CHEMISTRY, ORGANIC I



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Chemistry, Organic I

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CHAPTER OVERVIEW

1: Structure and Bonding

Chapter Objectives

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

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

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1.1: 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.

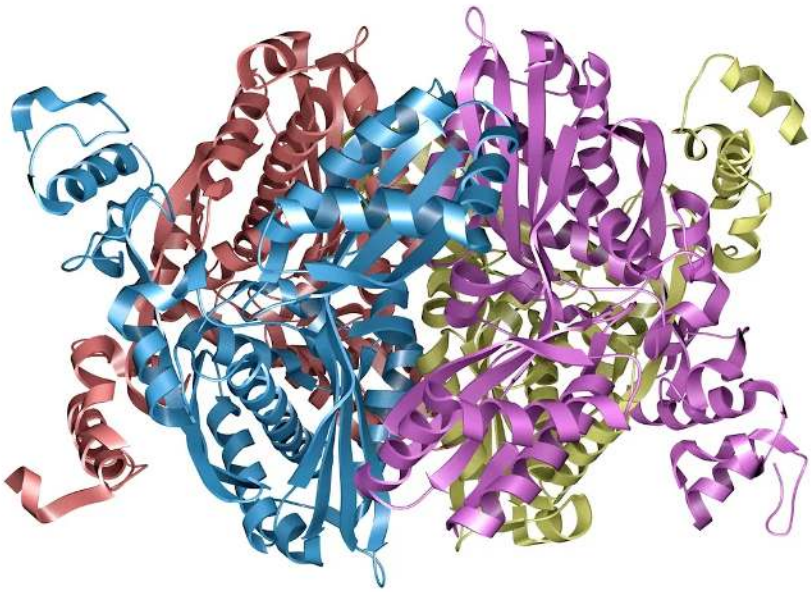
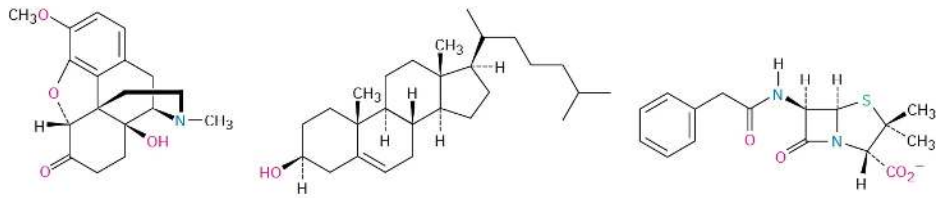


Figure 1.1.1: The enzyme HMG–CoA reductase, shown here as a so-called ribbon model, catalyzes a crucial step in the body's synthesis of cholesterol. Understanding how this enzyme functions has led to the development of drugs credited with saving millions of lives. (credit: image from the RCSB PDB (rcsb.org) 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.



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 1.1.2). 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.

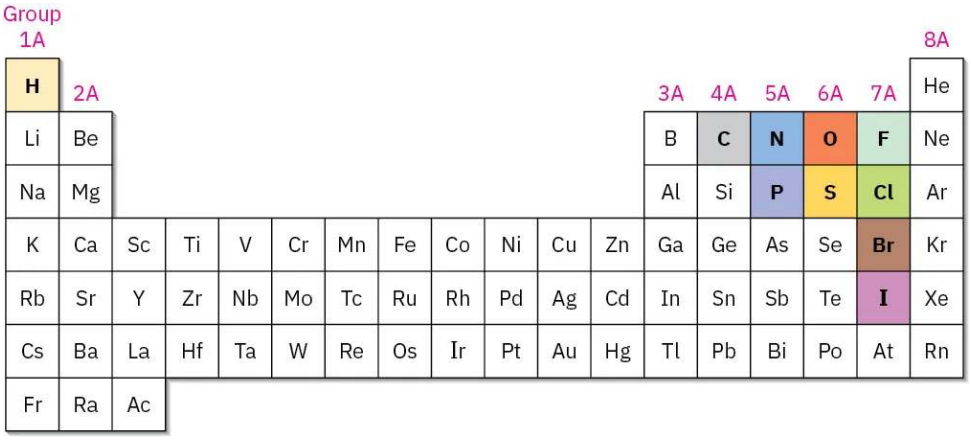


Figure 1.1.2: Carbon, hydrogen, and other elements commonly found in organic compounds are shown in the colors typically used to represent them.

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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1.2: 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 1.2.1). 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.

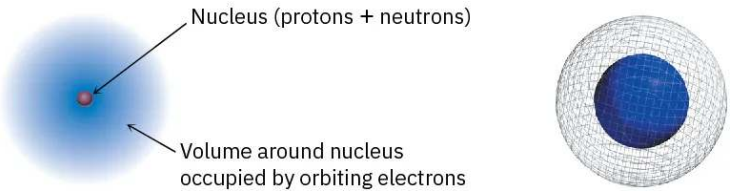


Figure 1.2.1: A schematic view of an atom. The dense, positively charged nucleus contains most of the atom's mass and is surrounded by negatively charged electrons. The three-dimensional view on the right shows calculated electron-density surfaces. Electron density increases steadily toward the nucleus 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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1.3: 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 1.3.1. The fifth *d* orbital is shaped like an elongated dumbbell with a doughnut around its middle.

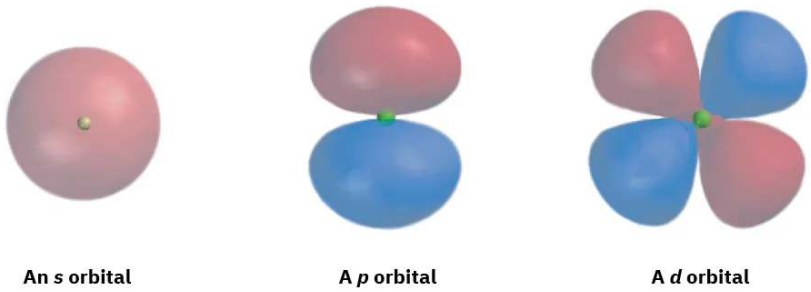


Figure 1.3.1: Representations of *s*, *p*, and *d* orbitals. An *s* orbital is spherical, a *p* orbital is dumbbell-shaped, and four of the five *d* orbitals are cloverleaf-shaped. Different lobes of p orbitals are often drawn for convenience as teardrops, but their actual shape is more like that of 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 1.3.2.

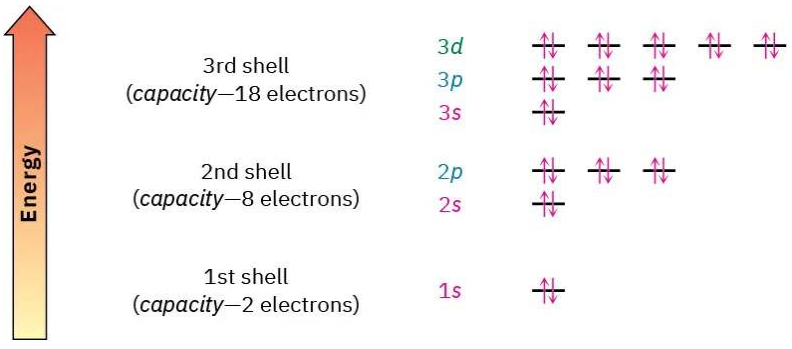


Figure 1.3.2: Energy levels of electrons in an atom. The first shell holds a maximum of 2 electrons in one **1*s***

orbital; the second shell holds a maximum of 8 electrons in one **2*s*** and three **2*p*** orbitals; the third shell holds a maximum of 18 electrons in one **3*s***, three **3*p***, and **3*d*** 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 **4*s*** orbital falls between **3*p*** and **3*d***.

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 1.3.3, 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 1.3.1 and Figure 1.3.3. 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.

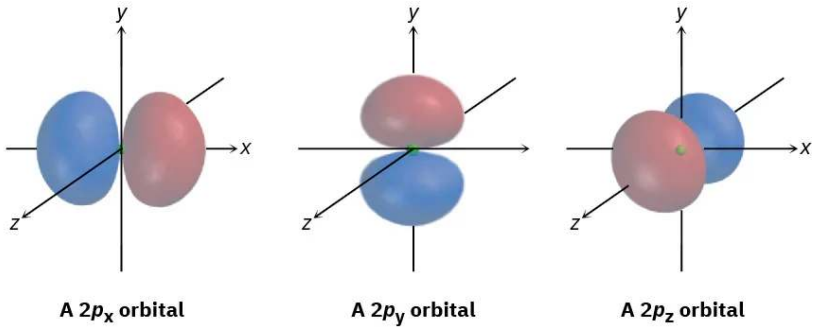


Figure 1.3.3: Shapes of the 2*p* orbitals. Each of the three mutually perpendicular, dumbbell-shaped orbitals has two lobes separated by a node. The two lobes have different algebraic signs in the corresponding wave function, as indicated by the different colors.

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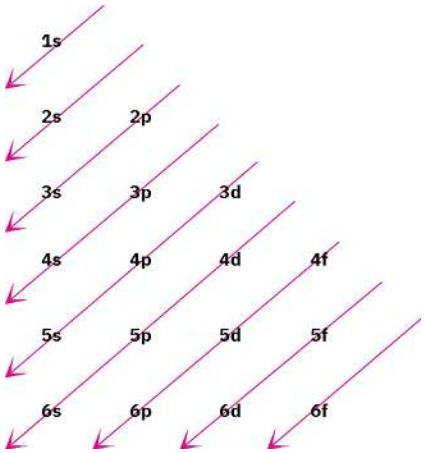
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1.4: Atomic Structure - Electron Configurations

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 4*s* orbital lies between the 3*p* and 3*d* orbitals in energy.



RULE 2

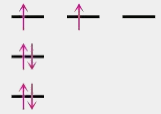
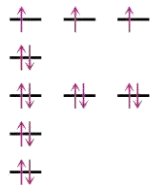
Electrons act in some ways as if they were spinning around an axis, somewhat as the earth spins. This spin can have two orientations, denoted as up (↑) and down (↓). Only two electrons can occupy an orbital, and they must have opposite spins, a statement called the *Pauli exclusion principle*.

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 1.4.1. Hydrogen, for instance, has only one electron, which must occupy the lowest-energy orbital. Thus, hydrogen has a 1*s* 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 1.4.1: Ground-State Electron Configurations of Some Elements

Element	Atomic number	Configuration
Hydrogen	1	
Carbon	6	
Phosphorus	15	

Exercise 1.4.1

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

a. Oxygen
b. Nitrogen
c. Sulfur

Answer

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 1.4.2

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

a. Magnesium
b. Cobalt
c. Selenium

Answer

a. 2
b. 2
c. 6

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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.

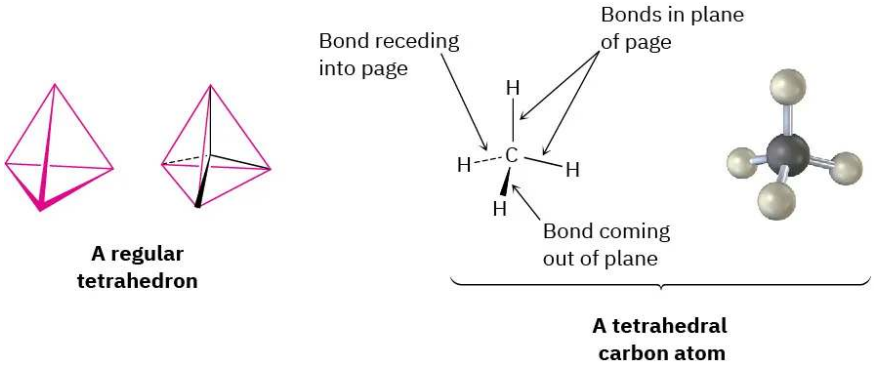


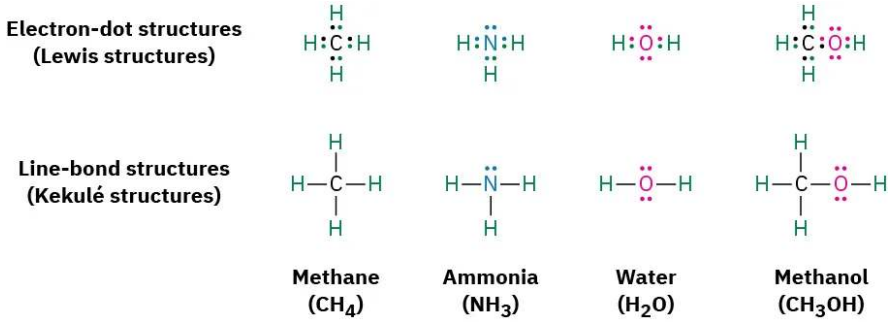
Figure 1.5.1: A representation of van’t Hoff’s tetrahedral carbon atom. The solid lines represent bonds in the plane of the paper, the heavy wedged line represents a bond coming out of the plane of the page toward the viewer, and the dashed line represents a bond going back behind the plane of the page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

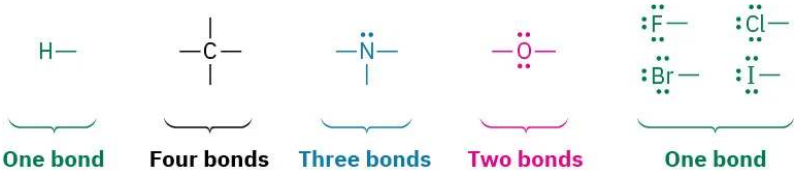
We know through observation that eight electrons (an electron *octet*) in an atom’s outermost shell, or valence shell, impart special stability to the noble-gas elements in group 8A of the periodic table: Ne (2 + *8*); Ar (2 + 8 + *8*); Kr (2 + 8 + 18 + *8*). We also know that the chemistry of the main-group 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.

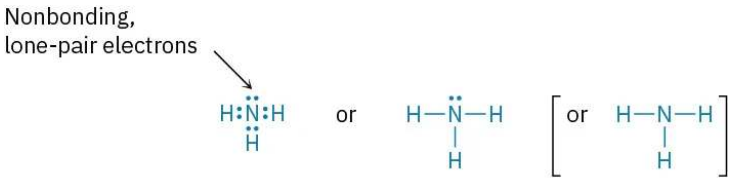
A simple way of indicating the covalent bonds in molecules is to use what are called Lewis structures, or electron-dot structures, in which the valence-shell electrons of an atom are represented as dots. Thus, hydrogen has one dot representing its 1*s* electron, carbon has four dots ($2s^2\ 2p^2$), oxygen 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 (1*s*) 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.



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_3?

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

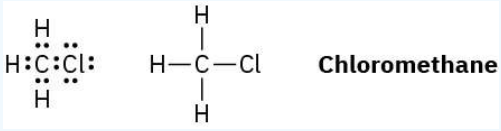
Draw both electron-dot and line-bond structures for chloromethane, CH_3Cl.

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

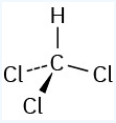


Chloromethane

Exercise 1.5.1

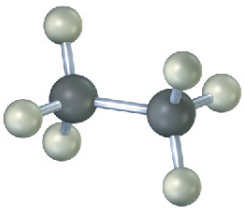
Draw a molecule of chloroform, $CHCl_3$, using solid, wedged, and dashed lines to show its tetrahedral geometry.

Answer



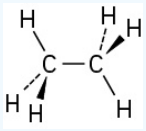
Exercise 1.5.2

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).



Ethane

Answer



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

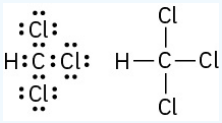
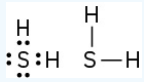
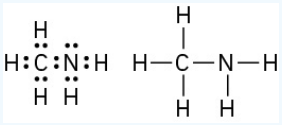
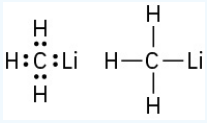
(a) CCl_4 (b) AlH_3 (c) CH_2Cl_2 (d) SiF_4 (e) CH_3NH_2

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

a. 
b. 
c. 
d. 

Exercise 1.5.5

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

Answer

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

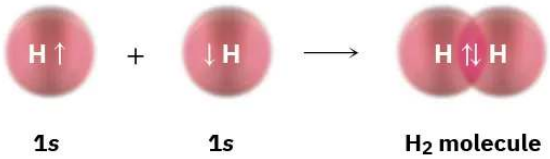
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1.6: Describing Chemical Bonds - Valence Bond Theory

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 1*s* 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 1.6.1. 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.

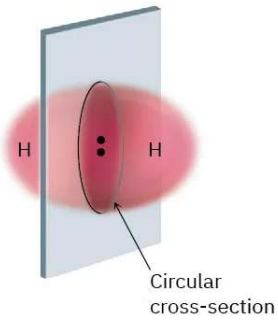


Figure 1.6.1: The cylindrical symmetry of the H–H σ bond in an H_2 molecule. The intersection of a plane cutting through the σ bond is a circle.

During the bond-forming reaction $2H\cdot \longrightarrow H2$, 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 1.6.2). 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.

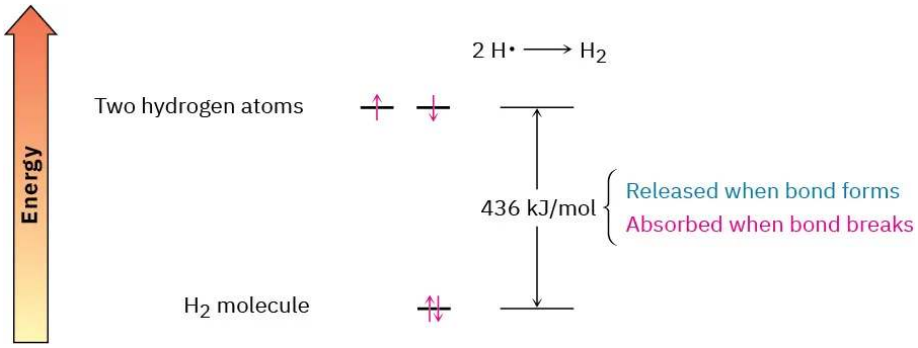


Figure 1.6.2: Relative energy levels of two H atoms and the H_2 molecule. The H_2 molecule has 436 kJ/mol (104 kcal/mol) less energy than the two separate H atoms, so 436 kJ/mol of energy is **released when the H–H bond forms**. Conversely, 436 kJ/mol is **absorbed when the H–H bond breaks**.

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 1.6.3). 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.

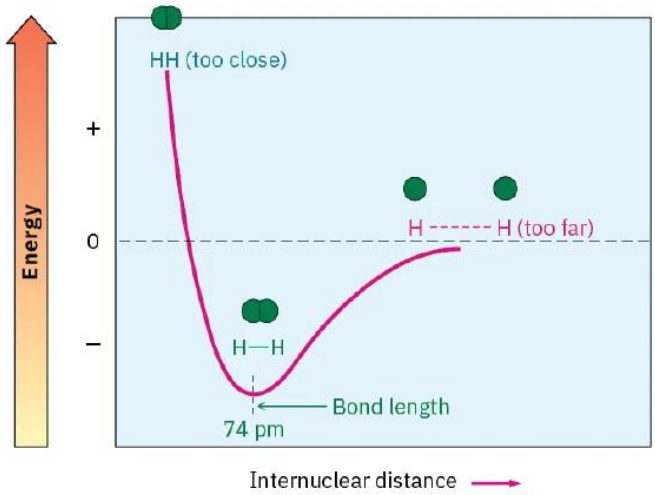


Figure 1.6.3: A plot of energy versus internuclear distance for two hydrogen atoms. The distance between nuclei at the minimum energy point is the **bond length.**

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1.7: 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 1.7.1, 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.

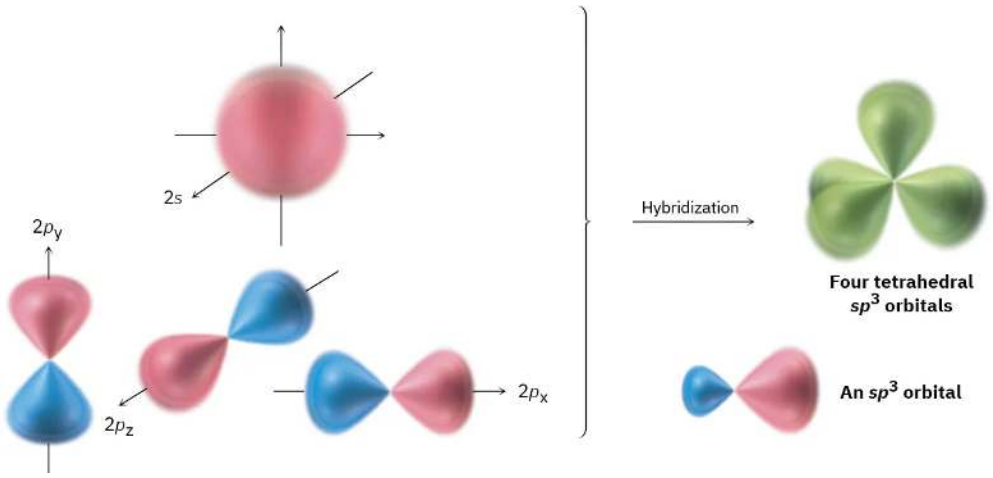


Figure 1.7.1: Four sp^3 hybrid orbitals , oriented toward the corners of a regular tetrahedron, are formed by the combination of an *s* orbital and three *p* orbitals (red/blue). The sp^3 hybrids have two lobes and are unsymmetrical about the nucleus, giving them a directionality and allowing them to 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 1*s* 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 1.7.2.

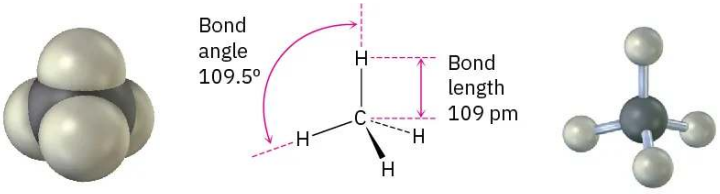


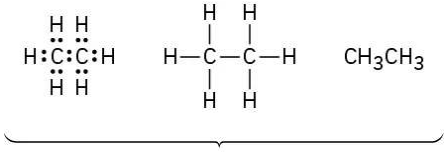
Figure 1.7.2: The structure of methane, showing its 109.5° bond angles.

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1.8: sp³ 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.



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 1.8.1). The remaining three sp^3 hybrid orbitals on each carbon overlap with the 1*s* 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°.

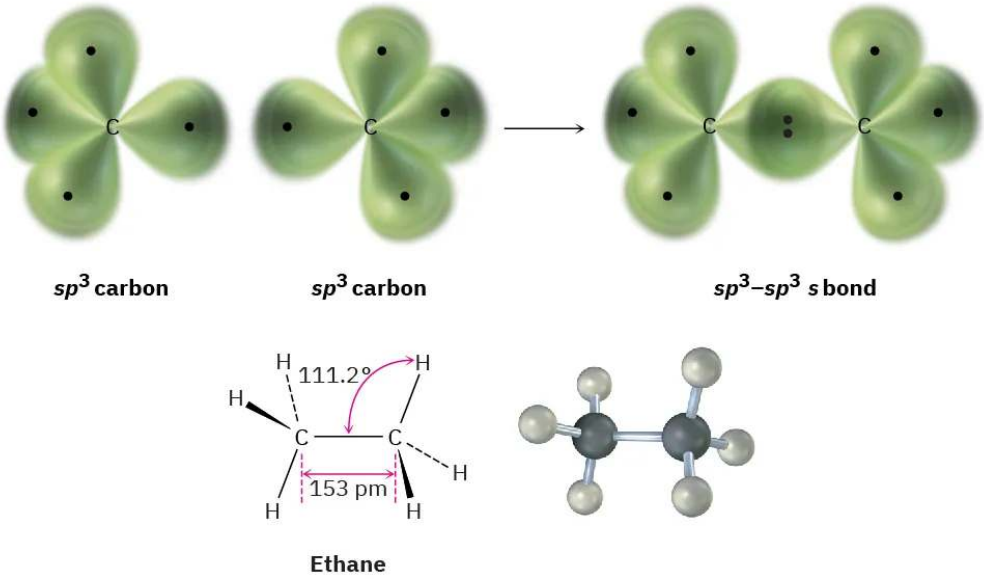
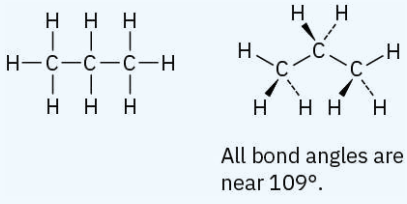


Figure 1.8.1: The structure of ethane. The carbon–carbon bond is formed by σ overlap of two ***sp*³ hybrid orbitals**. For clarity, the smaller lobes of the sp^3 hybrid orbitals are not shown.

? Exercise 1.8.1

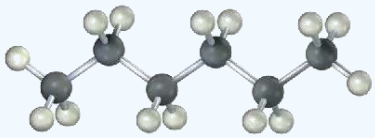
Draw a line-bond structure for propane, $CH_3CH_2CH_3$. Predict the value of each bond angle, and indicate the overall shape of the molecule.

Answer



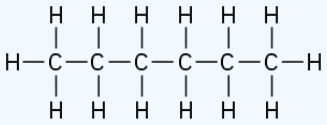
Exercise 1.8.2

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



Hexane

Answer



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1.9: sp² 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 1.9.1.

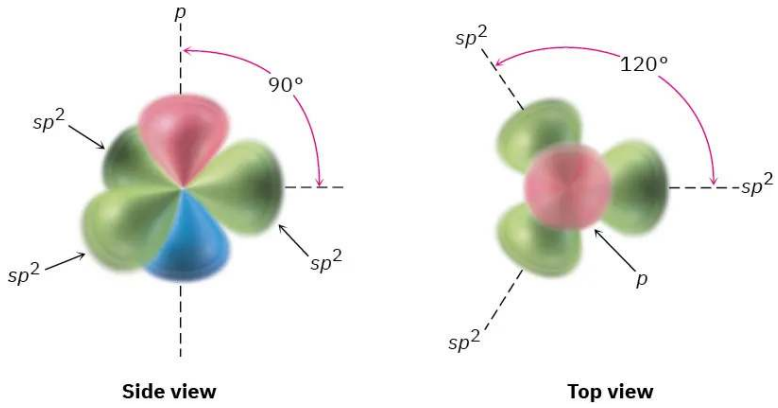


Figure 1.9.1: sp^2 Hybridization. The three equivalent ***sp*² hybrid orbitals** lie in a plane at angles of 120° to one another, and a single unhybridized ***p* orbital (red/blue)** is perpendicular to the sp^2 plane.

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 1.9.2). 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.

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).

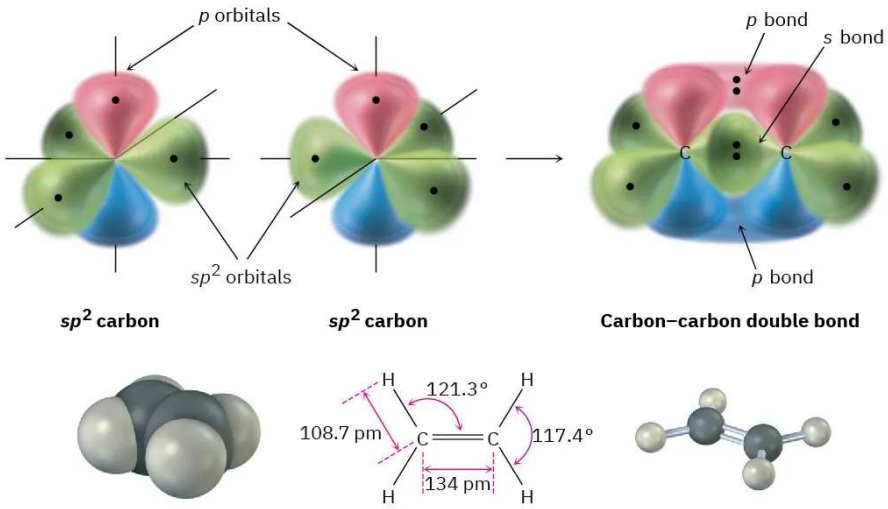


Figure 1.9.2: The structure of ethylene. One part of the double bond in ethylene results from σ (head-on) overlap of ***sp*^{2} hybrid orbitals** , and the other part results from π (sideways) overlap of unhybridized ***p* orbitals (red/blue)**. The π bond has regions of electron density above and below a line drawn between nuclei.

As you might expect, 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 1.9.1: Drawing Electron-Dot and Line-Bond Structures

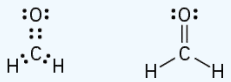
Commonly used in biology as a tissue preservative, formaldehyde, CH_2O, contains a carbon–*oxygen* double bond. Draw electron-dot and line-bond structures of formaldehyde, and indicate the hybridization of the carbon orbitals.

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**

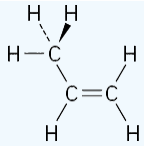
Like the carbon atoms in ethylene, the carbon atom in formaldehyde is in a double bond and its orbitals are therefore *sp*^{2}-hybridized.

? Exercise 1.9.1

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

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°.

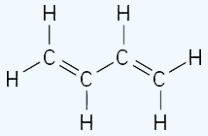


Exercise 1.9.2

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.

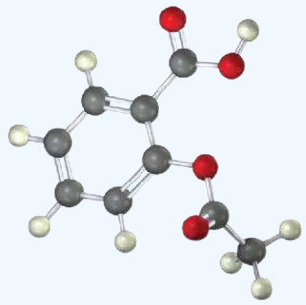
Answer

All carbons are sp^2, and all bond angles are near 120°.



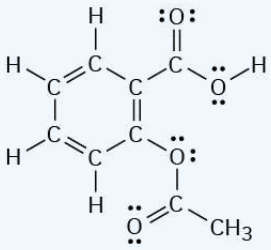
Exercise 1.9.3

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

All carbons except CH_3 are sp^2.



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1.10: 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 1.10.1.

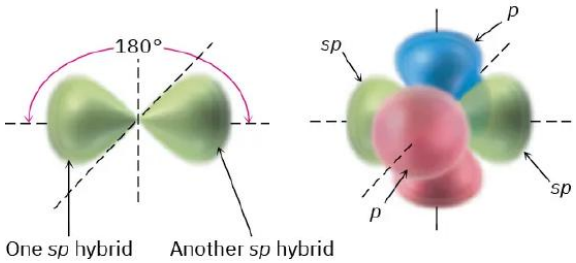


Figure 1.10.1: *sp* Hybridization. The two ***sp* hybrid orbitals** are oriented 180° away from each other, perpendicular to the two remaining ***p* orbitals (red/blue)**.

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 1.10.2).

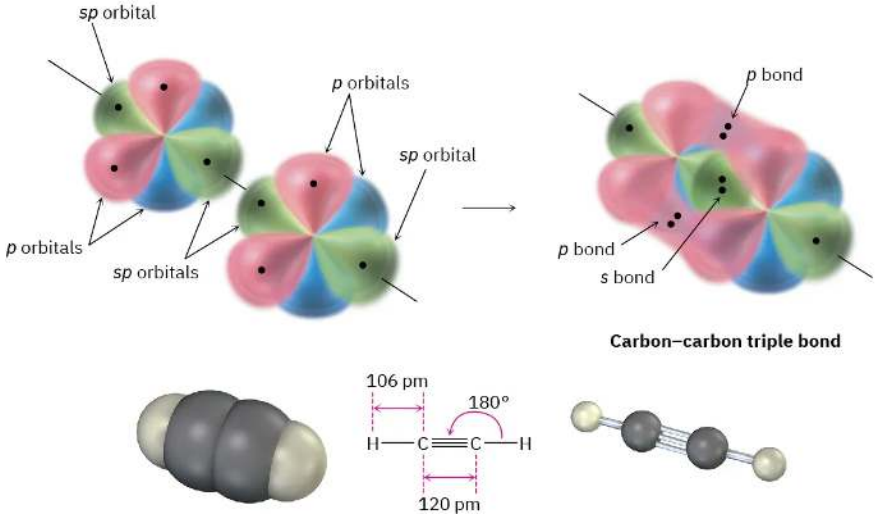


Figure 1.10.2: The structure of acetylene. The two carbon atoms are joined by one *sp*–*sp* σ bond and two *p*–*p* π bonds.

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 1.10.1.

Table 1.10.1 Comparison of C−C and C−H Bonds in Methane, Ethane, Ethylene, and Acetylene

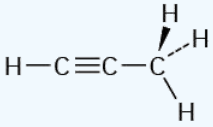
Molecule	Bond	Bond strength		Bond length (pm)
		(kJ/mol)	(kcal/mol)	
Methane, CH_4	$(sp^3)\,C-H$	439	105	109
Ethane, CH_3CH_3	$(sp^3)\,C-C\,(sp^3)$	377	90	153
	$(sp^3)\,C-H$	421	101	109
Ethylene, $H_2C=CH_2$	$(sp^2)\,C=C\,(sp^2)$	728	174	134
	$(sp^2)\,C-H$	464	111	109
Acetylene, $HC\equiv CH$	$(sp)C\equiv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

? Exercise 1.10.1

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

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°.



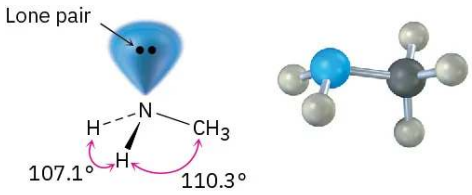
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1.11: Hybridization of Nitrogen, Oxygen, Phosphorus and Sulfur

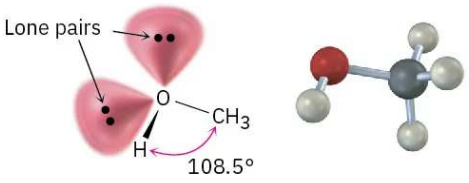
The valence-bond concept of orbital hybridization described in the previous four sections is not limited to carbon. Covalent bonds formed by other elements can also be described using hybrid orbitals. Look, for instance, at the nitrogen atom in methylamine (CH_3NH_2), an organic derivative of ammonia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

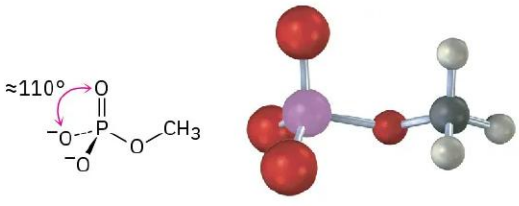
Like the carbon atom in methane and the nitrogen atom in methylamine, the oxygen atom in methanol (methyl alcohol) and many other organic molecules can be described as sp^3-hybridized. The C–O–H bond angle in methanol is 108.5°, very close to the 109.5° tetrahedral angle. Two of the four sp^3 hybrid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



Methanol
(methyl alcohol)

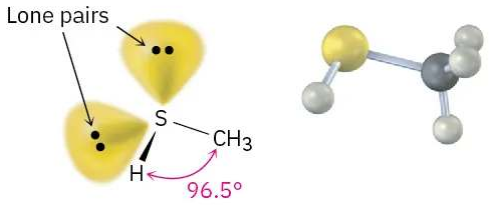
In the periodic table, phosphorus and sulfur are the third-row analogs of nitrogen and oxygen, and the bonding in both can be described using hybrid orbitals. Because of their positions in the third row, however, both phosphorus and sulfur can expand their outer-shell octets and form more than the typical 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.

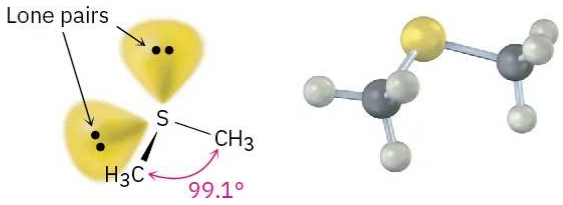


Methyl phosphate
(an organophosphate)

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

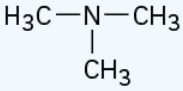


Dimethyl sulfide

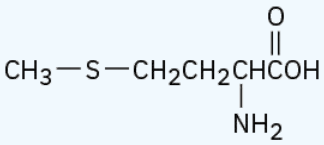
Exercise 1.11.1

Identify all nonbonding 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

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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1.12: 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 1*s* 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 1.12.1). Note that the additive combination is a single, egg-shaped, molecular orbital; it is not the same as the two overlapping 1*s* atomic orbitals of the valence bond description. Similarly, the subtractive combination is a single molecular orbital with the shape of an elongated dumbbell.

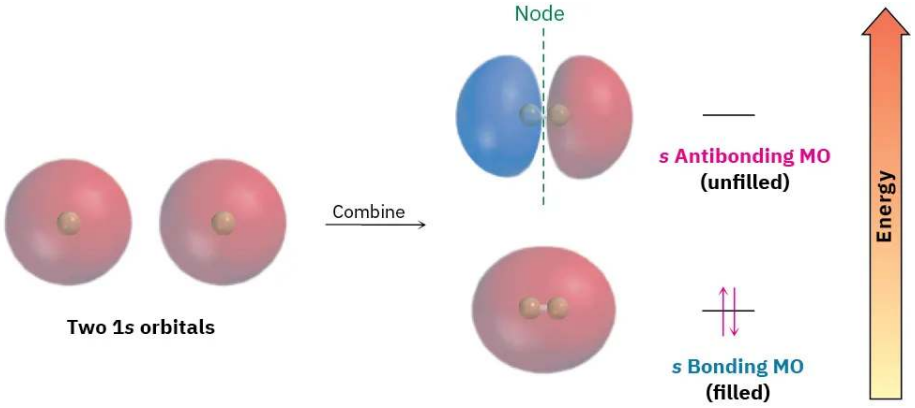


Figure 1.12.1: Molecular orbitals of H_2. Combination of two hydrogen 1*s* atomic orbitals leads to two H_2 molecular orbitals. The lower-energy, **bonding MO** is filled, and the higher-energy, **antibonding MO** is unfilled.

The additive combination is lower in energy than the two hydrogen 1*s* 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 1*s* 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 1.12.2, 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.

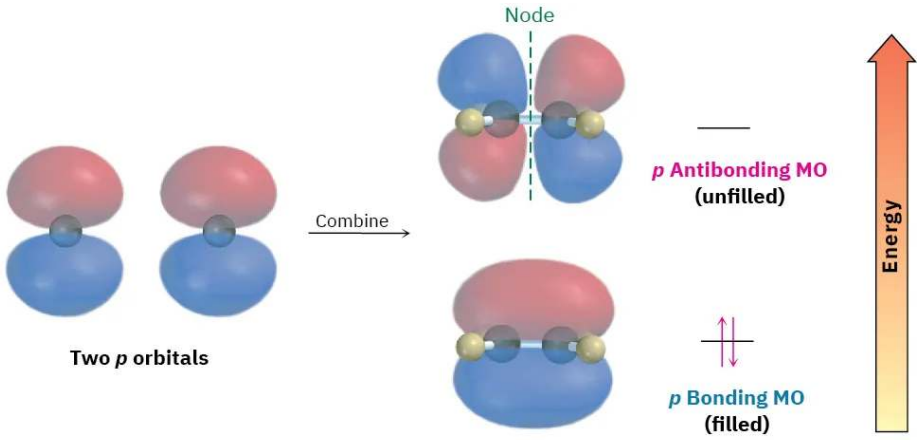


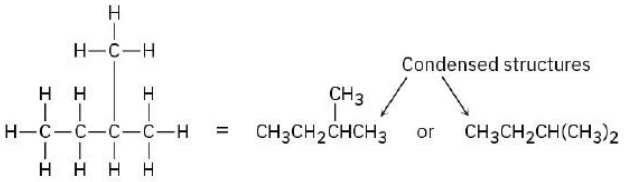
Figure 1.12.2: A molecular orbital description of the C–C π bond in ethylene. The lower-energy, $\boldsymbol{\pi}$ bonding MO results from an additive combination of *p* orbital lobes with the same algebraic sign and is filled. The higher-energy, $\boldsymbol{\pi}$ **antibonding MO** results from a subtractive combination of *p* orbital lobes with opposite algebraic signs and is unfilled.

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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 is 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.

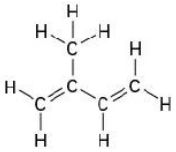
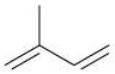
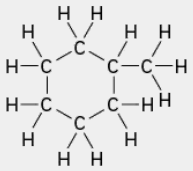
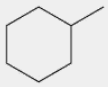
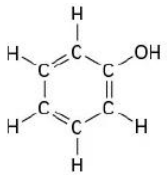
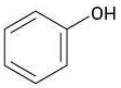
RULE 2

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.

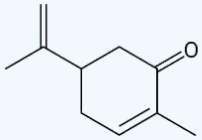
Table 1.13.1 Line-bond and Skeletal Structures for Some Compounds

Compound	Line-bond structure	Skeletal structure
Isoprene, C_5H_8		
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.

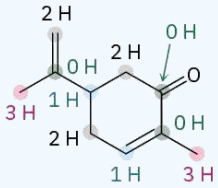


Carvone

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.

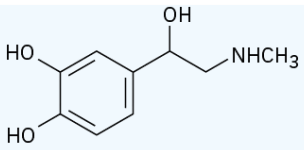
Solution



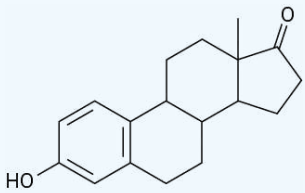
Carvone ($C_{10}H_{14}O$)

? 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?

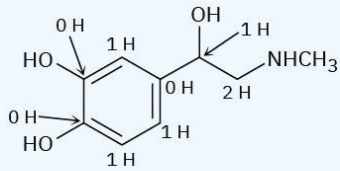


a. **Adrenaline**

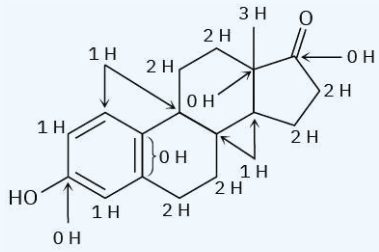


b. **Estrone (a hormone)**

Answer



a. Adrenaline—$C_9H_{13}NO_3$



b. Estrone—$C_{18}H_{22}O_2$

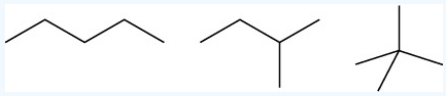
Exercise 1.13.2

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

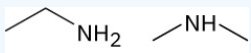
a. C_5H_{12}
b. C_2H_7N
c. C_3H_6O
d. C_4H_9Cl

Answer

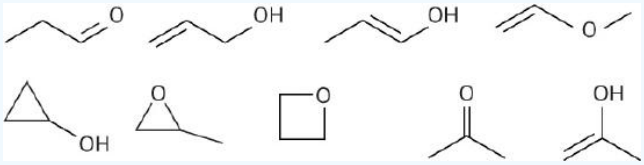
(a) There are numerous possibilities, such as:



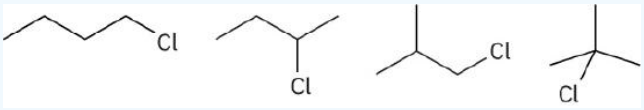
(b) There are numerous possibilities, such as:



(c) There are numerous possibilities, such as:

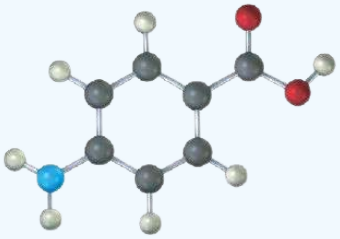


(d) There are numerous possibilities, such as:

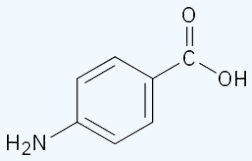


Exercise 1.13.3

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



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1.14: Chemistry Matters—Organic Foods- Risk versus Benefit

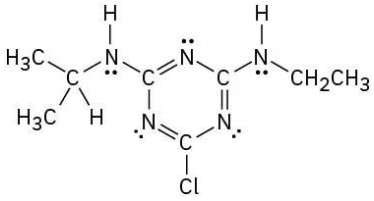
Contrary to what you may hear in supermarkets or on television, all foods are organic—that is, complex mixtures of organic molecules. Even so, when applied to food, the word *organic* has come to mean an absence of synthetic chemicals, typically pesticides, antibiotics, and preservatives. How concerned 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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1.15: Key Terms

- antibonding MO
- atomic number (*Z*)
- Aufbau principle
- bond angle
- bond length
- bond strength
- bonding MO
- condensed structure
- covalent bond
- electron shell
- electron-dot structure
- ground-state electron configuration
- Hund’s rule
- ionic bond
- isotope
- Kekulé structure
- Lewis structure
- line-bond structure
- lone-pair electrons
- mass number (*A*)
- molecular orbital (MO) theory
- molecule
- node
- nonbonding electron
- orbital
- organic chemistry
- Pauli exclusion principle
- pi (π) bond
- sigma (σ) bond
- skeletal structure
- *sp* hybrid orbital
- sp^2 hybrid orbital
- sp^3 hybrid orbital
- valence bond (VB) theory
- valence shell

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1.16: Summary

The purpose of this chapter has been to get you up to speed—to review some ideas about atoms, bonds, and molecular geometry. As we've seen, **organic chemistry** is the study of carbon compounds. Although a division into organic and inorganic chemistry occurred historically, there is no scientific reason for the division.

An atom consists of a positively charged nucleus surrounded by one or more negatively charged electrons. The electronic structure of an atom can be described by a quantum mechanical wave equation, in which electrons are considered to occupy **orbitals** around the nucleus. Different orbitals have different energy levels and different shapes. For example, *s* orbitals are spherical and *p* orbitals are dumbbell-shaped. The **ground-state electron configuration** of an atom can be found by assigning electrons to the proper orbitals, beginning with the lowest-energy ones.

A **covalent bond** is formed when an electron pair is shared between atoms. According to **valence bond (VB) theory**, electron sharing occurs by the overlap of two atomic orbitals. According to **molecular orbital (MO) theory**, bonds result from the mathematical combination of atomic orbitals to give molecular orbitals, which belong to the entire molecule. Bonds that have a circular cross-section and are formed by head-on interaction are called **sigma (σ) bonds**; bonds formed by sideways interaction of *p* orbitals are called **pi (π) bonds**.

In the valence bond description, carbon uses hybrid orbitals to form bonds in organic molecules. When forming only single bonds with tetrahedral geometry, carbon uses four equivalent sp^3 **hybrid orbitals**. When forming a double bond with planar geometry, carbon uses three equivalent sp^2 **hybrid orbitals** and one unhybridized *p* orbital. When forming a triple bond with linear geometry, carbon uses two equivalent ***sp* hybrid** orbitals and two unhybridized *p* orbitals. Other atoms such as nitrogen, phosphorus, oxygen, and sulfur also use hybrid orbitals to form strong, oriented bonds.

Organic molecules are usually drawn using either condensed structures or skeletal structures. In **condensed structures**, carbon–carbon and carbon–hydrogen bonds aren't shown. In **skeletal structures**, only the bonds and not the atoms are shown. A carbon atom is assumed to be at the ends and at the junctions of lines (bonds), and the correct number of hydrogens is supplied mentally.

Why You Should Work Problems

There's no surer way to learn organic chemistry than by working problems. Although careful reading and rereading of this text are important, reading alone isn't enough. You must also be able to use the information you've read and be able to apply your knowledge in new situations. Working problems gives you practice at doing this.

Each chapter in this book provides many problems of different sorts. The in-chapter problems are placed for immediate reinforcement of ideas just learned, while end-of-chapter problems provide additional practice and come in several forms. They often begin with a short section called "Visualizing Chemistry," which helps you see the microscopic world of molecules and provides practice for working in three dimensions. After the visualizations are many further problems, which are organized by topic. Early problems are primarily of the drill type, providing an opportunity for you to practice your command of the fundamentals. Later problems tend to be more thought-provoking, and some are real challenges.

As you study organic chemistry, take the time to work the problems. Do the ones you can, and ask for help on the ones you can't. If you're stumped by a particular problem, check the accompanying *Study Guide* and *Student Solutions Manual* for an explanation that should help clarify the difficulty. Working problems takes effort, but the payoff in knowledge and understanding is immense.

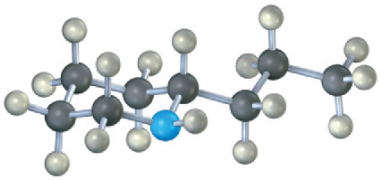
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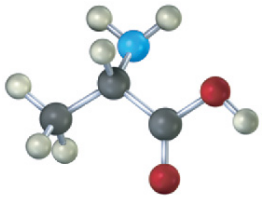
1.17: Additional Problems

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).

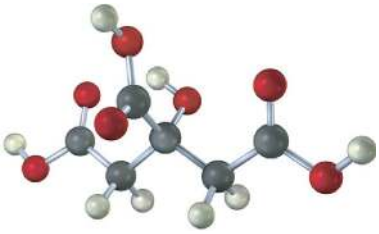


(a) Coniine (the toxic substance in poison hemlock)



(b) Alanine (an amino acid)

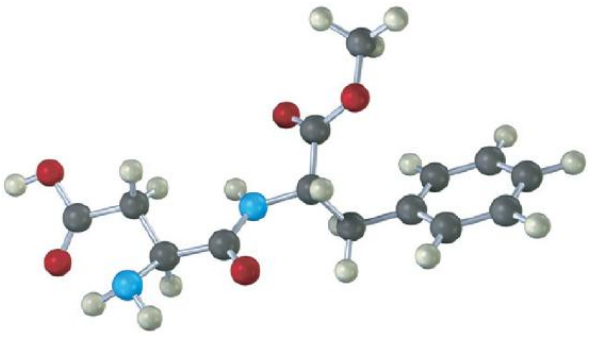
PROBLEM 1.19 The following model is a representation of citric acid, the key substance in the so-called citric acid cycle, by which food molecules are metabolized in the body. Only the connections between atoms are shown; multiple bonds are not indicated. Complete the structure by indicating the positions 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_2OH **(b)** $AlCl_2$ **(c)** CF_2Cl_2 **(d)** CH_2O

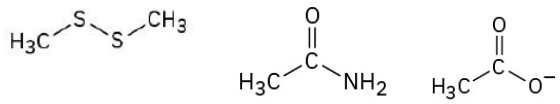
PROBLEM 1.25 Why can't molecules with the following formulas exist?

(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?

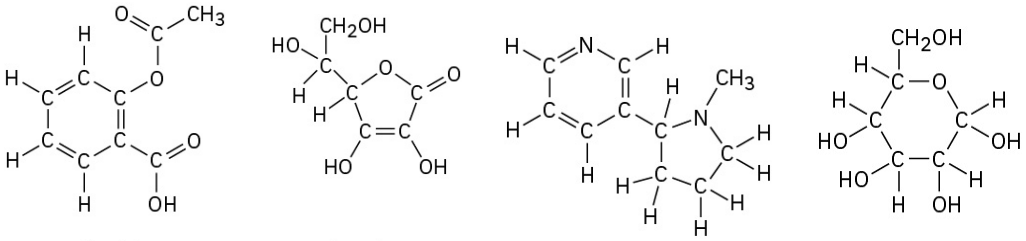
PROBLEM 1.27 Draw a line-bond structure for vinyl chloride, C_2H_3Cl, the starting material from which PVC poly(vinyl chloride) plastic is made.

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:



(a) Aspirin (acetylsalicylic acid) **(b)** Vitamin C (ascorbic acid) **(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

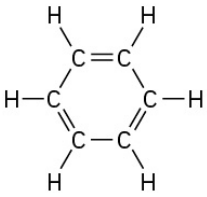
Hybridization

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?

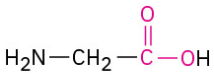
(a) Propane, $CH_3CH_2CH_3$ **(b)** 2-Methylpropene, $CH_3C(=CH_2)CH_3$ **(c)** But-1-en-3-yne, $H_2C{=}CH{-}C{\equiv}CH$ **(d)** Acetic acid, CH_3COOH

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



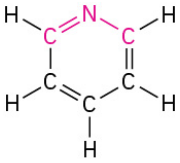
Benzene

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?



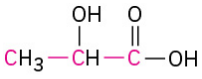
Glycine (an amino acid)

(a)



Pyridine

(b)



Lactic acid (in sour milk)

(c)

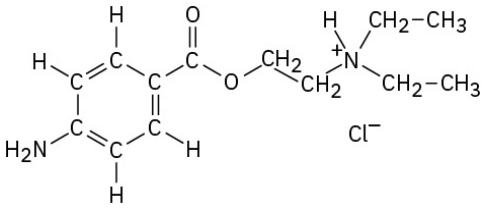
PROBLEM 1.38 Propose structures for molecules that meet the following descriptions:

(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

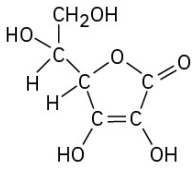
(c) Contains two *sp*-hybridized carbons and two sp^2-hybridized carbons

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



Procaine

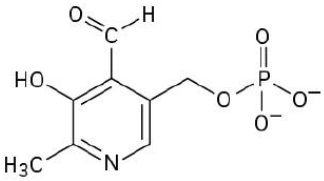
(a)



Vitamin C (ascorbic acid)

(b)

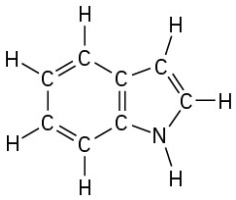
PROBLEM 1.40 Pyridoxal phosphate, a close relative of vitamin B_6, is involved in a large number of metabolic reactions. What is the hybridization and the bond angle for each nonterminal atom?



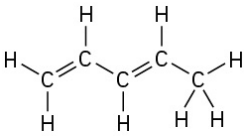
Pyridoxal phosphate

Skeletal Structures

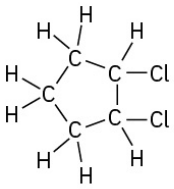
PROBLEM 1.41 Convert the following structures into skeletal drawings:



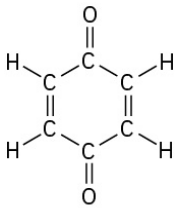
(a) **Indole**



(b) **1,3-Pentadiene**

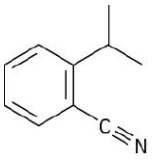


(c) **1,2-Dichlorocyclopentane**

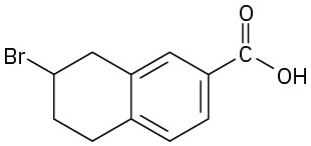


(d) **Benzoquinone**

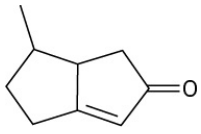
PROBLEM 1.42 How many hydrogens are bonded to each carbon atom in the following substances, and what is the molecular formula of each?



(a)

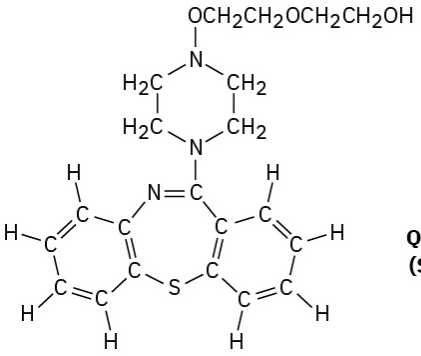


(b)



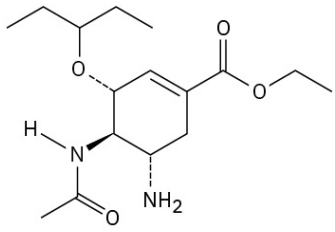
(c)

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.

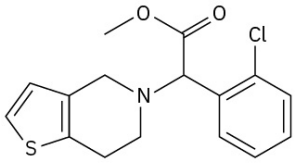


Quetiapine (Seroquel)

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.



(a) **Oseltamivir (Tamiflu)**



(b) **Clopidogrel (Plavix)**

General Problems

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

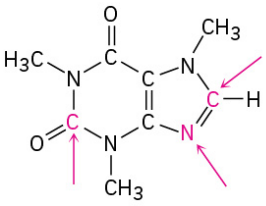


Cyclopentyne

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?

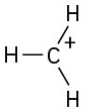
PROBLEM 1.47 Allene (see previous PROBLEM) is structurally related to carbon dioxide, CO_2. Draw a picture showing the orbitals involved in the σ and π bonds of CO_2, and identify the likely hybridization of carbon.

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.



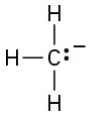
A carbocation

(a) How many valence electrons does the positively charged carbon atom have?

(b) What hybridization do you expect this carbon atom to have?

(c) 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.

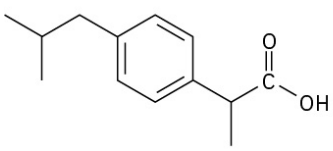
PROBLEM 1.52 Two different substances have the formula C_4H_{10}. Draw both, and tell how they differ.

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

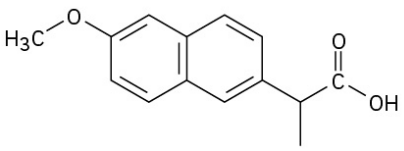
PROBLEM 1.54 Two different substances have the formula C_2H_6O. Draw both, and tell how they differ.

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.

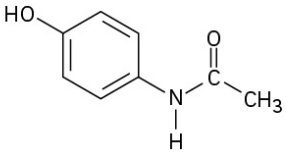
PROBLEM 1.56 Among the most common over-the-counter drugs you might find in a medicine cabinet are mild pain relievers such ibuprofen (Advil, Motrin), naproxen (Aleve), and acetaminophen (Tylenol).



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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CHAPTER OVERVIEW

2: Polar Covalent Bonds; Acids and Bases

Chapter Objectives

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

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

2.1: Why This Chapter?
2.2: Polar Covalent Bonds - Electronegativity
2.3: Polar Covalent Bonds - Dipole Moments
2.4: Formal Charges
2.5: Resonance
2.6: Rules for Resonance Forms
2.7: Drawing Resonance Forms
2.8: Acids and Bases - The Brønsted-Lowry Definition
2.9: Acid and Base Strength
2.10: Predicting Acid-Base Reactions from pKa Values
2.11: Organic Acids and Organic Bases
2.12: Acids and Bases - The Lewis Definition
2.13: Noncovalent Interactions Between Molecules
2.14: Chemistry Matters—Alkaloids- From Cocaine to Dental Anesthetics
2.15: Key Terms
2.16: Summary
2.17: Additional Problems

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2.1: 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 2.1.1: 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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2.2: 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 2.2.1).

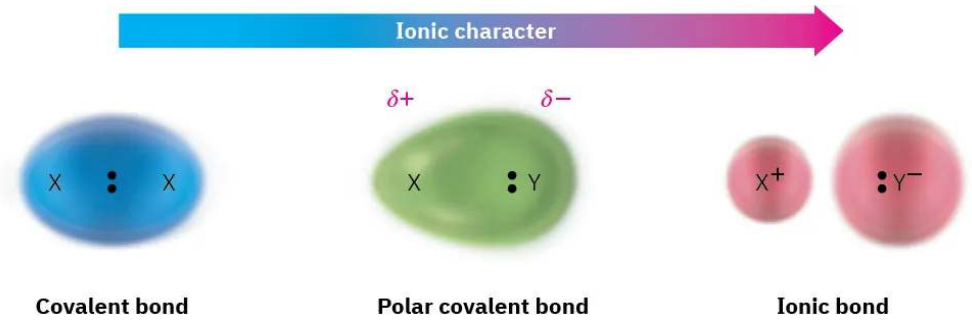


Figure 2.2.1: The continuum in bonding from covalent to ionic is a result of an unequal distribution of bonding electrons between atoms.

The symbol δ (lowercase Greek letter delta) means *partial* charge, either partial positive ($\delta+$) for the electron-poor atom or partial negative ($\delta-$) 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 2.2.2, 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 2.2.2 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, $\delta-$, and the electronegative atom with a partial negative charge, $\delta-$. An example is the C–O bond in methanol, CH_3OH (Figure 2.2.3*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 2.2.3*b*).

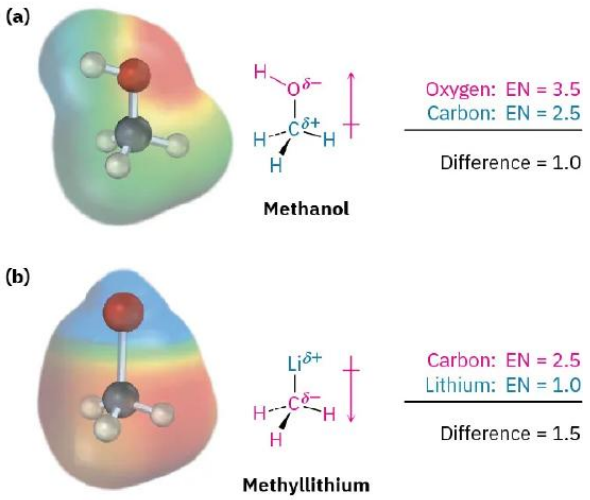


Figure 2.2.3: Polar covalent bonds. (a) Methanol, CH_3OH, has a polar covalent C–O bond, and **(b)** methyllithium, CH_3Li, has a polar covalent C–Li bond. The computer-generated representations, called electrostatic potential maps, use color to show calculated charge distributions, ranging from **red (electron-rich; $\delta-$)** to **blue (electron-poor; $\delta+$).**

Note in the representations of methanol and methyllithium in Figure 2.2.3 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 ($\delta+$), and the head of the arrow is electron-rich ($\delta-$).

Note also in Figure 2.2.3 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; $\delta-$) and electron-poor (blue; $\delta+$) 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 2.2.1

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

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

Exercise 2.2.2

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

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

Exercise 2.2.3

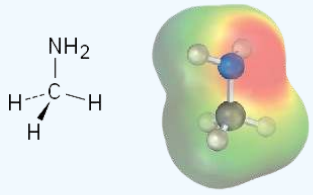
Use the electronegativity values shown in Figure 2.2.2 to rank the following bonds from least polar to most polar: $H_3C–Li$, $H_3C–K$, $H_3C–F$, $H_3C–MgBr$, $H_3C–OH$

Answer

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

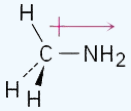
Exercise 2.2.4

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

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



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2.3: 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.

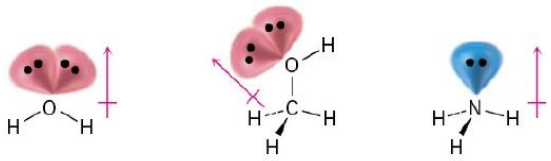
The dipole moment, μ (lowercase Greek letter mu), is defined as the magnitude of the charge Q at either end of the molecular dipole times the distance r between the charges, $\mu = Q \times r$. Dipole moments are expressed in *debyes* (D), where 1 D = 3.336×10^{-30} coulomb meters (C · m) in SI units. 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.

$$\mu = Q \times r$$
$$\mu = \left(1.60 \times 10^{-19}\text{C}\right)\left(100 \times 10^{-12}\ \text{m}\right)\left(\frac{1\text{D}}{3.336 \times 10^{-35}\text{C} - \text{m}}\right) = 4.80\text{D} \tag{2.3.1}$$

Dipole moments for some common substances are given in Table 2.3.1. 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.

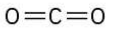
Table 2.3.1: Dipole Moments of Some Compounds

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		

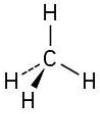


In contrast with water, methanol, and ammonia, molecules such as carbon dioxide, methane, ethane, and benzene have zero dipole moments. Because of the symmetrical structures of these molecules, the individual bond polarities and lone-pair contributions

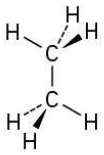
exactly cancel.



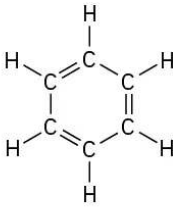
Carbon dioxide
(μ = 0)



Methane
(μ = 0)



Ethane
(μ = 0)



Benzene
(μ = 0)

Worked Example 2.3.1: Predicting the Direction of a Dipole Moment

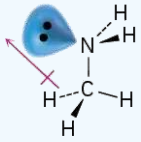
Make a three-dimensional drawing of methylamine, CH_3NH_2, and show the direction of its dipole moment (μ = 1.31).

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.



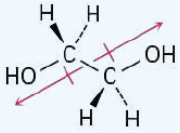
Methylamine
(μ = 1.31)

Exercise 2.3.1

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

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

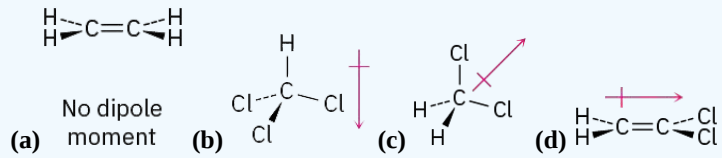


Exercise 2.3.2

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

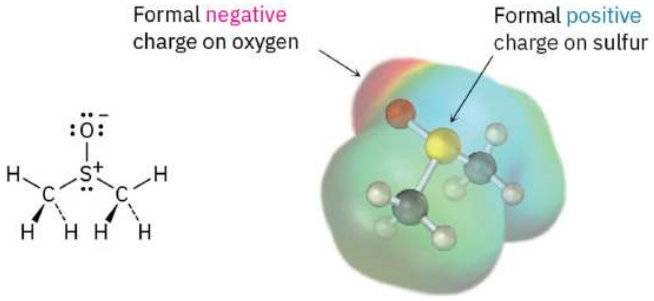


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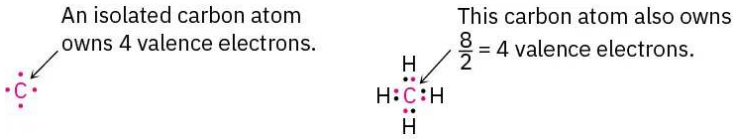
2.4: Formal Charges

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.

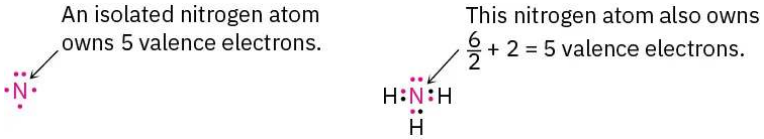


Dimethyl sulfoxide

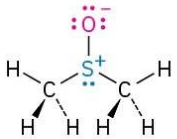
Formal charges, as the name suggests, are a formalism and don't imply the presence of actual ionic charges in a molecule. Instead, they're a device for electron "bookkeeping" and can be thought of in the following way: A typical covalent bond is formed when each atom donates one electron. Although the 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:

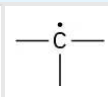
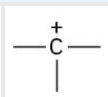
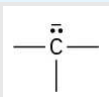
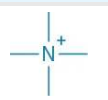
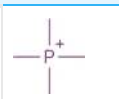
Oxygen valence electrons	= 6
Oxygen bonding electrons	= 2
Oxygen nonbonding electrons	= 6
Formal charge = 6 − 2/2 − 6	= −1

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.

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

A summary of commonly encountered formal charges and the bonding situations in which they occur is given in Table 2.4.1. 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 2.4.1: A Summary of Common Formal Charges

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

? Exercise 2.4.1

Calculate formal charges for the nonhydrogen 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

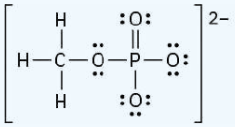
a. For carbon: FC = 4 − 8/2 − 0 = 0 For the middle nitrogen: FC = 5 − 8/2 − 0 = +1 For the end nitrogen: FC = 5 − 4/2 − 4 = −1

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

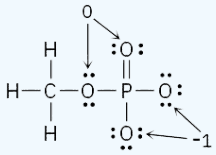
Exercise 2.4.2

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

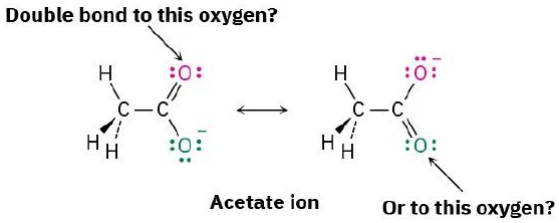


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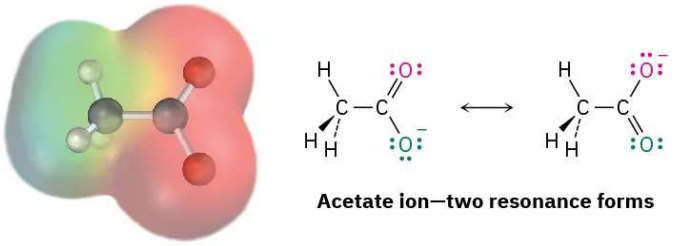
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2.5: Resonance

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?



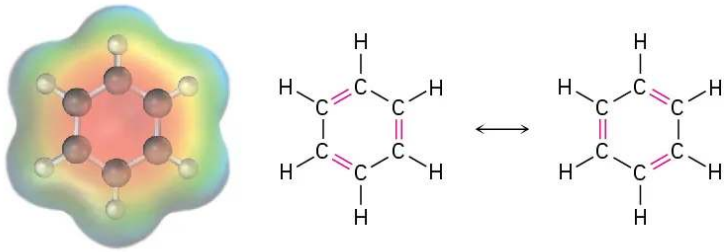
Although the two oxygen atoms in the acetate ion appear different in line-bond structures, experiments show that they are equivalent. Both carbon–oxygen bonds, for instance, are 127 pm in length, midway between the length of a typical C–O single bond (135 pm) and a typical C=O double bond (120 pm). In 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 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. We'll see in Chapter 15, for instance, that 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)

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2.6: Rules for Resonance Forms

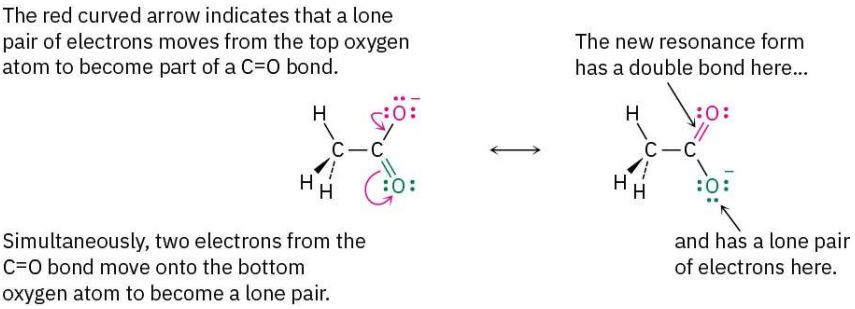
When first dealing with resonance forms, it's useful to have a set of guidelines that describe how to draw and interpret them. The following rules should be helpful:

RULE 1

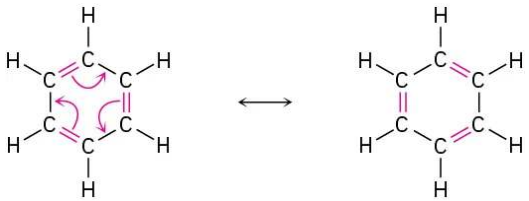
Individual resonance forms are imaginary, not real. The real structure is a composite, or resonance hybrid, of the different forms. Species such as the acetate ion and benzene are no different from any other. They have single, unchanging structures, and they don't switch back and forth between resonance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

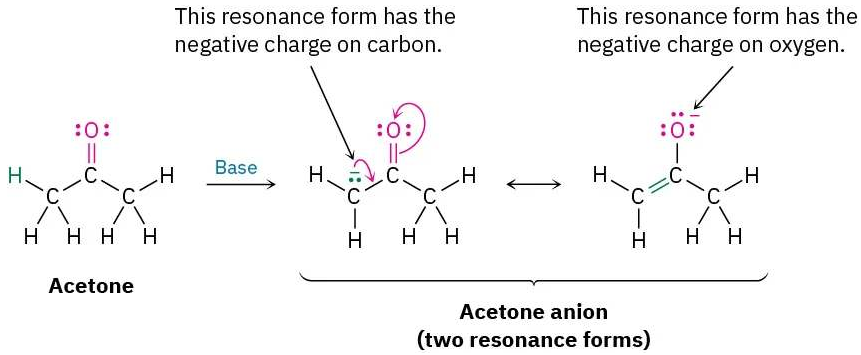


The situation with benzene is similar to that with acetate. The π electrons in the double bonds move, as shown with curved arrows, but the carbon and hydrogen atoms remain in place.



RULE 3

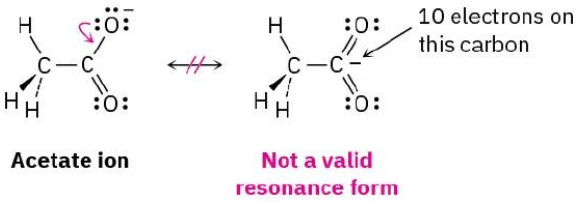
Different resonance forms of a substance don't have to be equivalent. As an example, we'll see in Chapter 22 that a compound such as acetone, which contains a C=O bond, can be converted into its anion by reaction with a strong base. The resultant anion has two resonance forms. One form contains a carbon–*oxygen* 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

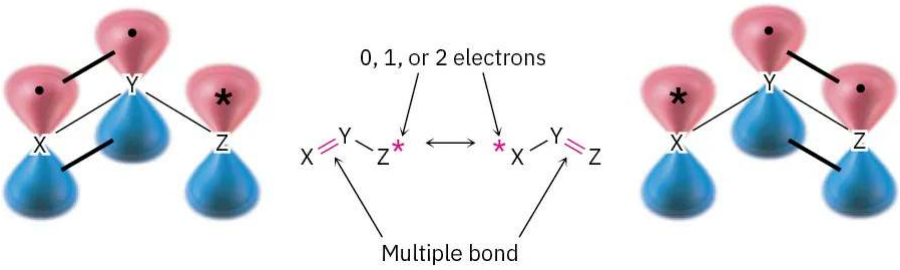
The resonance hybrid is more stable than any individual resonance form. In other words, resonance leads to stability. Generally speaking, the larger the number of resonance forms a substance has, the more stable the substance is, because its electrons are spread out over a larger part of the molecule and are closer to more nuclei. We'll see in Chapter 15, for instance, that a benzene ring is more stable because of resonance than might otherwise be expected.

