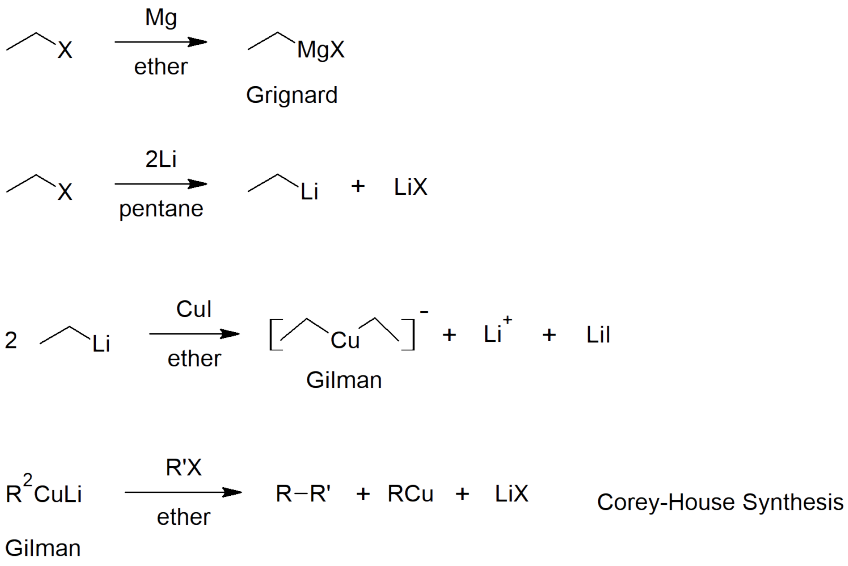
The allylic bromination of a symmetrical alkene with NBS, such as this cyclopentene, which affords one product.



However, with an unsymmetrical alkene and the delocalized unpaired electron forming various allylic resonances, several products are possible. For example, the NBS bromination of 4-methyl-cyclohexene leads to three products.



Reactions of Alkyl Halides



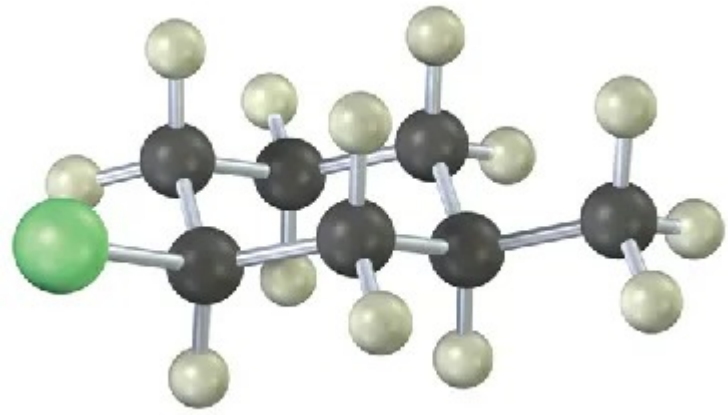
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- 10.4: Stability of the Allyl Radical - Resonance Revisited by Dietmar Kennepohl, Liza Chu, Sharon Wei, Steven Farmer is licensed CC BY-SA 4.0.

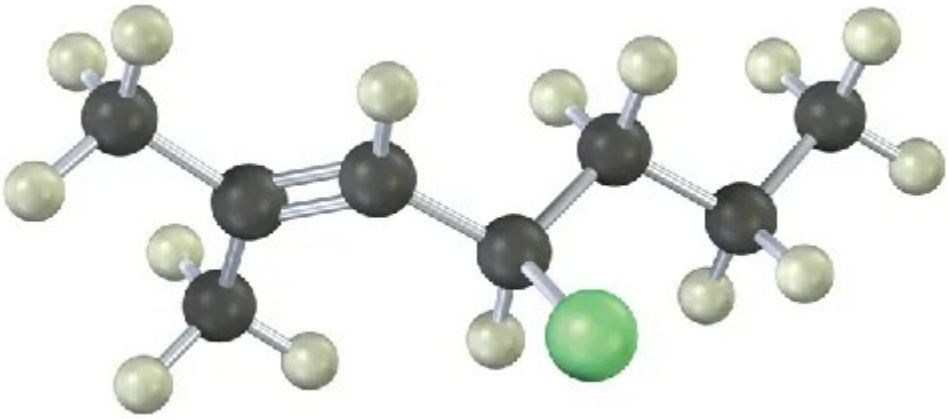
10.B: Additional Problems

Visualizing Chemistry

PROBLEM 10-14 Give IUPAC names for the following alkyl halides (green = Cl):

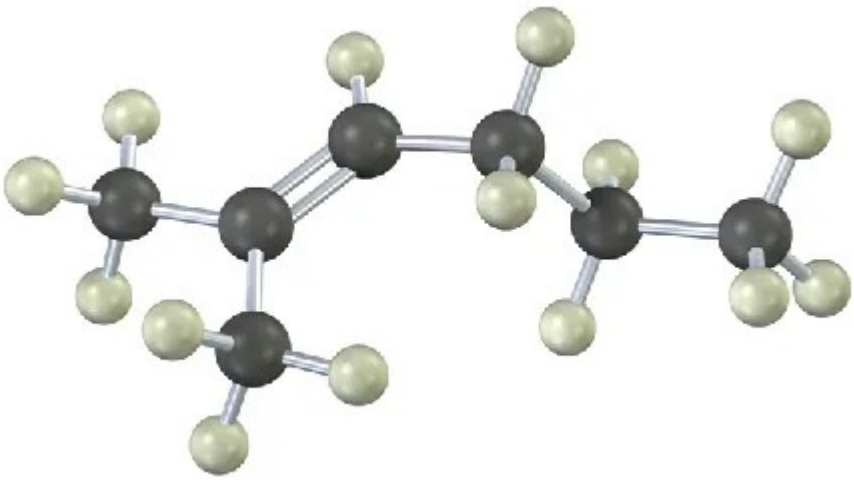


(a)



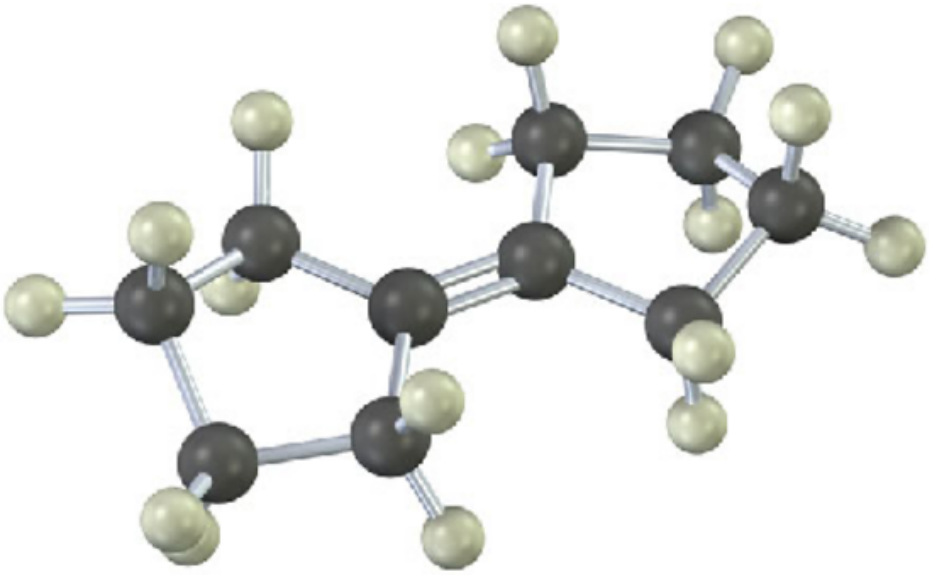
(b)

PROBLEM 10-15 Show the product(s) of reaction of the following alkenes with NBS:

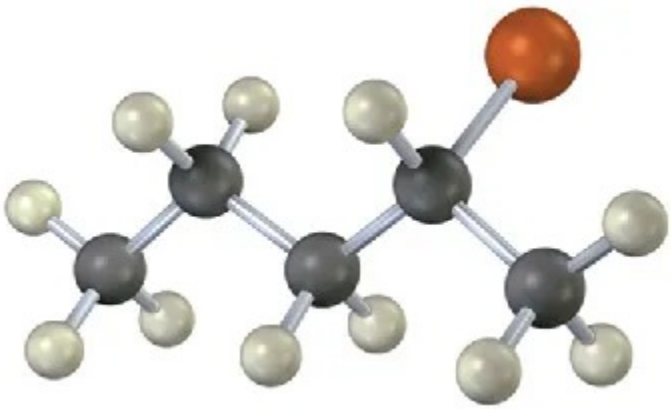


(a)

(b).

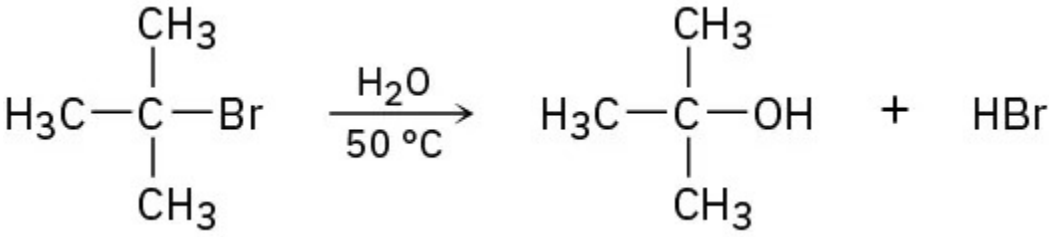


PROBLEM 10-16 The following alkyl bromide can be prepared by reaction of the alcohol (S)-2-pentanol with PBr_3. Name the compound, assign (*R*) or (S) stereochemistry, and tell whether the reaction of the alcohol results in the same stereochemistry or a change in stereochemistry (reddish brown = Br).



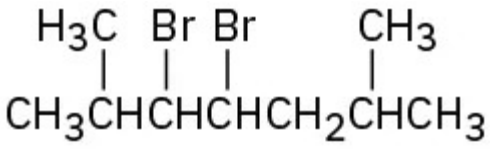
Mechanism Problems

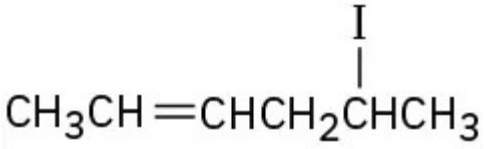
PROBLEM 10-17 In light of the fact that tertiary alkyl halides undergo spontaneous dissociation to yield a carbocation plus halide ion (see Problem 10-41), propose a mechanism for the following reaction.

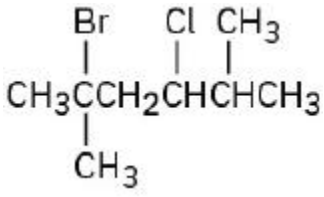


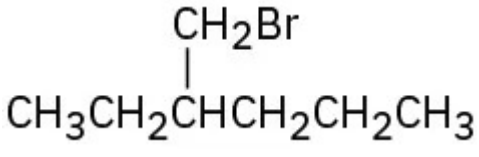
Naming Alkyl Halides

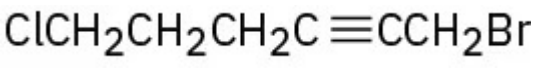
PROBLEM 10-18 Name the following alkyl halides:

(a) 

(b) 

(c) 

(d) 

(e) 

PROBLEM 10-19 Draw structures corresponding to the following IUPAC names:

(a) 2,3-Dichloro-4-methylhexane (b) 4-Bromo-4-ethyl-2-methylhexane

(c) 3-Iodo-2,2,4,4-tetramethylpentane (d) *cis*-1-Bromo-2-ethylcyclopentane

PROBLEM 10-20 Draw and name all the monochlorination products you might obtain from radical chlorination of the following compounds. Which of the products are chiral? Are any products optically active?

(a) 2-methylbutane (b) methylcyclopropane (c) 2,2-dimethylpentane

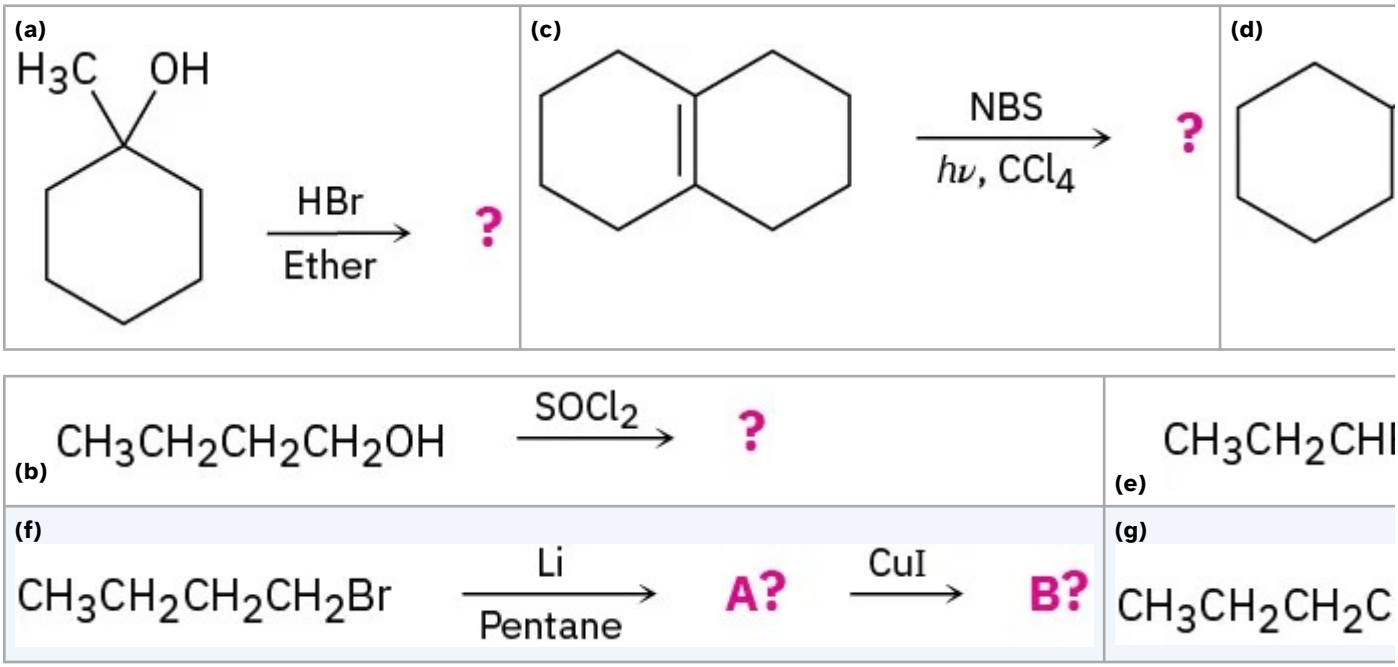
Synthesizing Alkyl Halides

PROBLEM 10-21 How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

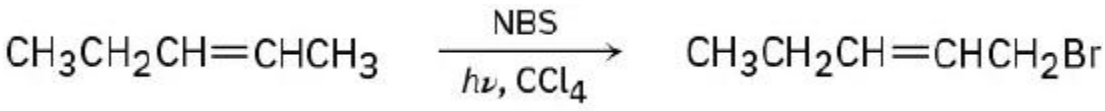
(a) Chlorocyclopentane (b) Methylcyclopentane (c) 3-Bromocyclopentene

(d) Cyclopentanol (e) Cyclopentylcyclopentane (f) 1,3-Cyclopentadiene

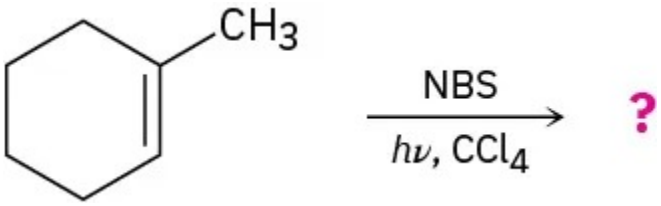
PROBLEM 10-22 Predict the product(s) of the following reactions:



PROBLEM 10-23 A chemist requires a large amount of 1-bromo-2-pentene as starting material for a synthesis and decides to carry out an NBS allylic bromination reaction. What is wrong with the following synthesis plan? What side products would form in addition to the desired product?

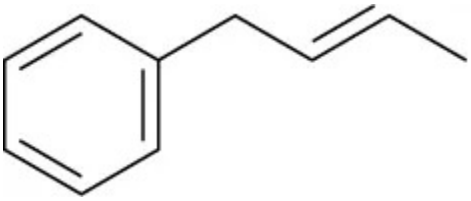


PROBLEM 10-24 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?



PROBLEM 10-25 What product(s) would you expect from the reaction of 1,4-hexadiene with NBS? What is the structure of the most stable radical intermediate?

PROBLEM 10-26 What product would you expect from the reaction of 1-phenyl-2-butene with NBS? Explain.

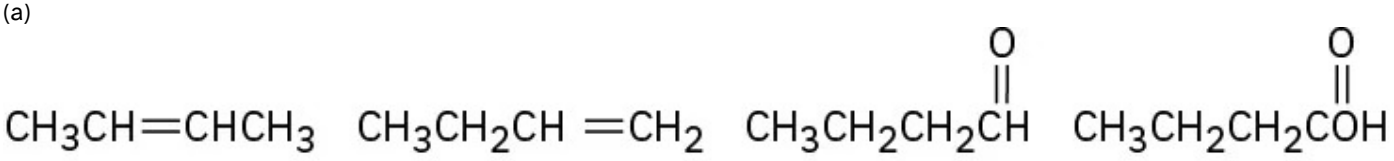


1-Phenyl-2-butene

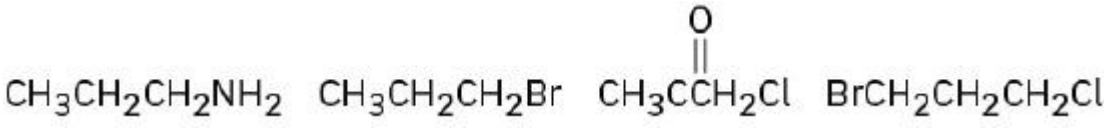
Oxidation and Reduction

PROBLEM 10-27 Rank the compounds in each of the following series in order of increasing oxidation level:

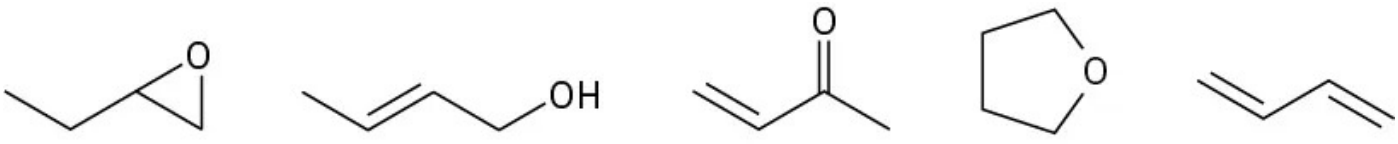
(a)



(b)



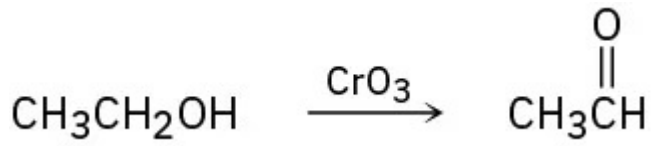
PROBLEM 10-28 Which of the following compounds have the same oxidation level, and which have different levels?



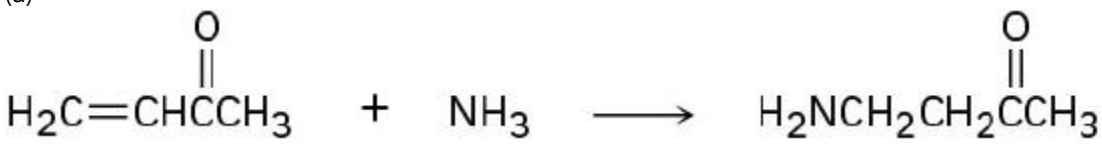
1 **2** **3** **4** **5**

PROBLEM 10-29 Tell whether each of the following reactions is an oxidation, a reduction, or neither:

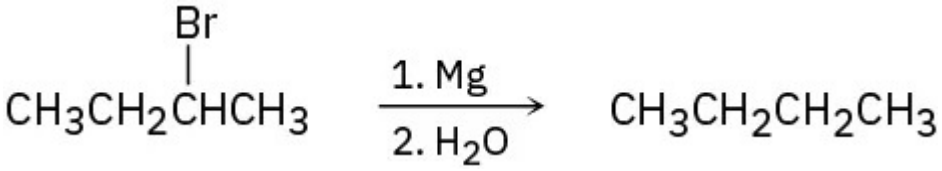
(a)



(b)



(c)



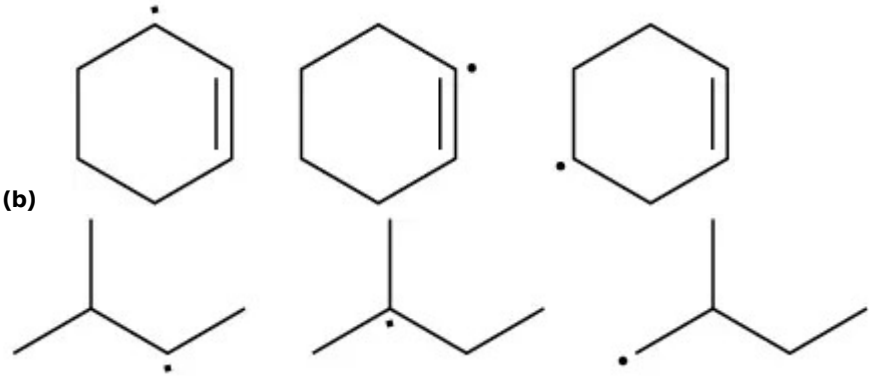
General Problems

PROBLEM 10-30 Arrange the following radicals from most stable to least stable.

(a)

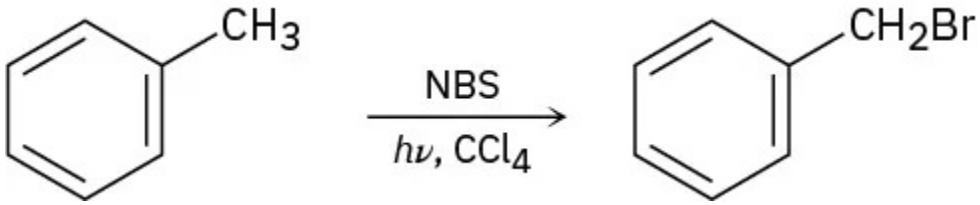


(b)



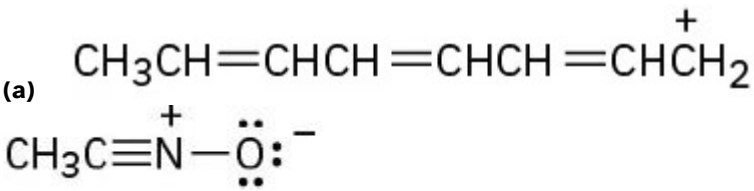
(c)

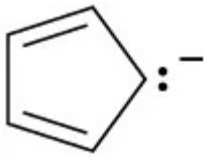
PROBLEM 10-31 Alkylbenzenes such as toluene (methylbenzene) react with NBS to give products in which bromine substitution has occurred at the position next to the aromatic ring (the *benzylic* position). Explain, based on the bond dissociation energies.



PROBLEM 10-32 Draw resonance structures for the benzyl radical, $C_6H_5CH_2\cdot$, the intermediate produced in the NBS bromination reaction of toluene (Problem 10-31).

PROBLEM 10-33 Draw resonance structures for the following species:

(a) 

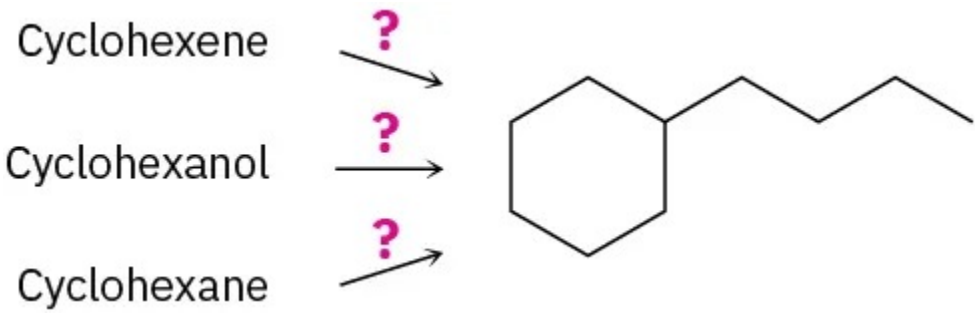
(b) 

(c)

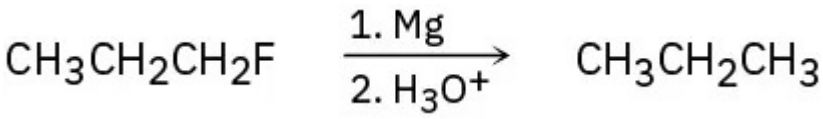
PROBLEM 10-34 (*S*)-3-Methylhexane undergoes radical bromination to yield optically inactive 3-bromo-3-methylhexane as the major product. Is the product chiral? What conclusions can you draw about the radical intermediate?

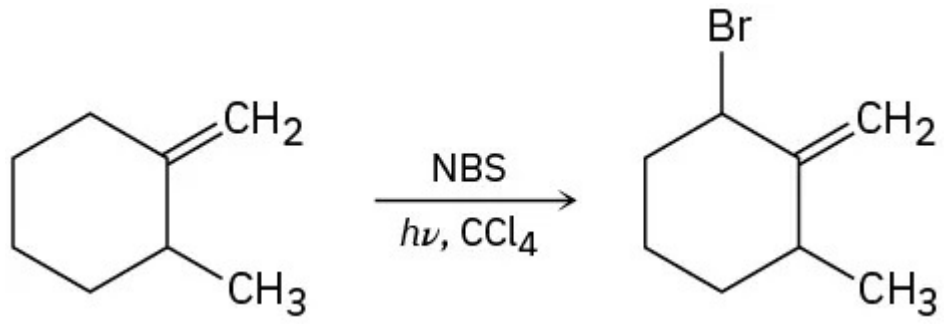
PROBLEM 10-35 Assume that you have carried out a radical chlorination reaction on (*R*)-2-chloropentane and have isolated (in low yield) 2,4-dichloropentane. How many stereoisomers of the product are formed, and in what ratio? Are any of the isomers optically active? (See Problem 10-34.)

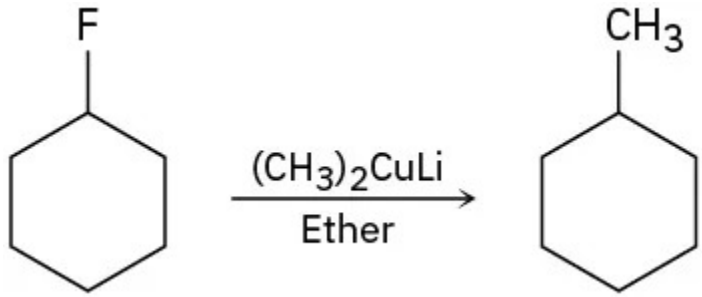
PROBLEM 10-36 How would you carry out the following syntheses?



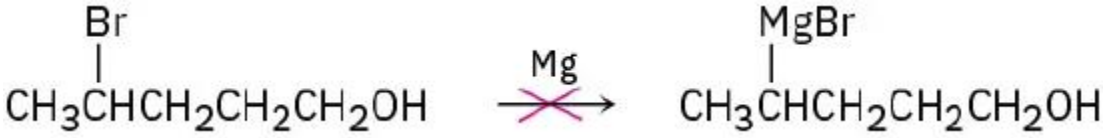
PROBLEM 10-37 The syntheses shown here are unlikely to occur as written. What is wrong with each?

(a) 

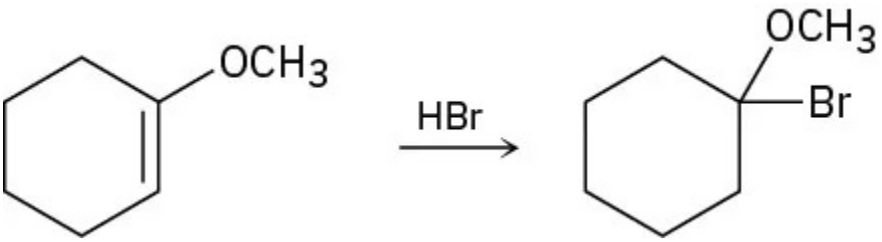
(b) 

(c) 

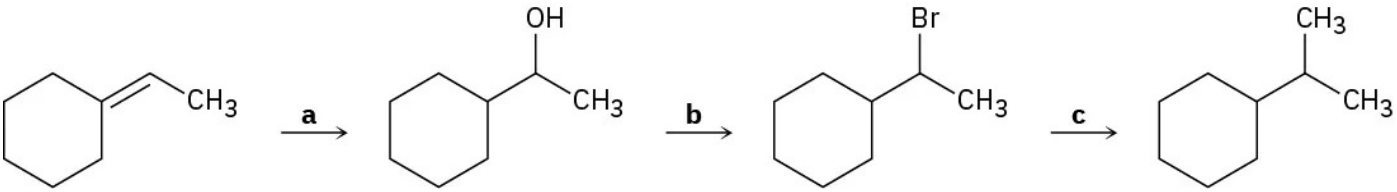
PROBLEM 10-38 Why do you suppose it's not possible to prepare a Grignard reagent from a bromo alcohol such as 4-bromo-1-pentanol? Give another example of a molecule that is unlikely to form a Grignard reagent.



PROBLEM 10-39 The addition of HBr to a double bond with an ether (–OR) substituent occurs regiospecifically to give a product in which the –Br and –OR are bonded to the same carbon. Draw the two possible carbocation intermediates in this electrophilic addition reaction, and explain using resonance why the observed product is formed.



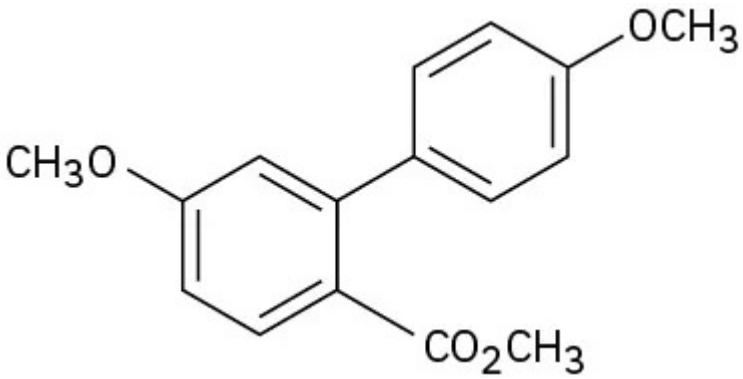
PROBLEM 10-40 Identify the reagents a–c in the following scheme:



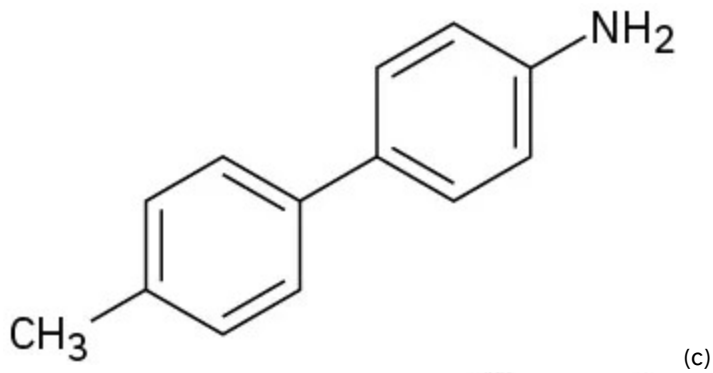
PROBLEM 10-41 Tertiary alkyl halides, R_3CX, undergo spontaneous dissociation to yield a carbocation, R_3C^+, plus halide ion. Which do you think reacts faster, $(CH_3)_3CBr$ or $H_2C{=}CHC(CH_3)_2Br$? Explain.

PROBLEM 10-42 Carboxylic acids (RCO_2H; $pK_a \approx 5$) are approximately 10^{11} times more acidic than alcohols (ROH; $pK_a \approx 16$). In other words, a carboxylate ion (RCO_2^-) is more stable than an alkoxide ion (RO^-). Explain using resonance.

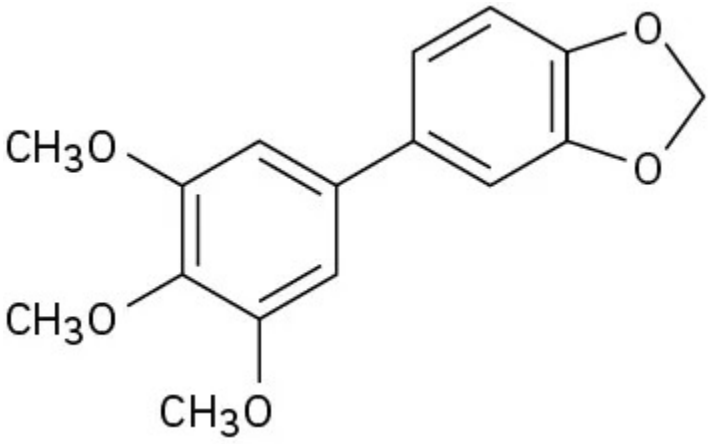
PROBLEM 10-43 How might you use a Suzuki–Miyaura reaction to prepare the biaryl compounds below? In each case, show the two potential reaction partners.



(a) **(b)**



(c)

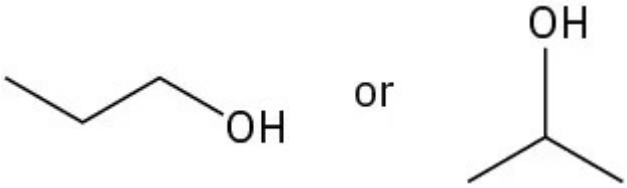


PROBLEM 10-44 The relative rate of radical bromination is 1:82:1640 for 1°:2°:3° hydrogens, respectively. Draw all of the monobrominated products that you might obtain from the radical bromination of the compounds below. Calculate the relative percentage of each.

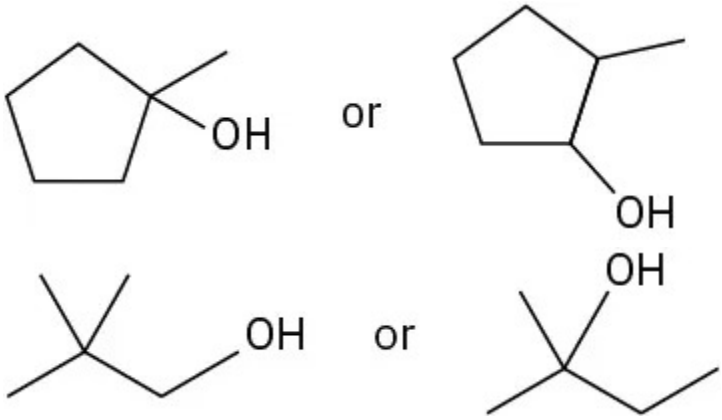
(a) methylcyclobutane (b) 3,3-dimethylpentane (c) 3-methylpentane

PROBLEM 10-45 Choose the alcohol from each pair below that would react faster with HX to form the corresponding alkyl halide.

(a)



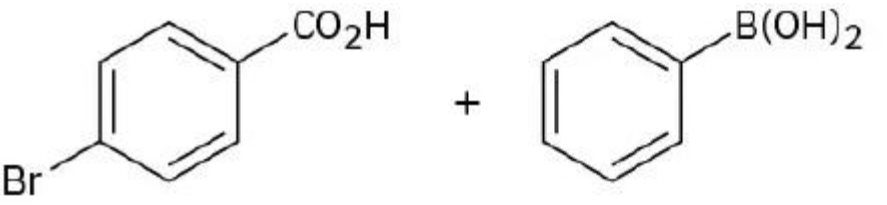
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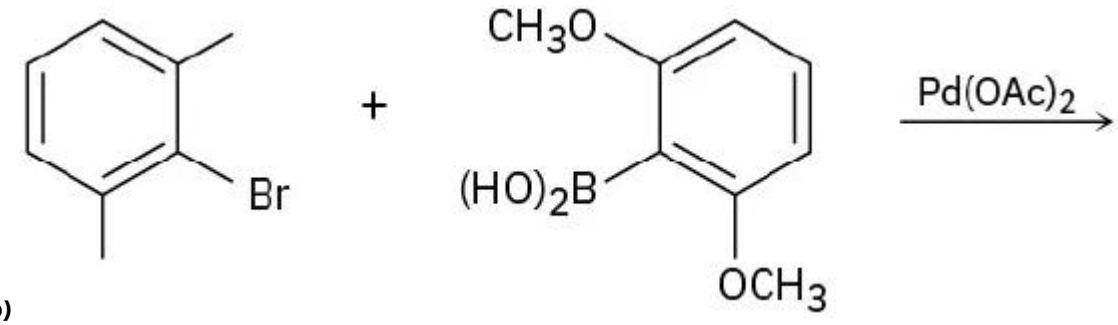
(c)

PROBLEM 10-46 Predict the product and provide the entire catalytic cycle for the following Suzuki–Miyaura reactions.

(a)

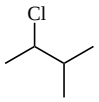


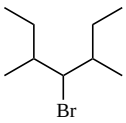
(b)

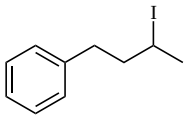


Additional Problems

PROBLEM 10-47 Predict the alcohol and reagent required for the synthesis of the following halides:







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11: REACTIONS OF ALKYL HALIDES- NUCLEOPHILIC SUBSTITUTIONS AND ELIMINATIONS

Learning Objectives

After you have completed Chapter 11, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use the reactions studied in this chapter with those from earlier ones when designing multistep syntheses.
- use the reactions and concepts discussed in this chapter to solve road map problems.
- define, and use in context, the key terms introduced.

In this course, you have already seen several examples of nucleophilic substitution reactions; now you will see that these reactions can occur by two different mechanisms. You will study the factors that determine which mechanism will be in operation in a given situation, and examine possible ways for increasing or decreasing the rates at which such reactions occur. The stereochemical consequences of both mechanisms will also be discussed. Elimination reactions often accompany nucleophilic substitution; so these reactions are also examined in this chapter. Again you will see that two different mechanisms are possible, and, as in the case of nucleophilic substitution reactions, chemists have learned a great deal about the factors that determine which mechanism will be observed when a given alkyl halide undergoes such a reaction.

11.0: Why This Chapter?

11.1: The Discovery of Nucleophilic Substitution Reactions

11.2: The SN2 Reaction

11.3: Characteristics of the SN2 Reaction

11.4: The SN1 Reaction

11.5: Characteristics of the SN1 Reaction

11.6: Predicting SN1 vs. SN2 mechanisms

11.7: Elimination Reactions- Zaitsev's Rule

11.8: The E2 Reaction and Mechanism

11.9: The E2 Reaction and Cyclohexane Conformation

11.10: The E1 and E1cB Reactions

11.11: Biological Reactions

11.12: Deciding between SN1, SN2, E1, and E2

11.13: Chemistry Matters—Green Chemistry

11.A: Nucleophilic Substitutions and Eliminations Reactions (Summary)

11.B: Additional Problems

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11.0: Why This Chapter?

Nucleophilic substitution and base-induced elimination are two of the most widely occurring and versatile reactions in organic chemistry, both in the laboratory and in biological pathways. We'll look at them closely in this chapter to see how they occur, what their characteristics are, and how they can be used. We'll begin with substitution reactions.



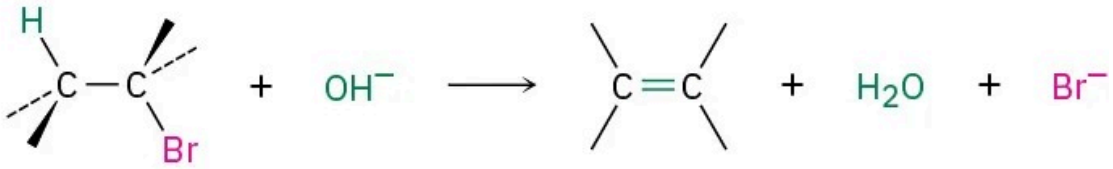
Figure 11.0.1: Competition occurs throughout nature. In chemistry, competition often occurs between alternative reaction pathways, such as in the substitution and elimination reactions of alkyl halides. (credit: modification of work "Bull moose fight" by Grand Teton, National Parks Service/Flickr, Public Domain)

We saw in the preceding chapter that the carbon–halogen bond in an alkyl halide is polar and that the carbon atom is electron-poor. Thus, alkyl halides are electrophiles, and much of their chemistry involves polar reactions with nucleophiles and bases. Alkyl halides do one of two things when they react with a nucleophile/base such as hydroxide ion: they either undergo *substitution* of the X group by the nucleophile, or they undergo *elimination* of HX to yield an alkene.

Substitution



Elimination



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11.1: The Discovery of Nucleophilic Substitution Reactions

Discovery of the nucleophilic substitution reaction of alkyl halides dates back to work carried out by the German chemist Paul Walden in 1896. Walden found that the pure enantiomeric (+)- and (–)-malic acids could be interconverted through a series of simple substitution reactions. When Walden treated (–)-malic acid with PCl_5, he isolated (+)-chlorosuccinic acid. This, on treatment with wet Ag_2O, gave (+)-malic acid. Similarly, reaction of (+)-malic acid with PCl_5 gave (–)-chlorosuccinic acid, which was converted into (–)-malic acid when treated with wet Ag_2O. The full cycle of reactions is shown in Figure 11.1.1.

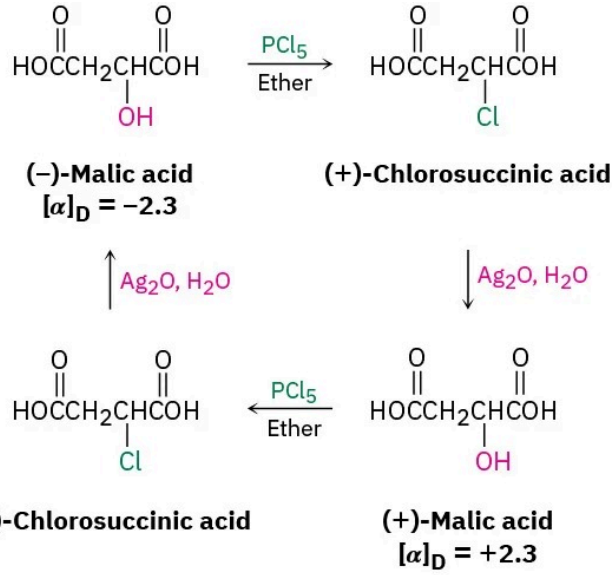


Figure 11.1.1: Walden's cycle of reactions interconverting (+)- and (–)-malic acids.

At the time, the results were astonishing. The eminent chemist Emil Fischer called Walden's discovery "the most remarkable observation made in the field of optical activity since the fundamental observations of Pasteur." Because (–)-malic acid was converted into (+)-malic acid, some reactions in the cycle must have occurred with a change, or inversion, of configuration at the chirality center. But which ones, and how? (Remember from Section 5.5 that the direction of light rotation and the configuration of a chirality center aren't directly related. You can't tell by looking at the sign of rotation whether a change in configuration has occurred during a reaction.)

Today, we refer to the transformations taking place in Walden's cycle as **nucleophilic substitution reactions** because each step involves the substitution of one nucleophile (chloride ion, Cl^-, or hydroxide ion, HO^-) by another. Nucleophilic substitution reactions are one of the most common and versatile reaction types in organic chemistry.



Following the work of Walden, further investigations were undertaken during the 1920s and 1930s to clarify the mechanism of nucleophilic substitution reactions and to find out how inversions of configuration occur. Among the first series studied was one that interconverted the two enantiomers of 1-phenyl-2-propanol (Figure 11.1.2). Although this particular series of reactions involves nucleophilic substitution of an alkyl *para*-toluenesulfonate (called a tosylate) rather than an alkyl halide, exactly the same type of reaction is involved as that studied by Walden. For all practical purposes, the entire tosylate group acts as if it were simply a halogen substituent. (In fact, when you see a tosylate substituent in a molecule, do a mental substitution and tell yourself that you're dealing with an alkyl halide.)

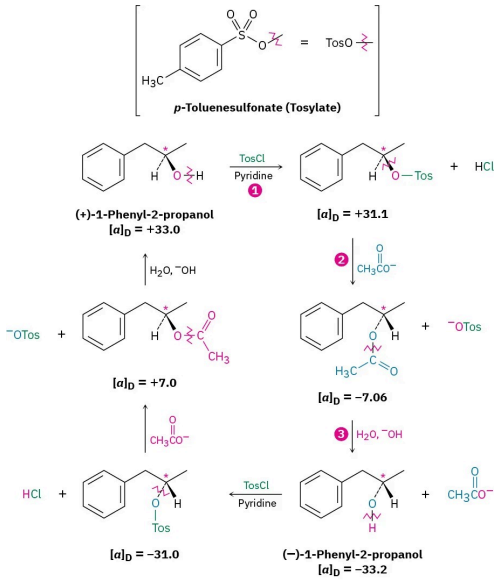
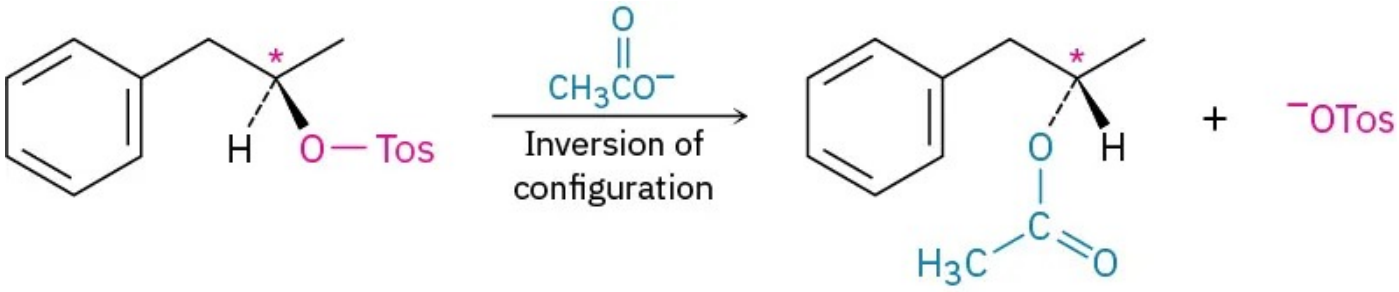


Figure 11.1.2: A Walden cycle interconverting (+) and (–) enantiomers of 1-phenyl-2-propanol. Chirality centers are marked by asterisks, and the bonds broken in each reaction are indicated by red wavy lines. The inversion of chirality occurs in step **2**, where acetate ion substitutes for tosylate ion.

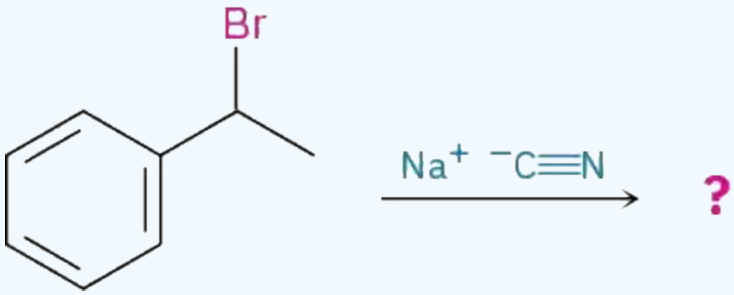
In the three-step reaction sequence shown in Figure 11.1.2, (+)-1-phenyl-2-propanol is interconverted with its (–) enantiomer, so at least one of the three steps must involve an inversion of configuration at the chirality center. Step **1**, formation of a tosylate, occurs by breaking the O–H bond of the alcohol rather than the C–O bond to the chiral carbon, so the configuration around the carbon is unchanged. Similarly, step **3**, hydroxide-ion cleavage of the acetate, takes place without breaking the C–O bond at the chirality center. Thus, the inversion of stereochemical configuration must take place in step **2**, the nucleophilic substitution of tosylate ion by acetate ion.



From this and nearly a dozen other series of similar reactions, researchers concluded that the nucleophilic substitution reaction of a primary or secondary alkyl halide or tosylate always proceeds with inversion of configuration. (Tertiary alkyl halides and tosylates, as we'll see shortly, give different stereochemical results and react by a different mechanism than the primary and secondary ones.)

Worked Example 11.1.1: Predicting the Stereochemistry of a Nucleophilic Substitution Reaction

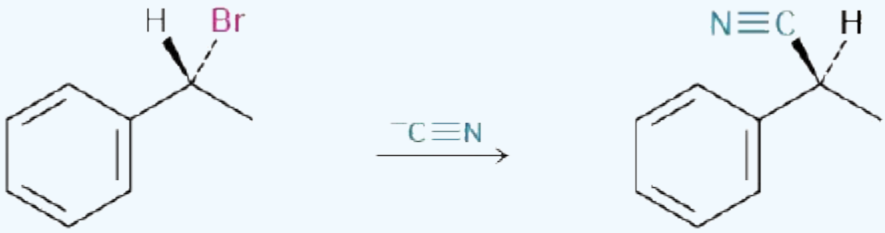
What product would you expect from a nucleophilic substitution reaction of (*R*)-1-bromo-1-phenylethane with cyanide ion, $^{-}C{\equiv}N$, as nucleophile? Show the stereochemistry of both reactant and product, assuming that inversion of configuration occurs.



Strategy

Draw the *R* enantiomer of the reactant, and then change the configuration of the chirality center while replacing the ⁻Br with a ⁻CN.

Solution



(*R*)-1-Bromo-1-phenylethane **(*S*)-2-Phenylpropanenitrile**

Exercise 11.1.1

What product would you expect from a nucleophilic substitution reaction of (S)-2-bromohexane with acetate ion, $CH_3CO_2^-$? Assume that inversion of configuration occurs, and show the stereochemistry of both the reactant and product.

Answer available at the end of this section.

Answers

Exercise 11.1.1

(*R*)-1-Methylpentyl acetate, $CH_3CO_2CH(CH_3)CH_2CH_2CH_2CH_3$

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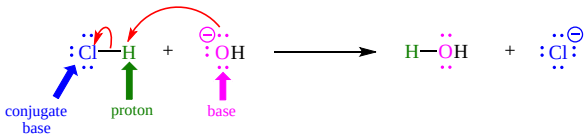
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11.2: The SN2 Reaction

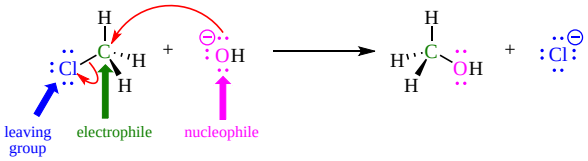
Brønsted-Lowry acid-base reactions

In many ways, the proton transfer process in a Brønsted-Lowry acid-base reaction can be thought of as simply a special kind of nucleophilic substitution reaction, one in which the electrophile is a hydrogen rather than a carbon.

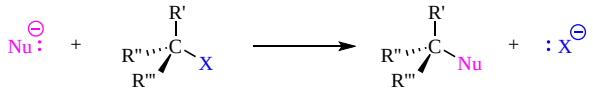
Acid-base reaction:



Nucleophilic substitution:

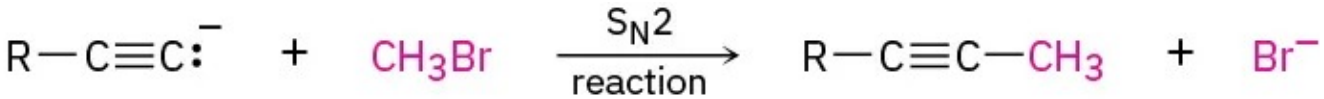


In both reaction types, we are looking at very similar players: an electron-rich species (the nucleophile/base) attacks an electron-poor species (the electrophile/proton), driving off the leaving group/conjugate base. Instead of showing a specific nucleophile like hydroxide, we will simply refer to the nucleophilic reactant as 'Nu'. Similarly, we will call the leaving group 'X'. We will see, as we study actual reactions, that leaving groups are sometimes negatively charged, sometimes neutral, and sometimes positively charged. We will also see some examples of nucleophiles that are negatively charged and some that are neutral. Therefore, in this general picture, we will not include a charge designation on the 'X' or 'Nu' species. We will generalize the three other groups bonded on the electrophilic central carbon as R_1, R_2, and R_3: these symbols could represent hydrogens as well as alkyl groups. Here, then, is the generalized picture of a concerted (single-step) nucleophilic substitution reaction.



R = alkyl or H

A wide array of substances can be prepared using nucleophilic substitution reactions. In fact, we've already seen examples in previous chapters. For instance, the reaction of an acetylide anion with an alkyl halide, discussed in Section 9.8, is an S_N2 reaction in which the acetylide nucleophile displaces a halide leaving group.



An acetylide anion

Order of Reaction

In almost all chemical reactions, there is a direct relationship between the rate at which the reaction occurs and the concentrations of the reactants. When we measure this relationship, we measure the kinetics of the reaction. For example, let's look at the kinetics of a simple nucleophilic substitution—the reaction of CH_3Br with OH^- to yield CH_3OH plus Br^-.



With a given temperature, solvent, and concentration of reactants, the substitution occurs at a certain rate. If we double the concentration of $\mathrm{OH^-}$, the frequency of encounters between reaction partners doubles and we find that the reaction rate also doubles. Similarly, if we double the concentration of $\mathrm{CH_3Br}$, the reaction rate again doubles. We call such a reaction, in which the rate is linearly dependent on the concentrations of two species, a second-order reaction. Mathematically, we can express this second-order dependence of the nucleophilic substitution reaction by setting up a **rate equation**. As either $[\mathrm{RX}]$ or $[^-\mathrm{OH}]$ changes, the rate of the reaction changes proportionately.

$$\begin{aligned} \text{Reaction rate} &= \text{Rate of disappearance of reactant} \\ &= \text{Rate of appearance of product} \\ &= k \times [\mathrm{RX}] \times [^-\mathrm{OH}] \end{aligned} \tag{11.2.1}$$

where

- $[\mathrm{RX}]$ is the $\mathrm{CH_3Br}$ concentration in molarity,
- $[^-\mathrm{OH}]$ is the $^-\mathrm{OH}$ concentration in molarity, and
- k is a constant value (the rate constant)

The S_N2 Mechanism

A mechanism that accounts for both the inversion of configuration and the second-order kinetics that are observed with nucleophilic substitution reactions was suggested in 1937 by the British chemists E. D. Hughes and Christopher Ingold, who formulated what they called the **S_N2 reaction**—short for *substitution, nucleophilic, bimolecular*. (**Bimolecular** means that two molecules, nucleophile and alkyl halide, take part in the step whose kinetics are measured.)

The essential feature of the S_N2 mechanism is that it takes place in a single step, without intermediates, when the incoming nucleophile reacts with the alkyl halide or tosylate (the *substrate*) from a direction opposite the group that is displaced (the **leaving group**). As the nucleophile comes in on one side of the substrate and bonds to the carbon, the halide or tosylate departs from the other side, thereby inverting the stereochemical configuration. The process is shown in Figure 11.2.1 for the reaction of (*S*)-2-bromobutane with HO^- to give (*R*)-2-butanol.

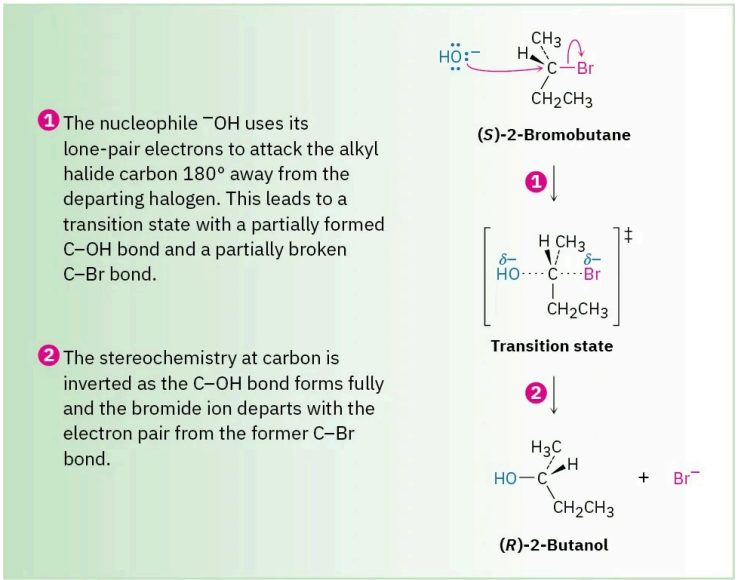


Figure 11.2.1: The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

As shown in Figure 11.2.1, the S_N2 reaction occurs when an electron pair on the nucleophile Nu:$^-$ forces out the group X:$^-$, which takes with it the electron pair from the former C–X bond. This occurs through a transition state in which the new Nu–C bond is partially formed at the same time that the old C–X bond is partially broken and in which the negative charge is shared by both the incoming nucleophile and the outgoing halide ion. The transition state for this inversion has the remaining three bonds to carbon in a planar arrangement (Figure 11.2.2).

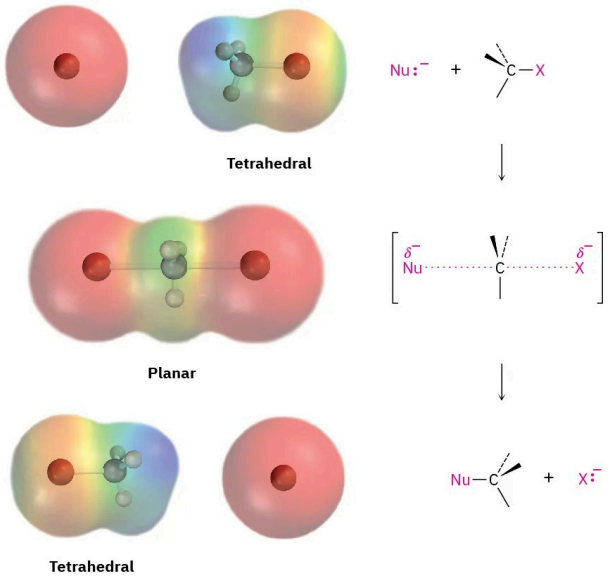


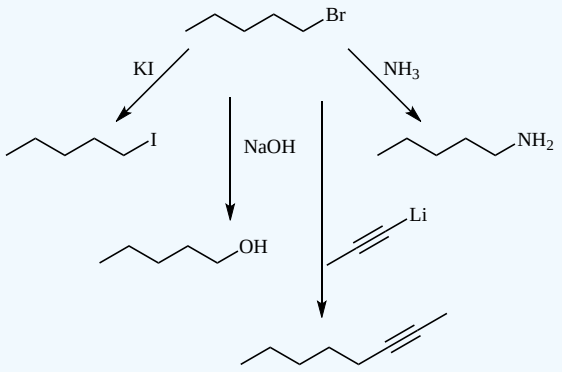
Figure 11.2.2: The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that the **negative charge** is delocalized in the transition state.

Example 11.2.1

What product(s) do you expect from the reaction of 1-bromopentane with each of the following reagents in an S_N2 reaction?

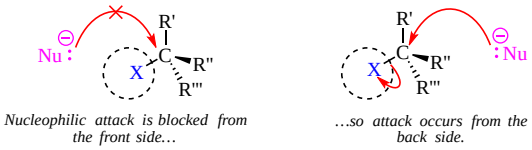
a) KI b) NaOH c) $CH_3C{\equiv}C\text{-}Li$ d) NH_3

Solution



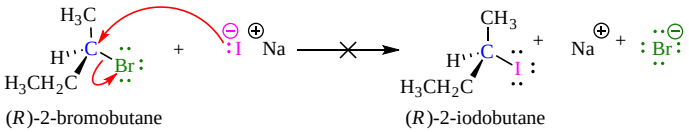
S_N2 Reactions Are Stereospecific

The mechanism proposed by Hughes and Ingold is fully consistent with experimental results, explaining both stereochemical and kinetic data. Thus, the requirement for a backside approach of the entering nucleophile (180° away from the departing X group) causes the stereochemistry of the substrate to invert, much like an umbrella turning inside-out in the wind. The Hughes–Ingold mechanism also explains why second-order kinetics are observed: the S_N2 reaction occurs in a single step that involves both alkyl halide and nucleophile. Two molecules are involved in the step whose rate is measured.

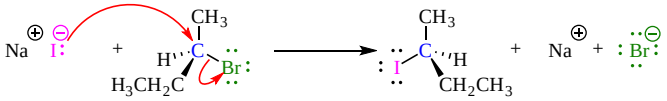


A stereospecific reaction is one in which different stereoisomers react to give different stereoisomers of the product. For example, if the substrate is an (*R*) enantiomer, a frontside nucleophilic attack results in retention of configuration, and the formation of the (*R*) enantiomer. A backside nucleophilic attack results in inversion of configuration, and the formation of the (S) enantiomer.

Frontside attack with retention of configuration:

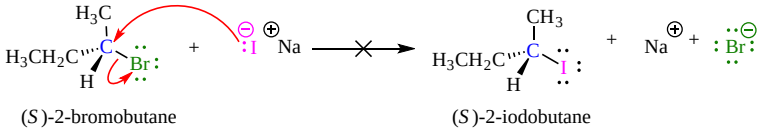


Backside attack with inversion of configuration:

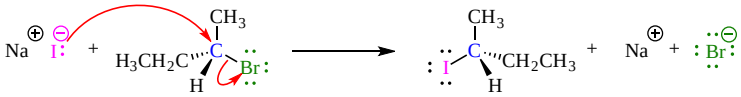


Conversely, if the substrate is an (S) enantiomer, a frontside nucleophilic attack results in retention of configuration and the formation of the (S) enantiomer. A backside nucleophilic attack results in inversion of configuration and the formation of the (*R*) enantiomer.

Frontside attack with retention of configuration:



Backside attack with inversion of configuration:



In conclusion, S_N2 reactions that begin with the (*R*) enantiomer as the substrate will form the (S) enantiomer as the product. Those that begin with the (S) enantiomer as the substrate will form the (*R*) enantiomer as the product. This concept also applies to both *cis* and trans substrates. If the *cis* configuration is the substrate, the resulting product will be *trans*. Conversely, if the *trans* configuration is the substrate, the resulting product will be *cis*.

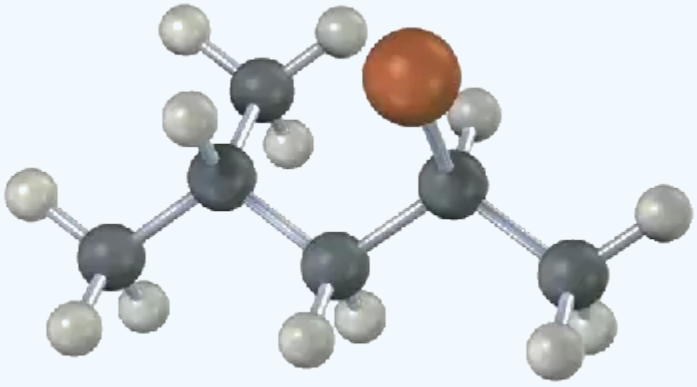
Exercise 11.2.1

What product would you expect to obtain from S_N2 reaction of $CH_3CO_2^-$ with (S)-2-bromopentane? Show the stereochemistry of both the reactant and product.

Answer available at the end of this section.

Exercise 11.2.2

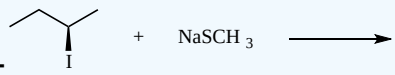
Assign configuration to the following substance, and draw the structure of the product that would result from nucleophilic substitution reaction with HS^- (reddish brown = Br):

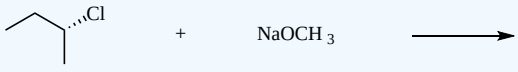


Answer available at the end of this section.

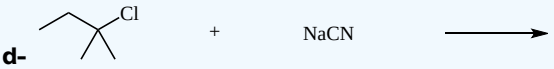
Exercise 11.2.3

Predict the structure of the product in this S_N2 reaction. Be sure to specify stereochemistry.

a- 

b- 

c- 

d- 

e- (*S*)-2-bromopentane + sodium hydroxide

Answer available at the end of this section.

Exercise 11.2.4

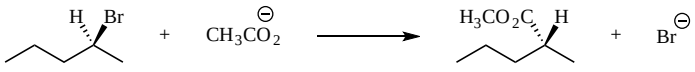
What product would you expect from S_N2 reaction of 1-bromobutane with each of the following?

a. NaI
b. KOH
c. H–C≡C–Li
d. NH_3

Answer available at the end of this section.

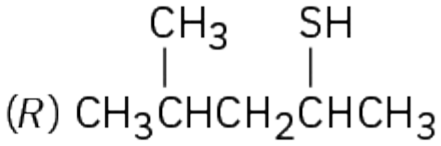
Answers

Exercise 11.2.1

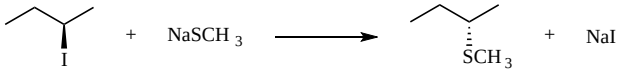


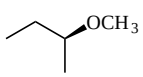
Exercise 11.2.2

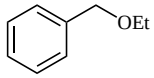
(S)-2-Bromo-4-methylpentane ⟶



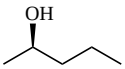
Exercise 11.2.3

a- 

b- 

c- 

d- no reaction (3^{o} alkyl halide)

e- 

Exercise 11.2.4

a. 1-Iodobutane
b. 1-Butanol
c. 1-Hexyne
d. Butylammonium bromide

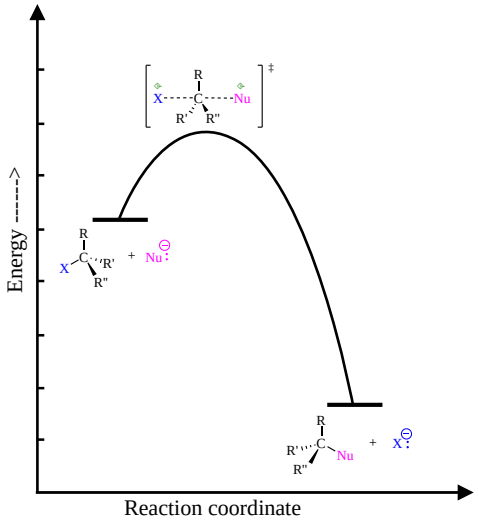
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11.3: Characteristics of the SN2 Reaction

Potential Energy Diagram for an S_N2 Reaction

The potential energy diagram for an S_N2 reaction is shown below. This is a single-step, concerted process so a single transition state is formed. A transition state, unlike a reaction intermediate, is a very short-lived species that cannot be isolated or directly observed. For an S_N2 reaction, the transition state directly determines the energy of activation, which must be overcome for the reaction to occur. Factors that affect the stability of the transition state affect the rate of the S_N2 reaction.



For an S_N2 reaction, the transition state represents the halfway point of the reaction. The C-Nu bond is in the process of forming and is represented by a dashed bond. The X-C bond is in the process of breaking and is also represented by a dash bond. The negative charge of the nucleophile is in the process of being transferred to the leaving groups. This is represented by both the nucleophile and the leaving group having a partial negative charge. The electrophilic carbon and the three 'R' substituents all lie on the same plane. Brackets and a double-dagger are placed around the structure to represent that it is a transition state.

Variables Affecting the Rate of Reaction

Now that the mechanism of S_N2 reactions is known, we need to explore the variables that influence them. Some S_N2 reactions are fast, while others are slow; some occur with high yield, and others with low yield. Understanding the factors involved is valuable when deciding whether a reaction proceeds via an S_N2 mechanism. Let's begin by recalling a few things about reaction rates in general.

The rate of a chemical reaction is determined by the activation energy $\Delta G‡$, the energy difference between the reactant ground state and the transition state. A change in reaction conditions can affect $\Delta G^‡$ either by changing the reactant energy level or by changing the transition-state energy level. (Figure 11.3.1)

- Lowering the reactant energy or raising the transition-state energy increases $\Delta G^‡$ and decreases the reaction rate.
- Raising the reactant energy or decreasing the transition-state energy decreases $\Delta G^‡$ and increases the reaction rate.

We'll see examples of all these effects as we look at S_N2 reaction variables.

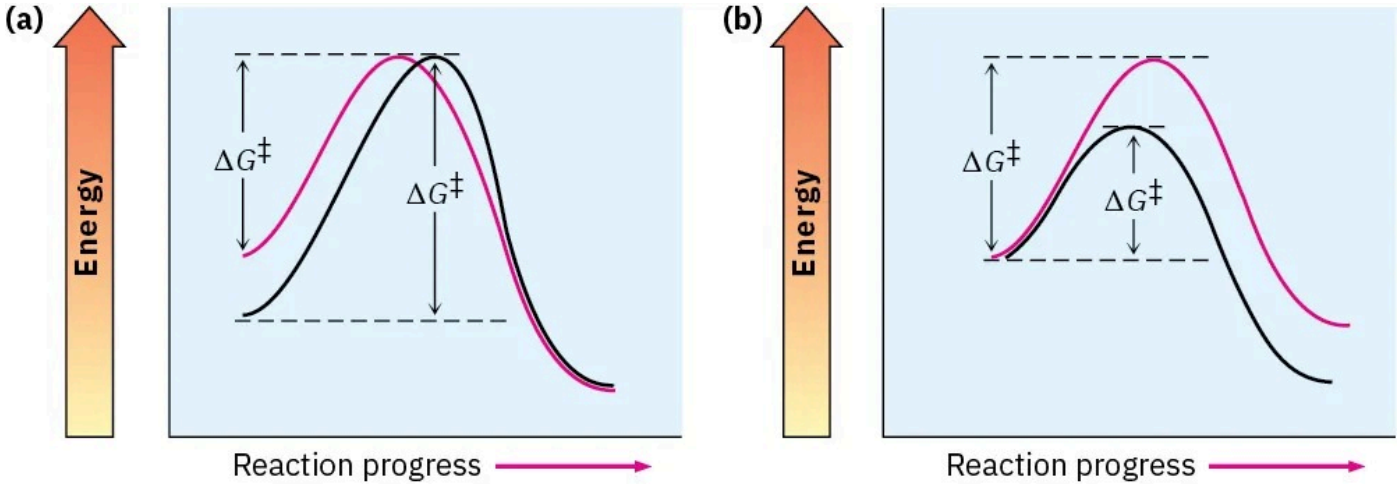
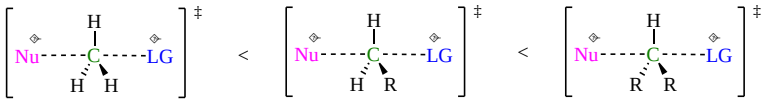


Figure 11.3.1: The effects of changes in reactant and transition-state energy levels on reaction rate. (a) A higher reactant energy level (red curve) corresponds to a faster reaction (smaller $\Delta G^{\ddagger}$). (b) A higher transition-state energy level (red curve) corresponds to a slower reaction (larger $\Delta G^{\ddagger}$).

Substrate: Steric Effects in the S_N2 Reaction

The first S_N2 reaction variable to look at is the structure of the substrate. Because the S_N2 transition state involves partial bond formation between the incoming nucleophile and the alkyl halide carbon atom, it seems reasonable that a hindered, bulky substrate should prevent easy approach of the nucleophile, making bond formation difficult.

Steric Repulsion of S_N2 Transition States



In other words, the transition state for the reaction of a sterically hindered substrate, whose carbon atom is “shielded” from the approach of the incoming nucleophile, is higher in energy and forms more slowly than the corresponding transition state for a less hindered substrate (Figure 11.3.2).

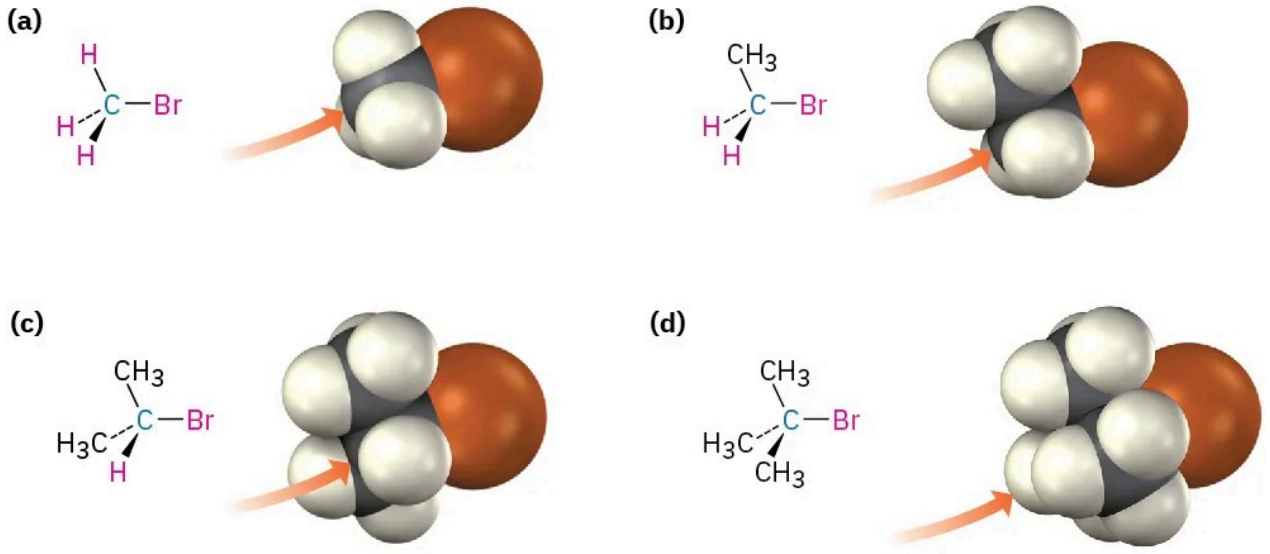
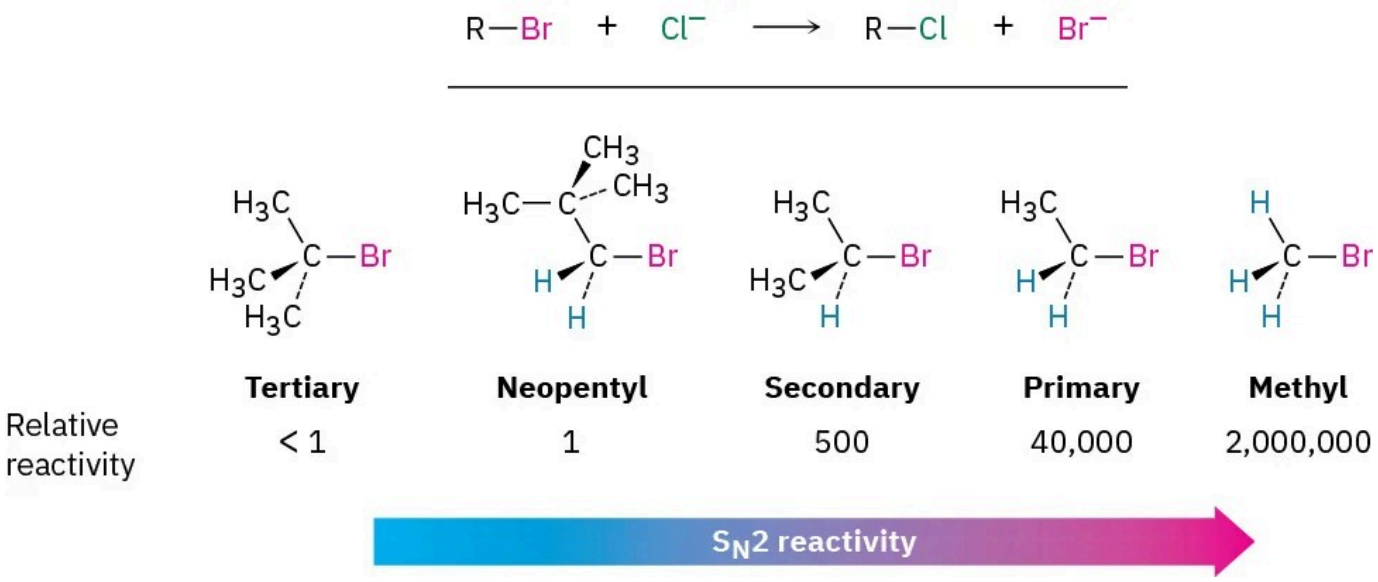


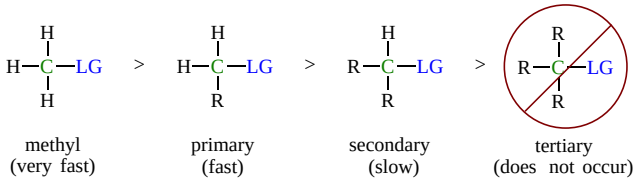
Figure 11.3.2: Steric hindrance to the S_N2 reaction. As the models indicate, the carbon atom in **(a)** bromomethane is readily accessible, resulting in a fast S_N2 reaction. The carbon atoms in **(b)** bromoethane (primary), **(c)** 2-bromopropane (secondary), and **(d)** 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.

As Figure 11.3.2 shows, the difficulty of the nucleophile approach increases as the three substituents bonded to the halo-substituted carbon atom increase in size. Methyl halides are by far the most reactive substrates in S_N2 reactions, followed by primary alkyl halides such as ethyl and propyl. Alkyl branching at the reacting center, as in isopropyl halides (2°), slows the reaction greatly, and further branching, as in *tert*-butyl halides (3°), effectively halts the reaction. Even branching one carbon away from the reacting center, as in 2,2-dimethylpropyl *(neopentyl)* halides, greatly hinders nucleophilic displacement. As a result, S_N2 reactions occur only at relatively unhindered sites and are normally useful only with methyl halides, primary halides, and a few simple secondary halides. Relative reactivities for some different substrates are as follows:

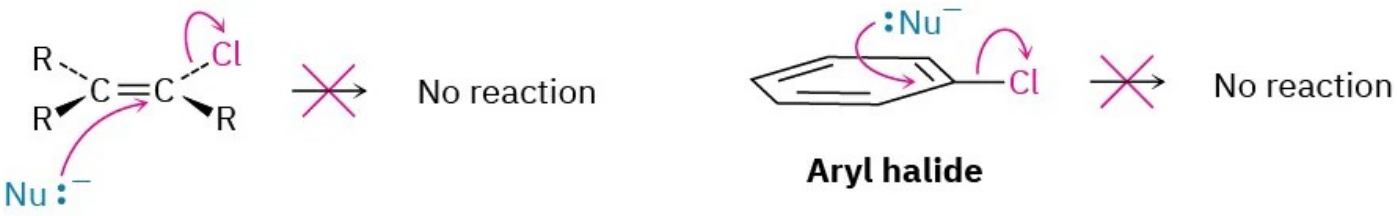


The diagram below illustrates this concept, showing that electrophilic carbons attached to three hydrogen atoms result in faster nucleophilic substitution reactions, in comparison to primary and secondary haloalkanes, which result in nucleophilic substitution reactions that occur at slower or much slower rates, respectively. Notice that a tertiary haloalkane, that which has three R groups attached, does not undergo nucleophilic substitution reactions at all. The addition of a third R group to this molecule creates a carbon that is entirely blocked.

S_N2 Displacement Reactivity of Haloalkanes



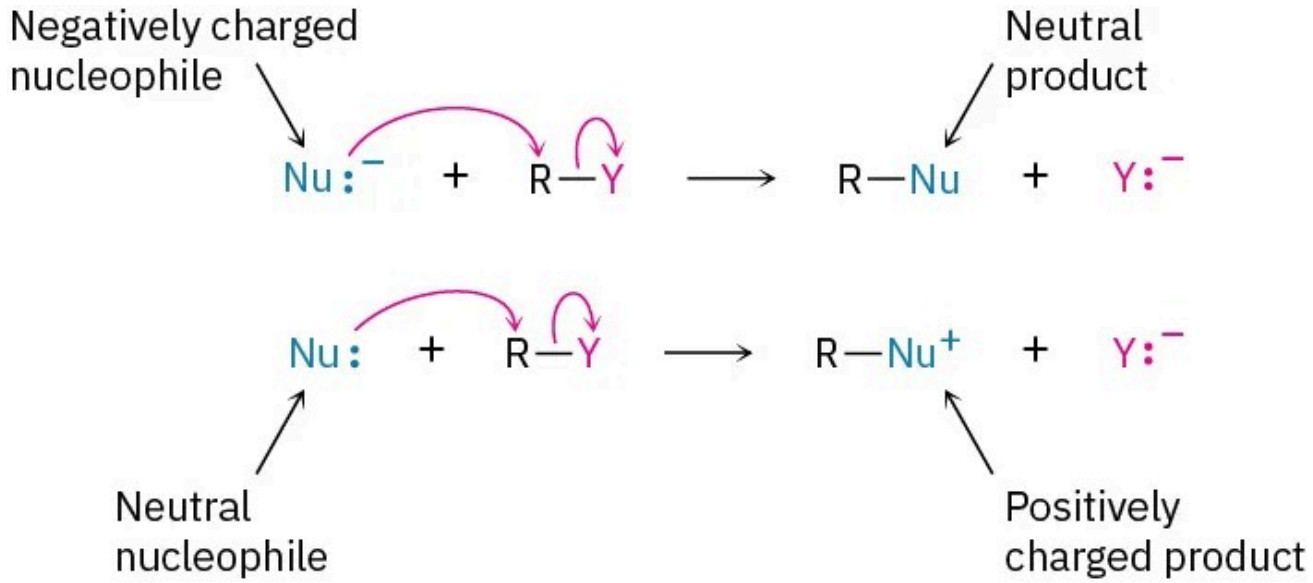
Vinylic halides (\(\ce{R2C=CR}\)) and aryl halides are not shown on this reactivity list because they are unreactive toward S_N2 displacement. This lack of reactivity is due to steric factors: the incoming nucleophile would have to approach in the plane of the carbon–carbon double bond and burrow through part of the molecule to carry out a backside displacement.



Vinylic halide

The Nucleophile

Another variable that has a significant effect on the S_N2 reaction is the nature of the nucleophile. Any compound, neutral or charged, which has lone pair electrons can act as a nucleophile, as long as it is a Lewis base. After an S_N2 reaction, neutral nucleophiles make positively charged products and negatively charged nucleophiles make neutral products. In general, negatively charged compounds tend to make better nucleophiles.

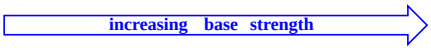


When thinking about nucleophiles, the first thing to recognize is that, for the most part, the same quality of 'electron-richness' that makes something nucleophilic also makes it basic: *nucleophiles can be bases, and bases can be nucleophiles*. It should not be surprising, then, that most of the trends in basicity that we have already discussed also apply to nucleophilicity.

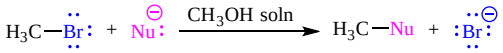
Some confusion in distinguishing basicity (base strength) and nucleophilicity (nucleophile strength) is inevitable. Since basicity is a less troublesome concept; it is convenient to start with it. Basicity refers to the ability of a base to accept a proton. Basicity may be related to the pK_a of the corresponding conjugate acid, as shown below. The strongest bases have the weakest conjugate acids and vice versa. The range of basicities included in the following table is remarkable, covering over fifty powers of ten! In general, as the pKa of the conjugate acid increases, the base becomes a stronger nucleophile. This, however, is not always the

case.

Base	$I^{(-)}$	$Cl^{(-)}$	H_2O	$CH_3CO_2^{(-)}$	$RS^{(-)}$	$CN^{(-)}$	$RO^{(-)}$	$NH_2^{(-)}$	$CH_3^{(-)}$
Conj. Acid	HI	HCl	$H_3O^{(+)}$	CH_3CO_2H	RSH	HCN	ROH	NH_3	CH_4
pK_a	-9	-7	0.0	4.8	8	9.1	16	33	48



Nucleophilicity is a more complex property. It commonly refers to the rate of substitution reactions at the halogen-bearing **carbon atom** of a reference alkyl halide, such as CH_3-Br. Thus the nucleophilicity of the $Nu:^{(-)}$ reactant in the following substitution reaction varies as shown in the chart below:



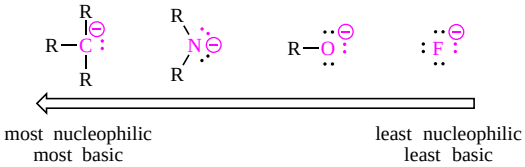
Nucleophilicity: $H_2O < CH_3CO_2^{(-)} < NH_3 < Cl^{(-)} < Br^{(-)} < HO^{(-)} < CH_3O^{(-)} < I^{(-)} < CN^{(-)} < CH_3S^{(-)}$



Periodic Trends in Nucleophilicity

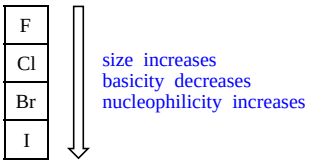
There are predictable periodic trends in nucleophilicity. Moving horizontally across the second row of the table, the trend in nucleophilicity parallels the trend in basicity:

The reasoning behind the horizontal nucleophilicity trend is the same as the reasoning behind the basicity trend: more electronegative elements hold their electrons more tightly and are less able to donate them to form a new bond. This horizontal trend also tells us that amines are more nucleophilic than alcohols, although both groups commonly act as nucleophiles in both laboratory and biochemical reactions.



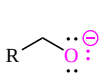
Recall that the basicity of atoms decreases as we move vertically down a column on the periodic table: thiolate ions are less basic than alkoxide ions, for example, and bromide ion is less basic than chloride ion, which in turn is less basic than fluoride ion. Recall also that this trend can be explained by considering the increasing size of the 'electron cloud' around the larger ions: the electron density inherent in the negative charge is spread around a larger area, which tends to increase stability (and thus reduce basicity).

As Size Increases, Basicity Decreases: In general, if we move from the top of the periodic table to the bottom of the periodic table, as shown in the diagram below, the size of an atom will increase. As size increases, basicity will decrease, meaning a species will be less likely to act as a base; that is, the species will be less likely to share its electrons and act as a nucleophile.

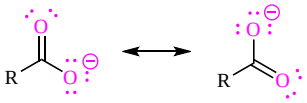


Resonance Effects on Nucleophilicity

Resonance effects also come into play when comparing the inherent nucleophilicity of different molecules. The reasoning involved is the same as that which we used to understand resonance effects on basicity. If the electron lone pair on a heteroatom is delocalized by resonance, it is inherently less reactive - meaning less nucleophilic, and also less basic. An alkoxide ion, for example, is more nucleophilic and more basic than a carboxylate group, even though in both cases the nucleophilic atom is a negatively charged oxygen. In the alkoxide, the negative charge is localized on a single oxygen, while in the carboxylate the charge is delocalized over two oxygen atoms by resonance.

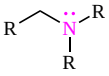


alkoxide ion
charge is localized on oxygen
more nucleophilic

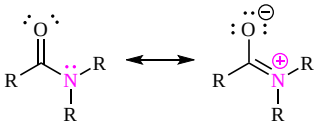


carboxylate ion
charge is delocalized over both oxygens
less nucleophilic

The nitrogen atom on an amide is less nucleophilic than the nitrogen of an amine, due to the resonance stabilization of the nitrogen lone pair provided by the amide carbonyl group.



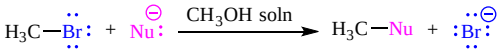
amine
more nucleophilic



amide
less nucleophilic

Order of Nucleophile Reactivity

Table 11.3.1 lists some nucleophiles in the order of their reactivity, shows the products of their reactions with bromomethane, and gives the relative rates of their reactions.



There are large differences in the rates at which various nucleophiles react.

Table 11.3.1: Some S_N2 Reactions with Bromomethane

Nucleophile		Product		Relative rate of reaction
Formula	Name	Formula	Name	
H_2O	Water	$CH_3OH_2^+$	Methylhydronium ion	1
$CH_3CO_2^-$	Acetate	$CH_3CO_2CH_3$	Methyl acetate	500
NH_3	Ammonia	$CH_3NH_3^+$	Methylammonium ion	700
Cl^-	Chloride	CH_3Cl	Chloromethane	1,000

Nucleophile		Product		Relative rate of reaction
Formula	Name	Formula	Name	
HO^-	Hydroxide	CH_3OH	Methanol	10,000
CH_3O^-	Methoxide	CH_3OCH_3	Dimethyl ether	25,000
I^-	Iodide	CH_3I	Iodomethane	100,000
^-CN	Cyanide	CH_3CN	Acetonitrile	125,000
HS^-	Hydrosulfide	CH_3SH	Methanethiol	125,000

What are the reasons for the reactivity differences observed in Table 11.3.1. Why do some reactants appear to be much more "nucleophilic" than others? The answers to these questions aren't straightforward. Part of the problem is that the term *nucleophilicity* is imprecise. The term is usually taken to be a measure of the affinity of a nucleophile for a carbon atom in the S_N2 reaction, but the reactivity of a given nucleophile can change from one reaction to the next. The exact nucleophilicity of a species in a given reaction depends on the substrate, the solvent, and even the reactant concentrations. Detailed explanations for the observed nucleophilicity aren't always simple, but some trends can be detected from the data of Table 11.3.1.

- **Nucleophilicity roughly parallels basicity** when comparing nucleophiles with the same reactive atom. Thus, OH^- is both more basic and more nucleophilic than acetate ion, $CH_3CO_2^-$, which in turn is more basic and more nucleophilic than H_2O. Since "nucleophilicity" is usually taken as the affinity of a Lewis base for a carbon atom in the S_N2 reaction and "basicity" is the affinity of a base for a proton, it's easy to see why there might be a correlation between the two kinds of behavior.
- **Nucleophilicity usually increases going down a column of the periodic table.** Thus, HS^- is more nucleophilic than HO^-, and the halide reactivity order is $I^- > Br^- > Cl^-$. Going down the periodic table, elements have their valence electrons in successively larger shells where they are successively farther from the nucleus, less tightly held, and consequently more reactive. This matter is complex, though, and the nucleophilicity order can change depending on the solvent.
- **Negatively charged nucleophiles are usually more reactive than neutral ones.** As a result, S_N2 reactions are often carried out under basic conditions rather than neutral or acidic conditions.

Exercise 11.3.1

Which substance in each of the following pairs is more reactive as a nucleophile? Explain.

a. $(CH_3)_2N^-$ or $(CH_3)_2NH$
b. $(CH_3)_3B$ or $(CH_3)_3N$
c. H_2O or H_2S

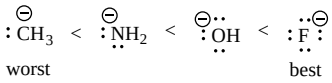
Answer available at the end of this section.

The Leaving Group

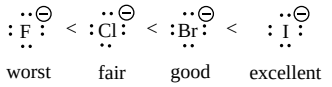
Another variable that can affect the S_N2 reaction is the nature of the group displaced by the incoming nucleophile, the leaving group.

As Electronegativity Increases, The Ability of the Leaving Group to Leave Increases

As mentioned previously, moving from left to right across the periodic table, electronegativity increases. With an increase in electronegativity, basicity decreases, and the ability of the leaving group to leave increases. This is because an increase in electronegativity results in a species that wants to hold onto its electrons rather than donate them. The following diagram illustrates this concept, showing $^-CH_3$ to be the worst leaving group and F^- to be the best leaving group. This particular example should only be used to facilitate your understanding of this concept. In real reaction mechanisms, these groups are not good leaving groups at all. For example, fluoride is such a poor leaving group that S_N2 reactions of fluoroalkanes are rarely observed.



As Size Increases, The Ability of the Leaving Group to Leave Increases: Here we revisit the effect size has on basicity. If we move down the periodic table, size increases. With an increase in size, basicity decreases, and the ability of the leaving group to leave increases. The relationship among the following halogens, unlike the previous example, is true to what we will see in upcoming reaction mechanisms.

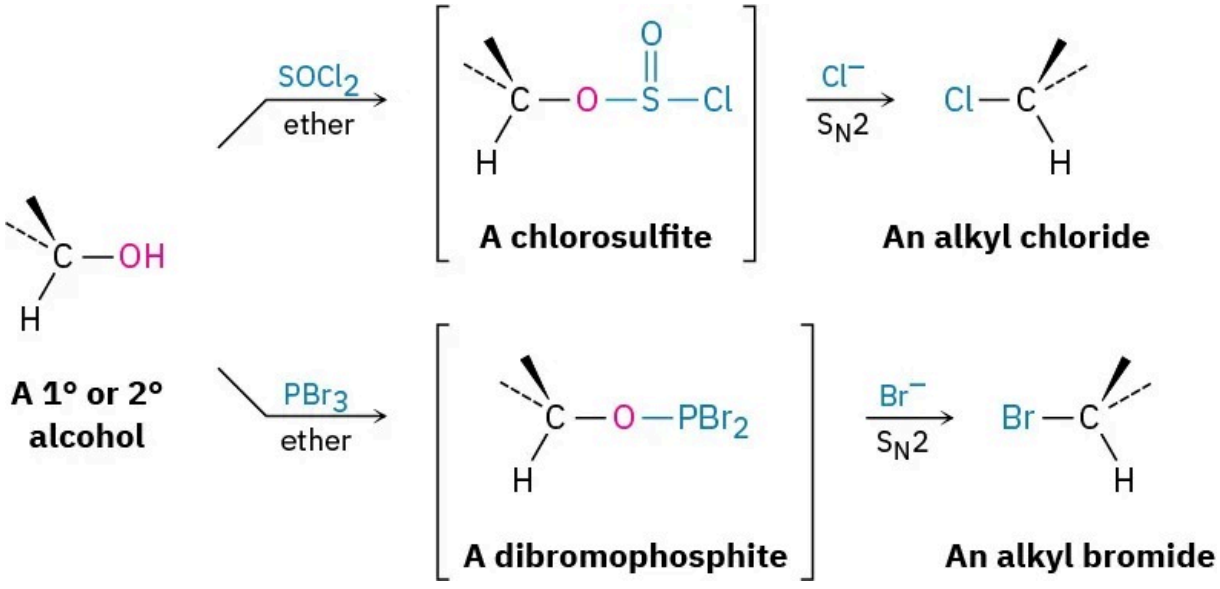


Because the leaving group is expelled with a negative charge in most S_N2 reactions, the best leaving groups are those that best stabilize the negative charge in the transition state. The greater the extent of charge stabilization by the leaving group, the lower the transition-state energy and the more rapid the reaction. But as we saw in Section 2.8, the groups that best stabilize a negative charge are also the weakest bases. Thus, weak bases such as Cl^-, Br^-, and tosylate ion make good leaving groups, while strong bases such as OH^- and NH_2^- make poor leaving groups.



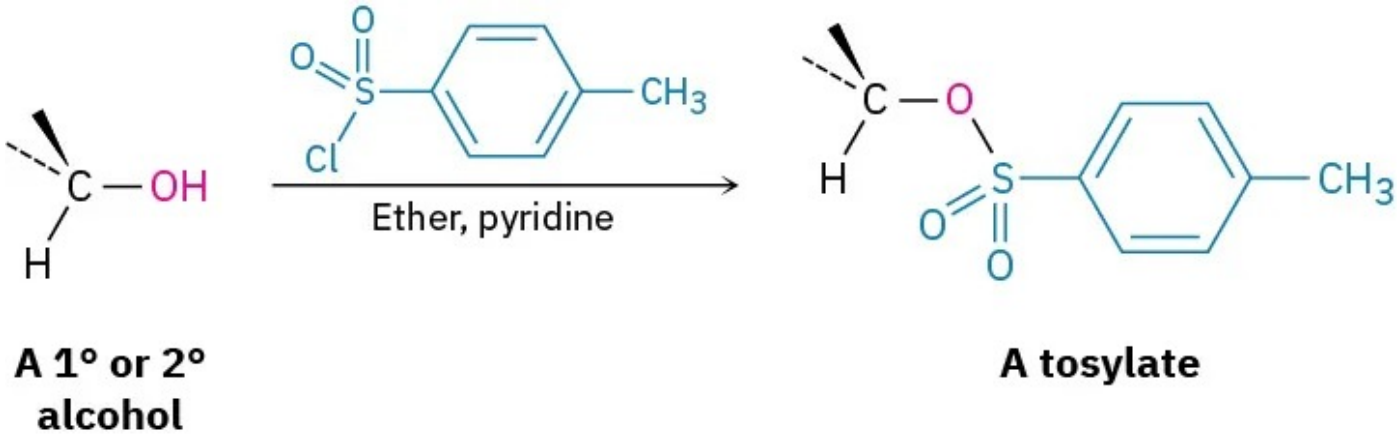
Alcohols are Poor Leaving Groups

It's just as important to know which are poor leaving groups as to know which are good, and the preceding data clearly indicate that F^-, HO^-, RO^-, and H_2N^- are not displaced by nucleophiles. In other words, alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions. To carry out an S_N2 reaction with an alcohol, it's necessary to convert the ^-OH into a better leaving group. This, in fact, is just what happens when a primary or secondary alcohol is converted into either an alkyl chloride by reaction with $SOCl_2$ or an alkyl bromide by reaction with PBr_3 (Section 10.5).



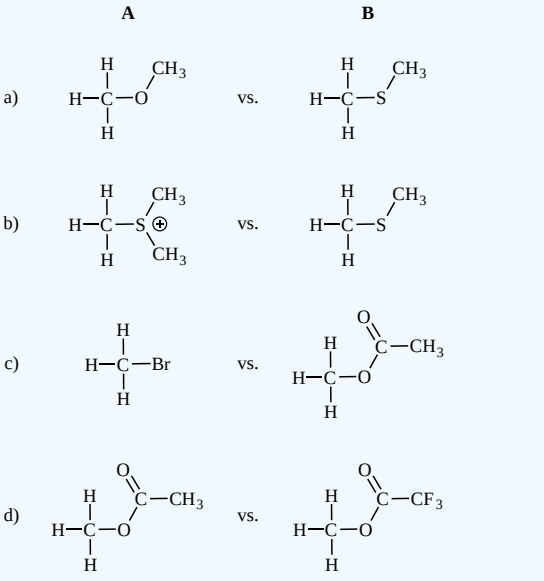
Alternatively, an alcohol can be made more reactive toward nucleophilic substitution by treating it with *para*-toluenesulfonyl

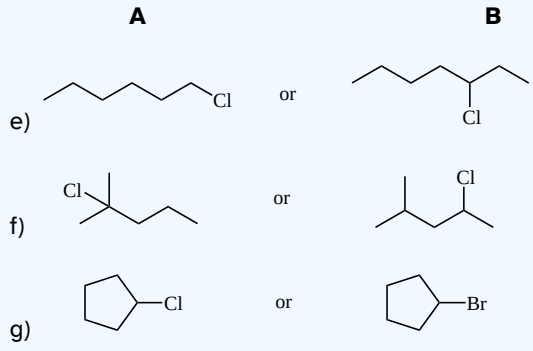
chloride to form a tosylate. As noted previously, tosylates are **even** more reactive than halides in nucleophilic substitutions. Note that tosylate formation does not change the configuration of the oxygen-bearing carbon because the C–O bond is not broken.

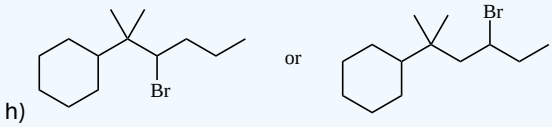


Exercise 11.3.2

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?





h) 

Answer available at the end of this section.

Exercise 11.3.4

Rank the following compounds in order of their expected reactivity toward S_N2 reaction:

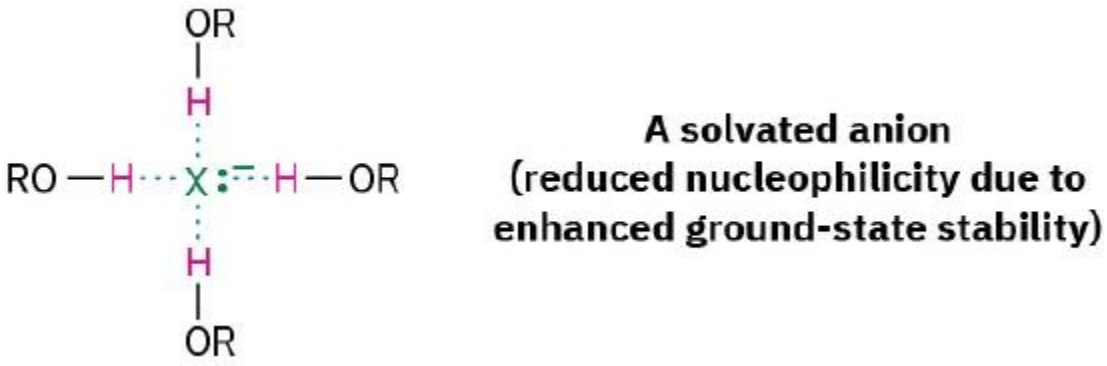
CH_3Br, CH_3OTos, $(CH_3)_3CCl$, $(CH_3)_2CHCl$

Answer available at the end of this section.

Influence of the Solvent

The rates of S_N2 reactions are strongly affected by the solvent. Protic solvents—those that contain an –OH or –NH group—are generally the worst for S_N2 reactions, while polar aprotic solvents, which are polar but don't have an –OH or –NH group, are the best.

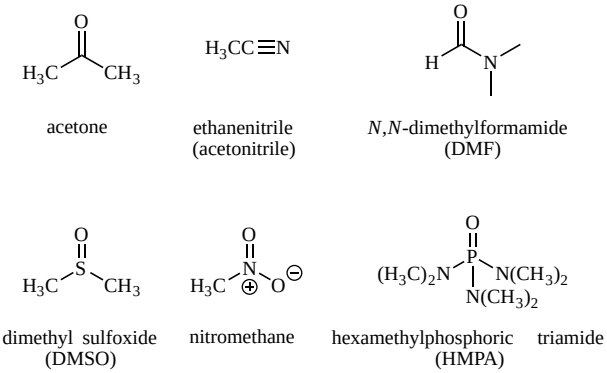
Protic solvents, such as methanol and ethanol, slow down S_N2 reactions by solvation of the reactant nucleophile. The solvent molecules hydrogen-bond to the nucleophile and form a cage around it, thereby lowering its energy and reactivity.



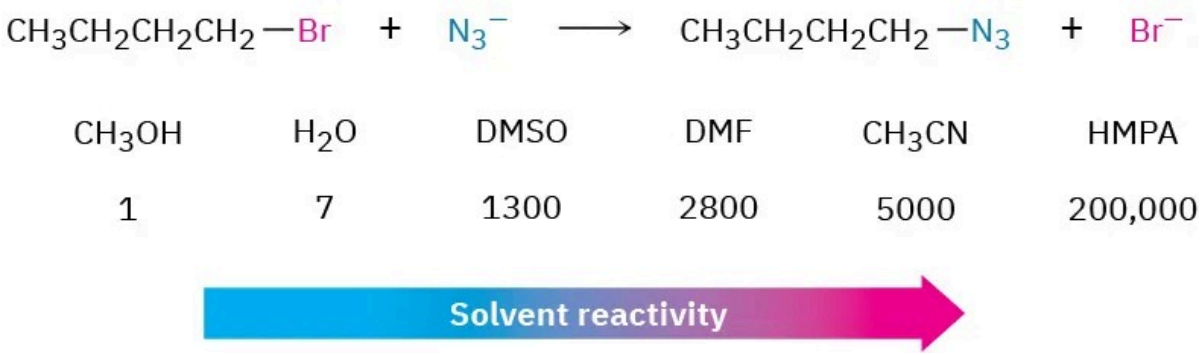
In contrast with protic solvents—which decrease the rates of S_N2 reactions by lowering the ground-state energy of the nucleophile—polar aprotic solvents increase the rates of S_N2 reactions by raising the ground-state energy of the nucleophile. Acetonitrile (CH_3CN), dimethylformamide [$(CH_3)_2NCHO$, abbreviated DMF], and dimethyl sulfoxide [$(CH_3)_2SO$, abbreviated DMSO] are particularly useful. A solvent known as hexamethylphosphoramide {$[(CH_3)_2N]_3PO$, abbreviated HMPA} can also be useful, but it should only be handled with great care and not be allowed to touch the eyes or skin. These solvents can dissolve many salts because of their high polarity, but they tend to solvate metal cations rather than nucleophilic anions. As a result, the bare, unsolvated anions have a greater nucleophilicity and S_N2 reactions take place at correspondingly increased rates.

Below are several polar aprotic solvents that are commonly used in the laboratory:

Polar Aprotic Solvents



For instance, a rate increase of 200,000 has been observed on changing from methanol to HMPA for the reaction of azide ion with 1-bromobutane.



Exercise 11.3.4

Organic solvents like benzene, ether, and chloroform are neither protic nor strongly polar. What effect would you expect these solvents to have on the reactivity of a nucleophile in S_N2 reactions?

Answer available at the end of this section.

Summary of Factors Affecting S_N2 Reactions

The effects on S_N2 reactions of the four variables—substrate structure, nucleophile, leaving group, and solvent—are summarized in the following statements and in the energy diagrams of Figure 11.3.3:

- **Substrate** Steric hindrance raises the energy of the S_N2 transition state, increasing $\Delta G^{\ddagger}$ and decreasing the reaction rate (Figure 11.3.3*a*). As a result, S_N2 reactions are best for methyl and primary substrates. Secondary substrates react slowly, and tertiary substrates do not react by an S_N2 mechanism.
- **Nucleophile** Basic, negatively charged nucleophiles are less stable and have a higher ground-state energy than neutral ones, decreasing $\Delta G^{\ddagger}$ and increasing the S_N2 reaction rate (Figure 11.3.3*b*).
- **Leaving group** Good leaving groups (more stable anions) lower the energy of the transition state, decreasing $\Delta G^{\ddagger}$ and increasing the S_N2 reaction rate (Figure 11.3.3*c*).
- **Solvent** Protic solvents solvate the nucleophile, thereby lowering its ground-state energy, increasing $\Delta G^{\ddagger}$, and decreasing the S_N2 reaction rate. Polar aprotic solvents surround the accompanying cation but not the nucleophilic anion, thereby raising the ground-state energy of the nucleophile, decreasing $\Delta G^{\ddagger}$, and increasing the reaction rate (Figure 11.3.3*d*).

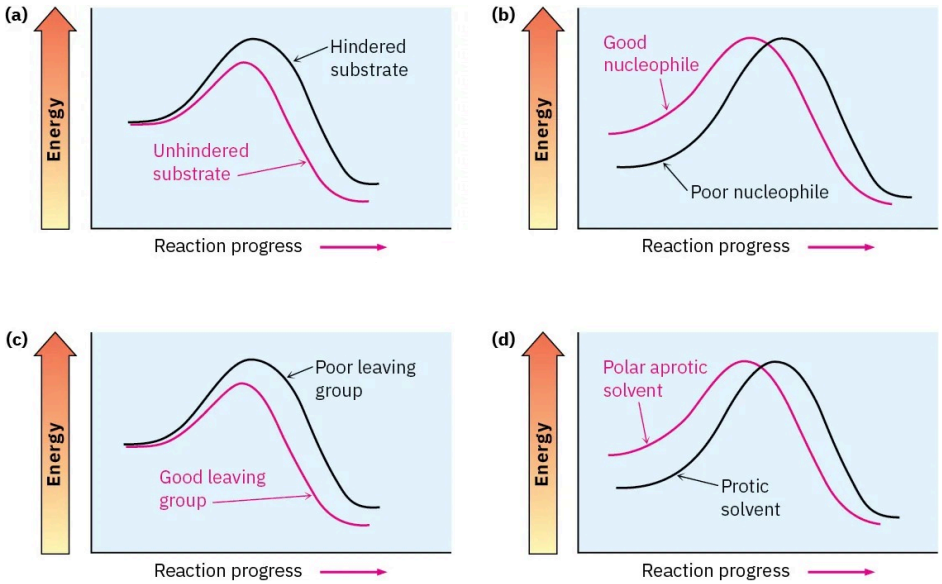


Figure 11.3.3: Energy diagrams showing the effects of (a) substrate, (b) nucleophile, (c) leaving group, and (d) solvent on S_N2 reaction rates. Substrate and leaving group effects are felt primarily in the transition state. Nucleophile and solvent effects are felt primarily in the reactant ground state.

Answers

Exercise 11.3.1

a. $(CH_3)_2N^-$
b. $(CH_3)_3N$
c. H_2S

Exercise 11.3.2

a. B (thiolate is a weaker base/better leaving group than alcohol)
b. A (sulfide is a better leaving group than thiolate (sulfide is neutral and not at all basic)
c. A (bromide ion is a weaker base/better leaving group than acetate – compare pK_a values of HBr and acetic acid).
d. B (inductive electron-withdrawing effect of fluorines makes trifluoroacetate a weaker base/better leaving group).
e. A. f. B. g. A. h. B.

Exercise 11.3.4

$CH_3OTos > CH_3Br > (CH_3)_2CHCl > (CH_3)_3CCl$

Exercise 11.3.4

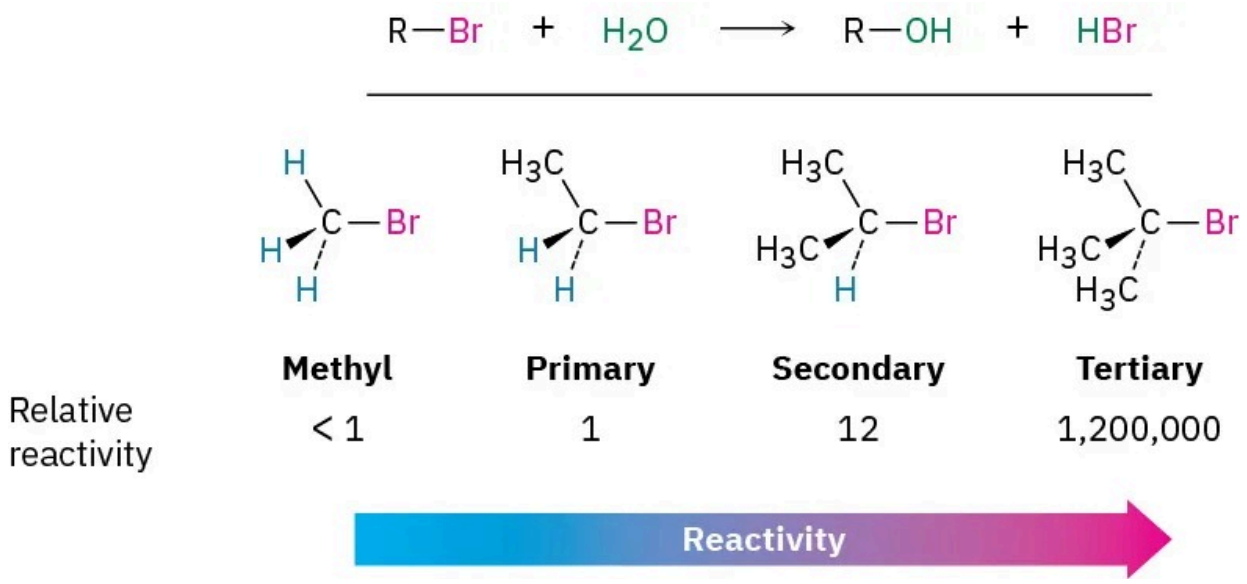
They will decrease the reactivity of the reaction.

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11.4: The SN1 Reaction

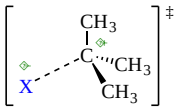
Most nucleophilic substitutions take place by the S_N2 pathway just discussed. The reaction is favored when carried out with an unhindered substrate and a negatively charged nucleophile in a polar aprotic solvent, but is disfavored when carried out with a hindered substrate and a neutral nucleophile in a protic solvent. You might therefore expect the reaction of a tertiary substrate (hindered) with water (neutral, protic) to be among the slowest of substitution reactions. Remarkably, however, the opposite is true. The reaction of the tertiary halide 2-bromo-2-methylpropane $(CH_3)_3CBr$ with H_2O to give the alcohol 2-methyl-2-propanol is more than *1 million times* faster than the corresponding reaction of CH_3Br to give methanol.



What's going on here? A nucleophilic substitution reaction is occurring—a hydroxyl group is replacing a halogen—yet the reactivity order seems backward. These reactions can't be taking place by the S_N2 mechanism we've been discussing, so we must therefore conclude that they are occurring by an alternative substitution mechanism. This alternative mechanism is called the **S_N1 reaction**, for *substitution, nucleophilic,* unimolecular. In contrast to the S_N2 reaction of CH_3Br with OH^-, the S_N1 reaction of $(CH_3)_3CBr$ with H_2O has a rate that depends only on the alkyl halide concentration and is independent of the H_2O concentration. In other words, the process is a first-order reaction; the concentration of the nucleophile does not appear in the rate equation. To explain this result, we need to know more about kinetic measurements.

Many organic reactions occur in several steps, one of which usually has a higher-energy transition state than the others and is therefore slower. We call this step with the highest transition-state energy the *rate-limiting step*, or **rate-determining step**. No reaction can proceed faster than its rate-limiting step, which acts as a kind of traffic jam, or bottleneck.

Because the first step of the mechanism is the rate-determining step, the first transition state will be the most important. During the first step, a carbon-leaving group bond in a neutral substrate is broken to form a carbocation intermediate and a leaving group anion. The breaking bond is represented as a dashed-partial bond in the transition state. A partial positive charge is shown on the carbon to represent the formation of a carbocation, and a partial negative charge is shown on the leaving group to represent the formation of an anion.



Transition State 1 ($[TS_1]^{‡}$)

2-Steps Potential Energy Diagram

In the S_N1 reaction of $(CH_3)_3CBr$ with H_2O, the fact that the nucleophile concentration does not appear in the first-order rate equation means that it is not involved in the rate-limiting step and must therefore be involved in some other, non-rate-limiting step. The energy diagram is shown in Figure 11.4.1.

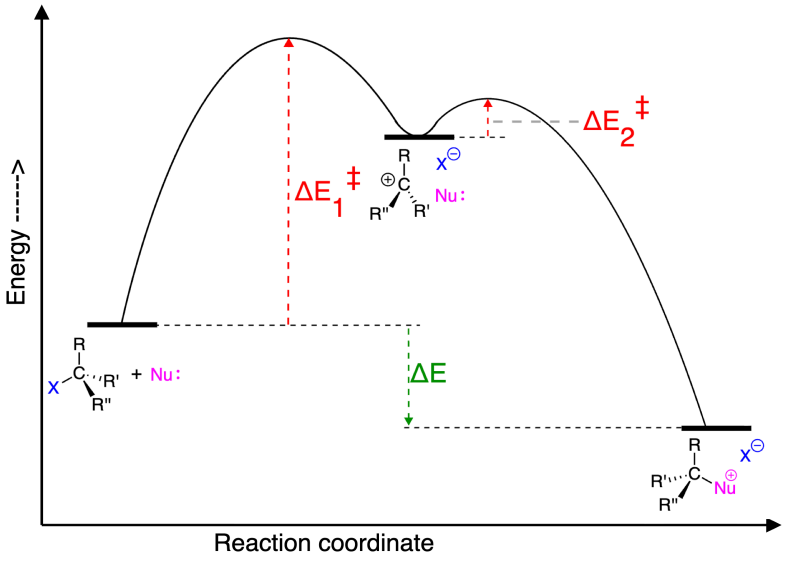


Figure 11.4.1: An energy diagram for an S_N1 reaction. The rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

Mechanism

Unlike what occurs in an S_N2 reaction, where the leaving group is displaced while the incoming nucleophile approaches, an S_N1 reaction takes place by loss of the leaving group *before* the nucleophile approaches. 2-Bromo-2-methylpropane spontaneously dissociates to the *tert*-butyl carbocation $(CH_3)_3C^+$, plus Br^- in a slow, rate-limiting step, and the intermediate carbocation is then immediately trapped by the nucleophile water in a faster second step. Thus, water is not a reactant in the step whose rate is measured. The mechanism shown in Figure 11.4.2 accounts for these observations.

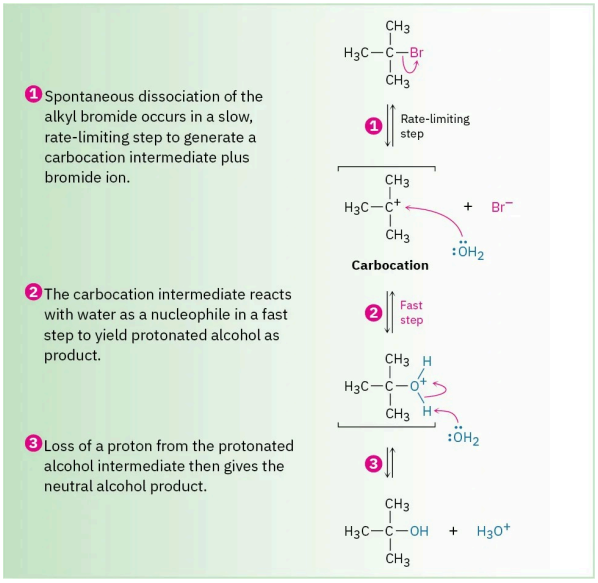
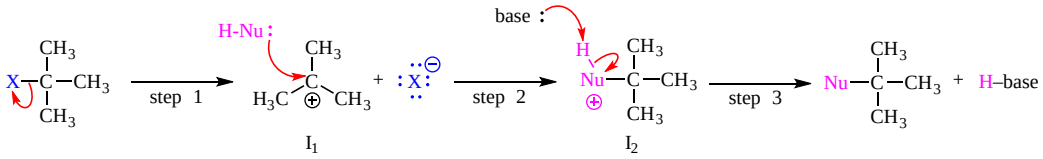


Figure 11.4.2: The mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H_2O involves three steps. Step 1—the spontaneous, unimolecular dissociation of the alkyl bromide to yield a carbocation—is rate-limiting.

3-Steps S_N1 Reactions



A potential energy diagram for this reaction shows that each of the two positively-charged intermediates (I_1 and I_2) can be visualized as a valley in the path of the reaction, higher in energy than both the reactant and product but lower in energy than the transition states. The first, bond-breaking step is the slowest, rate-determining step - notice it has the highest activation energy and leads to the highest-energy species, I_1, the carbocation intermediate. Step 2 is rapid: a new covalent bond forms between a carbocation and a water nucleophile, and no covalent bonds are broken. The third step represents a Bronsted-Lowry proton transfer, which is rapid, with low activation energy.

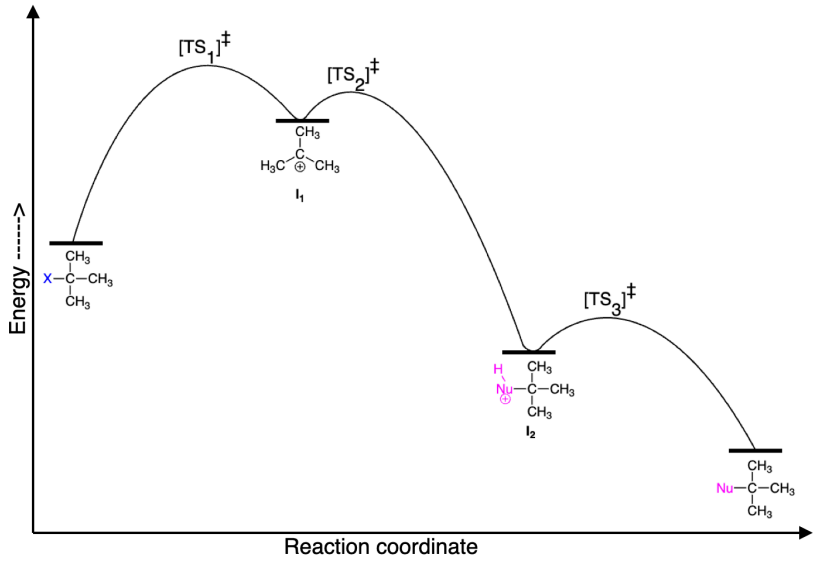


Figure 11.4.5: An energy diagram for an S_N1 reaction. The third step represents a Bronsted-Lowry proton transfer, which is rapid, with low activation energy.

Stereochemistry of the Product

Because an S_N1 reaction occurs through a carbocation intermediate, its stereochemical outcome is different from that of an S_N2 reaction. Carbocations, as we've seen, are planar, sp^2-hybridized, and achiral. Thus, if we carry out an S_N1 reaction on one enantiomer of a chiral reactant and go through an achiral carbocation intermediate, the product loses its optical activity (Section 8.12). That is, the pro-chiral intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic, 50 : 50 mixture of enantiomers (Figure 11.4.3).

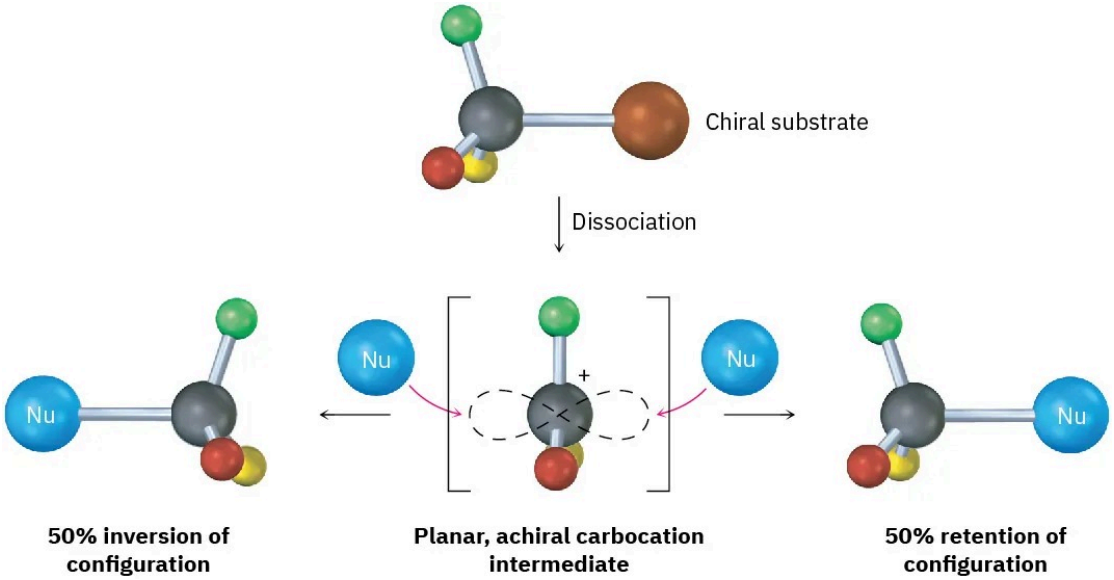
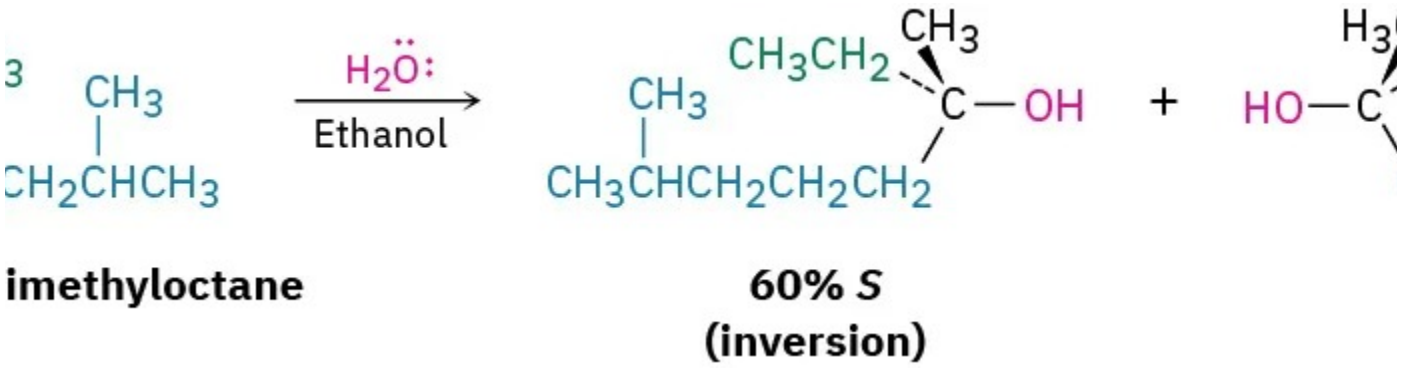


Figure 11.4.3: Stereochemistry of the S_N1 reaction. Because the reaction goes through an achiral intermediate, an enantiomerically pure reactant gives an optically inactive racemic product.

The conclusion that S_N1 reactions on enantiomerically pure substrates should give racemic products is nearly, but not exactly, what is found. In fact, few S_N1 displacements occur with complete racemization. Most give a minor (0–20%) excess of inversion.

The reaction of (*R*)-6-chloro-2,6-dimethyloctane with H_2O, for example, leads to an alcohol product that is approximately 80% racemized and 20% inverted (80% *R*,*S* + 20% *S* is equivalent to 40% *R* + 60% *S*).



This lack of complete racemization in S_N1 reactions is due to the fact that *ion pairs* are involved. According to this explanation, the dissociation of the substrate occurs to give a structure in which the two ions are still loosely associated and in which the carbocation is effectively shielded from reaction on one side by the departing anion. If a certain amount of substitution occurs before the two ions fully diffuse apart, then a net inversion of configuration will be observed (Figure 11.4.4).

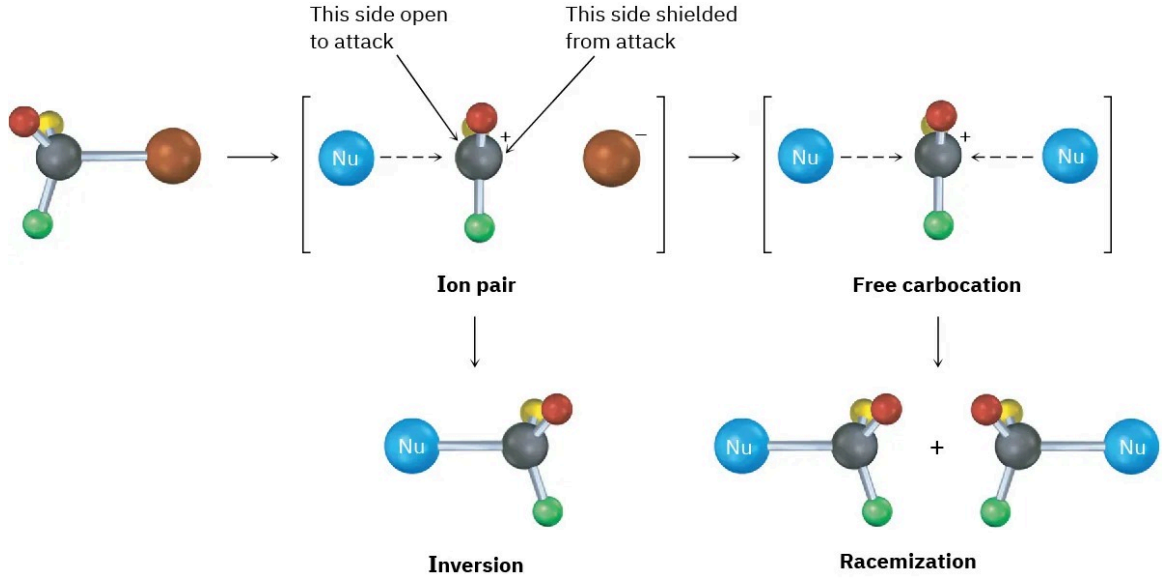


Figure 11.4.4: Ion pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.

Exercises

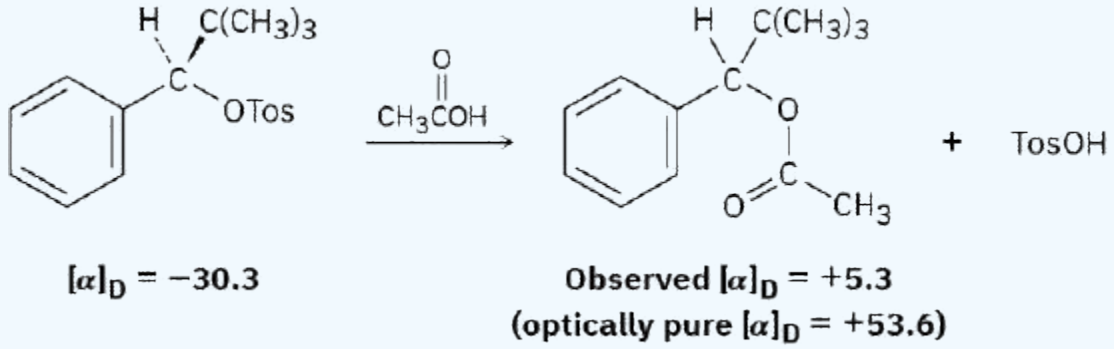
Exercise 11.4.1

What product(s) would you expect from the reaction of (*S*)-3-chloro-3-methyloctane with acetic acid? Show the stereochemistry of both reactant and product.

Answer available at the end of this section.

Exercise 11.4.2

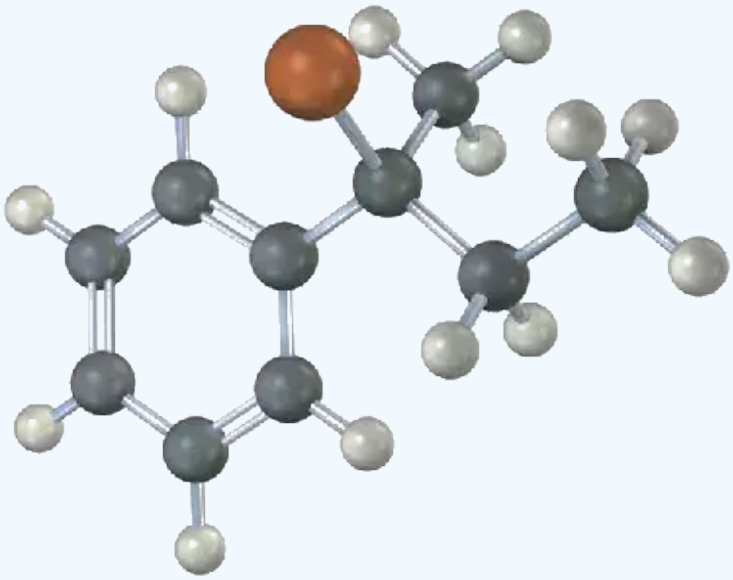
Among the many examples of S_N1 reactions that occur with incomplete racemization, the optically pure tosylate of 2,2-dimethyl-1-phenyl-1-propanol ($[\alpha]_D$ = –30.3) gives the corresponding acetate ($[\alpha]_D$ = +5.3) when heated in acetic acid. If complete inversion had occurred, the optically pure acetate would have had $[\alpha]_D$ = +53.6. What percentage racemization and what percentage inversion occurred in this reaction?



Answer available at the end of this section.

Exercise 11.4.3

Assign configuration to the following substrate, and show the stereochemistry and identity of the product you would obtain by S_N1 reaction with water (reddish brown = Br):



Answer available at the end of this section.

Answers

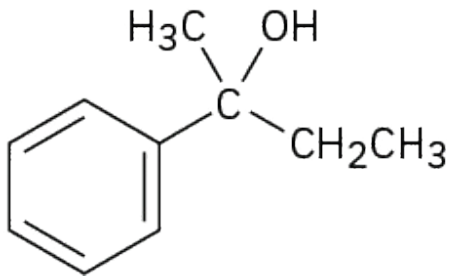
Exercise 11.4.1

Racemic 1-ethyl-1-methylhexyl acetate

Exercise 11.4.2

90.1% racemization, 9.9% inversion

Exercise 11.4.3

(*S*)-2-bromo-2-phenylbutane 

Racemic

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11.5: Characteristics of the SN1 Reaction

Just as the S_N2 reaction is strongly influenced by the structure of the substrate, the leaving group, the nucleophile, and the solvent, the S_N1 reaction is similarly influenced. Factors that lower $\Delta G^{\ddagger}$, either by lowering the energy level of the transition state or by raising the energy level of the ground state, favor faster S_N1 reactions. Conversely, factors that raise $\Delta G^{\ddagger}$, either by raising the energy level of the transition state or by lowering the energy level of the reactant, slow down the S_N1 reaction.

As discussed in the previous section, S_N1 reactions follow first-order kinetics due to a multi-step mechanism in which the rate-determining step consists of the ionization of the alkyl halide to form a carbocation.

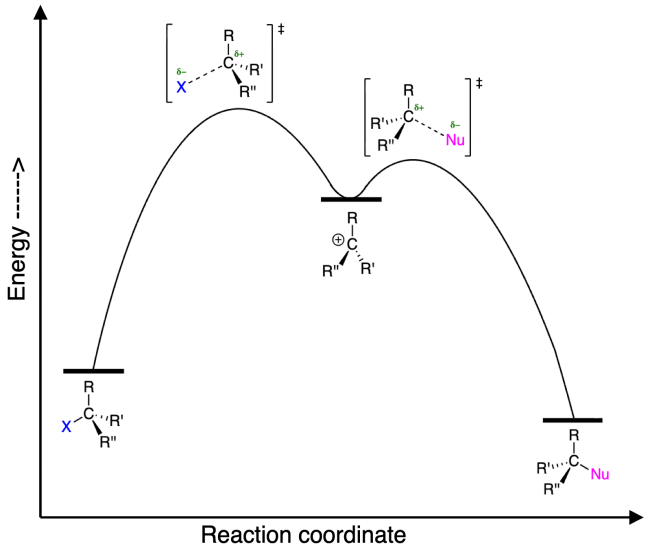
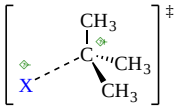


Figure 11.5.1: An energy diagram for an S_N1 reaction. The rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

Rate-Determining Step

The transition state for the rate-determining step shows the transition of an alkyl halide to a carbocation. Because the rate-determining step is endothermic, the Hammond postulate says that the transition state resembles, more closely, the carbocation intermediate. Factors that stabilize this intermediate will lower the energy of activation for the rate-determining step and cause the rate of reaction to increase. In general, a more stable carbocation intermediate allows for a faster S_N1 reaction rate.



Transition State 1 ($[TS_1]^{\ddagger}$)

The Substrate

According to the Hammond postulate, any factor that stabilizes a high-energy intermediate also stabilizes the transition state leading to that intermediate. Because the rate-limiting step in an S_N1 reaction is the spontaneous, unimolecular dissociation of the substrate to yield a carbocation, the reaction is favored whenever a stabilized carbocation intermediate is formed.

We saw in Section 10.4 that the stability order of alkyl carbocations is 3° > 2° > 1° > methyl. To this list we should also add the resonance-stabilized allyl and benzyl cations. Just as allylic radicals are unusually stable because the unpaired electron can be delocalized over an extended π orbital system (Section 10.4), so allylic and benzylic carbocations are unusually stable. (The word benzylic means "next to an aromatic ring.")

As Figure 11.5.2 indicates, an allylic cation has two resonance forms. In one form, the double bond is on the "left"; in the other form, it's on the "right." A benzylic cation has five resonance forms, all of which contribute to the overall resonance hybrid.

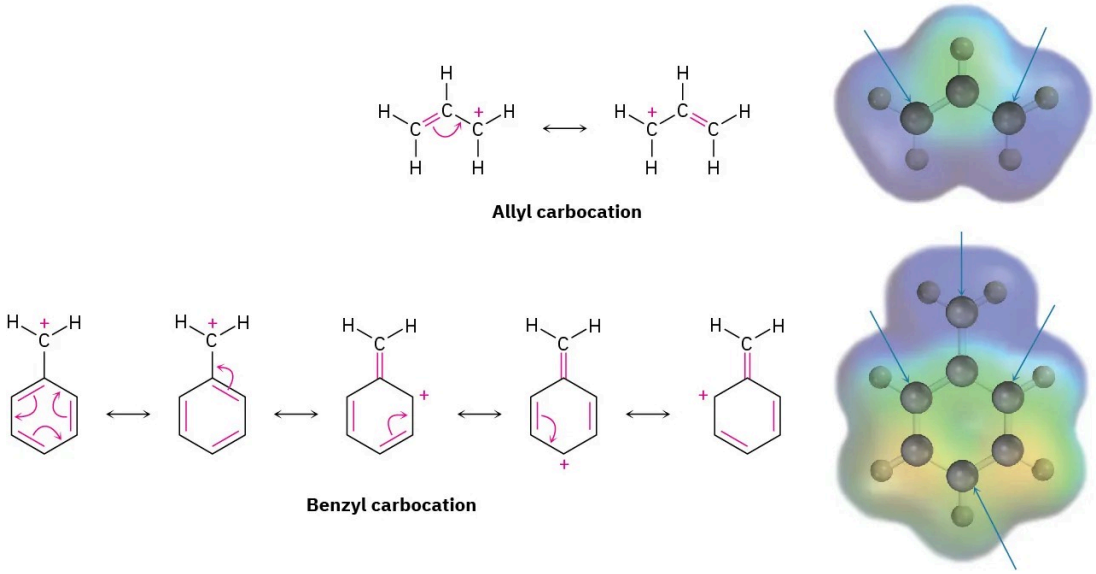
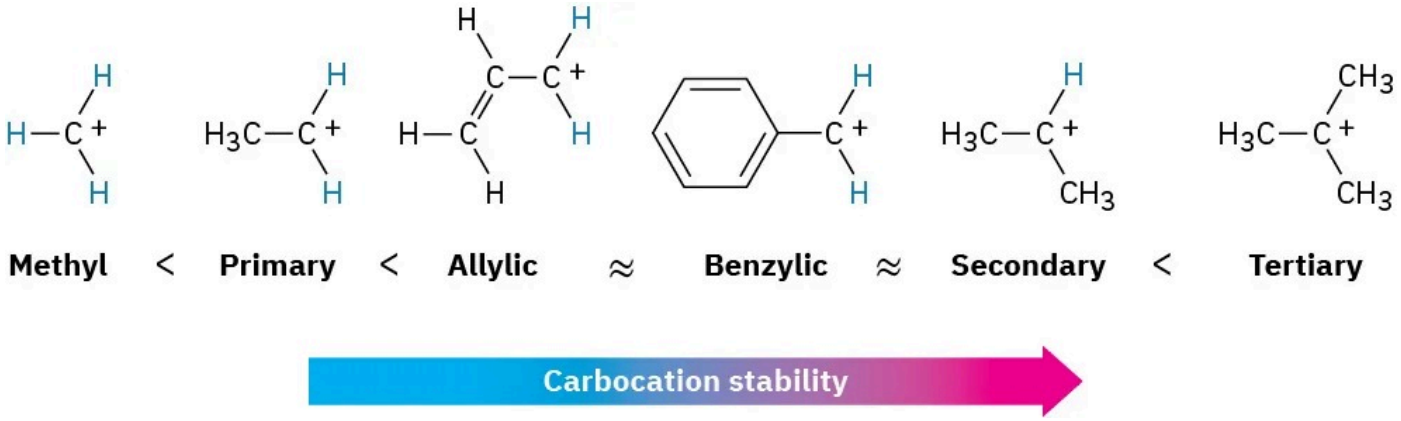
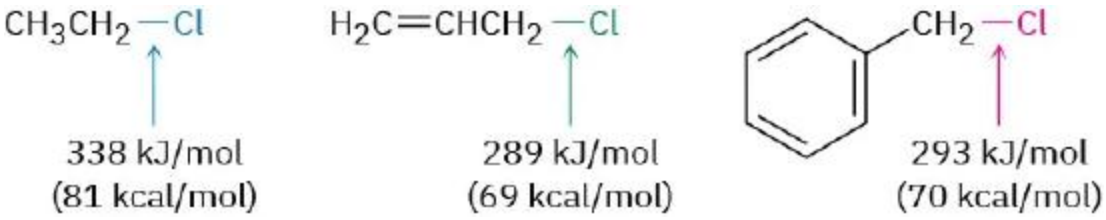


Figure 11.5.2: Resonance forms of allylic and benzylic carbocations. The positive charge is delocalized over the π system in both. **Electron-poor atoms** are indicated by blue arrows.

Because of resonance stabilization, a primary allylic or benzylic carbocation is about as stable as a secondary alkyl carbocation, and a secondary allylic or benzylic carbocation is about as stable as a tertiary alkyl carbocation. This stability order of carbocations is the same as the order of S_N1 reactivity for alkyl halides and tosylates.



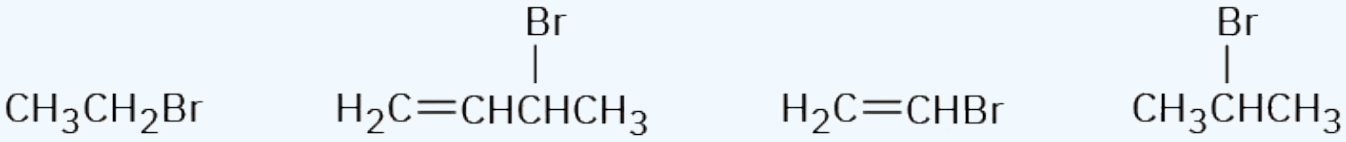
We should also note parenthetically that primary allylic and benzylic substrates are particularly reactive in S_N2 reactions as well as in S_N1 reactions. Allylic and benzylic C–X bonds are about 50 kJ/mol (12 kcal/mol) weaker than the corresponding saturated bonds and are therefore more easily broken.