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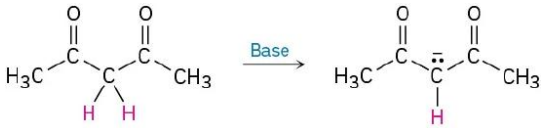
2.7: Drawing Resonance Forms

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:



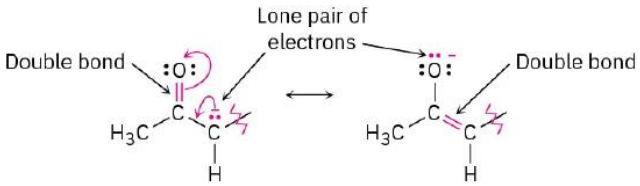
The atoms X, Y, and Z in the general structure might be C, N, O, P, S, or others, and the asterisk (*) might mean that the *p* orbital on atom Z is vacant, that it contains a single electron, or that it contains a lone pair of electrons. The two resonance forms differ simply by an exchange in position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

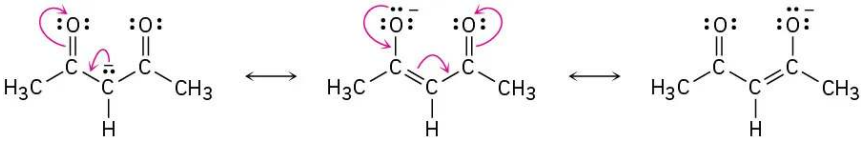


2,4-Pentanedione

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.

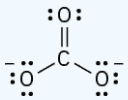


Just as there is a C=O bond to the left of the lone pair, there is a second C=O bond to the right. Thus, we can draw a total of three resonance structures for the 2,4-pentanedione anion.



Worked Example 2.7.1: Drawing Resonance Forms for an Anion

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



Carbonate ion

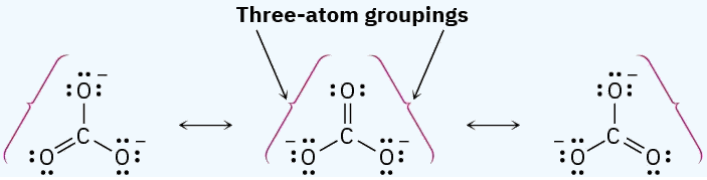
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Strategy

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 $\ddot{O}{=}C{-}\ddot{O}:^{-}$.

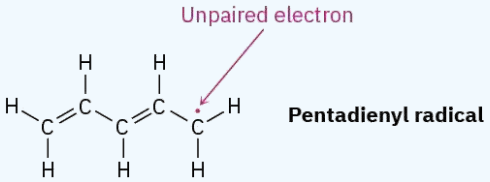
Solution

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 (·).

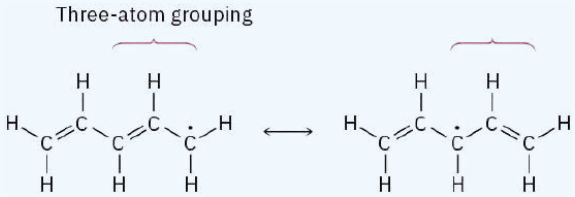


Strategy

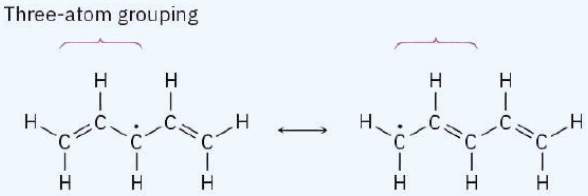
Find the three-atom groupings that contain a multiple bond next to an atom with a *p* orbital.

Solution

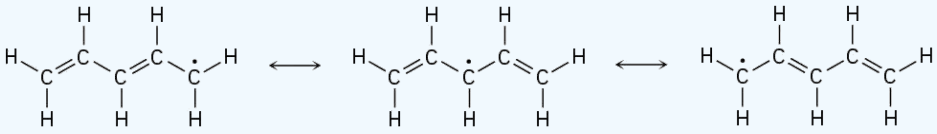
The unpaired electron is on a carbon atom next to a C=C bond, giving a typical three-atom grouping that has two resonance forms.



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.

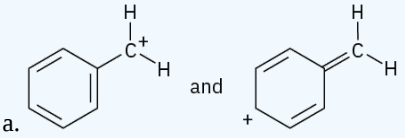


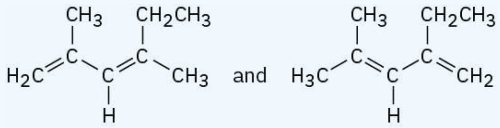
Thus, the three resonance forms for the pentadienyl radical are:



Exercise 2.7.1

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

a. 

b. 

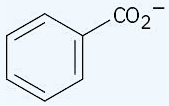
Answer

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

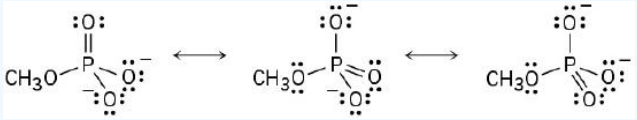
Exercise 2.7.2

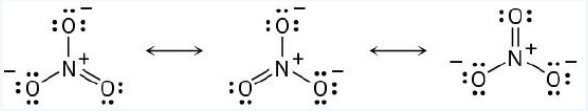
Draw the indicated number of resonance forms for each of the following substances:

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)

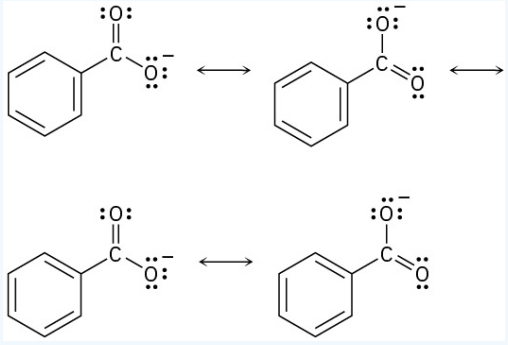


Answer

a. 

b. 

c. 

d. 

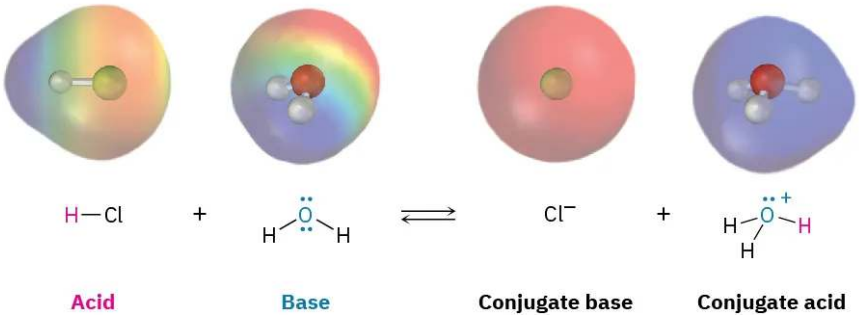
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2.8: Acids and Bases - The Brønsted-Lowry Definition

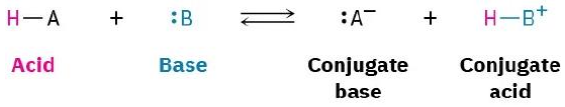
Perhaps the most important of all concepts related to electronegativity and polarity is that of *acidity* and *basicity*. We'll soon see, in fact, that the acid–base behavior of organic molecules explains much of their chemistry. You may recall from a course in general chemistry that two definitions 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.

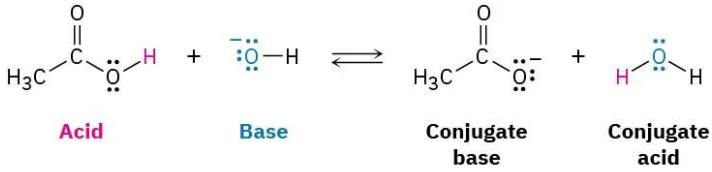


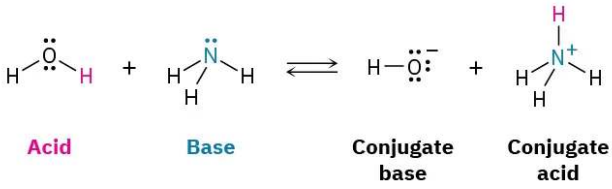
Chloride ion, the product that results when the acid HCl loses a proton, is called the conjugate base of the acid, and hydronium ion, the product that results when the base H_2O gains a proton, is called the conjugate acid of the base. Other common mineral acids such as H_2SO_4 and HNO_3 behave similarly,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

In a general sense,



For example:





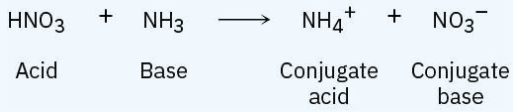
Notice that water can act either as an acid or as a base, depending on the circumstances. In its reaction with HCl, water is a base that accepts a proton to give the hydronium ion, H_3O^+. In its reaction with ammonia (NH_3), however, water is an acid that donates a proton to give ammonium ion (NH_4^+)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

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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



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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

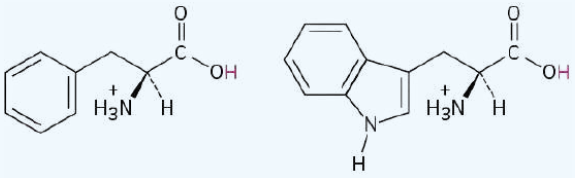
Notice also in Table 2.9.1 that there is an inverse relationship between the acid strength of an acid and the base strength of its conjugate base. A strong acid has a weak conjugate base, and a weak acid has a strong conjugate base. To understand this inverse relationship, think about what is happening 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

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

Phenylalanine is stronger.

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

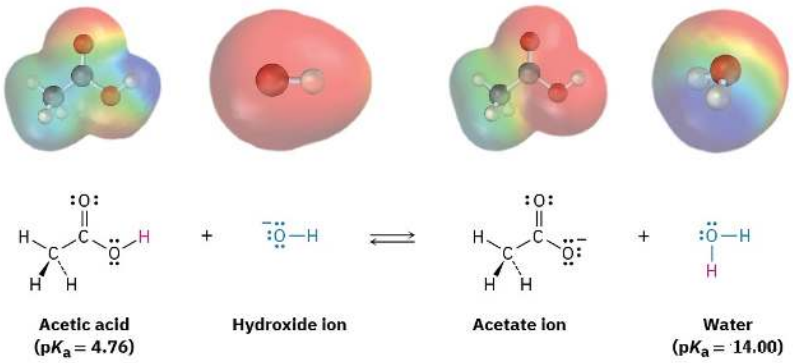
Water is a stronger acid.

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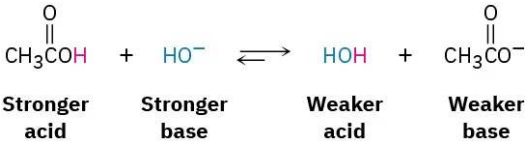
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2.10: Predicting Acid-Base Reactions from pKa Values

Compilations of pK_a values like those in Table 2.3 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.

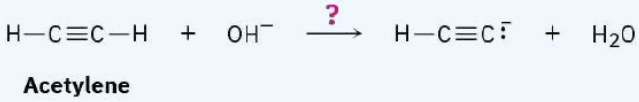


Another way to predict acid–base reactivity is to remember that the product conjugate acid in an acid–base reaction must be weaker and less reactive than the starting acid and the product conjugate base must be weaker and less reactive than the starting base. In the reaction of acetic acid with hydroxide 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 2.10.1: 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?



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 2.10.2: Calculating K$_a$ from pK$_a$

According to the data in Table 2.3, 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 2.10.1

Will either of the following reactions take place to a significant extent as written, according to the data in Table 2.3?

a. $HCN + CH_3CO_2^- Na^+ \xrightarrow{?} Na^+ {}^-CN + CH_3CO_2H$

b. $CH_3CH_2OH + Na^+ {}^-CN \xrightarrow{?} CH_3CH_2O^- Na^+ + HCN$

Answer

Neither reaction will take place.

Exercise 2.10.2

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

The reaction will take place.

Exercise 2.10.3

What is the K_a of HCN if its p$K_a = 9.31$?

Answer

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

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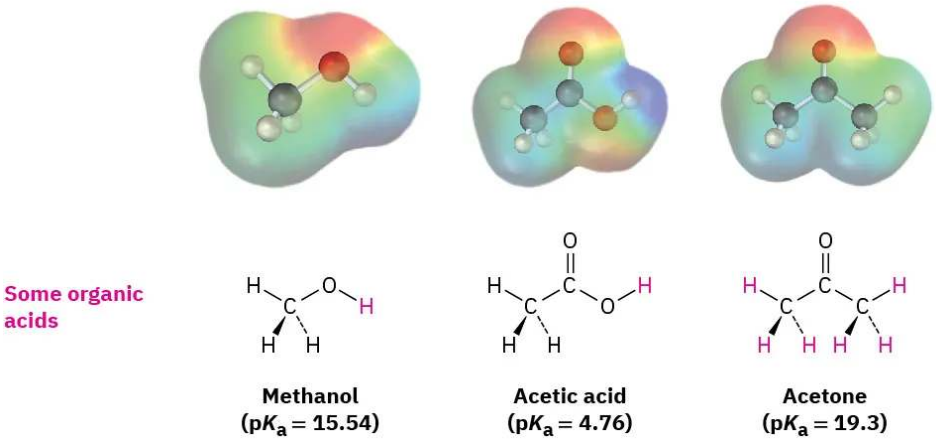
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2.11: Organic Acids and Organic Bases

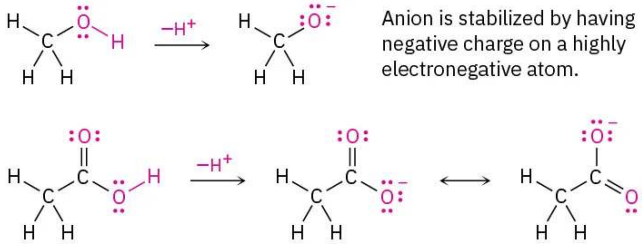
Many of the reactions we'll be seeing in future chapters, including practically all biological reactions, involve organic acids and organic bases. Although it's too early to go into the details of these processes now, you might keep the following generalities in mind:

Organic Acids

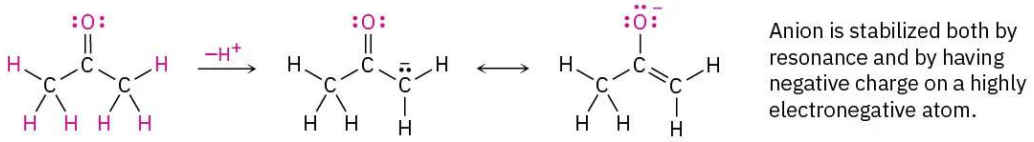
Organic acids are characterized by the presence of a positively polarized hydrogen atom (blue in electrostatic potential maps) and are of two main kinds: acids such as methanol and acetic acid that contain a hydrogen atom bonded to an electronegative oxygen atom (O–H) and those such as acetone (Section 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 (Section 2.5 and Section 2.6).



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.



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.

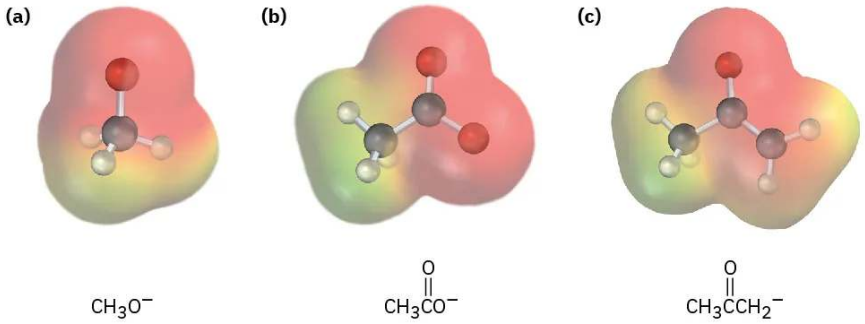
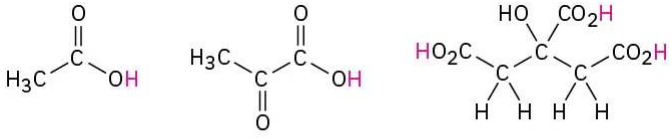


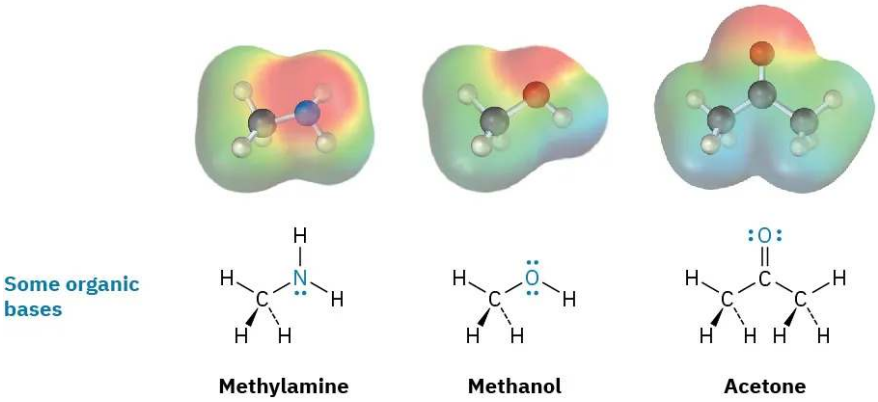
Figure 2.5 Electrostatic potential maps of the conjugate bases of **(a)** methanol, **(b)** acetic acid, and **(c)** acetone. The electronegative oxygen atoms stabilize the negative charge in all three.

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, $–CO_2^–$.

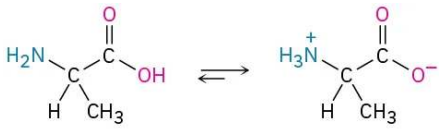


Organic Bases

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.



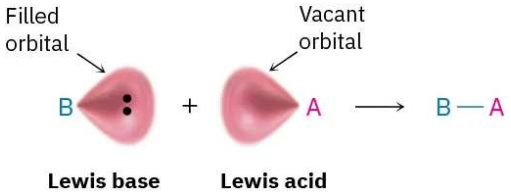
Alanine (uncharged form) **Alanine (zwitterion form)**

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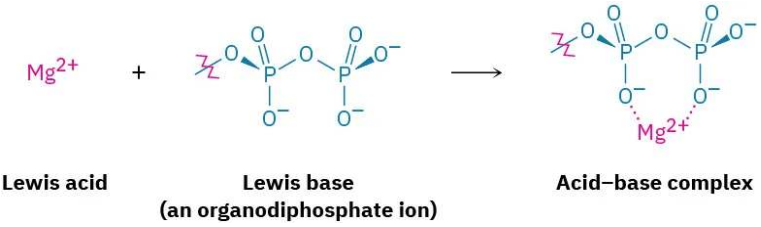
2.12: Acids and Bases - The Lewis Definition

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 1*s* 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.

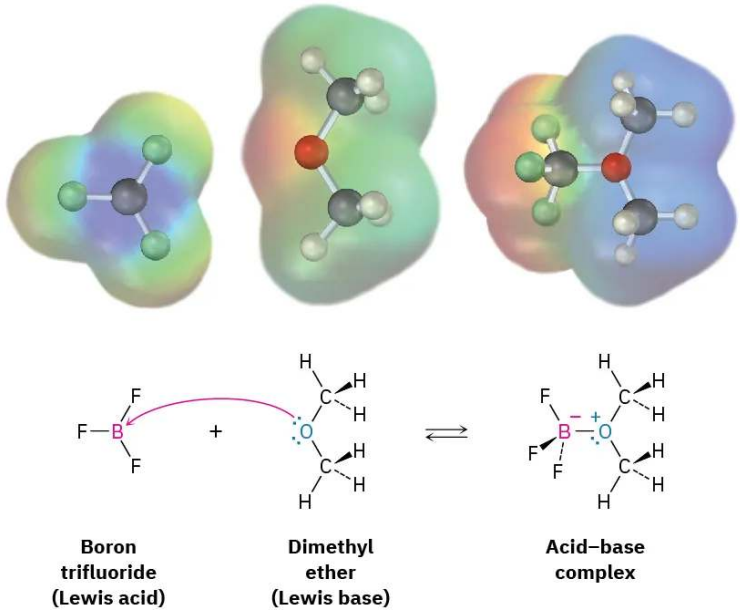
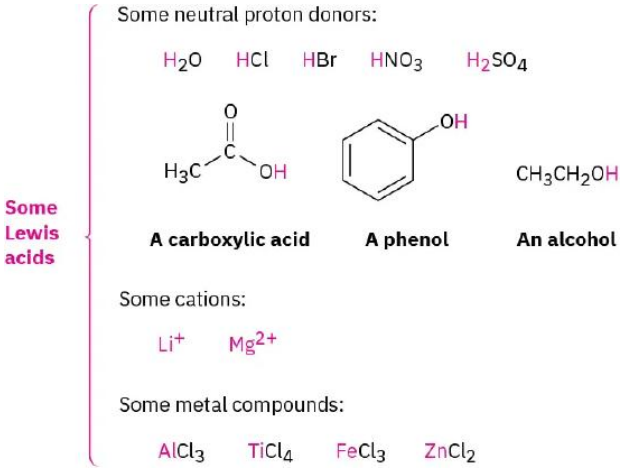


Figure 2.12.1: The reaction of boron trifluoride, a Lewis acid, with dimethyl ether, a Lewis base. The Lewis acid accepts a pair of electrons, and the Lewis base donates a pair of nonbonding electrons. Note how the movement of electrons from the Lewis base to the Lewis acid is indicated by a curved arrow. 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.

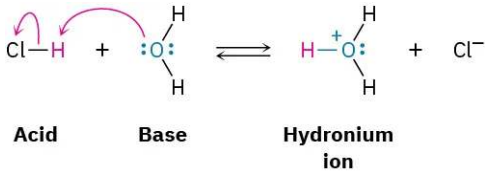
Look closely at the acid–base reaction in Figure 2.12.1, and notice how it's shown. Dimethyl ether, the Lewis base, donates an electron pair to a vacant valence orbital of the boron atom in BF_3, a Lewis acid. The direction of electron-pair flow from base to acid is shown using a curved arrow, just as 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:

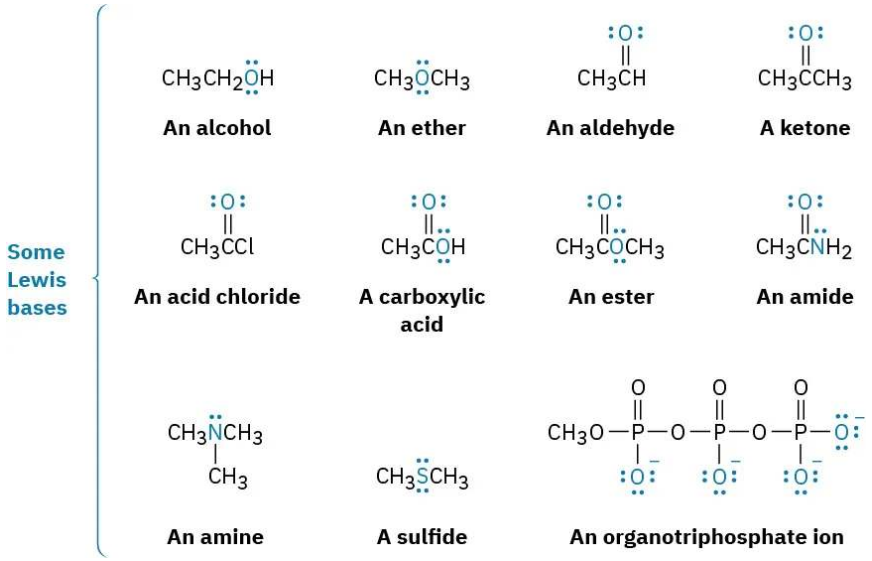


Lewis Bases

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^+.

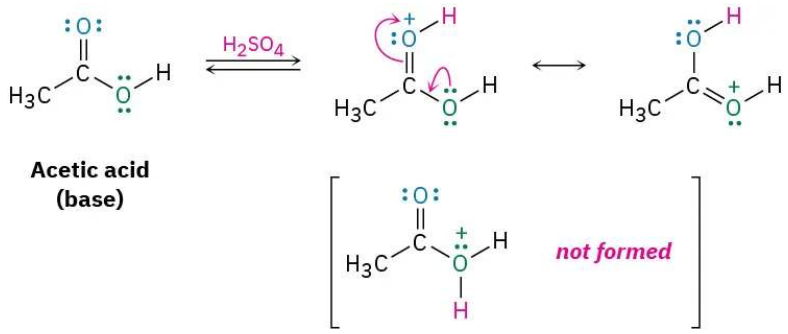


In a more general sense, most oxygen- and nitrogen-containing organic compounds can act as Lewis bases because they have lone pairs of electrons. A divalent oxygen compound has two lone pairs of electrons, and a trivalent nitrogen compound has one lone pair. Note in the following examples that some compounds 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^+.



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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.



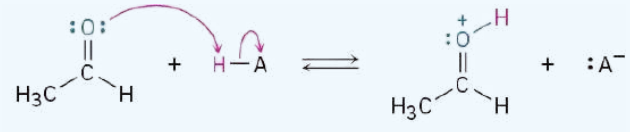
Worked Example 2.12.1: Using Curved Arrows to Show Electron Flow

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



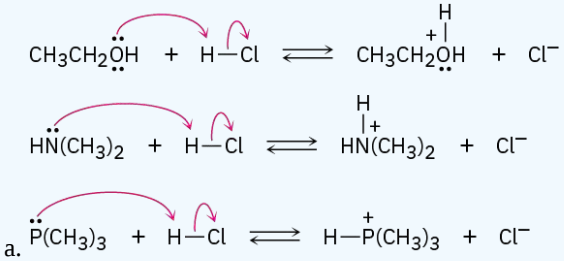
Acetaldehyde

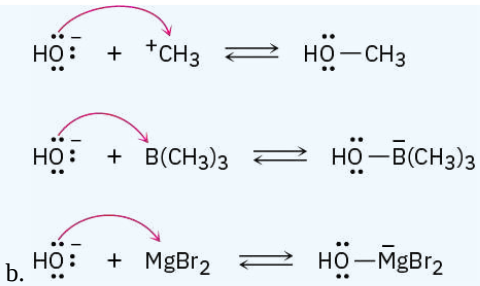
Exercise 2.12.1

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

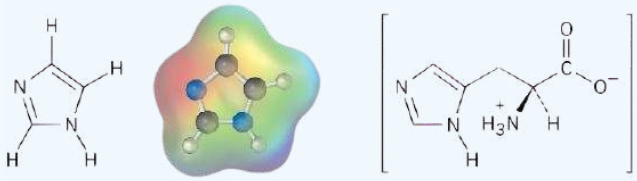




b.

Exercise 2.12.2

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

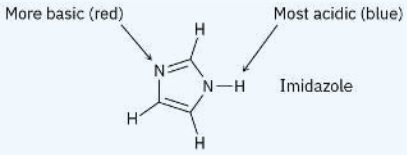


Imidazole Histidine

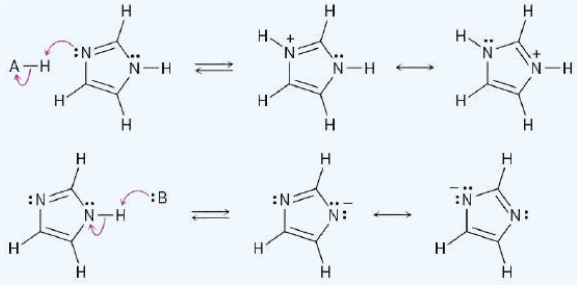
a. Look at the electrostatic potential map of imidazole, and identify the most acidic hydrogen atom and the most basic nitrogen atom.
b. Draw structures for the resonance forms of the products that result when imidazole is protonated by an acid and deprotonated by a base.

Answer

a.



b.



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2.13: Noncovalent Interactions Between Molecules

When thinking about chemical reactivity, chemists usually focus their attention on bonds, the covalent interactions between atoms within molecules. Also important, however, particularly in large biomolecules like proteins and nucleic acids, are a variety of interactions *between* molecules that strongly affect molecular properties. Collectively called either intermolecular forces, van der Waals forces, or noncovalent interactions, they are of several different types: dipole–dipole forces, dispersion forces, and hydrogen bonds.

Dipole–dipole forces occur between polar molecules as a result of electrostatic interactions among dipoles. The forces can be either attractive or repulsive depending on the orientation of the molecules—attractive when unlike charges are together and repulsive when like charges are together. The attractive geometry is lower in energy and therefore predominates (Figure 2.13.1).

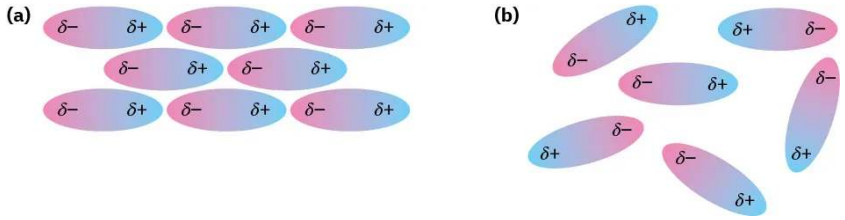


Figure 2.13.1: Dipole–dipole forces cause polar molecules (a) to attract one another when they orient with unlike charges together, but (b) to repel one another when they orient with like charges together.

Dispersion forces occur between all neighboring molecules and arise because the electron distribution within molecules is constantly changing. Although uniform on a time-averaged basis, the electron distribution even in nonpolar molecules is likely to be nonuniform at any given instant. One side of a molecule may, by chance, have a slight excess of electrons relative to the opposite side, giving the molecule a temporary dipole. This temporary dipole in one molecule causes a nearby molecule to adopt a temporarily opposite dipole, resulting in a tiny attraction between the two (Figure 2.13.2). Temporary molecular dipoles have only a fleeting existence and are constantly changing, but their cumulative effect is often strong enough to hold molecules close together so that a substance is a liquid or solid rather than a gas.

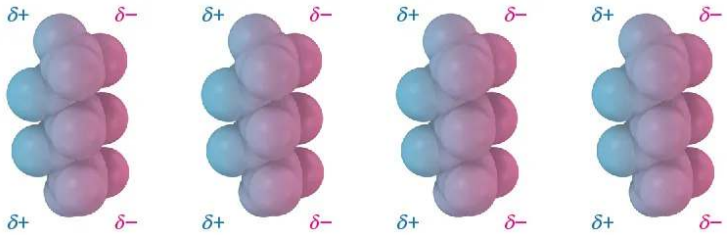
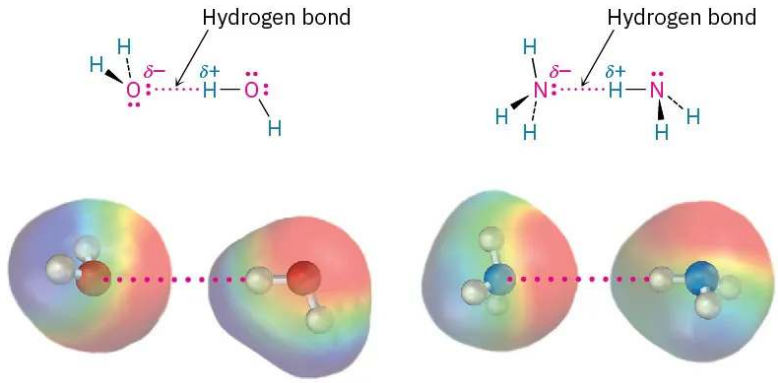
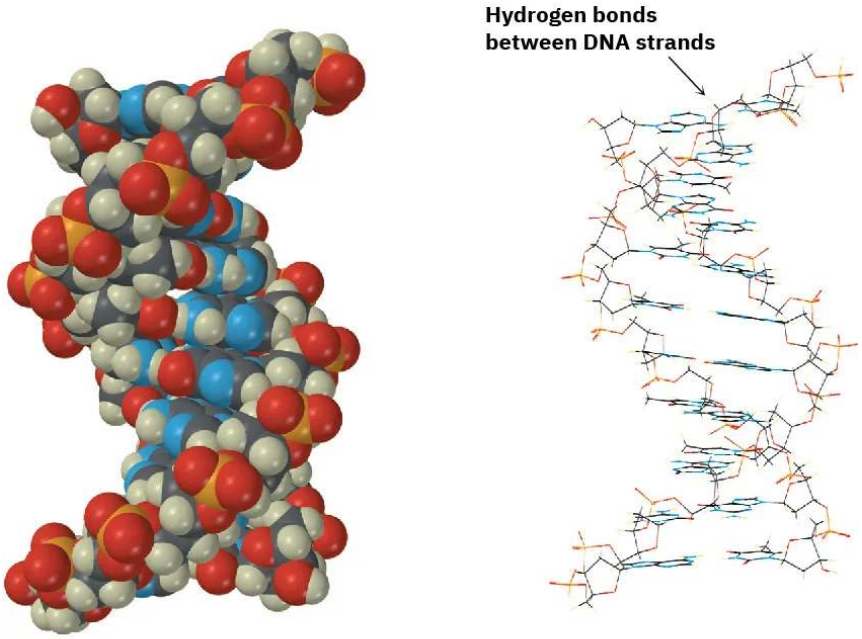


Figure 2.13.2: Attractive dispersion forces in nonpolar molecules are caused by temporary dipoles, as shown in these models of pentane, C_5H_{12}.

Perhaps the most important noncovalent interaction in biological molecules is the hydrogen bond, an attractive interaction between a hydrogen atom bonded to an electronegative O or N atom and an unshared electron pair on another O or N atom. In essence, a hydrogen bond is a very strong dipole–dipole interaction involving polarized O–H or N–H bonds. Electrostatic potential maps of water and ammonia clearly show the positively polarized hydrogens (blue) and the negatively polarized oxygens and nitrogens (red).

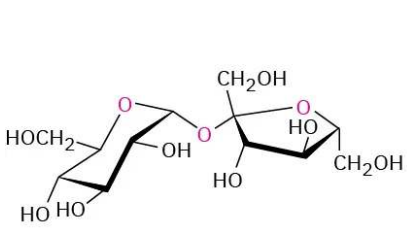


Hydrogen bonding has enormous consequences for living organisms. Hydrogen bonds cause water to be a liquid rather than a gas at ordinary temperatures, they hold enzymes in the shapes necessary for catalyzing biological reactions, and they cause strands of deoxyribonucleic acid (DNA) to pair up and coil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

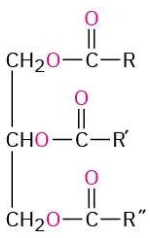


A deoxyribonucleic acid segment

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.



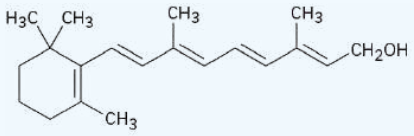
Sucrose (a disaccharide)



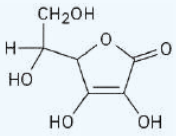
Animal fat—a triester (R, R′, R″ = C_{11}–C_{19} chains)

Exercise 2.13.1

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

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

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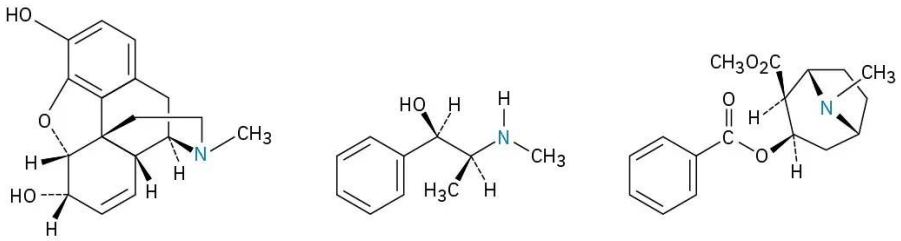
2.14: Chemistry Matters—Alkaloids- From Cocaine to Dental Anesthetics

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.



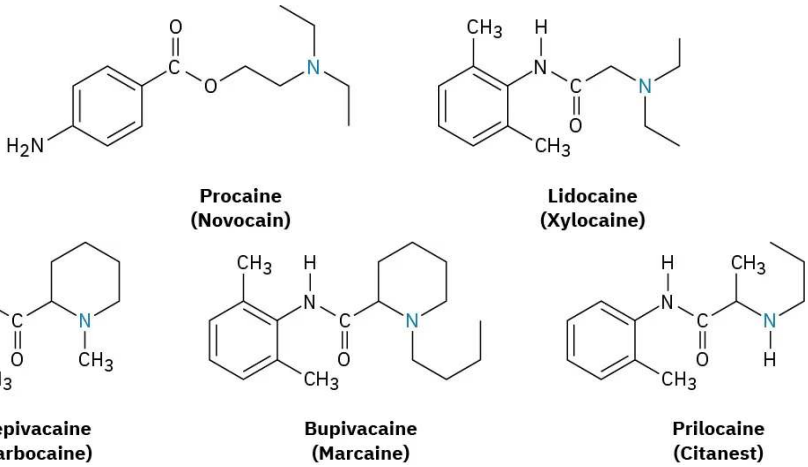
Figure 2.14.1: The coca bush *Erythroxylon coca*, native to upland rain forest areas of Colombia, Ecuador, Peru, Bolivia, and western Brazil, is the source of the alkaloid cocaine. (credit: "*Erythroxylum coca*" by Danna Guevara/Wikimedia Commons, CC BY 4.0)

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.



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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2.15: Key Terms

- acidity constant (K_a)
- alkaloid
- Brønsted–Lowry acid
- Brønsted–Lowry base
- conjugate acid
- conjugate base
- dipole moment (μ)
- dispersion force
- electronegativity (EN)
- electrostatic potential map
- formal charge
- hydrogen bond
- hydrophilic
- hydrophobic
- inductive effect
- intermolecular force
- Lewis acid
- Lewis base
- noncovalent interaction
- pK_a
- polar covalent bond
- resonance form
- resonance hybrid
- van der Waals force

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2.16: Summary

Understanding organic chemistry means knowing not just what happens but also why and how it happens at the molecular level. In this chapter, we've reviewed some of the ways that chemists describe and account for chemical reactivity, thereby providing a foundation for understanding the specific reactions that will be discussed in subsequent chapters.

Organic molecules often have **polar covalent bonds** as a result of unsymmetrical electron sharing caused by differences in the **electronegativity** of atoms. A carbon–oxygen bond is polar, for example, because oxygen attracts the shared electrons more strongly than carbon does. Carbon–hydrogen bonds are relatively nonpolar. Many molecules as a whole are also polar, owing to the presence of individual polar bonds and electron lone pairs. The polarity of a molecule is measured by its **dipole moment**, $\boldsymbol{\mu}$.

Plus (+) and minus (–) signs are often used to indicate the presence of **formal charges** on atoms in molecules. Assigning formal charges to specific atoms is a bookkeeping technique that makes it possible to keep track of the valence electrons around an atom and offers some clues about chemical reactivity.

Some substances, such as acetate ion and benzene, can't be represented by a single line-bond structure and must be considered as a **resonance hybrid** of two or more structures, none of which would be correct by themselves. The only difference between two **resonance forms** is in the location of their π and nonbonding electrons. The nuclei remain in the same places in both structures, and the hybridization of the atoms remains the same.

Acidity and basicity are closely related to the ideas of polarity and electronegativity. A **Brønsted–Lowry acid** is a compound that can donate a proton (hydrogen ion, H^+), and a **Brønsted–Lowry base** is a compound that can accept a proton. The strength of a Brønsted–Lowry acid or base is expressed by its **acidity constant, $\boldsymbol{K_a}$**, or by the negative logarithm of the acidity constant, **p$\boldsymbol{K_a}$**. The larger the pK_a, the weaker the acid. More useful is the Lewis definition of acids and bases. A **Lewis acid** is a compound that has a low-energy empty orbital that can accept an electron pair; Mg^{2+}, BF_3, $AlCl_3$, and H^+ are examples. A **Lewis base** is a compound that can donate an unshared electron pair; NH_3 and H_2O are examples. Most organic molecules that contain oxygen and nitrogen can act as Lewis bases toward sufficiently strong acids.

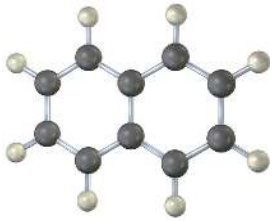
A variety of **noncovalent interactions** have a significant effect on the properties of large biomolecules. **Hydrogen bonding**—the attractive interaction between a positively polarized hydrogen atom bonded to an oxygen or nitrogen atom with an unshared electron pair on another O or N atom, is particularly important in giving proteins and nucleic acids their shapes.

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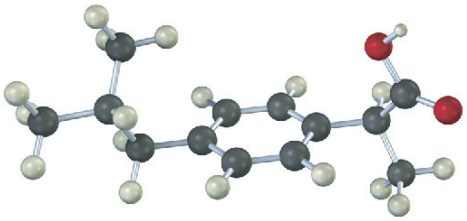
- **2.15: Summary** by OpenStax is licensed CC BY-NC-SA 4.0. Original source: https://openstax.org/details/books/organic-chemistry.

2.17: Additional Problems

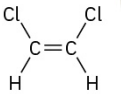
PROBLEM2-20 Fill in the multiple bonds in the following model of naphthalene, $C_{10}H_8$ (black = C, gray = H). How many resonance structures does naphthalene have? Draw them.

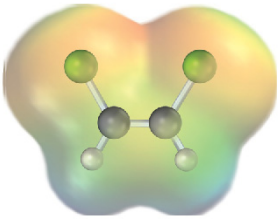


PROBLEM2-21 The following model is a representation of ibuprofen, a common over-the-counter pain reliever. Indicate the positions of the multiple bonds, and draw a skeletal structure (black = C, red = O, gray = H).

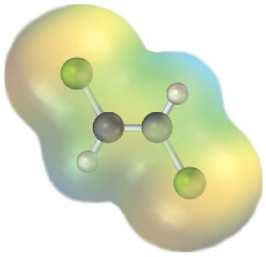


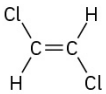
PROBLEM2-22 *cis*-1,2-Dichloroethylene and *trans*-1,2-dichloroethylene are *isomers*, compounds with the same formula but different chemical structures. Look at the following electrostatic potential maps, and tell whether either compound has a dipole moment.





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



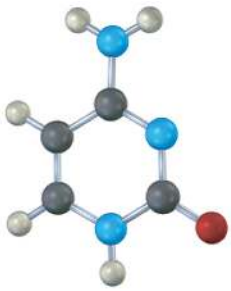


***trans*-1,2-Dichloroethylene**

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).



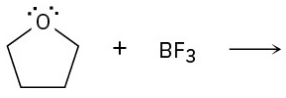
(a) Adenine

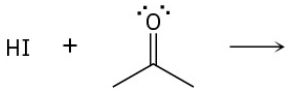


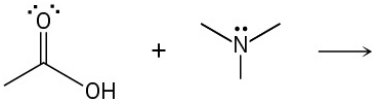
(b) Cytosine

Mechanism Problems

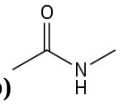
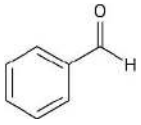
PROBLEM2-24 Predict the product(s) of the following acid/base reactions. Draw curved arrows to show the formation and breaking of bonds.

(a) 

(b) 

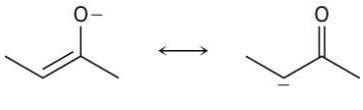
(c) 

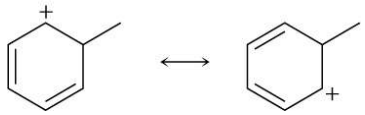
PROBLEM2-25 Use curved arrows to draw the protonated form of the following Lewis bases.

(a)  **(b)**  **(c)**  **(d)** 

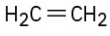
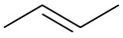
PROBLEM2-26 Use the curved-arrow formalism to show how the electrons flow in the resonance form on the left to give the one on the right.

(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

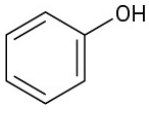
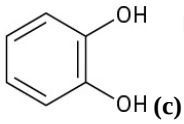
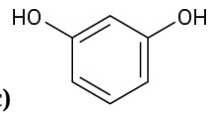
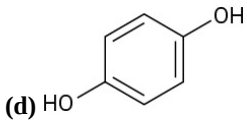
PROBLEM2-28 Identify the most electronegative element in each of the following molecules:

(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?

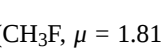
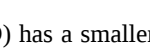
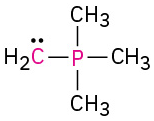
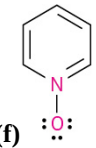
PROBLEM2-32 Phosgene, $Cl_2C{=}O$, has a smaller dipole moment than formaldehyde, $H_2C{=}{=}O$, even though it contains electronegative chlorine atoms in place of hydrogen. Explain.

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.

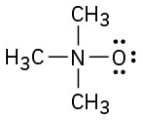
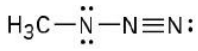
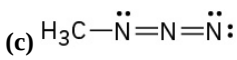
PROBLEM2-34 Methanethiol, CH_3SH, has a substantial dipole moment (μ = 1.52) even though carbon and sulfur have identical electronegativities. Explain.

Formal Charges

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

(a)  **(b)**  **(c)**  **(d)**  **(e)**  **(f)** 

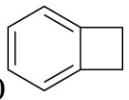
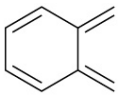
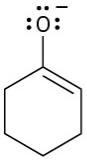
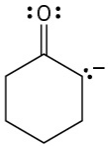
PROBLEM2-36 Assign formal charges to the atoms in each of the following molecules:

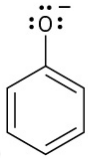
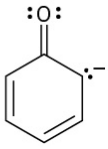
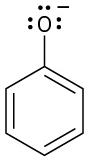
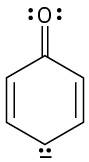
(a)  **(b)**  **(c)** 

Resonance

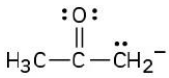
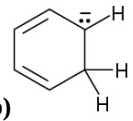
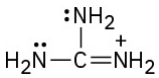
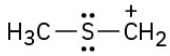
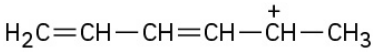
PROBLEM2-37

Which of the following pairs of structures represent resonance forms?

(a)  and  **(b)**  and 

(c)  and  **(d)**  and 

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

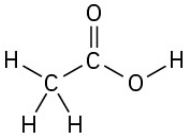
(a)  **(b)**  **(c)**  **(d)**  **(e)** 

PROBLEM2-39 1,3-Cyclobutadiene is a rectangular molecule with two shorter double bonds and two longer single bonds. Why do the following structures not represent resonance forms?



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

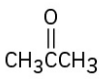
PROBLEM2-42 Draw electron-dot structures for the following molecules, indicating any unshared electron pairs. Which of the compounds are likely to act as Lewis acids and which as Lewis bases?

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

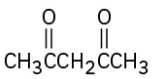
PROBLEM2-43 Write the products of the following acid–base reactions:

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

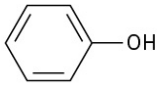
PROBLEM2-44 Rank the following substances in order of increasing acidity:



Acetone
(pK_a = 19.3)



2,4-Pentanedione
(pK_a = 9)



Phenol
(pK_a = 9.9)

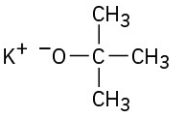


Acetic acid
(pK_a = 4.76)

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.)

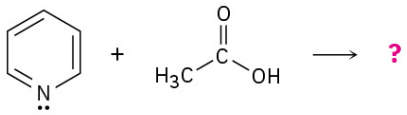
PROBLEM2-46 The ammonium ion (NH_4^+, pK_a = 9.25) has a lower pK_a than the methylammonium ion ($CH_3NH_3^+$, pK_a = 10.66). Which is the stronger base, ammonia (NH_3) or methylamine (CH_3NH_2)? Explain.

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:

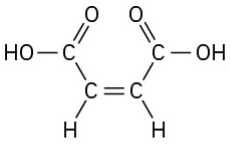
(a) Nitromethane, $K_a = 5.0 \times 10^{-11}$ **(b)** Acrylic acid, $K_a = 5.6 \times 10^{-5}$

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

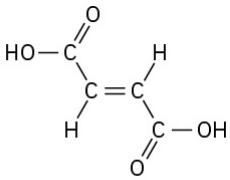
PROBLEM2-52 Sodium bicarbonate, $NaHCO_3$, is the sodium salt of carbonic acid (H_2CO_3), pK_a = 6.37. Which of the substances shown in Problem 2-44 will react significantly with sodium bicarbonate?

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

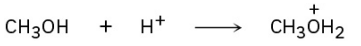


Fumaric acid

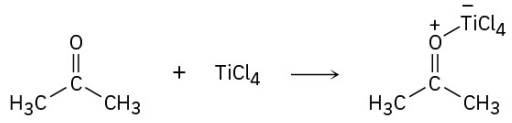
PROBLEM2-54 Assume that you have two unlabeled bottles, one of which contains phenol (pK_a = 9.9) and one of which contains acetic acid (pK_a = 4.76). In light of your answer to Problem 2-52, suggest a simple way to determine what is in each bottle.

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

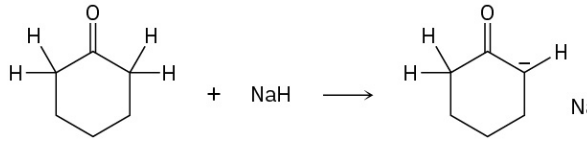
(a)



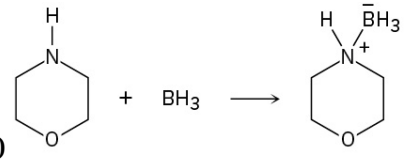
(b)



(c)

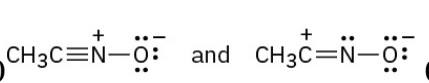


(d)

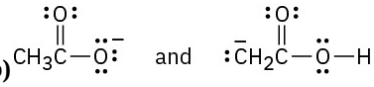


PROBLEM2-56 Which of the following pairs represent resonance structures?

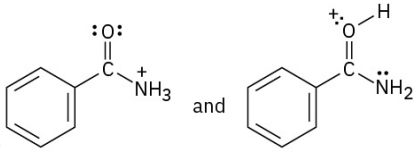
(a)



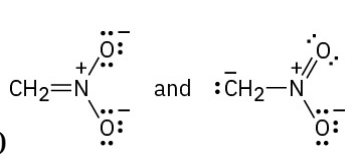
(b)



(c)

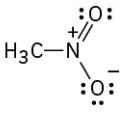


(d)

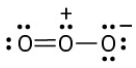


PROBLEM2-57 Draw as many resonance structures as you can for the following species, adding appropriate formal charges to each:

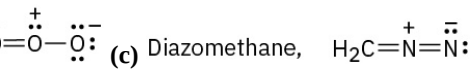
(a) Nitromethane,



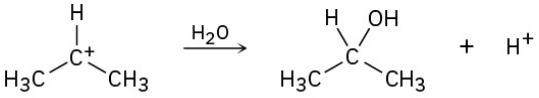
(b) Ozone,



(c) Diazomethane,

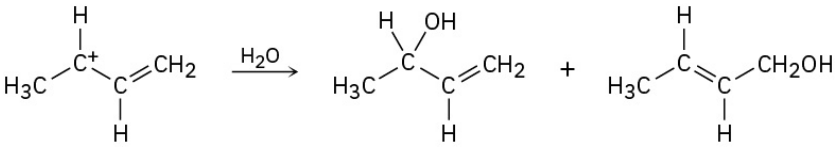


PROBLEM2-58 Carbocations, which contain a trivalent, positively charged carbon atom, react with water to give alcohols:

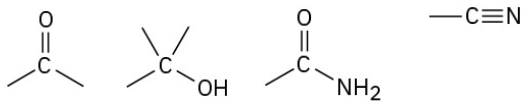


A carbocation **An alcohol**

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

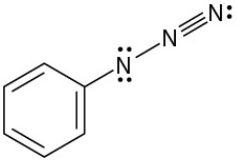


PROBLEM2-59 We'll see in the next chapter that organic molecules can be classified according to the functional groups they contain, where a functional group is a collection of atoms with a characteristic chemical reactivity. Use the electronegativity values given in Figure 2.3 to predict the direction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



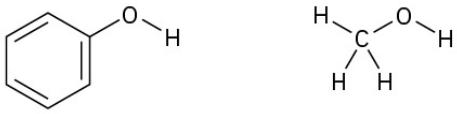
(a) Ketone (b) Alcohol (c) Amide (d) Nitrile

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.



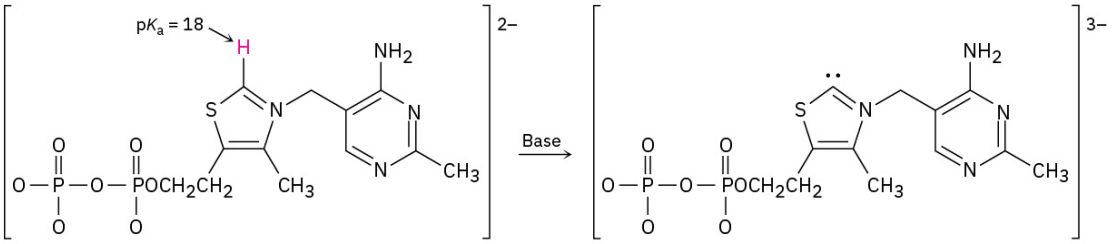
Azidobenzene

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.

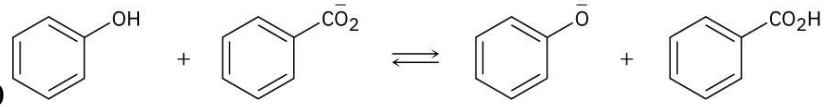


Thiamin diphosphate (TPP)

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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CHAPTER OVERVIEW

3: Organic Compounds- Alkanes and Their Stereochemistry

Learning Objectives

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

1. fulfill the detailed objectives listed under each section.
2. identify some of the commonest functional groups.
3. write the structures and names of the first ten straight-chain alkanes.
4. recognize and name the simple alkyl substituents, and give the systematic names for branched-chain alkanes.
5. briefly describe some of the processes used during the refining of petroleum.
6. briefly describe the physical properties of alkanes.
7. draw a number of possible conformations of some simple alkanes and alkane-like compounds, and represent the energies of such conformations on energy versus rotation diagrams.
8. define, and use in context, the key terms introduced in this chapter.

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

3.1: Why This Chapter?
3.2: Functional Groups
3.3: Alkanes and Alkane Isomers
3.4: Alkyl Groups
3.5: Naming Alkanes
3.6: Properties of Alkanes
3.7: Conformations of Ethane
3.8: Conformations of Other Alkanes
3.9: Chemistry Matters—Gasoline
3.10: Key Terms
3.11: Summary
3.12: Additional Problems

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3.1: Why This Chapter?

The group of organic compounds called *alkanes* are 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 3.1.1: The bristlecone pine is the oldest living organism on Earth. The waxy coating on its needles contains a mixture of organic compounds called alkanes, the subject of this chapter. (credit: "Gnarly Bristlecone Pine" by Rick Goldwaser/Flickr, CC BY 2.0)

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. We'll study the chemistry of specific families throughout much of this book, beginning in this chapter with a look at the simplest family, the *alkanes*.

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3.2: Functional Groups

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 3.2.1). This example is typical: *the chemistry of every organic molecule, regardless of size and complexity, is determined by the functional groups it contains.*

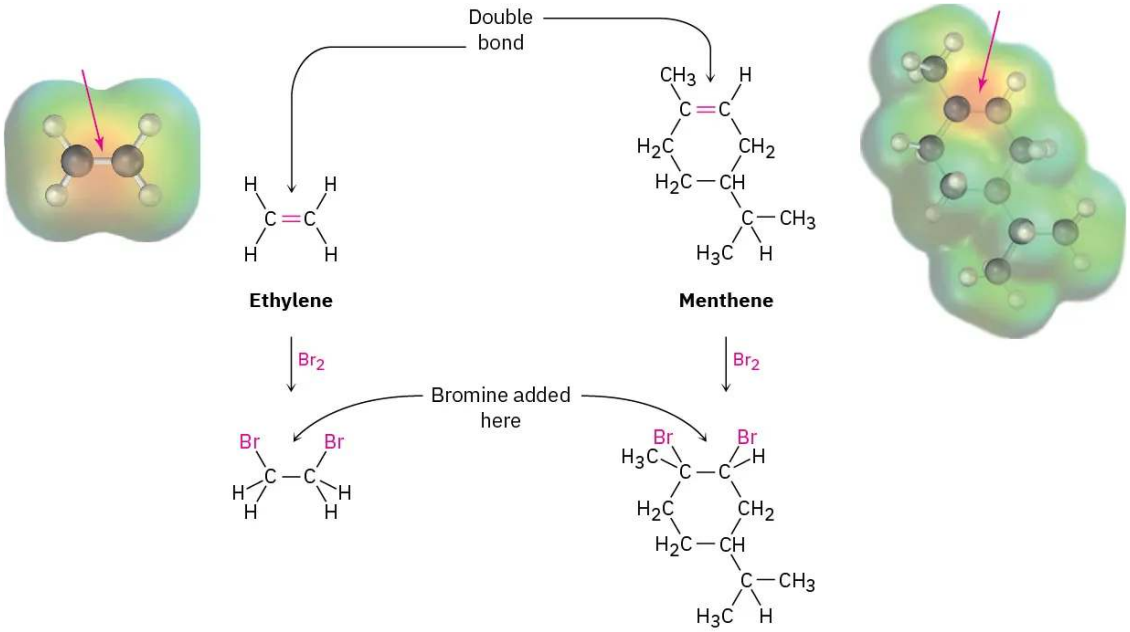


Figure 3.2.1: The reactions of ethylene and menthene with bromine. In both molecules, the carbon–carbon double-bond functional group has a similar polarity pattern, so both molecules react with Br_2 in the same way. The size and complexity of the molecules are not important.

Look at Table 3.2.1, 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.

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.

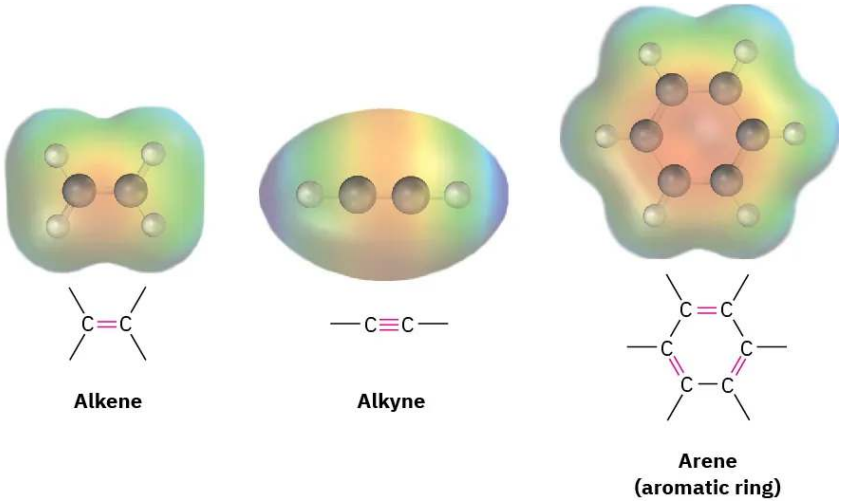
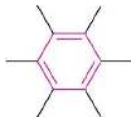
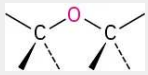
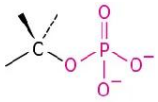
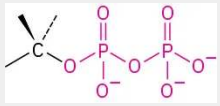
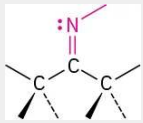
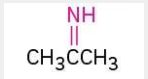
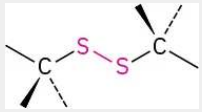
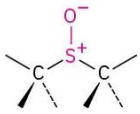
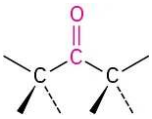
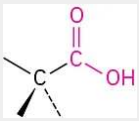
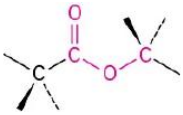
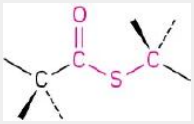
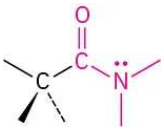
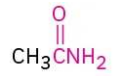
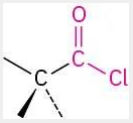
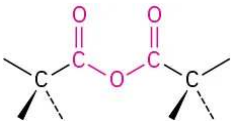


Table 3.2.1 Structures of Some Common Functional Groups

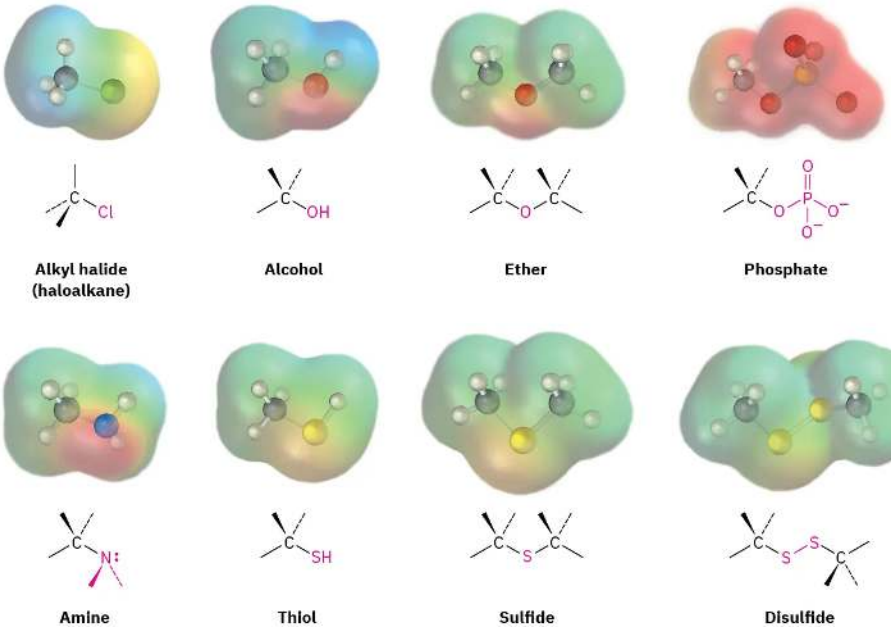
Name	Structure*	Name ending	Example
Alkene (double bond)		*-ene*	$H_2C{=}CH_2$ Ethene
Alkyne (triple bond)	–C≡C–	*-yne*	HC≡CH Ethyne
Arene (aromatic ring)		None	 Benzene
Halide	 (X=F, Cl, Br, I)	None	CH_3Cl Chloromethane
Alcohol		*-ol*	CH_3OH Methanol
Ether		*ether*	CH_3OCH_3 Dimethyl ether
Monophosphate		*phosphate*	$CH_3OPO_3^{2-}$ Methyl phosphate
Diphosphate		*diphosphate*	$CH_3OP_2O_6^{3-}$ Methyl diphosphate
Amine		*-amine*	CH_3NH_2 Methylamine
Imine (Schiff base)		None	 Acetone imine
Nitrile	–C≡N	*-nitrile*	CH3C≡N Ethanenitrile
Thiol		*-thiol*	CH_3SH Methanethiol
Sulfide		*sulfide*	CH_3SCH_3 Dimethyl sulfide
Disulfide		*disulfide*	CH_3SSCH_3 Dimethyl disulfide
Sulfoxide		*sulfoxide*	 Dimethyl sulfoxide

Name	Structure*	Name ending	Example
Aldehyde		*-al*	 Ethanal
Ketone		*-one*	 Propanone
Carboxylic acid		*-oic acid*	 Ethanoic acid
Ester		*-oate*	 Methyl ethanoate
Thioester		*-thioate*	 Methyl ethanethioate
Amide		*-amide*	 Ethanamide
Acid chloride		*-oyl chloride*	 Ethanoyl chloride
Carboxylic acid anhydride		*-oic anhydride*	 Ethanoic anhydride

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

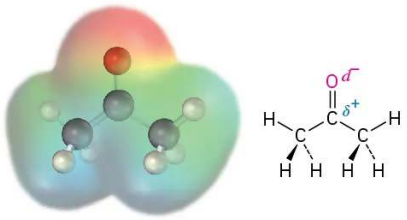
Functional Groups with Carbon Singly Bonded to an Electronegative Atom

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 ($–OPO_3^{2–}$), 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 ($\delta–$).

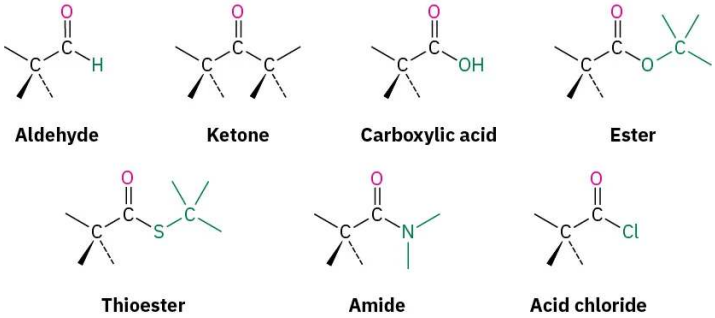


Functional Groups with a Carbon–Oxygen Double Bond (Carbonyl Groups)

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



? Exercise 3.2.1

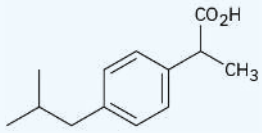
Use Table 3.2.1 to identify the functional groups in each of the following molecules:

Methionine, an amino acid:

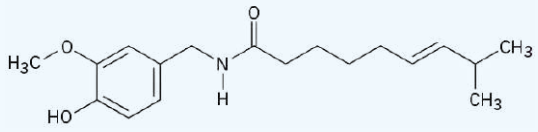
a. $CH_3SCH_2CH_2CH(NH_2)COOH$

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Ibuprofen, a pain reliever:

b. 

Capsaicin, the pungent substance in chili peppers:

c. 

Answer

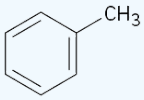
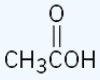
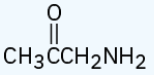
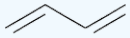
a. Sulfide, carboxylic acid, amine
b. Aromatic ring, carboxylic acid
c. Ether, alcohol, aromatic ring, amide, C=C bond

Exercise 3.2.2

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

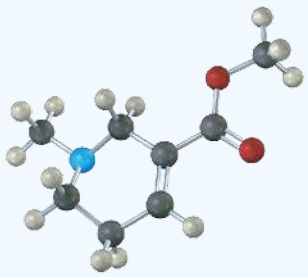
a. Alcohol
b. Aromatic ring
c. Carboxylic acid
d. Amine
e. Both ketone and amine
f. Two double bonds

Answer

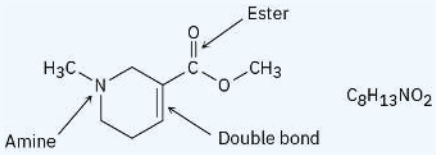
(a) **(b)**  **(c)**  **(d)** **(e)**  **(f)** 

Exercise 3.2.3

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

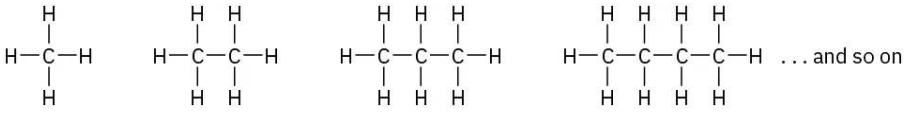


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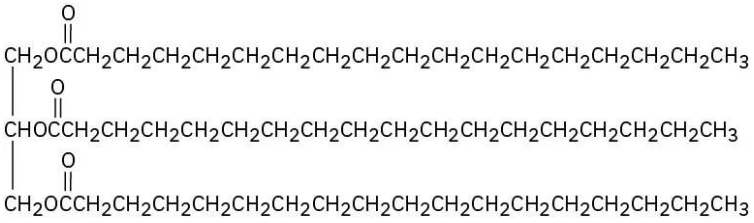
3.3: Alkanes and Alkane Isomers

Before beginning a systematic study of the different functional groups, let's look first 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." We'll see in **Section 27.2** that many animal fats contain long carbon chains similar to alkanes.



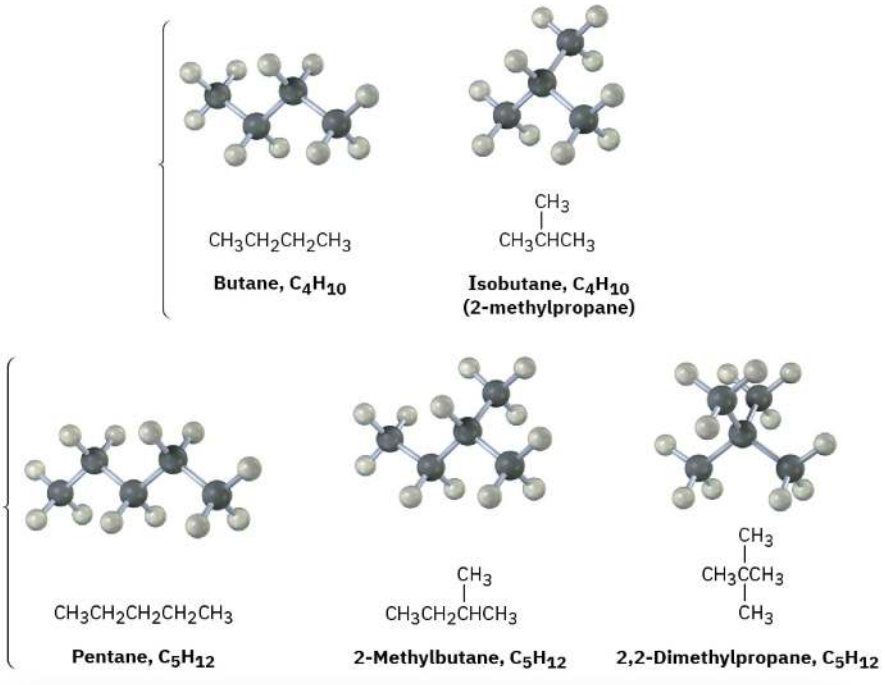
A typical animal fat

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, $CH_3CH_2CH_3$). 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.



Methane, CH_4 **Ethane, C_2H_6** **Propane, C_3H_8**

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.



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 3.3.1 shows, the number of possible alkane isomers increases dramatically with the number of carbon atoms.

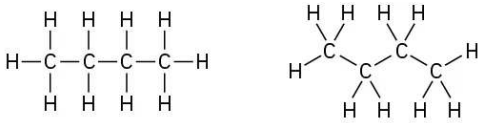
Table 3.3.1: Number of Alkane Isomers

Formula	Number of isomers	Formula	Number of isomers
C_6H_{14}	5	$C_{10}H_{22}$	75
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}	$CH_3CH(CH_3)CH_3$	and	$CH_3CH_2CH_2CH_3$
	2-Methylpropane (isobutane)		**Butane**
Different functional groups C_2H_6O	CH_3CH_2OH	and	CH_3OCH_3
	Ethanol		**Dimethyl ether**
Different position of functional groups C_3H_9N	$CH_3CH(NH_2)CH_3$	and	$CH_3CH_2CH_2NH_2$
	Isopropylamine		**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 3.3.2. 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 3.3.2 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 3.3.1: Drawing the Structures of Isomers

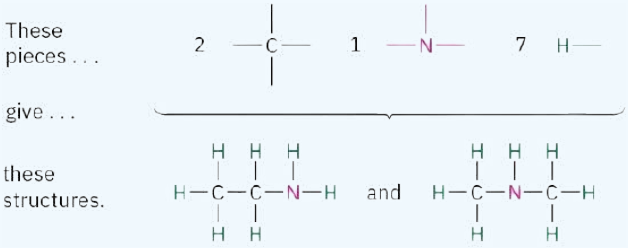
Propose structures for two isomers with the formula C_2H_7N.

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

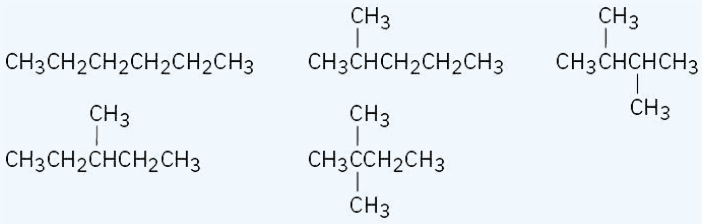
There are two isomeric structures. One has the connection C–C–N, and the other has the connection C–N–C.



Exercise 3.3.1

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

Answer

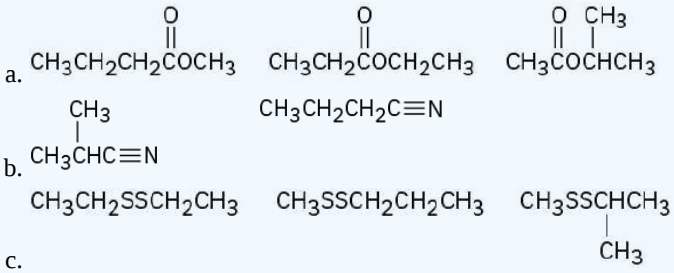


Exercise 3.3.2

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



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Exercise 3.3.3

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

a. Two
b. Four
c. Four

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3.4: 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 3.4.1. 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:

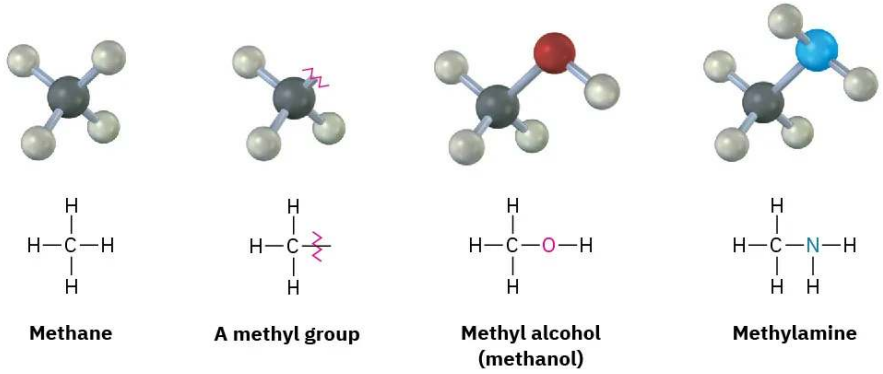
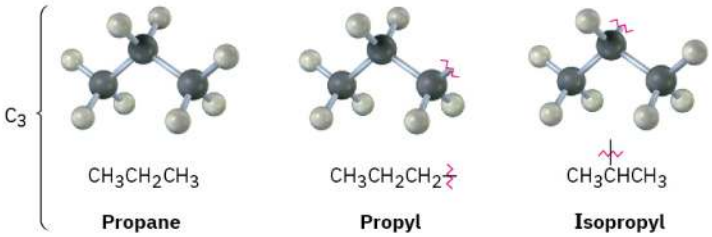


Table 3.4.1 Some Straight-Chain Alkyl Groups

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. Two 3-carbon alkyl groups and four 4-carbon alkyl groups are possible (Figure 3.4.1).



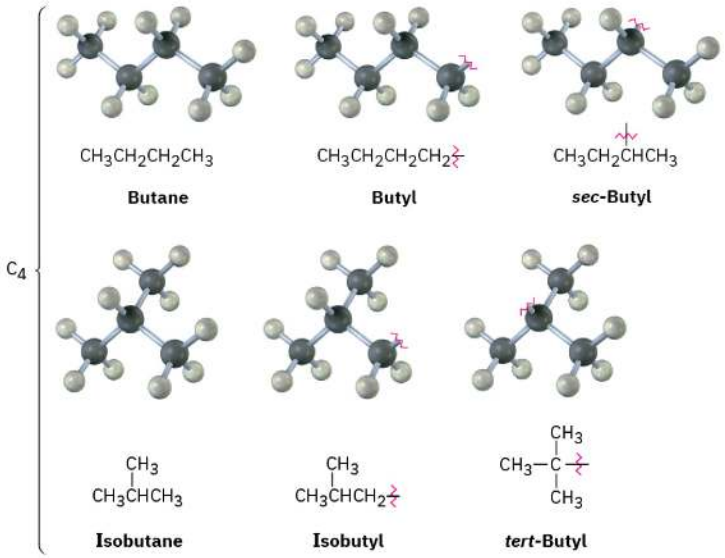


Figure 3.4.1: Alkyl groups generated from straight-chain alkanes.

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 3.4.1 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.**

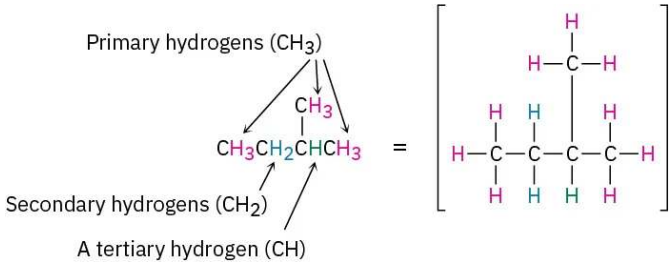
The symbol R is used here and throughout organic chemistry to represent a generalized organic group. The R group can be methyl, ethyl, propyl, or any of a multitude of others. You might think of **R** as representing the **R**est of the molecule, which isn't specified.

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?)

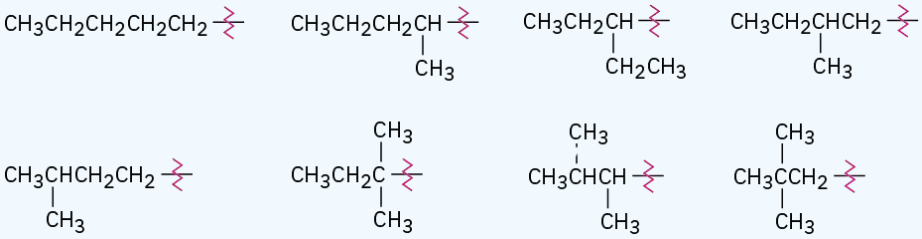


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Exercise 3.4.1

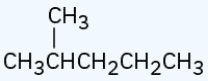
Draw the eight 5-carbon alkyl groups (pentyl isomers).

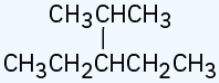
Answer

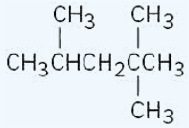


Exercise 3.4.2

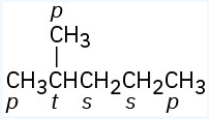
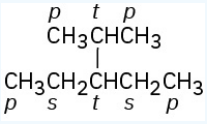
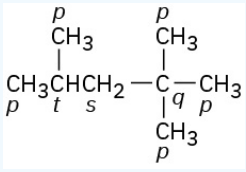
Identify the carbon atoms in the following molecules as primary, secondary, tertiary, or quaternary:

a. 

b. 

c. 

Answer

(a)  **(b)**  **(c)** 

Exercise 3.4.3

Identify the hydrogen atoms on the compounds shown in Problem 3.4.2 as primary, secondary, or tertiary.

Answer

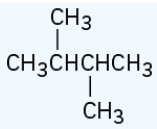
Primary carbons have primary hydrogens, secondary carbons have secondary hydrogens, and tertiary carbons have tertiary hydrogens.

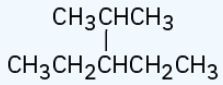
Exercise 3.4.4

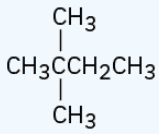
Draw structures of alkanes that meet the following descriptions:

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

a. 

b. 

c. 

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3.5: Naming Alkanes

In earlier times, when relatively few pure organic chemicals were known, 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.

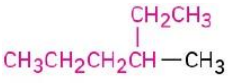


As we cover new functional groups in later chapters, the applicable IUPAC rules of nomenclature will be given. In addition, Appendix A at the back of this book gives an overall view of organic nomenclature and shows how compounds that contain more than one functional group are named. (If preferred, you 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.

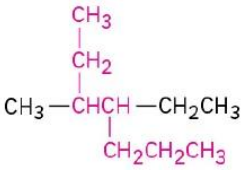
All but the most complex branched-chain alkanes can be named by following four steps. For a very few compounds, a fifth step is needed.

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."

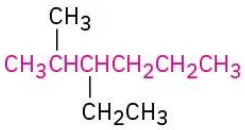


Named as a substituted hexane



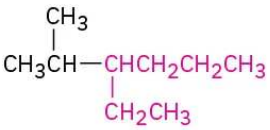
Named as a substituted heptane

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



Named as a hexane with *two* substituents

NOT



as a hexane with *one* substituent

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.



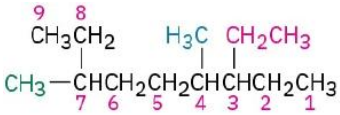
The first branch occurs at C3 in the proper system of numbering, not at C4.

(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

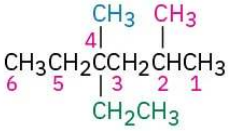
(a) Assign a number to each substituent to locate its point of attachment to the parent chain.



Named as a nonane

Substituents: On C3, CH_2CH_3 (3-ethyl)
On C4, CH_3 (4-methyl)
On C7, CH_3 (7-methyl)

(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.

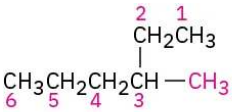


Named as a hexane

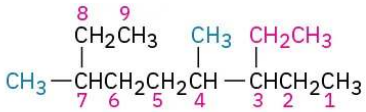
Substituents: On C2, CH_3 (2-methyl)
On C4, CH_3 (4-methyl)
On C4, CH_2CH_3 (4-ethyl)

STEP 4: Write the name as a single word

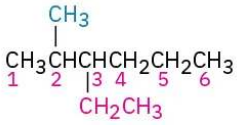
Use hyphens to separate the different prefixes, and use commas to separate numbers. If two or more different substituents are present, cite them in alphabetical order. If two or more identical substituents are present on the parent chain, use one of the multiplier prefixes *di-*, *tri-*, *tetra-*, and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



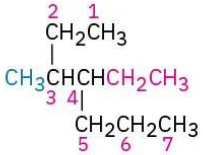
3-Methylhexane



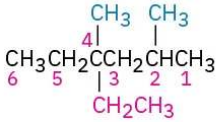
3-Ethyl-4,7-dimethylnonane



3-Ethyl-2-methylhexane



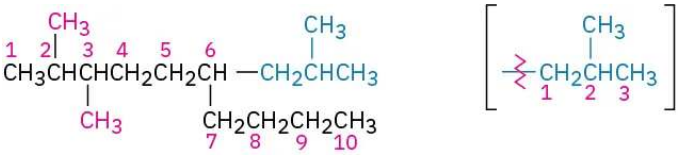
4-Ethyl-3-methylheptane



4-Ethyl-2,4-dimethylhexane

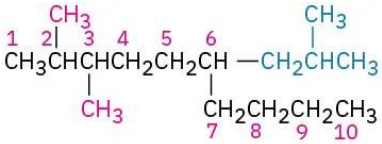
STEP 5: Name a branched substituent as though it were itself a compound

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.



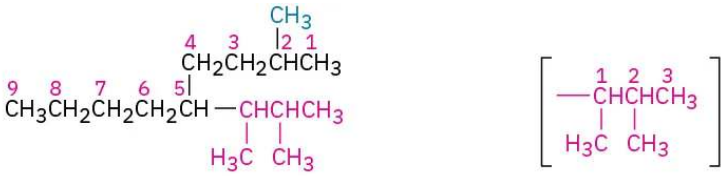
Named as a 2,3,6-trisubstituted decane **A 2-methylpropyl substituent**

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.



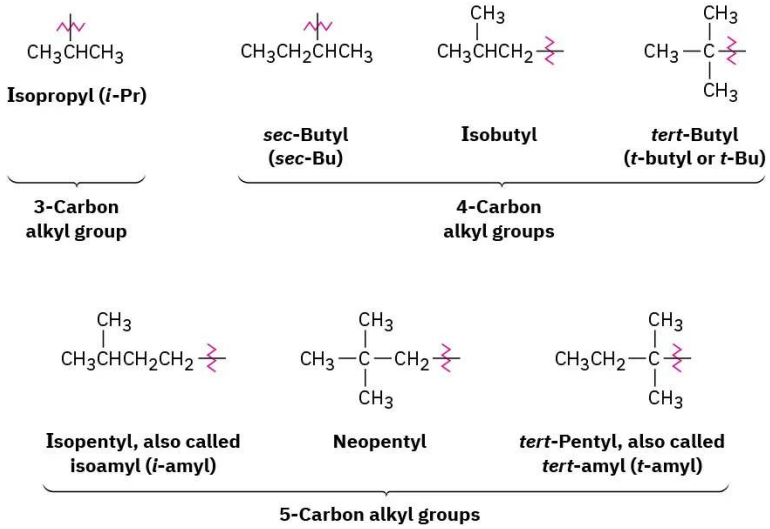
2,3-Dimethyl-6-(2-methylpropyl)decane

As a further example:



5-(1,2-Dimethylpropyl)-2-methylnonane **A 1,2-dimethylpropyl group**

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



Isopropyl (*i*-Pr)

3-Carbon alkyl group

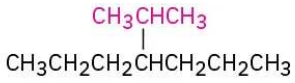
***sec*-Butyl (*sec*-Bu)** **Isobutyl** ***tert*-Butyl (*t*-butyl or *t*-Bu)**

4-Carbon alkyl groups

Isopentyl, also called isoamyl (*i*-amyl) **Neopentyl** ***tert*-Pentyl, also called *tert*-amyl (*t*-amyl)**

5-Carbon alkyl groups

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.

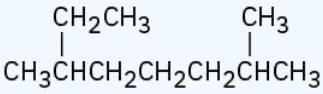


4-(1-Methylethyl)heptane or 4-Isopropylheptane

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 3.5.1: Naming Alkanes

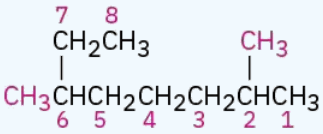
What is the IUPAC name for the following alkane?



Strategy

Find the longest continuous carbon chain in the molecule, and use that as the parent name. This molecule has a chain of eight carbons—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 3.5.2: Converting a Chemical Name into a Structure

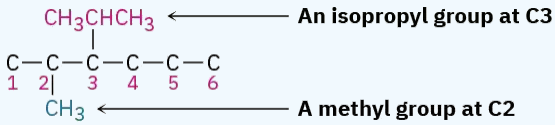
Draw the structure of 3-isopropyl-2-methylhexane.

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.

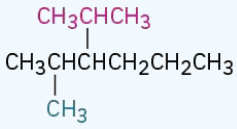
C–C–C–C–C–C Hexane

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



Finally, add hydrogens to complete the structure.

Solution



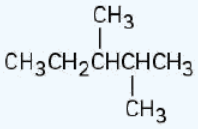
3-Isopropyl-2-methylhexane

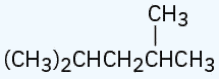
https://chem.libretexts.org/@go/page/563968

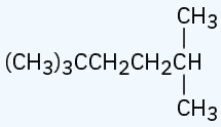
Exercise 3.5.1

Give IUPAC names for the following compounds:

a. The three isomers of C_5H_{12}

b. 

c. 

d. 

Answer

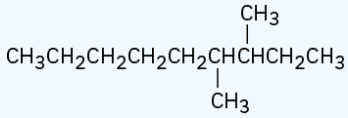
a. Pentane, 2-methylbutane, 2,2-dimethylpropane
b. 2,3-Dimethylpentane
c. 2,4-Dimethylpentane
d. 2,2,5-Trimethylhexane

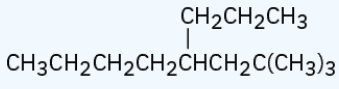
Exercise 3.5.2

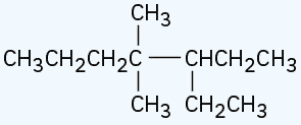
Draw structures corresponding to the following IUPAC names:

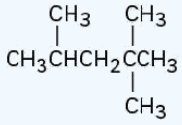
a. 3,4-Dimethylnonane
b. 3-Ethyl-4,4-dimethylheptane
c. 2,2-Dimethyl-4-propyloctane
d. 2,2,4-Trimethylpentane

Answer

a. 

b. 

c. 

d. 

Exercise 3.5.3

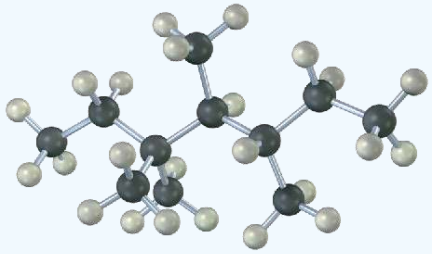
Name the eight 5-carbon alkyl groups you drew in Exercise 3.4.1.

Answer

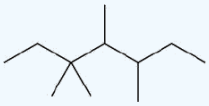
Pentyl, 1-methylbutyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl

Exercise 3.5.4

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



Answer



3,3,4,5-Tetramethylheptane

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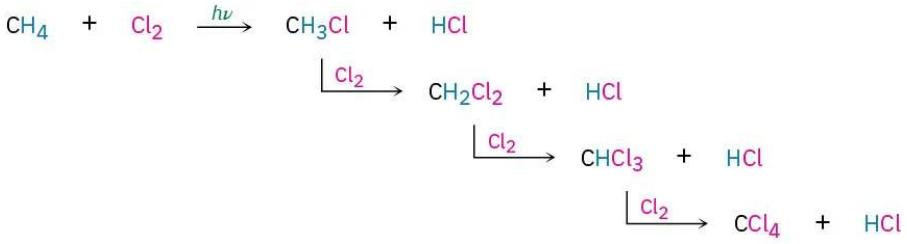
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3.6: Properties of Alkanes

Alkanes are sometimes referred to as *paraffins*, a word derived from the Latin *parum affinis*, meaning “little affinity.” This term aptly describes their behavior, for alkanes show little chemical affinity for other substances and are chemically inert to most laboratory reagents. They are also relatively inert biologically and are not often involved in the chemistry of living organisms. Alkanes do, however, react with oxygen, halogens, and a few other substances under appropriate conditions.Reaction with oxygen occurs during combustion in an engine or furnace when an alkane is used as a fuel. Carbon dioxide and water are formed as products, and a large amount of heat is released. For example, methane (natural gas) reacts with oxygen according to the equation

$$CH_4 + 2\,O_2 \longrightarrow CO_2 + 2\,H_2O + 890 \;\; kJ/mol \;(213\ kcal/mol) \tag{3.6.1}$$

The reaction of an alkane with Cl_2 occurs when a mixture of the two is irradiated with ultraviolet light (denoted *hυ*, where *υ* is the Greek letter *nu*). Depending on the time allowed and the relative amounts of the two reactants, a sequential substitution of the alkane hydrogen atoms by chlorine occurs, leading to a mixture of chlorinated products. Methane, for instance, reacts with Cl_2 to yield a mixture of CH_3Cl, CH_2Cl_2, $CHCl_3$, and CCl_4. We’ll look at this reaction in more detail in **Section 6.7**.



Alkanes show regular increases in both boiling point and melting point as molecular weight increases (Figure 3.6.1), an effect due to the presence of weak dispersion forces between molecules (Section 2.13). Only when sufficient energy is applied to overcome these forces does the solid melt or liquid boil. As you might expect, dispersion forces increase as molecular size increases, accounting for the higher melting and boiling points of larger alkanes.

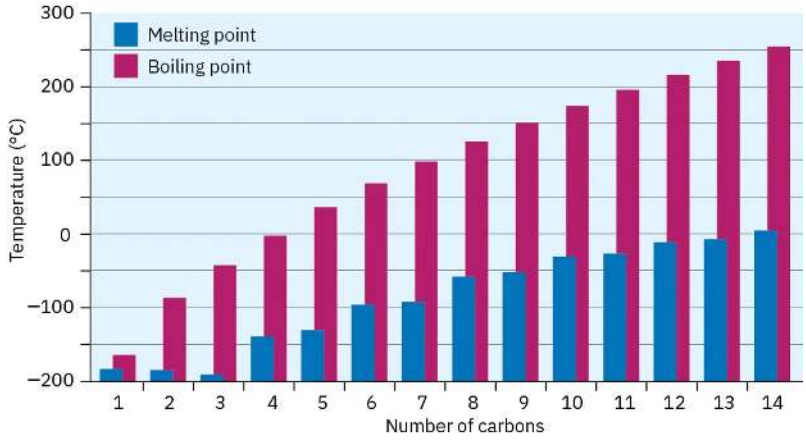


Figure 3.6.1: A plot of melting and boiling points versus number of carbon atoms for the C1–C14 straight-chain alkanes. There is a regular increase with molecular size.

Another effect seen in alkanes is that increased branching lowers an alkane’s boiling point. Thus, pentane has no branches and boils at 36.1 °C, isopentane (2-methylbutane) has one branch and boils at 27.85 °C, and neopentane (2,2-dimethylpropane) has two branches and boils at 9.5 °C. Similarly, octane boils at 125.7 °C, whereas isooctane (2,2,4-trimethylpentane) boils at 99.3 °C. Branched-chain alkanes are lower-boiling because they are more nearly spherical than straight-chain alkanes, have smaller surface areas, and consequently have smaller dispersion forces.

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3.7: 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 3.7.1).

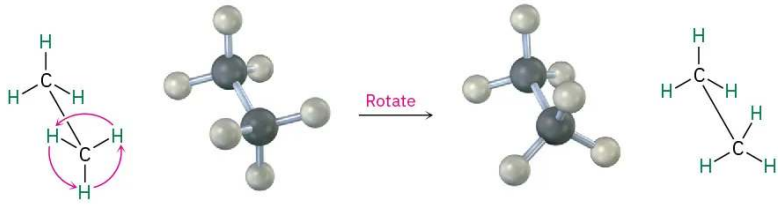


Figure 3.7.1: Rotation occurs around the carbon–carbon single bond in ethane because of σ bond cylindrical symmetry.

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 3.7.2. 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.

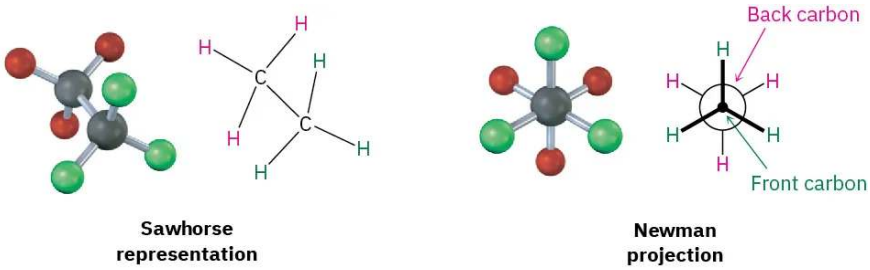
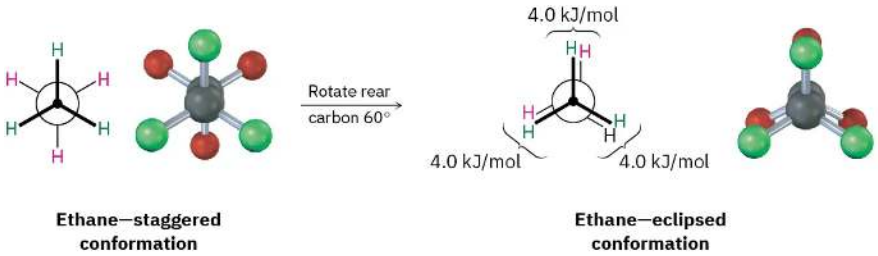


Figure 3.7.2: A sawhorse representation and a Newman projection of ethane. The sawhorse representation views the molecule from an oblique angle, while the Newman projection views the molecule end-on. Note that the molecular model of the Newman projection appears at first to have six atoms attached to 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 3.7.3.

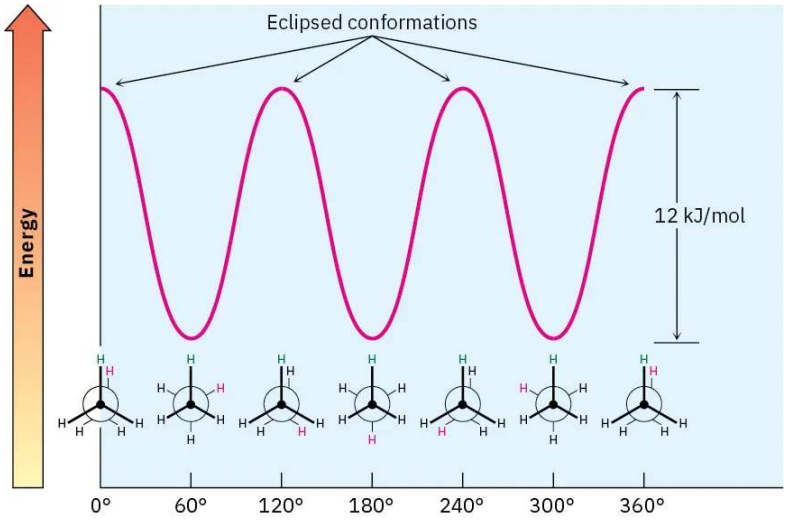


Figure 3.7.3: A graph of potential energy versus bond rotation in ethane. The staggered conformations are 12 kJ/mol lower in energy than the eclipsed conformations.

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3.8: 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 $14 - (2 \times 4.0) = 6.0$ kJ/mol (1.4 kcal/mol) to the eclipsing H ⟷ CH_3 interaction (Figure 3.8.1).

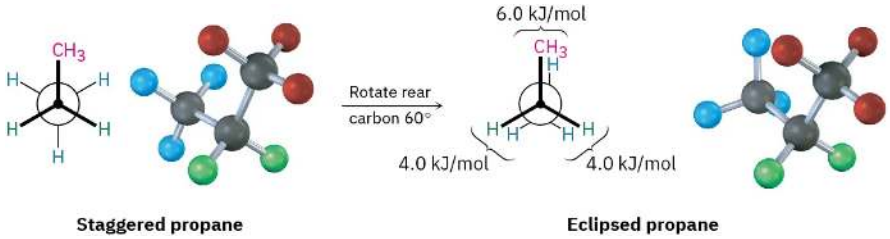
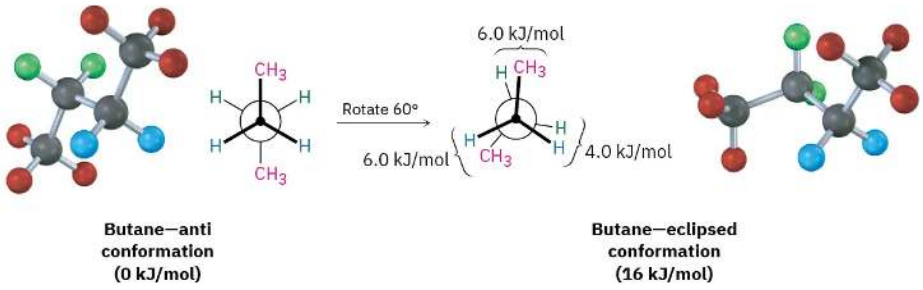
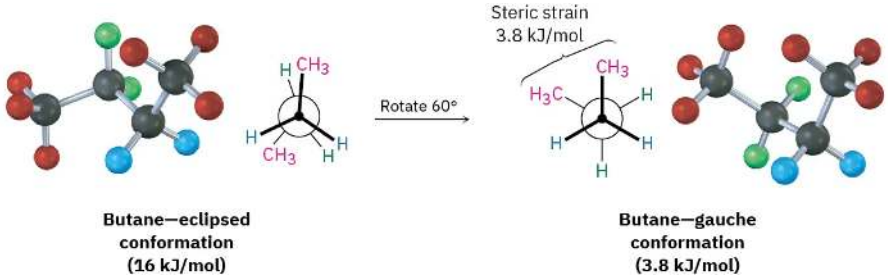


Figure 3.8.1: Newman projections of propane showing staggered and eclipsed conformations. The staggered conformer is lower in energy by 14 kJ/mol.

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).

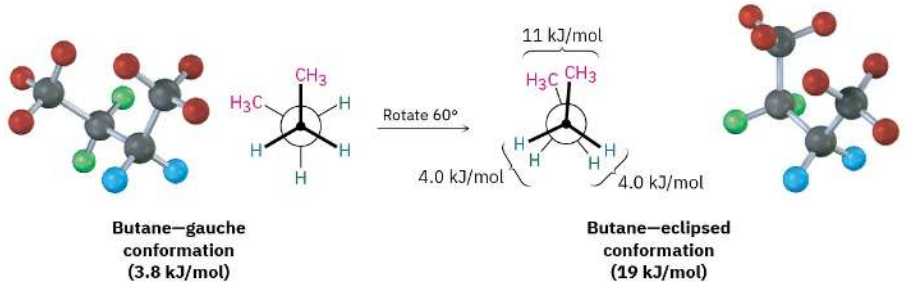


As bond rotation continues, an energy minimum is reached at the staggered conformation where the methyl groups are 60° apart. Called the gauche conformation, it lies 3.8 kJ/mol (0.9 kcal/mol) higher in energy than the anti conformation even though it has no eclipsing interactions. This energy difference 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.



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 $CH_3 \longleftrightarrow CH_3$ eclipsing interaction: total strain of 19 kJ/mol minus the strain of two $H \longleftrightarrow H$ eclipsing interactions (2 × 4.0 kcal/mol) equals 11 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 3.8.2.

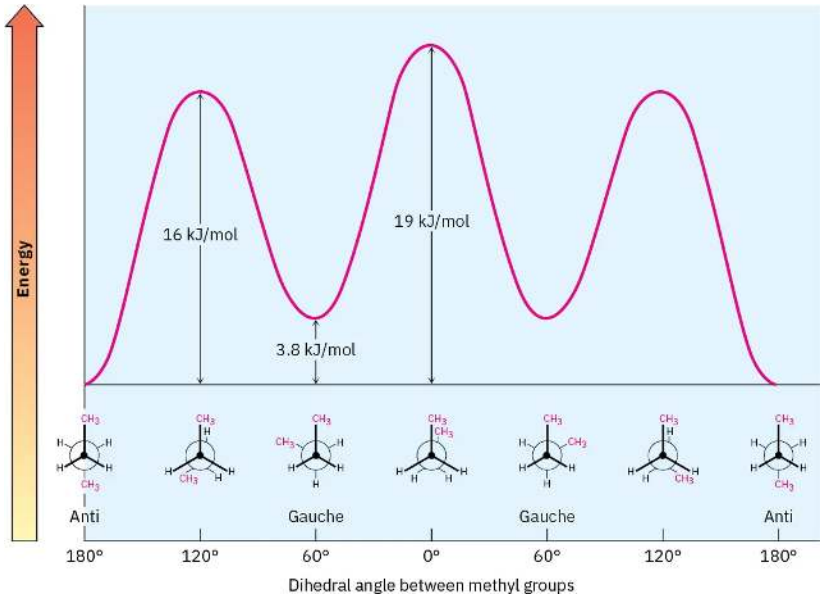


Figure 3.8.2: A plot of potential energy versus rotation for the C2−C3 bond in butane. The energy maximum occurs when the two methyl groups eclipse each other, and the energy minimum occurs when the two methyl groups are 180° apart (anti).

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 3.8.1.

Table 3.8.1: Energy Costs for Interactions in Alkane Conformers

Interaction	Cause	Energy cost	
		(kJ/mol)	(kcal/mol)
$H \longleftrightarrow H$ eclipsed	Torsional strain	4.0	1.0
$H \longleftrightarrow CH_3$ eclipsed	Mostly torsional strain	6.0	1.4
$CH_3 \longleftrightarrow CH_3$ eclipsed	Torsional and steric strain	11.0	2.6
$CH_3 \longleftrightarrow CH_3$ 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 3.8.3.

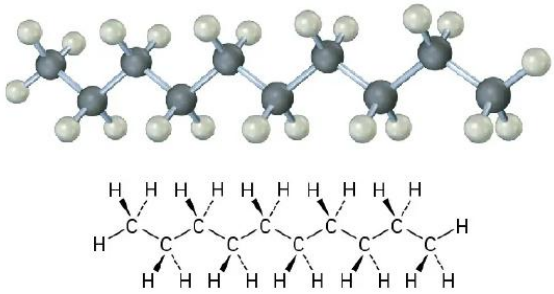


Figure 3.8.3: The most stable alkane conformation is the one in which all substituents are staggered and the carbon–carbon bonds are arranged anti, as shown in this model of decane.

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 3.8.1: 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

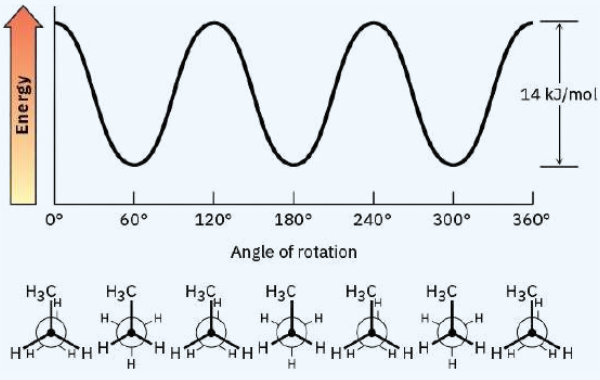


Most stable (staggered) Least stable (eclipsed)

Exercise 3.8.1

Make a graph of potential energy versus angle of bond rotation for propane, and assign values to the energy maxima.

Answer

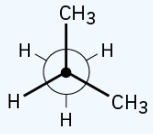


Exercise 3.8.2

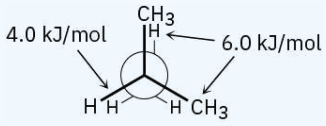
a. Draw a Newman projection of the most stable conformation.
b. Draw a Newman projection of the least stable conformation.
c. Make a graph of energy versus angle of rotation around the C2–C1 bond.
d. Assign relative values to the maxima and minima in your graph, given that an H ⟷ H eclipsing interaction costs 4.0 kJ/mol and an H ⟷ CH_3 eclipsing interaction costs 6.0 kJ/mol.

Answer

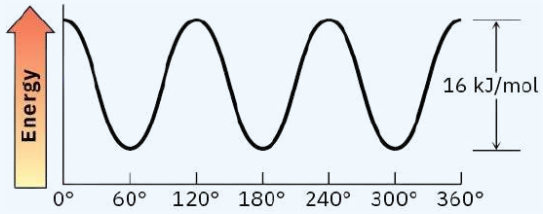
a.



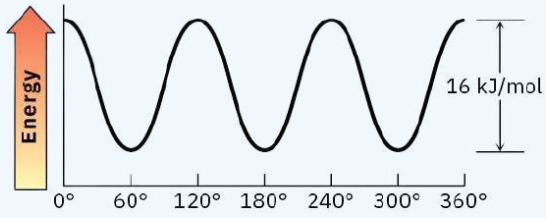
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c.



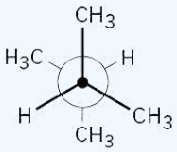
d.



Exercise 3.8.3

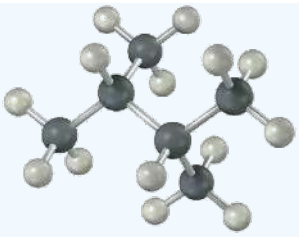
Sight along the C2–C3 bond of 2,3-dimethylbutane, and draw a Newman projection of the most stable conformation.

Answer

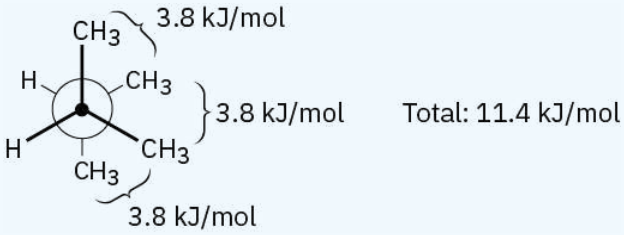


Exercise 3.8.4

Draw a Newman projection along the C2–C3 bond of the following conformation of 2,3-dimethylbutane, and calculate a total strain energy:



Answer



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3.9: 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.

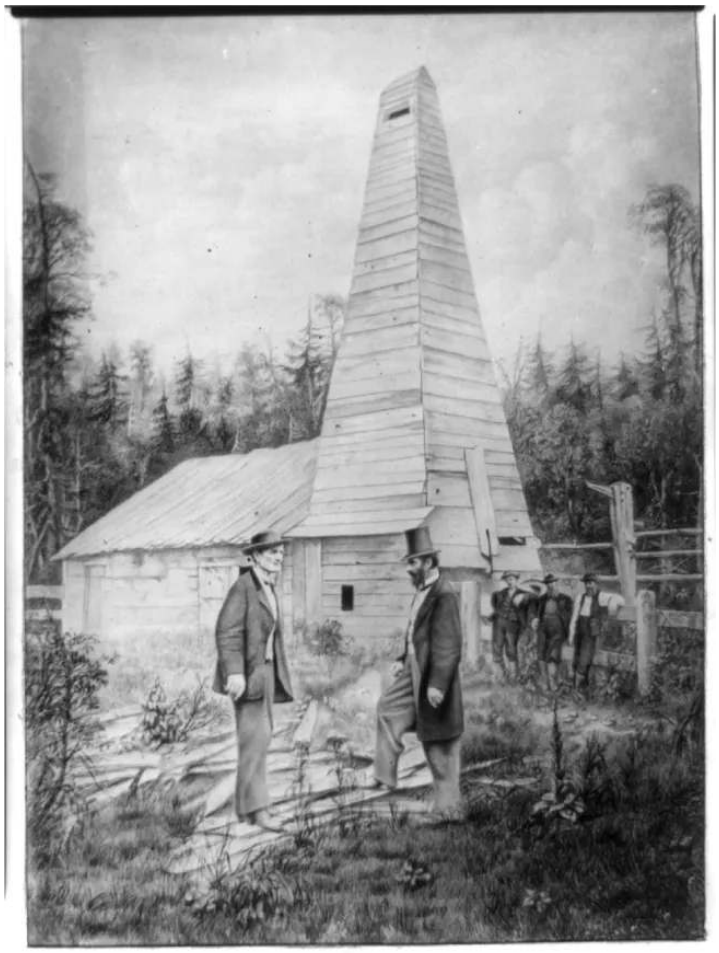


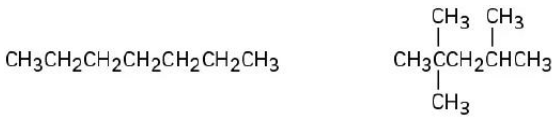
Figure 3.9.1: Gasoline is a finite resource. It won’t be around forever. (credit: “The first oil well” by Unknown/Library of Congress)

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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3.10: Key Terms

- alcohol
- aldehyde
- aliphatic
- alkane
- alkene
- alkyl group
- alkyl halide
- alkyne
- amide
- amine
- anti conformation
- arene
- branched-chain alkane
- carbonyl group
- carboxylic acid
- conformation
- conformational isomer
- conformer
- constitutional isomer
- eclipsed conformation
- ester
- ether
- functional group
- gauche conformation
- hydrocarbon
- isomer
- ketone
- Newman projection
- nitrile
- R group
- saturated
- sawhorse representation
- staggered conformation
- stereochemistry
- steric strain
- straight-chain alkane
- substituent
- sulfide
- thiol
- torsional strain

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3.11: Summary

Alkanes are relatively unreactive and rarely involved in chemical reactions, but they nevertheless provide a useful vehicle for introducing some important general ideas. In this chapter, we've used 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 **functional group** is a group of atoms within a larger molecule that has a characteristic chemical reactivity. Because functional groups behave in approximately the same way in all molecules where they occur, the chemical reactions of an organic molecule are largely determined by its functional groups.

Alkanes are a class of **saturated hydrocarbons** with the general formula C_nH_{2n+2}. They contain no functional groups, are relatively inert, and can be either **straight-chain** (*normal*) or **branched**. Alkanes are named by a series of IUPAC rules of nomenclature. Compounds that have the same chemical formula but different structures are called **isomers**. More specifically, compounds such as butane and isobutane, which differ in their connections between atoms, are called **constitutional isomers**.

Carbon–carbon single bonds in alkanes are formed by σ overlap of carbon sp^3 hybrid orbitals. Rotation is possible around σ bonds because of their cylindrical symmetry, and alkanes therefore exist in a large number of rapidly interconverting **conformations**. **Newman projections** make it possible to visualize the spatial consequences of bond rotation by sighting directly along a carbon–carbon bond axis. Not all alkane conformations are equally stable. The **staggered conformation** of ethane is 12 kJ/mol (2.9 kcal/mol) more stable than the **eclipsed conformation** because of **torsional strain**. In general, any alkane is most stable when all its bonds are staggered.

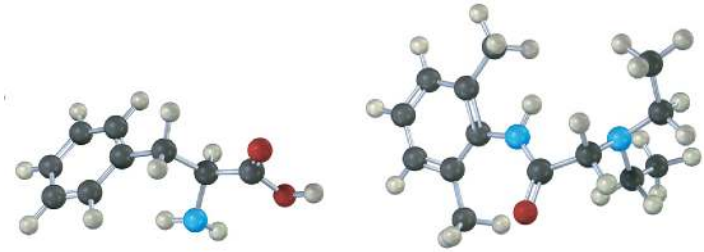
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3.12: Additional Problems

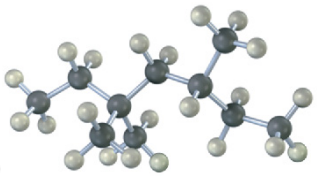
Visualizing Chemistry

PROBLEM 3-19 Identify the functional groups in the following substances, and convert each drawing into a molecular formula (red = O, blue = N).

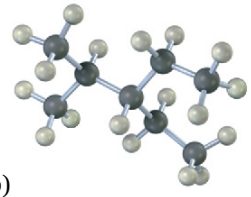


(a) Phenylalanine (b) Lidocaine

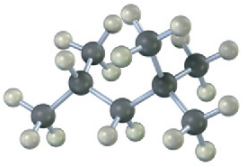
PROBLEM3-20 Give IUPAC names for the following alkanes, and convert each drawing into a skeletal structure.



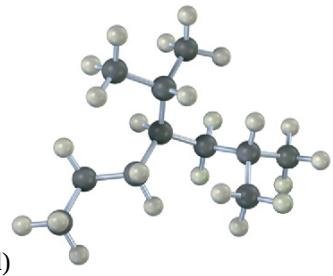
(a)



(b)



(c)



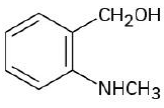
(d)

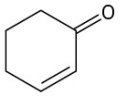
PROBLEM3-21 Draw a Newman projection along the C2–C3 bond of the following conformation of 2-butanol.

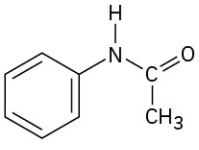


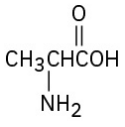
Functional Groups

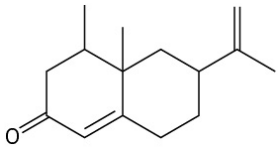
PROBLEM3-22 Locate and identify the functional groups in the following molecules.

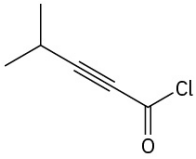
(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

PROBLEM3-23 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

PROBLEM3-24 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

PROBLEM3-25 Predict the hybridization of the carbon atom in each of the following functional groups:

(a) Ketone (b) Nitrile (c) Carboxylic acid

PROBLEM3-26 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.

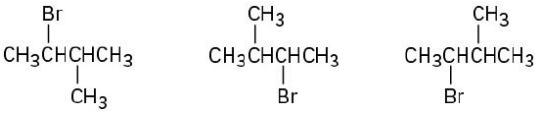
Isomers

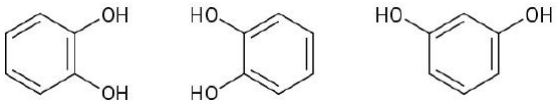
PROBLEM3-27 Draw structures that meet the following descriptions (there are many possibilities):

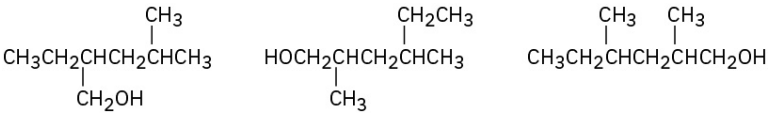
(a) Three isomers with the formula C_8H_{18}
(b) Two isomers with the formula $C_4H_8O_2$

PROBLEM3-28 Draw structures of the nine isomers of C_7H_{16}.

PROBLEM3-29 In each of the following sets, which structures represent the same compound and which represent different compounds?

(a) 

(b) 

(c) 

PROBLEM3-30 Seven constitutional isomers have the formula $C_4H_{10}O$. Draw as many as you can.

PROBLEM3-31 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 $C_4H_{10}O$

PROBLEM3-32 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

PROBLEM3-33 Draw and name all monobromo derivatives of pentane, $C_5H_{11}Br$.

PROBLEM3-34 Draw and name all monochloro derivatives of 2,5-dimethylhexane, $C_8H_{17}Cl$.

PROBLEM3-35 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

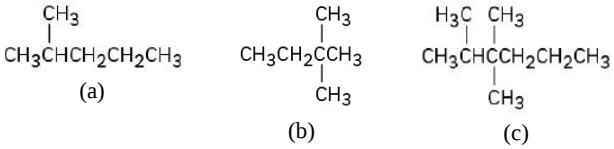
PROBLEM3-36 Draw a compound that:

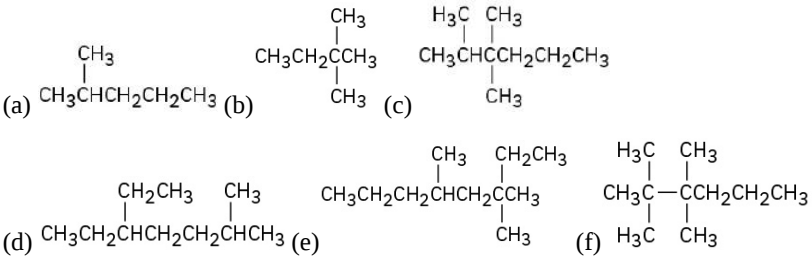
(a)Has only primary and tertiary carbons
(b) Has no secondary or tertiary carbons
(c) Has no secondary or tertiary carbons

PROBLEM3-37 Draw a compound that:

(a) Has nine primary hydrogens (b) Has only primary hydrogens

PROBLEM3-38 Give IUPAC names for the following compounds:





PROBLEM3-39 Name the five isomers of C_6H_{14}.

PROBLEM3-40 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

PROBLEM3-41 Propose structures and give IUPAC names for the following:

(a) A diethyldimethylhexane (b) A (3-methylbutyl)-substituted alkane

Conformations

PROBLEM3-42 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 $CH_3 \longleftrightarrow CH_3$ eclipsing interaction costs 11 kJ/mol (2.5 kcal/mol) and a $CH_3 \longleftrightarrow CH_3$ gauche interaction costs 3.8 kJ/mol (0.9 kcal/mol), make a quantitative plot of energy versus rotation about the C2–C3 bond.

PROBLEM3-43 What are the relative energies of the three possible staggered conformations around the C2–C3 bond in 2,3-dimethylbutane? (See Problem 3-42.)

PROBLEM3-44 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.

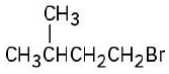
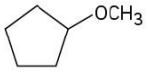
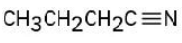
PROBLEM3-45Which conformation of 1,2-dibromoethane (Problem 3-44) would you expect to have the largest dipole moment? The observed dipole moment of 1,2-dibromoethane is μ = 1.0 D. What does this tell you about the actual conformation of the molecule?

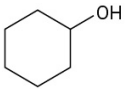
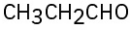
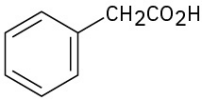
PROBLEM3-46 Draw the most stable conformation of pentane, using wedges and dashes to represent bonds coming out of the paper and going behind the paper, respectively.

PROBLEM3-47 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.

General Problems

PROBLEM3-48 For each of the following compounds, draw an isomer that has the same functional groups.

(a)  (b)  (c) 

(d)  (e)  (f) 

PROBLEM3-49 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?

PROBLEM3-50 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.

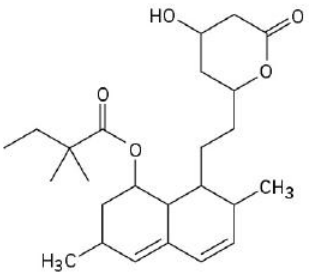
PROBLEM3-51 The barrier to rotation about the C–C bond in bromoethane is 15 kJ/mol (3.6 kcal/mol).

(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.

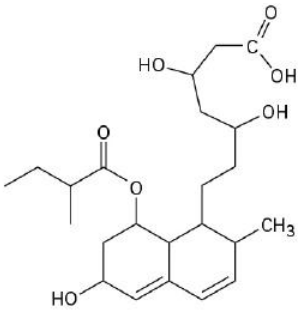
PROBLEM3-52 Increased substitution around a bond leads to increased strain. Take the four substituted butanes listed below, for example. For each compound, sight along the C2–C3 bond and draw Newman projections of the most stable and least stable conformations. Use the data in Table 3.5 to assign strain-energy 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

PROBLEM3-53 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.

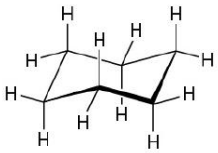


Simvastatin
(Zocor)

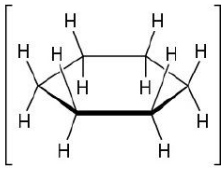


Pravastatin
(Pravachol)

PROBLEM3-54 In the next chapter we'll look at *cycloalkanes*—saturated cyclic hydrocarbons—and we'll see that the molecules generally adopt puckered, nonplanar conformations. Cyclohexane, for instance, has a puckered shape like a lounge chair rather than a flat shape. Why?

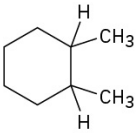


Nonplanar cyclohexane



Planar cyclohexane

PROBLEM3-55 We'll see in the next chapter that there are two isomeric substances, both named 1,2-dimethylcyclohexane. Explain.



1,2-Dimethylcyclohexane

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CHAPTER OVERVIEW

4: Organic Compounds - Cycloalkanes and their Stereochemistry

Learning Objectives

After you have completed Chapter 4, you should be able to

1. fulfill all of the detailed objectives listed under each individual section.
2. draw the *cis-trans* isomers of some simple disubstituted cycloalkanes, and write the IUPAC names of such compounds.
3. define, and use in context, the key terms introduced in this chapter.

This chapter deals with the concept of stereochemistry and conformational analysis in cyclic compounds. The causes of various ring strains and their effects on the overall energy level of a cycloalkane are discussed. We shall stress the stereochemistry of alicyclic compounds.

4.1: Why This Chapter?
4.2: Naming Cycloalkanes
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
4.12: Key Terms
4.13: Summary
4.14: Additional Problems

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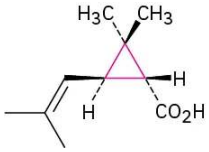
4.1: Why This Chapter?

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.



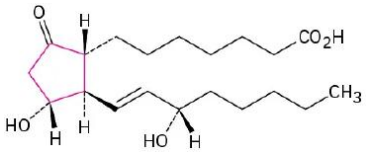
Figure 4.1.1: The musk gland of the male Himalayan musk deer secretes a substance once used in perfumery that contains cycloalkanes of 14 to 18 carbons. (credit: modification of work "Siberian musk deer in the tiaga" by ErikAdamsson/Wikimedia Commons, CC0 1.0)

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.



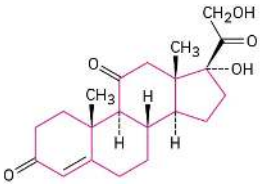
Chrysanthemic acid

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**.



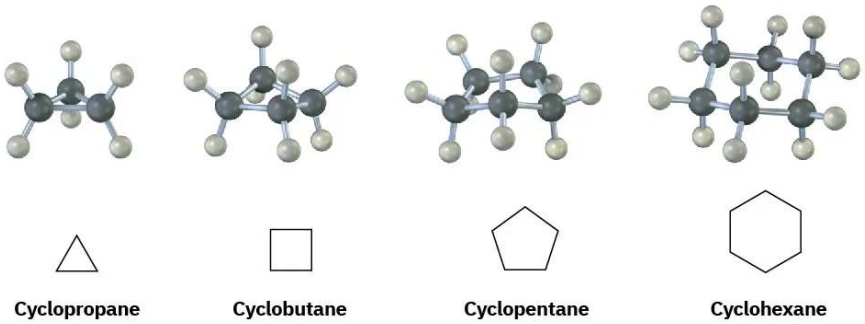
Cortisone

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4.2: 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 in (Section 3.5) for open-chain alkanes. For most compounds, there are only two steps.

STEP 1: Find the parent

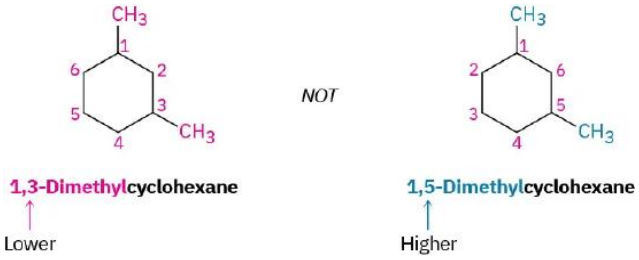
Count the number of carbon atoms in the ring and the number in the largest substituent. If the number of carbon atoms in the ring is equal to or greater than the number in the substituent, the compound is named as an alkyl-substituted cycloalkane. If the number of carbon atoms in the largest substituent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



Methylcyclopentane **1-Cyclopropylbutane**

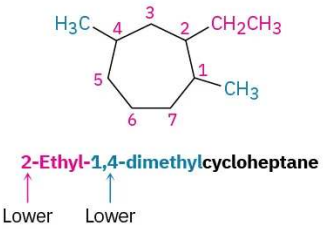
STEP 2: Number the substituents, and write the name

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.

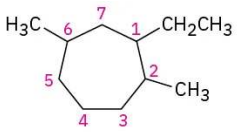


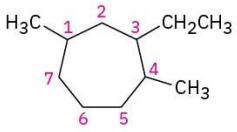
1,3-Dimethylcyclohexane *NOT* **1,5-Dimethylcyclohexane**

Lower Higher



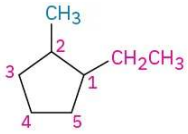
NOT





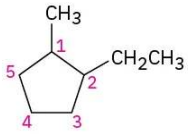
SUBSTEP 2a

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-.



1-Ethyl-2-methylcyclopentane

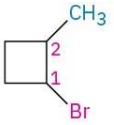
NOT



2-Ethyl-1-methylcyclopentane

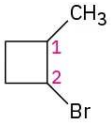
SUBSTEP 2b

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



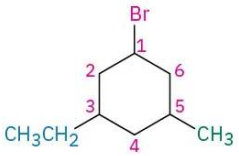
1-Bromo-2-methylcyclobutane

NOT

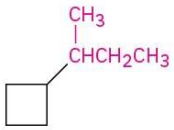


2-Bromo-1-methylcyclobutane

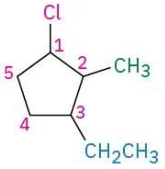
Some additional examples follow:



1-Bromo-3-ethyl-5-methylcyclohexane



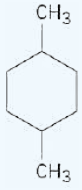
(1-Methylpropyl)cyclobutane or *sec*-butylcyclobutane



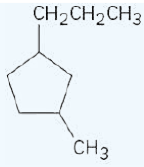
1-Chloro-3-ethyl-2-methylcyclopentane

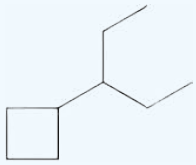
? Exercise 4.2.1

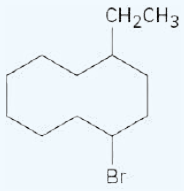
Give IUPAC names for the following cycloalkanes:

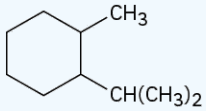
a. 

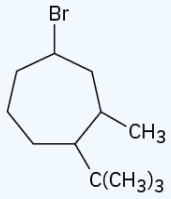
https://chem.libretexts.org/@go/page/563978

b. 

c. 

d. 

e. 

f. 

Answer

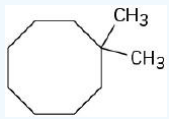
a. 1,4-Dimethylcyclohexane
b. 1-Methyl-3-propylcyclopentane
c. 3-Cyclobutylpentane
d. 1-Bromo-4-ethylcyclodecane
e. 1-Isopropyl-2-methylcyclohexane
f. 4-Bromo-1-*tert*-butyl-2-methylcycloheptane

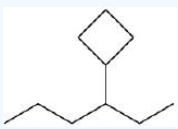
? Exercise 4.2.2

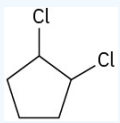
Draw structures corresponding to the following IUPAC names:

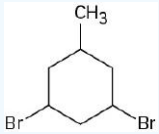
a. 1,1-Dimethylcyclooctane
b. 3-Cyclobutylhexane
c. 1,2-Dichlorocyclopentane
d. 1,3-Dibromo-5-methylcyclohexane

Answer

(a) 

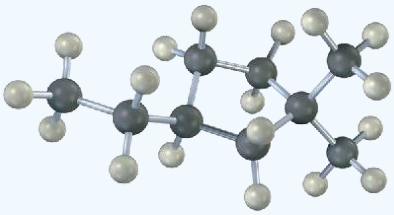
(b) 

(c) 

(d) 

Exercise 4.2.3

Name the following cycloalkane:



Answer

3-Ethyl-1,1-dimethylcyclopentane

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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 (Section 3.7 and Section 3.8), 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).

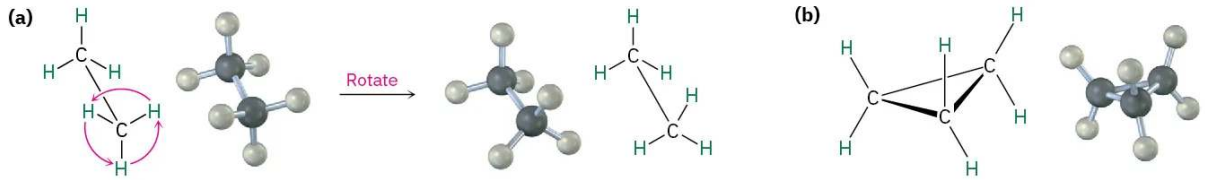
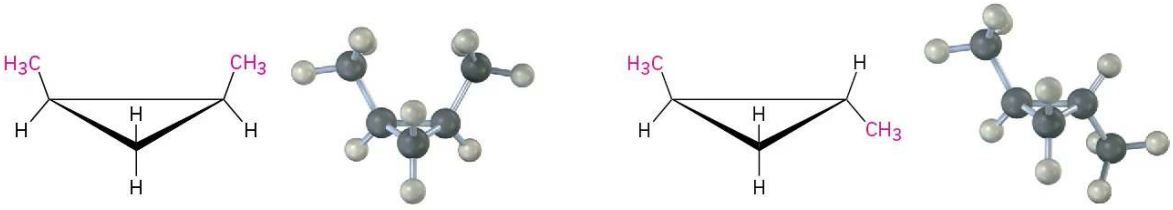


Figure 4.3.1: Bond rotation in ethane and cyclopropane. (a) Rotation occurs around the carbon–carbon bond in ethane, but **(b)** no rotation is possible around the carbon–carbon bonds in cyclopropane without breaking open the ring.

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.

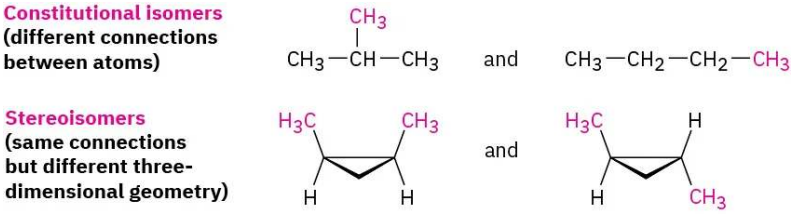
Because of their cyclic structures, cycloalkanes have two faces when viewed edge-on, a “top” face and a “bottom” face. As a result, isomerism is possible in substituted cycloalkanes. For example, there are two different 1,2-dimethylcyclopropane isomers, one with the two methyl groups on the same face 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.



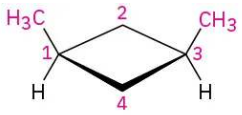
***cis*-1,2-Dimethylcyclopropane** ***trans*-1,2-Dimethylcyclopropane**

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.

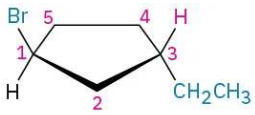
Unlike the constitutional isomers butane and isobutane, which have their atoms connected in a different order (Section 3.3), the two 1,2-dimethylcyclopropanes have the same order of connections but differ in the spatial orientation of the atoms. Such compounds, with atoms connected in the same order 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.



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.



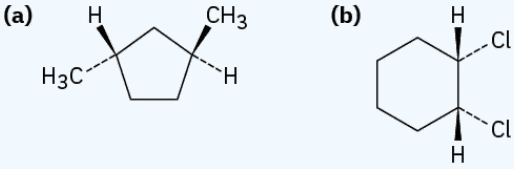
cis-1,3-Dimethylcyclobutane



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.

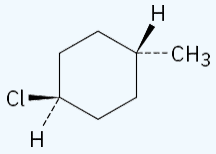
Solution

a. *trans*-1,3-Dimethylcyclopentane
b. *cis*-1,2-Dichlorocyclohexane

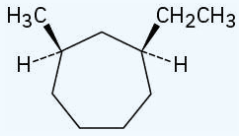
Exercise 4.3.1

Name the following substances, including the *cis*- or *trans*- prefix:

a.



b.



Answer

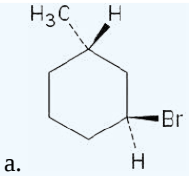
a. *trans*-1-Chloro-4-methylcyclohexane
b. *cis*-1-Ethyl-3-methylcycloheptane

Exercise 4.3.2

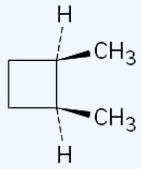
Draw the structures of the following molecules:

a. *trans*-1-Bromo-3-methylcyclohexane
b. *cis*-1,2-Dimethylcyclobutane
c. *trans*-1-*tert*-Butyl-2-ethylcyclohexane

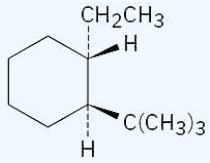
Answer



a.



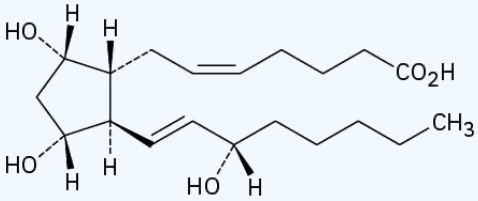
b.



c.

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



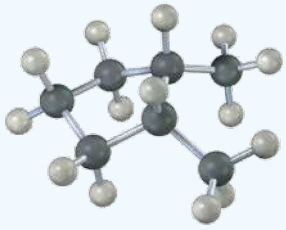
Prostaglandin $F_{2\alpha}$

Answer

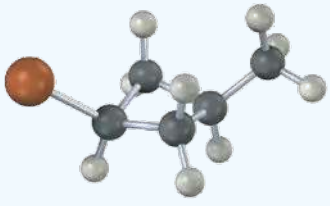
The two hydroxyl groups are cis. The two side chains are trans.

Exercise 4.3.4

Name the following substances, including the *cis*- or *trans*- prefix (red-brown = Br):



a.



b.

Answer

a. *cis*-1,2-Dimethylcyclopentane

b. *cis*-1-Bromo-3-methylcyclobutane

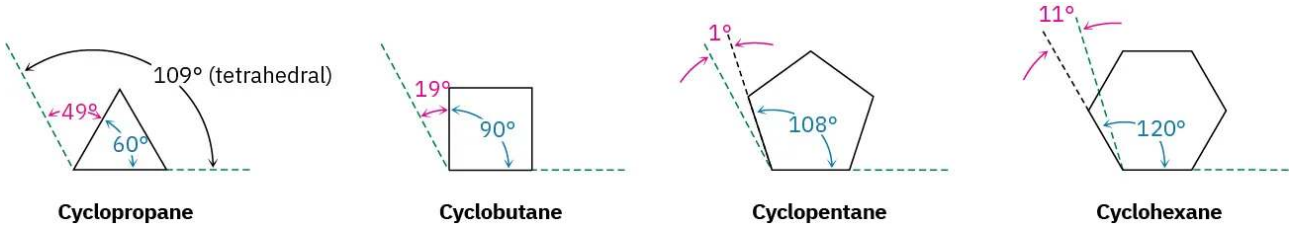
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4.4: Stability of Cycloalkanes - Ring Strain

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°.



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.

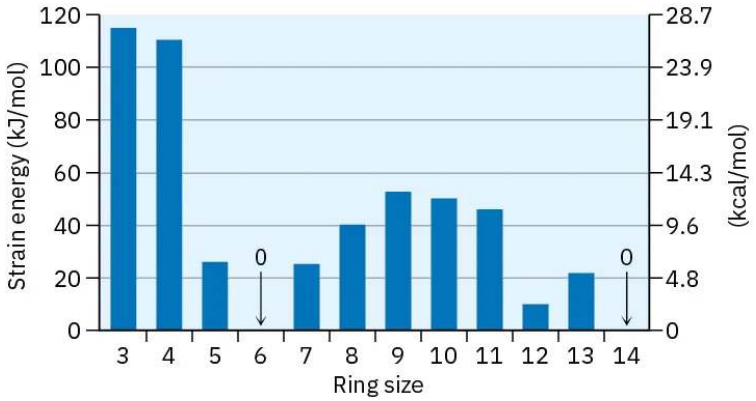


Figure 4.4.1: Cycloalkane strain energies, as calculated by taking the difference between cycloalkane heat of combustion per CH_2 and acyclic alkane heat of combustion per CH_2, and multiplying by the number of CH_2 units in a ring. Small and medium rings are strained, but cyclohexane rings and very 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 (Section 3.7) 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

Six interactions; 21% of strain

? 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

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).

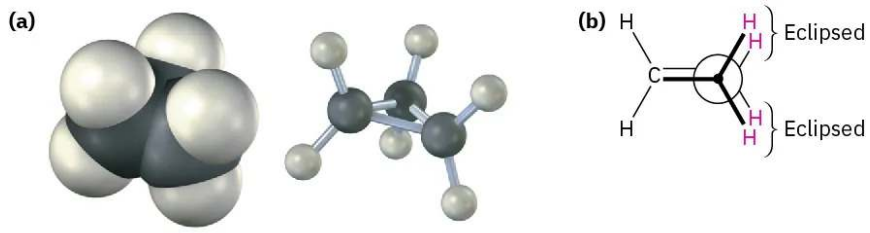
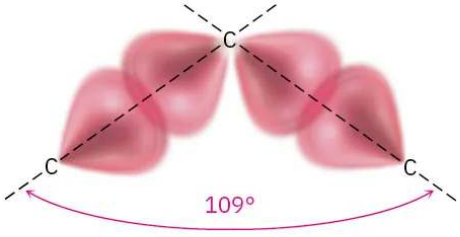
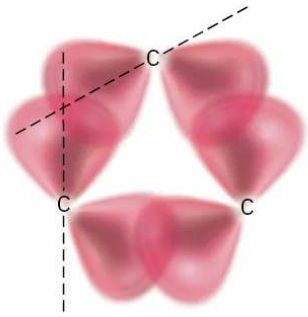


Figure 4.5.1: The structure of cyclopropane, showing the eclipsing of neighboring C−H bonds that gives rise to torsional strain. Part **(b)** is a Newman projection along a C−C bond.

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.

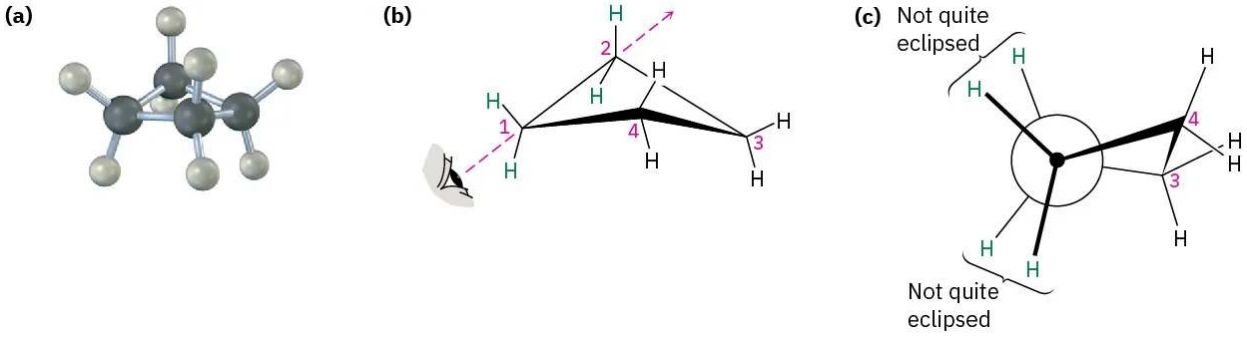


Figure 4.5.2: The conformation of cyclobutane. Part **(c)** is a Newman projection along a C−C bond, showing that neighboring C−H bonds are not quite eclipsed.

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).

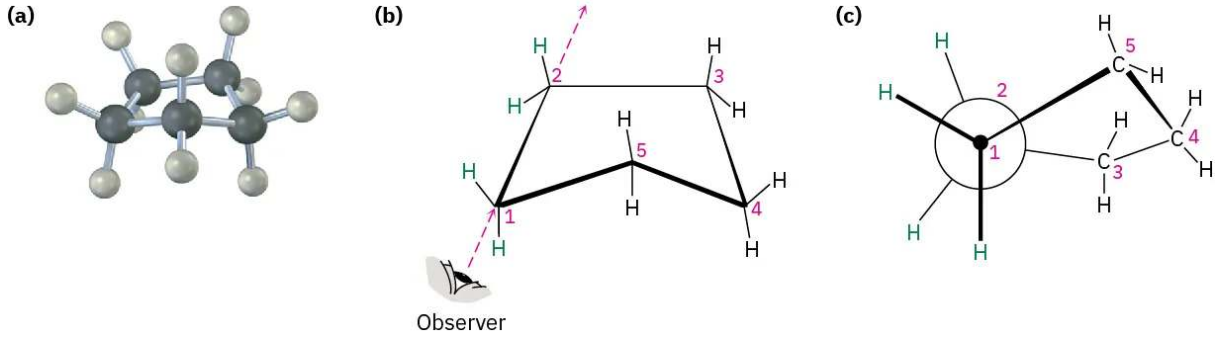


Figure 4.5.3: The conformation of cyclopentane. Carbons 1, 2, 3, and 4 are nearly coplanar, but carbon 5 is out of the plane. Part **(c)** is a Newman projection along the C1–C2 bond, showing that neighboring C−H bonds are nearly staggered.

? Exercise 4.5.1

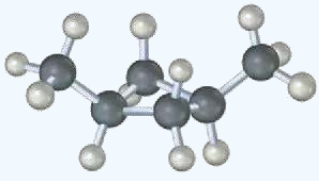
How many H ⟷ H eclipsing interactions would be present if cyclopentane were planar? Assuming an energy cost of 4.0 kJ/mol for each eclipsing interaction, how much torsional strain would planar cyclopentane have? Since the measured total strain of cyclopentane is 26 kJ/mol, how much of the torsional strain is relieved by puckering?

Answer

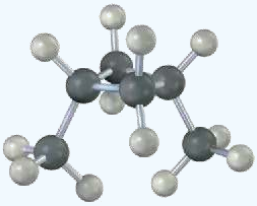
Ten eclipsing interactions; 40 kJ/mol; 35% is relieved.

? 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

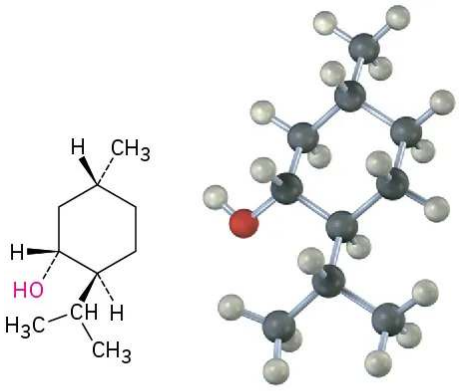
Conformation **(a)** is more stable because the methyl groups are farther apart.

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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.

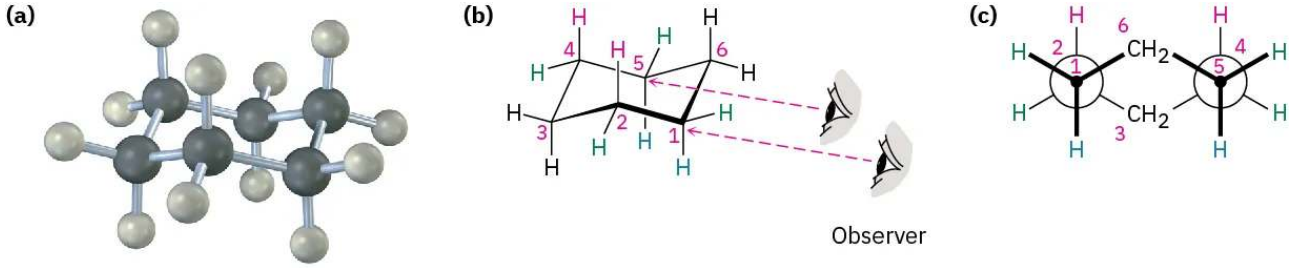


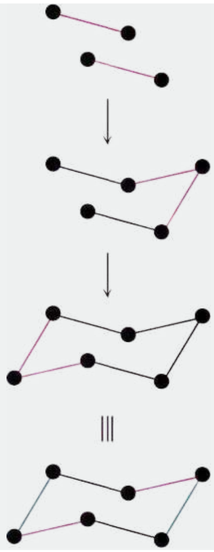
Figure 4.6.1: The strain-free chair conformation of cyclohexane. All C−C−C bond angles are 111.5°, close to the ideal 109° tetrahedral angle, and all neighboring C−H bonds are staggered.

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.

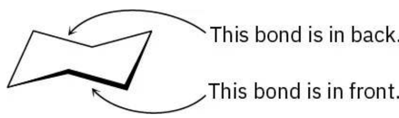
Chair Conformation of Cyclohexane

The chair conformation of cyclohexane can be drawn in three steps.