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Exercise 11.5.1

Rank the following substances in order of their expected S_N1 reactivity:



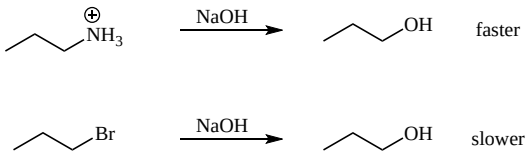
Answer available at the end of this section.

The Leaving Group

We said during the discussion of S_N2 reactivity that the best leaving groups are those that are most stable; that is, those that are the conjugate bases of strong acids. An identical reactivity order is found for the S_N1 reaction because the leaving group is directly involved in the rate-limiting step. Thus, the S_N1 reactivity order is



The two reactions below only vary by the different leaving groups in each reaction. The reaction with a more stable leaving group is significantly faster than the other. This is because the better leaving group leaves faster and thus the reaction can proceed faster.



Preparing a Better Leaving Group

Note that in the S_N1 reaction, which is often carried out under acidic conditions, neutral water is sometimes the leaving group. This occurs, for example, when an alkyl halide is prepared from a tertiary alcohol by reaction with HBr or HCl (Section 10.6). As shown in Figure 11.5.2,

1. Because the -OH group itself is a poor nucleophile, the mechanism starts with protonation to form a hydronium ion.
2. Neutral water is then lost as a leaving group to create the carbocation intermediate,
3. which then reacts with the halide ion nucleophile to provide the alkyl halide product.

Knowing that an S_N1 reaction is involved in the conversion of alcohols to alkyl halides explains why the reaction works well only for tertiary alcohols. Tertiary alcohols react fastest because they give the most stable carbocation intermediates.

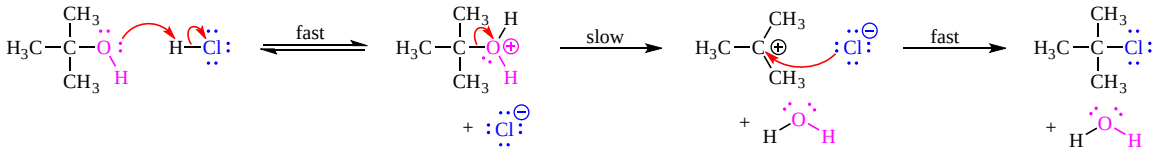
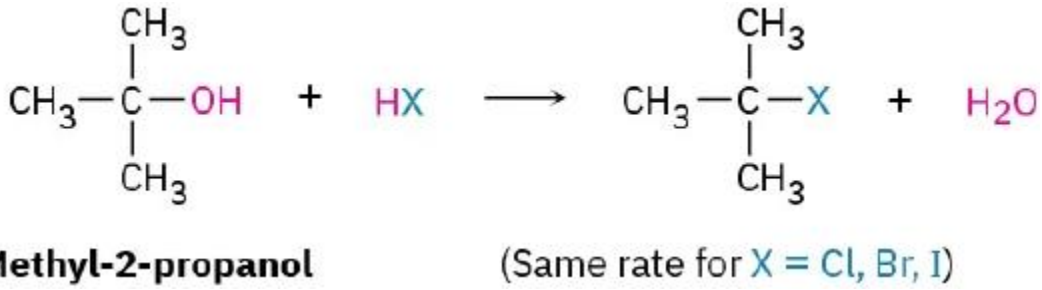


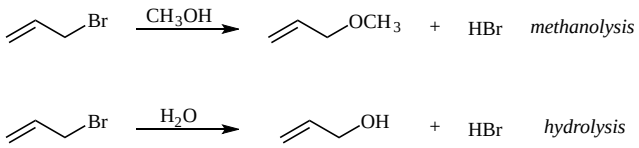
Figure 11.5.2: The S_N1 mechanism of a tertiary alcohol with HBr to yield an alkyl halide. Water is the leaving group (step **2**)

The Nucleophile

The nature of the nucleophile plays a major role in the S_N2 reaction but does not affect an S_N1 reaction. Because the S_N1 reaction occurs through a rate-limiting step in which the added nucleophile has no part, the nucleophile can't affect the reaction rate. The reaction of 2-methyl-2-propanol with HX, for instance, occurs at the same rate regardless of whether X is Cl, Br, or I. Furthermore, neutral nucleophiles are just as effective as negatively charged ones, so S_N1 reactions frequently occur under neutral or acidic conditions.

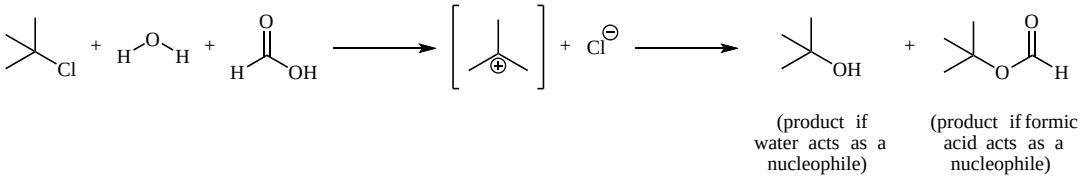


Note that S_N1 reactions in which the nucleophile is also the solvent are commonly called **solvolysis** reactions. The S_N1 reaction of allyl bromide in methanol is called **methanolysis**, while if water is the solvent, the reaction would be called **hydrolysis**:



The Strength of the Nucleophile

The strength of the nucleophile **does not affect the reaction rate of S_N1** because, as described previously, the nucleophile is not involved in the rate-determining step. However, if you have more than one nucleophile competing to bond to the carbocation, the strengths and concentrations of those nucleophiles affects the distribution of products that you will get. For example, if you have $(CH_3)_3CCl$ reacting in water and formic acid where the water and formic acid are competing nucleophiles, you will get two different products: $(CH_3)_3COH$ and $(CH_3)_3COCOH$. The relative yields of these products depend on the concentrations and relative reactivities of the nucleophiles.



The Solvent

What about the solvent? Do solvents have the same effect in S_N1 reactions that they have in S_N2 reactions? The answer is both

yes and no. Yes, solvents have a large effect on S_N1 reactions, but no, the reasons for the effects on S_N1 and S_N2 reactions are not the same. Solvent effects in the S_N2 reaction are due largely to stabilization or destabilization of the nucleophile *reactant,* while solvent effects in the S_N1 reaction are due largely to stabilization or destabilization of the *transition state*.

The Hammond postulate says that any factor stabilizing the intermediate carbocation should increase the rate of an S_N1 reaction. Solvation of the carbocation—the interaction of the ion with solvent molecules—has such an effect. Solvent molecules orient around the carbocation so that the electron-rich ends of the solvent dipoles face the positive charge (Figure 11.5.3), thereby lowering the energy of the ion and favoring its formation.

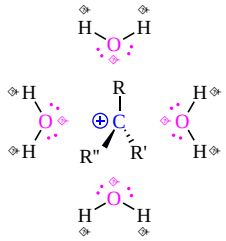


Figure 11.5.3: Solvation of a carbocation by water. The electron-rich oxygen atoms of solvent molecules orient around the positively charged carbocation and thereby stabilize it.

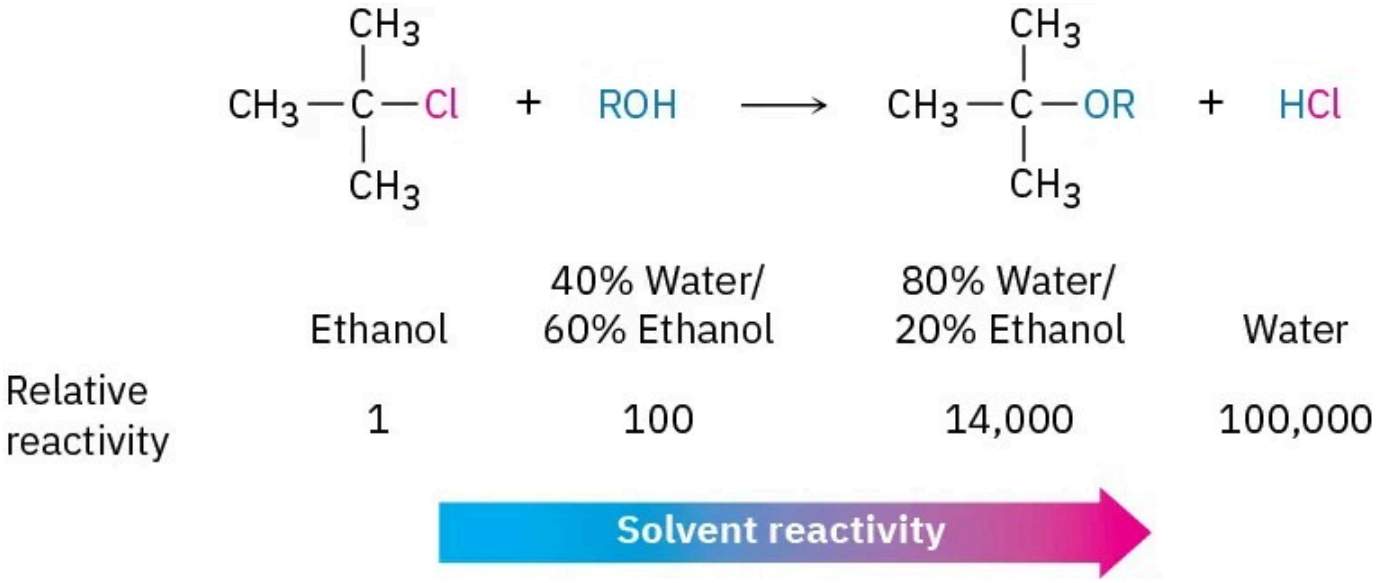
The properties of a solvent that contribute to its ability to stabilize ions by solvation are related to the solvent's polarity. S_N1 reactions take place much more rapidly in strongly polar solvents, such as water and methanol, than in less polar solvents, such as ether and chloroform.

The polarity and the ability of the solvent to stabilize the intermediate carbocation are very important, as shown by the relative rate data for a solvolysis (see table below). The dielectric constant of a solvent roughly provides a measure of the solvent's polarity. A dielectric constant below 15 is usually considered non-polar. Basically, the dielectric constant can be thought of as the solvent's ability to reduce the internal charge of the solvent. So for our purposes, the higher the dielectric constant, the more polar the substance, and in the case of SN1 reactions, the faster the rate.

Solvent	Dielectric Constant	Relative Rate
CH_3CO_2H	6	1
CH_3OH	33	4
H_2O	78	150,000

(Note that even though acetic acid is a highly polar molecule, it tends to make a dimer with itself, greatly reducing its dielectric constant)

In the reaction of 2-chloro-2-methylpropane, for example, a rate increase of 100,000 is observed upon going from ethanol (less polar) to water (more polar). The rate increases when going from a hydrocarbon solvent to water are so large that they can't be measured accurately.



It should be emphasized again that both the S_N1 and the S_N2 reaction show solvent effects, but that they do so for different reasons. S_N2 reactions are *disfavored* in protic solvents because the *ground-state energy* of the nucleophile is lowered by solvation. S_N1 reactions are *favored* in protic solvents because the *transition-state energy* leading to carbocation intermediate is lowered by solvation.

A Summary of S_N1 Reaction Characteristics

The effects on S_N1 reactions of the four variables—substrate, leaving group, nucleophile, and solvent—are summarized in the following statements:

- **Substrate:** The best substrates yield the most stable carbocations. As a result, S_N1 reactions are best for tertiary, allylic, and benzylic halides.
- **Leaving group:** Good leaving groups increase the reaction rate by lowering the energy level of the transition state for carbocation formation.
- **Nucleophile:** The nucleophile must be nonbasic to prevent a competitive elimination of HX (Section 11.7), but otherwise does not affect the reaction rate. Neutral nucleophiles work well.
- **Solvent:** Polar solvents with a high dielectric constant stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate.

Exercise

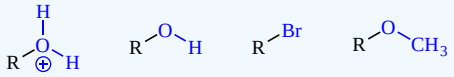
Exercise 11.5.2

3-bromo-1-pentene and 1-bromo-2-pentene, one is a secondary halide while the other is a primary halide, but both undergo S_N1 reaction at almost the same rate. Explain why this is.

Answer available at the end of this section.

Exercise 11.5.3

Put the following leaving groups highlighted in blue in order of decreasing leaving group ability



Answer available at the end of this section.

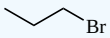
Exercise 11.5.4

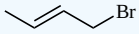
Which solvent would an S_N1 reaction occur faster in? H_2O or CH_3CN

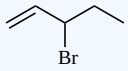
Answer available at the end of this section.

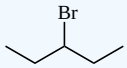
Exercise 11.5.5

Rank the following by increasing reactivity in an S_N1 reaction.

a) 

b) 

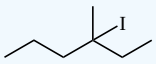
c) 

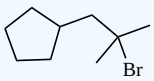
d) 

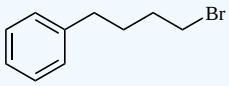
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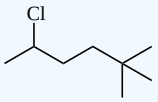
Exercise 11.5.6

Draw the solvolysis product expected when the compound is heated in ethanol vs water. Draw the expanded form of the solvent.

a) 

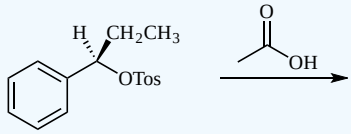
b) 

c) 

d) 

Exercise 11.5.7

Give the products of the following S_N1 reaction. Show stereochemistry.

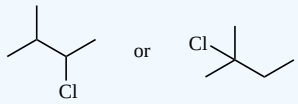


Answer available at the end of this section.

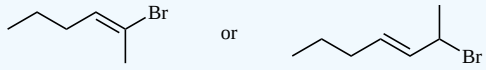
Exercise 11.5.8

Predict with compound in each pair will undergo an S_N1 reaction more quickly.

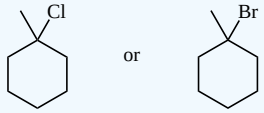
a)



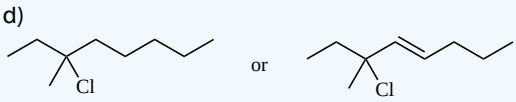
b)



c)



d)



Answer available at the end of this section.

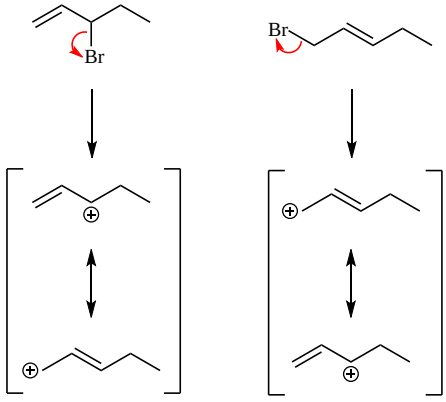
Answers

Exercise 11.5.1

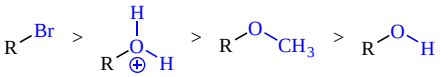
$H_2C{=}CHCH(Br)CH_3 > CH_3CH(Br)CH_3 > CH_3CH_2Br > H_2C{=}CHBr$

Exercise 11.5.2

They have the same intermediates when you look at the resonance forms.



Exercise 11.5.3



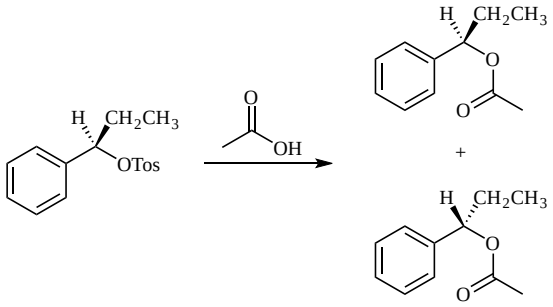
Exercise 11.5.4

An S_N1 reaction would occur faster in H_2O because it's polar protic, and would stabilize the carbocation, and CH_3CN is polar aprotic.

Exercise 11.5.5

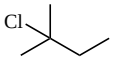
Consider the stability of the intermediate, the carbocation. (least reactive) A < D < B < C (most reactive)

Exercise 11.5.7

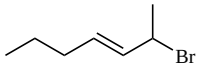


Exercise 11.5.8

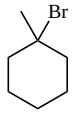
a)



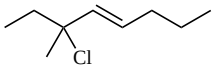
b)



c)



d)



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11.6: Predicting SN1 vs. SN2 mechanisms

Objectives

After completing this section, you should be able to

- compare the kinetics of S_N1 and S_N2 reactions.
- compare the stereochemical consequences of the S_N1 mechanism with those of the S_N2 mechanism.

Predicting S_N1 vs. S_N2 Mechanisms

When considering whether a nucleophilic substitution is likely to occur via an S_N1 or S_N2 mechanism, we really need to consider three factors:

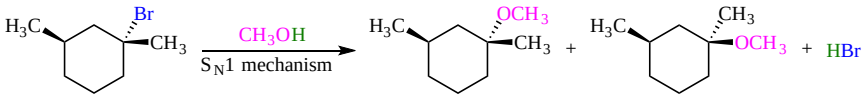
1) **The electrophile:** when the leaving group is attached to a methyl group or a primary carbon, an S_N2 mechanism is favored (here the electrophile is unhindered by surrounded groups, and any carbocation intermediate would be high-energy and thus unlikely). When the leaving group is attached to a tertiary, allylic, or benzylic carbon, a carbocation intermediate will be relatively stable and thus an S_N1 mechanism is favored.

2) **The nucleophile**: powerful nucleophiles, especially those with negative charges, favor the S_N2 mechanism. Weaker nucleophiles such as water or alcohols favor the S_N1 mechanism.

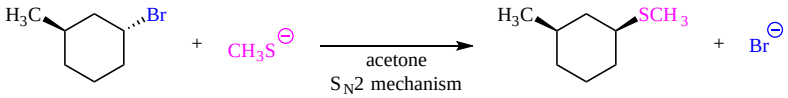
3) **The solvent**: Polar aprotic solvents favor the S_N2 mechanism by enhancing the reactivity of the nucleophile. Polar protic solvents favor the S_N1 mechanism by stabilizing the carbocation intermediate. S_N1 reactions are frequently solvolysis reactions.

Analysis

For example, the reaction below has a tertiary alkyl bromide as the electrophile, a weak nucleophile, and a polar protic solvent (we'll assume that methanol is the solvent). Thus we'd confidently predict an S_N1 reaction mechanism. Because substitution occurs at a chiral carbon, we can also predict that the reaction will proceed with racemization.

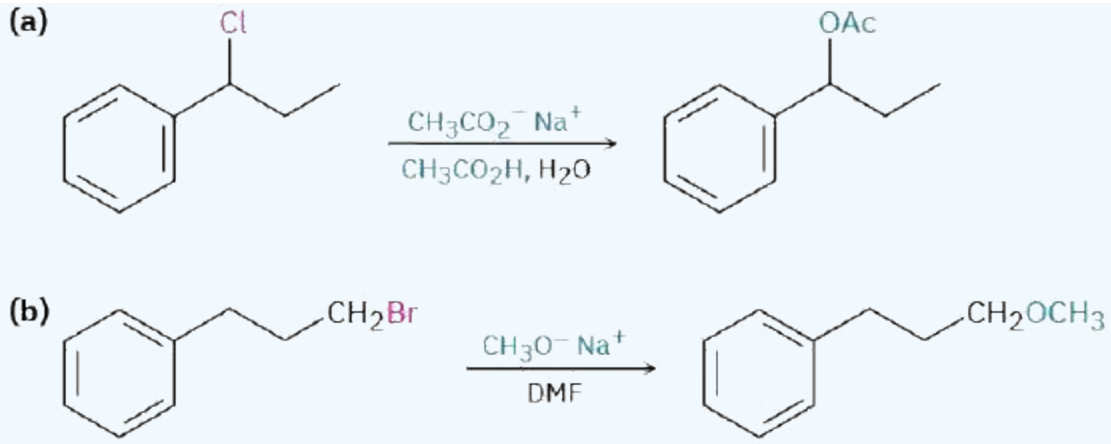


In the reaction below, on the other hand, the electrophile is a secondary alkyl bromide – with these, both S_N1 and S_N2 mechanisms are possible, depending on the nucleophile and the solvent. In this example, the nucleophile (a thiolate anion) is strong, and a polar aprotic solvent is used – so the S_N2 mechanism is heavily favored. The reaction is expected to proceed with inversion of configuration.



Worked Example 11.6.1: Predicting the Mechanism of a Nucleophilic Substitution Reaction

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:



Strategy

Look at the substrate, leaving group, nucleophile, and solvent. Then decide from the summaries at the ends of Section 11.3 and Section 11.5 whether an S_N1 or an S_N2 reaction is favored. S_N1 reactions are favored by tertiary, allylic, or benzylic substrates, by good leaving groups, by nonbasic nucleophiles, and by protic solvents. S_N2 reactions are favored by primary substrates, by good leaving groups, by good nucleophiles, and by polar aprotic solvents.

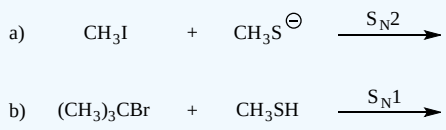
Solution

a. This is likely to be an S_N1 reaction because the substrate is secondary and benzylic, the nucleophile is weakly basic, and the solvent is protic.
b. This is likely to be an S_N2 reaction because the substrate is primary, the nucleophile is a good one, and the solvent is polar aprotic.

Exercise

Exercise 11.6.1

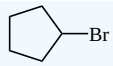
Consider two nucleophilic substitutions that occur uncatalyzed in solution. Assume that reaction A is S_N2, and reaction B is S_N1. Predict, in each case, what would happen to the rate of the reaction if the concentration of the nucleophile were doubled, while all other conditions remained constant.

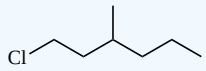


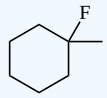
Answer available at the end of this section.

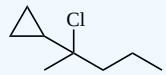
Exercise 11.6.2

Predict whether each compound below would be more likely to undergo a S_N2 or S_N1 reaction.

a) 

b) 

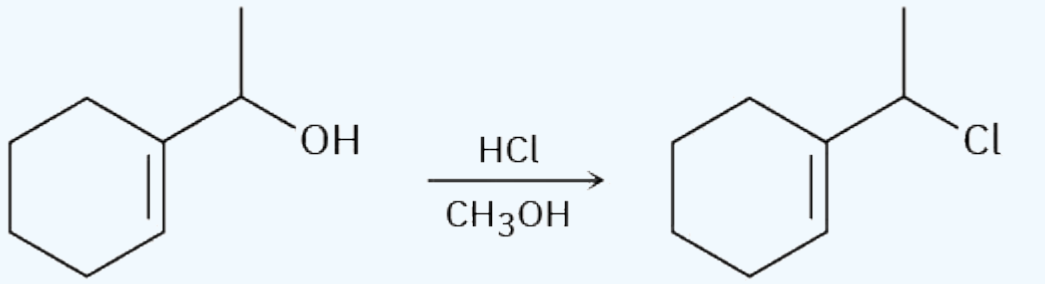
c) 

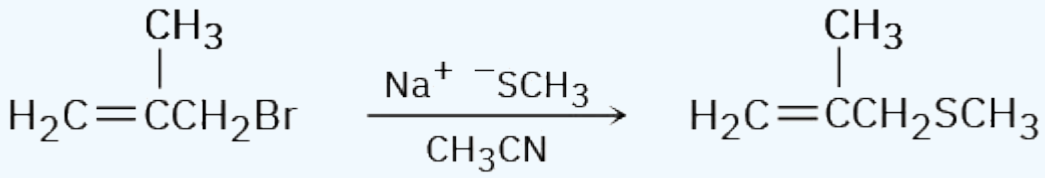
d) 

Answer available at the end of this section.

Exercise 11.6.3

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2:

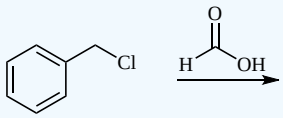
a. 

b. 

Answer available at the end of this section.

Exercise 11.6.4

Indicate the expected product and list why it occurs through S_N1 instead of S_N2?

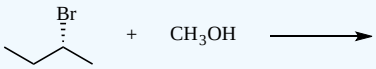


Answer available at the end of this section.

Exercise 11.6.5

a. Predict whether the following substitution reaction is likely to be S_N1 or S_N2. What are the products of the following reaction?

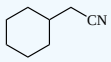
b. How could you change the reactants to favor the other substitution reaction?



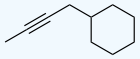
Answer available at the end of this section.

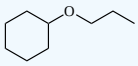
Exercise 11.6.6

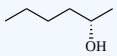
Show how each compound may be synthesized using nucleophilic substitution reactions.

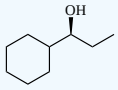
a) 

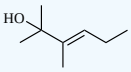
b) 

c) 

d) 

e) 

f) 

g) 

Answer available at the end of this section.

Answers

Exercise 11.6.1

For Reaction A, the rate law is rate = k[CH_3I][CH_3S^-]. Therefore, if the concentration of the nucleophile, CH_3S^-, is doubled and the concentration of the alkyl halide remains the same, then the reaction rate will double.

For Reaction B, the rate law is rate = k[$(CH_3)_3Br$]. Therefore, if the concentration of the nucleophile, CH_3SH, is doubled and the concentration of the alkyl halide remains the same, then reaction rate stays the same.

Exercise 11.6.2

a) Can undergo S_N1 or S_N2, depending on reaction conditions

b) S_N2 c) S_N1 d) S_N1

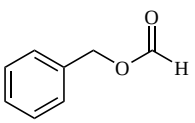
Exercise 11.6.3

a. S_N1 *poor leaving group, protic solvent, secondary cation intermediate

b. S_N2 *good leaving group, polar solvent, primary position.

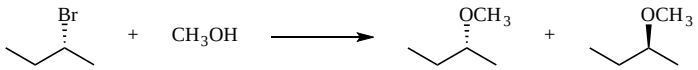
Exercise 11.6.4

This reaction occurs via S_N1 because Cl^- is a good leaving group, the intermediate carbocation is a stable benzylic cation, and the solvent is polar protic. This is an example of a solvolysis reaction because the nucleophile is also the solvent.



Exercise 11.6.5

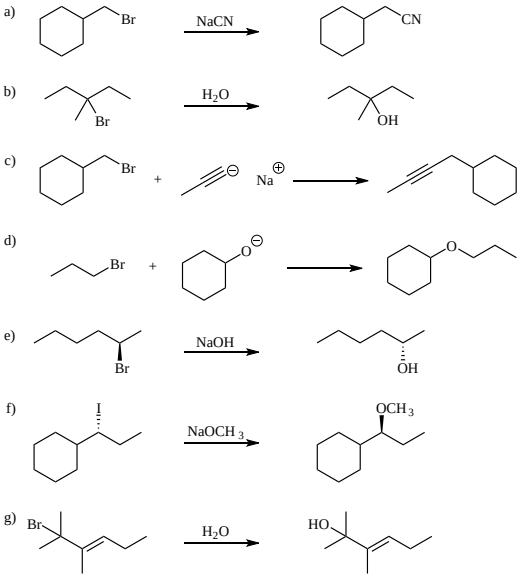
a. Reaction proceeds via S_N1 because the nucleophile is neutral, a secondary carbocation is formed, the solvent is polar protic, and Br- is a good leaving group.



racemic mixture

b. A stronger nucleophile such as $NaOCH_3$ should be used.

Exercise 11.6.6

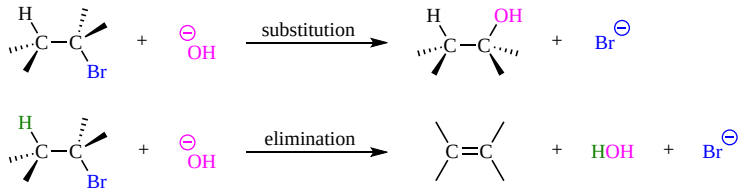


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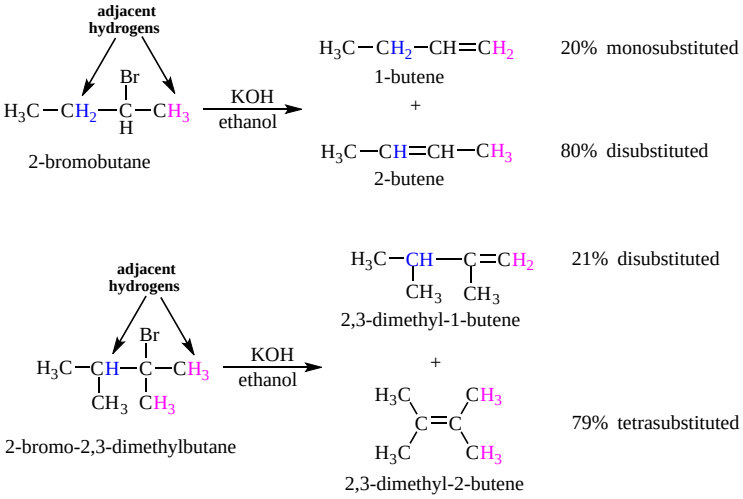
11.7: Elimination Reactions- Zaitsev's Rule

We said at the beginning of this chapter that two kinds of reactions can take place when a nucleophile/Lewis base reacts with an alkyl halide. The nucleophile can either substitute for the halide by reaction at carbon or can cause elimination of HX by reaction at a neighboring hydrogen:



Elimination reactions are more complex than substitution reactions for several reasons. One is the problem of regiochemistry. What product results by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

According to Zaitsev's rule, formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.



By using the strong base hydroxide, we direct these reactions toward elimination (rather than substitution). In both cases there are two different sets of adjacent hydrogens available to the elimination reaction (these are colored blue and magenta). If the rate of each possible elimination was the same, we might expect the amounts of the isomeric elimination products to reflect the number of hydrogens that could participate in that reaction. For example, since there are three 1°-hydrogens (magenta) and two 2°-hydrogens (blue) on beta-carbons in 2-bromobutane, statistics would suggest a 3:2 ratio of 1-butene and 2-butene in the products. This is not observed, and the latter predominates by 4:1. This departure from statistical expectation is even more pronounced in the second example, where there are six adjacent 1° hydrogens (magenta) compared with one 3°-hydrogen (blue). These results point to a strong favoring the more highly substituted product double bond predicted by **Zaitsev's Rule**.

Another factor that complicates a study of elimination reactions is that they can take place by different mechanisms, just as substitutions can. We'll consider three of the most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C–H and C–X bond-breaking.

ZAITSEV'S RULE

In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.

The E1, E2, and E1cB Reactions

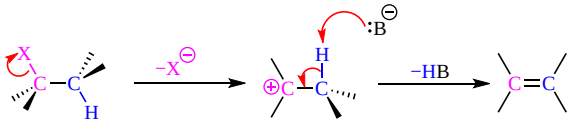
Elimination reactions take place by three common mechanisms, E1, E2, and E1cB, all of which break the H-C and X-C bonds at different points of their mechanism. In addition, the different mechanisms will have subtle effects on the reaction products which will be discussed later in this chapter.

- In the E1 reaction, the C–X bond breaks first to give a carbocation intermediate, which undergoes subsequent base abstraction of H^+ to yield the alkene.
- In the E2 reaction, base-induced C–H bond cleavage is simultaneous with C–X bond cleavage, giving the alkene in a single step.
- In the E1cB reaction (cB for "*conjugate base*"), base abstraction of the proton occurs first, giving a carbanion ($R:^-$) intermediate. This anion, the conjugate base of the reactant "acid," then undergoes loss of X^- in a subsequent step to give the alkene.

All three mechanisms occur frequently in the laboratory, but the E1cB mechanism predominates in biological pathways.

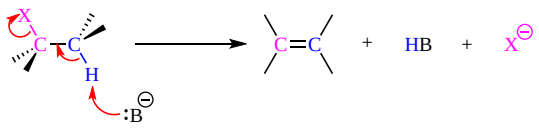
E1 Mechanism

This mechanism starts the breaking of the C-X to provide a carbocation intermediate. A base removes a hydrogen adjacent to the original electrophilic carbon. The electrons from the broken H-C bond move to form the pi bond of the alkene. In much the same fashion as the S_N1 mechanism, the first step of the mechanism is slow, making it the rate-determining step. This means that the reaction kinetics are unimolecular and first-order with respect to the substrate.



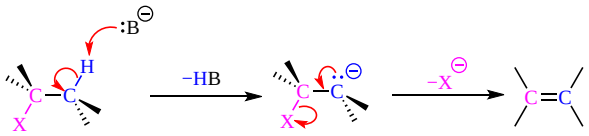
E2 Mechanism

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second-order kinetics and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the leaving group. The electrons of the broken H-C move to form the pi bond of the alkene. In doing this, the C-X bond is broken, causing the removal of the leaving group.



E1cB Mechanism

The E1cB mechanism starts with the base deprotonating a hydrogen adjacent to the leaving to form a carbanion. In the second step of the mechanism, the lone pair electrons of the carbanion move to become the pi bond of the alkene. This causes the C-X bond to break and the leaving group to be removed.



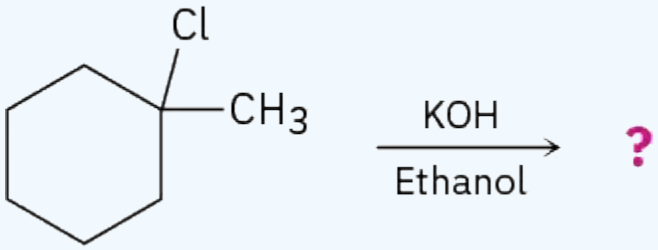
Predicting the Products of an Elimination Reaction

For most elimination reactions, the formation of the product involves the breaking of a C-X bond from the electrophilic carbon, the breaking of a C-H bond from a carbon adjacent to the electrophilic carbon, and the formation of a pi bond between these two carbons. Which elimination mechanism is being followed has little effect on these steps. The limitations of each elimination mechanism will be discussed later in this chapter.

To determine the possible products, it is vital to first identify the electrophilic carbon in the substrate. Next, identify all hydrogens on carbons directly adjacent to the electrophilic carbon. Each unique adjacent hydrogen has the possibility of forming a unique elimination product. Break a C-H bond from each unique group of adjacent hydrogens, then break the C-X bond. Finally, connect the adjacent carbon and the electrophilic carbon with a double bond. Repeat this process for each unique group of adjacent hydrogens. Finally, compare all of the possible elimination products. The product whose double bond has the most alkyl substituents will most likely be the preferred product.

Worked Example 11.7.1: Predicting the Product of an Elimination Reaction

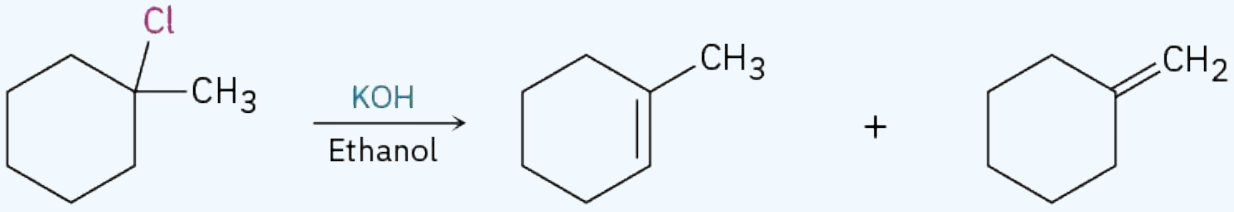
What product would you expect from reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?



Strategy

Treatment of an alkyl halide with a strong base such as KOH yields an alkene. To find the products in a specific case, locate the hydrogen atoms on each carbon next to the leaving group, and then generate the potential alkene products by removing HX in as many ways as possible. The major product will be the one that has the most highly substituted double bond—in this case, 1-methylcyclohexene.

Solution

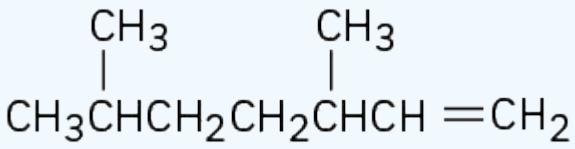


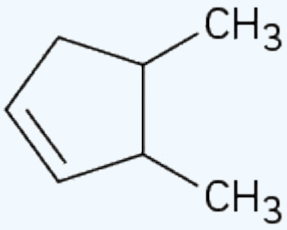
1-Chloro-1-methyl-cyclohexane | **1-Methylcyclohexene (major)** | **Methylenecyclohexane (minor)**

Exercises

Exercise 11.7.1

What alkyl halides might the following alkenes have been made from?

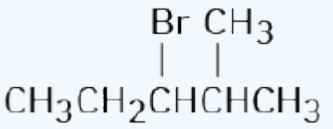
a. 

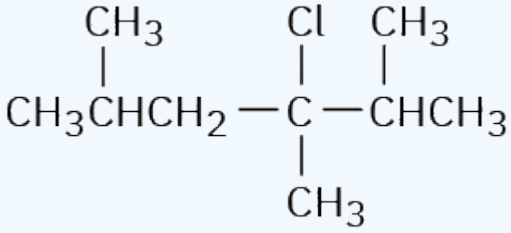
b. 

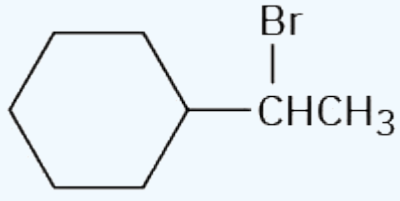
Answer available at the end of this section.

Exercise 11.7.2

Ignoring double-bond stereochemistry, what products would you expect from elimination reactions of the following alkyl halides? Which product will be the major product in each case?

a. 

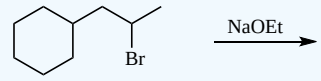
b. 

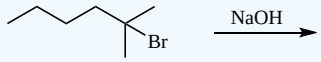
c. 

Answer available at the end of this section.

Exercise 11.7.3

Predict the major products of the following reactions.

a) 

b) 

c) 

Answer available at the end of this section.

Answers

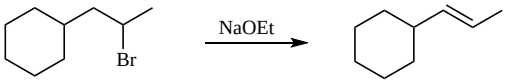
Exercise 11.7.1

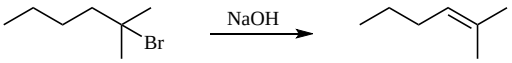
a. 1-Bromo-3,6-dimethylheptane
b. 4-Bromo-1,2-dimethylcyclopentane

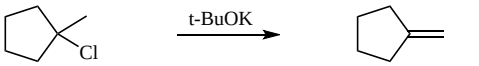
Exercise 11.7.2

a. Major: 2-methyl-2-pentene; minor: 4-methyl-2-pentene
b. Major: 2,3,5-trimethyl-2-hexene; minor: 2,3,5-trimethyl-3-hexene and 2-isopropyl-4-methyl-1-pentene
c. Major: ethylidenecyclohexane; minor: cyclohexylethylene

Exercise 11.7.3

a) 

b) 

c) 

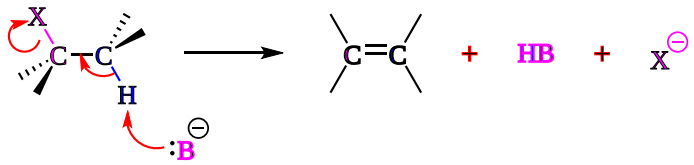
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11.8: The E2 Reaction and Mechanism

Introduction

E2, bimolecular elimination, was proposed in the 1920s by British chemist Christopher Kelk Ingold. E2 reactions are typically seen with secondary and tertiary alkyl halides, in the presence of a base (OH-, RO-, R_2N-). For a primary halide to undergo an E2 reaction, a strong sterically hindered base is usually required. The products of an E2 reaction follow Zaitsev's rule, the most substituted alkene is usually the major product.



E2 Mechanism

The E2 mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second-order kinetics and depends on the concentration of both the base and alkyl halide. The base removes a hydrogen from a carbon adjacent to the carbon with the leaving group. The electrons of the broken H-C bond move to form the pi bond of the neutral product alkene. In doing this, the C-X bond is broken, causing the removal of the leaving group. Overall, during this reaction, an electron pair is transferred from the base to the leaving group.

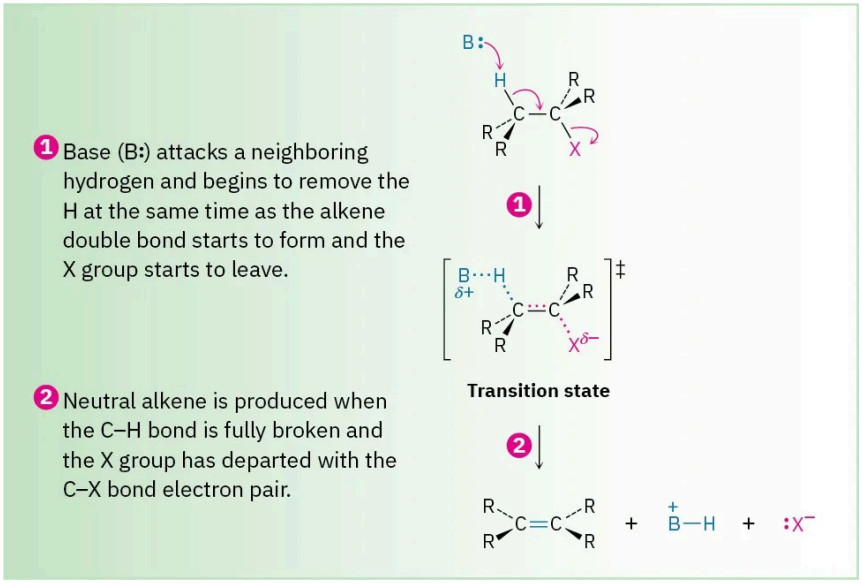


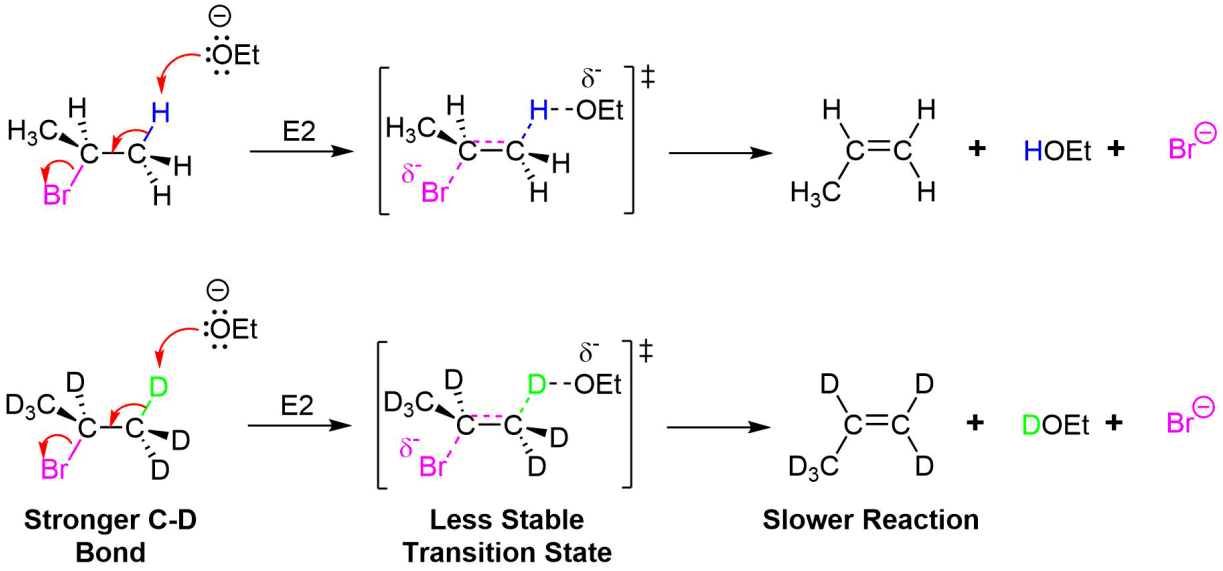
Figure 11.8.1: Mechanism of the E2 reaction of an alkyl halide. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.

Like the S_N2 reaction, the E2 reaction takes place in one step without intermediates. As the base begins to abstract H^+ from a carbon next to the leaving group, the C–H bond begins to break, a $C{=}C$ bond begins to form, and the leaving group begins to depart, taking with it the electron pair from the C–X bond.

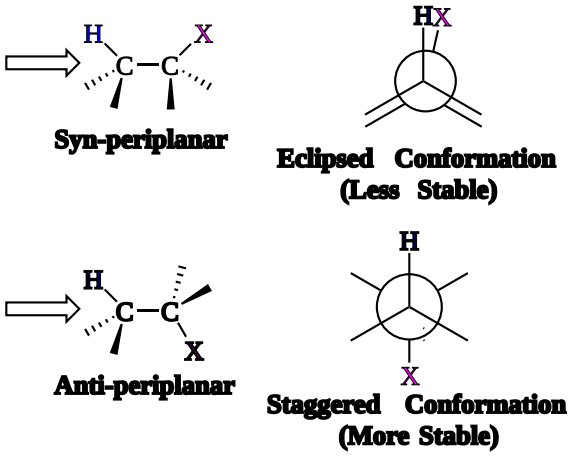
Evidence

Among the pieces of evidence supporting this mechanism is the fact that E2 reactions show second-order kinetics and follow the rate law: **rate = *k* × [RX] × [Base]**. That is, both the base and alkyl halide take part in the rate-limiting step.

Further evidence for the predicted mechanism for the E2 reaction was provided by experiments involving the **deuterium isotope effect** (DIE). The **deuterium isotope effect** (DIE) is a phenomenon associated with molecules that have had hydrogen (H) atoms isotopically substituted with deuterium (D) atoms, exhibiting different reaction rates. The bond dissociation energy for C-D bonds is about 5 kJ/mol stronger than the bond dissociation energy of C-H bonds. This difference in energy results in a reduction in the rate of reaction if the deuterium replacement occurs at a site of bond breaking in the rate-determining step of a reaction. So if the rate-limiting step involves a breaking of this bond, as it does at the E2 transition state, there will be a substantial decrease in reaction rates when comparing deuterated and non-deuterated analogues. Indeed, the reaction of 2-bromopropane with sodium ethoxide (NaOEt) is 6.7 times faster than its deuterated counterpart, providing evidence that the C-H bond is broken during the rate-determining step of the E2 mechanism. This is consistent with the predicted mechanism of the E2 reaction, consisting of a single concerted step. If the rate-determining step was the leaving group bond breaking first (as in an E1 reaction) the deuterium substitution would not have caused an observable change in reaction rate.



Another piece of mechanistic evidence involves the stereochemistry of E2 eliminations. As shown by a large number of experiments, E2 reactions occur with periplanar geometry, meaning that all four reacting atoms—the hydrogen, the two carbons, and the leaving group—lie in the same plane. Two such geometries are possible: syn-periplanar geometry, in which the H and the X are on the same side of the molecule, and anti periplanar geometry, in which the H and the X are on opposite sides of the molecule. Of the two, anti-periplanar geometry is energetically preferred because it allows the substituents on the two carbons to adopt a staggered relationship, whereas syn geometry requires that the substituents be eclipsed.



Periplanar Geometry

What's so special about periplanar geometry? Because the sp^3 σ orbitals in the reactant C–H and C–X bonds must overlap and become p π orbitals in the alkene product, there must also be some overlap in the transition state. This can occur most easily if all the orbitals are in the same plane to begin with—that is, if they're periplanar (Figure 11.8.2).

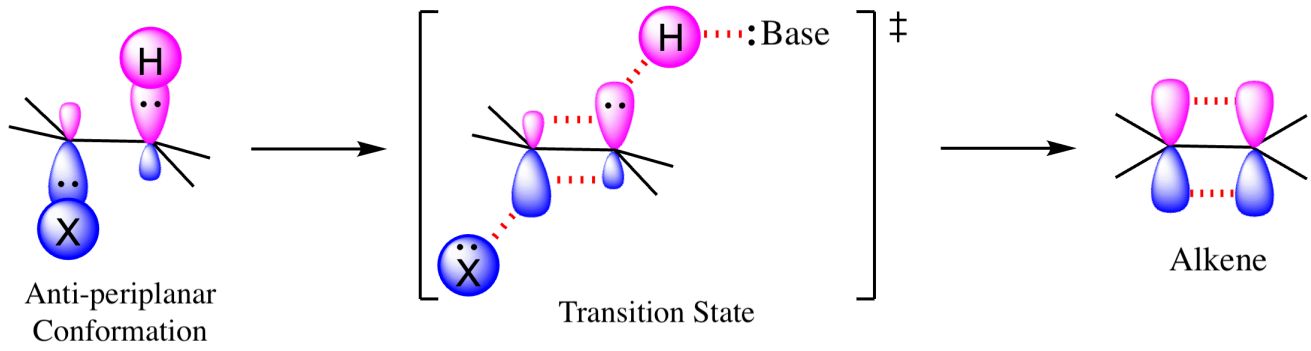
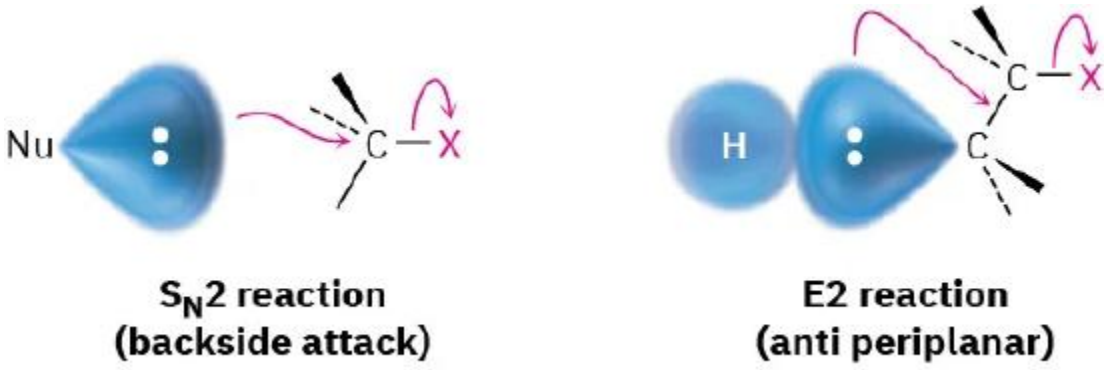
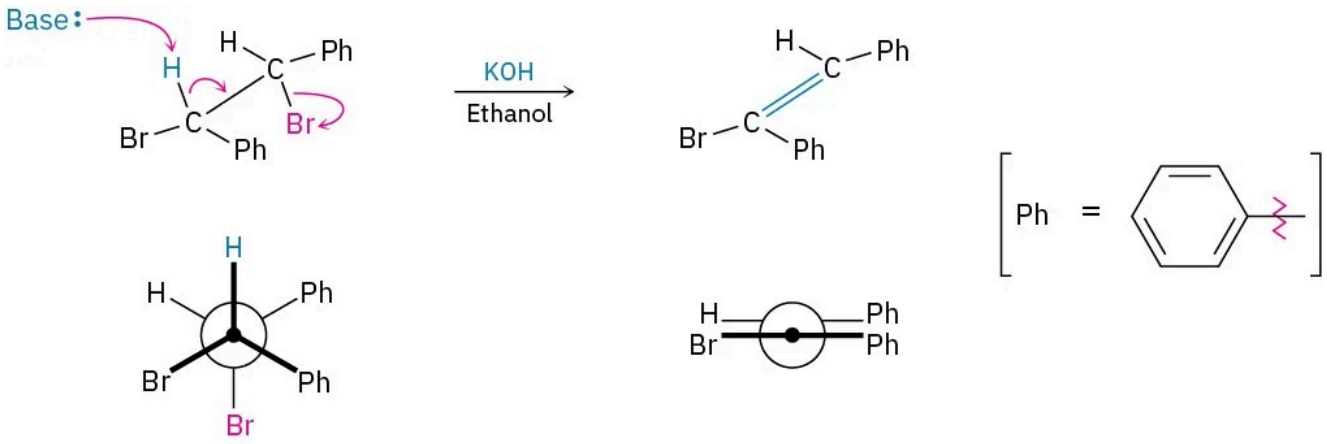


Figure 11.8.2: The transition state for the E2 reaction of an alkyl halide with base. Overlap of the developing p orbitals in the transition state requires periplanar geometry of the reactant.

Think of E2 elimination reactions with periplanar geometry as being similar to S_N2 reactions with 180° geometry. In an S_N2 reaction, an electron pair from the incoming nucleophile pushes out the leaving group on the opposite side of the molecule. In an E2 reaction, an electron pair from a neighboring C–H bond also pushes out the leaving group on the opposite side of the molecule.



Anti-periplanar geometry for E2 eliminations has specific stereochemical consequences that provide strong evidence for the proposed mechanism. To take just one example, *meso*-1,2-dibromo-1,2-diphenylethane undergoes E2 elimination on treatment with base to give only the *E* alkene. None of the isomeric *Z* alkene is formed because the transition state leading to the *Z* alkene would have to have syn-periplanar geometry and would thus be higher in energy.



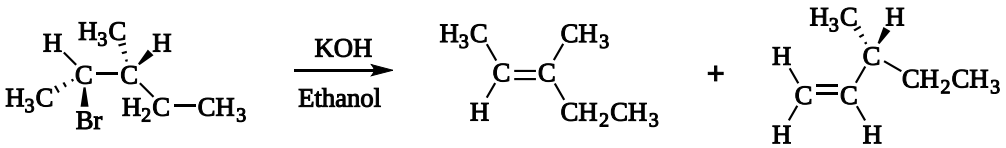
meso-1,2-Dibromo-1,2-diphenylethane (anti periplanar geometry)

(E)-1-Bromo-1,2-diphenylethylene

Predicting the Stereochemical Product of E2 Reactions

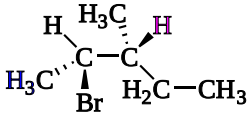
E2 reactions have the requirements of a leaving group and a hydrogen on a carbon adjacent to the leaving group carbon. For non-ringed compounds, the C-C can usually undergo free rotation to place the C-X and C-H bonds anti-periplanar to each other. Stereochemical considerations usually come into play when both of the carbons in the C-C bond are chiral. When these carbons are achiral but contain the other requirements for an E2 reaction, products lacking stereochemistry are usually produced.

When both of the carbons in the C-C bond are chiral, one carbon will have a leaving group, and the other carbon will have a single hydrogen. To consider the stereochemistry of an E2 product, start by creating a Newman projection looking down the C-C bond. Then rotate the C-C bond until the C-X and C-H bonds are in the anti position. The Newman projection now shows the relative positioning of the substituents on the C-C bond as they will appear in the double bond formed. It should be noted that if syn elimination were possible, a positional isomer of the double bond would be created. Consider the elimination products for (2R, 3R)-2-bromo-3-methylpentane.

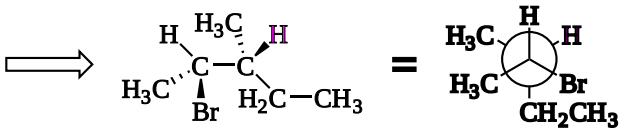


Major **Minor**

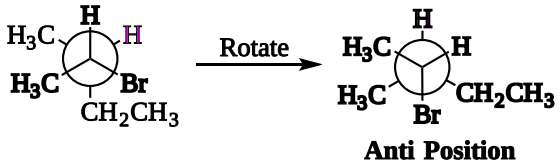
First, locate hydrogens on carbons adjacent to the leaving group. The compound used in this example has two unique sets of hydrogens.



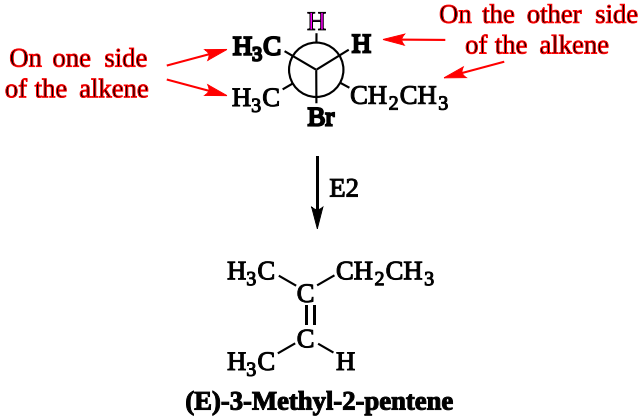
Because the adjacent hydrogen colored fuchsia is attached to a chiral carbon it require special consideration. Convert the structure into a Newman projection along the C-C bond that will for the alkene elimination product. The C-C bond can be view down either direction and still product the correct product.



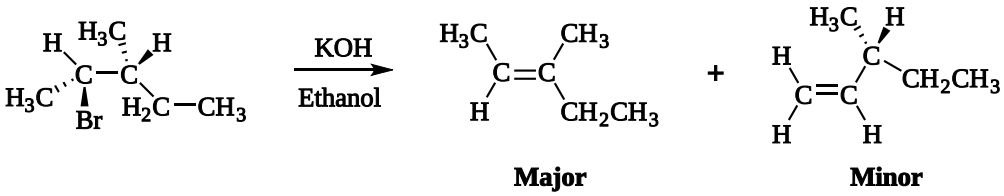
Then rotate such the the adjacent H and the leaving group are in the anti position.



This Newman projection shows the relative positioning of the substituents on the double bond formed. Note, none of the Z isomers is formed because it would require syn orientation of the H and Br.

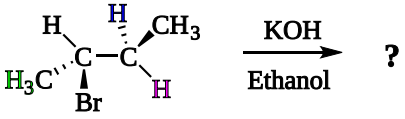


Lastly, consider the products made by other adjacent hydrogens and apply Zaitsev's rule to predict the preferred product.



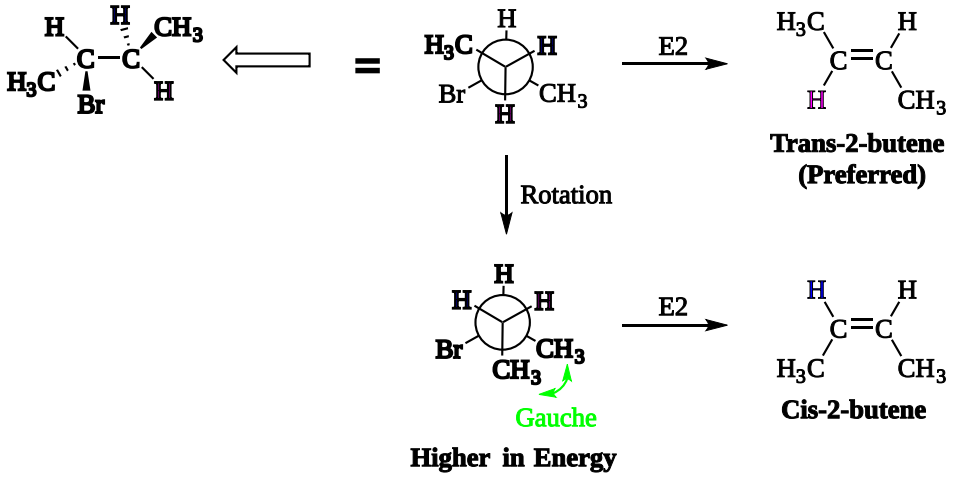
Determining *Cis* and *Trans* Products in an Elimination Reaction

Understanding that E2 reactions require an anti-periplanar geometry can explain why cis and trans alkene isomers can form as products. This occurs as an important exception to the rule that stereoisomers only form as elimination products when both of the carbons in the C-C bond forming the alkene are chiral. When considering the E2 reaction products of (R)-2-butane, there are two groups of hydrogens on carbons adjacent to the leaving group a CH_3 and a CH_2.

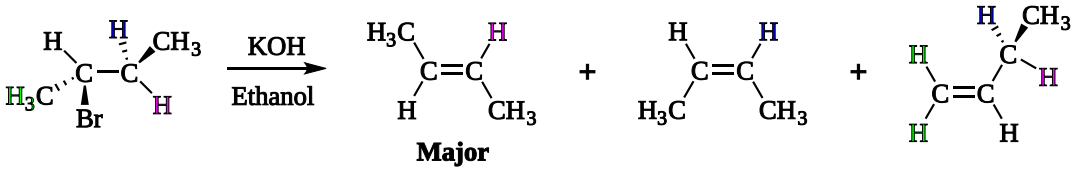


The carbon in the CH_2 group is achiral so both the H's appear to be equivalent. However, when the anti-periplanar geometry requirement is applied each hydrogen will produce its own unique product. Once the reactant is converted into a Newman projection it can be seen that the Br leaving group and the hydrogen colored blue are in the anti orientation and are ready to

be eliminated. It should also be noted that the two CH_3 groups are also in the anti position which gives them the least amount of steric interaction possible. Because the CH_3 groups are on opposite sides of the Newman projection the CH_3 groups will be on opposite sides of the alkene thus creating the product *trans*-2-butene. When the Newman projection is rotated such that the fuchsia colored hydrogen is anti to the Br leaving group, the two CH_3 groups are now on the same. This orientation creates the isomer *cis*-2-butene. However, to obtain this orientation the two CH_3 groups must overcome the steric strain associated with a gauche conformation. This makes the transition state leading the cis isomer higher in energy and more difficult to form. Because of this, the trans isomer will be the major product. It is clear that the two hydrogens of the CH_2 group are not equivalent despite their not being attached to a chiral carbon.



After considering all the products made during this E2 reaction the preferred product can be determined. The *cis* and *trans* isomer both have two alkene substituents while the third product only has one. Of the *cis* and *trans* isomer, the *trans* isomer is expected to be easier to form. Zaitsev's rule says that trans-2-butene will be the major product of this reaction.



Worked Example 11.8.1: Predicting the Double-Bond Stereochemistry of the Product in an E2 Reaction

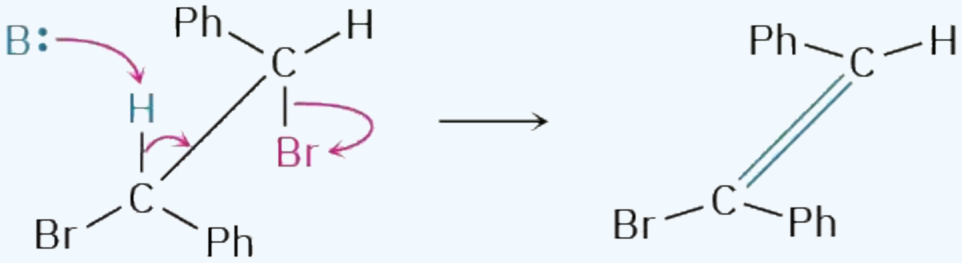
What stereochemistry do you expect for the alkene obtained by E2 elimination of (1S,2S)-1,2-dibromo-1,2-diphenylethane?

Strategy

Draw (1S,2S)-1,2-dibromo-1,2-diphenylethane so that you can see its stereochemistry and so that the –H and –Br groups to be eliminated are anti periplanar. Then carry out the elimination while keeping all substituents in approximately the same positions, and see what alkene results.

Solution

Anti periplanar elimination of HBr gives (*Z*)-1-bromo-1,2-diphenylethylene.



Exercises

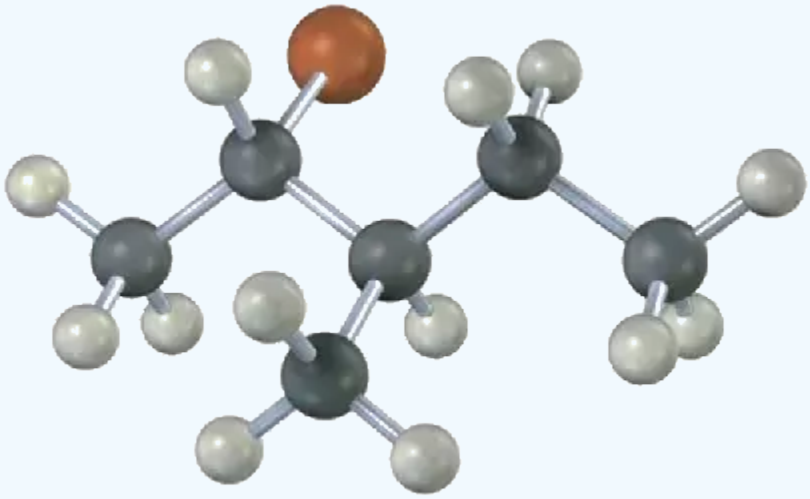
Exercise 11.8.1

What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

Answer available at the end of this section.

Exercise 11.8.2

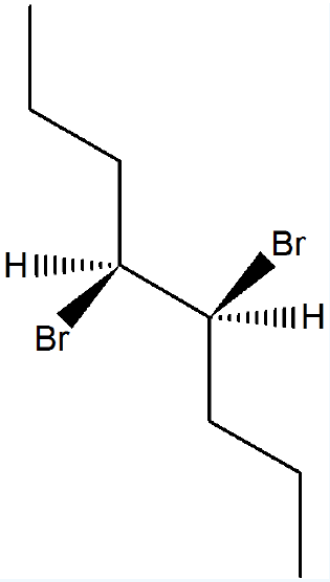
What stereochemistry do you expect for the trisubstituted alkene obtained by E2 elimination of the following alkyl halide on treatment with KOH? (reddish brown = Br.)



Answer available at the end of this section.

Exercise 11.8.3

What is the product of the following molecule in an E2 reaction? What is the stereochemistry?



Answer available at the end of this section.

Answers

Exercise 11.8.1

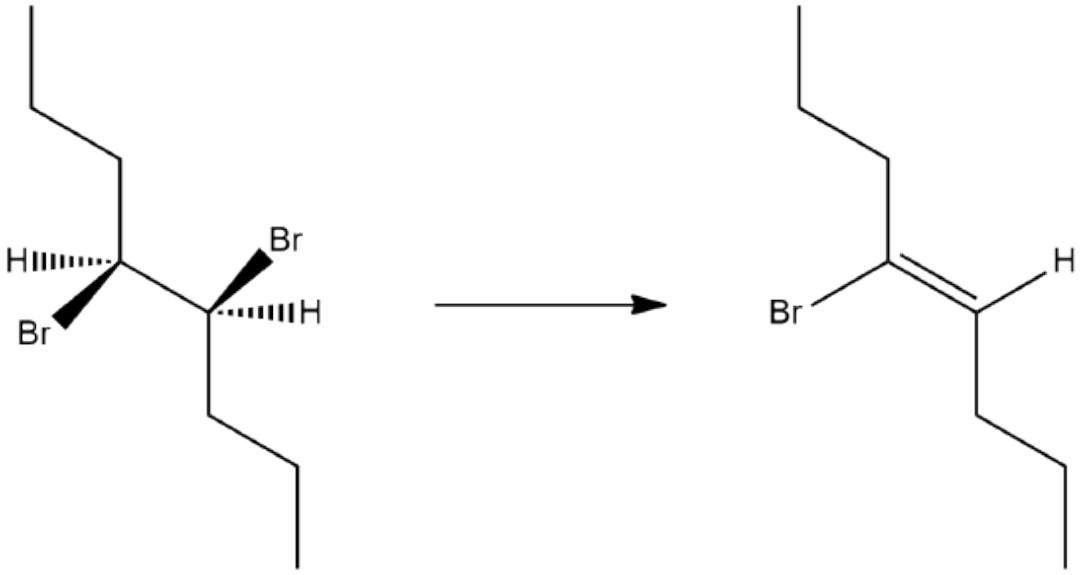
(*Z*)-1-Bromo-1,2-diphenylethylene

Exercise 11.8.2

(*Z*)-3-Methyl-2-pentene

Exercise 11.8.3

The stereochemistry is (*Z*) for the reaction.



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11.9: The E2 Reaction and Cyclohexane Conformation

Objectives

After completing this section, you should be able to

1. identify anti-periplanar arrangements of atoms in substituted cyclohexanes.
2. determine which cyclohexane conformation will generate a specific anti-periplanar arrangement.

Stereochemical Requirements of the E2 Reaction

Anti-periplanar geometry for E2 reactions is particularly important in cyclohexane rings, where chair geometry forces a rigid relationship between the substituents on neighboring carbon atoms (Section 4.8). The anti-periplanar requirement for E2 reactions overrides Zaitsev's rule and can be met in cyclohexanes only if the hydrogen and the leaving group are trans diaxial (Figure 11.9.1). If either the leaving group or the hydrogen is equatorial, E2 elimination can't occur.

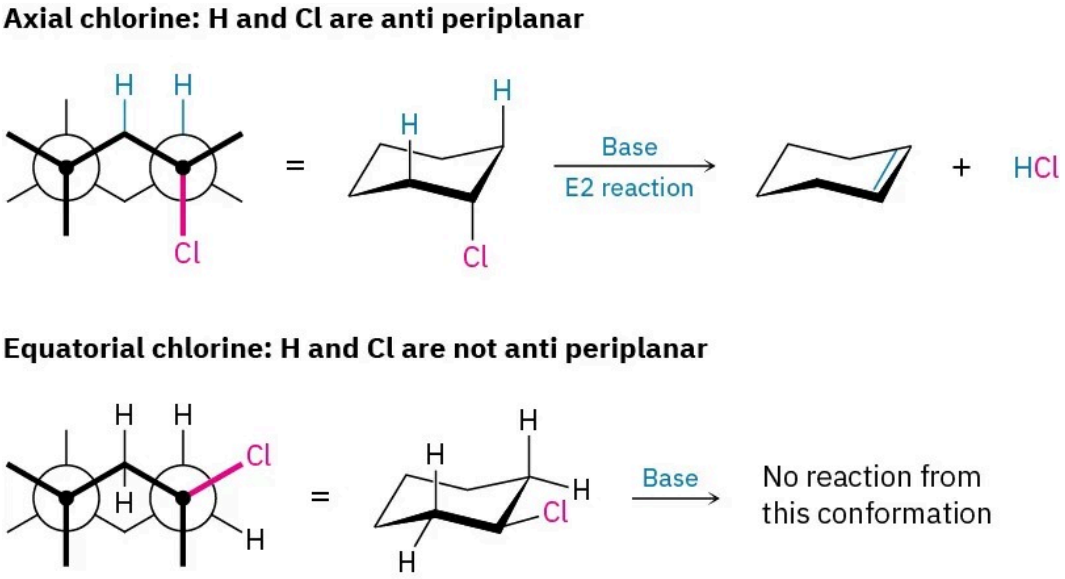


Figure 11.9.1: The geometric requirement for an E2 reaction in a substituted cyclohexane. The leaving group and the hydrogen must both be axial for anti-periplanar elimination to occur.

The elimination of HCl from the isomeric menthyl and neomenthyl chlorides shown in Figure 11.9.2 gives a good illustration of this trans-diaxial requirement. Neomenthyl chloride undergoes elimination of HCl on reaction with ethoxide ion 200 times faster than menthyl chloride. Furthermore, neomenthyl chloride yields 3-methene as the major alkene product, whereas menthyl chloride yields 2-methene.

The difference in reactivity between the isomeric methyl chlorides is due to the difference in their conformations. Neomenthyl chloride has the conformation shown in Figure 11.9.2*a*, with the methyl and isopropyl groups equatorial and the chlorine axial—a perfect geometry for E2 elimination. Loss of the hydrogen atom at C4 occurs easily to yield the more substituted alkene product, 3-menthene, as predicted by Zaitsev's rule.

Menthyl chloride, by contrast, has a conformation in which all three substituents are equatorial (Figure 11.9.2*b*). To achieve the necessary geometry for elimination, menthyl chloride must first ring-flip to a higher-energy chair conformation, in which all three substituents are axial. E2 elimination then occurs with loss of the only trans-diaxial hydrogen available, leading to the non-Zaitsev product 2-menthene. The net effect of the simple change in chlorine stereochemistry is a 200-fold change in reaction rate and a complete change of product. The chemistry of the molecule is controlled by its conformation.

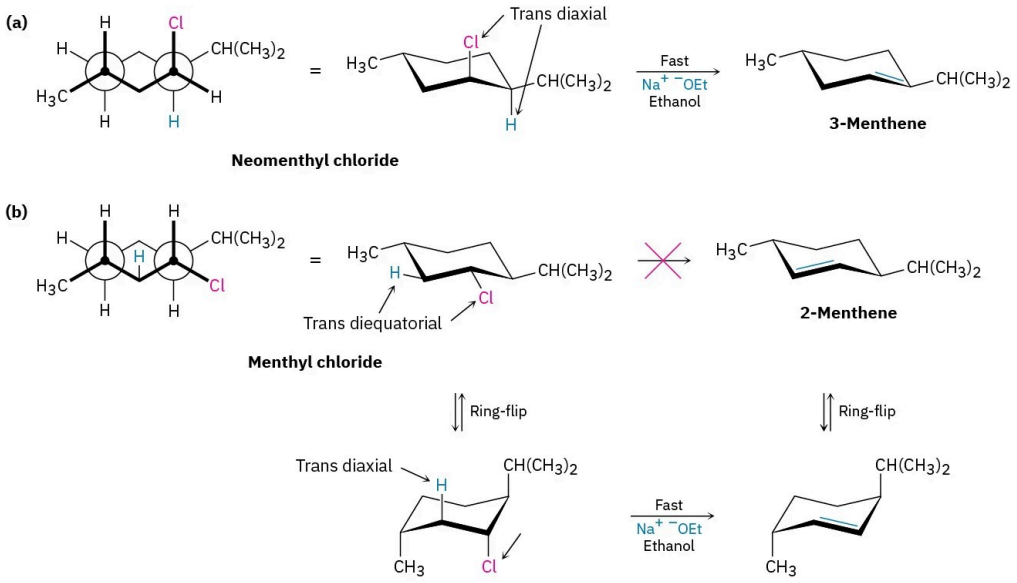


Figure 11.9.2: Dehydrochlorination of menthyl and neomenthyl chlorides. (a) Neomenthyl chloride loses HCl directly from its more stable conformation, but (b) menthyl chloride must first ring-flip to a higher energy conformation before HCl loss can occur. The abbreviation "Et" represents an ethyl group.

Worked Exercise 11.9.1

Which isomer would be expected to undergo E2 elimination quickly, cis or trans-1-bromo-4-tert-butylcyclohexane? Explain your answer.

Answer available at the end of this section.

Exercises

Exercise 11.9.1

Which of the following compounds will react faster in an E2 reaction; *trans*-1-bromo-2-isopropylcyclohexane or *cis*-1-bromo-2-isopropylcyclohexane?

Answer available at the end of this section.

Exercise 11.9.2

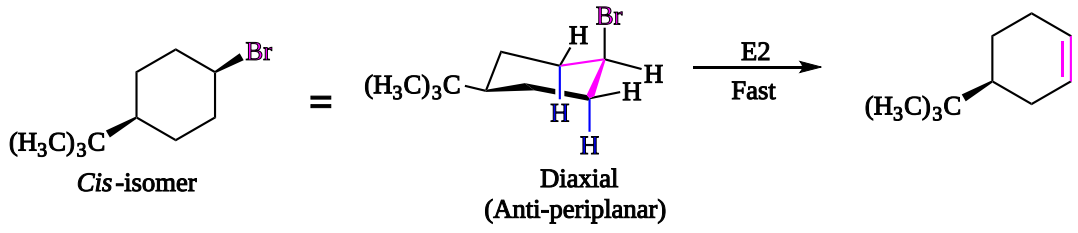
Which isomer would you expect to undergo E2 elimination faster, *trans*-1-bromo-4-*tert*-butylcyclohexane or *cis*-1-bromo-4-*tert*-butylcyclohexane? Draw each molecule in its more stable chair conformation, and explain your answer.

Answer available at the end of this section.

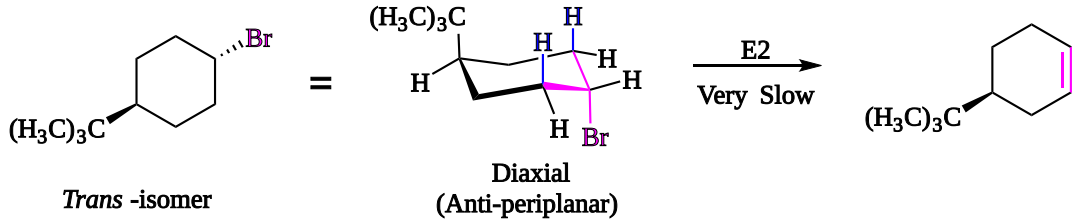
Answers

Worked Exercise 11.9.1

In the case of the 1-bromo-4-tert-butylcyclohexane isomers, the tert-butyl group is so large that it will always assume an equatorial orientation, leaving the bromine to be axial in the *cis*-isomer and equatorial in the *trans*-isomer. Because of symmetry, the two axial adjacent hydrogens in the *cis*-isomer react equally with base, resulting in rapid elimination to the same alkene (actually a racemic mixture). This reflects the fixed anti orientation of these hydrogens to the bromine atom. To assume a conformation having an axial bromine, the *trans*-isomer must tolerate serious crowding distortions. Such conformers are therefore present in extremely low concentration, and the rate of elimination is very slow. Indeed, substitution by hydroxide anion predominates in this situation.

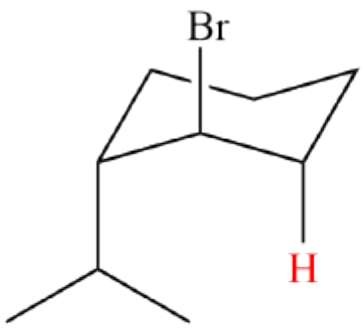


1-Bromo-4- *t*-butylcyclohexane

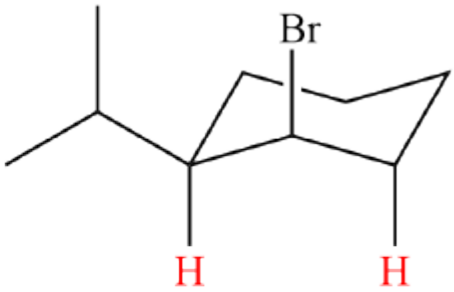


Exercise 11.9.1

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

Exercise 11.9.2

Cis isomer reacts faster because the bromine is axial.

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11.10: The E1 and E1cB Reactions

The E1 Reaction

Just as the E2 reaction is analogous to the S_N2 reaction, the S_N1 reaction has a close analog called the E1 reaction (for elimination, unimolecular). The E1 reaction can be formulated as shown in Figure 11.10.1, with the elimination of HCl from 2-chloro-2-methylpropane.

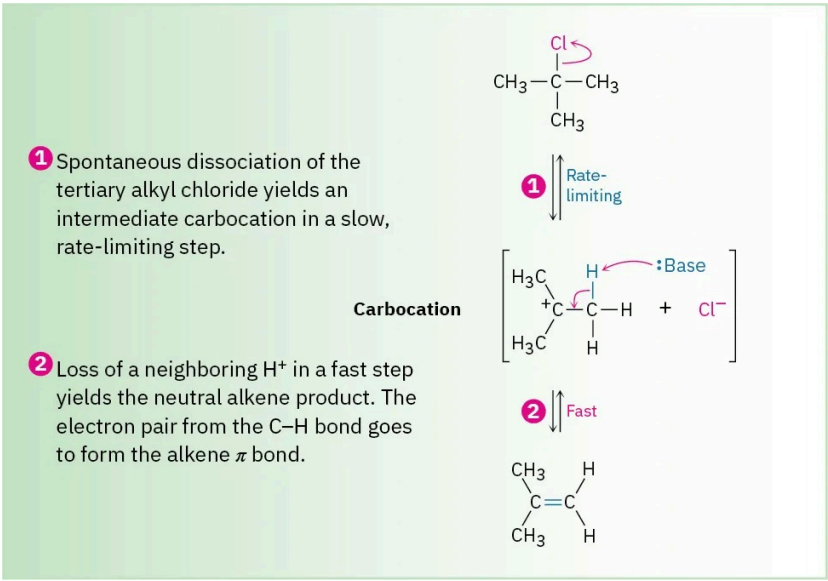
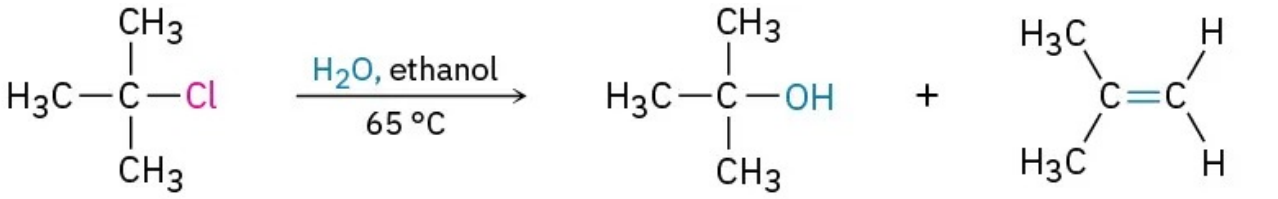


Figure 11.10.1: Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.

E1 eliminations begin with the same unimolecular dissociation to give a carbocation that we saw in the S_N1 reaction, but the dissociation is followed by loss of H^+ from the adjacent carbon rather than by substitution. In fact, the E1 and S_N1 reactions normally occur together whenever an alkyl halide is treated in a protic solvent with a nonbasic nucleophile. Thus, the best E1 substrates are also the best S_N1 substrates, and mixtures of substitution and elimination products are usually obtained. For example, when 2-chloro-2-methylpropane is warmed to 65 °C in 80% aqueous ethanol, a 64 : 36 mixture of 2-methyl-2-propanol (S_N1) and 2-methylpropene (E1) results.



2-Chloro-2-methylpropane | **2-Methyl-2-propanol (64%)** | **2-Methylpropene (36%)**

Much evidence has been obtained in support of the E1 mechanism. For example, E1 reactions show first-order kinetics, consistent with a rate-limiting, unimolecular dissociation process. Furthermore, E1 reactions show no deuterium isotope effect because rupture of the C–H (or C–D) bond occurs after the rate-limiting step rather than during it. Thus, we can't measure a rate difference between a deuterated and nondeuterated substrate.

A final piece of evidence involves the stereochemistry of elimination. Unlike the E2 reaction, where anti-periplanar geometry is

required, there is no geometric requirement on the E1 reaction because the halide and the hydrogen are lost in separate steps. We might therefore expect to obtain the more stable (Zaitsev's rule) product from E1 reaction, which is just what we find. To return to a familiar example, menthyl chloride loses HCl under E1 conditions in a polar solvent to give a mixture of alkenes in which the Zaitsev product, 3-menthene, predominates (Figure 11.10.2).

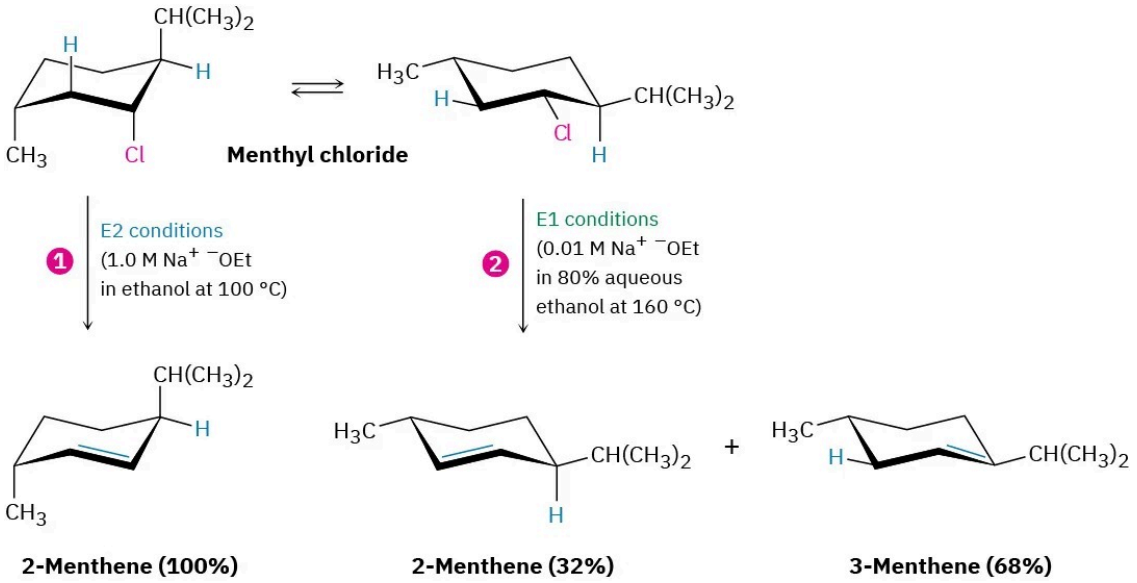
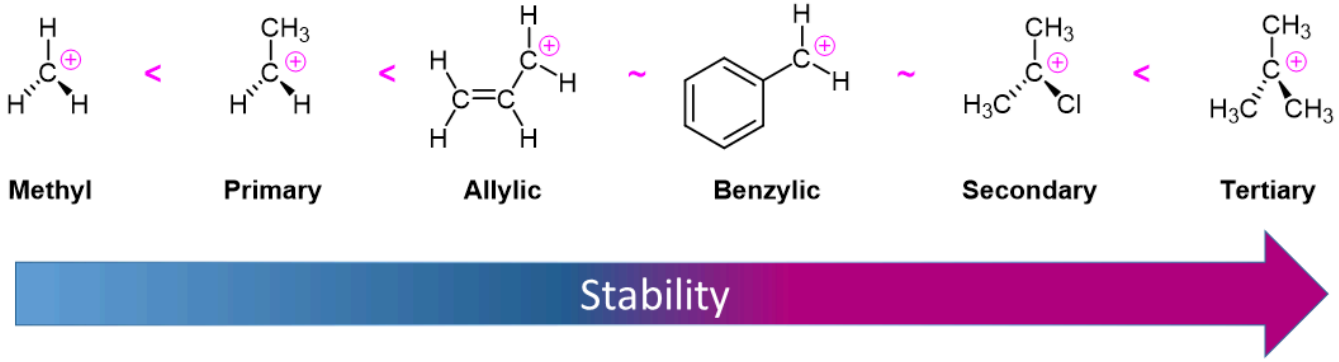


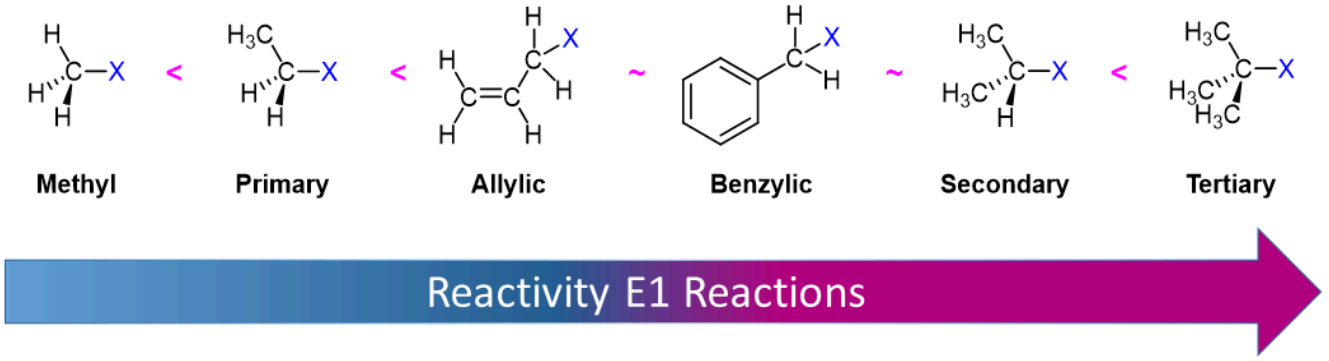
Figure 11.10.2: Elimination reactions of menthyl chloride. E2 conditions (**1**, strong base in 100% ethanol) lead to 2-menthene through an anti-periplanar elimination. E1 conditions (**2**, dilute base in 80% aqueous ethanol) lead to a mixture of 2-menthene and 3-menthene.

Alkyl Halide Reactivity in E1 Reactions

Due to the fact that E1 reactions create a carbocation intermediate, the reactivity of alkyl halides toward E1 reactions mirrors that present in S_N1 reactions.



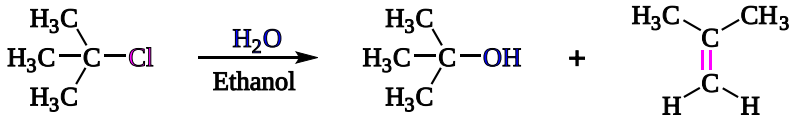
As expected, tertiary carbocations are favored over secondary, primary, and methyl carbocations. This is due to the phenomenon of hyperconjugation, which essentially allows a nearby C-C or C-H bond to interact with the p orbital of the carbon to bring the electrons down to a lower energy state. Thus, this has a stabilizing effect on the molecule as a whole. In general, primary and methyl carbocations do not proceed through the E1 pathway for this reason, unless there is a means of carbocation rearrangement to move the positive charge to a nearby carbon that is more stable. Secondary and Tertiary carbons form more stable carbocations, thus E1 reactions occur quite rapidly at these atoms.



Secondary carbocations can be subject to the E2 reaction pathway, but this generally occurs in the presence of a good/strong base. Adding a weak base to the reaction disfavors E2, essentially pushing towards the E1 pathway. In many instances, solvolysis occurs rather than using a base to deprotonate. This means heat is added to the solution, and the solvent itself deprotonates a hydrogen. The medium can affect the pathway of the reaction as well. Polar protic solvents may be used to hinder nucleophiles, thus disfavoring E2/S_N2 from occurring.

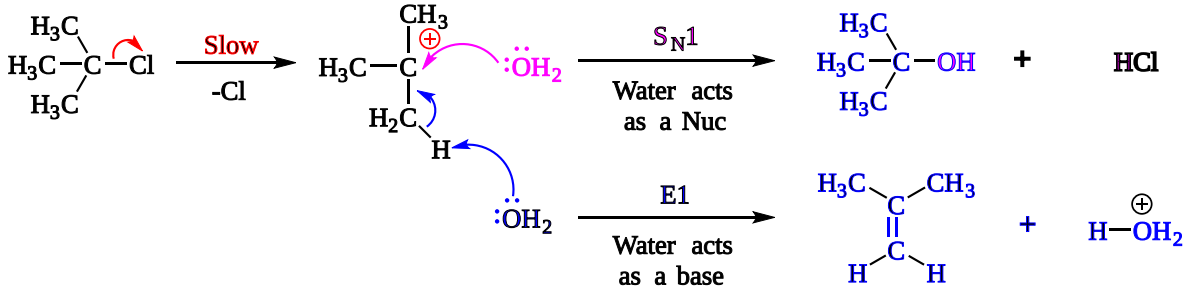
The Connection Between S_N1 and E1 Reactions

The E1 and S_N1 mechanisms both begin with the rate-determing step, the unimolecular removal of a leaving group to form a carbocation intermediate. Sharing the rate-determining step causes alkyl halides to produce both S_N1 substitution and E1 elimination products whenever they are reacted with nonbasic nucleophiles in a protic solvent. For example, the hydrolysis of *tert*-butyl chloride in a solution of water and ethanol gives a mixture of 2-methyl-2-propanol (60%) and 2-methylpropene (40%) at a rate independent of the water concentration.



2-Chloro-2-methylpropane → **2-Methyl-2-propanol (60%)** + **2-Methylpropene (40%)**

To produce the alcohol product, water attacks the carbocation as a nucleophile as part of an S_N1 reaction. To produce the alkene product, water acts as a base and deprotonates an adjacent hydrogen as part of an E1 reaction. As expected, the mechanisms of the two reactions have similar characteristics. They both show first-order kinetics; neither is much influenced by a change in the nucleophile/base, and both are relatively non-stereospecific.



To summarize, when carbocation intermediates are formed, them react further by one or more of the following modes:

1. The cation may bond to a nucleophile to give a substitution product.
2. The cation may transfer an adjacent proton to a base, giving an alkene product.
3. The cation may rearrange to a more stable carbocation, and then react by mode #1 or #2.

Comparing E1 and E2 Mechanisms

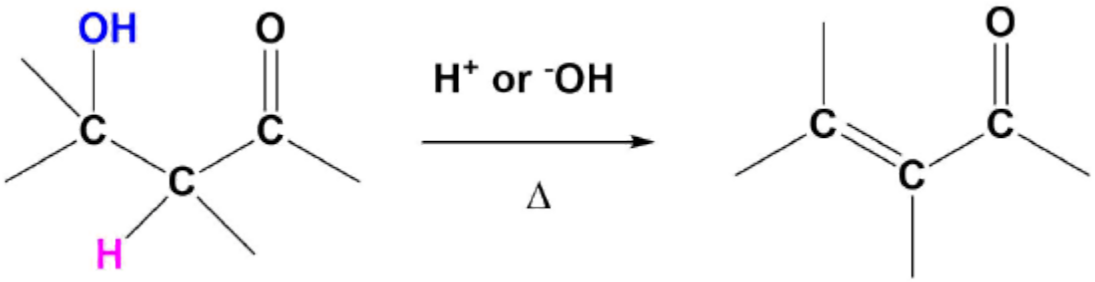
Three factors should be considered when determining whether an elimination reaction occurs via an E1 or E2 mechanism:

1. **The base:** strong bases favor the E2 mechanism, whereas E1 mechanisms only require a weak base.
2. **The solvent**: good ionizing solvents (polar protic) favor the E1 mechanism by stabilizing the carbocation intermediate.
3. **The alkyl halide:** primary alkyl halides have the only structure useful in distinguishing between the E2 and E1 pathways. Since primary carbocations do not form, only the E2 mechanism is possible.

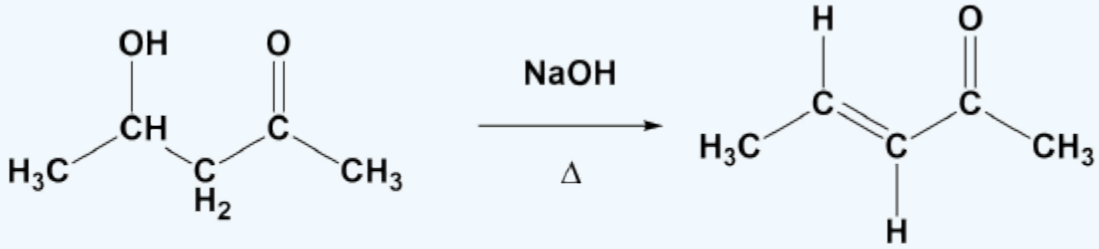
Reaction Parameter	E2	E1
alkyl halide structure	tertiary > secondary > primary	tertiary > secondary >>>> primary
nucleophile	high concentration of a strong base	weak base
mechanism	1-step	2-step
rate-limiting step	bimolecular transition state	carbocation formation
rate law	rate = k[R-X][Base]	rate = k[R-X]
solvent	not important	polar protic

The E1cB Reaction

The reaction is particularly common in substrates that have a poor leaving group, such as –OH, two carbons removed from a carbonyl group, as in HOC–CH–C═ O HOC –CH–C═O . The poor leaving group disfavors the alternative E1 and E2 possibilities, and the carbonyl group makes the adjacent hydrogen unusually acidic by resonance stabilization of the anion intermediate. We'll look at this acidifying effect of a carbonyl group in CHEM 232.

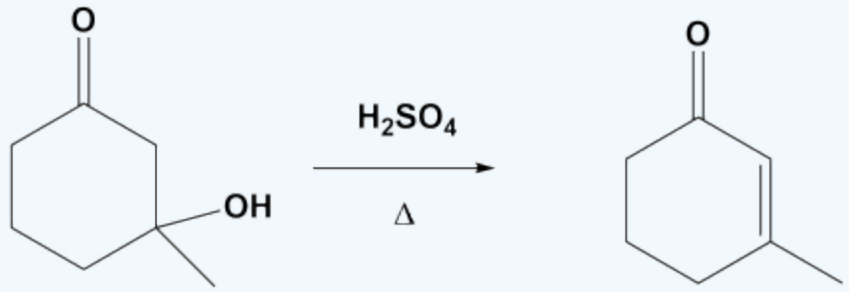


Example 11.10.1



4-Hydroxy-2-Pentanone

3-Penten-2-one

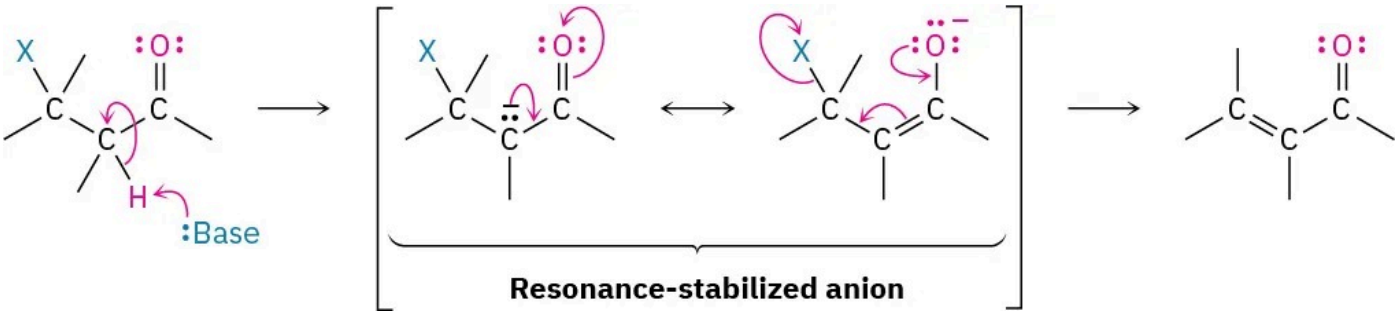


3-Hydroxy-3-methylcyclohexanone

3-Methyl-2-Cyclohexenone

E1cB Mechanism

In contrast to the E1 reaction, which involves a carbocation intermediate, the E1cB reaction takes place through a carbanion intermediate. Base-induced abstraction of a proton in a slow, rate-limiting step gives an anion, which expels a leaving group on the adjacent carbon.



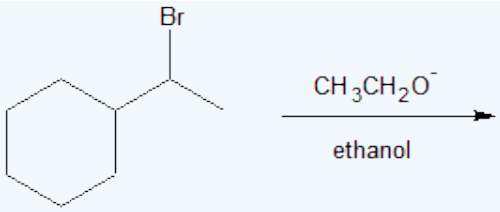
Note: The double bond always forms in conjugation with the carbonyl.

Exercises

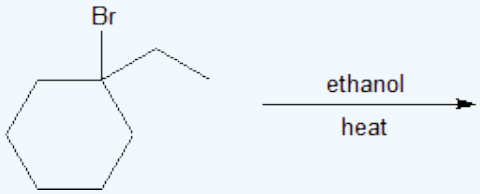
Exercise 11.10.1

Predict the dominant elimination mechanism (E1 or E2) for each reaction below. Explain your reasoning.

a)



b)

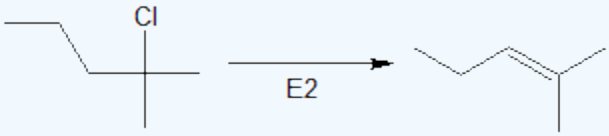


Answer available at the end of this section.

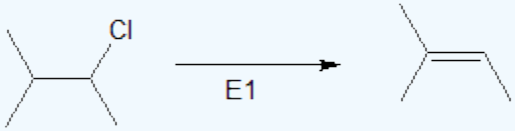
Exercise 11.10.2

Specify the reaction conditions to favor the indicated elimination mechanism.

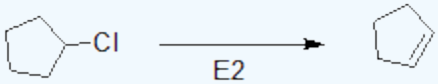
a)



b)



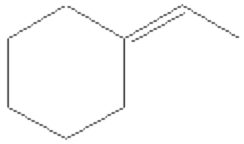
c)

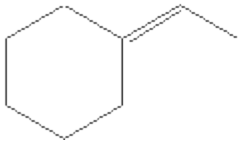


Answer available at the end of this section.

Answers

Exercise 11.10.1

a)  E2 reaction b/c secondary alkyl halide with a strong base.

b)  E1 reaction b/c tertiary alkyl halide with a weak base.

Exercise 11.10.2

a) strong base, such as hydroxide, an alkoxide, or equivalent
b) water or alcohol, or an equivalent weak base with heat
c) strong base, such as hydroxide, an alkoxide, or equivalent

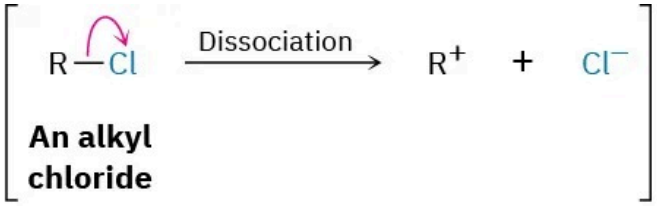
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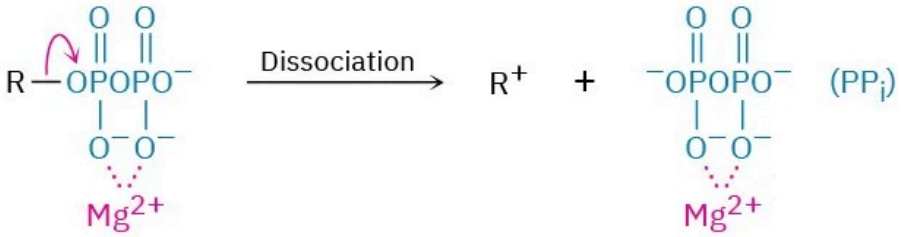
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11.11: Biological Reactions

Biological Substitution Reactions

Both S_N1 and S_N2 reactions are common in biological chemistry, particularly in the pathways for biosynthesis of the many thousands of plant-derived substances called terpenoids, which we saw briefly in Chapter 8 *Chemistry Matters* and will discuss in CHEM 232. Unlike what typically happens in the laboratory, however, the substrate in a biological substitution reaction is usually an organodiphosphate rather than an alkyl halide. Thus, the leaving group is the diphosphate ion, abbreviated PP_i, rather than a halide ion. In fact, it's useful to think of the diphosphate group as the "biological equivalent" of a halide. The dissociation of an organodiphosphate in a biological reaction is typically assisted by complexation to a divalent metal cation such as Mg^{2+} to help neutralize charge and make the diphosphate a better leaving group.





An organodiphosphate **Diphosphate ion**

As an example, two S_N1 reactions occur during the biosynthesis of geraniol, a fragrant alcohol found in roses and used in perfumery. Geraniol biosynthesis begins with dissociation of dimethylallyl diphosphate to give an allylic carbocation, which reacts with isopentenyl diphosphate (Figure 11.11.1). From the viewpoint of isopentenyl diphosphate, the reaction is an electrophilic alkene addition, but from the viewpoint of dimethylallyl diphosphate, the process is an S_N1 reaction in which the carbocation intermediate reacts with a double bond as the nucleophile.

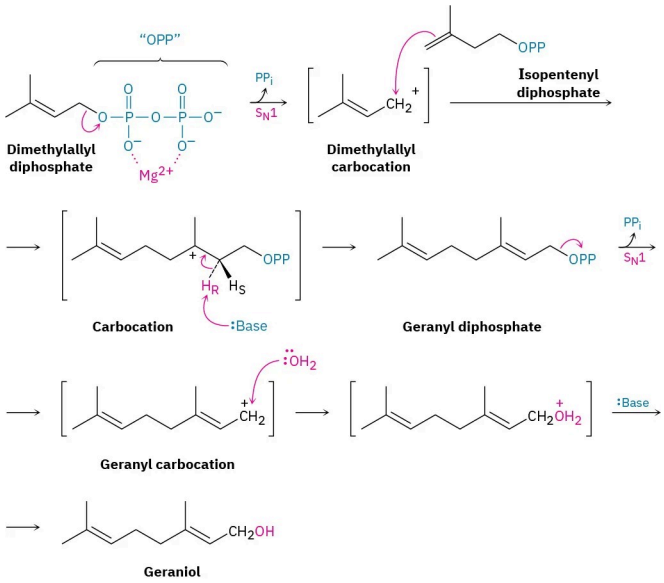


Figure 11.11.1: Biosynthesis of geraniol from dimethylallyl diphosphate. Two S_N1 reactions occur, both with diphosphate ion as the leaving group.

Following this initial S_N1 reaction, loss of the pro-*R* hydrogen gives geranyl diphosphate, itself an allylic diphosphate that dissociates a second time. Reaction of the geranyl carbocation with water in a second S_N1 reaction, followed by loss of a proton, then yields geraniol.

As another example, S_N2 reactions are involved in almost all biological methylations, which transfer a $-CH_3$ group from an electrophilic donor to a nucleophile. The donor is *S*-adenosylmethionine (abbreviated SAM), which contains a positively charged sulfur (a sulfonium ion, Section 5.12), and the leaving group is the neutral *S*-adenosylhomocysteine molecule. In the biosynthesis of epinephrine (adrenaline) from norepinephrine, for instance, the nucleophilic nitrogen atom of norepinephrine attacks the electrophilic methyl carbon atom of *S*-adenosylmethionine in an S_N2 reaction, displacing *S*-adenosylhomocysteine (Figure 11.11.2). In effect, *S*-adenosylmethionine is simply a biological equivalent of CH_3Cl.

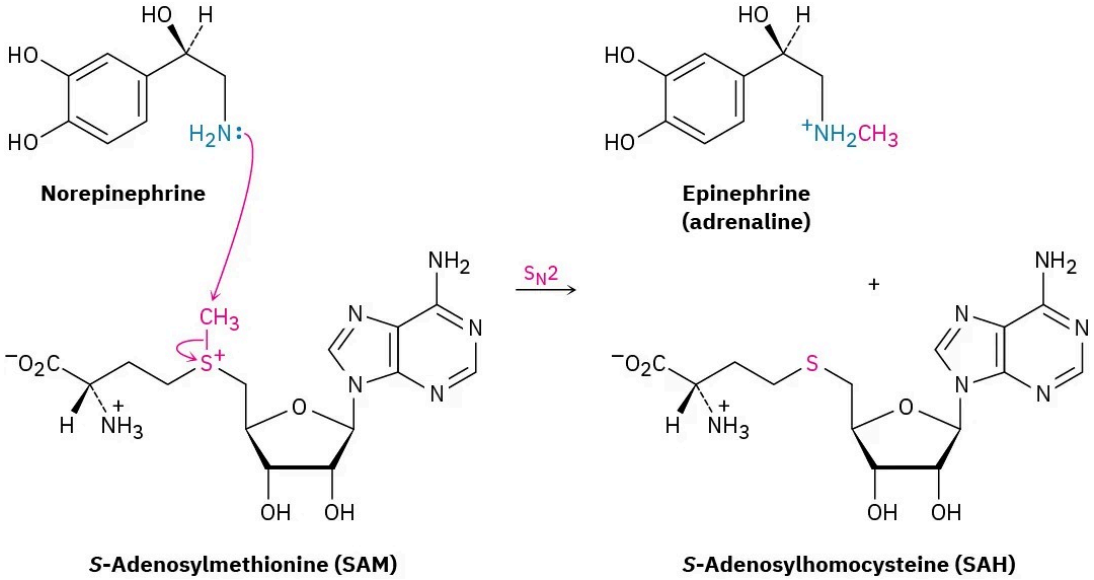


Figure 11.11.2: The biosynthesis of epinephrine from norepinephrine occurs by an S_N2 reaction with S-adenosylmethionine.

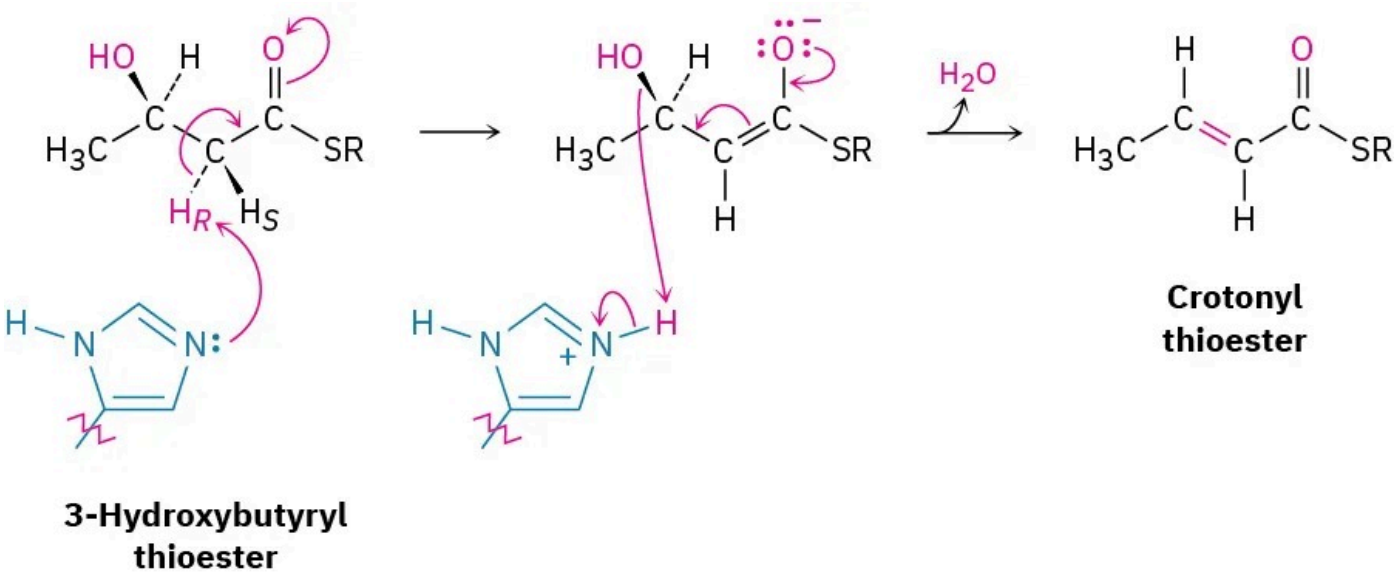
Exercise 11.11.1

Review the mechanism of geraniol biosynthesis shown in Figure 11.11.1, and propose a mechanism for the biosynthesis of limonene from linalyl diphosphate.

Answer available at the end of this section.

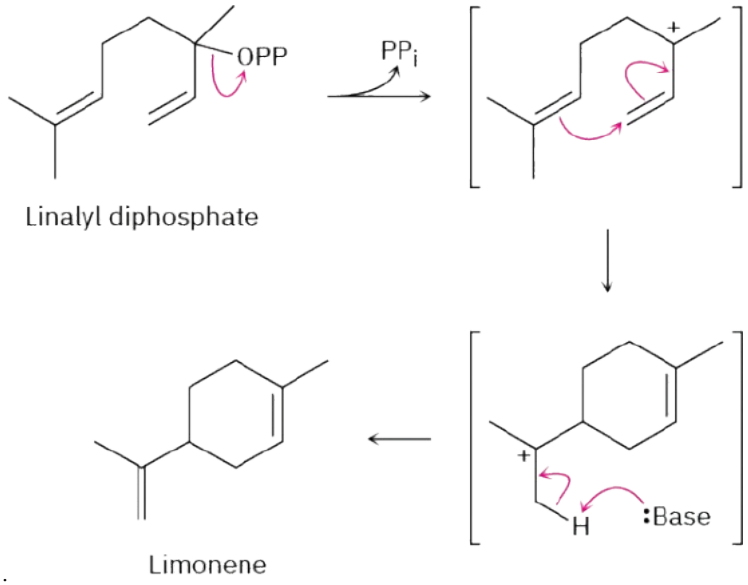
Biological Elimination Reactions

All three elimination reactions—E2, E1, and E1cB—occur in biological pathways, but the E1cB mechanism is particularly common. The substrate is usually an alcohol rather than an alkyl halide, and the H atom removed is usually adjacent to a carbonyl group, just as in laboratory reactions. Thus, 3-hydroxy carbonyl compounds are frequently converted to unsaturated carbonyl compounds by elimination reactions. A typical example occurs during the biosynthesis of fats and oils when a 3-hydroxybutyryl thioester is dehydrated to the corresponding unsaturated (crotonyl) thioester. The base in this reaction is a histidine amino acid in the enzyme, and the loss of the –OH group is assisted by simultaneous protonation.



Answers

Exercise 11.11.1



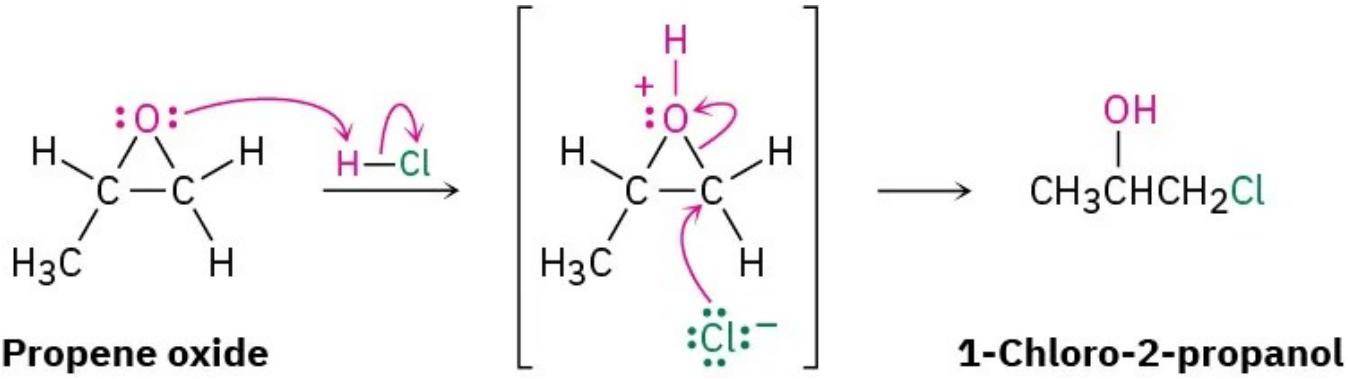
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11.12: Deciding between SN1, SN2, E1, and E2

S_N1, S_N2, E1, E1cB, E2—how can you keep it all straight and predict what will happen in any given case? Will substitution or elimination occur? Will the reaction be bimolecular or unimolecular? There are no rigid answers to these questions, but it's possible to recognize some trends and make some generalizations.

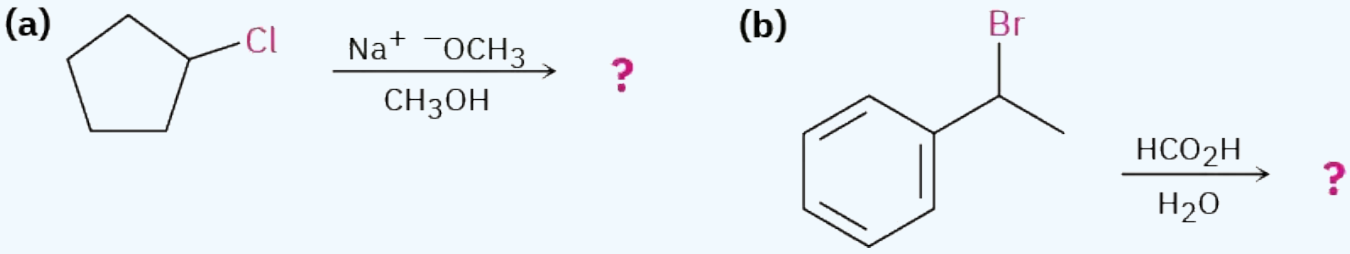
- **Primary substrates:** S_N2 substitution occurs if a good nucleophile is used, E2 elimination occurs if a strong, sterically hindered base is used, and E1cB elimination occurs if the leaving group is two carbons away from a carbonyl group.
- The one general exception to the rule that ethers don't typically undergo S_N2 reactions pertains to epoxides, the three-membered cyclic ethers that we saw in Section 8.7. Because of the angle strain in their three-membered ring, epoxides are much more reactive than other ethers. They react with aqueous acid to give 1,2-diols, as we saw in Section 8.7, and they react readily with many other nucleophiles as well. Propene oxide, for instance, reacts with HCl to give 1-chloro-2-propanol by an S_N2 backside attack on the less hindered primary carbon atom.



- **Secondary alkyl halides:** S_N2 substitution occurs if a weakly basic nucleophile is used in a polar aprotic solvent, E2 elimination predominates if a strong base is used, and E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group. Secondary allylic and benzylic alkyl halides can also undergo S_N1 and E1 reactions if a weakly basic nucleophile is used in a protic solvent.
- **Tertiary alkyl halides:** E2 elimination occurs when a base is used, but S_N1 substitution and E1 elimination occur together under neutral conditions, such as in pure ethanol or water. E1cB elimination takes place if the leaving group is two carbons away from a carbonyl group.

Worked Example 11.12.1: Predicting the Product and Mechanism of Reactions

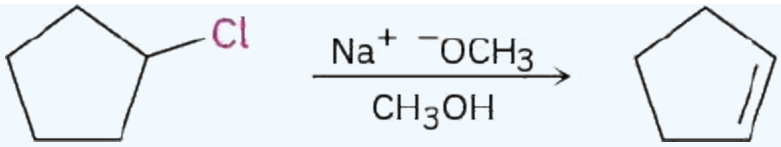
Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2, and predict the product of each:



Strategy

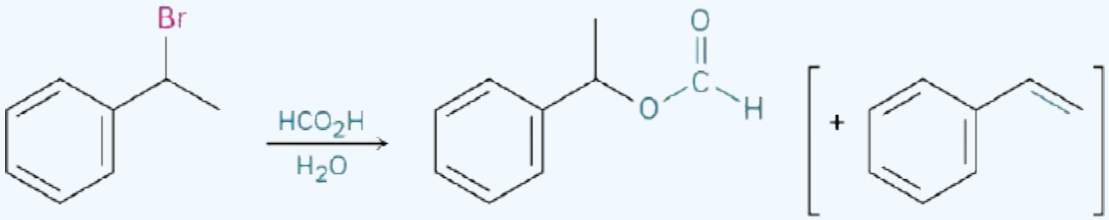
Look carefully in each reaction at the structure of the substrate, the leaving group, the nucleophile, and the solvent. Then decide from the preceding summary which kind of reaction is likely to be favored.

Solution



E2 reaction

(a) A secondary, nonallylic substrate can undergo an S_N2 reaction with a good nucleophile in a polar aprotic solvent but will undergo an E2 reaction on treatment with a strong base in a protic solvent. In this case, E2 reaction is likely to predominate.



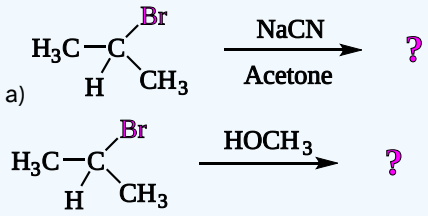
S_N1 E1

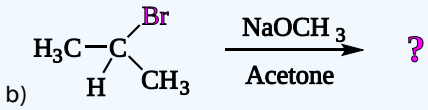
(b) A secondary benzylic substrate can undergo an S_N2 reaction on treatment with a nonbasic nucleophile in a polar aprotic solvent and will undergo an E2 reaction on treatment with a base. Under protic conditions, such as aqueous formic acid (HCO_2H), an S_N1 reaction is likely, along with some E1 reaction.

Exercises

Exercises11.12.1

1) For the following, please determine what kind of reaction is occurring and predict the product(s).





c)

Answer available at the end of this section.

Exercise 11.12.2

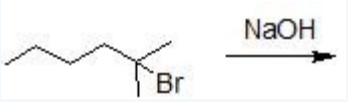
Identify the function of the following reagents. The reagents will be a strong/weak nucleophile and/or a strong/weak base.

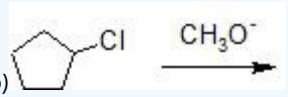
a) Cl^- b) NaH. c) t-BuO^- d) OH^- e) H_2O f) HS^- g) MeOH

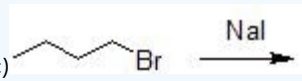
Answer available at the end of this section.

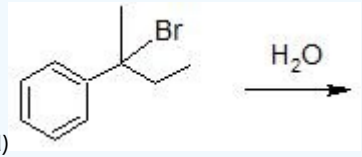
Exercise 11.12.3

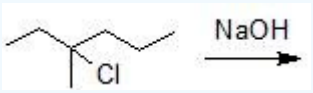
Identify the dominant reaction mechanism (S_N1, S_N2, E1, or E2) and predict the major product for the following reactions.

a) 

b) 

c) 

d) 

e) 

Answer available at the end of this section.

Exercise 11.12.4

Identify all the products of the following reactions and specify the major product.

Answer available at the end of this section.

Answer available at the end of this section.

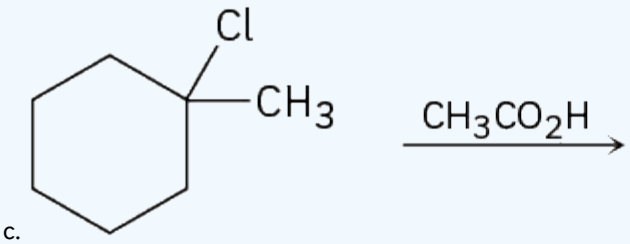
Exercise 11.12.5

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:

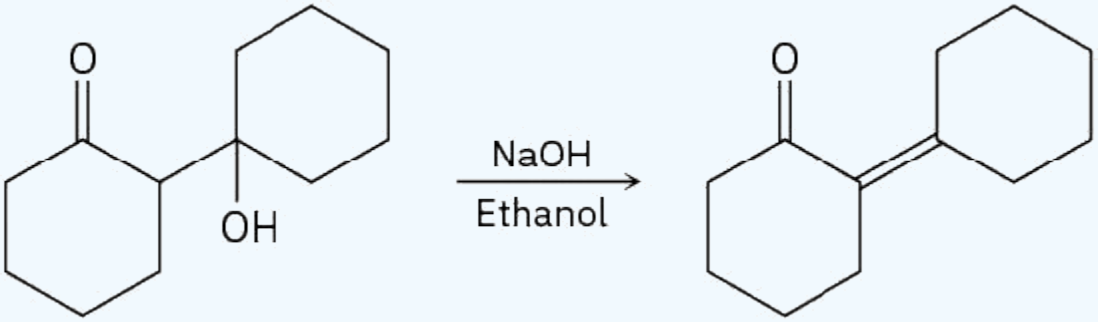
a. $CH_3CH_2CH_2CH_2Br \xrightarrow[THF]{NaN_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

b. $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[Ethanol]{KOH} CH_3CH_2CH{=}CHCH_3$

c.



d.



Answer available at the end of this section.

Exercise 11.12.6

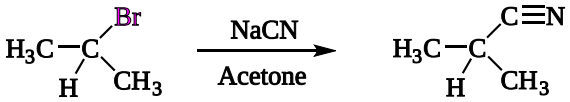
Answer available at the end of this section.

Answer available at the end of this section.

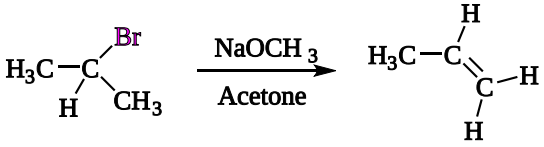
Answers

Exercises 11.12.1

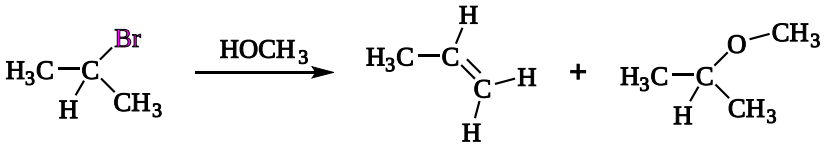
a) The substrate is a secondary halide, so the product is determined by the nature of the nucleophile used in the reaction. Cyanide (^{-}CN) is a good nucleophile, which is a weak base. The fact that the nucleophile is a weak base means that an E2 reaction is not favored. Also, the fact that cyanide is a good nucleophile means that S_N2 substitutions are favored over S_N1. When a secondary halide is reacted with a good nucleophile, which is a weak base, the preferred reaction is S_N2. After S_N2 substitution, the product is a nitrile.



b) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methoxide ($^{-}OCH_3$) is a strong base so it could prefer to remove a hydrogen from the substrate. This makes an E2 elimination the preferred reaction and an alkene the product.



c) The substrate is a secondary halide so the product is determined by the nature of the nucleophile used in the reaction. Methanol ($HOCH_3$) is a weak nucleophile that is a weak base. Being a weak base means that methanol is not capable of actively removing a hydrogen to cause an E2 reaction. Also, because methanol is a weak nucleophile is not capable of attacking the substrate and causing an S_N2 reaction. For the methanol nucleophile to react the substrate must first eject it leaving group to form the highly reactive carbocation intermediate. Formation of the carbocation is the rate-determining step for both the SN1 and E1 reactions, so they each form a separate product.



Exercise 11.12.2

a) Cl^- ; strong nucleophile. b) NaH ; strong base.

c) t-BuO^- ; strong base. d) OH^- ; strong nucleophile ; strong base.

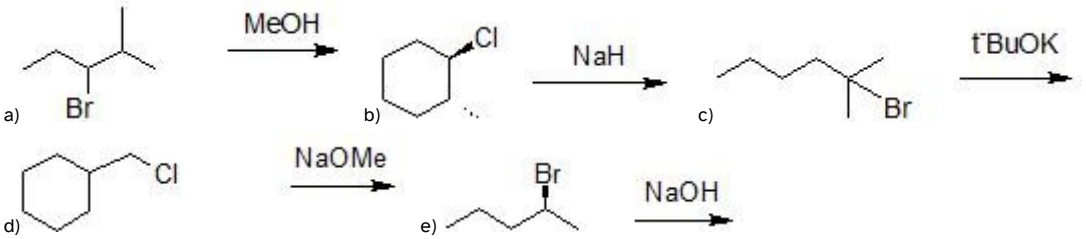
e) H_2O ; weak nucleophile ; weak base. f) HS^- ; strong nucleophile.

g) MeOH ; weak nucleophile ; weak base.

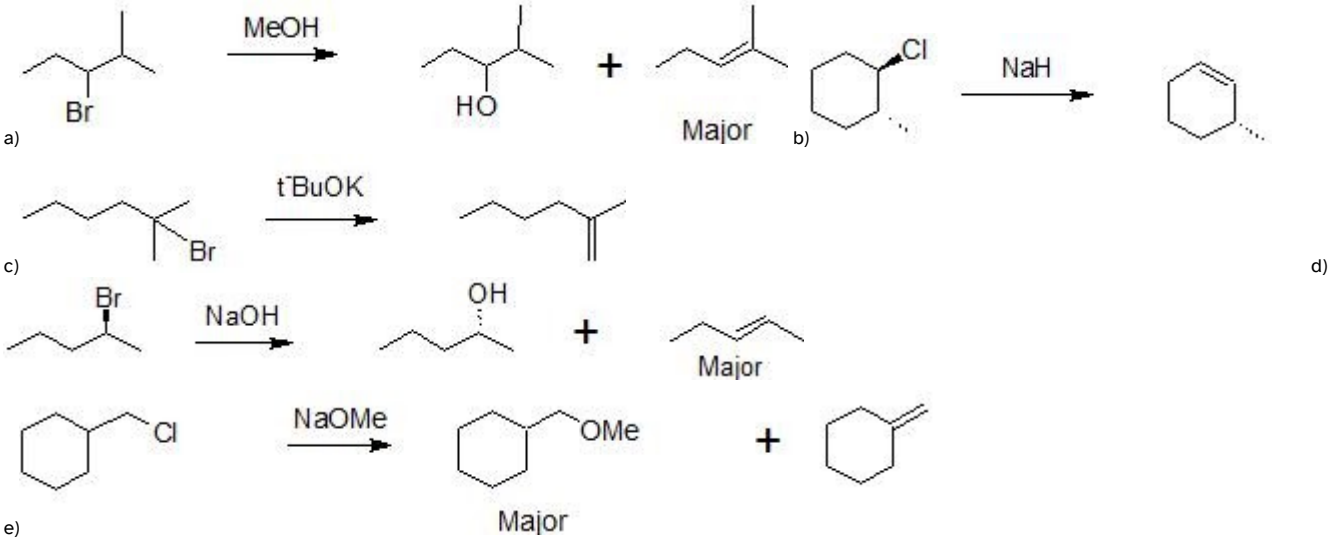
Exercise 11.12.3

a) E2, S_N1 b) S_N2, E2 c) S_N2 d) S_N1, E1 e) E2, S_N1

Exercise 11.12.4



Exercise 11.12.4



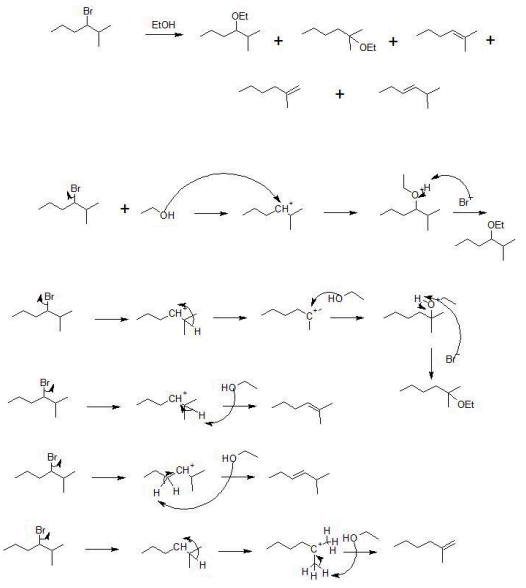
Exercise 11.12.5

a. S_N2 b. E2 c. S_N1 d. E1cB

Exercise 11.12.6

The following reaction yields five different products. Give the mechanisms for how each is formed.

Exercise 11.12.6



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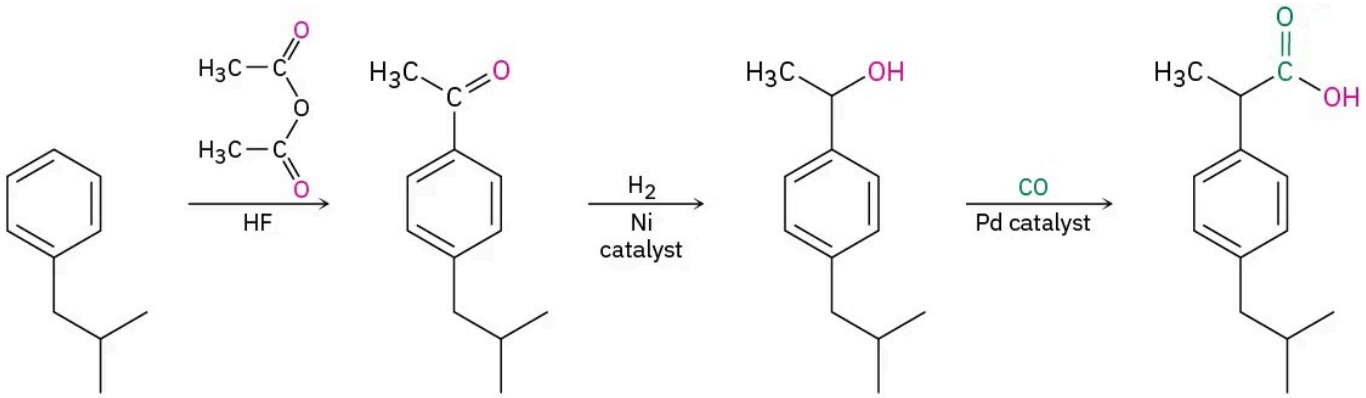
11.13: Chemistry Matters—Green Chemistry

Organic chemistry in the 20th century changed the world, giving us new medicines, food preservatives, insecticides, adhesives, textiles, dyes, building materials, composites, and all manner of polymers. But these advances did not come without a cost: Almost every chemical process produces waste that must be dealt with, including reaction solvents and toxic by-products that might evaporate into the air or be leached into groundwater if not disposed of properly. Even apparently harmless by-products must be safely buried or otherwise sequestered. As always, there's no such thing as a free lunch. With the good also comes the bad.

It may never be possible to make organic chemistry completely benign, but awareness of the environmental problems caused by many chemical processes has grown dramatically in recent years, giving rise to a movement called *green chemistry*. Green chemistry is the design and implementation of chemical products and processes that reduce waste and attempt to eliminate the generation of hazardous substances. There are 12 principles of green chemistry:

- **Prevent waste** – Waste should be prevented rather than treated or cleaned up after it has been created.
- **Maximize atom economy** – Synthetic methods should maximize the incorporation of all materials used in a process into the final product so that waste is minimized.
- **Use less hazardous processes** – Synthetic methods should use reactants and generate wastes with minimal toxicity to health and the environment.
- **Design safer chemicals** – Chemical products should be designed to have minimal toxicity.
- **Use safer solvents** – Minimal use should be made of solvents, separation agents, and other auxiliary substances in a reaction.
- **Design for energy efficiency** – Energy requirements for chemical processes should be minimized, with reactions carried out at room temperature if possible.
- **Use renewable feedstocks** – Raw materials should come from renewable sources when feasible.
- **Minimize derivatives** – Syntheses should be designed with minimal use of protecting groups to avoid extra steps and reduce waste.
- **Use catalysis** – Reactions should be catalytic rather than stoichiometric.
- **Design for degradation** – Products should be designed to be biodegradable at the end of their useful lifetimes.
- **Monitor pollution in real time** – Processes should be monitored in real time for the formation of hazardous substances.
- **Prevent accidents** – Chemical substances and processes should minimize the potential for fires, explosions, or other accidents.

The foregoing 12 principles may not all be met in most real-world applications, but they provide a worthy goal and they can make chemists think more carefully about the environmental implications of their work. Real success stories have occurred, and more are in progress. Approximately 7 million pounds per year of ibuprofen (6 billion tablets!) are now made by a "green" process that produces approximately 99% less waste than the process it replaces. Only three steps are needed, the anhydrous HF solvent used in the first step is recovered and reused, and the second and third steps are catalytic.



Isobutylbenzene **Ibuprofen**

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11.A: Nucleophilic Substitutions and Eliminations Reactions (Summary)

Concepts & Vocabulary

11.0 Introduction

- Alkyl halides react as electrophiles and undergo nucleophilic substitution and elimination reactions.

11.1 The Discovery of Nucleophilic Substitution Reactions

- Some nucleophilic substitution reactions invert stereochemistry at the reactive carbon.

11.2 The S_N2 Reaction

- Reaction steps with two molecules involved in the rate determining step are called bimolecular.
- A substitution mechanism that has the nucleophile entering at the same time the leaving group leaves, in a concerted step, is called S_N2 - substitution nucleophilic bimolecular.
- Concerted substitution mechanisms (S_N2) occur via backside attack, which causes inversion of the carbon where the reaction occurs.
- Rates of S_N2 reactions depend on concentration of nucleophile and alkyl halide.

11.3 Characteristics of the S_N2 Reaction

- S_N2 reactions are concerted.
- Sterically hindered substrates reduce S_N2 reaction rate.
- A **transition state** in a reaction mechanism is the highest energy point on a pathway from reactants to an intermediate or products.
- Larger groups (such as alkyl vs. hydrogen) cause greater steric repulsion in S_N2 **transition states**, reducing rates of S_N2 reactions.
- Groups that have electron-rich atoms are typically good nucleophiles.
- In general, stronger bases are better nucleophiles.
- Polar aprotic solvents increase rates of S_N2 reactions.
- Polar protic solvents decrease rates of S_N2 reactions.
- As basicity of leaving groups decreases, their ability to leave increases.

11.4 The S_N1 Reaction

- A substitution mechanism that occurs with the leaving group leaving in the first step, creating a carbocation intermediate, followed by the nucleophile entering is called S_N1 - substitution nucleophilic unimolecular.
- S_N1 reactions occur through a stepwise mechanism.
- The first step (dissociation) of an S_N1 mechanism is rate limiting.
- In S_N1 reactions the nucleophile is not involved in the rate limiting step, therefore nucleophile strength or concentration do not affect the rate.
- The intermediate for S_N1 mechanisms contains a planar carbocation. The nucleophile can then enter from either side of the molecule giving racemic products with no additional stereocenters in the molecule.

11.5 Characteristics of the S_N1 Reaction

- Polar solvents increase rates of S_N1 reactions.
- Better leaving groups increase rates of S_N1 and S_N2 reactions.
-

11.6 Predicting SN1 vs. SN2 mechanisms

- Predicting whether a reaction will follow an S_N1 or S_N2 mechanism requires analysis of:
  - Electrophile - primary favor S_N2, tertiary (and allyl or benzyl) favor S_N1, secondary depends on other factors
  - Nucleophile - strong favor S_N2, weak favor S_N1
  - Solvent - polar aprotic favor S_N2, polar protic favor S_N1

11.7 Elimination Reactions - Zaitsev's Rule

- The major product of Elimination reactions is the product with the more substituted double bond. This is known as Zaitsev's rule.

11.8 The E2 Reaction and Deuterium Isotope Effect

- The E2 mechanism is concerted with the base removing a proton and the leaving group leaving at the same time.
- Since E2 mechanisms are concerted, both the base and the electrophile are present in the rate equation.
- E2 reactions require strong bases and polar aprotic solvents.
- Kinetic Isotope Effects can provide evidence for E2 mechanisms since they can show when breaking of the C-H bond is part of the rate-determining step.

11.9 The E2 Reaction and Cyclohexane Conformation

- E2 reactions of cyclic structures show the necessity for anti-orientation of the proton being removed and the leaving group.

11.10 The E1 and E1cB Reactions

- E1 mechanisms begin with a leaving group leaving which forms a carbocation intermediate, which is then deprotonated in a second step.
- E1 mechanisms are step-wise.
- More substituted electrophiles are more reactive in E1 reactions.
- Zaitsev products are preferred, similarly to E2 reactions.
- E1 and S_N1 proceed via the same carbocation intermediate and the same rate-determining step so typically happen concurrently.
- E1cB reactions begin with deprotonation (usually resulting in a resonance stabilized carbanion), followed by loss of the leaving group in the second step.

11.11 Biological Reactions

- When biological substitution reactions occur, the electrophiles are often different, though the mechanisms are primarily the same.
- There are many important examples of biological elimination reactions.

11.12 Deciding between S_N1, S_N2, E1, and E2

Skills to Master

- Skill 11.1 Draw S_N1/S_N2 mechanisms showing appropriate stereochemistry.
- Skill 11.2 Explain when S_N1/S_N2 mechanisms are likely to occur.
- Skill 11.3 Describe/draw the intermediate for an S_N1 mechanism and transition state(s) for S_N1/S_N2 mechanisms.
- Skill 11.4 Write out rate laws for S_N1/S_N2 mechanisms.
- Skill 11.5 Differentiate between which mechanism is more likely between S_N1/S_N2.
- Skill 11.6 Draw reaction coordinate diagrams for S_N1/S_N2 mechanisms.
- Skill 11.7 Explain how the electrophile, nucleophile, leaving group, and solvent affect S_N1/S_N2 mechanisms.
- Skill 11.8 Recognize use of nucleophilic substitution and elimination reactions in biological systems.
- Skill 11.9 Draw E1/E2 mechanisms showing appropriate stereochemistry.
- Skill 11.10 Explain when E1/E2 mechanisms are likely to occur.
- Skill 11.11Describe/draw the intermediate for an E1 mechanism and transition state(s) for E1/E2mechanisms.
- Skill 11.12 Write out rate laws for E1/E2 mechanisms.
- Skill 11.13 Differentiate between which mechanism is more likely between E1/E2.

- Skill 11.14 Draw reaction coordinate diagrams for E1/E2 mechanisms.
- Skill 11.15 Explain how kinetic isotope effects can be used to support or refute a proposed mechanism.
- Skill 11.16 Draw an E1cB mechanism and explain when it is a viable option.
- Skill 11.17 Differentiate between which mechanism is more likely between S_N1/S_N2 and E1/E2.

Memorization Tasks (MT)

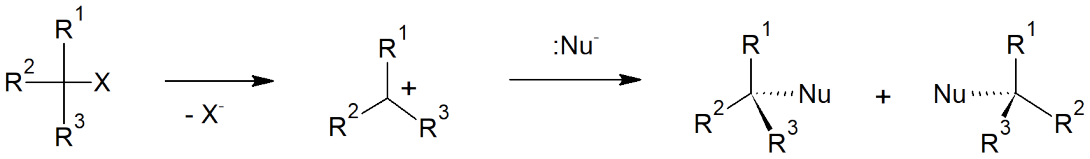
MT 11.1 Memorize the order of good leaving groups.

MT 11.2 Memorize which solvents are polar protic and polar aprotic.

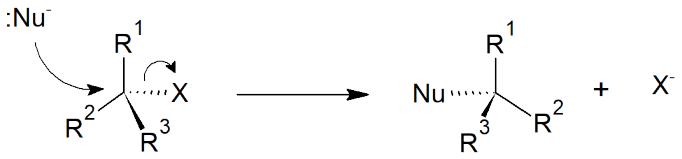
MT 11.3 Memorize the stability order of carbocations.