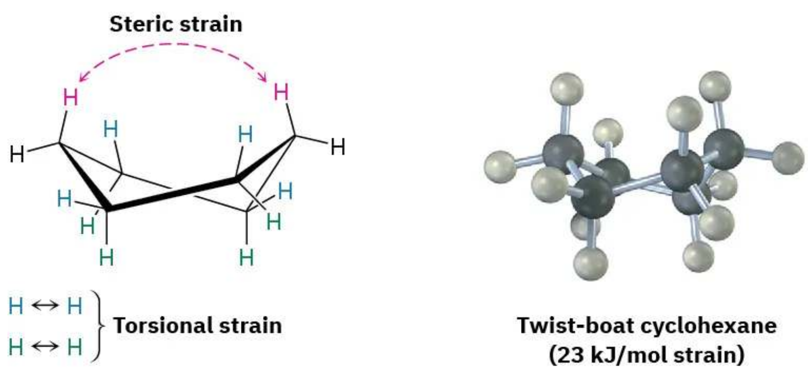
- **STEP 1:** Draw two parallel lines, slanted downward and slightly offset from each other. This means that four of the cyclohexane carbons lie in a plane.
- **STEP 2:** Place the topmost carbon atom above and to the right of the plane of the other four, and connect the bonds.
- **STEP 3:** Place the 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.

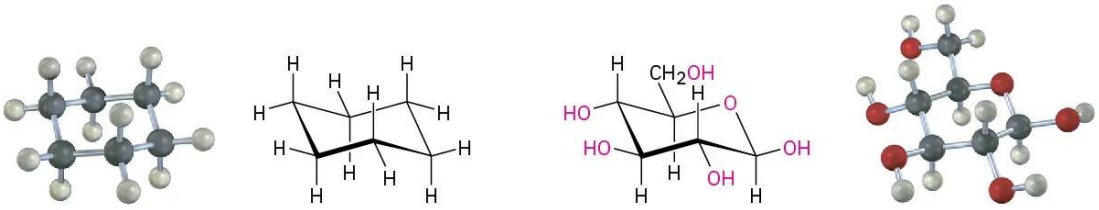


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4.7: Axial and Equatorial Bonds in Cyclohexane

The chair conformation of cyclohexane has many consequences. We'll see in **Section 11.10**, for instance, that the chemical behavior of many substituted cyclohexanes is influenced by their conformation. In addition, we'll see in **Section 25.6** 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**.

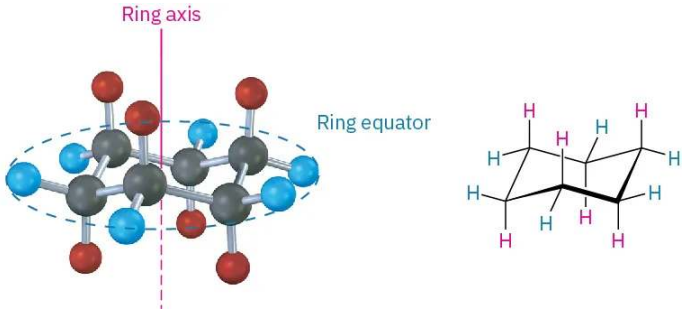


Figure 4.7.1: Axial and equatorial positions in chair cyclohexane. The six axial hydrogens are parallel to the ring axis, and the six equatorial hydrogens are in a band around the ring equator.

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).

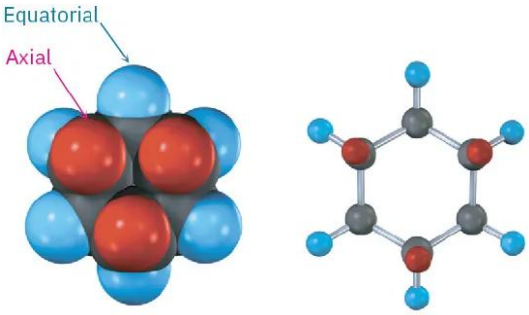


Figure 4.7.2: Alternating axial and equatorial positions in chair cyclohexane, looking directly down the ring axis. Each carbon atom has one axial and one equatorial position, and each face has alternating axial and equatorial positions.

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.

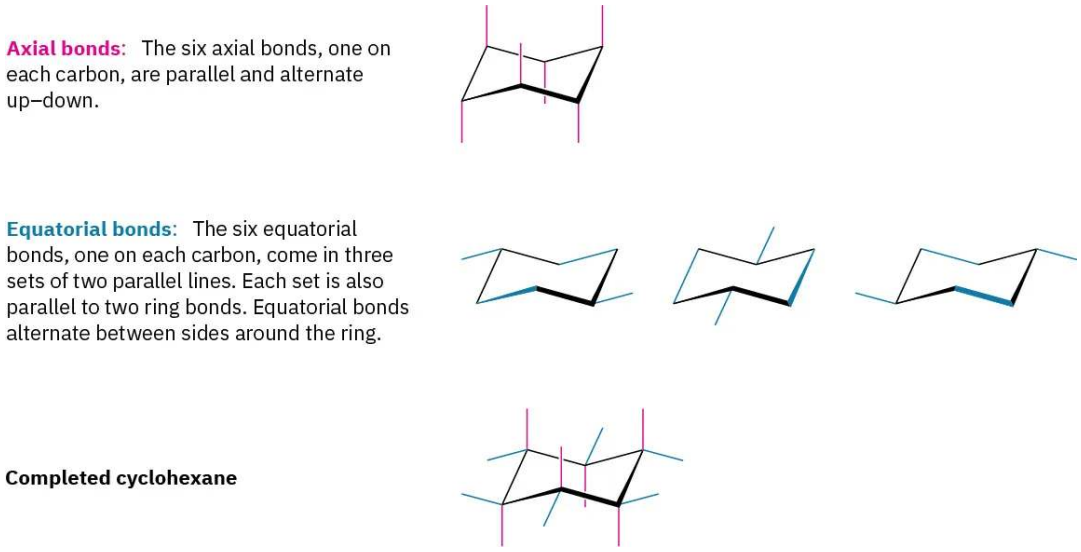


Figure 4.7.3: A procedure for drawing axial and equatorial bonds in chair cyclohexane.

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.

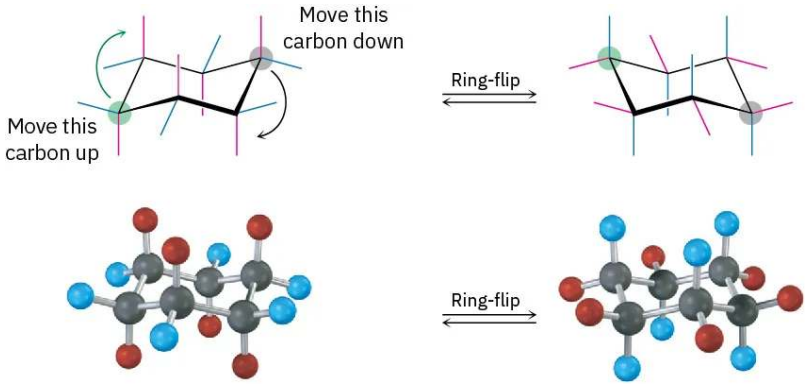
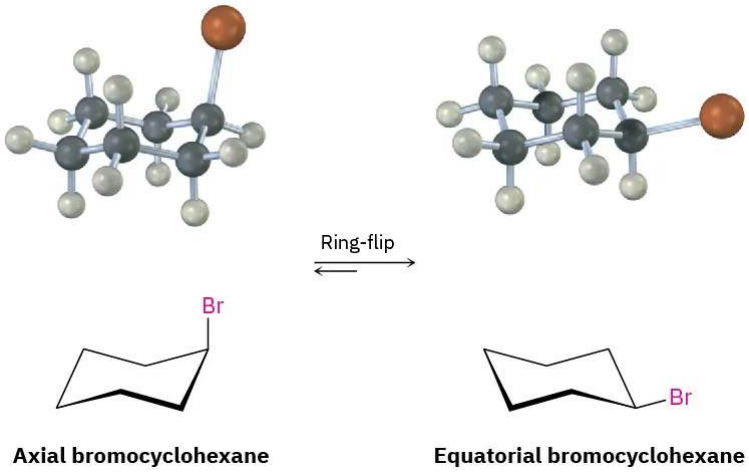


Figure 4.7.4: A ring-flip in chair cyclohexane interconverts axial and equatorial positions. What is **axial** in the starting structure becomes **equatorial** in the ring-flipped structure, and what is **equatorial** in the starting structure is **axial** after ring-flip.

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.



Axial bromocyclohexane **Equatorial bromocyclohexane**

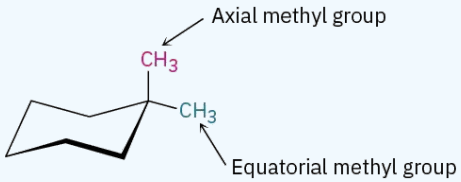
Worked Example 4.7.1: Drawing the Chair Conformation of a Substituted Cyclohexane

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 4.7.1

Draw two different chair conformations of cyclohexanol (hydroxycyclohexane), showing all hydrogen atoms. Identify each position as axial or equatorial.

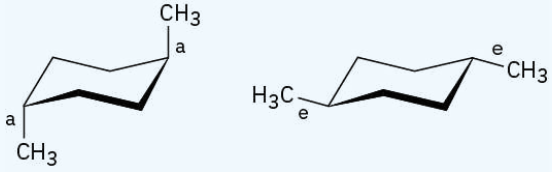
Answer



Exercise 4.7.2

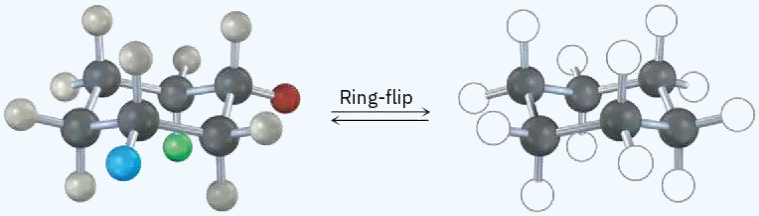
Draw two different chair conformations of *trans*-1,4-dimethylcyclohexane, and label all positions as axial or equatorial.

Answer



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

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.

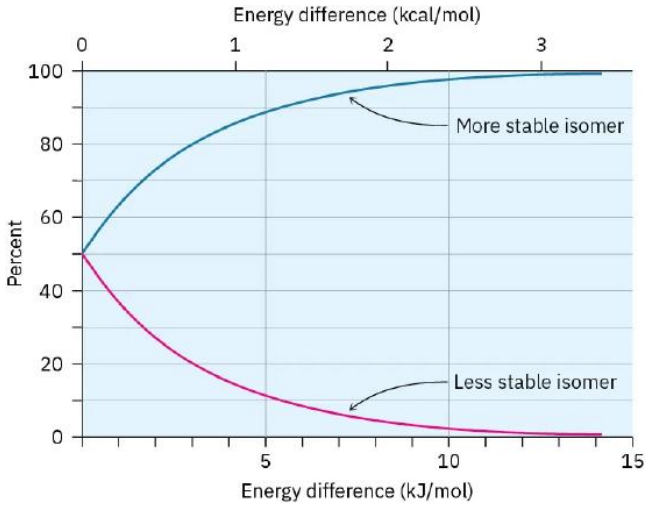


Figure 4.8.1: A plot of the percentages of two isomers at equilibrium versus the energy difference between them. The curves are calculated using the equation $\Delta E = -RT \ln K$.

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).

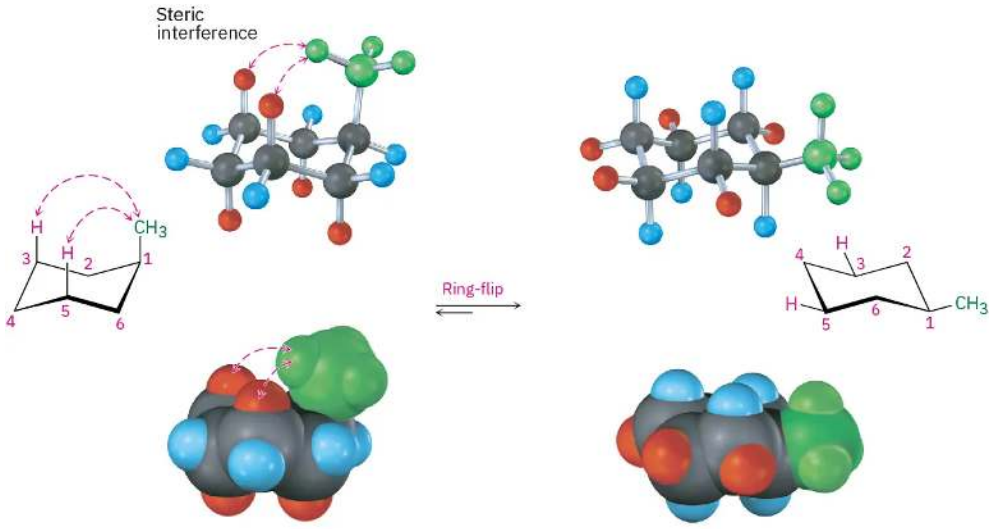


Figure 4.8.2: Interconversion of axial and equatorial methylcyclohexane, represented in several formats. The equatorial conformation is more stable than the axial conformation by 7.6 kJ/mol.

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.

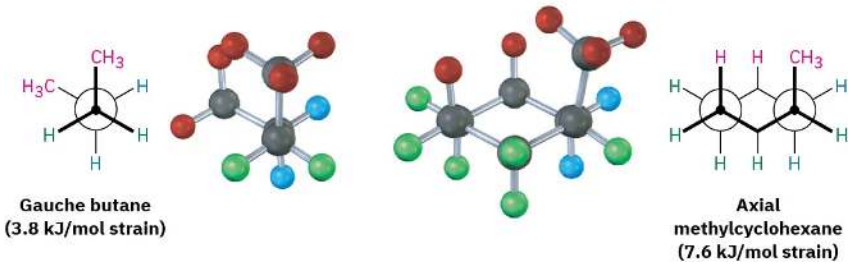
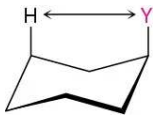


Figure 4.8.3: The origin of 1,3-diaxial interactions in methylcyclohexane. The steric strain between **an axial methyl group** and **an axial hydrogen atom** three carbons away is identical to the steric strain in gauche butane. (To display clearly the diaxial interactions in methylcyclohexane, two of 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

4.2 kJ/mol

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

Cyano group points straight up.

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

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.)

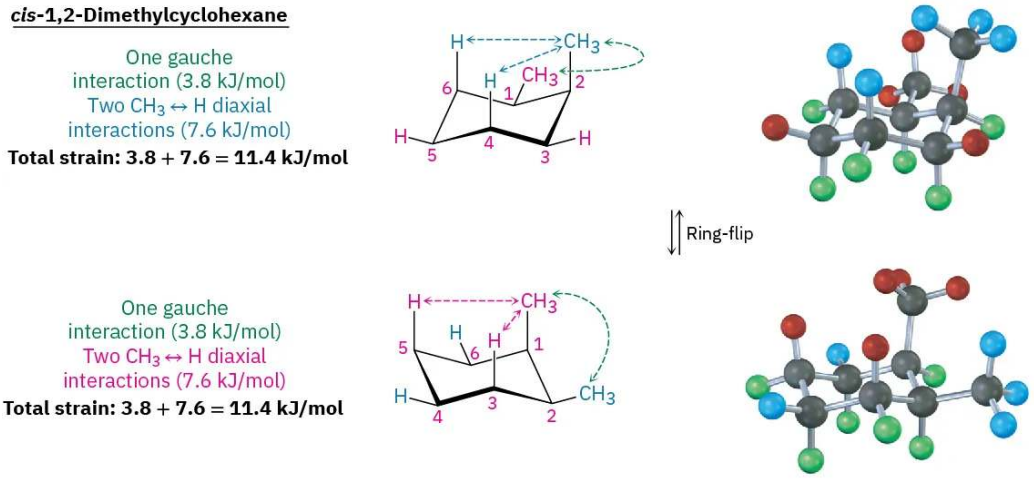


Figure 4.9.1: Conformations of *cis*-1,2-dimethylcyclohexane. The two chair conformations are equal in energy because each has one axial methyl group and one equatorial methyl group.

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.

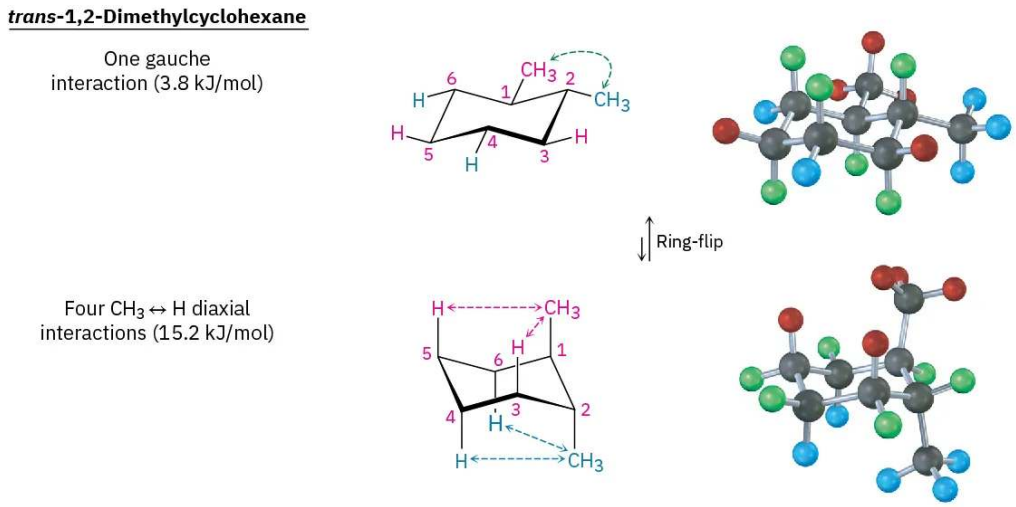
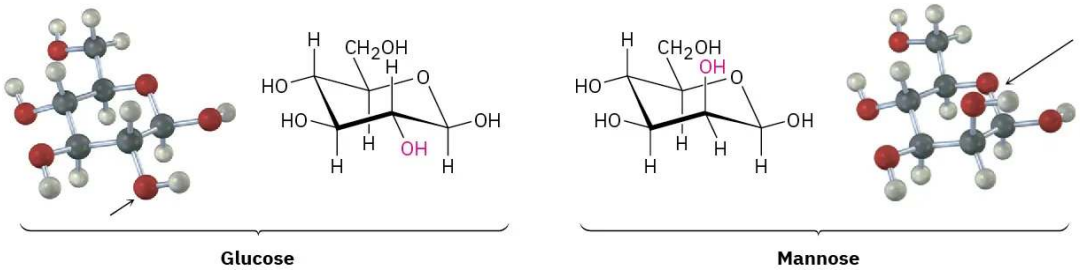


Figure 4.9.2: Conformations of *trans*-1,2-dimethylcyclohexane. The conformation with both methyl groups equatorial (top) is favored by 11.4 kJ/mol (2.7 kcal/mol) over the conformation with both methyl groups axial (bottom).

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:

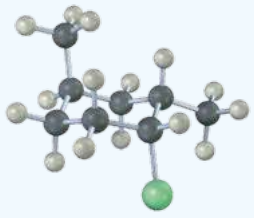
a. *trans*-1-Chloro-3-methylcyclohexane
b. *cis*-1-Ethyl-2-methylcyclohexane
c. *cis*-1-Bromo-4-ethylcyclohexane
d. *cis*-1-*tert*-Butyl-4-ethylcyclohexane

Answer

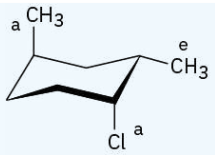
a. 2.0 kJ/mol (axial Cl)
b. 11.4 kJ/mol (axial CH_3)
c. 2.0 kJ/mol (axial Br)
d. 8.0 kJ/mol (axial CH_2CH_3)

? Exercise 4.9.2

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



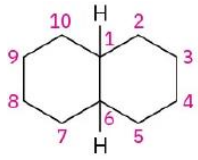
1-Chloro-2,4-dimethyl-cyclohexane
(less stable chair form)

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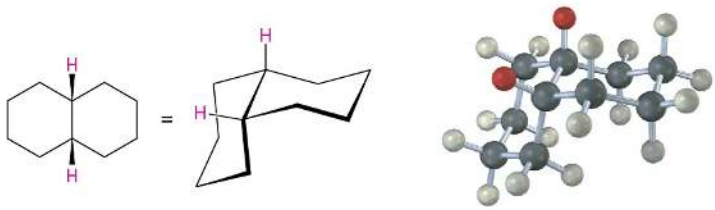
4.10: Conformations of Polycyclic Molecules

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.

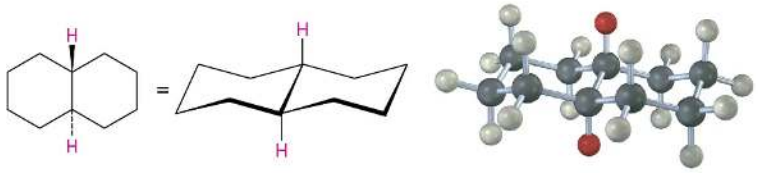


Decalin—two fused cyclohexane rings

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.



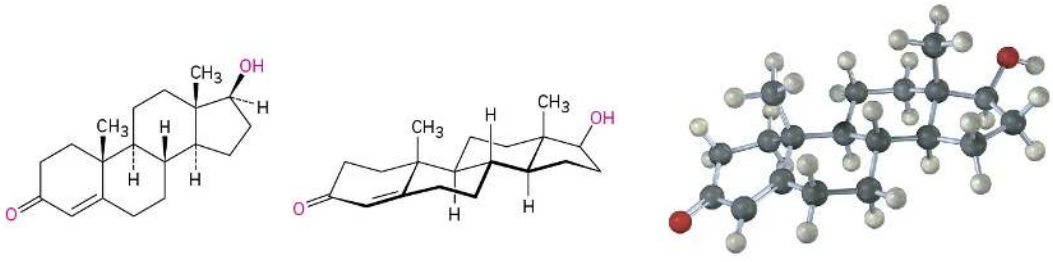
***cis*-Decalin**



***trans*-Decalin**

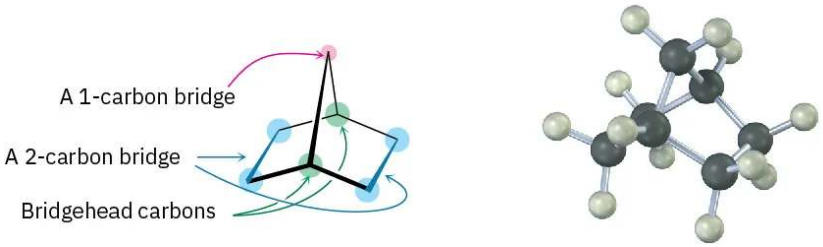
Figure 4.10.1: Representations of *cis*- and *trans*-decalin. **Hydrogen atoms** at the bridgehead carbons are on the same face of the rings in the cis isomer but on opposite faces in the trans isomer.

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)

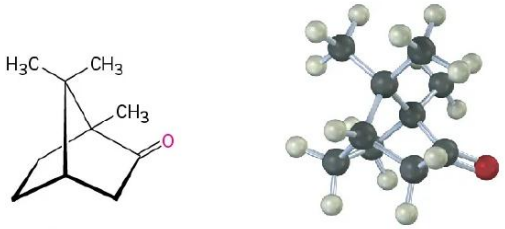
Another common ring system is the norbornane, or bicyclo[2.2.1]heptane, structure. Like decalin, norbornane is a bicycloalkane, so called because two rings would have to be broken open to generate an acyclic structure. Its systematic name, bicyclo[2.2.1]heptane, reflects the fact that the molecule has 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

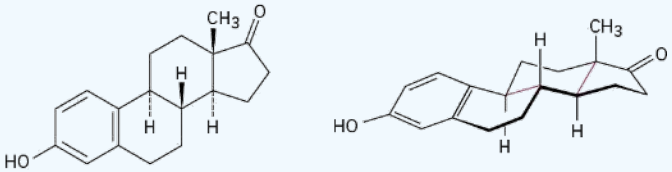
Which isomer is more stable, *cis*-decalin or *trans*-decalin (Figure 4.10.1)? Explain.

Answer

trans-Decalin is more stable because it has no 1,3-diaxial interactions.

? 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

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.

$$E_{\text{total}} = E_{\text{bond stretching}} + E_{\text{angle strain}} + E_{\text{torsional strain}} + E_{\text{van der Waals}}$$

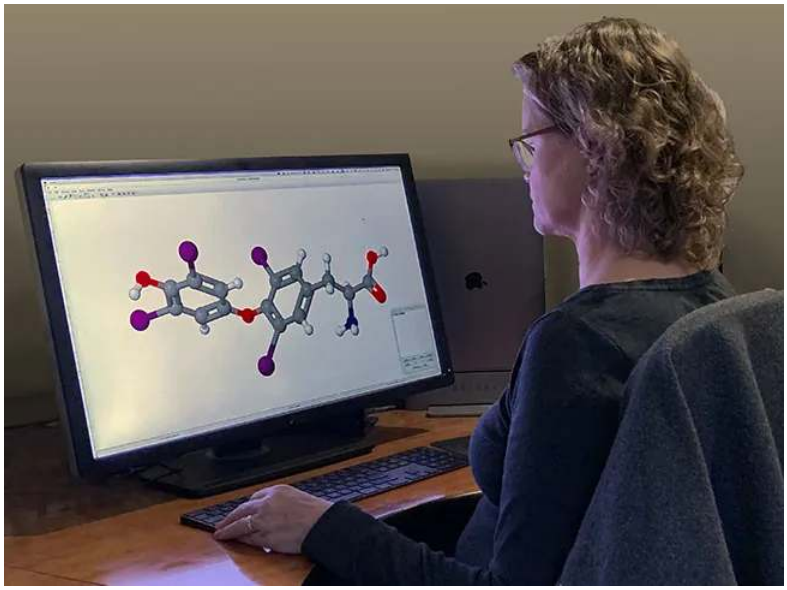


Figure 4.11.1: Computer programs make it possible to accurately represent molecular geometry. (credit: “Molecular geometry” by Jane Whitney/Flickr, CC BY 4.0)

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).

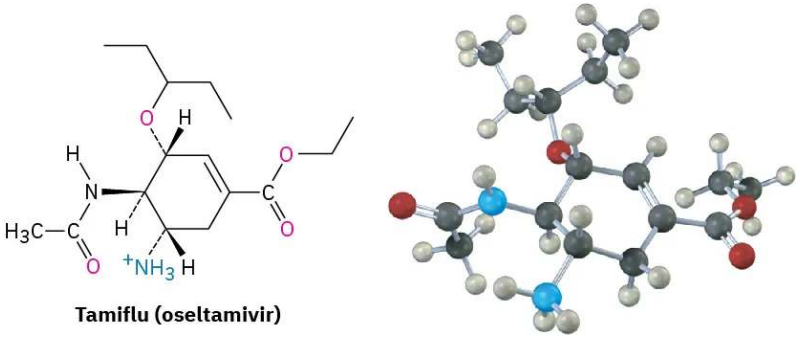


Figure 4.11.2: The structure of Tamiflu (oseltamivir), an antiviral agent active against type A influenza, along with a molecular model of its minimum-energy conformation as calculated by molecular mechanics.

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4.12: Key Terms

- alicyclic
- angle strain
- axial position (cyclohexane)
- boat cyclohexane
- Bridgehead atom
- chair conformation
- cis–trans isomers
- conformational analysis
- cycloalkanes
- 1,3-diaxial interaction
- Equatorial position (cyclohexane)
- polycyclic molecule
- ring-flip (cyclohexane)
- stereoisomer
- steric strain
- torsional strain
- twist-boat conformation

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4.13: Summary

Cyclic molecules are so commonly encountered throughout organic and biological chemistry that it's important to understand the consequences of their cyclic structures. Thus, we've taken a close look at cyclic structures in this chapter.

Cycloalkanes are saturated cyclic hydrocarbons with the general formula C_nH_{2n}. In contrast to open-chain alkanes, where nearly free rotation occurs around C−C bonds, rotation is greatly reduced in cycloalkanes. Disubstituted cycloalkanes can therefore exist as **cis–trans isomers**. The cis isomer has both substituents on the same side of the ring; the trans isomer has substituents on opposite sides. Cis–trans isomers are just one kind of **stereoisomer**—compounds that have the same connections between atoms but different three-dimensional arrangements.

Not all cycloalkanes are equally stable. Three kinds of strain contribute to the overall energy of a cycloalkane: (1) **angle strain** is the resistance of a bond angle to compression or expansion from the normal 109° tetrahedral value, (2) torsional strain is the energy cost of having neighboring C−H bonds eclipsed rather than staggered, and (3) steric strain is the repulsive interaction that arises when two groups attempt to occupy the same space.

Cyclopropane (115 kJ/mol strain) and cyclobutane (110.4 kJ/mol strain) have both angle strain and torsional strain. Cyclopentane is free of angle strain but has a substantial torsional strain due to its large number of eclipsing interactions. Both cyclobutane and cyclopentane pucker slightly away from planarity to relieve torsional strain.

Cyclohexane is strain-free because it adopts a puckered **chair conformation**, in which all bond angles are near 109° and all neighboring C–H bonds are staggered. Chair cyclohexane has two kinds of positions: **axial** and **equatorial**. Axial positions are oriented up and down, parallel to the ring axis, while equatorial positions lie in a belt around the equator of the ring. Each carbon atom has one axial and one equatorial position.

Chair cyclohexanes are conformationally mobile and can undergo a **ring-flip**, which interconverts axial and equatorial positions. Substituents on the ring are more stable in the equatorial position because axial substituents cause **1,3-diaxial interactions**. The amount of 1,3-diaxial steric strain caused by an axial substituent depends on its size.

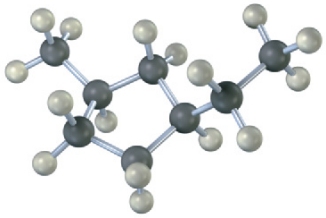
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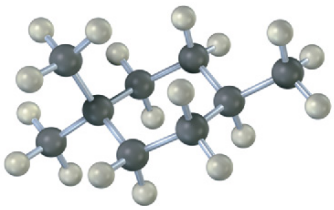
4.14: Additional Problems

Visualizing Chemistry

PROBLEM4-22 Name the following cycloalkanes:

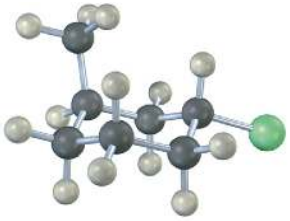


(a)

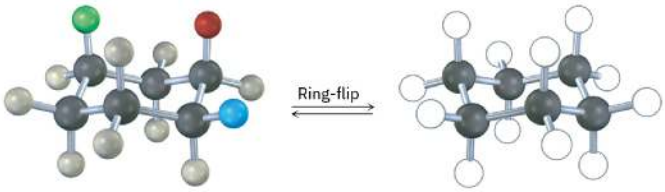


(b)

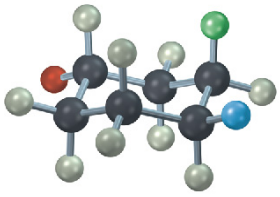
PROBLEM4-23 Name the following compound, identify each substituent as axial or equatorial, and tell whether the conformation shown is the more stable or less stable chair form (green = Cl):



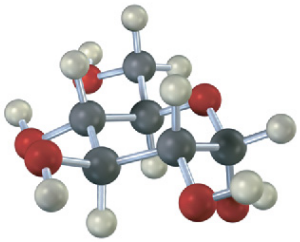
PROBLEM4-24 A trisubstituted cyclohexane with three substituents—red, green, and blue—undergoes a ring-flip to its alternate chair conformation. Identify each substituent as axial or equatorial, and show the positions occupied by the three substituents in the ring-flipped form.



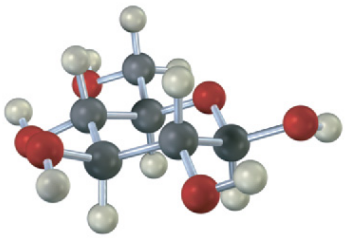
PROBLEM4-25 The following cyclohexane derivative has three substituents—red, green, and blue. Identify each substituent as axial or equatorial, and identify each pair of relationships (red–blue, red–green, and blue–green) as cis or trans.



PROBLEM4-26 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

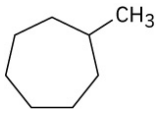


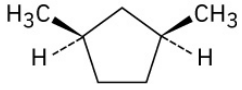
β-Glucose

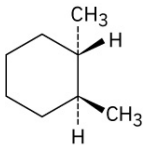
Cycloalkane Isomers

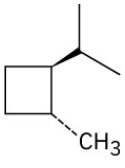
PROBLEM4-27 Draw the five cycloalkanes with the formula C_5H_{10}.

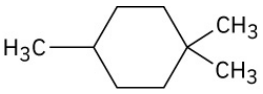
PROBLEM4-28 Give IUPAC names for the following compounds.

(a) 

(b) 

(c) 

(d) 

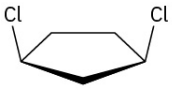
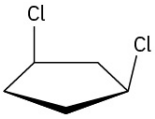
(e) 

PROBLEM4-29 Draw a stereoisomer of *trans*-1,3-dimethylcyclobutane.

PROBLEM4-30 Tell whether the following pairs of compounds are identical, constitutional isomers, stereoisomers, or unrelated.

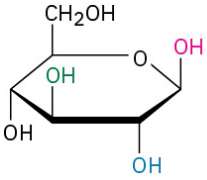
(a) *cis*-1,3-Dibromocyclohexane and *trans*-1,4-dibromocyclohexane

(b) 2,3-Dimethylhexane and 2,3,3-trimethylpentane

(c)  and 

PROBLEM4-31 Draw three isomers of *trans*-1,2-dichlorocyclobutane, and label them as either constitutional isomers or stereoisomers.

PROBLEM4-32 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.

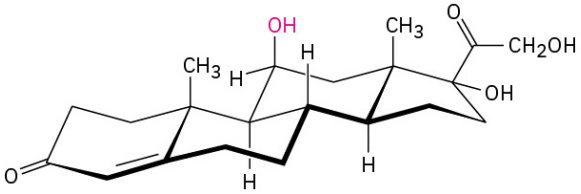


Glucose

PROBLEM4-33 Draw 1,3,5-trimethylcyclohexane using a hexagon to represent the ring. How many cis–trans stereoisomers are possible?

Cycloalkane Conformation and Stability

PROBLEM4-34 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

PROBLEM4-35 A 1,2-cis disubstituted cyclohexane, such as *cis*-1,2-dichlorocyclohexane, must have one group axial and one group equatorial. Explain.

PROBLEM4-36 A 1,2-trans disubstituted cyclohexane must have either both groups axial or both groups equatorial. Explain.

PROBLEM4-37 Why is a 1,3-cis disubstituted cyclohexane more stable than its trans isomer?

PROBLEM4-38 Which is more stable, a 1,4-trans disubstituted cyclohexane or its cis isomer?

PROBLEM4-39 *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.

PROBLEM4-40 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, $C_6H_{11}CN$

PROBLEM4-41 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

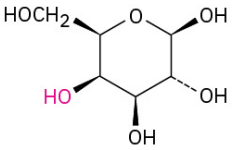
(d) 1,5-Trans disubstituted (e) 1,5-Cis disubstituted (f) 1,6-Trans disubstituted

Cyclohexane Conformational Analysis

PROBLEM4-42 Draw the two chair conformations of *cis*-1-chloro-2-methylcyclohexane. Which is more stable, and by how much?

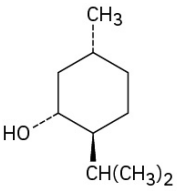
PROBLEM4-43 Draw the two chair conformations of *trans*-1-chloro-2-methylcyclohexane. Which is more stable?

PROBLEM4-44 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

PROBLEM4-45 Draw the two chair conformations of menthol, and tell which is more stable.



Menthol

PROBLEM4-46 There are four cis–trans isomers of menthol (Problem 4-45), including the one shown. Draw the other three.

PROBLEM4-47 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.

PROBLEM4-48 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.)

PROBLEM4-49 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?

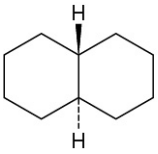
PROBLEM4-50 One of the two chair structures of *cis*-1-chloro-3-methylcyclohexane is more stable than the other by 15.5 kJ/mol (3.7 kcal/mol). Which is it? What is the energy cost of a 1,3-diaxial interaction between a chlorine and a methyl group?

General Problems

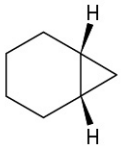
PROBLEM4-51 We saw in Problem 4-20 that *cis*-decalin is less stable than *trans*-decalin. Assume that the 1,3-diaxial interactions in *cis*-decalin are similar to those in axial methylcyclohexane [that is, one CH2 ↔ H interaction costs 3.8 kJ/mol (0.9 kcal/mol)], and calculate the magnitude of the energy difference between *cis*- and *trans*-decalin.

PROBLEM4-52 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.

PROBLEM4-53 *trans*-Decalin is more stable than its cis isomer, but *cis*-bicyclo[4.1.0]heptane is more stable than its trans isomer. Explain.

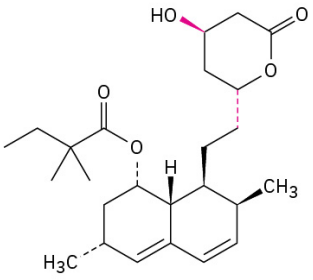


***trans*-Decalin**

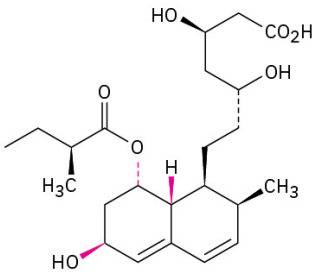


***cis*-Bicyclo[4.1.0]heptane**

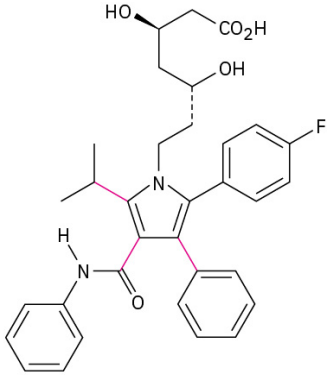
PROBLEM4-54 As mentioned in Problem 3-53, the statin drugs, such as simvastatin (Zocor), pravastatin (Pravachol), and atorvastatin (Lipitor) are the most widely prescribed drugs in the world.



Simvastatin (Zocor)



Pravastatin (Pravachol)



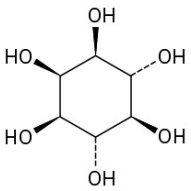
Atorvastatin (Lipitor)

(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?

PROBLEM4-55 *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**

PROBLEM4-56 How many cis–trans stereoisomers of *myo*-inositol (Problem 4-55) are there? Draw the structure of the most stable isomer.

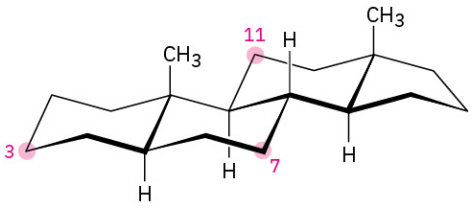
PROBLEM4-57 Julius Bredt, discoverer of the structure of camphor, proposed in 1935 that bicycloalkenes such as 1-norbornene, which have a double bond to a bridgehead carbon, are too strained to exist. Explain. (Making a molecular model will be helpful.



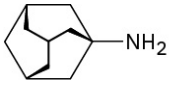
1-Norbornene

PROBLEM4-58 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



PROBLEM4-59 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.

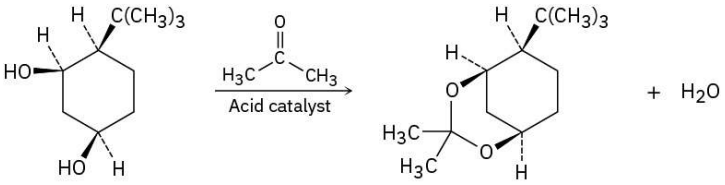


Amantadine

PROBLEM4-60 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.)

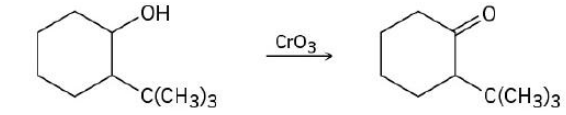


PROBLEM4-61 Ketones react with alcohols to yield products called *ketals*. Why does the all-cis isomer of 4-*tert*-butyl-1,3-cyclohexanediol react readily with acetone and an acid catalyst to form a ketal, but other stereoisomers do not react? In formulating your answer, draw the more stable chair conformations of all four stereoisomers and the product ketal for each one.



A ketal

PROBLEM4-62 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**

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CHAPTER OVERVIEW

5: Stereochemistry at Tetrahedral Centers

Learning Objectives

After you have completed Chapter 5, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use molecular models in solving problems on stereochemistry.
- solve road-map problems that include stereochemical information.
- define, and use in context, the new key terms.

This chapter introduces the concept of chirality, and discusses the structure of compounds containing one or two chiral centers. A convenient method of representing the three-dimensional arrangement of the atoms in chiral compounds is explained; furthermore, throughout the chapter , considerable emphasis is placed on the use of molecular models to assist in the understanding of the phenomenon of chirality. The chapter continues with an examination of stereochemistry—the three-dimensional nature of molecules. The subject is introduced using the experimental observation that certain substances have the ability to rotate plane-polarized light. Finally, certain reactions of alkenes are re-examined in the light of the new material encountered in this chapter.

5.1: Why This Chapter?
5.2: Enantiomers and the Tetrahedral Carbon
5.3: The Reason for Handedness in Molecules - Chirality
5.4: Optical Activity
5.5: Pasteur's Discovery of Enantiomers
5.6: Sequence Rules for Specifying Configuration
5.7: Diastereomers
5.8: Meso Compounds
5.9: Racemic Mixtures and the Resolution of Enantiomers
5.10: A Review of Isomerism
5.11: Chirality at Nitrogen, Phosphorus, and Sulfur
5.12: Prochirality
5.13: Chirality in Nature and Chiral Environments
5.14: Chemistry Matters—Chiral Drugs
5.15: Key Terms
5.16: Summary
5.17: Additional Problems

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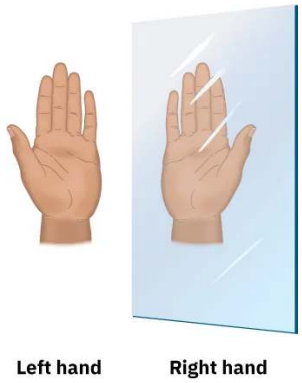
5.1: Why This Chapter?

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 5.1.1: 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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5.2: 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 5.2.1. 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.

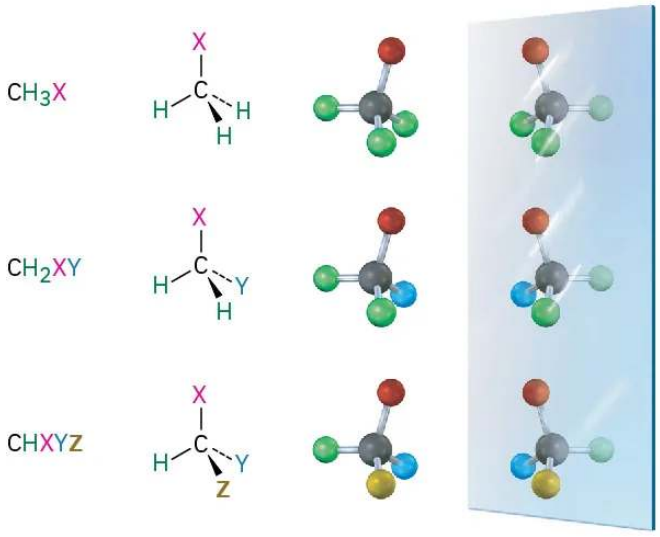
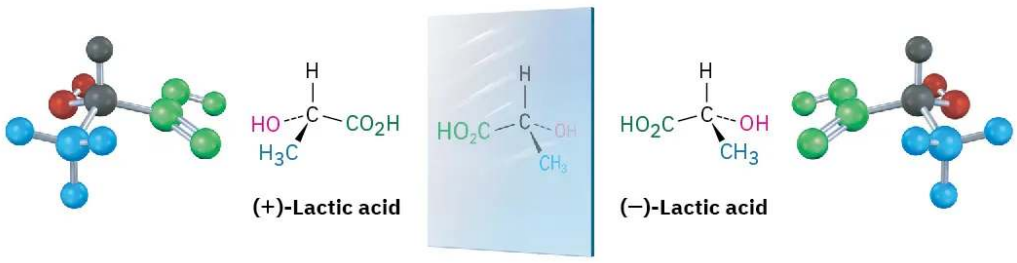


Figure 5.2.1: Tetrahedral carbon atoms and their mirror images. Molecules of the type CH_3X and CH_2XY are identical to their mirror images, but a molecule of the type CHXYZ is not. A CHXYZ molecule is related to its mirror image in the same way a right hand is related to a left hand.

A molecule that is not identical to its mirror image is a kind of stereoisomer (Section 4.3) 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 5.2.2).

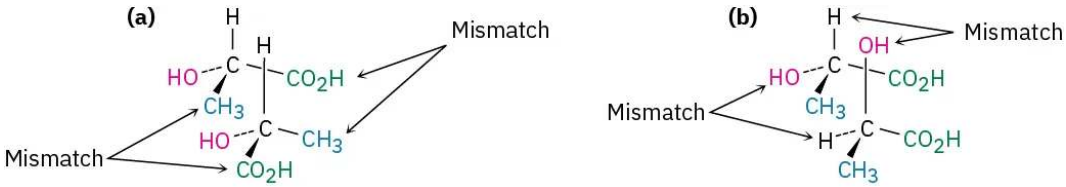


Figure 5.2.2: Attempts at superimposing the mirror-image forms of lactic acid. **(a)** When the −H and −OH substituents match up, the $-CO_2H$ and $-CH_3$ substituents don't; **(b)** when $-CO_2H$ and $-CH_3$ match up, −H and −OH don't. Regardless of how the molecules are oriented, they aren't identical.

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5.3: 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 5.3.1).

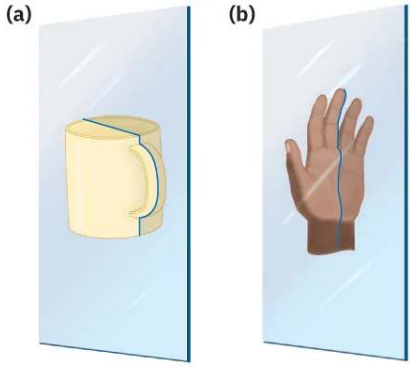


Figure 5.3.1: The meaning of symmetry plane. **(a)** An object like the coffee mug has a symmetry plane cutting through it so that right and left halves are mirror images. **(b)** An object like a hand has no symmetry plane; the right “half” of a hand is not a mirror image of the left half.

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 5.3.2 and is achiral, while lactic acid, $CH_3CH(OH)CO_2H$, has no plane of symmetry in any conformation and is chiral.

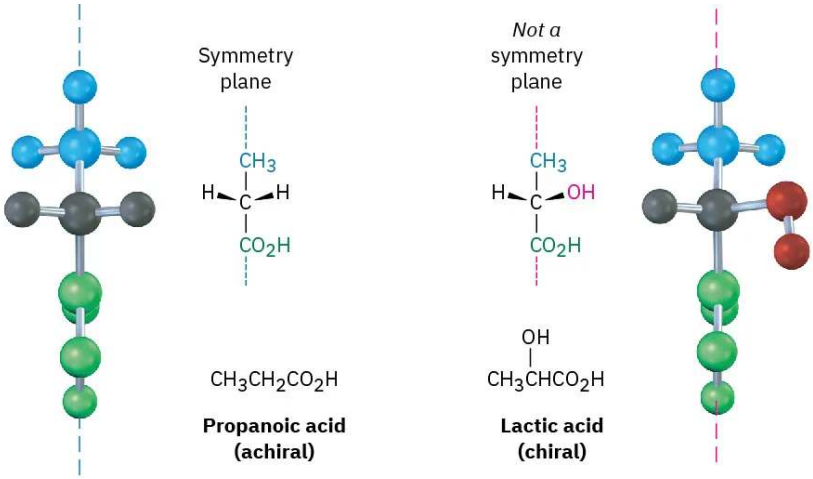
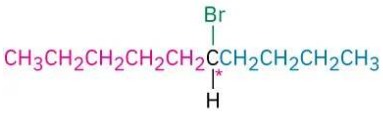


Figure 5.3.2: The achiral propanoic acid molecule versus the chiral lactic acid molecule. Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other. Lactic acid has no such symmetry plane.

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.



5-Bromodecane (chiral)

Substituents on carbon 5

—H

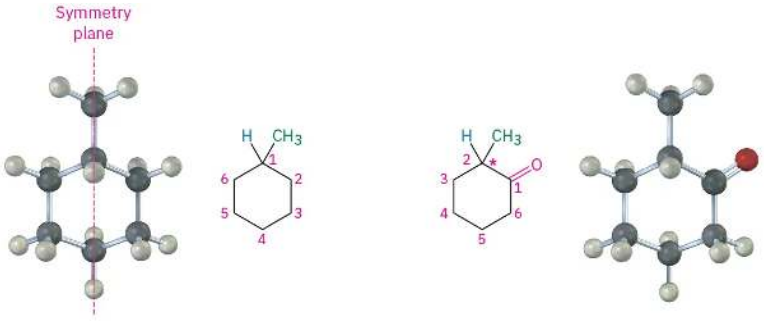
—Br

—$CH_2CH_2CH_2CH_3$ (butyl)

—$CH_2CH_2CH_2CH_2CH_3$ (pentyl)

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.

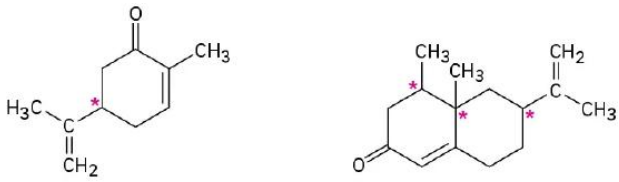
The situation is different for 2-methylcyclohexanone. 2-Methylcyclohexanone has no symmetry plane and is chiral because its C2 is bonded to four different groups: a $-CH_3$ group, an −H atom, a $-COCH_2-$ ring bond (C1), and a $-CH_2CH_2-$ ring bond (C3).



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 5.3.1: 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

Exercise 5.3.1

Which of the following objects are chiral?

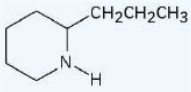
a. Soda can
b. Screwdriver
c. Screw
d. Shoe

Answer

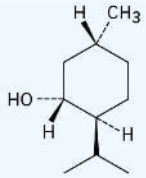
Chiral: screw, shoe

Exercise 5.3.2

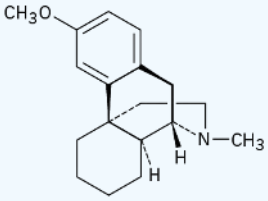
Which of the following molecules are chiral? Identify the chirality center(s) in each.

a. 

Coniine (poison hemlock)

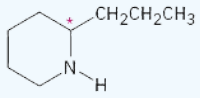
b. 

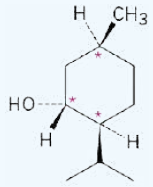
Menthol (flavoring agent)

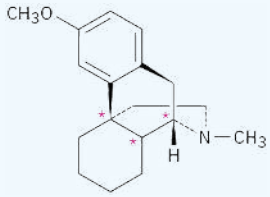
c. 

Dextromethorphan (cough suppressant)

Answer

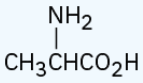
a. 

b. 

c. 

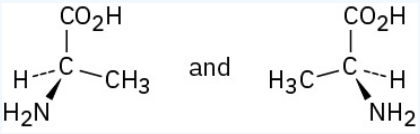
Exercise 5.3.3

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



Exercise 5.3.4

Identify the chirality centers in the following molecules (gray = H, black = C, red = O, green = Cl, yellow-green = F):



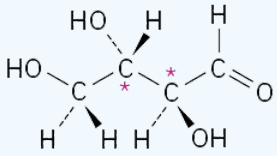
a.



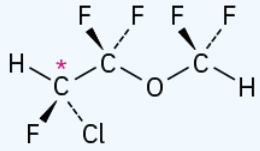
b.

Answer

a.



b.



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5.4: 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 5.4.1. 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.

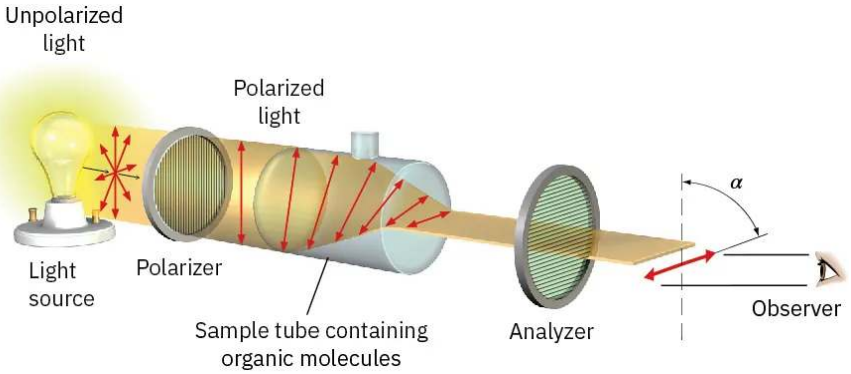


Figure 5.4.1: Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.

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.)

$$[\alpha]_D = \frac{\text{Observed rotation (degrees)}}{\text{Pathlength, } l\text{(dm)} \times \text{ Concentration, } c\text{ (g/cm}^3\text{)}} = \frac{\alpha}{l \times c}$$

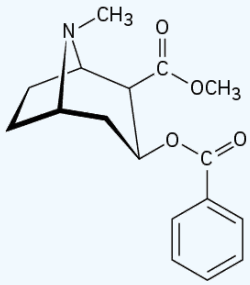
When optical rotations are expressed in this standard way, the specific rotation, $[\alpha]_D$, is a physical constant characteristic of a given optically active compound. For example, (+)-lactic acid has $[\alpha]_D = +3.82$, and (−)-lactic acid has $[\alpha]_D = -3.82$. That is, the two enantiomers 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 5.4.1.

Table 5.4.1 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 5.4.1: Calculating an Optical Rotation

A 1.20 g sample of cocaine, $[\alpha]_D = -16$, was dissolved in 7.50 mL of chloroform and placed in a sample tube having a pathlength of 5.00 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

$$\alpha = (-16)(0.500)(0.160) = -1.3^\circ.$$

Exercise 5.4.1

Is cocaine (Worked Example 5.4.1) dextrorotatory or levorotatory?

Answer

Levorotatory

Exercise 5.4.2

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

+16.1°

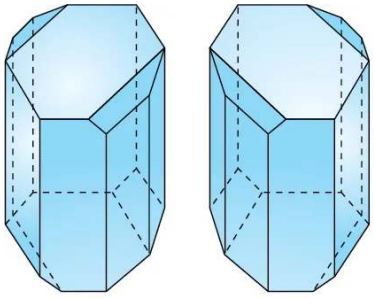
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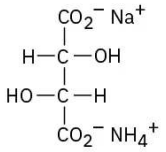
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5.5: Pasteur's Discovery of Enantiomers

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 5.5.1. 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.





Sodium ammonium tartrate

Figure 5.5.1: 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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5.6: 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:

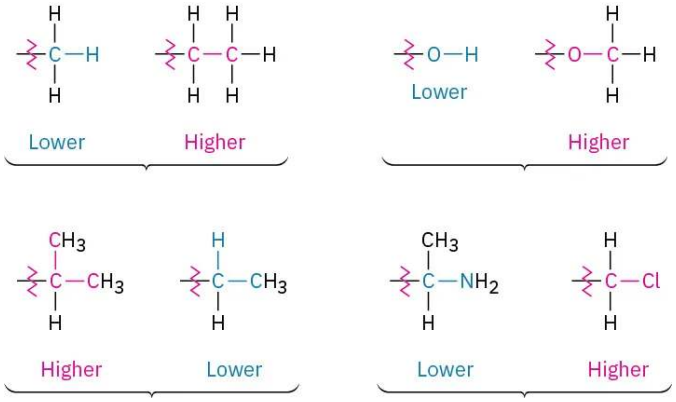
RULE 1

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

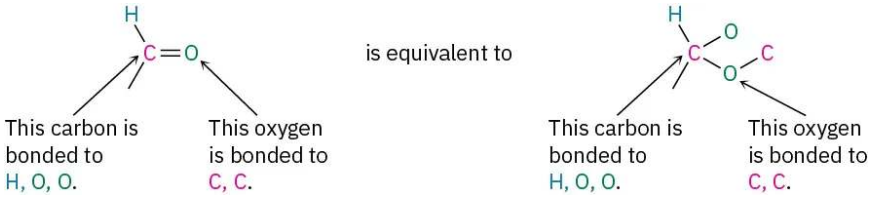
RULE 2

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:



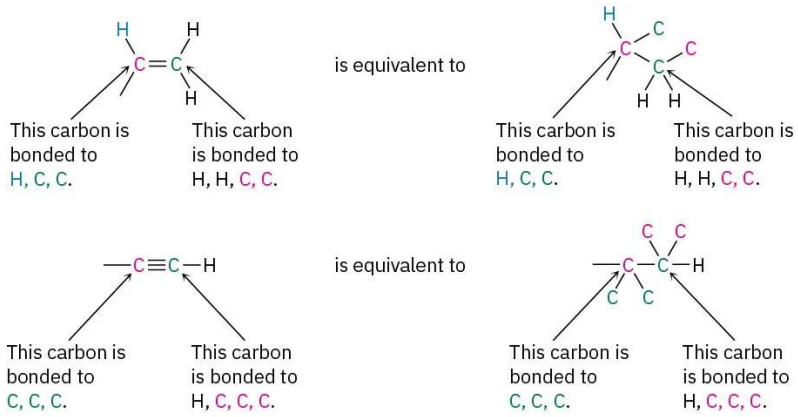
RULE 3

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:

https://chem.libretexts.org/@go/page/563997



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 5.6.1). 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.

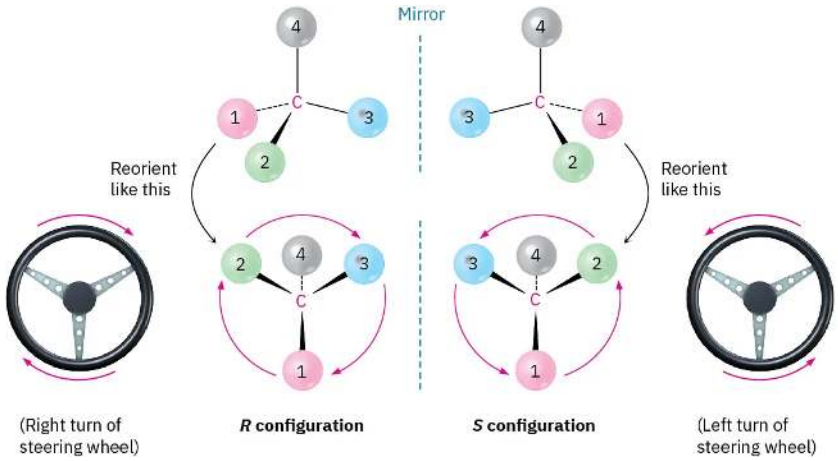


Figure 5.6.1: Assigning *R* and *S* configurations to chirality centers. When the molecule is oriented so that the lowest-ranked group (**4**) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel 1 → 2 → 3 is clockwise (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 5.6.2 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.

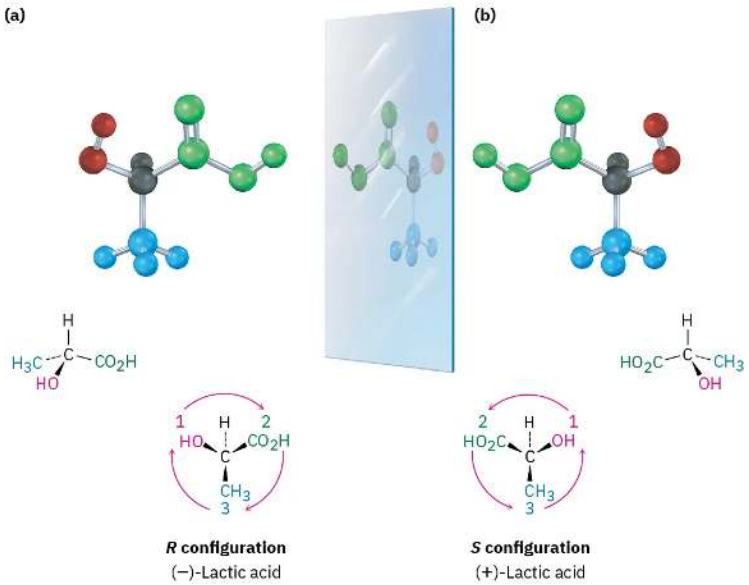


Figure 5.6.2: Assigning configuration to **(a)** (*R*)-(−)-lactic acid and **(b)** (*S*)-(+)-lactic acid.

Further examples are provided by naturally occurring (−)-glyceraldehyde and (+)-alanine, which both have the *S* configuration as shown in Figure 5.6.3. 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.

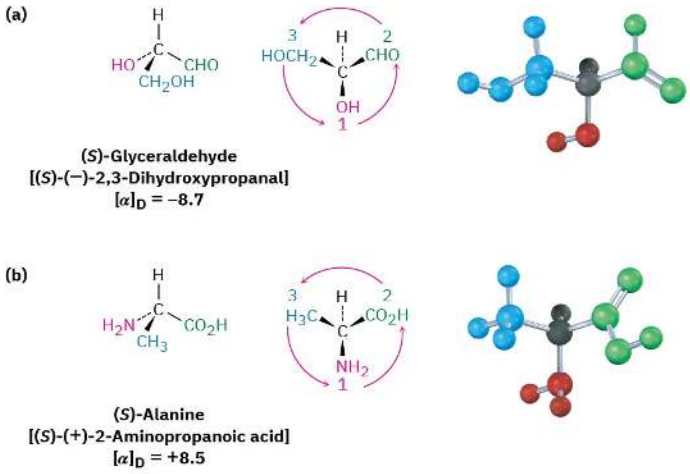
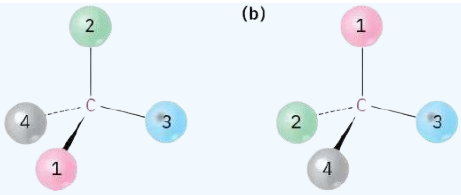


Figure 5.6.3: Assigning configuration to **(a)** (−)-glyceraldehyde. **(b)** (+)-alanine. Both happen to have the *S* configuration, although one is levorotatory and the other is dextrorotatory.

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 5.6.1: 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:

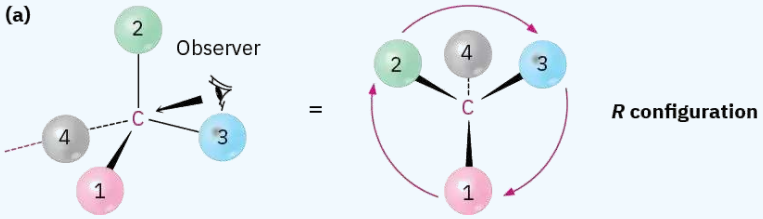


Strategy

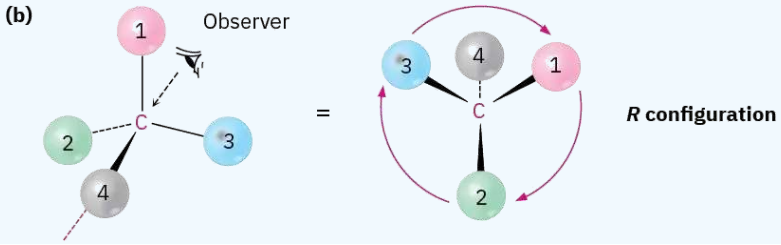
It takes practice to be able to visualize and orient a chirality center in three dimensions. You might start by indicating where the observer must be located—180° opposite the lowest-ranked group. Then imagine yourself in the position of the observer, and redraw what you would see.

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.



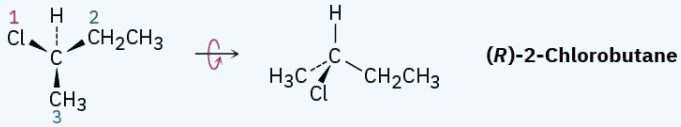
Worked Example 5.6.2: Drawing the Three-Dimensional Structure of a Specific Enantiomer

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



Exercise 5.6.1

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

a. $-Br$
b. $-Br$
c. $-CH_2CH_3$
d. $-OH$
e. $-CH_2OH$
f. $-CH{=}O$

Exercise 5.6.2

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. $-SH$, $-CH_2SCH_3$, $-CH_3$, $-SSCH_3$

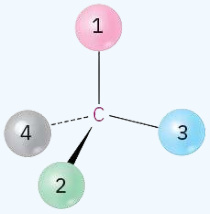
Answer

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. $-SSCH_3$, $-SH$, $-CH_2SCH_3$, $-CH_3$

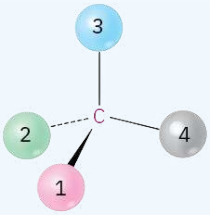
Exercise 5.6.1

Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:

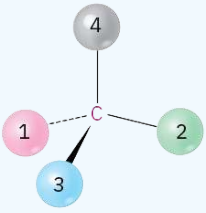
a.



b.



c.



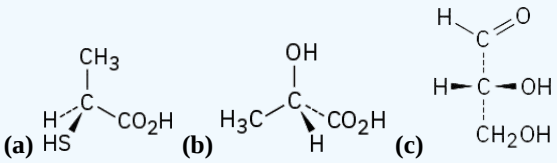
Answer

https://chem.libretexts.org/@go/page/563997

a. *S*
b. *R*
c. *S*

Exercise 5.6.4

Assign *R* or *S* configuration to the chirality center in each of the following molecules:

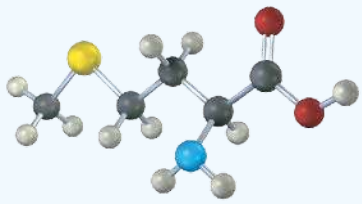


Answer

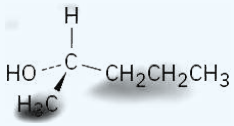
(a) *S* **(b)** *S* **(c)** *R*

Exercise 5.6.5

Assign *R* or *S* configuration to the chirality center in the following molecular model of the amino acid methionine (blue = N, yellow = S):



Answer



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5.7: 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 5.7.1. Check for yourself that the *R*,*S* configurations of all stereoisomers are correct.

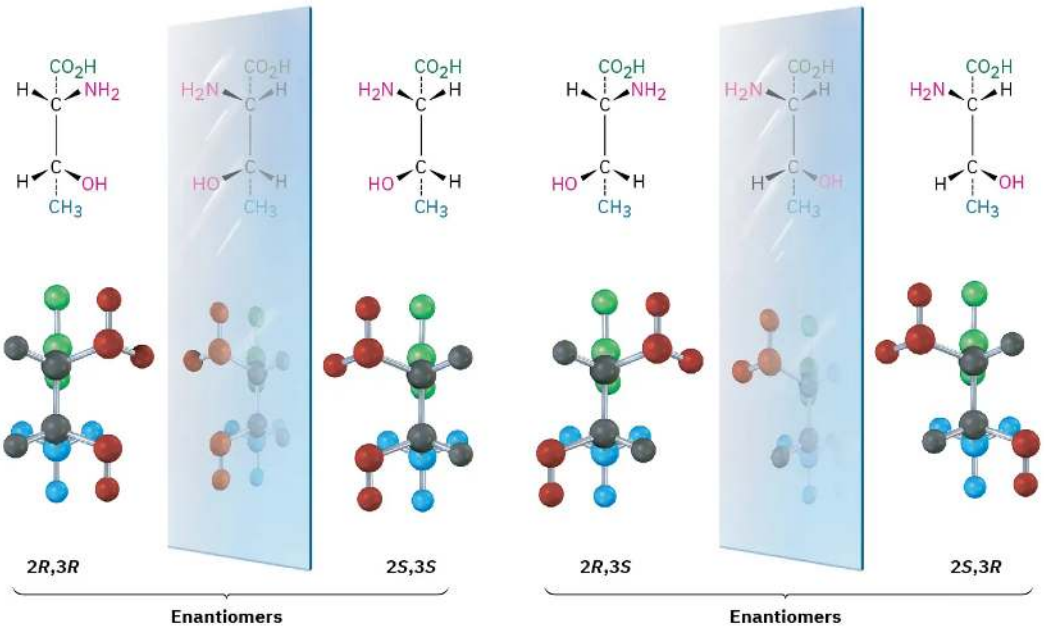


Figure 5.7.1: The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

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.*

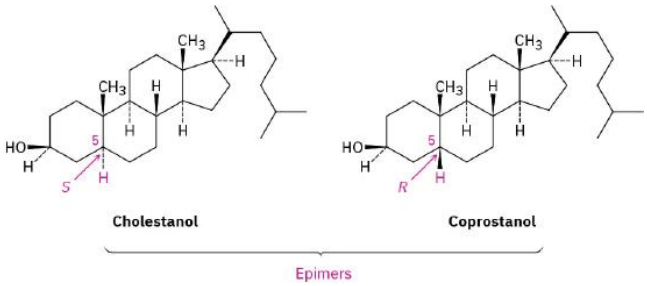
Diastereomers are stereoisomers that are not mirror images. Since we used the right-hand/left-hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and 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 5.7.1. 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 5.7.1 Relationships among the Four Stereoisomers of Threonine

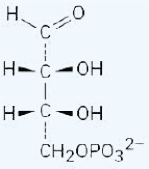
Stereoisomer	Enantiomer	Diastereomer
2*R*,3*R*	2*S*,3*S*	2*R*,3*S* and 2*S*,3*R*
2*S*,3*S*	2*R*,3*R*	2*R*,3*S* and 2*S*,3*R*
2*R*,3*S*	2*S*,3*R*	2*R*,3*R* and 2*S*,3*S*
2*S*,3*R*	2*R*,3*S*	2*R*,3*R* and 2*S*,3*S*

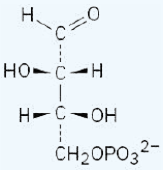
In the special case where two diastereomers differ at only one chirality center but are the same at all others, we say that the compounds are **epimers**. Cholestanol and coprostanol, for instance, are both found in human feces, and both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric* at C5.

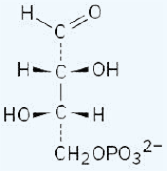


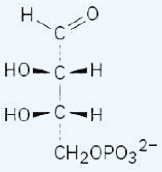
Exercise 5.7.1

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. 

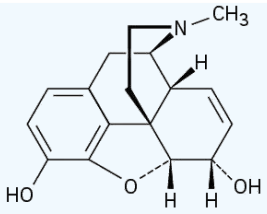
d. 

Answer

Compound **(a)** is D-erythrose 4-phosphate, **(d)** is its enantiomer, and **(b)** and **(c)** are diastereomers.

Exercise 5.7.2

How many chirality centers does morphine have? How many stereoisomers of morphine are possible in principle?



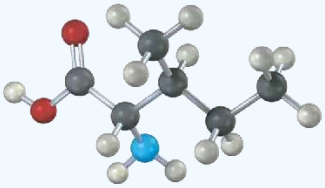
Morphine

Answer

Five chirality centers and $2^5 = 32$ stereoisomers

? Exercise 5.7.3

Assign *R* or *S* configuration to each chirality center in the following molecular model of the amino acid isoleucine (blue = N):



Answer

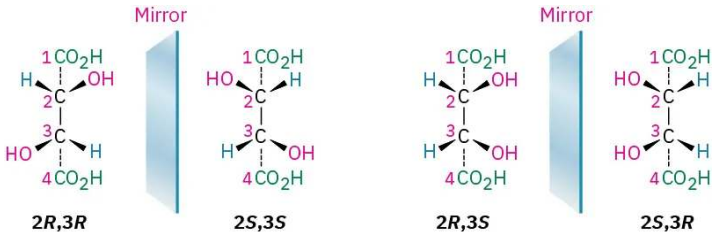
S,*S*

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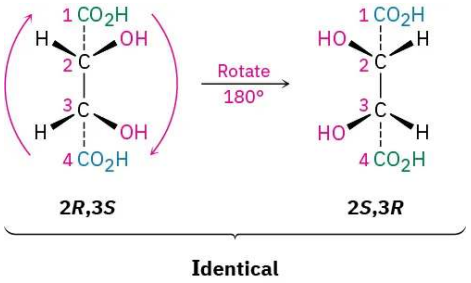
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5.8: Meso Compounds

Let's look at another example (Section 5.5) 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 2*S*,3*S* structures are nonsuperimposable mirror images and therefore represent a pair of enantiomers. A close look at the 2*R*,3*S* 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 5.8.1). 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.

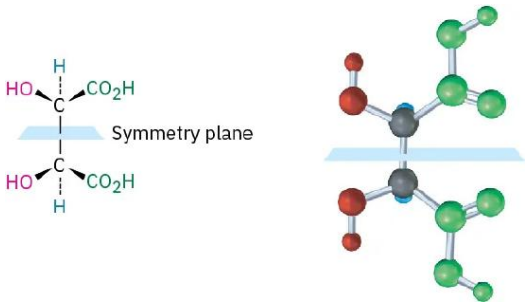


Figure 5.8.1: A symmetry plane through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral.

Some physical properties of the three stereoisomers are listed in Table 5.8.1. 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 5.8.1 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 5.8.1: Distinguishing Chiral Compounds from Meso Compounds

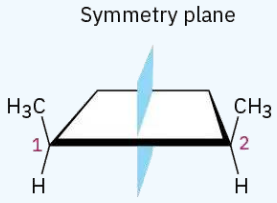
Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

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.

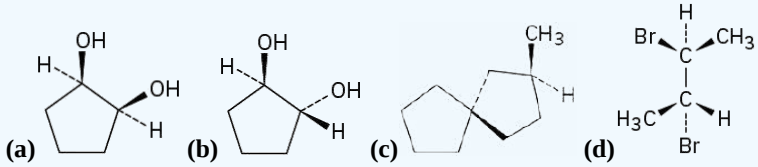
Solution

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.



Exercise 5.8.1

Which of the following structures represent meso compounds?



Answer

Compounds **(a)** and **(d)** are meso.

Exercise 5.8.2

Which of the following have a meso form? (Recall that the *-ol* suffix refers to an alcohol, ROH.)

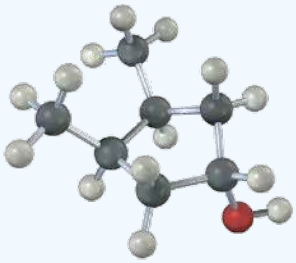
a. 2,3-Butanediol
b. 2,3-Pentanediol
c. 2,4-Pentanediol

Answer

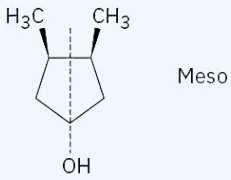
Compounds **(a)** and **(c)** have meso forms.

Exercise 5.8.3

Does the following structure represent a meso compound? If so, indicate the symmetry plane.



Answer



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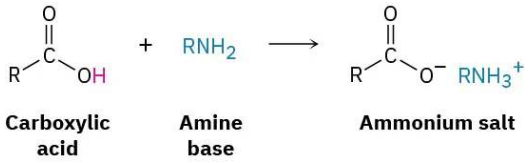
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5.9: Racemic Mixtures and the Resolution of Enantiomers

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 5.9.1).

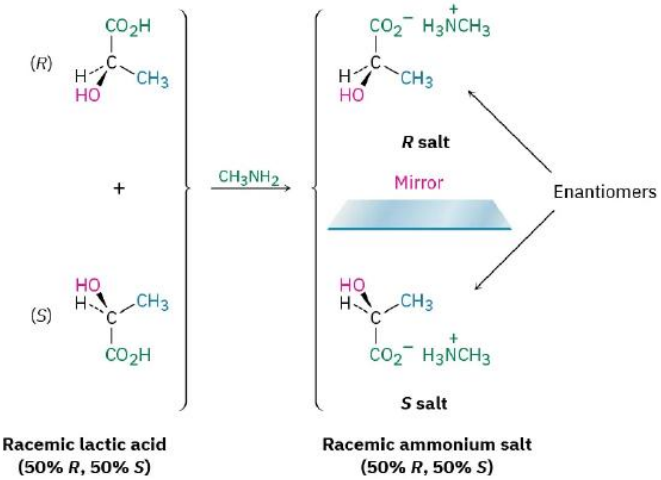


Figure 5.9.1: Reaction of racemic lactic acid with achiral methylamine gives a racemic mixture of ammonium salts.

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 5.9.2). (*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.

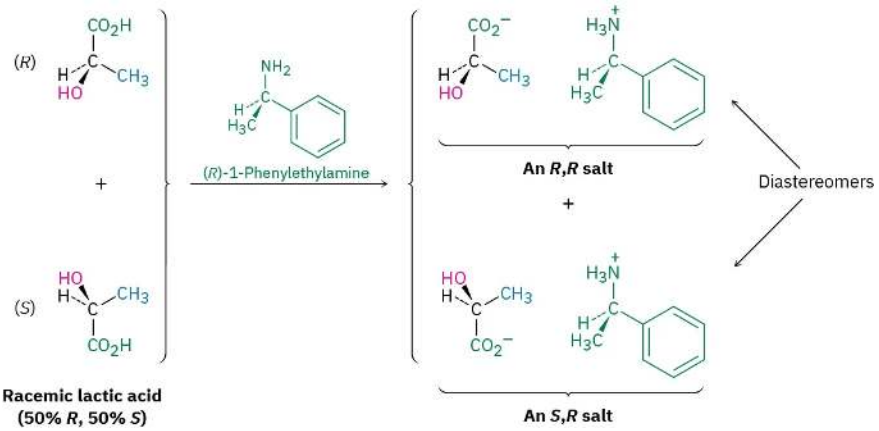
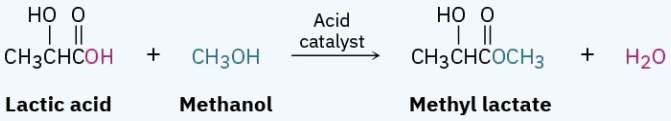


Figure 5.9.2: Reaction of racemic lactic acid with (*R*)-1-phenylethylamine yields a mixture of diastereomeric ammonium salts, which have different properties and can be separated.

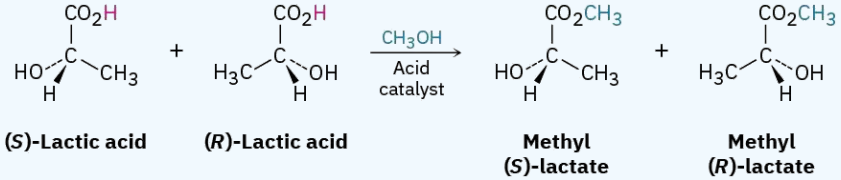
Worked Example 5.9.1: Predicting the Chirality of a Reaction Product

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?



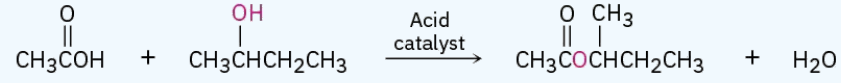
Solution

Reaction of a racemic acid with an achiral alcohol such as methanol yields a racemic mixture of mirror-image (enantiomeric) products.



Exercise 5.9.1

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?



Exercise 5.9.2

What stereoisomers would result from reaction of (±)-lactic acid with (*S*)-1-phenylethylamine, and what is the relationship between them?

Answer

> Two diastereomeric salts: (*R*)-lactic acid plus (*S*)-1-phenylethylamine and (*S*)-lactic acid plus (*S*)-1-phenylethylamine

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5.10: 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 5.10.1).

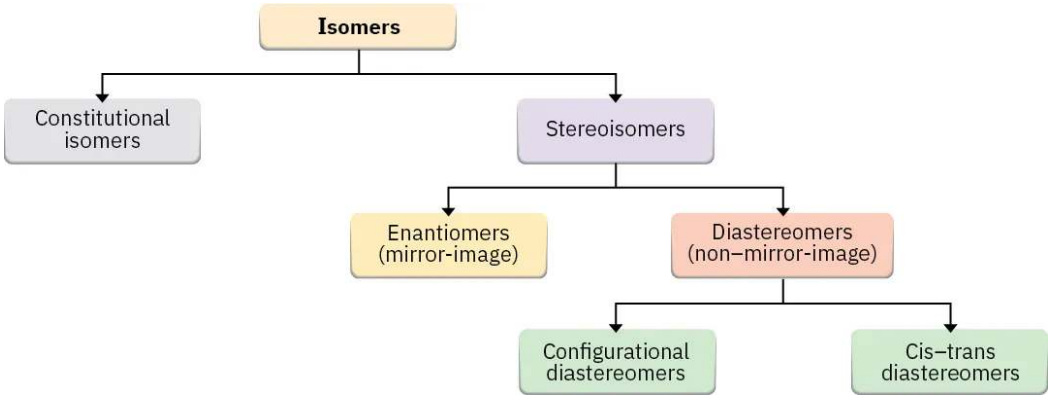


Figure 5.10.1: A summary of the different kinds of isomers.

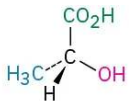
There are two fundamental types of isomers, both of which we've now encountered: constitutional isomers and stereoisomers.

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.

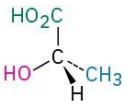
Different carbon skeletons	CH_3CHCH_3 (with CH_3 branch)	and	$CH_3CH_2CH_2CH_3$
	2-Methylpropane		**Butane**
Different functional groups	CH_3CH_2OH	and	CH_3OCH_3
	Ethyl alcohol		**Dimethyl ether**
Different position of functional groups	CH_3CHCH_3 (NH_2)	and	$CH_3CH_2CH_2NH_2$
	Isopropylamine		**Propylamine**

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)



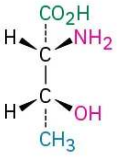
(*R*)-Lactic acid



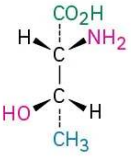
(*S*)-Lactic acid

Diastereomers (nonsuperimposable non–mirror-image stereoisomers)

Configurational diastereomers

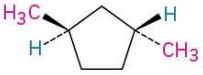


(2*R*,3*R*)-2-Amino-3-hydroxybutanoic acid



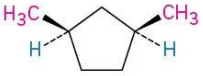
(2*R*,3*S*)-2-Amino-3-hydroxybutanoic acid

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 5.10.1

What kinds of isomers are the following pairs?

a. (*S*)-5-Chloro-2-hexene and chlorocyclohexane

b. (2*R*,3*R*)-Dibromopentane and (2*S*,3*R*)-dibromopentane

Answer

a. Constitutional isomers

b. Diastereomers

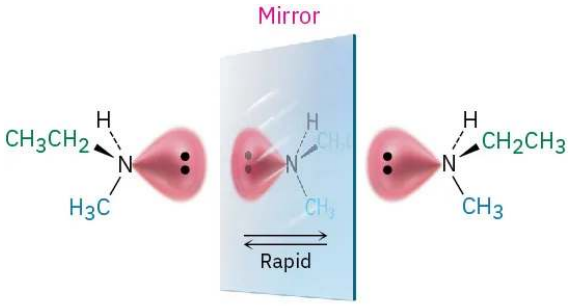
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5.11: Chirality at Nitrogen, Phosphorus, and Sulfur

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?

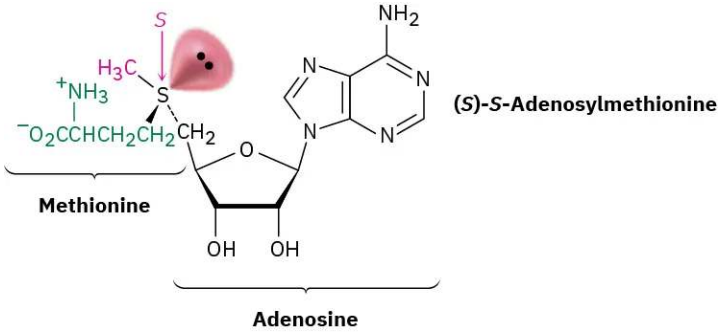
The answer is both yes and no. Yes in principle, but no in practice. It turns out that most trivalent nitrogen compounds undergo a rapid umbrella-like inversion that interconverts enantiomers, so we can't isolate individual enantiomers except in special cases.



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.

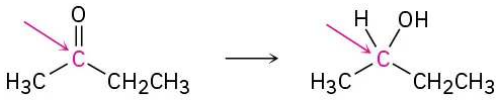


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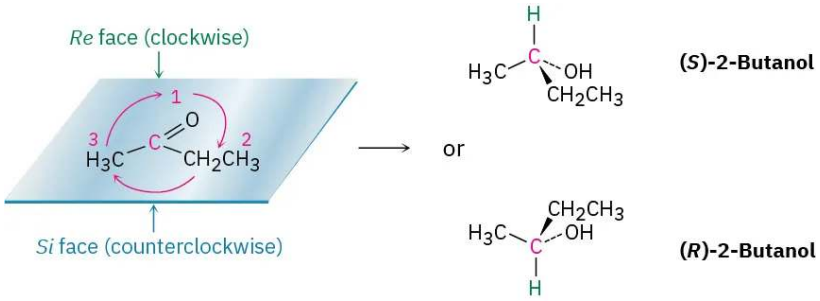
5.12: Prochirality

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 in **Section 17.5**.

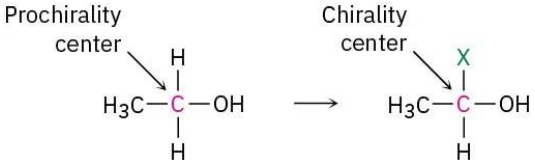


2-Butanone (prochiral) → **2-Butanol (chiral)**

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.

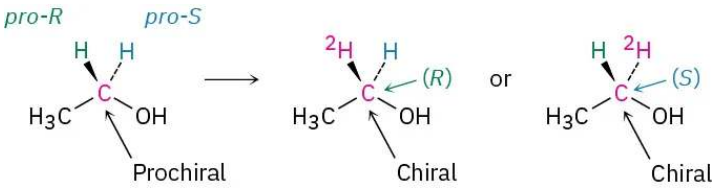


In addition to compounds with planar, sp^2-hybridized atoms, compounds with tetrahedral, sp^3-hybridized atoms can also be prochiral. An sp^3-hybridized atom is said to be a prochirality center if, by changing one of its attached groups, it becomes a chirality center. The $-CH_2OH$ carbon atom of ethanol, for instance, is a prochirality center because changing one of its attached −H atoms converts it into a chirality center.



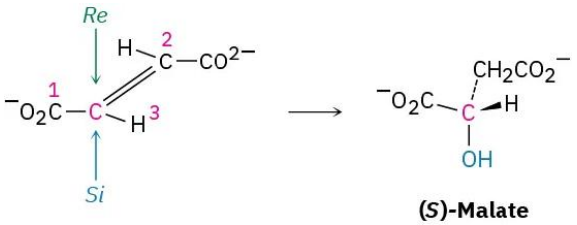
Ethanol

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*.

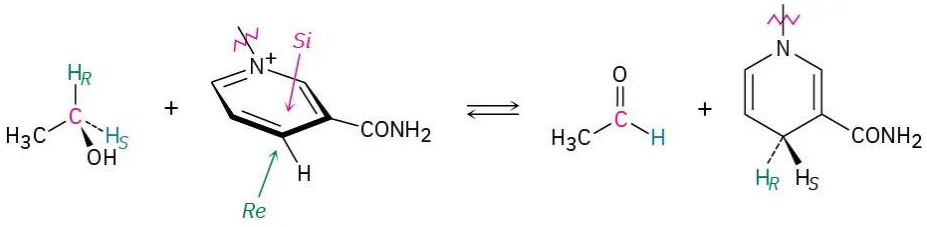


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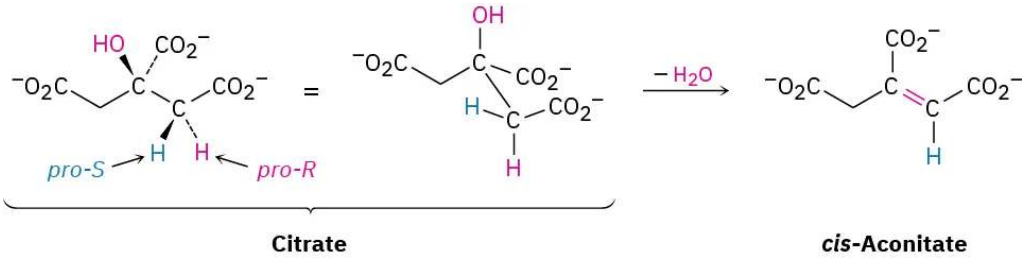
A large number of biological reactions involve prochiral compounds. One of the steps in the citric acid cycle by which food is metabolized, for instance, is the addition of H_2O to fumarate to give malate. Addition of ^-OH occurs on the Si face of a fumarate carbon and gives (*S*)-malate as product.



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^+.

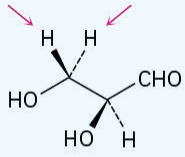


Determining the stereochemistry of reactions at prochirality centers is a powerful method for studying detailed mechanisms in biochemical reactions. As just one example, the conversion of citrate to *cis*-aconitate in the citric acid cycle has been shown to occur with loss of a pro-*R* hydrogen, implying that the OH and H groups leave from opposite sides of the molecule.

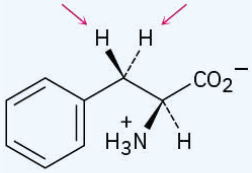


Exercise 5.12.1

Identify the indicated hydrogens in the following molecules as pro-*R* or pro-*S*:



a. **(*S*)-Glyceraldehyde**

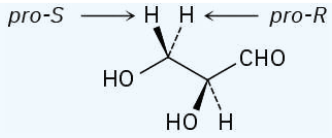


b. **Phenylalanine**

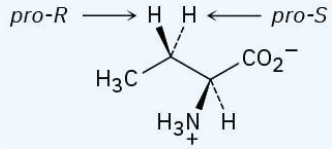
Answer

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a.



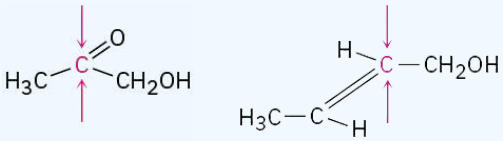
b.



Note: In the place of H_3C should read Ph=Phenyl group

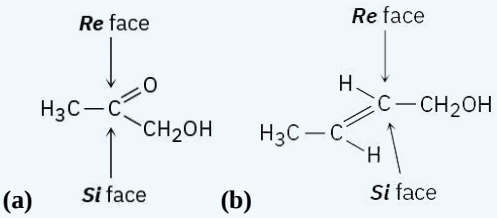
Exercise 5.12.2

Identify the indicated faces of carbon atoms in the following molecules as Re or Si:



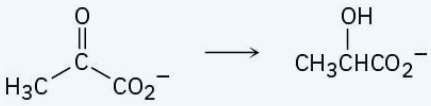
(a) Hydroxyacetone **(b) Crotyl alcohol**

Answer



Exercise 5.12.3

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?



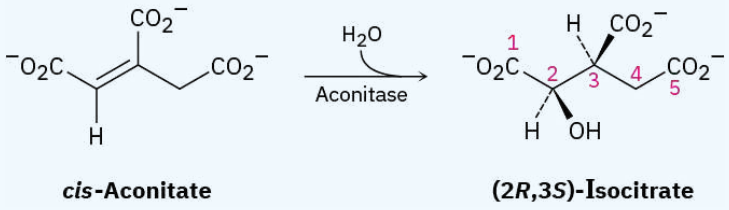
Pyruvate **Lactate**

Answer

(S)-Lactate

Exercise 5.12.4

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

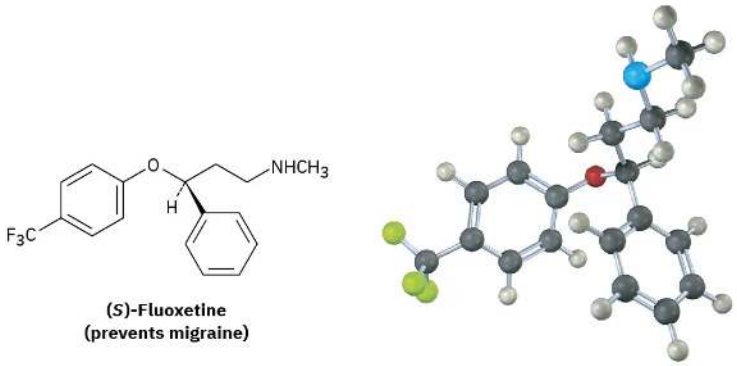
The −OH adds to the Re face of C2, and −H adds to the Re face of C3. The overall addition has anti-stereochemistry.

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5.13: 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.



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 5.13.1: one enantiomer fits the receptor perfectly, but the other does not.

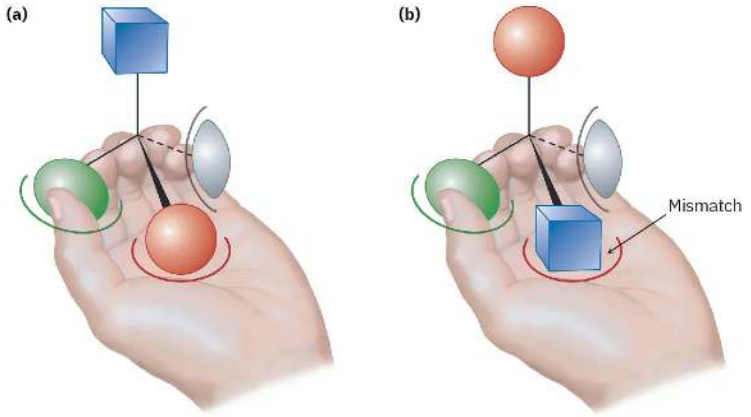


Figure 5.13.1: Interaction of a chiral object with a chiral receptor. A left hand interacts with a chiral object, much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: **green thumb**, **red palm**, and **gray pinkie finger**, with the **blue 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 5.13.1. 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 5.13.2a). 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 5.13.2b).

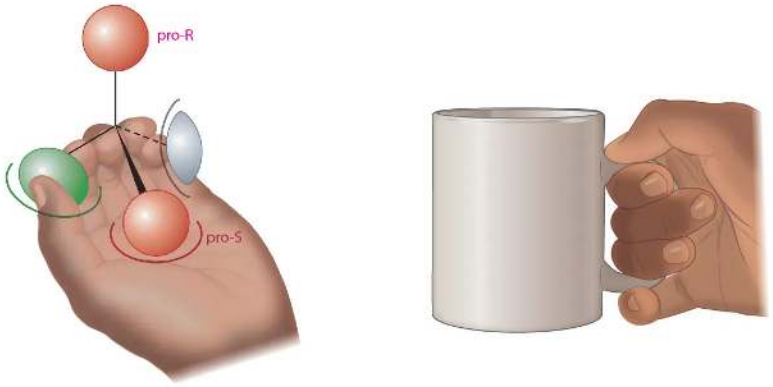


Figure 5.13.2: (a) When a prochiral molecule is held in a chiral environment, the **two seemingly identical substituents** are **distinguishable. (b)** Similarly, when an achiral coffee mug is held in the chiral environment of your hand, it's much easier to drink from one side than the other because the two sides of the mug are now distinguishable.

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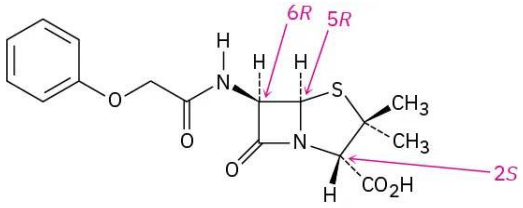
5.14: Chemistry Matters—Chiral Drugs

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.



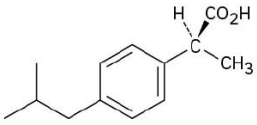
Figure 5.14.1: The *S* enantiomer of ibuprofen soothes the aches and pains of athletic injuries much more effectively than the *R* enantiomer. (credit: "World Athletic Championships 2007 in Osaka" by Eckhard Pecher/Wikimedia Commons, CC BY 2.5)

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.

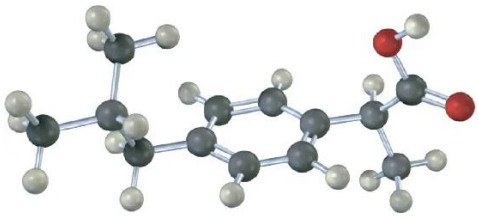


Penicillin V (2*S*,5*R*,6*R* configuration)

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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5.15: Key Terms

- absolute configuration
- achiral
- Cahn–Ingold–Prelog rules
- chiral
- chiral environment
- chirality center
- configuration
- dextrorotatory
- diastereomer
- enantiomer
- epimer
- levorotatory
- meso compound
- optically active
- prochiral
- prochirality center
- pro-*R* configuration
- pro-*S* configuration
- *R* configuration
- racemate
- Re face
- resolution
- *S* configuration
- Si face
- specific rotation, $[\alpha]_D$

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5.16: Summary

In this chapter, we've looked at some of the causes and consequences of molecular handedness—a topic of particular importance in understanding biological chemistry. The subject can be a bit complex but is so important that it's worthwhile spending time to become familiar with it.

An object or molecule that is not superimposable on its mirror image is said to be **chiral**, meaning "handed." A chiral molecule is one that does not have a plane of symmetry cutting through it so that one half is a mirror image of the other half. The most common cause of chirality in organic molecules is the presence of a tetrahedral, sp^3-hybridized carbon atom bonded to four different groups —a so-called **chirality center**. Chiral compounds can exist as a pair of nonsuperimposable mirror-image stereoisomers called **enantiomers**. Enantiomers are identical in all physical properties except for the direction in which they rotate plane-polarized light.

The stereochemical **configuration** of a chirality center can be specified as either ***R*** (*rectus*) or ***S*** (*sinister*) by using the **Cahn–Ingold–Prelog rules**. First rank the four substituents on the chiral carbon atom, and then orient the molecule so that the lowest-ranked group points directly back. If a curved arrow drawn in the direction of decreasing rank (1 → 2 → 3) for the remaining three groups is clockwise, the chirality center has the *R* configuration. If the direction is counterclockwise, the chirality center has the *S* configuration.

Some molecules have more than one chirality center. **Enantiomers** have opposite configuration at all chirality centers, whereas **diastereomers** have the same configuration in at least one center but opposite configurations at the others. **Epimers** are diastereomers that differ in configuration at only one chirality center. A compound with *n* chirality centers can have a maximum of 2^n stereoisomers.

A **meso compound** contains a chirality center but is achiral overall because it has a plane of symmetry. Racemic mixtures, or **racemates**, are 50 : 50 mixtures of (+) and (−) enantiomers. Racemates and individual diastereomers differ in their physical properties, such as solubility, melting point, and boiling point.

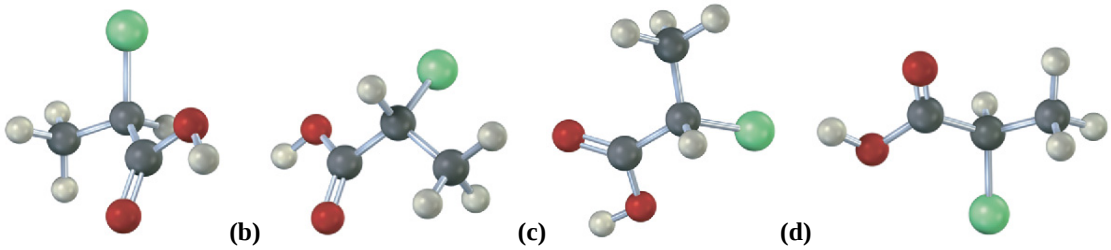
A molecule is **prochiral** if it can be converted from achiral to chiral in a single chemical step. A prochiral sp^2-hybridized atom has two faces, described as either **Re** or **Si**. An sp^3-hybridized atom is a **prochirality center** if, by changing one of its attached atoms, a chirality center results. The atom whose replacement leads to an *R* chirality center is **pro-*R*,** and the atom whose replacement leads to an *S* chirality center is **pro-*S*.**

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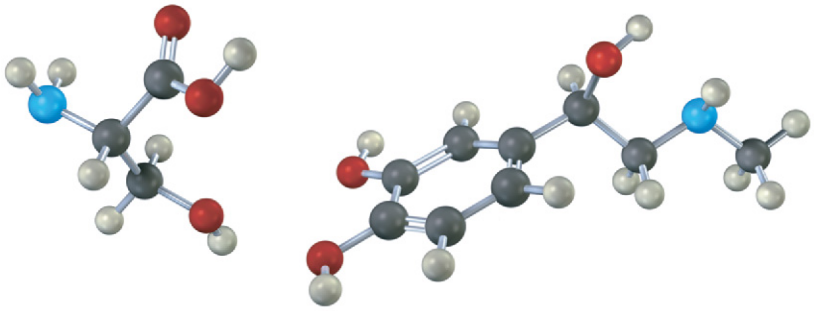
5.17: Additional Problems

PROBLEM5-26 Which of the following structures are identical? (Green = Cl.)



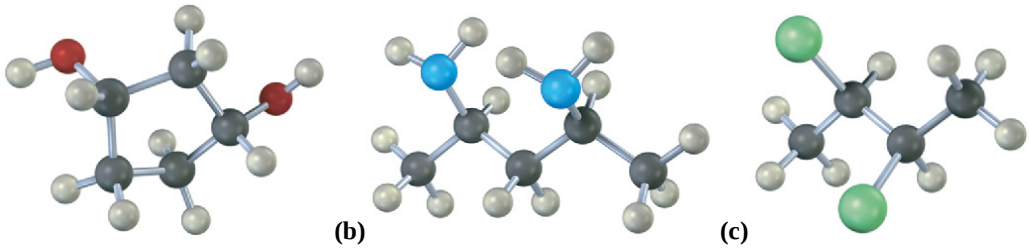
(a) **(b)** **(c)** **(d)**

PROBLEM5-27 Assign *R* or *S* configurations to the chirality centers in the following molecules (blue = N):



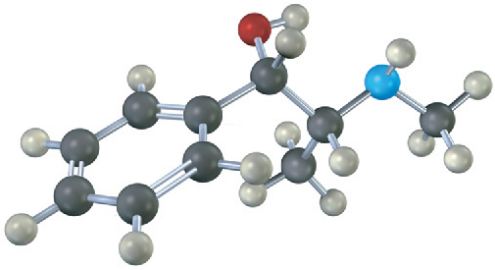
(a) **Serine** **(b)** **Adrenaline**

PROBLEM5-28 Which, if any, of the following structures represent meso compounds? (Blue = N, green = Cl.)

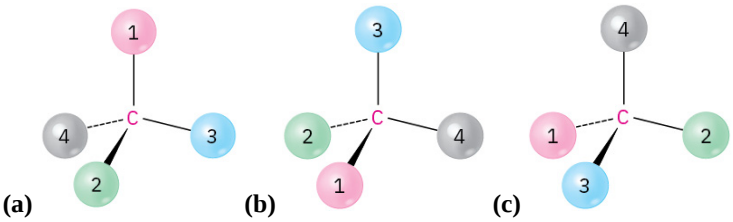


(a) **(b)** **(c)**

PROBLEM5-29 Assign *R* or *S* configuration to each chirality center in pseudoephedrine, an over-the-counter decongestant found in cold remedies (blue = N).



PROBLEM5-30 Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



Chirality and Optical Activity

PROBLEM5-31

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

PROBLEM5-32

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

PROBLEM5-33

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}

PROBLEM5-34

Eight alcohols have the formula $C_5H_{12}O$. Draw them. Which are chiral?

PROBLEM5-35

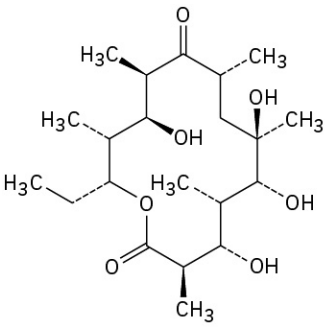
Draw compounds that fit the following descriptions:

(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

PROBLEM5-36

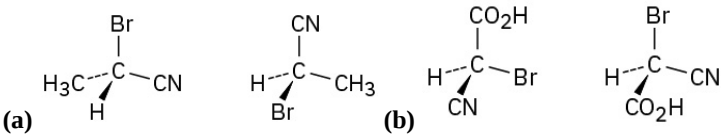
Erythronolide B is the biological precursor of erythromycin, a broad-spectrum antibiotic. How many chirality centers does erythronolide B have? Identify them.

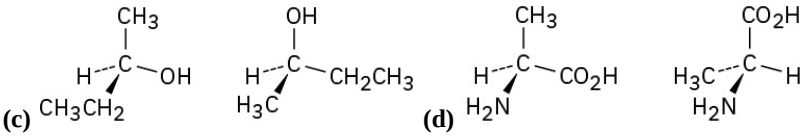


Erythronolide B

Assigning Configuration to Chirality Centers

PROBLEM5-37 Which of the following pairs of structures represent the same enantiomer, and which represent different enantiomers?





PROBLEM5-38

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?

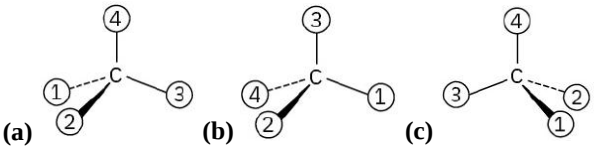
PROBLEM5-39 What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-2,4-octanediol?

PROBLEM5-40

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.)

PROBLEM5-41

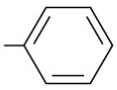
Orient each of the following drawings so that the lowest-ranked group is toward the rear, and then assign *R* or *S* configuration:



PROBLEM5-42

Assign Cahn–Ingold–Prelog rankings to the following sets of substituents:

(a) —CH=CH$_2$, —CH(CH$_3$)$_2$, —C(CH$_3$)$_3$, —CH$_2$CH$_3$

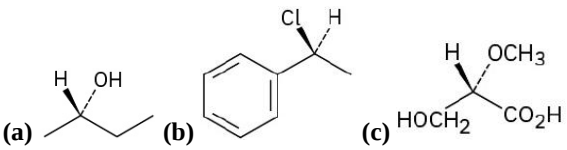
(b) —C≡CH, —CH=CH$_2$, —C(CH$_3$)$_3$, 

(c) —CO$_2$CH$_3$, —COCH$_3$, —CH$_2$OCH$_3$, —CH$_2$CH$_3$

(d) —C≡N, —CH$_2$Br, —CH$_2$CH$_2$Br, —Br

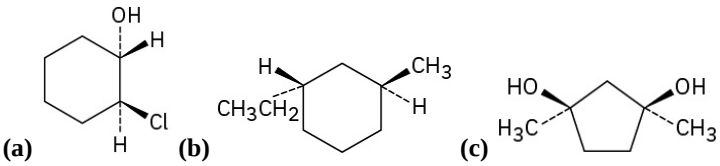
PROBLEM5-43

Assign *R* or *S* configurations to each chirality center in the following molecules:

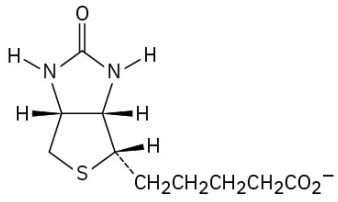


PROBLEM5-44

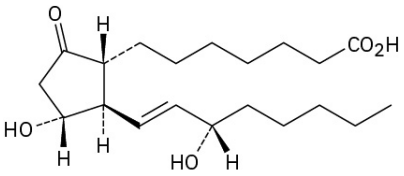
Assign *R* or *S* configuration to each chirality center in the following molecules:



PROBLEM5-45 Assign *R* or *S* configuration to each chirality center in the following biological molecules:



(a) **Biotin**



(b) **Prostaglandin E_1**

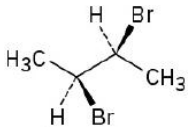
PROBLEM5-46

Draw tetrahedral representations of the following molecules:

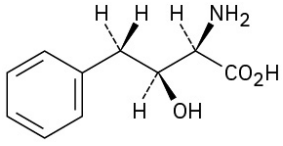
(a) (*S*)-2-Chlorobutane

(b) (*R*)-3-Chloro-1-pentene [$H_2C{=}CHCH(Cl)CH_2CH_3$]

PROBLEM5-47 Assign *R* or *S* configuration to each chirality center in the following molecules:

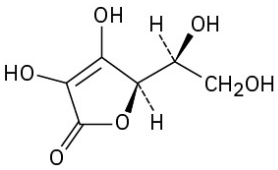


(a)



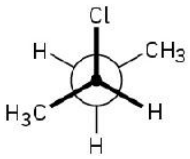
(b)

PROBLEM5-48 Assign *R* or *S* configurations to the chirality centers in ascorbic acid (vitamin C).

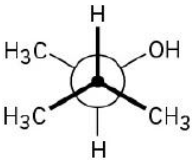


Ascorbic acid

PROBLEM5-49 Assign *R* or *S* stereochemistry to the chirality centers in the following Newman projections:

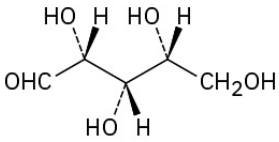


(a)



(b)

PROBLEM5-50 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

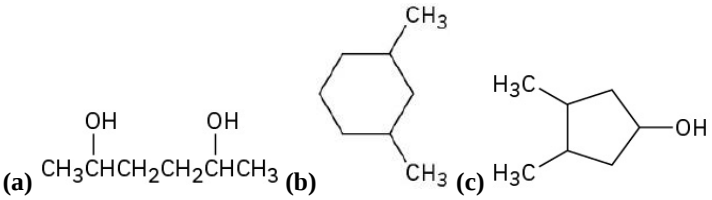
Meso Compounds

PROBLEM5-51 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*

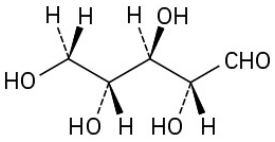
PROBLEM5-52 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:



(a) **(b)** **(c)**

PROBLEM5-53 Draw the structure of a meso compound that has five carbons and three chirality centers.

PROBLEM5-54 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:

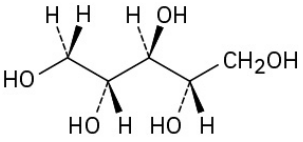


Ribose

(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.

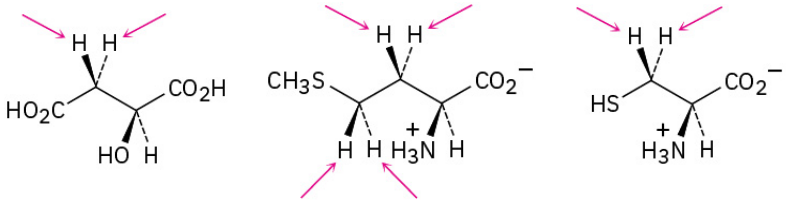
PROBLEM5-55 On reaction with hydrogen gas in the presence of a platinum catalyst, ribose (Problem 5-54) is converted into ribitol. Is ribitol optically active or inactive? Explain.



Ribitol

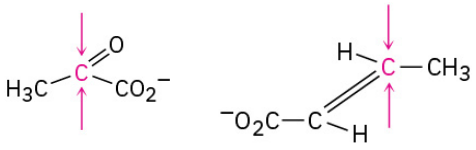
Prochirality

PROBLEM5-56 Identify the indicated hydrogens in the following molecules as pro-*R* or pro-*S:*



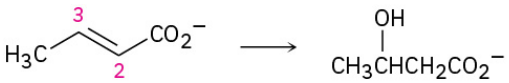
(a) **Malic acid** **(b)** **Methionine** **(c)** **Cysteine**

PROBLEM5-57 Identify the indicated faces in the following molecules as Re or Si:



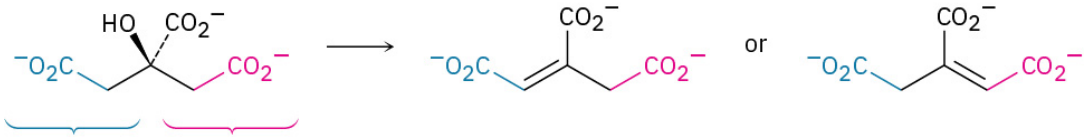
(a) **Pyruvate** **(b)** **Crotonate**

PROBLEM5-58 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.



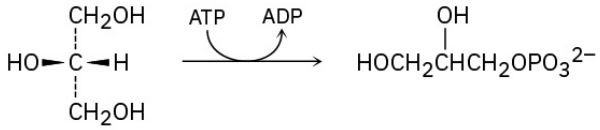
Crotonate **3-Hydroxybutyrate**

PROBLEM5-59 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?



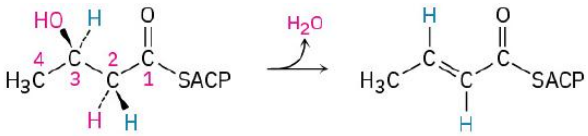
Citrate ***cis*-Aconitate**

PROBLEM5-60 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**

PROBLEM5-61 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

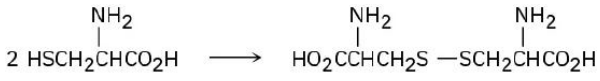
PROBLEM5-62 Draw all possible stereoisomers of 1,2-cyclobutanedicarboxylic acid, and indicate the interrelationships. Which, if any, are optically active? Do the same for 1,3-cyclobutanedicarboxylic acid.

PROBLEM5-63

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*.

PROBLEM5-64

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.

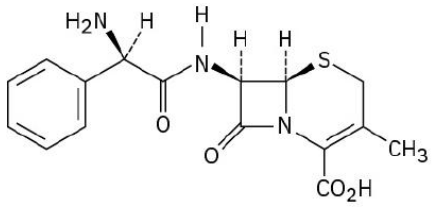


Cysteine **Cystine**

PROBLEM5-65 Draw tetrahedral representations of the following molecules:

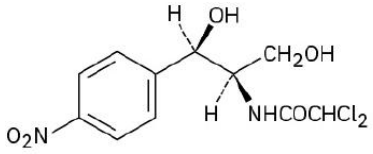
(a) The 2*S*,3*R* enantiomer of 2,3-dibromopentane **(b)** The meso form of 3,5-heptanediol

PROBLEM5-66 Assign *R* or *S* configurations to the chiral centers in cephalexin, trade-named Keflex, the most widely prescribed antibiotic in the United States.



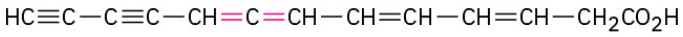
Cephalexin

PROBLEM5-67 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.



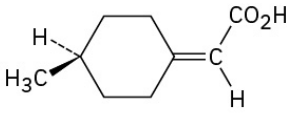
Chloramphenicol

PROBLEM5-68 *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

PROBLEM5-69 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

PROBLEM5-70 (*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?

PROBLEM5-71

How many stereoisomers of 2,4-dibromo-3-chloropentane are there? Draw them, and indicate which are optically active.

PROBLEM5-72

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?

PROBLEM5-73

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?

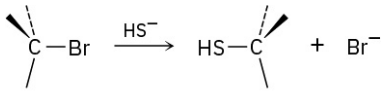
(c) What are the stereochemical relationships among the various stereoisomers of 1,3-dimethylcyclohexane?

PROBLEM5-74

cis-1,2-Dimethylcyclohexane is optically inactive even though it has two chirality centers. Explain.

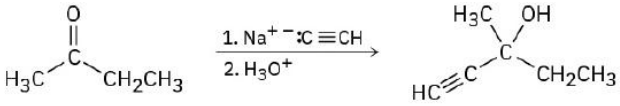
PROBLEM5-75

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

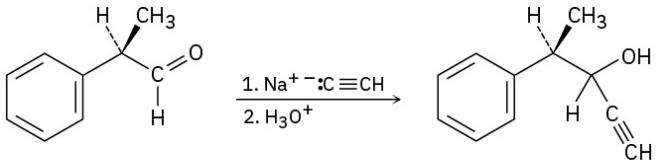
PROBLEM5-76 Ketones react with sodium acetylide (the sodium salt of acetylene, Na^{+-} : C≡CH) to give alcohols. For example, the reaction of sodium acetylide with 2-butanone yields 3-methyl-1-pentyn-3-ol:



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.

PROBLEM5-77 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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CHAPTER OVERVIEW

6: An Overview of Organic Reactions

Learning Objectives

After you have completed Chapter 6, you should be able to

1. fulfill the detailed objectives listed under each individual section.
2. identify the polarity pattern in the common functional groups, and explain the importance of being able to do so.
3. describe the essential differences between polar and radical reactions, and assign a given reaction to one of these two categories.
4. discuss how kinetic and thermodynamic factors determine the rate and extent of a chemical reaction.
5. use bond dissociation energies to calculate the $\Delta H°$ of simple reactions, and *vice versa*.
6. draw and interpret reaction energy diagrams.
7. define, and use in context, the new key terms.

This chapter is designed to provide a gentle introduction to the subject of reaction mechanisms. Two types of reactions are introduced—polar reactions and radical reactions. The chapter briefly reviews a number of topics you should be familiar with, including rates and equilibria, elementary thermodynamics and bond dissociation energies. You must have a working knowledge of these topics to obtain a thorough understanding of organic reaction mechanisms. Reaction energy diagrams are used to illustrate the energy changes that take place during chemical reactions, and to emphasize the difference between a reaction intermediate and a transition state.

6.1: Why This Chapter?
6.2: Kinds of Organic Reactions
6.3: How Organic Reactions Occur - Mechanisms
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: Radical Reactions
6.8: Describing a Reaction - Equilibria, Rates, and Energy Changes
6.9: Describing a Reaction - Bond Dissociation Energies
6.10: Describing a Reaction - Energy Diagrams and Transition States
6.11: Describing a Reaction- Intermediates
6.12: A Comparison between Biological Reactions and Laboratory Reactions
6.13: Chemistry Matters—Where Do Drugs Come From?
6.14: Key Terms
6.15: Summary
6.16: Additional Problems

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6.1: 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.

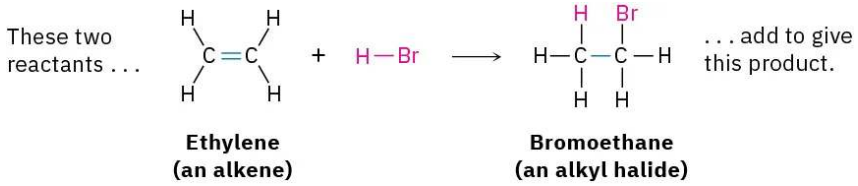
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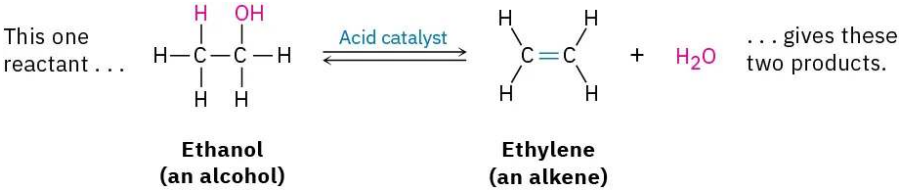
6.2: Kinds of Organic Reactions

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*.

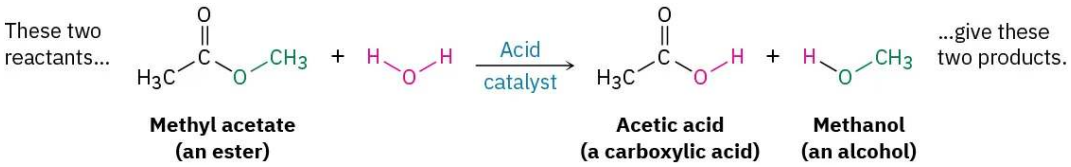
- Addition reactions occur when two reactants add together to form a single product with no atoms "left over." An example that we'll be studying soon is the reaction of an alkene, such as ethylene, with HBr to yield an alkyl bromide.



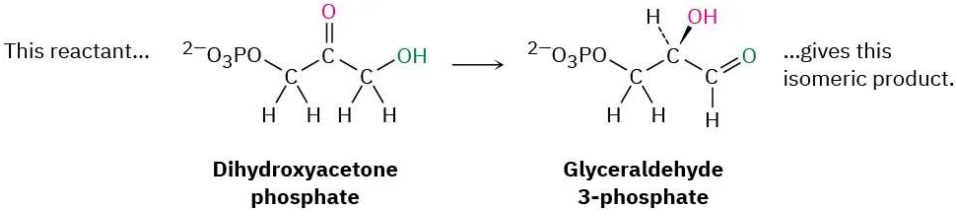
- Elimination reactions are, in a sense, the opposite of addition reactions. They occur when a single reactant splits into two products, often with the formation of a small molecule such as water or HBr. An example is the acid-catalyzed reaction of an alcohol to yield water and an alkene.



- 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.



Exercise 6.2.1

Classify each of the following reactions as an addition, elimination, substitution, or rearrangement:

a. $CH_3Br + KOH \longrightarrow CH_3OH + KBr$
b. $CH_3CH_2Br \longrightarrow H_2C{=}CH_2 + HBr$
c. $H_2C{=}CH_2 + H_2 \longrightarrow CH_3CH_3$

Answer

a. Substitution
b. Elimination

c. Addition

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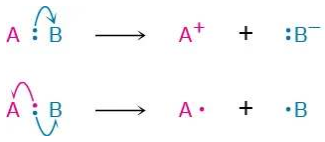
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6.3: How Organic Reactions Occur - Mechanisms

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*, and the symmetrical cleavage is said to be *homolytic*.

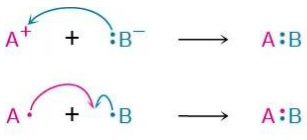
We'll develop this point in more detail later, but note for now that the movement of *two* electrons in the unsymmetrical process is indicated using a full-headed curved arrow (↷), whereas the movement of *one* electron in the symmetrical process is indicated using a half-headed, or "fishhook," arrow (↶).



Unsymmetrical bond-breaking (polar):
two bonding electrons stay with one product.

Symmetrical bond-breaking (radical):
one bonding electron stays with each product.

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.



Unsymmetrical bond-making (polar):
two bonding electrons are donated by one reactant.

Symmetrical bond-making (radical):
one bonding 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.

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 in Chapter 30.

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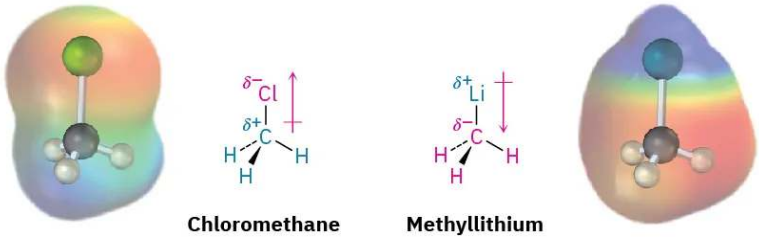
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6.4: Polar Reactions

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 2.2 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 2.2, 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.

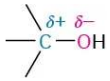
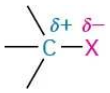
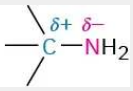
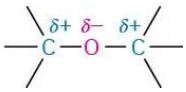
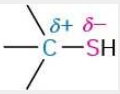
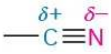
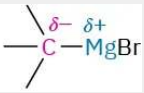
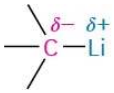
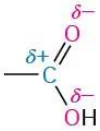
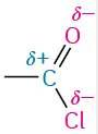
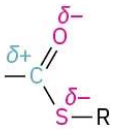
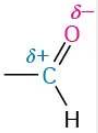
Elements such as oxygen, nitrogen, fluorine, and chlorine are more electronegative than carbon, so a carbon atom bonded to one of these atoms has a partial positive charge ($\delta+$). Metals are less electronegative than carbon, so a carbon atom bonded to a metal has a partial negative charge ($\delta-$). 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).



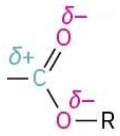
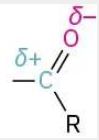
Chloromethane **Methyllithium**

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.

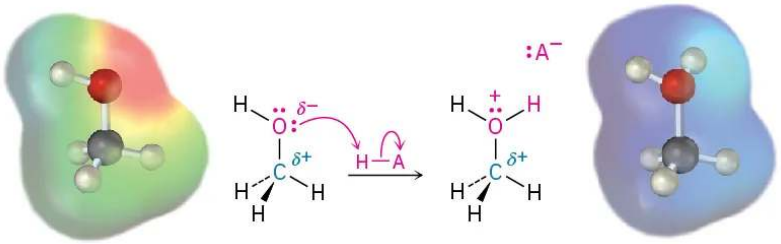
Table 6.4.1: Polarity Patterns in Some Common Functional Groups

Compound type	Functional group structure
Alcohol	
Alkene	 Symmetrical, nonpolar
Alkyl halide	
Amine	
Ether	
Thiol	
Nitrile	
Grignard reagent	
Alkyllithium	
Carbonyl	
Carboxylic acid	
Carboxylic acid chloride	
Thioester	
Aldehyde	

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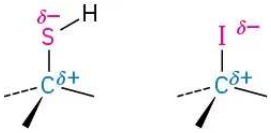
Compound type	Functional group structure
Ester	
Ketone	

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.



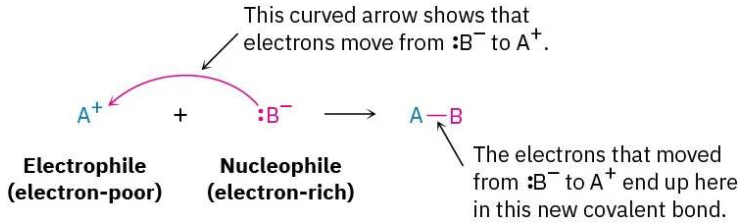
Methanol—weakly electron-poor carbon **Protonated methanol—strongly electron-poor carbon**

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 6.2).

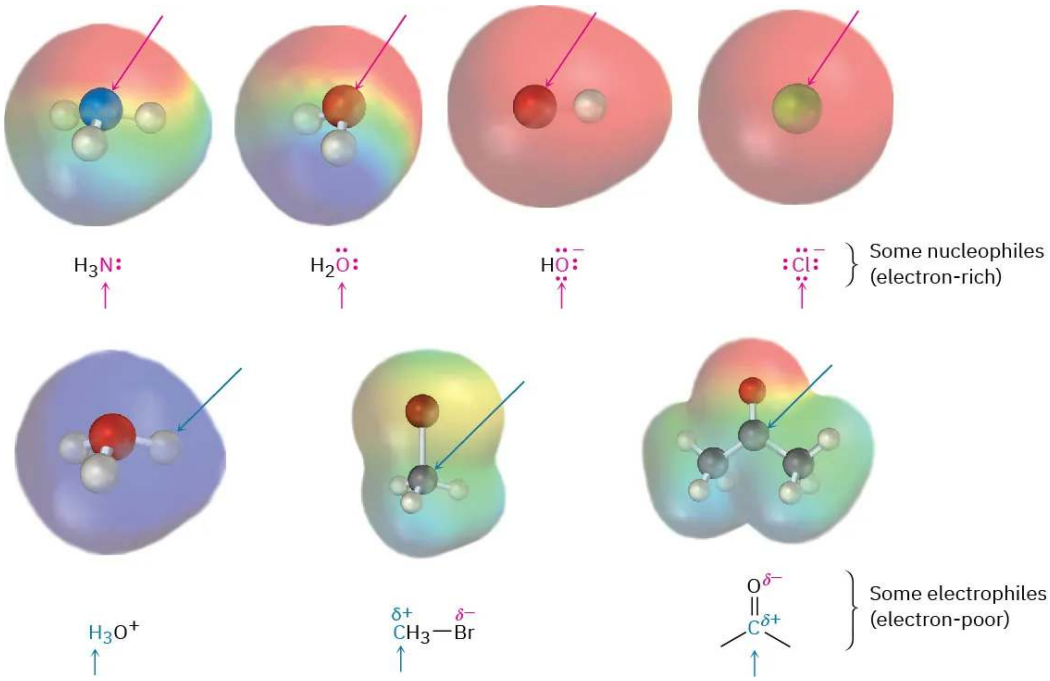


Figure 6.2: Some nucleophiles and electrophiles. Electrostatic potential maps identify the nucleophilic **(negative)** and electrophilic **(positive)** atoms.

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

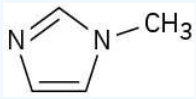
A nucleophile has an electron-rich site, either because it is negatively charged or because it has a functional group containing an atom that has a lone pair of electrons. An electrophile has an electron-poor site, either because it is positively charged or because it has a functional group containing 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.

? 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. 

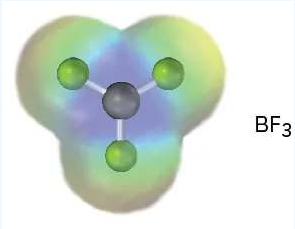
d. 

Answer

a. Carbon is electrophilic.
b. Sulfur is nucleophilic.
c. Nitrogens are nucleophilic (for reasons that will be explained in Chapter 15).
d. Oxygen is nucleophilic; carbon is electrophilic.

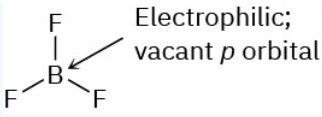
? Exercise 6.4.2

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

Electrophile; Boron has a vacant *p* orbital.

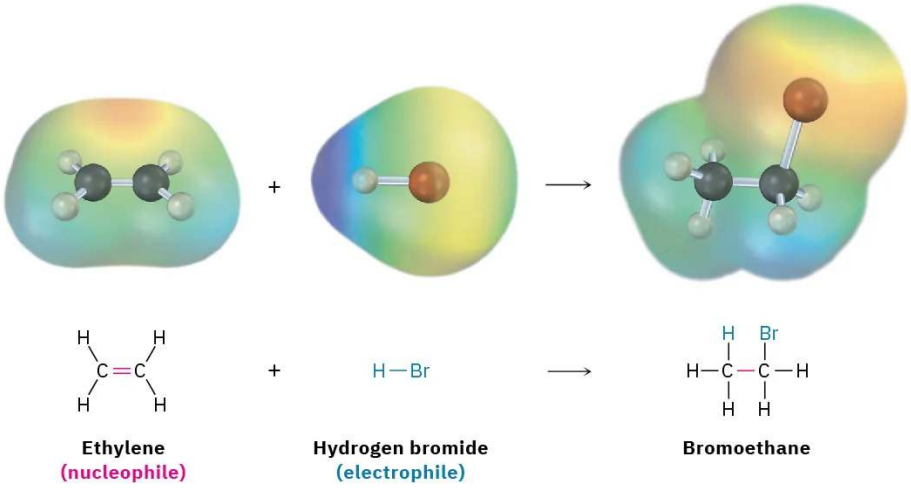


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6.5: An Example of a Polar Reaction - Addition of HBr to Ethylene

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 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.

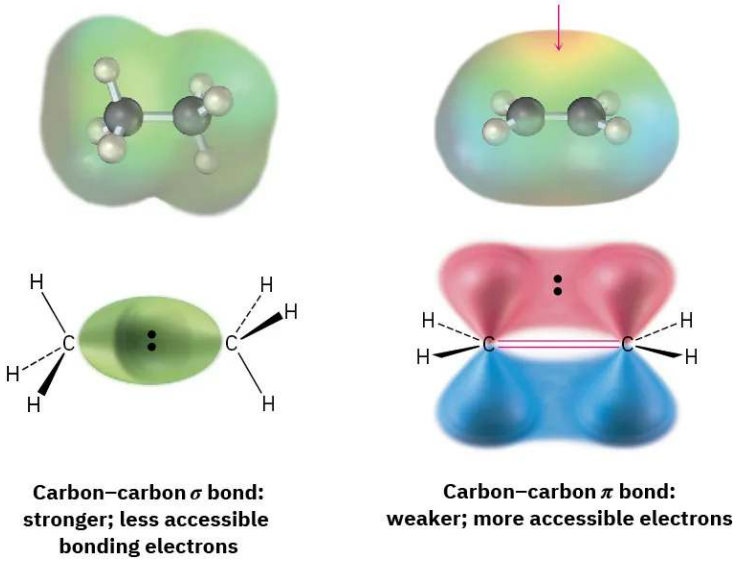


Figure 6.5.1: A comparison of carbon–carbon single and double bonds. A double bond is both more accessible to approaching reactants than a single bond and more electron-rich (more nucleophilic). An electrostatic potential map of ethylene indicates that the double bond is the region of **highest negative 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^-.

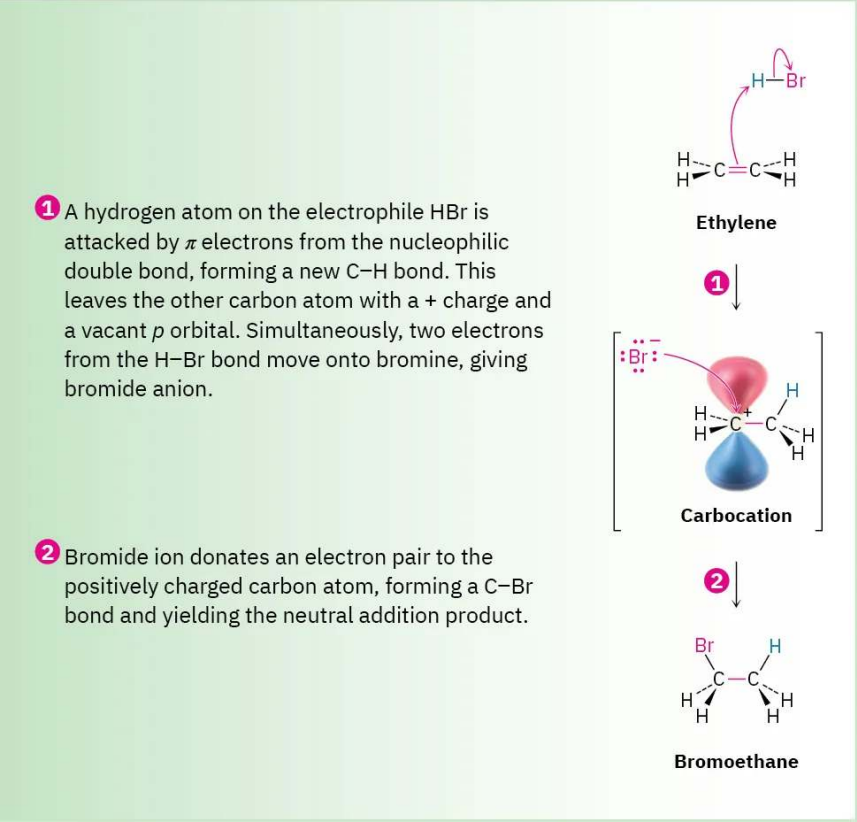


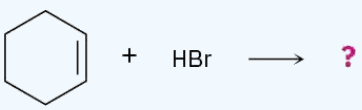
Figure 6.5.2: The electrophilic addition reaction of ethylene and HBr. The reaction takes place in two steps, both of which involve electrophile–nucleophile interactions.

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.

? Exercise 6.5.1

What product would you expect from the reaction of cyclohexene with HBr? With HCl?



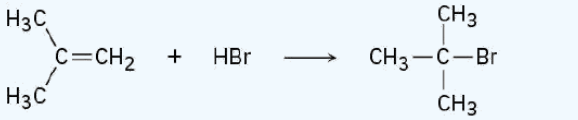
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Answer

Bromocyclohexane; chlorocyclohexane.

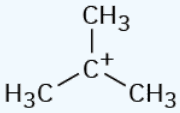
? Exercise 6.5.2

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



The mechanism is shown in Figure 6.5.2.

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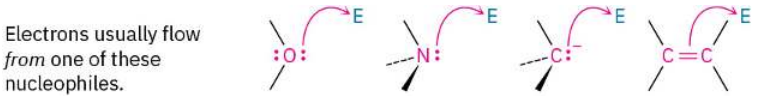
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6.6: Using Curved Arrows in Polar Reaction Mechanisms

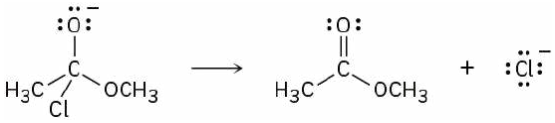
It takes practice to use curved arrows properly in reaction mechanisms, but there are a few rules and a few common patterns you should look for that will help you become more proficient:

RULE 1

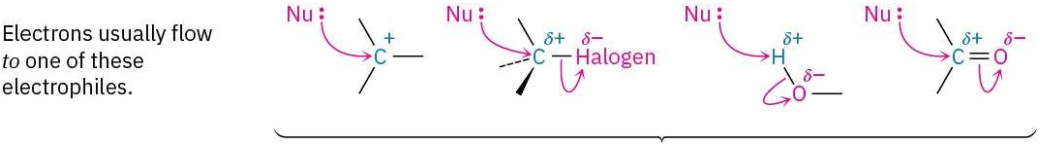
Electrons move *from* a nucleophilic source (Nu: or Nu:$^-$) *to* an electrophilic sink (E or E$^+$). The nucleophilic source must have an electron pair available, usually either as a lone pair or in a multiple bond.



For example:

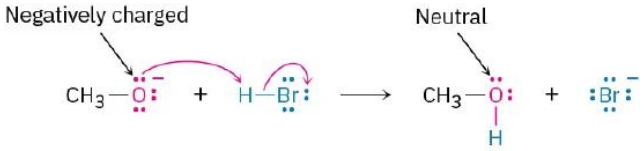


The electrophilic sink must be able to accept an electron pair, usually because it has either a positively charged atom or a positively polarized atom in a functional group. For example:

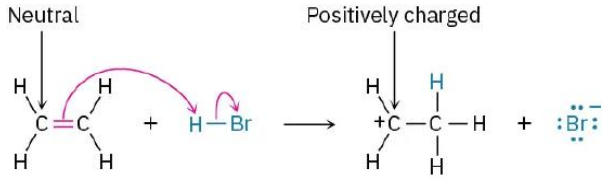


RULE 2

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:

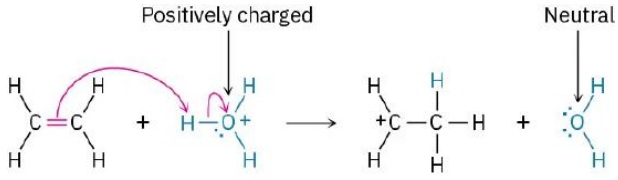


If the nucleophile is neutral, the atom that donates the electron pair acquires a positive charge. For example:



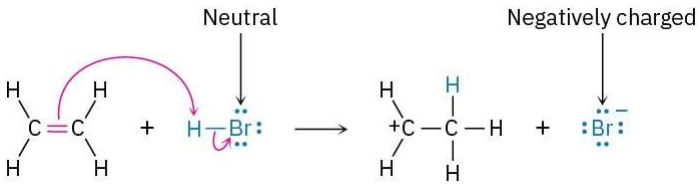
RULE 3

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.

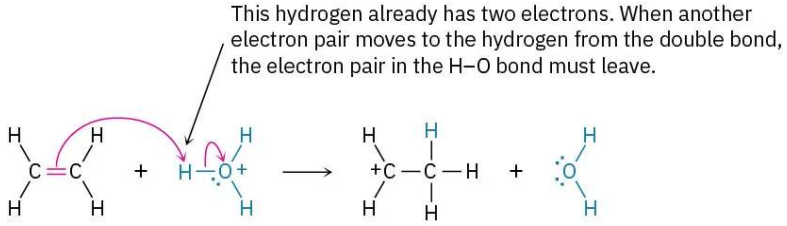
Carbon and hydrogen do not typically stabilize a negative charge. For example:



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

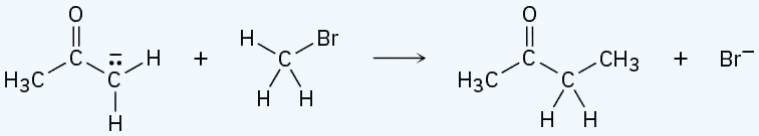
The octet rule must be followed. That is, no second-row atom can be left with ten electrons (or four for hydrogen). If an electron pair moves *to* an atom that already has an octet (or two electrons for hydrogen), another electron pair must simultaneously move from that atom to maintain the octet. When 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 6.2 gives another example of drawing curved arrows.

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 the 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

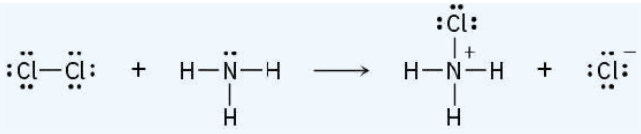


Exercise 6.6.1

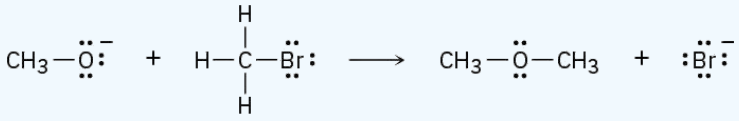
Add curved arrows to the following polar reactions to indicate the flow of electrons in each:

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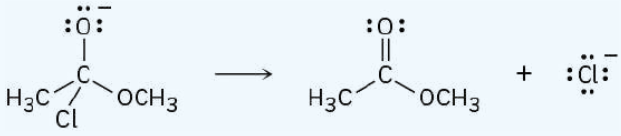
a.



b.



c.



Answer

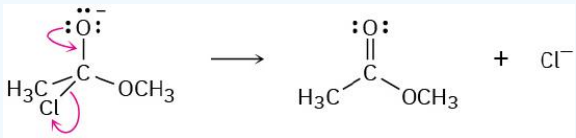
a.



b.

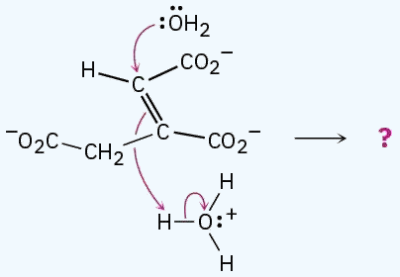


c.

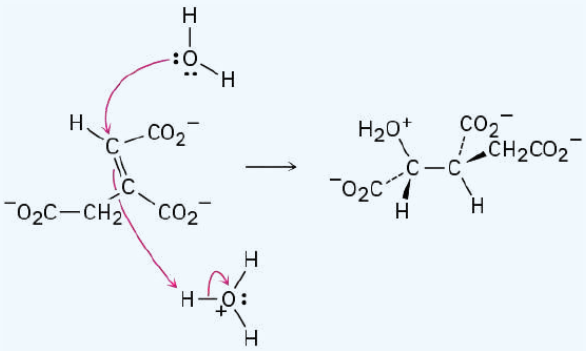


Exercise 6.6.2

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



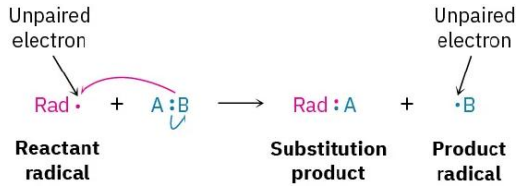
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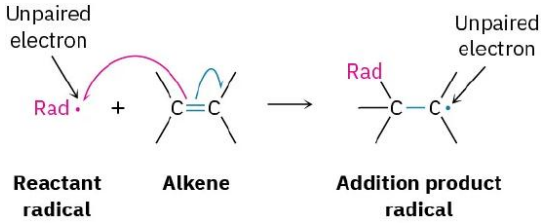
6.7: Radical Reactions

Radical reactions are much less common than polar reactions but are nevertheless important in some industrial processes and biological pathways. We'll look at them in more detail in **Sections 10.3** and **10.4** but will briefly see how they occur at this point.

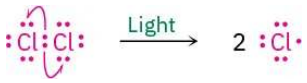
A radical is highly reactive because it contains an atom with an odd number of electrons (usually seven) in its valence shell, rather than a noble-gas octet. The radical can achieve a valence-shell octet in several ways however. For instance, it might abstract an atom and one bonding electron from another reactant, leaving behind a new radical. The net result is a radical substitution reaction.



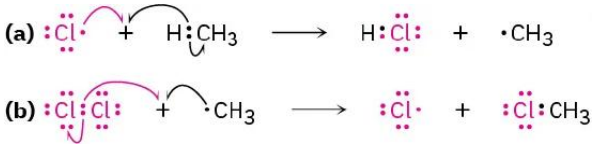
Alternatively, a reactant radical might add to a double bond, taking one electron from the double bond and yielding a new radical. The net result is a radical addition reaction.



An example of an industrially useful radical reaction is the reaction of chlorine with methane to yield chloromethane, which is used to manufacture the solvents dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$). The process begins with irradiation of Cl_2 with ultraviolet light to break the relatively weak Cl−Cl bond of Cl_2 and produce chlorine radicals (·Cl).

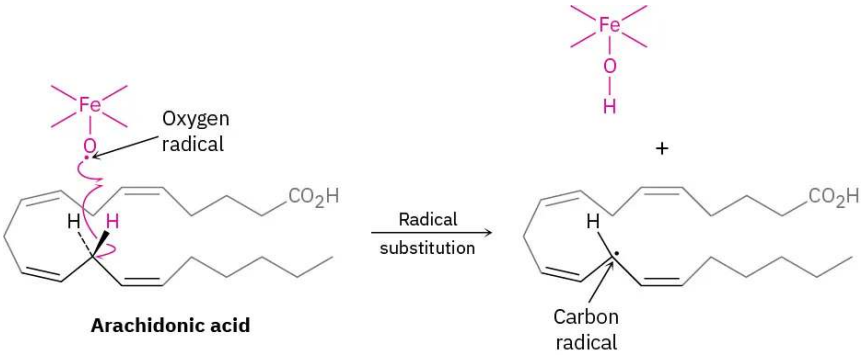


Chlorine radicals then react with methane by abstracting a hydrogen atom to give HCl and a methyl radical (·CH_3) that reacts further with Cl_2 to give chloromethane plus a new chlorine radical that cycles back and repeats the first step. Thus, once the sequence has started, it becomes a self-sustaining cycle of repeating steps (**a**) and (**b**), making the overall process a chain reaction.