Summary of Reactions

Nucleophilic Substitutions



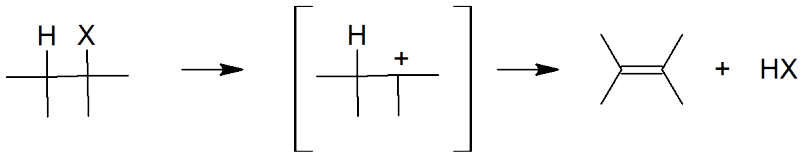
S_N1 (racemic mix of *R* and *S* products)



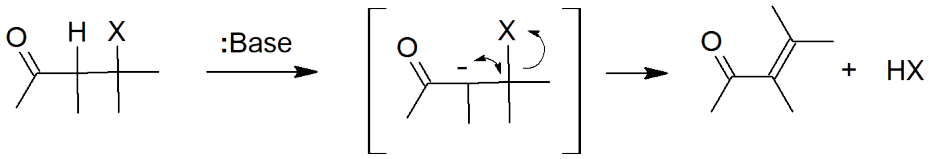
S_N2 (inverted product)

Eliminations

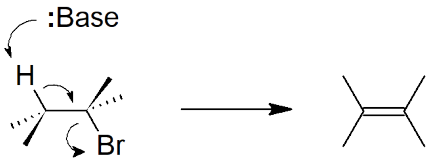
E1



E1cB



E2



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11.B: Additional Problems

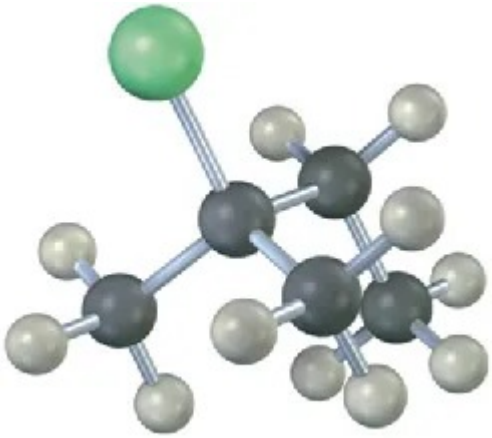
Visualizing Chemistry

PROBLEM 11-21 Write the product you would expect from the reaction of each of the following alkyl halides with (1) $Na^+ \ ^-SCH_3$ and (2) $Na^+ \ ^-OH$ (green = Cl):

(a)



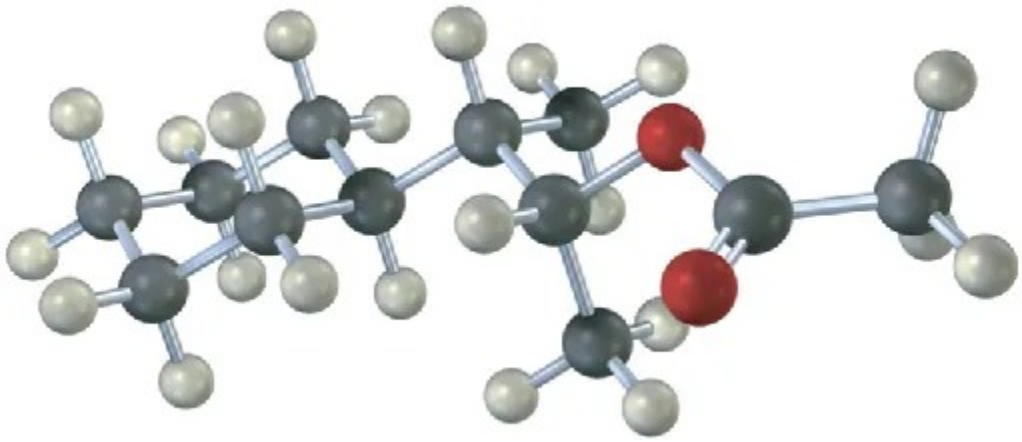
(b)



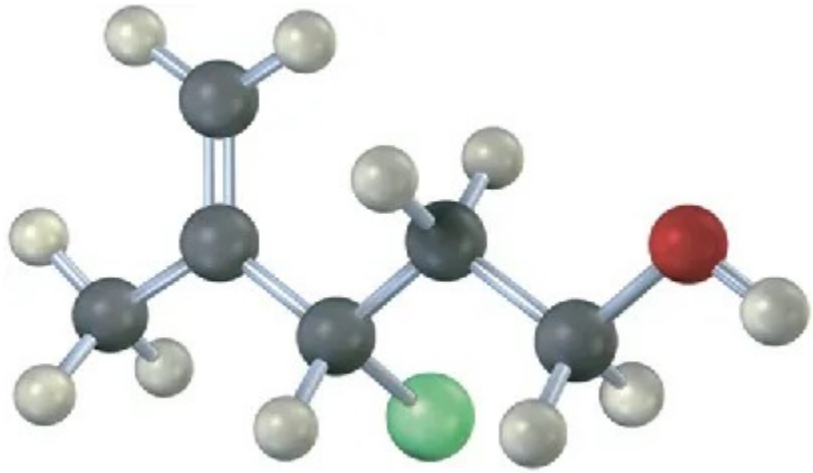
(c)



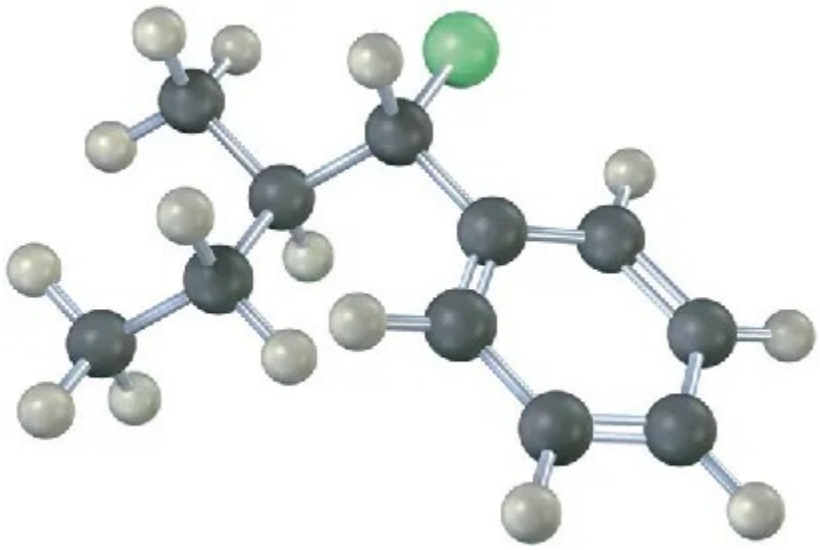
PROBLEM 11-22 From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing all stereochemistry.



PROBLEM 11-23 Assign *R* or *S* configuration to the following molecule, write the product you would expect from S_N2 reaction with NaCN, and assign *R* or *S* configuration to the product (green = Cl):



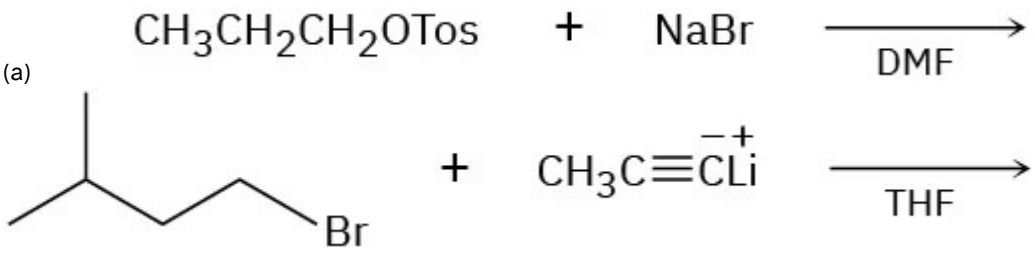
PROBLEM 11-24 Draw the structure and assign *Z* or *E* stereochemistry to the product you expect from E2 reaction of the following molecule with NaOH (green = Cl):



Mechanism Problems

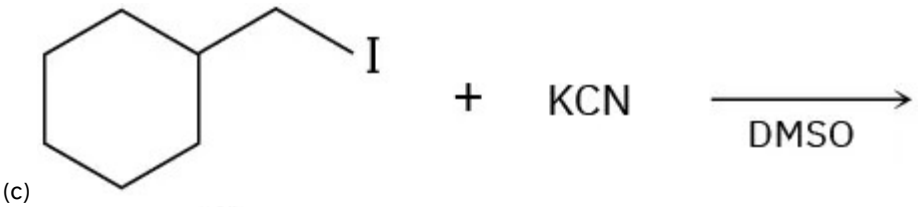
PROBLEM 11-25 Predict the product(s) and show the mechanism for each of the following reactions. What do the mechanisms have in common? Why?

(a)

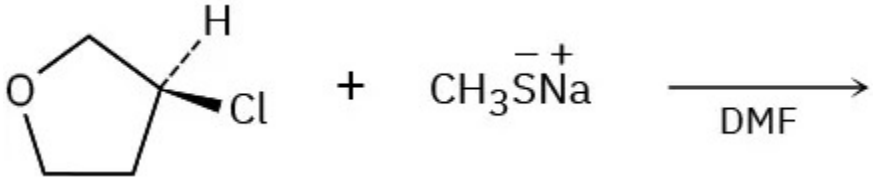


(b)

(c)

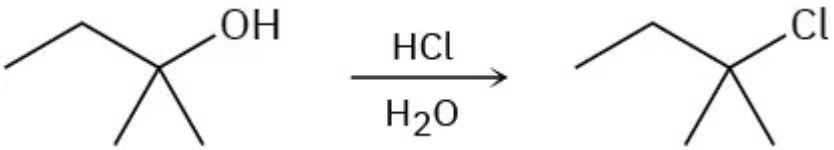


(d)

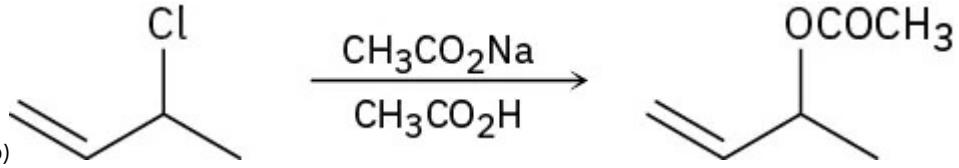


PROBLEM 11-26 Show the mechanism for each of the following reactions. What do the mechanisms have in common? Why?

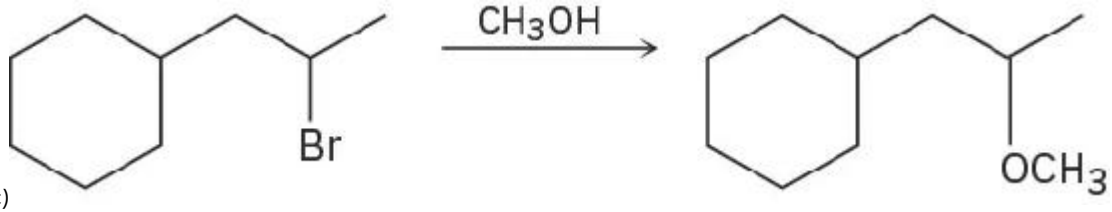
(a)



(b)

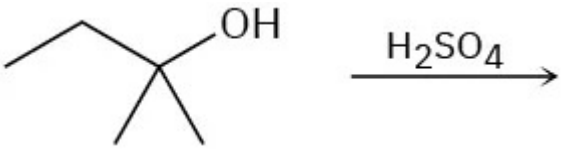


(c)

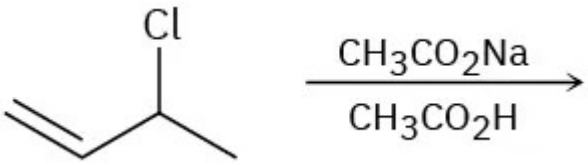


PROBLEM 11-27 Predict the product(s) for each of the following elimination reactions. In each case, show the mechanism. What do the mechanisms have in common? Why?

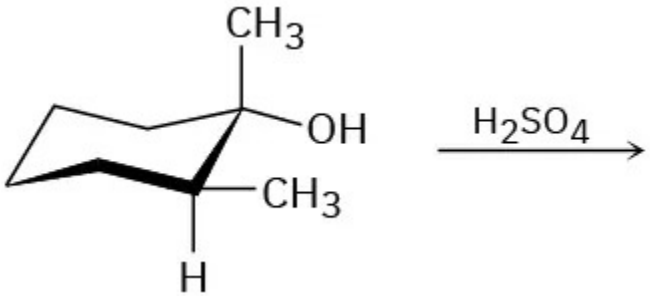
(a)



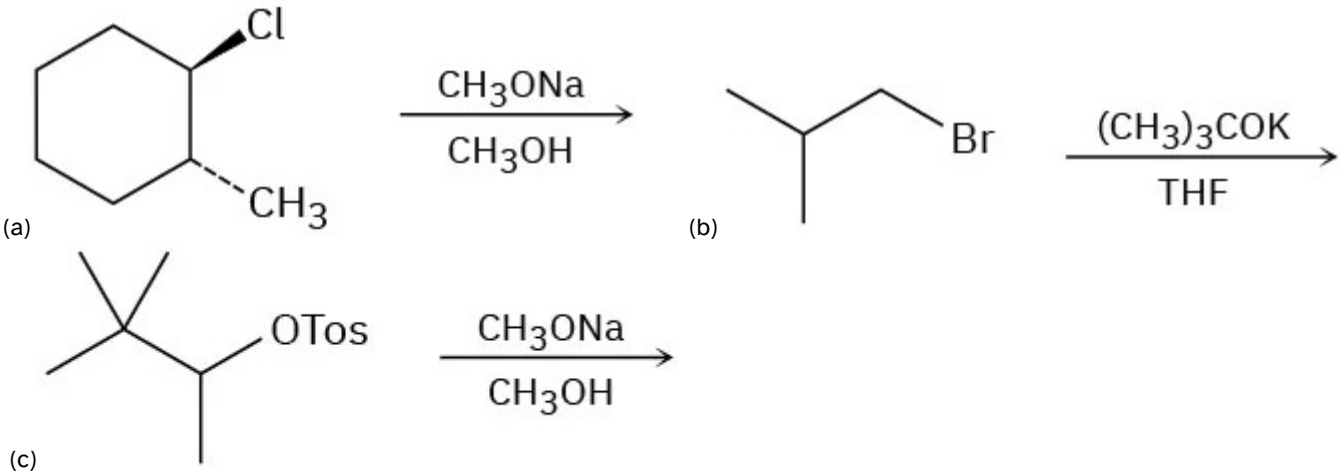
(b)



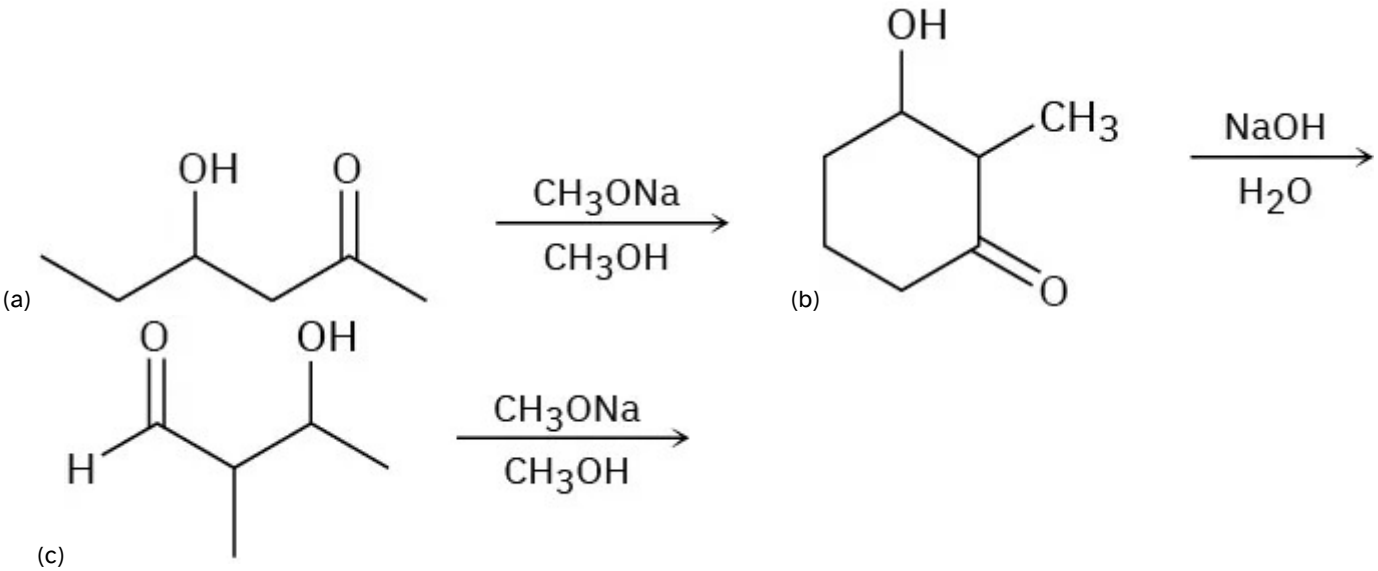
(c)



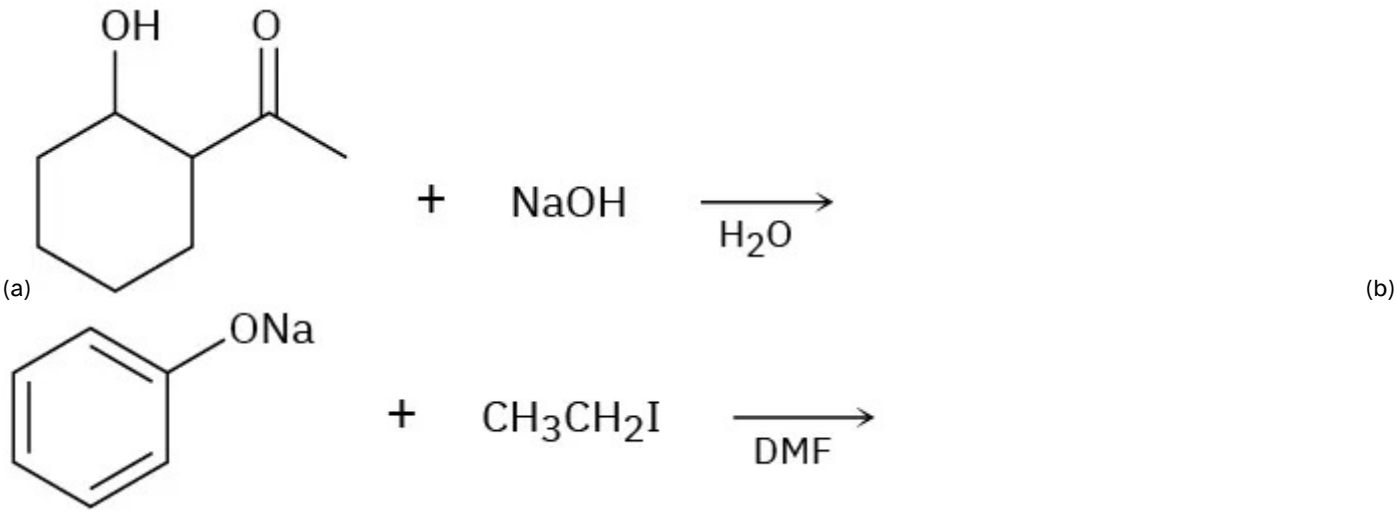
PROBLEM 11-28 Predict the product(s) for each of the following elimination reactions. In each case, show the mechanism. What do the mechanisms have in common? Why?



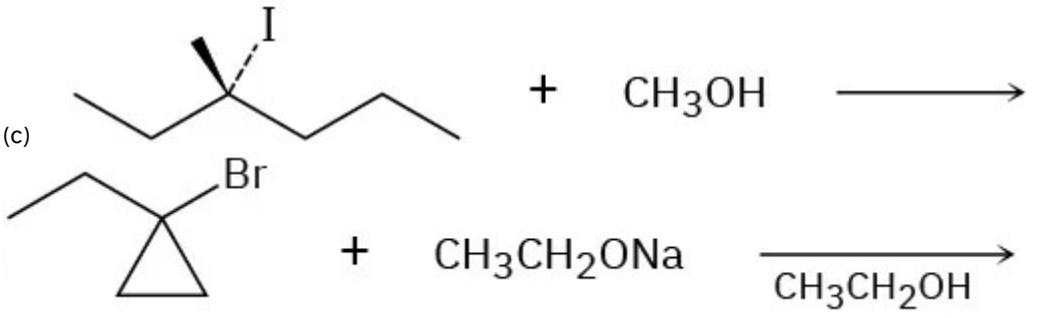
PROBLEM 11-29 Predict the product(s) for each of the following elimination reactions. In each case, show the mechanism. What do the mechanisms have in common? Why?



PROBLEM 11-30 Predict the product of each of the following reactions, and indicate if the mechanism is likely to be S_N1, S_N2, E1, E2, or E1cB.

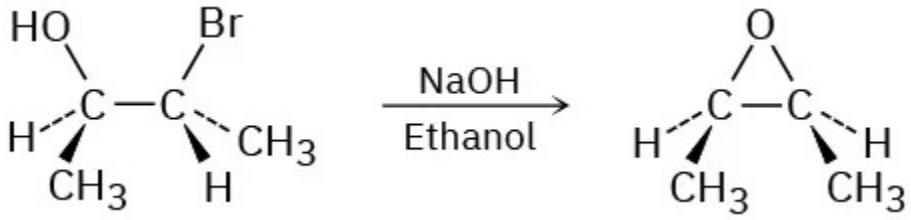


(c)

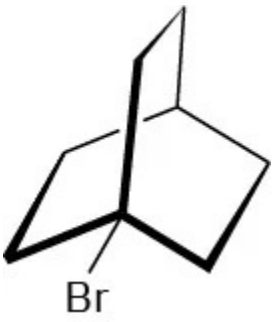


(d)

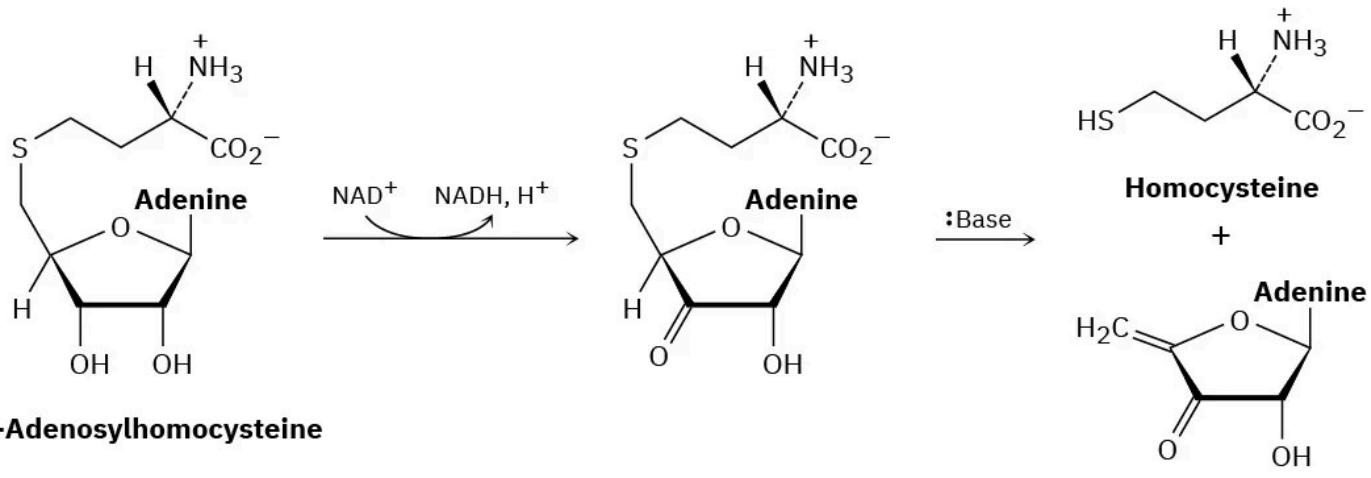
PROBLEM 11-31 We saw in Section 8.7 that bromohydrins are converted into epoxides when treated with base. Propose a mechanism, using curved arrows to show the electron flow.



PROBLEM 11-32 The following tertiary alkyl bromide does not undergo a nucleophilic substitution reaction by either S_N1 or S_N2 mechanisms. Explain.



PROBLEM 11-33 Metabolism of *S*-adenosylhomocysteine (Section 11.6) involves the following sequence. Propose a mechanism for the second step.

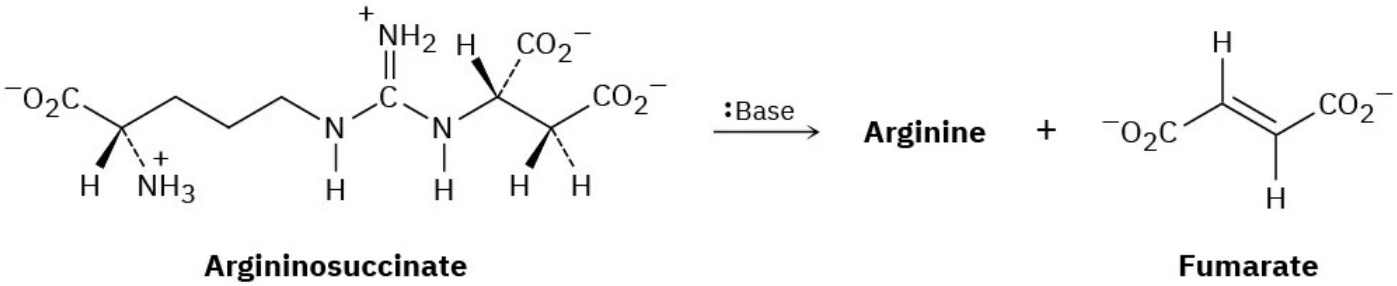


***S*-Adenosylhomocysteine**

PROBLEM 11-34 Reaction of iodoethane with CN^- yields a small amount of *isonitrile,* $CH_3CH_2N{\equiv}C$, along with the nitrile

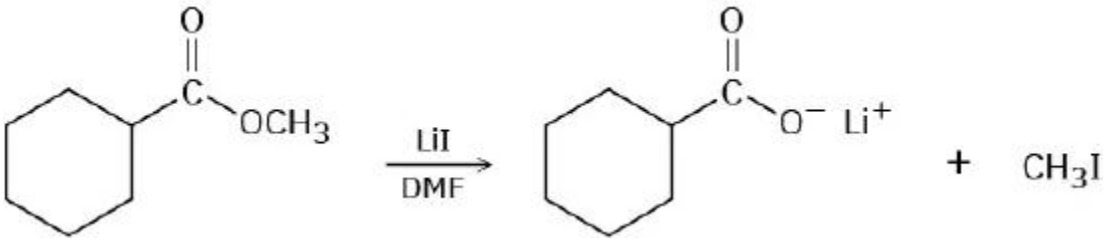
$CH_3CH_2C{\equiv}N$ as the major product. Write electron-dot structures for both products, assign formal charges as necessary, and propose mechanisms to account for their formation.

PROBLEM 11-35 One step in the urea cycle for ridding the body of ammonia is the conversion of argininosuccinate to the amino acid arginine plus fumarate. Propose a mechanism for the reaction, and show the structure of arginine.



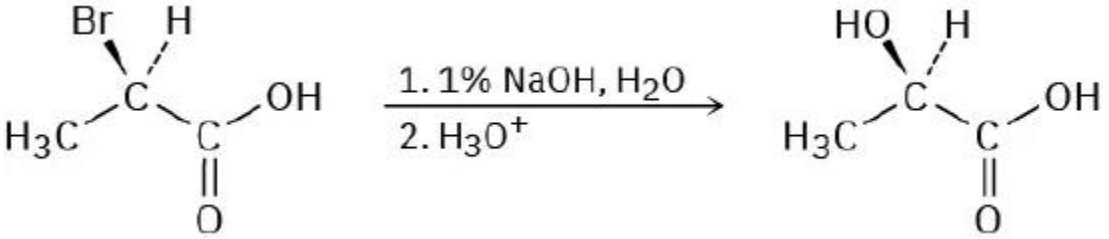
Argininosuccinate **Fumarate**

PROBLEM 11-36 Methyl esters (RCO_2CH_3) undergo a cleavage reaction to yield carboxylate ions plus iodomethane on heating with LiI in dimethylformamide:

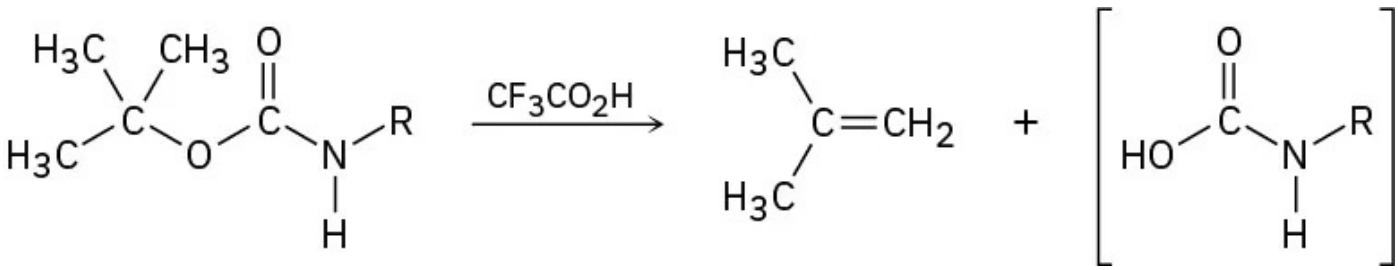


The following evidence has been obtained: (1) The reaction occurs much faster in DMF than in ethanol. (2) The corresponding ethyl ester ($RCO_2CH_2CH_3$) cleaves approximately 10 times more slowly than the methyl ester. Propose a mechanism for the reaction. What other kinds of experimental evidence could you gather to support your hypothesis?

PROBLEM 11-37 S_N2 reactions take place with inversion of configuration, and S_N1 reactions take place with racemization. The following substitution reaction, however, occurs with complete *retention* of configuration. Propose a mechanism. (Hint: two inversions = retention.)



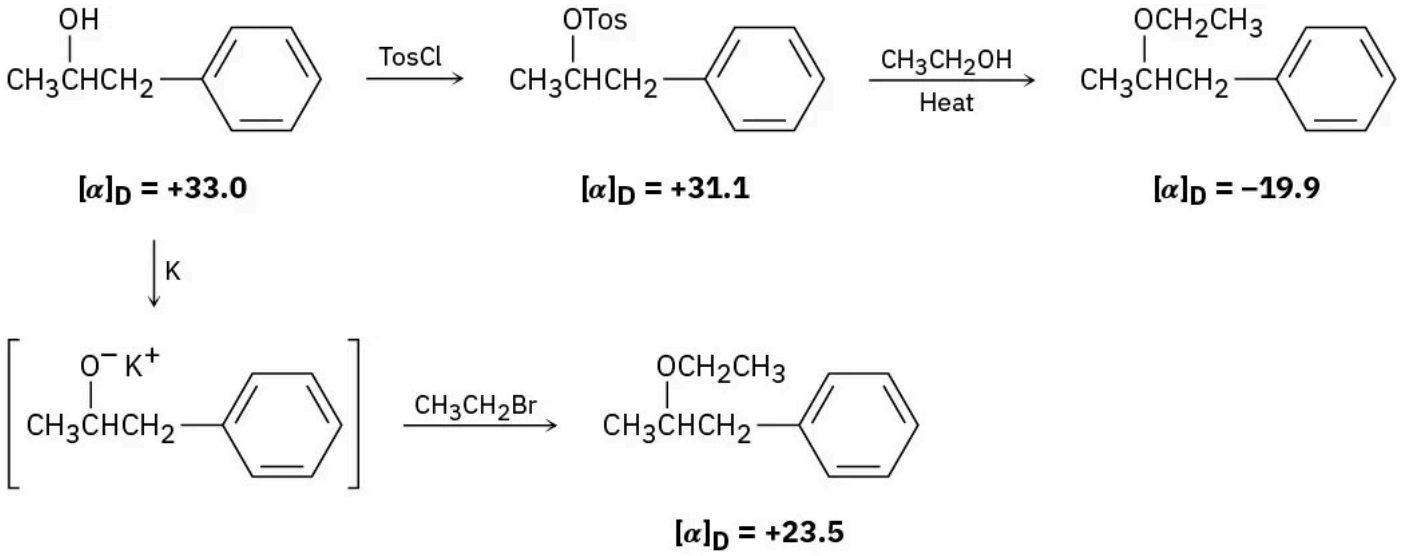
PROBLEM 11-38 Propose a mechanism for the following reaction, an important step in the laboratory synthesis of proteins:



Nucleophilic Substitution Reactions

PROBLEM 11-39 Draw all isomers of C_4H_9Br, name them, and arrange them in order of decreasing reactivity in the S_N2 reaction.

PROBLEM 11-40 The following Walden cycle has been carried out: Explain the results, and indicate where inversion occurs.



PROBLEM 11-41 Which compound in each of the following pairs will react faster in an S_N2 reaction with OH^-?

(a) CH_3Br or CH_3I (b) CH_3CH_2I in ethanol or in dimethyl sulfoxide

(c) $(CH_3)_3CCl$ or CH_3Cl (d) $H_2C{=}CHBr$ or $CH_2C{=}CHCH_2Br$

PROBLEM 11-42 Which reactant in each of the following pairs is more nucleophilic? Explain.

(a) $^-NH_2$ or NH_3 (b) H_2O or $CH_3CO_2^-$ (c) BF_3 or F^- (d) $(CH_3)_3P$ or $(CH_3)_3N$ (e) I^- or Cl^- (f) $^-C{\equiv}N$ or $^-OCH_3$

PROBLEM 11-43 What effect would you expect the following changes to have on the rate of the S_N2 reaction of 1-iodo-2-methylbutane with cyanide ion?

(a) The CN^- concentration is halved, and the 1-iodo-2-methylbutane concentration is doubled.

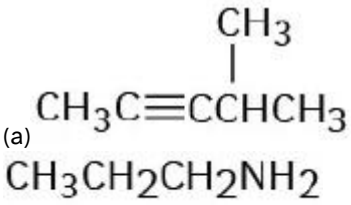
(b) Both the CN^- and the 1-iodo-2-methylbutane concentrations are tripled.

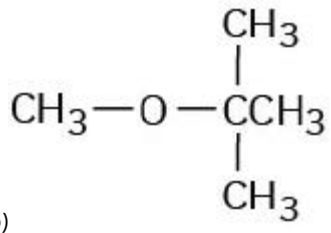
PROBLEM 11-44 What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?

(a) The concentration of the halide is tripled.

(b) The concentration of the ethanol is halved by adding diethyl ether as an inert solvent.

PROBLEM 11-45 How might you prepare each of the following using a nucleophilic substitution reaction at some step?

(a) 

(b) 

(c) 

(d)

PROBLEM 11-46 Which reaction in each of the following pairs would you expect to be faster?

(a) The S_N2 displacement by I^- on CH_3Cl or on CH_3OTos

(b) The S_N2 displacement by $CH_3CO_2^-$ on bromoethane or on bromocyclohexane

(c) The S_N2 displacement on 2-bromopropane by $CH_3CH_2O^-$ or by CN^-

(d) The S_N2 displacement by $HC{\equiv}CC^-$ on bromomethane in benzene or in acetonitrile

PROBLEM 11-47 Predict the product and give the stereochemistry resulting from the reaction of each of the following nucleophiles with (*R*)-2-bromooctane:

(a) ^-CN. (b) $CH_3CO_2^-$ (c) CH_3S^-

PROBLEM 11-48 (*R*)-2-Bromooctane undergoes racemization to give (±)-2-bromooctane when treated with NaBr in dimethyl sulfoxide. Explain.

Elimination Reactions

PROBLEM 11-49 Propose structures for compounds that fit the following descriptions:

(a) An alkyl halide that gives a mixture of three alkenes on E2 reaction

(b) An organohalide that will not undergo nucleophilic substitution

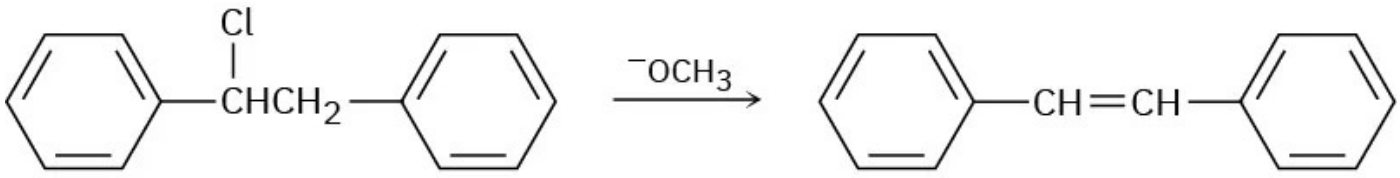
(c) An alkyl halide that gives the non-Zaitsev product on E2 reaction

(d) An alcohol that reacts rapidly with HCl at 0 °C

PROBLEM 11-50 What products would you expect from the reaction of 1-bromopropane with each of the following?

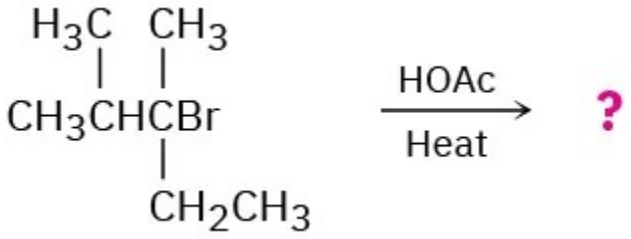
(a) $NaNH_2$ (b) $KOC(CH_3)_3$ (c) NaI (d) NaCN (e) $NaC{\equiv}CH$ (f) Mg, then H_2O

PROBLEM 11-51 1-Chloro-1,2-diphenylethane can undergo E2 elimination to give either *cis*- or *trans*-1,2-diphenylethylene (stilbene). Draw Newman projections of the reactive conformations leading to both possible products, and suggest a reason why the *trans* alkene is the major product.



1-Chloro-1,2-diphenylethane ***trans*-1,2-Diphenylethylene**

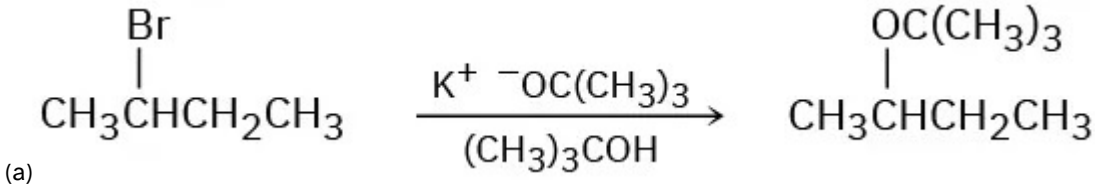
PROBLEM 11-52 Predict the major alkene product of the following E1 reaction:



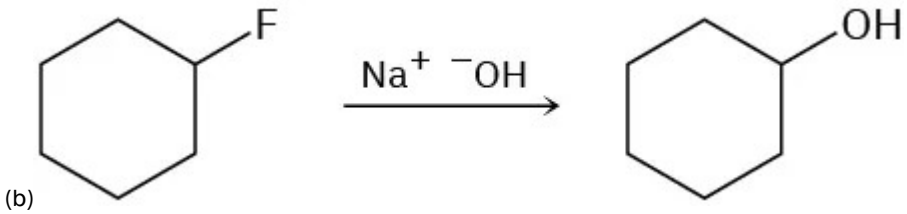
PROBLEM 11-53 There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

General Problems

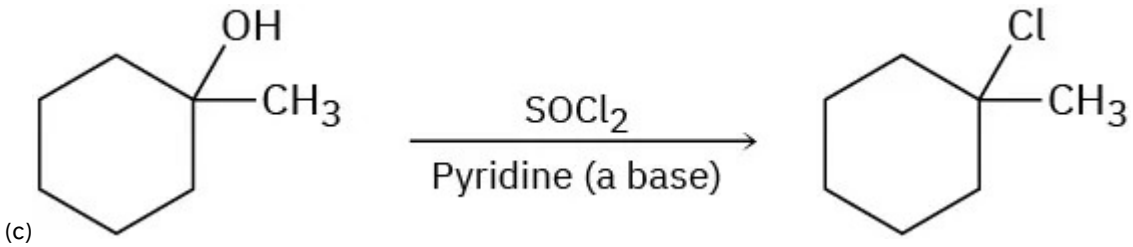
PROBLEM 11-54 The following reactions are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.



(a)



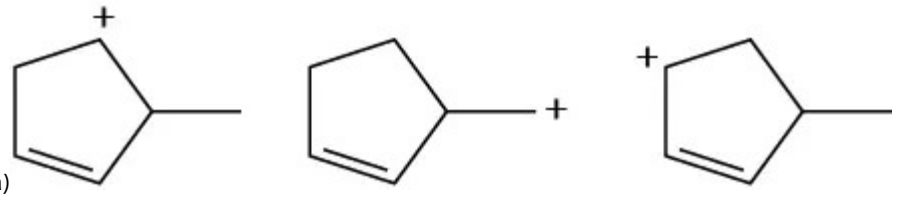
(b)



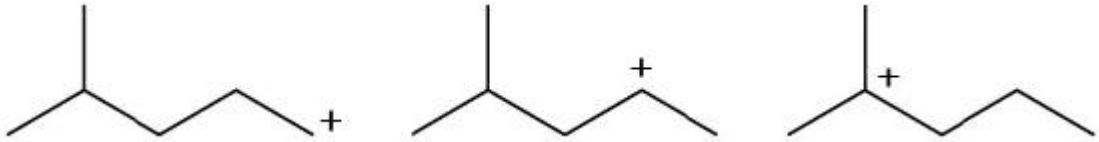
(c)

PROBLEM 11-55 Arrange the following carbocations in order of increasing stability.

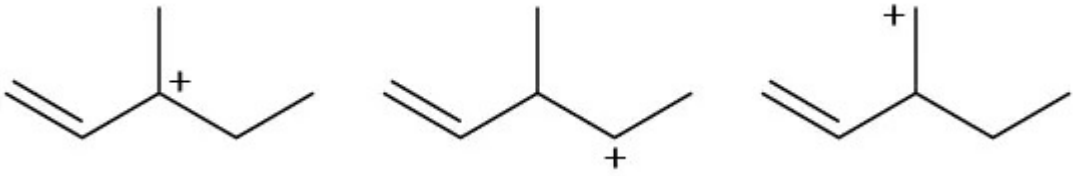
(a)



(b)

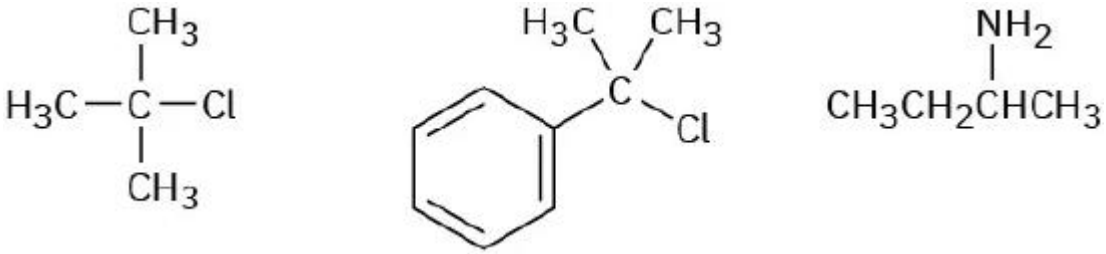


(c)

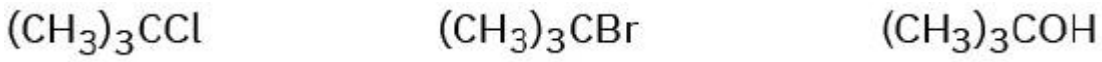


PROBLEM 11-56 Order each of the following sets of compounds with respect to S_N1 reactivity:

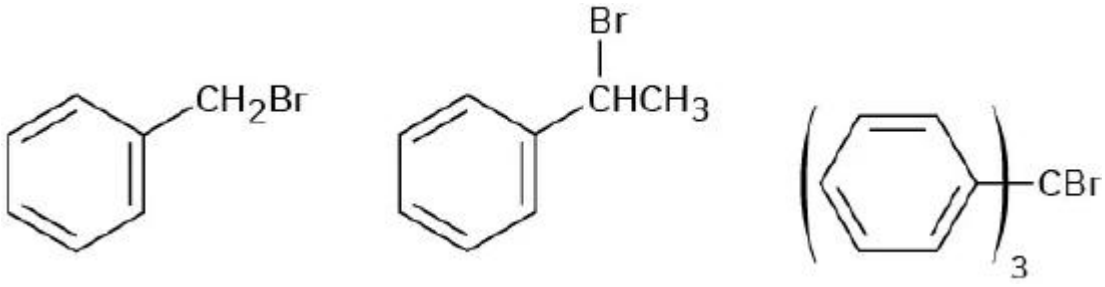
(a)



(b)

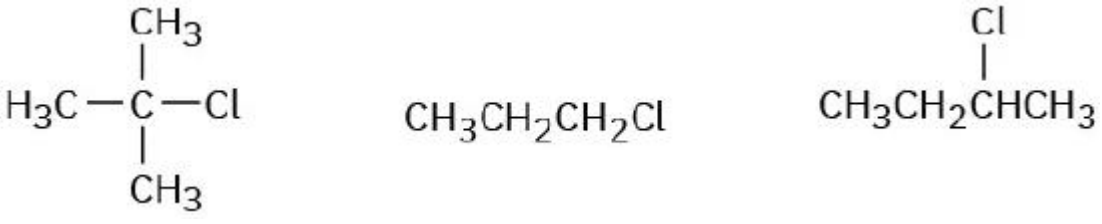


c)

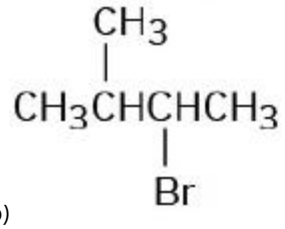


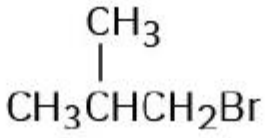
PROBLEM 11-57 Order each of the following sets of compounds with respect to S_N2 reactivity:

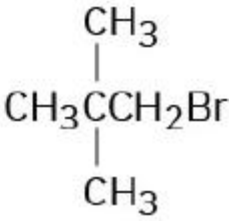
(a)



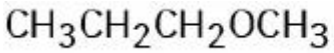
(b)

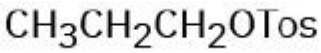


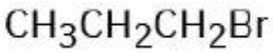




(c)

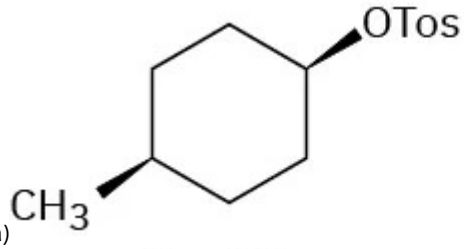


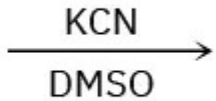




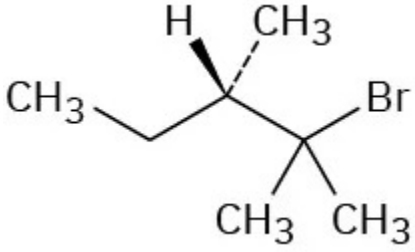
PROBLEM 11-58 Predict the major product(s) of each of the following reactions. Identify those reactions where you would expect the product mixture to rotate plane-polarized light.

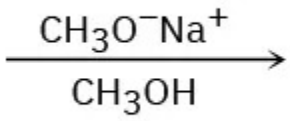
(a)



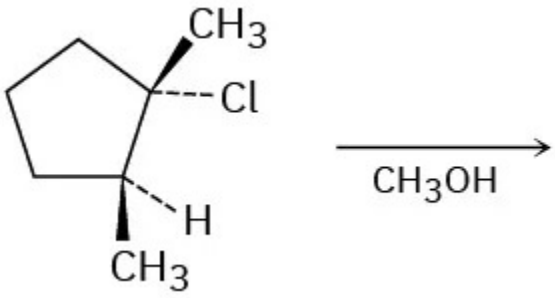


(b)

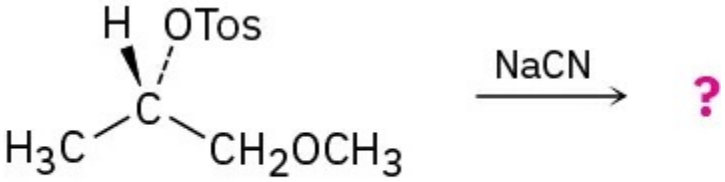




(c)

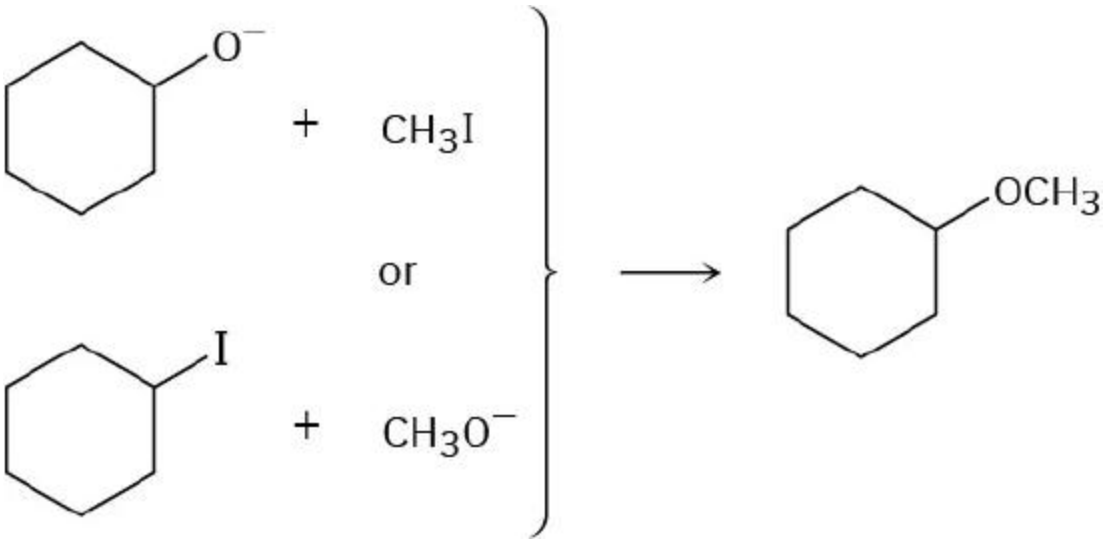


PROBLEM 11-59 Reaction of the following S tosylate with cyanide ion yields a nitrile product that also has S stereochemistry. Explain.

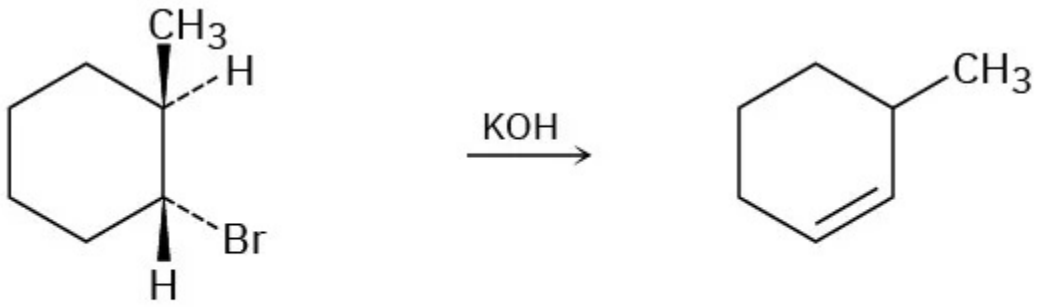


(*S* stereochemistry)

PROBLEM 11-60 Ethers can often be prepared by S_N2 reaction of alkoxide ions, RO^-, with alkyl halides. Suppose you wanted to prepare cyclohexyl methyl ether. Which of the following two possible routes would you choose? Explain.

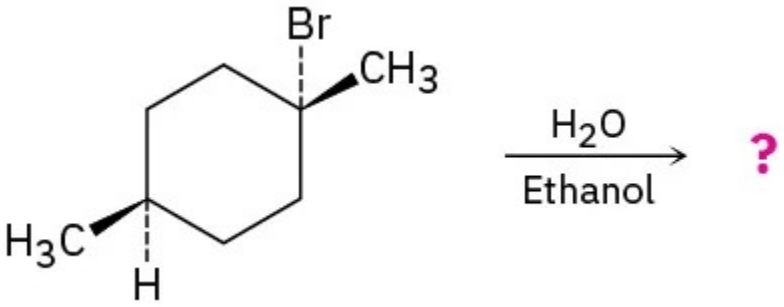


PROBLEM 11-61 How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?

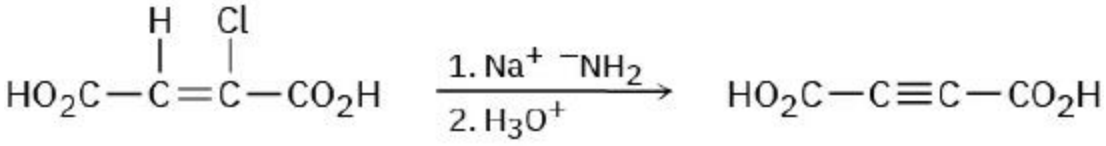


***trans*-1-Bromo-2-methylcyclohexane** **3-Methylcyclohexene**

PROBLEM 11-62 Predict the product(s) of the following reaction, indicating stereochemistry where necessary:

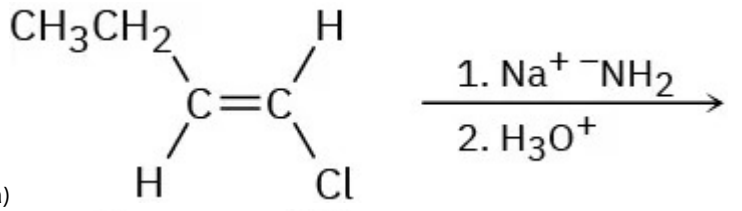


PROBLEM 11-63 Alkynes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (*Z*)-2-chloro-2-butenedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?

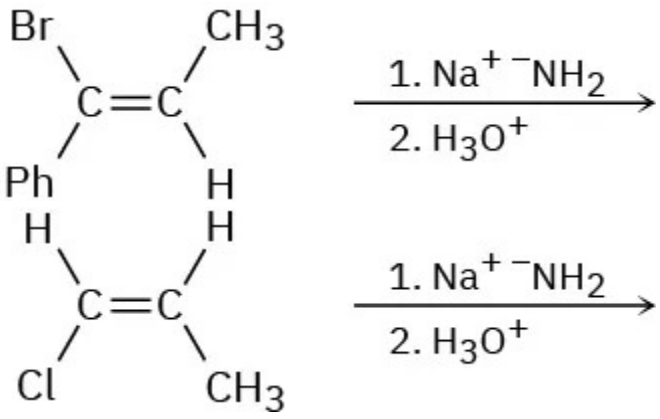


PROBLEM 11-64 Based on your answer to Problem 11-63, predict the product(s) and show the mechanism for each of the following reactions.

(a)

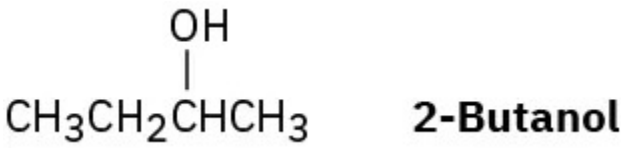


(b)



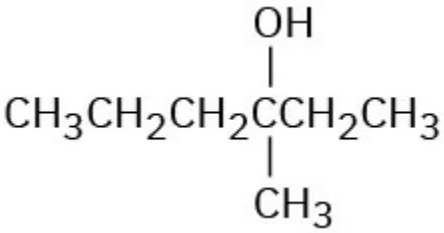
(c)

PROBLEM 11-65 (S)-2-Butanol slowly racemizes on standing in dilute sulfuric acid. Explain.



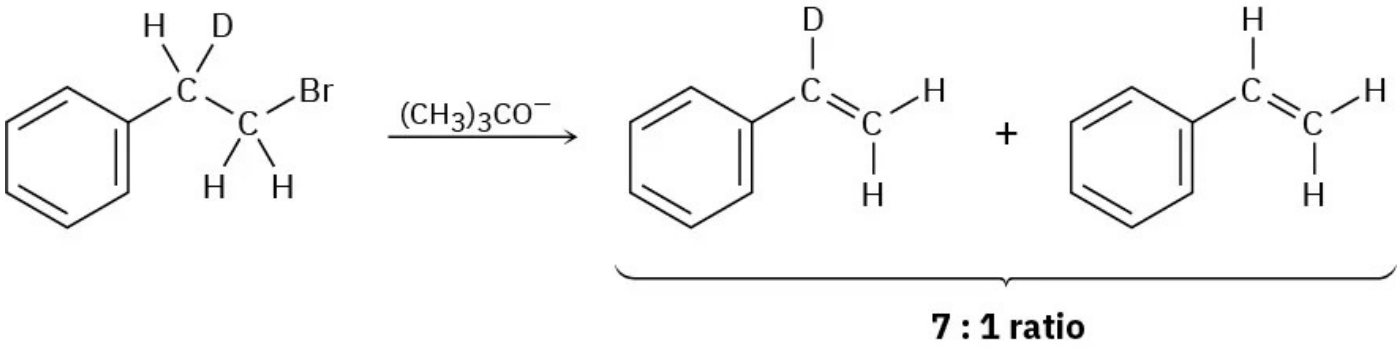
2-Butanol

PROBLEM 11-66 The reaction of HBr with (*R*)-3-methyl-3-hexanol leads to racemic 3-bromo-3-methylhexane. Explain.



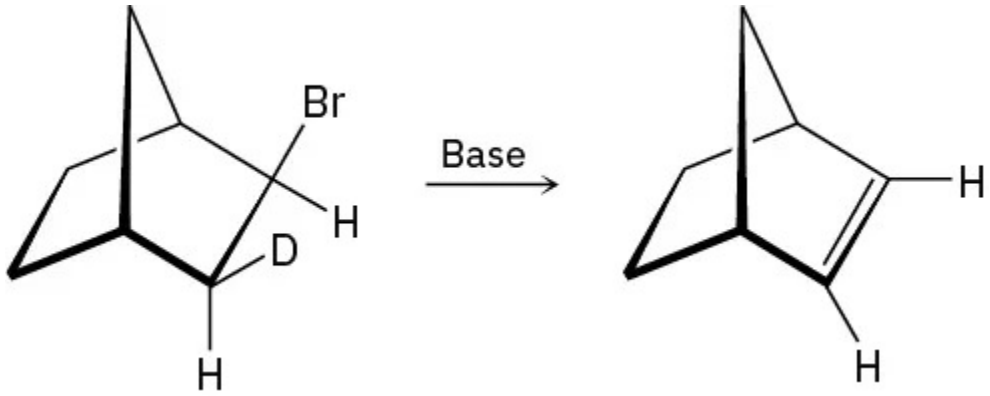
3-Methyl-3-hexanol

PROBLEM 11-67 Treatment of 1-bromo-2-deuterio-2-phenylethane with a strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in an approximately 7:1 ratio. Explain.



PROBLEM 11-68 Propose a structure for an alkyl halide that gives only (*E*)-3-methyl-2-phenyl-2-pentene on E2 elimination. Make sure you indicate the stereochemistry.

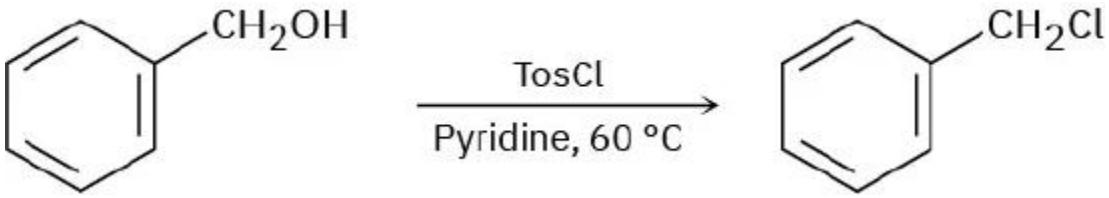
PROBLEM 11-69 Although anti-periplanar geometry is preferred for E2 reactions, it isn't absolutely necessary. The following deuterated bromo compound reacts with strong base to yield an undeuterated alkene. A syn elimination has occurred. Make a molecular model of the reactant, and explain the result.



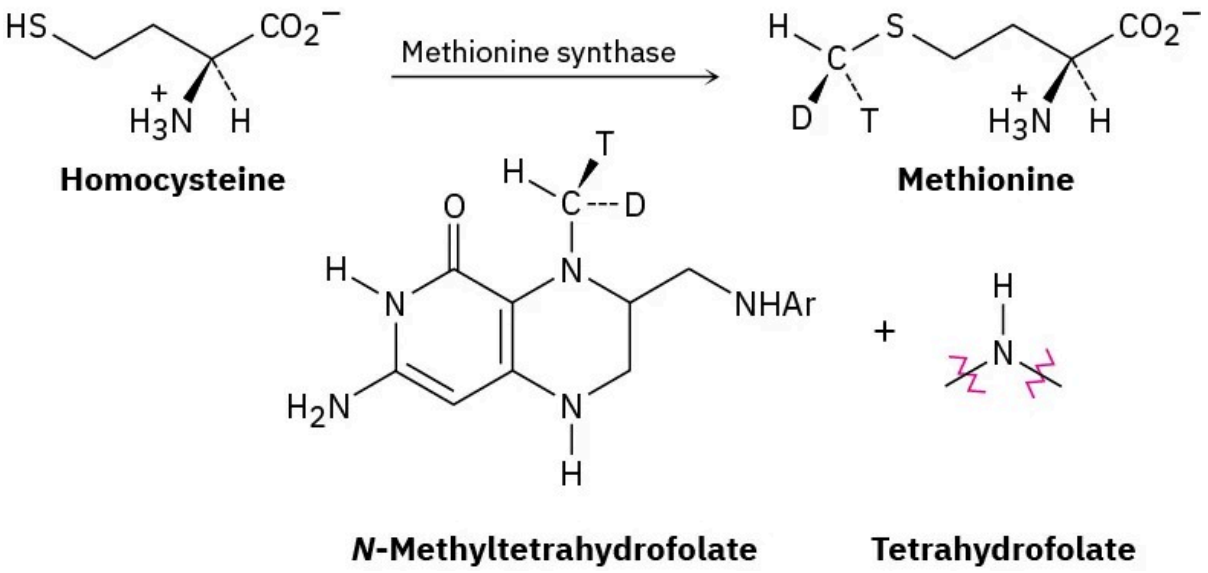
PROBLEM 11-70 The reaction of 1-chlorooctane with $CH_3CO_2^-$ to give octyl acetate is greatly accelerated by adding a small quantity of iodide ion. Explain.

PROBLEM 11-71 Compound X is optically inactive and has the formula $C_{16}H_{16}Br_2$. On treatment with a strong base, X gives hydrocarbon Y, $C_{16}H_{14}$. Compound Y absorbs 2 equivalents of hydrogen when reduced over a palladium catalyst and reacts with ozone to give two fragments. One fragment, Z, is an aldehyde with formula C_7H_6O. The other fragment is glyoxal, $(CHO)_2$. Write the reactions involved, and suggest structures for X, Y, and Z. What is the stereochemistry of X?

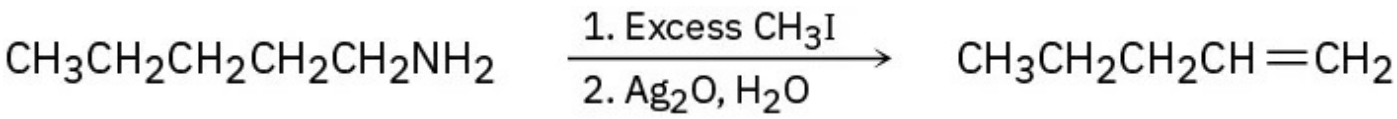
PROBLEM 11-72 When a primary alcohol is treated with *p*-toluenesulfonyl chloride at room temperature in the presence of an organic base such as pyridine, a tosylate is formed. When the same reaction is carried out at a higher temperature, an alkyl chloride is often formed. Explain.



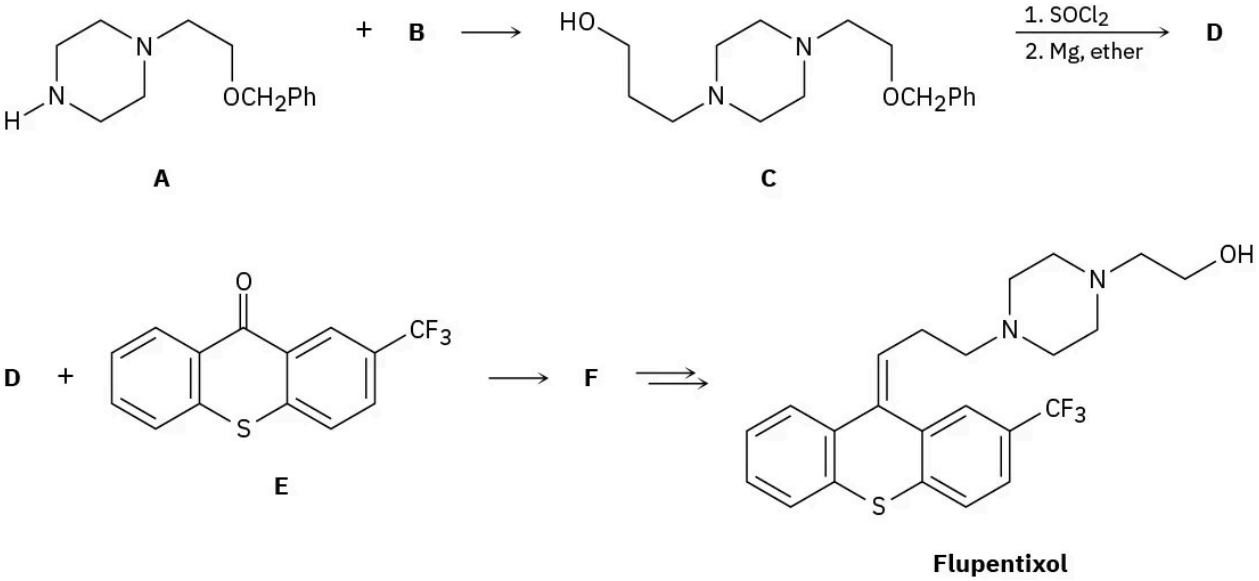
PROBLEM 11-73 The amino acid methionine is formed by a methylation reaction of homocysteine with *N*-methyltetrahydrofolate. The stereochemistry of the reaction has been probed by carrying out the transformation using a donor with a "chiral methyl group," which contains protium (H), deuterium (D), and tritium (T) isotopes of hydrogen. Does the methylation reaction occur with inversion or retention of configuration?



PROBLEM 11-74 Amines are converted into alkenes by a two-step process called the Hofmann elimination. S_N2 reaction of the amine with an excess of CH_3I in the first step yields an intermediate that undergoes E2 reaction when treated with silver oxide as a base. Pentylamine, for example, yields 1-pentene. Propose a structure for the intermediate, and explain why it readily undergoes elimination.



PROBLEM 11-75 The antipsychotic drug flupentixol is prepared by the following scheme:



(a) What alkyl chloride B reacts with amine A to form C?

(b) Compound C is treated with $SOCl_2$, and the product is allowed to react with magnesium metal to give a Grignard reagent D. What is the structure of D?

(c) We'll see in CHEM 232 that Grignard reagents add to ketones, such as E, to give tertiary alcohols, such as F. Because of the

newly formed chirality center, compound F exists as a pair of enantiomers. Draw both, and assign *R*,*S* configurations.

(d) Two stereoisomers of flupentixol are subsequently formed from F, but only one is shown. Draw the other isomer, and identify the type of stereoisomerism.

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12: ALCOHOLS

Learning Objectives

When you have completed Chapter 12, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. design a multi-step synthesis using any of the reactions introduced in this chapter, together with any number of the reactions discussed previously.
3. solve “road-map” problems requiring a knowledge of alcohol chemistry.
4. define, and use in context, the key terms introduced in this chapter.

In this chapter, we examine the chemistry of the alcohol family of compounds. Alcohols can undergo a wide variety of reactions, and because of this reactivity and because they can be prepared in a number of different ways, alcohols occupy an important position in organic chemistry.

The discussion begins with an outline of the nomenclature of alcohols and phenols. We review the physical properties of these compounds, and discuss methods used to obtain the lower members of the series on an industrial scale. A detailed discussion of the laboratory preparation of alcohols follows, with particular emphasis on those methods that involve either the reduction of a carbonyl compound or the use of a Grignard reagent.

Certain reactions of alcohols were discussed in previous chapters. In this chapter, we concentrate on the oxidation of alcohols to carbonyl compounds. We also introduce the concept of protecting a sensitive functional group during an organic synthesis. The discussion then turns to the uses of phenols, their preparation and their chemical reactivity.

Infrared, nuclear magnetic resonance and mass spectroscopy each can provide valuable information about alcohols and phenols, and we illustrate the application of these techniques to the identification of unknown alcohols and phenols with a number of examples.

12.0: Why This Chapter?

12.1: Properties of Alcohols and Phenols

12.2: Preparation of Alcohols- A Review

12.3: Alcohols from Carbonyl Compounds- Reduction

12.4: Alcohols from Carbonyl Compounds - Grignard Reagents

12.5: Reactions of Alcohols

12.6: Oxidation of Alcohols

12.7: Protection of Alcohols

12.8: Chemistry Matters—Ethanol- Chemical, Drug, and Poison

12.A: Alcohols (Summary)

12.B: Additional Problems

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- 17: Alcohols and Phenols by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

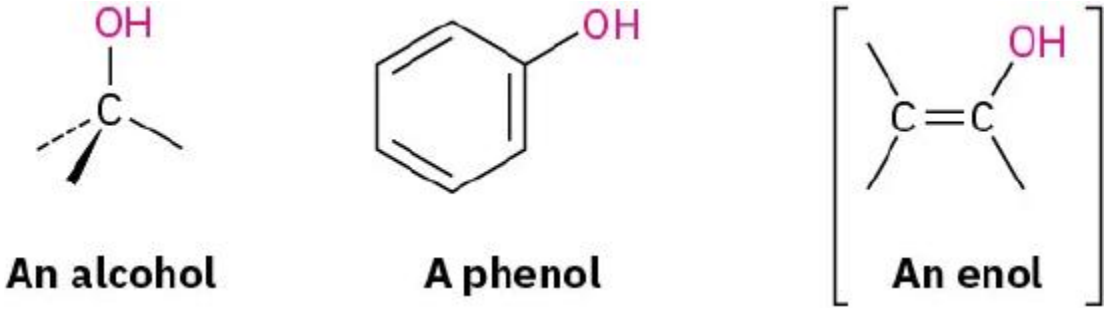
12.0: Why This Chapter?

Up to this point, we've focused on developing some general ideas of organic reactivity, looking at the chemistry of hydrocarbons and alkyl halides, and examining some of the tools used in structural studies. With that background, it's now time to begin a study of the oxygen-containing functional groups that lie at the heart of organic and biological chemistry. We'll look at alcohols in this chapter and move on to carbonyl compounds in CHEM 232.

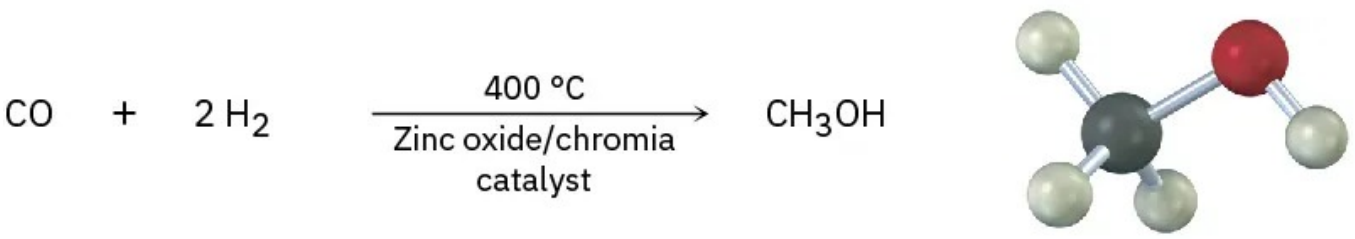


Figure 12.0.1: The phenol resveratrol, found in the skin of red grapes, continues to be studied for its potential anti-cancer, antiarthritic, and hypoglycemic properties. (credit: "Weinreben-Ötlingen" by Pierre Likissas/Wikimedia Commons, CC BY 3.0)

Alcohols and phenols can be thought of as organic derivatives of water in which one of water's hydrogens is replaced by an organic group: H–O–H versus R–O–H and Ar–O–H. In practice, the name *alcohol* is restricted to compounds that have their –OH group bonded to a saturated, sp^3-hybridized carbon atom, while compounds with their –OH group bonded to a vinylic, sp^2-hybridized carbon are called *enols*.

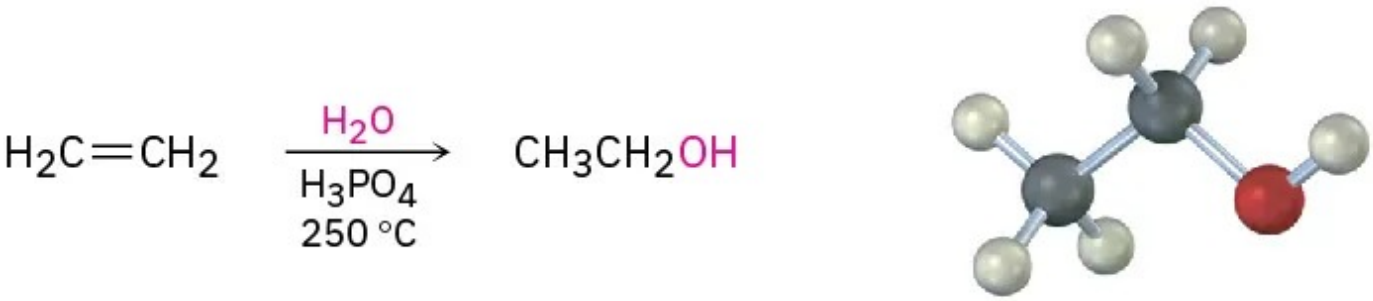


Alcohols occur widely in nature and have many industrial and pharmaceutical applications. Methanol, for instance, is one of the most important of all industrial chemicals. Historically, methanol was prepared by heating wood in the absence of air and thus came to be called *wood alcohol*. Today, approximately 173 million tons (50 billion gallons) of methanol is manufactured worldwide each year, most of it by catalytic reduction of carbon monoxide with hydrogen gas. Methanol is toxic to humans, causing blindness in small doses (15 mL) and death in larger amounts (100–250 mL). Industrially, it is used both as a solvent and as a starting material for production of formaldehyde (CH_2O) and acetic acid (CH_3CO_2H).



Ethanol was one of the first organic chemicals to be prepared and purified. Its production by fermentation of grains and sugars has been carried out for perhaps 9000 years, and its purification by distillation goes back at least as far as the 12th century. Today, approximately 88 million tons (26 billion gallons) of ethanol are produced worldwide each year, most of it by fermentation of corn, barley, sorghum, and other plant sources. Almost all of this ethanol is used for bus and automobile fuel.

Ethanol for industrial use as a solvent or chemical intermediate is largely obtained by acid-catalyzed hydration of ethylene at high temperature.



Phenols occur widely throughout nature and also serve as intermediates in the industrial synthesis of products as diverse as adhesives and antiseptics. Phenol itself is a general disinfectant found in coal tar; methyl salicylate is a flavoring agent found in oil of wintergreen; and urushiols are the allergenic constituents of poison oak and poison ivy. Note that the word *phenol* is the name both of the specific compound (hydroxybenzene) and of the class of compounds.



Phenol (also known as carbolic acid)

Methyl salicylate

Urushiols (R = different C_{15} alkyl and alkenyl chains)

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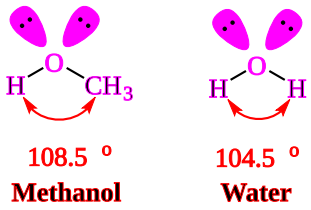
12.1: Properties of Alcohols and Phenols

Objectives

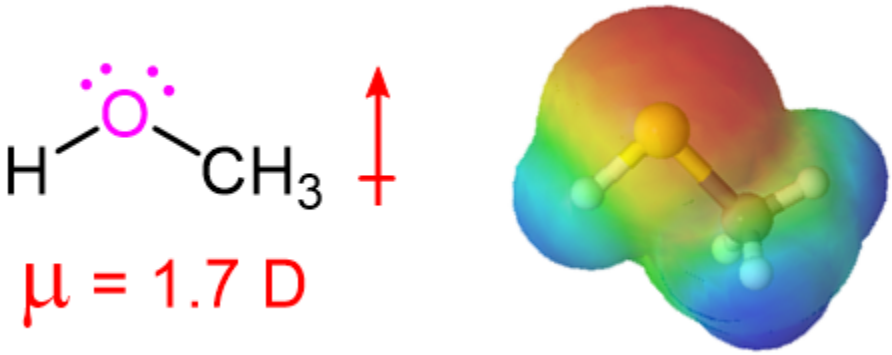
After completing this section, you should be able to

1. explain why the boiling points of alcohols and phenols are much higher than those of alkanes, ethers, etc., of similar molecular mass.
2. discuss the factors that are believed to determine the acidity of alcohols and phenols.
3. list a given series of alcohols or phenols in order of increasing or decreasing acidity.
4. explain the difference in acidity between two given alcohols or phenols.
5. explain why phenols are more acidic than alcohols.
6. explain, in terms of inductive and resonance effects, why a given substituted phenol is more or less acidic than phenol itself.
7. write equations for the reactions of given alcohols and phenols with strong bases, such as sodium hydride and sodium amide.

Alcohols and phenols have nearly the same geometry around the oxygen atom as water. The R–O–H bond angle has an approximately tetrahedral value (108.5° in methanol, for instance), and the oxygen atom is sp^3-hybridized.



The presence of a highly electronegative oxygen confers a measure of polar character to alcohols. Much of the electron density of alcohol is drawn towards the oxygen, giving alcohols a relatively high dipole moment (1.7 D for Methanol).



The Dipole Moment of Methanol

Boiling Points of Alcohols

Also, like water, alcohols, and phenols have higher boiling points than expected because of hydrogen bonding (Section 2.12). A positively polarized –OH hydrogen atom from one molecule is attracted to a lone pair of electrons on the electronegative oxygen atom of another molecule, resulting in a weak force that holds the molecules together (Figure 12.1.1). These intermolecular

attractions must be overcome for a molecule to break free from the liquid and enter the vapor state, so the boiling temperature is raised. For example, 1-propanol (MW = 60), butane (MW = 58), and chloroethane (MW = 65) have similar molecular weights, yet 1-propanol boils at 97 °C, compared with –0.5 °C for the alkane and 12.5 °C for the chloroalkane.

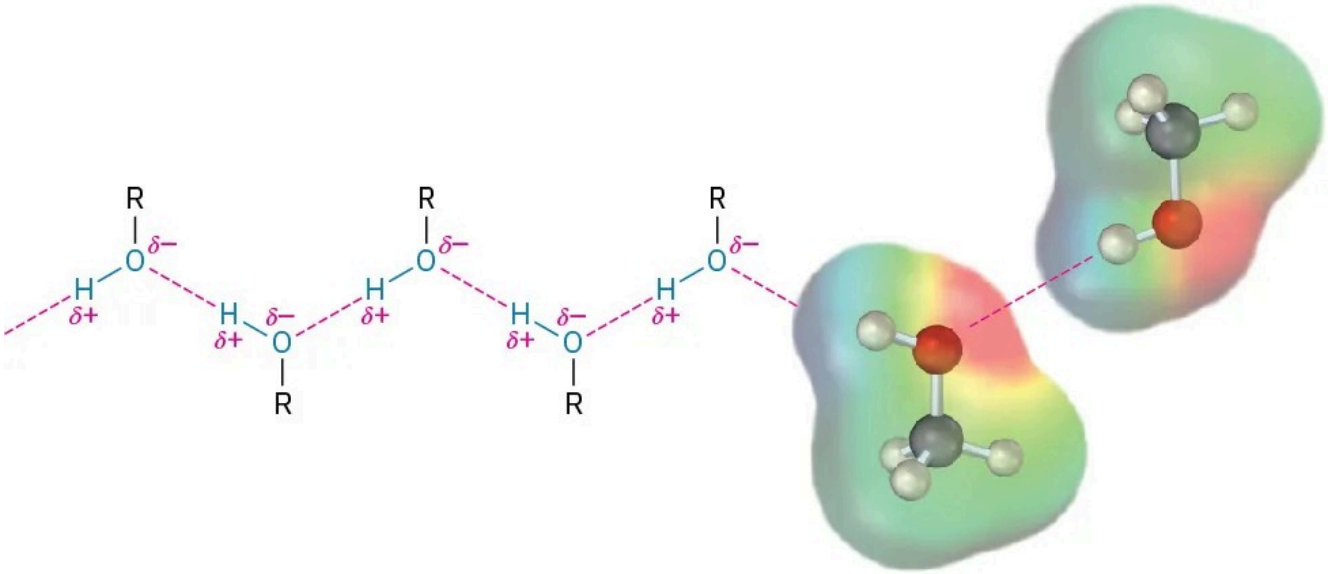


Figure 12.1.1: Hydrogen-bonding in alcohols and phenols. The attraction between a positively polarized –OH hydrogen and a negatively polarized oxygen holds molecules together. The electrostatic potential map of methanol shows the **positively polarized** –OH hydrogen and the **negatively polarized** oxygen.

This table shows that alcohols (in blue) have higher boiling points than haloalkanes and alkanes with the equivalent molecular weight. It also shows that the boiling points of alcohols increase with the number of carbon atoms.

Table 12.1.1: Physical Properties of Selected Alcohols, Haloalkanes, and Alkanes

Compound	IUPAC Name	Molecular Weight (g/mol)	Melting Point (°C)	Boiling Point (°C)
CH_3OH	Methanol	32.0	-97.8	65.0
CH_3Cl	Chloromethane	50.5	-97.7	-24.2
CH_3CH_2OH	Ethanol	46.1	-114.7	78.5
$CH_3CH_2CH_2CH_3$	Butane	58.1	-140.	-1
$CH_3CH_2CH_2OH$	1-Propanol	60.1	-126.5	97.4
CH_3CH_2Cl	Chloroethane	64.5	-136.4	12.3
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72.2	-130	36.3
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74.1	-89.5	117.3
$CH_3(CH_2)_4OH$	1-Pentanol	88.1	-79	138

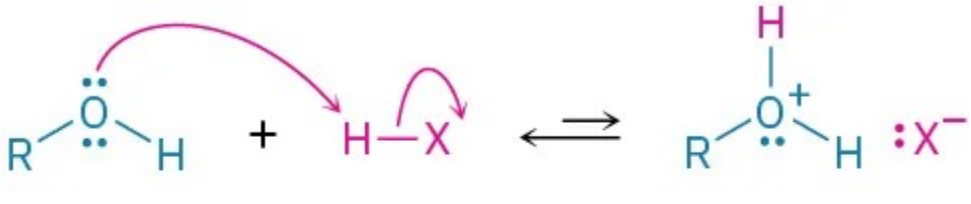
Solubility of Alcohols in Water

Alcohols and water have the ability to form hydrogen bonds with one another, which tends to make the two liquids miscible. Small alcohols are completely soluble in water; mixing them in any proportion yields 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.

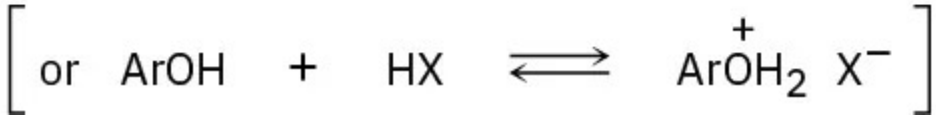
Acid-Base Properties of Alcohols

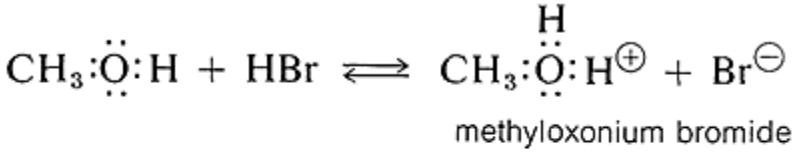
Another similarity with water is that alcohols and phenols are both weakly basic and weakly acidic. Alcohols are weak bases similar in strength to water and can accept protons from strong acids to form the conjugate acid called oxonium ions (ROH_2^+). An example is the reaction of methanol with hydrogen bromide to give methyloxonium bromide, which is analogous to the formation of hydroxonium bromide from the reaction of hydrogen bromide and water:

As weak bases, they are reversibly protonated by strong acids to yield oxonium ions, ROH_2^+.

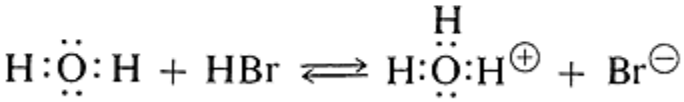


An alcohol **An oxonium ion**





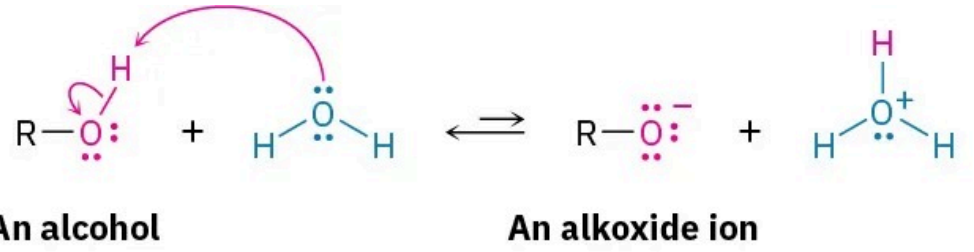
methyloxonium bromide



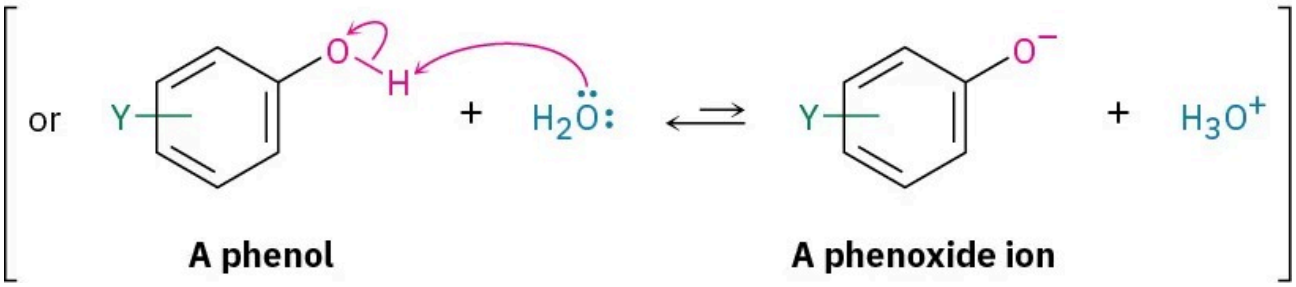
hydroxonium bromide

Acidic behavior of Alcohols

In aqueous solutions, alcohols dissociate slightly by donating a hydrogen to water. This creates the alcohol's conjugate base, called an alkoxide ion (RO^-), along with hydronium (H_3O^+). The acid ionization constant (K_a) of ethanol is about 10^{-18}, which is slightly less than that of water. Alcohols, such as ethanol, can be deprotonated to form their conjugate base by reaction with a stronger base, such as sodium amide ($NaNH_2$), sodium hydride (NaH), or Grignard reagents (RMgBr). Alkoxides can also be formed using sodium or potassium metal, which reacts vigorously but controllably with alcohols.



An alcohol **An alkoxide ion**



A phenol **A phenoxide ion**

The strength of any acid HA in water can be expressed by an acidity constant, K_a.

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

with

$$pK_a = -\log K_a$$

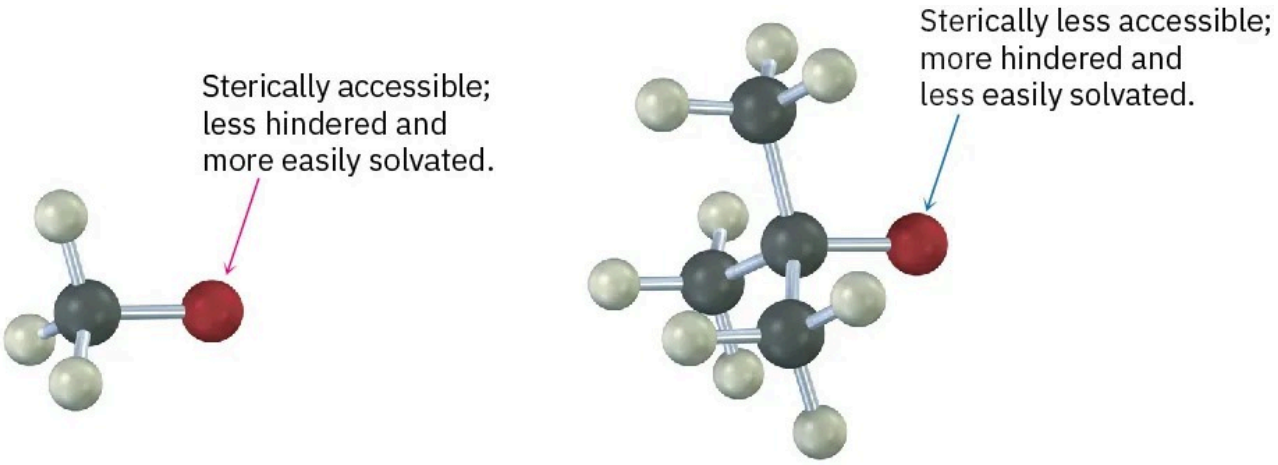
Compounds with a smaller K_a and larger pK_a are less acidic, whereas compounds with a larger K_a and smaller pK_a are more acidic. As shown in Table 12.1.1, simple alcohols like methanol and ethanol are about as acidic as water, but the more highly substituted *tert*-butyl alcohol is somewhat weaker. Substituent groups also have a significant effect: 2,2,2-trifluoroethanol is approximately 3700 times stronger than ethanol, for instance. Phenols and *thiols,* the sulfur analogs of alcohols, are substantially more acidic than water.

Table 12.1.1 *Acidity Constants of Some Alcohols and Phenols*

Compound	pK_a	
$(CH_3)_3COH$ t-butanol	18	Weaker acid
CH_3CH_2OH ethanol	16	
H_2O	15.74	
CH_3OH	15.54	
CF_3CH_2OH	12.43	
p-Aminophenol	10.46	
CH_3SH	10.3	
p-Methylphenol	10.17	
Phenol	9.89	
p-Chlorophenol	9.38	
p-Nitrophenol	7.15	
Acetic Acid	4.76	Stronger acid
2,4-dinitrophenol	4.1	

Compound	pK_a	
2,4,6-trinitrophenol	0.3	

The effect of alkyl substitution on alcohol acidity is due primarily to solvation of the alkoxide ion formed on acid dissociation. The more readily the alkoxide ion is solvated by water, the more stable it is, the more its formation is energetically favored, and the greater the acidity of the parent alcohol. For example, the oxygen atom of an unhindered alkoxide ion, such as that from methanol, is sterically accessible and is easily solvated by water. The oxygen atom of a hindered alkoxide ion, however, such as that from *tert*-butyl alcohol, is less easily solvated and is therefore less stable.



Methoxide ion, CH_3O^-
(pK_a = 15.54)

***tert*-Butoxide ion, $(CH_3)_3CO^-$**
(pK_a = 18)

Inductive effects (Section 16.4) are also important in determining alcohol acidities. Electron-withdrawing halogen substituents, for instance, stabilize an alkoxide ion by spreading the charge over a larger volume, thus making the alcohol more acidic. Compare, for instance, the acidities of ethanol (pK_a = 16) and 2,2,2-trifluoroethanol (pK_a = 12.43), or of *tert*-butyl alcohol (pK_a = 18) and nonafluoro-*tert*-butyl alcohol (pK_a = 5.4).

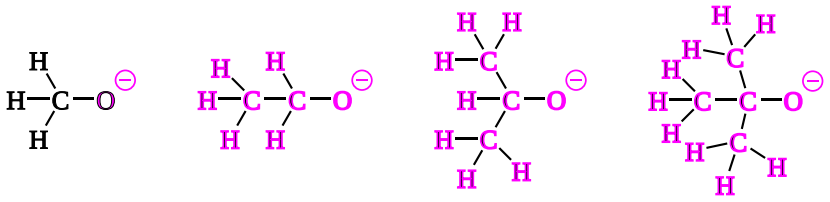
Electron-withdrawing groups stabilize the alkoxide ion and lower the pK_a of the alcohol.



pK_a = 5.4 versus pK_a = 18

Acidity of Alcohols in Aqueous Solution

In general, alcohols in aqueous solution are slightly less acidic than water. The order of acidity of various liquid alcohols generally is water > primary > secondary > tertiary ROH. By this we mean that the pK_a is reduced as R is changed from primary to secondary to tertiary; therefore, *tert*-butyl alcohol is less acidic than ethanol. This trend is explained by the importance of solvation in equilibrium. In solution, the larger alkoxide ions, are less well solvated than the smaller ions, because fewer solvent molecules can be accommodated around the negatively charged oxygen in the larger ions. The acidity of alcohols, therefore, decreases as the size of the conjugate base increases. This trend can be clearly seen when comparing alkoxide size to the pKa of the corresponding alcohol listed in Table 12.1.2.

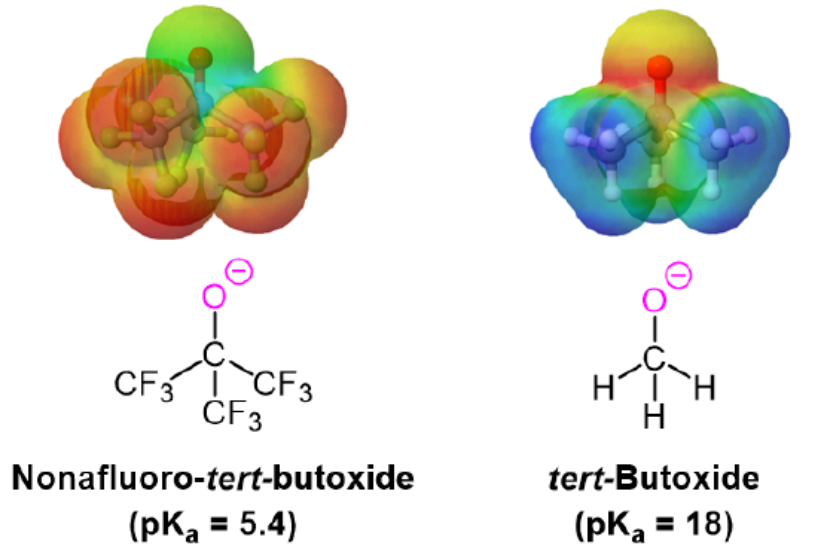


$$ROH + OH^- \rightleftharpoons RO^- + HOH$$

Table 12.1.2*: The pKa's of various alcohols*

R	Name	pK_{a1}
H	water	14.0
CH_3	methanol	15.5
CH_3CH_2	ethanol	15.9
$(CH_3)_2CH$	propan-2-ol (isopropyl alcohol)	16.5
$(CH_3)_3C$	2-methylpropan-2-ol (*tert*-butanol)	17
C_6H_5 (phenyl)	phenol	9.95

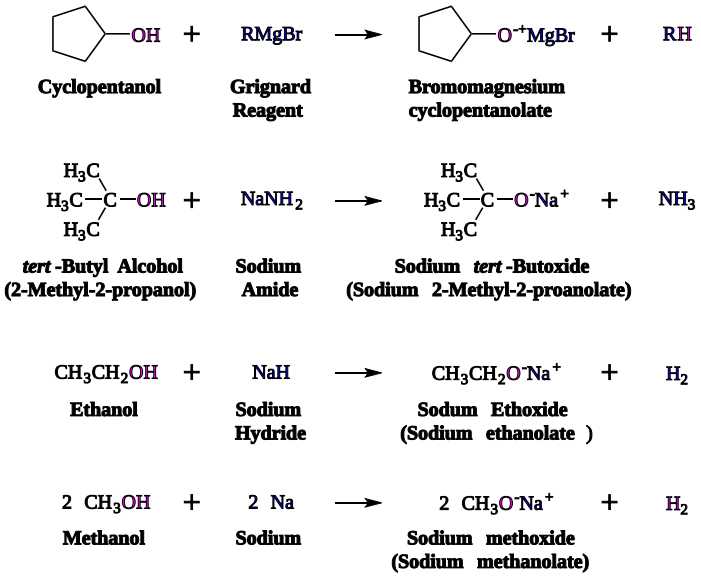
The addition of an electron-withdrawing group, such as an electronegative halogen, can increase the acid strength of an alcohol by stabilizing its alkoxide conjugate base through induction (**Section 2.10**). The electron-withdrawing group helps to spread out the electron density of the alkoxide's negative charge, which has a stabilizing effect. The inductive effect is cumulative, such that the acid strength of an alcohol becomes stronger (Lower pK_a) as the number of halogens increases. The presence of nine fluorines in nonafluoro-*tert*-butyl alcohol decreases its pK_a to 5.4 which is significantly more acidic than *tert*-butyl alcohol (pK_a = 18). The electron-withdrawing effect of the fluorines is clearly seen when comparing the electrostatic potential maps of the corresponding alkoxides. In *tert*-butoxide, the molecule's electron density is firmly centered around the oxygen, as shown by the orange/yellow color. In nonafluoro-*tert*-butoxide, the molecule's electron density is almost completely removed from the oxygen and shifted to the fluorines.



Reaction of Alcohols with Strong Bases

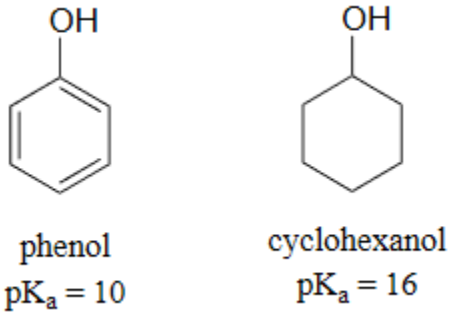
Because alcohols are weak acids, they don't react with weak bases, such as amines or bicarbonate ion, and they only react to a

limited extent with metal hydroxides such as NaOH. Alcohols do, however, react with alkali metals and with strong bases such as sodium hydride (NaH), sodium amide ($NaNH_2$), and Grignard reagents (RMgX). Alkoxides are themselves bases that are frequently used as reagents in organic chemistry. They are named systematically by adding the *-ate* suffix to the name of the alcohol. Methanol becomes methanolate, for instance.

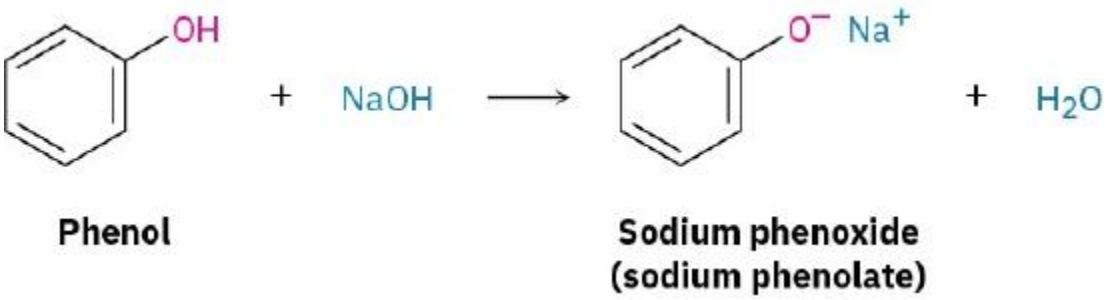


Acidity of Phenol

Phenols are about a million times more acidic than alcohols (Table 12.1.1). The reason for this increasing acidity is the stability of the conjugate base through resonance effects. An excellent example of this effect is seen in phenol, which is roughly a million times more acidic than cyclohexanol.



Phenol is acidic enough to be deprotonated by weaker bases, such as sodium hydroxide (NaOH), to form the phenoxide ion. They are therefore soluble in dilute aqueous NaOH and can often be separated from a mixture simply by basic extraction into aqueous solution, followed by re-acidification.



Phenols are more acidic than alcohols because the phenoxide anion is resonance-stabilized. The increased acidity of phenol is caused by the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring. As a result, the negative charge is no longer entirely localized on the oxygen, but is spread throughout the whole ion, allowing it to be highly stabilized.

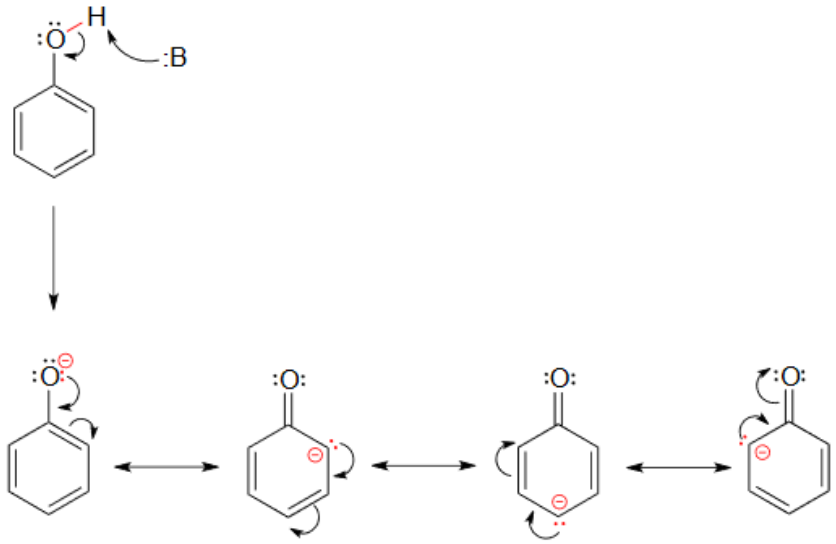


Figure 12.1.2: The resonance-stabilized phenoxide ion is more stable than expected because the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom being delocalized by resonance to three different carbons on the aromatic ring; spreading over the aromatic ring in the phenoxide ion.

Delocalization of the negative charge over the ortho and para positions of the aromatic ring results in increased stability of the phenoxide anion relative to undissociated phenol and in a consequently lower $\Delta G°$ for dissociation. Figure 12.1.2 compares electrostatic potential maps of an alkoxide ion (CH_3O^-) with phenoxide ion to show how the negative charge in phenoxide ion is delocalized from oxygen to the ring.

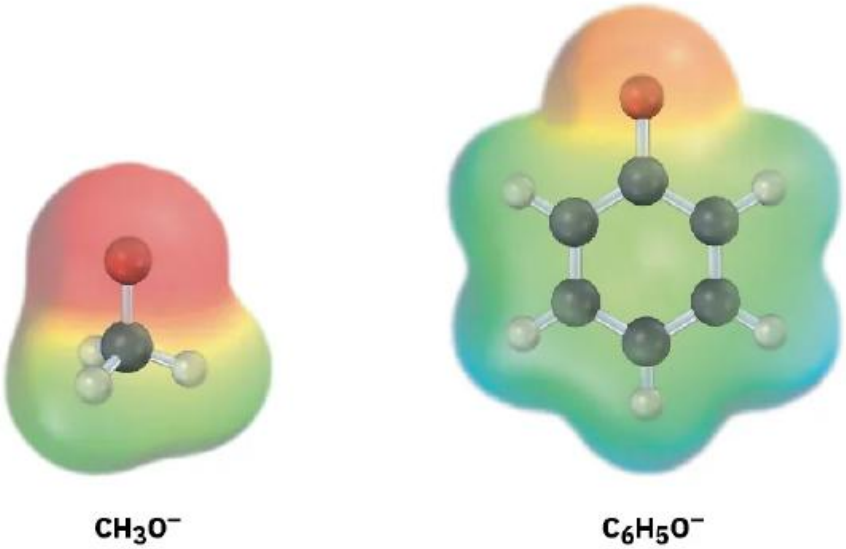


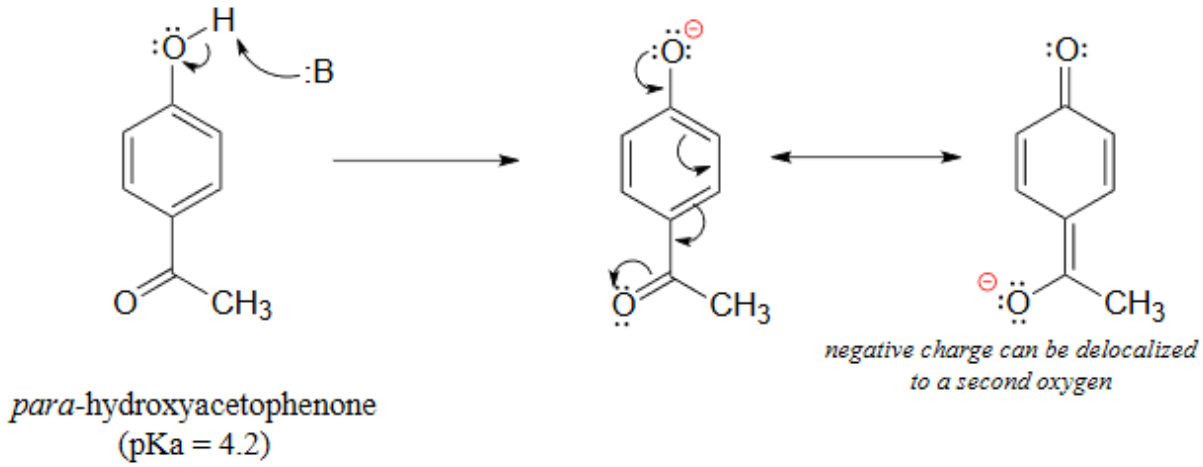
Figure 12.1.3: The resonance-stabilized phenoxide ion is more stable than an alkoxide ion. Electrostatic potential maps show that the **negative charge** is concentrated on the oxygen atom in the methoxide ion but is spread over the aromatic ring in the phenoxide ion.

Acidity of Substituted Phenols

Substituted phenols can be either more acidic or less acidic than phenol itself, depending on whether the substituent is electron-

withdrawing or electron-donating. Phenols with an electron-donating substituent are less acidic because these substituents concentrate the charge.

Phenols with an electron-withdrawing substituent, such as a nitro or carbonyl on the aromatic ring, are more acidic because these substituents delocalize the negative charge. For the conjugate base of the phenol derivative below, an additional resonance contributor can be drawn in which the negative formal charge is placed on the carbonyl oxygen.



para-hydroxyacetophenone
(pKa = 4.2)

Now the negative charge on the conjugate base can be spread out over two oxygens (in addition to three aromatic carbons). The phenol acid therefore has a pK_a similar to that of a carboxylic acid, where the negative charge on the conjugate base is also delocalized to two oxygen atoms. The ketone group on the aromatic ring is acting as an electron-withdrawing group and 'pulling' electron density towards itself, through both inductive and resonance effects.

The acidifying effect of an electron-withdrawing substituent is particularly noticeable in phenols with a nitro group at the ortho or para position.

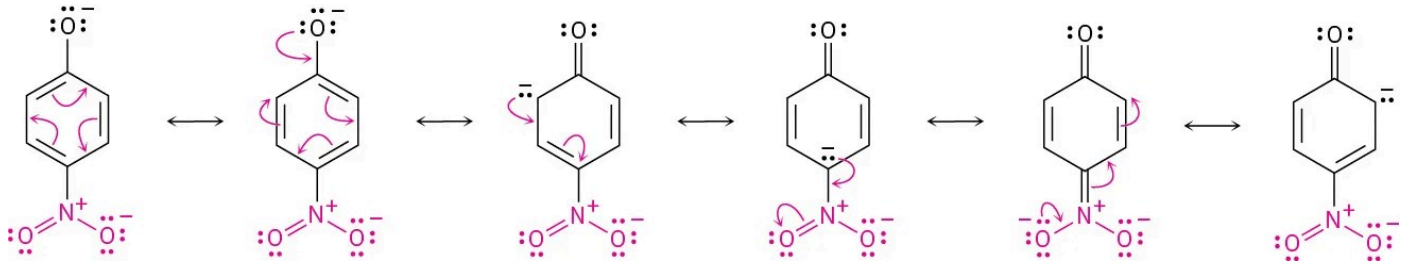
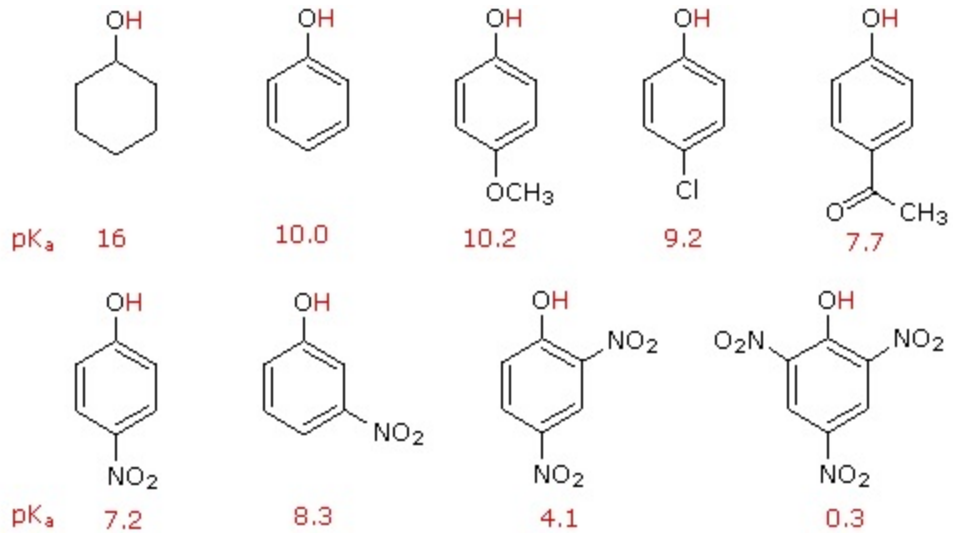


Figure 12.1.4: The resonance-stabilized phenoxide ion is more stable than expected because the negative charge and a set of lone pair electrons from the phenoxide's oxygen atom are delocalized by resonance to three different carbons on the aromatic ring and an additional oxygen on the nitro group, increasing the acidity of the phenol.

It is noteworthy that the influence of a nitro substituent is over ten times stronger in the *para*-location than it is meta, despite the fact that the latter position is closer to the hydroxyl group. This occurs since nitro groups at the meta position cannot accept the negative charge through resonance. Furthermore additional nitro groups have an additive influence if they are positioned *ortho* or *para* locations to the hydroxide. The trinitro compound shown at the lower right is a very strong acid called picric acid.

Lastly, if an electron-donating group is attached to an aromatic ring, as in *p*-methoxyphenol, the phenoxide ion is destabilized, which causes a decrease in acidity in the corresponding phenol.



Worked Example 12.1.1: Predicting the Relative Acidity of a Substituted Phenol

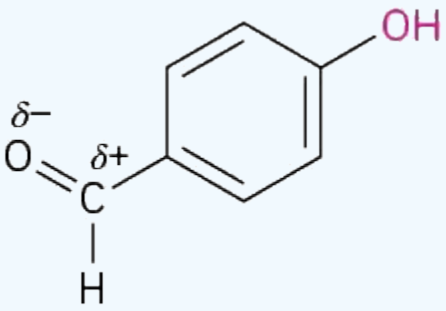
Is *p*-hydroxybenzaldehyde more acidic or less acidic than phenol?

Strategy

Identify the substituent on the aromatic ring, and decide whether it is electron-donating or electron-withdrawing. Electron-withdrawing substituents make the phenol more acidic by stabilizing the phenoxide anion, and electron-donating substituents make the phenol less acidic by destabilizing the anion.

Solution

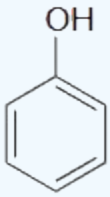
We saw in Section 16.4 that a carbonyl group is electron-withdrawing. Thus, ***p***-hydroxybenzaldehyde is more acidic (pK_a = 7.9) than phenol (pK_a = 9.89).



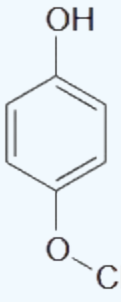
***p*-Hydroxybenzaldehyde**
(pK_a = 7.9)

Worked Example 12.1.2

Using resonance structures, please explain why 4-methoxyphenol is less acidic than phenol.



pKa = 10



pKa = 10.6

Answer available at the end of this section.

Exercises

Exercise 12.1.1

The following data for isomeric four-carbon alcohols show that there is a decrease in boiling point with increasing substitution of the OH-bearing carbon. How might you account for this trend?

1-Butanol, bp 117.5 °C
2-Butanol, bp 99.5 °C
2-Methyl-2-propanol, bp 82.2 °C

Answer available at the end of this section.

Exercise 12.1.2

Predict which compound of each pair is more soluble in water and explain your reasoning.

a. Butan-1-ol or pentan-1-ol
b. Phenol or cyclohexanol
c. Octan-1,3-diol or octan-1-ol
d. 1-Chlorohexane or hexan-1-ol

Answer available at the end of this section.

Exercise 12.1.3

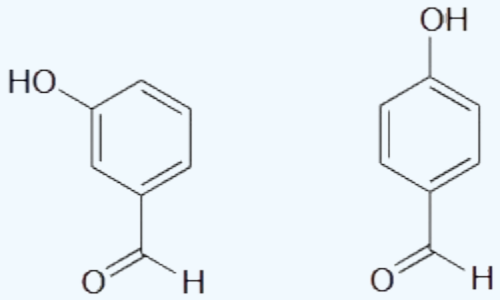
Predict which compound has the higher boiling point and explain your reasoning.

a. Water or ethanol
b. Butan-1-ol or octan-1-ol
c. Hexan-2-ol or hexan-2-one

Answer available at the end of this section.

Exercise 12.1.4

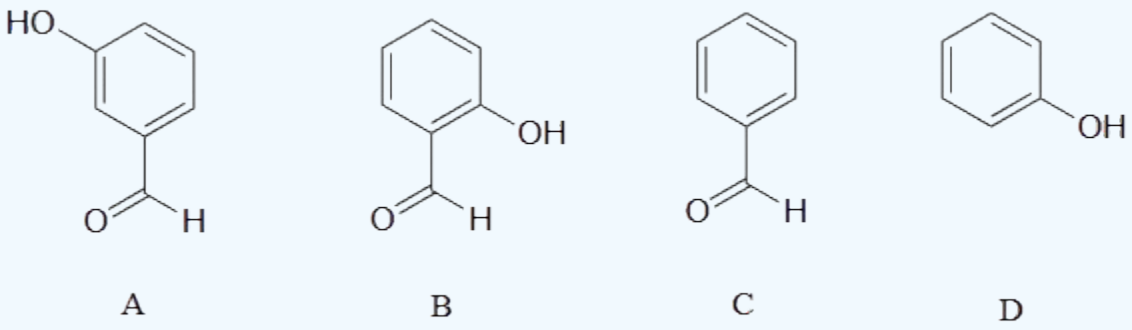
The position of the electron-withdrawing substituent relative to the phenol hydroxyl is very important in terms of its effect on acidity. Which of the two substituted phenols below is more acidic? Use resonance drawings to explain your answer.



Answer available at the end of this section.

Exercise 12.1.5

Rank the four compounds below from most acidic to least.



A B C D

Answer available at the end of this section.

Exercise 12.1.6

Rank the following substances in order of increasing acidity:

a. $(CH_3)_2CHOH$, $HC{\equiv}CH$, $(CF_3)_2CHOH$, CH_3OH
b. Phenol, p-methylphenol, p-(trifluoromethyl)phenol
c. Benzyl alcohol, phenol, p-hydroxybenzoic acid

Answer available at the end of this section.

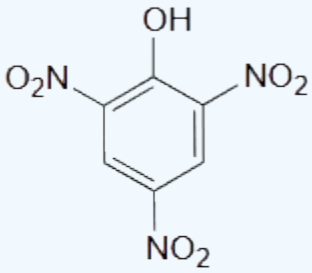
Exercise 12.1.7

p-Nitrobenzyl alcohol is more acidic than benzyl alcohol, but *p*-methoxybenzyl alcohol is less acidic. Explain.

Answer available at the end of this section.

Exercise 12.1.8

Use a resonance argument to explain why picric acid has such a low pKa.



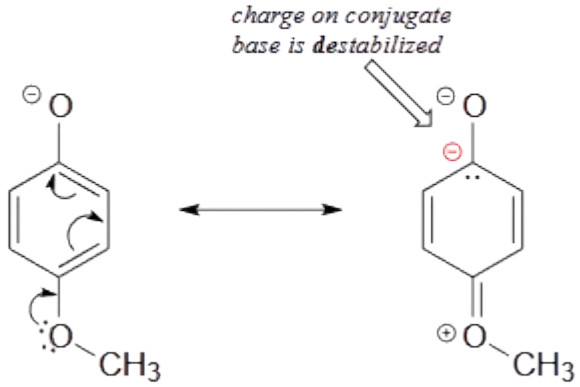
picric acid
pKa = 0.25

Answer available at the end of this section.

Answers

Worked Example 12.1.2

The methoxy group is an electron-donating group by resonance. A resonance contributor can be drawn in which a formal negative charge is placed on the carbon adjacent to the negatively-charged phenolate oxygen.



Because of like-charge repulsion, this destabilizes the negative charge on the phenolate oxygen, making the corresponding phenol less acidic.

Exercise 12.1.1

Hydrogen-bonding is more difficult in hindered alcohols.

Exercise 12.1.2

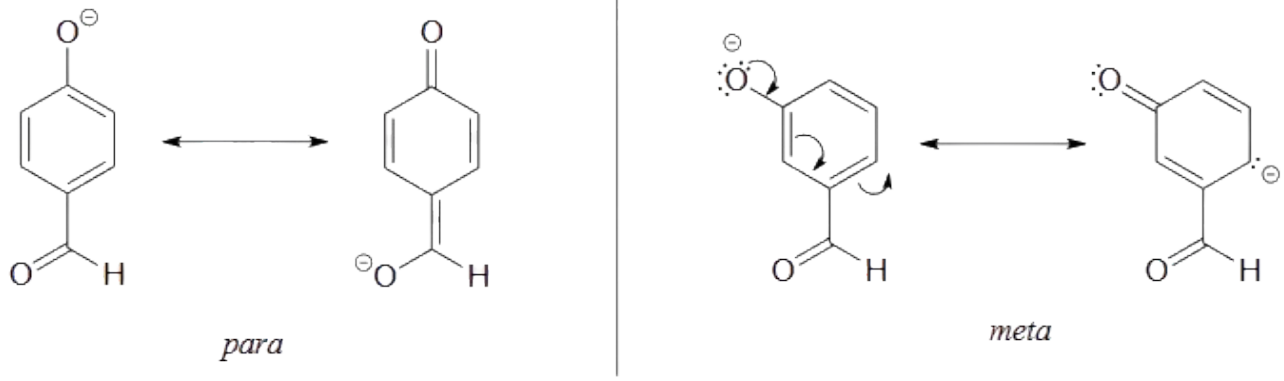
1. Butan-1-ol is more soluble in water because it has a smaller hydrophobic region compared to pentan-1-ol, allowing butan-1-ol to interact with water better.
2. Phenol is more soluble in water than cyclohexanol because of the more polar character of its ring. phenol is able to interact with water better 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.

Exercise 12.1.3

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.

Exercise 12.1.4

The para-subsituted phenol is more acidic, because the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. This is not possible when the aldehyde group is in the meta position



Exercise 12.1.5

Compound B is the strongest acid due to electron-withdrawing resonance effects-the negative charge on the conjugate base can be delocalized to the aldehyde oxygen. Compound A is the 2nd strongest acid -while the negative charge on the conjugate base cannot be delocalized to the aldehyde oxygen due to the *meta*-position, the aldehyde none the less has a stabilizing, electron-withdrawing inductive effect. Compound D is ranked #3 -it is phenol, and does not have any electron-withdrawing substituents on the ring as do B and A. Compound C is the least acidic -neither the phenyl group nor the aldehyde are even slightly acidic.

Exercise 12.1.6

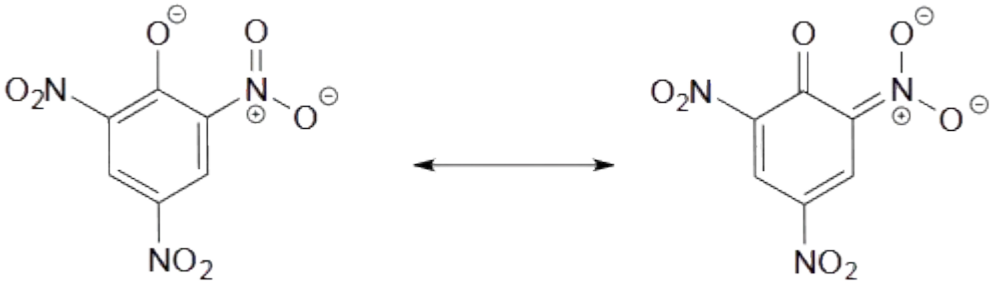
1. $HC{\equiv}CH < (CH_3)_2CHOH < CH_3OH < (CF_3)_2CHOH$
2. p-Methylphenol < Phenol < p-(Trifluoromethyl)phenol
3. Benzyl alcohol < Phenol < p-Hydroxybenzoic acid

Exercise 12.1.7

The electron-withdrawing nitro group stabilizes an alkoxide ion, but the electron-donating methoxyl group destabilizes the anion.

Exercise 12.1.8

The negative charge on the conjugate base of picric acid can be delocalized to oxygen atoms on all threeof the nitro groups. One such resonance contributor is shown below. This extensive delocalization means that the conjugate base is very stable, and the conjugate acid is thus a very strong acid.



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12.2: Preparation of Alcohols- A Review

Alcohols occupy a central position in organic chemistry. They can be prepared from many other kinds of compounds (alkenes, alkyl halides, ketones, esters, and aldehydes, among others), and they can be transformed into an equally wide assortment of compounds (Figure 12.2.1).

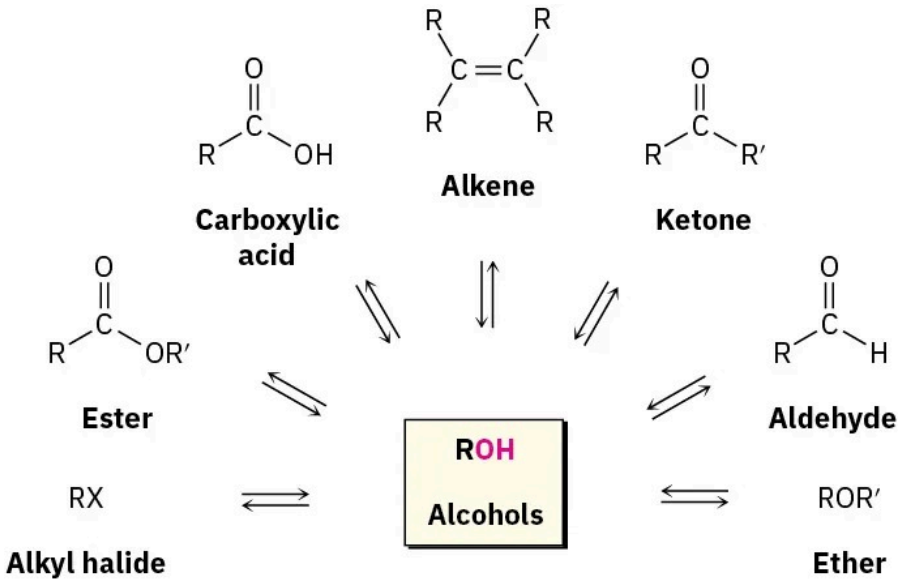
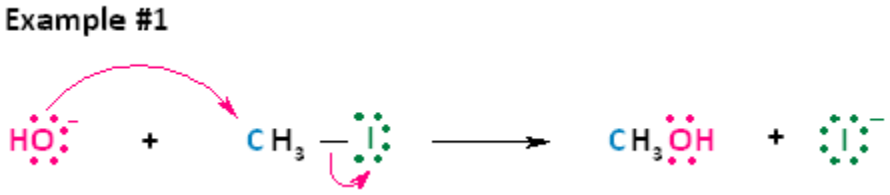


Figure 12.2.1: The central position of alcohols in organic chemistry. Alcohols can be prepared from, and converted into, many other kinds of compounds.

We've already seen several methods of alcohol synthesis:

Alcohols from Substitution Reactions

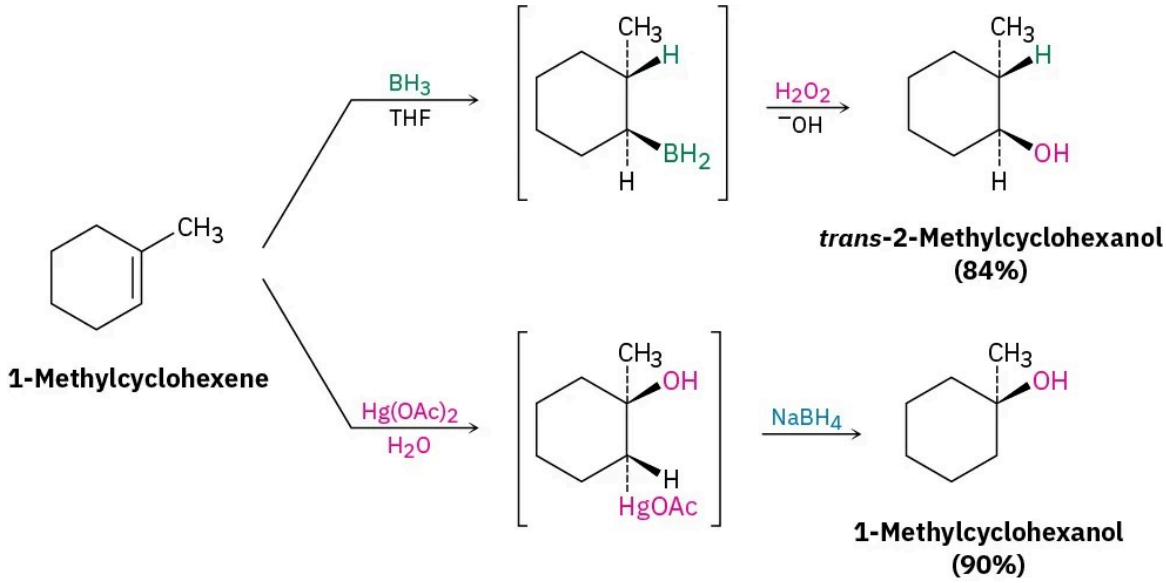
Methyl and primary alkyl halides can be converted to alcohols by using an S_N2 reaction with OH^- as a nucleophile (**Section 11.5**). Also, secondary and tertiary alkyl halides can be converted to alcohols by an S_N1 reaction using water as the nucleophile (and it can even be the solvent). Recall that S_N1 reactions are promoted in polar, protic solvents (**Section 11.7**).



The Synthesis of Methanol Using an S_N2 Reaction

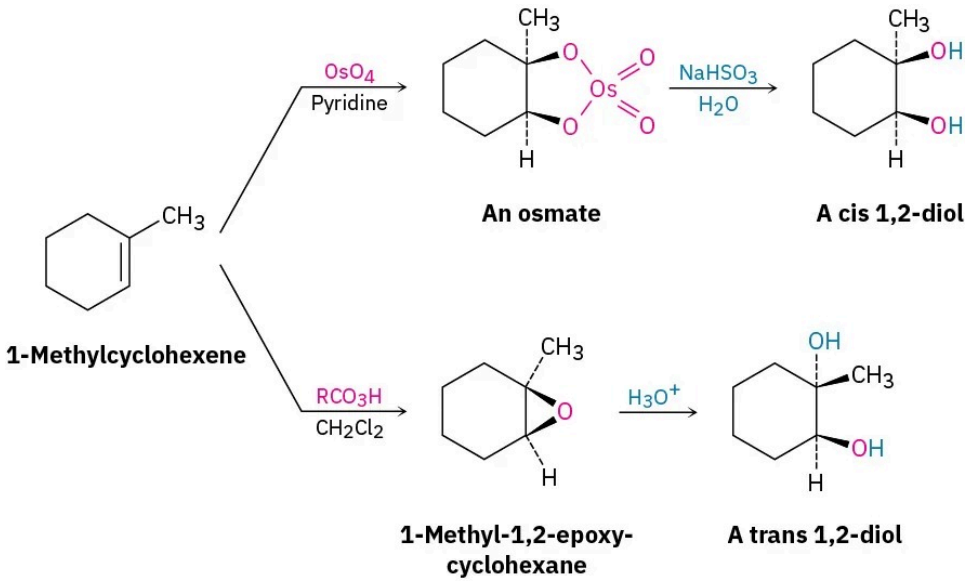
Alcohols from Alkenes

- Alcohols can be prepared by hydration of alkenes. Because the direct hydration of alkenes with aqueous acid is generally a poor reaction in the laboratory, two indirect methods are commonly used. Hydroboration–oxidation yields the syn, non-Markovnikov hydration product (Section 8.5), whereas oxymercuration–demercuration yields the Markovnikov hydration product (Section 8.4).



Diols from Alkenes

- 1,2-Diols can be prepared either by direct hydroxylation of an alkene with OsO_4 followed by reduction with $NaHSO_3$ or by acid-catalyzed hydrolysis of an epoxide (Section 8.7). The OsO_4 reaction occurs with syn stereochemistry to give a cis diol, and epoxide opening occurs with anti stereochemistry to give a trans diol.

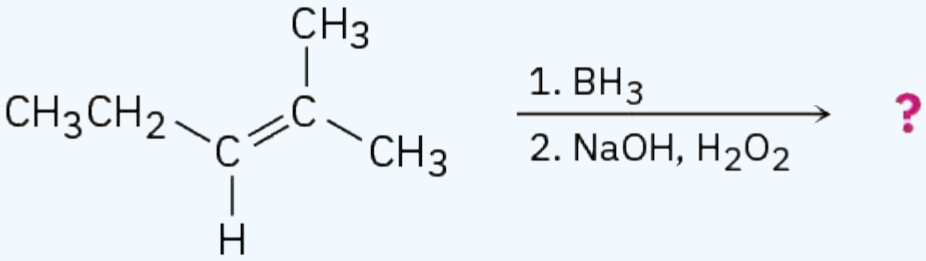


Exercises

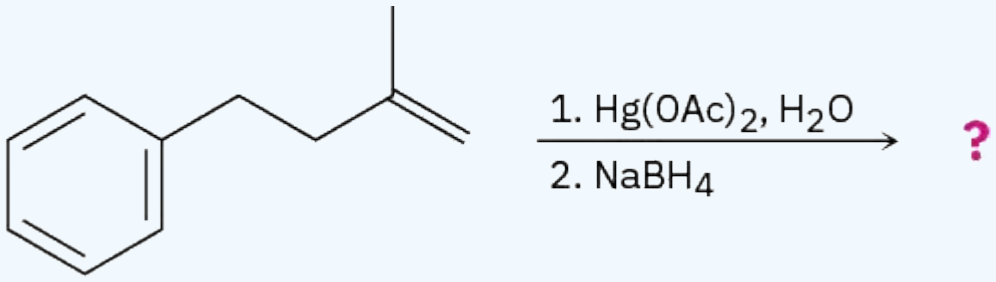
Exercise 12.2.1

Predict the products of the following reactions:

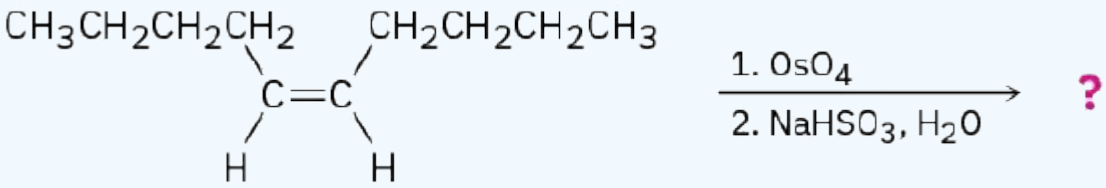
a.



b.



a.



Answer available at the end of this section.

Answers

Exercise 12.2.1

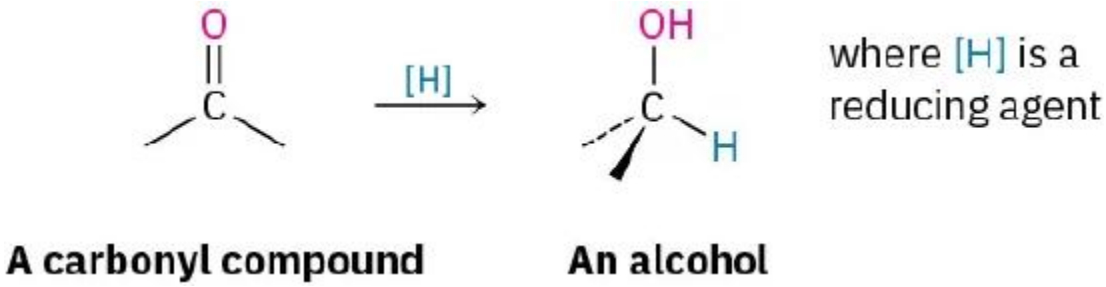
a. 2-Methyl-3-pentanol
b. 2-Methyl-4-phenyl-2-butanol
c. meso-5,6-Decanediol

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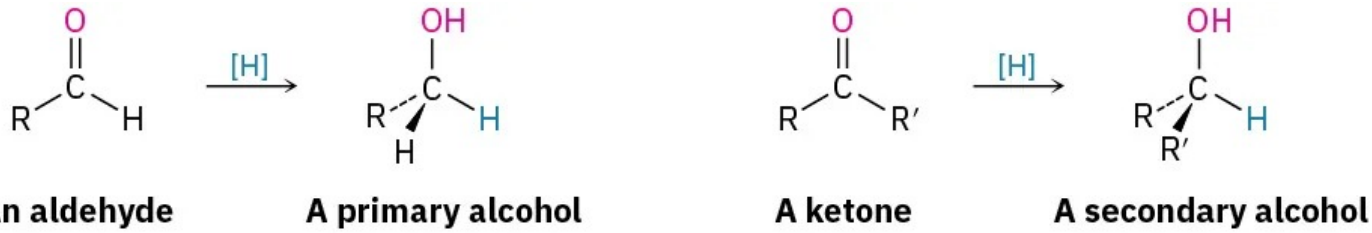
12.3: Alcohols from Carbonyl Compounds- Reduction

The most general method for preparing alcohols, both in the laboratory and in living organisms, is by reduction of a carbonyl compound. Just as reduction of an alkene adds hydrogen to a C=C bond to give an alkane (Section 8.6), reduction of a carbonyl compound adds hydrogen to a C=O bond to give an alcohol. All kinds of carbonyl compounds can be reduced, including aldehydes, ketones, carboxylic acids, and esters.



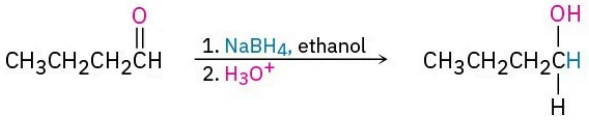
Reduction of Aldehydes and Ketones

Aldehydes are easily reduced to give primary alcohols, and ketones are reduced to give secondary alcohols.



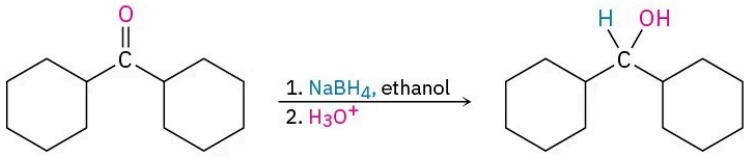
Dozens of reagents are used in the laboratory to reduce aldehydes and ketones, depending on the circumstances, but sodium borohydride, $NaBH_4$, is usually chosen because of its safety and ease of handling. Sodium borohydride is a white, crystalline solid that can be weighed in the open atmosphere and used in either water or alcohol solution.

Aldehyde reduction



Butanal — **1-Butanol (85%) (a 1° alcohol)**

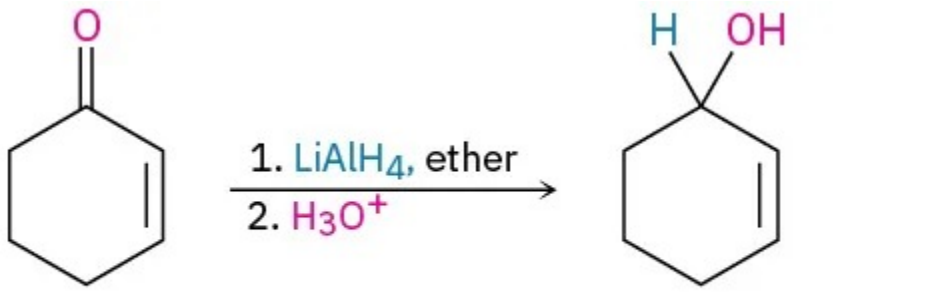
Ketone reduction



Dicyclohexyl ketone — **Dicyclohexylmethanol (88%) (a 2° alcohol)**

Lithium aluminum hydride, $LiAlH_4$, is another reducing agent often used for reduction of aldehydes and ketones. A grayish powder

that is soluble in ether and tetrahydrofuran, $LiAlH_4$ is much more reactive than $NaBH_4$ but also much more dangerous. It reacts violently with water and decomposes explosively when heated above 120 °C.



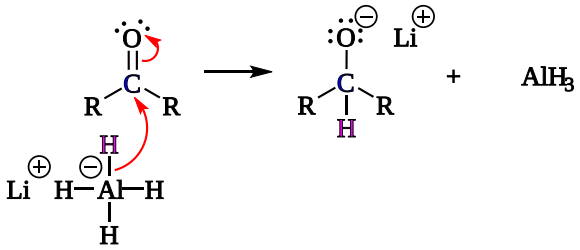
2-Cyclohexenone **2-Cyclohexenol (94%)**

Mechanism

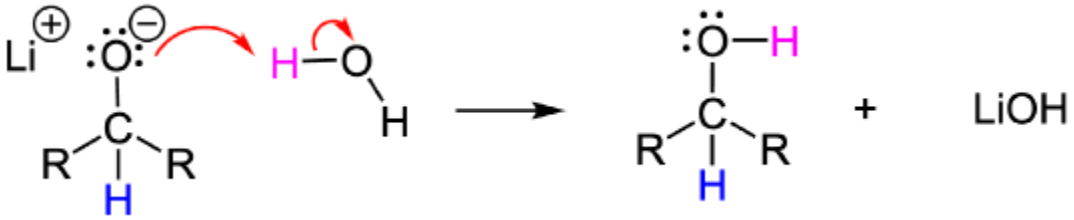
Both $NaBH_4$ and $LiAlH_4$ act as if they were a source of the hydride anion nucleophile. The hydride anion undergoes nucleophilic addition to the carbonyl carbon to form a C-H single bond and form a tetrahedral alkoxide ion intermediate. The alkoxide ion is subsequently converted to an alcohol by reaction with a proton source. In the $LiAlH_4$ reduction, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the borohydride reduction, the hydroxylic solvent system achieves this hydrolysis automatically. The lithium, sodium, boron and aluminum end up as soluble inorganic salts.

Note! The reaction and the corresponding mechanism of hydride reductions of carbonyls is fairly complicated. The following mechanism has been simplified for easier understanding..

1) Nucleophilic attack to form a tetrahedral alkoxide intermediate



2) Protonation to form an alcohol



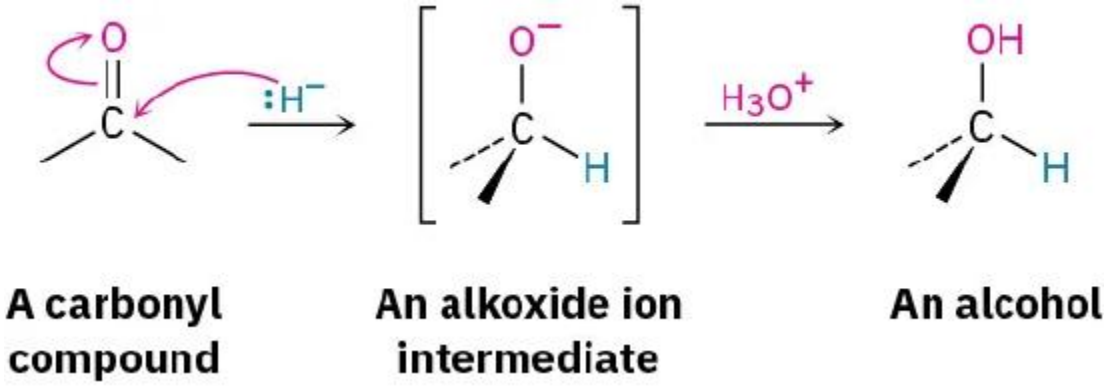
In metal hydride reductions, the resulting alkoxide salts are insoluble and need to be hydrolyzed (with care) before the alcohol product can be isolated. In the sodium borohydride reduction, the methanol solvent system achieves this hydrolysis automatically. In the lithium aluminum hydride reduction, water is usually added in a second step. The lithium, sodium, boron, and aluminum end up as soluble inorganic salts at the end of either reaction. Note! $LiAlH_4$ and $NaBH_4$ are both capable of reducing aldehydes and ketones to the corresponding alcohol.