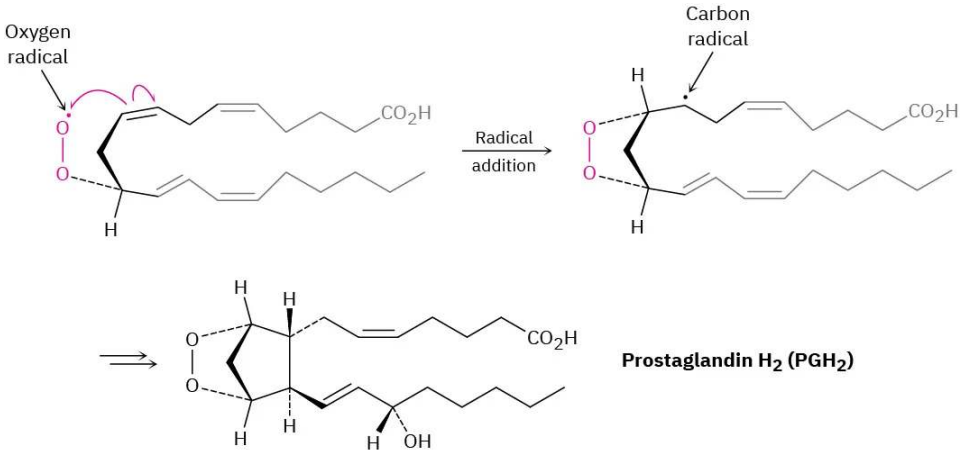
As a biological example of a radical reaction, look at the synthesis of *prostaglandins*, a large class of molecules found in virtually all body tissues and fluids. A number of pharmaceuticals are based on or derived from prostaglandins, including medicines that induce labor during childbirth, reduce 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)

Exercise 6.7.1

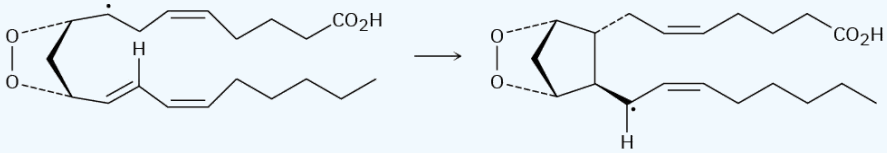
Radical chlorination of alkanes is not generally useful because mixtures of products often result when more than one kind of C−H bond is present in the substrate. Draw and name all monochloro substitution products $C_6H_{13}Cl$ you might obtain by reaction of 2-methylpentane with Cl_2.

Answer

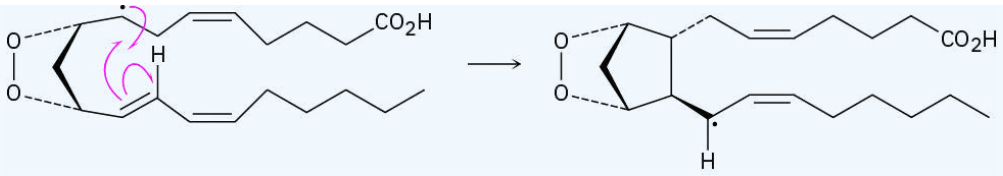
1-Chloro-2-methylpentane, 2-chloro-2-methylpentane, 3-chloro-2-methylpentane, 2-chloro-4-methylpentane, 1-chloro-4-methylpentane.

Exercise 6.7.2

Using curved fishhook arrows, propose a mechanism for the formation of the cyclopentane ring of prostaglandin H_2.



Answer



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6.8: 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 $[\mathrm{C}]^c[\mathrm{D}]^d$ is much larger than the reactant concentration term $[\ \mathrm{A}]^a[\ \mathrm{B}]^b$, 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:

$$K_{\mathrm{eq}} = \frac{[\mathrm{CH_3CH_2Br}]}{[\mathrm{H_2C{=}CH_2}][\mathrm{HBr}]} = 7.1 \times 10^7 \tag{6.8.1}$$

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%).

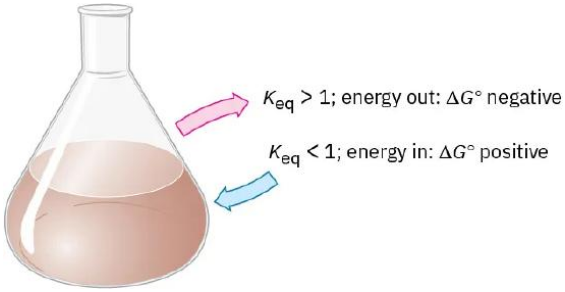
What determines the magnitude of the equilibrium constant? For a reaction to have a favorable equilibrium constant and proceed as written, the energy of the products must be lower than the energy of the reactants. In other words, energy must be released. This situation is analogous to that of a rock 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:

$$\Delta G = G_{products} - G_{reactants}. \tag{6.8.2}$$

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

$$\Delta G^\circ = -RT \ln K_{eq} \tag{6.8.3}$$

or

$$K_{eq} = e^{-\Delta G^\circ / RT} \tag{6.8.4}$$

where

$$\begin{aligned} &R = 8.314 \text{ J/(K} \cdot \text{mol)} = 1.987 \text{cal/(K} \cdot \text{mol)} \\ &T = \text{ Kelvin temperature} \\ &e = 2.718 \\ &\ln K_{eq} = \text{ natural logarithm of } K_{eq} \end{aligned} \tag{6.8.5}$$

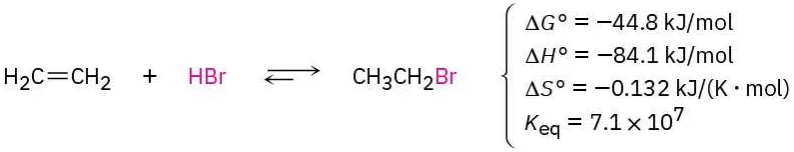
For example, the reaction of ethylene with HBr (Equation 6.8.2) has $K_{eq} = 7.1 \times 10^7$, so $\Delta G° = -44.8$ kJ/mol (−10.7 kcal/mol) at 298 K:

$$\begin{aligned} &K_{eq} = 7.1 \times 10^7 \text{ and } \ln K_{eq} = 18.08 \\ &\Delta G^\circ = -RT \ln K_{eq} = -[8.314 \text{ J/(K} \cdot \text{mol)}](298 \text{ K})(18.08) \\ &= -44,800 \text{ J/mol} = -44.8 \text{ kJ/mol} \end{aligned} \tag{6.8.6}$$

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.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{6.8.7}$$

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

$$\text{A} \longrightarrow \text{B} + \text{C}$$

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

$$A + B \longrightarrow C$$

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 6.8.1 describes the thermodynamic terms more fully.

Table 6.8.1: 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?

? Exercise 6.8.1

Which reaction is more energetically favored, one with $\Delta G° = -44$ kJ/mol or one with $\Delta G° = +44$ kJ/mol?

Answer

Negative $\Delta G°$ is favored.

? Exercise 6.8.2

Which reaction is more exergonic, one with K_{eq}=1000 or one with K_{eq}=0.001?

Answer

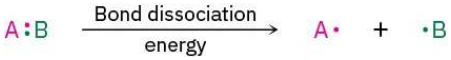
Larger K_{eq} is more exergonic.

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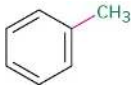
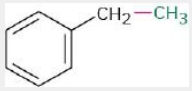
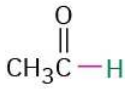
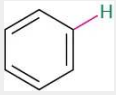
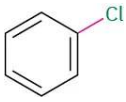
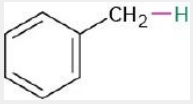
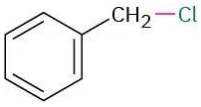
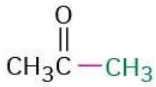
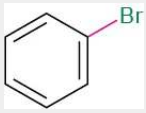
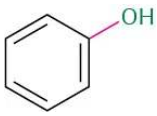
6.9: Describing a Reaction - Bond Dissociation Energies

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).



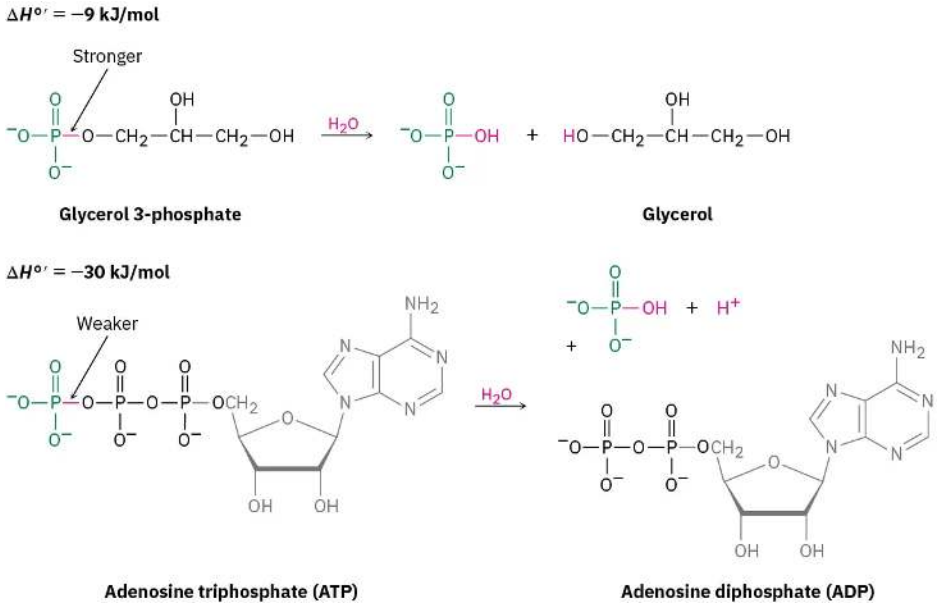
Each specific bond has its own characteristic strength, and extensive tables of such data are available. For example, a C−H bond in methane has a bond dissociation energy D = 439.3 kJ/mol (105.0 kcal/mol), meaning that 439.3 kJ/mol must be added to break a C−H bond of methane to give the two radical 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 6.9.1 lists some other bond strengths.

Table 6.9.1: 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	$(CH_3)_2CH$—CI	354	$(CH_3)_2CH$—CH_3	369
H—CI	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	$(CH_3)_3C$—CI	352	H_2C=$CHCH_2$—CH 3	318
CI—CI	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—CI	396		374
CH_3—CI	350	H_2C=$CHCH_2$—H	369	HO—H	497
CH_3—Br	294	H_2C=$CHCH_2$—CI	298	HO—OH	211
CH_3—I	239		472	CH_3O—H	440
CH_3—OH	385		400	CH_3S—H	366
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.

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 ($\Delta H^{\circ\prime} = -9$ kJ/mol), but when ATP reacts with water, 30 kJ/mol of heat is released ($\Delta H^{\circ\prime} = -30$ 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.

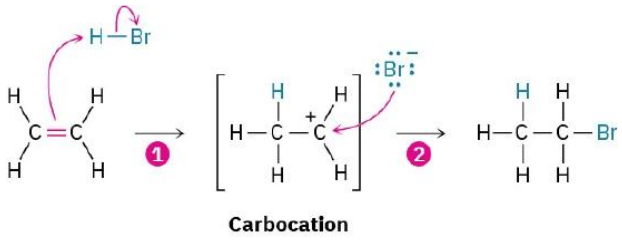


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6.10: Describing a Reaction - Energy Diagrams and Transition States

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 6.10.1. 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.

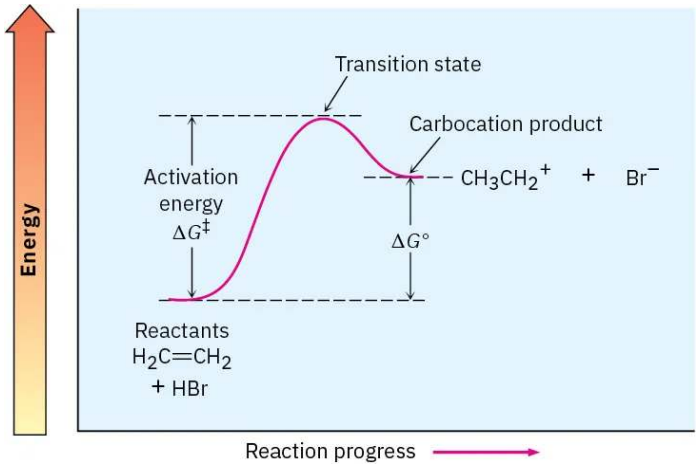


Figure 6.10.1: An energy diagram for the first step in the reaction of ethylene with HBr. The energy difference between reactants and the transition state, $\Delta G^{\ddagger}$, defines the reaction rate. The energy difference between reactants and carbocation product, $\Delta G°$, defines the position 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 6.10.1. 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 6.10.2).

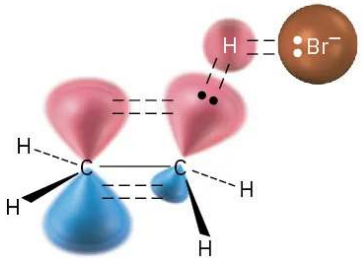


Figure 6.10.2: A hypothetical transition-state structure for the first step of the reaction of ethylene with HBr. The C=C π bond and H−Br bond are just beginning to break, and the C−H bond is just beginning to form.

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 6.10.3 illustrates some different possibilities.

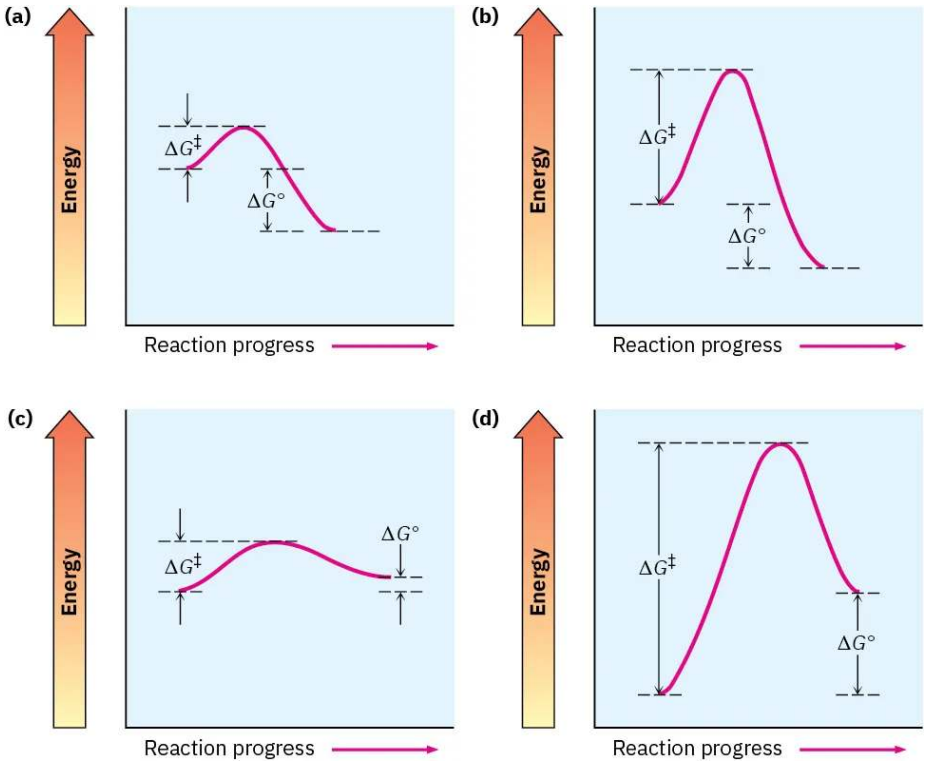


Figure 6.10.3: Some hypothetical energy diagrams: **(a)** a fast exergonic reaction (low $\Delta G^{\ddagger}$, negative $\Delta G°$); **(b)** a slow exergonic reaction (high $\Delta G^{\ddagger}$, negative $\Delta G°$); **(c)** a fast endergonic reaction (small $\Delta G^{\ddagger}$, small positive $\Delta G°$); **(d)** a slow endergonic reaction (high $\Delta G^{\ddagger}$, positive $\Delta G°$).

? Exercise 6.10.1

Which reaction is faster, one with $\Delta G^{\ddagger}$ = +45 kJ/mol or one with $\Delta G^{\ddagger}$ = +70 kJ/mol?

Answer

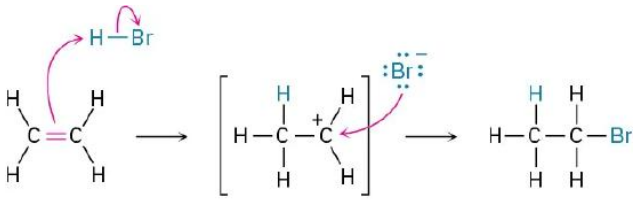
Lower $\Delta G^{\ddagger}$ is faster.

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6.11: 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.



Reaction Intermediate

We call the carbocation, which exists only transiently during the course of the multistep reaction, a reaction intermediate. 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 6.11.1. 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 6.11.1, 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.

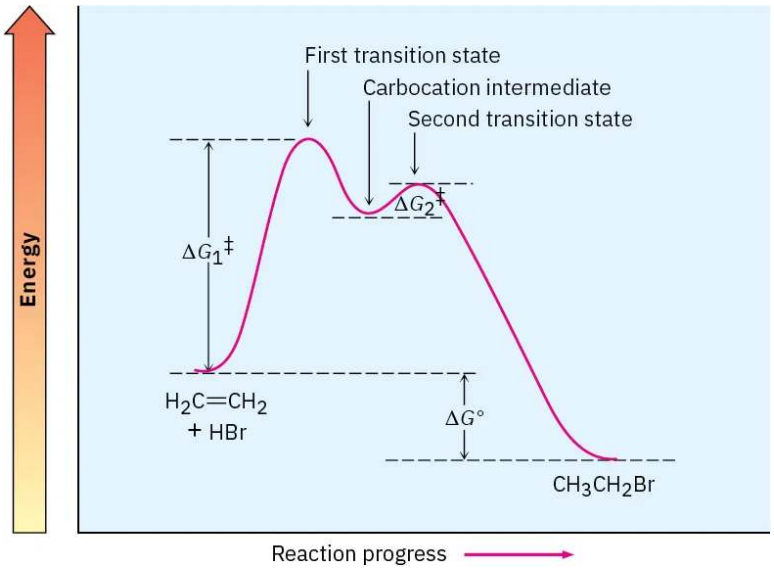


Figure 6.11.1: An energy diagram for the reaction of ethylene with HBr. Two separate steps are involved, each with its own activation energy ($\Delta G^{\ddagger}$) and free-energy change ($\Delta G°$). The overall $\Delta G^{\ddagger}$ for the complete reaction is the energy difference between reactants 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 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 6.11.2.

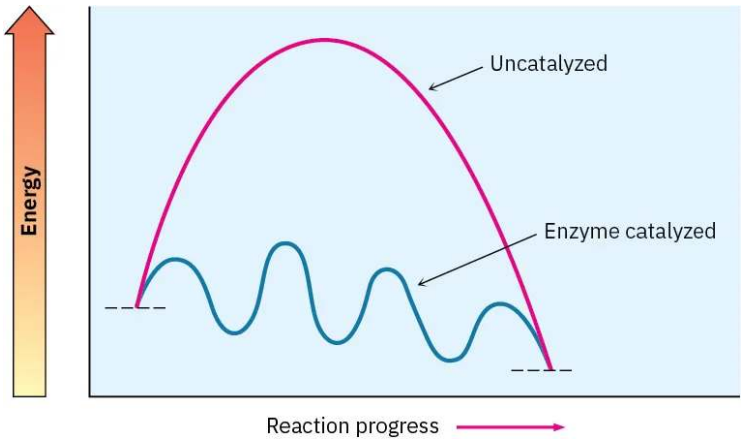


Figure 6.11.2: Energy diagrams for a typical, enzyme-catalyzed biological reaction and an **uncatalyzed laboratory reaction**. The biological reaction involves many steps, each of which has a relatively small activation energy and small energy change. The end result is the same, however.

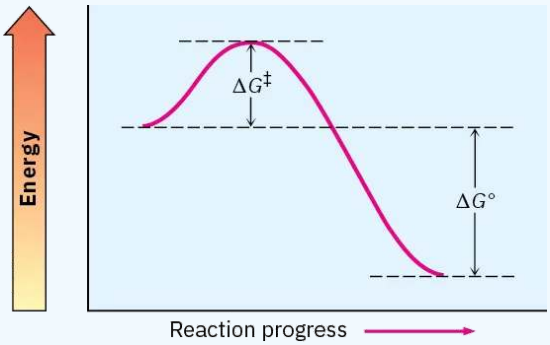
Worked Example 6.11.1: Drawing a Reaction Energy Diagram

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



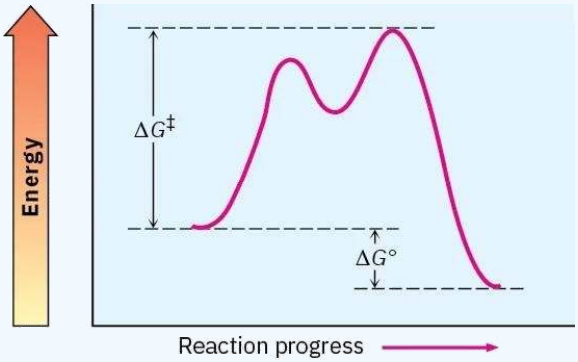
Worked Example 6.11.2: Drawing a Reaction Energy Diagram

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 $\Delta G°$.

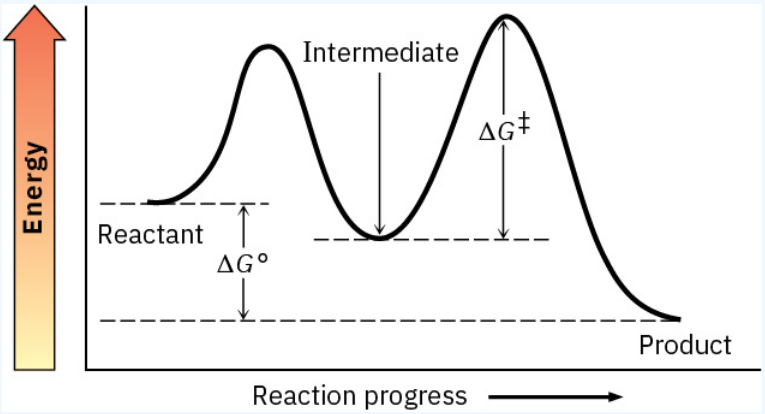
Solution



Exercise 6.11.1

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



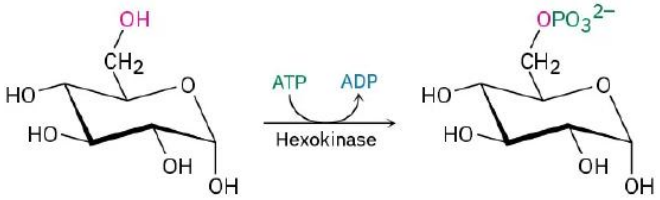
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6.12: A Comparison between Biological Reactions and Laboratory Reactions

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 **Section 26.11**, 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 6.12.1 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.

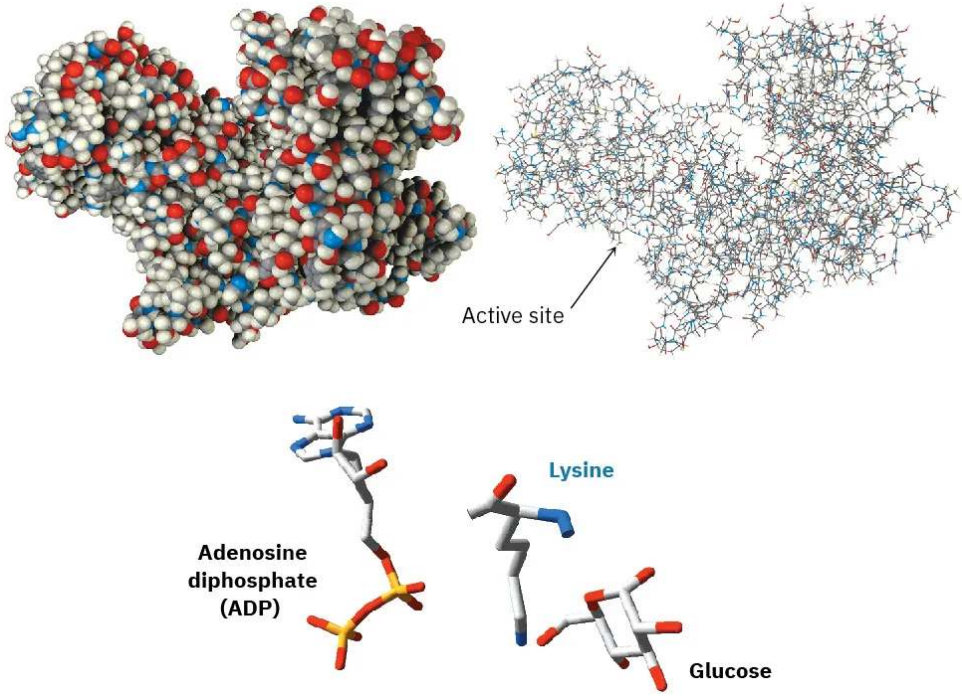
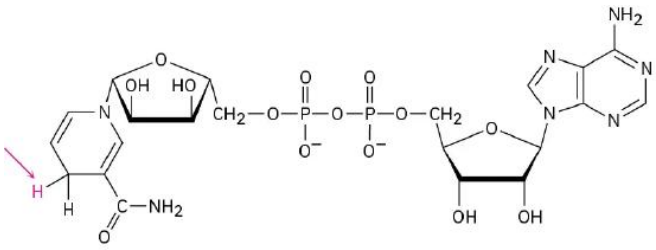


Figure 6.12.1: Models of hexokinase in space-filling and wire-frame formats, showing the cleft that contains the active site where substrate binding and reaction catalysis occur. At the bottom is an X-ray crystal structure of the enzyme active site, showing the positions of both glucose and ADP as well 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 6.12.1 summarizes some of the differences between laboratory and biological reactions.

Table 6.12.1: 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 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

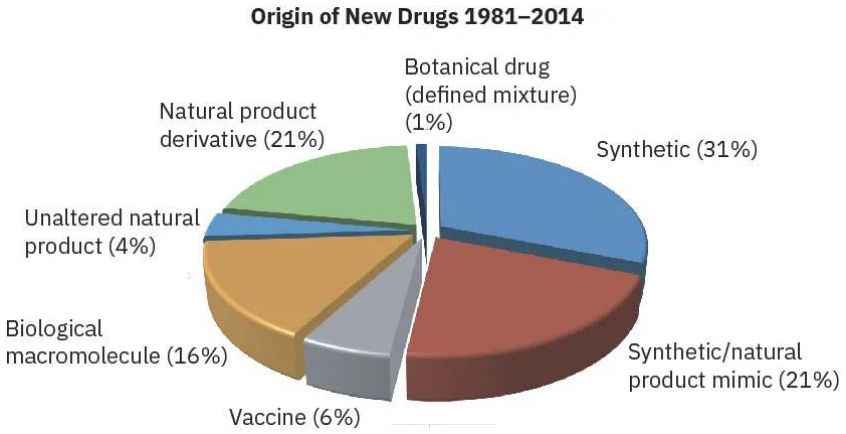
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6.13: Chemistry Matters—Where Do Drugs Come From?

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%.



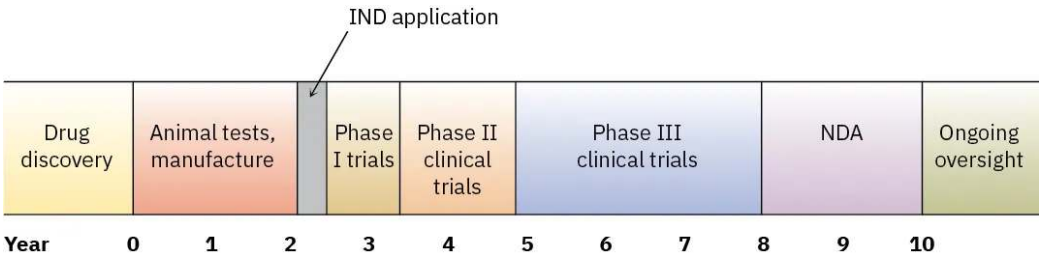
Many years of work go into screening many thousands of substances to identify a single compound that might ultimately gain approval as an NME. But after that single compound has been identified, the work has just begun because it takes an average of 9 to 10 years for a drug to make it through the approval 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 6.13.1: 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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6.14: Key Terms

- activation energy ($\Delta G^{\ddagger}$)
- active site
- addition reaction
- bond dissociation energy (D)
- carbocation
- electrophile
- elimination reaction
- endergonic
- endothermic
- enthalpy change (ΔH)
- entropy change (ΔS)
- enzyme
- exergonic
- exothermic
- Gibbs free-energy change (ΔG)
- heat of reaction
- nucleophile
- polar reaction
- polarizability
- radical
- radical reaction
- reaction coordinate
- reaction intermediate
- reaction mechanism
- rearrangement reaction
- substitution reaction
- transition state

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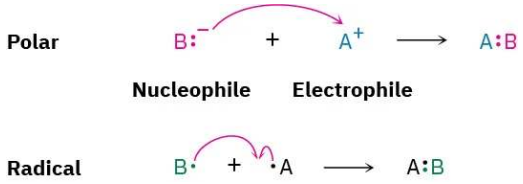
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6.15: Summary

All chemical reactions, whether in the laboratory or in living organisms, follow the same chemical rules. 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've taken a brief look at the fundamental kinds of organic reactions, we've seen why reactions occur, and we've seen how reactions can be described.

There are four common kinds of reactions: **addition reactions** take place when two reactants add together to give a single product; **elimination reactions** take place when one reactant splits apart to give two products; **substitution reactions** take place when two reactants exchange parts to give two new products; and **rearrangement reactions** take place when one reactant undergoes a reorganization of bonds and atoms to give an isomeric product.

A full description of how a reaction occurs is called its **mechanism**. There are two general kinds of mechanisms by which most reactions take place: **radical** mechanisms and **polar** mechanisms. Polar reactions, the more common type, occur because of an attractive interaction between a **nucleophilic** (electron-rich) site in one molecule and an **electrophilic** (electron-poor) site in another molecule. A bond is formed in a polar reaction when the nucleophile donates an electron pair to the electrophile. This transfer of electrons is indicated by a curved arrow showing the direction of electron travel from the nucleophile to the electrophile. Radical reactions involve species that have an odd number of electrons. A bond is formed when each reactant donates one electron.



The energy changes that take place during reactions can be described by considering both rates (how fast the reactions occur) and equilibria (how much the reactions occur). The position of a chemical equilibrium is determined by the value of the **free-energy change (Δ*G*)** for the reaction, where $\Delta G = \Delta H - T\Delta S$. The **enthalpy** term (ΔH) corresponds to the net change in strength of chemical bonds broken and formed during the reaction; the **entropy** term (ΔS) corresponds to the change in the amount of molecular randomness during the reaction. Reactions that have negative values of ΔG release energy, are said to be **exergonic**, and have favorable equilibria. Reactions that have positive values of ΔG absorb energy, are said to be **endergonic**, and have unfavorable equilibria.

A reaction can be described pictorially using an energy diagram that follows the reaction course from reactants through transition state to product. The **transition state** is an activated complex occurring at the highest-energy point of a reaction. The amount of energy needed by reactants to reach this high point is the **activation energy, $\Delta G^{\ddagger}$**. The higher the activation energy, the slower the reaction.

Many reactions take place in more than one step and involve the formation of a **reaction intermediate**. An intermediate is a species that lies at an energy minimum between steps on the reaction curve and is formed briefly during the course of a reaction.

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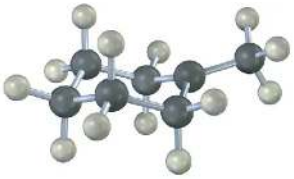
6.16: Additional Problems

Visualizing Chemistry

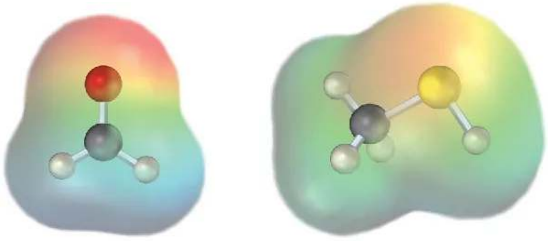
PROBLEM 6-14 The following alkyl halide can be prepared by the addition of HBr to two different alkenes. Draw the structures of both (reddish-brown = Br).



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.

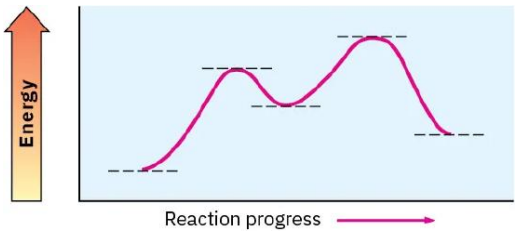


PROBLEM 6-16 Electrostatic potential maps of **(a)** formaldehyde (CH_2O) and **(b)** methanethiol (CH_3SH) are shown. Is the formaldehyde carbon atom likely to be electrophilic or nucleophilic? What about the methanethiol sulfur atom? Explain.



(a) **Formaldehyde** (b) **Methanethiol**

PROBLEM 6-17 Look at the following energy diagram:

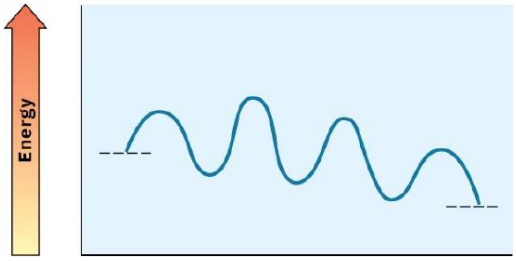


(a) Is $\Delta G°$ for the reaction positive or negative? Label it on the diagram.

(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?

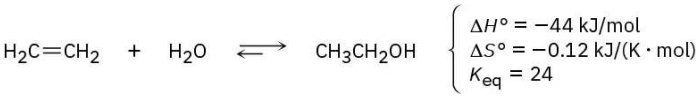
PROBLEM 6-20 Draw an energy diagram for a one-step reaction with $K_{eq} < 1$. Label the parts of the diagram corresponding to reactants, products, transition state, $\Delta G°$, and $\Delta G^{‡}$. Is $\Delta G°$ positive or negative?

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.

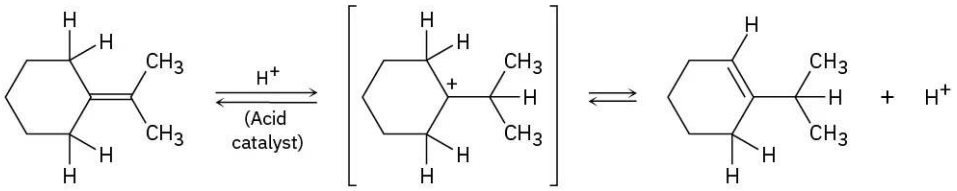
PROBLEM 6-23 Draw an energy diagram for a reaction with $K_{eq} = 1$. What is the value of $\Delta G°$ in this reaction?

PROBLEM 6-24 The addition of water to ethylene to yield ethanol has the following thermodynamic parameters:



- (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**

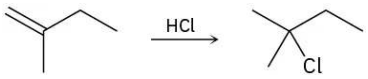
At equilibrium, the product mixture contains about 30% isopropylidenecyclohexane and about 70% 1-isopropylcyclohexene.

- (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 $\Delta G^{‡}$?
- (c) Draw an energy diagram for the reaction.

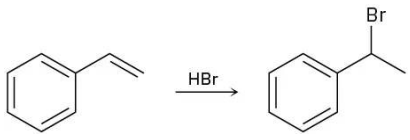
PROBLEM 6-26 Add curved arrows to the mechanism shown in Problem 6-25 to indicate the electron movement in each step.

PROBLEM 6-27 Draw the complete mechanism for each of the following polar reactions.

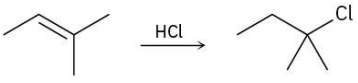
(a)



(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) Cl· +

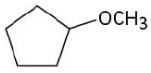
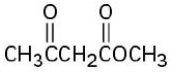
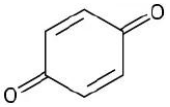
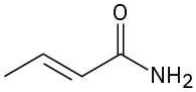
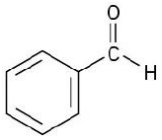


(b) 

(c) 

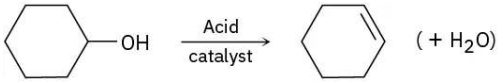
Polar Reactions

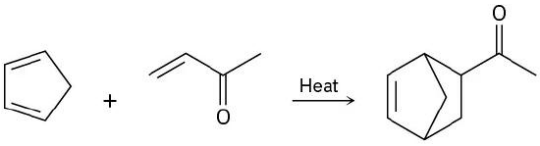
PROBLEM 6-29 Identify the functional groups in the following molecules, and show the polarity of each:

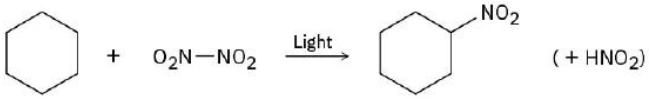
(a) $CH_3CH_2C{\equiv}N$ (b)  (c)  (d)  (e)  (f) 

PROBLEM 6-30 Identify the following reactions as additions, eliminations, substitutions, or rearrangements:

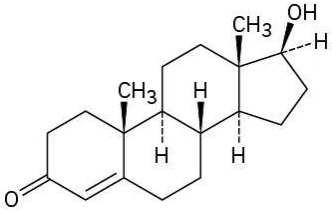
(a) $CH_3CH_2Br + NaCN \longrightarrow CH_3CH_2CN\ (+ NaBr)$

(b) 

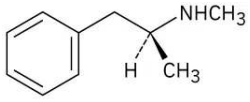
(c) 

(d) 

PROBLEM 6-31 Identify the likely electrophilic and nucleophilic sites in each of the following molecules:



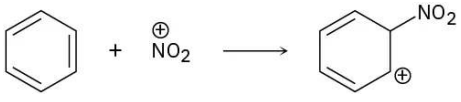
(a) **Testosterone**

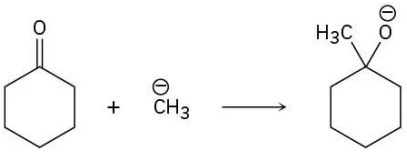


(b) **Methamphetamine**

PROBLEM 6-32 Identify the electrophile and the nucleophile.

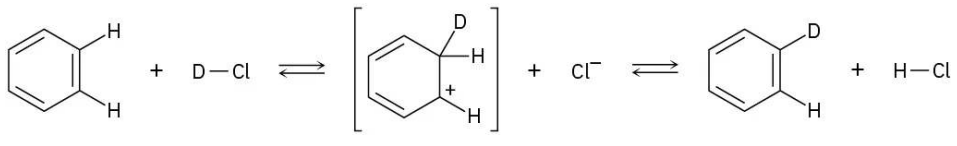
(a) $N_3^{\ominus} + CH_3Cl \longrightarrow CH_3N_3 + Cl^{\ominus}$

(b) 

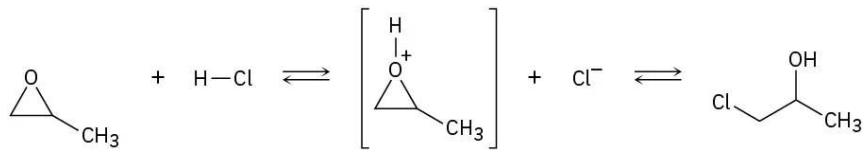
(c) 

PROBLEM 6-33 Add curved arrows to the following polar reactions to indicate the flow of electrons in each:

(a)

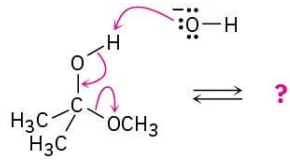


(b)

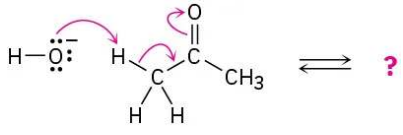


PROBLEM 6-34 Follow the flow of electrons indicated by the curved arrows in each of the following polar reactions, and predict the products that result:

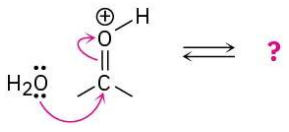
(a)



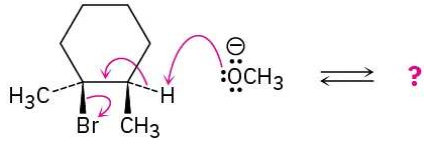
(b)



(c)



(d)



Radical Reactions

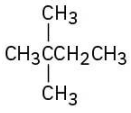
PROBLEM 6-35 Radical chlorination of pentane is a poor way to prepare 1-chloropentane, but radical chlorination of neopentane, $(CH_3)_4C$, is a good way to prepare neopentyl chloride, $(CH_3)_3CCH_2Cl$. Explain.

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?

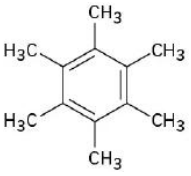
(a) CH_3CH_3 **(b)** $CH_3CH_2CH_3$ **(c)**



(d)



(e) $CH_3C{\equiv}CCH_3$ **(f)**

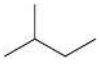


PROBLEM 6-37 Draw the different monochlorinated constitutional isomers you would obtain by the radical chlorination of the following compounds.

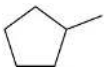
(a)



(b)



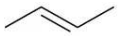
(c)



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">+.

(a)



(b)



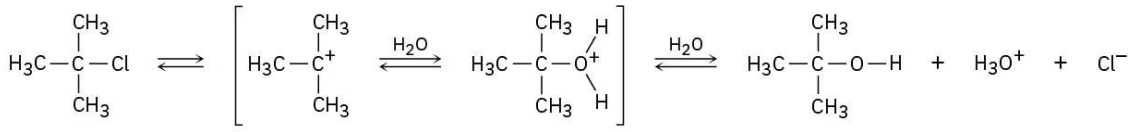
(c)



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.

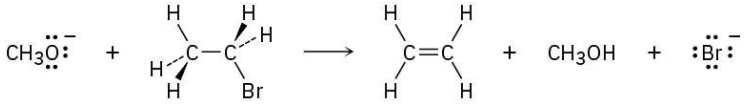
PROBLEM 6-41 Add curved arrows to the mechanism shown in Problem 6-40 to indicate the electron movement in each step.

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:

$$HO^- + CH_3Cl \rightleftarrows CH_3OH + Cl^-$$

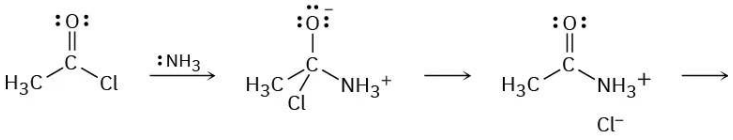
The value of $\Delta H°$ for the reaction is −75 kJ/mol, and the value of $\Delta S°$ is +54 J/(K·mol). What is the value of $\Delta G°$ (in kJ/mol) at 298 K? Is the reaction exothermic or endothermic? Is it exergonic or endergonic?

PROBLEM 6-43 Methoxide ion (CH_3O^-) reacts with bromoethane in a single step according to the following equation:

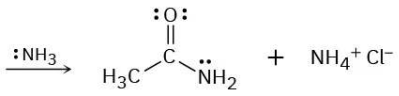


Identify the bonds broken and formed, and draw curved arrows to represent the flow of electrons during the reaction.

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

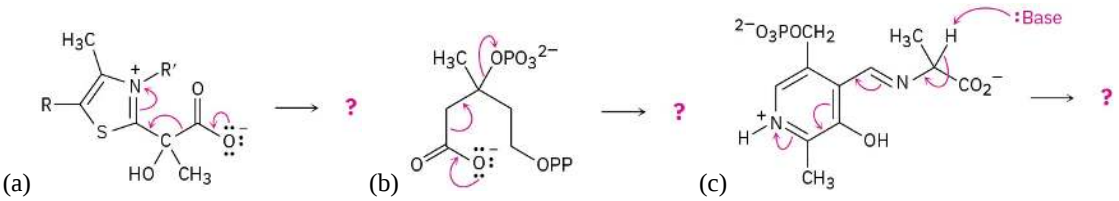
PROBLEM 6-45 The naturally occurring molecule α-terpineol is biosynthesized by a route that includes the following step:



Carbocation **Isomeric 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:



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?

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CHAPTER OVERVIEW

7: Alkenes - Structure and Reactivity

Learning Objectives

After you have completed Chapter 7, you should be able to fulfill all of the detailed objectives listed under each individual section:

1. describe the importance of alkenes to the chemical industry.
2. use the concept of “degree of unsaturation” in determining chemical structures.
3. describe the electronic structure and geometry of alkenes.
4. describe the factors that influence alkene stability, and determine the relative stability of a number of given alkenes.
5. write the IUPAC name of a given alkene, and draw the structure of any alkene, given its IUPAC name.
6. determine whether a given alkene has an *E* configuration or a *Z* configuration.
7. explain why alkenes are more reactive than alkanes.
8. 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.
9. 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.

7.1: Why This Chapter?
7.2: Industrial Preparation and Use of Alkenes
7.3: Calculating Degree of Unsaturation
7.4: Naming Alkenes
7.5: Cis-Trans Isomerism in Alkenes
7.6: Alkene Stereochemistry and the E,Z Designation
7.7: Stability of Alkenes
7.8: Electrophilic Addition Reactions of Alkenes
7.9: Orientation of Electrophilic Additions - Markovnikov's Rule
7.10: Carbocation Structure and Stability
7.11: The Hammond Postulate
7.12: Evidence for the Mechanism of Electrophilic Additions - Carbocation Rearrangements
7.13: Chemistry Matters - Bioprospecting - Hunting for Natural Products
7.14: Key Terms
7.15: Summary
7.16: Additional Problems

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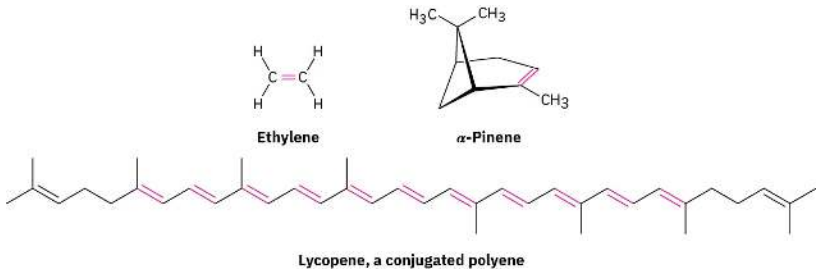
7.1: Why This Chapter?

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 7.1.1: 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.



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7.2: 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 7.2.1).

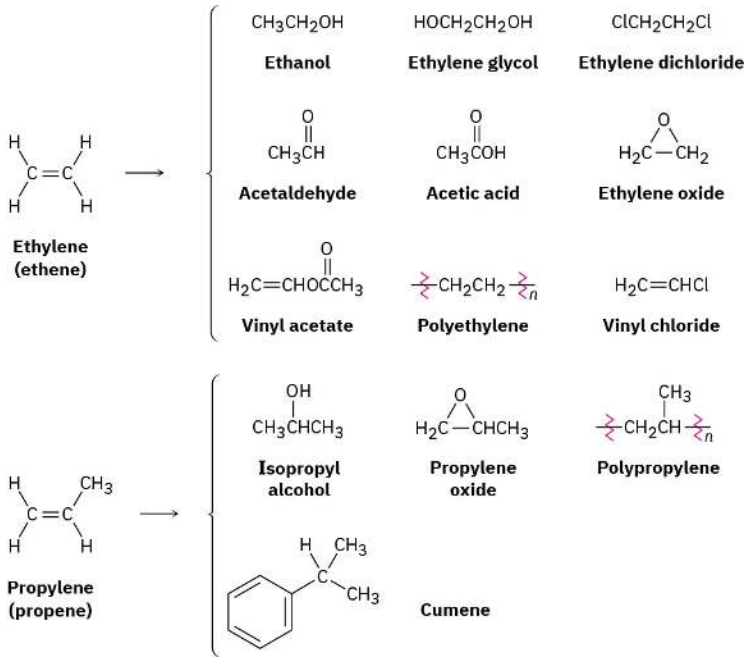
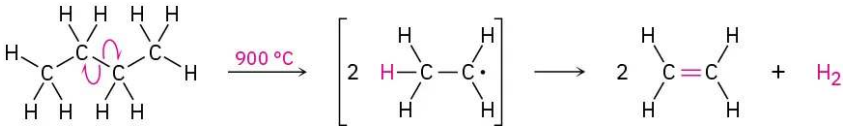


Figure 7.2.1: Compounds derived industrially from ethylene and propylene.

Ethylene, propylene, and butene are synthesized from (C_2–C_8) alkanes by a process called *steam cracking* at temperatures up to 900 °C.

$$CH_3(CH_2)_nCH_3 \quad [n = 0\text{–}6] \xrightarrow{850\text{–}900\ ^\circ C,\ \text{steam}} H_2 + H_2C{=}CH_2 + CH_3CH{=}CH_2 + CH_3CH_2CH{=}CH_2$$

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.

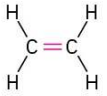
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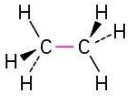
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7.3: Calculating Degree of Unsaturation

Because of 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.



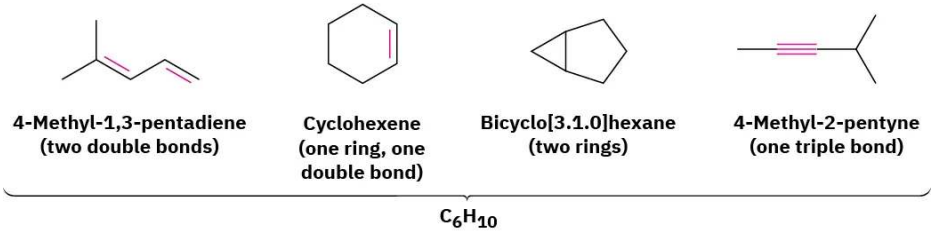
Ethylene: C_2H_4
(Fewer hydrogens—*Unsaturated*)



Ethane: C_2H_6
(More hydrogens—*Saturated*)

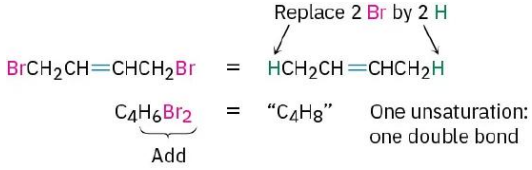
In general, each ring or double bond in a molecule corresponds to a loss of two hydrogens from the alkane formula C_nH_{2n+2}. Knowing this relationship, it's possible to work backward from a molecular formula to calculate a molecule's degree of unsaturation—the number of rings and/or multiple bonds present in the molecule.

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}. 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.

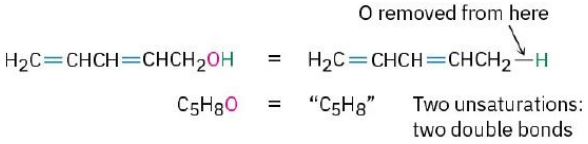


Similar calculations can be carried out for compounds containing elements other than just carbon and hydrogen.

- **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.

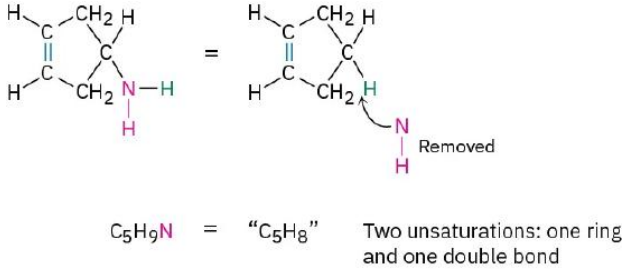


- **Organooxygen compounds (C, H, O)** Oxygen forms two bonds, so it doesn't affect the formula of an equivalent hydrocarbon and can be ignored when calculating the degree of unsaturation. You can convince yourself of this by seeing what happens when an oxygen atom is inserted into an alkane bond: C−C becomes C−O−C or C−H becomes C−O−H, and there is no change in the number of hydrogen atoms. For example, the formula C_5H_8O is equivalent to the hydrocarbon formula C_5H_8 and thus corresponds to two degrees of unsaturation.



- **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 this extra hydrogen atom 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.



C_5H_9N = "C_5H_8" Two unsaturations: one ring and one double bond

To summarize:

- **Add** the number of halogens to the number of hydrogens.
- **Ignore** the number of oxygens.
- **Subtract** the number of nitrogens from the number of hydrogens.

Exercise 7.3.1

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

a. 1
b. 2
c. 2

Exercise 7.3.2

Calculate the degree of unsaturation in each of the following formulas:

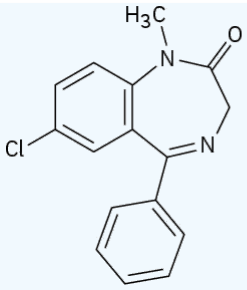
a. C_6H_5N
b. $C_6H_5NO_2$
c. $C_8H_9Cl_3$
d. $C_9H_{16}Br_2$
e. $C_{10}H_{12}N_2O_3$
f. $C_{20}H_{32}ClN$

Answer

a. 5
b. 5
c. 3
d. 1
e. 6
f. 5

Exercise 7.3.3

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

$C_{16}H_{13}ClN_2O$

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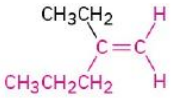
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7.4: Naming Alkenes

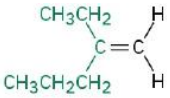
Alkenes are named using a series of rules similar to those for alkanes (Section 3.4), with the suffix *-ene* used instead of *-ane* to identify the functional group. There are three steps to this process.

STEP 1: **Name the parent hydrocarbon**

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



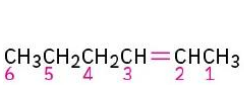
Named as a *pentene* *NOT*

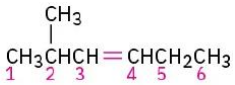


as a hexene, since the double bond is not contained in the six-carbon chain

STEP 2: **Number the carbon atoms in the chain**

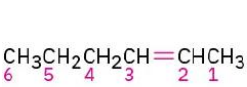
Begin at the end nearer the double bond or, if the double bond is equidistant from the two ends, begin at the end nearer the first branch point. This rule ensures that the double-bond carbons receive the lowest possible numbers.



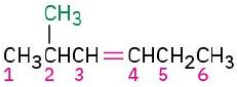


STEP 3: **Write the full name**

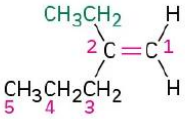
Number the substituents according to their positions in the chain, and list them alphabetically. Indicate the position of the double bond by giving the number of the first alkene carbon and placing that number directly before the parent name. If more than one double bond is present, indicate the position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



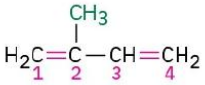
2-Hexene



2-Methyl-3-hexene

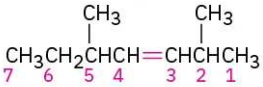


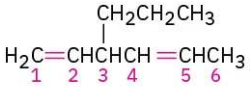
2-Ethyl-1-pentene



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.

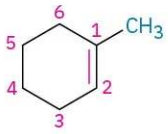




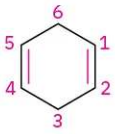
Newer naming system: **2,5-Dimethylhept-3-ene** **3-Propylhexa-1,4-diene**

(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.

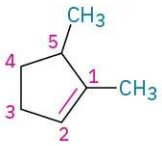


1-Methylcyclohexene



1,4-Cyclohexadiene

(New: Cyclohexa-1,4-diene)

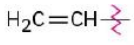


1,5-Dimethylcyclopentene

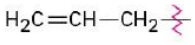
For historical reasons, there are a few alkenes whose names are firmly entrenched in common usage but don't conform to the rules. For example, the alkene derived from ethane should be called *ethene*, but the name *ethylene* has been used for so long that it is accepted by IUPAC. Table 7.4.1 lists several 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 7.4.1: Common Names of Some Alkenes

Compound	Systematic name	Common name
$H_2C{=}CH_2$	Ethene	Ethylene
$CH_3CH{=}CH_2$	Propene	Propylene
$CH_3C(CH_3){=}CH_2$	2-Methylpropene	Isobutylene
$H_2C{=}C(CH_3){-}CH{=}CH_2$	2-Methyl-1,3-butadiene	Isoprene

? Exercise 7.4.1

Give IUPAC names for the following compounds:

a. $H_2C{=}CHCH(CH_3)C(CH_3)_2CH_3$

b. $CH_3CH_2CH{=}C(CH_3)CH_2CH_3$

c. $CH_3CH{=}CHCH(CH_3){=}CHCH(CH_3)CH_3$

d. $CH_3CH_2CH_2CH{=}CHCH(CH_2CH_3)CH_2CH_3$

Answer

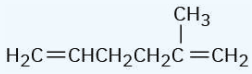
a. 3,4,4-Trimethyl-1-pentene
b. 3-Methyl-3-hexene
c. 4,7-Dimethyl-2,5-octadiene
d. 6-Ethyl-7-methyl-4-nonene

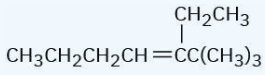
Exercise 7.4.2

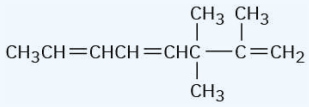
Draw structures corresponding to the following IUPAC names:

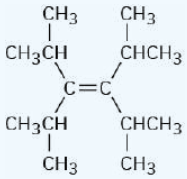
a. 2-Methyl-1,5-hexadiene
b. 3-Ethyl-2,2-dimethyl-3-heptene
c. 2,3,3-Trimethyl-1,4,6-octatriene
d. 3,4-Diisopropyl-2,5-dimethyl-3-hexene

Answer

a. 

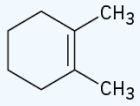
b. 

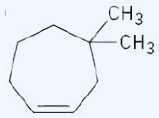
c. 

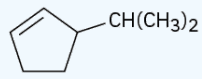
d. 

Exercise 7.4.3

Name the following cycloalkenes:

a. 

b. 

c. 

Answer

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

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7.5: 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 3.7), 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 7.5.1). 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.

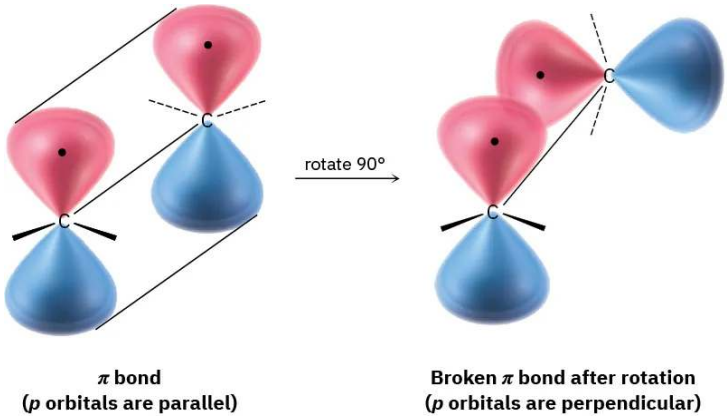


Figure 7.5.1: The π bond must break for rotation to take place around a carbon–carbon double bond.

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 7.5.2).

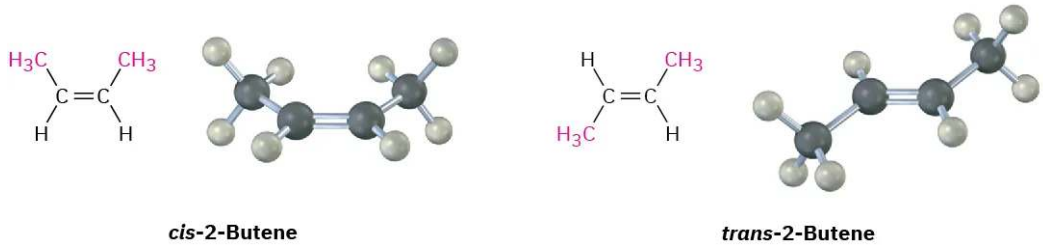


Figure 7.5.2: Cis and trans isomers of 2-butene. The cis isomer has the two methyl groups on the same side of the double bond, and the trans isomer has methyl groups on opposite sides.

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 7.5.3).

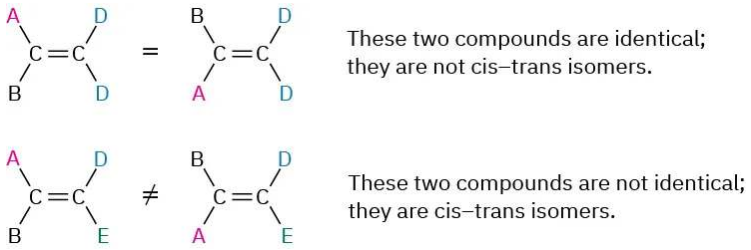
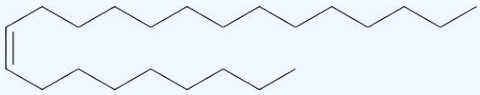


Figure 7.5.3: The requirement for cis–trans isomerism in alkenes. Compounds that have one of their carbons bonded to two identical groups can't exist as cis–trans isomers. Only when both carbons are bonded to two different groups is cis–trans isomerism possible.

Exercise 7.5.1

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



Exercise 7.5.2

Which of the following compounds can exist as pairs of cis–trans isomers? Draw each pair, and indicate the geometry of each isomer.

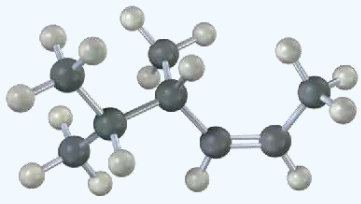
a. $CH_3CH{=}CH_2$
b. $(CH_3)_2C{=}CHCH_3$
c. $CH_3CH_2CH{=}CHCH_3$
d. $(CH_3)_2C{=}C(CH_3)CH_2CH_3$
e. $ClCH{=}CHCl$
f. $BrCH{=}CH$

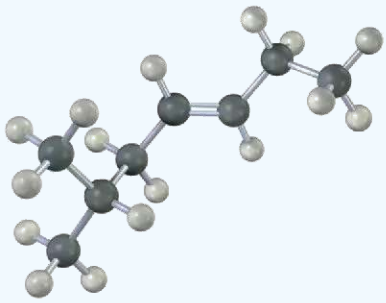
Answer

Compounds (c), (e), and (f) have cis–trans isomers.

Exercise 7.5.3

Name the following alkenes, including a cis or trans designation:

a. 

b. 

Answer

a. cis-4,5-Dimethyl-2-hexene
b. trans-6-Methyl-3-heptene

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7.6: 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.

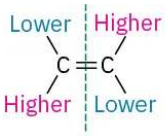
RULE 2

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.

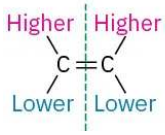
RULE 3

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.)

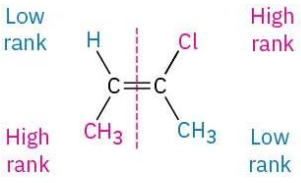


E double bond
(Higher-ranked groups
are on opposite sides.)

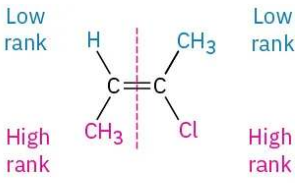


Z double bond
(Higher-ranked groups
are on the same side.)

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.



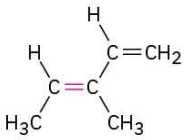
(a) (*E*)-2-Chloro-2-butene



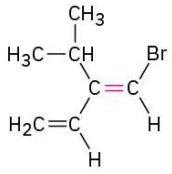
(b) (*Z*)-2-Chloro-2-butene

In the following examples observe the configuration, and identify the high rank groups that make the assignment correct:

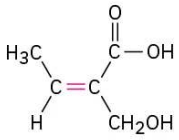
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(*E*)-3-Methyl-1,3-pentadiene



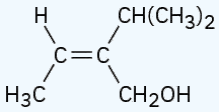
(*E*)-1-Bromo-2-isopropyl-1,3-butadiene



(*Z*)-2-Hydroxymethyl-2-butenoic acid

Worked Example 7.6.1: Assigning E and Z Configurations to Alkenes

Assign *E* or *Z* configuration to the double bond in the following compound:

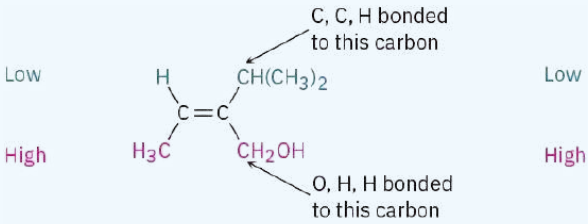


Strategy

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 7.6.2

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

a. $-CH_3$
b. −Cl
c. $-CH=CH_2$
d. $-OCH_3$
e. −CH=O
f. −CH=O

Exercise 7.6.3

Rank the substituents in each of the following sets according to the sequence rules:

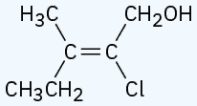
a. $-CH_3$, $-OH$, $-H$, $-Cl$
b. $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CH_2OH$
c. $-CO_2H$, $-CH_2OH$, $-C{\equiv}N$, $-CH_2NH_2$
d. $-CH_2CH_3$, $-C{\equiv}CH$, $-C{\equiv}N$, $-CH_2OCH_3$

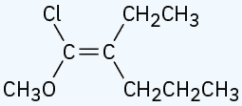
Answer

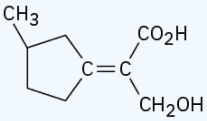
a. $-Cl$, $-OH$, $-CH_3$, $-H$
b. $-CH_2OH$, $-CH{=}CH_2$, $-CH_2CH_3$, $-CH_3$
c. $-CO_2H$, $-CH_2OH$, $-C \equiv N$, $-CH_2NH_2$
d. $-CH_2OCH_3$, $-C{\equiv}N$, $-C{\equiv}CH$, $-CH_2CH_3$

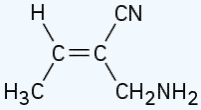
Exercise 7.6.4

Assign *E* or *Z* configuration to the following alkenes:

a. 

b. 

c. 

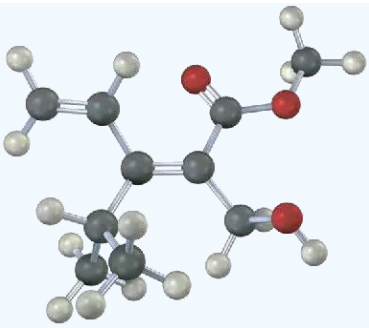
d. 

Answer

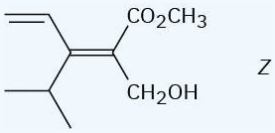
a. Z
b. E
c. Z
d. E

Exercise 7.6.5

Assign stereochemistry (*E* or *Z*) to the double bond in the following compound, and convert the drawing into a skeletal structure (red = O):



Answer



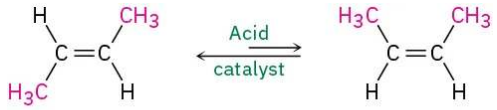
Z

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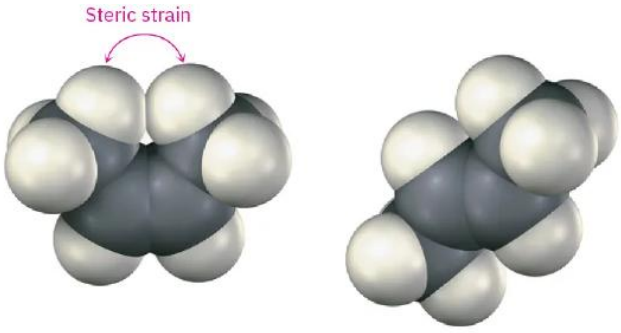
7.7: Stability of Alkenes

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.



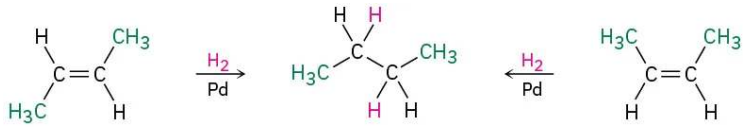
Trans (76%) **Cis (24%)**

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**

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.



***trans*-2-Butene** **Butane** ***cis*-2-Butene**

Energy diagrams for the hydrogenation reactions of *cis*- and *trans*-2-butene are shown in Figure 7.7.1. 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.

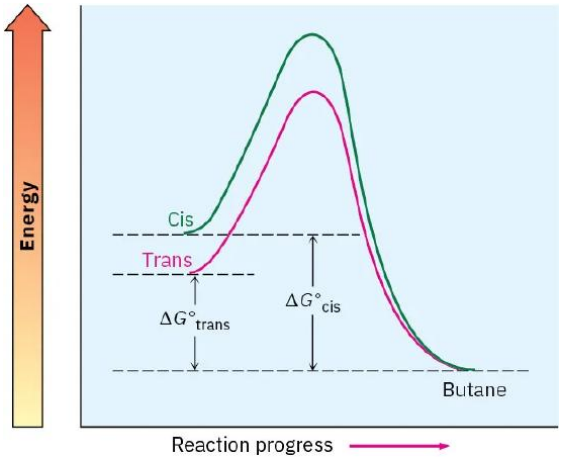
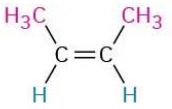
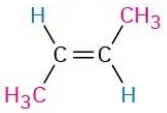


Figure 7.7.1: Energy diagrams for hydrogenation of *cis*- and *trans*-2-butene. The cis isomer is higher in energy than the trans isomer by about 2.8 kJ/mol and therefore releases more energy when hydrogenated.

If we were to measure the so-called heats of hydrogenation ($\Delta H°_{\text{hydrog}}$) for two double-bond isomers and find their difference, we could determine the relative stabilities of cis and trans isomers without having to measure an equilibrium position. *cis*-2-Butene, for instance, has $\Delta H°_{\text{hydrog}}$ = −119 kJ/mol(−28.3 kcal/mol), while *trans*-2-butene has $\Delta H°_{\text{hydrog}}$ = −115 kJ/mol(−27.4 kcal/mol)—a difference of 4 kJ/mol.



Cis isomer
$\Delta H°_{\text{hydrog}}$ = −120 kJ/mol



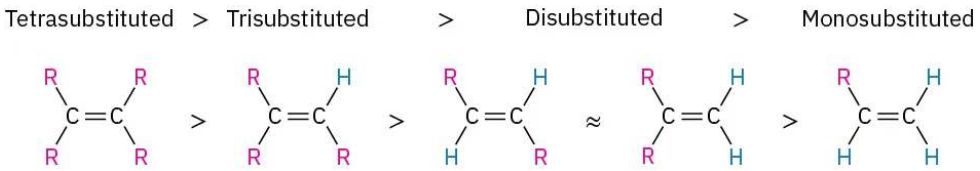
Trans isomer
$\Delta H°_{\text{hydrog}}$ = −116 kJ/mol

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.

Tabke 7.7.1: Heats of Hydrogenation of Some Alkenes

Substitution	Alkene	$\Delta H°_{\text{hydrog}}$ (kJ/mol)	$\Delta H°_{\text{hydrog}}$ (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

Tabke 7.7.1 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 7.7.2. The more substituents present on the double bond, the more hyperconjugation occurs and the more stable the alkene.

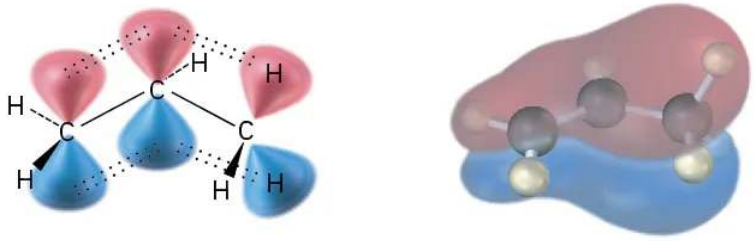


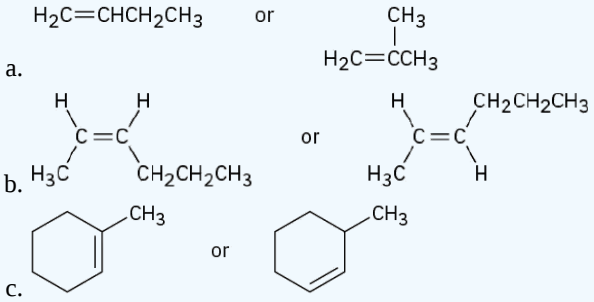
Figure 7.7.2: Hyperconjugation is a stabilizing interaction between the C=C π orbital and adjacent C−H σ bonds on substituents. The more substituents there are, the greater the stabilization of the alkene.

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.



Exercise 7.7.1

Name the following alkenes, and tell which compound in each pair is more stable:



Answer

2-Methylpropene is more stable than 1-butene

trans-2-Hexene is more stable than cis-2-hexene

1-Methylcyclohexene is more stable than 3-methylcyclohexene

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7.8: 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 7.8.1 for an electrophilic addition reaction.