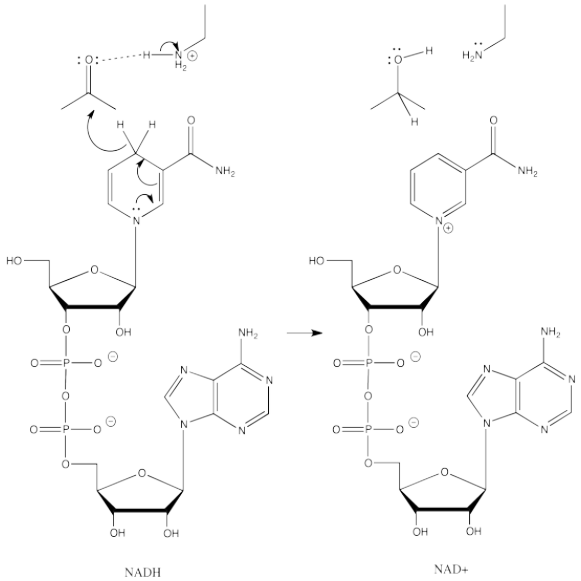
Biological Reduction

Aldehydes, ketones and alcohols are very common features in biological molecules. Converting between these compounds is a frequent event in many biological pathways. However, semi-anionic compounds like sodium borohydride don't exist in the cell. Instead, a number of biological hydride donors play a similar role.

NADH is a common biological reducing agent. NADH is an acronym for nicotinamide adenine dinucleotide hydride. Instead of an anionic donor that provides a hydride to a carbonyl, NADH is actually a neutral donor. It supplies a hydride to the carbonyl under very specific circumstances. In doing so, it forms a cation, NAD^+. However, NAD^+ is stabilized by the fact that its nicotinamide ring is aromatic; the ring is not aromatic in NADH.

We'll defer a detailed discussion of these reductions until next semester. For the moment, we'll note that they involve the addition of a nucleophilic hydride ion ($:H^-$) to the positively polarized, electrophilic carbon atom of the carbonyl group. The initial product is an alkoxide ion, which is protonated by the addition of H_3O^+ in a second step to yield the alcohol product.





In living organisms, aldehyde and ketone reductions are carried out by either of the coenzymes NADH (reduced nicotinamide adenine dinucleotide) or NADPH (reduced nicotinamide adenine dinucleotide phosphate). Although these biological "reagents" are much more complex structurally than $NaBH_4$ or $LiAlH_4$, the mechanisms of laboratory and biological reactions are similar. The coenzyme acts as a hydride-ion donor to give an alkoxide anion, and the intermediate anion is then protonated by acid. An example is the reduction of acetoacetyl ACP to β-hydroxybutyryl ACP, a step in the biological synthesis of fats (Figure 12.3.1). Note that the pro-*R* hydrogen of NADPH is the one transferred in this example. Enzyme-catalyzed reactions usually occur with high specificity, although it's not usually possible to predict the stereochemical result before the fact.

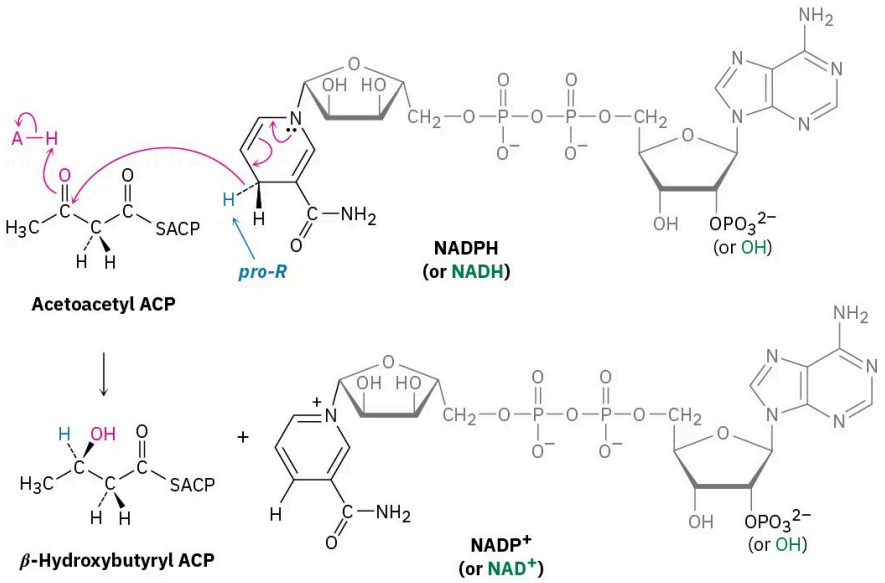
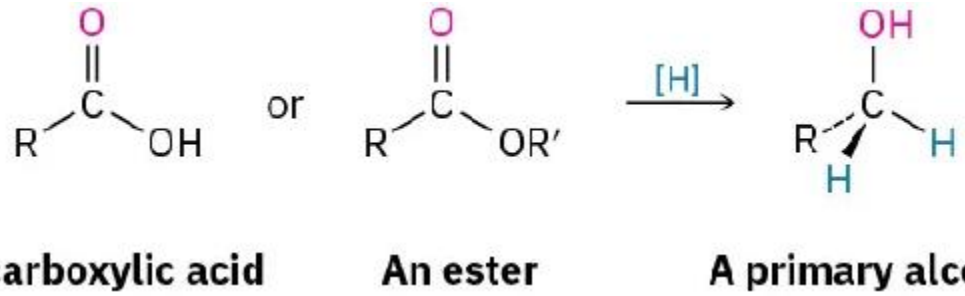


Figure 12.3.1: The biological reduction of a ketone (acetoacetyl ACP) to an alcohol (β-hydroxybutyryl ACP) by NADPH.

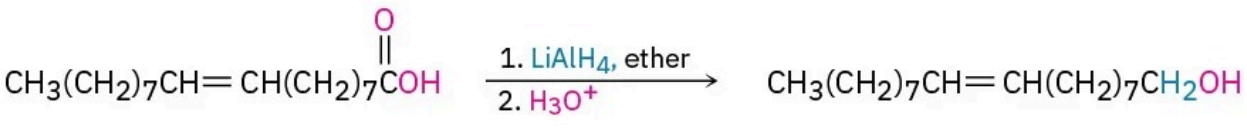
Reduction of Carboxylic Acids and Esters

Carboxylic acids and esters are reduced to give primary alcohols.



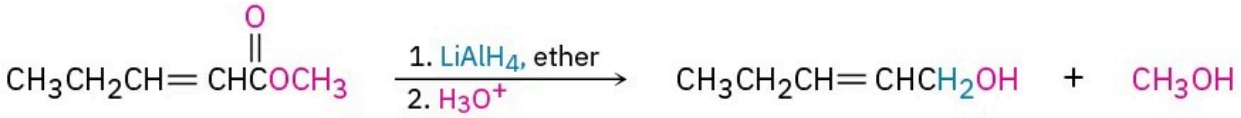
These reactions aren't as rapid as the reductions of aldehydes and ketones. $NaBH_4$ reduces esters very slowly and does not reduce carboxylic acids at all. Instead, carboxylic acid and ester reductions are usually carried out with the more reactive reducing agent $LiAlH_4$. All carbonyl groups, including acids, esters, ketones, and aldehydes, are reduced by $LiAlH_4$. Note that one hydrogen atom is delivered to the carbonyl carbon atom during aldehyde and ketone reductions, but that two hydrogens become bonded to the former carbonyl carbon during carboxylic acid and ester reductions. We'll defer a discussion of the mechanisms of these reactions until next semester.

Carboxylic acid reduction



9-Octadecenoic acid (oleic acid) — **9-Octadecen-1-ol (87%)**

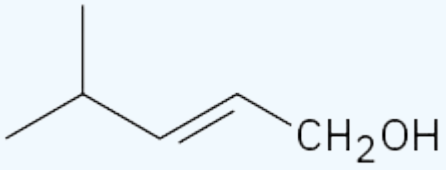
Ester reduction

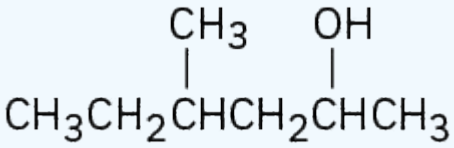


Methyl 2-pentenoate — **2-Penten-1-ol (91%)**

Worked Example 12.3.1: Identifying a Reactant, Given the Product

What carbonyl compounds would you reduce to obtain the following alcohols?

a. 

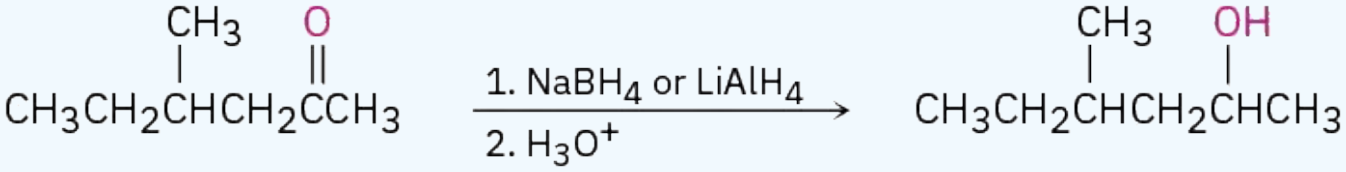
b. 

Strategy

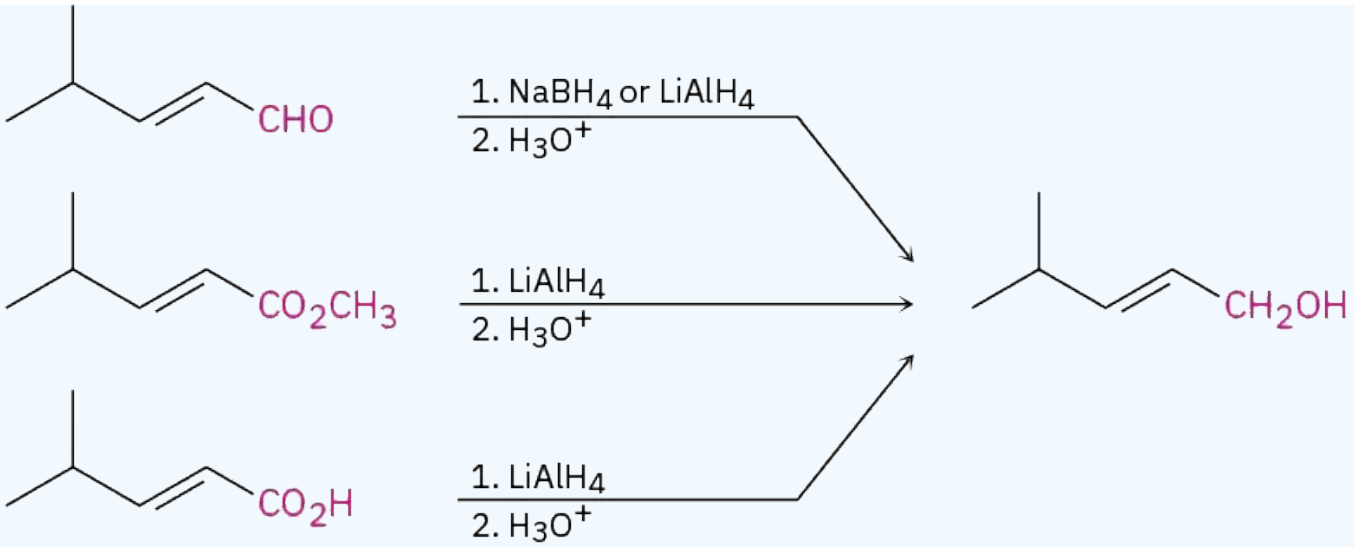
Identify the target alcohol as primary, secondary, or tertiary. A primary alcohol can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid; a secondary alcohol can be prepared by reduction of a ketone; and a tertiary alcohol can't be prepared by reduction.

Solution

a. The target molecule is a secondary alcohol, which can be prepared only by reduction of a ketone. Either $NaBH_4$ or $LiAlH_4$ can be used.



a. The target molecule is a primary alcohol, which can be prepared by reduction of an aldehyde, an ester, or a carboxylic acid. $LiAlH_4$ is needed for the ester and carboxylic acid reductions.



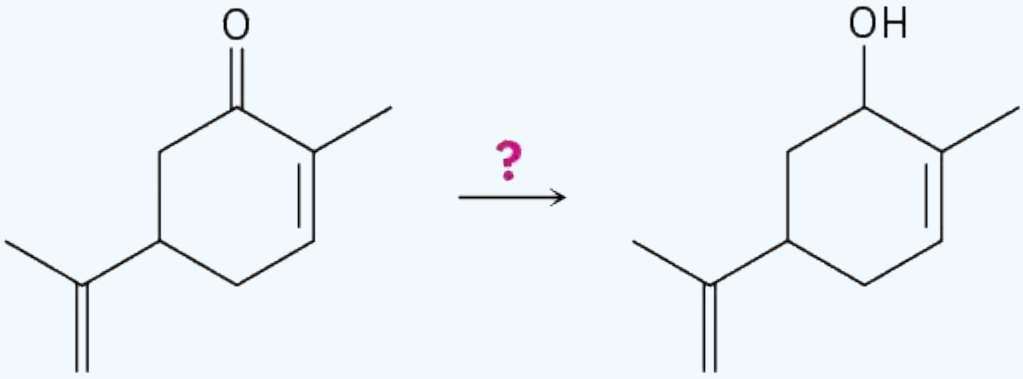
Exercises

Exercise 12.3.1

What reagent would you use to accomplish each of the following reactions?

a. 

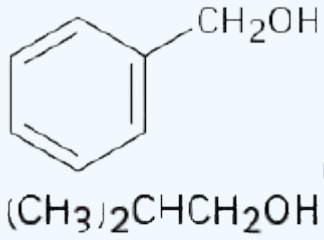
b. 

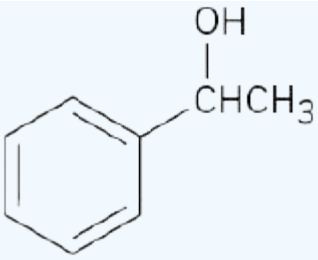
c. 

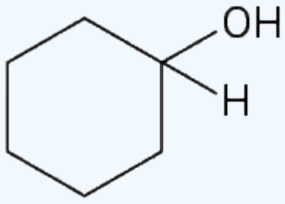
Answer available at the end of this section.

Exercise 12.3.2

What carbonyl compounds give the following alcohols on reduction with $LiAlH_4$? Show all possibilities.

a. 

b. 

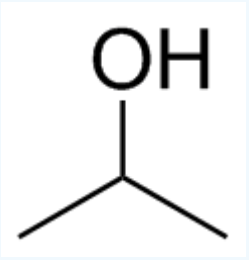
c. 

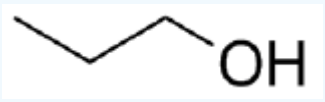
d.

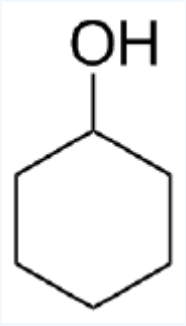
Answer available at the end of this section.

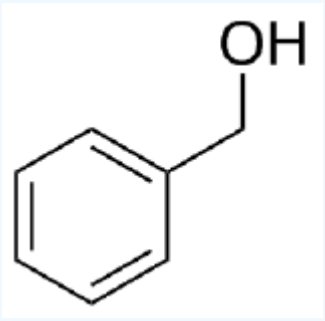
Exercise 12.3.3

Give the aldehyde, ketone, or carboxylic acid (there can be multiple answers) that could be reduced to form the following alcohols.

a) 

b) 

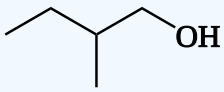
c) 

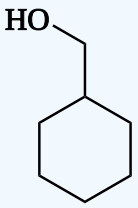
d) 

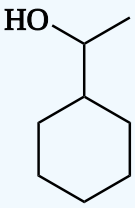
Answer available at the end of this section.

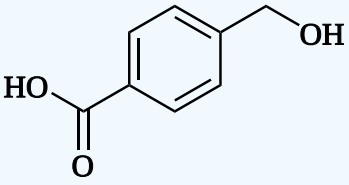
Exercise 12.3.4

Given the following alcohol, draw the structure from which it could be derived using only $NaBH_4$.

A) 

B) 

C) 

D) 

Answer available at the end of this section.

Answers

Exercise 12.3.1

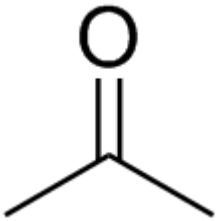
a. $NaBH_4$
b. $LiAlH_4$
c. $LiAlH_4$

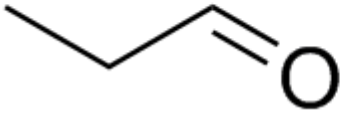
Exercise 12.3.2

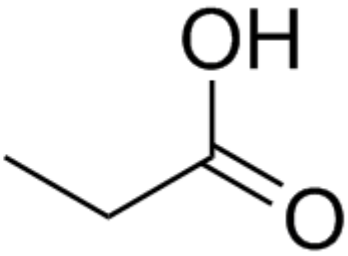
a. Benzaldehyde or benzoic acid (or ester)

b. Acetophenone
c. Cyclohexanone
d. 2-Methylpropanal or 2-methylpropanoic acid (or ester)

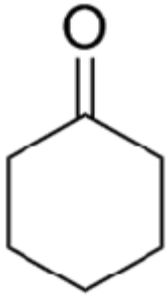
Exercise 12.3.3

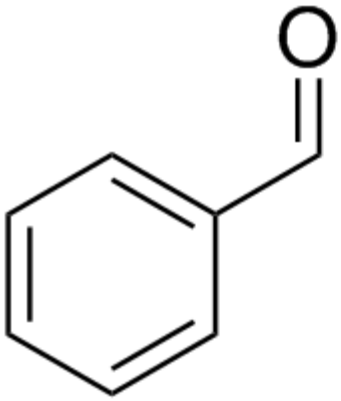
a) 

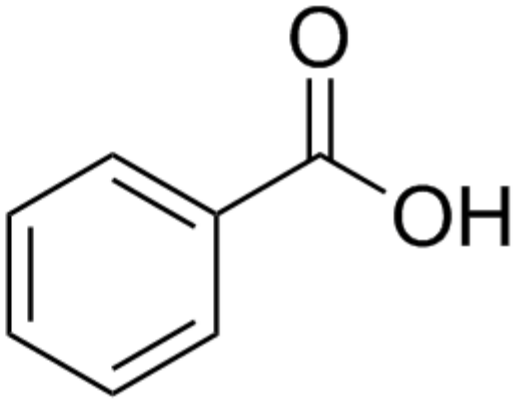
b) 

or 

c)



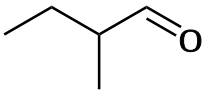


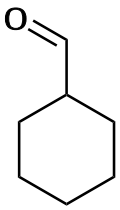
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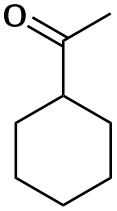
d)

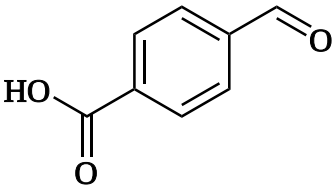
Exercise 12.3.4

Note: $NaBH_4$ is only a strong enough reducing agent to reduce ketones and aldehydes.

A) 

B) 

C) 

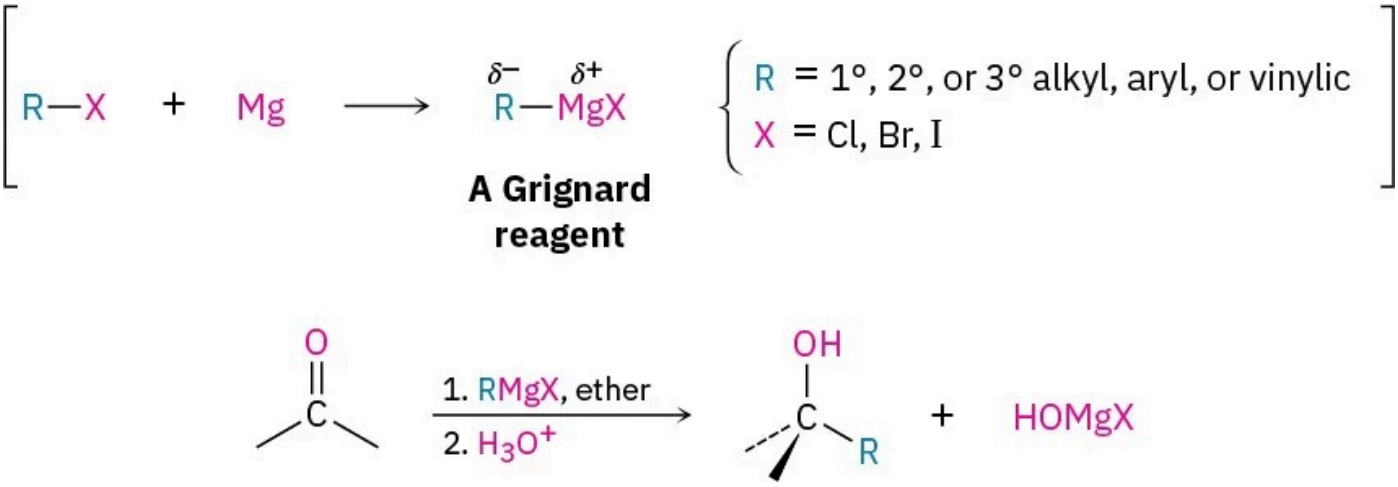
D) 

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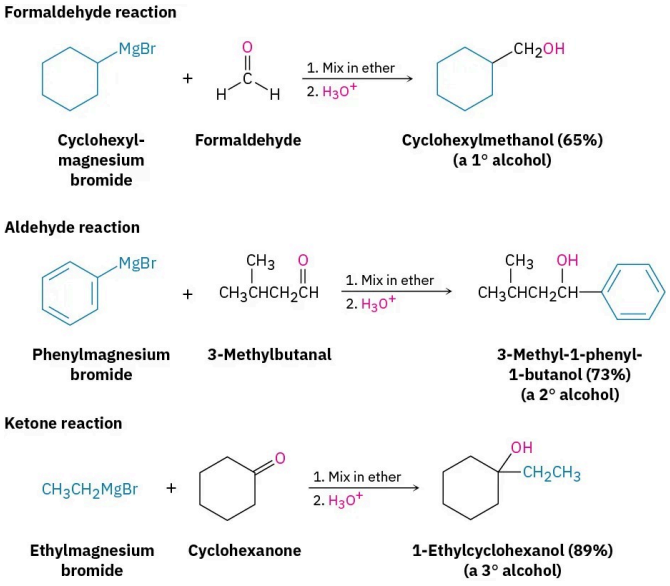
12.4: Alcohols from Carbonyl Compounds - Grignard Reagents

Grignard reagents (RMgX), prepared by reaction of organohalides with magnesium (Section 10.6), react with carbonyl compounds to yield alcohols in much the same way that hydride reducing agents do. Just as carbonyl reduction involves addition of a hydride ion nucleophile to the $C{=}O$ bond, Grignard reaction involves addition of a carbanion nucleophile ($R{:}^{-}{}^{+}MgX$).



The nucleophilic addition reaction of Grignard reagents to carbonyl compounds has no direct counterpart in biological chemistry because organomagnesium compounds are too strongly basic to exist in an aqueous medium. Nevertheless, the reaction is worth understanding for two reasons. First, the reaction is an unusually broad and useful method of alcohol synthesis and demonstrates again the relative freedom with which chemists can operate in the laboratory. Second, the reaction does have an indirect biological counterpart, for we'll see in Chapter 23 that the addition of stabilized carbon nucleophiles to carbonyl compounds is used in almost all metabolic pathways as the major process for forming carbon–carbon bonds.

As examples of their addition to carbonyl compounds, Grignard reagents react with formaldehyde, $H_2C{=}O$, to give primary alcohols, with aldehydes to give secondary alcohols, and with ketones to give tertiary alcohols.



Esters react with Grignard reagents to yield tertiary alcohols in which two of the substituents bonded to the hydroxyl-bearing

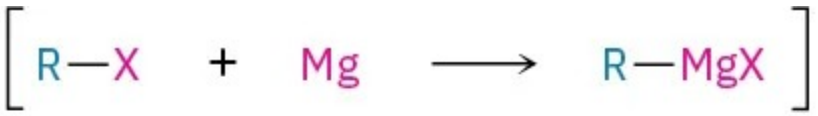
carbon have come from the Grignard reagent, just as $LiAlH_4$ reduction of an ester adds two hydrogens.

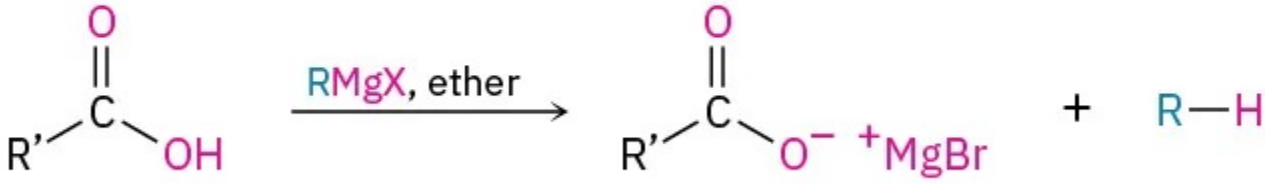


Ethyl pentanoate

2-Methyl-2-hexanol (85%)
(a 3° alcohol)

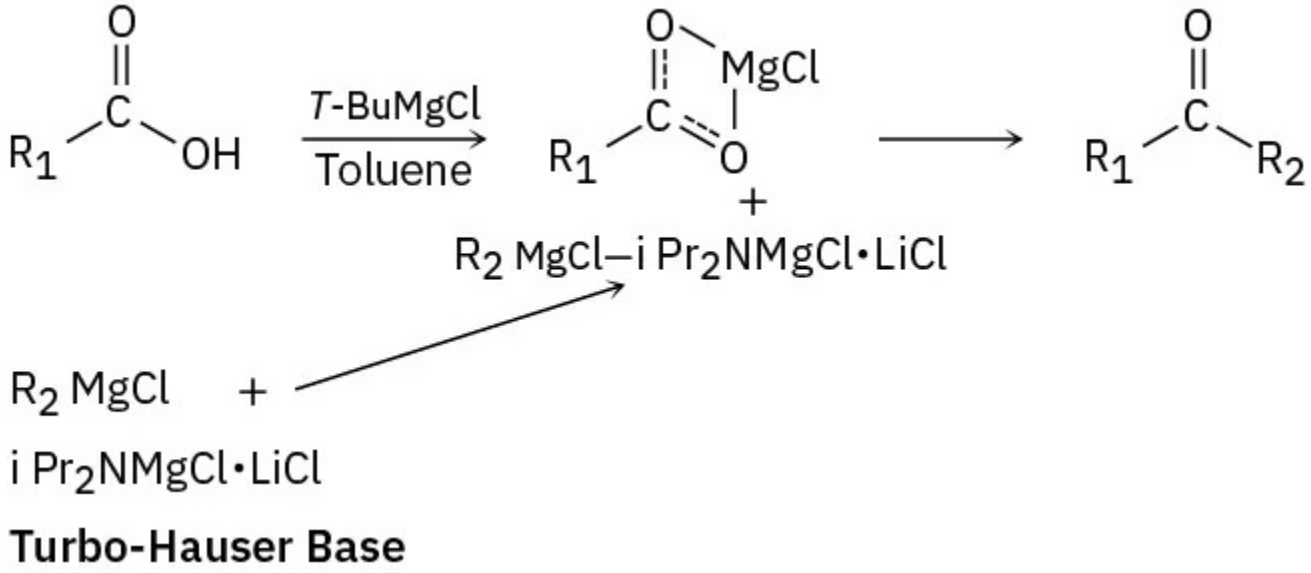
Carboxylic acids don't give addition products when treated directly with Grignard reagents because the acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid.





A carboxylic acid **A carboxylic acid salt**

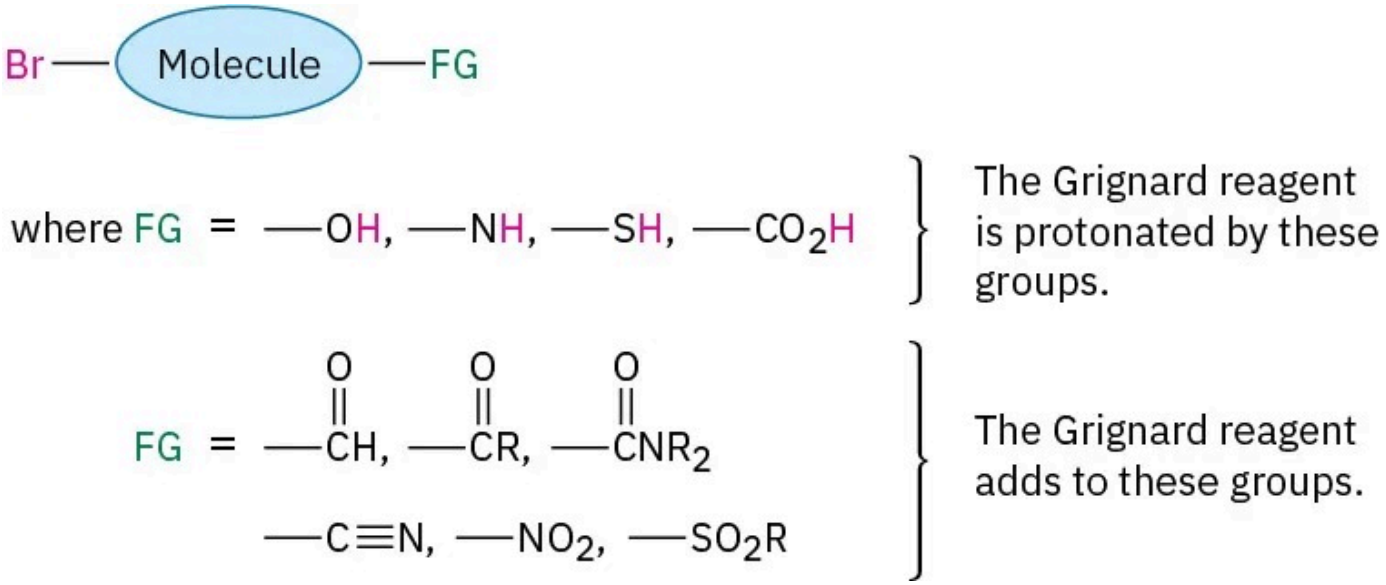
Carboxylic acids do, however, react with Grignard reagents to give ketones if they are first treated with *i*-Pr_2NMgCl-LiCl, called the *turbo*-Hauser base, to form a complex and increase the electrophilicity of the carboxylate anion toward nucleophilic addition with a Grignard reagent.



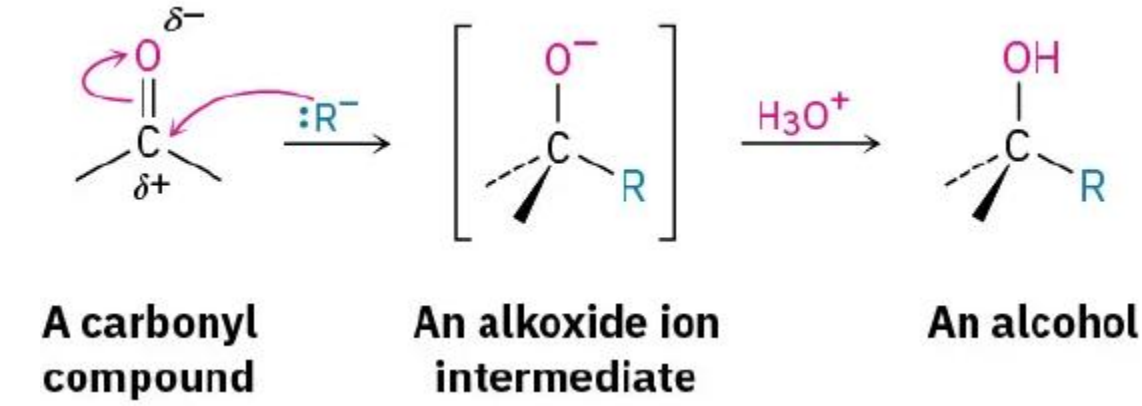
Turbo-Hauser Base

The Grignard reaction, although useful, does have limitations. One major problem is that a Grignard reagent can't be prepared from an organohalide if other reactive functional groups are present in the same molecule. For example, a compound that is both an alkyl halide and a ketone can't form a Grignard reagent because it would react with itself. Similarly, a compound that is both an alkyl halide and a carboxylic acid, alcohol, or amine can't form a Grignard reagent because the acidic $RCO_2\mathbf{H}$, RO**H**, or $RN\mathbf{H_2}$

hydrogen present in the same molecule would react with the basic Grignard reagent as rapidly as it forms. In general, Grignard reagents can't be prepared from alkyl halides that contain the following functional groups (FG):



As with the reduction of carbonyl compounds discussed in the previous section, we'll defer a detailed treatment of the Grignard reactions until Chapter 19. For the moment, it's sufficient to note that Grignard reagents act as nucleophilic carbanions (:R^-) and that their addition to a carbonyl compound is analogous to the addition of hydride ion. The intermediate is an alkoxide ion, which is protonated by addition of H_3O^+ in a second step.



Worked Example 17.3: Using a Grignard Reaction to Synthesize an Alcohol

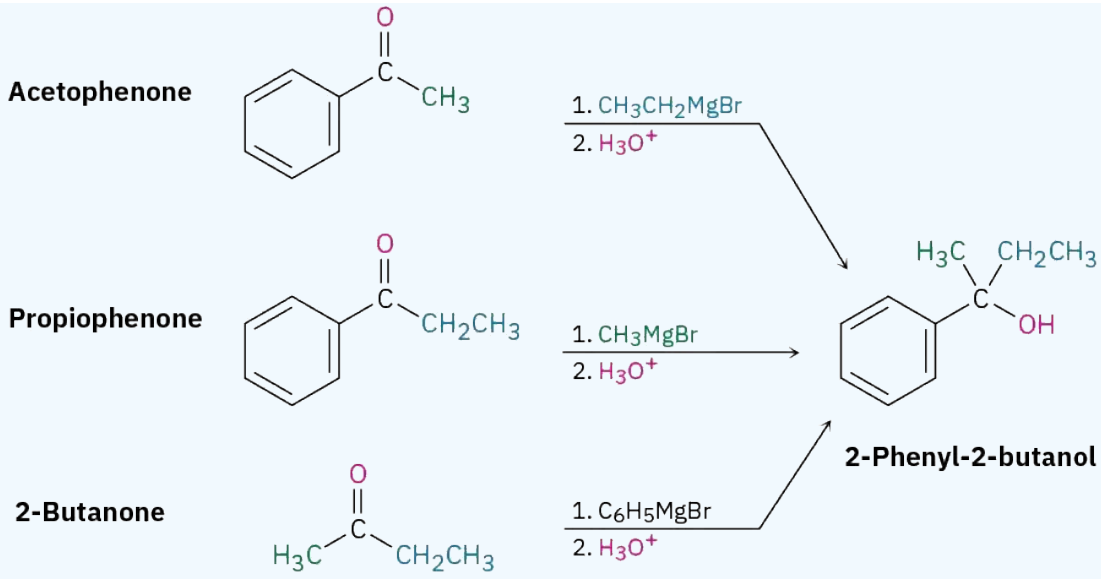
How could you use the addition of a Grignard reagent to a ketone to synthesize 2-phenyl-2-butanol?

Strategy

Draw the product, and identify the three groups bonded to the alcohol carbon atom. One of the three will have come from the Grignard reagent, and the remaining two will have come from the ketone.

Solution

2-Phenyl-2-butanol has a methyl group, an ethyl group, and a phenyl group (–C_6H_5) attached to the alcohol carbon atom. Thus, the possibilities are addition of ethylmagnesium bromide to acetophenone, addition of methylmagnesium bromide to propiophenone, and addition of phenylmagnesium bromide to 2-butanone.



Worked Example 17.4: Using a Grignard Reaction to Synthesize an Alcohol

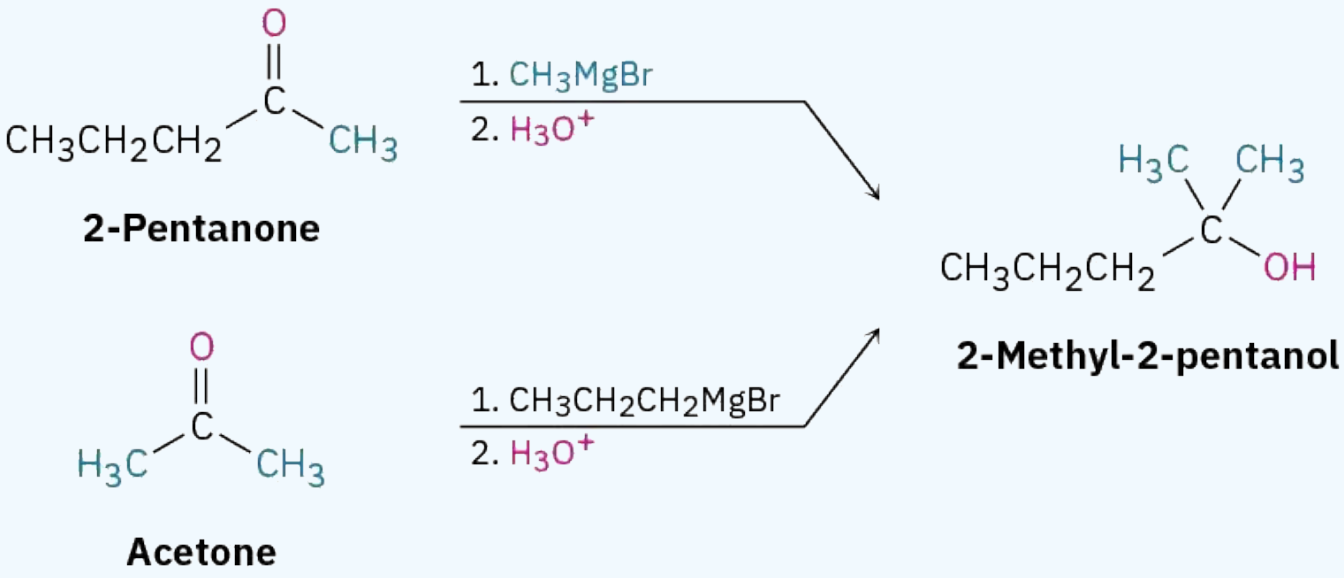
How could you use the reaction of a Grignard reagent with a carbonyl compound to synthesize 2-methyl-2-pentanol?

Strategy

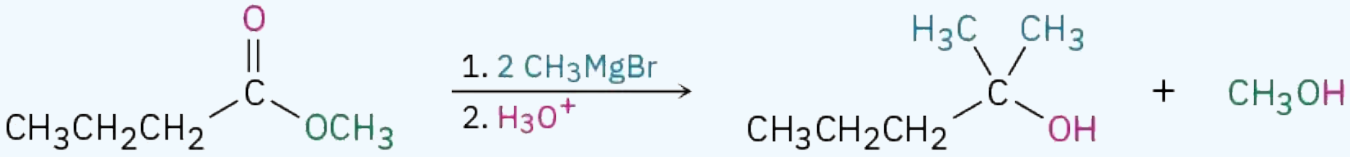
Draw the product, and identify the three groups bonded to the alcohol carbon atom. If the three groups are all different, the starting carbonyl compound must be a ketone. If two of the three groups are identical, the starting carbonyl compound could be either a ketone or an ester.

Solution

In the present instance, the product is a tertiary alcohol with two methyl groups and one propyl group. Starting from a ketone, the possibilities are addition of methylmagnesium bromide to 2-pentanone and addition of propylmagnesium bromide to acetone.



Starting from an ester, the only possibility is addition of methylmagnesium bromide to an ester of butanoic acid, such as methyl butanoate.



Methyl butanoate **2-Methyl-2-pentanol**

Exercise 12.4.1

Show the products obtained from addition of methylmagnesium bromide to the following compounds:

a. Cyclopentanone
b. Benzophenone (diphenyl ketone)
c. 3-Hexanone

Answer available at the end of this section.

Exercise 12.4.2

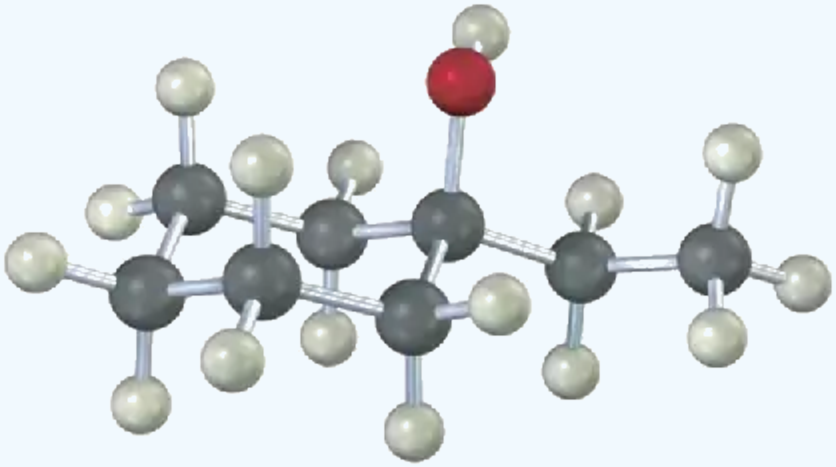
Use a Grignard reaction to prepare the following alcohols:

a. 2-Methyl-2-propanol
b. 1-Methylcyclohexanol
c. 3-Methyl-3-pentanol
d. 2-Phenyl-2-butanol
e. Benzyl alcohol
f. 4-Methyl-1-pentanol

Answer available at the end of this section.

Exercise 12.4.3

Use the reaction of a Grignard reagent with a carbonyl compound to synthesize the following compound:



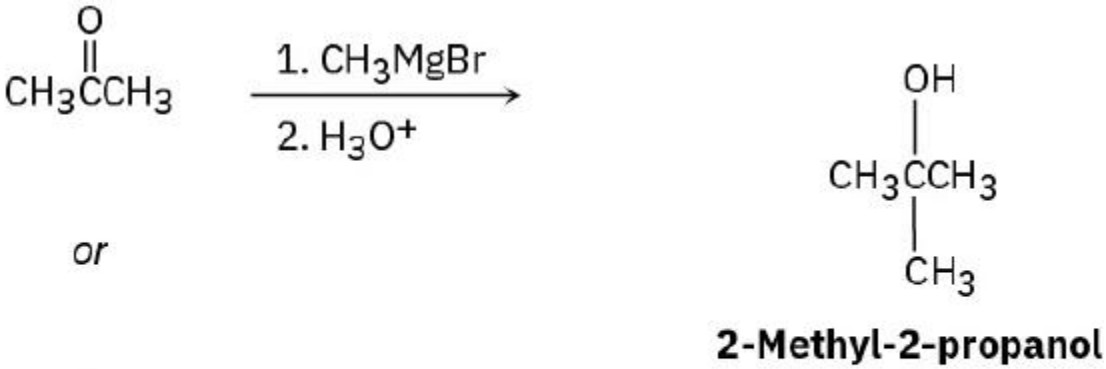
Answer available at the end of this section.

Answers

Exercise 12.4.1

a. 1-Methylcyclopentanol
b. 1,1-Diphenylethanol
c. 3-Methyl-3-hexanol

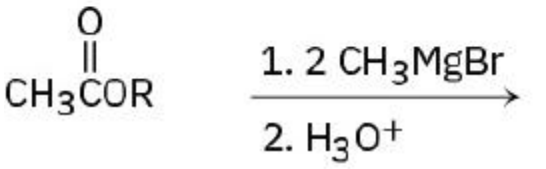
Exercise 12.4.2



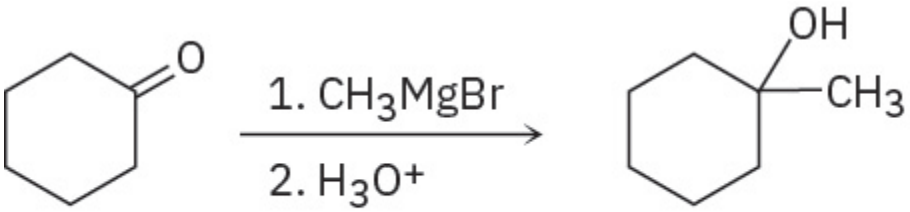
or

2-Methyl-2-propanol

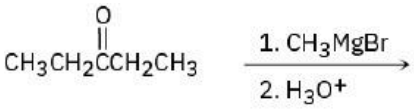
a.



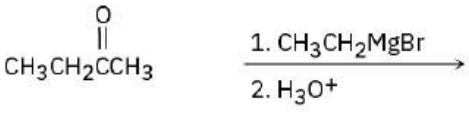
b.

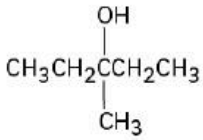


1-Methylcyclohexanol



or

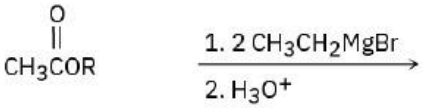


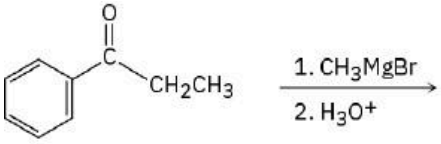


3-Methyl-3-pentanol

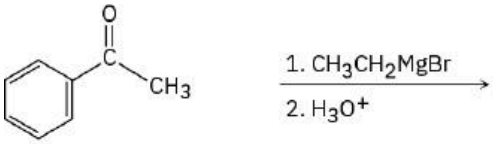
or

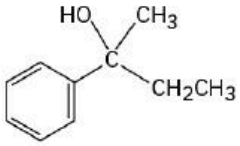
c.





or

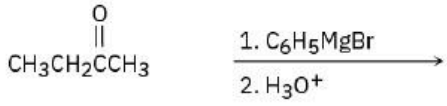




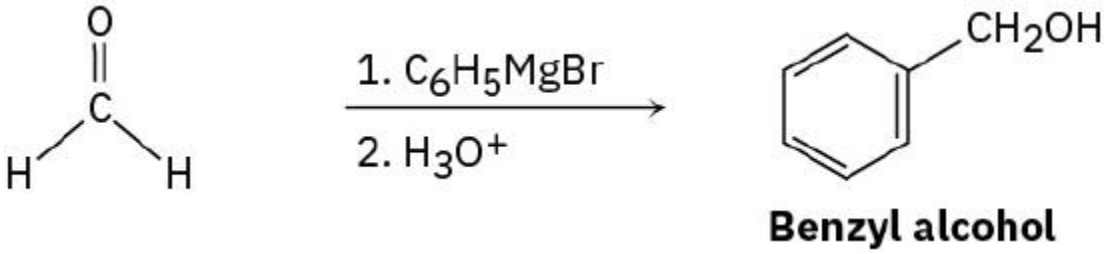
2-Phenyl-2-butanol

or

d.

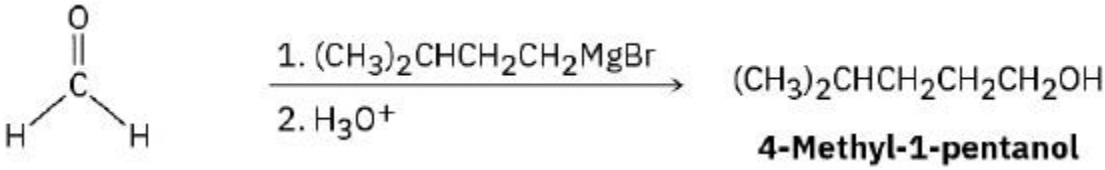


e.



Benzyl alcohol

f.



4-Methyl-1-pentanol

Exercise 12.4.3

Cyclohexanone + CH_3CH_2MgBr

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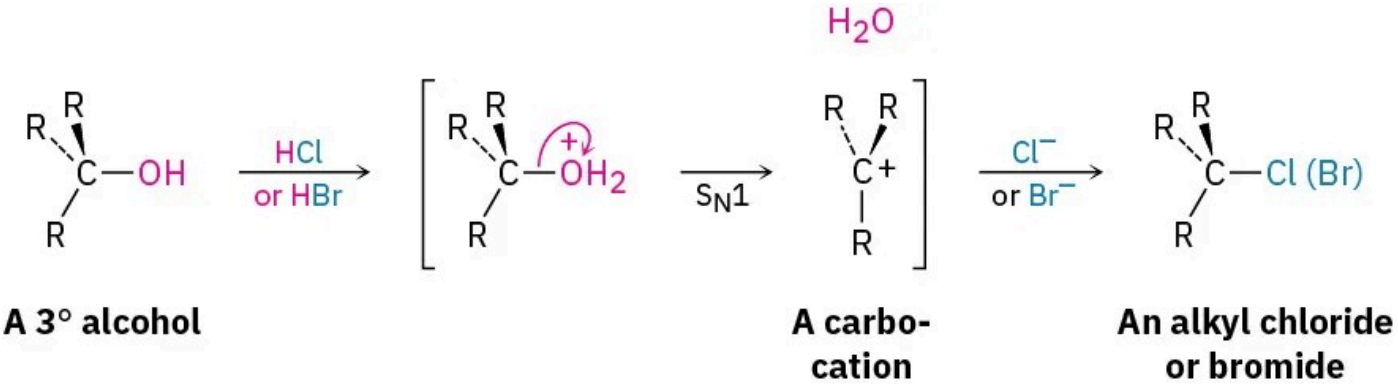
12.5: Reactions of Alcohols

We've already seen several reactions of alcohols—their conversion into alkyl halides and tosylates in Section 10.5 and their dehydration to give alkenes in Section 8.1—albeit without mechanistic details. Let's now look at those details.

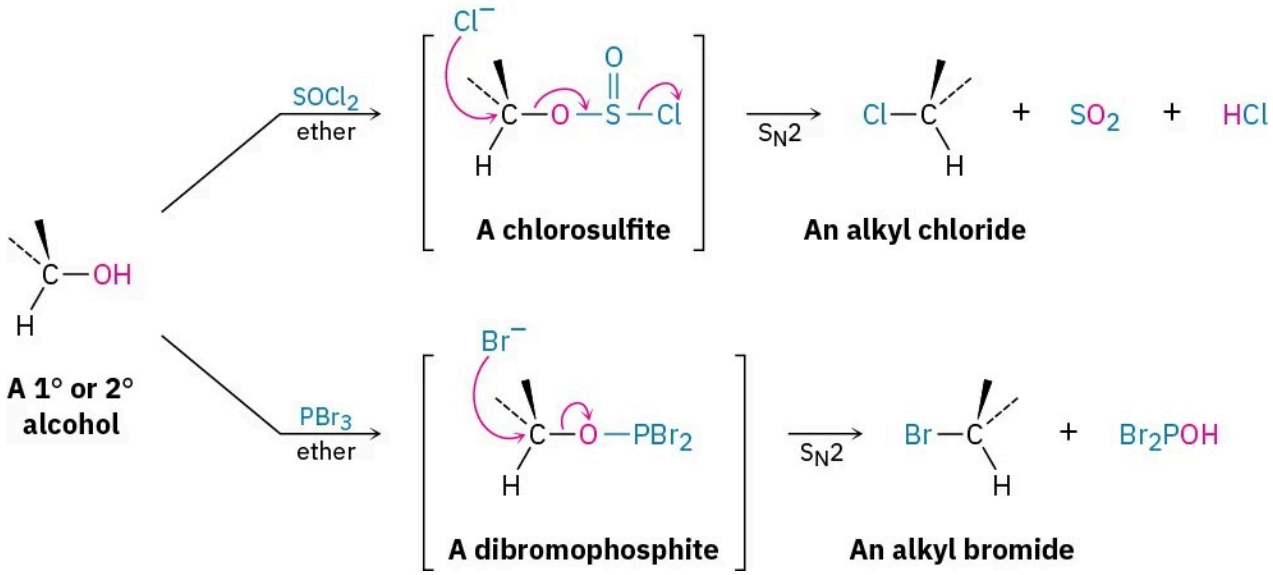
Conversion of Alcohols into Alkyl Halides

Tertiary alcohols react with either HCl or HBr at 0 °C by an S_N1 mechanism through a carbocation intermediate. Primary and secondary alcohols are much more resistant to acid, however, and are best converted into halides by treatment with either $SOCl_2$ or PBr_3 through an S_N2 mechanism.

The reaction of a tertiary alcohol with HX takes place by an S_N1 mechanism when acid protonates the hydroxyl oxygen atom. Water is expelled to generate a carbocation, and the cation reacts with nucleophilic halide ion to give the alkyl halide product.

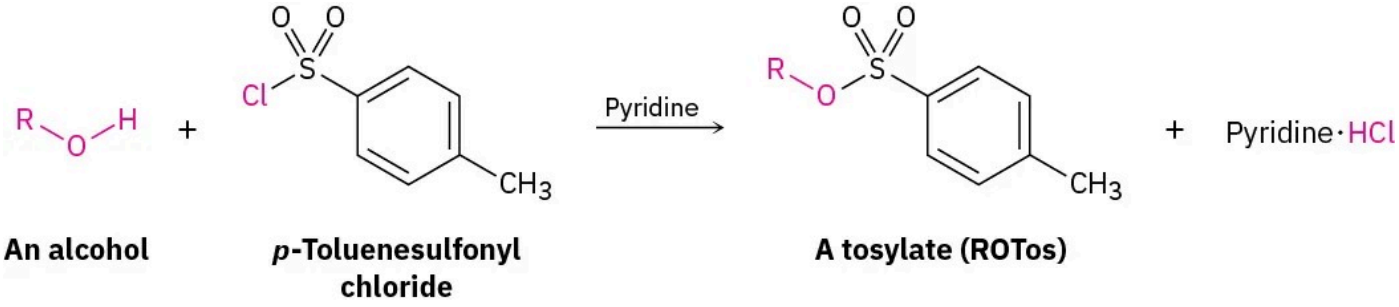


The reactions of primary and secondary alcohols with $SOCl_2$ and PBr_3 take place by S_N2 mechanisms. Hydroxide ion itself is too poor a leaving group to be displaced by nucleophiles in S_N2 reactions, but reaction of an alcohol with $SOCl_2$ or PBr_3 converts the –OH into a much better leaving group, either a chlorosulfite (–OSOCl) or a dibromophosphite ($-OPBr_2$), which is readily expelled by backside nucleophilic substitution.



Conversion of Alcohols into Tosylates

Alcohols react with *p*-toluenesulfonyl chloride (tosyl chloride, *p*-TosCl) in pyridine solution to yield alkyl tosylates, ROTos (Section 11.1). Only the O–H bond of the alcohol is broken in this reaction; the C–O bond remains intact, so no change of configuration occurs if the oxygen is attached to a chirality center. The resultant alkyl tosylates behave much like alkyl halides, undergoing both S_N1 and S_N2 substitution reactions.



One of the most important reasons for using tosylates in S_N2 reactions is stereochemical. The S_N2 reaction of an alcohol with an alkyl halide proceeds with two inversions of configuration—one to make the halide from the alcohol and one to substitute the halide—and yields a product with the same stereochemistry as the starting alcohol. The S_N2 reaction of an alcohol with a tosylate, however, proceeds with only one inversion and yields a product of opposite stereochemistry to the starting alcohol. Figure 12.5.1 shows a series of reactions on the *R* enantiomer of 2-octanol that illustrates these stereochemical relationships.

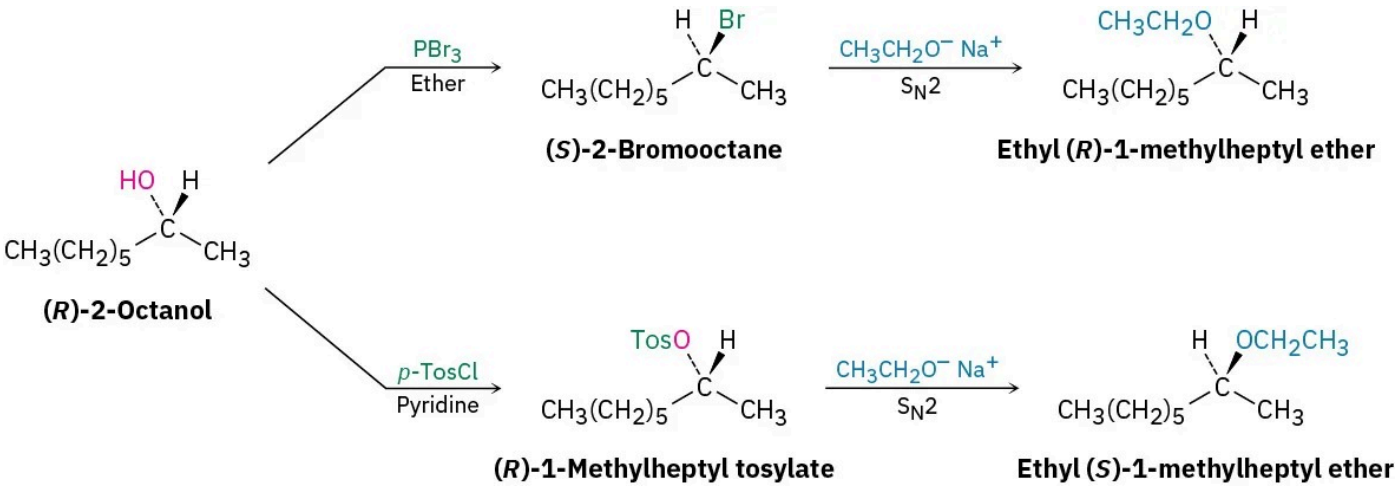
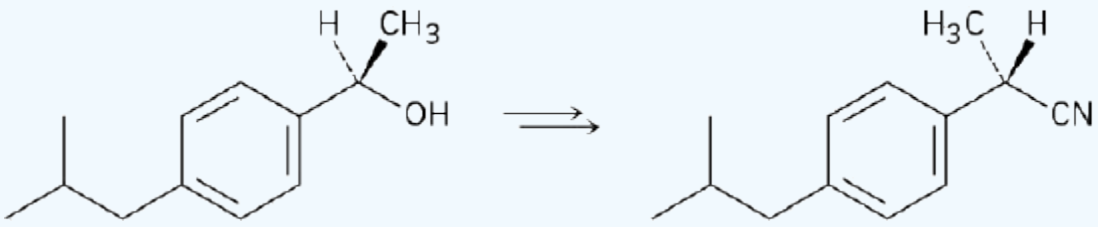


Figure 12.5.1: Stereochemical consequences of S_N2 reactions on derivatives of (*R*)-2-octanol. Substitution through the halide gives a product with the same stereochemistry as the starting alcohol; substitution through the tosylate gives a product with opposite stereochemistry to the starting alcohol.

Exercise 12.5.1

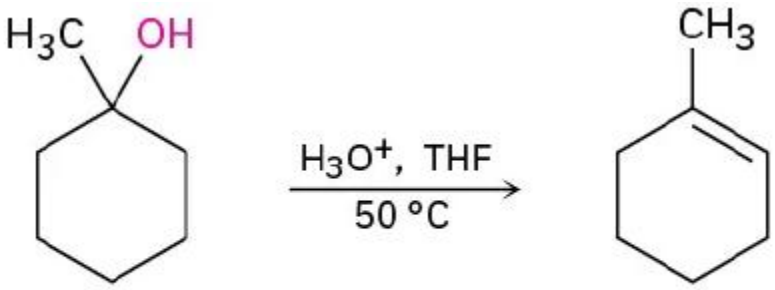
How would you carry out the following transformation, a step used in the commercial synthesis of (S)-ibuprofen?



Answer available at the end of this section.

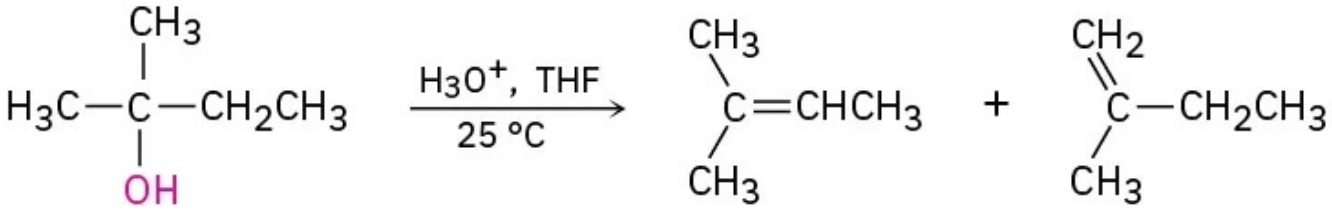
Dehydration of Alcohols to Yield Alkenes

A third important reaction of alcohols, both in the laboratory and in biological pathways, is their dehydration to give alkenes. Because of the usefulness of the reaction, a number of methods have been devised for carrying out dehydrations. One method that works particularly well for tertiary alcohols is the acid-catalyzed reaction discussed in Section 8.1. For example, treatment of 1-methylcyclohexanol with warm, aqueous sulfuric acid in a solvent such as tetrahydrofuran results in loss of water and formation of 1-methylcyclohexene.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**

Acid-catalyzed dehydrations usually follow Zaitsev's rule (Section 11.7) and yield the more stable alkene as the major product. Thus, 2-methyl-2-butanol gives primarily 2-methyl-2-butene (trisubstituted double bond) rather than 2-methyl-1-butene (disubstituted double bond).



2-Methyl-2-butanol

2-Methyl-2-butene (trisubstituted)

Major product

2-Methyl-1-butene (disubstituted)

Minor product

This reaction is an E1 process (Section 11.10) and occurs by the three-step mechanism shown in Figure 12.5.2 on the next page. Protonation of the alcohol oxygen is followed by unimolecular loss of water to generate a carbocation intermediate and final loss of a proton from the neighboring carbon atom to complete the process. As with most E1 reactions, tertiary alcohols react fastest because they lead to stabilized, tertiary carbocation intermediates. Secondary alcohols can be made to react, but the conditions are severe (75% H_2SO_4, 100 °C) and sensitive molecules don't survive.

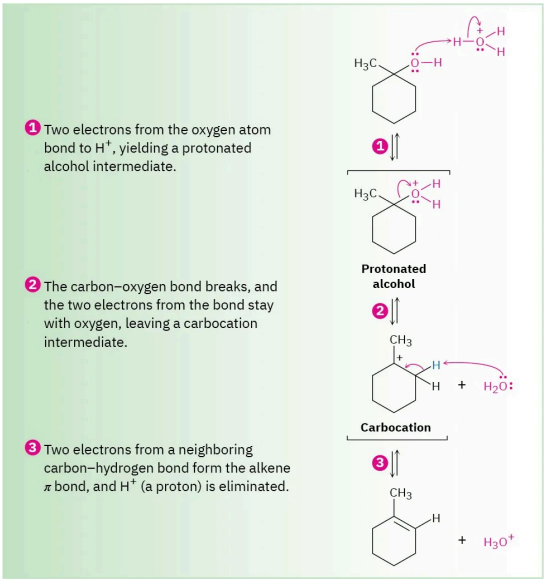
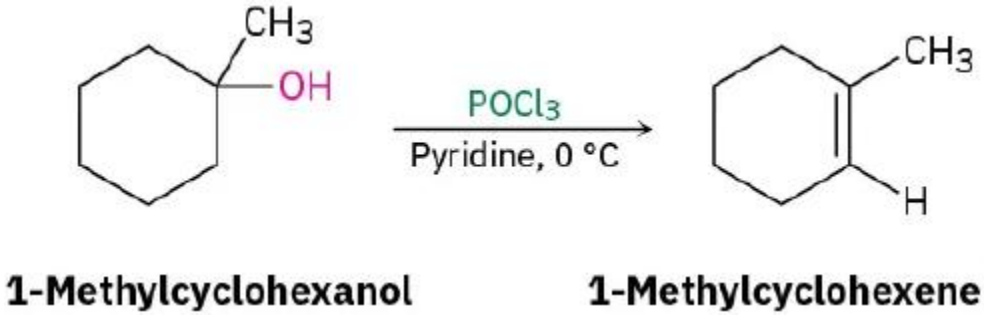


Figure 12.5.2: Mechanism for the acid-catalyzed dehydration of a tertiary alcohol to yield an alkene. The process is an E1 reaction and involves a carbocation intermediate.

To circumvent the need for strong acid and allow the dehydration of secondary alcohols in a gentler way, reagents have been developed that are effective under mild, basic conditions. One such reagent, phosphorus oxychloride ($POCl_3$) in the basic amine solvent pyridine, is often able to effect the dehydration of secondary and tertiary alcohols at 0 °C.



1-Methylcyclohexanol **1-Methylcyclohexene (96%)**

Alcohol dehydrations carried out with $POCl_3$ in pyridine take place by an E2 mechanism, as shown in Figure 12.5.3. Because hydroxide ion is a poor leaving group (Section 11.3), direct E2 elimination of water from an alcohol does not occur. On reaction with $POCl_3$, however, the –OH group is converted into a dichlorophosphate ($–OPOCl_2$), which is a good leaving group and is readily eliminated. Pyridine is both the reaction solvent and the base that removes a neighboring proton in the E2 elimination step.

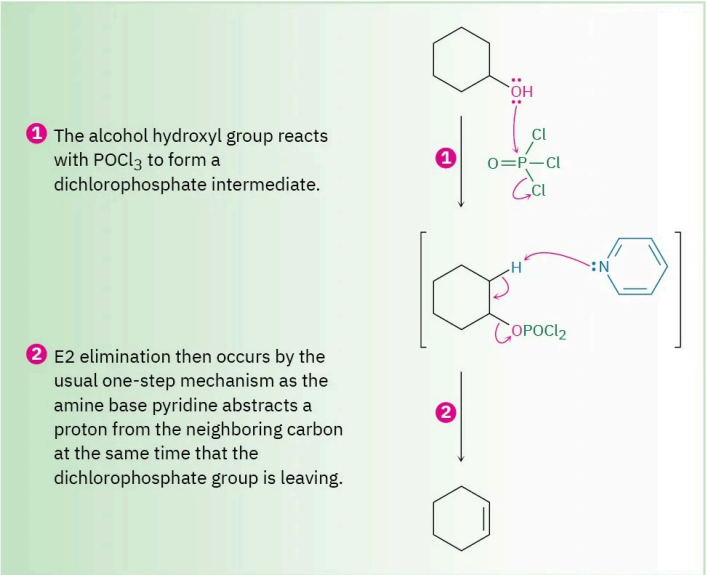
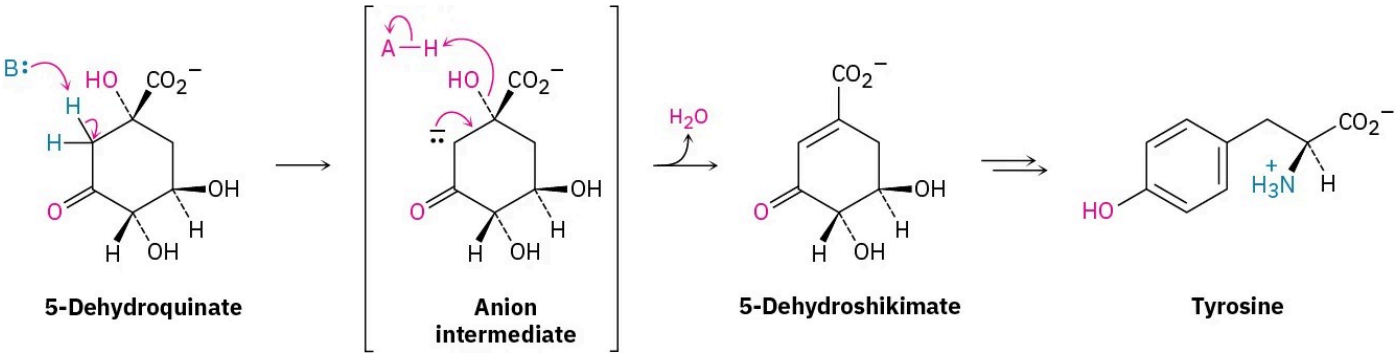


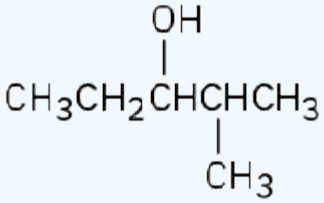
Figure 12.5.3: Mechanism for the dehydration of secondary and tertiary alcohols by reaction with $POCl_3$ in pyridine. The reaction is an E2 process.

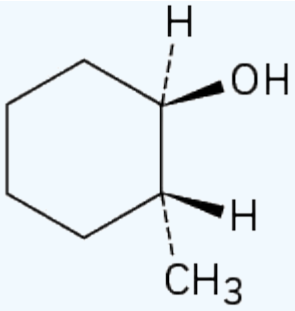
As noted in Section 11.11, biological dehydrations are also common and usually occur by an E1cB mechanism on a substrate in which the –OH group is two carbons away from a carbonyl group. One example occurs in the biosynthesis of the aromatic amino acid tyrosine. A base (:B) first abstracts a proton from the carbon adjacent to the carbonyl group, and the anion intermediate then expels the –OH group with simultaneous protonation by an acid (HA) to form water.

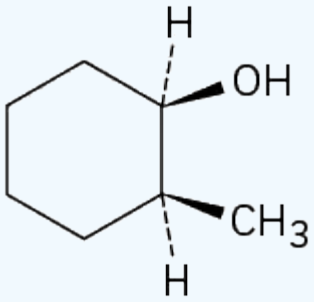


Exercise 12.5.2

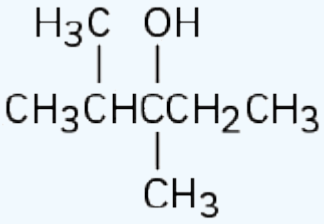
What product(s) would you expect from dehydration of the following alcohols with $POCl_3$ in pyridine? Indicate the major product in each case.

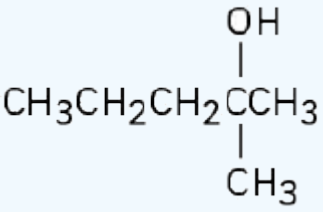
a. 

b. 

c. 

d.

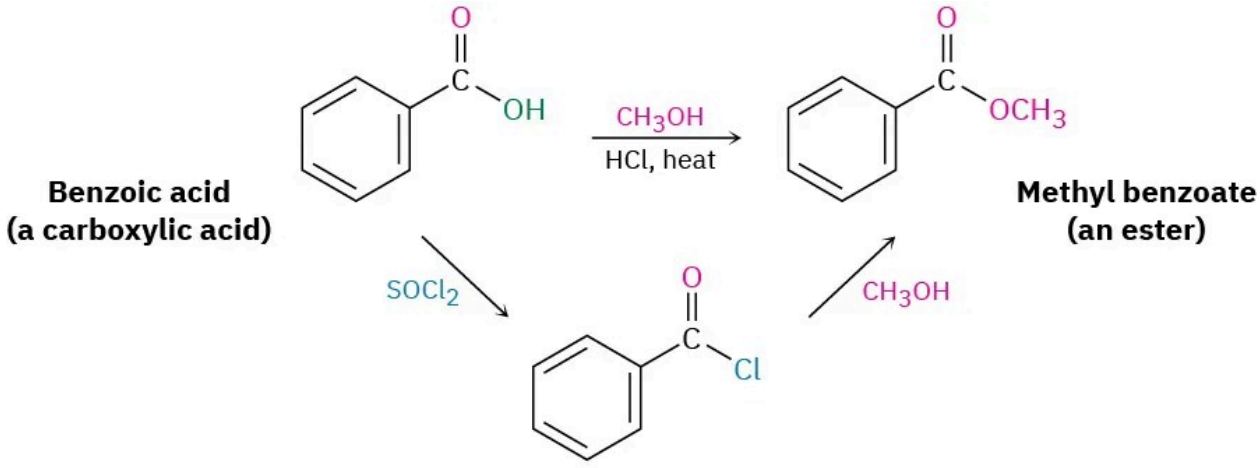


e. 

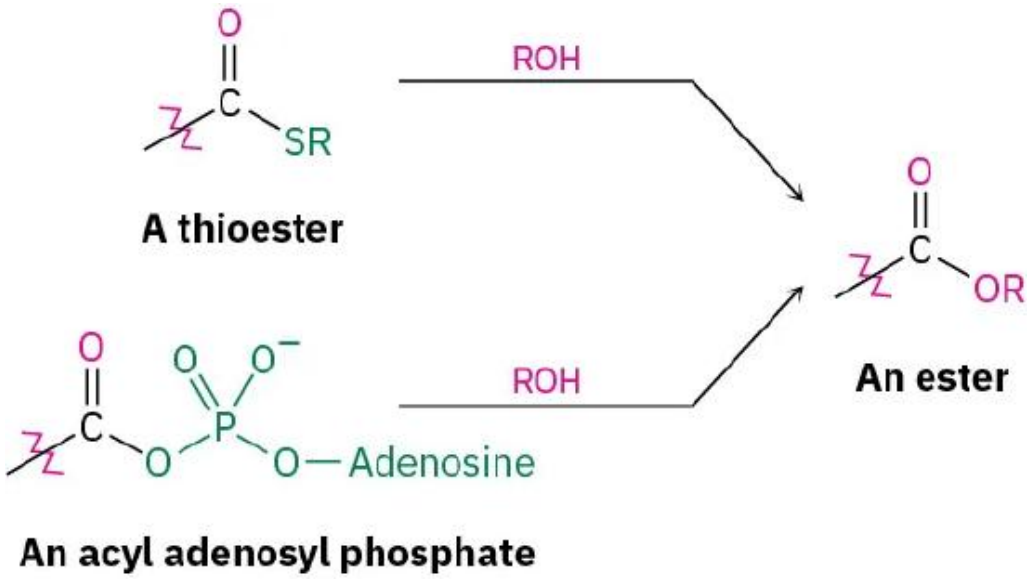
Answer available at the end of this section.

Conversion of Alcohols into Esters

Alcohols react with carboxylic acids to give esters, a reaction that is common in both the laboratory and living organisms. In the laboratory, the reaction can be carried out in a single step if a strong acid is used as catalyst. More frequently, though, the reactivity of the carboxylic acid is enhanced by first converting it into a carboxylic acid chloride, which then reacts with the alcohol.



In living organisms, a similar process occurs, though a thioester or acyl adenosyl phosphate acts as substrate rather than a carboxylic acid chloride. We'll look at the mechanisms of these reactions in Chapter 21.



Answers

Exercise 12.5.1

1. p-TosCl, pyridine; 2. NaCN

Exercise 12.5.2

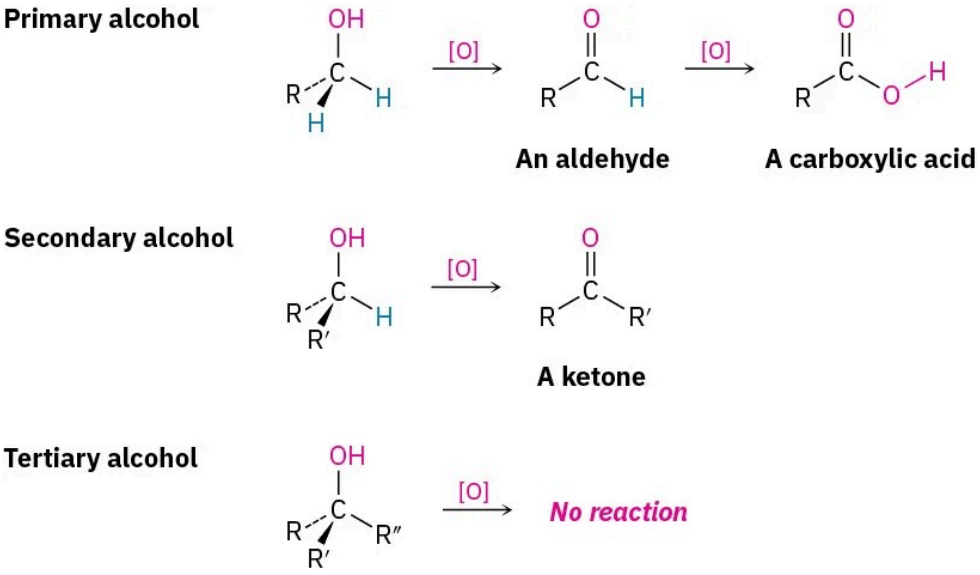
a. 2-Methyl-2-pentene
b. 3-Methylcyclohexene
c. 1-Methylcyclohexene
d. 2,3-Dimethyl-2-pentene
e. 2-Methyl-2-pentene

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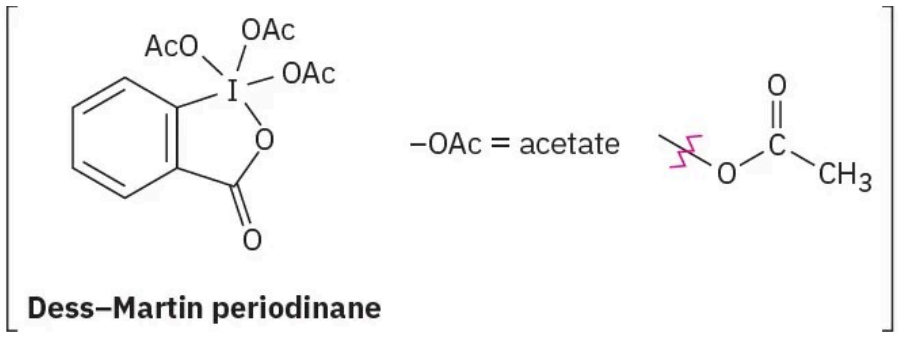
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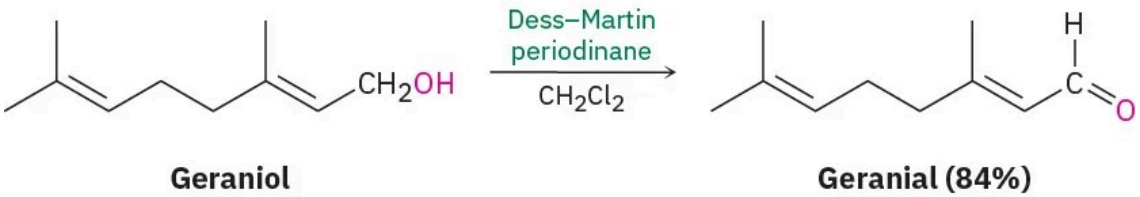
12.6: Oxidation of Alcohols

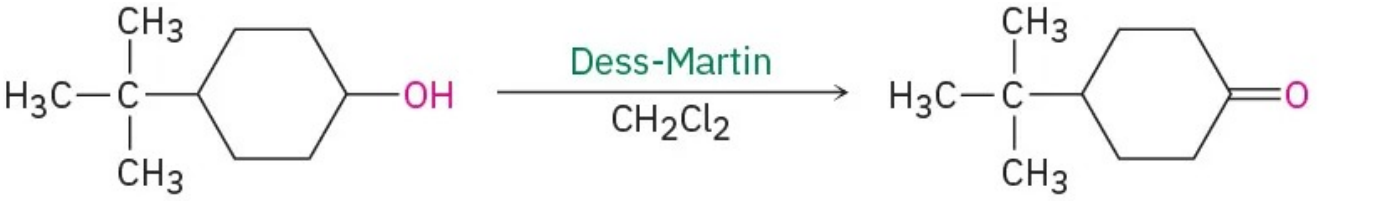
Perhaps the most valuable reaction of alcohols is their oxidation to give carbonyl compounds—the opposite of the reduction of carbonyl compounds to give alcohols. Primary alcohols are oxidized either to aldehydes or carboxylic acids, and secondary alcohols are oxidized to ketones, but tertiary alcohols don't normally react with most oxidizing agents.



Primary and secondary alcohols can be oxidized by any of a number of reagents, including CrO_3 in aqueous acetic acid and $KMnO_4$ in aqueous NaOH, but chromium-based reagents are rarely used today because of their toxicity and fire danger. Today, primary and secondary alcohols are oxidized to aldehydes and ketones, respectively, using the iodine-containing *Dess–Martin periodinane* in dichloromethane solution.

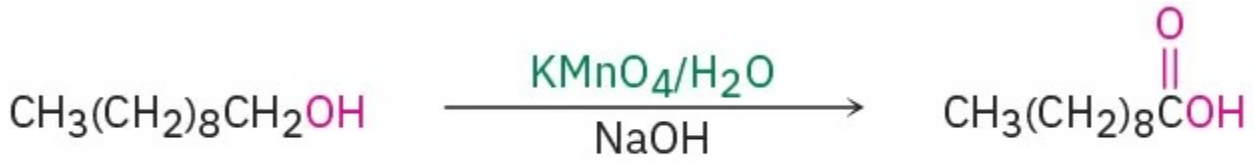






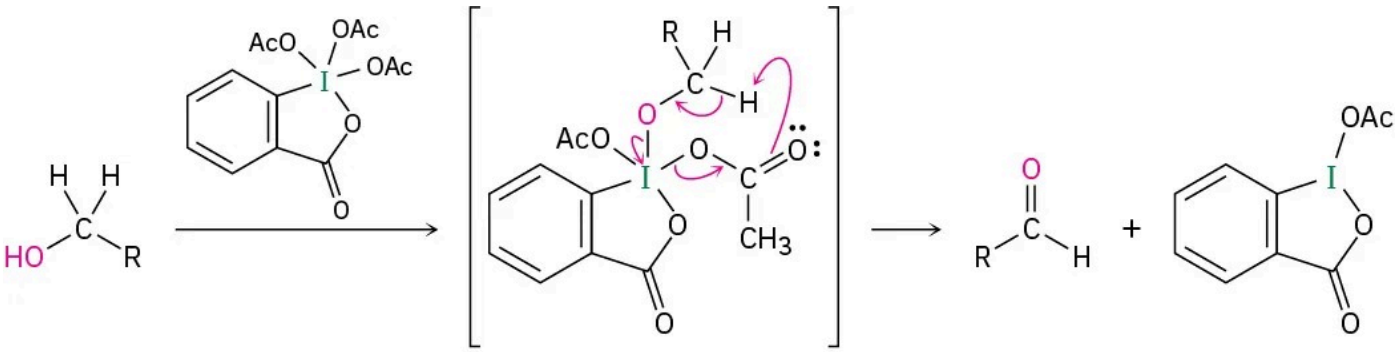
4-*tert*-Butylcyclohexanol **4-*tert*-Butylcyclohexanone (91%)**

Primary alcohols are oxidized to carboxylic acids by heating with $KMnO_4$ in a basic aqueous solution. An aldehyde is involved as an intermediate in the $KMnO_4$ reaction but can't usually be isolated because it is further oxidized too rapidly.

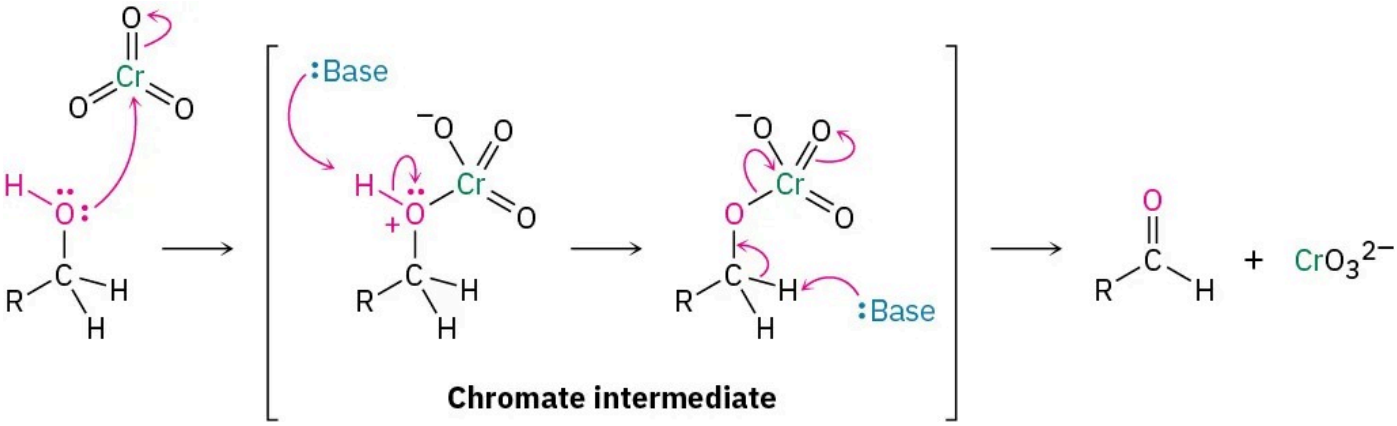


1-Decanol **Decanoic acid (93%)**

All these oxidations occur by a mechanism that is closely related to the E2 reaction (Section 11.8). In the Dess–Martin oxidation, for instance, the first step involves a substitution reaction between the alcohol and the I(V) reagent to form a new periodinane intermediate, followed by expulsion of reduced I(III) as the leaving group. Similarly, when a Cr(VI) reagent, such as CrO_3, is the oxidant, reaction with the alcohol gives a chromate intermediate followed by expulsion of a reduced Cr(VI) species.



Periodinane intermediate



Chromate intermediate

Biological alcohol oxidations are the opposite of biological carbonyl reductions and are facilitated by the coenzymes NAD^+ and

$NADP^+$. A base removes the –OH proton, and the alkoxide ion transfers a hydride ion to the coenzyme. An example is the oxidation of *sn*-glycerol 3-phosphate to dihydroxyacetone phosphate, a step in the biological metabolism of fats (Figure 12.6.1). Note that addition occurs exclusively on the Re face of the NAD^+ ring, adding a hydrogen with pro-*R* stereochemistry.

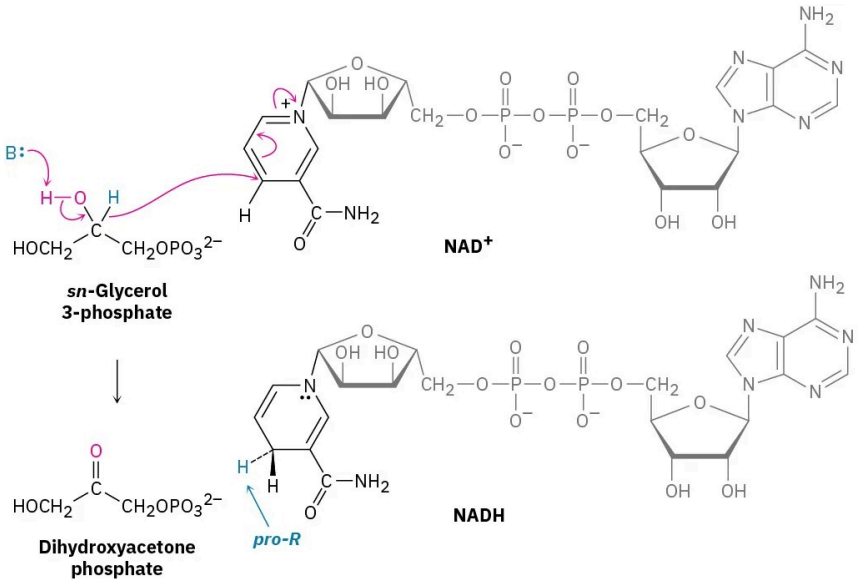
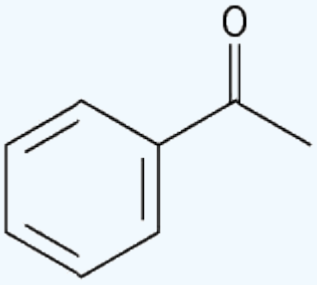


Figure 12.6.1: The biological oxidation of an alcohol (*sn*-glycerol 3-phosphate) to give a ketone (dihydroxyacetone phosphate). This mechanism is the exact opposite of the ketone reduction shown previously in Figure 17.5.

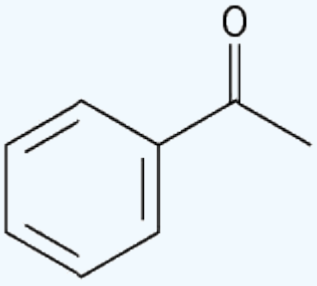
Exercise 12.6.1

What alcohols would give the following products on oxidation?

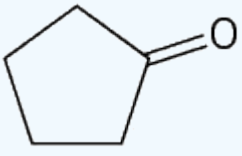
a.



b.



c.



Answer available at the end of this section.

Exercise 12.6.2

What products would you expect from oxidation of the following compounds with the Dess–Martin periodinane?

a. 1-Hexanol
b. 2-Hexanol
c. Hexanal

Answer available at the end of this section.

Answers

Exercise 12.6.1

a. 1-Phenylethanol
b. 2-Methyl-1-propanol
c. Cyclopentanol

Exercise 12.6.2

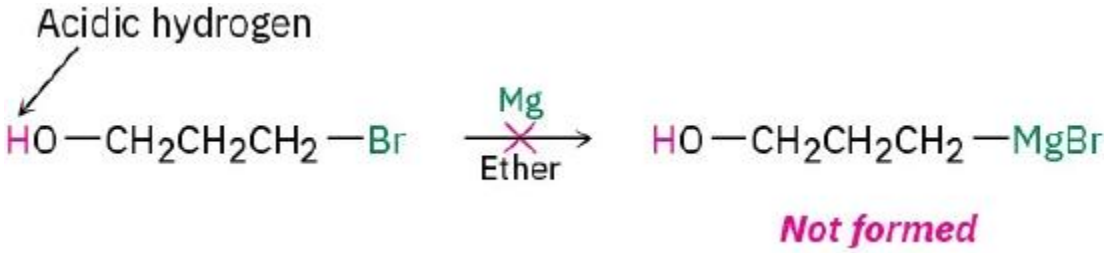
a. Hexanoic acid, hexanal
b. 2-Hexanone
c. Hexanoic acid, no reaction

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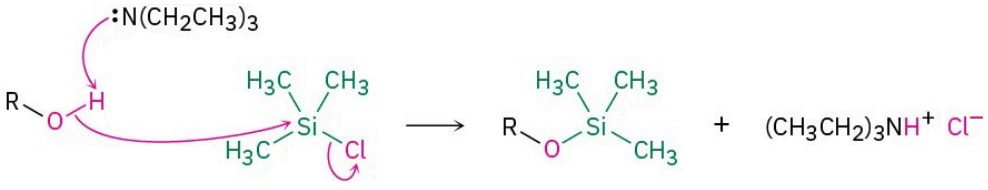
12.7: Protection of Alcohols

It often happens, particularly during the synthesis of complex molecules, that one functional group in a molecule interferes with an intended reaction on another functional group elsewhere in the same molecule. We saw earlier in this chapter, for instance, that a Grignard reagent can't be prepared from an alcohol-containing halidel because the C–Mg bond is not compatible with the presence of an acidic –OH group in the same molecule.



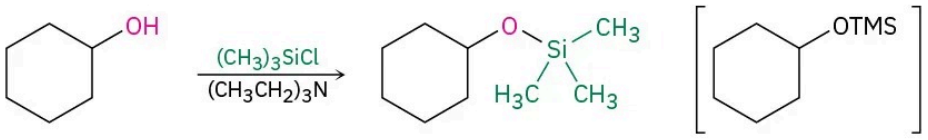
When this kind of incompatibility arises, it's sometimes possible to circumvent the problem by *protecting* the interfering functional group. Protection involves three steps: (**1**) introducing a protecting group to block the interfering function, (**2**) carrying out the desired reaction, and (**3**) removing the protecting group.

One of the more common methods of alcohol protection involves reaction with a chlorotrialkylsilane, Cl–SiR_3, to yield a trialkylsilyl ether, R′–O–SiR_3. (Chloro-*tert*-butyldimethylsilane), usually abbreviated either TBS or TBDMS is often used, as is chlorotrimethylsilane (TMS), and the reaction is carried out in the presence of a base, such as triethylamine, to help form the alkoxide anion from the alcohol and to remove the HCl by-product from the reaction.



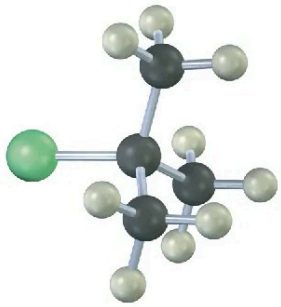
An alcohol | **Chlorotrimethyl-silane** | **A trimethylsilyl (TMS) ether**

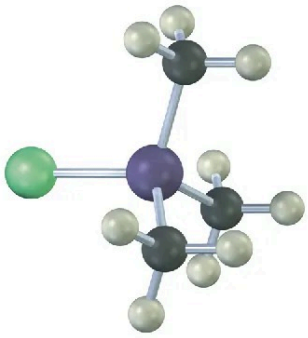
For example:

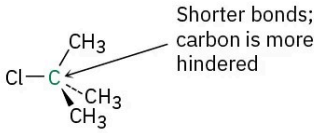


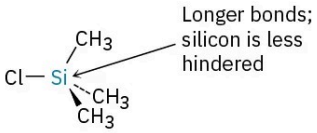
Cyclohexanol | **Cyclohexyl trimethylsilyl ether (94%)**

The ether-forming step is an S_N2-like reaction of the alkoxide ion on the silicon atom, with concurrent loss of the leaving chloride anion. Unlike most S_N2 reactions, though, this reaction takes place at a *tertiary* center—a trialkyl-substituted silicon atom. The reaction occurs because silicon, a third-row atom, is larger than carbon and forms longer bonds. In addition, three alkyl substituents attached to silicon offer little steric hindrance to ether formation.



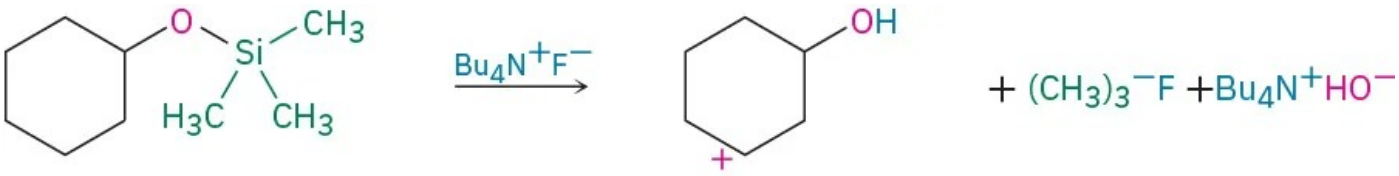






C–C bond length: 154 pm **C–Si bond length: 195 pm**

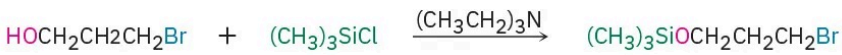
Like most other ethers, which we'll study in the next chapter, trialkylsilylethers are relatively unreactive. They have no acidic hydrogens and don't react with oxidizing agents, reducing agents, or Grignard reagents. They do, however, react with aqueous acid or with fluoride ion to regenerate the alcohol. Tetrabutylammonium fluoride is often used.



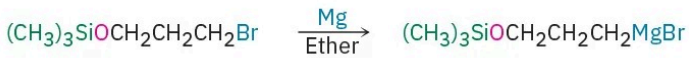
Cyclohexyl trimethylsilyl ether **Cyclohexanol**

To solve the problem posed at the beginning of this section, note that it's possible to use an alcohol-containing halide in a Grignard reaction by employing a protection sequence. For example, we can add 3-bromo-1-propanol to acetaldehyde by the route shown in Figure 12.7.1.

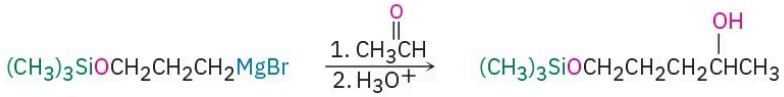
Step 1 Protect alcohol:



Step 2a Form Grignard reagent:



Step 2b Do Grignard reaction:



Step 3 Remove protecting group:



Figure 12.7.1: Use of a trialkylsilyl-protected alcohol during a Grignard reaction.

Exercise 12.7.1

Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF to deprotect the silyl ether.

Answer available at the end of this section.

Answers

Exercise 12.7.1

S_N2 reaction of F^- on silicon with displacement of alkoxide ion.

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12.8: Chemistry Matters—Ethanol- Chemical, Drug, and Poison

The production of ethanol by fermentation of grains and sugars is one of the oldest known organic reactions, going back at least 8000 years in the Middle East and perhaps as many as 9000 years in China. Fermentation is carried out by adding yeast to an aqueous sugar solution, where enzymes break down carbohydrates into ethanol and CO_2. As noted in the chapter introduction, approximately 26 billion gallons of ethanol is produced each year by fermentation of corn and sugar, with essentially the entire amount used to make bus and automobile fuel.

$$C_6H_{12}O_6 \xrightarrow{\text{Yeast}} 2\,CH_3CH_2OH + 2\,CO_2$$

A carbohydrate

Ethanol is classified medically as a central nervous system (CNS) depressant. Its effects—that is, being drunk—resemble the human response to anesthetics. There is an initial excitability and increase in sociable behavior, but this results from depression of inhibition rather than from stimulation. At a blood alcohol concentration of 0.1% to 0.3%, motor coordination is affected, accompanied by loss of balance, slurred speech, and amnesia. When blood alcohol concentration rises to between 0.3% and 0.4%, nausea and loss of consciousness occur. Above 0.6%, spontaneous respiration and cardiovascular regulation are affected, ultimately leading to death. The LD_{50} of ethanol is 10.6 g/kg (Chapter 1 *Chemistry Matters*).

The passage of ethanol through the body begins with its absorption in the stomach and small intestine, followed by rapid distribution to all body fluids and organs. In the pituitary gland, ethanol inhibits the production of a hormone that regulates urine flow, causing increased urine production and dehydration. In the stomach, ethanol stimulates production of acid. Throughout the body, ethanol causes blood vessels to dilate, resulting in flushing of the skin and a sensation of warmth as blood moves into capillaries beneath the surface. The result is not a warming of the body, but an increased loss of heat at the surface.



Figure 12.8.1: The Harger Drunkometer was the first breath analyzer, introduced in 1938 to help convict drunk drivers. (credit: "Unidentified police officer with a Harger "Drunkometer" breathalyzer" by Florida Memory, State Library and Archives of Florida/Wikimedia Commons, Public Doman)

Ethanol metabolism occurs mainly in the liver and proceeds by oxidation in two steps, first to acetaldehyde (CH_3CHO) and then to acetic acid (CH_3CO_2H). When continuously present in the body, ethanol and acetaldehyde are toxic, leading to the devastating physical and metabolic deterioration seen in people with chronic alcohol use disorder. The liver usually suffers the worst damage

since it is the major site of alcohol metabolism.

Approximately 17,000 people are killed each year in the United States in alcohol-related automobile accidents. Thus, all 50 states have made it illegal to drive with a blood alcohol concentration (BAC) above 0.08%. Fortunately, simple tests have been devised for measuring blood alcohol concentration. The original breath analyzer test measured alcohol concentration in expired air by the color change occurring when the bright-orange oxidizing agent potassium dichromate ($K_2Cr_2O_7$) reduced to blue-green chromium(III). Current consumer devices use a conductivity sensor, and tests used by law-enforcement agencies use IR spectroscopy to measure blood-alcohol levels in expired air. Just breathe into the machine, and let the spectrum tell the tale.

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12.A: Alcohols (Summary)

Concepts & Vocabulary

12.0 Introduction

- Alcohols have hydroxide groups (OH) bonded to an sp^3 carbon.
- Enols have a hydroxide bonded to an sp^2 carbon that is not part of an aromatic ring, a vinyl carbon.
- Phenols have a hydroxide bonded to an sp^2 carbon that is part of an aromatic ring, an aryl carbon.

12.1 Naming Alcohols and Phenols

- Alcohols can be described as methyl, primary, secondary or tertiary, based on the number of alkyl groups attached to the carbon bonded to OH.
- Alcohols are named following IUPAC rules, by dropping the -e of an alkane and replacing with -ol.

12.2 Properties of Alcohols and Phenols

- Alcohols, enols and phenols all have significantly higher boiling points than alkanes, due to hydrogen bonding.
- Small alcohols are soluble in water.
- Alcohols are amphoteric, they act as an acid when reacting with bases and as a base when reacting with acids.
- Phenols are more acidic than alcohols due to resonance delocalization of the negative charge in the phenoxide conjugate base.
- Substituent groups on an aromatic ring that withdraw electron density increase the acidity of phenols, while substituent groups that donate electron density decrease acidity of phenols.

12.3 Preparation of Alcohols: A Review

- Alcohols can be prepared from alkyl halides by reacting with hydroxide.
- Alcohols can be prepared from alkenes by reaction with acid/water or oxymercuration to form the more substituted alcohol.
- Alcohols can be prepared from alkenes by hydroboration/oxidation to form the less substituted alcohol.
- Diols can be prepared from alkenes by first forming an epoxide, then ring opening the epoxide to form an anti-diol.
- Diols can be prepared from alkenes by reacting with osmium tetraoxide, then reducing off the osmium to form syn-diols.

12.4 Alcohols from Carbonyl Compounds: Reduction

- Organic reduction can be defined by increasing the number of bonds to hydrogen.
- Aldehydes and ketones can be reduced to alcohols with several different hydride donor reagents.
- NADH is an example of a biological reducing agent, which donates a hydride to carbonyl groups, reducing them to an alcohol.
- Carboxylic acids and esters can be reduced to alcohols with a strong reducing agent such as lithium aluminum hydride $LiAlH_4$.

12.5 Alcohols from Carbonyl Compounds: Grignard Reaction

- One of the most important organometallic groups of molecules are Grignard reagents, which are alkyl magnesium halides.
- Grignard reagents, like other organometallic compounds, include a nucleophilic alkyl group that can react with many different electrophiles.
- Grignard reagents will add to aldehydes and ketones forming alcohol products.
- Grignard reagents will add twice to ester molecules, forming alcohol products.
- Grignard reagents are strong bases, therefore the will not undergo nucleophilic addition reactions with molecules that have protons that are even slightly acidic such as: alcohols, carboxylic acids, alkynes, and amines or amides that have an N-H bond.

12.6 Reactions of Alcohols

- Alcohols can be converted into alkyl halides directly by reaction with strong hydrogen halides. This works best for 3^{o} alcohols.
- Conversion of 1^{o} and 2^{o} alcohols into alkyl halides commonly use thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3).
- To activate an alcohol in order to make the hydroxide a good leaving group, tosylates (toluenesulfonates) and mesylates (methanesulfonates) can be formed.
- Alcohols can be dehydrated by heating in strong acid solution to form an alkene.
- Alcohols react with acid chlorides to form esters.

12.7 Oxidation of Alcohols

- Primary and secondary alcohols can be oxidized with various chromium reagents, while tertiary alcohols are not.
- Secondary alcohols are oxidized to ketones.
- Primary alcohols are oxidized to carboxylic acids using chromium trioxide or dichromate compounds.
- Primary alcohols can be stopped in their oxidation at aldehydes by reacting with pyridinium chlorochromate or Dess-Martin periodinane.

12.8 Protection of Alcohols

- Protection of a functional group is useful when that functional group may interfere with an intended reaction.
- Protection converts a functional group into a non-interfering derivative molecule through a reaction that can be easily reversed to remove the protecting group.
- Protection consists of a series of reactions that include protect, perform intended reactions, and deprotect.
- Alcohols can be protected as silyl ethers by reacting with chlorotrialkyl silanes.

12.9 Phenols and Their Uses

- Phenols can be prepared from chlorobenzene or isopropylbenzene.
- Phenol and phenol derivatives (such as resorcinol) are used as germicides and antiseptics.
- Bisphenol A (BPA) has controversially been used to create polycarbonate plastics such as water bottles.

12.10 Reactions of Phenols

- Phenols can react with strong electrophiles (such as in Friedel-Crafts reactions).
- Phenols react with strong oxidizing agents including Jones reagent or silver oxide to form quinones.

12.11 Spectroscopy of Alcohols and Phenols

- Alcohols are among the most identifiable functional groups in infrared spectroscopy due to the strong, wide absorbance around 3400 cm^{-1}.
- Alcohol peaks are much more difficult to recognize in ^{1}H NMR, since OH hydrogens are relatively reactive and can exchange with hydrogens from the solvent, they are often weak absorptions without strong, sharp peaks.
- Hydroxide protons are not split in ^{1}H NMR.
- Loss of hydroxide in mass spectroscopy can lead to loss of a fragment with 17 m/z.

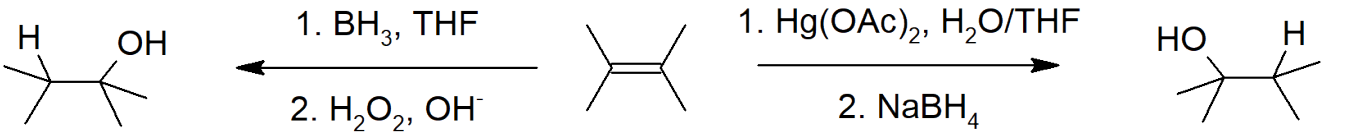
Skills to Master

- Skill 12.1 Identify types of alcohols.
- Skill 12.2 Name molecules with hydroxide groups using IUPAC rules.
- Skill 12.3 Describe properties related to intermolecular forces (including hydrogen bonding).
- Skill 12.4 Explain acid-base properties of alcohols and phenols.
- Skill 12.5 Describe how additional functional groups affect the acidity of phenols.
- Skill 12.6 Draw mechanisms to form alcohols from alkyl halides.
- Skill 12.7 Draw mechanisms to form alcohols from alkenes.
- Skill 12.8 Draw mechanisms to form alcohols by reduction reactions.
- Skill 12.9 Draw mechanisms to form alcohols by reaction of carbonyl compounds with Grignard reagents (and other organometallics).
- Skill 12.10 Draw mechanisms for conversion of alcohols to alkyl halides.
- Skill 12.11 Draw mechanisms for conversion of alcohols to tosylates.

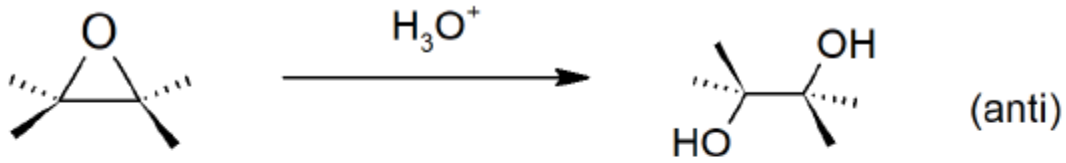
- Skill 12.12 Draw mechanisms for dehydration of alcohols to alkenes.
- Skill 12.13 Draw mechanisms for conversion of alcohols to esters.
- Skill 12.14 Draw mechanisms for oxidation of alcohols to aldehydes, ketones, and carboxylic acids.
- Skill 12.15 Write out syntheses that incorporate protection and deprotection of alcohols.

Summary of Reactions

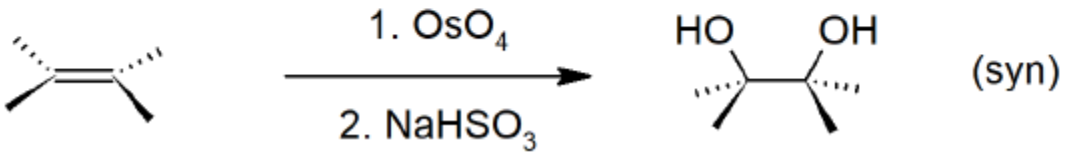
Alcohol Preparation (Hydrolysis)



(non-Markovnikov) (Markovnikov)

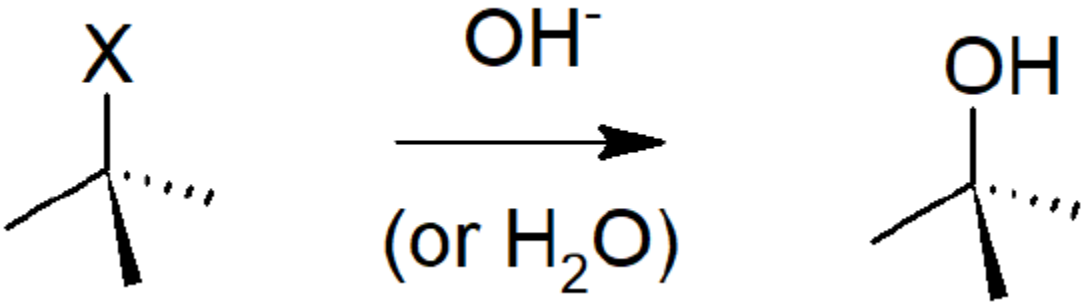


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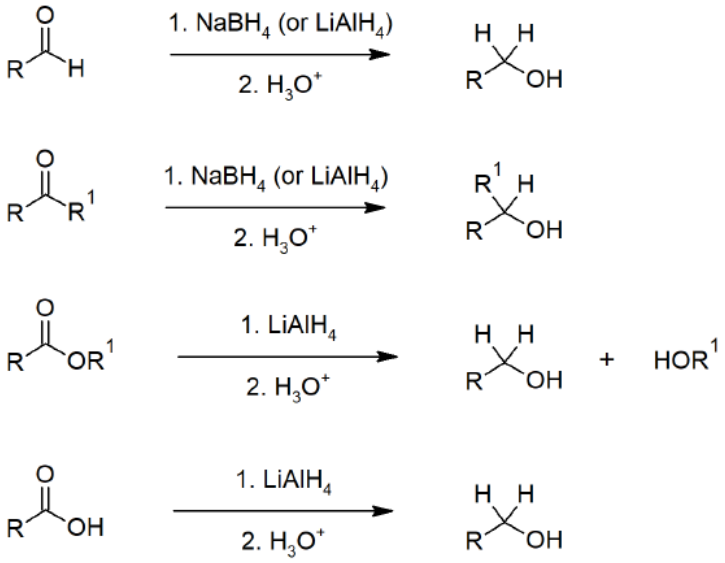


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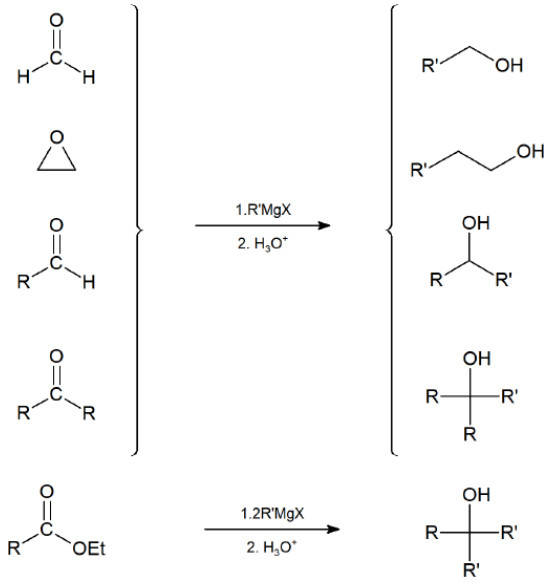
Alcohol Preparation (from Organohalide)



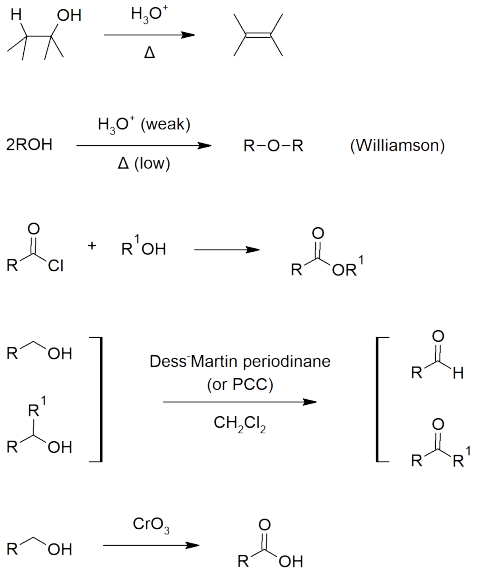
Alcohol Preparation (Reducing the Carbonyl)



Alcohol Preparation (Grignard Additions)



Alcohol Reactions



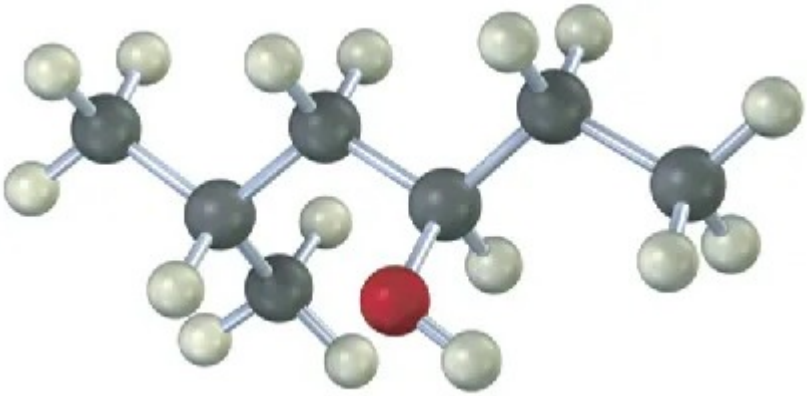
This page titled 12.A: Alcohols (Summary) is shared under a CC BY-SA 4.0 license and was authored, remixed, and/or curated by Dietmar Kennepohl & Steven Farmer.

- 17.S: Alcohols and Phenols (Summary) by Dietmar Kennepohl, Layne Morsch, Steven Farmer is licensed CC BY-SA 4.0.

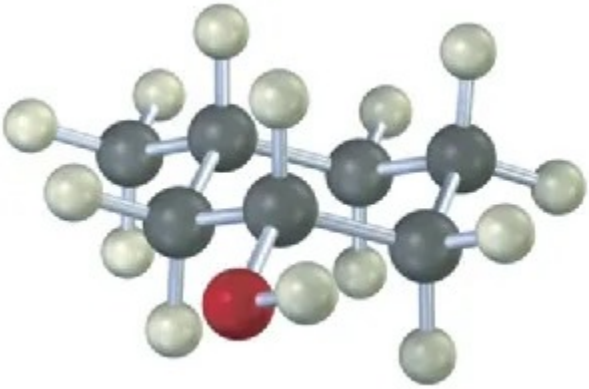
12.B: Additional Problems

Visualizing Chemistry

PROBLEM 12-20 Give IUPAC names for the following compounds:

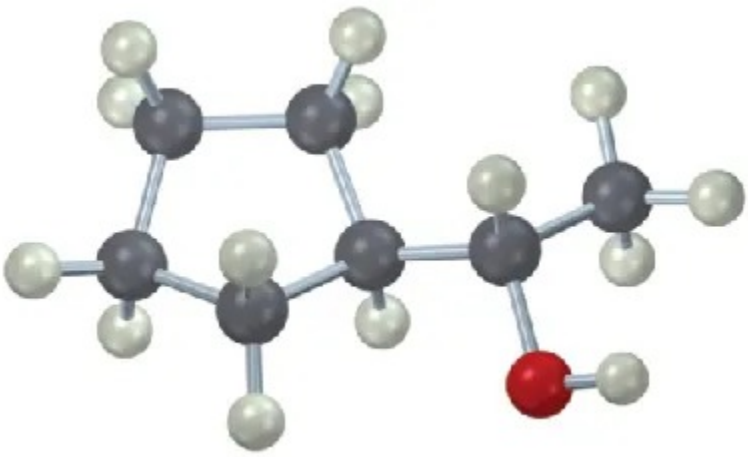


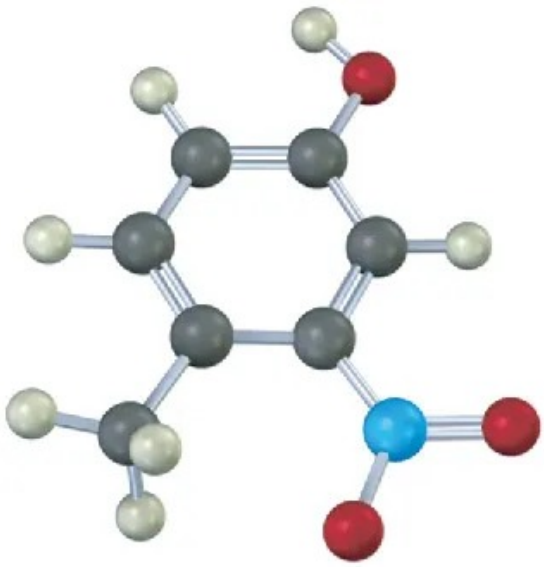
(a)



(b)

(c)

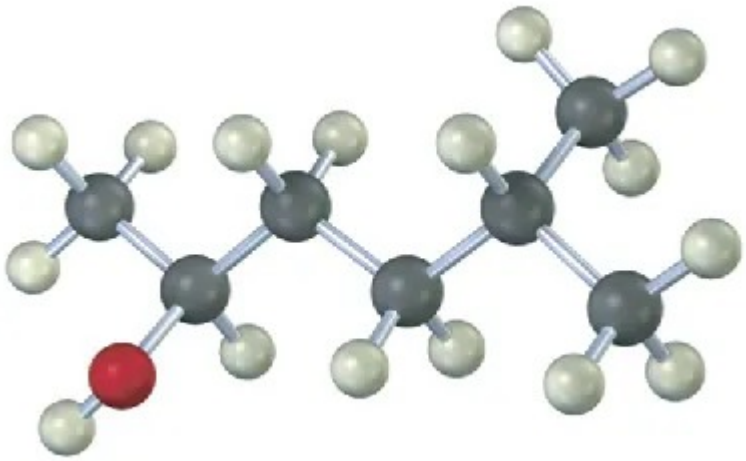




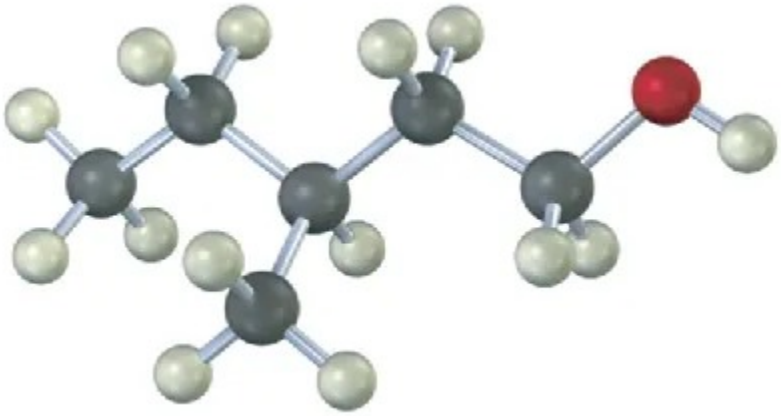
(d)

PROBLEM 12-21 Draw the structure of the carbonyl compound(s) from which each of the following alcohols might have been

prepared, and show the products you would obtain by treatment of each alcohol with (1) Na metal, (2) $SOCl_2$, and (3) Dess–Martin periodinane.

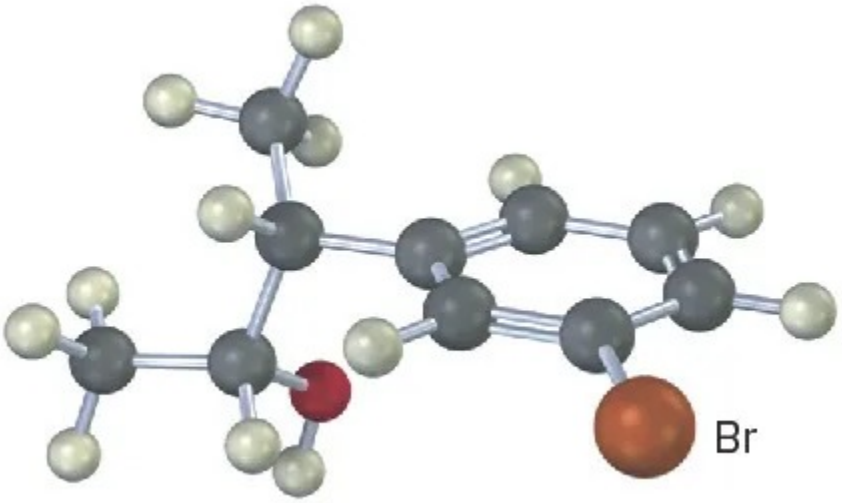


(a)



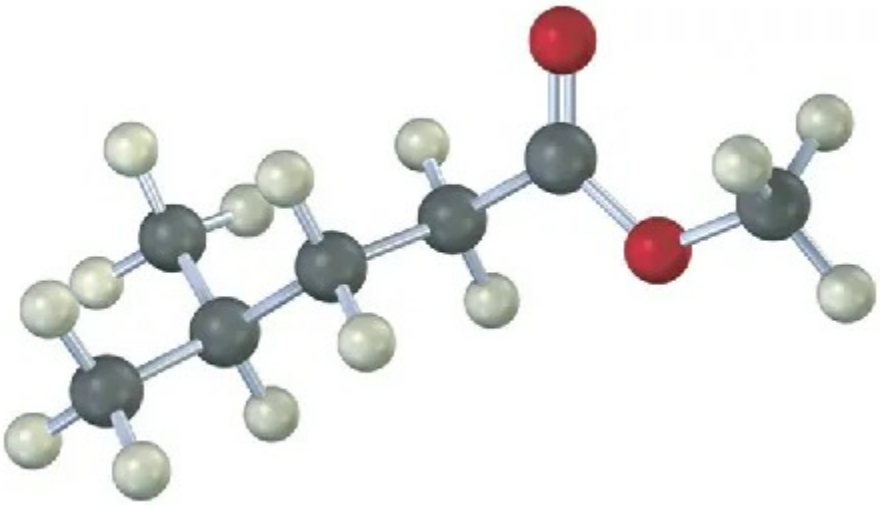
(b)

PROBLEM 12-22 Predict the product from the reaction of the following substance (reddish brown = Br) with: (a) PBr_3 (b) Aqueous H_2SO_4 (c) $SOCl_2$ (d) Dess–Martin periodinane (e) Br_2, $FeBr_3$

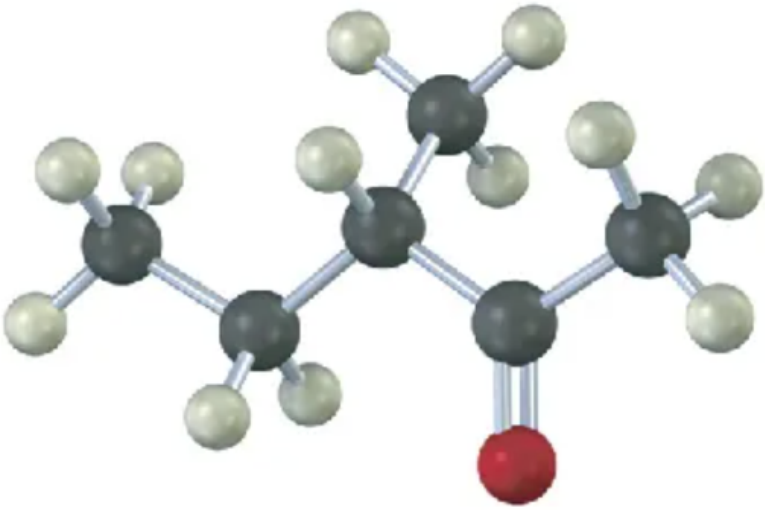


PROBLEM 12-25 Predict the product from the reaction of the following substance with: (a) $NaBH_4$; then H_3O^+ (b) $LiAlH_4$; then

H_3O^+ (c) 2 CH_3CH_2MgBr; then H_3O^+

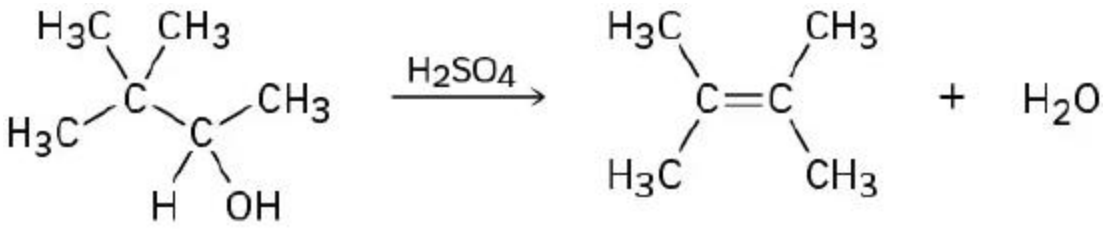


PROBLEM 12-24 Name and assign *R* or *S* stereochemistry to the product(s) you would obtain by reaction of the following substance with ethylmagnesium bromide. Is the product chiral? Is it optically active? Explain.

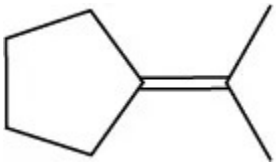


Mechanism Problems

PROBLEM 12-25 Evidence for the intermediate carbocations in the acid-catalyzed dehydration of alcohols comes from the observation that rearrangements sometimes occur. Propose a mechanism to account for the formation of 2,3-dimethyl-2-butene from 3,3-dimethyl-2-butanol.

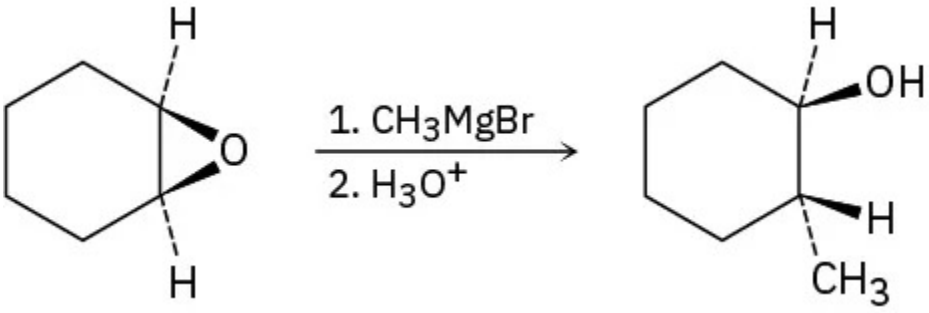


PROBLEM 12-26 Acid-catalyzed dehydration of 2,2-dimethylcyclohexanol yields a mixture of 1,2-dimethylcyclohexene and isopropylidenecyclopentane. Propose a mechanism to account for the formation of both products.

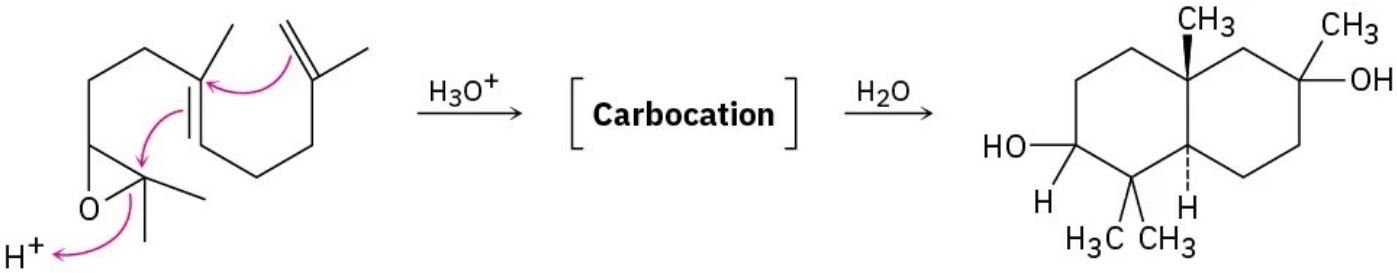


Isopropylidenecyclopentane

PROBLEM 12-27 Epoxides react with Grignard reagents to yield alcohols. Propose a mechanism.



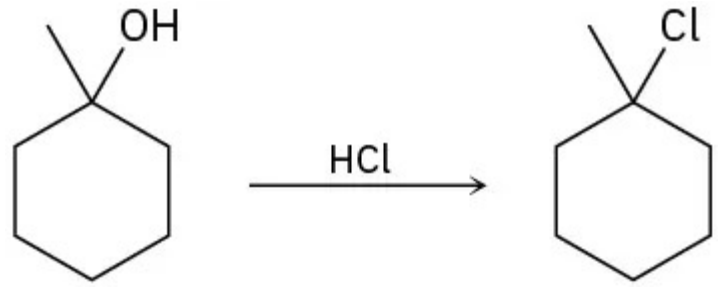
PROBLEM 12-28 Treatment of the following epoxide with aqueous acid produces a carbocation intermediate that reacts with water to give a diol product. Show the structure of the carbocation, and propose a mechanism for the second step.



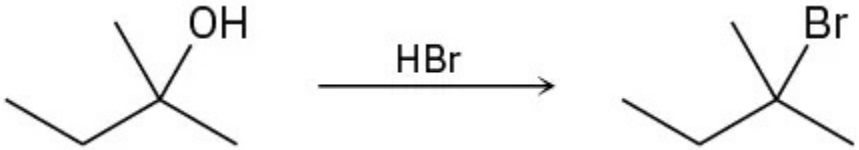
PROBLEM 12-29 Reduction of 2-butanone with $NaBH_4$ yields 2-butanol. Is the product chiral? Is it optically active? Explain.

PROBLEM 12-30 The conversion of 3° alcohols into 3° alkyl halides under acidic conditions involves two cationic intermediates. For each reaction, draw the complete mechanism using curved arrows.

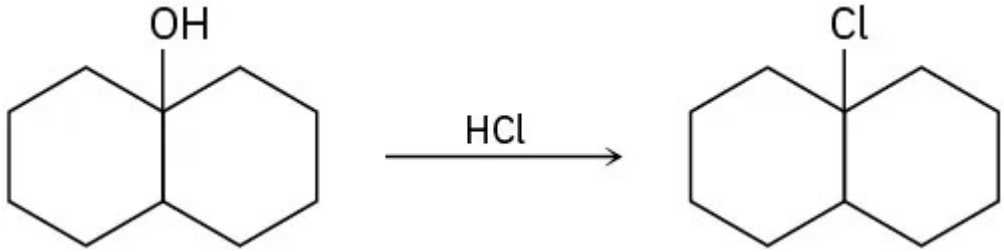
(a)



(b)

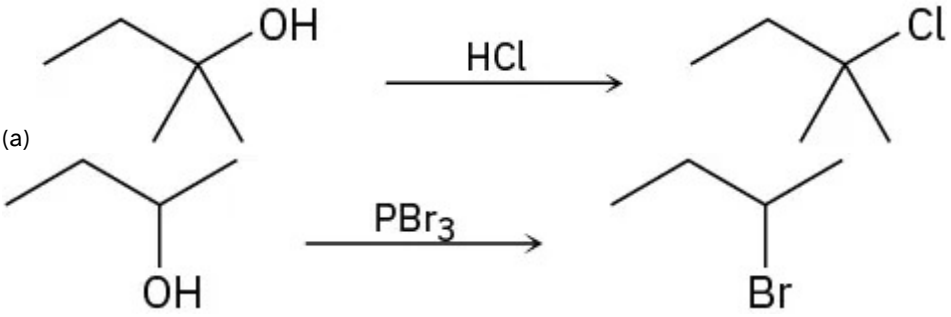


(c)



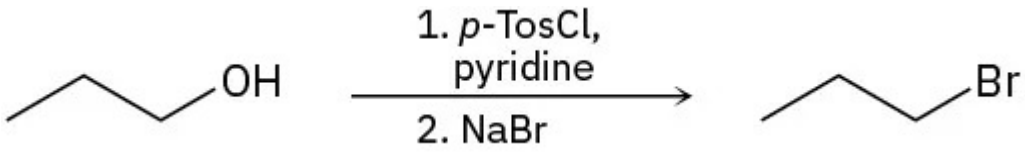
PROBLEM 12-31 Identify the type of substitution mechanism (S_N1, S_N2) involved in the conversion of the following alcohols into the corresponding alkyl halide.

(a)



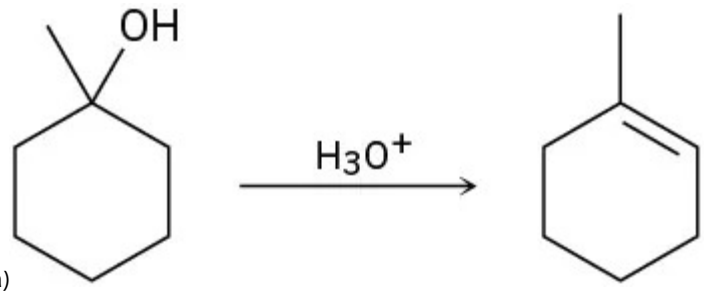
(b)

(c)

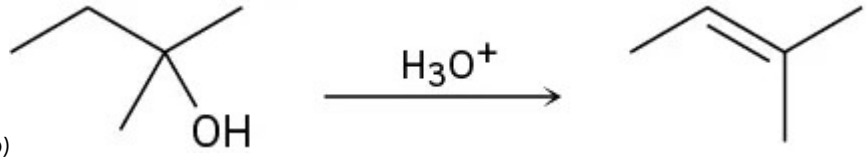


PROBLEM 12-32 The conversion of 3° alcohols into alkenes under acidic conditions involves two cationic intermediates. For each reaction, draw the complete mechanism using curved arrows.

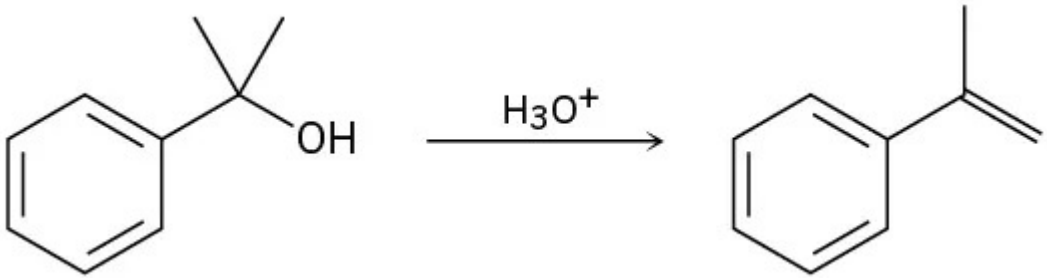
(a)



(b)

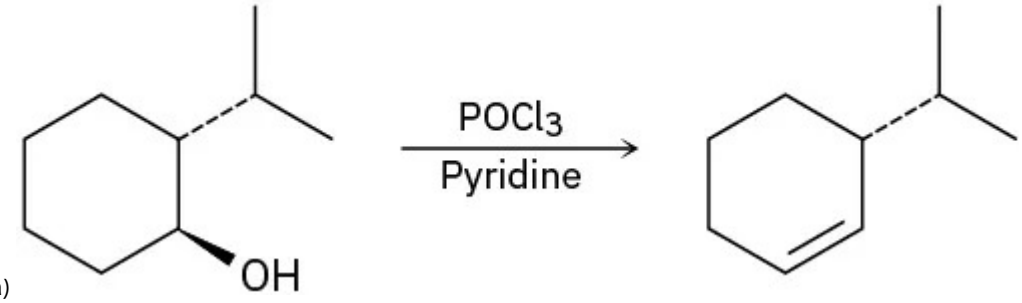


c)

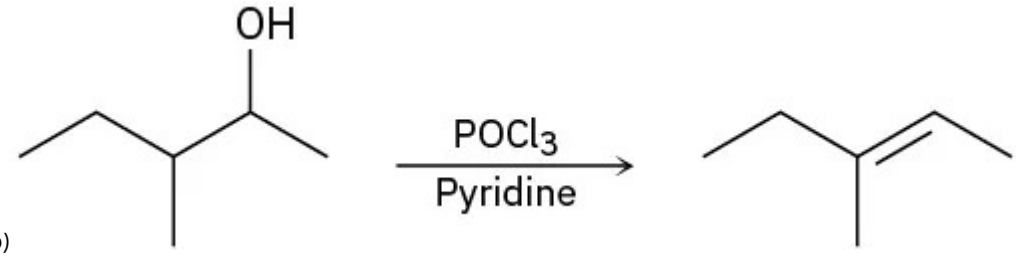


PROBLEM 12-33 For each reaction, write the mechanism using curved arrows for the conversion of the alcohol into the corresponding alkene with $POCl_3$. In each case, explain the regiochemistry of the elimination.

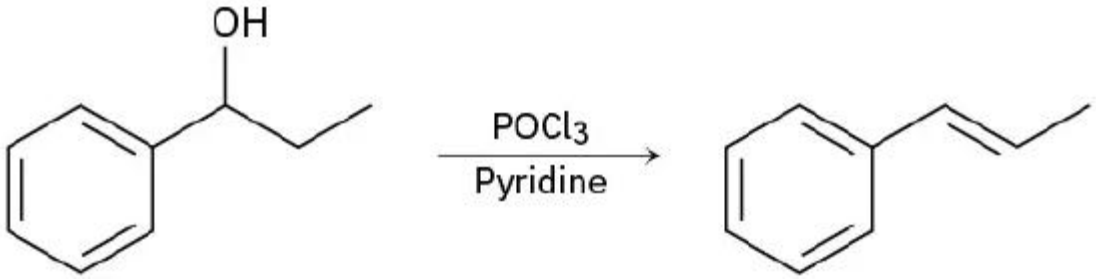
(a)



(b)



(c)



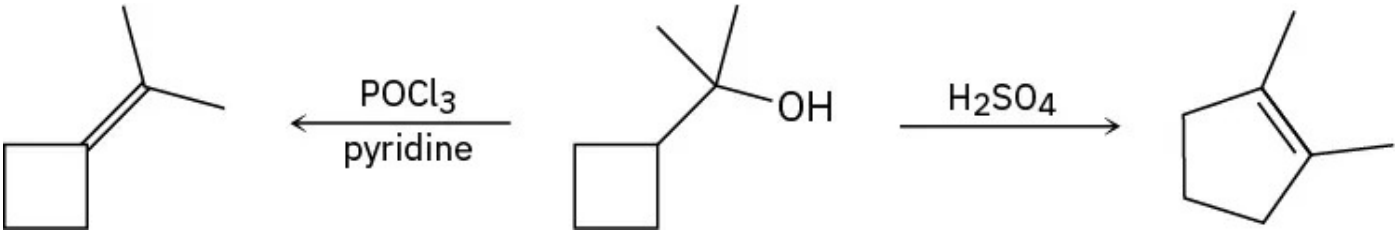
PROBLEM 12-34 The trimethylsilyl (TMS) protecting group is one of several silicon-protecting groups for alcohols. For each reaction, draw the mechanism for the protection of (*R*)-3-bromo-1-butanol with the following silyl chlorides, using triethylamine as the base:

(a) *tert*-butyldimethylsilyl chloride (TBS-Cl)

(b) triisopropylsilyl chloride (TIPS-Cl)

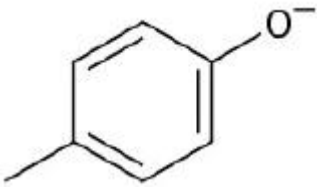
(c) triethylsilyl chloride (TES-Cl)

PROBLEM 12-35 When the following alcohol is treated with $POCl_3$ and pyridine, the expected elimination product is formed. However, when the same alcohol is treated with H_2SO_4, the elimination product is 1,2-dimethylcyclopentene. Propose a mechanism for each pathway to account for these differences.

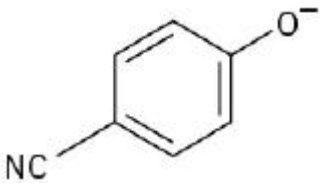


PROBLEM 12-36 Phenols generally have lower pK_a's than alcohols because of resonance stabilization with the aromatic ring. Draw all of the resonance contributors for the following phenolate ions.

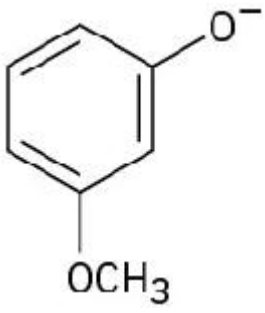
(a)



(b)

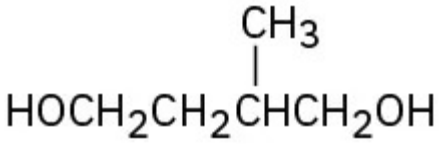


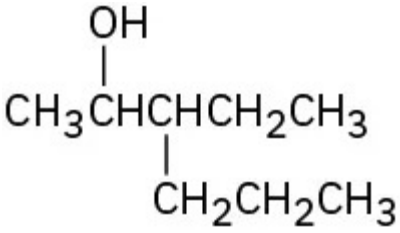
(c)

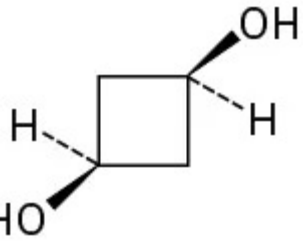


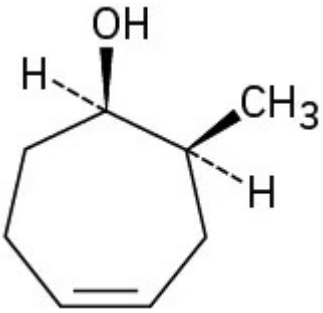
Naming Alcohols

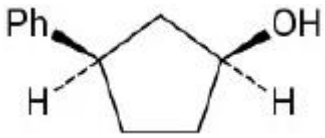
PROBLEM 12-37 Give IUPAC names for the following compounds:

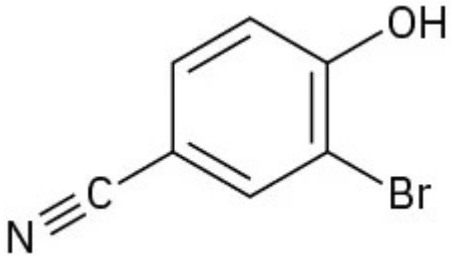
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM 12-38 Draw and name the eight isomeric alcohols with formula $C_5H_{12}O$.