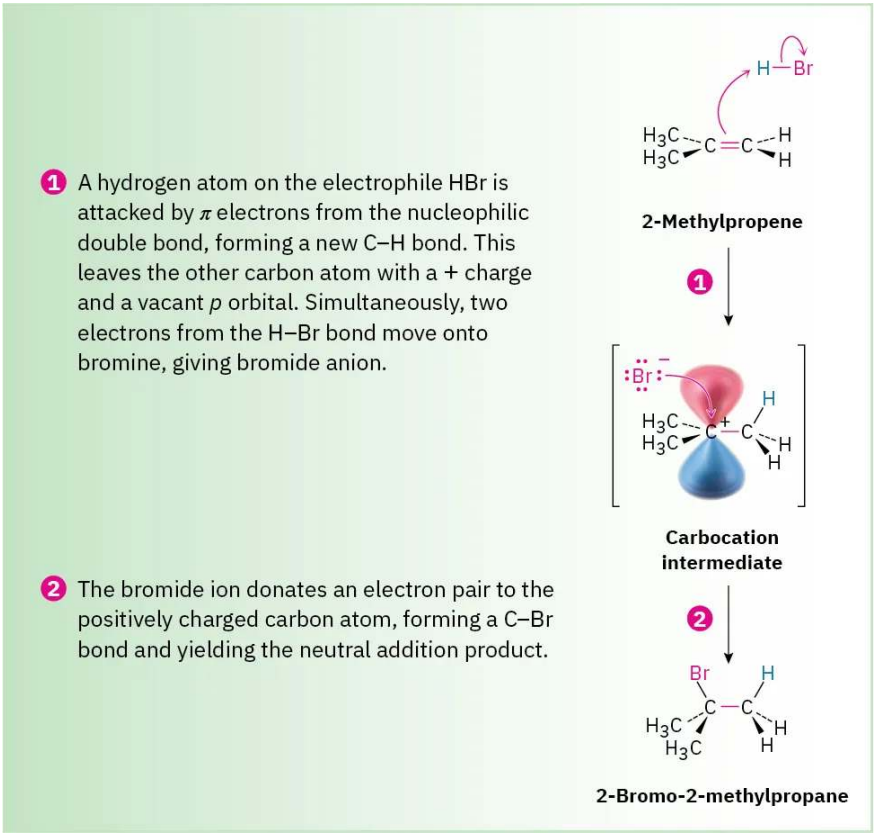


Figure 7.8.1: Mechanism of the electrophilic addition of HBr to 2-methylpropene. The reaction occurs in two steps, protonation and bromide addition, and involves a carbocation intermediate.

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 7.8.1. 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 7.8.2) 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 7.8.2 by the fact that $\Delta G_1^{\ddagger}$ is larger than $\Delta G_2^{\ddagger}$.

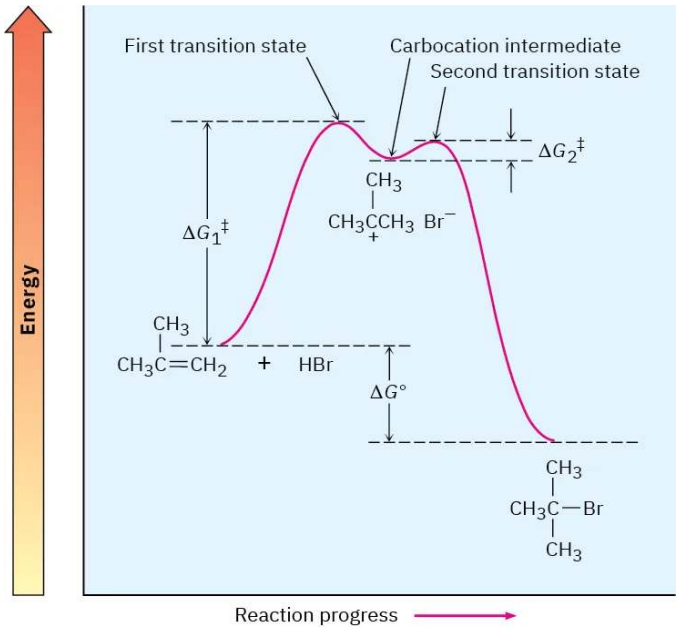
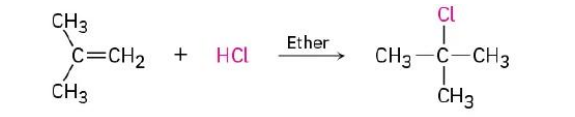


Figure 7.8.2: Energy diagram for the two-step electrophilic addition of HBr to 2-methylpropene. The first step is slower than the second step.

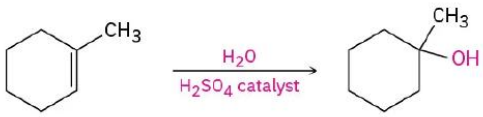
Electrophilic addition to alkenes is successful not only with HBr but with HCl, HI, and H_2O as well. Note that HI is usually generated in the reaction mixture by treating potassium iodide with phosphoric acid and that a strong acid catalyst is needed for the addition of water.



2-Methylpropene **2-Chloro-2-methylpropane (94%)**



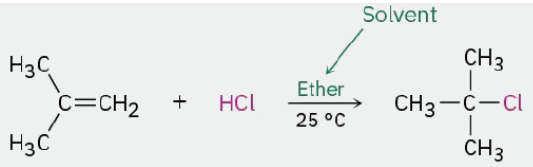
1-Pentene **(HI)** **2-Iodopentane**



1-Methylcyclohexene **1-Methylcyclohexanol**

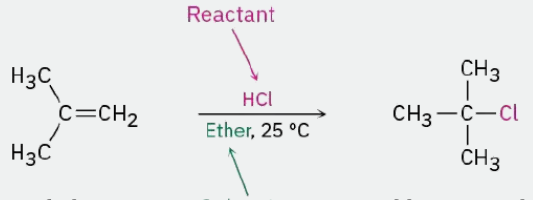
Writing Organic Reactions

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.



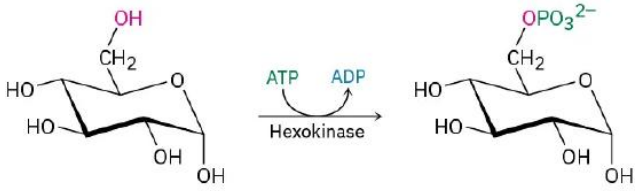
2-Methylpropene **2-Chloro-2-methyl-propane**

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.



2-Methylpropene **2-Chloro-2-methyl-propane**

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



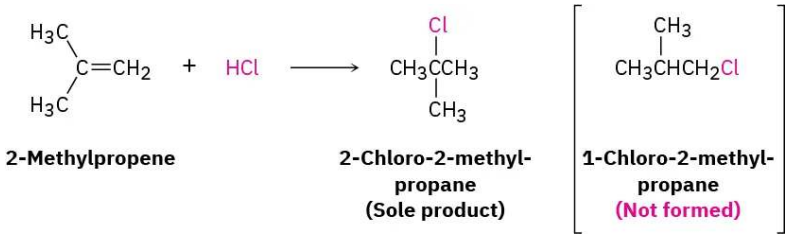
Glucose **Glucose 6-phosphate**

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7.9: Orientation of Electrophilic Additions - Markovnikov's Rule

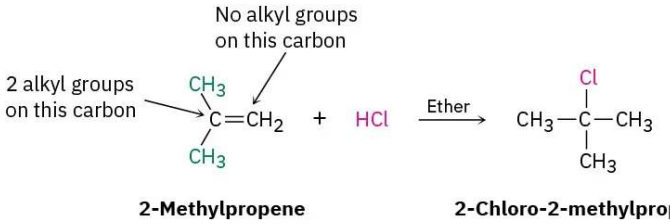
Look carefully at the electrophilic addition reactions shown in the previous section. In each case, an unsymmetrically substituted alkene has given a single addition product rather than the mixture that might be expected. For example, 2-methylpropene might react with HCl to give both 2-chloro-2-methylpropane 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.

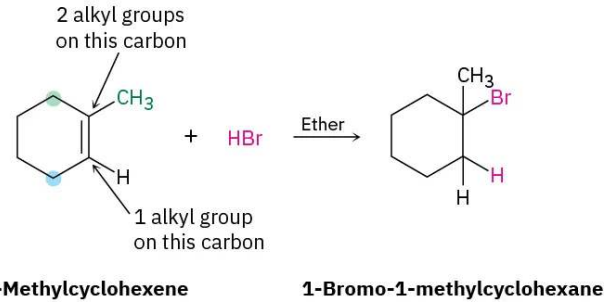


After looking at the results of many such reactions, the Russian chemist Vladimir Markovnikov proposed in 1869 what has become known as Markovnikov's rule.

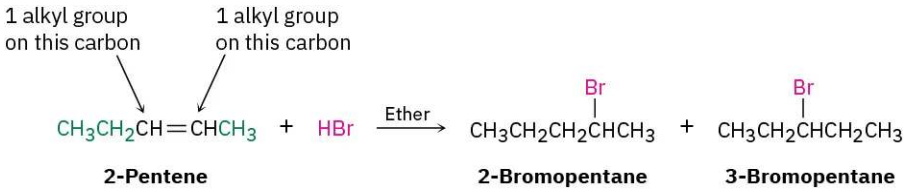
Markovnikov's Rule

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.

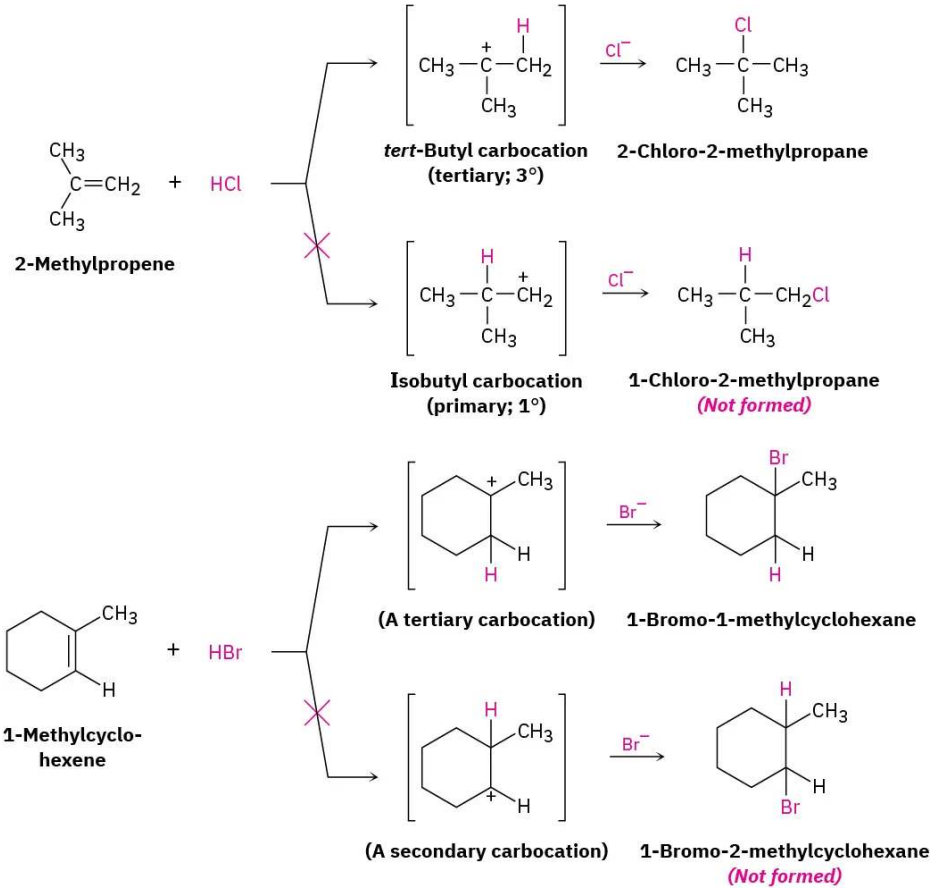


Because carbocations are involved as intermediates in these electrophilic addition reactions, Markovnikov's rule can be restated in the following way:

Markovnikov's Rule Restated

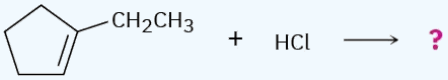
In the addition of HX to an alkene, the more highly substituted carbocation is formed as the intermediate rather than the less highly substituted one.

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 7.9.1: Predicting the Product of an Electrophilic Addition Reaction

What product would you expect from reaction of HCl with 1-ethylcyclopentene?

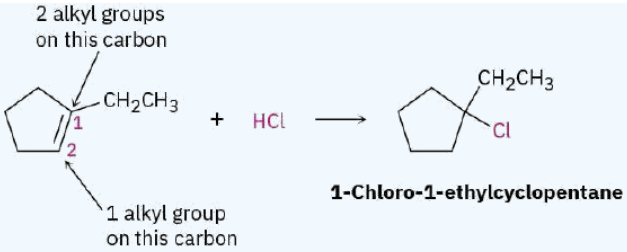


Strategy

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

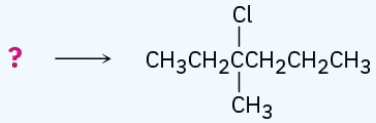
The expected product is 1-chloro-1-ethylcyclopentane.



1-Chloro-1-ethylcyclopentane

Worked Example 7.9.1: Synthesizing a Specific Compound

What alkene would you start with to prepare the following alkyl halide? There may be more than one possibility.

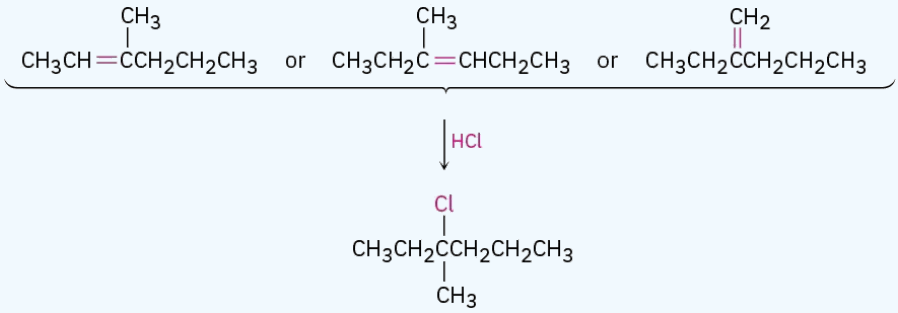


Strategy

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.

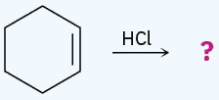
Solution

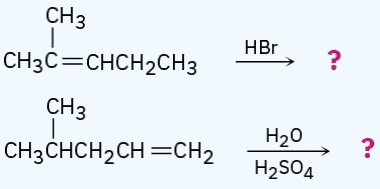
There are three possibilities, all of which could give the desired product according to Markovnikov's rule.



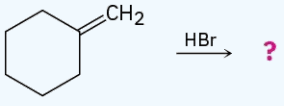
Exercise 7.9.1

Predict the products of the following reactions:

a. 

b. 

c. (Addition of H_2O occurs.)

d. 

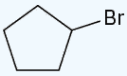
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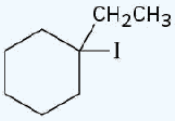
Answer

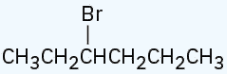
a. Chlorocyclohexane
b. 2-Bromo-2-methylpentane
c. 4-Methyl-2-pentanol
d. 1-Bromo-1-methylcyclohexane

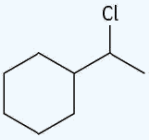
? Exercise 7.9.2

What alkenes would you start with to prepare the following products? (a)

a. 

b. 

c. 

d. 

Answer

a. Cyclopentene
b. 1-Ethylcyclohexene or ethylidenecyclohexane
c. 3-Hexene
d. Vinylcyclohexane (cyclohexylethylene)

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7.10: 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 7.10.1. 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.

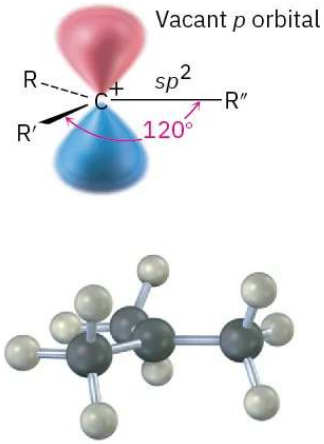
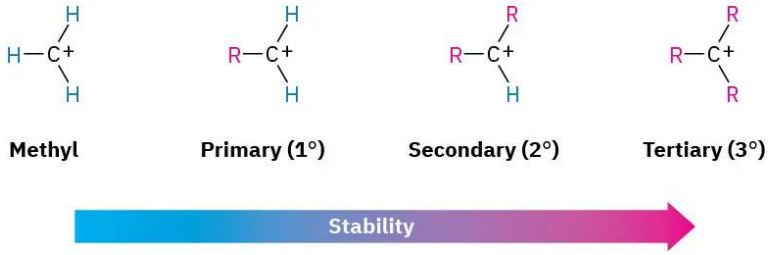


Figure 7.10.1: The structure of a carbocation. The trivalent carbon is sp^2-hybridized and has a vacant p orbital perpendicular to the plane of the carbon and three attached groups.

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 7.10.2, 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 7.10.2 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.

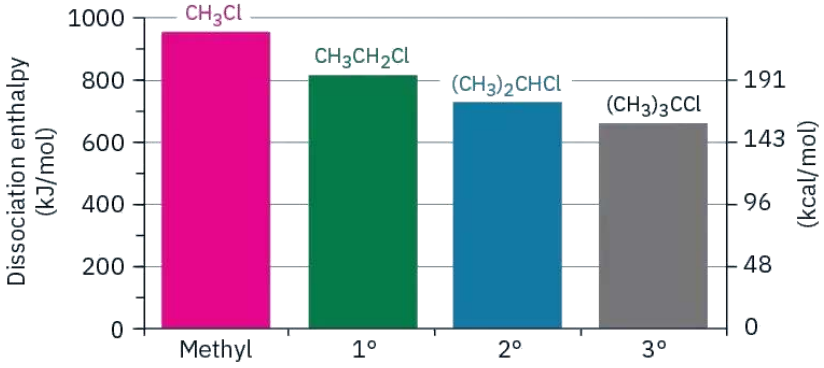


Figure 7.10.2: A plot of dissociation enthalpy versus substitution pattern for the gas-phase dissociation of alkyl chlorides to yield carbocations. More highly substituted alkyl halides dissociate more easily than less highly substituted ones.

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 7.10.3).

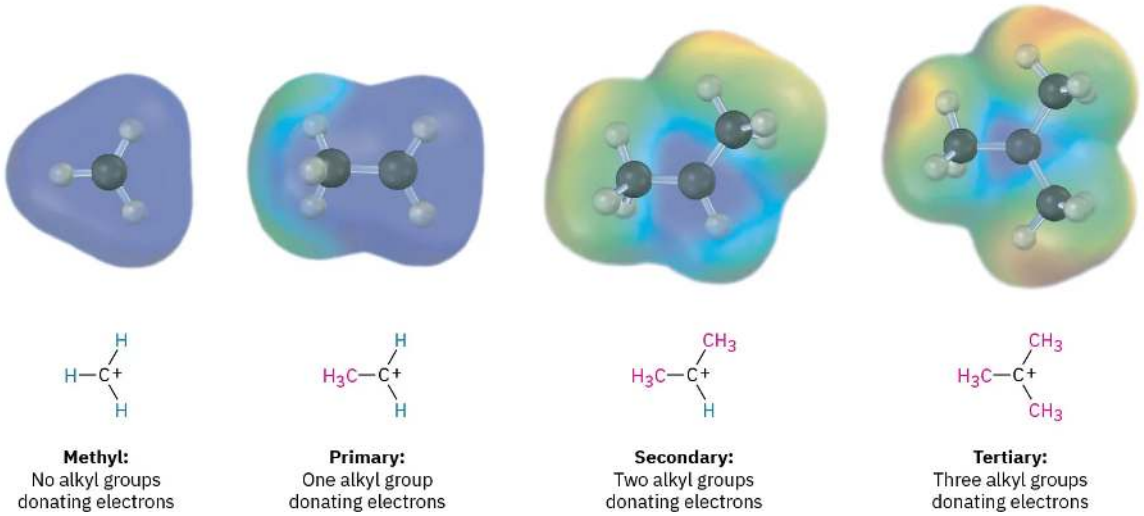


Figure 7.10.3: A comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups that are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron-poor (blue in electrostatic 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 7.10.4 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.

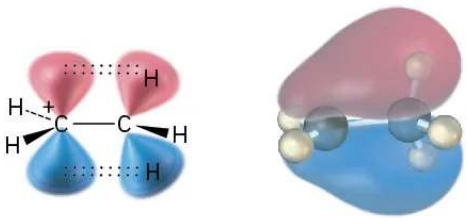
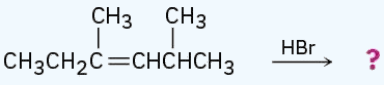
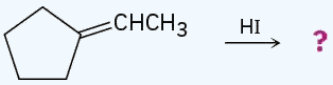


Figure 7.10.4: Stabilization of the ethyl carbocation, $CH_3CH_2^+$, through hyperconjugation. Interaction of neighboring C−H σ bonds with the vacant p orbital stabilizes the cation and lowers its energy. The molecular orbital shows that only the two C−H bonds more parallel to the cation p orbital are oriented properly. The C−H bond perpendicular to the cation p orbital can't take part properly.

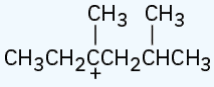
Exercise 7.10.1

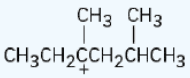
Show the structures of the carbocation intermediates you would expect in the following reactions:

a. 

b. 

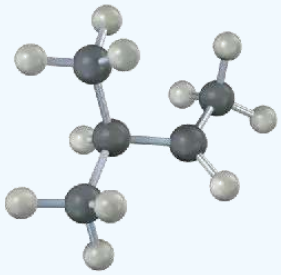
Answer

a. 

b. 

Exercise 7.10.2

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

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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7.11: 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 7.11.1, 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.

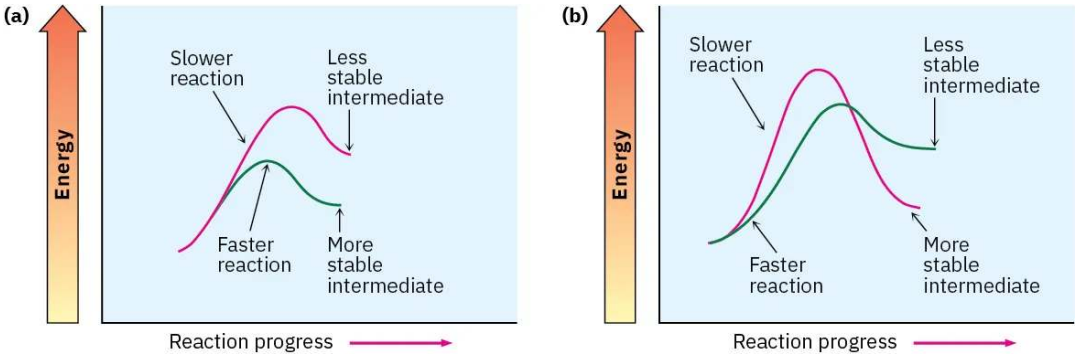


Figure 7.11.1: Energy diagrams for two similar competing reactions. In **(a)**, the faster reaction yields the more stable intermediate. In **(b)**, the slower reaction yields the more stable intermediate. The curves shown in **(a)** represent the typical situation.

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 7.11.2, 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.

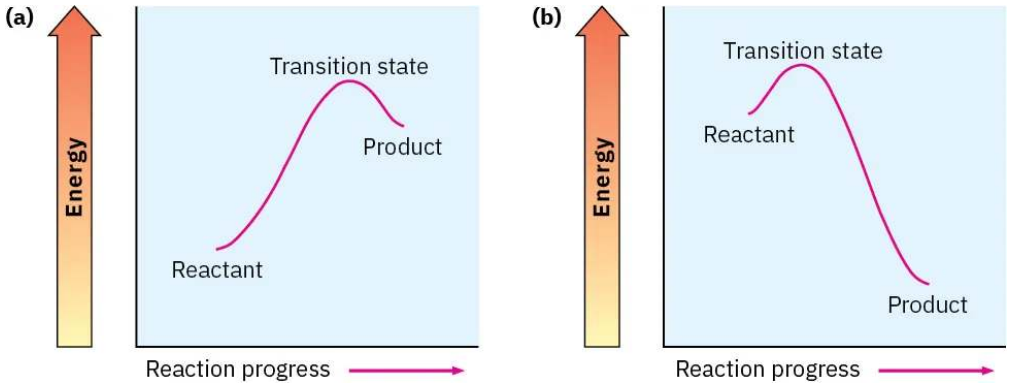


Figure 7.11.2: Energy diagrams for endergonic and exergonic steps. **(a)** In an endergonic step, the energy levels of transition state and *product* are closer. **(b)** In an exergonic step, the energy levels of transition state and *reactant* are closer.

In an endergonic reaction (Figure 7.11.2a), 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 7.11.2b), 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 7.11.3).

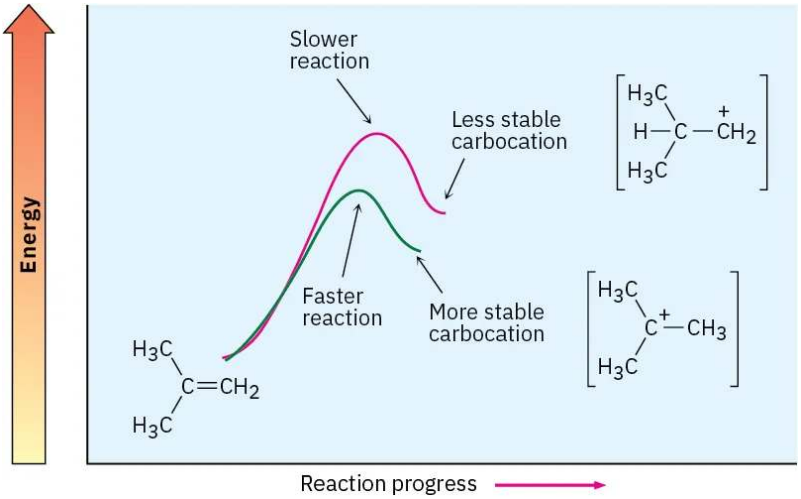


Figure 7.11.3: Energy diagrams for carbocation formation. The more stable tertiary carbocation is formed faster **(green curve)** because its increased stability lowers the energy of the transition state leading to it.

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 7.11.4). 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.

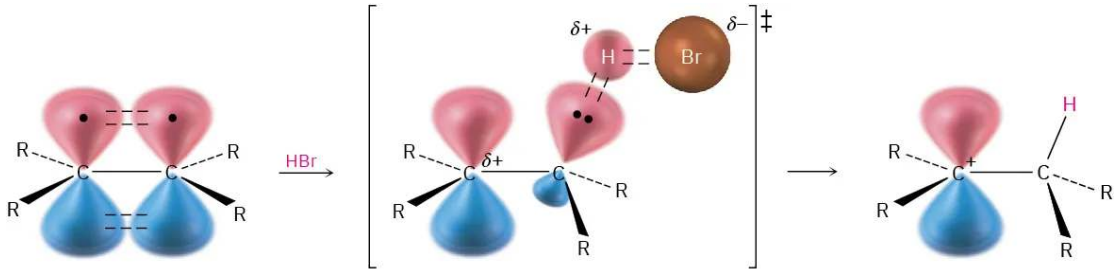


Figure 7.11.4: The hypothetical structure of a transition state for alkene protonation. The transition state is closer in both energy and structure to the carbocation than to the alkene. Thus, an increase in carbocation stability (lower $\Delta G°$) also causes an increase in transition-state stability (lower $\Delta G^{\ddagger}$), thereby increasing the rate of its formation.

? Exercise 7.11.1

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

The second step is exergonic; the transition state resembles the carbocation.

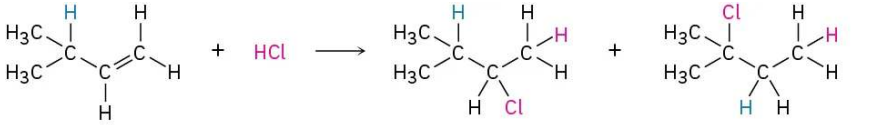
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7.12: Evidence for the Mechanism of Electrophilic Additions - Carbocation Rearrangements

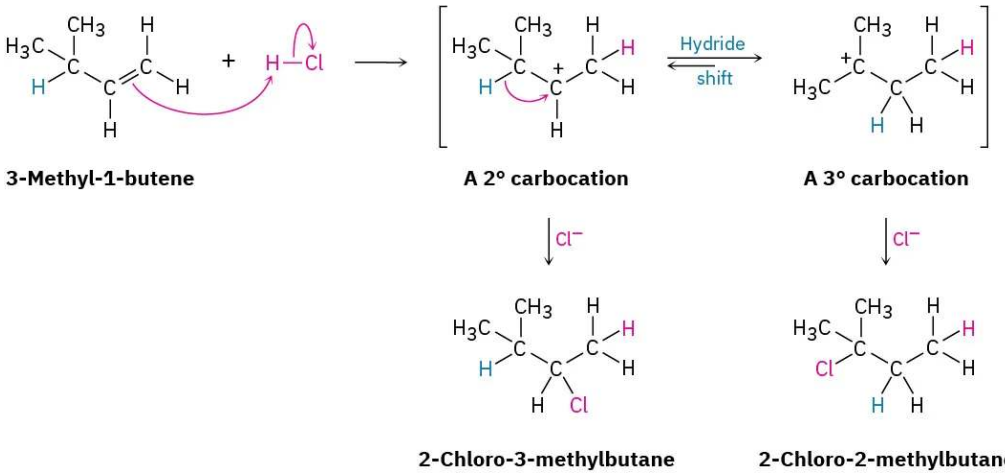
How do we know that the carbocation mechanism for electrophilic addition reactions of alkenes is correct? The answer is that we *don't* know it's correct; at least we don't know with complete certainty. Although an incorrect reaction mechanism can be disproved by demonstrating that it doesn't account 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%)**

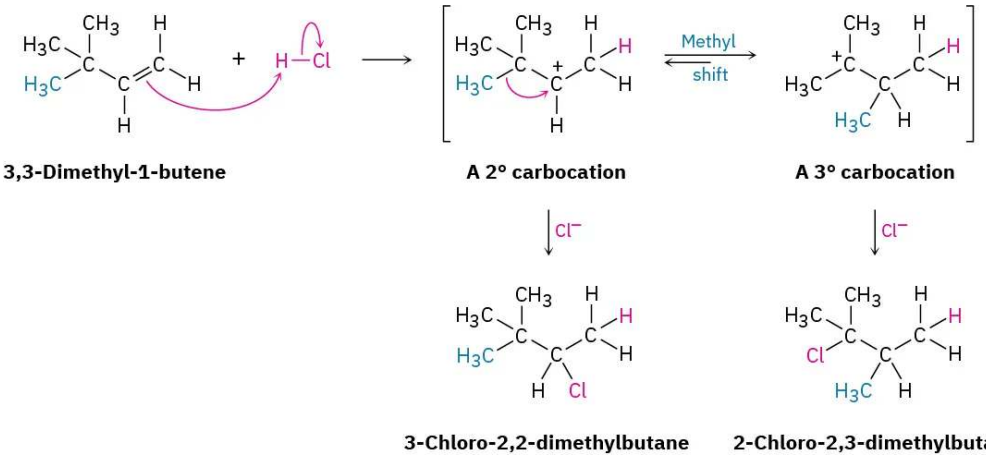
If the reaction takes place in a single step, it would be difficult to account for rearrangement, but if the reaction takes place in several steps, rearrangement is more easily explained. Whitmore suggested that it is a carbocation intermediate that undergoes rearrangement. The secondary carbocation 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**

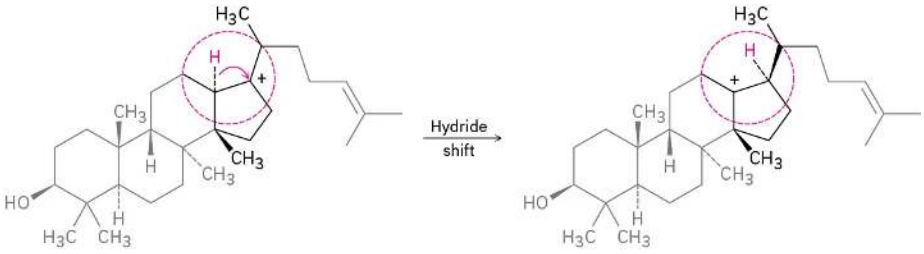
Carbocation rearrangements can also occur by the shift of an alkyl group with its electron pair. For example, reaction of 3,3-dimethyl-1-butene with HCl leads to an equal mixture of unrearranged 3-chloro-2,2-dimethylbutane and rearranged 2-chloro-2,3-dimethylbutane. In this instance, a secondary carbocation 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.

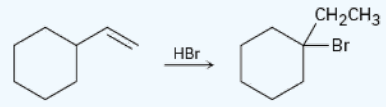


A tertiary carbocation | **An isomeric tertiary carbocation**

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.

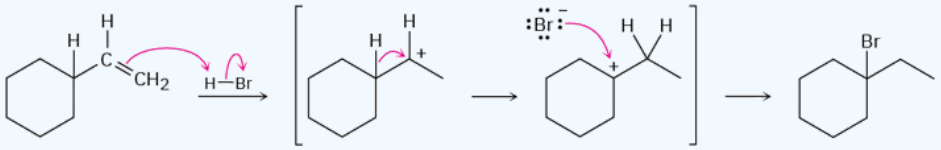
? Exercise 7.12.1

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



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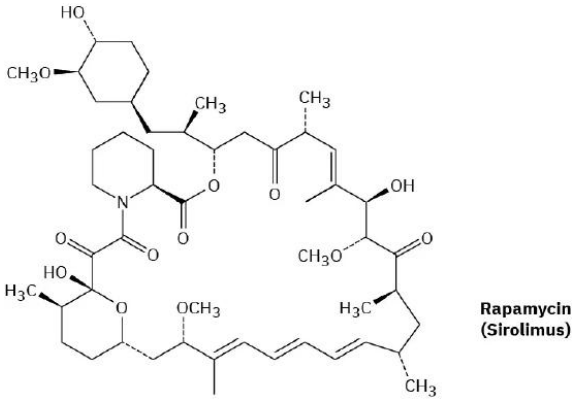
7.13: Chemistry Matters - Bioprospecting - Hunting for Natural Products

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 7.13.1: 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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7.14: Key Terms

- alkene ($R_2C{=}CR_2$)
- allyl group
- degree of unsaturation
- *E* configuration
- *E*,*Z* system
- electrophilic addition reaction
- Hammond postulate
- hydride shift
- hyperconjugation
- Markovnikov's rule
- methylene group
- regiospecific reaction
- unsaturated
- vinyl group
- *Z* configuration

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7.15: Summary

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've looked at some consequences of alkene stereoisomerism and at the details of the broadest class of alkene reactions—the electrophilic addition reaction.

An **alkene** is a hydrocarbon that contains a carbon–carbon double bond. Because they contain fewer hydrogens than alkanes with the same number of carbons, alkenes are said to be **unsaturated**.

Because rotation around the double bond can't occur, substituted alkenes can exist as cis–trans stereoisomers. The configuration of a double bond can be specified by applying the Cahn–Ingold–Prelog sequence rules, which rank the substituents on each double-bond carbon. If the higher-ranking groups on each carbon are on the same side of the double bond, the configuration is ***Z*** (*zusammen*, "together"); if the higher-ranking groups on each carbon are on opposite sides of the double bond, the configuration is ***E*** (*entgegen*, "apart").

Alkene chemistry is dominated by **electrophilic addition reactions**. When HX reacts with an unsymmetrically substituted alkene, **Markovnikov's rule** predicts that the H will add to the carbon having fewer alkyl substituents and the X group will add to the carbon having more alkyl substituents. Electrophilic additions to alkenes take place through carbocation intermediates formed by reaction of the nucleophilic alkene π bond with electrophilic H^+. Carbocation stability follows the order

$$\text{Tertiary (3°)} > \text{Secondary (2°)} > \text{Primary (1°)} > \text{Methyl}$$

$$R_3C^+ > R_2CH^+ > RCH_2{}^+ > CH_3{}^+$$

Markovnikov's rule can be restated by saying that, in the addition of HX to an alkene, a more stable carbocation intermediate is formed. This result is explained by the **Hammond postulate**, which says that the transition state of an exergonic reaction step structurally resembles the reactant, whereas the transition state of an endergonic reaction step structurally resembles the product. Since an alkene protonation step is endergonic, the stability of the more highly substituted carbocation is reflected in the stability of the transition state leading to its formation.

Evidence in support of a carbocation mechanism for electrophilic additions comes from the observation that structural rearrangements often take place during reaction. Rearrangements occur by shift of either a hydride ion, $:H^-$ (a **hydride shift**), or an alkyl anion, $:R^-$, from a carbon atom to the neighboring positively charged carbon. This results in isomerization of a less stable carbocation to a more stable one.

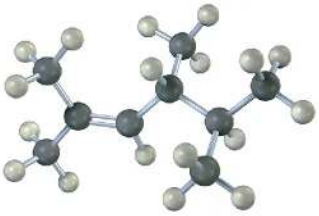
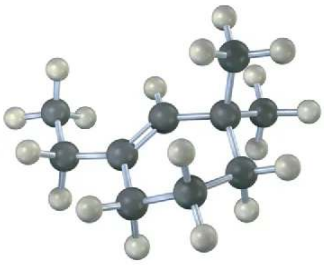
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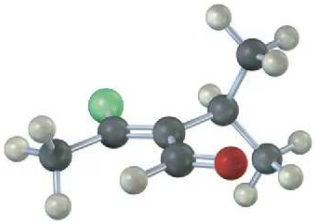
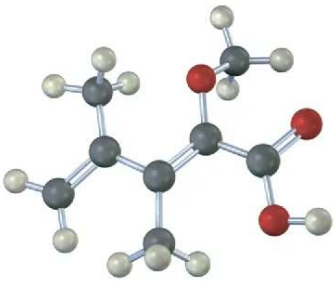
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7.16: Additional Problems

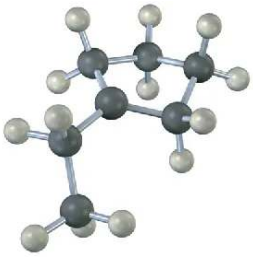
Visualizing Chemistry

PROBLEM7-22 Name the following alkenes, and convert each drawing into a skeletal structure:

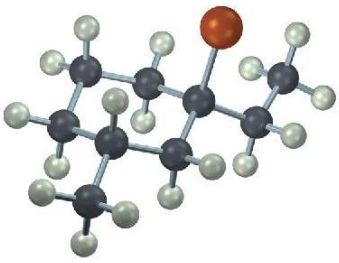
(a)  (b) 

PROBLEM7-23 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) 

PROBLEM7-24 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.

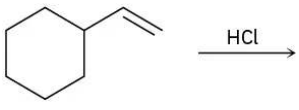


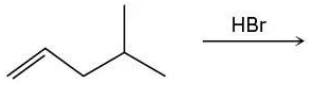
PROBLEM7-25 The following alkyl bromide can be made by HBr addition to three different alkenes. Show their structures.

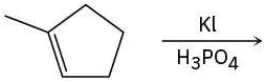


Mechanism Problems

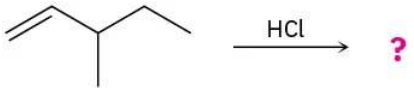
PROBLEM7-26 Predict the major product and show the complete mechanism for each of the following electrophilic addition reactions.

(a) 

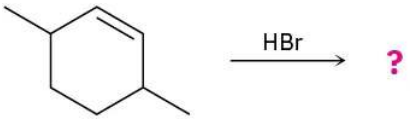
(b) 

(c) 

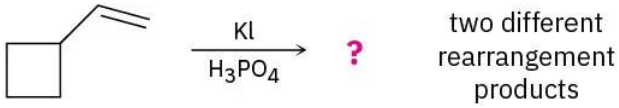
PROBLEM7-27 Each of the following electrophilic addition reactions involves a carbocation rearrangement. Predict the product and draw the complete mechanism of each using curved arrows. (a)



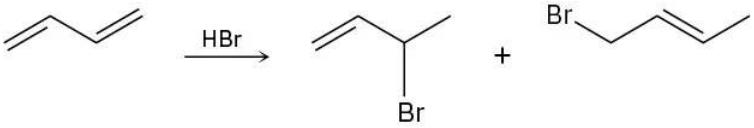
(b)



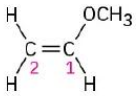
(c)



PROBLEM7-28 When 1,3-butadiene reacts with 1 mol of HBr, two isolable products result. Propose mechanisms for both.

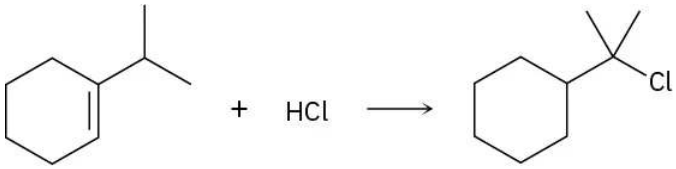


PROBLEM7-29 When methyl vinyl ether reacts with a strong acid, H^+ adds to C2 instead of C1 or the oxygen atom. Explain.

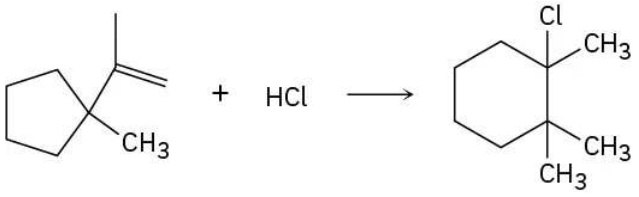


Methyl vinyl ether

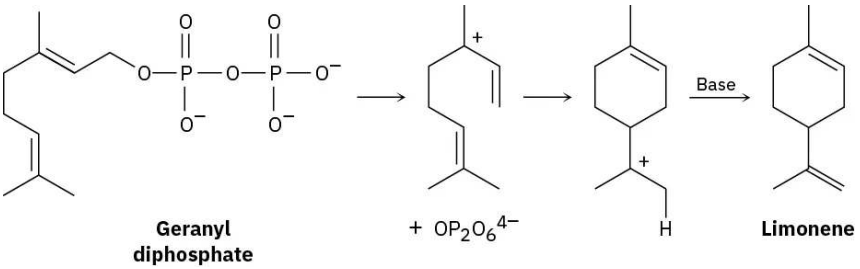
PROBLEM7-30 Addition of HCl to 1-isopropylcyclohexene yields a rearranged product. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.



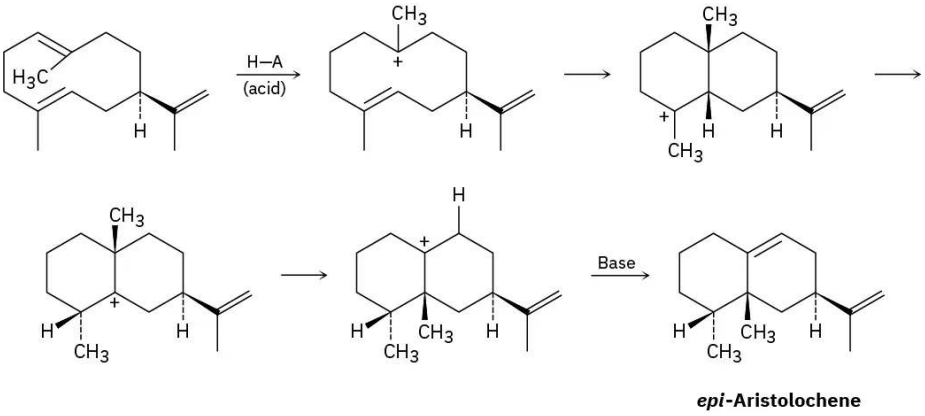
PROBLEM7-31 Addition of HCl to 1-isopropenyl-1-methylcyclopentane yields 1-chloro-1,2,2-trimethylcyclohexane. Propose a mechanism, showing the structures of the intermediates and using curved arrows to indicate electron flow in each step.



PROBLEM7-32 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.)



PROBLEM7-33 *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 a 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) $C_8H_{10}ClNO$

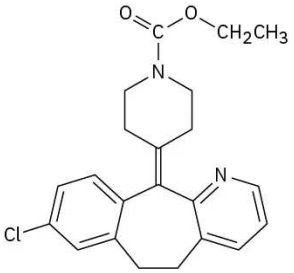
PROBLEM 7-35 How many hydrogens does each of the following compounds have?

(a) $C_8H_?O_2$, has two rings and one double bond

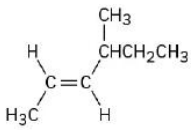
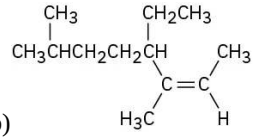
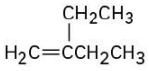
(b) $C_7H_?N$, has two double bonds

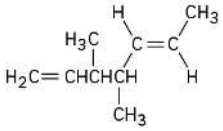
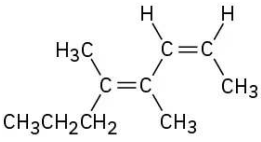
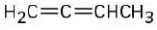
(c) $C_9H_?NO$, has one ring and three double bonds

PROBLEM7-36 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.)



PROBLEM 7-37 Name the following alkenes:

(a)  (b)  (c) 

(d)  (e)  (f) 

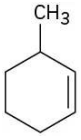
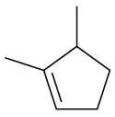
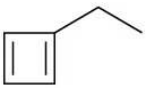
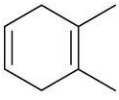
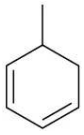
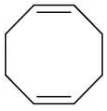
PROBLEM 7-38 Draw structures corresponding to the following systematic names:

(a) (4*E*)-2,4-Dimethyl-1,4-hexadiene **(b)** *cis*-3,3-Dimethyl-4-propyl-1,5-octadiene

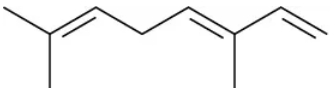
(c) 4-Methyl-1,2-pentadiene **(d)** (3*E*,5*Z*)-2,6-Dimethyl-1,3,5,7-octatetraene

(e) 3-Butyl-2-heptene **(f)** *trans*-2,2,5,5-Tetramethyl-3-hexene

PROBLEM 7-39 Name the following cycloalkenes:

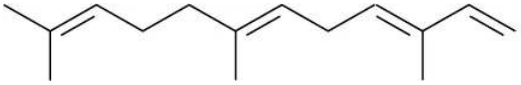
(a)  (b)  (c)  (d)  (e)  (f) 

PROBLEM7-40 Ocimene is a triene found in the essential oils of many plants. What is its IUPAC name, including stereochemistry?



Ocimene

PROBLEM7-41 α-Farnesene is a constituent of the natural wax found on apples. What is its IUPAC name, including stereochemistry?



α-Farnesene

Menthene, a hydrocarbon found in mint plants, has the systematic name 1-isopropyl-4-**PROBLEM 7**-42 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

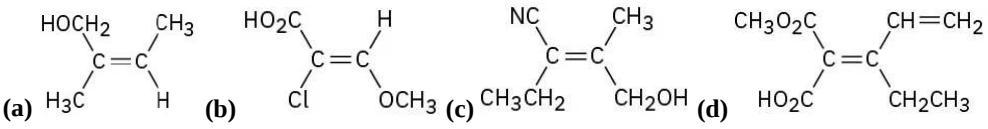
PROBLEM 7-45 Rank the following sets of substituents according to the Cahn–Ingold–Prelog sequence rules:

(a) $-CH_3, -Br, -H, -I$ **(b)** $-OH, -OCH_3, -H, -CO_2H$

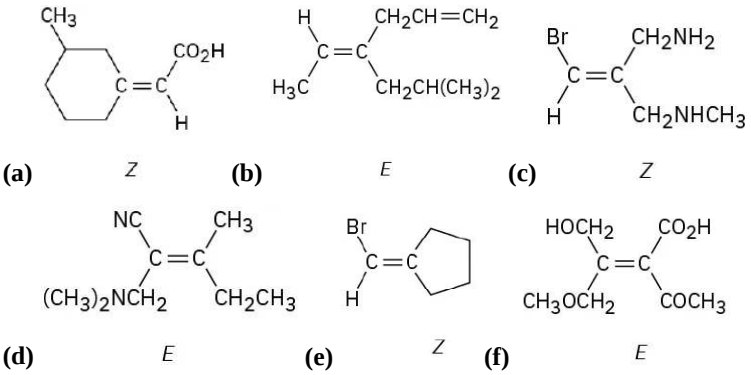
(c) $-CO_2H, -CO_2CH_3, -CH_2OH, -CH_3$ **(d)** $-CH_3, -CH_2CH_3, -CH_2CH_2OH, -\overset{\overset{O}{\|}}{C}CH_3$

(e) $-CH{=}CH_2, -CN, -CH_2NH_2, -CH_2Br$ **(f)** $-CH{=}CH_2, -CH_2CH_3, -CH_2OCH_3, -CH_2OH$

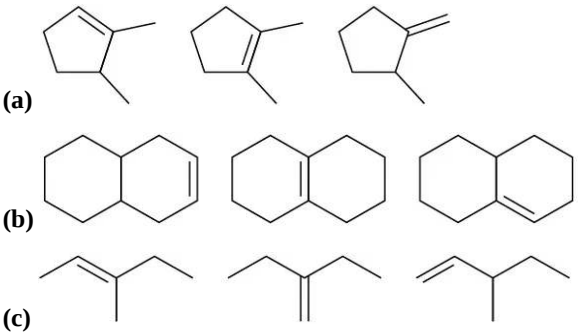
Problem 7-46 Assign *E* or *Z* configuration to each of the following compounds:



Problem 7-47 Which of the following *E*,*Z* designations are correct, and which are incorrect?



Problem 7-48 Rank the double bonds according to their increasing stability.



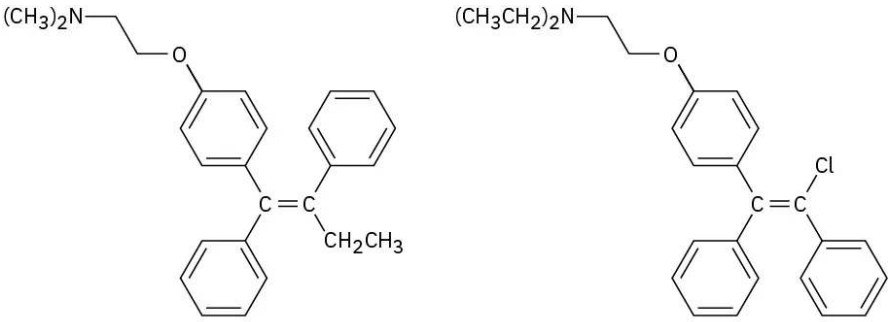
Problem 7-49 *trans*-2-Butene is more stable than *cis*-2-butene by only 4 kJ/mol, but *trans*-2,2,5,5-tetramethyl-3-hexene is more stable than its cis isomer by 39 kJ/mol. Explain.

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.



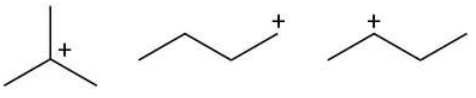
Tamoxifen
(anticancer)

Clomiphene
(fertility treatment)

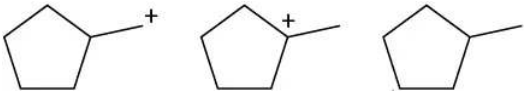
Carbocations and Electrophilic Addition Reactions

Problem 7-54 Rank the following carbocations according to their increasing stability.

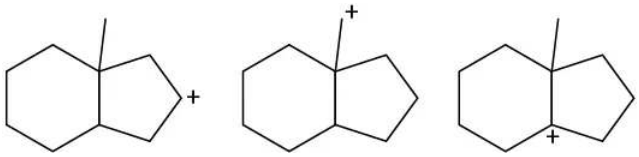
https://chem.libretexts.org/@go/page/564042



(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)



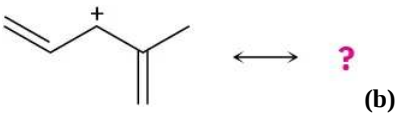
(b)



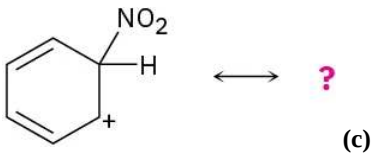
(c)



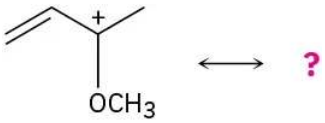
Problem 7-56 The following carbocations can be stabilized by resonance. Draw all the resonance forms that would stabilize each carbocation. (a)



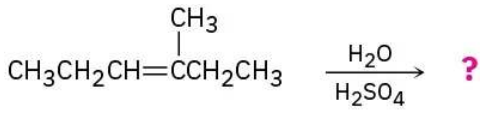
(b)



(c)

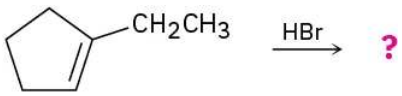


Problem 7-57 Predict the major product in each of the following reactions:

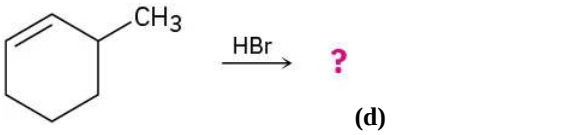


(a) (Addition of H_2O occurs.)

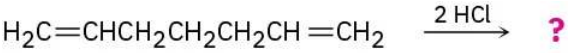
(b)



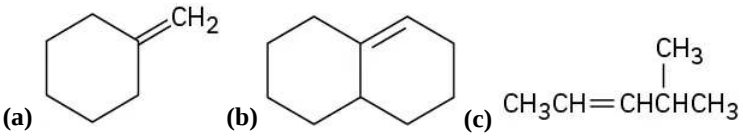
(c)



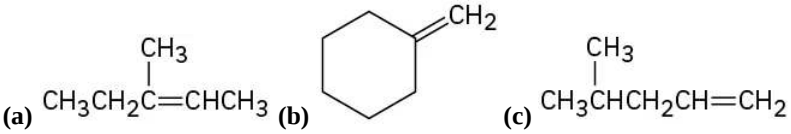
(d)



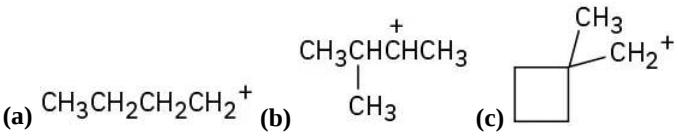
Problem 7-58 Predict the major product from addition of HBr to each of the following alkenes:



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.



Problem 7-60 Each of the following carbocations can rearrange to a more stable ion. Propose structures for the likely rearrangement products.

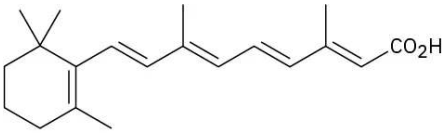


General Problems

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?

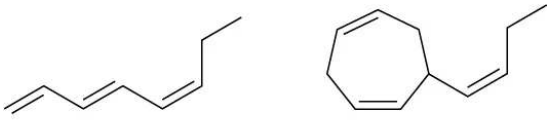
Problem 7-62 The heat of hydrogenation for allene (Problem 7-61) to yield propane is −295 kJ/mol, and the heat of hydrogenation for a typical monosubstituted alkene, such as propene, is −125 kJ/mol. Is allene more stable or less stable than you might expect for a diene? Explain.

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)

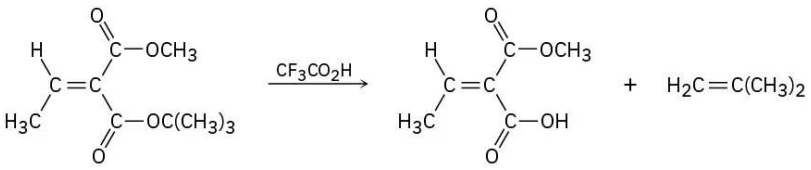
Problem 7-64 Fucoserratene and ectocarpene are sex pheromones produced by marine brown algae. What are their systematic names? (Ectocarpene is difficult; make your best guess, and then check your answer in the *Student Solutions Manual*.)



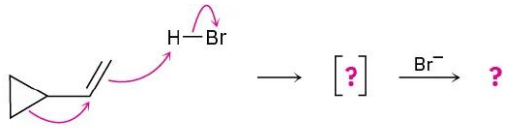
Fucoserratene **Ectocarpene**

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.

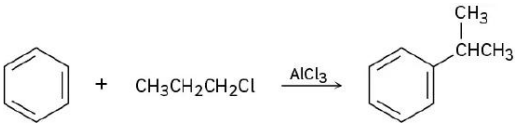


Isobutyl cation ***tert*-Butyl cation**

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 $AlCl_3$ ($R{-}Cl + AlCl_3 \longrightarrow R^+ + AlCl_4^-$). How can you explain the observation that 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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CHAPTER OVERVIEW

8: Alkenes - Reactions and Synthesis

As you have seen, addition reactions dominate the chemistry of alkenes. This chapter shows how a variety of reagents can add to alkenes; how hydrogen bromide can be made to add to alkenes in a non-Markovnikov manner; and how alkene molecules can be cleaved into easily identifiable parts. First, you will examine the preparation of alkenes by elimination reactions.

8.1: Why This Chapter?
8.2: Preparation of Alkenes - A Preview of Elimination Reactions
8.3: Halogenation of Alkenes - Addition of X_2
8.4: Halohydrins from Alkenes - Addition of HO-X
8.5: Hydration of Alkenes - Addition of H_2O by Oxymercuration
8.6: Hydration of Alkenes - Addition of H_2O by Hydroboration
8.7: Reduction of Alkenes - Hydrogenation
8.8: Oxidation of Alkenes - Epoxidation and Hydroxylation
8.9: Oxidation of Alkenes - Cleavage to Carbonyl Compounds
8.10: Addition of Carbenes to Alkenes - Cyclopropane Synthesis
8.11: Radical Additions to Alkenes - Chain-Growth Polymers
8.12: Biological Additions of Radicals to Alkenes
8.13: Stereochemistry of Reactions - Addition of H_2O to an Achiral Alkene
8.14: Stereochemistry of Reactions - Addition of H_2O to a Chiral Alkene
8.15: Chemistry Matters—Terpenes- Naturally Occurring Alkenes
8.16: Key Terms
8.17: Summary
8.18: Summary of Reactions
8.19: Additional Problems

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8.1: 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 8.1.1: 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.

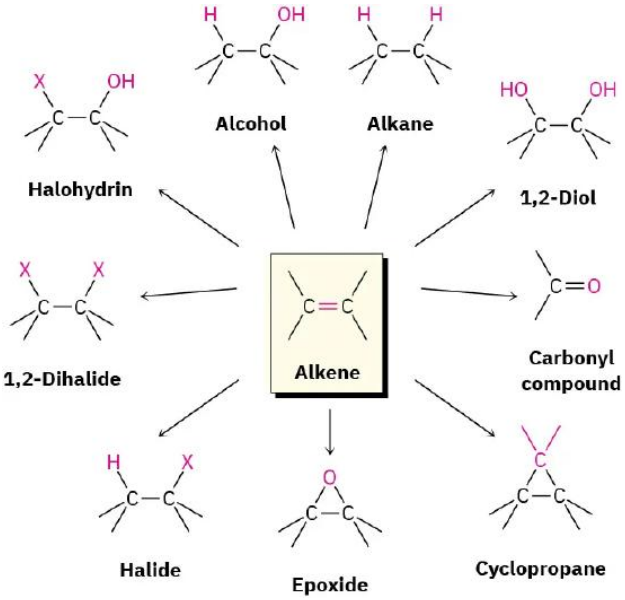


Figure 8.1.2: Some useful alkene reactions.

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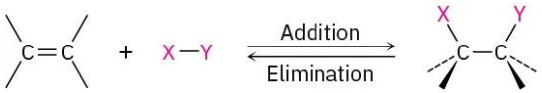
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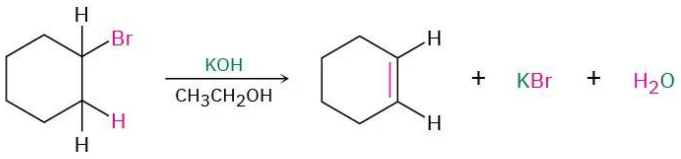
8.2: Preparation of Alkenes - A Preview of Elimination Reactions

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.

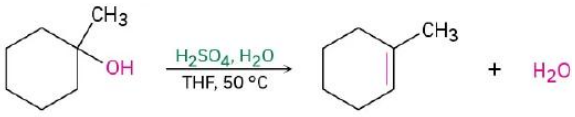


The two most common elimination reactions are dehydrohalogenation—the loss of HX from an alkyl halide—and dehydration—the loss of water from an alcohol. Dehydrohalogenation usually occurs by reaction of an alkyl halide with strong base such as potassium hydroxide. For example, bromocyclohexane yields cyclohexene when treated with KOH in ethanol solution.



Bromocyclohexane **Cyclohexene (81%)**

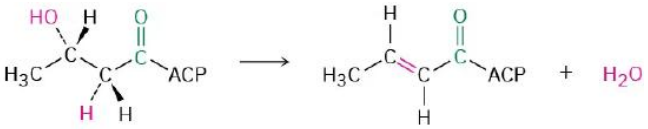
Dehydration is often carried out in the laboratory by treatment of an alcohol with a strong acid. For example, when 1-methylcyclohexanol is warmed with aqueous sulfuric acid in tetrahydrofuran (THF) solvent, loss of water occurs and 1-methylcyclohexene is formed.



1-Methylcyclohexanol **1-Methylcyclohexene (91%)**



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 8.2.1

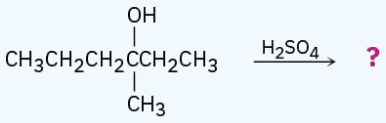
One problem with elimination reactions is that mixtures of products are often formed. For example, treatment of 2-bromo-2-methylbutane with KOH in ethanol yields a mixture of two alkene products. What are their likely structures?

Answer

2-Methyl-2-butene and 2-methyl-1-butene.

Exercise 8.2.2

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

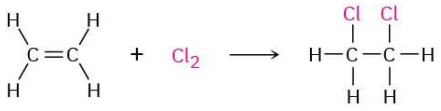
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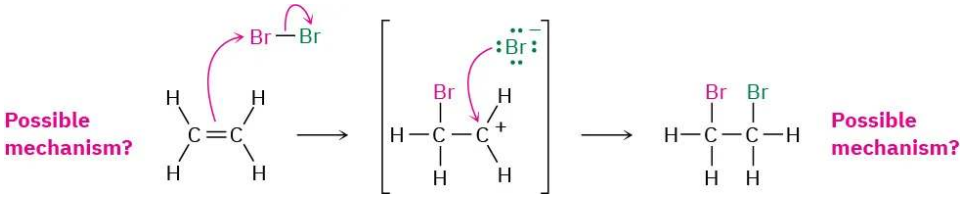
8.3: Halogenation of Alkenes - Addition of X_2

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.



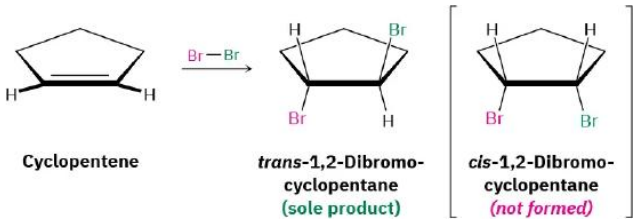
Ethylene **1,2-Dichloroethane (ethylene dichloride)**

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.



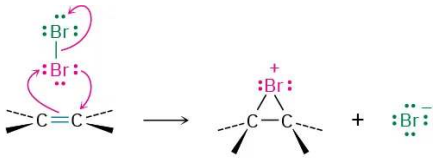
Although this mechanism seems plausible, it's not fully consistent with known facts. In particular, it doesn't explain the stereochemistry of the addition reaction. That is, the mechanism doesn't account for which product stereoisomer is formed.

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.



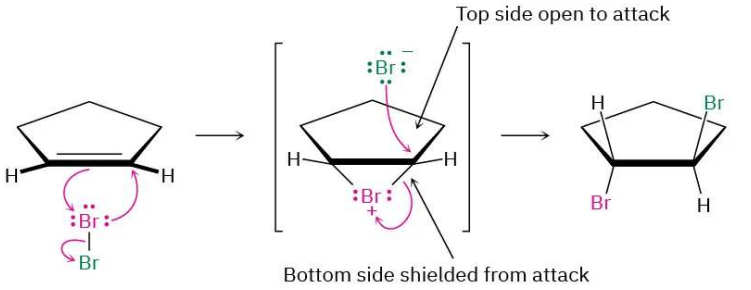
Cyclopentene ***trans*-1,2-Dibromo-cyclopentane (sole product)** ***cis*-1,2-Dibromo-cyclopentane *(not formed)***

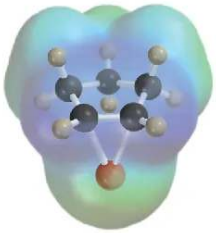
An explanation for the observed stereochemistry of addition was suggested in 1937 by George Kimball and Irving Roberts, who proposed that the reaction intermediate is not a carbocation but is instead a bromonium ion, \(\ce{R2Br^{+}}\), formed by electrophilic addition of Br^+ to the alkene. (Similarly, 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^-.



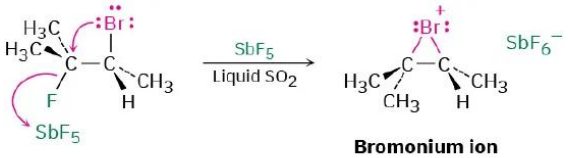
An alkene **A bromonium ion**

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.

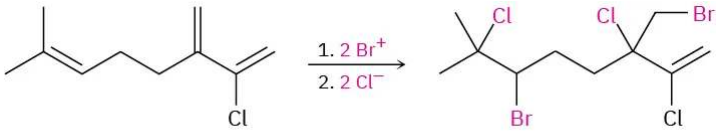




The bromonium ion postulate, made more than 85 years ago to explain the stereochemistry of halogen addition to alkenes, is a remarkable example of deductive logic in chemistry. Arguing from experimental results, chemists were able to make a hypothesis about the intimate mechanistic details of alkene electrophilic reactions. Subsequently, strong evidence supporting the mechanism came from the work of George Olah at the University of Southern California, who prepared and studied stable solutions of cyclic bromonium ions in liquid SO_2. There's no question that bromonium ions exist.



Alkene halogenation reactions occur in nature just as they do in the laboratory but are limited primarily to marine organisms living in halide-rich environments. These biological halogenation reactions are carried out by enzymes called *haloperoxidases*, which use H_2O_2 to oxidize Br^- or Cl^- ions to a biological equivalent of Br^+ or Cl^+. Electrophilic addition to the double bond of a substrate molecule then yields a bromonium or chloronium ion intermediate just as in the laboratory, and reaction with another halide ion completes the process. Halomon, for example, an antitumor pentahalide isolated from red alga, is thought to arise by a route that involves twofold addition of BrCl through the corresponding bromonium ions.



? Exercise 8.3.1

What product would you expect to obtain from the addition of Cl_2 to 1,2-dimethylcyclohexene? Show the stereochemistry of the product.

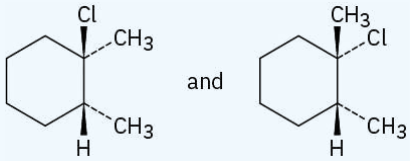
Answer

trans-1,2-Dichloro-1,2-dimethylcyclohexane.

Exercise 8.3.2

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

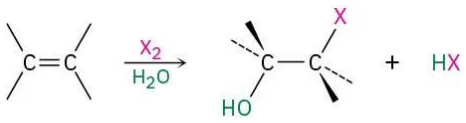


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8.4: Halohydrins from Alkenes - Addition of HO-X

Another example of an electrophilic addition is the reaction an alkene with either Br_2 or Cl_2 in the presence of water to yield a 1,2-halo alcohol, called a halohydrin.



An alkene **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 addition of HO−Br to the alkene by the pathway shown in Figure 8.4.1.

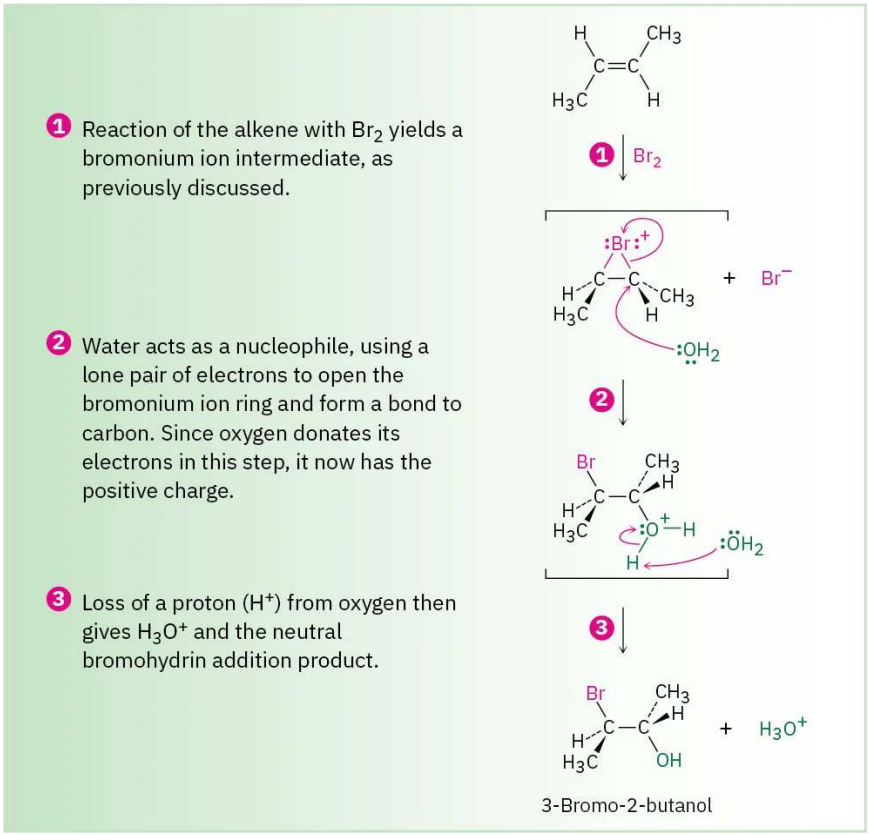
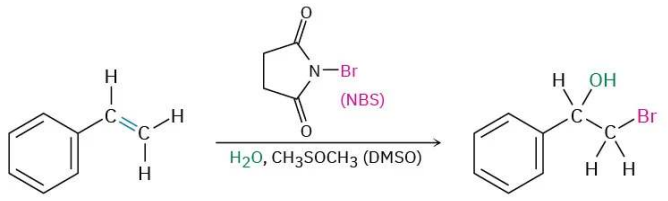


Figure 8.4.1: Bromohydrin formation by reaction of an alkene with Br_2 in the presence of water. Water acts as a nucleophile in step 2 to react with the intermediate bromonium ion.

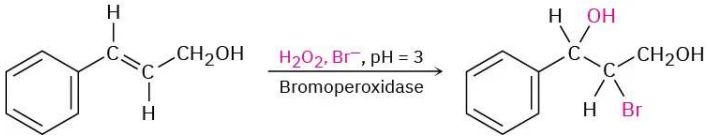
In practice, few alkenes are soluble in water, and bromohydrin formation is often carried out in a solvent such as aqueous dimethyl sulfoxide, CH_3SOCH_3 (DMSO), using a reagent called *N*-bromosuccinimide (NBS) as a source of Br_2. NBS is a stable, easily handled compound that slowly decomposes in water 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.

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:



? Exercise 8.4.1

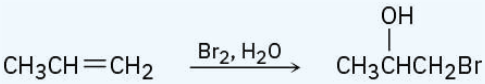
What product would you expect from the reaction of cyclopentene with NBS and water? Show the stereochemistry.

Answer

trans-2-Bromocyclopentanol

? Exercise 8.4.2

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

Markovnikov

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8.5: Hydration of Alkenes - Addition of H_2O by Oxymercuration

Water adds to alkenes to yield alcohols, a process called hydration. The reaction takes place on 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 8.5.1, 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.

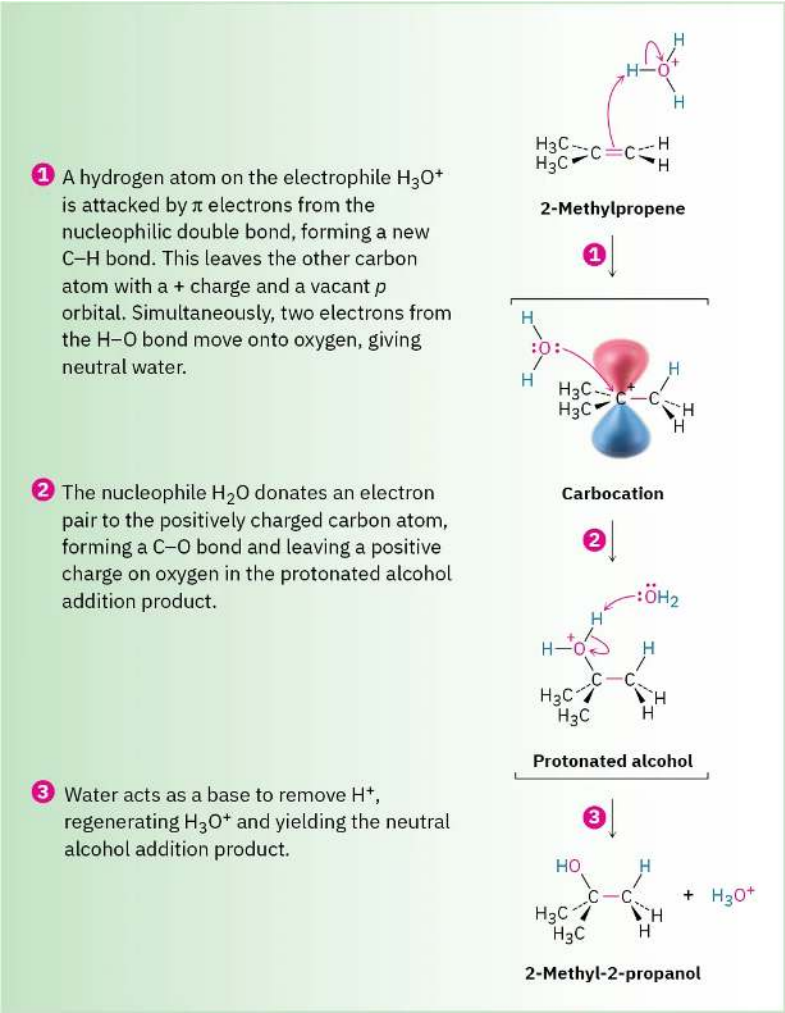
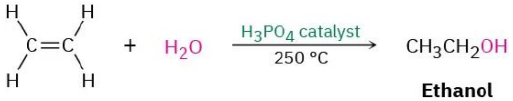


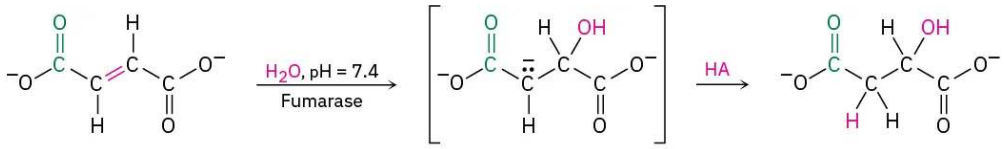
Figure 8.5.1: Mechanism of the acid-catalyzed hydration of an alkene to yield an alcohol. Protonation of the alkene gives a carbocation intermediate, which reacts with water. The initial product is then deprotonated.