PROBLEM 12-39 Draw structures corresponding to the following IUPAC names:

(a) *Trans*-3-Chlorocycloheptanol

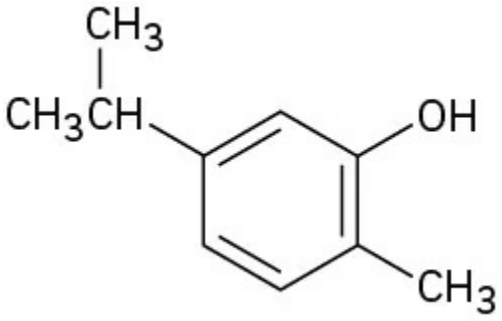
(b) 2-Ethyl-2-buten-1-ol

(c) *o*-(2-Hydroxyethyl)phenol

(d) 3-Methyl-1-phenyl-1-butanol

PROBLEM 12-40 Bombykol, the sex pheromone secreted by the female silkworm moth has the formula $C_{16}H_{28}O$ and the systematic name (10*E*,12*Z*)-10,12-hexadecadien-1-ol. Draw bombykol, showing the correct geometry for the two double bonds.

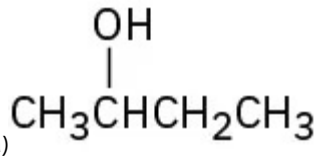
PROBLEM 12-41 Carvacrol is a naturally occurring substance isolated from oregano, thyme, and marjoram. What is its IUPAC name?

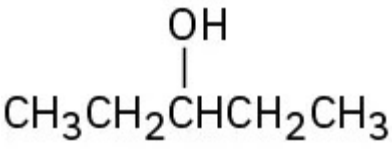


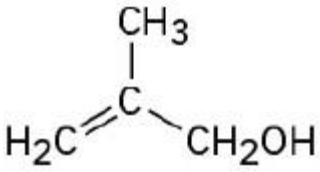
Carvacrol

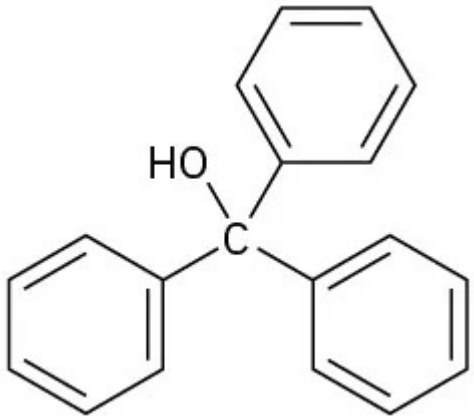
Synthesizing Alcohols

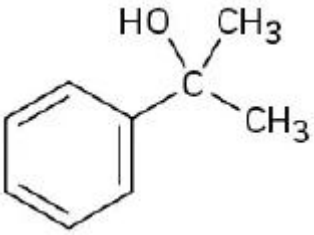
PROBLEM 12-42 What Grignard reagent and what carbonyl compound might you start with to prepare the following alcohols:

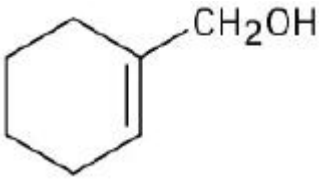
(a) 

(b) 

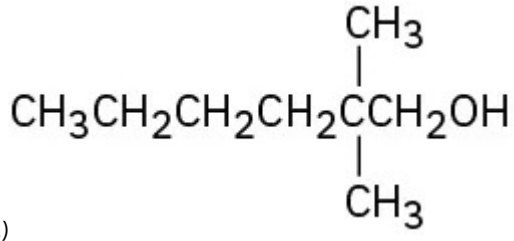
(c) 

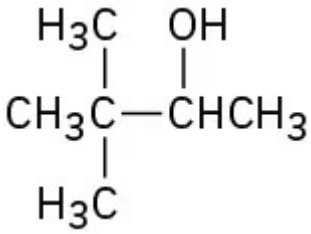
(d) 

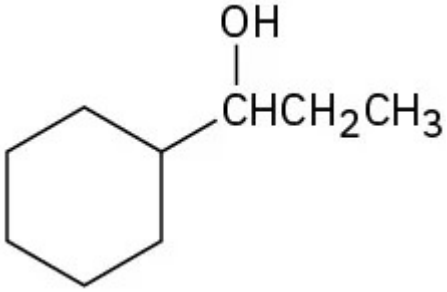
(e) 

(f) 

PROBLEM 12-43 What carbonyl compounds would you reduce to prepare the following alcohols: List all possibilities.

(a) 

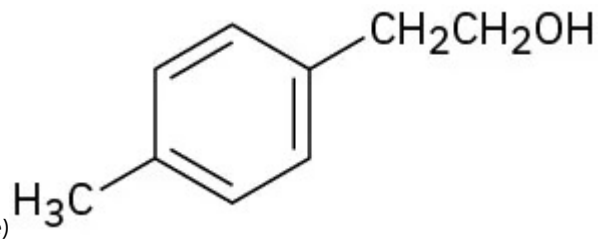
(b) 

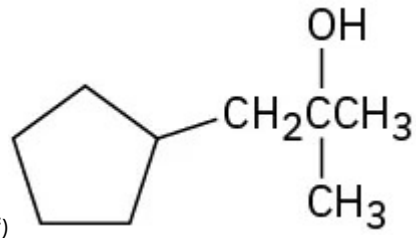
(c) 

PROBLEM 12-44 What carbonyl compounds might you start with to prepare the following compounds by Grignard reaction? List all possibilities.

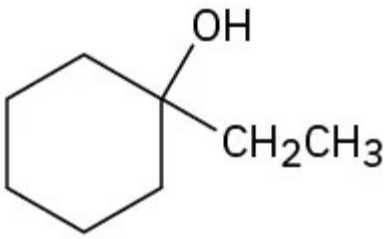
(a) 2-Methyl-2-propanol (b) 1-Ethylcyclohexanol

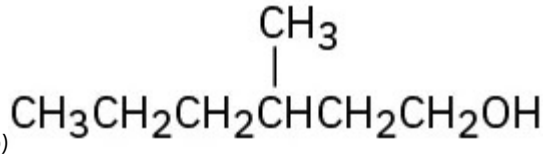
(c) 3-Phenyl-3-pentanol (d) 2-Phenyl-2-pentanol

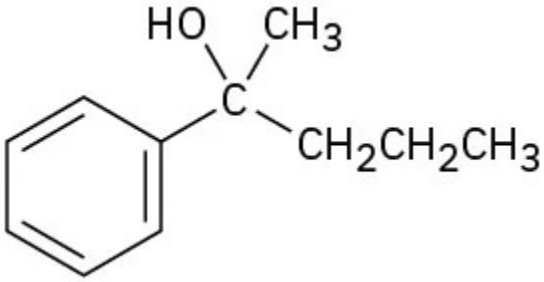
(e) 

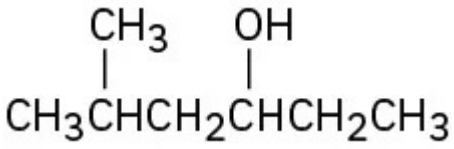
(f) 

PROBLEM 12-45 How would you synthesize the following alcohols, starting with benzene and other alcohols of six or fewer carbons as your only organic reagents?

(a) 

(b) 

(c) 

(d) 

Reactions of Alcohols

PROBLEM 12-46 What products would you obtain from reaction of 1-pentanol with the following reagents:

(a) PBr_3 (b) $SOCl_2$ (c) Dess–Martin periodinane

PROBLEM 12-47 How would you prepare the following compounds from 2-phenylethanol: More than one step may be required.

(a) Styrene ($PhCH{=}CH_2$) (b) Phenylacetaldehyde ($PhCH_2CHO$) (c) Phenylacetic acid ($PhCH_2CO_2H$) (d) Benzoic acid

(e) Ethylbenzene (f) Benzaldehyde (g) 1-Phenylethanol (h) 1-Bromo-2-phenylethane

PROBLEM 12-48 How would you prepare the following compounds from 1-phenylethanol: More than one step may be required.

(a) Acetophenone ($PhCOCH_3$) (b) Benzyl alcohol (c) *m*-Bromobenzoic acid (d) 2-Phenyl-2-propanol

PROBLEM 12-49 How would you prepare the following substances from cyclopentanol: More than one step may be required.

(a) Cyclopentanone (b) Cyclopentene (c) 1-Methylcyclopentanol (d) *trans*-2-Methylcyclopentanol

PROBLEM 12-50 What products would you expect to obtain from the reaction of 1-methylcyclohexanol with the following reagents?

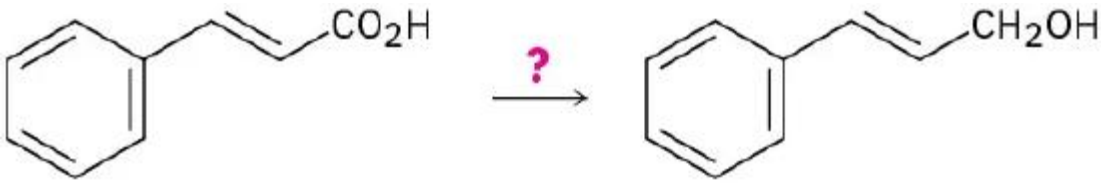
(a) HBr (b) NaH (c) H_2SO_4

General Problems

PROBLEM 12-51 How would you carry out the following transformations?

(a) 

(b)

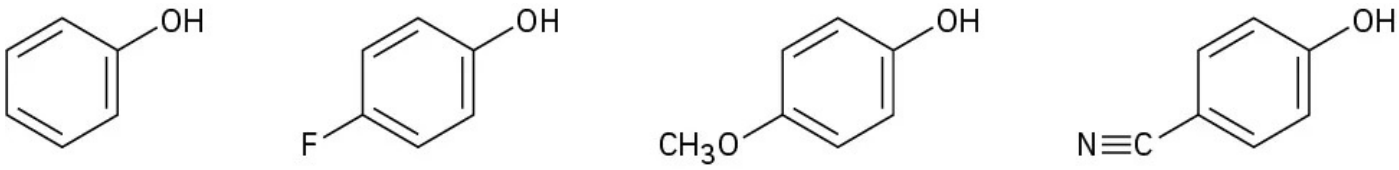


(c)

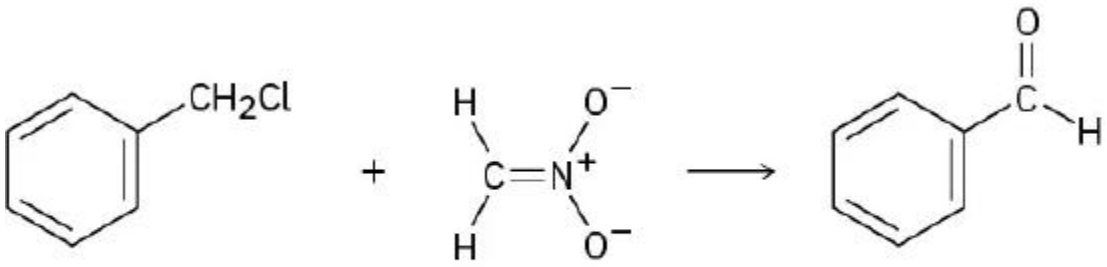


PROBLEM 12-52 Removed

PROBLEM 12-53 Rank the following substituted phenols in order of increasing acidity, and explain your answer:

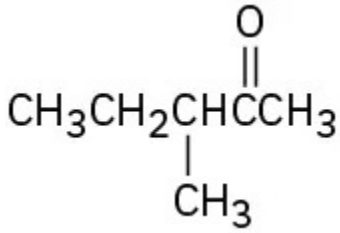


PROBLEM 12-54 Benzyl chloride can be converted into benzaldehyde by treatment with nitromethane and base. The reaction involves initial conversion of nitromethane into its anion, followed by S_N2 reaction of the anion with benzyl chloride and subsequent E2 reaction. Write the mechanism in detail, using curved arrows to indicate the electron flow in each step.



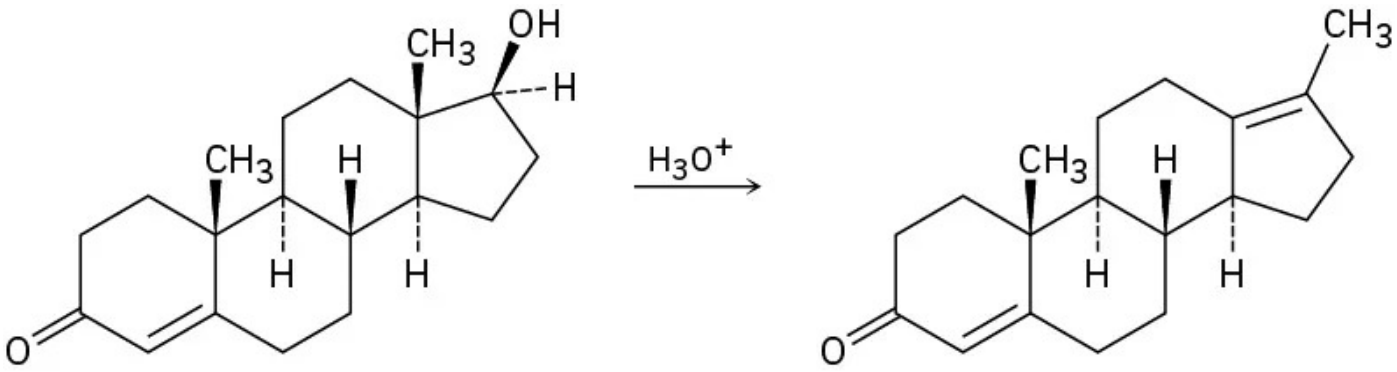
Benzyl chloride **Nitromethane anion** **Benzaldehyde**

PROBLEM 12-55 Reaction of (S)-3-methyl-2-pentanone with methylmagnesium bromide followed by acidification yields 2,3-dimethyl-2-pentanol. What is the stereochemistry of the product? Is the product optically active?



3-Methyl-2-pentanone

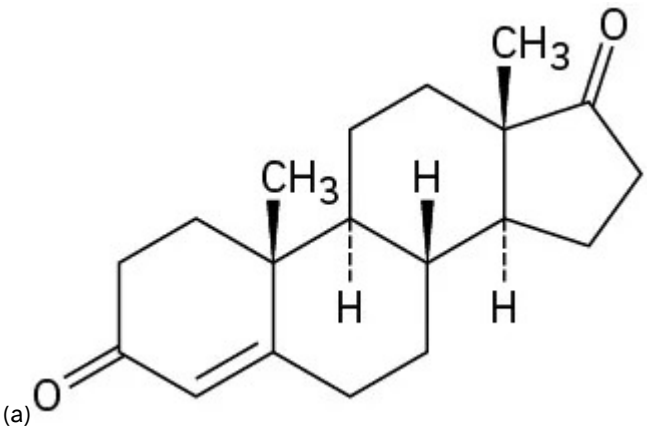
PROBLEM 12-56 Testosterone is one of the most important male steroid hormones. When testosterone is dehydrated by treatment with acid, rearrangement occurs to yield the product shown. Propose a mechanism to account for this reaction.



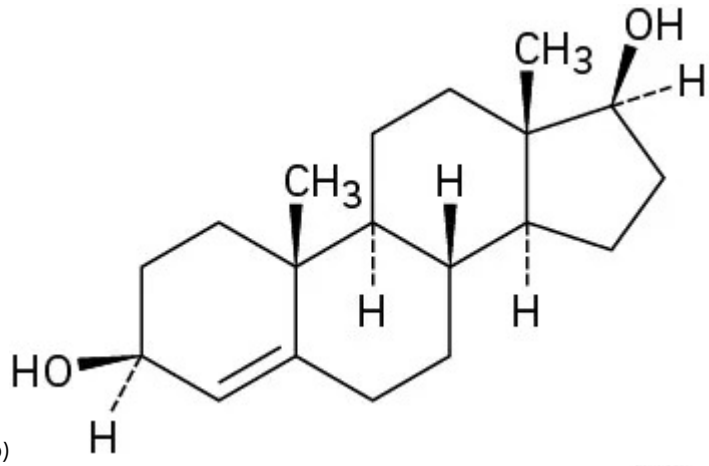
Testosterone

PROBLEM 12-57 Starting from testosterone (Exercise $12.B.56$), how would you prepare the following substances?

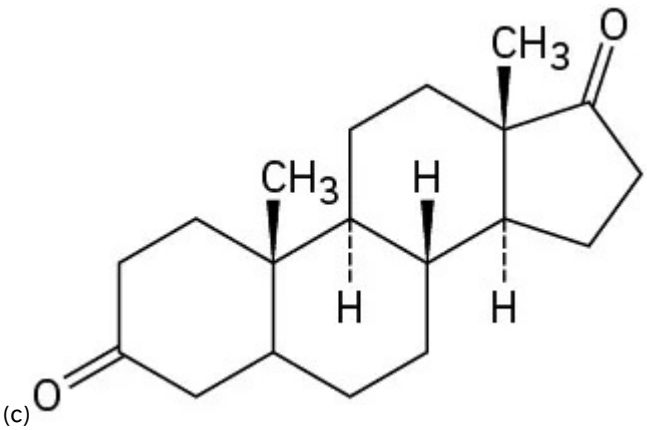
(a)



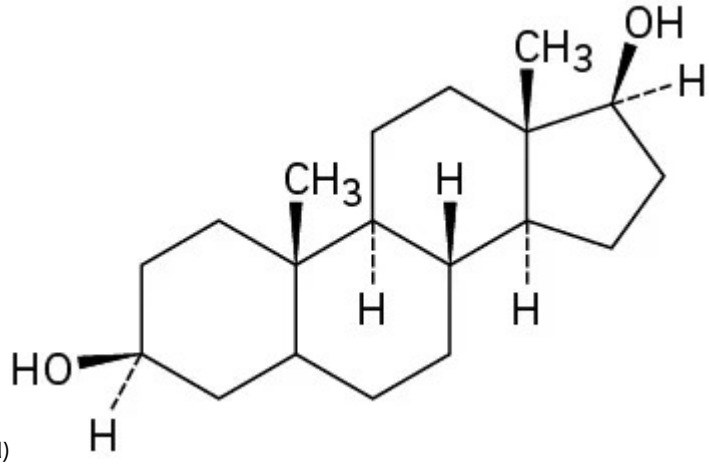
(b)



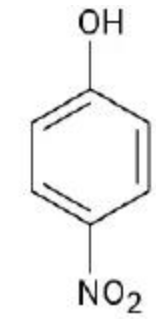
(c)

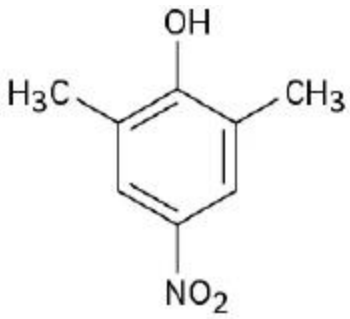


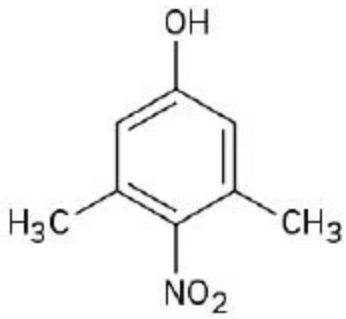
(d)



PROBLEM 12-58 *p*-Nitrophenol and 2,6-dimethyl-4-nitrophenol both have pK_a = 7.15, but 3,5-dimethyl-4-nitrophenol has pK_a = 8.25. Why is 3,5-dimethyl-4-nitrophenol so much less acidic?





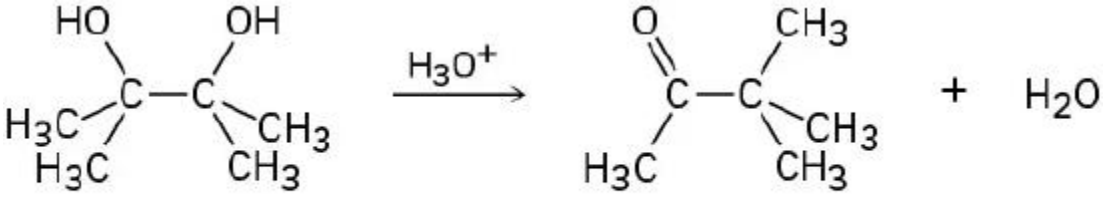


pK_a = 7.15 **pK_a = 7.15** **pK_a = 8.25**

PROBLEM 12-59 Compound **A**, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 25 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Write the reactions involved, and identify **A** and **B**.

PROBLEM 12-60 Dehydration of *trans*-2-methylcyclopentanol with $POCl_3$ in pyridine yields predominantly 3-methylcyclopentene. Is the stereochemistry of this dehydration syn or anti?

PROBLEM 12-61 2,3-Dimethyl-2,3-butanediol has the common name *pinacol*. On heating with aqueous acid, pinacol rearranges to *pinacolone,* 3,3-dimethyl-2-butanone. Suggest a mechanism for this reaction.

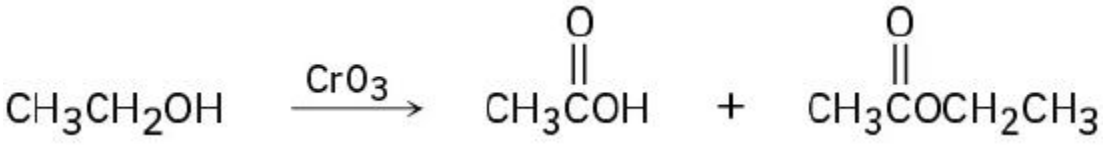


Pinacol **Pinacolone**

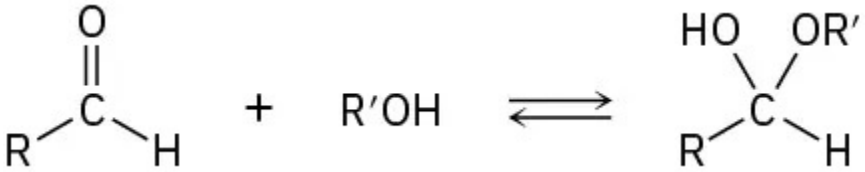
PROBLEM 12-62 As a rule, axial alcohols oxidize somewhat faster than equatorial alcohols. Which would you expect to oxidize faster, *cis*-4-*tert*-butylcyclohexanol or *trans*-4-*tert*-butylcyclohexanol? Draw the more stable chair conformation of each molecule.

PROBLEM 12-63 Removed

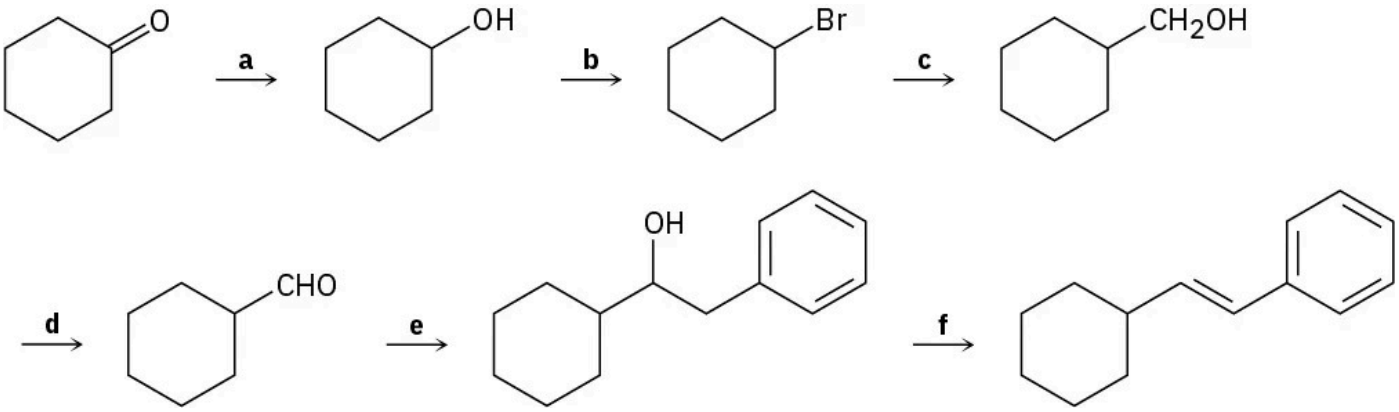
PROBLEM 12-64 A problem often encountered in the oxidation of primary alcohols to carboxylic acids is that esters are sometimes produced as by-products. For example, oxidation of ethanol yields acetic acid and ethyl acetate:



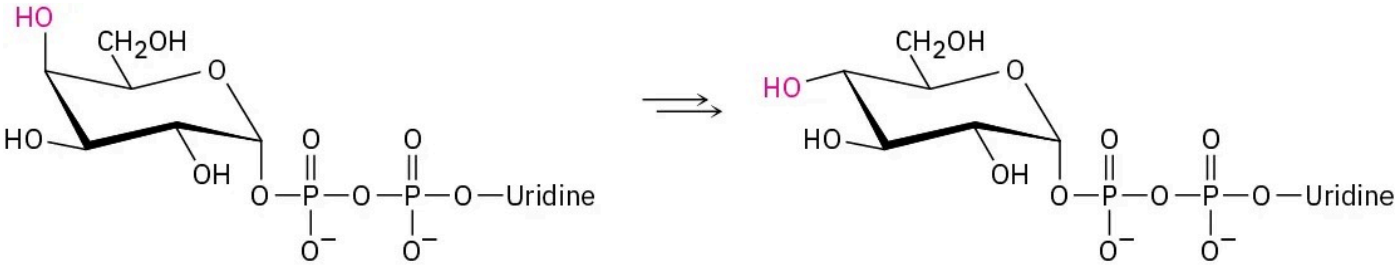
Propose a mechanism to account for the formation of ethyl acetate. Take into account the reversible reaction between aldehydes and alcohols:



PROBLEM 12-65 Identify the reagents **a**–**f** in the following scheme:



PROBLEM 12-66 Galactose, a constituent of the disaccharide lactose found in dairy products, is metabolized by a pathway that includes the isomerization of UDP-galactose to UDP-glucose, where UDP = uridylyl diphosphate. The enzyme responsible for the transformation uses NAD^+ as cofactor. Propose a mechanism.



UDP-galactose **UDP-glucose**

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13: STRUCTURE DETERMINATION - MASS SPECTROMETRY AND INFRARED SPECTROSCOPY

Learning Objectives

After you have completed Chapter 13, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems that include mass spectral data, infrared data, or both.
3. define, and use in context, the key terms introduced.

The processes of identifying and characterizing organic compounds are of great importance to the working organic chemist. With modern instrumental techniques, these tasks can now be accomplished much more readily than in the past. In this chapter, you will learn about two spectroscopic techniques (mass spectroscopy and infrared spectroscopy) that are used to identify organic compounds.

13.0: Why This Chapter?

13.1: Spectroscopy and the Electromagnetic Spectrum

13.2: Infrared Spectroscopy

13.3: Interpreting Infrared Spectra

13.4: Infrared Spectra of Some Common Functional Groups

13.5: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments

13.6: Interpreting Mass Spectra

13.7: Mass Spectroscopy and Natural Abundances of Isotopes

13.8: Mass Spectrometry of Some Common Functional Groups

13.9: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

13.10: Chemistry Matters—X-Ray Crystallography

13.A: Structure Determination - Mass Spectrometry and Infrared Spectroscopy (Summary)

13.B: Additional Problems

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13.0: Why This Chapter?

Finding the structures of new molecules, whether small ones synthesized in the laboratory or large proteins and nucleic acids found in living organisms, is central to progress in chemistry and biochemistry. We can only scratch the surface of structure determination in this book, but after reading this and the following two chapters, you should have a good idea of the range of structural techniques available and of how and when each is used.



Figure 13.0.1: More than a thousand different chemical compounds have been isolated from coffee. Their structures were determined using various spectroscopic techniques. (credit: "Coffee, Espresso" by John Beans/myfriendscoffee.com, CC BY 4.0)

Every time a reaction is run, the products must be identified, and every time a new compound is found in nature, its structure must be determined. Determining the structure of an organic compound was a difficult and time-consuming process until the mid-20th century, but powerful techniques and specialized instruments are now routinely used to simplify the problem. In this and the next two chapters, we'll look at four such techniques—mass spectrometry (MS), infrared (IR) spectroscopy, ultraviolet spectroscopy (UV), and nuclear magnetic resonance spectroscopy (NMR)—and we'll see the kind of information that can be obtained from each.

Mass spectrometry	What is the size and formula?
Infrared spectroscopy	What functional groups are present?
Ultraviolet spectroscopy	Is a conjugated π electron system present?
Nuclear magnetic resonance spectroscopy	What is the carbon–hydrogen framework?

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13.1: Spectroscopy and the Electromagnetic Spectrum

Infrared, ultraviolet, and nuclear magnetic resonance spectroscopies differ from mass spectrometry in that they are nondestructive and involve the interaction of molecules with electromagnetic energy rather than with an ionizing source. Before beginning a study of these techniques, however, let's briefly review the nature of radiant energy and the electromagnetic spectrum.

Visible light, X rays, microwaves, radio waves, and so forth are all different kinds of electromagnetic radiation. Collectively, they make up the electromagnetic spectrum, shown in Figure 13.1.1. The electromagnetic spectrum is arbitrarily divided into regions, with the familiar visible region accounting for only a small portion, from 3.8×10^{-7} m to 7.8×10^{-7} m in wavelength. The visible region is flanked by the infrared and ultraviolet regions.

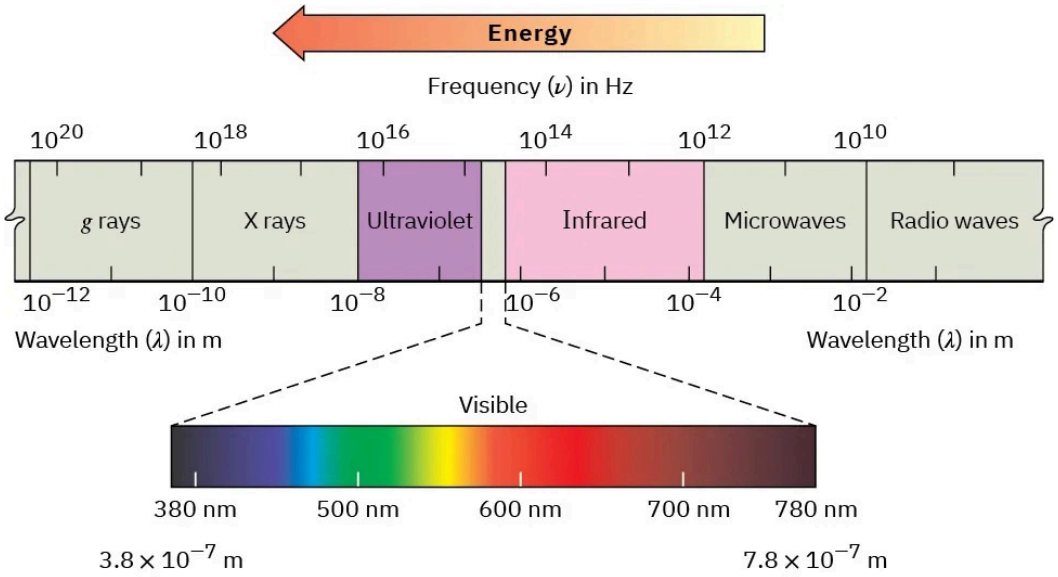


Figure 13.1.1: The electromagnetic spectrum covers a continuous range of wavelengths and frequencies, from radio waves at the low-frequency end to gamma (γ) rays at the high-frequency end. The familiar visible region accounts for only a small portion near the middle of the spectrum.

Electromagnetic radiation is often said to have dual behavior. In some respects, it has the properties of a particle, called a photon, yet in other respects it behaves as an energy wave. Like all waves, electromagnetic radiation is characterized by a *wavelength*, a *frequency*, and an *amplitude* (Figure 13.1.2). The wavelength, λ (Greek lambda), is the distance from one wave maximum to the next. The frequency, ν (Greek nu), is the number of waves that pass by a fixed point per unit time, usually given in reciprocal seconds (s^{-1}), or hertz, Hz (1 Hz = 1 s^{-1}). The amplitude is the height of a wave, measured from midpoint to peak. The intensity of radiant energy, whether a feeble glow or a blinding glare, is proportional to the square of the wave's amplitude.

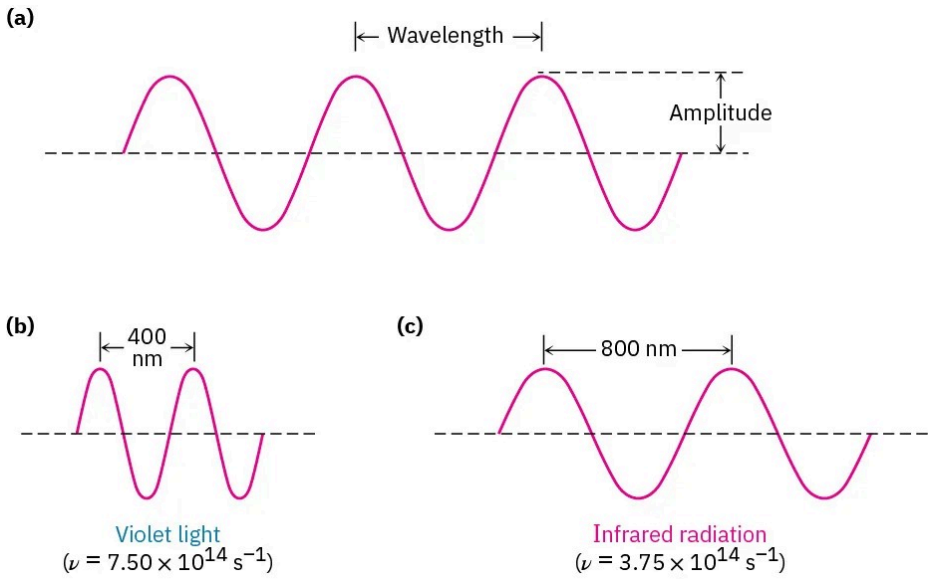


Figure 13.1.2: Electromagnetic waves are characterized by a wavelength, a frequency, and an amplitude. **(a)** Wavelength (λ) is the distance between two successive wave maxima. Amplitude is the height of the wave measured from the center. **(b)–(c)** What we perceive as different kinds of electromagnetic radiation are simply waves with different wavelengths and frequencies.

Multiplying the wavelength of a wave in meters (m) by its frequency in reciprocal seconds (s^{-1}) gives the speed of the wave in meters per second (m/s). The rate of travel of all electromagnetic radiation in a vacuum is a constant value, commonly called the "speed of light" and abbreviated c. Its numerical value is defined as exactly 2.997 924 58 × 10^8 m/s, usually rounded off to 3.00 × 10^8 m/s.

$$\text{Wavelength} \times \text{Frequency} = \text{Speed}$$

$$\lambda(\text{m}) \times \nu\left(\text{s}^{-1}\right) = c(\text{ m/s})$$

$$\lambda = \frac{c}{v} \tag{13.1.1}$$

or

$$\nu = \frac{c}{\lambda} \tag{13.1.2}$$

Just as matter comes only in discrete units called atoms, electromagnetic energy is transmitted only in discrete amounts called **quanta**. The amount of energy ε corresponding to 1 quantum of energy (1 **photon**) of a given frequency ν is expressed by the Planck equation

$$\varepsilon = h\nu = \frac{hc}{\lambda} \tag{13.1.3}$$

where h is Planck's constant (6.62 × 10^{-34} J · s = 1.58 × 10^{-34} cal · s).

The Planck equation says that the energy of a given photon varies directly with its frequency ν but inversely with its wavelength λ. High frequencies and short wavelengths correspond to high-energy radiation such as gamma rays; low frequencies and long wavelengths correspond to low-energy radiation such as radio waves. Multiplying ε by Avogadro's number N_A gives the same equation in more familiar units, where E represents the energy of Avogadro's number (one "mole") of photons of wavelength λ:

$$E = \frac{N_A hc}{\lambda}$$

$$= \frac{1.20 \times 10^{-4}\text{ kJ/mol}}{\lambda(\text{ m})}$$

$$= \frac{2.86 \times 10^{-5}\text{kcal/mol}}{\lambda(\text{ m})}$$

When an organic compound is exposed to a beam of electromagnetic radiation, it absorbs energy of some wavelengths but passes, or transmits, energy of other wavelengths. If we irradiate the sample with energy of many different wavelengths and determine which are absorbed and which are transmitted, we can measure the absorption spectrum of the compound.

An example of an absorption spectrum—that of ethanol exposed to infrared radiation—is shown in Figure 13.1.3. The horizontal axis records the wavelength, and the vertical axis records the intensity of the various energy absorptions in percent transmittance. The baseline corresponding to 0% absorption (or 100% transmittance) runs along the top of the chart, so a downward spike means that energy absorption has occurred at that wavelength.

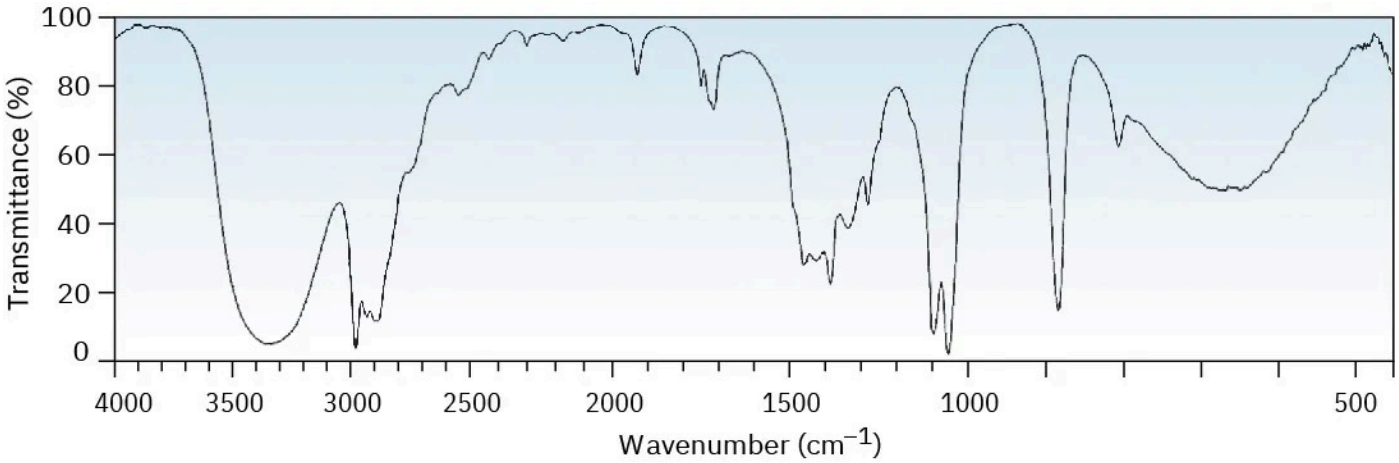


Figure 13.1.3: An infrared absorption spectrum for ethanol, CH_3CH_2OH. A transmittance of 100% means that all the energy is passing through the sample, whereas a lower transmittance means that some energy is being absorbed. Thus, each downward spike corresponds to an energy absorption.

The energy a molecule gains when it absorbs radiation must be distributed over the molecule in some way. With infrared radiation, the absorbed energy causes bonds to stretch and bend more vigorously. With ultraviolet radiation, the energy causes an electron to jump from a lower-energy orbital to a higher-energy one. Different radiation frequencies affect molecules in different ways, but each provides structural information when the results are interpreted.

There are many kinds of spectroscopies, which differ according to the region of the electromagnetic spectrum used. We'll look at three: infrared spectroscopy, ultraviolet spectroscopy, and nuclear magnetic resonance spectroscopy. Let's begin by seeing what happens when an organic sample absorbs infrared energy.

Worked Example 13.1.1: Correlating Energy and Frequency of Radiation

Which is higher in energy, FM radio waves with a frequency of 1.015×10^8 Hz (101.5 MHz) or visible green light with a frequency of 5×10^{14} Hz?

Strategy

Remember the equations $\varepsilon = h\nu$ and $\varepsilon = hc/\lambda$, which say that energy increases as frequency increases and as wavelength decreases.

Solution

Since visible light has a higher frequency than radio waves, it is higher in energy.

Exercise 13.1.1

Which has higher energy, infrared radiation with $\lambda = 1.0 \times 10^{-6}$ m or an X ray with $\lambda = 3.0 \times 10^{-9}$ m? Radiation with $\nu = 4.0 \times 10^9$ Hz or with $\lambda = 9.0 \times 10^{-6}$ m?

Answer available at the end of this section.

Exercise 13.1.2

Calculate the energies in KJ/mol of each of the following kinds of radiation:

a. A gamma ray with $\lambda = 5.0 \times 10^{-11}$ m.
b. An X-ray with $\lambda = 3.0 \times 10^{-9}$ m.
c. Ultraviolet light with $\nu = 6.0 \times 10^{15}$ Hz.
d. Visible light with $\nu = 7.0 \times 10^{14}$ Hz.
e. Infrared radiation with $\lambda = 2.0 \times 10^{-5}$ m.
f. Microwave radiation with $\nu = 5.0 \times 10^{11}$ Hz.

Answer available at the end of this section.

Answers

Exercise 13.1.1

X-ray energy is higher; $\lambda = 9.0 \times 10^{-6}$ m is higher in energy.

Exercise 13.1.2

a. 2.4×10^{6} kJ/mol
b. 4.0×10^{4} kJ/mol
c. 2.4×10^{3} kJ/mol
d. 2.8×10^{2} kJ/mol
e. 6.0 kJ/mol
f. 4.0×10^{-2} kJ/mol

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13.2: Infrared Spectroscopy

In infrared (IR) spectroscopy, the IR region of the electromagnetic spectrum covers the range from just above the visible (7.8 × 10^{-7} m) to approximately 10^{-4} m, but only the midportion from 2.5 × 10^{-6} m to 2.5 × 10^{-5} m is used by organic chemists (Figure 13.2.1. Wavelengths within the IR region are usually given in micrometers (1 μm = 10^{-6} m), and frequencies are given in wavenumbers rather than in hertz. The wavenumber $\tilde{\nu}$ is the reciprocal of wavelength in centimeters and is therefore expressed in units of cm^{-1}.

$$\text{Wavenumber: } \tilde{\nu}\left(\text{ cm}^{-1}\right) = \frac{1}{\lambda(\text{ cm})}$$

Thus, the useful IR region is from 4000 to 400 cm^{-1}, corresponding to energies of 48.0 kJ/mol to 4.80 kJ/mol (11.5–1.15 kcal/mol).

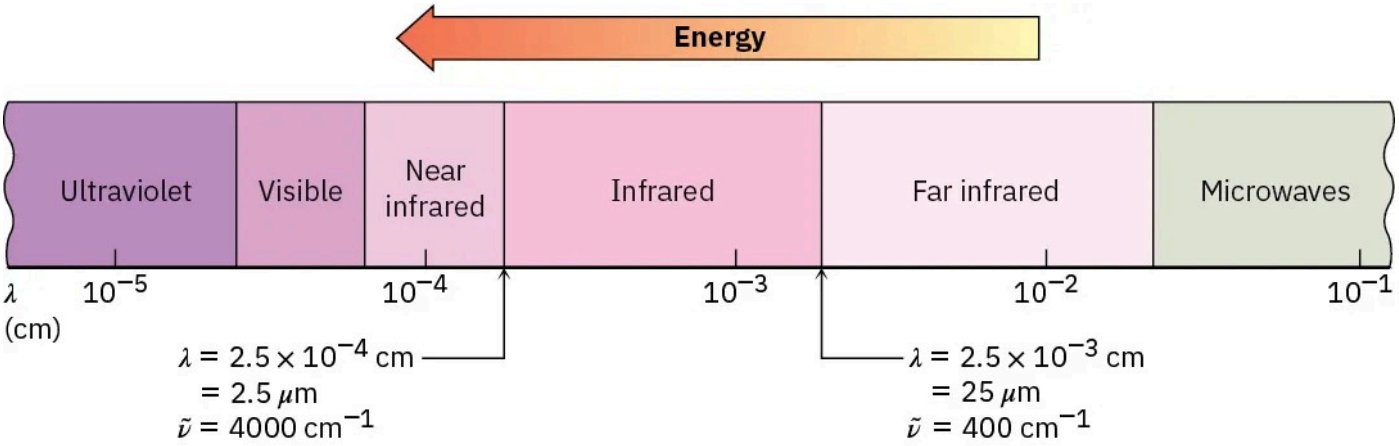
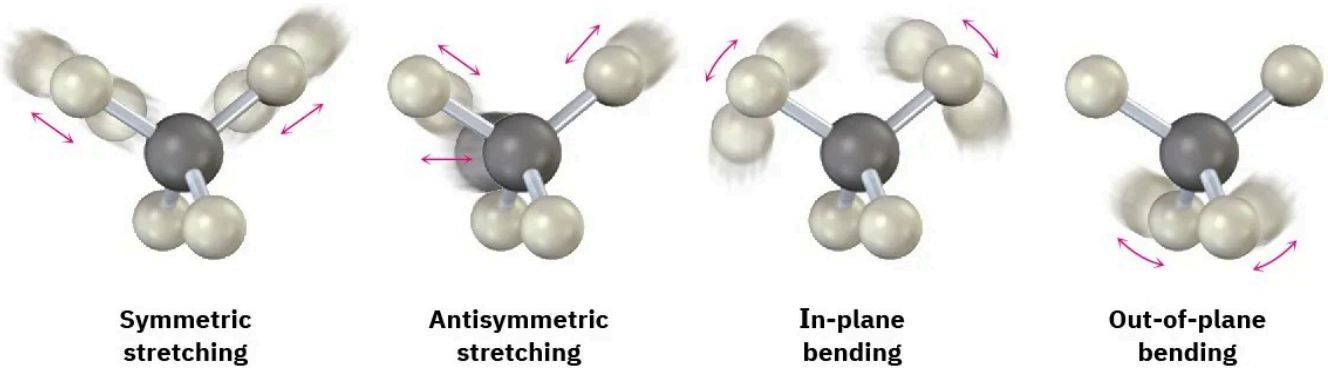


Figure 13.2.1: The infrared and adjacent regions of the electromagnetic spectrum.

Why does an organic molecule absorb some wavelengths of IR radiation but not others? All molecules have a certain amount of energy and are in constant motion. Their bonds stretch and contract, atoms wag back and forth, and other molecular vibrations occur. Some of the kinds of allowed vibrations are shown below:



The amount of energy a molecule contains is not continuously variable but is *quantized*. That is, a molecule can stretch or bend only at specific frequencies corresponding to specific energy levels. Take bond stretching, for example. Although we usually speak of bond lengths as if they were fixed, the numbers given are really averages. In fact, a typical C–H bond with an average bond length of 110 pm is actually vibrating at a specific frequency, alternately stretching and contracting as if there were a spring connecting the two atoms.

When a molecule is irradiated with electromagnetic radiation, energy is absorbed if the frequency of the radiation matches

the frequency of the vibration. The result of this energy absorption is an increased amplitude for the vibration; in other words, the “spring” connecting the two atoms stretches and compresses a bit further. Since each frequency absorbed by a molecule corresponds to a specific molecular motion, we can find what kinds of motions a molecule has by measuring its IR spectrum. By interpreting these motions, we can find out what kinds of bonds (functional groups) are present in the molecule.

$$\text{IR spectrum} \rightarrow \text{What molecular motions?} \rightarrow \text{What functional groups?}$$

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13.3: Interpreting Infrared Spectra

The complete interpretation of an IR spectrum is difficult because most organic molecules have dozens of different bond stretching and bending motions, and thus have dozens of absorptions. On the one hand, this complexity is a problem because it generally limits the laboratory use of IR spectroscopy to pure samples of fairly small molecules—little can be learned from IR spectroscopy about large, complex biomolecules. On the other hand, this complexity is useful because an IR spectrum acts as a unique fingerprint of a compound. In fact, the complex region of the IR spectrum, from 1500 cm^{-1} to around 400 cm^{-1}, is called the *fingerprint region*. If two samples have identical IR spectra, they are almost certainly identical compounds.

Fortunately, we don't need to interpret an IR spectrum fully to get useful structural information. Most functional groups have characteristic IR absorption bands that don't change much from one compound to another. The C=O absorption of a ketone is almost always in the range 1680 to 1750 cm^{-1}; the O–H absorption of an alcohol is almost always in the range 3400 to 3650 cm^{-1}; the C=C absorption of an alkene is almost always in the range 1640 to 1680 cm^{-1}; and so forth. By learning where characteristic functional-group absorptions occur, it's possible to get structural information from IR spectra. Table 13.3.1 lists the characteristic IR bands of some common functional groups.

Table 13.3.1: Characteristic IR Absorptions of Some Functional Groups

Functional Group		Absorption (cm^{-1})	Intensity
Alkane	C–H	2850–2960	Medium
Alkene	=C–H	3020–3100	Medium
	C=C	1640–1680	Medium
Alkyne	≡C–H	3300	Strong
	C≡C	2100–2260	Medium
Alkyl halide	C–Cl	600–800	Strong
	C–Br	500–600	Strong
Alcohol	O–H	3400–3650	Strong, broad
	C–O	1050–1150	Strong
Arene	C–H	3030	Weak
Aromatic ring		1660–2000	Weak
		1450–1600	Medium
Amine	N–H	3300–3500	Medium
	C–N	1030–1230	Medium
Carbonyl compound	C=O	1670–1780	Strong
	Aldehyde	1730	Strong
	Ketone	1715	Strong
	Ester	1735	Strong
	Amide	1690	Strong
	Carboxylic acid	1710	Strong
Carboxylic acid	O–H	2500–3100	Strong, broad
Nitrile	C≡N	2210–2260	Medium
Nitro	NO_2	1540	Strong

% transmittance as a measurement of Intensity

The vertical axis is '% transmittance', which tells how strongly light was absorbed at each frequency. The solid line traces the % transmittance values at each wavelength passing through the sample. At the high end of the axis, 100% transmittance means no absorption occurred at that frequency. Lower % transmittance values indicate that some of the energy is absorbed by the compound, resulting in downward spikes. The spikes are called **absorption bands** in an IR spectrum.

The absorption bands in IR spectra have different intensities, which can usually be referred to as strong (s), medium (m), weak (w), broad, and sharp. The intensity of an absorption band depends on the bond polarity; a more polar bond shows a more intense absorption band. The intensity also depends on the number of bonds responsible for the absorption; the absorption band with more bonds involved has higher intensity.

Looking at the IR spectra example, $\mathrm{C{=}O}$ shows a characteristic strong absorption at 1720 cm^{-1}, while $\mathrm{C{=}C}$ shows a characteristic medium to weak absorption at 1660 cm^{-1}.

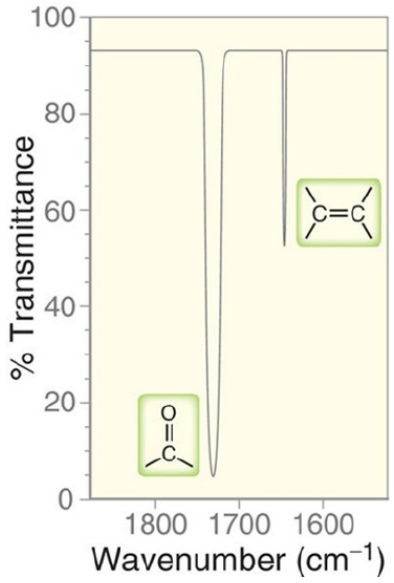


Figure 13.3.1: IR spectra example of different peak intensities.

Wavenumber as a measurement of Bond strength

Look at the IR spectra of hexane, 1-hexene, and 1-hexyne in Figure 13.3.1 to see an example of how IR spectroscopy can be used. Although all three IR spectra contain many peaks, there are characteristic absorptions of $\mathrm{C{=}C}$ and C≡C& functional groups that allow the three compounds to be distinguished. Thus, 1-hexene shows a characteristic $\mathrm{C{=}C}$ absorption at 1660 cm^{-1} and a vinylic =C–H absorption at 3100 cm^{-1}, whereas 1-hexyne has a C≡C absorption at 2100 cm^{-1} and a terminal alkyne ≡C–H absorption at 3300 cm^{-1}.

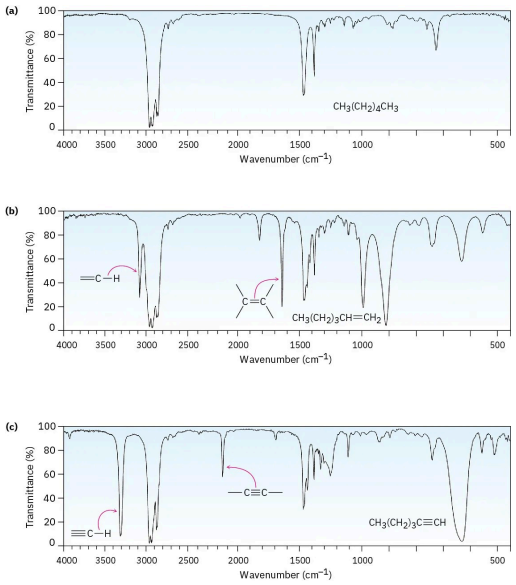


Figure 13.3.2: IR spectra of (a) hexane, (b) 1-hexene, and (c) 1-hexyne. Spectra like these are easily obtained from sub-milligram amounts of material in a few minutes using commercially available instruments.

It helps in remembering the position of specific IR absorptions to divide the IR region from 4000 cm^{-1} to 400 cm^{-1} into four parts, as shown in Figure 13.3.2.

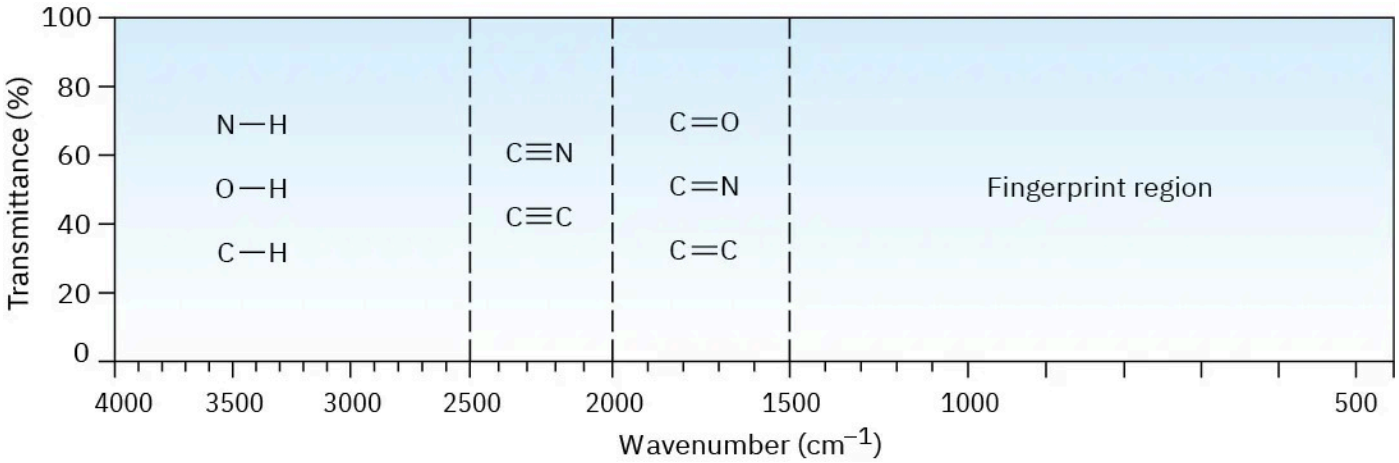


Figure 13.3.3: The four regions of the infrared spectrum: single bonds to hydrogen, triple bonds, double bonds, and fingerprint.

- The region from 4000 to 2500 cm^{-1} corresponds to absorptions caused by N–H, C–H, and O–H single-bond stretching motions. N–H and O–H bonds absorb in the 3300 to 3600 cm^{-1} range; C–H bond stretching occurs near 3000 cm^{-1}.
- The region from 2500 to 2000 cm^{-1} is where triple-bond stretching occurs. Both C≡N and C≡C bonds absorb here.
- The region from 2000 to 1500 cm^{-1} is where double bonds (C=O, C=N, and C=C) absorb. Carbonyl groups generally absorb in the range 1680 to 1750 cm^{-1}, and alkene stretching normally occurs in the narrow range of 1640 to 1680 cm^{-1}.
- The region below 1500 cm^{-1} is the fingerprint portion of the IR spectrum. A large number of absorptions due to a variety of C–C, C–O, C–N, and C–X single-bond vibrations occur here.

Why do different functional groups absorb where they do? As noted previously, a good analogy is that of two weights (atoms) connected by a spring (a bond). Short, strong bonds vibrate at a higher energy and higher frequency than do long, weak bonds, just as a short, strong spring vibrates faster than a long, weak spring. Thus, triple bonds absorb at a higher frequency than double bonds, which in turn absorb at a higher frequency than single bonds. In addition, C–H, O–H, and N–H bonds vibrate at a higher frequency than bonds between heavier C, O, and N atoms.

Worked Example 13.3.1: Distinguishing Isomeric Compounds by IR Spectroscopy

Acetone (CH_3COCH_3) and 2-propen-1-ol ($H_2C{=}CHCH_2$) are isomers. How could you distinguish them by IR spectroscopy?

Strategy

Identify the functional groups in each molecule, and refer to Table 13.3.1.

Solution

Acetone has a strong C=O absorption at 1715 cm^{-1}, while 2-propen-1-ol has an –OH absorption at 3500 cm^{-1} and a C=C absorption at 1660 cm^{-1}.

Exercise 13.3.1

What functional groups might the following molecules contain?

a. A compound with a strong absorption at 1710 cm^{-1}
b. A compound with a strong absorption at 1540 cm^{-1}
c. A compound with strong absorptions at 1720 cm^{-1} and 2500 to 3100 cm^{-1}

Answer available at the end of this section.

Exercise 13.3.2

How might you use IR spectroscopy to distinguish between the following pairs of isomers?

a. CH_3CH_2OH and CH_3OCH_3
b. Cyclohexane and 1-hexene
c. $CH_3CH_2CO_2H$ and $HOCH_2CH_2CHO$

Answer available at the end of this section.

Answers

Exercise 13.3.1

a. Ketone or aldehyde
b. Nitro compound
c. Carboxylic acid

Exercise 13.3.2

a. CH_3CH_2OH has an –OH absorption.
b. 1-Hexene has a double-bond absorption.

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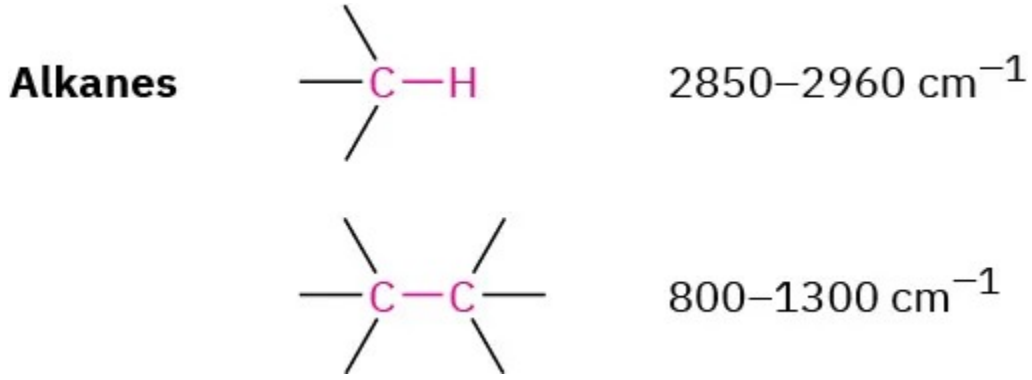
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13.4: Infrared Spectra of Some Common Functional Groups

As each functional group is discussed in future chapters, the spectroscopic properties of that group will be described. For the present, we'll point out some distinguishing features of the hydrocarbon functional groups already studied and briefly preview some other common functional groups. We should also point out, however, that in addition to interpreting absorptions that *are* present in an IR spectrum, it's also possible to get structural information by noticing which absorptions are *not* present. If the spectrum of a compound has no absorptions at 3300 and 2150 cm^{-1}, the compound is not a terminal alkyne; if the spectrum has no absorption near 3400 cm^{-1}, the compound is not an alcohol; and so on.

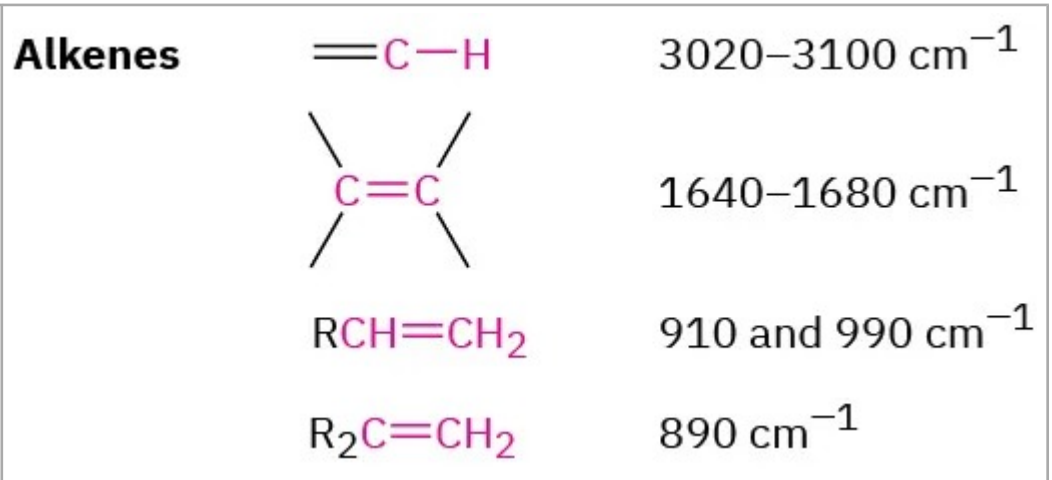
Alkanes

The IR spectrum of an alkane is fairly uninformative because no functional groups are present, and all absorptions are due to C–H and C–C bonds. Alkane C–H bonds show a strong absorption from 2850 to 2960 cm^{-1}, and saturated C–C bonds show a number of bands in the 800 to 1300 cm^{-1} range. Since most organic compounds contain saturated alkane-like portions, most organic compounds have these characteristic IR absorptions. The C–H and C–C bands are clearly visible in the three spectra shown previously.



Alkenes

Alkenes show several characteristic stretching absorptions. Vinylic =C–H bonds absorb from 3020 to 3100 cm^{-1}, and alkene C=C bonds usually absorb near 1650 cm^{-1}, although in some cases, their peaks can be rather small and difficult to see clearly when the alkene is symmetric, or nearly so. Both absorptions are visible in the 1-hexene spectrum in Figure 13.3.2(b).

Alkenes have characteristic =C–H out-of-plane bending absorptions in the 700 to 1000 cm^{-1} range, thereby allowing the substitution pattern on a double bond to be determined (Figure 13.4.1). For example, monosubstituted alkenes such as 1-hexene show strong characteristic bands at 910 and 990 cm^{-1}, and 1,1-disubstituted alkenes ($R_2C{=}CH_2$) have an intense band at 890 cm^{-1}.	

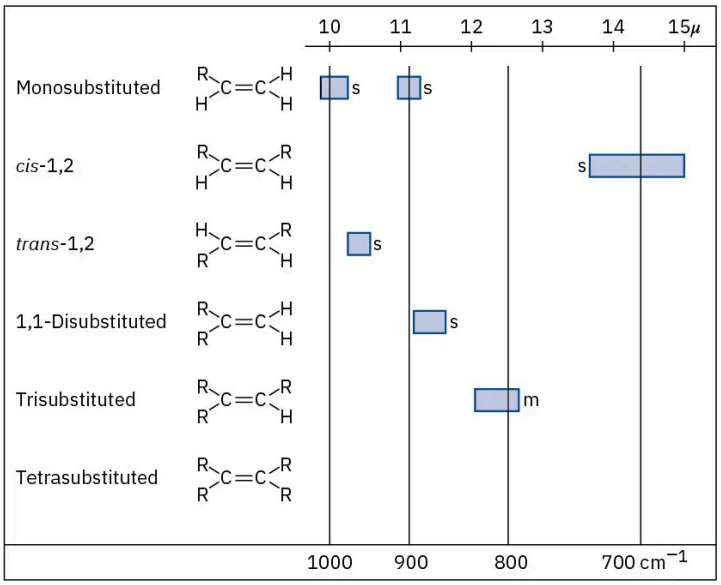
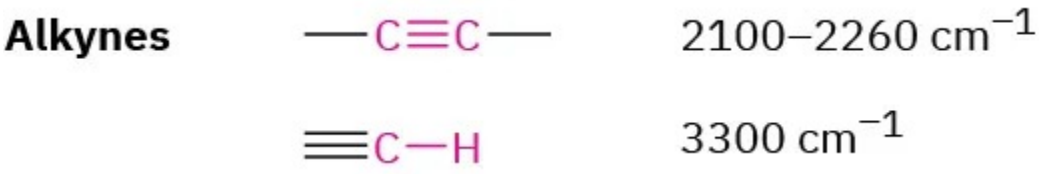


Figure 13.4.1: C–H out-of-plane bending vibrations for substituted alkenes.

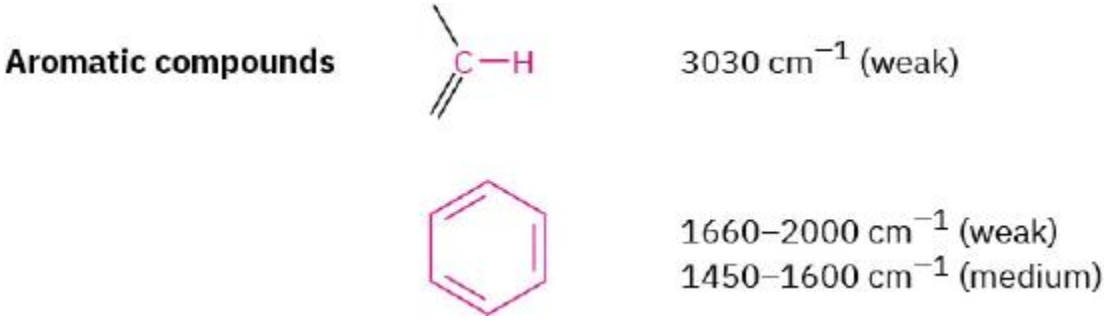
Alkynes

Alkynes show a C≡C stretching absorption at 2100 to 2260 cm^{-1}, an absorption that is much more intense for terminal alkynes than for internal alkynes. Terminal alkynes such as 1-hexyne also have a characteristic ≡C–H stretching absorption at 3300 cm^{-1} (Figure 13.3.2(c)). This band is diagnostic for terminal alkynes because it is fairly intense and quite sharp.



Aromatic Compounds

Aromatic compounds, such as benzene, have a weak C–H stretching absorption at 3030 cm^{-1}, just to the left of a typical saturated C–H band. In addition, they have a series of weak absorptions in the 1660 to 2000 cm^{-1} range and a series of medium-intensity absorptions (always two intense peaks) in the 1450 to 1600 cm^{-1} region (due to complex molecular motions of the entire ring).



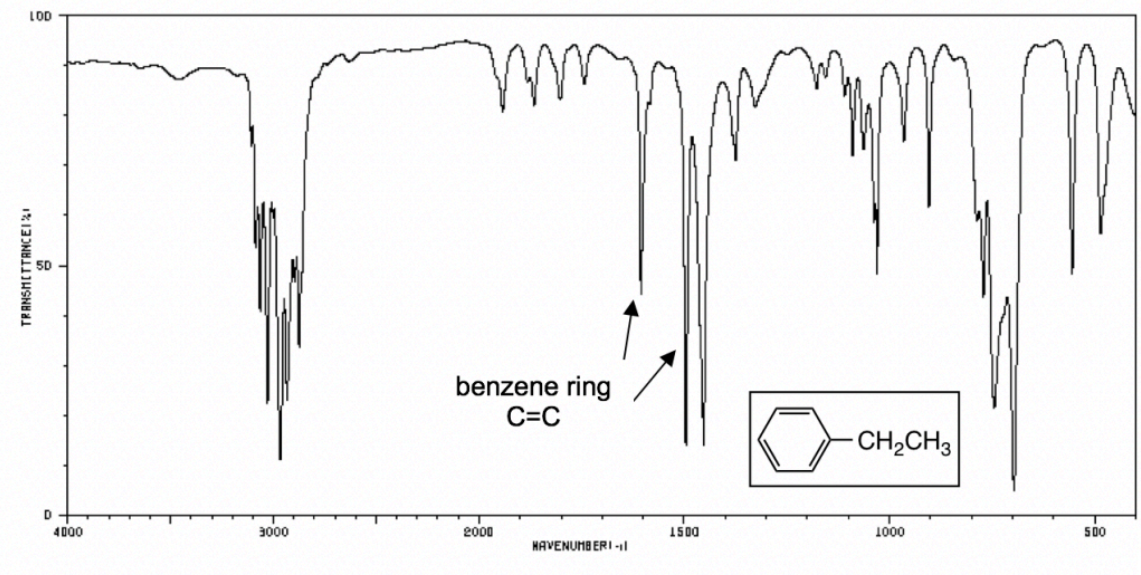


Figure 13.4.2: a series of weak absorptions between 1660 and 2000 cm^{-1} and a series of medium-intensity absorptions between 1450 and 1600 cm^{-1}.

The C–H out-of-plane bending region for benzene derivatives, between 650 and 1000 cm^{-1}, gives valuable information about the ring's substitution pattern (Figure 13.4.3), similar to how it does for the substitution pattern of alkenes.

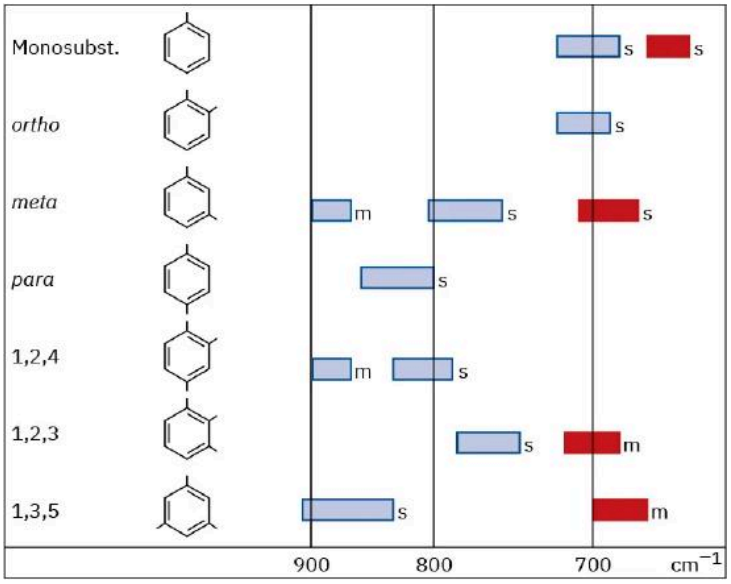


Figure 13.4.3: C–H out-of-plane bending vibrations for substituted benzenes.

Alcohols

Alcohols have a strong C–O stretching absorption near 1050 cm^{-1} and a characteristic O–H stretching absorption between 3300 and 3600 cm^{-1}.

The O–H functional group of alcohols is easy to spot. Alcohols have a characteristic band in the range 3400 to 3650 cm^{-1} that is usually broad and intense. Hydrogen bonding between O–H groups is responsible for making the absorbance so broad. If an O–H stretch is present, it's hard to miss this band or to confuse it with anything else.

Alcohols —O—H 3400–3650 cm^{-1} (broad, intense)

The exact position of the O–H stretch depends on the extent of hydrogen-bonding in the molecule. Unassociated alcohols show a fairly sharp absorption near 3600 cm^{-1}, whereas hydrogen-bonded alcohols show a broader absorption in the 3300 to 3400 cm^{-1} range. The hydrogen-bonded hydroxyl absorption appears at 3350 cm^{-1} in the IR spectrum of cyclohexanol (Figure 13.4.4).

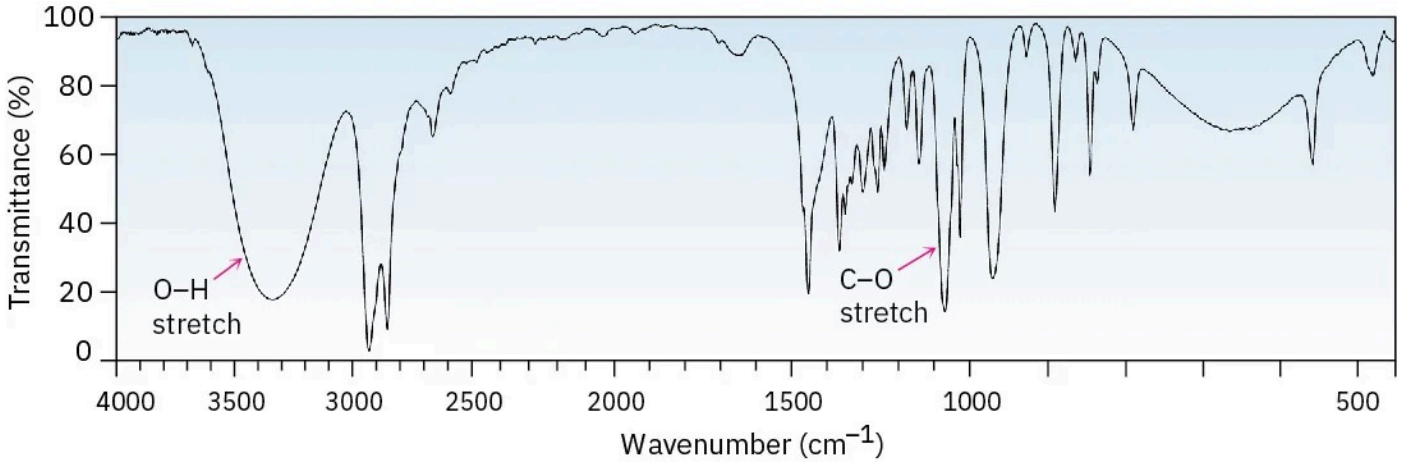


Figure 13.4.4: IR spectrum of cyclohexanol. Characteristic O–H and C–O stretching absorptions are indicated.

Amines

The N–H functional group of amines is also easy to spot in the IR, with a characteristic absorption in the 3300 to 3500 cm^{-1} range. Although alcohols absorb in the same range, an N–H absorption band is much sharper and less intense than an O–H band.

Amines —N(—H)— 3300–3500 cm^{-1} (sharp, medium intensity)

Primary amines (R–NH_2) have two absorbances—one for the symmetric stretching mode and one for the asymmetric mode (Figure 13.4.5). Secondary amines (R_2N–H) only have one N–H stretching absorbance in this region.

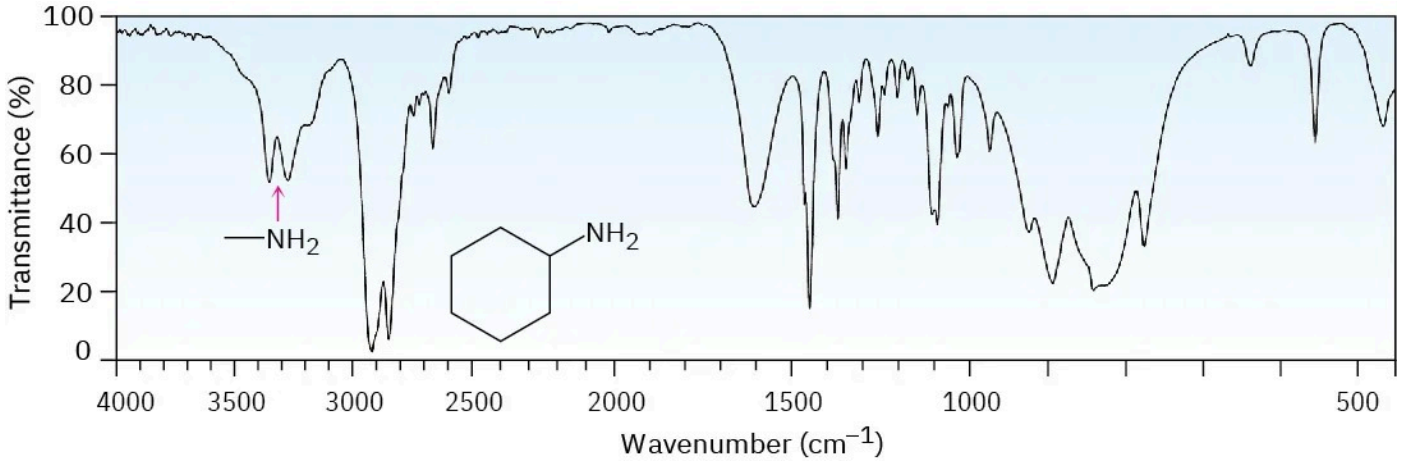


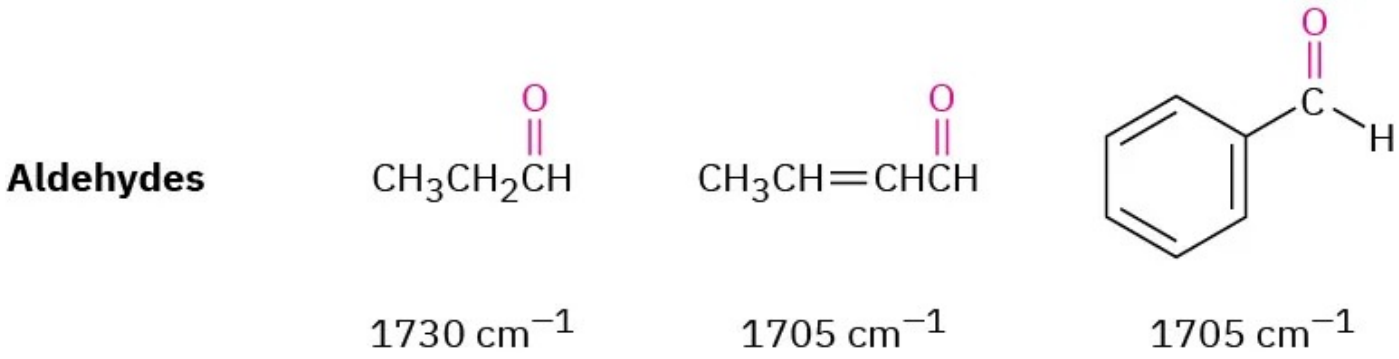
Figure 13.4.5: IR spectrum of cyclohexylamine.

Carbonyl Compounds

Carbonyl functional groups are the easiest to identify of all IR absorptions because of their sharp, intense peak in the range 1670 to 1780 cm^{-1}. Most importantly, the exact position of absorption within this range can often be used to identify the exact kind of carbonyl functional group—aldehyde, ketone, ester, and so forth.

ALDEHYDES

The carbonyl(C=O) stretching vibration band of saturated aldehydes absorbs at 1730 cm^{-1} (Figure 13.4.6); aldehydes next to either a double bond or an aromatic ring absorb at 1705 cm^{-1}.



The C–H group attached to the carbonyl is responsible for the characteristic IR absorbance for aldehydes at 2750 and 2850 cm^{-1}. Although these are not very intense, the absorbance at 2750 cm^{-1} is useful for distinguishing between an aldehyde and a ketone.

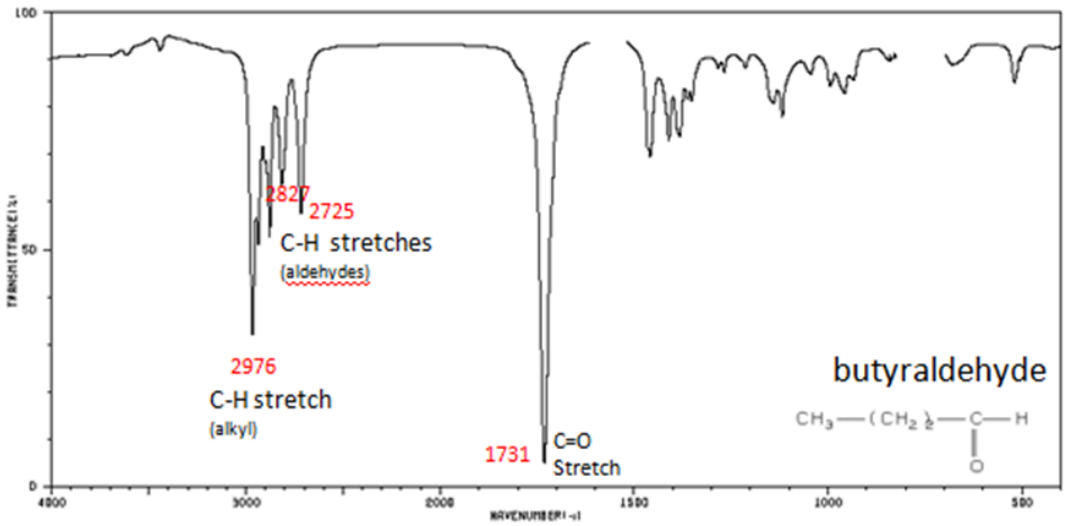


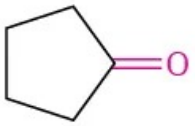
Figure 13.4.6: Infrared Spectrum of Butyraldehyde

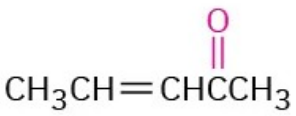
KETONES

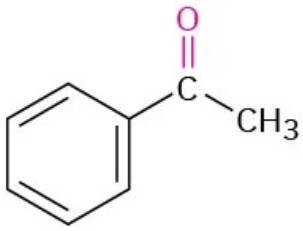
The carbonyl (C=O) stretching vibration band of saturated open-chain ketones and six-membered cyclic ketones absorbs at 1715 cm^{-1}. Ring strain stiffens the C=O bond, making five-membered cyclic ketones absorb at 1750 cm^{-1}, and four-membered cyclic ketones absorb at 1780 cm^{-1}, about 20 to 30 cm^{-1} lower than the corresponding saturated ketone (Figure 13.4.7).

Ketones









1715 cm^{-1} 1750 cm^{-1} 1690 cm^{-1} 1690 cm^{-1}

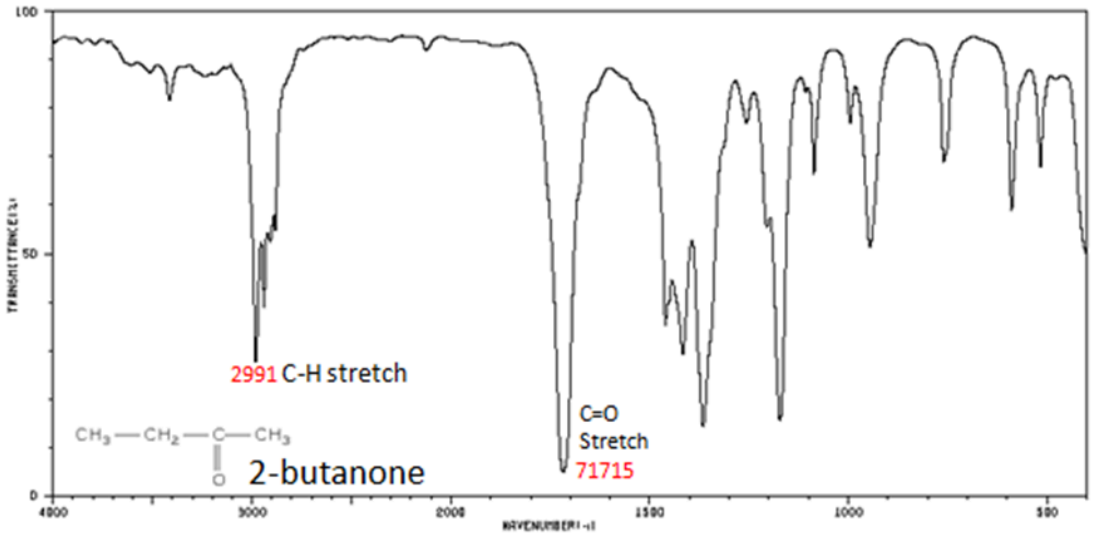


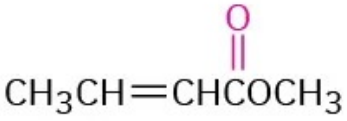
Figure 13.4.7: Infrared Spectrum of 2-Butanone. Note the C=O band should be read as 1715.

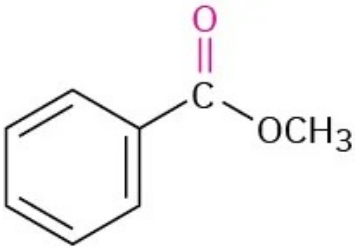
ESTERS

Saturated esters have a C=O absorbance at 1735 cm^{-1} and two strong absorbances in the 1300 to 1000 cm^{-1} range from the C–O portion of the functional group. Like other carbonyl functional groups, esters next to either an aromatic ring or a double bond absorb at 1715 cm^{-1}, about 20 to 30 cm^{-1} lower than a saturated ester.

Esters







1735 cm^{-1} 1715 cm^{-1} 1715 cm^{-1}

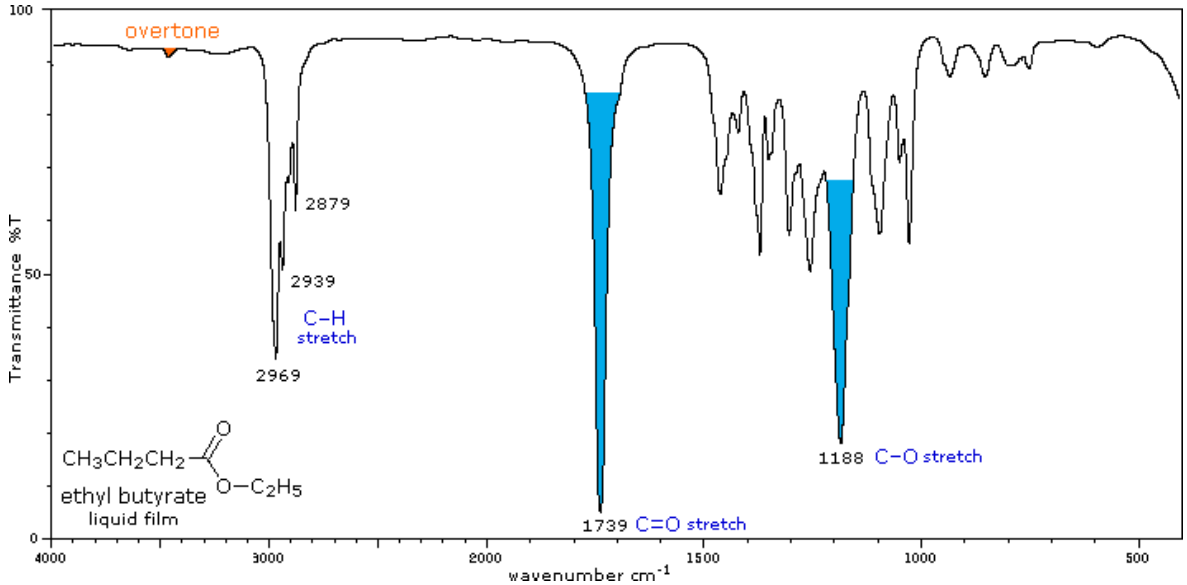
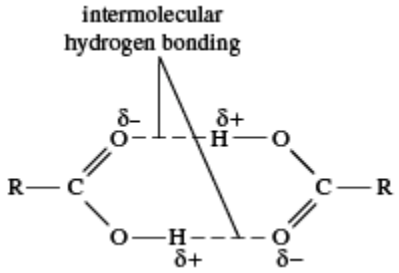


Figure 13.4.8: The Infrared Spectrum of ethyl butanoate. Carbonyl (1739 cm^{-1}) and carbon-oxygen single bond (1188 cm^{-1}) peaks of an ester

CARBOXYLIC ACIDS

The carboxyl group is associated with two characteristic infrared stretching absorptions, which change markedly with hydrogen bonding. 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 Hydrogen Bonding Dimer of Carboxylic Acids

The spectrum of propionic acid (propanoic acid) dissolved in CCl_4, shown below, is illustrative. The smaller peaks protruding near 2655 and 2560 cm^{-1} are characteristic of the dimer. In ether solvents, a sharper hydrogen-bonded monomer absorption near 3500 cm-1 is observed, due to competition of the ether oxygen as a hydrogen bond acceptor. The carbonyl stretching frequency of the dimer is found near 1710 cm^{-1}, but is increased by 25 cm^{-1} or more in the monomeric state. Other characteristic stretching and bending absorptions are marked in the spectrum.

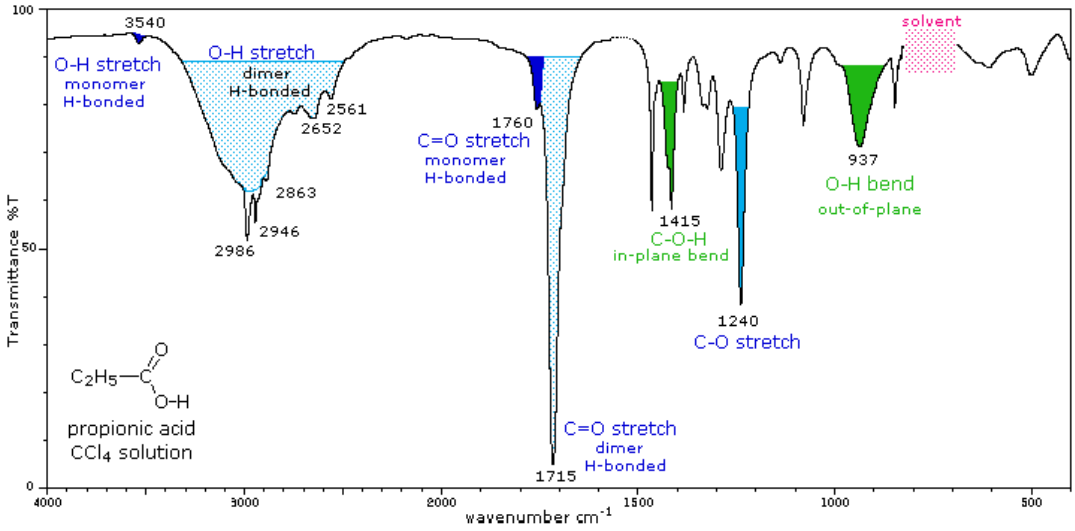


Figure 13.4.9: The Infrared Spectrum of Propanoic Acid

Combination of Simple Functional Groups with an Aromatic Ring

The IR spectrum of phenylacetylene, shown in Figure 13.4.10, gives an example, clearly showing the following absorbances: ≡C–H stretch at 3300 cm^{-1}, C–H stretches from the benzene ring at 3000 to 3100 cm^{-1}, C=C stretches of the benzene ring between 1450 and 1600 cm^{-1}, and out-of-plane bending of the ring's C–H groups, indicating monosubstitution at 750 cm^{-1}.

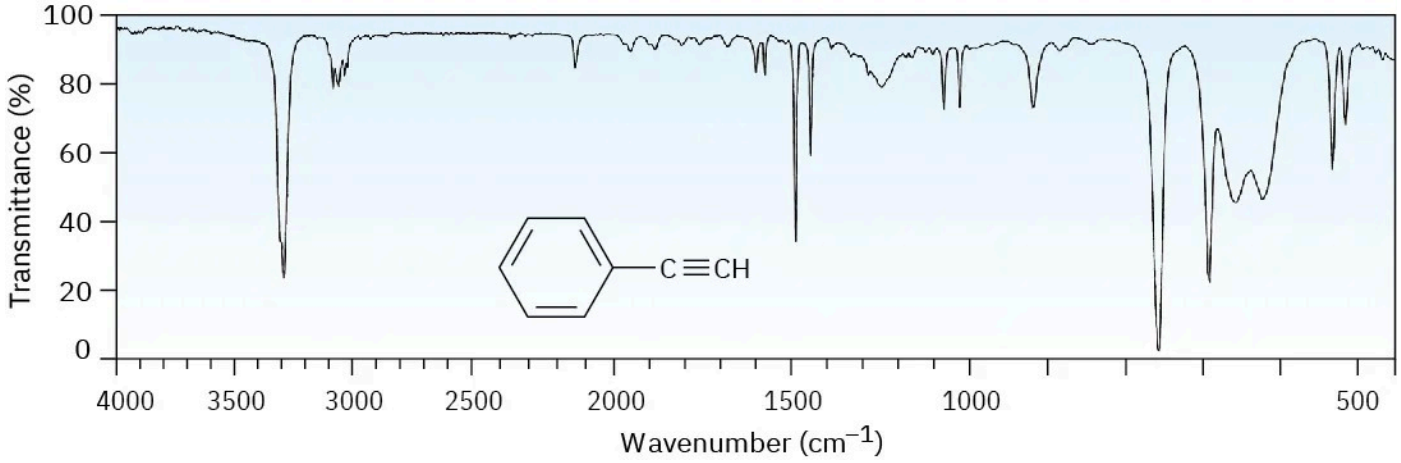


Figure 13.4.10: C–H out-of-plane bending vibrations for substituted benzenes.

Phenols also show a characteristic broad IR absorption at 3500 cm^{-1} due to the –OH group, as well as the usual 1500 and 1600 cm^{-1} aromatic bands (Figure 13.4.11). In phenol itself, monosubstituted aromatic-ring peaks are visible at 690 and 760 cm^{-1}.

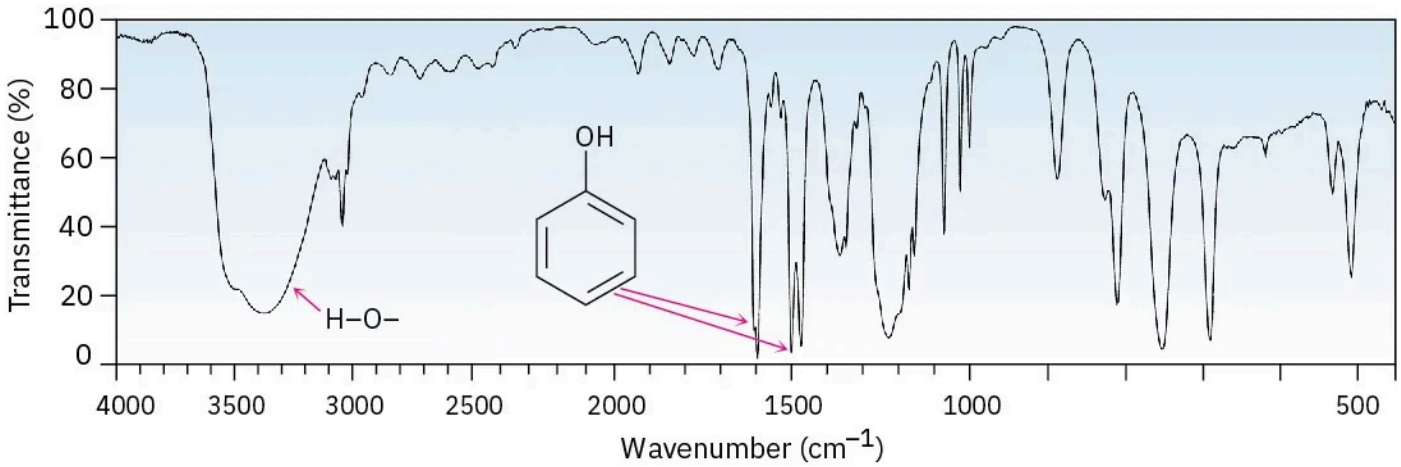


Figure 13.4.11: IR spectrum of phenol.

Benzaldehyde also shows a characteristic broad IR absorption at 1700 cm^{-1}. The C–H group attached to the carbonyl is responsible for the characteristic IR absorbance for aldehydes at 2750 and 2850 cm^{-1}. The two aromatic bands appear at the usual range, between 1500 and 1600 cm^{-1} (Figure 13.4.12). The monosubstituted aromatic-ring peaks are visible at 690 and 760 cm^{-1}.

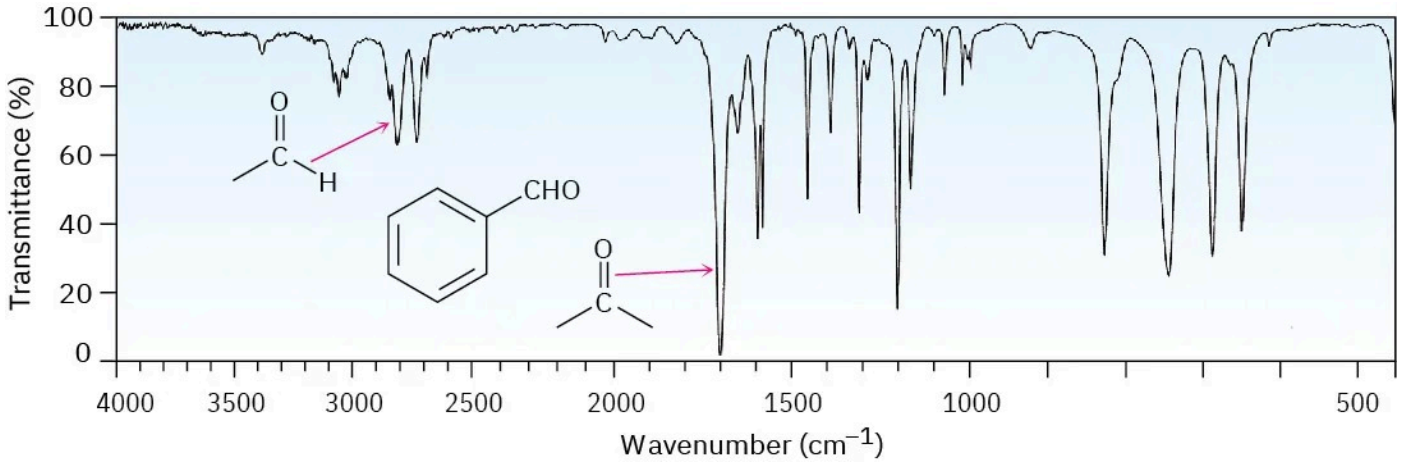
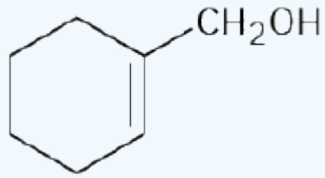
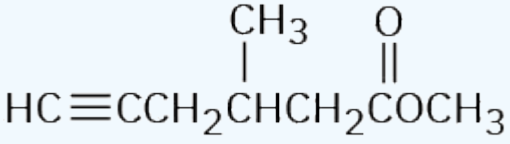


Figure 13.4.12: The IR spectrum of benzaldehyde.

Worked Example 13.4.1: Predicting IR Absorptions of Compounds

Where might the following compounds have IR absorptions?

a. 

b. 

Strategy

Identify the functional groups in each molecule, and then check IR Table to see where those groups absorb.

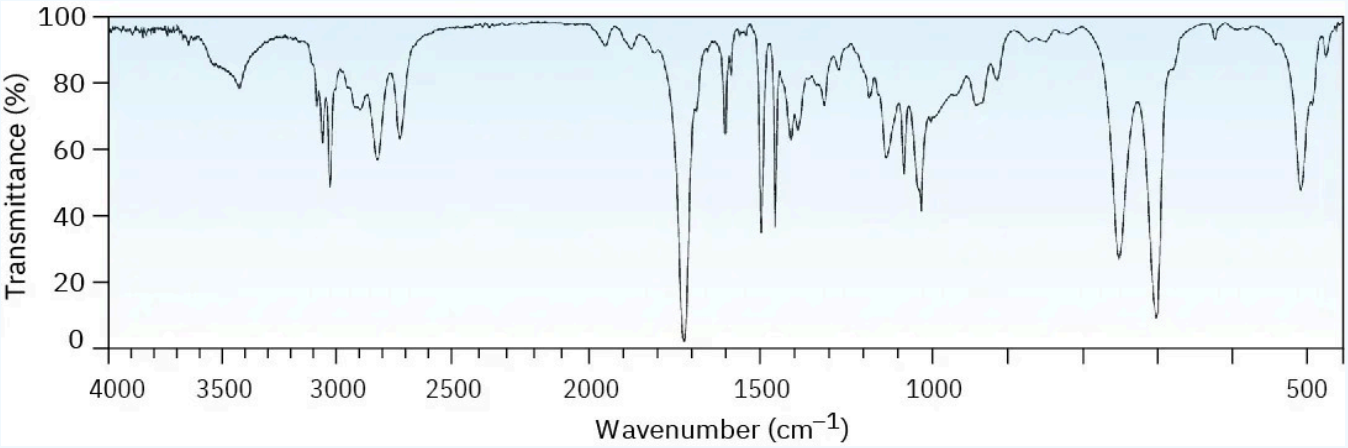
Solution

a. *Absorptions:* 3400 to 3650 cm^{-1} (O–H), 3020 to 3100 cm^{-1} (=C–H), 1640 to 1680 cm^{-1} (C=C). This molecule has an alcohol O–H group and an alkene double bond.

b. *Absorptions:* 3300 cm^{-1} (≡C–H), 2100 to 2260 cm^{-1} (C≡C), 1735 cm^{-1} (C=O). This molecule has a terminal alkyne triple bond and a saturated ester carbonyl group.

Worked Example 13.4.2: Identifying Functional Groups from an IR Spectrum

The IR spectrum of an unknown compound is shown below. What functional groups does the compound contain?

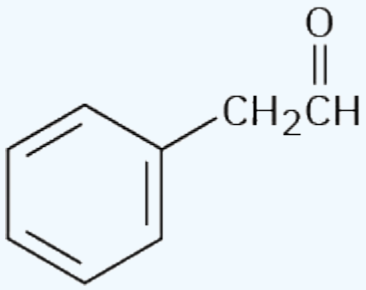


Strategy

All IR spectra have many absorptions, but those useful for identifying specific functional groups are usually found in the region from 1500 cm^{-1} to 3300 cm^{-1}. Pay particular attention to the carbonyl region (1670 to 1780 cm^{-1}), the aromatic region (1660 to 2000 cm^{-1}), the triple-bond region (2000 to 2500 cm^{-1}), and the C–H region (2500 to 3500 cm^{-1}).

Solution

The spectrum shows an intense absorption at 1725 cm^{-1} due to a carbonyl group (perhaps an aldehyde, –CHO), a series of weak absorptions from 1800 to 2000 cm^{-1} characteristic of aromatic compounds, and a C–H absorption near 3030 cm^{-1}, also characteristic of aromatic compounds. In fact, the compound is phenylacetaldehyde.



Phenylacetaldehyde

Exercises

Exercise 13.4.1

Assume that you need to prepare 5-cholesten-3-one from cholesterol. How could you use IR spectroscopy to tell whether the reaction was successful? What differences would you look for in the IR spectra of the starting material and the product?

Answer available at the end of this section.

Exercise 13.4.2

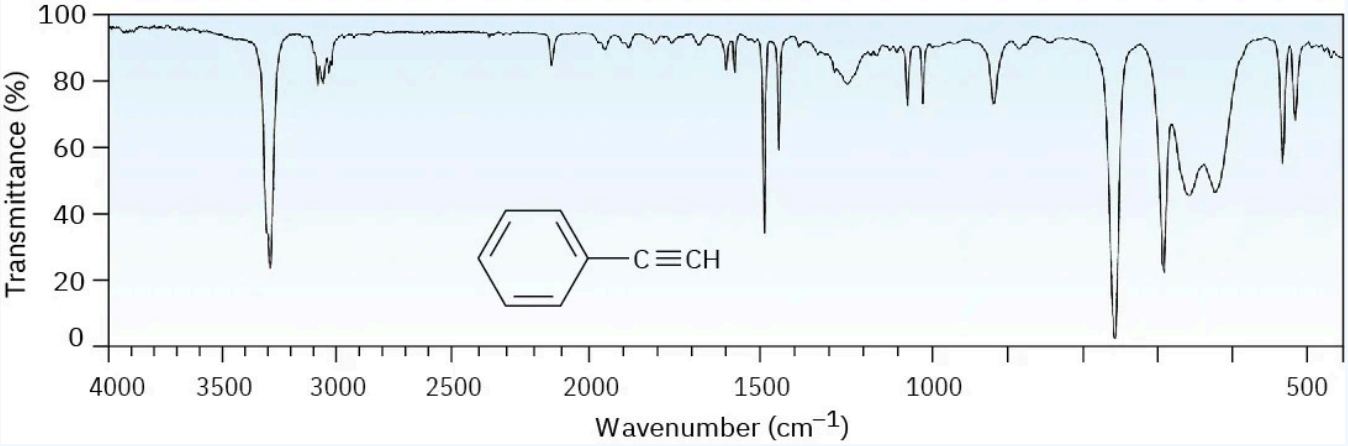
Where might the following compounds have IR absorptions?

a. **b.** **c.** **d.**

Answer available at the end of this section.

Exercise 13.4.3

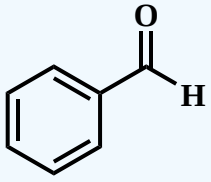
The IR spectrum of phenylacetylene is shown below. What absorption bands can you identify?

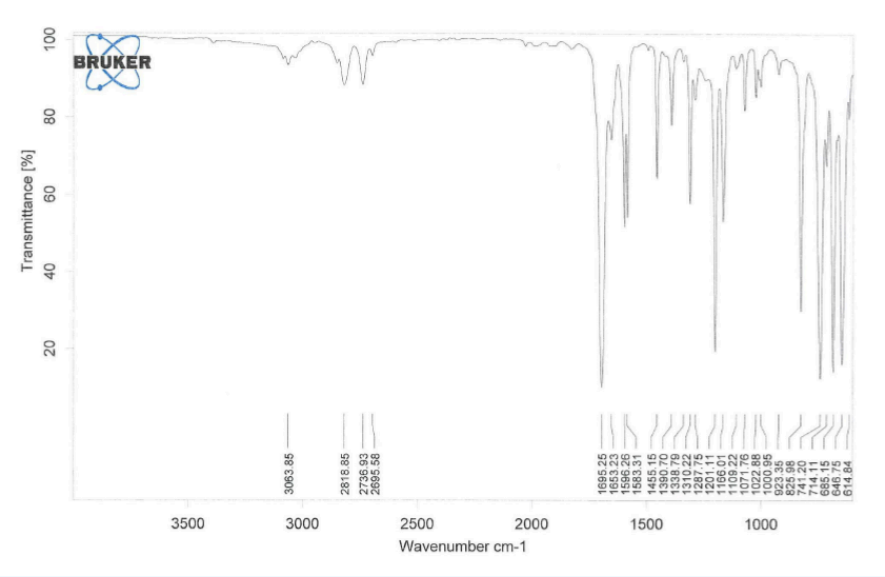


Answer available at the end of this section.

Exercise 13.4.4

What notable peaks in the IR spectrum verify that benzaldehyde is present?

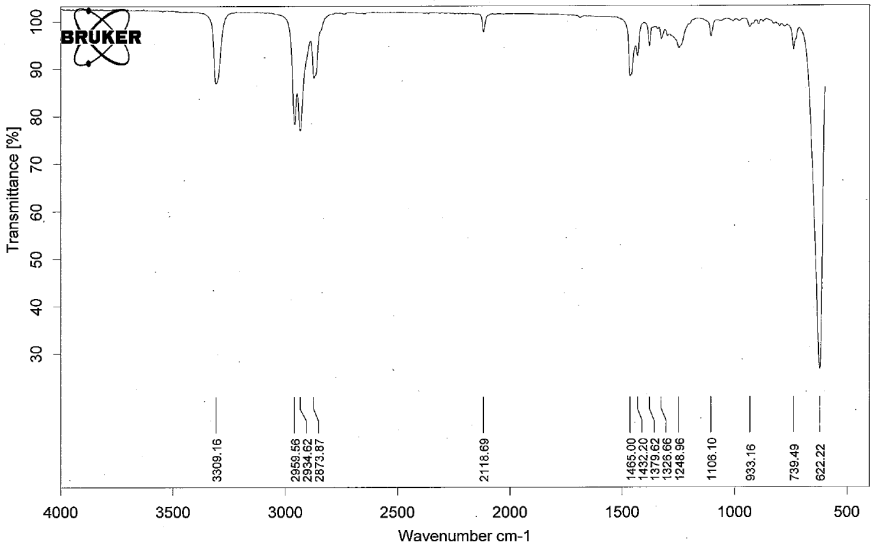




Answer available at the end of this section.

Exercise 13.4.5

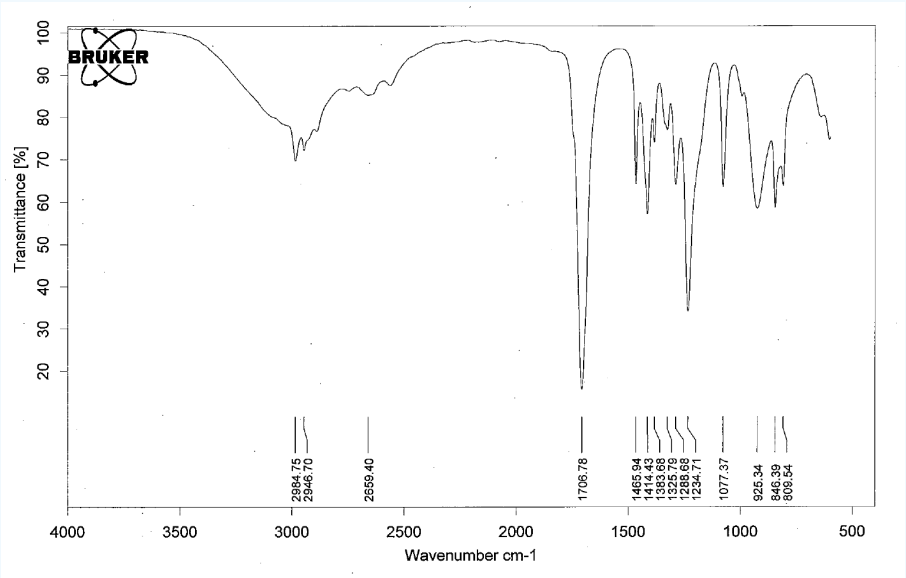
What functional group is present in the spectrum below?



Answer available at the end of this section.

Exercise 13.4.6

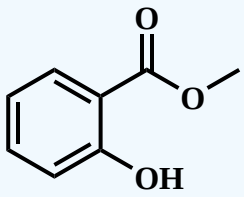
What functional group is present in the spectrum below?

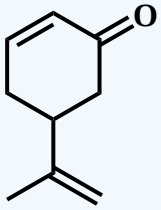


Answer available at the end of this section.

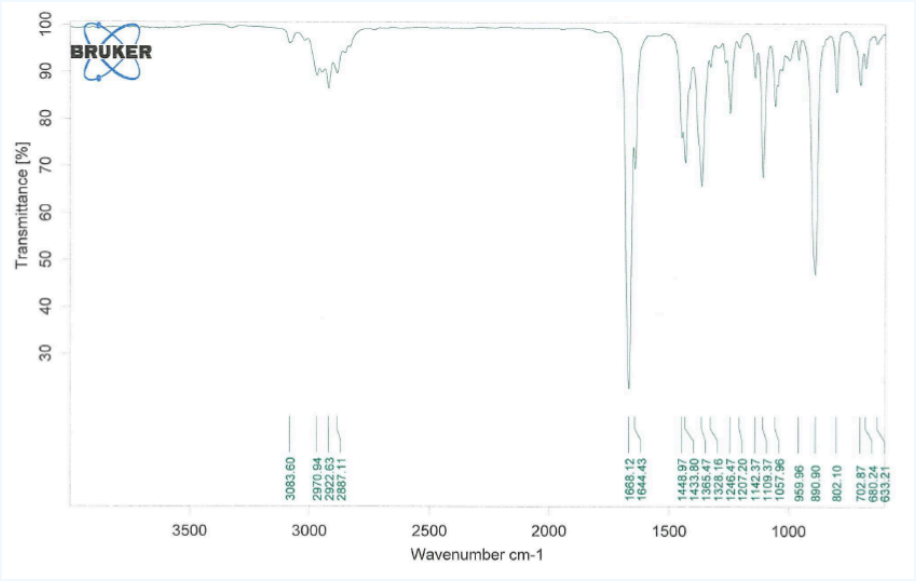
Exercise 13.4.7

Which IR spectrum goes with which molecule below?

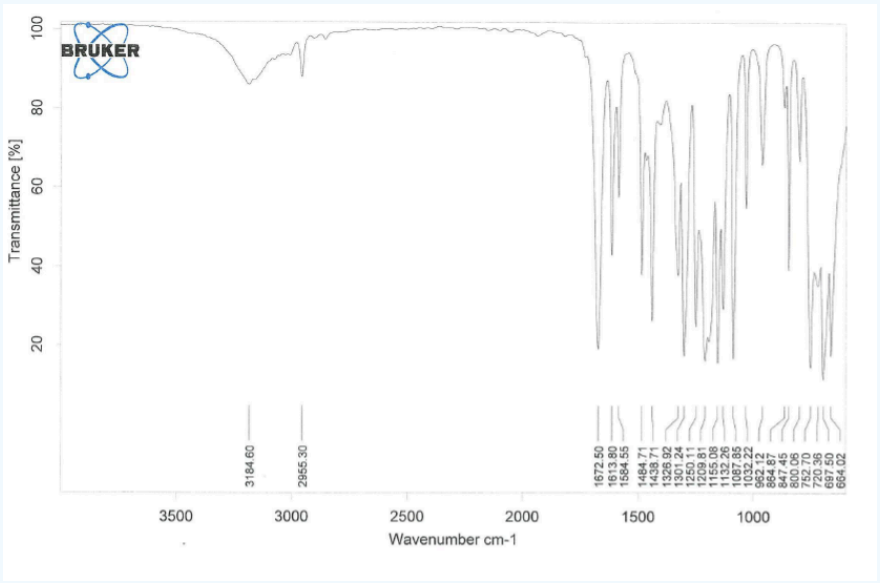
Molecule A: 

Molecule B: 

IR spectrum 1:



IR spectrum 2:



Answer available at the end of this section.

Answers

Exercise 13.4.1

Disappearance of $-\mathrm{OH}$ absorption; appearance of $\mathrm{C{=}O}$

Exercise 13.4.2

a.1715, 1640, 1250 cm^{-1} **b.**1730, 2100, 3300 cm^{-1}

c. 1720, 2500–3100, 3400–3650 cm^{-1} **d.** 1690, 1650, 2230 cm^{-1}

Exercise 13.4.3

1450–1600 cm^{-1}: aromatic ring; 2100 cm^{-1}: C≡C; 3300 cm^{-1}: C≡C–H

Exercise 13.4.4

Frequency (cm^{-1})	Functional Group
3063	Csp2-H
2818 and 2736	aldehyldic proton
1695	C=O
1653-1455	aromatic ring

Exercise 13.4.5

Alkyne

Exercise 13.4.6

Carboxylic Acid

Exercise 13.4.7

Molecule A is Spectrum 2. Molecule B is Spectrum 1.

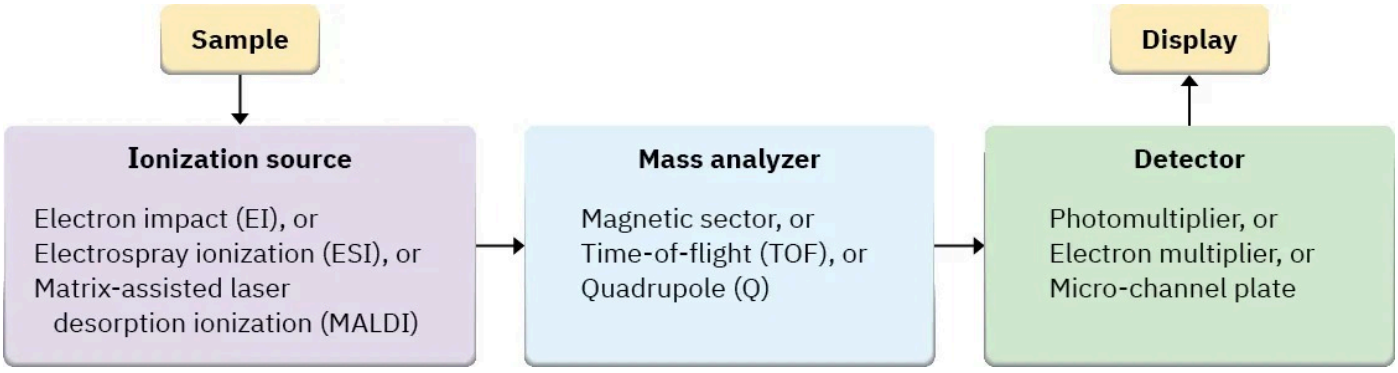
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13.5: Mass Spectrometry of Small Molecules - Magnetic-Sector Instruments

At its simplest, mass spectrometry (MS) is a technique for measuring the mass, and therefore the molecular weight (MW), of a molecule. In addition, it's often possible to gain structural information about a molecule by measuring the masses of the fragments produced when molecules are broken apart.

More than 20 different kinds of commercial mass spectrometers are available depending on the intended application, but all have three basic parts: an *ionization source* in which sample molecules are given an electrical charge, a *mass analyzer* in which ions are separated by their mass-to-charge ratio, and a *detector* in which the separated ions are observed and counted.



Among the most common mass spectrometers used for routine purposes in the laboratory is the electron-impact, magnetic-sector instrument shown schematically in Figure 13.5.1.

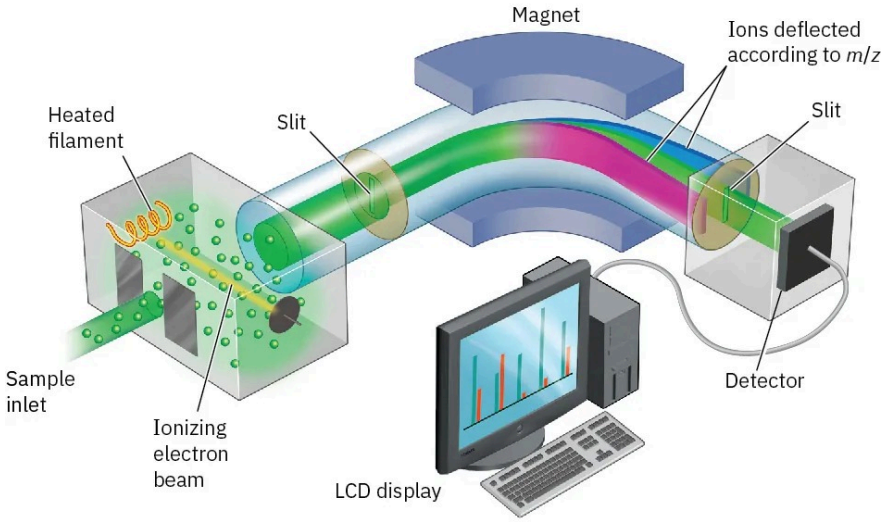
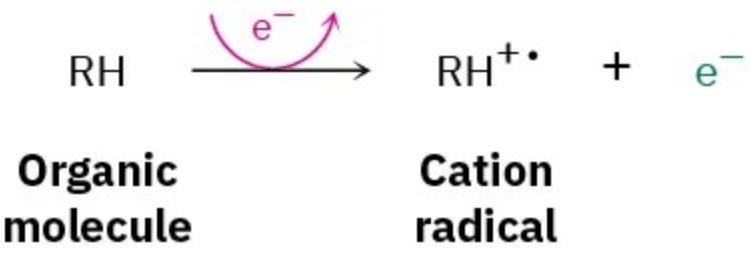


Figure 13.5.1: Representation of an electron-ionization, magnetic-sector mass spectrometer. Molecules are ionized by collision with high-energy electrons, causing some of the molecules to fragment. Passage of the charged fragments through a magnetic field then sorts them according to their mass.

A small amount of sample is vaporized into the ionization source, where it is bombarded by a stream of high-energy electrons. The energy of the electron beam can be varied but is commonly around 70 electron volts (eV), or 6700 kJ/mol. When a high-energy electron strikes an organic molecule, it dislodges a valence electron from the molecule, producing a cation radical—*cation* because the molecule has lost an electron and now has a positive charge; *radical* because the molecule now has an odd number of electrons.



Electron bombardment transfers so much energy that most of the cation radicals fragment after formation. They break apart into smaller pieces, some of which retain the positive charge and some of which are neutral. The fragments then flow through a curved pipe in a strong magnetic field, which deflects them into different paths according to their mass-to-charge ratio (*m/z*). Neutral fragments are not deflected by the magnetic field and are lost on the walls of the pipe, but positively charged fragments are sorted by the mass spectrometer onto a detector, which records them as peaks at the various *m/z* ratios. Since the number of charges *z* on each ion is usually 1, the value of *m/z* for each ion is simply its mass *m*. Masses up to approximately 2500 atomic mass units (amu) can be analyzed by this type of instrument.

Another common type of mass spectrometer uses what is called a quadrupole mass analyzer, which has a set of four solid rods is arranged parallel to the direction of the ion beam, with an oscillating electrostatic field is generated in the space between the rods. For a given field, only one *m/z* value will make it through the quadrupole region. The others will crash into the rods or the walls of the instrument and never reach the detector Figure 13.5.2.

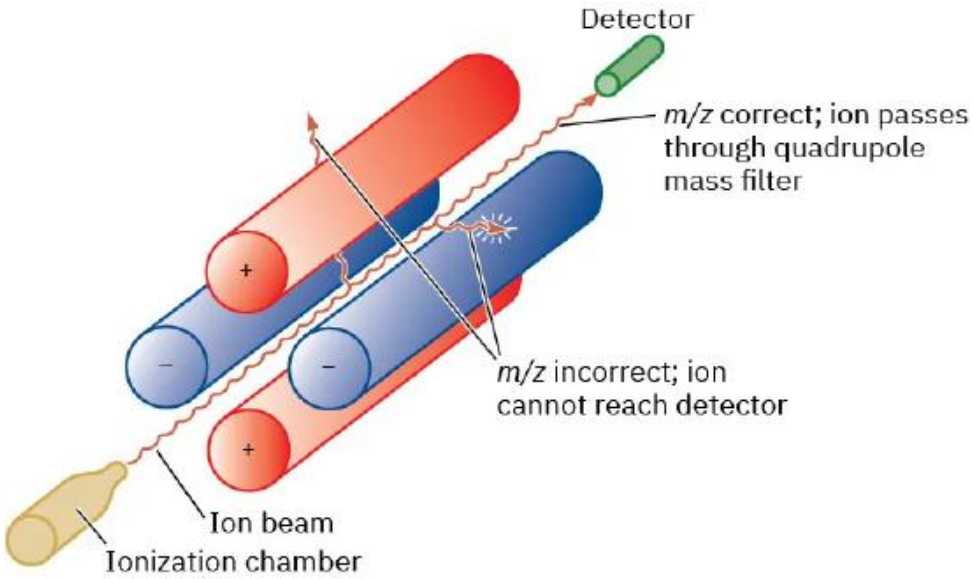


Figure 13.5.2: Representation of a quadrupole mass analyzer. Only ions of a certain *m/z* will reach the detector; other ions will collide with the rods.

The mass spectrum of a compound is typically presented as a bar graph, with masses (*m/z* values) on the *x* axis and intensity, or relative abundance of ions of a given *m/z* striking the detector, on the *y* axis. The tallest peak, assigned an intensity of 100%, is called the base peak, and the peak that corresponds to the unfragmented cation radical is called the parent peak, or the *molecular ion* (M^+, or simply *M*). Figure 13.5.3 shows the mass spectrum of propane.

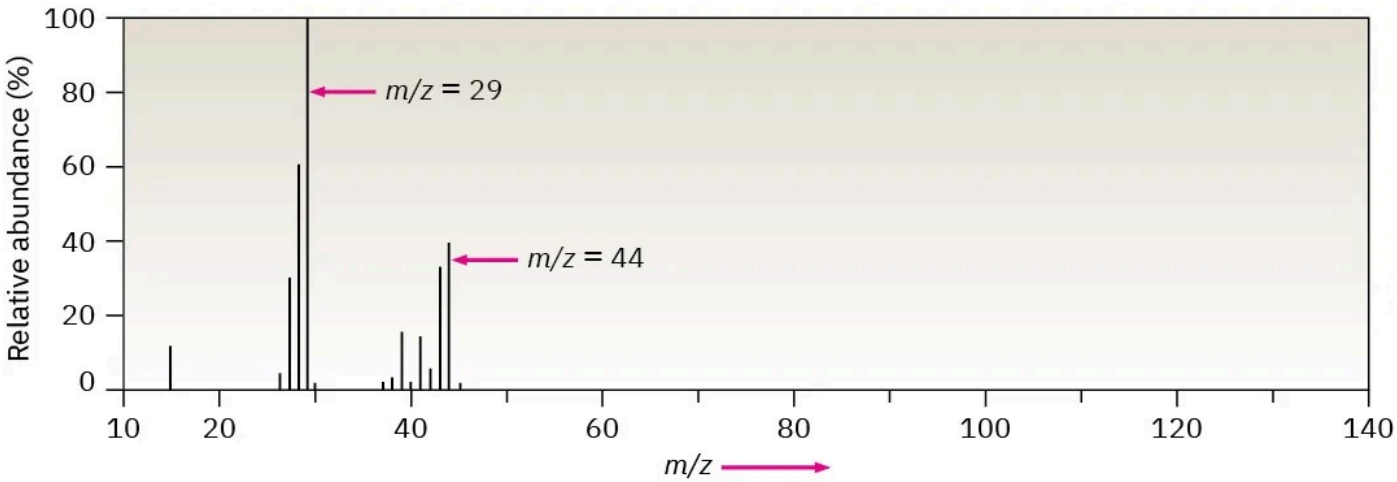


Figure 13.5.3: Mass spectrum of propane (C_3H_8; MW = 44).

Mass spectral fragmentation patterns are usually complex, and the molecular ion is often not the base peak. The mass spectrum of propane in Figure 13.5.3, for instance, shows a molecular ion at *m/z* = 44 that is only about 30% as high as the base peak at *m/z* = 29. In addition, many other fragment ions are present.

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13.6: Interpreting Mass Spectra

What kinds of information can we get from a mass spectrum?

The most obvious information is the sample's molecular weight, which can be invaluable in itself. If we were given samples of hexane (MW = 86), 1-hexene (MW = 84), and 1-hexyne (MW = 82), for example, mass spectrometry would easily distinguish them.

Some instruments, called *double-focusing mass spectrometers*, have two magnetic sectors in their mass analyzers, giving these spectrometers have such high resolution that they provide mass measurements accurate to 5 ppm, or about 0.0005 amu, making it possible to distinguish between two formulas with the same nominal mass. For example, both C_5H_{12} and C_4H_8O have MW = 72, but they differ slightly beyond the decimal point: C_5H_{12} has an exact mass of 72.0939 amu, whereas C_4H_8O has an exact mass of 72.0575 amu. A high-resolution instrument can easily distinguish between them. Note, however, that exact mass measurements refer to molecules with specific isotopic compositions. Thus, the sum of the exact atomic masses of the specific isotopes in a molecule is measured—1.007 83 amu for ^{1}H, 12.000 00 amu for ^{12}C, 14.003 07 amu for ^{14}N, 15.994 91 amu for ^{16}O, and so on—rather than the sum of the average atomic masses of elements, as found on a periodic table.

Unfortunately, not every compound shows a molecular ion in its electron-impact mass spectrum. Although M^+ is usually easy to identify if it's abundant, some compounds, such as 2,2-dimethylpropane, fragment so easily that no molecular ion is observed (Figure 13.6.1). In such cases, alternative "soft" ionization methods that don't use electron bombardment can prevent or minimize fragmentation.

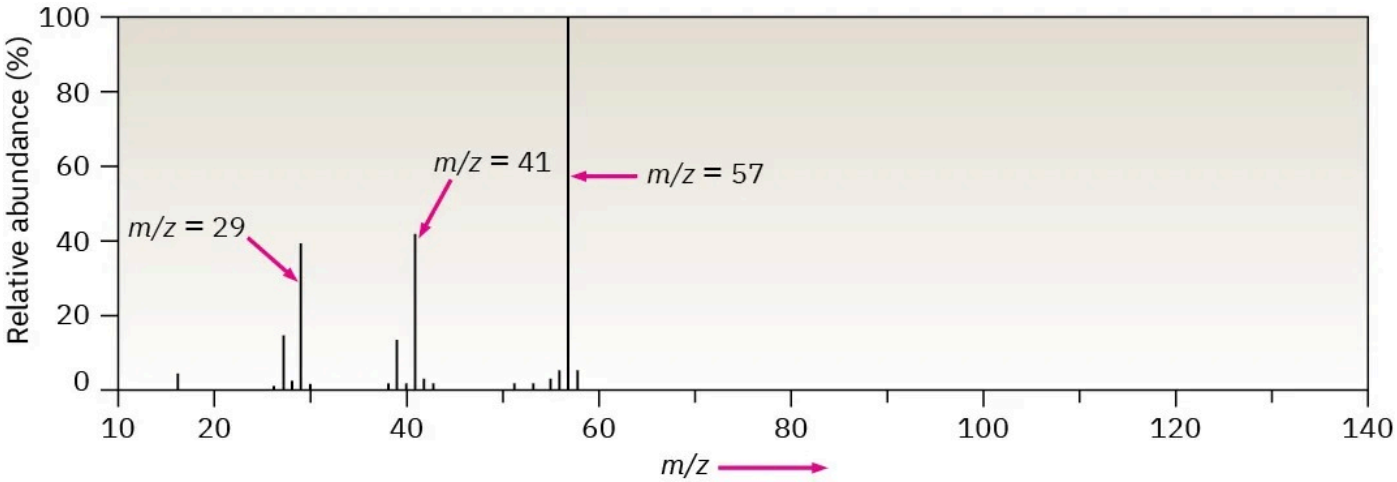


Figure 13.6.1: Mass spectrum of 2,2-dimethylpropane (C_5H_{12}; MW = 72). No molecular ion is observed when electron-impact ionization is used. What do you think is the formula and structure of the M^+ peak at *m/z* = 57?

Knowing the molecular weight allows narrowing the choices of molecular formula considerably. For example, if the mass spectrum of an unknown compound shows a molecular ion at *m/z* = 110, the molecular formula is likely to be C_8H_{14}, $C_7H_{10}O$, $C_6H_6O_2$, or $C_6H_{10}N_2$. There are always a number of molecular formulas possible for all but the lowest molecular weights, and a computer can easily generate a list of the choices.

A further point about mass spectrometry, noticeable in the spectra of both propane (Figure 13.6.2) and 2,2-dimethylpropane (Figure 13.6.1), is that the peak for the molecular ion is not at the highest *m/z* value. There is also a small peak at M + 1 due to the presence of different isotopes in the molecules. Although ^{12}C is the most abundant carbon isotope, a small amount (1.10% natural abundance) of ^{13}C is also present. Thus, a certain percentage of the molecules analyzed in the mass spectrometer are likely to contain a ^{13}C atom, giving rise to the observed M + 1 peak. In addition, a small amount of ^{2}H (deuterium; 0.015% natural abundance) is present, making a further contribution to the M + 1 peak.

Mass spectral fragmentation patterns are usually complex, and the molecular ion is often not the base peak. The mass spectrum of propane in Figure 13.6.2, for instance, shows a molecular ion at *m/z* = 44 that is only about 30% as high as the base peak at

m/z = 29. In addition, many other fragment ions are present.

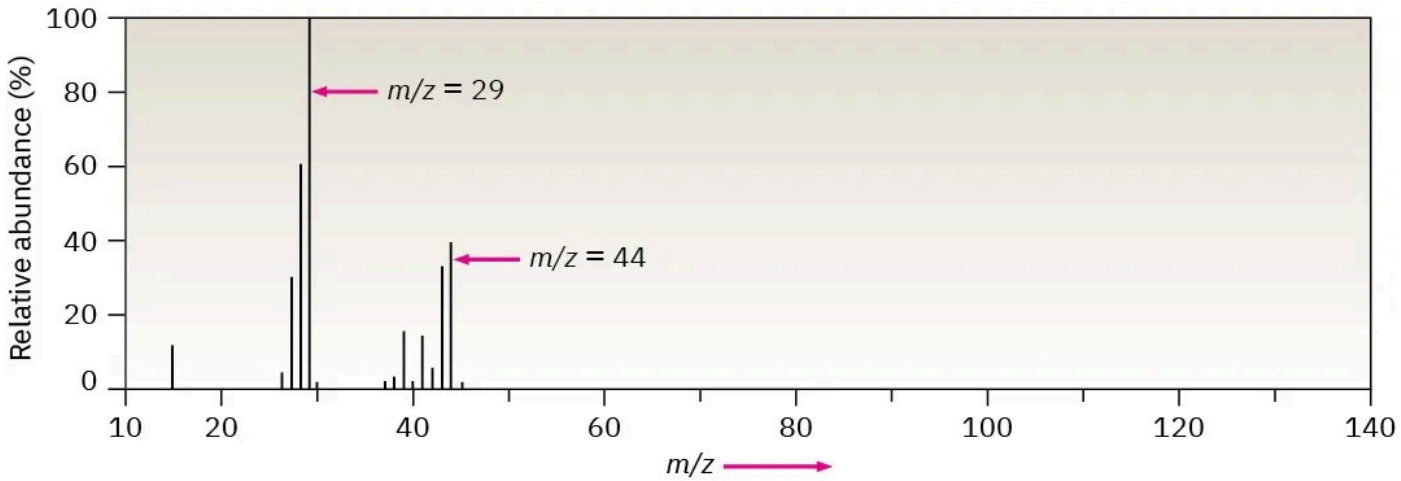


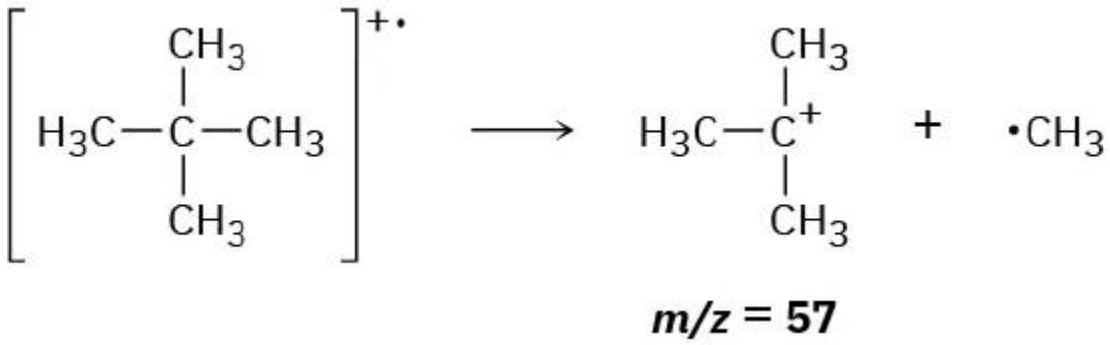
Figure 13.6.2: Mass spectrum of propane (C_3H_8; MW = 44).

Molecular Fingerprint

Mass spectrometry would be useful even if molecular weight and formula were the only information that could be obtained, but in fact, it provides much more. For one thing, the mass spectrum of a compound serves as a kind of "molecular fingerprint." Every organic compound fragments in a unique way depending on its structure, and the likelihood of two compounds having identical mass spectra is small. Thus, it's sometimes possible to identify an unknown by computer-based matching of its mass spectrum to one of the more than 785,0̸61 searchable spectra recorded in a database called the *Registry of Mass Spectral Data*.

It's also possible to derive structural information about a molecule by interpreting its fragmentation pattern. Fragmentation occurs when the high-energy cation radical flies apart by spontaneous cleavage of a chemical bond. One of the two fragments retains the positive charge and is a carbocation, while the other fragment is a neutral radical.

Not surprisingly, the positive charge often remains with the fragment that is best able to stabilize it. In other words, a relatively stable carbocation is often formed during fragmentation. For example, 2,2-dimethylpropane tends to fragment in such a way that the positive charge remains with the *tert*-butyl group. 2,2-Dimethylpropane therefore has a base peak at *m/z* = 57, corresponding to $C_4H_9^+$ (Figure 13.6.1).



Because mass-spectral fragmentation patterns are usually complex, it's often difficult to assign structures to fragment ions. Most hydrocarbons fragment in many ways, as demonstrated by the mass spectrum of hexane in Figure 13.6.3. The hexane spectrum shows a moderately abundant molecular ion at *m/z* = 86 and fragment ions at *m/z* = 71, 57, 43, and 29. Since all the carbon–carbon bonds of hexane are electronically similar, all break to a similar extent, giving rise to the observed mixture of ions.

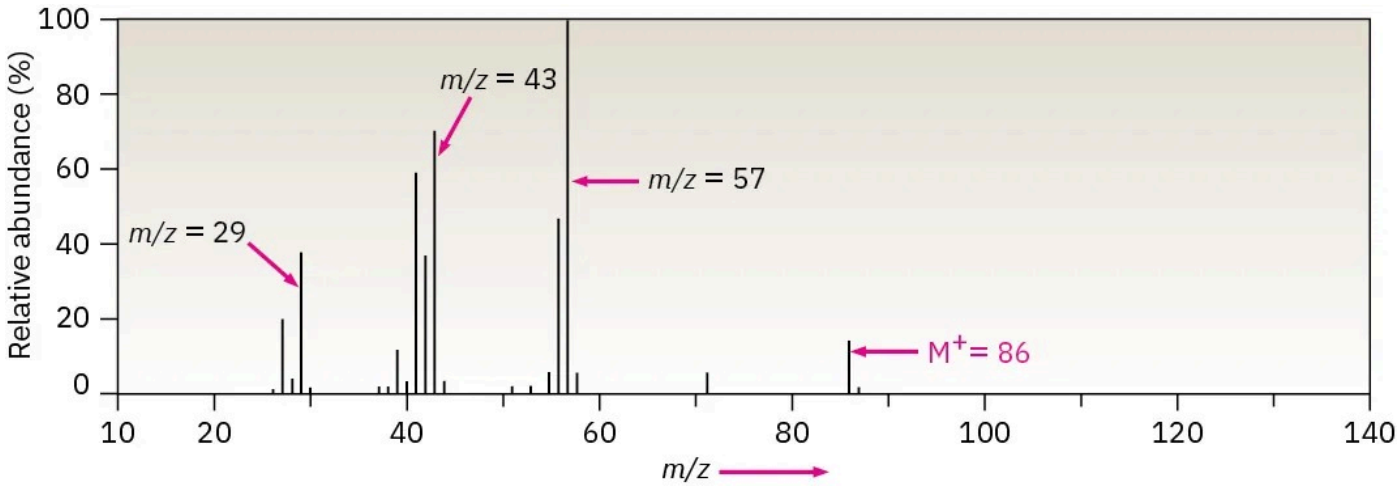


Figure 13.6.3: Mass spectrum of hexane (C_6H_{14}; MW = 86). The base peak is at *m/z* = 57, and numerous other ions are present.

Figure 13.6.4 shows how the hexane fragments might arise. The loss of a methyl radical (CH_3, M = 15) from the hexane cation radical (M^+ = 86) gives rise to a fragment of mass 86 – 15 = 71; the loss of an ethyl radical (C_2H_5, M = 29) accounts for a fragment of mass 86 – 29 = 57; the loss of a propyl radical (C_3H_7, M = 43) accounts for a fragment of mass 86 – 43 = 43; and the loss of a butyl radical accounts for a fragment of mass 29. With practice, it's sometimes possible to analyze the fragmentation pattern of an unknown compound and work backward to a structure that is compatible with the data.

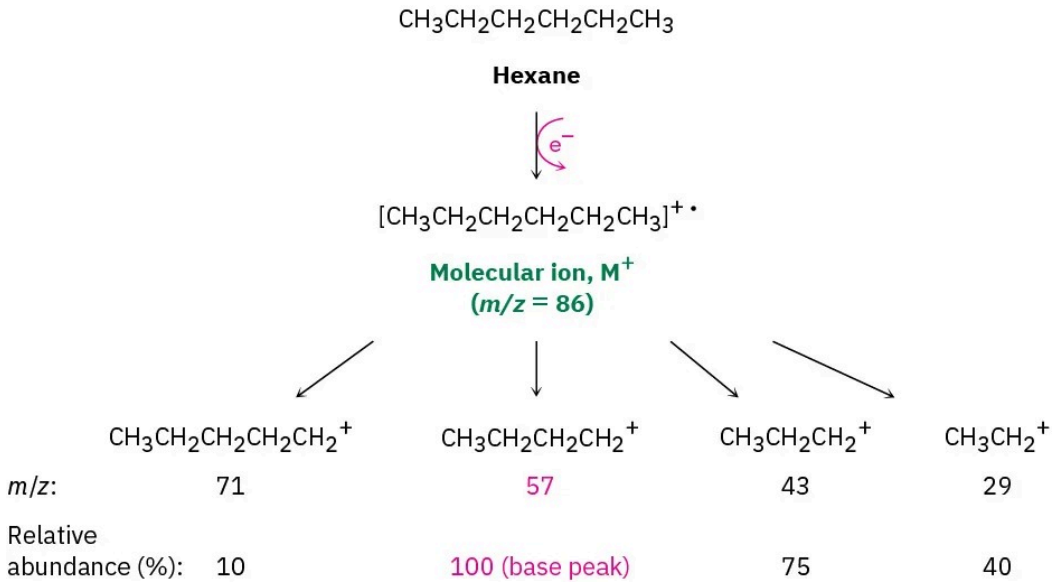


Figure 13.6.4: Fragmentation of hexane in a mass spectrometer.

We'll see in the next section and in later chapters that specific functional groups, such as alcohols, ketones, aldehydes, and amines, show specific kinds of mass spectral fragmentations that can be interpreted to provide structural information.

Worked Example 12.1: Using Mass Spectra to Identify Compounds

Assume that you have two unlabeled samples, one of methylcyclohexane and the other of ethylcyclopentane. How could you use mass spectrometry to tell them apart? The mass spectra of both are shown in Figure 13.6.5.

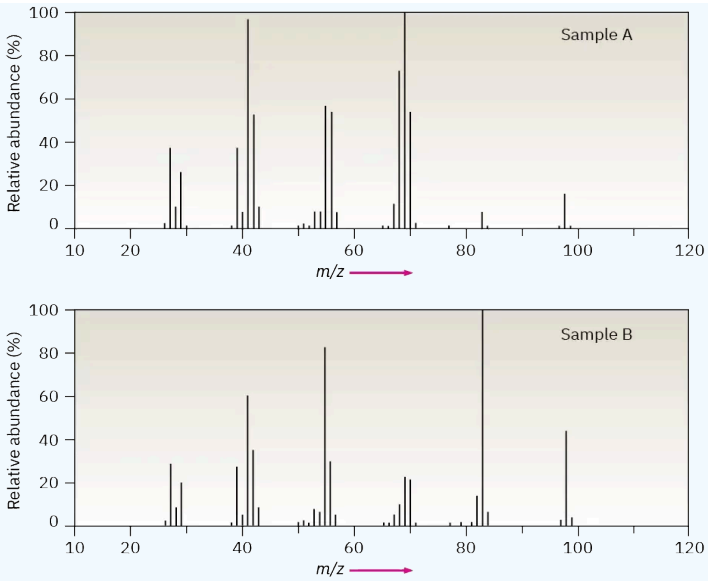


Figure 13.6.5: Mass spectra of unlabeled samples A and B for Worked Example 12.1.

Strategy

Look at the possible structures and decide on how they differ. Then think about how any of these differences in structure might give rise to differences in mass spectra. Methyl cyclohexane, for instance, has a $-CH_3$ group, and ethylcyclopentane has a $-CH_2CH_3$ group, which should affect the fragmentation patterns.

Solution

Both mass spectra show molecular ions at $M^+ = 98$, corresponding to C_7H_{14}, but they differ in their fragmentation patterns. Sample **A** has its base peak at $m/z = 69$, corresponding to the loss of a CH_2CH_3 group (29 mass units), but **B** has a rather small peak at $m/z = 69$. Sample **B** shows a base peak at $m/z = 83$, corresponding to the loss of a CH_3 group (15 mass units), but sample **A** has only a small peak at $m/z = 83$. We can therefore be reasonably certain that **A** is ethylcyclopentane and **B** is methylcyclohexane.

Exercise 13.6.1

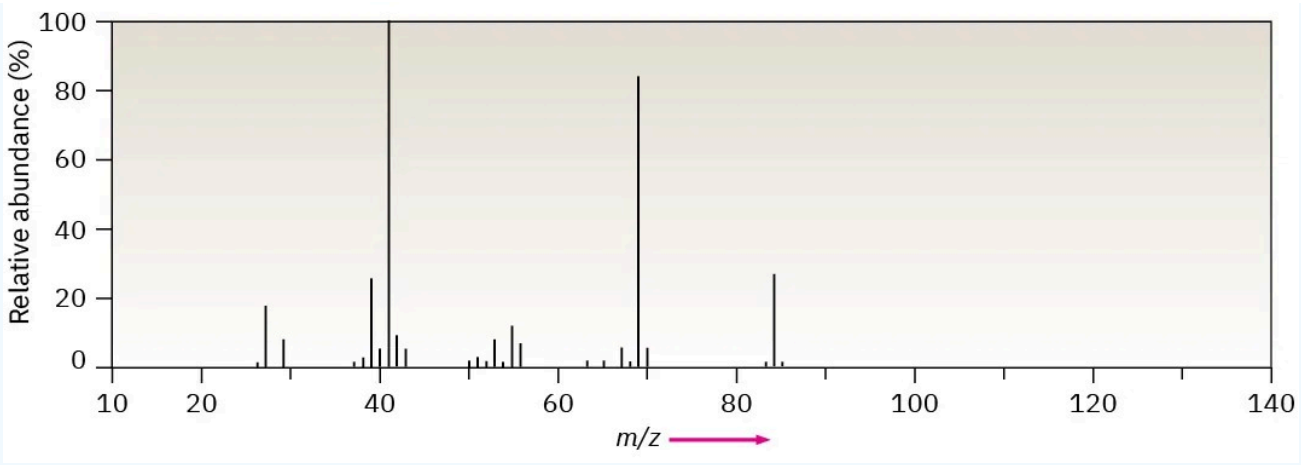
The sex hormone testosterone contains only C, H, and O and has a mass of 288.2089 amu, as determined by high-resolution mass spectrometry. What is the likely molecular formula of testosterone?

Answer available at the end of this section.

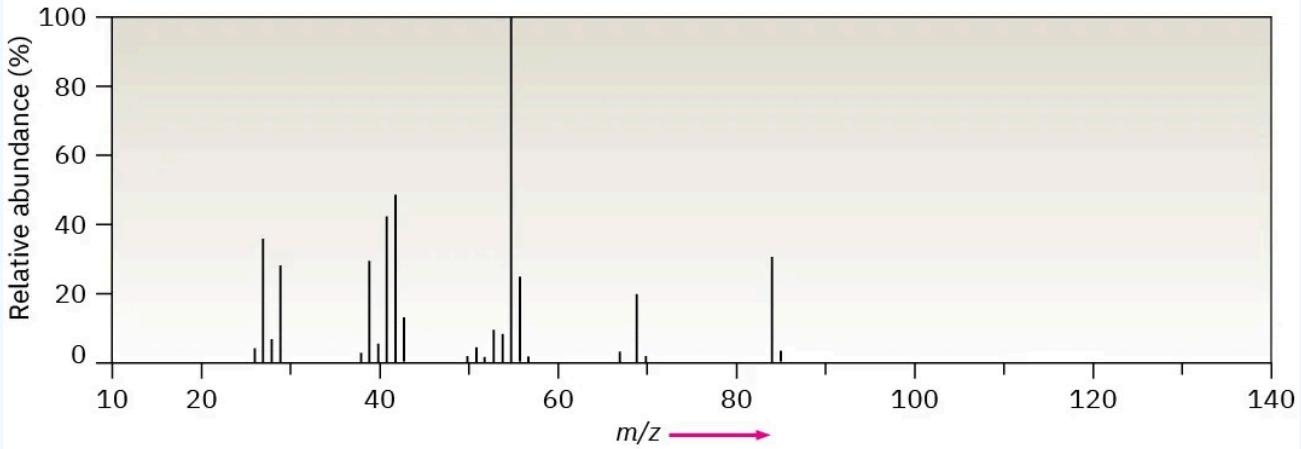
Exercise 13.6.2

Two mass spectra are shown in Figure 13.6.6. One spectrum is that of 2-methyl-2-pentene; the other is of 2-hexene. Which is which? Explain

a.



b.



Answer available at the end of this section.

Answers

Exercise 13.6.1

$C_{19}H_{28}O_2$

Exercise 13.6.2

a. 2-Methyl-2-pentene
b. 2-Hexene

Explanation: Note the relative abundances of the group of peaks around 40 amu in **(a)** vs the 55 amu in **(b)**. The larger fragments in **(a)** come from the preferential breaking of all of the three-carbon chain fragments from both fragments on either side of the double-bond, whereas the 4-carbon chain in 2-hexene splits at the alkene, resulting in the peaks around 55 amu.

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13.7: Mass Spectroscopy and Natural Abundances of Isotopes

Mass spectra of 2-propanone, 2-butanone, and propanal are shown in Figure $13.7.1$. Each peak represents ions of particular masses formed as the result of fragmentation of the molecule produced by electron impact into CH_3^+, $CH_3CH_2^+$, CH_3CO^+, and so on. The "cracking patterns" are, of course, functions of the energy of the bombarding electrons and serve as an extraordinarily individual fingerprint of the particular molecules. For instance, 2-propanone and propanal are isomers, yet their cracking patterns are strikingly different.

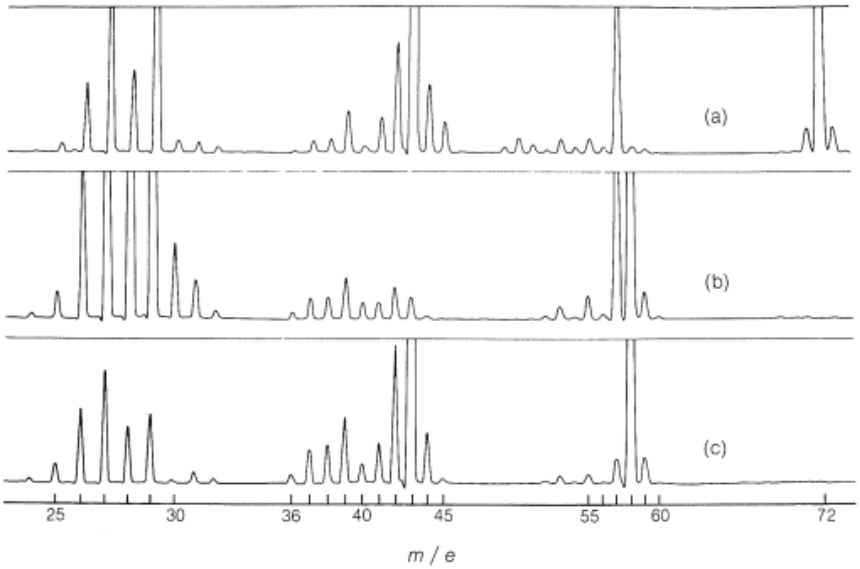


Figure $13.7.1$: The mass spectra of (a) 2-butanone, (b) propanal, and (c) 2-propanone. These spectra were supplied through the courtesy of Dr. D. P. Stevenson of the Shell Development Company.

The peak that is highest in mass number is of considerable importance because it corresponds to the parent molecule M minus one electron (designated as M^+) and provides a highly accurate method for measuring molecular weights. Incorrect molecular weights will be obtained if the positive ion, M^+, becomes fragmented before it reaches the collector, or if two fragments combine to give a fragment heavier than M^+. The peak of M^+ is especially weak with alcohols and branched-chain hydrocarbons, which readily undergo fragmentation by loss of water or side-chain groups. With such compounds the peak corresponding to M^+ may be 0.1% or less of the highest peak in the spectrum, which is called the **base peak** and usually is assigned an arbitrary intensity of 100.

The pressure of the sample in the ion source of a mass spectrometer is usually about 10^{-5} mm, and, under these conditions, buildup of fragments to give significant peaks with m/e greater than M^+ is rare. One exception to this is the formation of $(M+1)^+$ peaks resulting from transfer of a hydrogen atom from M to M^+. The relative intensities of such $(M+1)^+$ peaks are usually sensitive to the sample pressure and may be identified in this way.

With the molecular weight available from the M^+ peak with reasonable certainty, the next step is to determine the *molecular formula*. If the resolution of the instrument is sufficiently high, quite exact masses can be measured, which means that ions with m/e values differing by one part in 50,000 can be distinguished. At this resolution, it is possible to determine the elemental composition of each ion from its exact m/e value.

Many mass spectrometers in routine use are incapable of resolving ions with m/e values that differ by less than one mass unit. In this event, the determination of elemental composition can be determined by the method of *isotope abundance*. We will illustrate this with the following simple example.

The highest peaks corresponding to M^+ in the mass spectrum of an unknown sample have m/e equal to 64 and 66 with relative intensities of 3:1. What is the elemental composition? The 3:1 abundance ratio is uniquely characteristic of the chlorine isotopes,

^{35}Cl:^{37}Cl = 3:1. The mass peaks at 64 and 66 are therefore both molecular ions; the 64 peak is of an ion containing ^{35}Cl and the 66 peak is of an ion containing ^{37}Cl. The remaining atoms in the molecule must add up to $(64 - 35) = 29$, or $(66 - 37) = 29$ mass units. There are several possible combinations of C, H, N, and O that give mass 29; they are N_2H, CHO, CH_3N, and C_2H_5.[15] Of these, the combination with Cl that makes the most chemical sense is C_2H_5, and the formula of the molecule therefore is C_2H_5Cl , chloroethane.

This example illustrates how m/e values of *ions that differ only in isotopic composition can be used to determine elemental compositions*. The important isotopes for this purpose in addition to those of chlorine are the stable isotopes of natural abundance, ^{13}C (1.1%), ^{15}N (0.37%), ^{17}O (0.04%), and ^{18}O (0.20%). As a further example, suppose that we have isolated a hydrocarbon and have determined from its mass spectrum that $M^+ = 86$ mass units. In the absence of any combination reactions there will be an $(M + 1)^+$ ion corresponding to the same molecular ion but with *one* ^{13}C ion in place of ^{12}C. The intensity ratio $(M + 1)^+/M^+$ will depend on the number of carbon atoms present, because the more carbons there are, the greater the probability will be that one of them is ^{13}C. The greater the probability, the larger the $(M + 1)^+/M^+$ ratio. For n carbons, we expect

$$\frac{\text{abundance of } (M+1)^+}{\text{abundance of } M^+} = n \times \%^{13}\text{C abundance}/100 \tag{13.7.1}$$

If the measured $(M + 1)^+/M^+$ ratio is 6.6:100, then

$$\frac{6.6}{100} = n \times 1.1/100 \tag{13.7.2}$$

$$n = 6 \tag{13.7.3}$$

The only hydrocarbon formula with $M^+ = 86$ and $n = 6$ is C_6H_{14}.

Nitrogen (as ^{15}N) and oxygen (as ^{17}O) also contribute to $(M + 1)^+$, if present, while ^{18}O and *two* ^{13}C's contribute to $(M + 2)^+$. The calculated intensities of $(M + 1)^+$ and $(M + 2)^+$ relative to M^+ (as 100) are tabulated in Table 1 for elemental composition of ions up to C_{20}. The table applies to fragment ions as well as molecular ions, but the intensity data from fragment ions is very often complicated by overlapping peaks.

Table 1: *Isotopic Contributions for Carbon and other Elements to Intensities of $(M + 1)^+$ and $(M + 2)^+$ relative to M^+ (100)*

C_n	$(M+1)^+$	$(M+2)^+$	C_n	$(M+1)^+$	$(M+2)^+$
C_1	1.1	0.000	C_{11}	12.1	0.67
C_2	2.2	0.012	C_{12}	13.2	0.80
C_3	3.3	0.036	C_{13}	14.2	0.94
C_4	4.4	0.073	C_{14}	15.4	1.10
C_5	5.5	0.12	C_{15}	16.5	1.27
C_6	6.6	0.18	C_{16}	17.6	1.46
C_7	7.7	0.25	C_{17}	18.7	1.65
C_8	8.8	0.34	C_{18}	19.8	1.86
C_9	9.9	0.44	C_{19}	20.9	2.07
C_{10}	11.0	0.54	C_{20}	22.0	2.30

For each additional element present, add per atom
$(M + 1)^+$ ^{15}N, 0.37; ^{17}O, 0.04; ^{33}S, 0.80
$(M + 2)^+$ ^{18}O, 0.20; ^{34}S, 4.44; ^{37}Cl, 32.5; ^{81}Br, 98

Halides

The fact that some elements have two common isotopes gives their mass spectra a distinctive appearance. Chlorine, for example, exists as two isotopes, ^{35}Cl and ^{37}Cl, in roughly a 3 : 1 ratio. In a sample of chloroethane, three out of four molecules contain a ^{35}Cl atom and one out of four has a ^{37}Cl atom. In the mass spectrum of chloroethane (Figure 13.7.2) we see the molecular ion (M) at *m/z* = 64 for ions that contain a ^{35}Cl and another peak at *m/z* = 66, called the M + 2 peak, for ions containing a ^{37}Cl. The ratio of the relative abundance of M : M + 2 is about 3 : 1, a reflection of the isotopic abundances of chlorine.

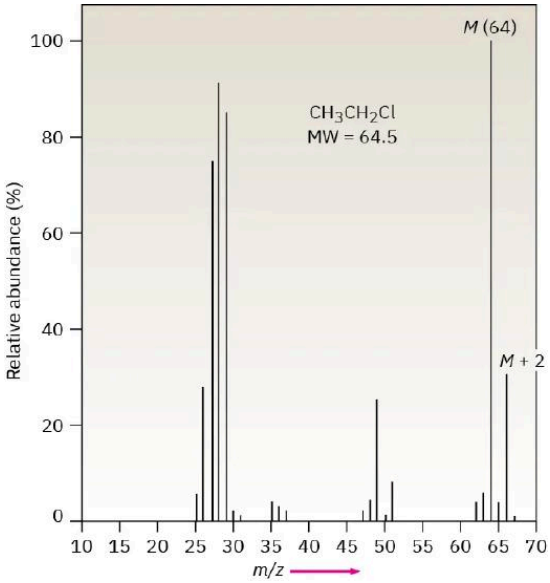


Figure 13.7.2: Mass spectrum of chloroethane.

In the case of bromine, the isotopic distribution is 50.7% ^{79}Br and 49.3% ^{81}Br. In the mass spectrum of 1-bromohexane (Figure 13.7.3) the molecular ion appears at *m/z* = 164 for ^{79}Br-containing ions and the M + 2 peak is at *m/z* = 166 for ^{81}Br-containing ions. The ions at *m/z* = 135 and 137 are informative as well. The two nearly equally large peaks tell us that the ions at those *m/z* values still contain the bromine atom. The peak at *m/z* = 85, on the other hand, does not contain bromine because there is not a large peak at *m/z* = 87.

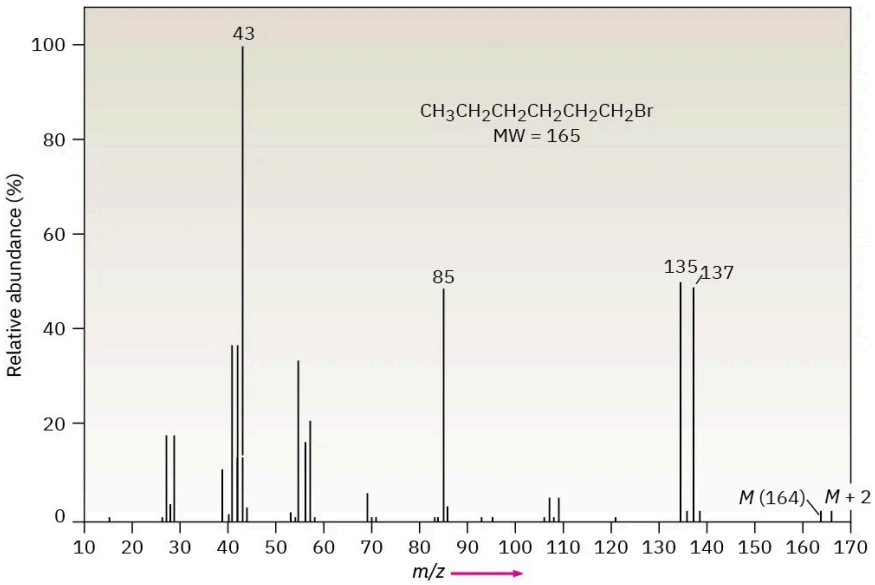


Figure 13.7.3: Mass spectrum of 1-bromohexane.

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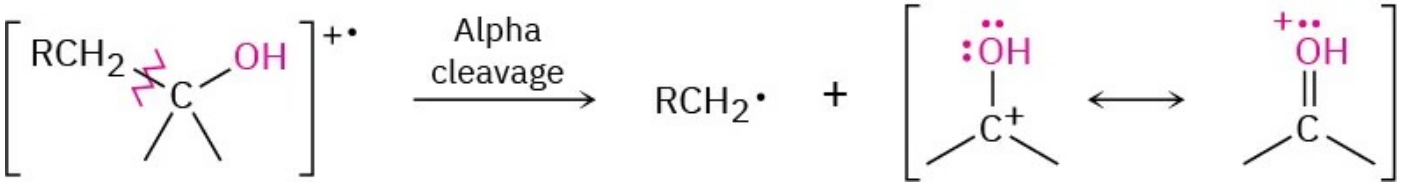
- 12.3: Mass Spectrometry of Some Common Functional Groups by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

13.8: Mass Spectrometry of Some Common Functional Groups

As each functional group is discussed in future chapters, mass-spectral fragmentations characteristic of that group will be described. As a preview, though, we'll point out some distinguishing features of several common functional groups.

Alcohols

Alcohols undergo fragmentation in a mass spectrometer by two pathways: *alpha cleavage* and *dehydration*. In the α-cleavage pathway, the C–C bond nearest the hydroxyl group is broken, yielding a neutral radical and a resonance-stabilized oxygen-containing cation.



This type of fragmentation is seen in the spectrum of 2-pentanol in Figure 13.8.1 as the positively charged fragment remains (For this molecule: $C_2H_5O^+$) with a m/z = 45.

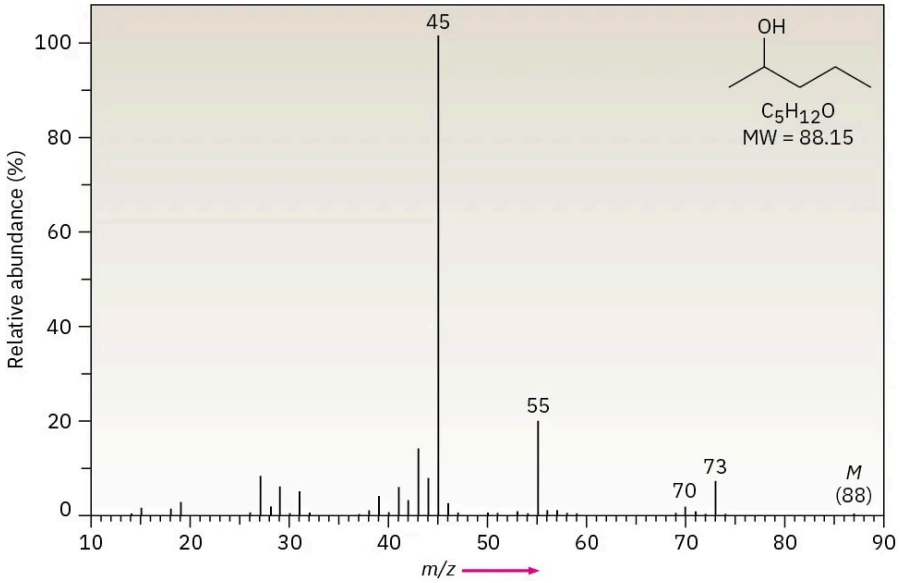
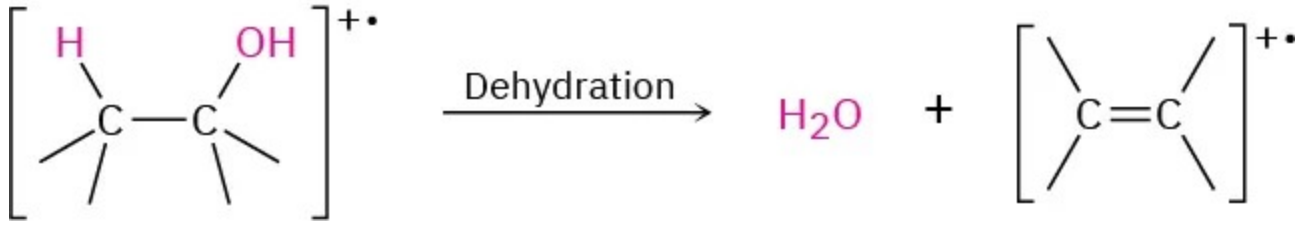


Figure 13.8.1: Mass spectrum of 2-pentanol.

In the dehydration pathway, water is eliminated, yielding an alkene radical cation that is 18 amu lighter than M^+ (otherwise marked as M^+-18). For simplicity, we have drawn the dehydration below as an E2-type process. Often, the hydrogen that is lost is not beta to the hydroxyl. Only a small peak from dehydration is observed in the spectrum of 2-pentanol at m/z = 70 (Figure 13.8.1).



Mass Spectrum of 1-butanol

Both fragmentation modes are apparent in the mass spectrum of 1-butanol (Figure 13.8.2). The peak at *m/z* = 56 is due to loss of water from the molecular ion, and the peak at *m/z* = 31 is due to an alpha cleavage.

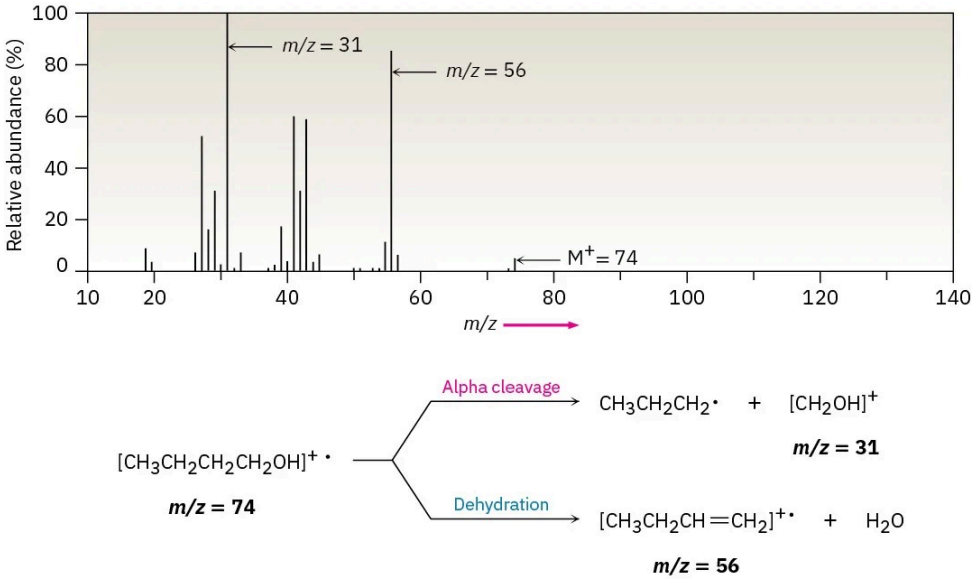
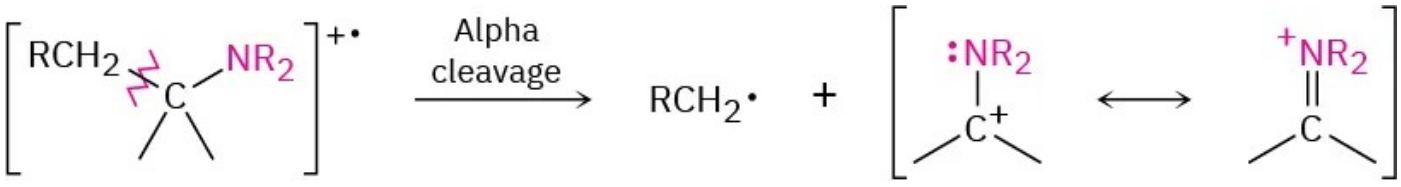


Figure 13.8.2: Mass spectrum of 1-butanol (M^+ = 74). Dehydration gives a peak at *m/z* 56, and alpha-cleavage fragmentation gives a peak at *m/z* 31.

Amines

The **nitrogen rule** of mass spectrometry says that a compound with an odd number of nitrogen atoms has an odd-numbered molecular weight. The logic behind the rule comes from the fact that nitrogen is trivalent, thus requiring an odd number of hydrogen atoms. The presence of nitrogen in a molecule is often detected simply by observing its mass spectrum. An odd-numbered molecular ion usually means that the unknown compound has one or three nitrogen atoms, and an even-numbered molecular ion usually means that the compound has either zero or two nitrogen atoms.

Aliphatic amines undergo a characteristic *α* cleavage in a mass spectrometer, similar to that observed for alcohols. A C–C bond nearest the nitrogen atom is broken, yielding an alkyl radical and a resonance-stabilized, nitrogen-containing cation.



The mass spectrum of triethylamine has a base peak at *m/z* = 86, which arises from an alpha cleavage resulting in the loss of a

methyl group (Figure 13.8.3).

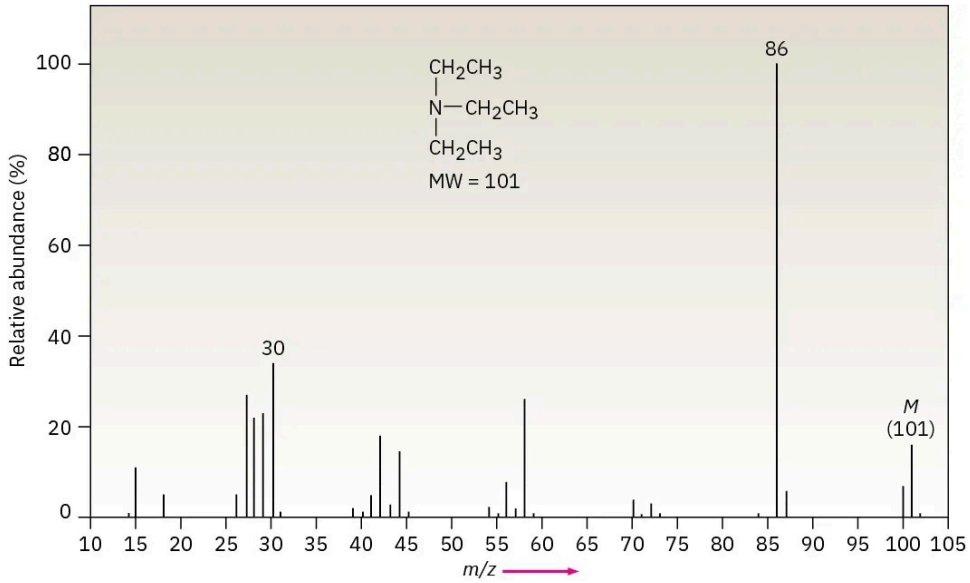
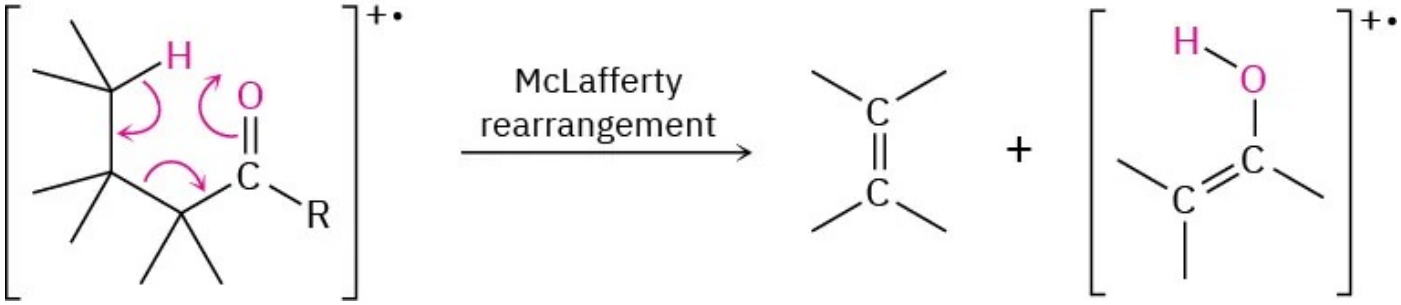


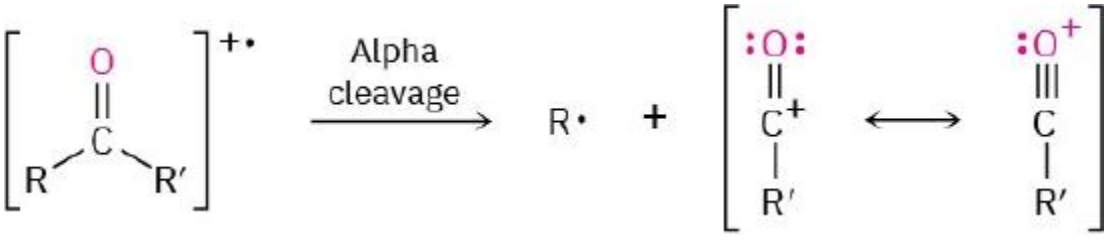
Figure 13.8.3: Mass spectrum of triethylamine.

Carbonyl Compounds

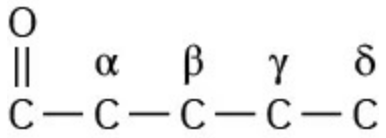
Ketones and aldehydes that have a hydrogen on a carbon three atoms away from the carbonyl group undergo a characteristic mass-spectral cleavage called the **McLafferty rearrangement**. The hydrogen atom is transferred to the carbonyl oxygen, a C–C bond between the alpha and beta carbons is broken, and a neutral alkene fragment is produced. The charge remains with the oxygen-containing fragment.



In addition, ketones and aldehydes frequently undergo α cleavage of the bond between the carbonyl carbon and the neighboring carbon to yield a neutral radical and a resonance-stabilized acyl cation. Because the carbon neighboring the carbonyl carbon is called the alpha carbon, the reaction is called an alpha cleavage.



(To be more general about neighboring positions in carbonyl compounds, Greek letters are used in alphabetical order: alpha, beta, gamma, delta, and so on.)



The mass spectrum of butyrophenone illustrates both alpha cleavage and the McLafferty rearrangement (Figure 13.8.4). Alpha cleavage of the propyl substituent results in the loss of C_3H_7 = 43 mass units from the parent ion at *m/z* = 148 to give the fragment ion at *m/z* = 105. A McLafferty rearrangement of butyrophenone results in the loss of ethylene, C_2H_4 = 28 mass units, from the parent leaving the ion at *m/z* = 120.

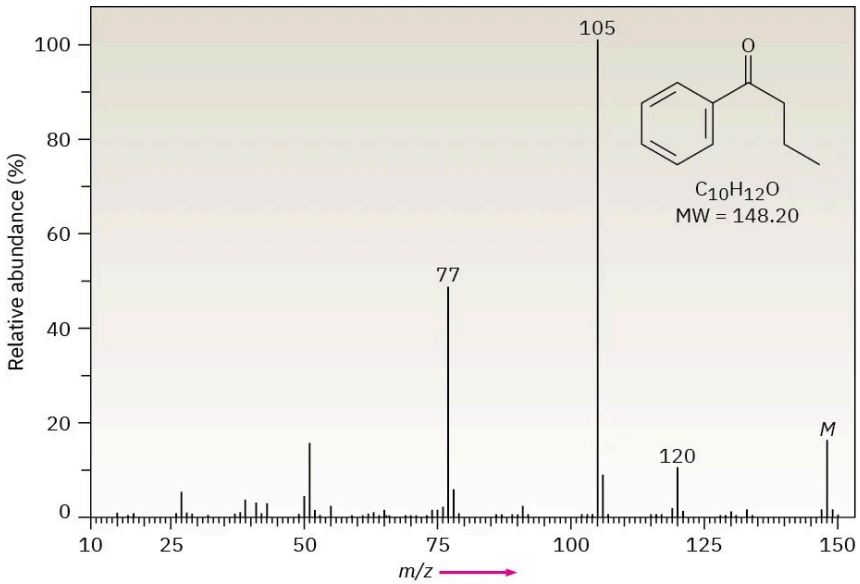


Figure 13.8.4: Mass spectrum of butyrophenone.

Worked Example 13.8.1: Identifying Fragmentation Patterns in a Mass Spectrum

The mass spectrum of 2-methyl-3-pentanol is shown in Figure 13.8.5. What fragments can you identify?

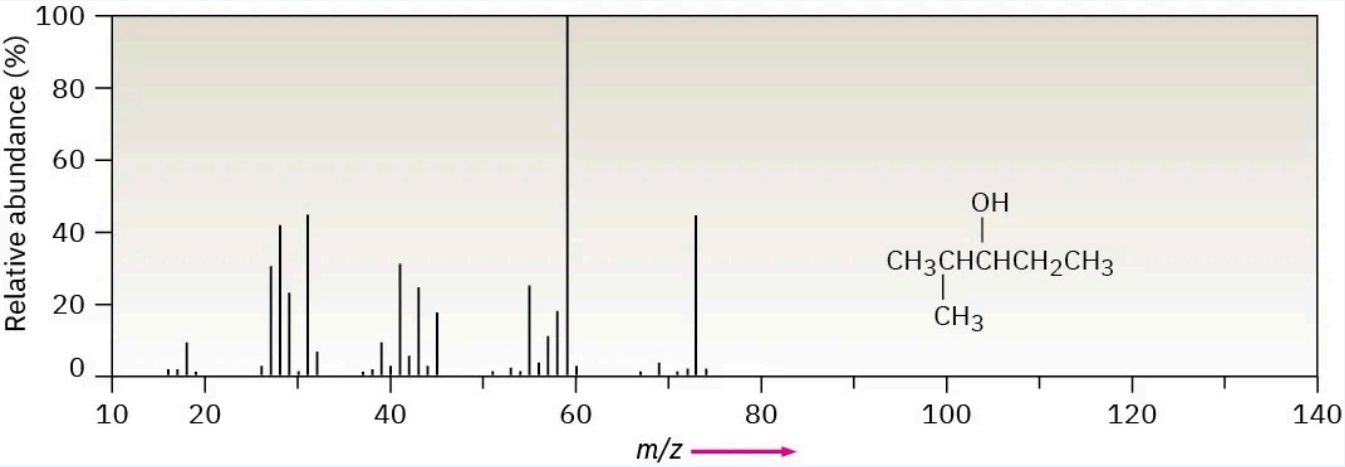


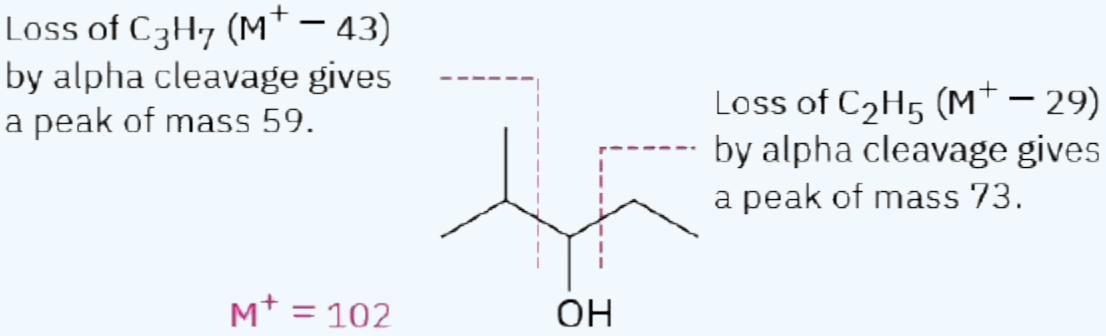
Figure 13.8.5: Mass spectrum of 2-methyl-3-pentanol, for Worked Example 12.2.

Strategy

Calculate the mass of the molecular ion, and identify the functional groups in the molecule. Then write the fragmentation processes you might expect, and compare the masses of the resultant fragments with the peaks present in the spectrum.

Solution

2-Methyl-3-pentanol, an open-chain alcohol, has M^+ = 102 and might be expected to fragment by α cleavage and by dehydration. These processes would lead to fragment ions of *m/z* = 84, 73, and 59. Of the three expected fragments, dehydration is not observed (no *m/z* = 84 peak), but both α cleavages take place (*m/z* = 73, 59).



Exercises

Exercise 13.8.1

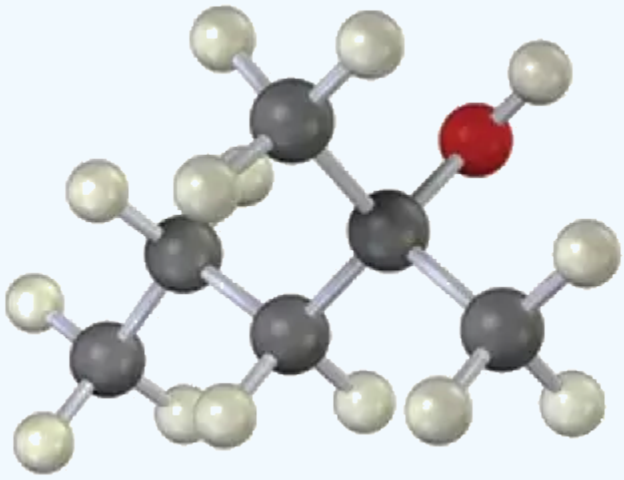
What are the masses of the charged fragments produced in the following cleavage pathways?

a. Alpha cleavage of 2-pentanone ($CH_3COCH_2CH_2CH_3$)
b. Dehydration of cyclohexanol (hydroxycyclohexane)
c. McLafferty rearrangement of 4-methyl-2-pentanone [$CH_3COCH_2CH(CH_3)_2$]
d. Alpha cleavage of triethylamine [$(CH_3CH_2)_3N$]

Answer available at the end of this section.

Exercise 13.8.2

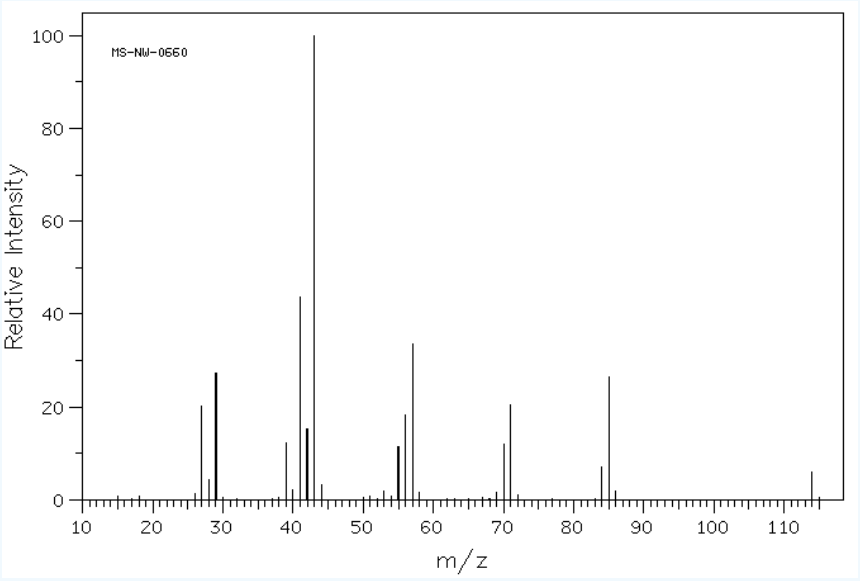
List the masses of the parent ion and of several fragments you might expect to find in the mass spectrum of the following molecule:



Answer available at the end of this section.

Exercise 13.8.3

The following figure shows the mass spectrum of a saturated hydrocarbon (containing only carbon and hydrogen with only single bonds between carbons, not double bonds).



1. Draw five different structures that would have the molecular weight of this compound.
2. Choose three smaller m/z values from the spectrum and draw one structure for each of them. Note that these fragments will not have complete Lewis structures.

Answer available at the end of this section.

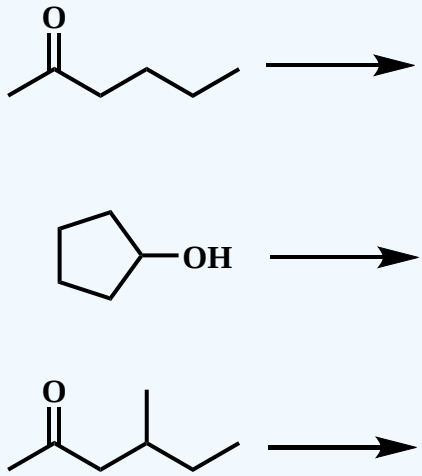
Exercise 13.8.4

Caffeine has a mass of 194.19 amu, determined by mass spectrometry, and contains C, N, H, O. What is a molecular formula for this molecule?

Answer available at the end of this section.

Exercise 13.8.5

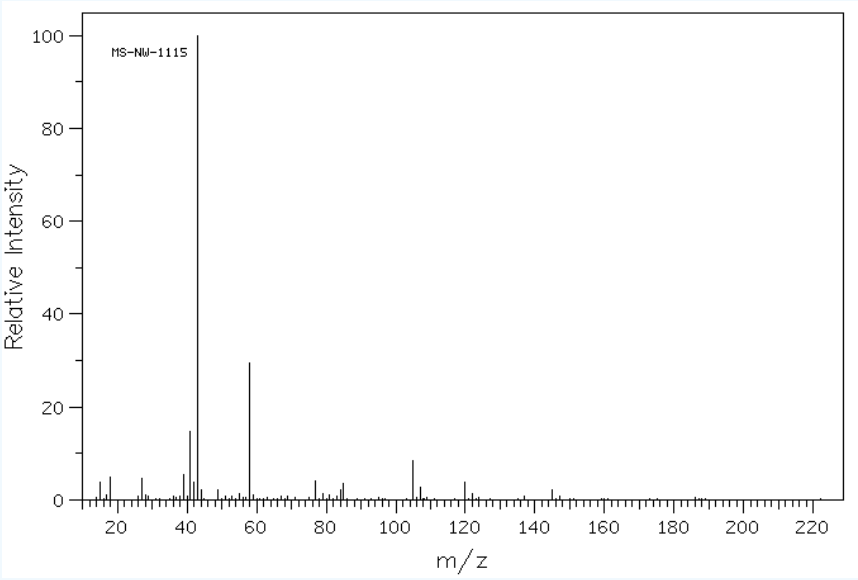
What are the masses of all the components in the following fragmentations?



Answer available at the end of this section.

Exercise 13.8.6

5-Chloro-2-pentanone has the mass spectrum shown. Which peak represents the M^+? Which is the base peak? Why is there a peak at 122? Explain what the fragment for the base peak would be.



Answer available at the end of this section.

Source: SDBSWeb : https://sdbs.db.aist.go.jp/sdbs/cgi-bin/cre_frame_disp.cgi?sdbsno=10178 (National Institute of Advanced Industrial Science and Technology, 16 August 2022)

Answers

Exercise 13.8.1

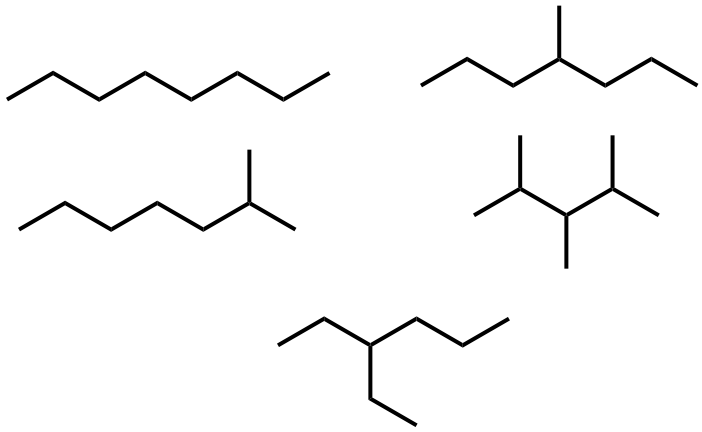
(a) 43, 71 **(b)** 82 **(c)** 58 **(d)** 86

Exercise 13.8.2

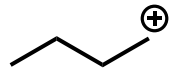
102 (M^+), 84 (dehydration), 87 (alpha cleavage), 59 (alpha cleavage)

Exercise 13.8.3

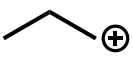
1. Molecular Weight = 114, which cooresponds to a C_8H_{18} hydrocarbon. There is the possibility of 18 isomers, but here are a few isomers:



2. m/z = 57; $[CH_3CH_2CH_2CH_2]^+$



m/z = 43; $[CH_3CH_2CH_2]^+$



m/z = 29; $[CH_3CH_2]^+$

Exercise 13.8.4

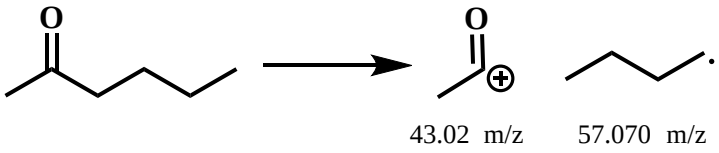
$C_8H_{10}N_4O_2$

C = 12 × 8 = 96 ; N = 14 × 4 = 56 ; H = 1 × 10 = 10 ; O = 2 × 16 = 32

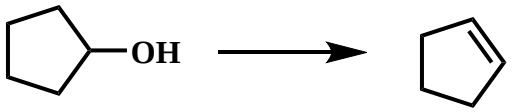
96+56+10+32 = 194 g/mol

Exercise 13.8.5

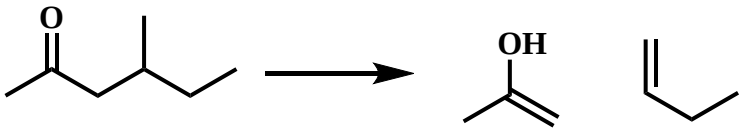
The first undergoes an alpha cleavage. The second undergoes a dehydration. The final one goes through a McLafferty rearrangement.



43.02 m/z 57.070 m/z



68.06 m/z 18.01 m/z



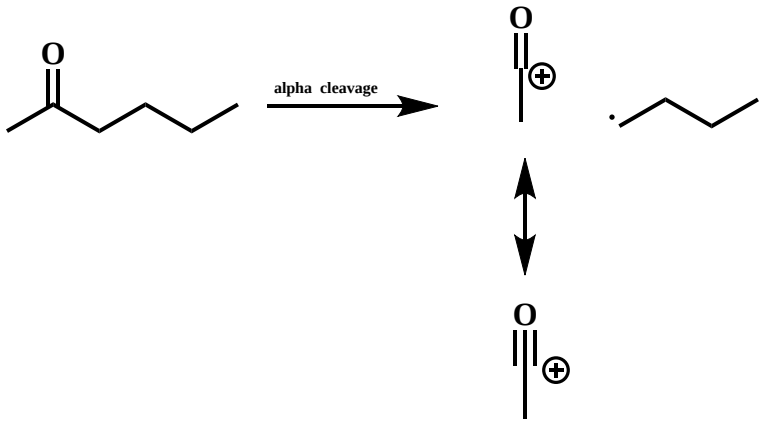
58.04 m/z 46.06 m/z

Exercise 13.8.6

M+ = 120 ; base peak = 43

The m/z peak at 122 is the M + 2 peak. It occurs because chlorine has two isotopes ^{35}C and ^{37}C in a 3:1 ratio.

The m/z = 43 occurs due to the alpha cleavage. The acylium ion has an m/z of 43. This fragment is particularly stable due to resonance.



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13.9: Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

MS analyses of sensitive biological samples rarely use magnetic sector ionization. Instead, they typically use either electrospray ionization (*ESI*) or matrix-assisted laser desorption ionization (*MALDI*), typically linked to a time-of-flight (*TOF*) mass analyzer. Both ESI and MALDI are soft ionization methods that produce charged molecules with little fragmentation, even with sensitive biological samples of very high molecular weight.

In an ESI source, as a sample solution exits the tube, it is subjected to a high voltage that causes the droplets to become charged. The sample molecules gain one or more protons from charged solvent molecules in the droplet. The volatile solvent quickly evaporates, giving variably protonated sample molecules ($M + H_n^{n+}$). In a MALDI source, the sample is adsorbed onto a suitable matrix compound, such as 2,5-dihydroxybenzoic acid, which is ionized by a short burst of laser light. The matrix compound then transfers the energy to the sample and protonates it, forming $M + H_n^{n+}$ ions.Following ion formation, the variably protonated sample molecules are electrically focused into a small packet with a narrow spatial distribution, and the packet is given a sudden kick of energy by an accelerator electrode. As each molecule in the packet is given the same energy,

$$E = \frac{mv^2}{2}$$

it begins moving with a velocity that depends on the square root of its mass,

$$v = \sqrt{\frac{2E}{m}}.$$

Lighter molecules move faster, and heavier molecules move slower. The analyzer itself—the *drift tube*—is simply an electrically grounded metal tube inside which the different charged molecules become separated as they move at different velocities and take different amounts of time to complete their flight.

The Time of Flight technique is considerably more sensitive than the magnetic sector alternative, and protein samples of up to 100 kilodaltons (100,000 amu) can be separated with a mass accuracy of 3 ppm. Figure 13.9.1 shows a MALDI–TOF spectrum of chicken egg-white lysozyme, MW = 14,306.7578 daltons. Biochemists generally use the unit *dalton*, abbreviated Da, instead of amu, although the two are equivalent (1 dalton = 1 amu).

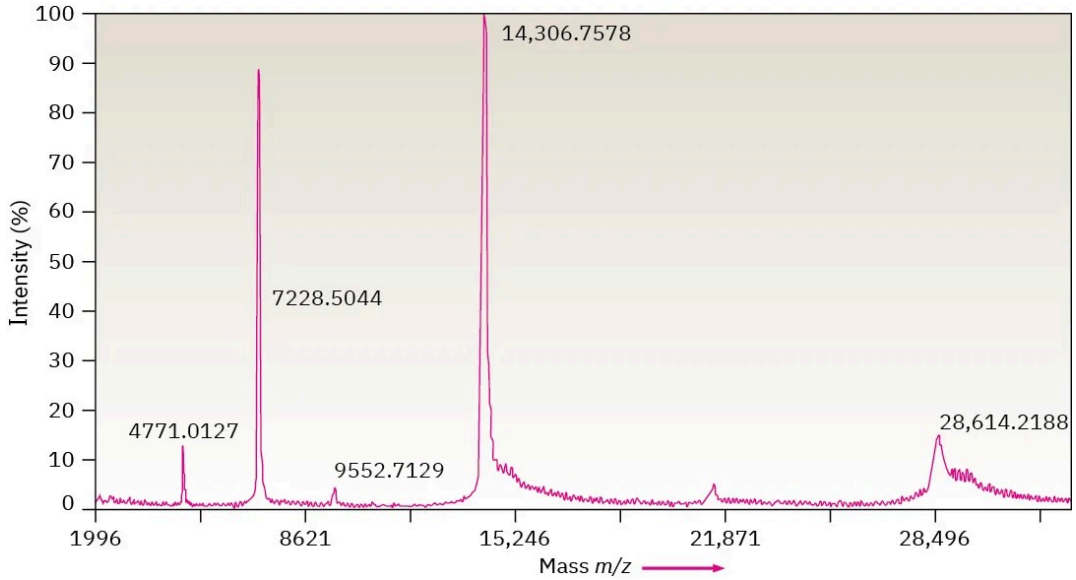


Figure 13.9.1: MALDI–TOF mass spectrum of chicken egg-white lysozyme. The peak at 14,306.7578 daltons (amu) is due to the monoprotonated protein, $M + H^+$, and the peak at 28,614.2188 daltons is due to an impurity formed by dimerization of the protein. Other peaks at lower *m/z* values are various protonated species, $M + H_n^{n+}$.

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13.10: Chemistry Matters—X-Ray Crystallography

The various spectroscopic techniques described in this and the next two chapters are enormously important in chemistry and have been fine-tuned to such a degree that the structure of almost any molecule can be found. Nevertheless, wouldn't it be nice if you could simply look at a molecule and "see" its structure with your eyes?

Determining the three-dimensional shape of an object around you is easy—you just look at it, let your eyes focus the light rays reflected from the object, and let your brain assemble the data into a recognizable image. If the object is small, you use a microscope and let the microscope lens focus the visible light. Unfortunately, there is a limit to what you can see, even with the best optical microscope. Called the diffraction limit, you can't see anything smaller than the wavelength of light you are using for the observation. Visible light has wavelengths of several hundred nanometers, but atoms in molecules have dimensions on the order of 0.1 nm. Thus, to see a molecule—whether a small one in the laboratory or a large, complex enzyme with a molecular weight in the tens of thousands—you need wavelengths in the 0.1 nm range, which corresponds to X rays.

Let's say that we want to determine the structure and shape of an enzyme or other biological molecule. The technique used is called **X-ray crystallography**. First, the molecule is crystallized (which often turns out to be the most difficult and time-consuming part of the entire process) and a small crystal of 0.4 to 0.5 mm on its longest axis is glued to the end of a glass fiber. The fiber and attached crystal are then mounted in an instrument called an X-ray diffractometer, which consists of a radiation source, a sample positioning and orienting device that can rotate the crystal in any direction, a detector, and a controlling computer.

Once mounted in the diffractometer, the crystal is irradiated with X rays, usually so-called Cu-K_α radiation with a wavelength of 0.154 nm. When the X rays strike the enzyme crystal, they interact with electrons in the molecule and are scattered into a diffraction pattern which, when detected and visualized, appears as a series of intense spots against a null background.

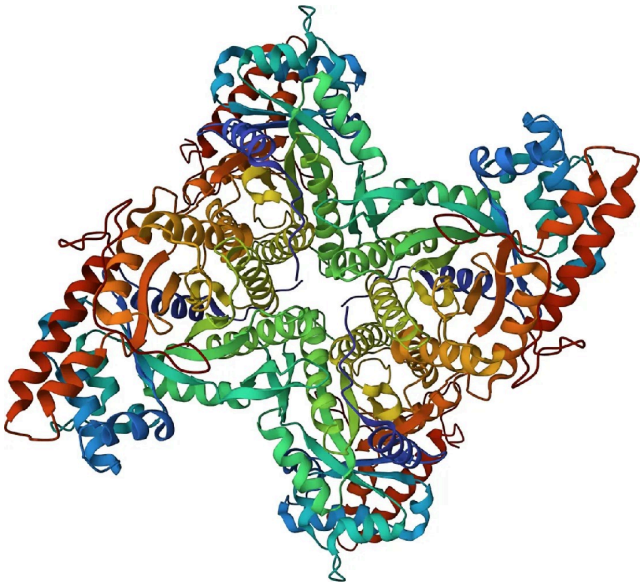


Figure 13.10.1: The structure of human muscle fructose-1,6-bisphosphate aldolase, as determined by X-ray crystallography. (credit: modification of work Protein Data Bank, 1ALD. PDB ID: 1ALD, Gamblin, S.J. Davies, G.J. Grimes, J.M. Jackson, R.M. Littlechild, J.A. Watson, H.C. (1991) J. Mol. Biol. 219: 573-576, CC BY 1.0.)

Manipulation of the diffraction pattern to extract three-dimensional molecular data is a complex process, but the final result is an electron-density map of the molecule. Because electrons are largely localized around atoms, any two centers of electron density located within bonding distance of each other are assumed to represent bonded atoms, leading to a recognizable chemical structure. So important is this structural information for biochemistry that an online database of approximately 145,000 biological substances has been created. Operated by Rutgers University and funded by the U.S. National Science Foundation, the Protein Data Bank (PDB) is a worldwide repository for processing and distributing three-dimensional structural data for biological macromolecules. We'll see how to access the PDB in the Chapter 26 *Chemistry Matters*.

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13.A: Structure Determination - Mass Spectrometry and Infrared Spectroscopy (Summary)

Concepts & Vocabulary

13.0 Introduction

- Spectroscopy describes several techniques used by chemists to understand chemical structures and bonds.

13.1 Spectroscopy and the Electromagnetic Spectrum

- Electromagnetic radiation is composed of waves where shorter wavelengths correspond to higher energy radiation.
- Electromagnetic radiation can also be thought of as a stream of particles called **photons**.
- The electromagnetic spectrum is made up of many types of radiation including infrared, ultraviolet, and visible lights as well as x-rays, gamma rays, microwaves, and radio waves.
- Molecular spectroscopy works by exposing a chemical sample to electromagnetic radiation. It will only absorb radiation with energy that corresponds to some excited state, while all other energies will pass through unabsorbed.

13.2 Infrared Spectroscopy

- When infrared radiation is absorbed, molecules will move to a higher vibrational energy state.
- Examples of molecular vibrations include bending and stretching of bonds. These vibrations can be symmetric or asymmetric.
- In general, more polar bonds have stronger IR absorption.
- IR spectra typically use wavenumbers (cm^{-1}) as units for the x-axis.
- The y-axis for IR spectra is usually % transmittance, with 100% at the top of the spectrum and absorbances looking like valleys (or downward peaks).

13.3 Interpreting Infrared Spectra

- Functional groups have standard regions within the IR spectrum where they absorb.
- The general regions include hydrogen bonding (O-H and N-H), carbon-hydrogen bonds, triple bonds, carbonyls, alkenes, and the fingerprint region.

13.4 Infrared Spectra of Some Common Functional Groups

13.5 Mass Spectrometry of Small Molecules - Magnetic Sector Instruments

- Mass spectrometers consist of an **ion source**, **mass analyzer** and detector.
- There are several common **ion sources** including **electron ionization** and **chemical ionization**.
- Upon ionization, a molecular ion is formed (the molecule after losing a single electron) which will break into smaller pieces (fragments).
- Fragments that are charged will appear in the mass spectrum and are helpful in identifying the parent molecule.
- The most abundant ion in a mass spectrum is called the **base peak**.
- The ion with the same mass as the parent molecule is called the **molecular ion**.
- The x-axis of a mass spectrum is **m/z** - the mass to charge ratio, which in practice equals the mass of the ion.

13.6 Interpreting Mass Spectra

- Uncharged particles do not appear in mass spectra.
- The y-axis of a mass spectrum is the relative abundance, with the base peak set at 100 as the most abundant ion.
- The abundance of ions is related to their stability.

13.8 Mass Spectrometry and Natural Abundances of Isotopes

- Isotopes of carbon and hydrogen lead to common M+1 peaks.

13.8 Mass Spectrometry of Some Common Functional Groups

13.9 Mass Spectrometry in Biological - Time-of-flight (TOF) Instruments

Skills to Master

- Skill 13.1 Determine specific atoms from mass spectra based on molecular ion and M+2 peaks (N, Cl, Br).
- Skill 13.2 Interpret mass spectra fragments - recognizing common fragments.
- Skill 13.3 Interpret infrared spectra to determine functional groups that are present or absent.
- Skill 13.4 Identify the presence of alcohols by IR, and MS.

Memorization Tasks (MT)

MT - Memorize common mass spectra fragments.

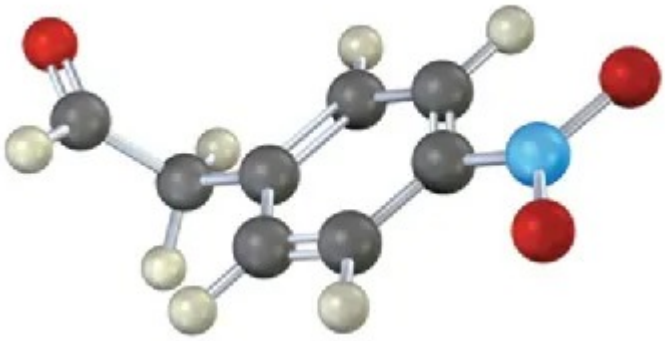
MT - Memorize common functional group regions in infrared spectroscopy.

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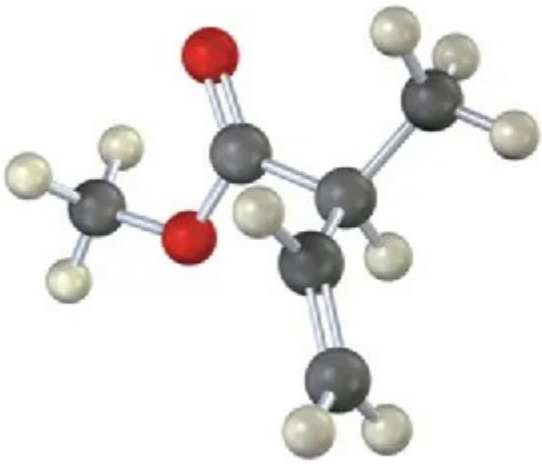
13.B: Additional Problems

Visualizing Chemistry

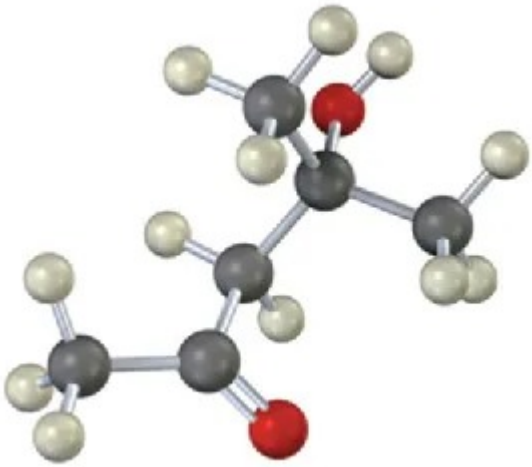
PROBLEM 13-12 Where in the IR spectrum would you expect each of the following molecules to absorb?



(a)

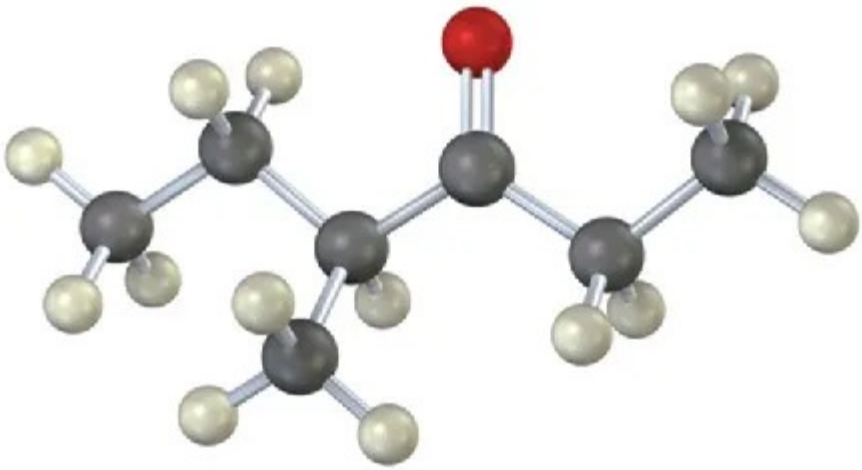


(b)

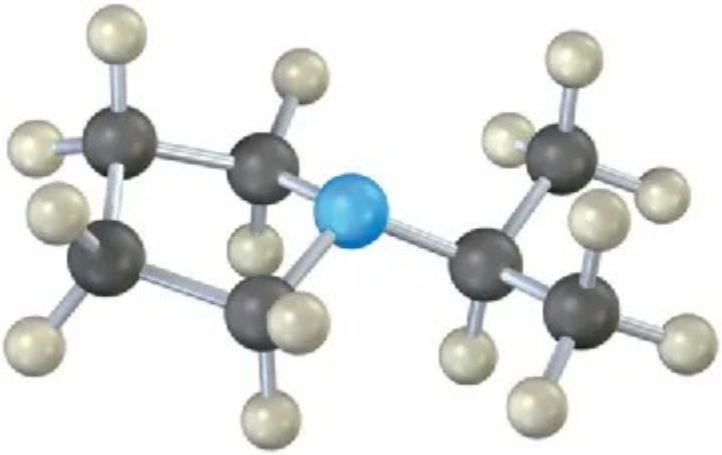


(c)

PROBLEM 13-13 Show the structures of the fragments you would expect in the mass spectra of the following molecules:



(a) (b)



Mass Spectrometry

PROBLEM 13-14 Propose structures for compounds that fit the following mass-spectral data:

(a) A hydrocarbon with $M^+ = 132$

(b) A hydrocarbon with $M^+ = 166$

(c) A hydrocarbon with $M^+ = 84$

PROBLEM 13-15 Write molecular formulas for compounds that show the following molecular ions in their high-resolution mass spectra, assuming that C, H, N, and O might be present. The exact atomic masses are: 1.007 83 (^{1}H), 12.000 00 (^{12}C), 14.003 07 (^{14}N), 15.994 91 (^{16}O).

(a) $M^+ = 98.0844$ (b) $M^+ = 123.0320$

PROBLEM 13-16 Camphor, a saturated monoketone from the Asian camphor tree, is used among other things as a moth repellent and as a constituent of embalming fluid. If camphor has $M^+ = 152.1201$ by high-resolution mass spectrometry, what is its molecular formula? How many rings does camphor have?

PROBLEM 13-17 The nitrogen rule of mass spectrometry says that a compound containing an odd number of nitrogens has an

odd-numbered molecular ion. Conversely, a compound containing an even number of nitrogens has an even-numbered M^+ peak. Explain.

PROBLEM 13-18 In light of the nitrogen rule mentioned in Problem 12-17, what is the molecular formula of pyridine, $M^+ = 79$?

PROBLEM 13-19 Nicotine is a diamino compound isolated from dried tobacco leaves. Nicotine has two rings and $M^+ = 162.1157$ by high-resolution mass spectrometry. Give a molecular formula for nicotine, and calculate the number of double bonds.

PROBLEM 13-20 The hormone cortisone contains C, H, and O, and shows a molecular ion at $M^+ = 360.1937$ by high-resolution mass spectrometry. What is the molecular formula of cortisone? (The degree of unsaturation for cortisone is 8.)

PROBLEM 13-21 Halogenated compounds are particularly easy to identify by their mass spectra because both chlorine and bromine occur naturally as mixtures of two abundant isotopes. Recall that chlorine occurs as ^{35}Cl (75.8%) and ^{37}Cl (24.2%); and bromine occurs as ^{79}Br (50.7%) and ^{81}Br (49.3%). At what masses do the molecular ions occur for the following formulas? What are the relative percentages of each molecular ion?

(a) Bromomethane, CH_3Br (b) 1-Chlorohexane, $C_6H_{13}Cl$

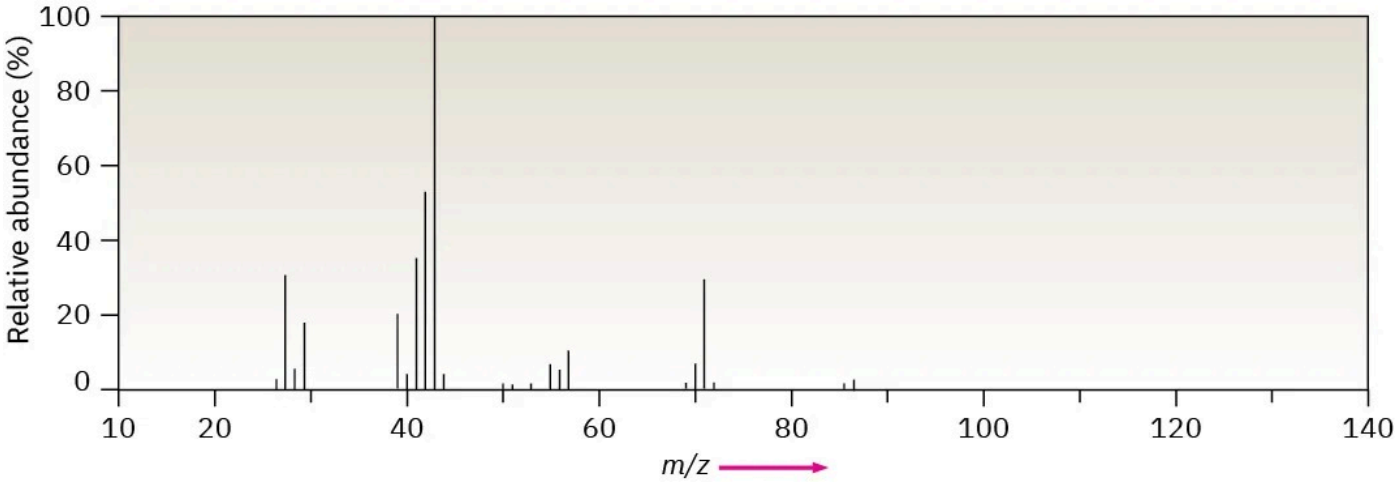
PROBLEM 13-22 By knowing the natural abundances of minor isotopes, it's possible to calculate the relative heights of M^+ and M + 1 peaks. If ^{13}C has a natural abundance of 1.10%, what are the relative heights of the M^+ and M + 1 peaks in the mass spectrum of benzene, C_6H_6?

PROBLEM 13-23 Propose structures for compounds that fit the following data:

(a) A ketone with $M^+ = 86$ and fragments at *m/z* = 71 and *m/z* = 43

(b) An alcohol with $M^+ = 88$ and fragments at *m/z* = 73, *m/z* = 70, and *m/z* = 59

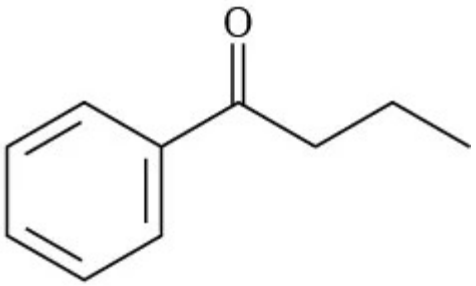
PROBLEM 13-24 2-Methylpentane (C_6H_{14}) has the mass spectrum shown. Which peak represents M^+? Which is the base peak? Propose structures for fragment ions of *m/z* = 71, 57, 43, and 29. Why does the base peak have the mass it does?



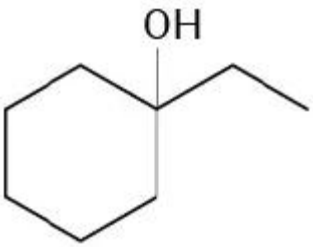
PROBLEM 13-25 Assume that you are in a laboratory carrying out the catalytic hydrogenation of cyclohexene to cyclohexane. How could you use a mass spectrometer to determine when the reaction is finished?

PROBLEM 13-26 What fragments might you expect in the mass spectra of the following compounds?

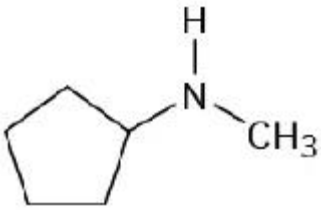
(a)



(b)



(c)



Infrared Spectroscopy

PROBLEM 13-27 How might you use IR spectroscopy to distinguish among the three isomers 1-butyne, 1,3-butadiene, and 2-butyne?

PROBLEM 13-28 Would you expect two enantiomers such as (*R*)-2-bromobutane and (S)-2-bromobutane to have identical or different IR spectra? Explain.

PROBLEM 13-29 Would you expect two diastereomers such as *meso*-2,3-dibromobutane and (2*R*,3*R*)-dibromobutane to have identical or different IR spectra? Explain.

PROBLEM 13-30 Propose structures for compounds that meet the following descriptions:

(a) C_5H_8, with IR absorptions at 3300 and 2150 cm^{-1}

(b) C_4H_8O, with a strong IR absorption at 3400 cm^{-1}

(c) C_4H_8O, with a strong IR absorption at 1715 cm^{-1}

(d) C_8H_{10}, with IR absorptions at 1600 and 1500 cm^{-1}

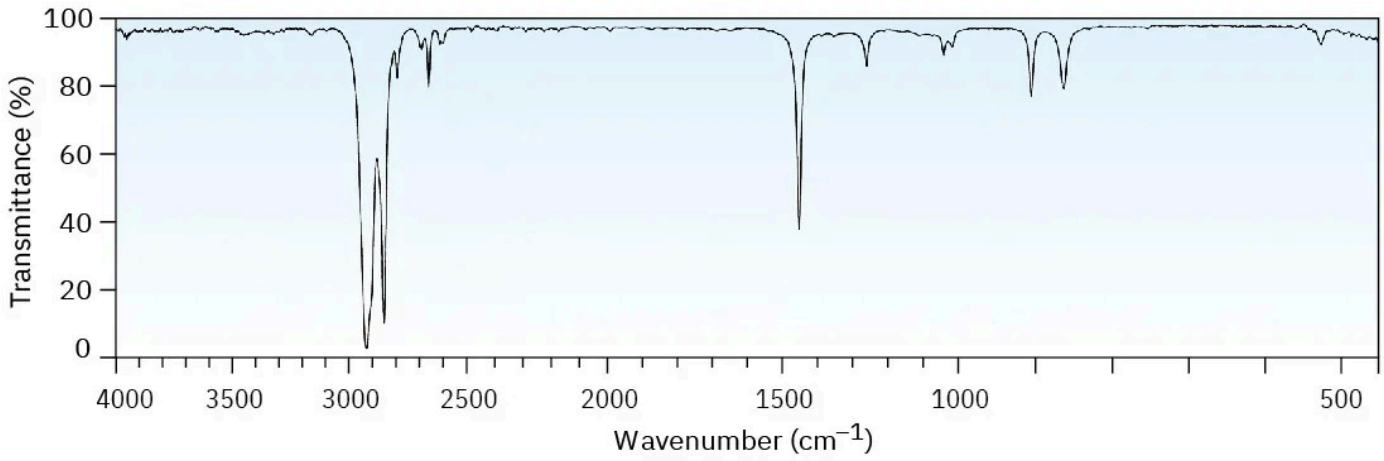
PROBLEM 13-31 How could you use infrared spectroscopy to distinguish between the following pairs of isomers?

(a) $HC{\equiv}CCH_2NH_2$ and $CH_3CH_2C{\equiv}N$

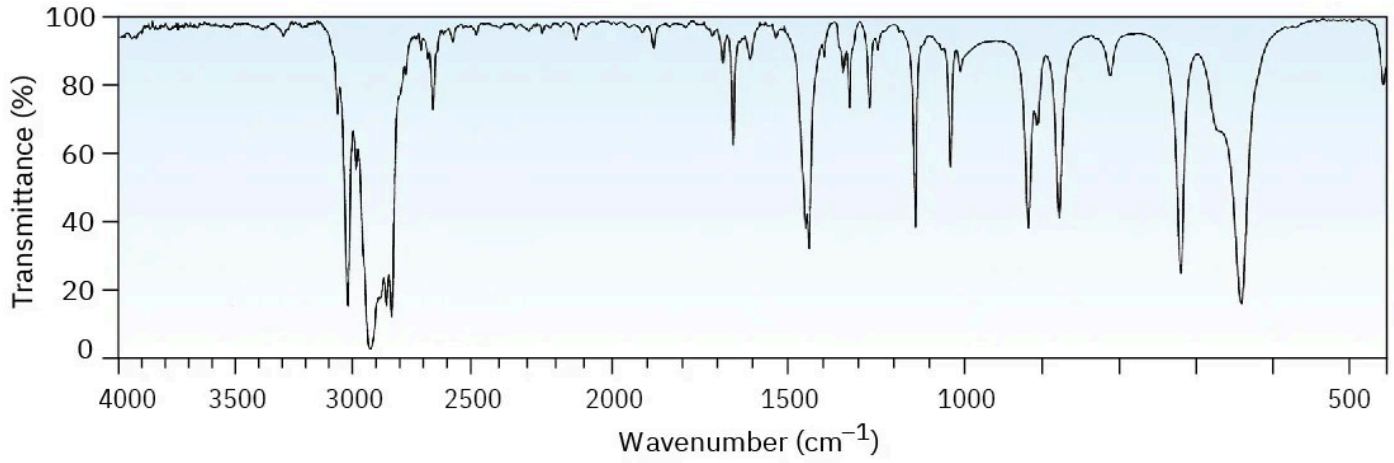
(b) CH_3COCH_3 and CH_3CH_2CHO

PROBLEM 13-32 Two infrared spectra are shown. One is the spectrum of cyclohexane, and the other is the spectrum of cyclohexene. Identify them, and explain your answer.

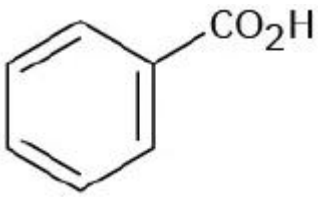
(a)

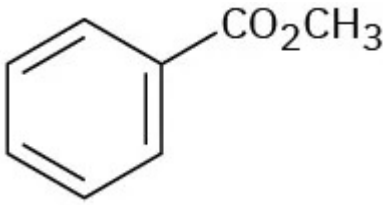


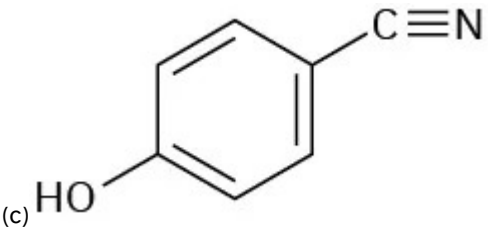
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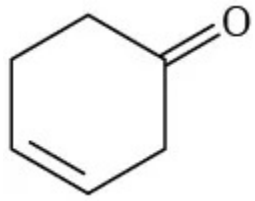


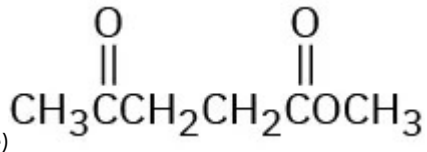
PROBLEM 13-33 At what approximate positions might the following compounds show IR absorptions?

(a) 

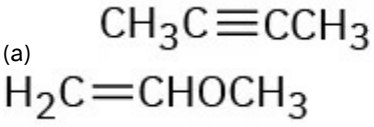
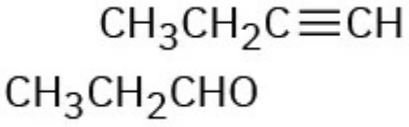
(b) 

(c) 

(d) 

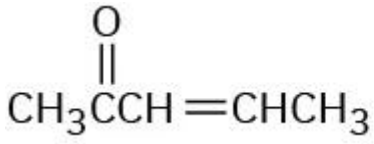
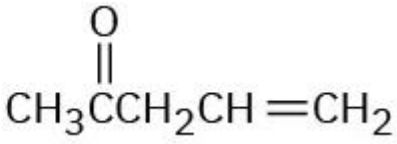
(e) 

PROBLEM 13-34 How would you use infrared spectroscopy to distinguish between the following pairs of constitutional isomers?

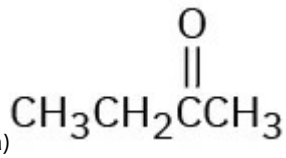
(a)  and 

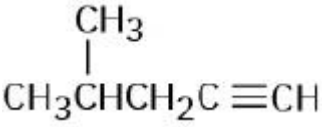
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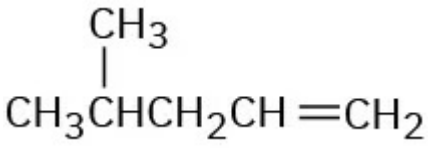
(c)

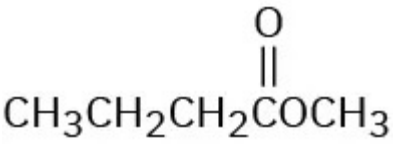
(b)  and 

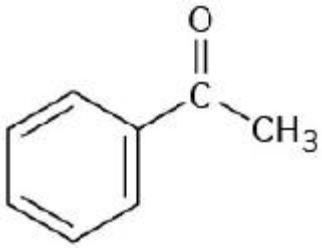
PROBLEM 13-35 At what approximate positions might the following compounds show IR absorptions?

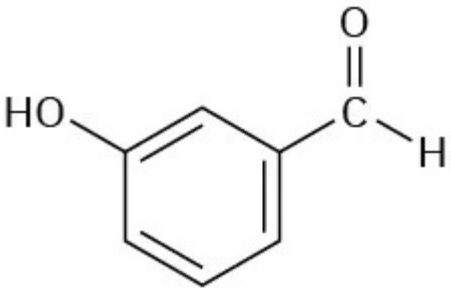
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM 13-36 Assume that you are carrying out the dehydration of 1-methylcyclohexanol to yield 1-methylcyclohexene. How could you use infrared spectroscopy to determine when the reaction is complete?

PROBLEM 13-37 Assume that you are carrying out the base-induced dehydrobromination of 3-bromo-3-methylpentane to yield an alkene. How could you use IR spectroscopy to tell which of the three possible elimination products is formed, if one includes *E/Z* isomers?

General Problems

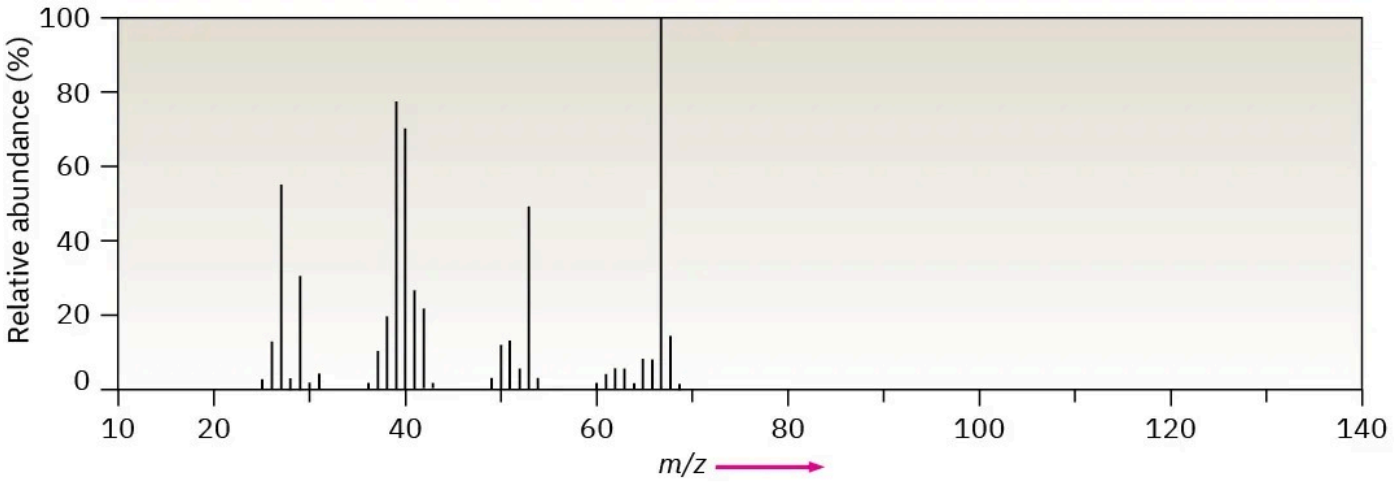
PROBLEM 13-38 Which is stronger, the C=O bond in an ester (1735 cm^{-1}) or in a saturated ketone (1715 cm^{-1})? Explain

PROBLEM 13-39 Carvone is an unsaturated ketone responsible for the odor of spearmint. If carvone has M^+ = 150 in its mass spectrum and contains three double bonds and one ring, what is its molecular formula?

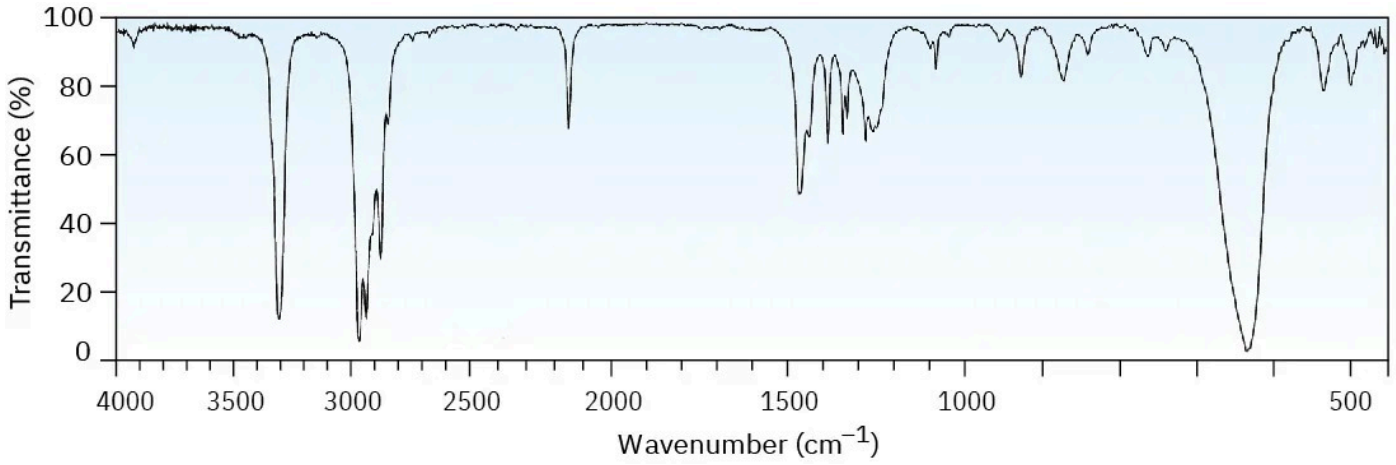
PROBLEM 13-40 Carvone (Problem 39) has an intense IR absorption at 1690 cm^{-1}. What kind of ketone does carvone contain?

PROBLEM 13-41 The mass spectrum **(a)** and the infrared spectrum **(b)** of an unknown hydrocarbon are shown. Propose as many structures as you can.

(a)

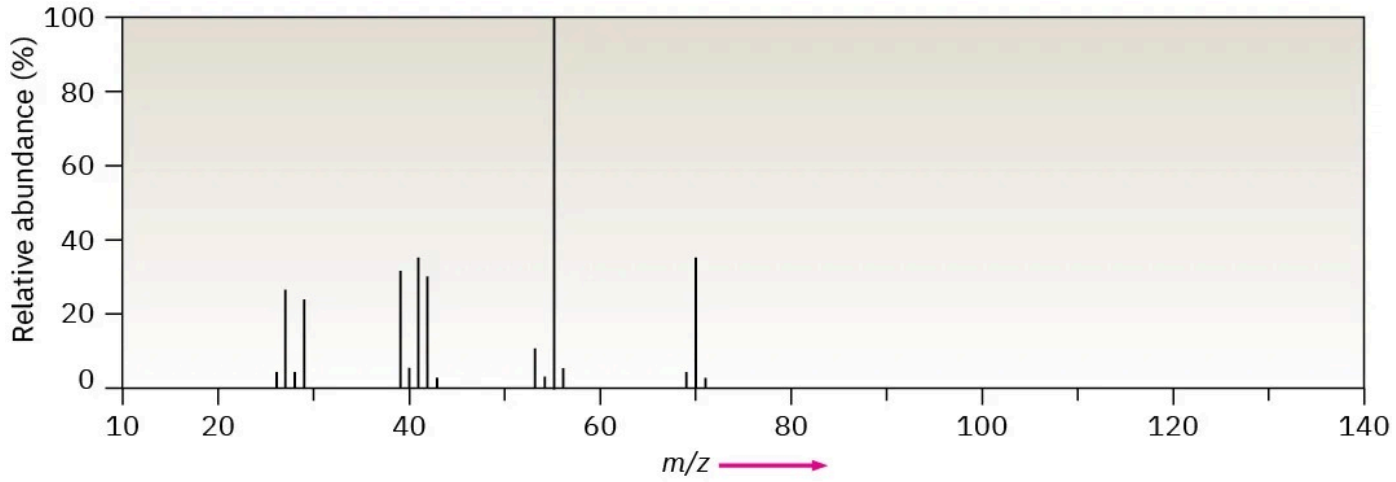


(b)

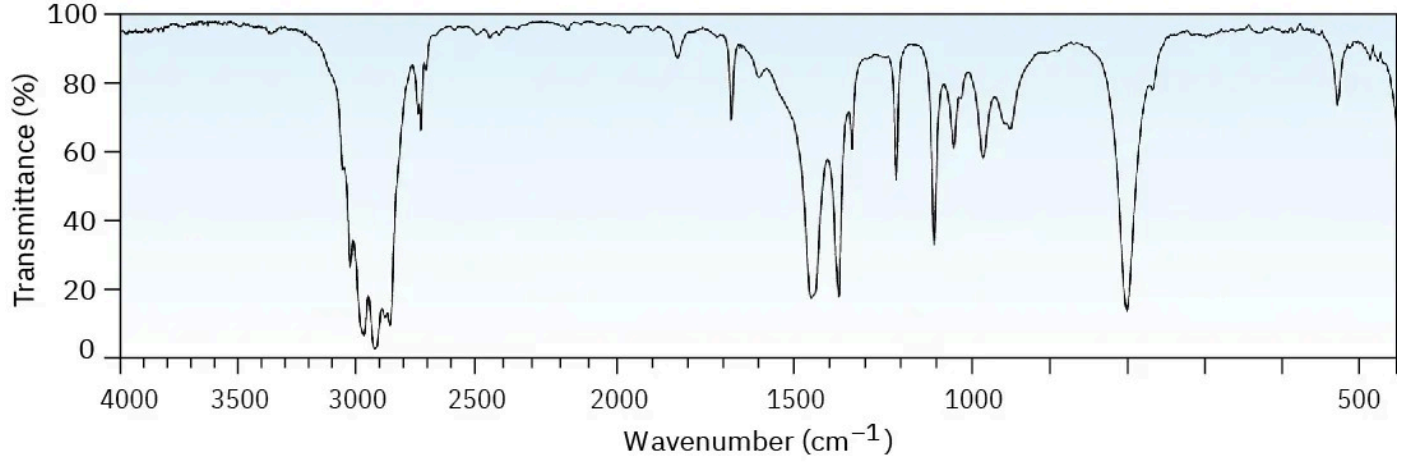


PROBLEM 13-42 The mass spectrum **(a)** and the infrared spectrum **(b)** of another unknown hydrocarbon are shown. Propose as many structures as you can.

(a)



(b)

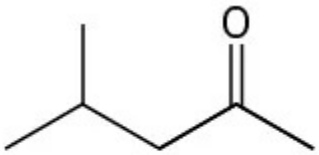


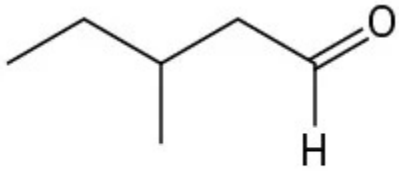
PROBLEM 13-43 Propose structures for compounds that meet the following descriptions:

(a) An optically active compound $C_5H_{10}O$ with an IR absorption at 1730 cm^{-1}

(b) A non-optically active compound C_5H_9N with an IR absorption at 2215 cm^{-1}

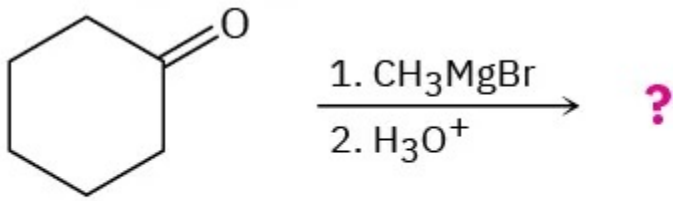
PROBLEM 13-44 4-Methyl-2-pentanone and 3-methylpentanal are isomers. Explain how you could tell them apart, both by mass spectrometry and by infrared spectroscopy.





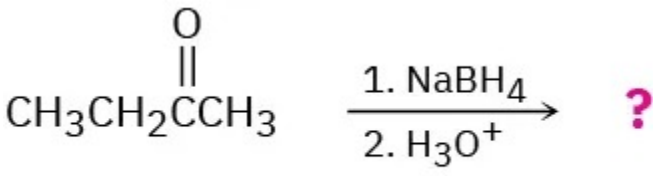
4-Methyl-2-pentanone **3-Methylpentanal**

PROBLEM 13-45 Grignard reagents (alkylmagnesium halides) undergo a general and very useful reaction with ketones. Methylmagnesium bromide, for example, reacts with cyclohexanone to yield a product with the formula $C_7H_{14}O$. What is the structure of this product if it has an IR absorption at 3400 cm^{-1}?



Cyclohexanone

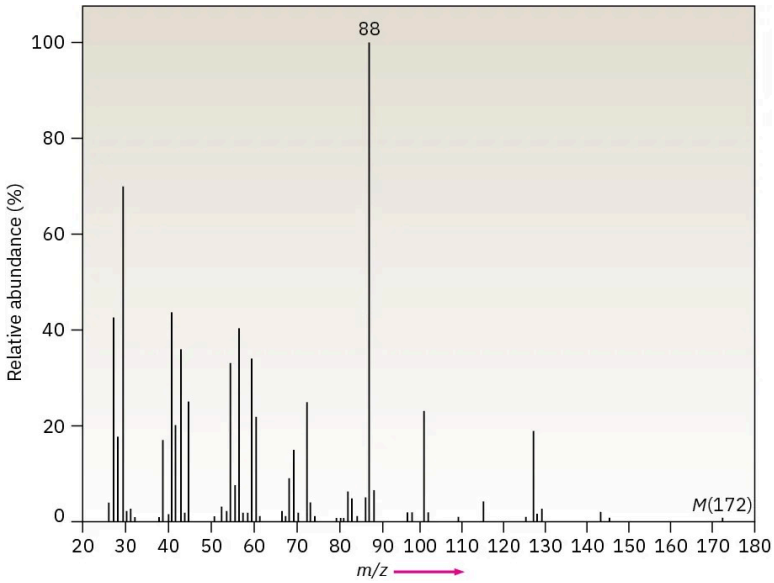
PROBLEM 13-46 Ketones undergo a reduction when treated with sodium borohydride, $NaBH_4$. What is the structure of the compound produced by the reaction of 2-butanone with $NaBH_4$ if it has an IR absorption at 3400 cm^{-1} and M^+ = 74 in the mass spectrum?



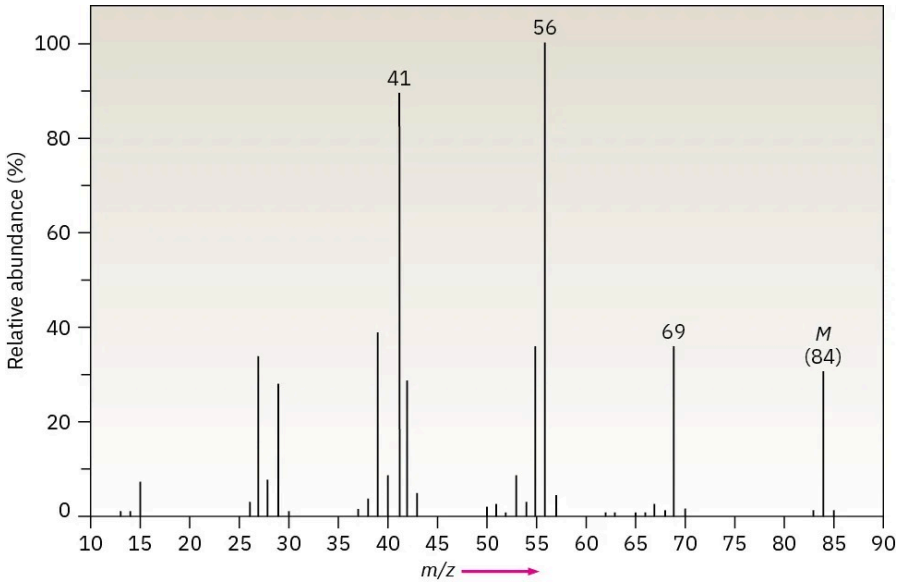
2-Butanone

PROBLEM 13-47 Nitriles, R–C≡N, undergo a hydrolysis reaction when heated with aqueous acid. What is the structure of the compound produced by hydrolysis of propanenitrile, $CH_3CH_2C{\equiv}N$, if it has IR absorptions from 2500–3100 cm^{-1} and at 1710 cm^{-1}, and has M^+ = 74?

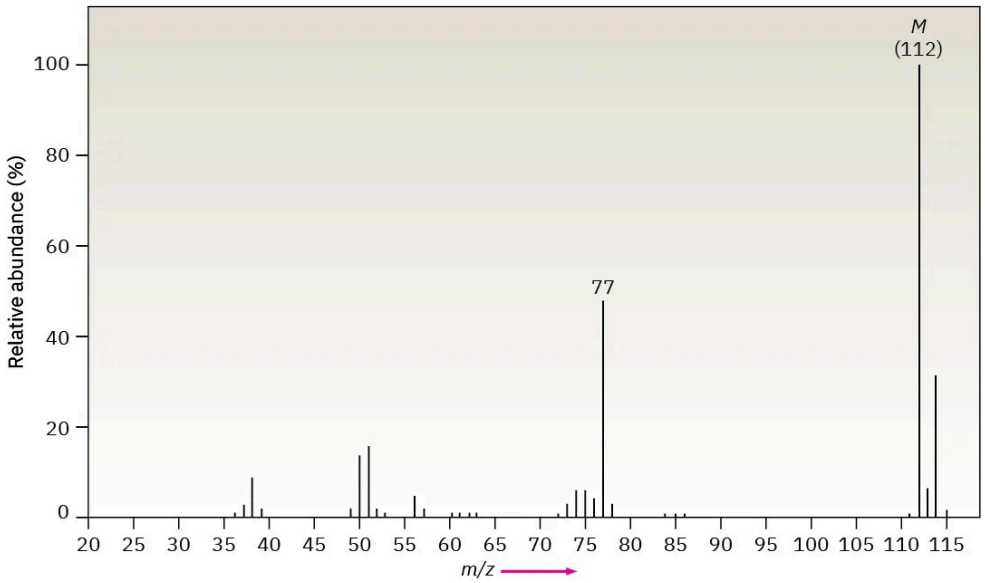
PROBLEM 13-48 The infrared spectrum of the compound with the following mass spectrum lacks any significant absorption above 3000 cm^{-1}. There is a prominent peak near 1740 cm^{-1} and another strong peak near 1200 cm^{-1}. Propose a structure.



PROBLEM 13-49 The infrared spectrum of the compound with the following mass spectrum has a medium-intensity peak at about 1650 cm^{-1}. There is also a C–H out-of-plane bending peak near 880 cm^{-1}. Propose a structure.



PROBLEM 13-50 The infrared spectrum of the compound with the following mass spectrum has strong absorbances at 1584, 1478, and 1446 cm^{-1}. Propose a structure.



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14: STRUCTURE DETERMINATION - NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

Learning Objectives

- fulfill all of the detailed objectives listed under each individual section.
- Solve road-map problems, which may require the interpretation of ^{1}H NMR spectra in addition to other spectral data.
- Define and use in context the key terms introduced.

In Chapter 13, you learned how an organic chemist could use two spectroscopic techniques, mass spectroscopy and infrared spectroscopy, to assist in determining the structure of an unknown compound. This chapter introduces a third technique, nuclear magnetic resonance (NMR). The two most common forms of NMR spectroscopy, ^{1}H NMR and ^{13}C NMR, will be discussed, the former in much more detail than the latter. Nuclear magnetic resonance spectroscopy is a very powerful tool, particularly when used in combination with other spectroscopic techniques.

14.0: Why This Chapter?

14.1: Nuclear Magnetic Resonance Spectroscopy

14.2: Acquiring a NMR Spectrum

14.3: The Shielding Effect

14.4: Proton Equivalence

14.5: Chemical Shifts in ^{1}H NMR Spectroscopy

14.6: ^{1}H NMR Signal Integration and Splitting

14.7: More Complex Spin-Spin Splitting Patterns

14.8: Uses of ^{1}H NMR Spectroscopy

14.9: Characteristics of ^{13}C NMR Spectroscopy

14.10: DEPT ^{13}C NMR Spectroscopy

14.11: H-NMR and C-NMR of Alcohols and Phenols

14.12: Uses of ^{13}C NMR Spectroscopy

14.13: Constructing Partial Structures

14.14: Combined Spectra for Structure Elucidation

14.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)

14.A: Structure Determination - NMR Spectroscopy (Summary)

14.B: Additional Problems

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14.0: Why This Chapter?

Nuclear magnetic resonance (NMR) spectroscopy has far-reaching applications in many scientific fields, particularly in chemical structure determination. Although we'll just give an overview of the subject in this chapter, focusing on NMR applications with small molecules, more advanced NMR techniques are also used in biological chemistry to study protein structure and folding.



Figure 14.0.1: NMR spectroscopy is an invaluable aid in carrying out the design and synthesis of new drugs. (credit: modification of work by Unknown/Pxhere, CC0 1.0)

Nuclear magnetic resonance (NMR) spectroscopy is the most valuable spectroscopic technique available to organic chemists. It's the method of structure determination that organic chemists usually turn to first.

We saw in the chapter on Structure Determination: Mass Spectrometry and Infrared Spectroscopy that mass spectrometry gives a molecule's formula and infrared spectroscopy identifies a molecule's functional groups. Nuclear magnetic resonance spectroscopy complements these other techniques by mapping a molecule's carbon–hydrogen framework. Taken together, MS, IR, and NMR make it possible to determine the structures of even very complex molecules.

Mass spectrometry	Molecular size and formula
Infrared spectroscopy	Functional groups present
NMR spectroscopy	Map of carbon–hydrogen framework

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14.1: Nuclear Magnetic Resonance Spectroscopy

NMR-active Nuclei

The basis for NMR is the phenomenon that some atomic nuclei spin about their axes and as a result generate their own magnetic field, or < strong>magnetic moment, therefore these nuclei are called **NMR-active**. Not all nuclei have a magnetic moment, though; only those nuclei with an odd number of protons and/or neutrons have. Fortunately nuclei that are important for organic compounds, such as the ^{1}H isotope of hydrogen, the ^{13}C isotope of carbon, the ^{14}N isotope of nitrogen, ^{19}F and the ^{31}P are all NMR-active and therefore can be observed by NMR. Other nuclei, such as the common ^{12}C isotopes of carbon and ^{16}O isotope of oxygen, do not have magnetic moments, and cannot be directly observed by NMR.

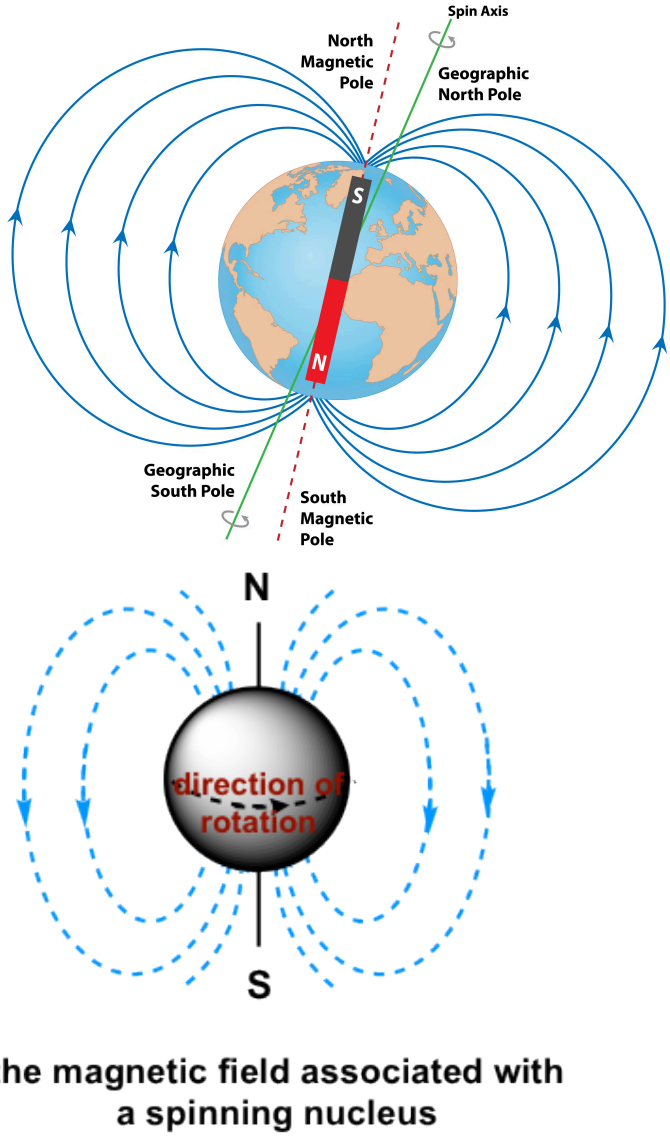


Figure 14.1.1: The magnetic field associated with (a) The spinning Earth (b) A spinning Nucleus

Many kinds of nuclei behave as if they were spinning about an axis, somewhat as the Earth spins daily. Because they're positively charged, these spinning nuclei act like tiny magnets and can interact with an external magnetic field, denoted $\boldsymbol{B}_0$. Not all nuclei

act this way, but fortunately for organic chemists, both the proton (^{1}H) and the ^{13}C nucleus do have spins. The more common ^{12}C isotope, however, does not have nuclear spin. (In speaking about NMR, the words *proton* and *hydrogen* are often used interchangeably, since a hydrogen nucleus is just a proton.) Let's see what the consequences of nuclear spin are and how we can use the results.

Spin State and Magnetic Resonance

In the absence of an external magnetic field, the spins of magnetic nuclei are oriented randomly. When a sample containing these nuclei is placed between the poles of a strong magnet, however, the nuclei adopt specific orientations, much as a compass needle orients in the earth's magnetic field. A spinning ^{1}H or ^{13}C nucleus can orient so that its own tiny magnetic field is aligned either with (parallel to) or against (antiparallel to) the external field. The two orientations don't have the same energy, however, and aren't equally likely. The parallel orientation is slightly lower in energy by an amount that depends on the strength of the external field, making this spin state very slightly favored over the antiparallel orientation (Figure 14.1.2).

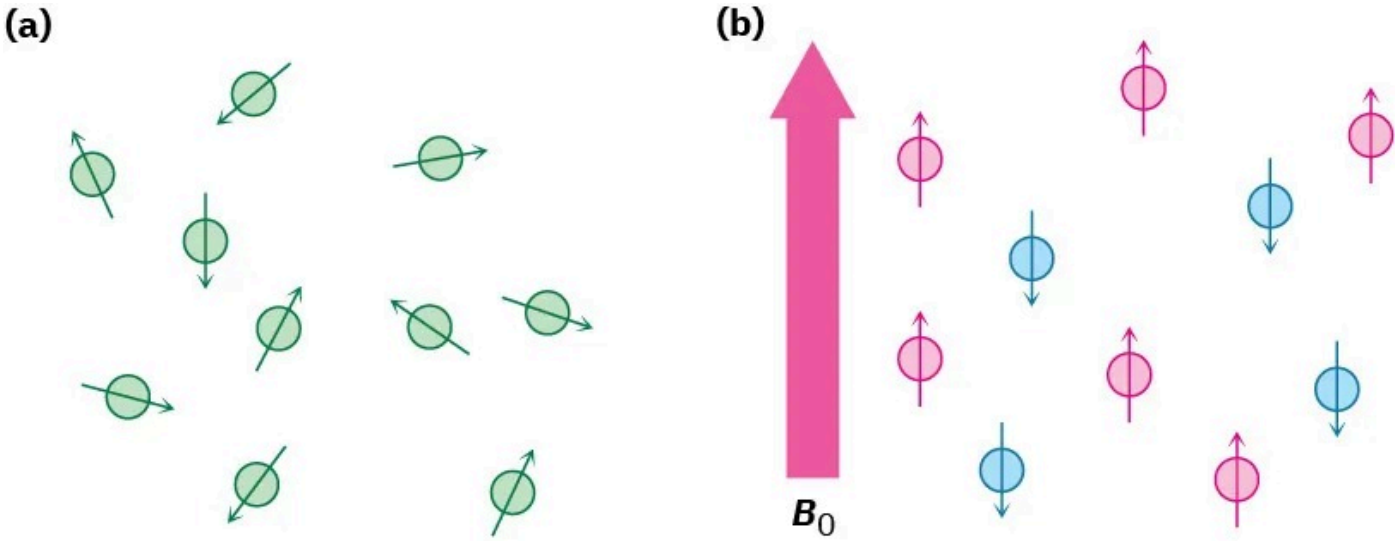


Figure 14.1.2: (a) Nuclear spins are oriented randomly in the absence of an external magnetic field but (b) have a specific orientation in the presence of an external field, B_0. Some of the spins (red) are aligned parallel to the external field while others (blue) are antiparallel. The parallel spin state is slightly lower in energy and therefore favored.

If the oriented nuclei are irradiated with electromagnetic radiation of the proper frequency, energy absorption occurs and the lower-energy spin state "flips" to the higher-energy state. When this spin-flip occurs, the magnetic nuclei are said to be in resonance with the applied radiation—hence the name *nuclear magnetic resonance*.

The exact frequency necessary for resonance depends both on the strength of the external magnetic field, the identity of the nucleus, and the electronic environment of the nucleus. If a very strong magnetic field is applied, the energy difference between the two spin states is larger and higher-frequency (higher-energy) radiation is required for a spin-flip. If a weaker magnetic field is applied, less energy is required to effect the transition between nuclear spin states (Figure 14.1.3).

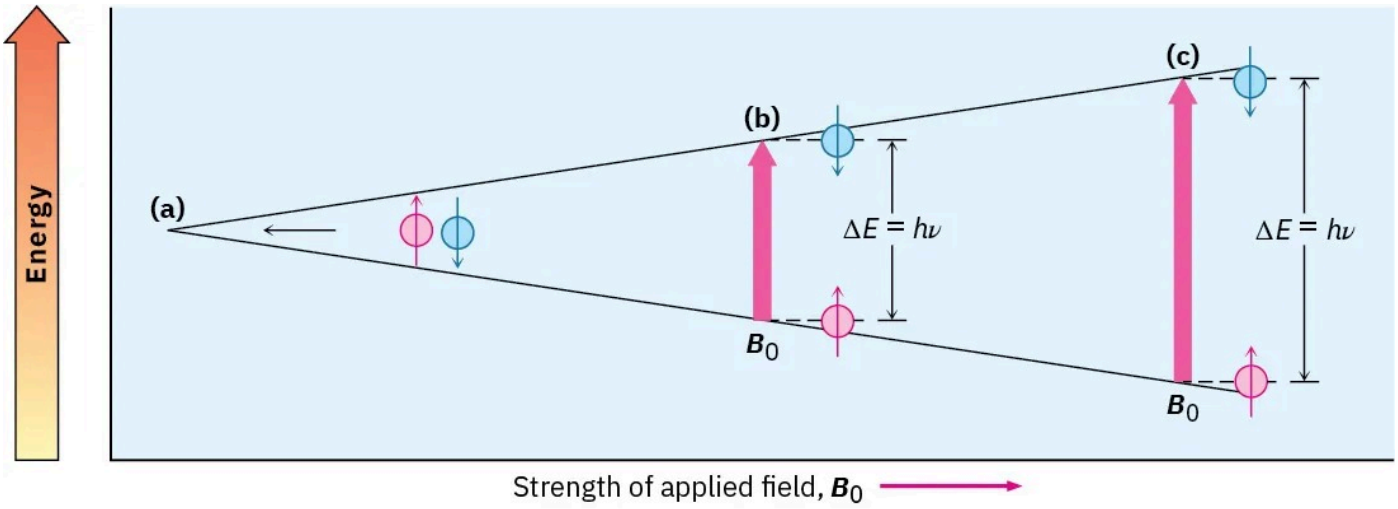


Figure 14.1.3: The energy difference ΔE between nuclear spin states depends on the strength of the applied magnetic field. Absorption of energy with frequency ν converts a nucleus from a lower spin state to a higher spin state. **(a)** Spin states have equal energies in the absence of an applied magnetic field but **(b)** have unequal energies in the presence of a magnetic field. At ν = 200 MHz, $\Delta E = 8.0 \times 10^{-5}$ kJ/mol (1.9×10^{-5} kcal/mol). **(c)** The energy difference between spin states is greater at larger applied fields. At ν = 500 MHz, $\Delta E = 2.0 \times 10^{-4}$ kJ/mol.

In practice, superconducting magnets that produce enormously powerful fields up to 23.5 tesla (T) are sometimes used, but field strengths in the range of 4.7 to 7.0 T are more common. At a magnetic field strength of 4.7 T, so-called radiofrequency (rf) energy in the 200 MHz range (1 MHz = 10^6 Hz) brings a ^{1}H nucleus into resonance, and rf energy of 50 MHz brings a ^{13}C nucleus into resonance. At the highest field strength currently available in commercial instruments (23.5 T), 1000 MHz energy is required for ^{1}H spectroscopy. These energies needed for NMR are much smaller than those required for IR spectroscopy; 200 MHz rf energy corresponds to only 8.0×10^{-5} kJ/mol versus the 4.8 to 48 kJ/mol needed for IR spectroscopy.

^{1}H and ^{13}C nuclei are not unique in their ability to exhibit the NMR phenomenon. All nuclei with an odd number of protons (^{1}H, ^{2}H, ^{14}N, ^{19}F, ^{31}P, for example) and all nuclei with an odd number of neutrons (^{13}C, for example) show magnetic properties. Only nuclei with even numbers of both protons and neutrons (^{12}C, ^{16}O, ^{32}S) do not give rise to magnetic phenomena (Table 14.1.1).

Table 14.1.1: The NMR Behavior of Some Common Nuclei

Magnetic nuclei	^{1}H	^{13}C	^{2}H	^{14}N	^{19}F	^{31}P
Nonmagnetic nuclei	^{12}C	^{16}O	^{32}S			

Exercise 14.1.1

The amount of energy required to spin-flip a nucleus depends both on the strength of the external magnetic field and on the nucleus. At a field strength of 4.7 T, rf energy of 200 MHz is required to bring a ^{1}H nucleus into resonance, but energy of only 187 MHz will bring a ^{19}F nucleus into resonance. Calculate the amount of energy required to spin-flip a ^{19}F nucleus. Is this amount greater or less than that required to spin-flip a ^{1}H nucleus?

Answer available at the end of this section.

Exercise 14.1.2

Calculate the amount of energy required to spin-flip a proton in a spectrometer operating at 300 MHz. Does increasing the spectrometer frequency from 200 to 300 MHz increase or decrease the amount of energy necessary for resonance?

Answer available at the end of this section.

Answers

Exercise 14.1.1

- 7.5×10^{-5} kJ/mol for ^{19}F
- 8.0×10^{-5} kJ/mol for ^{1}H

Exercise 14.1.2

1.2×10^{-4} kJ/mol

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14.2: Acquiring a NMR Spectrum

NMR Spectrometer

The operation of a basic NMR spectrometer is illustrated in Figure 14.2.1. An organic sample is dissolved in a suitable solvent (usually deuteriochloroform, $CDCl_3$, which has no hydrogens) and placed in a thin glass tube between the poles of a magnet. The strong magnetic field causes the ^{1}H and ^{13}C nuclei in the molecule to align in one of the two possible orientations, and the sample is irradiated with rf energy. If the frequency of the rf irradiation is held constant and the strength of the applied magnetic field is varied, each nucleus comes into resonance at a slightly different field strength. A sensitive detector monitors the absorption of rf energy, and its electronic signal is then amplified and displayed as a peak.

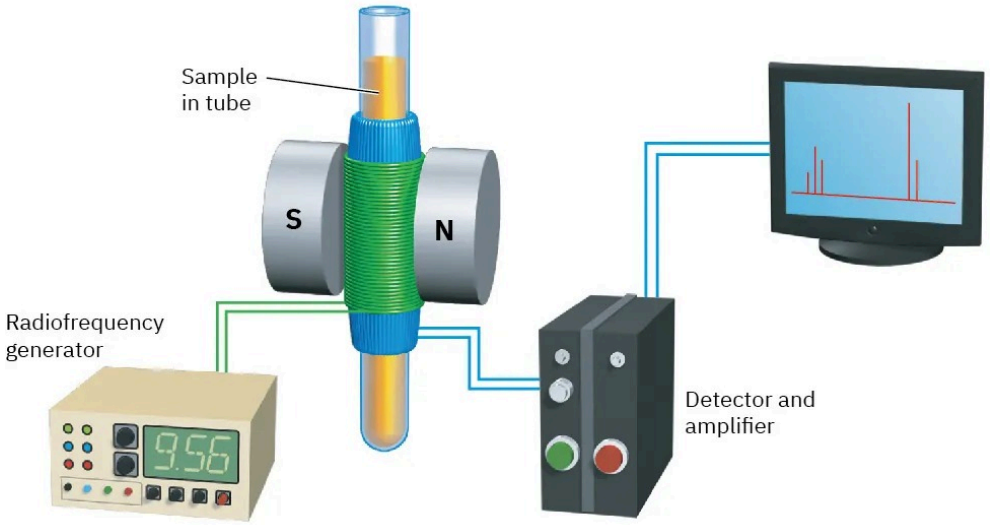


Figure 14.2.1: Schematic operation of a basic NMR spectrometer. A thin glass tube containing the sample solution is placed between the poles of a strong magnet and irradiated with rf energy.

NMR Spectra

NMR spectra are displayed on charts that show the applied field strength increasing from left to right (Figure 14.2.2). Thus, the left part of the chart is the low-field, or **downfield**, side, and the right part is the high-field, or **upfield**, side. Nuclei that absorb on the downfield side of the chart require a lower field strength for resonance, implying that they have less shielding. Nuclei that absorb on the upfield side require a higher field strength for resonance, implying that they have more shielding.

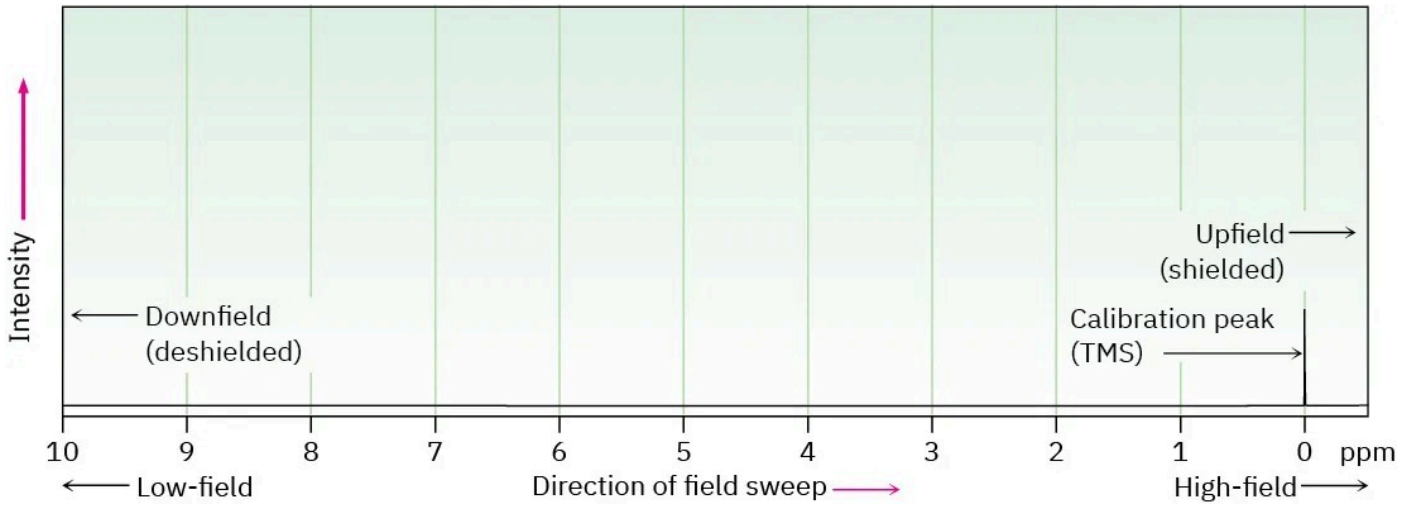


Figure 14.2.2: The NMR chart. The downfield, deshielded side is on the left, and the upfield, shielded side is on the right. The tetramethylsilane (TMS) absorption is used as reference point.

To define the position of an absorption, the NMR chart is calibrated and a reference point is used. In practice, a small amount of tetramethylsilane [TMS; $(CH_3)_4Si$] is added to the sample so that a reference absorption peak is produced when the spectrum is run. TMS is used as reference for both ^1H and ^{13}C measurements because in both cases it produces a single peak that occurs upfield of other absorptions normally found in organic compounds. The ^1H and ^{13}C spectra of methyl acetate in Figure 13.4 have the TMS reference peak indicated.The position on the chart at which a nucleus absorbs is called its **chemical shift**. The chemical shift of TMS is set as the zero point, and other absorptions normally occur downfield, to the left on the chart. NMR charts are calibrated using an arbitrary scale called the **delta (δ) scale**, where 1 δ equals 1 part-per-million (1 ppm) of the spectrometer operating frequency. For example, if we were measuring the ^1H NMR spectrum of a sample using an instrument operating at 200 MHz, 1 δ would be 1 part per million of 200,000,000 Hz, or 200 Hz. If we were measuring the spectrum using a 500 MHz instrument, 1 δ = 500 Hz. The following equation can be used for any absorption:

$$\delta = \frac{\text{Observed chemical shift (number of Hz away from TMS)}}{\text{Spectrometer frequency in}} \tag{14.2.1}$$

Although this method of calibrating NMR charts may seem complex, there's a good reason for it. As we saw earlier, the rf frequency required to bring a given nucleus into resonance depends on the spectrometer's magnetic field strength. But because there are many different kinds of spectrometers with many different magnetic field strengths available, chemical shifts given in frequency units (Hz) vary from one instrument to another. Thus, a resonance that occurs at 120 Hz downfield from TMS on one spectrometer might occur at 600 Hz downfield from TMS on another spectrometer with a more powerful magnet.

By using a system of measurement in which NMR absorptions are expressed in relative terms (parts per million relative to spectrometer frequency) rather than absolute terms (Hz), it's possible to compare spectra obtained on different instruments. *The chemical shift of an NMR absorption in δ units is constant, regardless of the operating frequency of the spectrometer.* A ^1H nucleus that absorbs at 2.0 δ on a 200 MHz instrument also absorbs at 2.0 δ on a 500 MHz instrument.

The range in which most NMR absorptions occur is quite narrow. Almost all ^1H NMR absorptions occur from 0 to 10 δ downfield from the proton absorption of TMS, and almost all ^{13}C absorptions occur from 1 to 220 δ downfield from the carbon absorption of TMS. Thus, there is a likelihood that accidental overlap of nonequivalent signals will occur. The advantage of using an instrument with higher field strength (say, 500 MHz) rather than lower field strength (200 MHz) is that different NMR absorptions are more widely separated at the higher field strength. The chances that two signals will accidentally overlap are therefore lessened, and interpretation of spectra becomes easier. For example, two signals that are only 20 Hz apart at 200 MHz (0.1 ppm) are 50 Hz apart at 500 MHz (still 0.1 ppm).

Exercise 14.2.1

The following ^1H NMR peaks were recorded on a spectrometer operating at 200 MHz. Convert each into δ units.

a. $CHCl_3$; 1454 Hz
b. CH_3Cl; 610 Hz
c. CH_3OH; 693 Hz
d. CH_2Cl_2; 1060 Hz

Answer available at the end of this section.

Exercise 14.2.2

When the ^1H NMR spectrum of acetone, CH_3COCH_3, is recorded on an instrument operating at 200 MHz, a single sharp resonance at 2.1 δ is seen.

a. How many hertz downfield from TMS does the acetone resonance correspond to?
b. If the ^1H NMR spectrum of acetone is recorded at 500 MHz, what would the position of the absorption be in δ units?
c. How many hertz downfield from TMS does this 500 MHz resonance correspond to?

Answer available at the end of this section.

Answers

Exercise 14.2.1

a.7.27 δ **b.**3.05 δ **c.**3.46 δ **d.**5.30 δ

Exercise 14.2.2

a.420 Hz **b.**2.1 δ **c.**1050 Hz

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14.3: The Shielding Effect

Shielding and Deshielding

From the description thus far, you might expect all ^{1}H nuclei in a molecule to absorb energy at the same frequency and all ^{13}C nuclei to absorb at the same frequency. If so, we would observe only a single NMR absorption signal in the ^{1}H or ^{13}C spectrum of a molecule, a situation that would be of little use. In fact, the absorption frequency is not the same for all ^{1}H or all ^{13}C nuclei. Electrons surround all nuclei in molecules. When an external magnetic field is applied to a molecule, the electrons moving around nuclei set up tiny local magnetic fields of their own. These local magnetic fields act in opposition to the applied field so that the effective field actually felt by the nucleus is a bit weaker than the applied field.

Figure 14.3.1 shows for hydrogen atoms in any bonds, such as C-H, O-H etc, the external magnetic field B_0 causes the s electrons to circulate in a way that generate an induced local magnetic field (B_{local}) at the proton, and the direction of the local field B_{local} is opposite to the external field B_0. The proton thus experiences a net magnetic field, which is called B_{eff}, that is smaller than the applied magnetic field:

$$B_{\text{effective}} = B_{\text{applied}} - B_{\text{local}}$$

As a result, the proton responses to a lower frequency (resonance frequency is proportional to the magnetic field as mentioned early). This Blocal, to a small but significant degree, shields the proton from experiencing the full force of B0, so this effect is called the shielding effect. Different hydrogen atoms in organic structures are in different electronic environments, have different electron density, therefore have different B_{local} and different B_{eff} as well. That is why different hydrogens (and protons) are in different resonance frequency and show different signals in the spectrum.

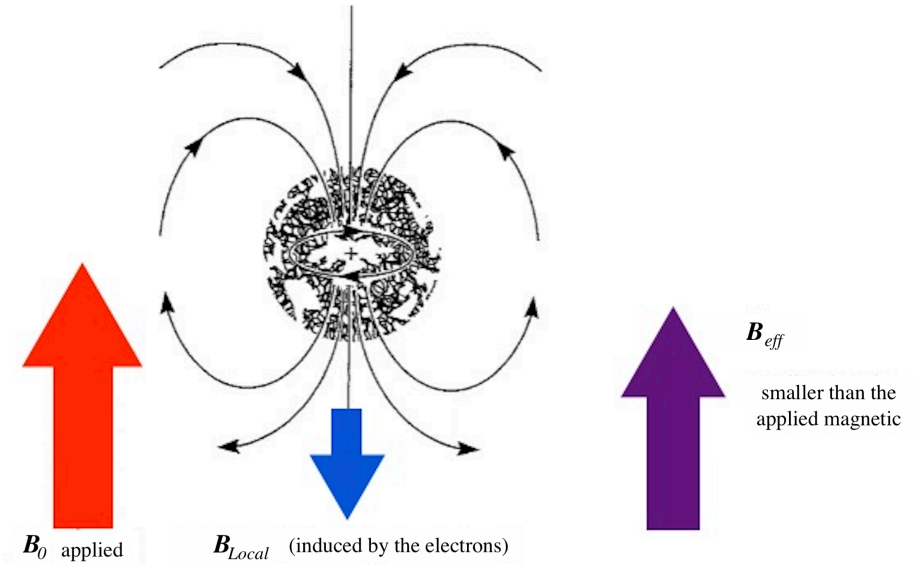


Figure 14.3.1: the external magnetic field B_0 causes the s electrons to circulate in a way that generates an induced local magnetic field (B_{local}) at the proton, and the direction of the local field B_{local} is opposite to the external field B_0. The proton thus experiences a net magnetic field, which is called B_{eff}.

Effect of Shielding

For hydrogen atoms close to electronegative groups, electronegative groups withdraw electron density from nearby atoms, thus diminishing the shielding of the protons by circulating electrons. The hydrogen atoms near an electronegative group are said to be **deshielded** from the external magnetic field and have a higher resonance frequency than those shielded protons. As the electronegativity of the substituent increases, so does the extent of the deshielding effect, as shown in the examples below.

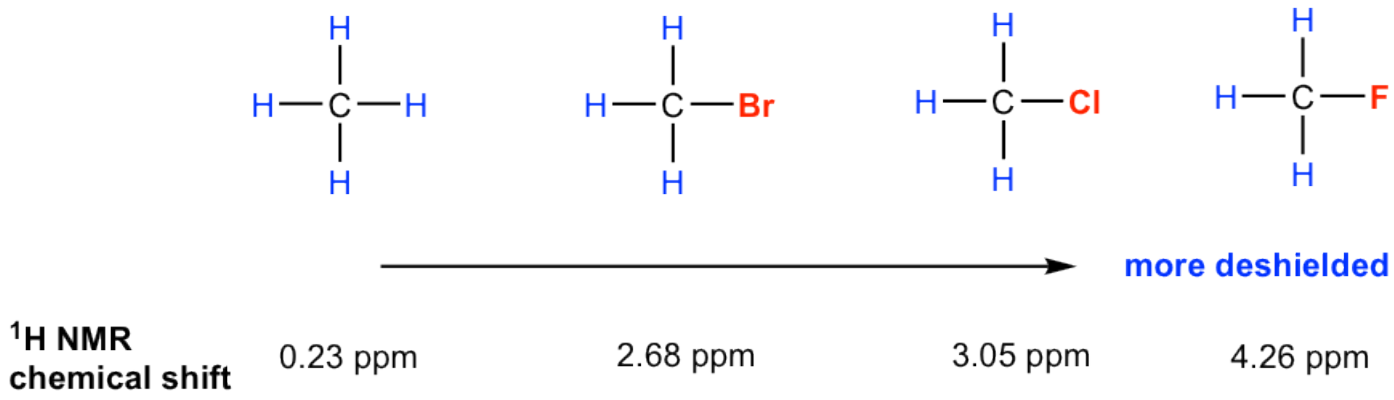


Figure 14.3.2 a: H atoms get more deshielded when the electronegativity of the substituent increases.

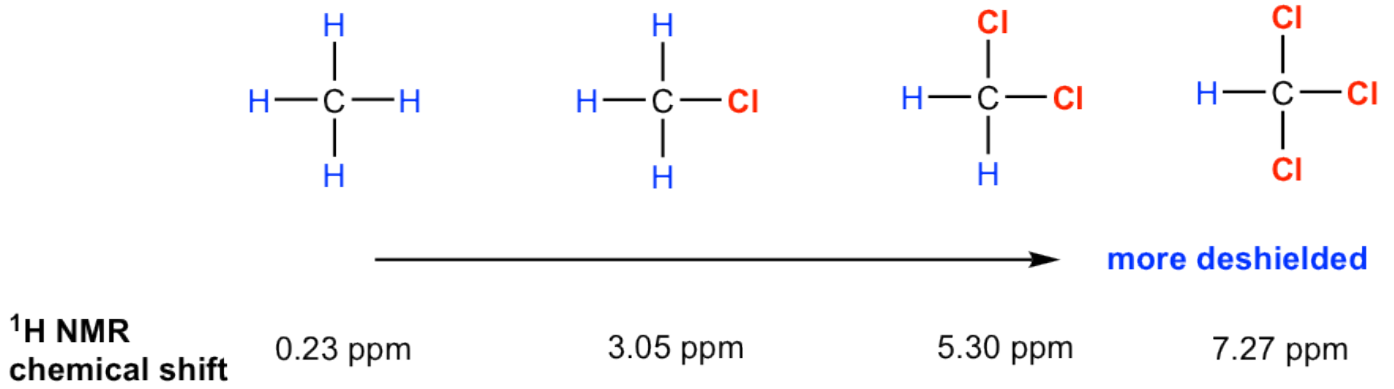


Figure 14.3.2 b: H atoms get more deshielded when more electronegative substituents are involved.

Chemical Shift

In describing this effect of local fields, we say that nuclei experience **shielding** from the full effect of the applied field by the surrounding electrons. Because each chemically distinct nucleus in a molecule is in a slightly different electronic environment, each nucleus is shielded to a slightly different extent, and the effective magnetic field felt by each is slightly different. These tiny differences in the effective magnetic fields experienced by different nuclei can be detected, and we thus see a distinct NMR signal for each chemically distinct ^{13}C or ^{1}H nucleus in a molecule. As a result, an NMR spectrum effectively maps the carbon–hydrogen framework of an organic molecule. With practice, it's possible to read this map and derive structural information.

Figure 14.3.3 shows both the ^{1}H and the ^{13}C NMR spectra of methyl acetate, $CH_3CO_2CH_3$. The horizontal axis shows the effective field strength felt by the nuclei, and the vertical axis indicates the intensity of absorption of rf energy. Each peak in the NMR spectrum corresponds to a chemically distinct ^{1}H or ^{13}C nucleus in the molecule. Note that NMR spectra are formatted with the zero absorption line at the bottom, whereas IR spectra are formatted with the zero absorption line at the top; Chapter 13. Note also that ^{1}H and ^{13}C spectra can't be observed simultaneously on the same spectrometer because different amounts of energy are required to spin-flip the different kinds of nuclei. The two spectra must be recorded separately.

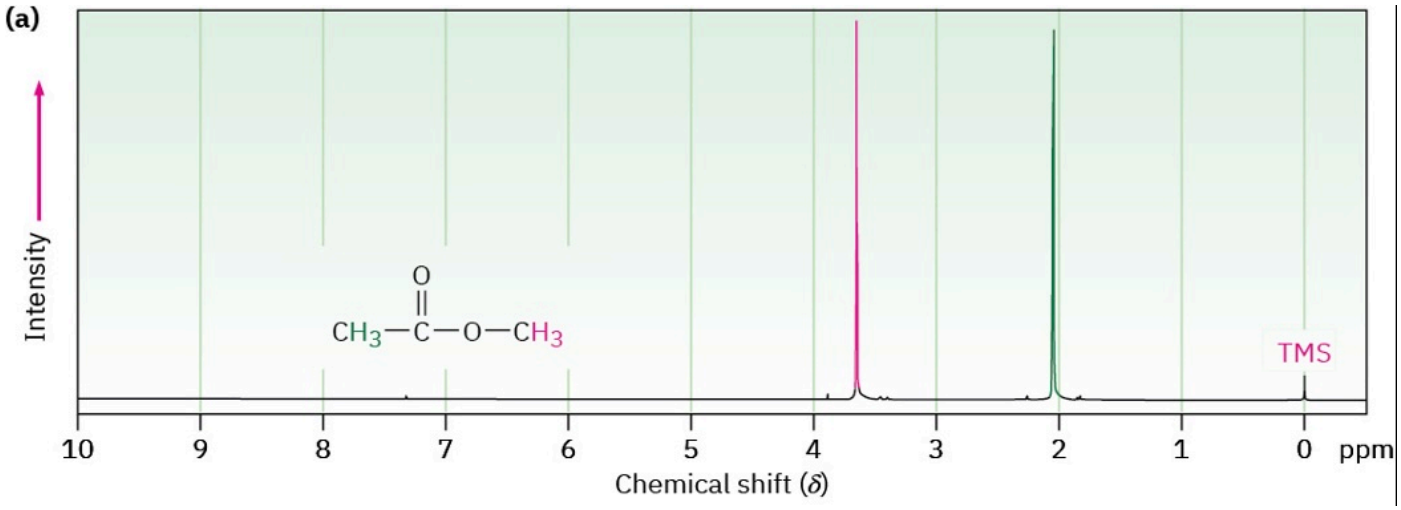


Figure 14.3.3 (a): The ^{1}H NMR spectrum. The small peak labeled “TMS” at the far right of the spectrum is a calibration peak.

The ^{13}C NMR spectrum of methyl acetate in Figure 14.3.3b shows three peaks, one for each of the three chemically distinct carbon atoms in the molecule. The ^{1}H NMR spectrum in Figure 14.3.3a shows only two peaks; however, even though methyl acetate has six hydrogens. One peak is due to the $CH_3C{=}O$ hydrogens, and the other to the $-OCH_3$ hydrogens. Because the three hydrogens in each methyl group have the same electronic environment, they are shielded to the same extent and are said to be equivalent. Chemically equivalent nuclei always show the same absorption. The two methyl groups themselves, however, are not equivalent, so the two sets of hydrogens absorb at different positions.

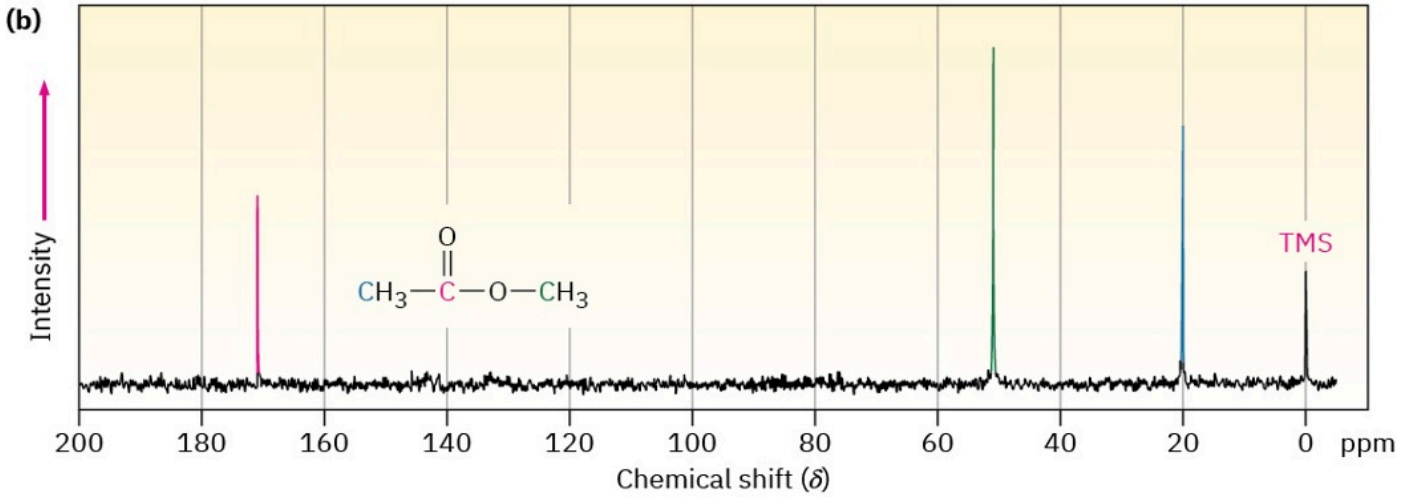


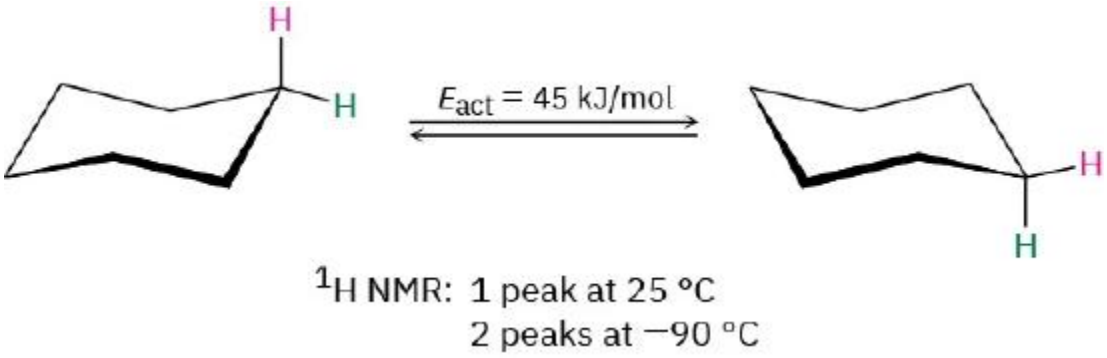
Figure 14.3.3 (b): the proton-decoupled ^{13}C NMR spectrum of methyl acetate, $CH_3CO_2CH_3$.

Effect of Time on Not-Equivalent Shielding

NMR spectroscopy differs from IR spectroscopy in that the timescales of the two techniques are quite different. The absorption of infrared energy by a molecule giving rise to a change in vibrational amplitude is an essentially instantaneous process (about 10^{-13} s), but the NMR process is much slower (about 10^{-3} s). This difference in timescales between IR and NMR spectroscopy is analogous to the difference between cameras operating at very fast and very slow shutter speeds. The fast camera (IR) takes an instantaneous picture and freezes the action. If two rapidly interconverting species are present, IR spectroscopy records the spectrum of both. The slow camera (NMR), however, takes a blurred, time-averaged picture. If two species interconverting faster than 10^{3} times per second are present in a sample, NMR records only a single, averaged spectrum, rather than separate spectra of the two discrete species.

Because of this blurring effect, NMR spectroscopy can be used to measure the rates and activation energies of very fast chemical

processes. In cyclohexane, for example, a ring-flip (Chapter 4) occurs so rapidly at room temperature that axial and equatorial hydrogens can't be distinguished by NMR; only a single, averaged ^{1}H NMR absorption is seen for cyclohexane at 25 °C. At –90 °C, however, the ring-flip is slowed down enough that two absorption peaks are visible, one for the six axial hydrogens and one for the six equatorial hydrogens. Knowing the temperature and the rate at which signal blurring begins to occur, it's possible to calculate that the activation energy for the cyclohexane ring-flip is 45 kJ/mol (10.8 kcal/mol).



Exercise 14.3.1

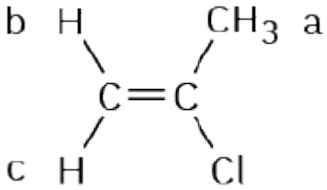
2-Chloropropene shows signals for three kinds of protons in its ^{1}H NMR spectrum. Explain.

Answer available at the end of this section.

Answers

Exercise 14.3.1

The vinylic C – H protons are nonequivalent.



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14.4: Proton Equivalence

Understanding the basics of NMR theory gets us ready to move on to the most important and practical part in this section, which is how to understand the ^{1}H NMR spectrum and elucidate the structure of a compound from ^{1}H NMR spectrum information. Let's first take a look at an actual ^{1}H NMR spectrum.

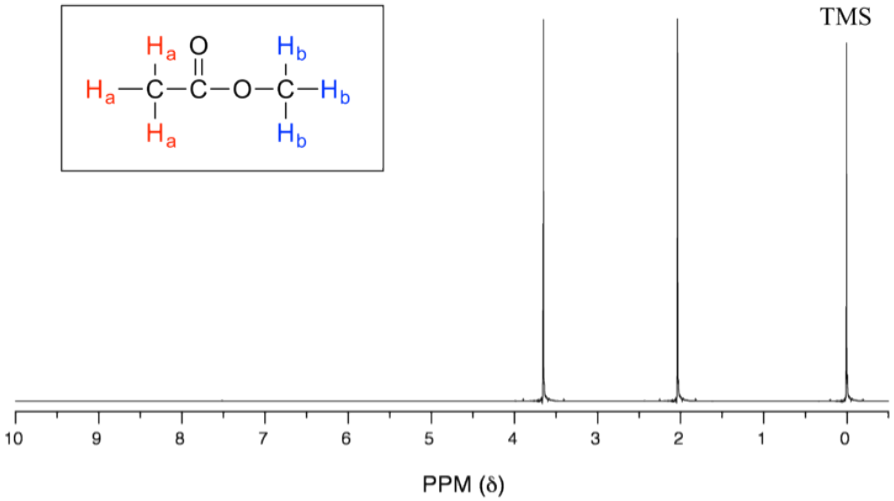


Figure 14.4.1: The 1H NMR spectrum of methyl acetate

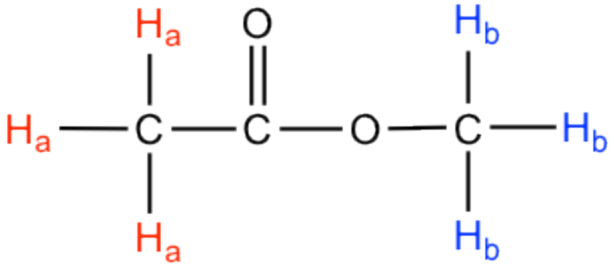
Generally, the information about the structure of a molecule can be obtained from four aspects of a typical ^{1}H NMR spectrum:

- Chemical equivalent and non-equivalent protons (total number of signals)
- Chemical shift
- Integration
- Signal splitting

Chemical Equivalent and Non-Equivalent Protons

In the above ^{1}H NMR spectrum of methyl acetate (Figure 14.4.1:), we can see that there are three signals. The peak at the far right is for the standard reference compound tetramethylsilane (TMS, more discussions in chemical shift section), not for the compound. So the compound methyl acetate shows two signals in ^{1}H NMR spectrum. Why only two signals for a compound containing a total of six hydrogens?

This is because of chemical equivalence. The six total hydrogens can be divided into two groups: the three **Ha** protons in the methyl group bonded to the C=O are in the same chemical environment and are therefore chemically equivalent. All chemical equivalent hydrogens have the same resonance frequency when applied to an external magnetic field, so they show only one signal in a 1H NMR spectrum. The three **H_b** protons in the methyl group bonded with O atom are chemical equivalent as well and show the other signal. That is why there are two signals in total for compound methyl acetate.



the three H_as are chemical equivalent

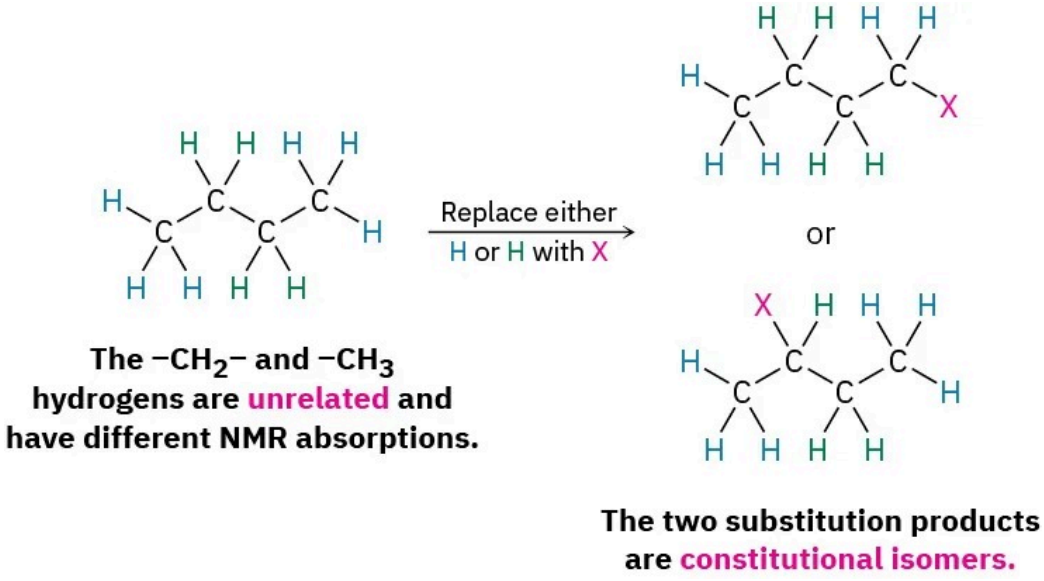
the three H_bs are chemical equivalent

The ability to recognize chemically equivalent and non-equivalent protons in a molecule is very important in understanding the NMR spectrum. For the compound with the given structure, we can predict how many signals there are in the 1H NMR spectrum. On the other side, if the ^{1}H NMR spectrum is available for an unknown compound, counting the number of signals in the spectrum tells us the number of different sets of protons in the molecule, and that is very important information to determine the structure of the compound.

Homotopic, Enantiotopic, or Diasterotopic CH_2 Protons

For relatively small molecules, a quick look at the structure is often enough to decide how many kinds of protons are present and thus how many NMR absorptions might appear. If in doubt, though, the equivalence or nonequivalence of two protons can be determined by comparing the structures that would be formed if each hydrogen were replaced by an X group. There are four possibilities.

- One possibility is that the protons are chemically unrelated and thus nonequivalent. If so, the products formed on substitution of H by X would be different constitutional isomers. In butane, for instance, the $-CH_3$ protons are different from the $-CH_2-$ protons. They therefore give different products on substitution by X than the $-CH_2$ protons and would likely show different NMR absorptions.



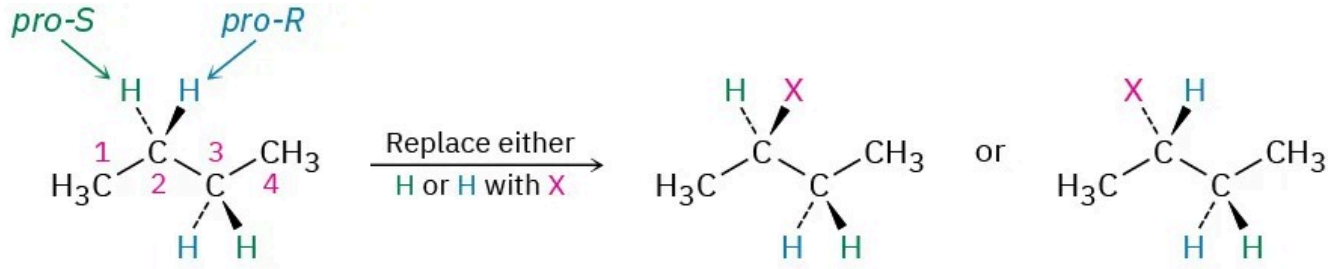
- A second possibility is that the protons are chemically identical and thus electronically equivalent. If so, the same product would be formed regardless of which H is substituted by X. In butane, for instance, the six $-CH_3$ hydrogens on C1 and C4 are identical, would give the identical structure on substitution by X, and would show an identical NMR absorption. Such protons are said to be homotopic.



The six $-CH_3$ hydrogens are homotopic and have the same NMR absorption.

Only one substitution product is possible.

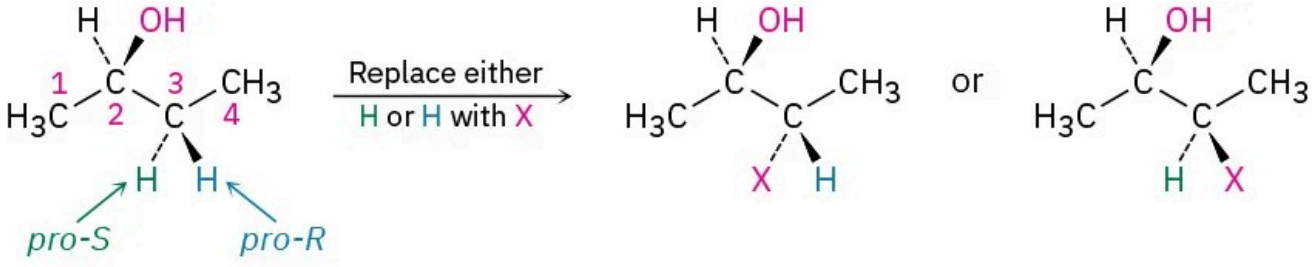
- The third possibility is a bit more subtle. Although they might at first seem homotopic, the two $-CH_2-$ hydrogens on C2 in butane (and the two $-CH_2-$ hydrogens on C3) are in fact not identical. Substitution by X of a hydrogen at C2 (or C3) would form a new chirality center, so different enantiomers (Section 5.1) would result, depending on whether the pro-*R* or pro-*S* hydrogen had been substituted (Section 5.11). Such hydrogens, whose substitution by X would lead to different enantiomers, are said to be enantiotopic. Enantiotopic hydrogens, even though not identical, are nevertheless electronically equivalent and thus have the same NMR absorption.



The two hydrogens on C2 (and on C3) are enantiotopic and have the same NMR absorption.

The two possible substitution products are enantiomers.

- The fourth possibility arises in chiral molecules, such as (*R*)-2-butanol. The two $-CH_2-$ hydrogens at C3 are neither homotopic nor enantiotopic. Because substitution of a hydrogen at C3 would form a *second* chirality center, different diastereomers (Section 5.6) would result, depending on whether the pro-*R* or pro-S hydrogen had been substituted. Such hydrogens, whose substitution by X leads to different diastereomers, are said to be diastereotopic. Diastereotopic hydrogens are neither chemically nor electronically equivalent. They are completely different and would likely show different NMR absorptions.



The two hydrogens on C3 are diastereotopic and have different NMR absorptions.

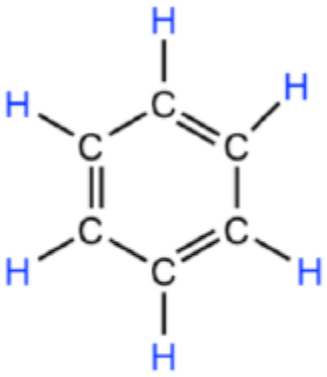
The two possible substitution products are diastereomers.

Note

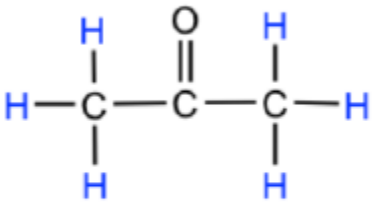
As you probably already realized, chemical equivalence or non-equivalence in NMR is closely related to *symmetry*. The protons that are symmetric to each other by a certain plane of symmetry are chemically equivalent.

Here, we will go through several examples for the first situation: predicting the number of signals in a 1H NMR spectrum given the structure of a compound. To do that, we need to count the number of distinct sets of protons in the molecule.

For each of the following molecules, the chemically equivalent protons are labeled in the same *color* to facilitate understanding.



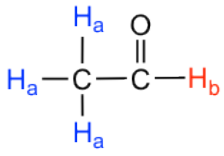
benzene



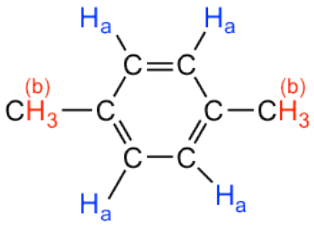
acetone

- **Benzene:** all six protons are chemically equivalent (have the same bonding and are in the same chemical environment) to each other and have the same resonance frequency in a 1H NMR experiment, therefore show only **one** signal.
- **Acetone:** both methyl groups (two CH_3) are bonded with the C=O bond, so they are in the same chemical environment, and as a result, all six protons are chemically equivalent, showing only **one** signal.

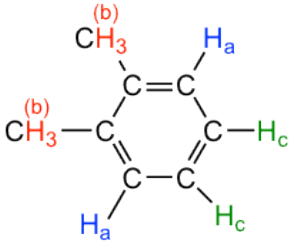
The molecules in the next figure contain more sets of chemically equivalent protons.



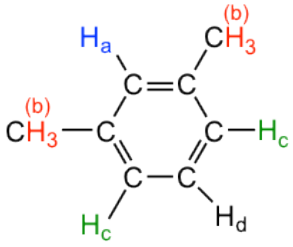
acetaldehyde



1,4-dimethylbenzene



1,2-dimethylbenzene



1,3-dimethylbenzene

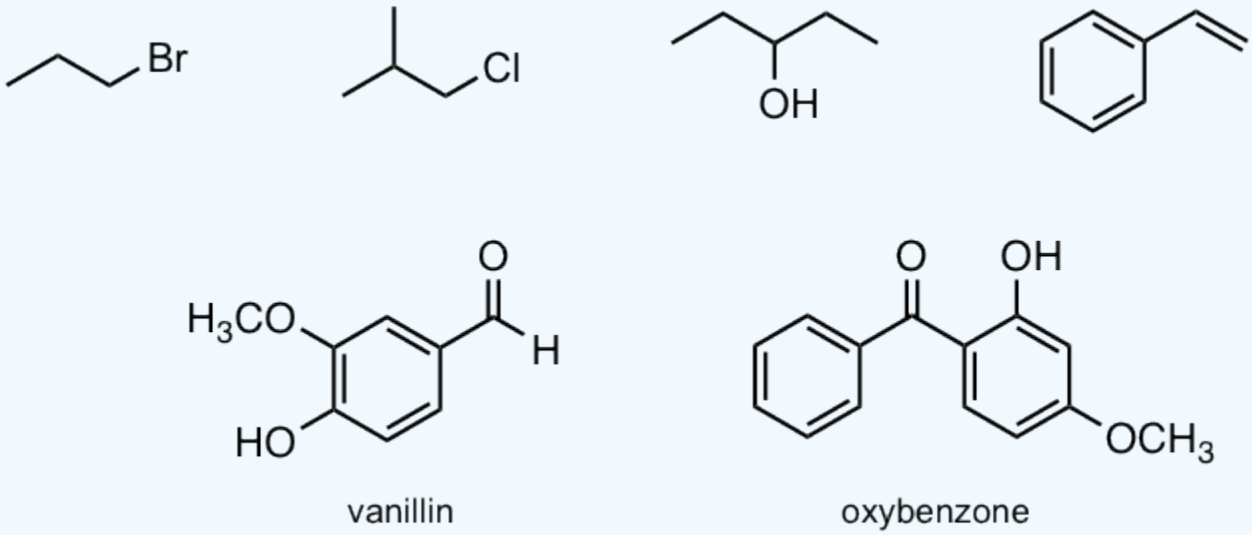
- **Acetaldehyde:** The three Ha protons in the methyl group are chemically equivalent, and they are all bonded to an sp^3-hybridized carbon; but they are different from the Hb proton that is bonded to an sp^2–sp^2-hybridized carbonyl carbon. **Two** signals total in ^{1}H NMR spectrum.
- **1,4-dimethylbenzene:** all four aromatic protons are chemically equivalent because of the symmetry. The two methyl groups are equivalent to each other as well. **Two** signals total in ^{1}H NMR spectrum.
- **1,2-dimethylbenzene:** both H_a protons are adjacent to a methyl substituent, while both H_c protons are two carbons away. So the four aromatic protons are divided to *two* sets. Both methyl groups are in the same bonding and symmetric to each other; they are equivalent. **Three** signals total in ^{1}H NMR spectrum.
- **1,3-dimethylbenzene:** H_b is situated between two methyl groups, the two H_c protons are one carbon away from a methyl group, and H_d is two carbons away from a methyl group. Therefore, the four aromatic protons can be divided into *three* sets.

The two methyl groups are equivalent. **Four** signals total in ^{1}H NMR spectrum.

Exercises

Exercise 14.4.1

How many ^{1}H NMR signals would you predict for each of the following molecules?



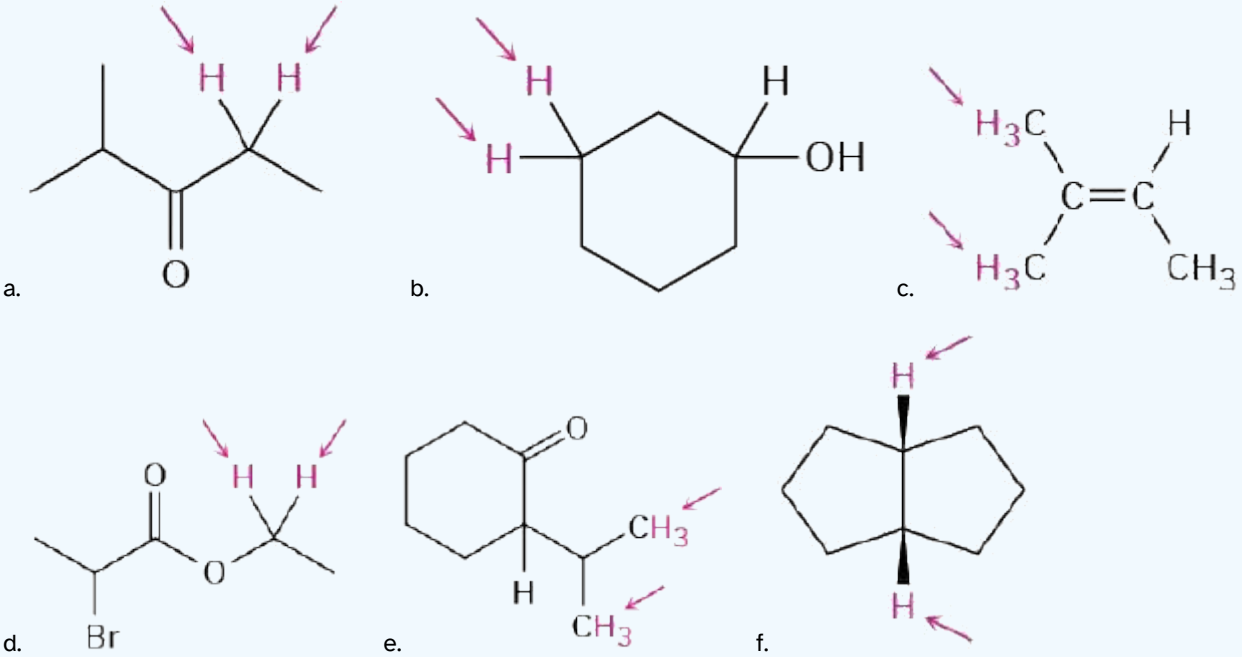
vanillin

oxybenzone

Answer available at the end of this section.

Exercise 14.4.2

Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



Answer available at the end of this section.

Exercise 14.4.3

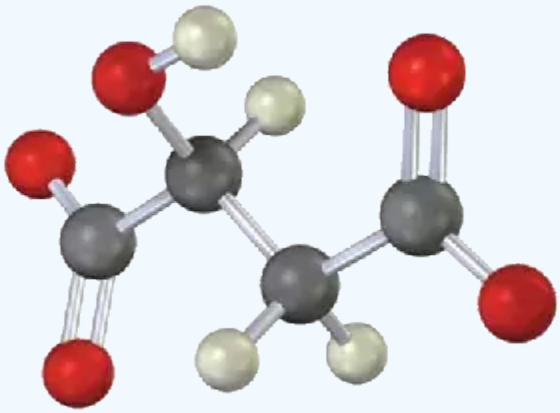
How many kinds of electronically nonequivalent protons are present in each of the following compounds, and thus how many NMR absorptions might you expect in each?

a. CH_3CH_2Br b. $CH_3OCH_2CH(CH_3)_2$ c. $CH_3CH_2CH_2NO_2$ d. Methylbenzene e. 2-Methyl-1-butene f. *cis*-3-Hexene

Answer available at the end of this section.

Exercise 14.4.4

How many absorptions would you expect (*S*)-malate, an intermediate in carbohydrate metabolism, to have in its ^1H NMR spectrum? Explain.

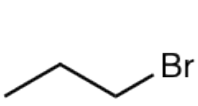


(*S*)-Malate

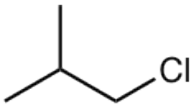
Answer available at the end of this section.

Answers

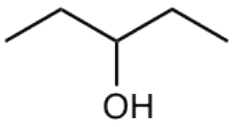
Exercise 14.4.1



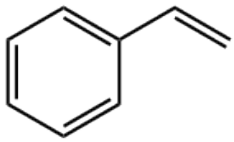
3



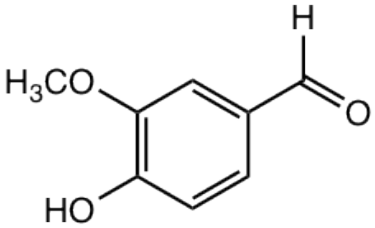
3



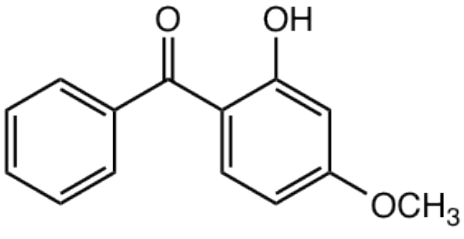
4



5



6



10

Exercise 14.4.2

a. Enantiotopic. b. Diastereotopic. c. Diastereotopic. d. Diastereotopic. e. Diastereotopic. f. Homotopic

Exercise 14.4.3

a. 2. b. 4 c. 3. d. 4. e. 5. f. 3.

Exercise 14.4.4

4

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14.5: Chemical Shifts in ^{1}H NMR Spectroscopy

As mentioned previously, differences in chemical shifts are caused by the small local magnetic field of electrons surrounding different nuclei. As seen in the ^{1}H NMR spectrum of methyl acetate (Figure 14.5.1), the *x*-axis units of NMR spectrum are in ppm (not in Hz as we would expect for frequency), and the two signals stand at different position along the *x*-axis. Let's explain how that works and what information can be obtained.

Shielded vs Deshielded

The position of a signal along the *x*-axis of an NMR spectra is called **chemical shift,** or **δ,** of the signal. Chemical shift is determined by the structural electronic environment of the nuclei producing that signal. Protons in different chemical environments (non-equivalent) show signals at different chemical shifts. The *direction* of the chemical shift scale on *the x*-axis is opposite to what we are familiar with, that is, the smaller value is at the right-hand side, and the larger value is at the left-hand side.

- Smaller chemical shift (**δ**) values correspond with lower resonance frequency;
- Larger chemical shift (**δ**) values correspond with higher resonance frequency.

By **convention**, the right-hand side of an NMR spectrum with smaller chemical shift values is called **upfield**, and the left-hand direction is called **downfield** (Figure 14.5.1).

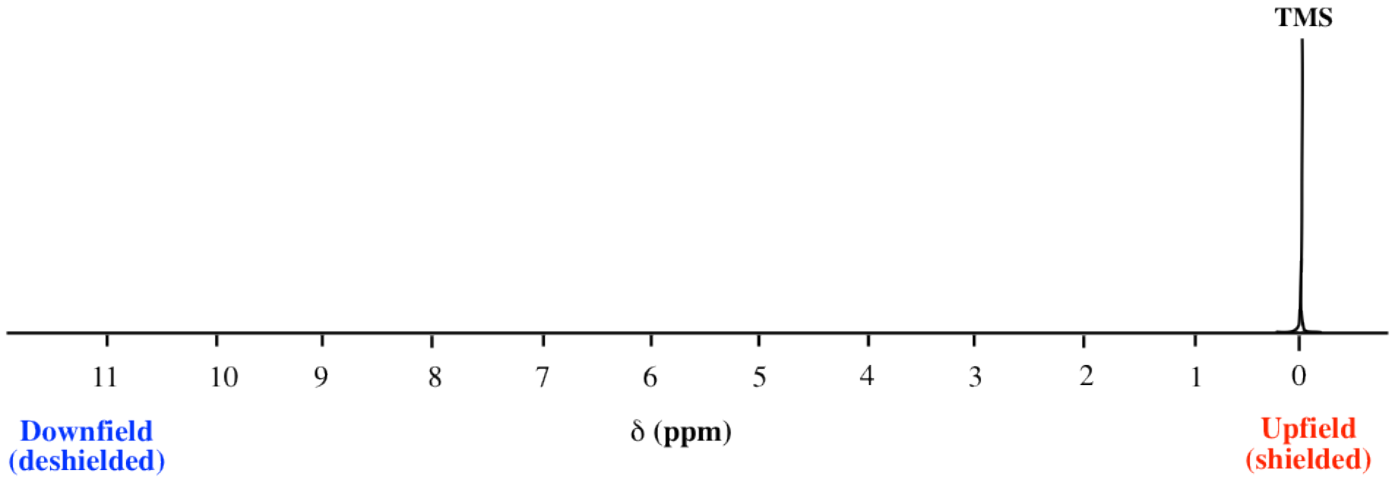


Figure 14.5.1: The chemical shift scale in H NMR spectra

For protons that are **shielded**, because of the B_{local} caused by circulating electrons, the magnetic field experienced by the proton, B_{eff}, is smaller than the applied external field, B_o, so the protons resonate at a lower frequency and have smaller chemical shift values.

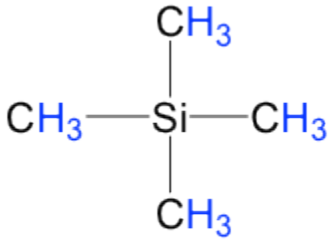
- Shielded protons have a lower resonance frequency and smaller chemical shift (**δ**) values;
- Deshielded protons have a higher resonance frequency and larger chemical shift (**δ**) values.

Reference

In a ^{1}H NMR spectrum, the absorption of the protons of **TMS** (tetramethylsilane) is defined as "**zero**" on the chemical shift (**δ**) scale, and the absorption of other protons is reported as a relative shift compared with that of TMS.

TMS was chosen as a reference compound and defined as "**zero**" for several reasons. Since silicon is less electronegative than carbon, the hydrogens of TMS are in a high electron-density environment, therefore are highly shielded with a very low resonance

frequency and rarely interfere with the signals of other compounds. Also, there are twelve equivalent hydrogens in TMS that show a *single* signal, so the signal is rather strong even with a very small amount of TMS. TMS is also quite inert and easy to remove with a boiling point of 27°C. A small amount of TMS was added to the sample as an internal standard for NMR measurement, and removed by evaporation afterwards. However, for contemporary NMR spectrometers (including bench-top NMR), it is no longer necessary to add TMS, as the computer can electronically calibrate the chemical shift based on the solvent's resonance frequencies.



tetramethylsilane (TMS)

The unit of chemical shift (**δ**) is **ppm**. The 'ppm' label stands for 'parts per million'. The chemical shift relative to TMS, in ppm, is defined by the formula below.

The reason for using a relative value of chemical shift in ppm, rather than the actual resonance frequency in Hz is that every NMR instrument will have a different magnetic field strength, so the actual value of resonance frequencies expressed in Hz will be different on different instruments – remember that ΔE for the magnetic transition of a nucleus depends upon the strength of the externally applied magnetic field B_o. However, the chemical shift expressed in ppm will always be the same whether measured with an instrument operating at 400 MHz or 60 MHz. In the ^{1}H NMR of methyl acetate, the two signals at 2.0 and 3.6 ppm represent the two sets of protons in methyl acetate that have resonance frequencies about 2.0 and 3.6 parts per million higher than the resonance frequency of the TMS protons. If, for example, the spectrum is measured by the 400 MHz NMR spectrometer, then the chemical shift in Hz will be 800 Hz and 1440 Hz, respectively.

Chemical Shift

Most ^{1}H chemical shifts fall within the range 0 to 12 *δ*, which can be divided into the five regions shown in Figure 14.5.2. By remembering the positions of these regions, it's often possible to tell at a glance what kinds of protons a molecule contains.

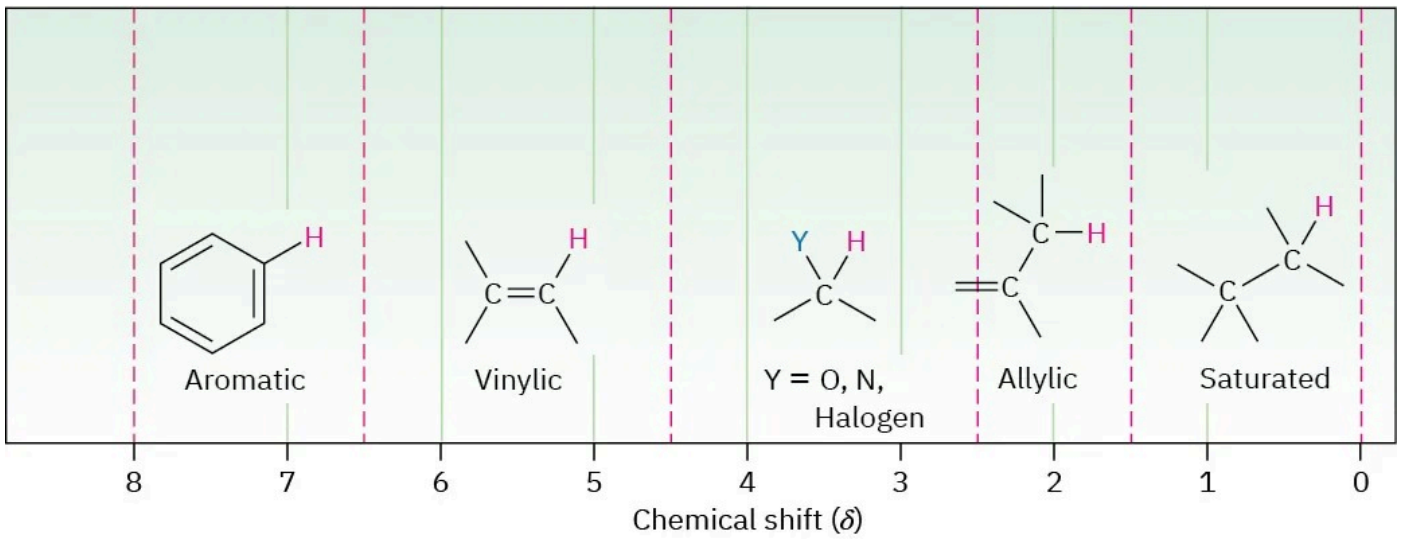


Figure 14.5.2: "Oversimplified" Regions of the ^{1}H NMR Spectrum

Table 14.5.1 shows the correlation of ^{1}H chemical shift with electronic environment in more detail. In general, protons bonded to saturated, sp^3-hybridized carbons absorb at higher fields, whereas protons bonded to sp^2-hybridized carbons absorb at lower fields. Protons on carbons that are bonded to electronegative atoms, such as N, O, or halogen, also absorb at lower fields.

The importance of chemical shift information lies in its ability to provide critical clues about *molecular structures*. Several highlights here:

- Usually, the hydrogens in C-H bond, without any other functional groups nearby, are in the range of 1-2 ppm;
- For hydrogen in C-H bond beside a double bond, like C=C or C=O bond, the signal goes downfield to 2-2.5 ppm;
- With electronegative atoms connected on the carbon, like O-C-H, the hydrogens get deshielded and the chemical shift moves further downfield to 3-4 ppm;
- The hydrogens bonded directly to the double bond carbon have the chemical shift at around 4.5-6 pm;
- The aromatic hydrogens (H on benzene ring) show a chemical shift around 7 ppm;
- The chemical shift of hydrogens in OH (alcohol) or NH (amine) group varies in a rather large range, from 1-5 ppm;
- The hydrogen in aldehyde (-CHO) and carboxylic acid (COOH) groups has chemical shifts that are downfield, at about 9-10 ppm and 10-12 ppm, respectively.

Note

When referring to the chemical shift table (or chart) for a given compound, keep in mind that the exact value may vary slightly within the given range, and differences of up to 0.5 ppm may occur, depending on the specific structure and the solvent used.

Nuclei that are more strongly shielded by electrons require a higher applied field to bring them into resonance, so they absorb on the right side of the NMR chart. Nuclei that are less strongly shielded need a lower applied field for resonance, so they absorb on the left of the NMR chart.

Table 14.5.1: Approximate Proton Chemical Shifts of Common Functional Groups

Type of Proton	Chemical Shift (ppm)	Type of Proton	Chemical Shift (ppm)
$R-CH_3$	0.9 – 1.2	$X-CH_2R$ (X: Cl, Br, I)	3.1 – 3.8
$R-CH_2$	1.2 – 1.5	R—OH	variable, 1 – 5
$R-CH$	1.4 – 1.9	$R-NH_2$	variable, 1 – 5
$C=C-CHR_2$	1.5 – 2.5	$C=C-H$	4.5 – 6.0
$R-C(=O)-CH_3$	2.0 – 2.6	Ar—H	6.0 – 8.5
$Ar-CH_3$	2.2 – 2.5	$R-C(=O)-H$	9.5 – 10.5
$R-C\equiv C-H$	2.5 – 3.0	$R-C(=O)-OH$	10 – 13
$(H)R-O-CH_3$	3.3 – 4.0		

With chemical shift information available, we can now assign the signals in the ^{1}H NMR spectrum of methyl acetate. According to the chemical shift table, the protons in the CH_3 group beside the C=O bond are supposed to be in the range of 2-3 ppm, and the protons in the CH_3 group connected with O directly have a δ value of about 3-4 ppm. So the 2.0 ppm signal corresponds to the Ha group, and the 3.6 ppm signal corresponds to the **Hb** group.

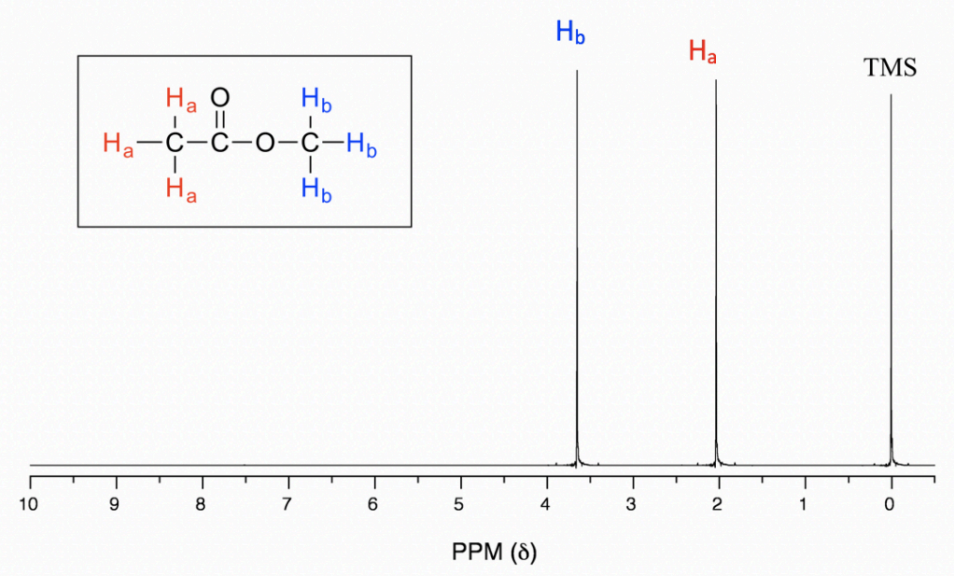
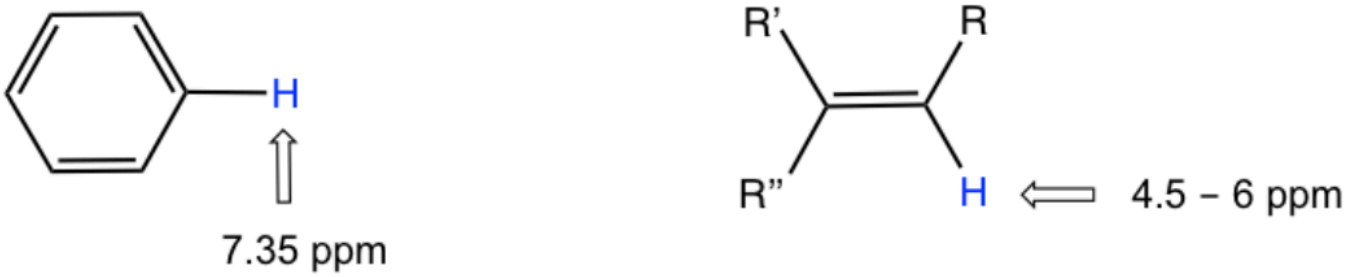


Figure 14.5.3: The 1H NMR spectrum of methyl acetate with signals assignment

Chemical Shift of Protons Near π Electrons — Anisotropy Effect

The chemical shift values of aromatic and vinylic protons (those directly bonded to an alkene carbon) resonate much further downfield (higher frequency, higher chemical shift) than can be accounted for by the deshielding effect of nearby electronegative atoms alone. These chemical shifts result from the anisotropy effect.



Let's investigate the aromatic protons first. In benzene ring (and many other aromatic structures), the total six π electrons form a delocalized π bond around the ring (more discussions in Organic II). When the molecule is exposed to the external magnetic field $\mathbf{B_o}$, these π electrons begin to circulate in a ring current and generate their own **induced magnetic field** $B_{induced}$. Whether shielding or deshielding occurs depends on the *location* of the protons in the induced magnetic field, a phenomenon known as **the anisotropy effect** (meaning "non-uniformity"). This can be explicitly illustrated in the figure below by comparing points **A** and **B**.

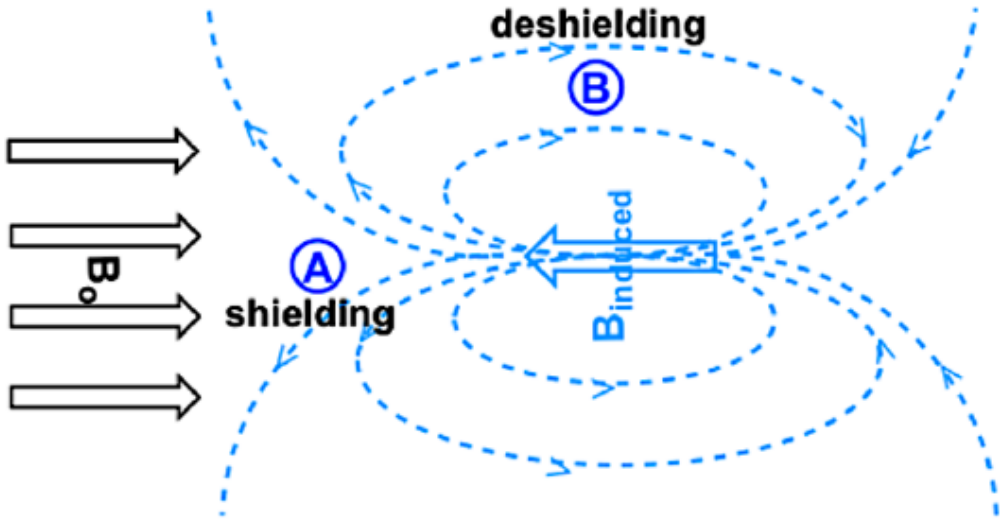


Figure 14.5.4: Anisotropy effect of the induced magnetic field B(induced)

If a proton is at point **A**, it feels the induced magnetic field pointing in the opposite direction of B_o, so the proton experiences the **shielding** effect. For the proton at point **B**, however, it experiences the induced magnetic field in the same direction as Bo, so it experiences **a deshielding** effect.

The protons on the benzene ring are at the position equivalent of 'point **B**', which means that the induced current in this region of space is oriented in the *same* direction as B_0, so it *add*s to B_0 and results in a deshielding effect, and the benzene protons resonate at a higher frequency and have larger chemical shifts.

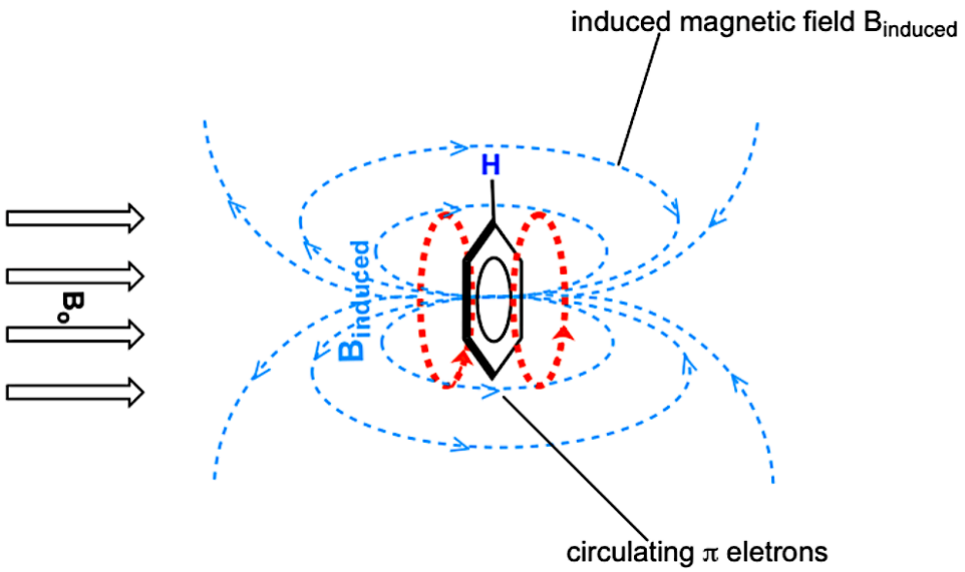


Figure 14.5.5: Anisotropy effect of Benzene ring: aromatic protons are at the location with deshielding effect, where the $B_{(induced\ by\ the\ ring)}$ is in the same direction as the B_o

As a result, due to the anisotropy of the induced field generated by the circulating π electrons, the benzene protons are highly deshielded. Their chemical shift is far downfield, in the range of 6.5–8.5 ppm.

Anisotropy is also responsible for the downfield (high frequency) chemical shifts of vinylic protons (4–6.5 ppm) and aldehyde protons (9.5–11 ppm). The π electrons in these groups also circulate in such a way to generate an induced magnetic field that *adds* to the external field B_o in the spots occupied by the protons. Carboxylic acid protons are even further downfield (9.5–12 ppm) due to the combined influence of the electronegative oxygen atom and the nearby π bond.

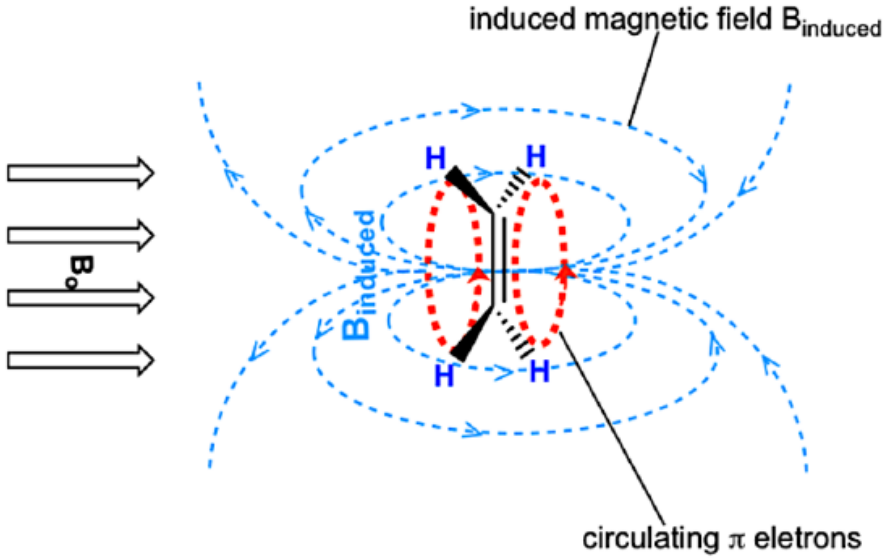


Figure 14.5.6: Anisotropy Effect of Alkene: Vinylic protons are at the location with deshielding effect, where the $B_{(induced\ by\ the\ ring)}$ is in the same direction as the B_o

Worked Example 14.5.1: Predicting Chemical Shifts in ^{1}H NMR Spectra

Methyl 2,2-dimethylpropanoate $(CH_3)_2CCO_2CH_3$ has two peaks in its ^{1}H NMR spectrum. What are their approximate chemical shifts?

Strategy

Identify the types of hydrogen atoms in the molecule, and note whether each is alkyl, vinylic, or adjacent;to an electronegative atom. Then predict where each absorbs, using Figure 14.5.2 if necessary.

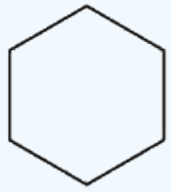
Solution

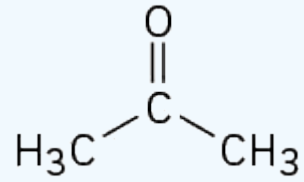
The $-OCH_3$ protons absorb around 3.5 to 4.0 δ because they are on a carbon bonded to oxygen. The $(CH_3)_3C-$ protons absorb near 1.0 δ because they are typical alkane-like protons.

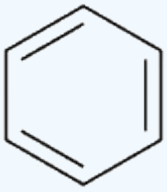
Exercises

Exercise 14.5.1

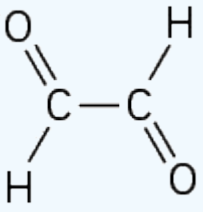
Each of the following compounds has a single ^1H NMR peak. Approximately where would you expect each compound to absorb?

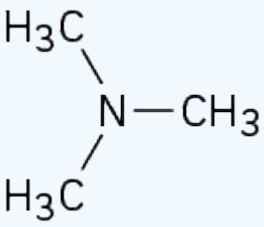
a. 

b. 

c. 

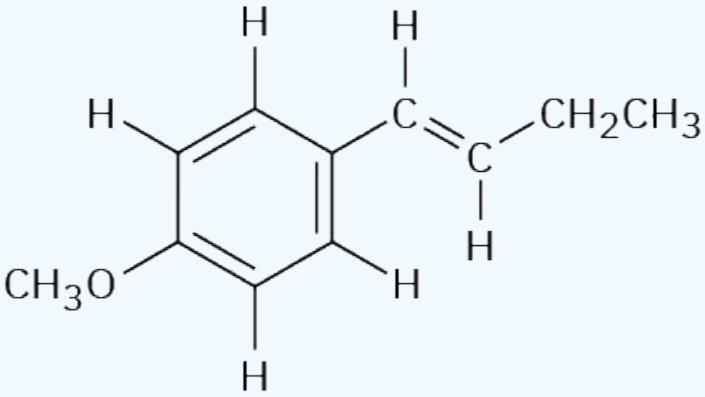
d. CH_2Cl_2

e. 

f. 

Answer available at the end of this section.

Exercise 14.5.2



Identify the different types of protons in the following molecule, and tell where you would expect each to absorb:

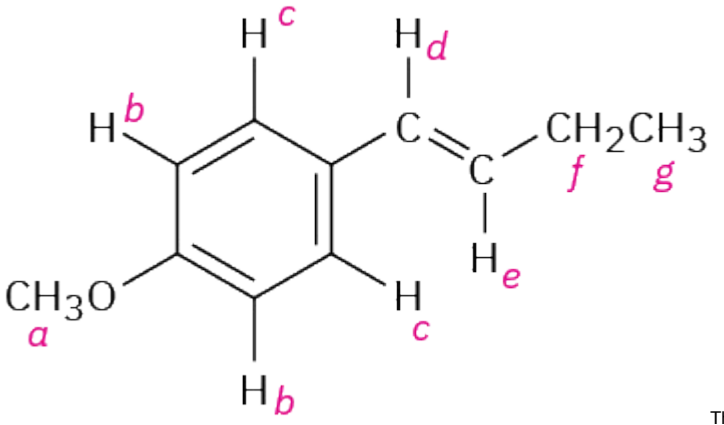
Answer available at the end of this section.

Answers

Exercise 14.5.1

a. 1.43 δ b. 2.17 δ c. 7.37 δ d. 5.30 δ e. 9.70 δ f. 2.12 δ

Exercise 14.5.2



There are seven kinds of protons labeled. The types and expected range of absorption of each follow. ***a:*** ether, 3.5–4.5 δ; ***b:*** aryl, 6.5–8.0 δ; ***c:*** aryl, 6.5–8.0; ***d:*** vinylic, 4.5–6.5 δ; ***e:*** vinylic, 4.5–6.5 δ; ***f:*** alkyl (secondary), 1.2–1.6 δ; ***g:*** alkyl (primary), 0.7–1.3 δ.

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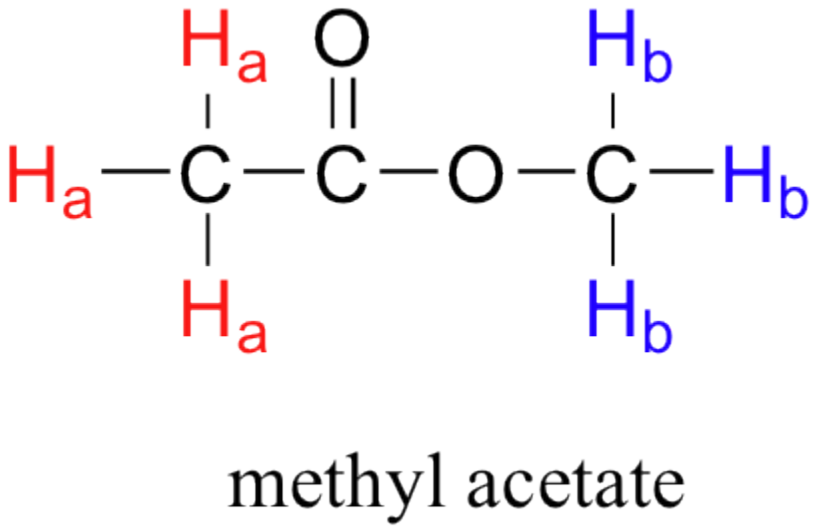
14.6: ^{1}H NMR Signal Integration and Splitting

Integration of Signal Areas

Signal integration in NMR (Nuclear Magnetic Resonance) spectroscopy is crucial for quantifying the relative number of nuclei contributing to each signal in the spectrum. This process involves measuring the area under each peak in the NMR spectrum, which directly correlates to the abundance of the corresponding nuclei in the sample.

The computer in the NMR instrument can be instructed to mathematically integrate the area under a signal or group of signals. The **signal integration** process is very useful in ^{1}H NMR spectrum, because ***the area under a signal is proportional to the number of protons to which the signal corresponds*.**

As an example, methyl acetate, the Ha and H_b peaks would integrate to approximately the same area, because they both correspond to a set of three equivalent protons.



methyl acetate

Now, take a look at the spectrum of *para*-xylene (IUPAC name 1,4-dimethylbenzene). The Figure 14.6.1 is the ^{1}H NMR spectrum of 1,4-dimethylbenzene with integration line (blue lines). The integration line generated by the computer is always in a curved shape that resembles steps. The integration numbers are also generated by the computer together with the curve, which shows the relative area of each signal.

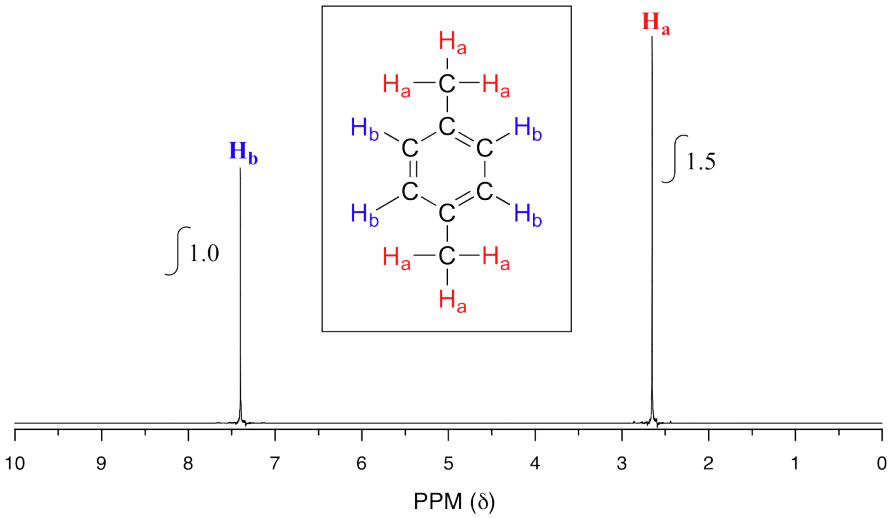


Figure 14.6.1: The 1H NMR spectrum of 1,4-dimethylbenzene with integration

As we discussed earlier, the molecule of 1,4-dimethylbenzene has two sets of equivalent protons: the four aromatic (H_a) protons and the six methyl (H_b) protons. The integration of the area under the peak at 2.6 ppm is 1.5 times greater than the area under the peak at 7.4 ppm. ***Please note that the integration number show the relative ratio of the number of protons, not the actual number*. The ratio 1.5 to 1 here matches the ratio of the actual numbers 6 to 4.** This integration information, along with the chemical shift knowledge we have learned before, allows us to assign the peaks: the peak at 7.4 ppm corresponds to protons (Ha) on the benzene ring, and the peak at 2.6 ppm corresponds to two methyl groups (Hb).

Signal Splitting (Coupling)

In the ^{1}H NMR spectra that we have seen so far, each set of protons generates a *single* NMR signal. This is not that common for ^{1}HNMR actually. In fact, the 1H NMR spectra of most organic molecules contain signals that are 'split' into two or more peaks, which is called **splitting** (or **coupling**). The spectra with peak splitting may look more complicated; however, this splitting behavior provides very useful information about the structure of a compound.

Let's consider the spectrum for 1,1,2-trichloroethane (Figure 14.6.2). In this and in other spectra to follow, the expansions of individual signals are shown so that the signal splitting patterns are recognizable.

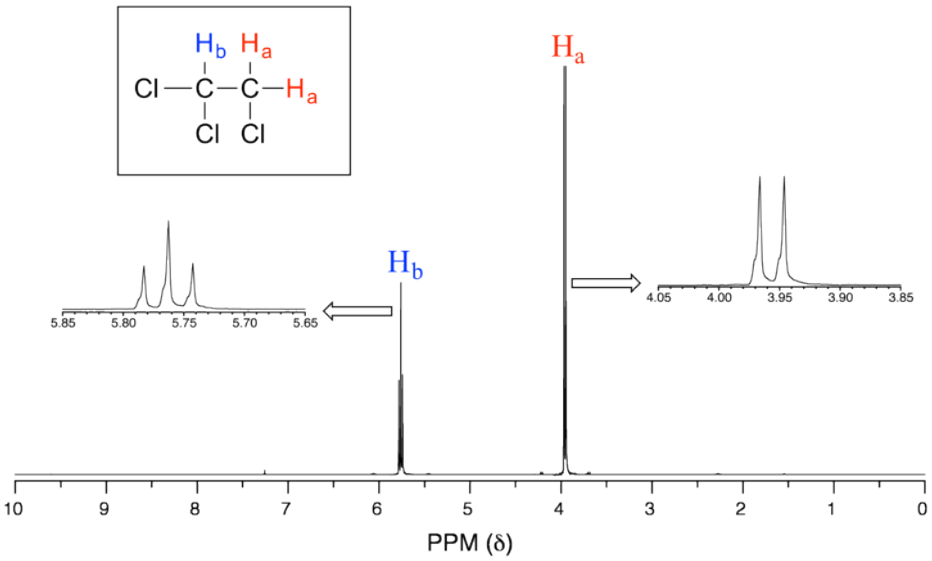


Figure 14.6.2: The 1H NMR spectrum of 1,1,2-trichloroethane with signal splitting

The signal at 3.96 ppm, corresponding to the two Ha protons, is split into two peaks of equal height (and area) – this is referred to as a **doublet.** The Hb signal at 5.76 ppm, on the other hand, is split into three peaks, with the middle peak higher than the two outside peaks and the integration ratio between the three peaks is 1:2:1, such splitting signal is called a **triplet**.

Signal splitting is caused by **spin-spin coupling**, a term that describes the magnetic interactions between non-equivalent hydrogen atoms that are with 2 or 3 bonds of the hydrogens producing the signal. The nearby protons have a magnetic moment that can be either against or with the external magnetic field, therefore splitting the energy levels of the protons whose signal is being observed, resulting in the splitting of the signal into multiple peaks (the terms 'splitting' and 'coupling' are often used interchangeably when discussing NMR).

The most typical coupling we observed in this course is from non-equivalent vicinal hydrogens that are 3 bonds away, that is, the hydrogens on adjacent carbons. This is also called **vicinal coupling** or **three-bond coupling**.

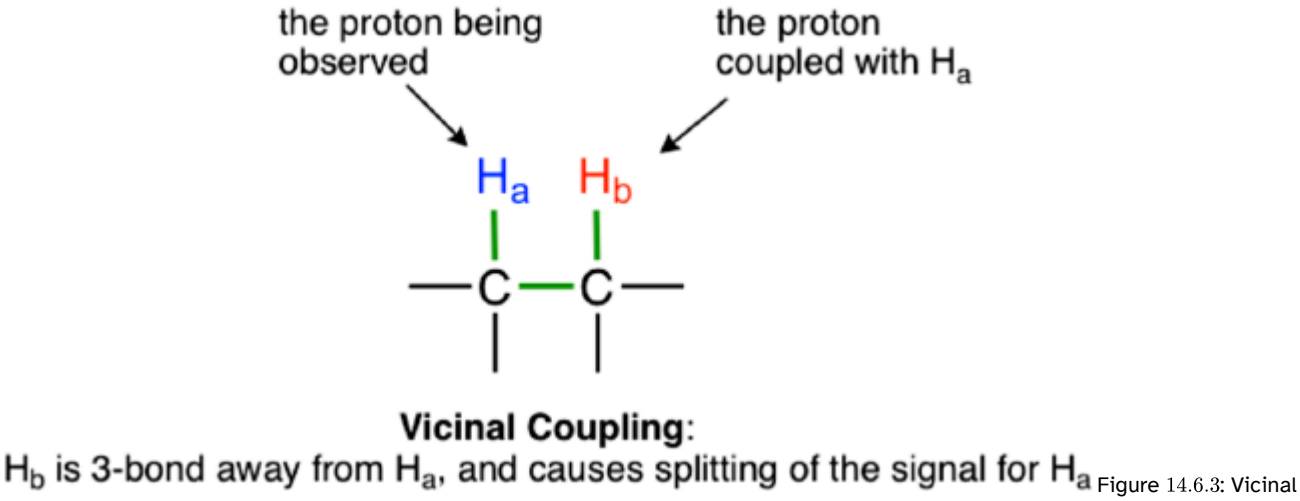


Figure 14.6.3: Vicinal Coupling

A simple rule that applies for predicting the number of peaks (or splitting pattern) expected from coupling, and the rule in ^{1}H NMR is:

number of peaks = **n + 1**

(n is the number of vicinal non-equivalent hydrogens)

We will examine the splitting pattern with different numbers of n:

- When n=0, the signal is a **singlet**, or has only one peak, as the signals observed in Figure 14.6.1.
- When n=1, the signal is a **doublet** with two peaks. The area ratio of the two peaks for a doublet is 1:1. The space between the two peaks is called coupling constant, J_{ab}, measured in Hz.

  For the example of compound 1,1,2-trichloromethane, the **H_a** proton signal fits this situation. With only one vicinal proton, **H_b**, on the adjacent carbon, the signal of **H_a** shows as a doublet, as observed in Figure 14.6.4.

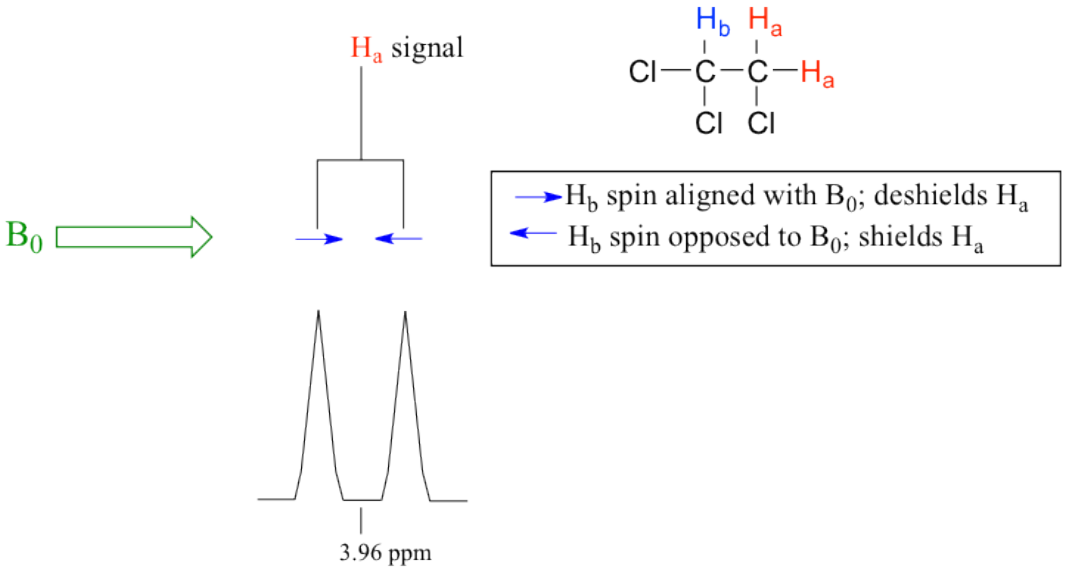


Figure 14.6.4: the **Ha** proton signal of 1,1,2-trichloromethane

- When n=2, the signal is a **triplet** with three peaks. The three peaks of the triplet have an area ratio of 1:2:1.

  In the same compound, 1,1,2-trichloromethane, the signal of the **H_b** proton fits into this situation. With two vicinal protons, 2 H_a, on the adjacent carbon, the signal of **H_b** shows as a triplet, as observed in Figure 14.6.5.

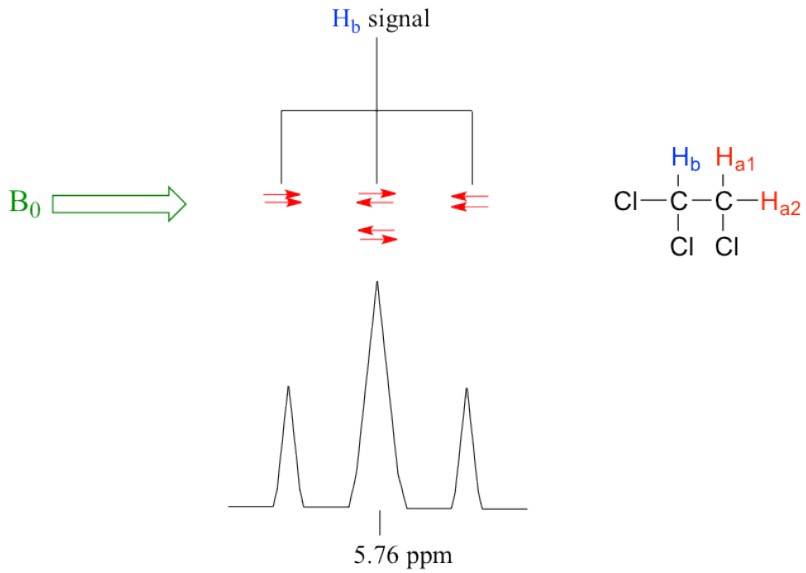


Figure 14.6.5: the **H_b** proton signal of 1,1,2-trichloromethane

- When n=3, the signal is a **quartet,** which means four peaks. The four peaks of the quartet have the area ratio of 1:3:3:1.

  For the spectrum of ethyl acetate (Figure 14.6.6), the signal of **H_b** is a quartet, because there are three vicinal protons 3 **H_c** on the adjacent carbon. Please note that the carbon with **H_b** connected with oxygen on the other side, and there are no hydrogen atoms on that oxygen atom, so only the coupling with three vicinal protons applies.

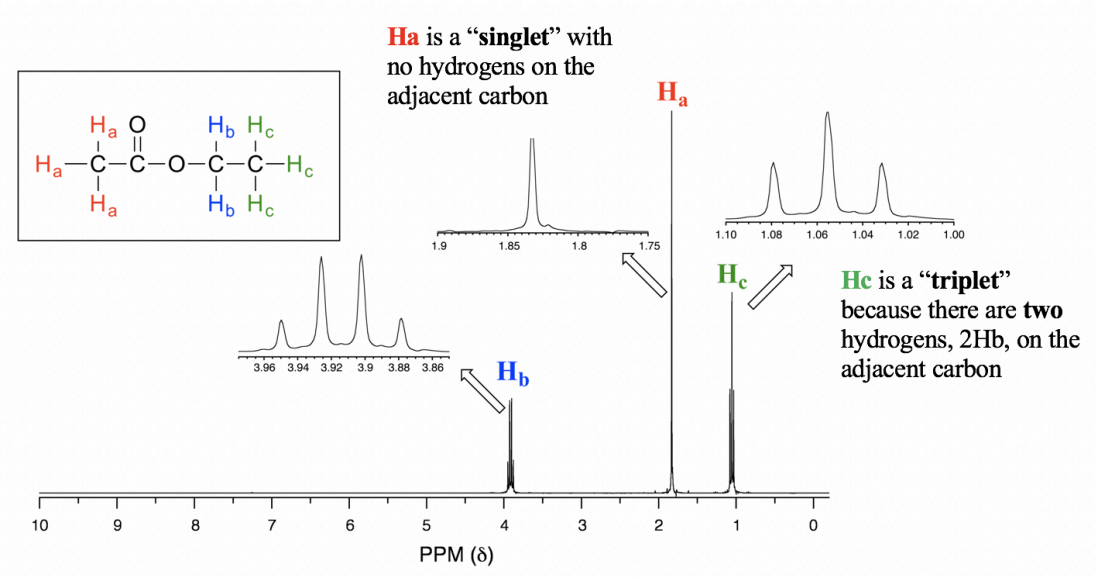


Figure 14.6.6: The 1H NMR spectrum of ethyl acetate with signals splitting

- When n≥4, the signal can be called a **multiplet**. Theoretically, with n increasing, the signal is split into more peaks and the total number of peaks is "n+1". However, the small peaks on the sides may or may not be able to be observed since they might be merged into noise. The signal with more than four peaks is generally called a multiplet, and it is not that critical to tell exactly how many peaks are involved in a multiplet.

For the spectrum of ethyl acetate (Figure 14.6.7), 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.

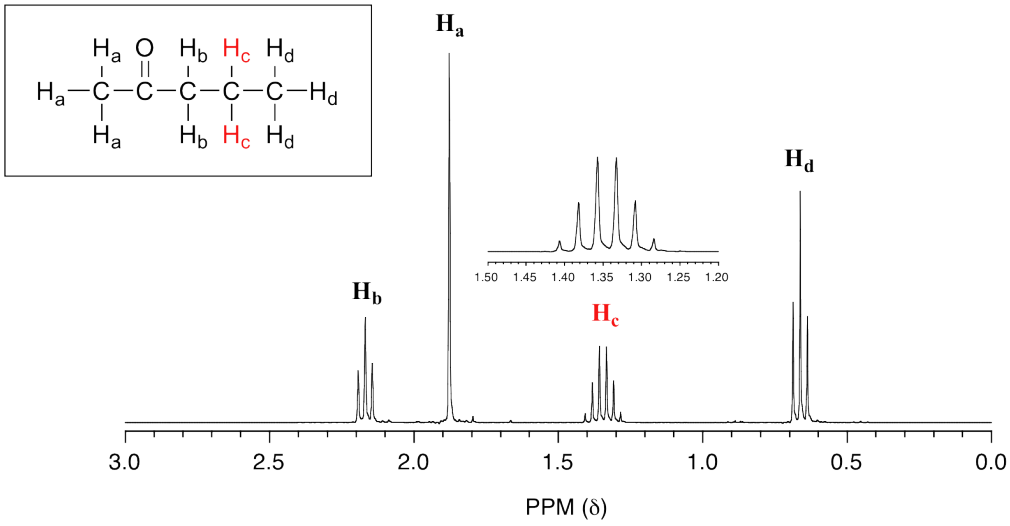


Figure 14.6.7: The 1H NMR spectrum of propyl acetate with signals splitting

Extra notes about signal splitting:

1. Splitting (coupling) ***only*** occurs between ***nonequivalent*** protons. For equivalent protons, there is no coupling. In the spectrum of succinic acid (Figure 14.6.8), for example, the protons on the two middle carbons are equivalent (Ha), so there is no coupling between them, and they show a singlet.

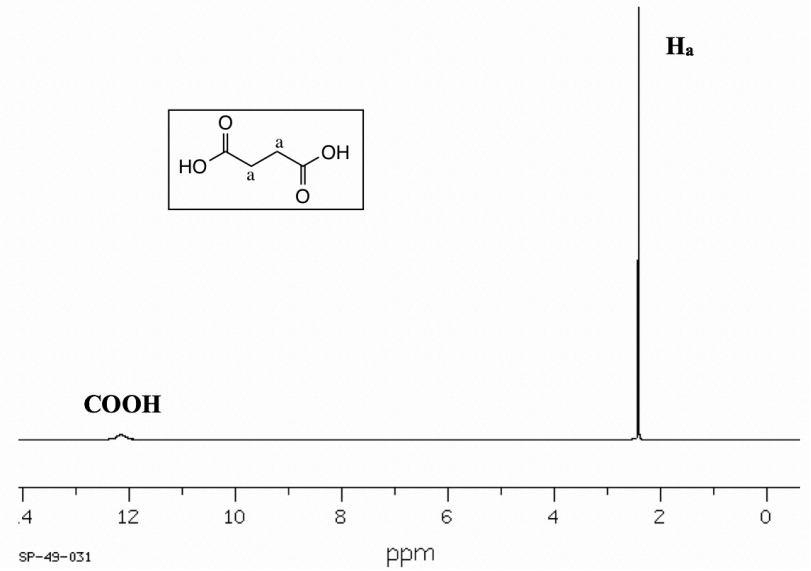


Figure 14.6.8: 1H NMR spectrum of succinic acid

2. Protons in OH or NH generally do not couple with vicinal hydrogens. OH and NH protons are acidic enough to rapidly exchange between different molecules, so the neighboring protons never actually 'feel' their influence. See the specific example of 1-heptanol spectrum in Figure 14.6.9:

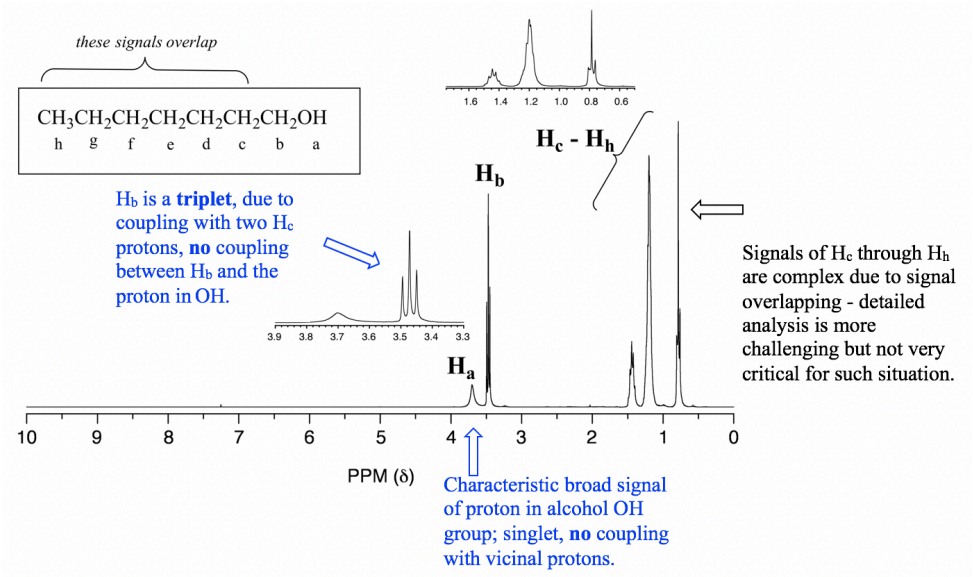


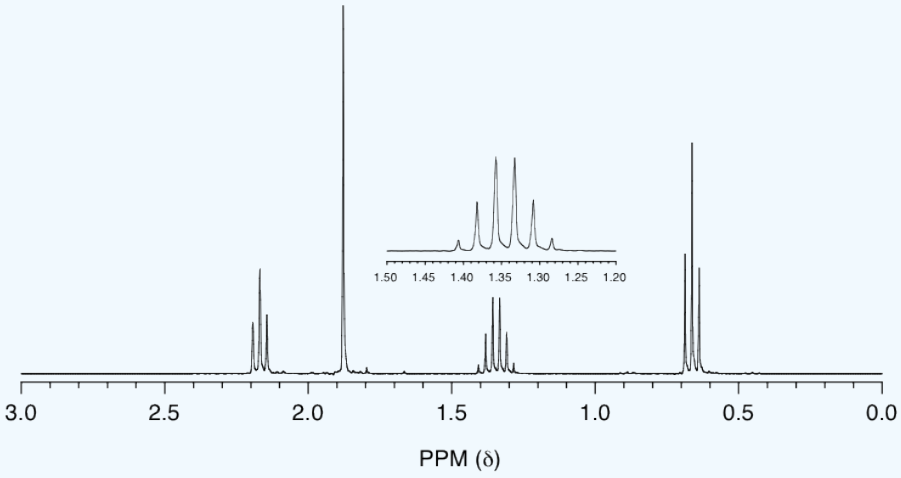
Figure 14.6.9: The ^{1}H NMR spectrum of 1-heptanol

^{1}H NMR Practice

With the structure of a compound given, we can apply all the knowledge about 1H NMR to assign the signals in the spectrum, that is, to identify which hydrogen(s) a certain signal comes from.

Worked Example 14.6.1: Signal assignment based on the given structure

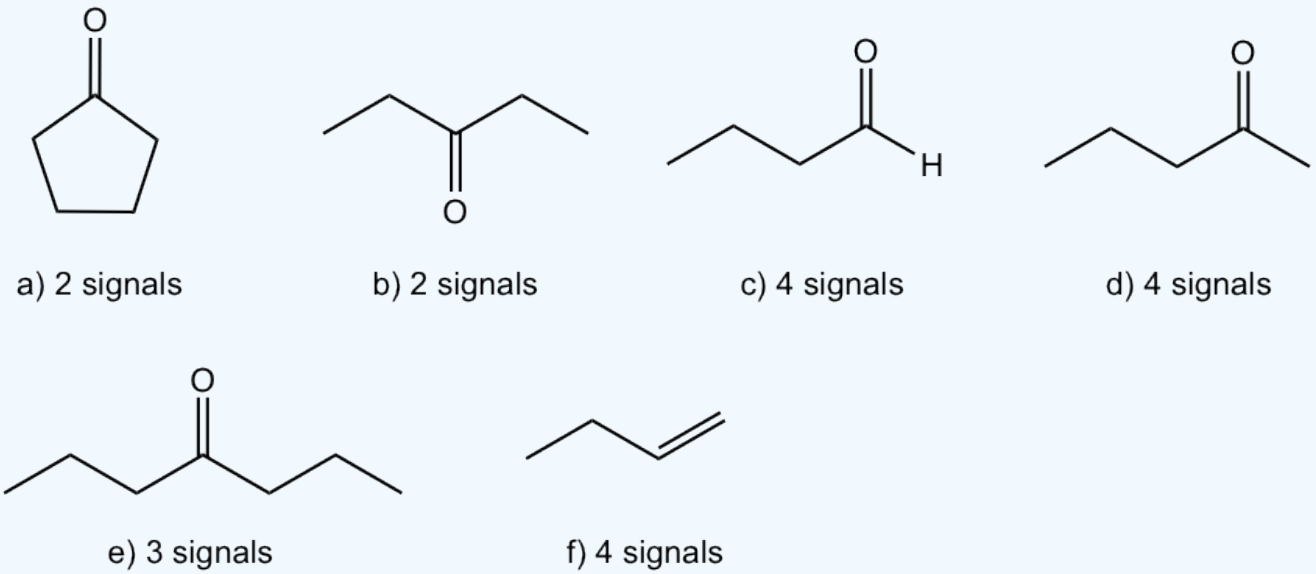
Match the ^{1}H NMR spectrum below to its corresponding compound and assign all signals.



a) cyclopentanone b) 3-pentanone c) butaldehyde

d) 2-pentanone e) 4-heptanone f) 1-butene

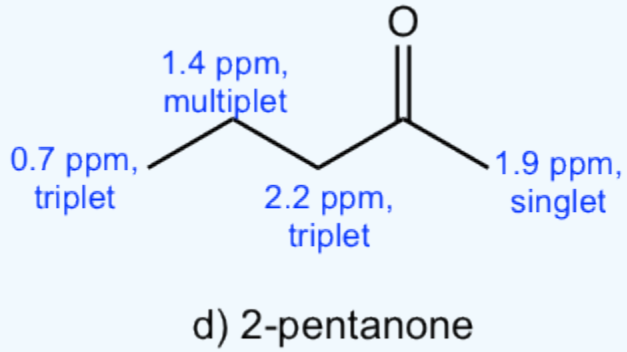
Approach: It is a good idea to draw the structure of each compound and try to see which matches the spectrum.



The spectrum has four signals: triplet (~0.7 ppm), multiplet (~1.4 ppm), singlet (~1.9 ppm) and triplet (~2.2 ppm). Based on the structure of each compound, compounds c), d), and f) should have four signals in the 1H NMR spectrum.

- There are no signals at about 9 ppm for the aldehyde hydrogen in the spectra, so the spectrum is **not** for compound c), butaldehyde.
- There are no signals at about 4~5 ppm for the alkene hydrogens in the spectra, so the spectrum is **not** for compound f), 1-butene.
- The signals in the spectrum match what is expected for compound d), 2-pentanone.

Solution: The spectrum is for 2-pentanone.



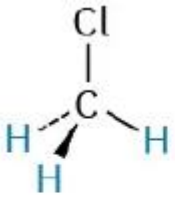
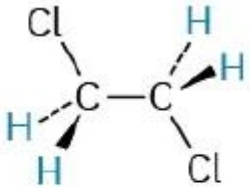
d) 2-pentanone

Structure Determination based on ^{1}H NMR spectrum

A lot of valuable information about a compound's structure can be obtained from a 1H NMR spectrum. For a summary, analyzing the four features of the spectrum is critical to elucidate the structure of a compound:

- The **number of signals** indicates how many different sets of protons there are in the molecule;
- The **chemical shift** of the signal tells us about the electronic environment of each set of protons;
- The **integration** under each signal provides information about how many protons there are in the set being measured (keep in mind that the integration values are for the *ratio*, not the actual number of protons);
- The **splitting pattern** of each signal tells about the number of protons on atoms *adjacent* to the one whose signal is being measured.

Spin–spin splitting in ^{1}H NMR can be summarized by three rules:

RULE 1 **Chemically equivalent protons don't show spin–spin splitting.** Equivalent protons may be on the same carbon or on different carbons, but their signals don't split.	 **Three C–H protons are chemically equivalent; no splitting occurs.**	 **Four C–H protons are chemically equivalent; no splitting occurs.**

RULE 2 **The signal of a proton with *n* equivalent neighboring protons is split into a multiplet of *n* + 1 peaks with coupling constant *J*.** Protons that are farther than two carbon atoms apart don't usually couple. However, they sometimes show weak coupling when they are separated by a π bond.	
RULE 3 **Two groups of protons coupled to each other have the same coupling constant, *J*.**	

The spectrum of *para*-methoxypropiophenone in Figure 14.6.10 further illustrates these three rules. The downfield absorptions at 6.91 and 7.93 δ are due to the four aromatic-ring protons. There are two kinds of aromatic protons, each of which gives a signal that is split into a doublet by its neighbor. The $-OCH_3$ signal is unsplit and appears as a sharp singlet at 3.84 δ. The $-CH_2-$ protons next to the carbonyl group appear at 2.93 δ in the region expected for protons on carbon next to an unsaturated center, and their signal is split into a quartet by coupling with the protons of the neighboring methyl group. The methyl protons appear as a triplet at 1.20 δ in the usual upfield region.

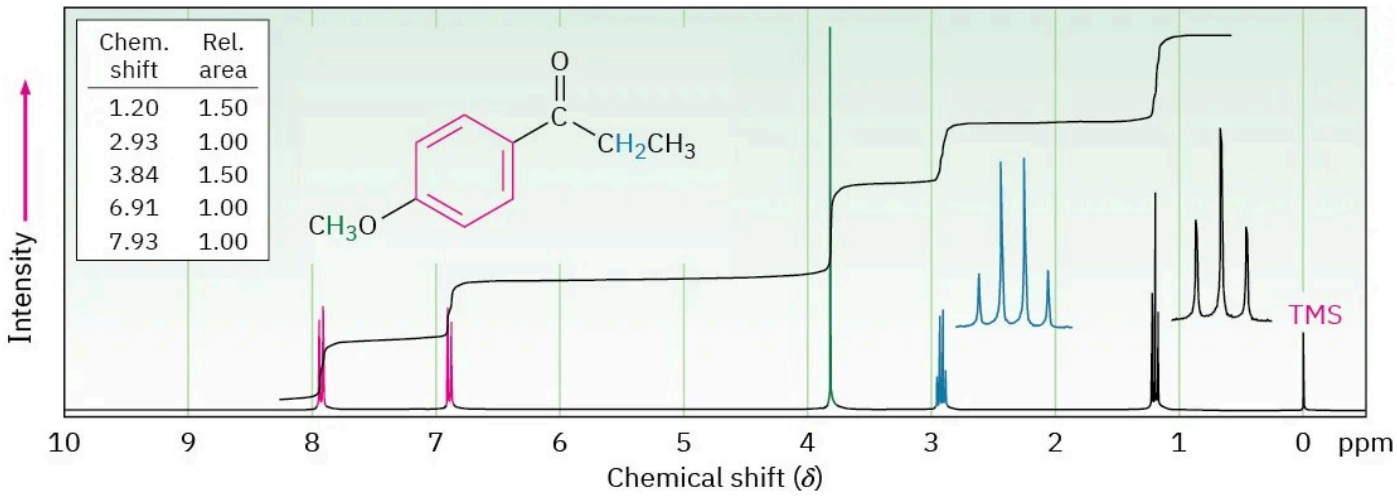


Figure 14.6.10: The ^{1}H NMR spectrum of *para*-methoxypropiophenone.

Worked Example 14.6.1: Assigning a Chemical Structure from a 1H NMR Spectrum

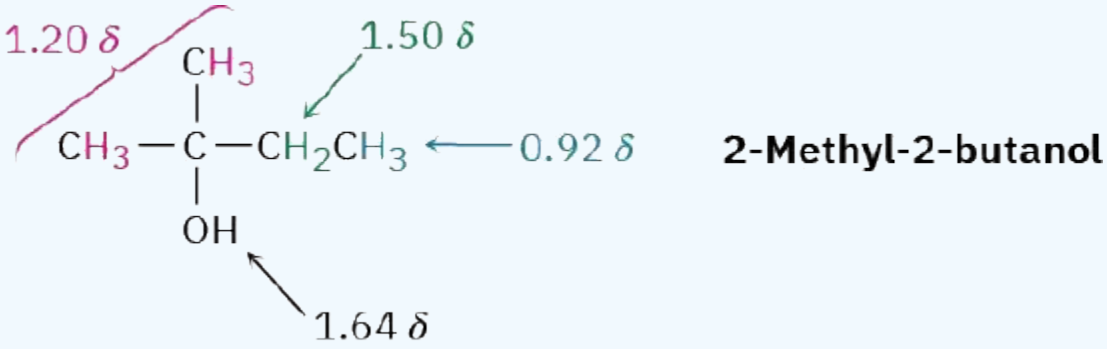
Propose a structure for a compound, $C_5H_{12}O$, that fits the following ^1H NMR data: 0.92 δ (3 H, triplet, J = 7 Hz), 1.20 δ (6 H, singlet), 1.50 δ (2 H, quartet, J = 7 Hz), 1.64 δ (1 H, broad singlet).

Strategy

It's best to begin solving structural problems by calculating a molecule's degree of unsaturation. In the present instance, a formula of $C_5H_{12}O$ corresponds to a saturated, open-chain molecule, either an alcohol or an ether.

To interpret the NMR information, let's look at each absorption individually. The three-proton absorption at 0.92 δ is due to a methyl group in an alkane-like environment, and the triplet-splitting pattern implies that the CH_3 is next to a CH_2. Thus, our molecule contains an ethyl group, CH_3CH_2–. The six-proton singlet at 1.20 δ is due to two equivalent alkane-like methyl groups attached to a carbon with no hydrogens, $(CH_3)_2C$, and the two-proton quartet at 1.50 δ is due to the CH_2 of the ethyl group. All 5 carbons and 11 of the 12 hydrogens in the molecule are now accounted for. The remaining hydrogen, which appears as a broad one-proton singlet at 1.64 δ, is probably due to an OH group, since there is no other way to account for it. Putting the pieces together gives the structure: 2-methyl-2-butanol.

Solution



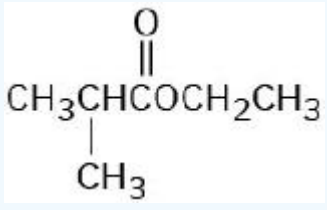
2-Methyl-2-butanol

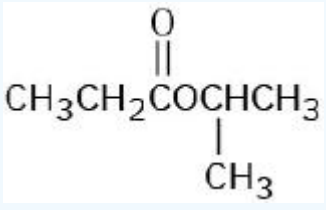
Exercises

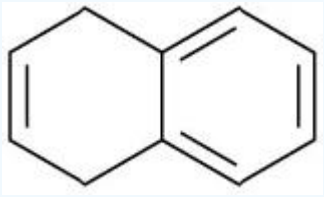
Exercise 14.6.1

Predict the splitting patterns you would expect for each proton in the following molecules:

a. $CHBr_2CH_3$ b. $CH_3OCH_2CH_2Br$ c. $ClCH_2CH_2CH_2Cl$

d. 

e. 

f. 

Answer available at the end of this section.

Exercise 14.6.2

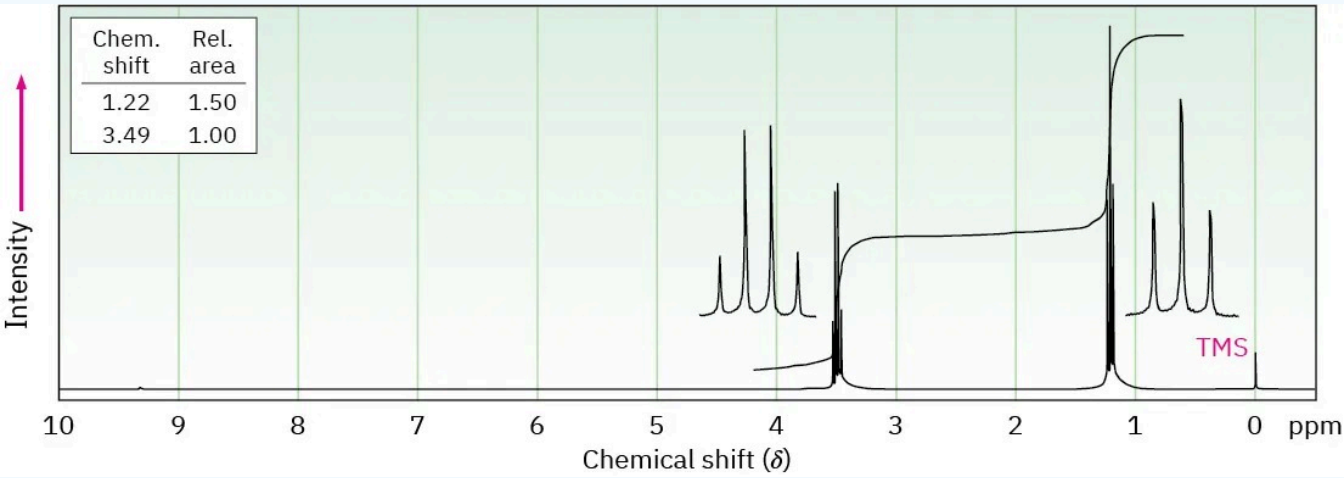
Draw structures for compounds that meet the following descriptions:

a. C_2H_6O; one singlet
b. C_3H_7Cl; one doublet and one septet
c. $C_4H_8Cl_2O$; two triplets
d. $C_4H_8O_2$; one singlet, one triplet, and one quartet

Answer available at the end of this section.

Exercise 14.6.3

The integrated ^1H NMR spectrum of a compound of formula $C_4H_{10}O$ is shown below. Propose a structure.



Answer available at the end of this section.

Answers

Exercise 14.6.1

a. $-CHBr_2$, quartet; $-CH_3$, doublet
b. CH_3O-, singlet; $-OCH_2-$, triplet; $-CH_2Br$, triplet
c. $ClCH_2-$, triplet; $-CH_2-$, quintet
d. CH_3-, triplet; $-CH_2-$, quartet; $-CH-$, septet; $(CH_3)_2$, doublet
e. CH_3-, triplet; $-CH_2-$, quartet; $-CH-$, septet; $(CH_3)_2$, doublet
f. =CH, triplet, $-CH_2-$, doublet, aromatic C–H, two multiplets

Exercise 14.6.2

a. CH_3OCH_3
b. $CH_3CH(Cl)CH_3$
c. $ClCH_2CH_2OCH_2CH_2Cl$
d. $CH_3CH_2CO_2CH_3$ or $CH_3CO_2CH_2CH_3$

Exercise 14.6.3

$CH_3CH_2OCH_2CH_3$

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- 13.4: Integration of ^1H NMR Absorptions - Proton Counting by Dietmar Kennepohl, Steven Farmer, Tim Soderberg is licensed CC BY-SA 4.0.
- 13.7: More Complex Spin-Spin Splitting Patterns by Dietmar Kennepohl, Steven Farmer, Tim Soderberg is licensed CC BY-SA 4.0.
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14.7: More Complex Spin-Spin Splitting Patterns

In the ^{1}H NMR spectra we've seen so far, the chemical shifts of different protons have been distinct and the spin–spin splitting patterns have been straightforward. It often happens, however, that different kinds of hydrogens in a molecule have accidentally overlapping signals. The spectrum of toluene (methylbenzene) in Figure 14.7.1, for example, shows that the five aromatic ring protons give a complex, overlapping pattern, even though they aren't all equivalent.

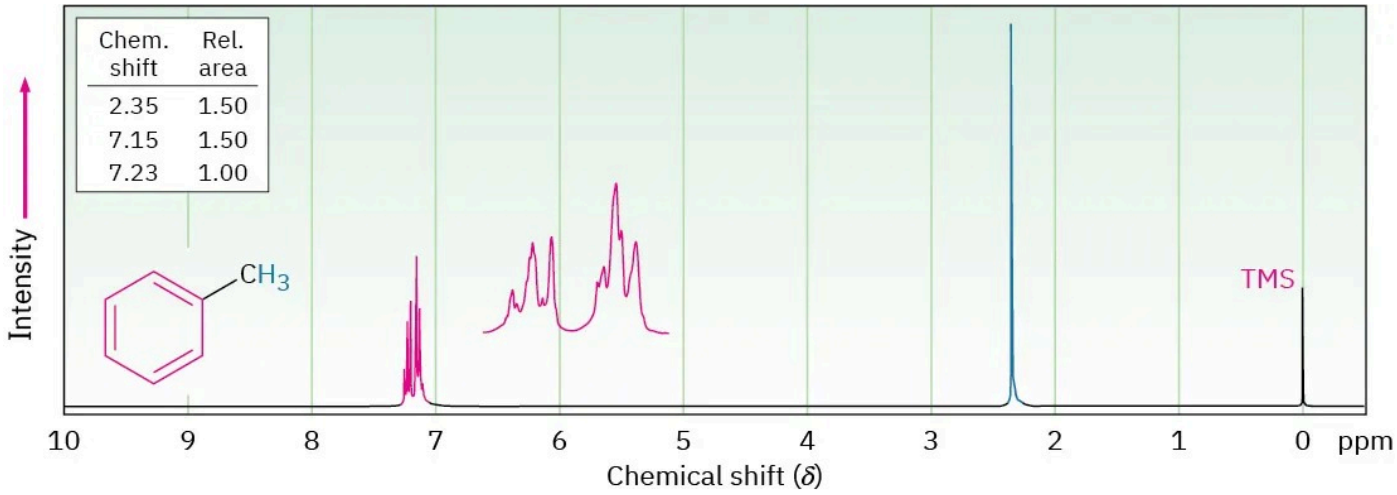


Figure 14.7.1: The ^{1}H NMR spectrum of toluene, showing the accidental overlap of the five nonequivalent aromatic ring protons.

Yet another complication in ^{1}H NMR spectroscopy arises when a signal is split by two or more *nonequivalent* kinds of protons, as is the case with *trans*-cinnamaldehyde, isolated from oil of cinnamon (Figure 14.7.2). Although the $n + 1$ rule predicts splitting caused by equivalent protons, splittings caused by nonequivalent protons are more complex.

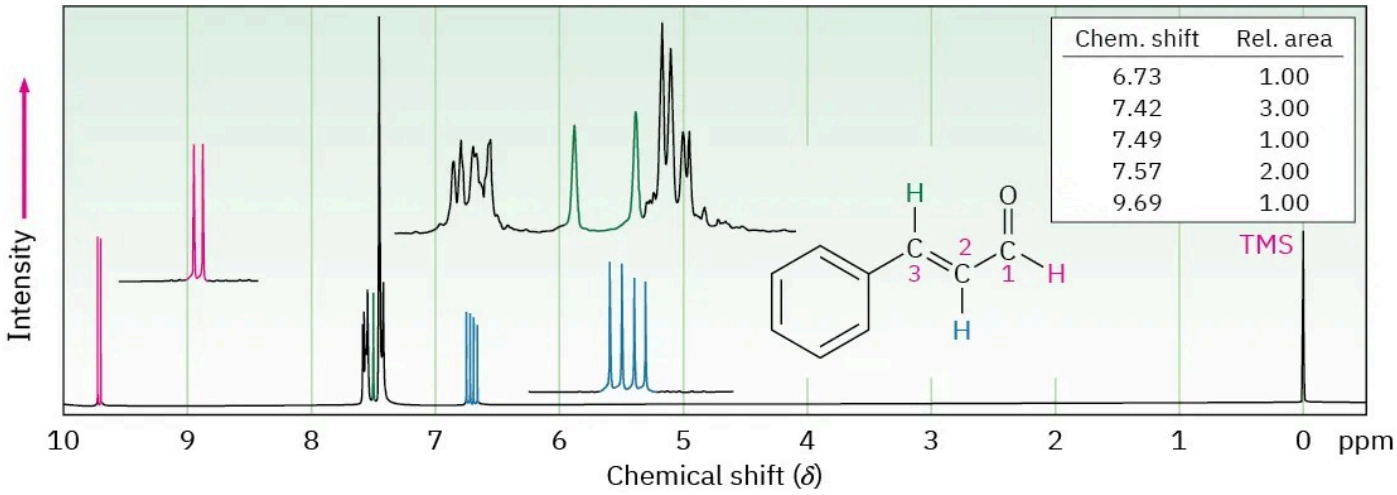


Figure 14.7.2: The ^{1}H NMR spectrum of *trans*-cinnamaldehyde. The signal of the proton at C2 (blue) is split into four peaks—a doublet of doublets—by the two nonequivalent neighboring protons.

To understand the ^{1}H NMR spectrum of *trans*-cinnamaldehyde, we have to isolate the different parts and look at the signal of each proton individually.

- The five aromatic proton signals (black in Figure 14.7.2) overlap into a complex pattern with a large peak at 7.42 δ and a broad absorption at 7.57 δ.
- The aldehyde proton signal at C1 (**red**) appears in the normal downfield position at 9.69 δ and is split into a doublet with J = 6 Hz by the adjacent proton at C2.

- The vinylic proton at C3 (**green**) is next to the aromatic ring and is therefore shifted downfield from the normal vinylic region. This C3 proton signal appears as a doublet centered at 7.49 δ. Because it has one neighbor proton at C2, its signal is split into a doublet, with J = 12 Hz.
- The C2 vinylic proton signal (**blue**) appears at 6.73 δ and shows an interesting, four-line absorption pattern. It is coupled to the two nonequivalent protons at C1 and C3 with two different coupling constants: $J_{1\text{-}2}$ = 6 Hz and $J_{2\text{-}3}$ = 12 Hz.

A good way to understand the effect of multiple coupling, such as that occurring for the C2 proton of *trans*-cinnamaldehyde, is to draw a *tree diagram*, like that in Figure 14.7.3. The diagram shows the individual effect of each coupling constant on the overall pattern. Coupling with the C3 proton splits the signal of the C2 proton in *trans*-cinnamaldehyde into a doublet with J =12 Hz. Further coupling with the aldehyde proton then splits each peak of the doublet into new doublets with J = 6 Hz, and we therefore observe a four-line spectrum for the C2 proton.

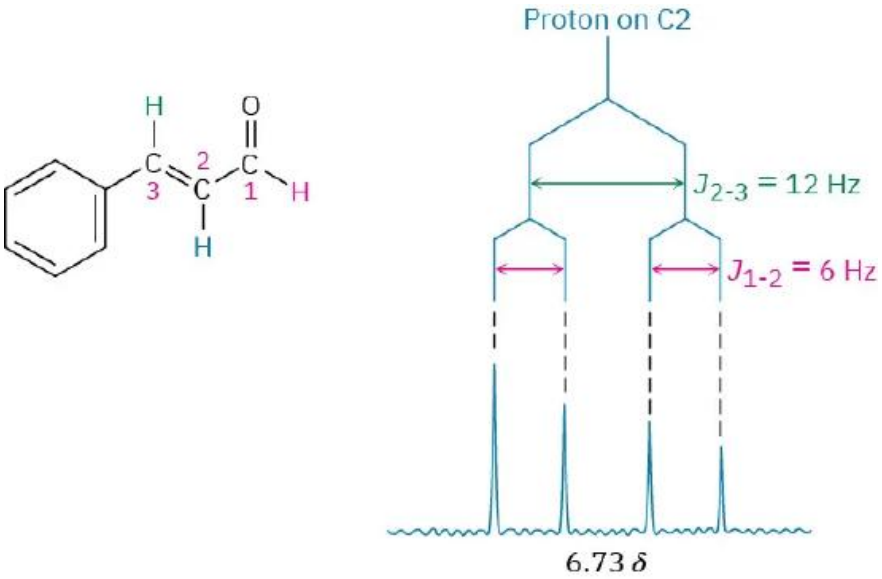


Figure 14.7.3: A tree diagram for the C2 proton of *trans*-cinnamaldehyde shows how it is coupled to the C1 and C3 protons with different coupling constants.

One further trait evident in the cinnamaldehyde spectrum is that the four peaks of the C2 proton signal are not all the same size. The two left-hand peaks are somewhat larger than the two right-hand peaks. Such a size difference occurs whenever coupled nuclei have similar chemical shifts—in this case, 7.49 δ for the C3 proton and 6.73 δ for the C2 proton. The peaks nearer the signal of the coupled partner are always larger, and the peaks farther from the signal of the coupled partner are always smaller. Thus, the left-hand peaks of the C2 proton multiplet at 6.73 δ are closer to the C3 proton absorption at 7.49 δ and are larger than the right-hand peaks. At the same time, the right-hand peak of the C3 proton doublet at 7.49 δ is larger than the left-hand peak because it is closer to the C2 proton multiplet at 6.73 δ. This skewing effect on multiplets is often useful because it indicates where to look in the spectrum to find the coupled partner: toward the larger peaks.

Exercise 14.7.1

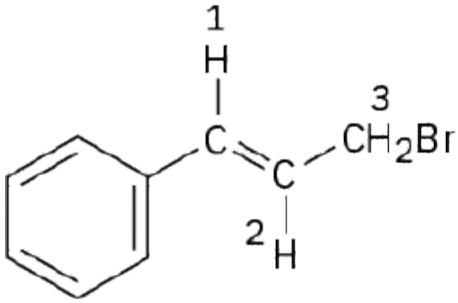
3-Bromo-1-phenyl-1-propene shows a complex NMR spectrum in which the vinylic proton at C2 is coupled with both the C1 vinylic proton (J = 16 Hz) and the C3 methylene protons (J = 8 Hz). Draw a tree diagram for the C2 proton signal, and account for the fact that a five-line multiplet is observed.

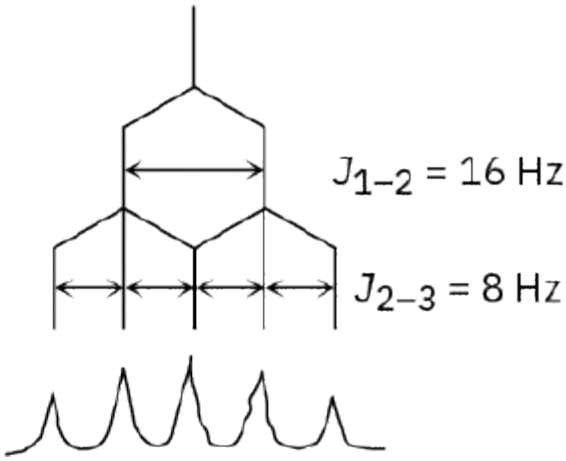
Answer available at the end of this section.

Answers

Exercise 14.7.1

$J_{1\text{–}2}$ = 16 Hz; $J_{2\text{–}3}$ = 8 Hz





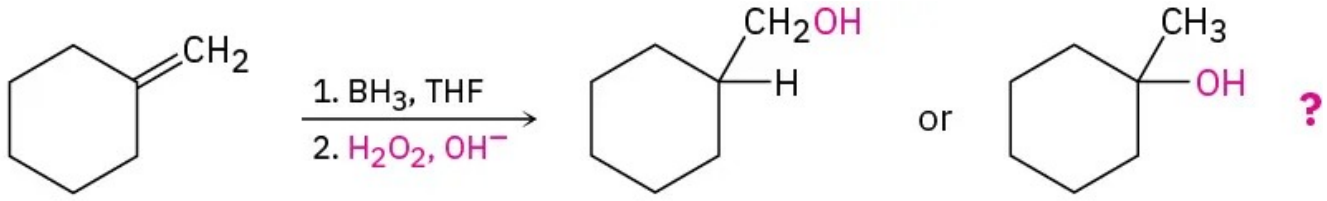
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14.8: Uses of ^{1}H NMR Spectroscopy

NMR is used to help identify the product of nearly every reaction run in the laboratory. For example, we said in Section 8.5 that hydroboration–oxidation of alkenes occurs with non-Markovnikov regiochemistry to yield the less highly substituted alcohol. With the help of NMR, we can now prove this statement.

Does hydroboration–oxidation of methylenecyclohexane yield cyclohexylmethanol or 1-methylcyclohexanol?



Methylenecyclohexane **Cyclohexylmethanol** **1-Methylcyclohexanol**

The ^{1}H NMR spectrum of the reaction product is shown in Figure 14.8.1a. The spectrum shows a two-proton peak at 3.40 δ, indicating that the product has a $-CH_2-$ group bonded to an electronegative oxygen atom ($-CH_2OH$). Furthermore, the spectrum shows no large three-proton singlet absorption near 1 δ, where we would expect the signal of a quaternary $-CH_3$ group to appear. (Figure 14.8.1b) gives the spectrum of 1-methylcyclohexanol, the alternative product.) Thus, it's clear that cyclohexylmethanol is the reaction product.

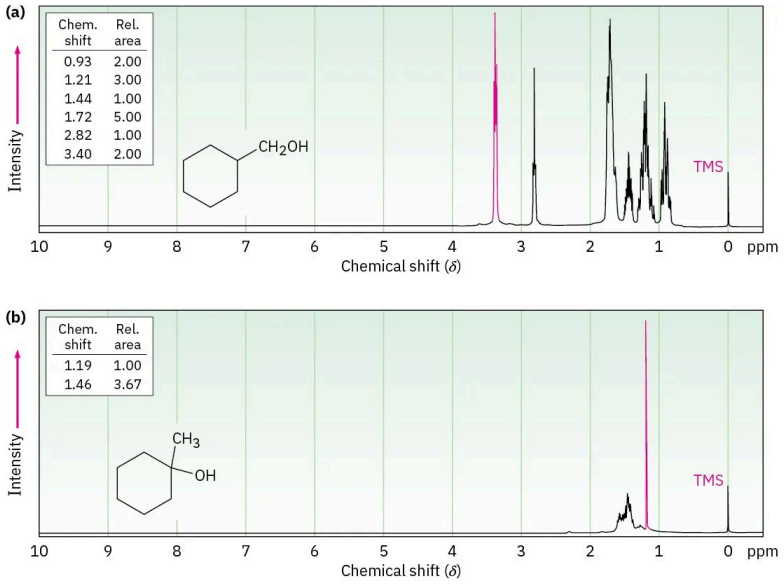


Figure 14.8.1: (a) The ^{1}H NMR spectrum of cyclohexylmethanol, the product from hydroboration–oxidation of methylenecyclohexane, and (b) the ^{1}H NMR spectrum of 1-methylcyclohexanol, the possible alternative reaction product.

Exercise

Exercise 14.8.1

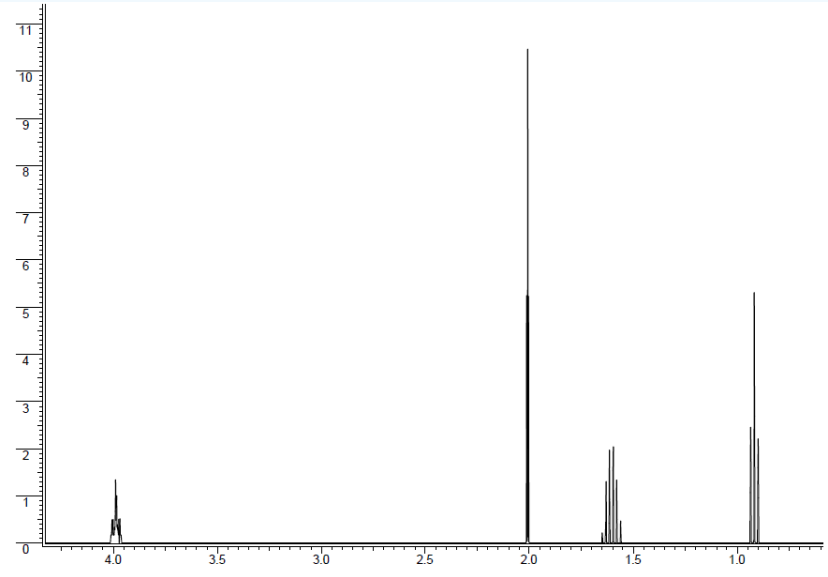
How could you use ^{1}H NMR to determine the regiochemistry of electrophilic addition to alkenes? For example, does addition of HCl to 1-methylcyclohexene yield 1-chloro-1-methylcyclohexane or 1-chloro-2-methylcyclohexane?

Answer available at the end of this section.

Exercise 14.8.2

Determine the structure for the unknown molecule with the molecular formula of $C_5H_{10}O_2$.

^{1}H NMR: The ratio of protons is 2:3:2:3. J = 7 Hz for all coupling.

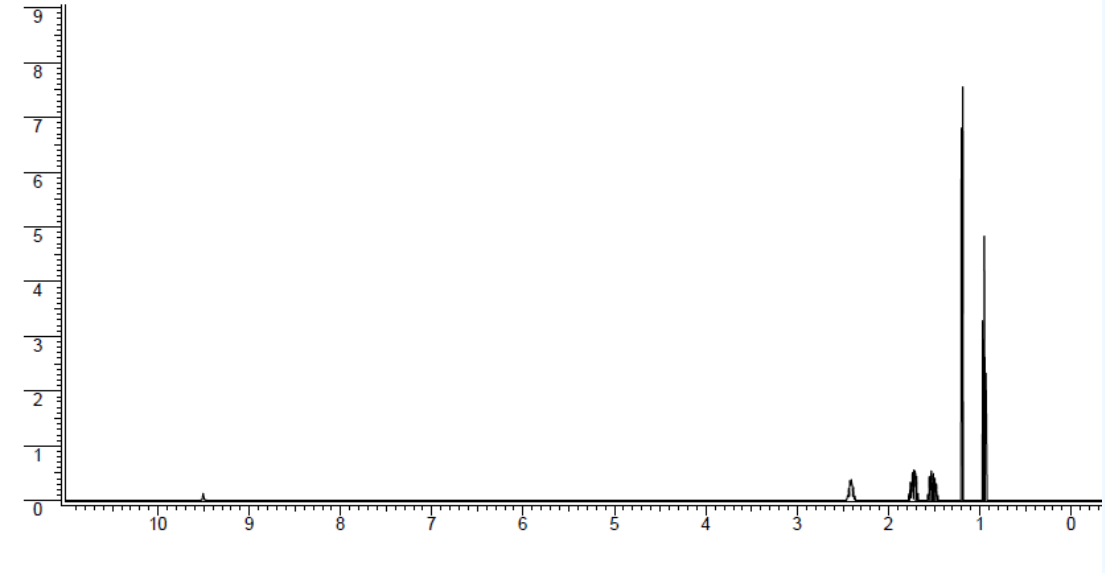


Answer available at the end of this section.

Exercise 14.8.3

Determine the structure for the unknown molecule with the molecular formula of $C_5H_{10}O_2$.

^{1}H NMR: The ratio of protons is 1:1:1:1:3:3. The peak at 9.5 ppm is a singlet. The peak at 2.41 ppm is sextet (J = 7 Hz). The peak at 1.72 ppm is a multiplet (J = 7Hz, 25 Hz). The peak at 1.53 ppm is a multiplet (J = 7 Hz, 25 Hz). The peak at 1.20ppm is a doublet (J = 7 Hz). The peak at 0.95 ppm is a triplet (J = 7 Hz).

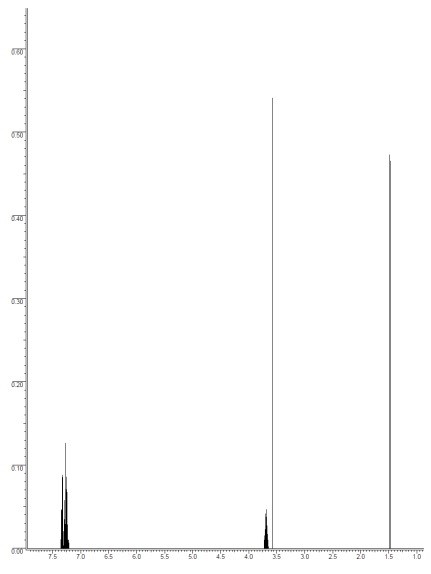


Answer available at the end of this section.

Exercise 14.8.4

Determine the structure for the unknown molecule with the molecular formula of $C_{10}H_{12}O_2$.

^{1}H NMR: The ratio of protons is 5:1:3:3. The peak at 7.5 ppm is a multiplet. The peak at 3.70 ppm is a quartet (J = 7 Hz). The peak at 3.58 ppm is a singlet. The peak at 1.48 ppm is a doublet (J = 7 Hz).

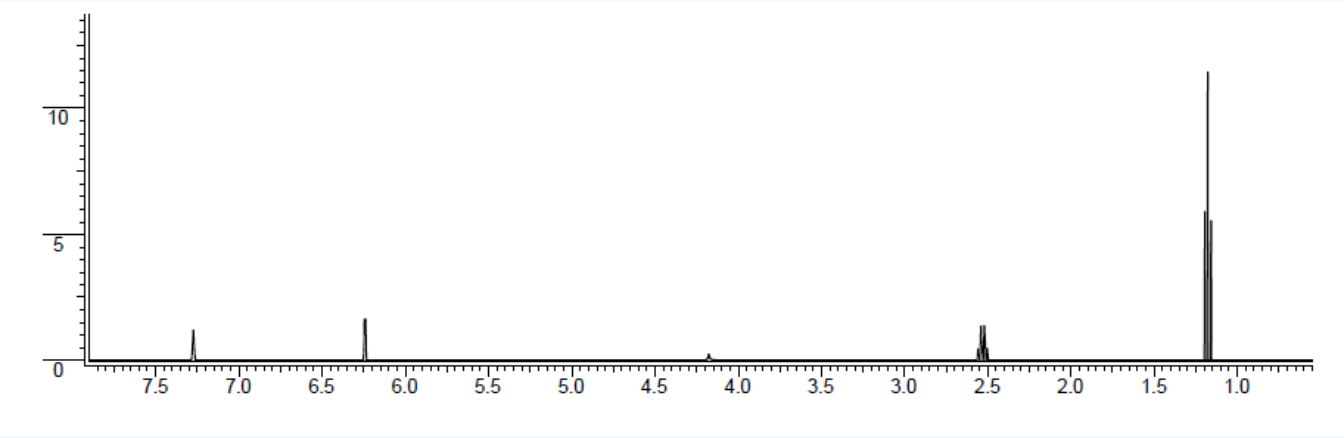


Answer available at the end of this section.

Exercise 14.8.5

Determine the structure for the unknown molecule with the molecular formula of $C_{10}H_{15}N$.

^{1}H NMR: The ratio of protons is 1:2:2:4:6. The peak at 7.3 ppm is a triplet (J = 2Hz) and the peak at 6.24 ppm is a doublet (J = 2 Hz).

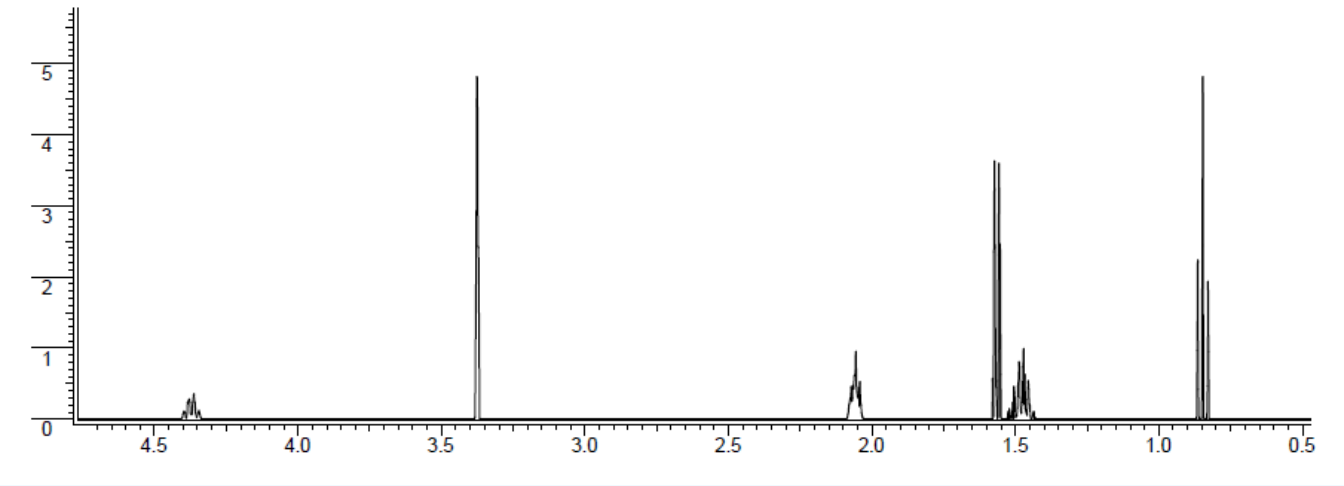


Answer available at the end of this section.

Exercise 14.8.6

Determine the structure for the unknown molecule with the molecular formula of $C_7H_{14}O$.

^{1}H NMR: The ratio of protons is 1:3:2:3:2:3. The peak at 4.36 ppm is a triplet of quartets (J = 17 Hz and 7Hz). The peak at 3.37 ppm is a singlet. The peak at 2.04 ppm is a doublet of triplets (J = 17 Hz and 7Hz). The peak at 1.56 ppm is a doublet (J = 7 Hz). The peak at 1.48 ppm is a sextet (J = 7 Hz). The peak at 0.85 ppm is a triplet (J = 7 Hz).



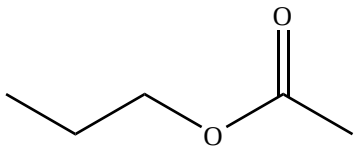
Answer available at the end of this section.

Answers

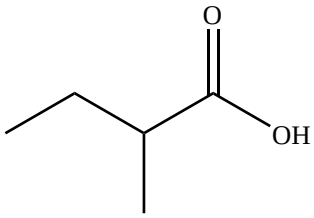
Exercise 14.8.1

1-Chloro-1-methylcyclohexane has a singlet methyl absorption.

Exercise 14.8.2

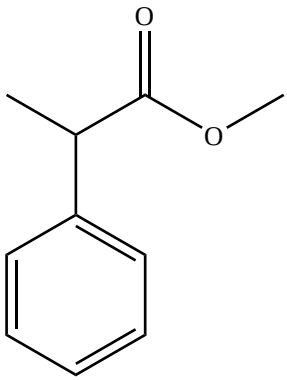


Exercise 14.8.3

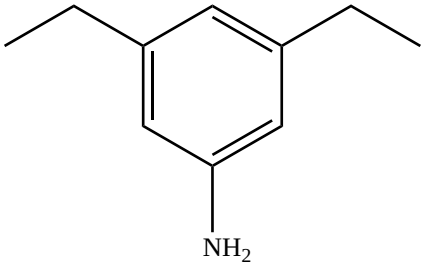


Note: The -CH_2- protons are diastereotopic, so they show up differently in ^{1}H NMR spectra.

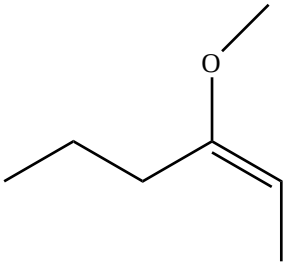
Exercise 14.8.4



Exercise 14.8.5



Exercise 14.8.6



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14.9: Characteristics of ^{13}C NMR Spectroscopy

^{13}C NMR Spectroscopy - Signal Averaging and FT-NMR

In some ways, it's surprising that carbon NMR is even possible. After all, ^{12}C, the most abundant carbon isotope, has no nuclear spin and can't be seen by NMR. Carbon-13 is the only naturally occurring carbon isotope with a nuclear spin, but its natural abundance is only 1.1%. Thus, only about 1 of every 100 carbon atoms in an organic sample can be observed by NMR. The problem of low abundance has been overcome, however, by the use of *signal averaging* and *Fourier-transform NMR* (FT–NMR). Signal averaging increases instrument sensitivity, and FT–NMR increases instrument speed.

The low natural abundance of ^{13}C means that any individual NMR spectrum is extremely "noisy." That is, the signals are so weak that they are cluttered with random background electronic noise, as shown in Figure 14.9.1a. If, however, hundreds or thousands of individual runs are added together by a computer and then averaged, a greatly improved spectrum results (Figure 14.9.1b). Background noise, because of its random nature, increases very slowly as the runs are added, while the nonzero signals stand out clearly. Unfortunately, the value of signal averaging is limited when using the method of NMR spectrometer operation described in Section 13.2, because it takes about 5 to 10 minutes to obtain a single spectrum. Thus, a faster way to obtain spectra is needed if signal averaging is to be used.

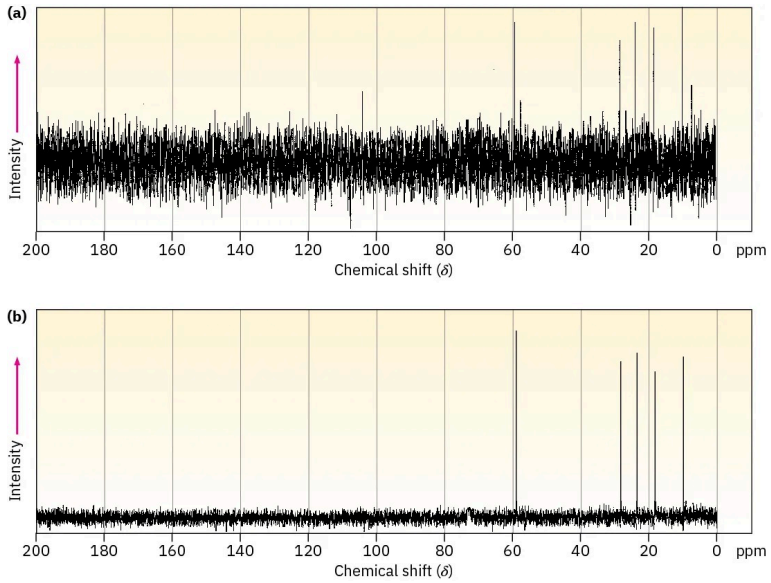


Figure 14.9.1: Carbon-13 NMR spectra of 1-pentanol, $CH_3CH_2CH_2CH_2CH_2OH$. Spectrum **(a)** is a single run showing the high level of background noise. Spectrum **(b)** is an average of 200 runs.

In the method of NMR spectrometer operation described in Section 13.2, the rf frequency is held constant while the strength of the magnetic field is varied so that all signals in the spectrum are recorded sequentially. In the FT–NMR technique used by modern spectrometers, however, all the signals are recorded simultaneously. A sample is placed in a magnetic field of constant strength and is irradiated with a short pulse of rf energy that covers the entire range of useful frequencies. All ^{1}H or ^{13}C nuclei in the sample resonate at once, giving a complex, composite signal that is mathematically manipulated using so-called Fourier transforms and then displayed in the usual way. Because all resonance signals are collected at once, it takes only a few seconds rather than a few minutes to record an entire spectrum.

Combining the speed of FT–NMR with the sensitivity enhancement of signal averaging is what gives modern NMR spectrometers their power. Literally thousands of spectra can be taken and averaged in a few hours, resulting in sensitivity so high that a ^{13}C NMR spectrum can be obtained from less than 0.1 mg of sample and a ^{1}H spectrum can be recorded from only a few *micro*grams.

One further question needs to be answered before moving forward with our discussion of ^{13}C NMR. Why is spin–spin splitting

seen only for ^{1}H NMR? Why is there no splitting of *carbon* signals into multiplets in ^{13}C NMR? After all, you might expect that the spin of a given ^{13}C nucleus would couple with the spin of an adjacent magnetic nucleus, either ^{13}C or ^{1}H.

No coupling of a ^{13}C nucleus with nearby carbons is seen because their low natural abundance makes it unlikely that two ^{13}C nuclei will be adjacent. No coupling of a ^{13}C nucleus with nearby hydrogens is seen because ^{13}C spectra are normally recorded using *broadband decoupling*. At the same time that the sample is irradiated with a pulse of rf energy to cover the carbon resonance frequencies, it is also irradiated by a second band of rf energy covering all the hydrogen resonance frequencies. This second irradiation makes the hydrogens spin-flip so rapidly that their local magnetic fields average to zero and no coupling with carbon spins occurs.

Factors on ^{13}C NMR Spectra

At its simplest, ^{13}C NMR makes it possible to count the number of different carbon atoms in a molecule. Look at the ^{13}C NMR spectra of 1-pentanol (Figure 14.9.1) shown previously and ethyl acetate (Figure 14.9.2). In each case, a single sharp resonance line is observed for each different carbon atom.

Most ^{13}C resonances are between 0 and 220 ppm downfield from the TMS reference line, with the exact chemical shift of each ^{13}C resonance dependent on that carbon's electronic environment within the molecule. Figure 14.9.1 shows the correlation of chemical shift with environment.

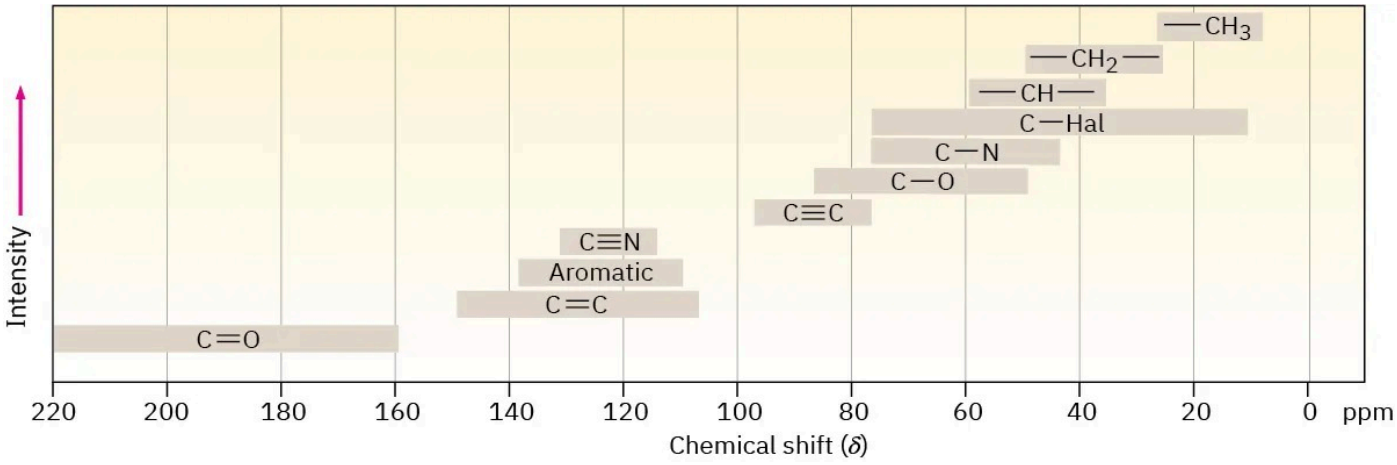


Figure 14.9.1: Chemical shift correlations for ^{13}C NMR.

The factors that determine chemical shifts are complex, but it's possible to make some generalizations from the data in Figure 14.9.1. One trend is that a carbon atom's chemical shift is affected by the electronegativity of nearby atoms. Carbons bonded to oxygen, nitrogen, or halogen absorb downfield (to the left) of typical alkane carbons. Because electronegative atoms attract electrons, they pull them away from neighboring carbon atoms, causing those carbons to be deshielded and to resonate at a lower field.

Another trend is that sp^3-hybridized carbons generally absorb from 0 to 90 δ, while sp^2 carbons absorb from 110 to 220 δ. Carbonyl carbons (C=O) are particularly distinct in ^{13}C NMR and are always found at the low-field end of the spectrum, from 160 to 220 δ. Figure 14.9.2 shows the ^{13}C NMR spectra of 2-butanone and *para*-bromoacetophenone and indicates the peak assignments. Note that the C=O carbons are at the left edge of the spectrum in each case.

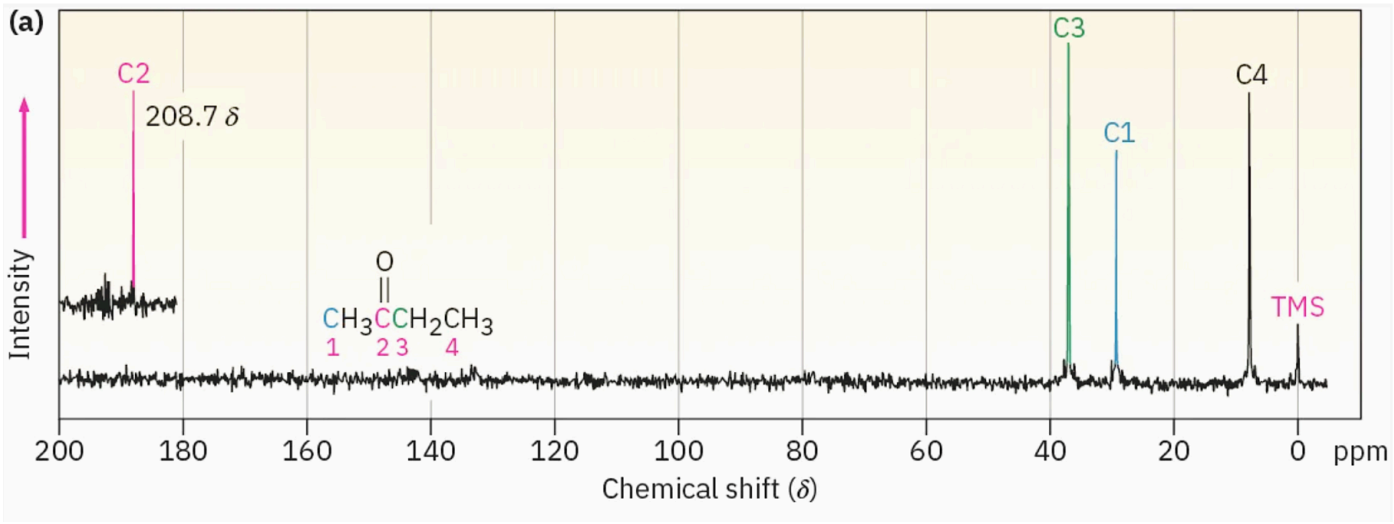


Figure 14.9.2: Carbon-13 NMR spectra of (a) 2-butanone.

A second interesting point about both spectra in Figure 14.9.2 is that the peaks aren't uniform in size. Some peaks are larger than others, even though they are one-carbon resonances (except for the two 2-carbon peaks of *para*-bromoacetophenone). This difference in peak size is a general feature of broadband-decoupled ^{13}C NMR spectra, and explains why we can't integrate ^{13}C NMR spectra in the same way we integrate the resonances in a ^{1}H NMR spectrum. The local environment of each carbon atom determines not only its chemical shift but also the time it takes for the nuclei to return to their equilibrium state after receiving a pulse of rf radiation and flipping their spins. Quaternary carbons, regardless of their hybridization state or substituents, typically give smaller resonances than primary, secondary, or tertiary carbons.

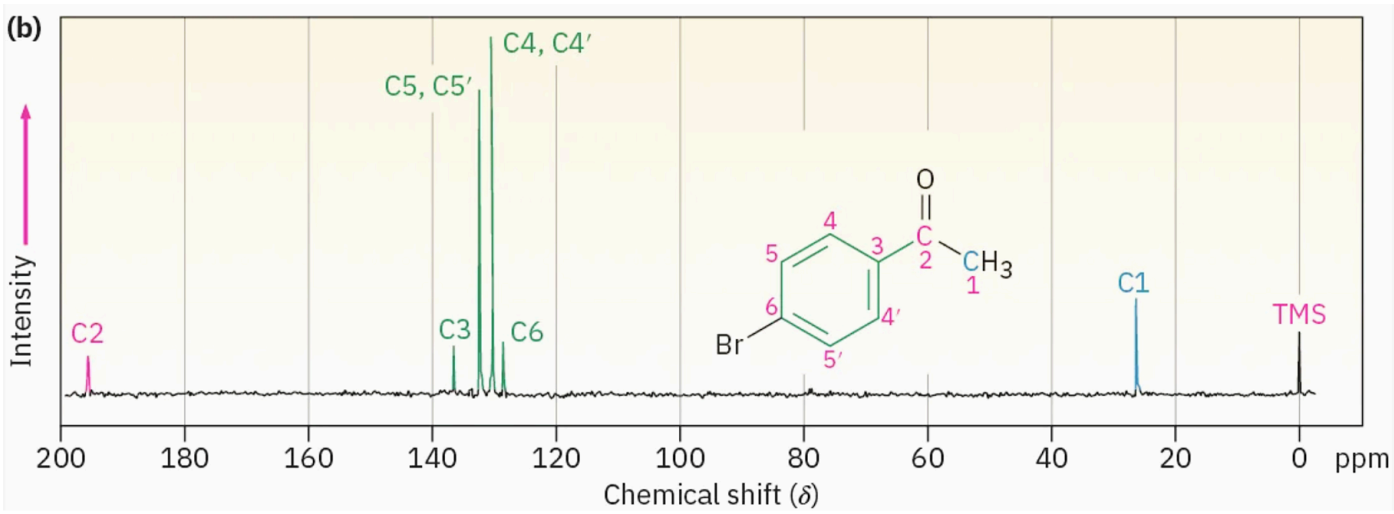
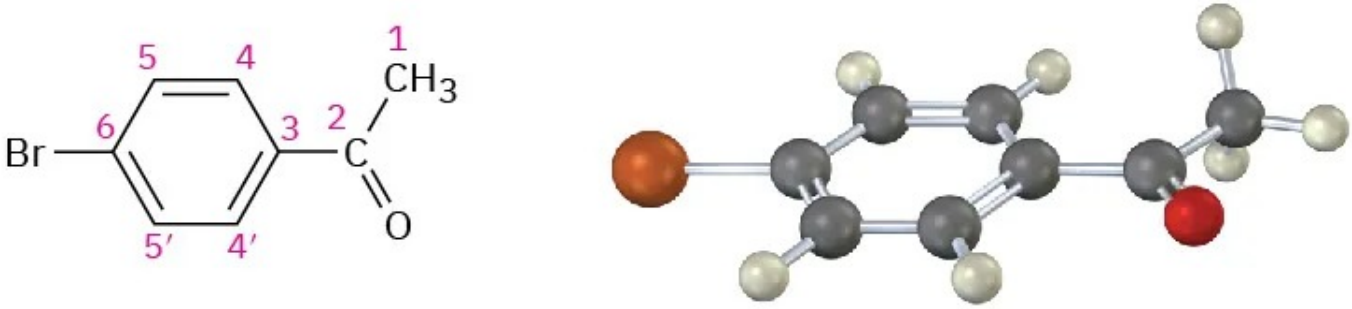


Figure 14.9.2: Carbon-13 NMR spectra of (b) *para*-bromoacetophenone.

The ^{13}C NMR spectrum of *para*-bromoacetophenone is interesting in several ways. Note particularly that only six carbon absorptions are observed, even though the molecule contains eight carbons. *para*-bromoacetophenone has a symmetry plane that makes ring carbons 4 and 4′, and ring carbons 5 and 5′ equivalent. (Remember from Section 2.4 that aromatic rings have two resonance forms.) Thus, the aromatic carbons show only four absorptions in the range 128 to 137 δ.



para-Bromoacetophenone

Worked Example 14.9.1: Predicting Chemical Shifts in ^{13}C NMR Spectra

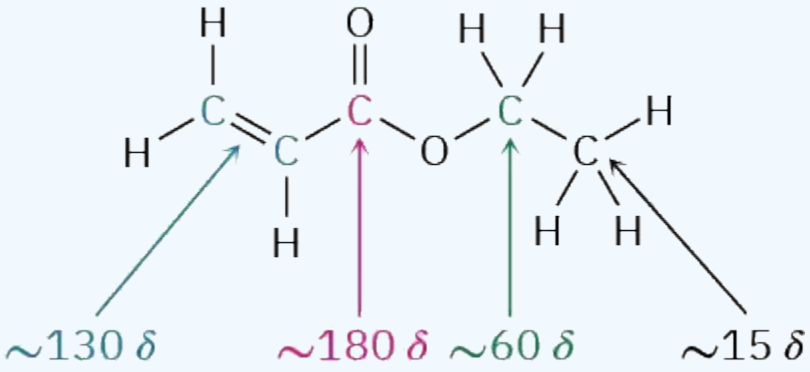
At what approximate positions would you expect ethyl acrylate, $H_2C{=}CHCO_2CH_2CH_3$, to show ^{13}C NMR absorptions?

Strategy

Identify the distinct carbons in the molecule, and note whether each is alkyl, vinylic, aromatic, or in a carbonyl group. Then predict where each absorbs, using Figure 14.9.1 as necessary.

Solution

Ethyl acrylate has five chemically distinct carbons: two different C=C, one C=O, one O–C, and one alkyl C. From Figure 14.9.1 , the likely absorptions are



The actual absorptions are at 14.1, 60.5, 128.5, 130.3, and 166.0 δ.

Exercises

Exercise 14.9.1

Predict the number of carbon resonance lines you would expect in the ^{13}C NMR spectra of the following compounds:

a.Methylcyclopentane **b.**1-Methylcyclohexene **c.**1,2-Dimethylbenzene **d.**2-Methyl-2-butene **e.** **f.**

Answer available at the end of this section.

Exercise 14.9.2

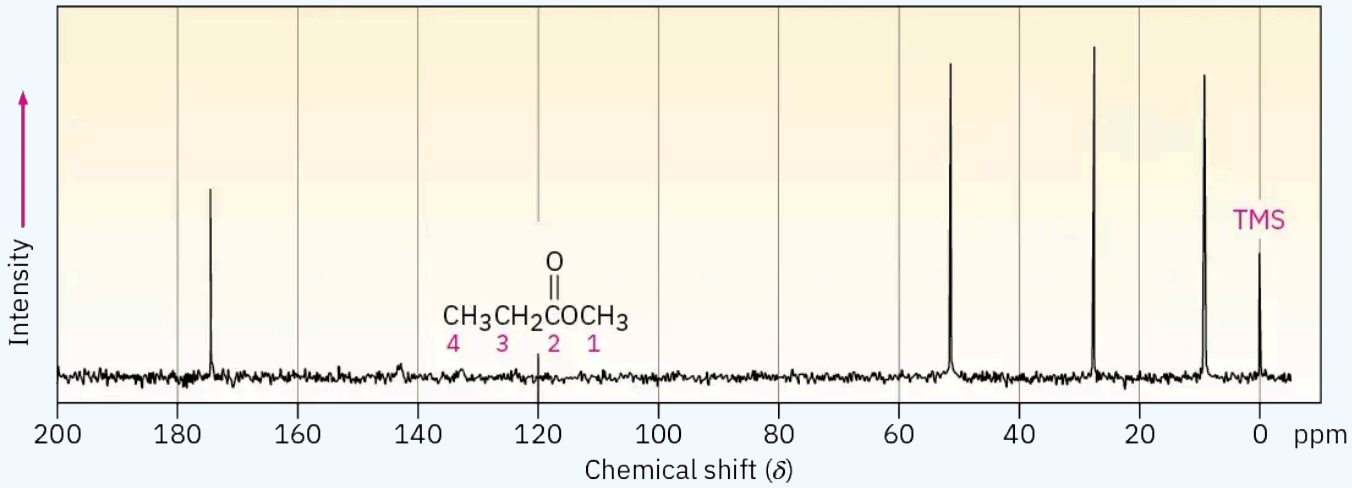
Propose structures for compounds that fit the following descriptions:

a. A hydrocarbon with seven lines in its ^{13}C NMR spectrum
b. A six-carbon compound with only five lines in its ^{13}C NMR spectrum
c. A four-carbon compound with three lines in its ^{13}C NMR spectrum

Answer available at the end of this section.

Exercise 14.9.3

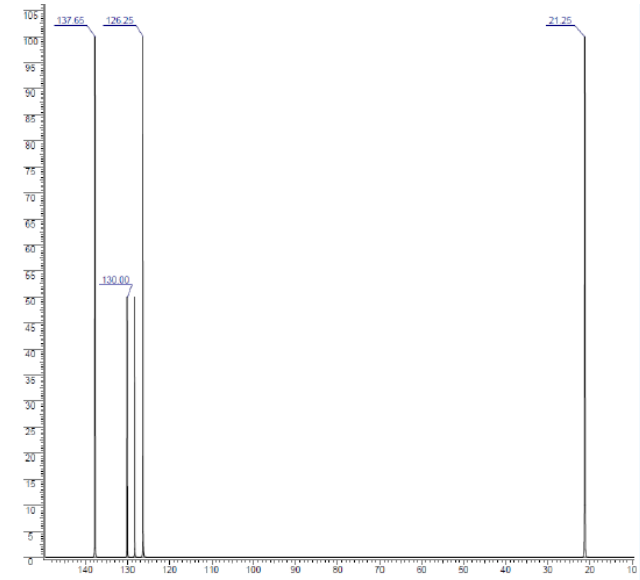
Classify the resonances in the ^{13}C NMR spectrum of methyl propanoate, $CH_3CH_2CO_2CH_3$:



Answer available at the end of this section.

Exercise 14.9.4

Which isomer of ortho, meta, or para xylene do you have based on the ^{13}C NMR spectrum?

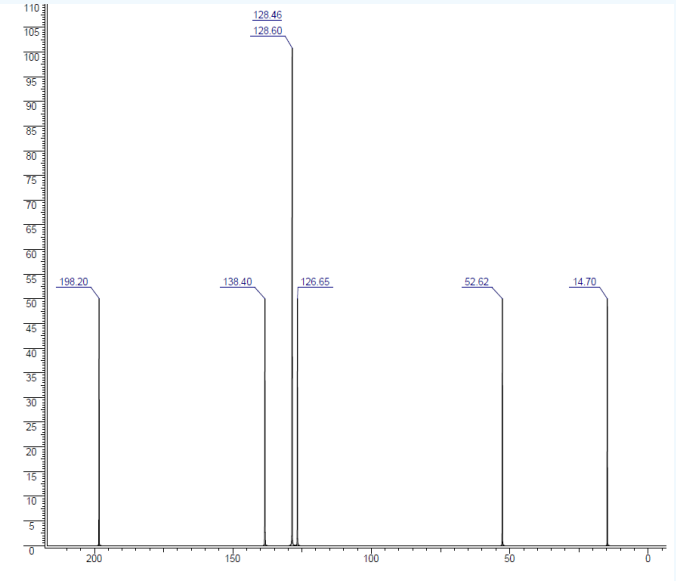


Answer available at the end of this section.

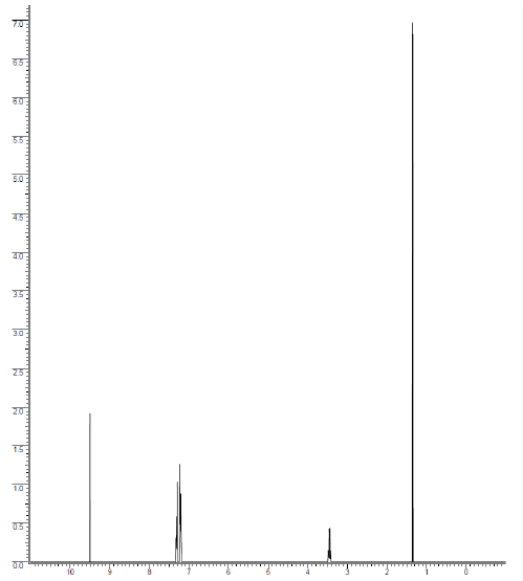
Exercise 14.9.5

Propose a structure using the spectral data below for $C_9H_{10}O$.

^{13}C broadband decoupled spectrum:



^{1}H NMR spectrum: Integration: 1 (doublet; J = 1 Hz):5 (multiplet):1 (quartet of doublets;J = 7 Hz and 1 Hz):3 (doublet; J = 7 Hz)



Answer available at the end of this section.

Answers

Exercise 14.9.1

a.4 **b.**7 **c.**4 **d.**5 **e.**5 **f.**7

Exercise 14.9.2

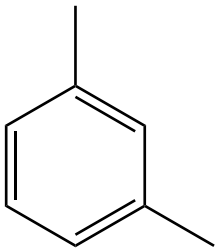
a. 1,3-Dimethylcyclopentene
b. 2-Methylpentane
c. 1-Chloro-2-methylpropane

Exercise 14.9.3

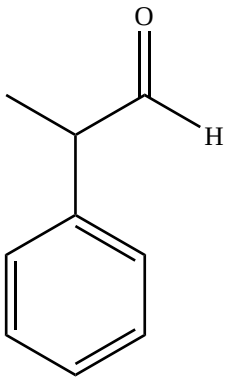
$-CH_3$, 9.3 δ; $-CH_2-$, 27.6 δ; C=O, 174.6 δ; $-OCH_3$, 51.4 δ

Exercise 14.9.4

There are 5 different carbons in the spectrum with four different aromatic carbons. *p*-Xylene would have 2 types of aromatic carbons and *o*-xylene would have 3 types. *m*-Xylene is the only one with 4 different types of aromatic carbons, which fits this spectrum. The methyl groups would all be similary, so not a point of difference.



Exercise 14.9.5



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14.10: DEPT ^{13}C NMR Spectroscopy

Numerous techniques developed in recent years have made it possible to obtain enormous amounts of information from ^{13}C NMR spectra. Among these techniques is one called *DEPT–NMR*, for *distortionless enhancement by polarization transfer,* which makes it possible to distinguish between signals due to CH_3, CH_2, CH, and quaternary carbons. That is, the number of hydrogens attached to each carbon in a molecule can be determined.

A DEPT experiment is usually done in three stages, as shown in Figure 14.10.1 for 6-methyl-5-hepten-2-ol. The first stage is to run an ordinary spectrum (called a broadband-decoupled spectrum) to locate the chemical shifts of all carbons. Next, a second spectrum called a DEPT-90 is run, using special conditions under which only signals due to CH carbons appear. Signals due to CH_3, CH_2, and quaternary carbons are absent. Finally, a third spectrum called a DEPT-135 is run, using conditions under which CH_3 and CH resonances appear as positive signals, CH_2 resonances appear as negative signals—that is, as peaks below the baseline—and quaternary carbons are again absent.

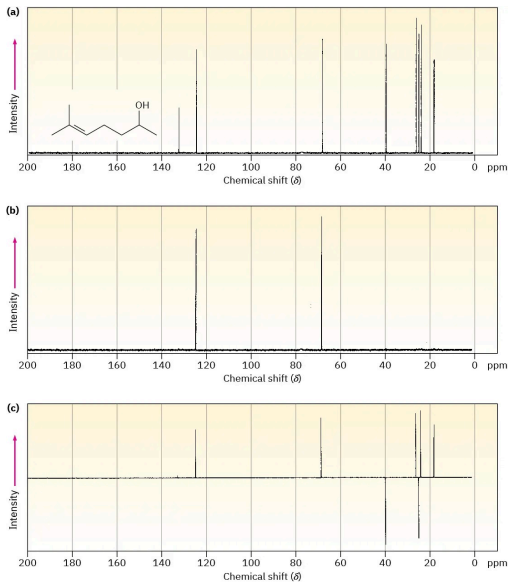


Figure 14.10.1: DEPT–NMR spectra for 6-methyl-5-hepten-2-ol. Part **(a)** is an ordinary broadband-decoupled spectrum, which shows signals for all eight carbons. Part **(b)** is a DEPT-90 spectrum, which shows only signals for the two CH carbons. Part **(c)** is a DEPT-135 spectrum, which shows positive signals for the two CH and three CH_3 carbons and negative signals for the two CH_2 carbons.

Putting together the information from all three spectra makes it possible to tell the number of hydrogens attached to each carbon. The CH carbons are identified in the DEPT-90 spectrum, the CH_2 carbons are identified as negative peaks in the DEPT-135 spectrum, the CH_3 carbons are identified by subtracting the CH peaks from the positive peaks in the DEPT-135 spectrum, and quaternary carbons are identified by subtracting all peaks in the DEPT-135 spectrum from the peaks in the broadband-decoupled spectrum.

Broadband-decoupled	DEPT-90	DEPT-135
C, CH, CH_2, CH_3	CH	CH_3, CH are positive CH_2 is negative

C	Subtract DEPT-135 from broadband-decoupled spectrum
CH	DEPT-90
CH_2	Negative DEPT-135
CH_3	Subtract DEPT-90 from positive DEPT-135

Worked Example 14.10.1: Assigning a Chemical Structure from a 13C NMR Spectrum

Propose a structure for an alcohol, $C_4H_{10}O$, that has the following ^{13}C NMR spectral data:

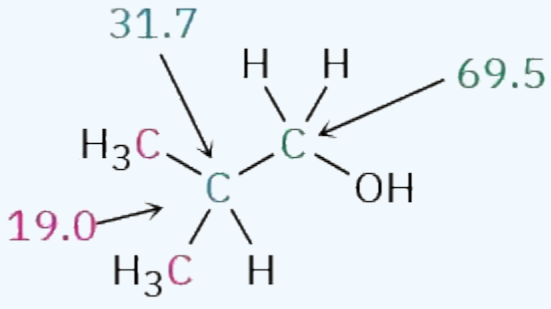
- Broadband decoupled ^{13}C NMR: 19.0, 31.7, 69.5 δ;
- DEPT-90: 31.7 δ;
- DEPT-135: positive peak at 19.0 δ, negative peak at 69.5 δ.

Strategy

As noted in Section 7.2, it usually helps with compounds of known formula but unknown structure to calculate the compound's degree of unsaturation. In the present instance, a formula of $C_4H_{10}O$ corresponds to a saturated, open-chain molecule.

To gain information from the ^{13}C data, let's begin by noting that the unknown alcohol has four carbon atoms, yet has only three NMR absorptions, which implies that two of the carbons must be equivalent. Looking at chemical shifts, two of the absorptions are in the typical alkane region (19.0 and 31.7 δ), while one is in the region of a carbon bonded to an electronegative atom (69.5 δ)—oxygen in this instance. The DEPT-90 spectrum tells us that the alkyl carbon at 31.7 δ is tertiary (CH); the DEPT-135 spectrum tells us that the alkyl carbon at 19.0 δ is a methyl (CH_3) and that the carbon bonded to oxygen (69.5 δ) is secondary (CH_2). The two equivalent carbons are probably both methyls bonded to the same tertiary carbon, $(CH_3)_2CH$–. We can now put the pieces together to propose a structure: 2-methyl-1-propanol.

Solution



2-Methyl-1-propanol

Exercises

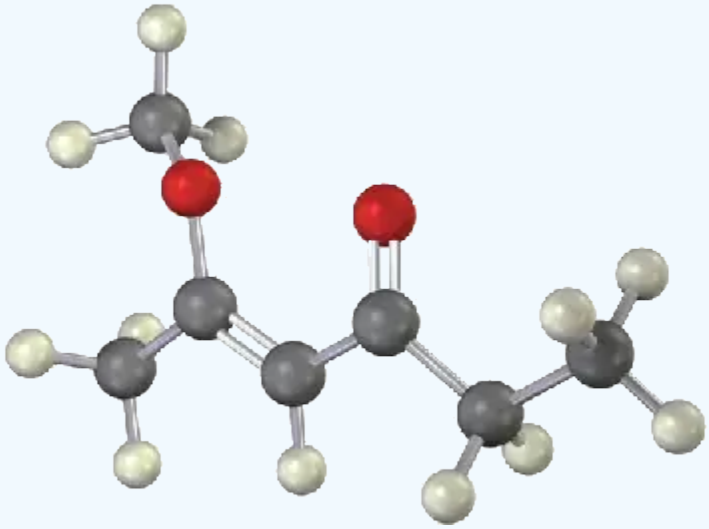
Exercise 14.10.1

Assign a chemical shift to each carbon in 6-methyl-5-hepten-2-ol (Figure 14.10.1).

Answer available at the end of this section.

Exercise 14.10.2

Estimate the chemical shift of each carbon in the following molecule. Predict which carbons will appear in the DEPT-90 spectrum, which will give positive peaks in the DEPT-135 spectrum, and which will give negative peaks in the DEPT-135 spectrum.



Answer available at the end of this section.

Exercise 14.10.3

Propose a structure for an aromatic hydrocarbon, $C_{11}H_{16}$, that has the following ^{13}C NMR spectral data:

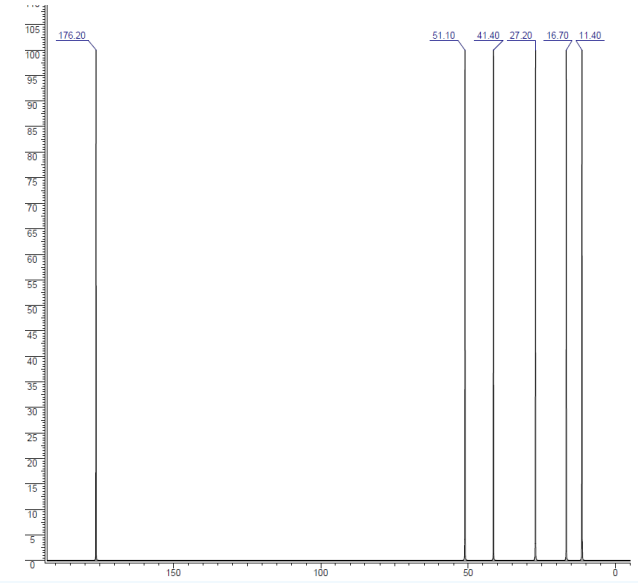
Broadband decoupled: 29.5, 31.8, 50.2, 125.5, 127.5, 130.3, 139.8 δ
DEPT-90: 125.5, 127.5, 130.3 δ
DEPT-135: positive peaks at 29.5, 125.5, 127.5, 130.3 δ; negative peak at 50.2 δ

Answer available at the end of this section.

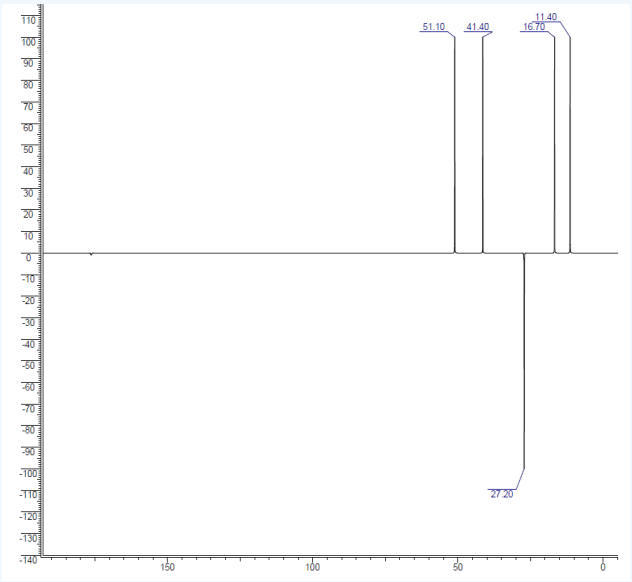
Exercise 14.10.4

Propose a structure using the spectral data below for $C_6H_{12}O_2$.

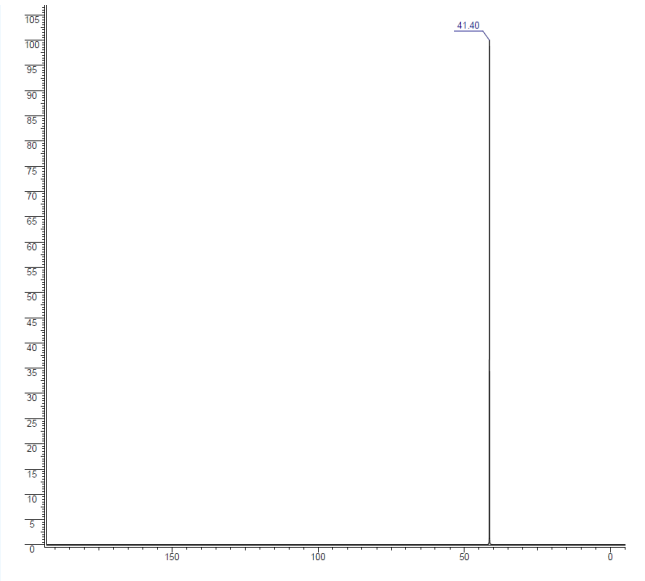
^{13}C broadband decoupled spectrum:



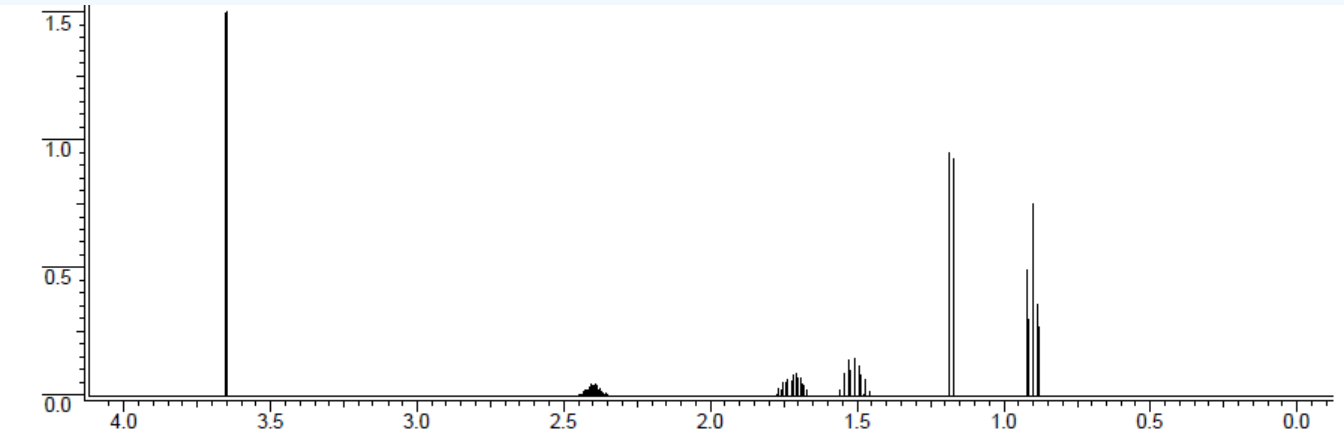
DEPT-135:



DEPT-90:



^{1}H NMR spectrum: Integration: 3 (singlet):1 (sextet; J = 8 Hz):1 (multiplet;J = 25 Hz and 8 Hz):1(multiplet; J = 25 Hz and 8 Hz):3 (doublet; J = 8 Hz):3 (triplet; J = 8 Hz)

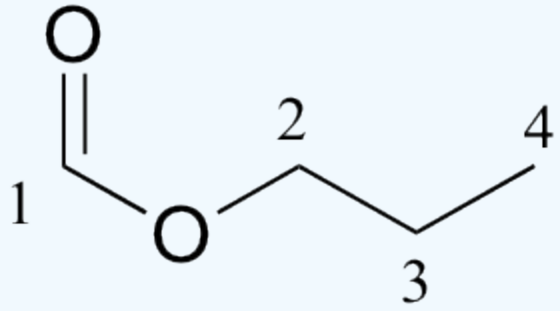


Answer available at the end of this section.

Exercise 14.10.5

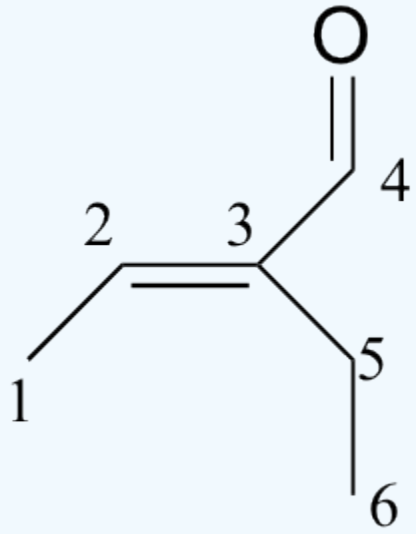
^{13}C-NMR data is given for the molecules shown below. Complete the peak assignment column of each NMR data table.

a)



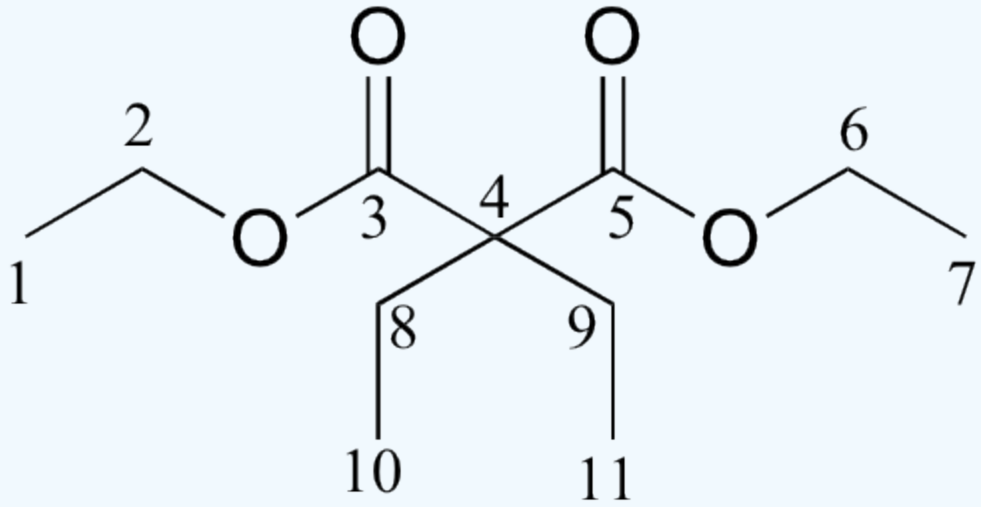
δ	DEPT	carbon #
161.12	CH	
65.54	CH_2	
21.98	CH_2	
10.31	CH_3	

b)



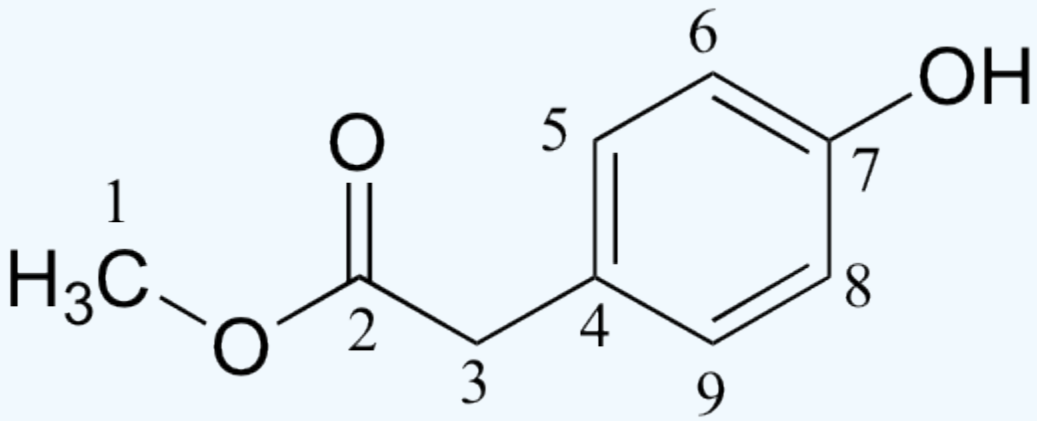
δ	DEPT	carbon #
194.72	C	
149.10	C	
146.33	CH	
16.93	CH_2	
14.47	CH_3	
12.93	CH_3	

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	

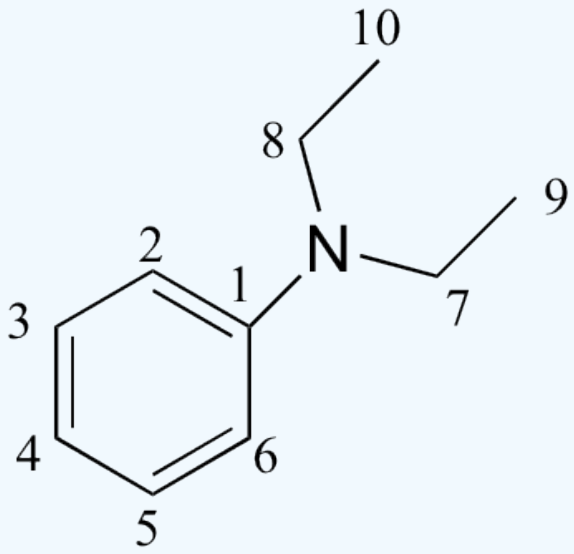
d)



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)

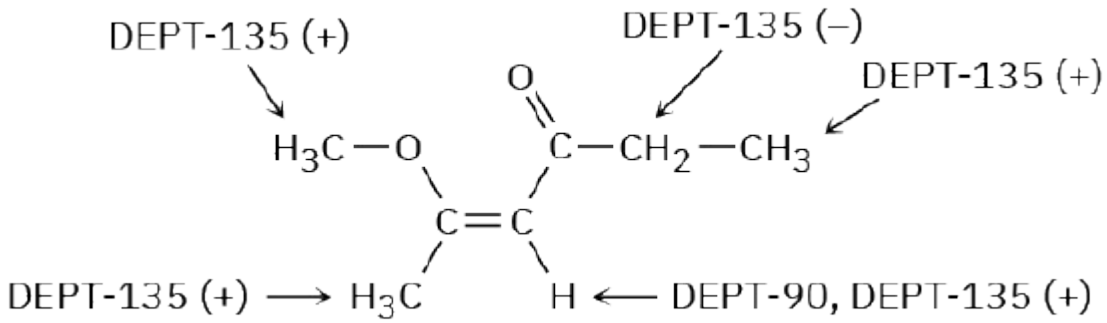


δ	DEPT	carbon #
147.79	C	
129.18	CH	
115.36	CH	
111.89	CH	
44.29	CH_2	
12.57	CH_3	

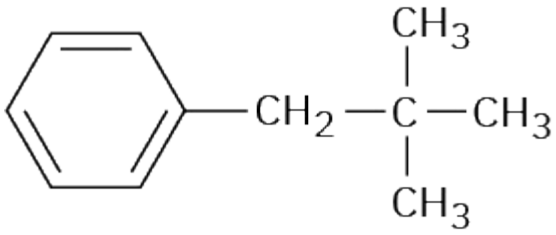
Answers

Exercise 14.10.1

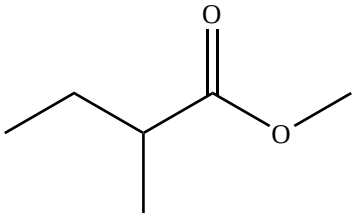
Exercise 14.10.2



Exercise 14.10.3



Exercise 14.10.4



Structure:

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14.11: H-NMR and C-NMR of Alcohols and Phenols

Objectives

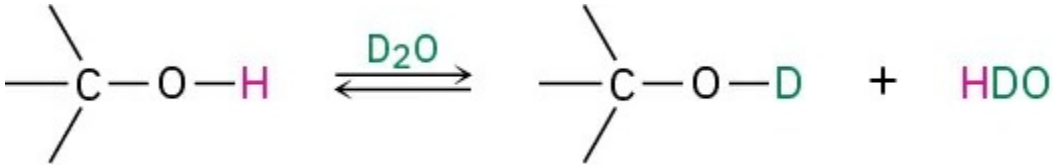
After completing this section, you should be able to

a. Describe the characteristic features of the proton NMR spectra of alcohols and phenols.
- **a.** Explain how deuterium oxide (D_2O) can be used to assist in the identification of the signal caused by the presence of the O-H proton in the ^1H NMR spectrum of an alcohol.
- **b.** Predict the general form (i.e., number of peaks, approximate chemical shifts, and splitting pattern) of the proton NMR of a given alcohol or phenol.
- **c.** Predict the general form (i.e., number of peaks, and approximate chemical shifts) of the Carbon NMR of a given alcohol or phenol

Determining the Position of an -OH Peak in ^1H NMR

Aliphatic Alcohols

Alcohols also show characteristic absorptions in the ^1H NMR spectrum. Hydrogens on the oxygen-bearing carbon atom are deshielded by the electron-withdrawing effect of the nearby oxygen, and their absorptions occur in the range 3.4 to 4.5 δ. Spin–spin splitting, however, is not usually observed between the O–H proton of an alcohol and the neighboring protons on carbon. Most samples contain small amounts of acidic impurities, which catalyze an exchange of the O–H proton on a timescale so rapid that the effect of spin–spin splitting is removed. It's often possible to take advantage of this rapid proton exchange to identify the position of the O–H absorption. If a small amount of deuterated water, D_2O, is added to an NMR sample tube, the O–H proton is rapidly exchanged for deuterium, and the hydroxyl absorption disappears from the spectrum.



Typical spin–spin splitting *is* observed between protons on the oxygen-bearing carbon and other neighbors. For example, the signal of the two –CH_2O– protons in 1-propanol is split into a triplet by coupling with the neighboring –CH_2– protons (Figure 14.11.1).

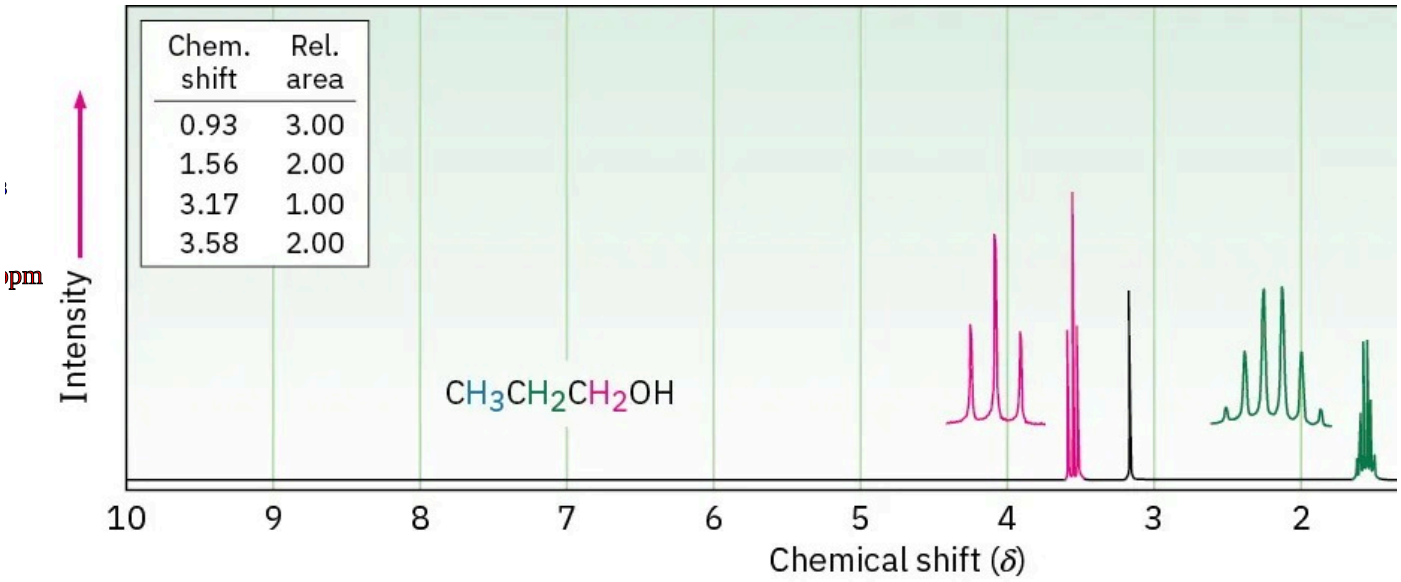


Figure 14.11.1: ^{1}H NMR spectrum of 1-propanol. The protons on the oxygen-bearing carbon are split into a triplet at 3.58 δ.

Aromatic Alcohols, Phenols

Phenols, like all aromatic compounds, show ^{1}H NMR absorptions near 6.5 to 8 δ, the expected position for aromatic-ring protons. These peaks will exhibit splitting typical of aromatic protons. The protons directly attached to the alcohol oxygen of phenols appear in the region of 3 to 8 δ. These peaks tend to appear as short, broad singlets, similar to other alcohols. In neither case are these absorptions uniquely diagnostic for phenols, since other kinds of protons absorb in the same range.

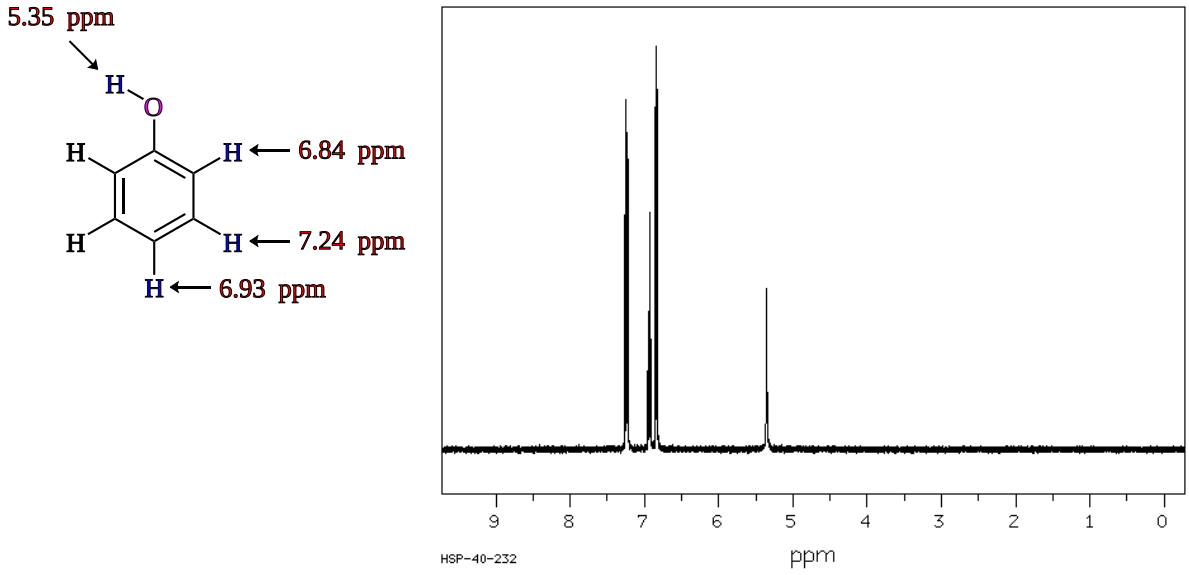


Figure 14.11.2: ^{1}H NMR spectrum of phenol.

Exercises

Exercise 14.11.1

When the ^{1}H NMR spectrum of an alcohol is run in dimethyl sulfoxide (DMSO) solvent rather than in chloroform, exchange of the O–H proton is slow and spin–spin splitting is seen between the O–H proton and C–H protons on the adjacent carbon. What spin multiplicities would you expect for the hydroxyl protons in the following alcohols?

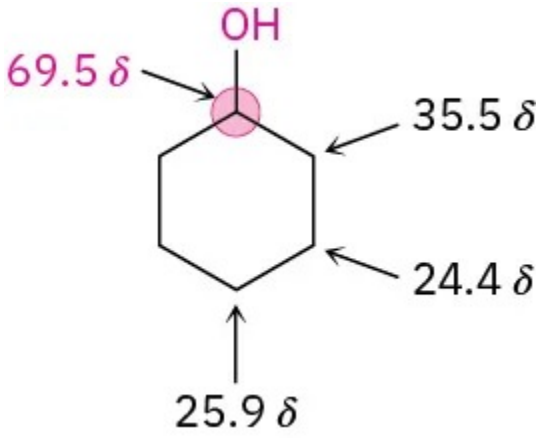
a.2-Methyl-2-propanol **b.**Cyclohexanol **c.**Ethanol **d.**2-Propanol **e.**Cholesterol **f.**1-Methylcyclohexanol

Answer available at the end of this section.

Determining the Position of a C-OH in ^{13}C NMR

Aliphatic Alcohols

Carbon atoms bonded to electron-withdrawing –OH groups are deshielded and appear at a lower field in the ^{13}C NMR spectrum than do typical alkane carbons. Most alcohol carbon absorptions fall in the range 50 to 70 δ, as shown in the following drawing for cyclohexanol:



- While carbons adjacent to the alcohol oxygen appear in the distinctive region of 50-70 ppm in the ^{13}C NMR spectrum, carbons at a two-bond distance show a softer deshielding effect and appear at slightly lower fields.

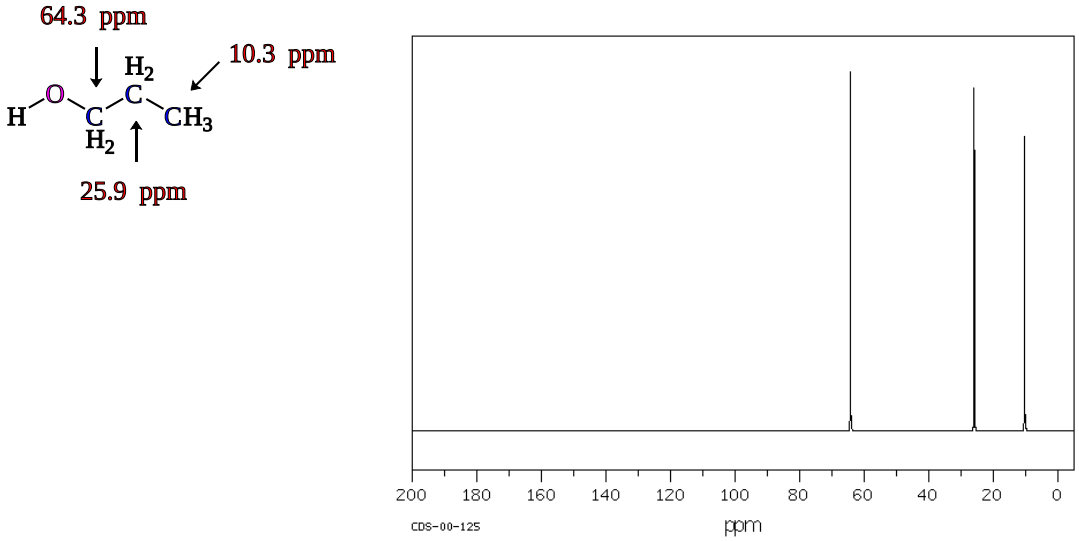


Figure 14.11.3: ^{1}C NMR spectrum of 1-propanol. The oxygen-bearing carbon appears at 64.3 δ.

Aromatic Alcohols, Phenols

- Due to the electronegative oxygen, the aromatic carbon attached to the -OH group is shifted downfield to 155 ppm.
- The other carbons in the phenol ring appear in the region typical for aromatic carbons of 125-150 ppm.

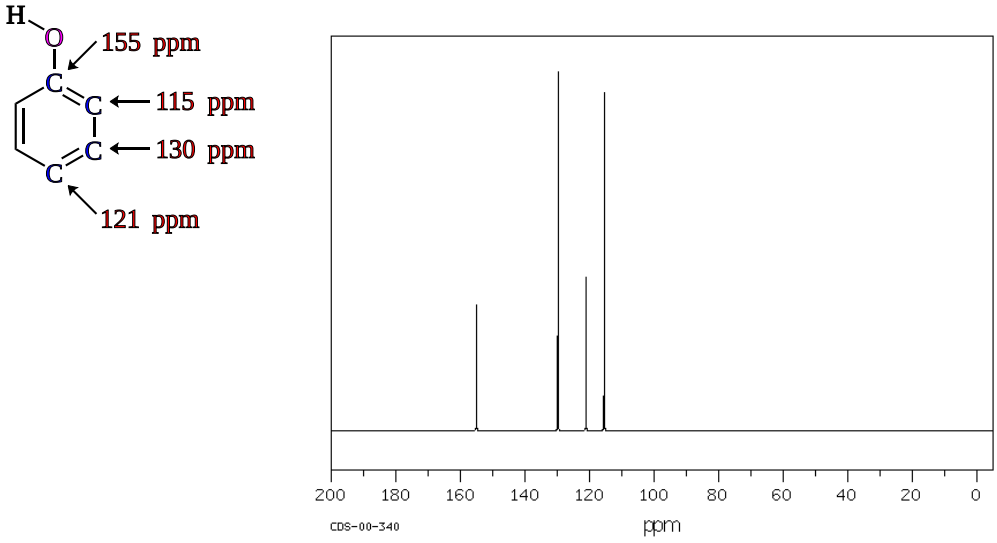


Figure 14.11.4: ^{1}C NMR spectrum of 1-propanol. The oxygen-bearing carbon appears at 64.3 δ.

Answers

Exercise 14.11.1

a.Singlet **b.**Doublet **c.**Triplet **d.**Doublet **e.**Doublet **f.**Singlet

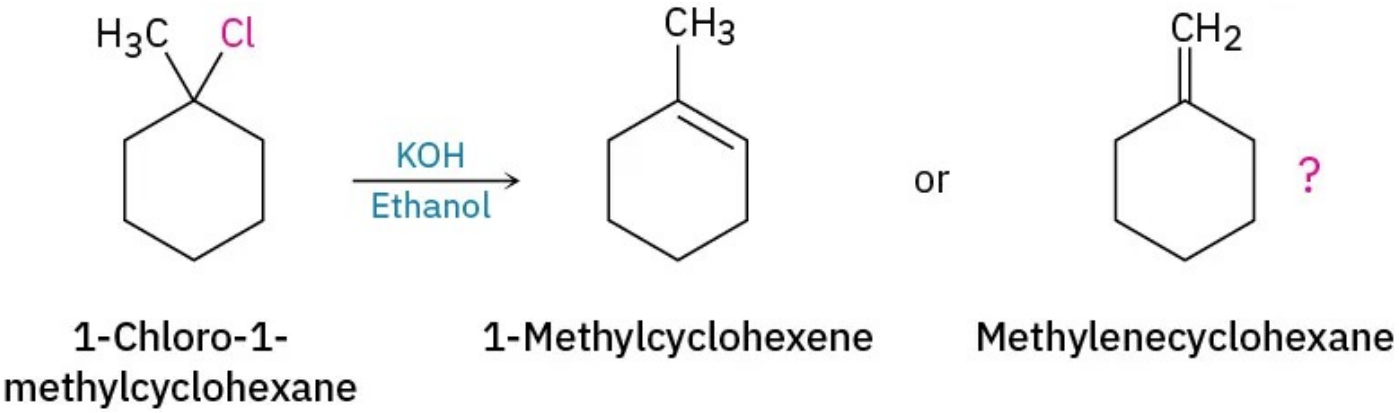
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14.12: Uses of ^{13}C NMR Spectroscopy

The information derived from ^{13}C NMR spectroscopy is extraordinarily useful for structure determination. Not only can we count the number of nonequivalent carbon atoms in a molecule, we can also get information about the electronic environment of each carbon and find how many protons are attached to each. As a result, we can address many structural questions that go unanswered by IR spectroscopy or mass spectrometry.

Here's an example: how do we know that the E2 reaction of an alkyl halide follows Zaitsev's rule (Section 11.7)? Does treatment of 1-chloro-1-methylcyclohexane with a strong base give predominantly the trisubstituted alkene 1-methylcyclohexene or the disubstituted alkene methylenecyclohexane?



1-Methylcyclohexene will have five sp^3-carbon resonances in the 20 to 50 δ range and two sp^2-carbon resonances in the 100 to 150 δ range. Methylenecyclohexane, however, because of its symmetry, will have only three sp^3-carbon resonance peaks and two sp^2-carbon peaks. The spectrum of the actual reaction product, shown in Figure 14.12.1, clearly identifies 1-methylcyclohexene as the product of this E2 reaction.

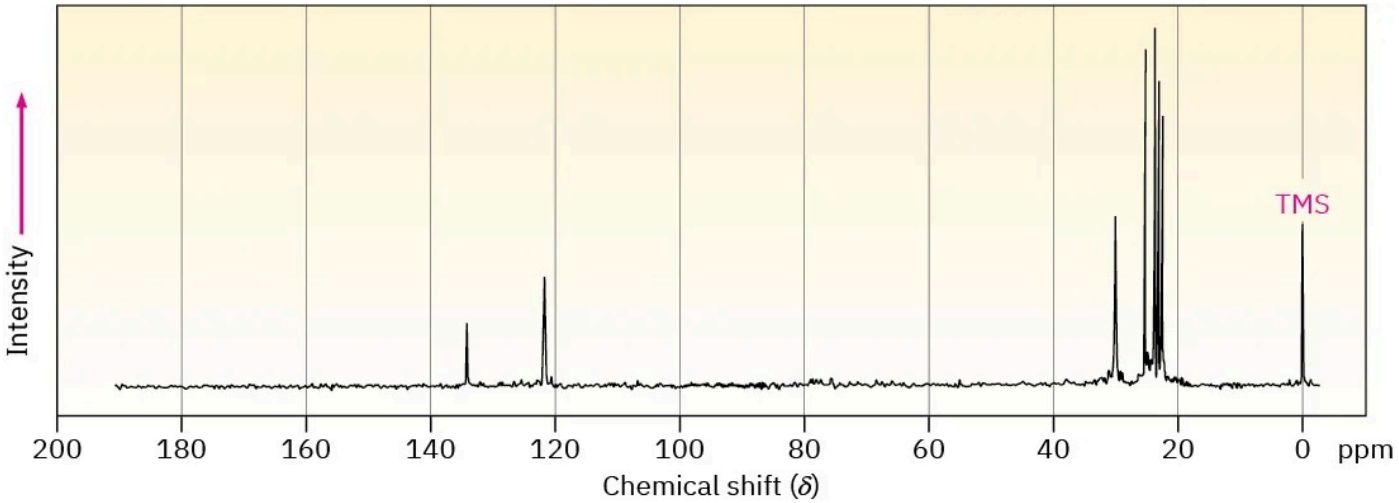


Figure 14.12.1: The ^{13}C NMR spectrum of 1-methylcyclohexene, the E2 reaction product from treatment of 1-chloro-1-methylcyclohexane with base.

Exercise 14.12.1

We saw in Section 9.3 that addition of HBr to a terminal alkyne leads to the Markovnikov addition product, with the Br bonding to the more highly substituted carbon. How could you use ^{13}C NMR to identify the product of the addition of 1 equivalent of HBr to 1-hexyne?

Answer available at the end of this section.

Answers

Exercise 14.12.1

A DEPT-90 spectrum would show two absorptions for the non-Markovnikov product (RCH=CHBr) but no absorptions for the Markovnikov product ($RBrC=CH_2$).

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14.13: Constructing Partial Structures

When you look at an IR spectrum, you immediately see little chunks of the structure, because you see individual bonds. You know at a glance that the compound contains a C=O bond or an O-H bond. That can be very reassuring, because you can quickly imagine what you are dealing with.

NMR spectra often take more work. You may have to put pencil to paper to come up with a structure. The work pays off, because you can get a much more detailed picture of the structure.

Step by Step

Let's start with a ^{13}C NMR spectrum. Suppose you had peaks in the spectrum at 200, 35, and 15 ppm. We might assign these three peaks as follows:

shift (ppm)	partial structure
200	sp^2 **C**=O
35	sp^3 **C**-C=O
30	sp^3 **C**-C=O
15	sp^3 **C**-C

We are saying that the first carbon is in the sp^2 (trigonal planar) region and that it is so far downfield because of a double bond to oxygen. The other two carbons are in the sp^3 or tetrahedral region. One of them isn't very far downfield; it is probably just attached to another sp^3 carbon. The other two, at 35 and 30 ppm, are both a little further downfield. That's roughly the right place for a tetrahedral carbon attached to a trigonal-planar carbon; that is, these carbons are each attached to either a double bond or a carbonyl.

In the partial structure, we always **bold** or underline the carbon that corresponds to the peak we are discussing. If you don't do that, it isn't clear whether the peak at 30 comes from a carbon next to the carbonyl (C=O), or the carbon in the carbonyl itself. Also, at the peak at 15, we want to make it clear that we are talking about a single carbon atom; leaving the partial structure as C-C implies that this spectroscopy observes bonds, but it does not. IR spectroscopy observes bonds. ^{13}C NMR spectroscopy observes carbon atoms.

Now, suppose we look at the ^{1}H NMR spectrum for the same compound. Maybe we will see three peaks this time. There is a quartet integrating for 2H at 2.3 ppm, a singlet integrating for 3H at 2.1 ppm, and a triplet integrating for 3H at 1.1 ppm. We enter those characteristics in a table. This time, there are three features to explain for each peak.

shift	integ.	multipl.	partial structure
2.3	2H	quartet	CH_3-C**H_2**-C=O
2.1	3H	singlet	C**H_3**-C=O
1.1	3H	triplet	C**H_3**-CH2

First, we need to explain the shift. All of these peaks are in the upfield end of the spectrum (below 5 ppm), so they are likely from hydrogens on sp^3 or tetrahedral carbons. The first two are slightly downfield, just past 2 ppm. That suggests that the sp3 carbons they are attached to may, in turn, be attached to sp2 carbons: either double bonds or carbonyls. We already know there is a carbonyl from the ^{13}C spectrum, so let's assume that's what is causing the shift near 2 ppm. The third peak, at 1.1 ppm, is in the normal range; this hydrogen is on a tetrahedral carbon, likely attached to other tetrahedral carbons.

To demonstrate what the integration is telling us, we just show the correct number of hydrogens. There are two hydrogens responsible for the peak at 2.3 ppm. Three others are responsible for the peak at 2.1 ppm, and another three give rise to the peak at 1.1 ppm.

Finally, we need to explain the multiplicity. The peak at 2.3 ppm is a quartet, so by the "n+1" rule it must be next to a CH_3 group. The peak at 1.1 ppm is a triplet, so it must be next to a CH_2 group. (It does not take long to figure out that these two peaks represent hydrogens that are next to each other.) Finally, the peak at 2.1 ppm is a singlet. It has no hydrogen neighbors at all.

Notice that we do not need to know the structure to fill in these partial structures. We are just writing down what the data is telling us. From there, it isn't very far to determine the overall structure.

Exercise 14.13.1

Fill in partial structures for the following peaks.

a) 10.1 ppm, 1H, triplet b) 3.4 ppm, 1H, septet c) 7.3 ppm, 2H, triplet

d) 5.4 ppm, 1H, quartet e) 1.4 ppm, 2H, sextet f) 8.0 ppm, 1H, singlet

g) 2.1 ppm, 3H, singlet h) 6.8 ppm, 2H, doublet i) 0.9 ppm, 6H, doublet

Answer available at the end of this section.

Exercise 14.13.2

Identify the errors in the following partial structures:

a) 3.6 ppm, 2H, triplet, C**H**$_2$-CH_2 b) 2.1 ppm, 2H, singlet, C**H**$_3$-C=C

c) 7.4 ppm, 2H, doublet, CH=C**H**$_2$-C d) 1.8 ppm, 2H, quintet, C**H**$_2$-CH_4

e) 7.8 ppm, 1H, triplet, -C**H**=CH_2 f) 1.7 ppm, 1H, nonet, NH_2-C**H**$(CH_3)_2$

Answer available at the end of this section.

Answers

Exercise 14.13.1

Aromatic (benzene etc) peaks are labeled "Ar" to distinguish from alkene peaks that show up further upfield (lower shift). Also, some peaks may be in two symmetric positions and are labeled with "x2".

a) 10.1 ppm, 1H, triplet, CH_2-C**H**=O b) 3.4 ppm, 1H, septet, O-C**H**$(CH_3)_2$

c) 7.3 ppm, 2H, triplet, CH=C**H**-CH x 2 (Ar) d) 5.4 ppm, 1H, quartet, CH_3-C**H**=C

e) 1.4 ppm, 2H, sextet, CH_3-C**H**$_2$-CH_2 f) 8.0 ppm, 1H, singlet, C=C**H**-C (Ar)

g) 2.1 ppm, 3H, singlet, C**H**$_3$-C=C or C**H**$_3$-C=O or C**H**$_3$-N; need context to choose

h) 6.8 ppm, 2H, doublet, CH=C**H**-C x 2 (Ar) i) 0.9 ppm, 6H, doublet, CH-C**H**$_3$ x 2

Exercise 14.13.2

Identify the errors in the following partial structures:

a) 3.6 ppm, 2H, triplet, C**H**$_2$-CH_2 the first carbon must be attached to O to have a shift at 3.6 ppm

b) 2.1 ppm, 2H, singlet, C**H**$_3$-C=C the integral says only 2H, not 3H

c) 7.4 ppm, 2H, doublet, CH=C**H**$_2$-C the shift implies aromatic, so there can only be one H per carbon; must be symmetry

d) 1.8 ppm, 2H, quintet, C**H**$_2$-CH_4 there can't be four hydrogens on one carbon; must be some hydrogens on each side

e) 7.8 ppm, 1H, triplet, -C**H**=CH_2 the shift implies aromatic, so there can only be one H per carbon; must be one one each side

f) 1.7 ppm, 1H, nonet, NH2-C**H**(CH3)2, an attached nitrogen would shift this hydrogen past 2 ppm; also, coupling is rarely seen across O or N, so the two neighboring H on the left are probably on a carbon.

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14.14: Combined Spectra for Structure Elucidation

There are many ways we can use NMR spectroscopy to analyze compounds. One common application is determining the structure of an unknown. Given the MS, IR, ^{13}C and ^{1}H NMR spectra, what might be the structure of an unknown sample?

IR Spectrum

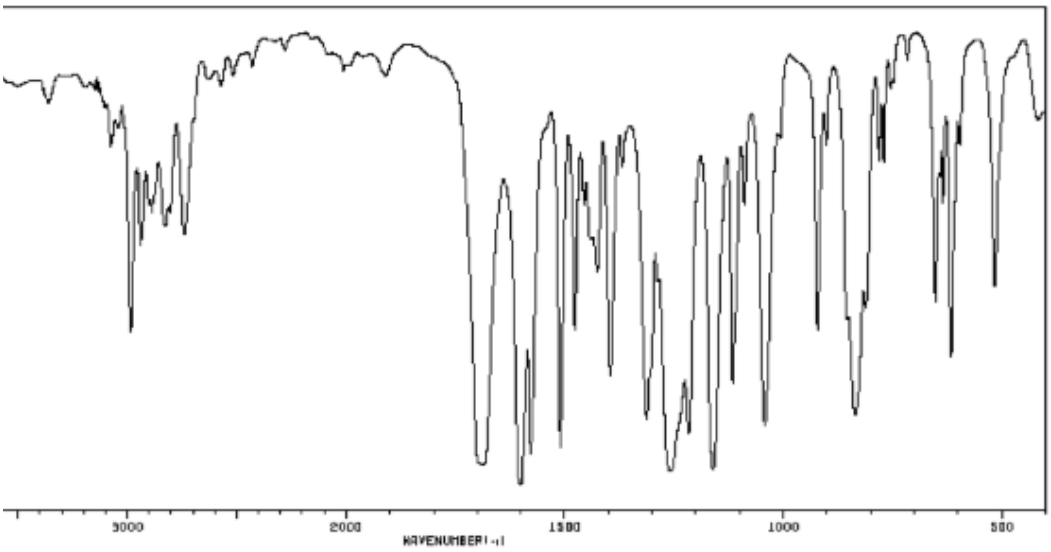
It is often easiest to start with the IR spectrum.

- Identify at least three peaks in the IR spectrum. Which peaks seem to tell you the most information about this compound?
- Don't think with your head; think with your hands. Write down ideas on the spectrum.
- If you are working on a formal proof of structure, on a class test, or a lab report, you may be required to enter your data in a table correlating wavenumber with peak assignment:

cm^{-1}	asst

For example, a student might obtain the following IR spectrum.Figure 14.14.1

From that information, she constructs the following table. She might even write this table, by hand, directly on her spectrum. She makes useful notes on the edges and might even include some guesses, which she later crosses out but does not erase. She is assisted in this task by consulting an IR table, which suggests what some of these peaks might mean.



frequency (cm^{-1})	description	assignme
3400	weak, broad	OH (wa
2990	medium, sharp	sp3 C-H
2800 & 2700	medium, sharp	aldehy
1700	strong	C=O
1250	strong	C-O
1150	strong	(C-O ?
825	strong	C=C-H

Figure 14.14.1: IR spectrum of unknown sample and the student-constructed table

Remember:

- Make special note of what atoms are present in the compound: C, H, N, O...
- Also note your initial ideas about specific functional groups that may be present.
- If you are unsure of an assignment, put a question mark beside it to signal this uncertainty.
- Some data may need to be discarded later if it is not consistent with other data.

^{13}C NMR Spectra

- How many different carbons are there, based on the number of peaks in the spectrum? This is the first step in estimating the molecular formula.
- Do you have reason to believe there is symmetry in the structure? In the entire compound or just part of it? Adjust the number of carbons you think you are dealing with.
- As in IR spectroscopy, begin assigning peaks, either on the spectrum or, if required, in a table:

ppm	asst

For example, a student might obtain the following ^{13}C NMR spectrum. From that information, she puts together the following table:

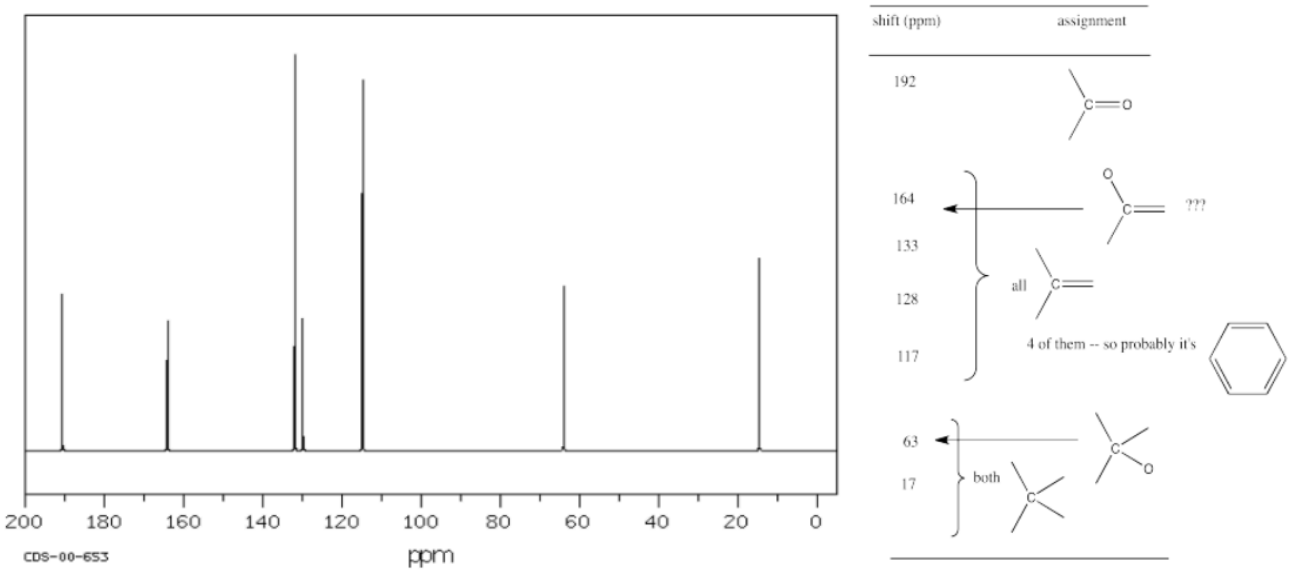


Figure 14.14.2: ^{13}C NMR spectrum of unknown sample and the student-constructed table

Remember:

- You will be able to assign all peaks in the NMR spectrum, not just a few, like in IR.

As in ^{13}C NMR, you should be able to assign all peaks in the ^{1}H NMR spectrum. You may be able to do so by making notes on the spectrum. If you think you know the structure, you may be able to draw it and note which peak belongs with which proton.

^{1}H NMR Spectra

A formal proof of structure might require a table of H assignments. This table demonstrates your ability to read the spectrum. Can you decide what ratio of protons is suggested by the integral line? Can you decide whether a peak is a quartet?

ppm	int	mult	partial structure	assignment

- The partial structure column should explain the shift, integration, and multiplicity for the peak in that row. It should not show any other information from elsewhere in the structure. This restriction forces you to demonstrate a thorough understanding of the data in a way that "getting the right answer" does not.
- The partial structure column is best filled in with drawings rather than words. The drawing is a partial structure. The partial structure will show the assigned protons at that shift, as well as the neighboring protons; you need to distinguish between them in your picture. Most people circle, underline, or **bold** the assigned protons.
- When finished with the partial structure column, you should be able to link the partial structures together to make an entire structure in the assignment column.

An example of a spectrum and its accompanying data table is given below. Here is the spectrum and the student-constructed data table:

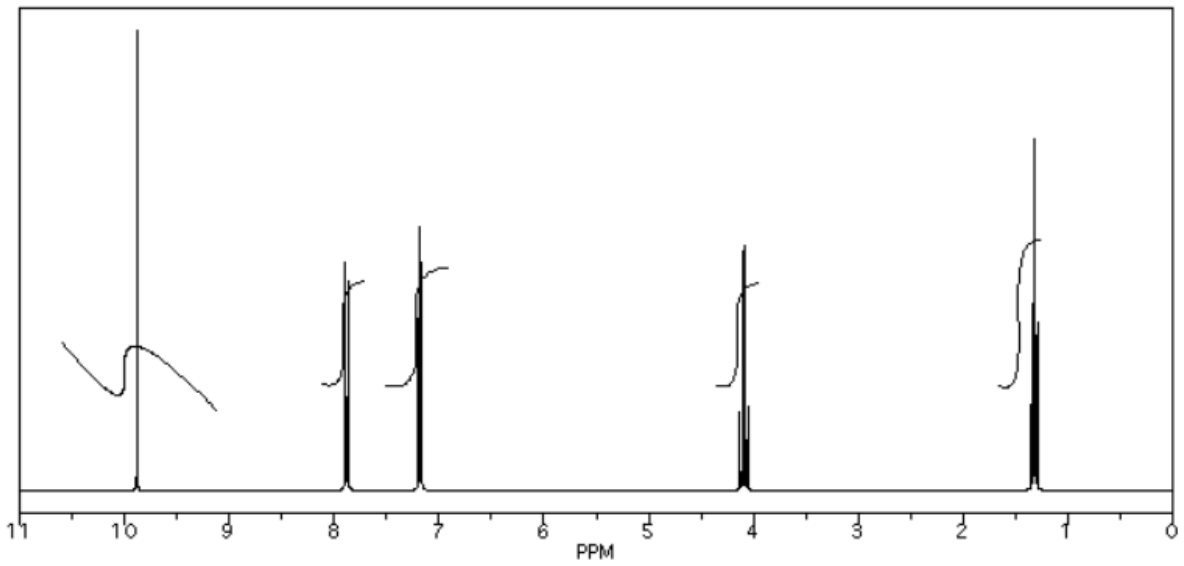


Figure $14.14.3a$: ^{1}H NMR spectrum of unknown sample

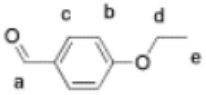
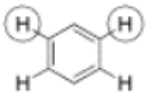
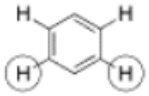
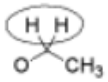
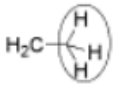
	shift	integration	int(n)	multiplicity	partial structure	assignment
a	9.7 ppm	11 mm	1H	singlet		
b	7.5 ppm	23 mm	2H	doublet		
c	8.1 ppm	21 mm	2H	doublet		
d	3.8 ppm	24 mm	2H	quartet		
e	1.2 ppm	35 mm	3H	triplet		

Figure 14.14.3*b*: Student-constructed table of ^{1}H NMR spectrum of unknown sample

Things to note:

- This student has used two integration columns instead of just one.
  - The first column shows the integral height measured from the spectrum with a ruler.
  - The second column contains the minimum ratio calculated from the measurement. This ratio is easier to use.
- Also note that the peak at 9.7 ppm has a poor integral. There is either a "phasing" or a "level & tilt" problem here that can be corrected using the NMR software, but this is sometimes difficult to do. If she had taken an automatic printout of this integral measurement, she would have gotten a strange number; in this case, it would be about -5, because the end of the integral line is lower than the start. It clearly isn't a negative number of hydrogens, though. She has instead measured the vertical rise in the integral and recorded that; it isn't perfect, but is a fair estimate in this case.

Additional Tools

There are a couple of additional tools that can help to confirm the structure at this point. Alternatively, if the structure remains elusive, these tools might help generate some ideas.

Chemical Formula

The First tool is the chemical formula. Once we have NMR tables, we can begin guessing at the number of carbons and hydrogens in the structure. With the addition of an IR table, we can begin to infer the presence of other atoms, such as oxygen or nitrogen.

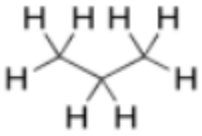
For example, in the ^{13}C NMR table above, there were seven peaks. That means there are probably at least seven carbons. We can start off the molecular formula as C_7. However, there may be additional carbons if there is some symmetry. There may also be a few carbons that do not show up very well in the spectrum. If you have ever obtained a real ^{13}C NMR spectrum, you will know that carbonyl peaks can be hard to find, especially if there are no hydrogens attached to the carbonyl. In the table above, it looked like there was benzene, so maybe there were really six carbons in the aromatic region, and not just four carbons. That would mean the formula, so far, is C_9.

In the ^{1}H NMR table, the integrals added up to 10H. So, maybe the formula is C_9H_{10}.

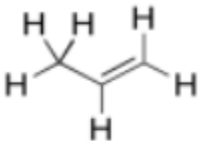
Furthermore, the IR table suggested the possible presence of two different oxygen atoms. The formula may actually be $C_9H_{10}O_2$.

Degrees of Unsaturation

Once we have a formula, one of the most important pieces is "units of unsaturation" or "degrees of unsaturation" (DU). The DU is the result of a formal comparison of the C/H ratio in the compound to that in a normal alkane. In a normal alkane, the formula is always C_nH_{2n+2}. If you picture a long hydrocarbon chain, there will be two hydrogens on each carbon along the chain, plus one more hydrogen at either end of the chain. However, an alkene contains one pi bond, and at the site of that pi bond there are two hydrogen atoms missing from that alkane formula. A simple alkene always has the formula C_nH_{2n}. That missing pair of hydrogens in the formula is called a degree of unsaturation.

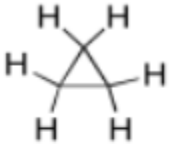


C_3H_8



C_3H_6

1 degree of unsaturation

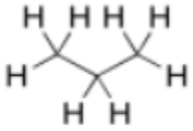


C_3H_6

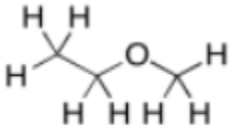
1 degree of unsaturation

The same thing also happens to the formula if there is a ring present. One DU can correspond to the presence of a double bond or a ring. If DU=2, there may be two double bonds, two rings, or one of each.

If there are oxygen atoms present in the formula, we can just ignore them and pay attention to the hydrocarbon part. Conceptually, because oxygen forms two bonds, we can think of it as squeezing in between any two atoms in a hydrocarbon structure to form a new compound. The ratio of carbon to hydrogen is unchanged. If there is a degree of unsaturation in a formula containing oxygen, it simply indicates the presence of a ring or a double bond, as in a hydrocarbon.

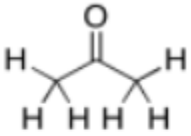


C_3H_8



C_3H_8O

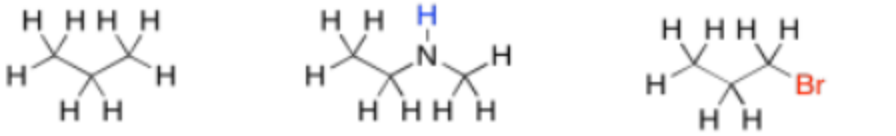
no degrees of unsaturation



C_3H_6O

1 degree of unsaturation (1 double bond)

Sometimes, if other atoms are present, we need to adjust the formula to account for them. For example, whenever a halogen is present in the structure, it conceptually replaces a hydrogen atom. In order for a halogen to be found in the structure, there would have to be one fewer hydrogen atom in order to open up a spot for the halogen. To account for the presence of a halogen, we need to add one hydrogen atom to the formula, then compare it with the standard alkane formula.



C_3H_8 C_3H_9N C_3H_7Br

subtract 1 H per N

add 1 H per halogen

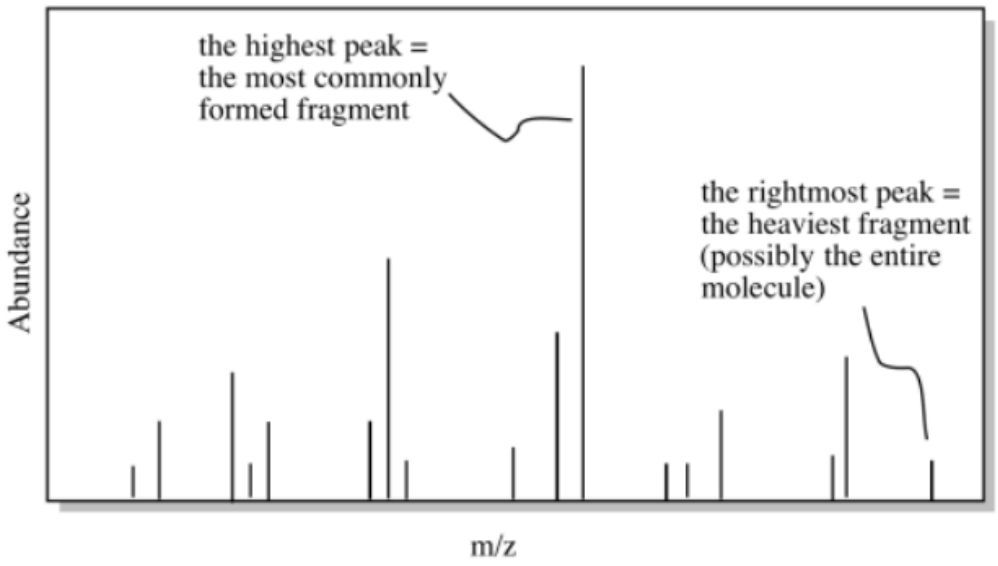
no degrees of unsaturation

no degrees of unsaturation

Nitrogen, on the other hand, has three bonds. Unlike oxygen, if we squeeze it in between two other atoms, it still needs one extra bond. It always adds an extra hydrogen atom to the formula. To account for the presence of nitrogen, we need to subtract 1 H from the formula, then compare it with the standard alkane formula.

In the formula we just calculated, we have $C_9H_{10}O_2$. We can ignore the oxygens and look at the C_9H_{10}. If this were a saturated hydrocarbon with nine carbons, its formula would be C_9H_{20} (since 2 x 9 + 2 = 20). We are missing five pairs of hydrogens, so DU = 5. That is a lot. However, if we have one benzene in the structure, that would account for three double bonds and one ring all at once. That is four degrees of unsaturation. An additional carbonyl would bring the number up to the required five. If we had not yet arrived at the idea of a benzene ring, this comparison might prompt us to consider it. Alternatively, if we knew about the benzene but hadn't yet spotted the carbonyl, we might be on the lookout for it now.

Once we have a possible formula, another useful tool is mass spectrometry (MS). Even if you don't know much about mass spectrometry, the basic idea is simple. A mass spectrometer takes a molecule and bashes it into little pieces, then measures the molecular weights of each fragment. If you are lucky when you run the experiment, some of the molecules are left intact, and you get the molecular weight of the entire molecule, too.

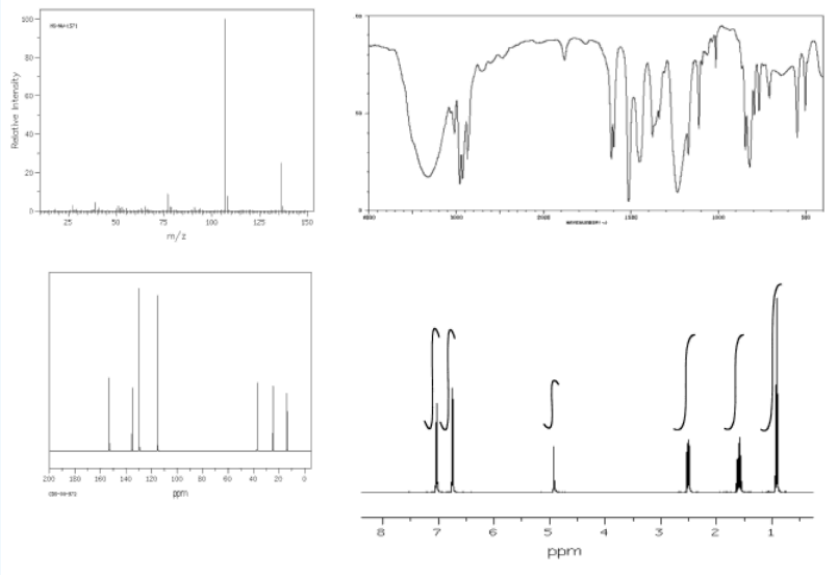


If we calculate the molecular weight using the formula and compare it with the molecular weight determined from the mass spectrum, we might confirm that we are on the right track. Alternatively, maybe our calculated molecular weight will come up short. If we are off by 16, maybe we have missed an oxygen atom somewhere. If we are off by 14, maybe we have missed a carbon and a pair of hydrogens. This information might help us to correct some mistakes.

In the example above, the formula yields a molecular weight of 150 g/mol. If the mass spectrum did not match, we would want to check our work to see if we had overlooked something.

Exercise 14.14.3

Using the approach outlined above, build a case for the structure of the compound represented by the data below.



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- 4.12: Constructing Partial Structures in NMR Spectroscopy and Combined Structure Determination by Chris Schaller is licensed CC BY-NC 3.0. Original source: https://employees.csbsju.edu/cschaller/ROBI2.htm.

14.15: Chemistry Matters—Magnetic Resonance Imaging (MRI)

As practiced by organic chemists, NMR spectroscopy is a powerful method of structure determination. A small amount of sample, typically a few milligrams or less, is dissolved in a small amount of solvent, the solution is placed in a thin glass tube, and the tube is placed into the narrow (1–2 cm) gap between the poles of a strong magnet. Imagine, though, that a much larger NMR instrument were available. Instead of a few milligrams, the sample size could be tens of kilograms; instead of a narrow gap between magnet poles, the gap could be large enough for a whole person to climb into so that an NMR spectrum of body parts could be obtained. That large instrument is exactly what's used for *magnetic resonance imaging (MRI)*, a diagnostic technique of enormous value to the medical community.

Like NMR spectroscopy, MRI takes advantage of the magnetic properties of certain nuclei, typically hydrogen, and of the signals emitted when those nuclei are stimulated by radiofrequency energy. Unlike what happens in NMR spectroscopy, though, MRI instruments use data manipulation techniques to look at the three-dimensional *location* of magnetic nuclei in the body rather than at the chemical nature of the nuclei. As noted, most MRI instruments currently look at hydrogen, present in abundance wherever there is water or fat in the body.



Figure 14.15.1 If you're a runner, you really don't want this to happen to you. The MRI of this left knee shows bone formation in the tissue in a patient with osteochondroma. (credit: "Osteochondroma MRI" by Michael R Carmont, Sian Davies, Daniel Gey van Pittius and Robin Rees/ Wikimedia Commons, CC BY 2.0)

The signals detected by MRI vary with the density of hydrogen atoms and with the nature of their surroundings, allowing identification of different types of tissue and even allowing the visualization of motion. For example, the volume of blood leaving the heart in a single stroke can be measured, and heart motion can be observed. Soft tissues that don't show up well on X-ray images can be seen clearly, allowing diagnosis of brain tumors, strokes, and other conditions. This technique is also valuable in diagnosing damage to knees or other joints and is a noninvasive alternative to surgical explorations.

Several types of atoms in addition to hydrogen can be detected by MRI, and the applications of images based on ^{31}P atoms are being explored. This approach holds great promise for studies of metabolism.

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14.A: Structure Determination - NMR Spectroscopy (Summary)

Concepts & Vocabulary

14.0: Why This Chapter?

14.1: Nuclear Magnetic Resonance Spectroscopy

14.5: Chemical Shifts in ^{1}H NMR Spectroscopy

14.6: ^{1}H NMR Signal Integration and Splitting

14.7: More Complex Spin-Spin Splitting Patterns

14.8: Uses of ^{1}H NMR Spectroscopy

14.1 Nuclear Magnetic Resonance Spectroscopy

- An applied magnetic field orients nuclei from random to aligned with or against the field. The nuclei absorb EM radiation of a frequency with energy that matches this energy gap.

14.2 Acquiring a NMR Spectrum

- Nuclei in an applied field can align with the magnetic field (+1/2) or against the magnetic field (-1/2). The difference in the energy of these two states is the resonant frequency of that atom.
- To allow comparison between NMR spectra from instruments of differing field strength, the x-axis is reported as chemical shift, rather than frequency.
- **Chemical shift** is defined as the frequency of absorbance (in Hz) divided by the resonant frequency of the instrument (in MHz), thus the units are PPM (parts per million).
- Tetramethylsilane is used as a standard reference with its **chemical shift** set to 0 PPM (since these protons are highly shielded).

14.3 The Shielding Effect

- Higher **chemical shifts** are called downfield, while lower shifts are called upfield.
- Nearby electrons shield the nuclei from the induced magnetic field, thus reducing their chemical shift. Atoms of higher electronegativity pull some of this electron density away from the nuclei, causing increased **chemical shift**. This is called **deshielding**.
- Pi electrons in a compound generate their own magnetic field that influences the shielding of nearby atoms. This is most clearly exemplified by benzene protons that are highly unshielded (chemical shifts of 6.5-8 PPM).
- Protons involved in hydrogen bonding exhibit variable chemical shifts and often do not absorb at a single frequency, leading to broader peaks

14.4 Proton Equivalence

- Equivalent protons (protons in identical electrical environments) only give 1 signal.
- To determine the number of ^{1}H NMR signals expected, symmetry of a molecule needs to be examined to find equivalent protons.
- Protons with different stereochemistry are not equivalent.
- Protons on chiral molecules that are diastereotopic (would create a diastereomer if replaced) are not equivalent.

14.5 Chemical Shifts in ^{1}H NMR Spectroscopy

- Chemical shifts of protons are shifted upfield (higher ppm) by electronegative groups attached to the same carbon (and to a

lesser effect when attached to nearby carbons).
- Aromatic protons appear between 6.5 and 8 ppm.
- Chemical shifts of O-H and N-H bonds vary with temperature and concentration.

14.5 Integration of ^{1}H NMR Absorptions - Proton Counting

- The are under a ^{1}H NMR signal is proportional to the number of hydrogens that caused the signal.

14.6 Spin-Spin Splitting in ^{1}H NMR Spectra

- ^{1}H signals are split into multiple peaks by neighboring H atoms whose spins can add to or subtract from the magnetic field.
- Spin-spin coupling yields n+1 peaks where n is the number of neighboring protons.
- Multiplets formed from spin-spin splitting follow specific symmetry based on the number of neighboring protons.
- The distance between peaks in a signal is called a coupling constant.

14.7 More Complex Spin-Spin Splitting Patterns

- ^{1}H NMR signals can overlap, making interpretation more difficult.
- Signals can distort where the peaks are not completely symmetrical in shape.
- When neighboring protons are nonequivalent, the coupling constant can be different leading to complex sets of peaks.
- Some complex multiplets can be identified, such as a doublet of doublets, but others cannot and are referred to as multiplets.

14.8 Uses of ^{1}H NMR Spectroscopy

- ^{1}H NMR can help identify components of a mixture or determine which product was formed in a reaction.

14.9: Characteristics of ^{13}C NMR Spectroscopy

14.10: DEPT ^{13}C NMR Spectroscopy

14.11: H-NMR and C-NMR of Alcohols and Phenols

14.12: Uses of ^{13}C NMR Spectroscopy

14.13: Constructing Partial Structures in NMR Spectroscopy and Combined Structure Determination

14.14: Chemistry Matters—Magnetic Resonance Imaging (MRI)

Skills to Master

- Skill 14.1 Interpretation of ^{1}H NMR Spectra.

Memorization Tasks (MT)

MT 14.1 Memorize chemical shift patterns in ^{1}H NMR. (not specific values but ranges)

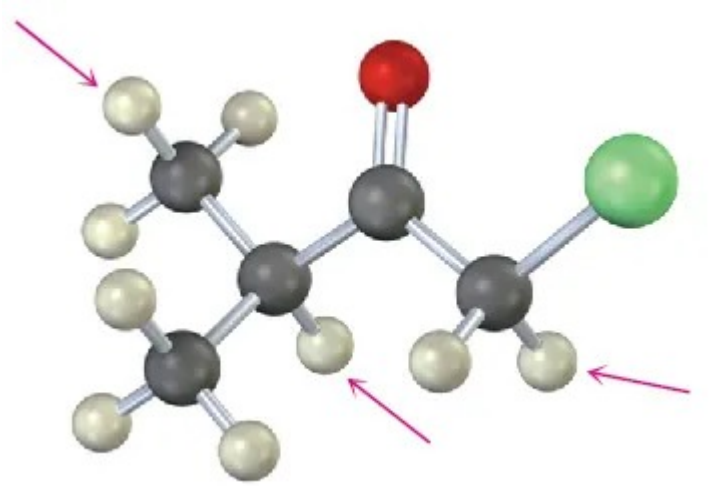
MT 14.2 Memorize spin-spin splitting patterns (N+1)

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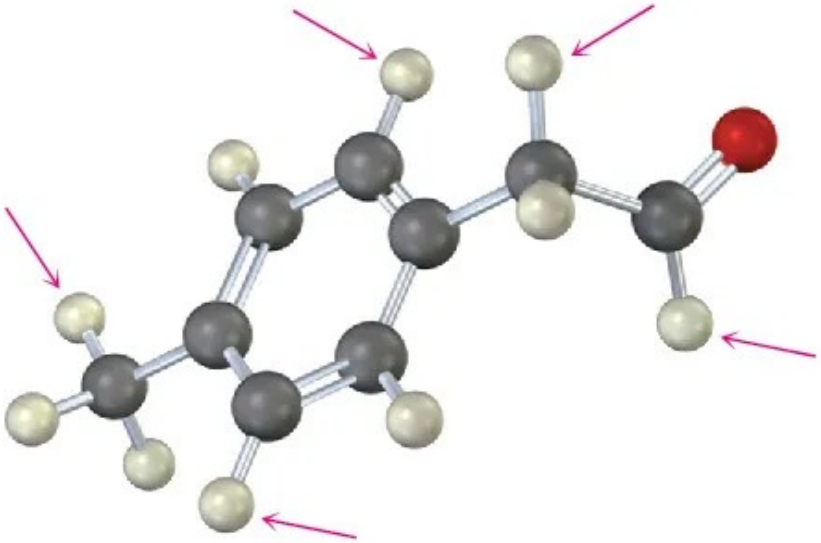
14.B: Additional Problems

Visualizing Chemistry

PROBLEM 14-24 Into how many peaks would you expect the ^{1}H NMR signals of the indicated protons to be split? (Green = Cl.)

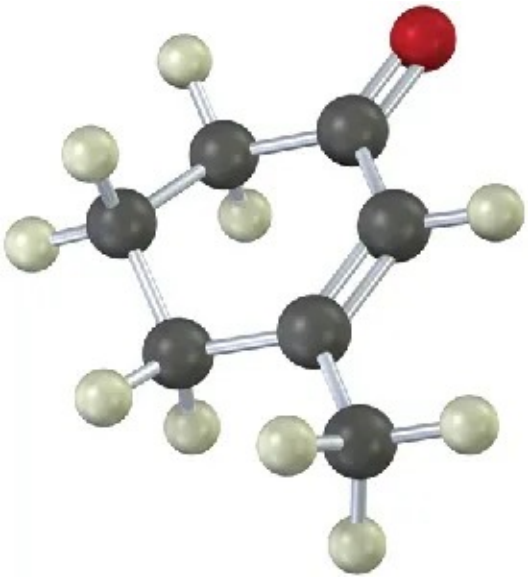


(a)

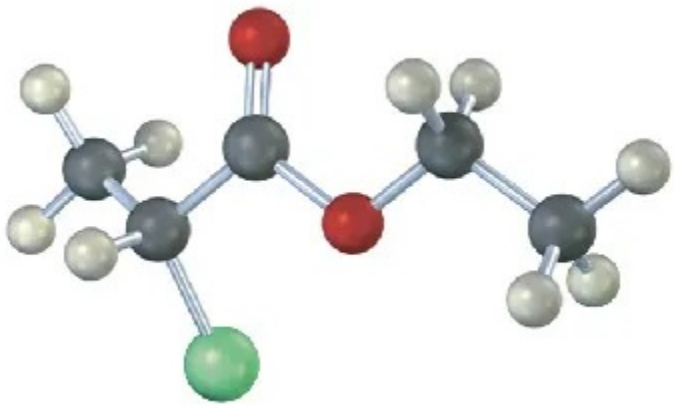


(b)

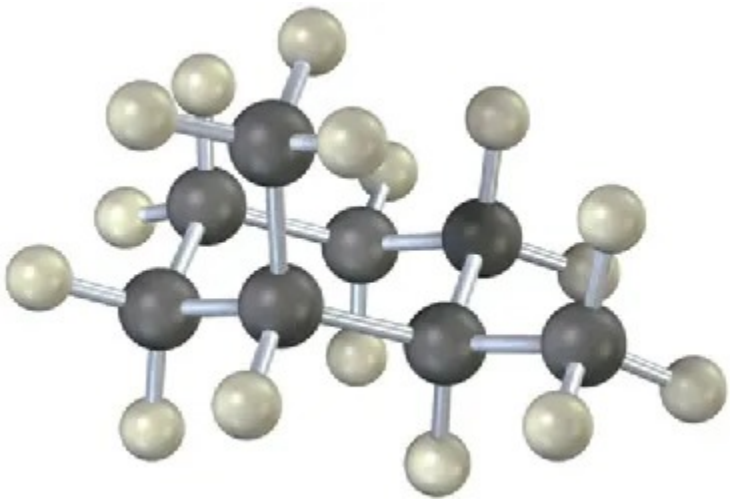
PROBLEM 14-25 How many absorptions would you expect the following compound to have in its ^{1}H and ^{13}C NMR spectra?



PROBLEM 14-26 Sketch what you might expect the ^{1}H and ^{13}C NMR spectra of the following compound to look like (green = Cl):

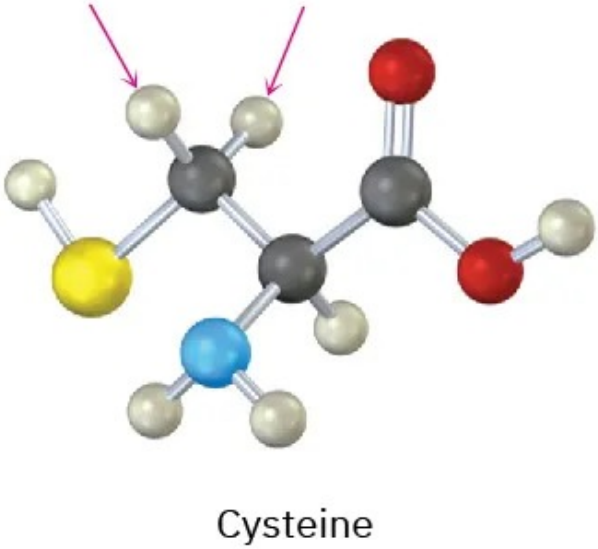


PROBLEM 14-27 How many electronically nonequivalent kinds of protons and how many kinds of carbons are present in the following compound? Don't forget that cyclohexane rings can ring-flip.

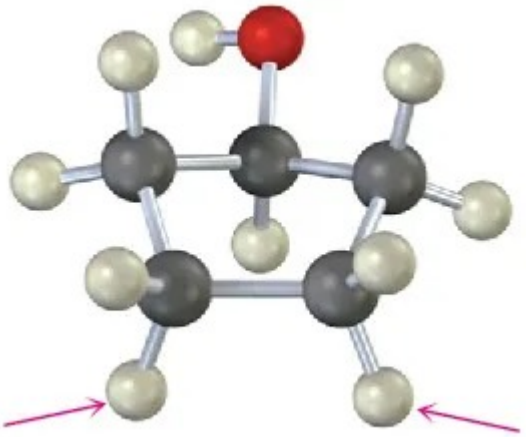


PROBLEM 14-28 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or

diastereotopic.



(a)



(b)

Chemical Shifts and NMR Spectroscopy

PROBLEM 14-29 Identify the indicated protons in the following molecules as unrelated, homotopic, enantiotopic, or diastereotopic. The following ^{1}H NMR absorptions were obtained on a 200 MHz spectrometer and are reported in hertz downfield from the TMS standard. Convert the absorptions to δ units.

(a) 436 Hz (b) 956 Hz (c) 1504 Hz

PROBLEM 14-30 The following ^{1}H NMR absorptions were obtained on a spectrometer operating at 300 MHz. Convert the chemical shifts from δ units to hertz downfield from TMS. (a) 2.1 δ (b) 3.45 δ (c) 6.30 δ (d) 7.70 δ

PROBLEM 14-31 When measured on a 200 MHz spectrometer, chloroform ($CHCl_3$) shows a single sharp absorption at 7.3 δ.

(a) How many parts per million downfield from TMS does chloroform absorb?

(b) How many hertz downfield from TMS would chloroform absorb if the measurement were carried out on a 360 MHz spectrometer?

(c) What would be the position of the chloroform absorption in δ units when measured on a 360 MHz spectrometer?

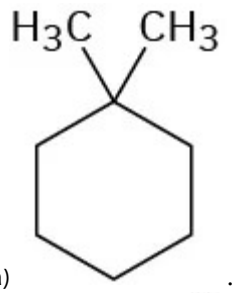
PROBLEM 14-32 Why do you suppose accidental overlap of signals is much more common in ^{1}H NMR than in ^{13}C NMR?

PROBLEM 14-33 (a) Is a nucleus that absorbs at 6.50 δ more shielded or less shielded than a nucleus that absorbs at 3.20 δ?

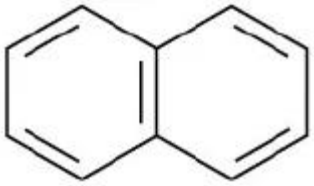
(b) Does the nucleus that absorbs at 6.50 δ require a stronger applied field or a weaker applied field to come into resonance than the one that absorbs at 3.20 δ?

^{1}H NMR Spectroscopy

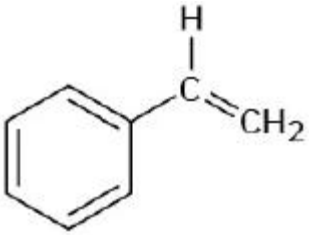
PROBLEM 14-34 How many types of nonequivalent protons are present in each of the following molecules?



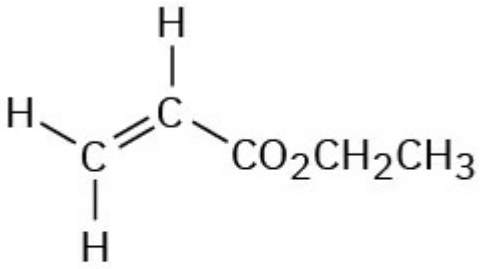
(a) . **(b)** $CH_3CH_2CH_2OCH_3$



(c) Naphthalene



(d) Styrene

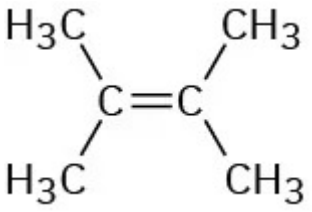


(e) Ethyl acrylate

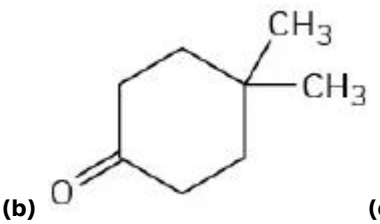
PROBLEM 14-35 The following compounds all show a single line in their ^1H NMR spectra. List them in order of expected increasing chemical shift:

CH_4, CH_2Cl_2, cyclohexane, CH_3COCH_3, $H_2C=CH_2$, benzene

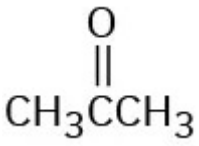
PROBLEM 14-36 How many signals would you expect each of the following molecules to have in its ^1H and ^{13}C spectra?



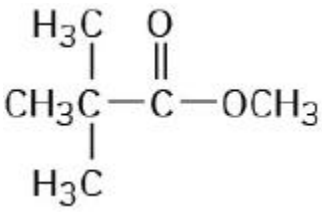
(a)



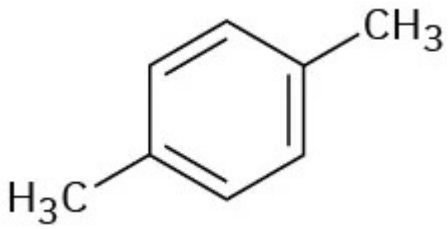
(b)



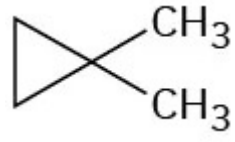
(c)



(d)



(e)



(f)

Problem 13-37 Propose structures for compounds with the following formulas that show only one peak in their ^1H NMR spectra:

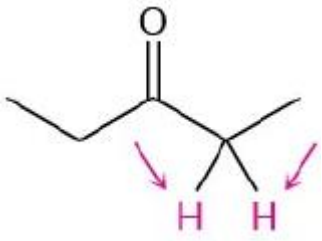
(a) C_5H_{12} **(b)** C_5H_{10} **(c)** $C_4H_8O_2$

PROBLEM 14-38 Predict the splitting pattern for each kind of hydrogen in the following molecules:

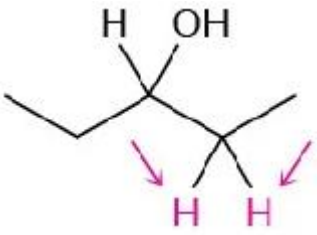
(a) $(CH_3)_3CH_3$ **(b)** $CH_3CH_2CO_2CH_3$ **(c)** *trans*-2-Butene

PROBLEM 14-39 Predict the splitting pattern for each kind of hydrogen in isopropyl propanoate, $CH_3CH_2CO_2CH(CH_3)_2$.

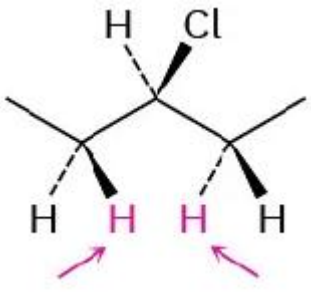
PROBLEM 14-40 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



(a)

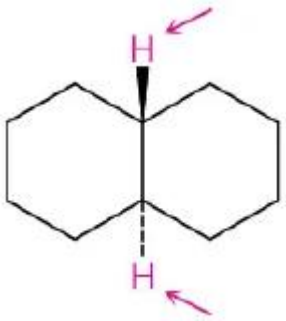


(b)

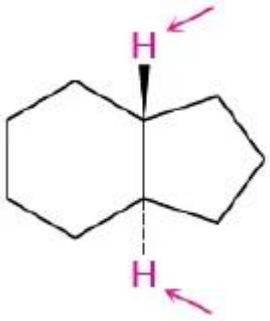


(c)

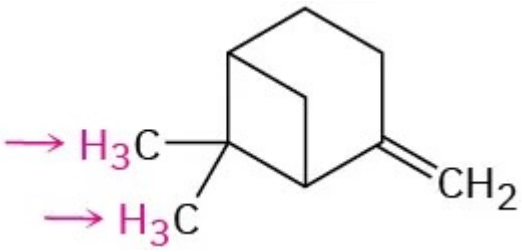
PROBLEM 14-41 Identify the indicated sets of protons as unrelated, homotopic, enantiotopic, or diastereotopic:



(a)

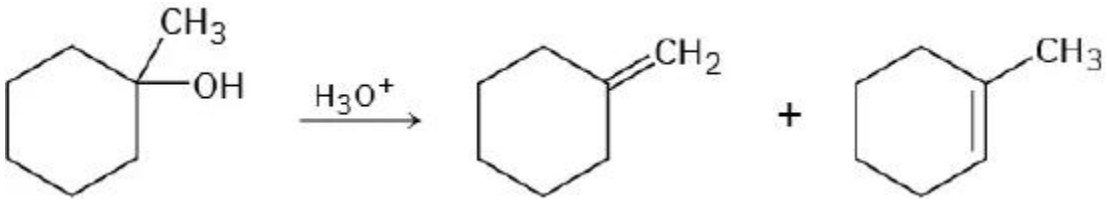


(b)



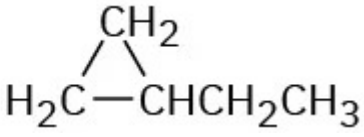
(c)

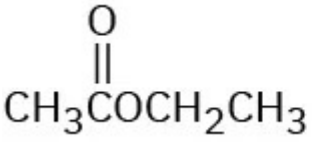
PROBLEM 14-42 The acid-catalyzed dehydration of 1-methylcyclohexanol yields a mixture of two alkenes. How could you use ^{1}H NMR to help you decide which was which?

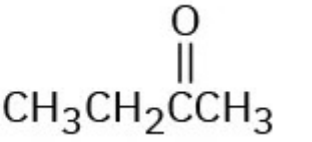


PROBLEM 14-43 ^{1}H NMR to distinguish between the following pairs of isomers?

(a) $CH_3CH{=}CHCH_2CH_3$ and $CH_3CH_2OCH_2CH_3$

(b)  and $CH_3OCH_2CH_2CH_3$

(c)  and $H_2C{=}C(CH_3)CCH_3$

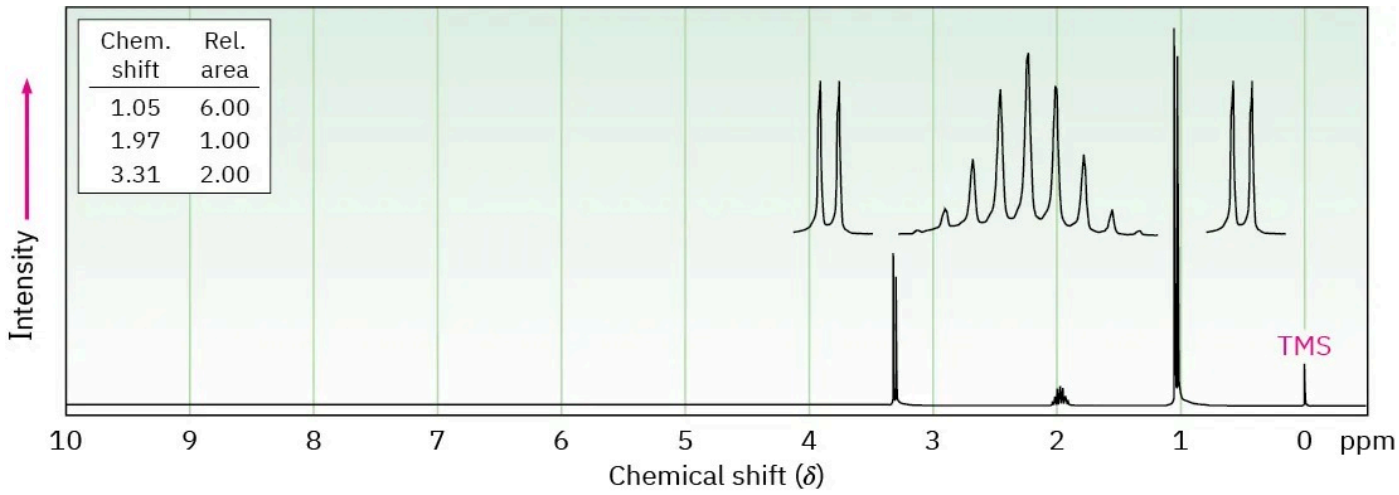
(d)  and $CH_3CH{=}CHCCH_3$

PROBLEM 14-44 Propose structures for compounds that fit the following ^{1}H NMR data:

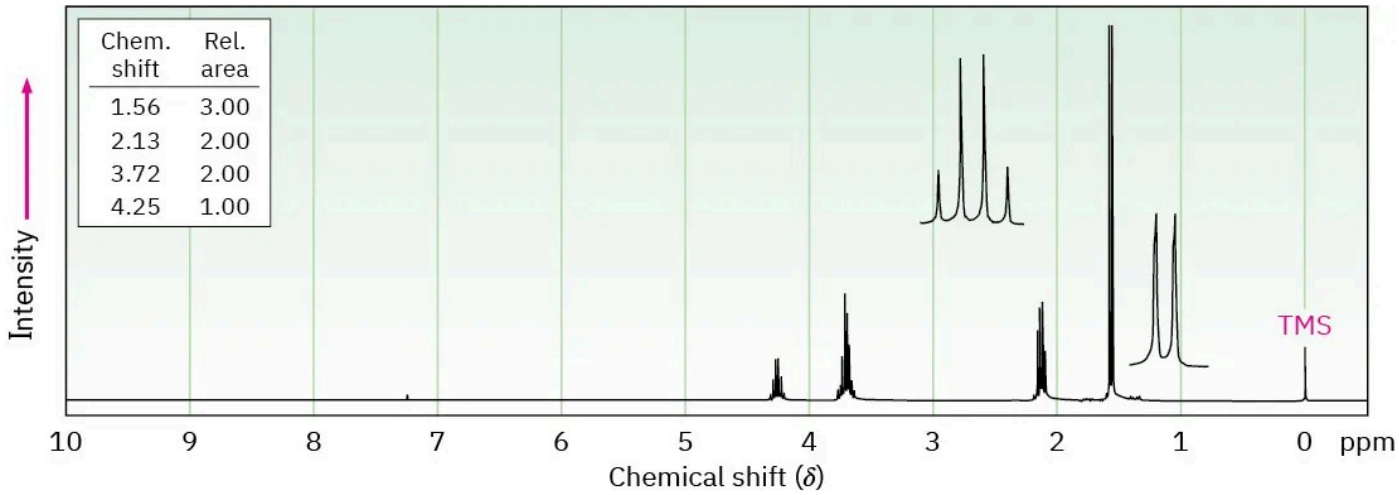
(a) $C_5H_{10}O$	**(b) C_3H_5Br**
0.95 δ (6 H, doublet, J = 7 Hz) 2.10 δ (3 H, singlet) 2.43 δ (1 H, multiplet)	2.32 δ (3 H, singlet) 2.32 δ (3 H, singlet) 2.32 δ (3 H, singlet)

PROBLEM 14-45 Propose structures for the two compounds whose ^{1}H NMR spectra are shown.

(a) C_4H_9Br



(b) $C_4H_8Cl_2$



^{13}C NMR Spectroscopy

PROBLEM 14-46 How many ^{13}C NMR absorptions would you expect for *cis*-1,3-dimethylcyclohexane? For *trans*-1,3-dimethylcyclohexane? Explain.

PROBLEM 14-47 How many absorptions would you expect to observe in the ^{13}C NMR spectra of the following compounds?

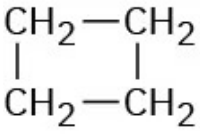
(a) 1,1-Dimethylcyclohexane _____. **(b)** $CH_3CH_2OCH_3$ _____.

(c) *tert*-Butylcyclohexane _____. **(d)** 3-Methyl-1-pentyne _____.

(e) *cis*-1,2-Dimethylcyclohexane _____. **(f)** Cyclohexanone _____.

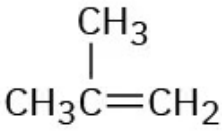
PROBLEM 14-48 Suppose you ran a DEPT-135 spectrum for each substance in Problem 47. Which carbon atoms in each molecule would show positive peaks, and which would show negative peaks?

PROBLEM 14-49 How could you use ^{1}H and ^{13}C NMR to help distinguish the following isomeric compounds of the formula C_4H_8?

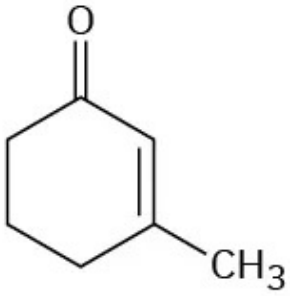


$H_2C{=}CHCH_2CH_3$

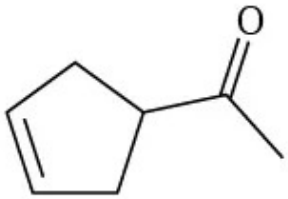
$CH_3CH{=}CHCH_3$



PROBLEM 14-50 How could you use ^{1}H NMR, ^{13}C NMR, and IR spectroscopy to help you distinguish between the following structures?

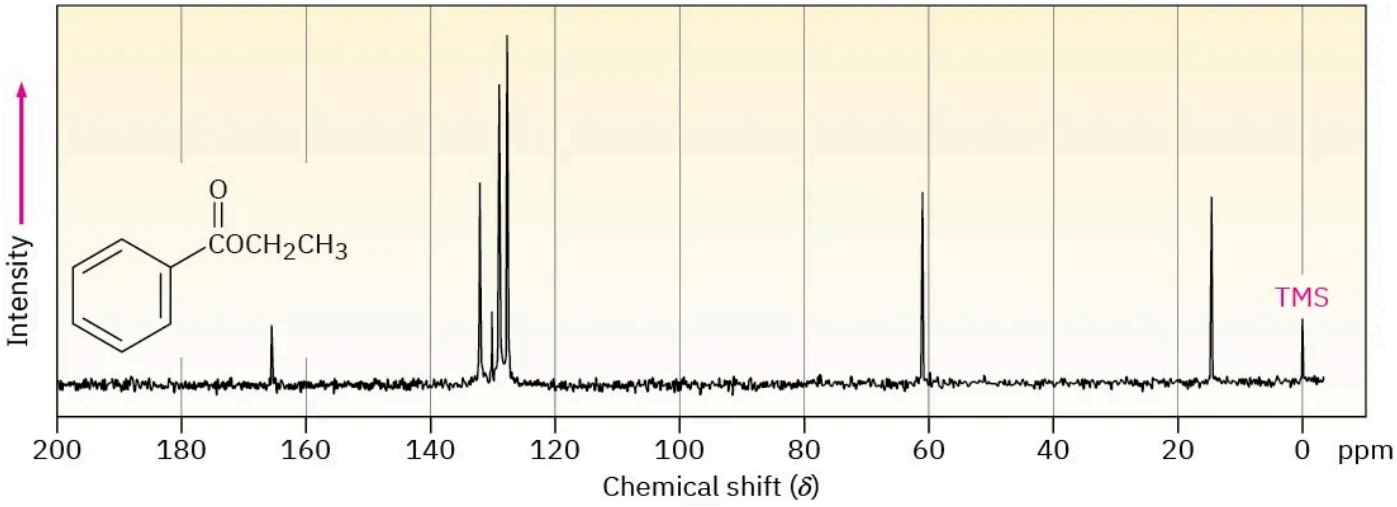


3-Methyl-2-cyclohexenone



3-Cyclopentenyl methyl ketone

PROBLEM 14-51 Assign as many resonances as you can to specific carbon atoms in the ^{13}C NMR spectrum of ethyl benzoate.



General Problems

PROBLEM 14-52 Assume that you have a compound with the formula C_3H_6O.

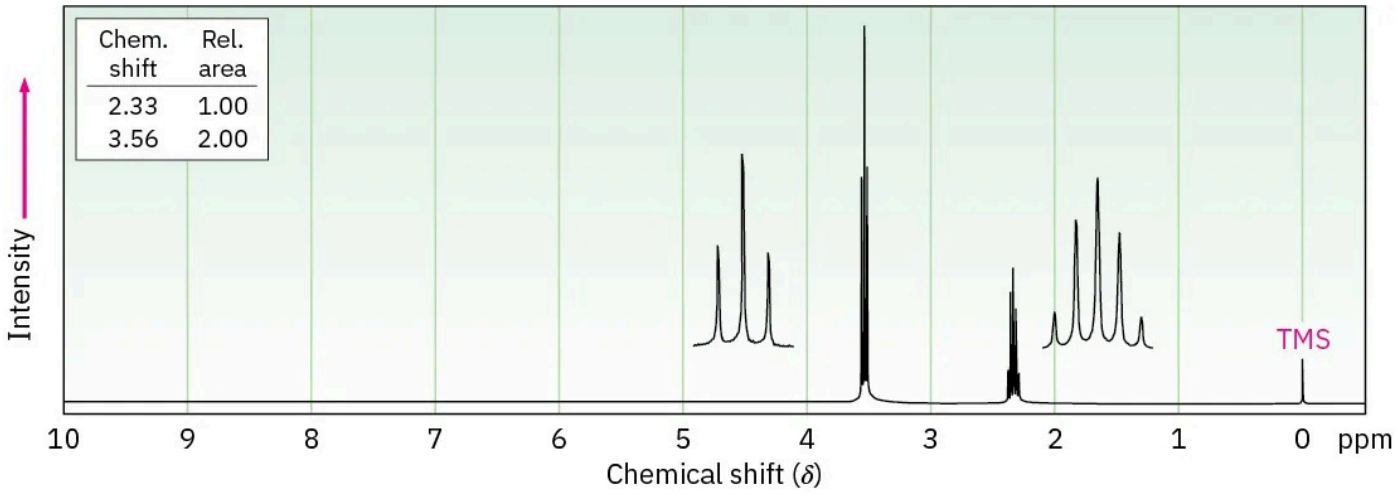
(a) How many double bonds and/or rings does your compound contain?

(b) Propose as many structures as you can that fit the molecular formula.

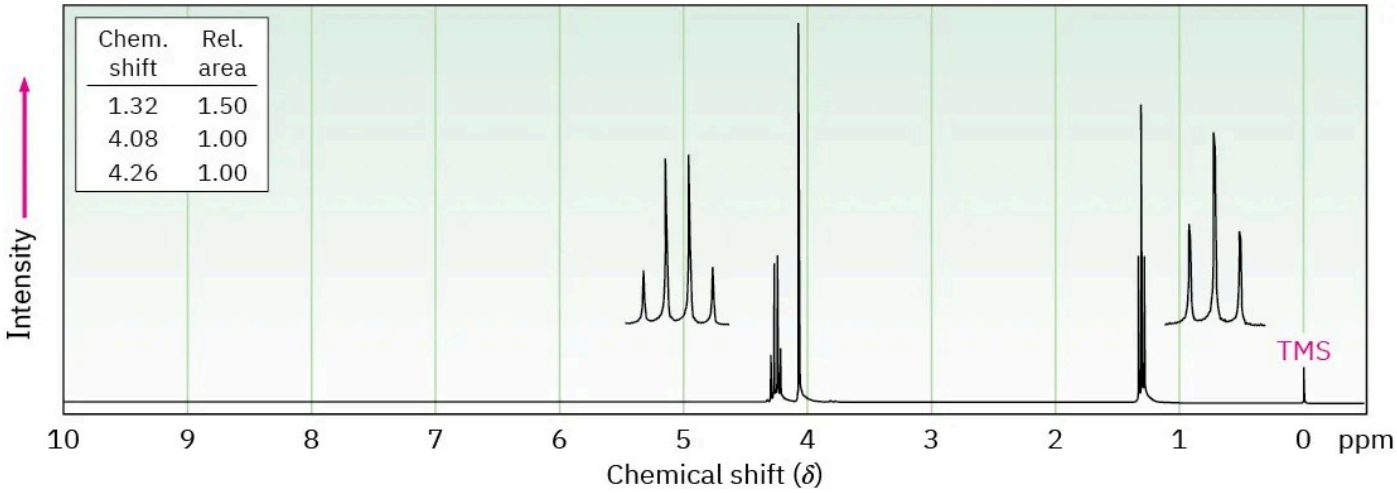
(c) If your compound shows an infrared absorption peak at 1715 cm^{-1}, what functional group does it have?

(d) If your compound shows a single ^1H NMR absorption peak at 2.1 δ, what is its structure?

PROBLEM 14-53 The compound whose ^1H NMR spectrum is shown has the molecular formula $C_3H_6Br_2$. Propose a structure.



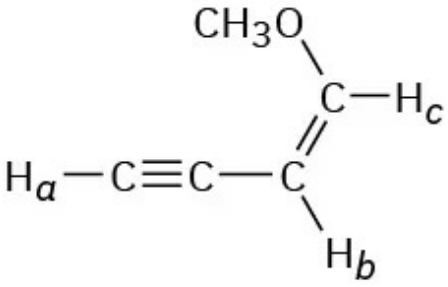
PROBLEM 14-54 The compound whose ^1H NMR spectrum is shown has the molecular formula $C_4H_7O_2Cl$ and has an infrared absorption peak at 1740 cm^{-1}. Propose a structure.



PROBLEM 14-55 Propose structures for compounds that fit the following ^1H NMR data:

(a) **$C_4H_6Cl_2$** 2.18 δ (3 H, singlet) 4.16 δ (2 H, doublet, J = 7 Hz) 5.71 δ (1 H, triplet, J = 7 Hz)	**(b) $C_{10}H_{14}$** 1.30 δ (9 H, singlet) 7.30 δ (5 H, singlet)
(c) C_4H_7BrO 2.11 δ (3 H, singlet) 3.52 δ (2 H, triplet, J = 6 Hz) 4.40 δ (2 H, triplet, J = 6 Hz)	**(d) $C_9H_{11}Br$** 2.15 δ (2 H, quintet, J = 7 Hz) 2.75 δ (2 H, triplet, J = 7 Hz) 3.38 δ (2 H, triplet, J = 7 Hz) 7.22 δ (5 H, singlet)

PROBLEM 14-56 Long-range coupling between protons more than two carbon atoms apart is sometimes observed when π bonds intervene. An example is found in 1-methoxy-1-buten-3-yne. Not only does the acetylenic proton, H_a, couple with the vinylic proton H_b, it also couples with the vinylic proton H_c, four carbon atoms away. Construct tree diagrams that account for the observed splitting patterns of H_a, H_b, and H_c. The data are:

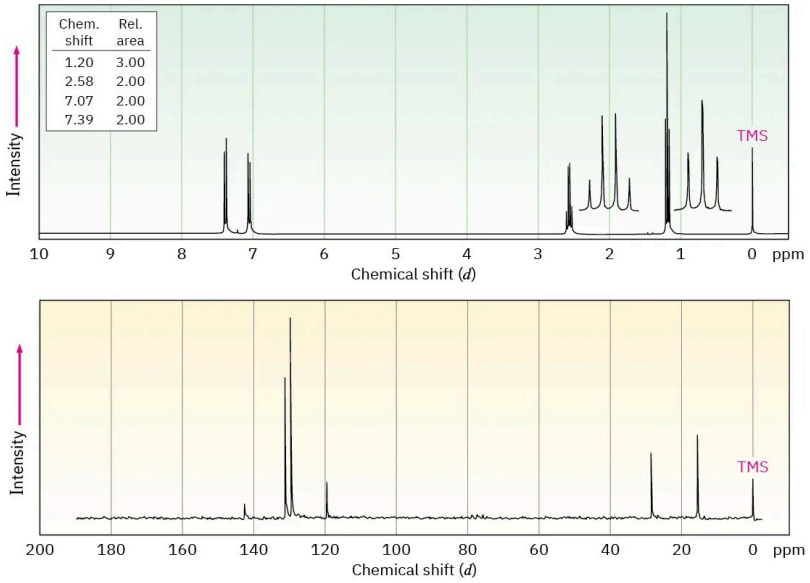


H_a (3.08 δ) H_b (4.52 δ) H_c (6.35 δ)

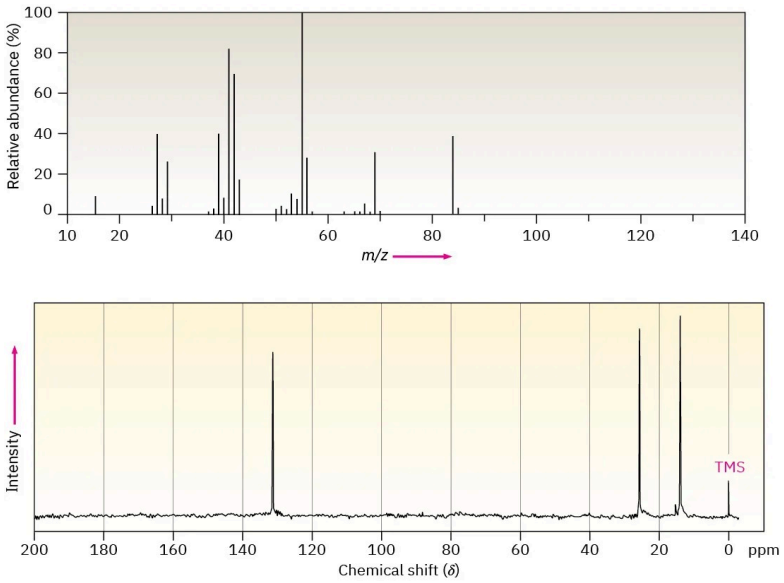
$J_{a\text{-}b}$ = 3 Hz $J_{a\text{-}c}$ = 1 Hz $J_{b\text{-}c}$ = 7 Hz

1-Methoxy-1-buten-3-yne

PROBLEM 14-57 The ^1H and ^{13}C NMR spectra of compound **A**, C_8H_9Br, are shown. Propose a structure for **A**, and assign peaks in the spectra to your structure.

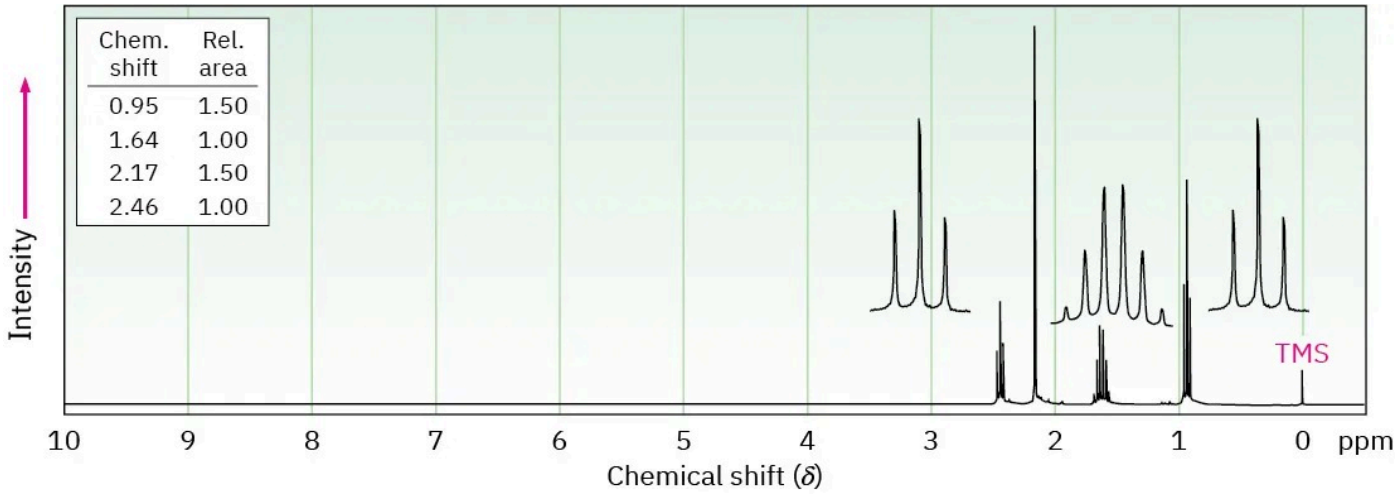


PROBLEM 14-59 The mass spectrum and ^{13}C NMR spectrum of a hydrocarbon are shown. Propose a structure for this hydrocarbon, and explain the spectral data.

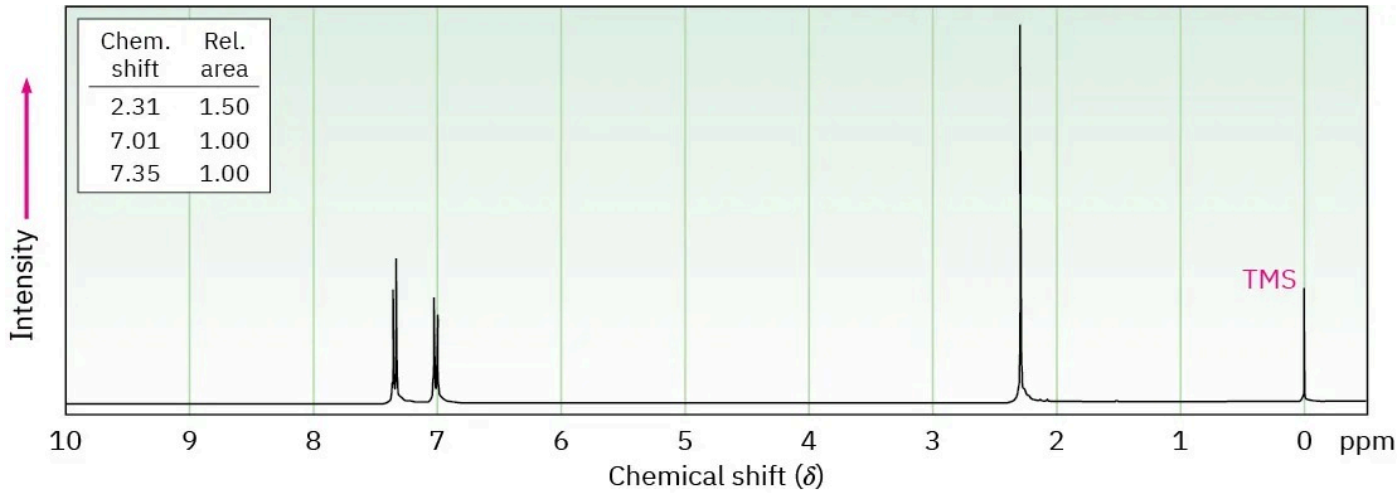


PROBLEM 14-58 Propose structures for the three compounds whose ^{1}H NMR spectra are shown.

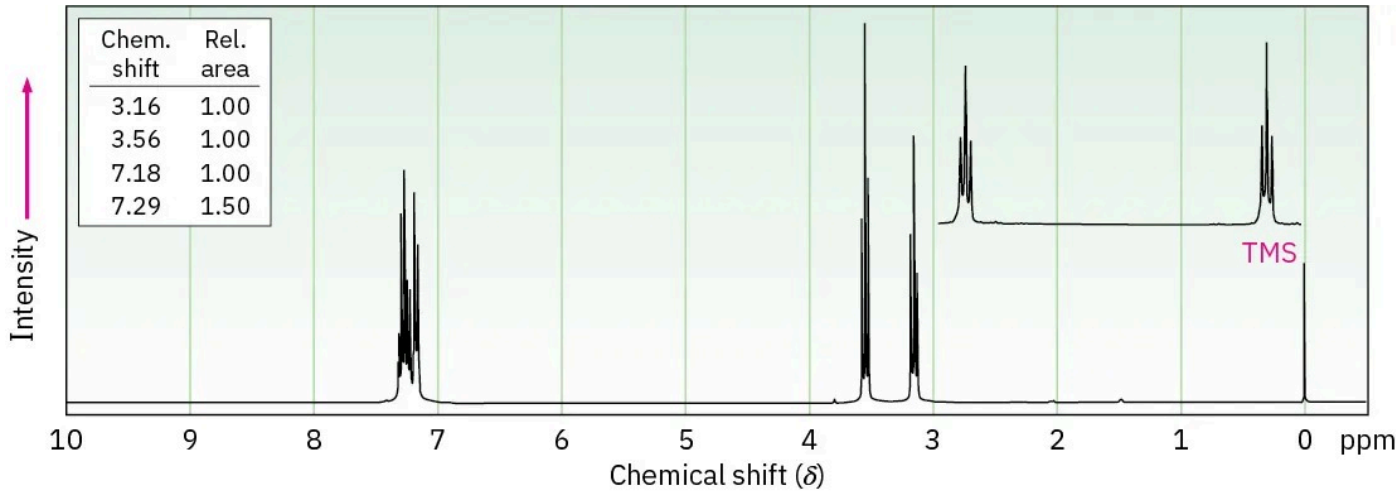
(a) $C_5H_{10}O$



(b) C_7H_7Br


Chem. shift
Rel. area
2.31
1.50
7.01
1.00
7.35
1.00
TMS
Intensity
10
9
8
7
6
5
4
3
2
1
0
ppm
Chemical shift (δ)

(c) C_8H_9Br


Chem. shift
Rel. area
3.16
1.00
3.56
1.00
7.18
1.00
7.29
1.50
TMS
Intensity
10
9
8
7
6
5
4
3
2
1
0
ppm
Chemical shift (δ)

PROBLEM 14-60 Compound **A**, a hydrocarbon with M^+ = 96 in its mass spectrum, has the following ^{13}C spectral data. On reaction with BH_3, followed by treatment with basic H_2O_2, **A** is converted into **B**, whose ^{13}C spectral data are also given. Propose structures for **A** and **B**.

Compound A

Broadband-decoupled ^{13}C NMR: 26.8, 28.7, 35.7, 106.9, 149.7 δ
DEPT-90: no peaks
DEPT-135: no positive peaks *;* negative peaks at 26.8, 28.7, 35.7, 106.9 δ

Compound B

Broadband-decoupled ^{13}C NMR: 26.1, 26.9, 29.9, 40.5, 68.2 δ
DEPT-90: 40.5 δ
DEPT-135: positive peak at 40.5 δ*;* negative peaks at 26.1, 26.9, 29.9, 68.2 δ

PROBLEM 14-61 Propose a structure for compound **C**, which has M^+= 86 in its mass spectrum, an IR absorption at 3400 cm^{-1}, and the following ^{13}C NMR spectral data:

Compound C

Broadband-decoupled ^{13}C NMR: 30.2, 31.9, 61.8, 114.7, 138.4 δ
DEPT-90: 138.4 δ
DEPT-135: positive peak at 138.4 δ; negative peaks at 30.2, 31.9, 61.8, 114.7 δ

PROBLEM 14-62 Compound **D** is isomeric with compound **C** (Problem 61) and has the following ^{13}C NMR spectral data. Propose a structure.

Compound D

Broadband-decoupled ^{13}C NMR: 9.7, 29.9, 74.4, 114.4, 141.4 δ
DEPT-90: 74.4, 141.4 δ
DEPT-135: positive peaks at 9.7, 74.4, 141.4 δ*;* negative peaks at 29.9, 114.4 δ

PROBLEM 14-63 Propose a structure for compound **E**, $C_7H_{12}O_2$, which has the following ^{13}C NMR spectral data:

Compound E

Broadband-decoupled ^{13}C NMR: 19.1, 28.0, 70.5, 129.0, 129.8, 165.8 δ
DEPT-90: 28.0, 129.8 δ
DEPT-135: positive peaks at 19.1, 28.0, 129.8 δ*;* negative peaks at 70.5, 129.0 δ

PROBLEM 14-64 Compound **F**, a hydrocarbon with M^+ = 96 in its mass spectrum, undergoes reaction with HBr to yield compound **G**. Propose structures for **F** and **G**, whose ^{13}C NMR spectral data are given below.

Compound F

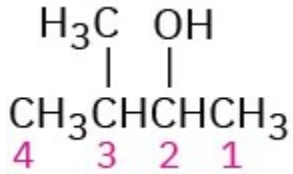
Broadband-decoupled ^{13}C NMR: 27.6, 29.3, 32.2, 132.4 δ
DEPT-90: 132.4 δ
DEPT-135: positive peak at 132.4 δ*;* negative peaks at 27.6, 29.3, 32.2 δ

Compound G

Broadband-decoupled ^{13}C NMR: 25.1, 27.7, 39.9, 56.0 δ
DEPT-90: 56.0 δ

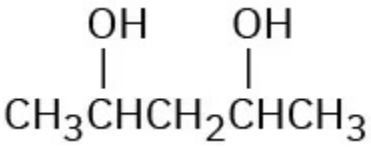
DEPT-135: positive peak at 56.0 *δ;* negative peaks at 25.1, 27.7, 39.9 *δ*

PROBLEM 14-65 3-Methyl-2-butanol has five signals in its ^{13}C NMR spectrum at 17.90, 18.15, 20.00, 35.05, and 72.75 *δ*. Why are the two methyl groups attached to C3 nonequivalent? Making a molecular model should be helpful.



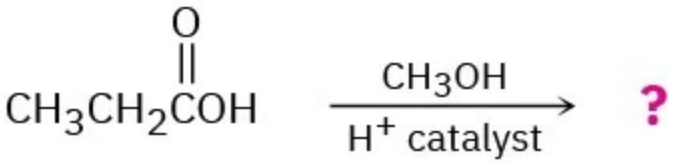
3-Methyl-2-butanol

PROBLEM 14-66 A ^{13}C NMR spectrum of commercially available 2,4-pentanediol, shows *five* peaks at 23.3, 23.9, 46.5, 64.8, and 68.1 *δ*. Explain.



2,4-Pentanediol

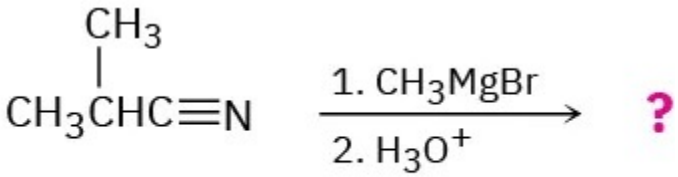
PROBLEM 14-67 Carboxylic acids (RCO_2H) react with alcohols (R′OH) in the presence of an acid catalyst. The reaction product of propanoic acid with methanol has the following spectroscopic properties. Propose a structure.



Propanoic acid

- MS: $M^+ = 88$
- IR: 1735 cm^{-1}
- ^1H NMR: 1.11 *δ* (3 H, triplet, *J* = 7 Hz); 2.32 *δ* (2 H, quartet, *J* = 7 Hz);
- 3.65 *δ* (3 H, singlet)
- ^{13}C NMR: 9.3, 27.6, 51.4, 174.6 *δ*

PROBLEM 14-68 Nitriles (RC≡N) react with Grignard reagents (R′MgBr). The reaction product from 2-methylpropanenitrile with methylmagnesium bromide has the following spectroscopic properties. Propose a structure.

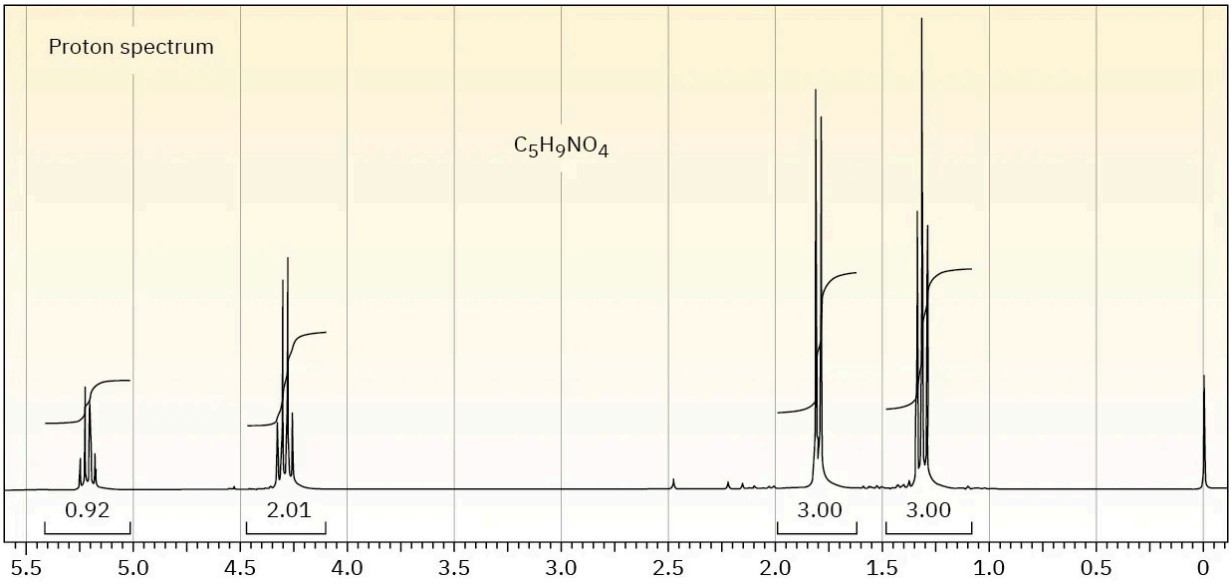


2-Methylpropanenitrile

- MS: $M^+ = 86$
- IR: 1715 cm^{-1}
- ^1H NMR: 1.05 *δ* (6 H, doublet, *J* = 7 Hz); 2.12 *δ* (3 H, singlet);
- 2.67 *δ* (1 H, septet, *J* = 7 Hz)
- ^{13}C NMR: 18.2, 27.2, 41.6, 211.2 *δ*

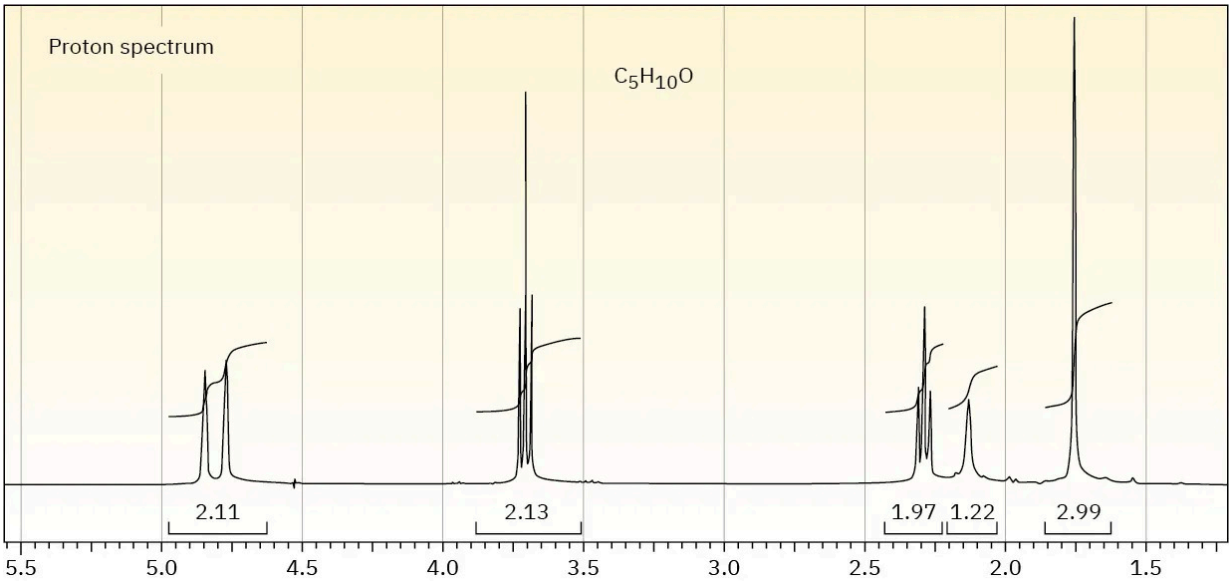
PROBLEM 14-69 The proton NMR spectrum is shown for a compound with the formula $C_5H_9NO_4$. The infrared spectrum displays strong bands at 1750 and 1562 cm^{-1} and a medium-intensity band at 1320 cm^{-1}. The normal carbon-13 and the DEPT experimental results are tabulated. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
14	Positive	No peak
16	Positive	No peak
63	Negative	No peak
83	Positive	Positive
165	No peak	No peak



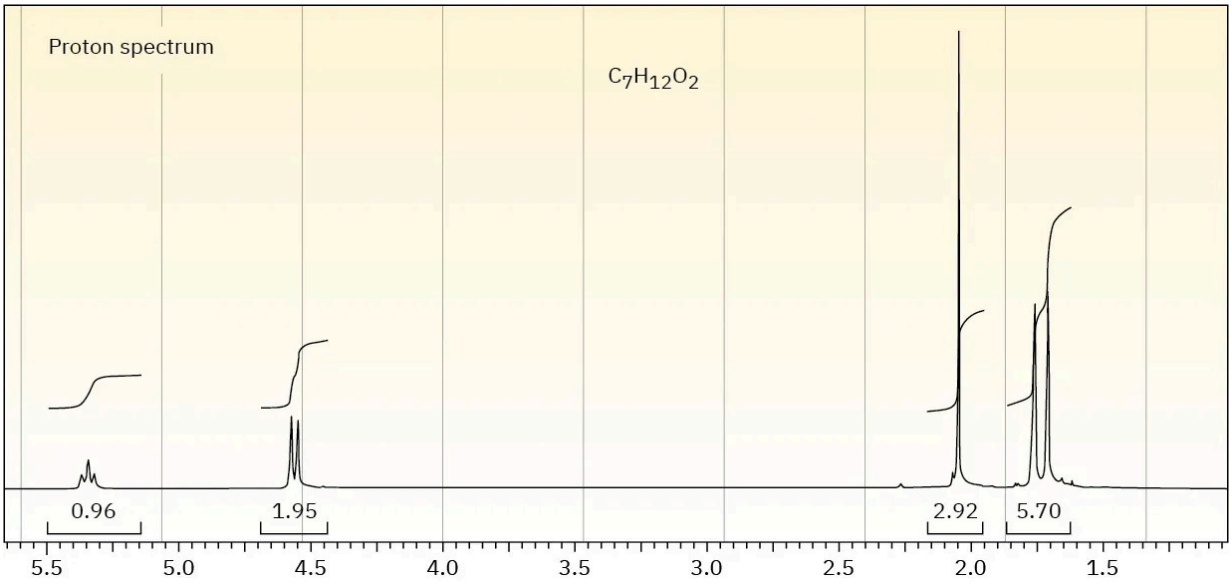
PROBLEM 14-70 The proton NMR spectrum of a compound with the formula $C_5H_{10}O$ is shown. The normal carbon-13 and the DEPT experimental results are tabulated. The infrared spectrum shows a broad peak at about 3340 cm^{-1} and a medium-sized peak at about 1651 cm^{-1}. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
22.2	Positive	No peak
40.9	Negative	No peak
60.2	Negative	No peak
112.5	Negative	No peak
142.3	No peak	No peak



PROBLEM 14-71 The proton NMR spectrum of a compound with the formula $C_7H_{12}O_2$ is shown. The infrared spectrum displays a strong band at 1738 cm^{-1} and a weak band at 1689 cm^{-1}. The normal carbon-13 and the DEPT experimental results are tabulated. Draw the structure of this compound.

Normal Carbon (ppm)	DEPT-135	DEPT-90
18	Positive	No peak
21	Positive	No peak
26	Positive	No peak
61	Negative	No peak
119	Positive	Positive
139	No peak	No peak
171	No peak	No peak



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acid strength
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GLOSSARY

S

Sample Word 1 | Sample Definition 1

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