Most ethanol throughout the world is now made by fermentation of biological precursors, such as corn and sugar, but acid-catalyzed alkene hydration is particularly suited to large-scale industrial procedures, and approximately 90,000 tons of ethanol is manufactured each year in the United States by hydration of ethylene. The reaction is of little value in the laboratory, however, because it requires high temperatures—250 °C in the case of ethylene—and strongly acidic conditions.



Acid-catalyzed hydration of double bonds is also uncommon in biological pathways. Instead, biological hydrations usually require that the double bond be adjacent to a carbonyl group for reaction to proceed. Fumarate, for instance, is hydrated to give malate as one step in the citric acid cycle of food metabolism. Note that the requirement for an adjacent carbonyl group in the addition of water is the same as in Section 8.2 for the elimination of water. We'll see the reason for this requirement in **Section 19.14**, but will

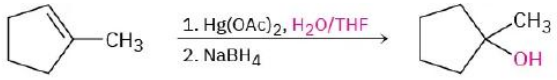
note for now that the reaction is not an electrophilic addition but instead occurs through a mechanism that involves formation of an anion intermediate followed by protonation by an acid HA.



Fumarate **Anion intermediate** **Malate**

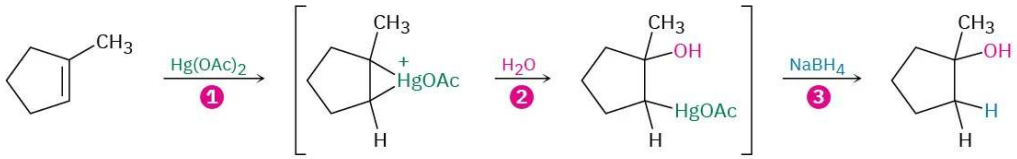
When it comes to circumventing problems like those with acid-catalyzed alkene hydrations, laboratory chemists have a great advantage over the cellular "chemists" in living organisms. Laboratory chemists are not constrained to carry out their reactions in water solution; they can choose from any of a large number of solvents. Laboratory reactions don't need to be carried out at a fixed temperature; they can take place over a wide range of temperatures. And laboratory reagents aren't limited to containing carbon, oxygen, nitrogen, and a few other elements; they can contain any element in the periodic table.

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:



1-Methylcyclopentene **1-Methylcyclopentanol (92%)**

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 8.5.2). 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.



1-Methyl-cyclopentene **Mercurinium ion** **Organomercury compound** **1-Methyl-cyclopentanol (92% yield)**

Figure 8.5.2: 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 8.5.1

What products would you expect from oxymercuration–demercuration of the following alkenes?

a. $CH_3CH_2CH_2CH{=}CH_2$

b. $CH_3C(CH_3){=}CHCH_2CH_3$

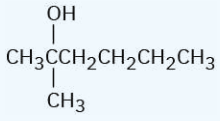
Answer

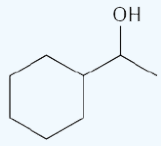
a. 2-Pentanol

b. 2-Methyl-2-pentanol

Exercise 8.5.2

From what alkenes might the following alcohols have been prepared?

a. 

b. 

Answer

a. Oxymercuration of 2-methyl-1-hexene or 2-methyl-2-hexene

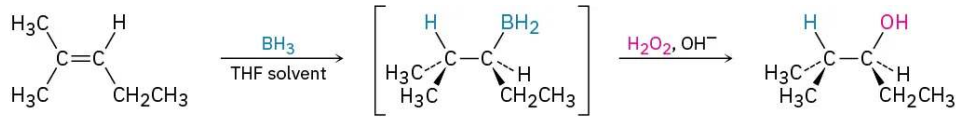
b. Oxymercuration of cyclohexylethylene or hydroboration of ethylidenecyclohexane

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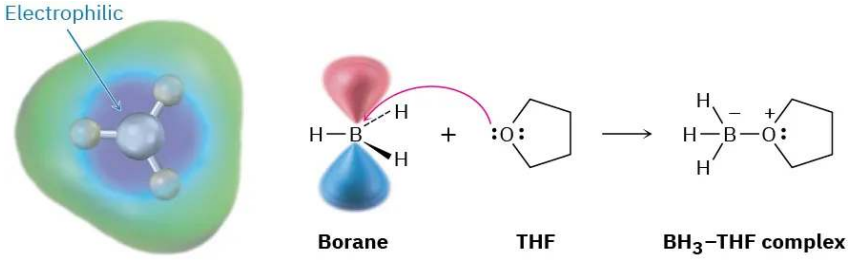
8.6: Hydration of Alkenes - Addition of H_2O by Hydroboration

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:



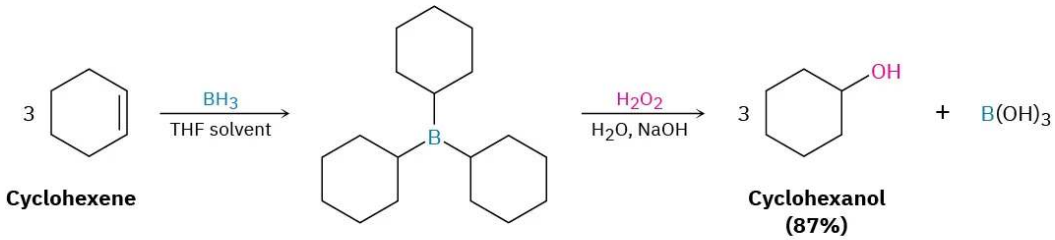
2-Methyl-2-pentene | **Organoborane intermediate** | **2-Methyl-3-pentanol**

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.



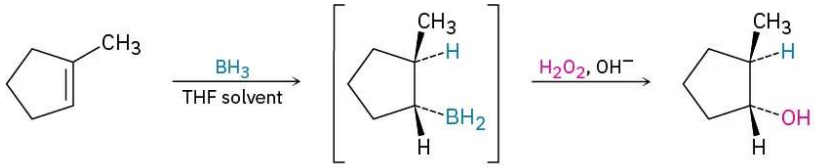
Borane | **THF** | **BH_3–THF complex**

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.



1-Methyl-cyclopentene | **Organoborane intermediate** | ***trans*-2-Methyl-cyclopentanol (85% yield)**

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 8.6.1). 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.

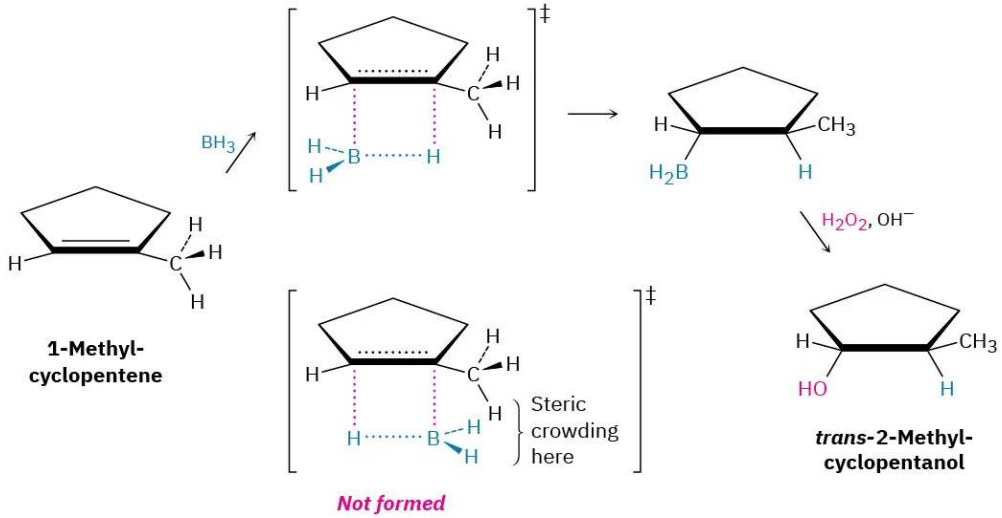


Figure 8.6.1: Mechanism of alkene hydroboration. The reaction occurs in a single step in which the C−H and C−B bonds form at the same time and on the same face of the double bond. The lower energy, more rapidly formed transition state is the one with less steric crowding, leading to non-Markovnikov regiochemistry.

Worked Example 8.1: Predicting the Products of a Hydration Reaction

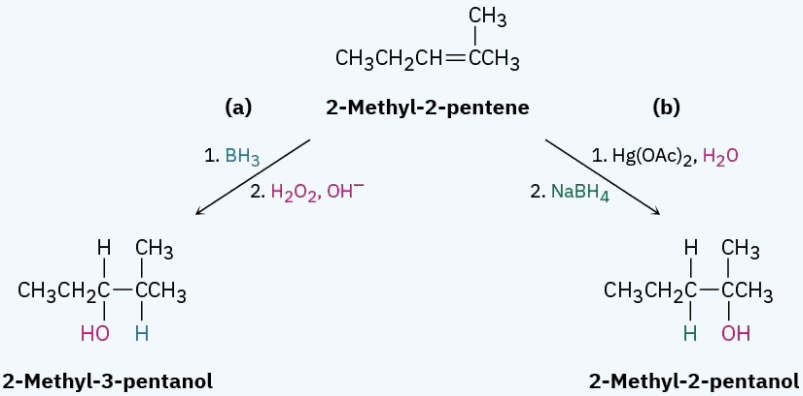
What products would you obtain from reaction of 2-methyl-2-pentene with:

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.

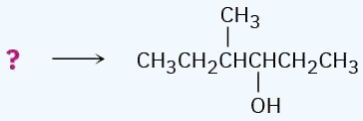
Solution



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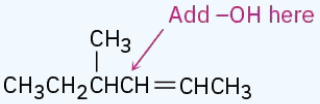
Worked Example 8.2: Synthesizing an Alcohol

How might you prepare the following alcohol?

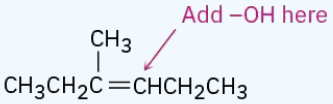


Strategy

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.



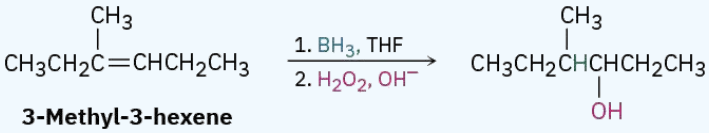
4-Methyl-2-hexene



3-Methyl-3-hexene

4-Methyl-2-hexene has a disubstituted double bond, 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

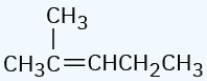


3-Methyl-3-hexene

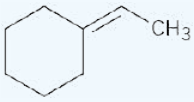
Exercise 8.6.1

Show the structures of the products you would obtain by hydroboration–oxidation of the following alkenes:

a.

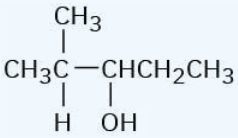


b.

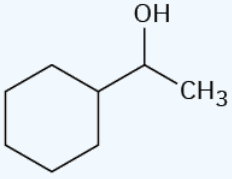


Answer

a.



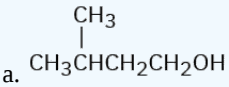
b.

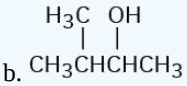


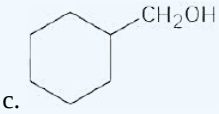
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Exercise 8.6.2

What alkenes might be used to prepare the following alcohols by hydroboration–oxidation?

a. 

b. 

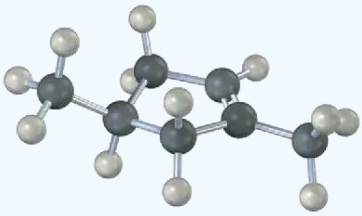
c. 

Answer

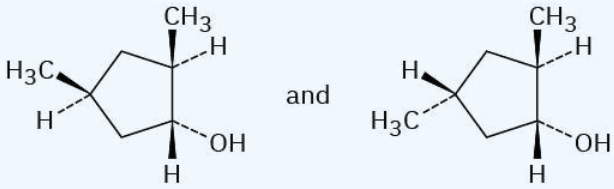
a. 3-Methyl-1-butene
b. 2-Methyl-2-butene
c. Methylenecyclohexane

Exercise 8.6.3

The following cycloalkene gives a mixture of two alcohols on hydroboration followed by oxidation. Draw the structures of both, and explain the result.



Answer



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8.7: Reduction of Alkenes - Hydrogenation

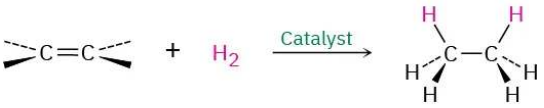
Alkenes react with H_2 in the presence of a metal catalyst such as palladium or platinum to yield the corresponding saturated alkanes. We describe the result by saying that the double bond has been hydrogenated, or *reduced*. Note that the word *reduction* is used somewhat differently in organic chemistry 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

Increases electron density on carbon by:

- forming this: C–H or
- breaking one of these: C–O, C–N, C–X

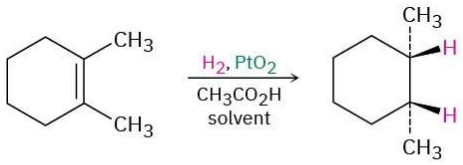
A reduction:



An alkene **An alkane**

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, a reagent known as *Adams' catalyst* after its discoverer, Roger Adams at the University of Illinois.

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.



1,2-Dimethyl-cyclohexene **_cis_-1,2-Dimethyl-cyclohexane (82%)**

As shown in Figure 8.7.1, 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.

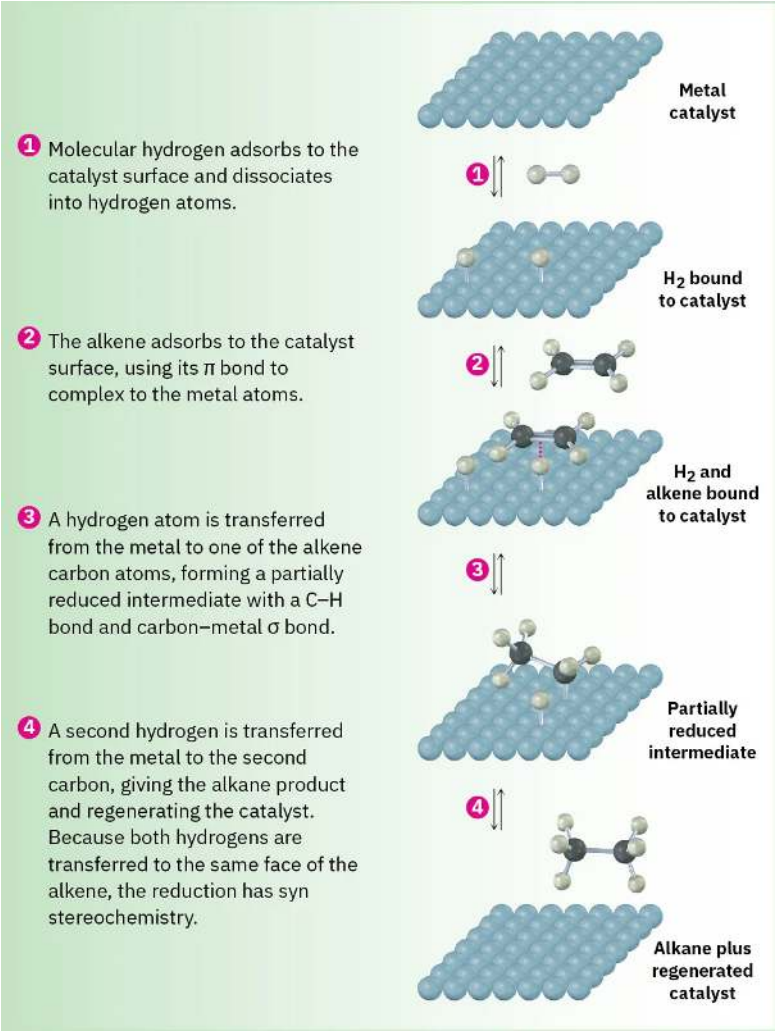
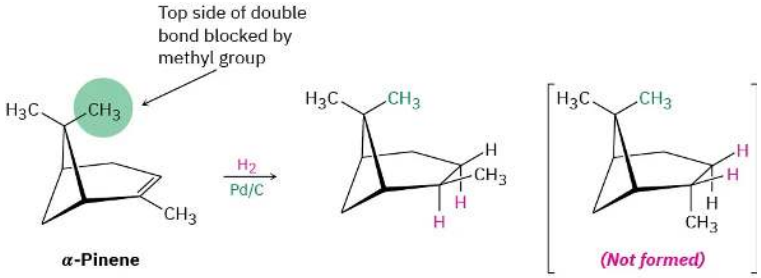
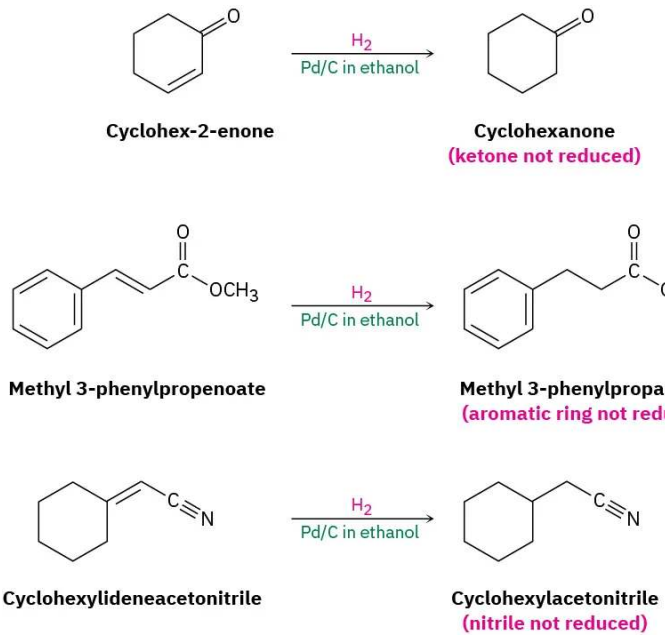


Figure 8.7.1: Mechanism of alkene hydrogenation. The reaction takes place with syn stereochemistry on the surface of insoluble catalyst particles.

An interesting feature of catalytic hydrogenation is that the reaction is extremely sensitive to the steric environment around 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 8.7.2). As we'll see in **Section 27.2**, vegetable oils are triesters of glycerol, $HOCH_2CH(OH)CH_2OH$, with three long-chain carboxylic acids called *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 eaten and digested, the free trans fatty acids are released, raising blood cholesterol levels and potentially contributing to coronary problems.

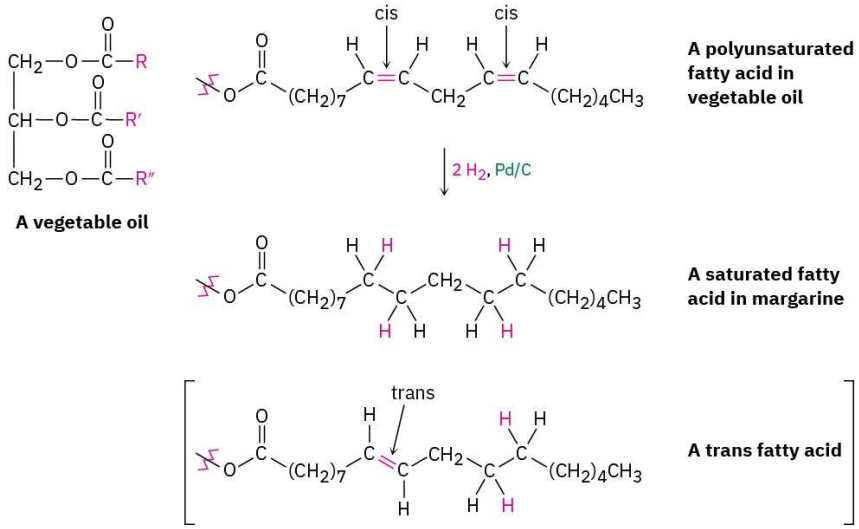


Figure 8.7.2: Catalytic hydrogenation of polyunsaturated fats leads primarily to saturated products, along with a small amount of isomerized trans fats.

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 8.7.3).

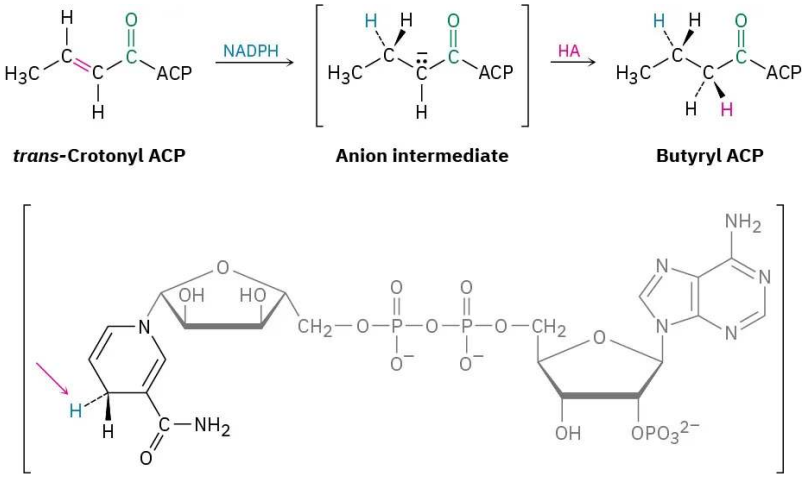
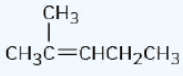
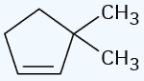


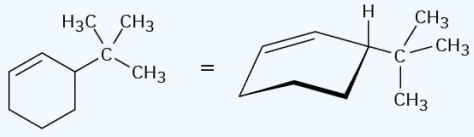
Figure 8.7.3: Reduction of the carbon–carbon double bond in *trans*-crotonyl ACP, a step in the biosynthesis of fatty acids. **One hydrogen** is delivered from NADPH as a hydride ion, H:⁻; the **other hydrogen** is delivered by protonation of the anion intermediate with an acid, HA.

Exercise 8.7.1

What product would you obtain from catalytic hydrogenation of the following alkenes?

a. 

b. 

c. 

Answer

a. 2-Methylpentane

b. 1,1-Dimethylcyclopentane

c. *tert*-Butylcyclohexane

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8.8: Oxidation of Alkenes - Epoxidation and Hydroxylation

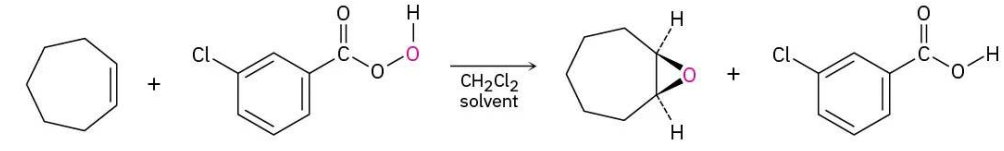
Like the word *reduction* used in the previous section for the addition of hydrogen to a double bond, the word *oxidation* has a slightly different meaning in organic chemistry than what you might have previously learned. In general chemistry, an oxidation is defined as the loss of one or more electrons by an atom. In organic chemistry, however, an oxidation is a reaction that results in a loss of electron density for 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 an *oxidation* often adds oxygen, while a *reduction* often adds hydrogen.

Oxidation

Decreases electron density on carbon by:

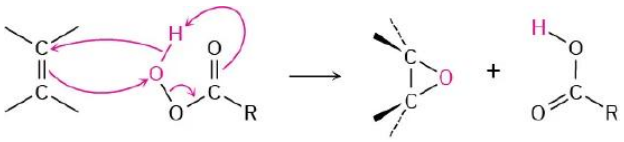
- forming one of these: C–O, C–N, C–X
- or breaking this: C–H

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:



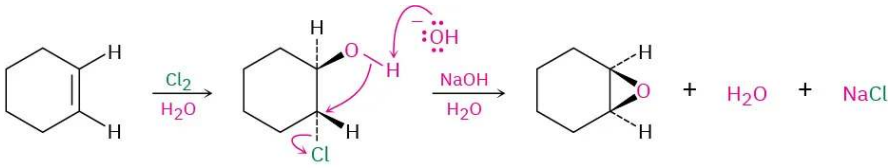
Cycloheptene | ***meta*-Chloroperoxy-benzoic acid** | **1,2-Epoxy-cycloheptane** | ***meta*-Chloro-benzoic acid**

Peroxyacids transfer an oxygen atom to the alkene with syn stereochemistry—both 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.



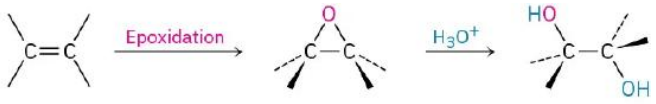
Alkene | **Peroxyacid** | **Epoxide** | **Acid**

Another method for the synthesis of epoxides involves the use of halohydrins, prepared by 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.



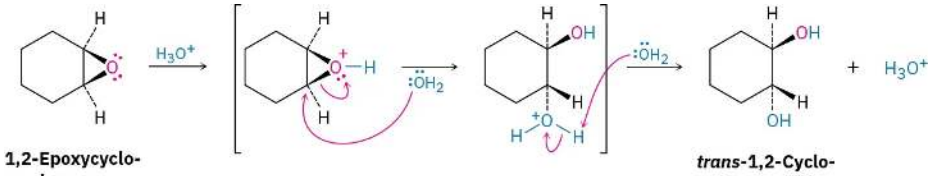
Cyclohexene | ***trans*-2-Chloro-cyclohexanol** | **1,2-Epoxycyclohexane (73%)**

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 204 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.

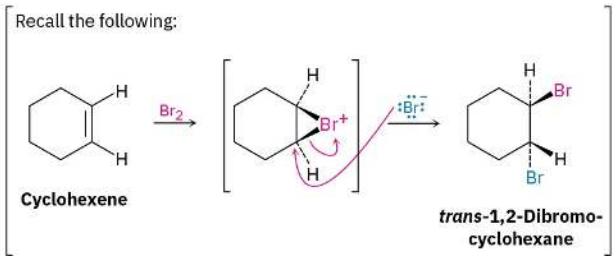


An alkene **An epoxide** **A 1,2-diol**

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. We'll look at epoxide chemistry in more detail in **Section 18.7**.

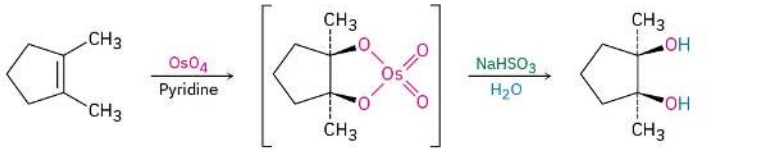


1,2-Epoxycyclohexane ***trans*-1,2-Cyclohexanediol (86%)**



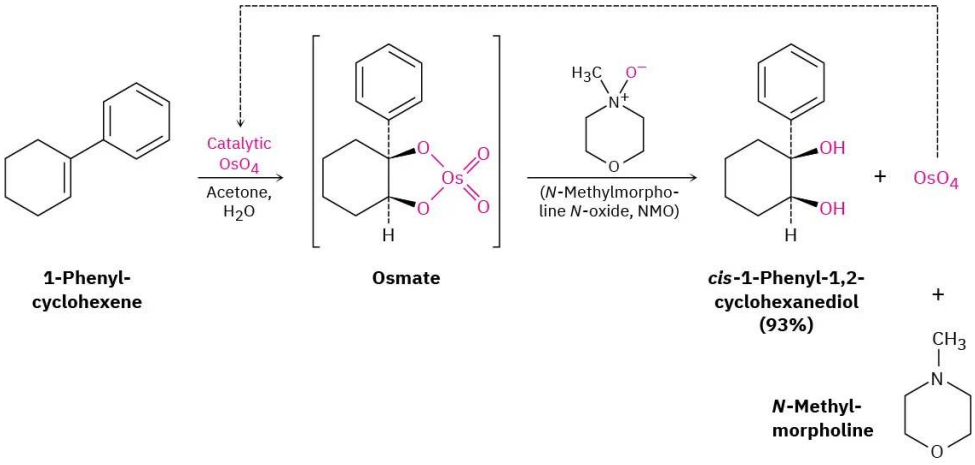
Cyclohexene ***trans*-1,2-Dibromocyclohexane**

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%)**

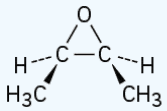
Because OsO_4 is both very expensive and *very* toxic, the reaction is usually carried out using only a small, catalytic amount of OsO_4 in the presence of a stoichiometric amount of a safe and inexpensive co-oxidant such as *N*-methylmorpholine *N*-oxide, abbreviated NMO. The initially formed osmate intermediate reacts rapidly with NMO to yield the product diol plus *N*-methylmorpholine and reoxidized OsO_4, which reacts with more alkene in a catalytic cycle.



Exercise 8.8.1

What product would you expect from the reaction of *cis*-2-butene with *meta*-chloroperoxybenzoic acid? Show the stereochemistry.

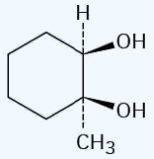
Answer

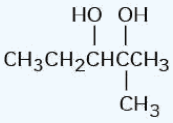


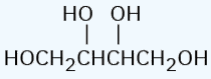
cis-2,3-Epoxybutane

Exercise 8.8.2

Starting with an alkene, how would you prepare each of the following compounds?

a. 

b. 

c. 

Answer

a. 1-Methylcyclohexene
b. 2-Methyl-2-pentene
c. 1,3-Butadiene

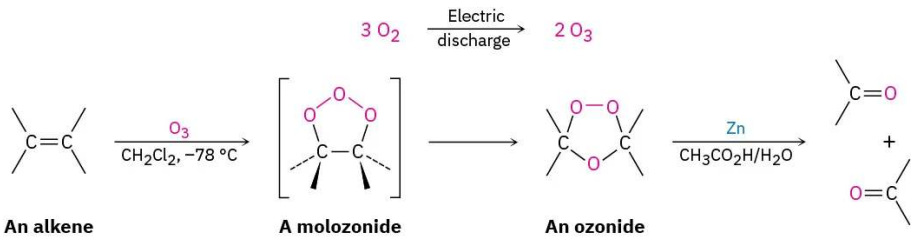
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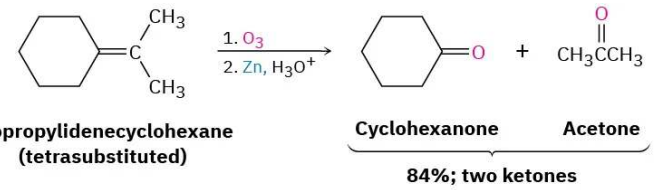
8.9: Oxidation of Alkenes - Cleavage to Carbonyl Compounds

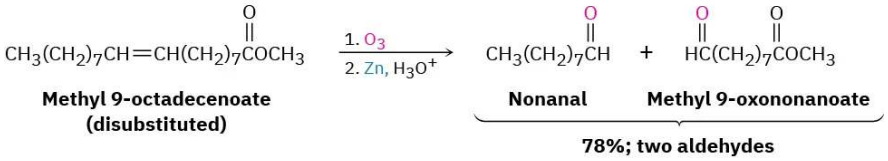
In all the alkene addition reactions we've seen thus far, the carbon–carbon double bond has been converted into a single bond but the carbon skeleton has been unchanged. There are, however, powerful oxidizing reagents that will cleave C=C bonds and produce two carbonyl-containing fragments.

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.

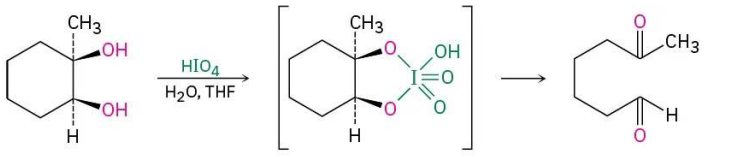




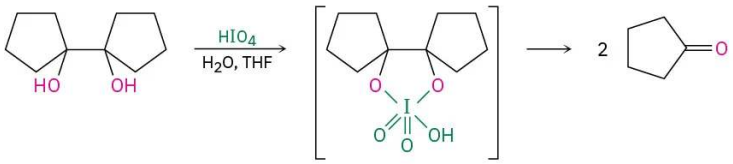
Several oxidizing reagents other than ozone also cause double-bond cleavage, although such reactions are not often used. For example, potassium permanganate ($KMnO_4$) in neutral or acidic solution cleaves alkenes to give carbonyl-containing products. If hydrogens are present on the double bond, carboxylic acids are produced; if two hydrogens are present on one carbon, CO_2 is formed.



In addition to direct cleavage with ozone or $KMnO_4$, an alkene can also be cleaved in a two-step process by initial hydroxylation to a 1,2-diol, as discussed in the previous section, followed by treatment of the diol with periodic acid, HIO_4. If the two −OH groups are in an open chain, two carbonyl compounds result. If the two −OH groups are on a ring, a single, open-chain dicarbonyl compound is formed. As indicated in the following examples, the cleavage reaction takes place through a cyclic periodate intermediate.



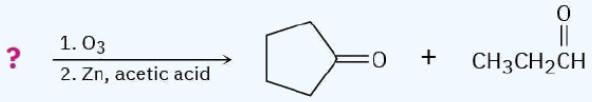
A 1,2-diol | **Cyclic periodate intermediate** | **6-Oxoheptanal (86%)**



A 1,2-diol | **Cyclic periodate intermediate** | **Cyclopentanone (81%)**

Worked Example 8.9.1: Predicting the Reactant in an Ozonolysis Reaction

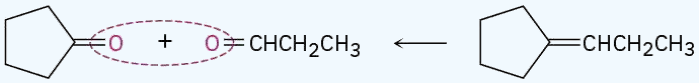
What alkene would yield a mixture of cyclopentanone and propanal on treatment with ozone followed by reduction with zinc?



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 8.9.1

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

a. $CH_3COCH_2CH_2CH_2CH_2CO_2H$
b. $CH_3COCH_2CH_2CH_2CH_2CHO$

Exercise 8.9.2

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

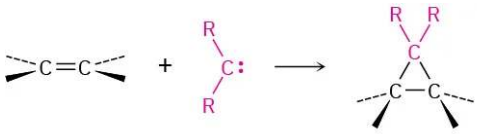
a. 2-Methylpropene
b. 3-Hexene

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8.10: 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.



An alkene **A carbene** **A cyclopropane**

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 8.10.1, the loss of a proton from $CHCl_3$ gives trichloromethanide anion, $^{-}$:CCl_2, which spontaneously expels a Cl^- ion to yield dichlorocarbene, :CCl_2.

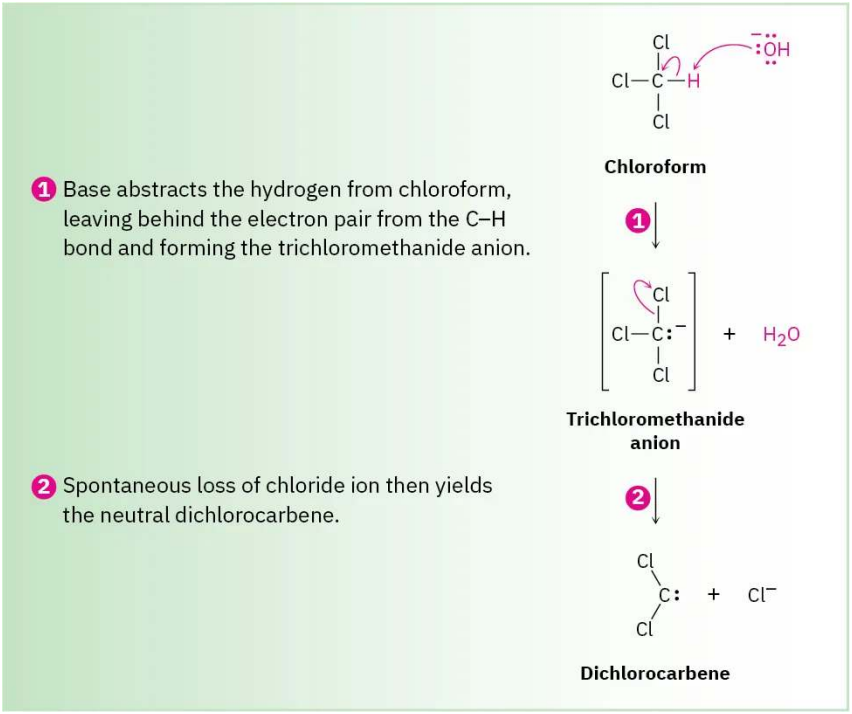


Figure 8.10.1: Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base. Deprotonation of CHCl3 gives the trichloromethanide anion, $^{-}$: CCl_2, which spontaneously expels a Cl^- ion.

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 8.10.2).

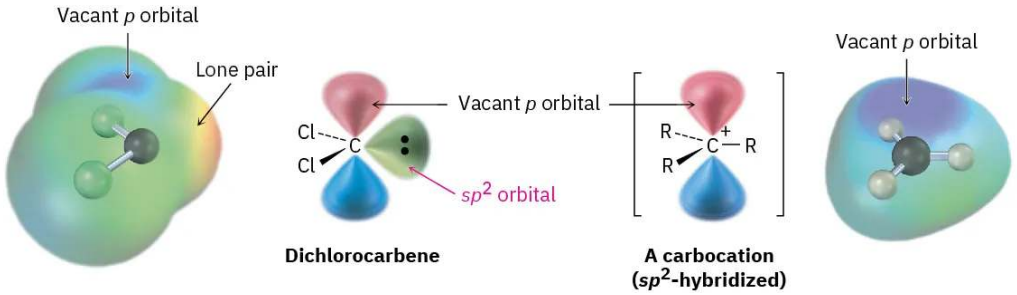
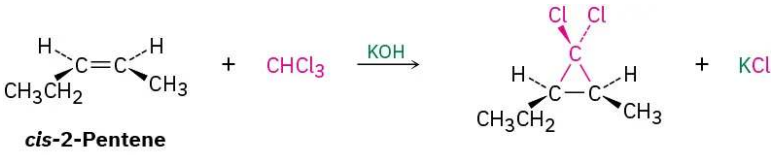
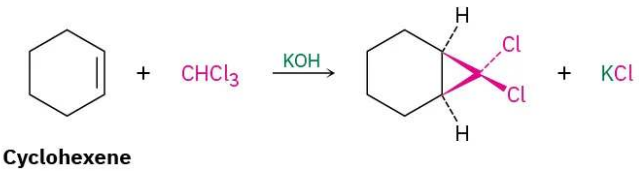


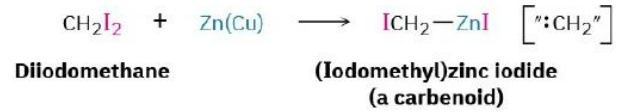
Figure 8.10.2: The structure of dichlorocarbene. Electrostatic potential maps show how **the positive region** coincides with the empty *p* orbital in both dichlorocarbene and a carbocation (CH_3^+). The **negative region** in the dichlorocarbene map coincides with the lone-pair electrons.

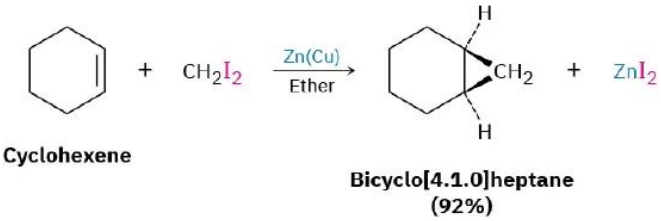
If dichlorocarbene is generated in the presence of an alkene, addition to the double bond occurs and a dichlorocyclopropane is formed. As the reaction of dichlorocarbene with *cis*-2-pentene demonstrates, the addition is stereospecific, meaning that only a single stereoisomer is formed as product. Starting from a cis alkene, for instance, only cis-disubstituted cyclopropane is produced; starting from a trans alkene, only trans-disubstituted cyclopropane is produced.





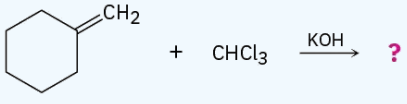
The best method for preparing nonhalogenated cyclopropanes is by a process called the Simmons–Smith reaction. First investigated at the DuPont company, this reaction does not involve a free carbene. Rather, it utilizes a *carbenoid*—a metal-complexed reagent with carbene-like reactivity. When diiodomethane 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.

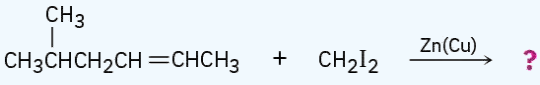




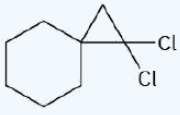
? Exercise 8.10.1

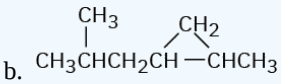
What products would you expect from the following reactions?

a. 

b. 

Answer

a. 

b. 

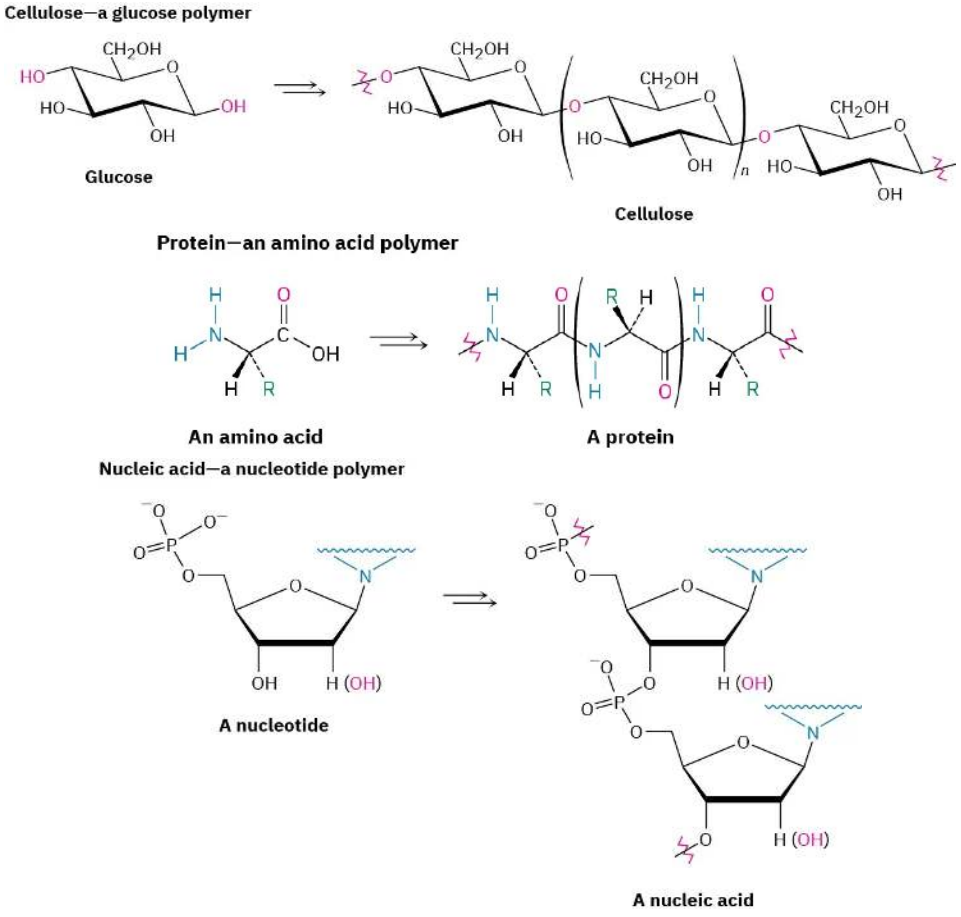
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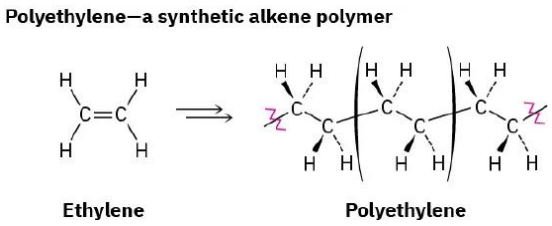
8.11: Radical Additions to Alkenes - Chain-Growth Polymers

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.

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.



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.

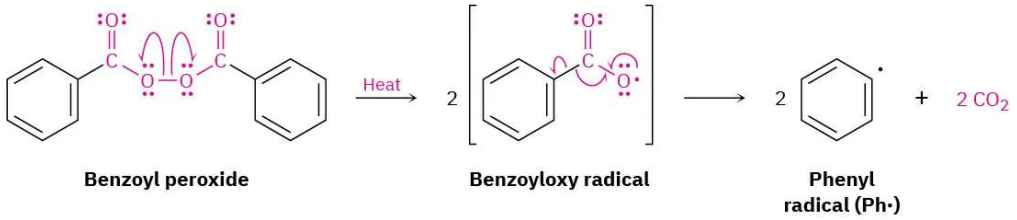


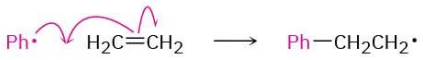
Polyethylene and other simple alkene polymers are called chain-growth polymers because they are formed in a chain-reaction process in which an initiator adds to a carbon–carbon double bond to yield a reactive intermediate. The intermediate then reacts

with a second molecule of monomer to yield a new intermediate, which reacts with a third monomer unit, and so on.

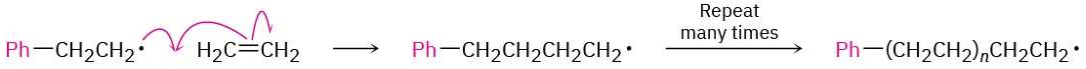
Historically, ethylene polymerization was carried out at high pressure (1000–3000 atm) and high temperature (100–250 °C) in the presence of a radical initiator such as benzoyl peroxide. Like many radical reactions, the mechanism of ethylene polymerization occurs in three steps: initiation, propagation, 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.





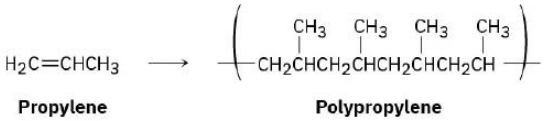
- **Propagation:** Polymerization occurs when the carbon radical formed in the initiation step adds to another ethylene molecule to yield another radical. Repetition of the process for hundreds or thousands of times builds the polymer chain.

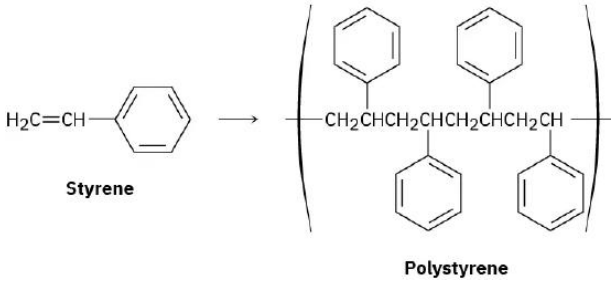


- **Termination:** The chain process is eventually ended by a reaction that consumes the radical. The combination of two growing chains is one possible chain-terminating reaction.

$$2R - CH_2CH_2\cdot \longrightarrow R - CH_2CH_2CH_2CH_2 - R$$

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.





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 ($RCH_2\cdot$) or a secondary radical ($R_2CH\cdot$). Just as in electrophilic addition reactions, however, we find that only the more highly substituted, secondary radical is formed.

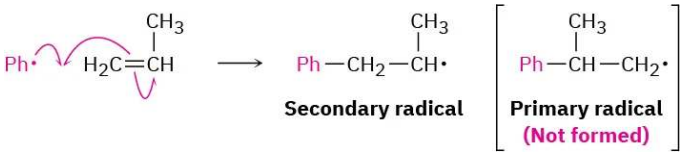


Figure 8.11.1 shows some commercially important alkene polymers, their uses, and the monomers from which they are made.

Figure 8.11.1: Some Alkene Polymers and Their Uses

Monomer	Formula	Trade or common name of polymer	Uses
Ethylene	\(\ce{H2C=CH2}\)	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
Methyl methacrylate	$H_2C{=}C(CH_3)CO_2CH_3$	Plexiglas, Lucite	Paint, sheets, moldings
Vinyl acetate	$H_2C{=}CHOCOCH_3$	Poly(vinyl acetate)	Paint, adhesives, foams

Worked Example 8.11.1: Predicting the Structure of a Polymer

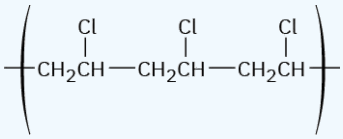
Show the structure of poly(vinyl chloride), a polymer made from $H_2C{=}CHCl$, by drawing several repeating units.

Strategy

Mentally break the carbon–carbon double bond in the monomer unit, and form single bonds by connecting numerous units together.

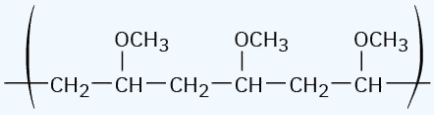
Solution

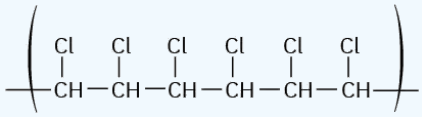
The general structure of poly(vinyl chloride) is



Exercise 8.11.1

Show the monomer units you would use to prepare the following polymers:

a. 

b. 

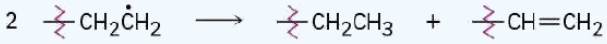
Answer

a. $H_2C{=}CHOCH_3$

b. $ClCH{=}CHCl$

Exercise 8.11.2

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



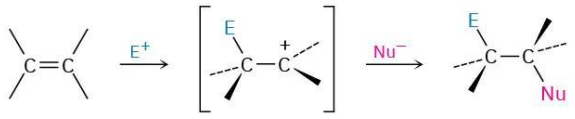
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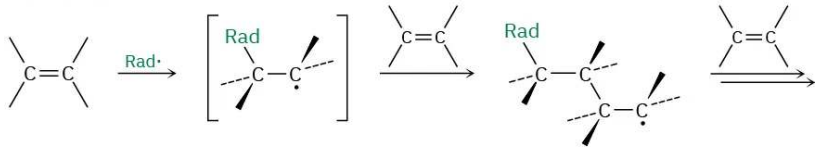
8.12: Biological Additions of Radicals to Alkenes

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 8.12.1, 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.

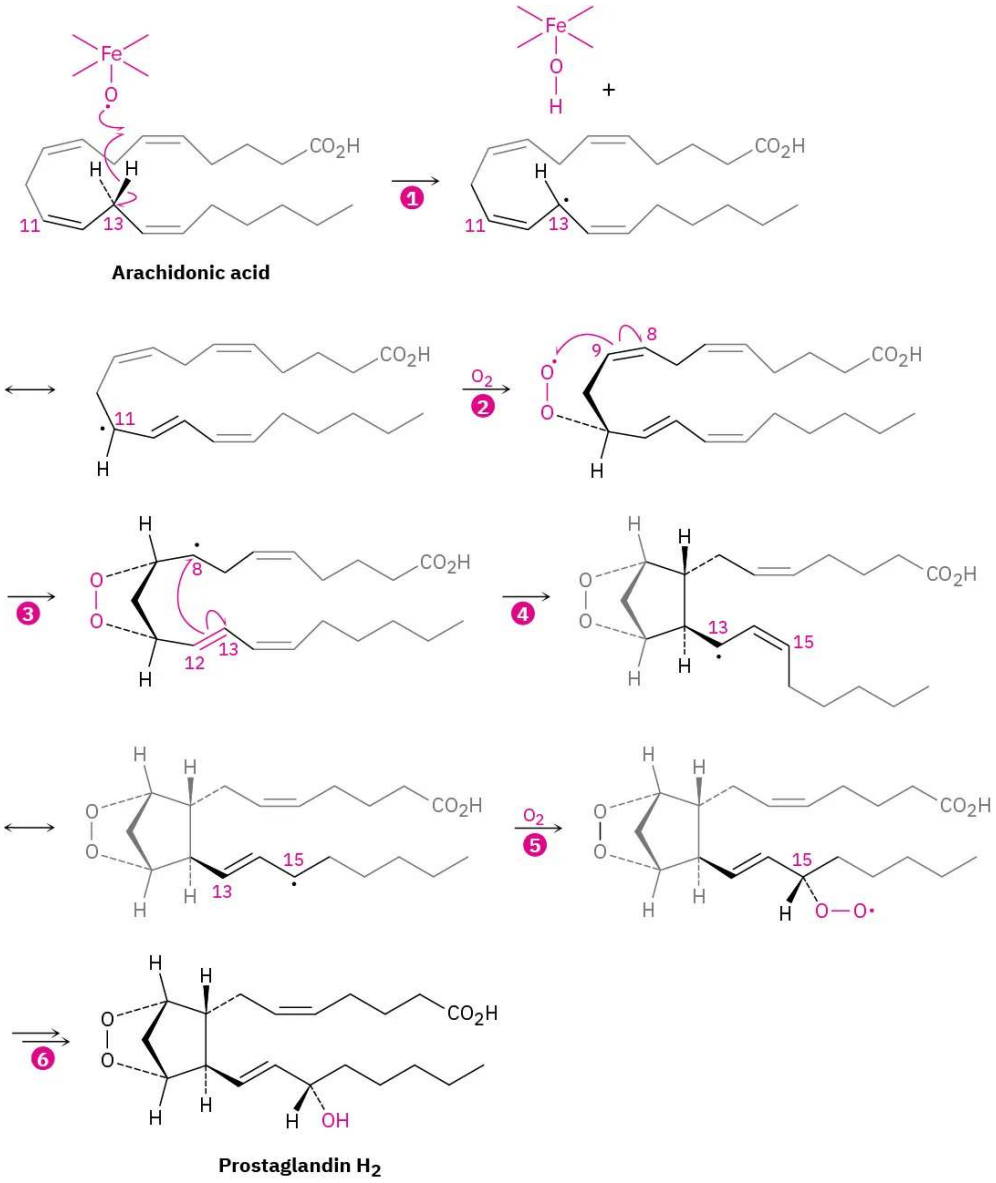


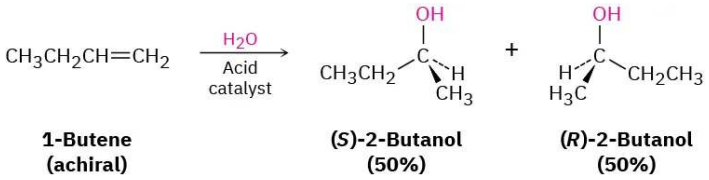
Figure 8.12.1: Pathway for the biosynthesis of prostaglandins from arachidonic acid. Steps **2** and **5** are radical addition reactions to O_2; steps **3** and **4** are radical additions to carbon–carbon double bonds.

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8.13: Stereochemistry of Reactions - Addition of H_2O to an Achiral Alkene

Most of the biochemical reactions that take place in the body, as well as many organic reactions in the laboratory, yield products with chirality 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 8.13.1, 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.

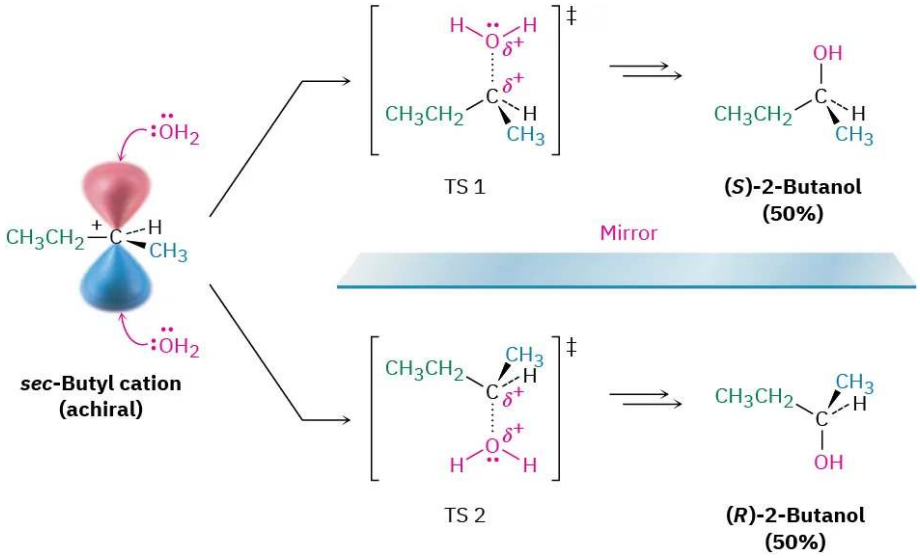
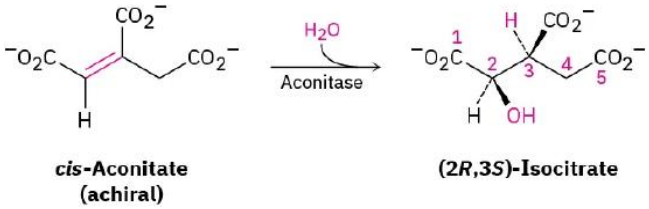


Figure 8.13.1: Reaction of H_2O with the carbocation resulting from protonation of 1-butene. Reaction from the top leads to *S* product and is the mirror image of reaction from the bottom, which leads to *R* product. Because they are energetically identical, they are equally likely and lead to a racemic mixture of products. The dotted C···O bond in the transition state indicates partial bond formation.

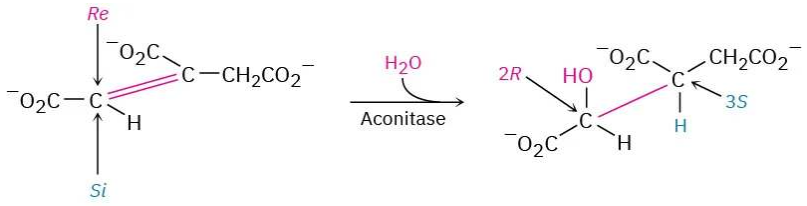
As a general rule, the formation of a new chirality center by achiral reactants always leads to a racemic mixture of enantiomeric products. Put another way, optical activity can't appear from nowhere; an optically active product can only result by starting with an optically active reactant or chiral environment (Section 5.13).

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 (usually called *cis*-aconitate) to give isocitrate.



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Even though *cis*-aconitate is achiral, only the (2*R*,3*S*) enantiomer of the product is formed. As discussed in Section 5.12 and Section 5.13, *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.



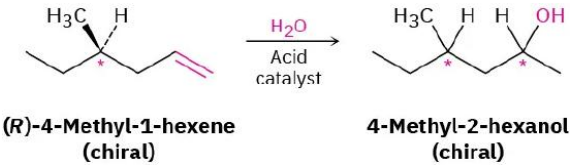
***cis*-Aconitate** **(2*R*,3*S*)-Isocitrate**

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8.14: Stereochemistry of Reactions - Addition of H_2O to a Chiral Alkene

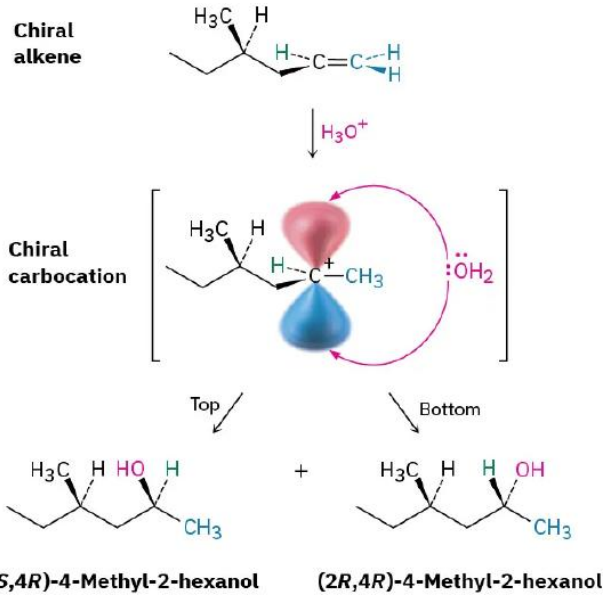
The reaction discussed in the previous section involves an addition to an achiral reactant and forms an optically inactive, racemic mixture of two enantiomeric products. What would happen, though, if we were to carry out the reaction on a single enantiomer of a chiral reactant? For example, what stereochemical result would be obtained from 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 chirality centers and so has 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).

What about the configuration at C2, the newly formed chirality center? As shown in Figure 8.14.1, 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 (2*S*,4*R*)-4-methyl-2-hexanol, are formed in unequal amounts, and the mixture is optically active.



(2*S*,4*R*)-4-Methyl-2-hexanol **(2*R*,4*R*)-4-Methyl-2-hexanol**

Figure 8.14.1: 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 2*S*,4*R* products is formed in unequal amounts because reaction of the chiral carbocation intermediate is not equally likely from top and bottom. The product 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.

Exercise 8.14.1

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

An optically inactive, non-50 : 50 mixture of two racemic pairs: (2*R*,4*R*) + (2*S*,4*S*) and (2*R*,4*S*) + (2*S*,4*R*)

Exercise 8.14.2

What products are formed from hydration of 4-methylcyclopentene? What can you say about the relative amounts of the products?

Answer

Non-50 : 50 mixture of two racemic pairs: (1*S*,3*R*) + (1*R*,3*S*) and (1*S*,3*S*) + (1*R*,3*R*)

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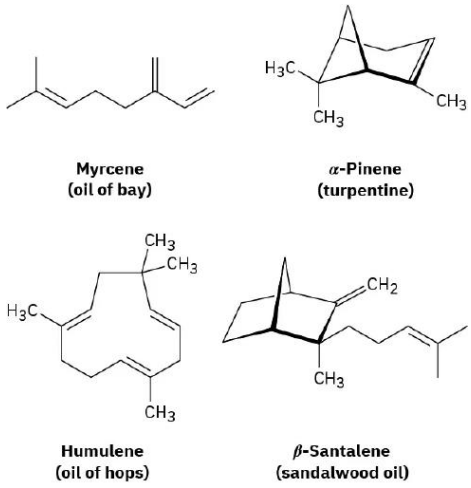
8.15: Chemistry Matters—Terpenes- Naturally Occurring Alkenes

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.

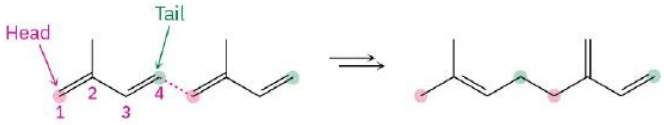


Figure 8.15.1: The wonderful fragrance of leaves from the California bay laurel is due primarily to myrcene, a simple terpene. (credit: "California Bay Umbellularia californica" by Don Loaire/Flickr, CC BY 2.0)

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:

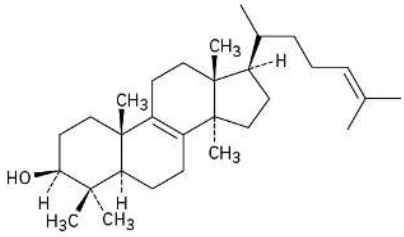


Regardless of their apparent structural differences, all terpenoids are related. According to a formalism called the isoprene rule, they can be thought of as arising from head-to-tail joining of 5-carbon isoprene units (2-methyl-1,3-butadiene). Carbon 1 is the head of the isoprene unit, and carbon 4 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.



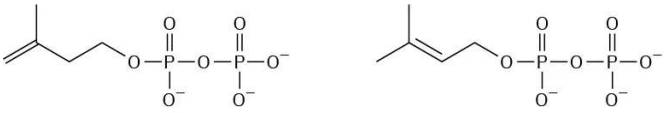
Two isoprene units **Myrcene**

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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8.16: Key Terms

- anti stereochemistry
- bromonium ion
- carbene, R_2C
- chain-growth polymer
- epoxide
- glycol
- halohydrin
- hydroboration
- hydrogenated
- hydroxylation
- monomer
- oxidation
- oxirane
- oxymercuration–demercuration
- ozonide
- polymer
- reduction
- Simmons–Smith reaction
- stereospecific
- syn stereochemistry

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8.17: Summary

With the background needed to understand organic reactions now covered, this chapter has begun the systematic description of major functional groups.

Alkenes are generally prepared by an elimination reaction, such as dehydrohalogenation, the elimination of HX from an alkyl halide, or dehydration, the elimination of water from an alcohol. The converse of this elimination reaction is the addition of various substances to the alkene double bond to give saturated products.

HCl, HBr, and HI add to alkenes by a two-step electrophilic addition mechanism. Initial reaction of the nucleophilic double bond with H^+ gives a carbocation intermediate, which then reacts with halide ion. Bromine and chlorine add to alkenes via three-membered-ring **bromonium ion** or chloronium ion intermediates to give addition products having **anti stereochemistry**. If water is present during the halogen addition reaction, a **halohydrin** is formed.

Hydration of an alkene—the addition of water—is carried out by either of two procedures, depending on the product desired. **Oxymercuration–demercuration** involves electrophilic addition of Hg^{2+} to an alkene, followed by trapping of the cation intermediate with water and subsequent treatment with $NaBH_4$. **Hydroboration** involves addition of borane (BH_3) followed by oxidation of the intermediate organoborane with alkaline H_2O_2. The two hydration methods are complementary: oxymercuration–demercuration gives the product of Markovnikov addition, whereas hydroboration–oxidation gives the product with non-Markovnikov **syn stereochemistry**.

Alkenes are **reduced** by addition of H_2 in the presence of a catalyst such as platinum or palladium to yield alkanes, a process called catalytic **hydrogenation**. Alkenes are also **oxidized** by reaction with a peroxyacid to give **epoxides**, which can be converted into trans-1,2-diols by acid-catalyzed hydrolysis. The corresponding cis-1,2-diols can be made directly from alkenes by **hydroxylation** with OsO_4. Alkenes can also be cleaved to produce carbonyl compounds by reaction with ozone, followed by reduction with zinc metal. In addition, alkenes react with divalent substances called **carbenes, R_2C:**, to give cyclopropanes. Nonhalogenated cyclopropanes are best prepared by treatment of the alkene with CH_2I_2 and zinc–copper, a process called the **Simmons–Smith reaction**.

Alkene **polymers**—large molecules resulting from repetitive bonding of many hundreds or thousands of small **monomer** units—are formed by chain-reaction polymerization of simple alkenes. Polyethylene, polypropylene, and polystyrene are examples. As a general rule, radical addition reactions are not common in the laboratory but occur frequently in biological pathways.

Many reactions give chiral products. If the reactants are optically inactive, the products are also optically inactive. If one or both of the reactants is optically active, the products can also be optically active.

Learning Reactions

What's seven times nine? Sixty-three, of course. You didn't have to stop and figure it out; you knew the answer immediately because you long ago learned the multiplication tables. Learning the reactions of organic chemistry requires the same approach: reactions have to be learned for quick recall if they are to be useful.

Different people take different approaches to learning reactions. Some people make flashcards; others find studying with friends to be helpful. To help guide your study, most chapters in this book end with a summary of the reactions just presented. In addition, the accompanying *Study Guide and Student Solutions Manual* has several appendixes that organize organic reactions from other perspectives. Fundamentally, though, there are no shortcuts. Learning organic chemistry does take effort.

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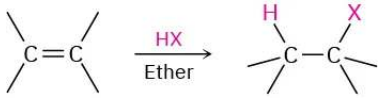
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8.18: Summary of Reactions

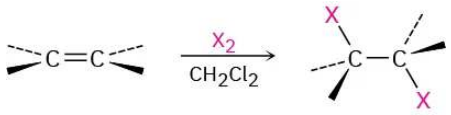
No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.

1. Addition reactions of alkenes

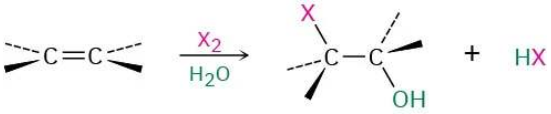
   a. Addition of HCl, HBr, and HI (Section 7.8 and Section 7.9)
   Markovnikov regiochemistry occurs, with H adding to the less highly substituted alkene carbon and halogen adding to the more highly substituted carbon.



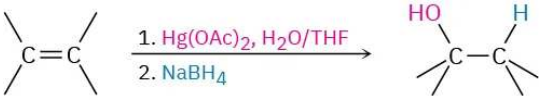
- Addition of halogens Cl_2 and Br_2 (Section 8.3)
  Anti addition is observed through a halonium ion intermediate.



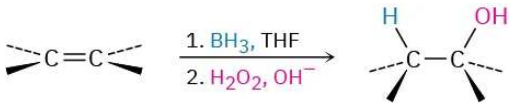
- Halohydrin formation (Section 8.4)
  Markovnikov regiochemistry and anti stereochemistry occur.



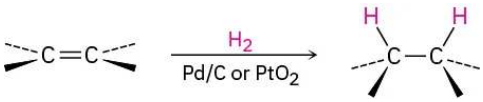
- Addition of water by oxymercuration–demercuration (Section 8.5)
  Markovnikov regiochemistry occurs.



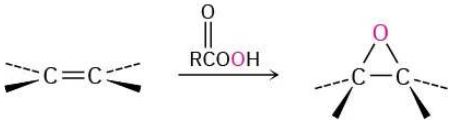
- Addition of water by hydroboration–oxidation (Section 8.6)
  Non-Markovnikov syn addition occurs.



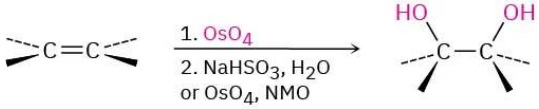
- Catalytic hydrogenation (Section 8.7)
  Syn addition occurs.



- Epoxidation with a peroxyacid (Section 8.8)
  Syn addition occurs.



- Hydroxylation with OsO_4 (Section 8.8)
  Syn addition occurs.

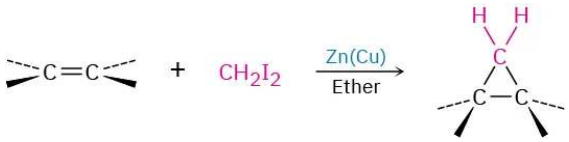


- Addition of carbenes to yield cyclopropanes (Section 8.10)

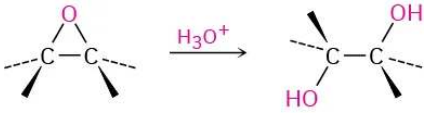
  (1) Dichlorocarbene addition



(2) Simmons–Smith reaction

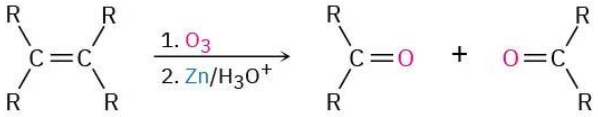


- Hydroxylation by acid-catalyzed epoxide hydrolysis (Section 8.8)
  Anti stereochemistry occurs.

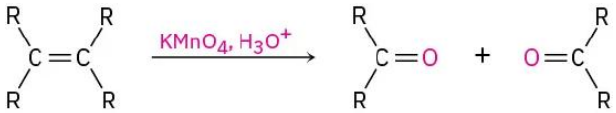


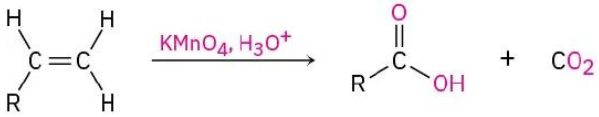
- Oxidative cleavage of alkenes (Section 8.9)

  a. Reaction with ozone followed by zinc in acetic acid

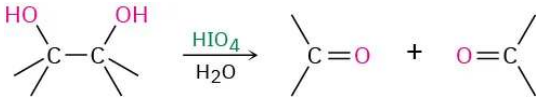


  b. Reaction with $KMnO_4$ in acidic solution





- Cleavage of 1,2-diols (Section 8.9)



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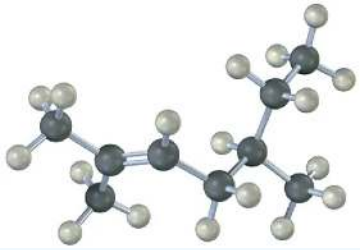
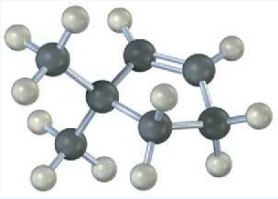
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8.19: Additional Problems

Visualizing Chemistry

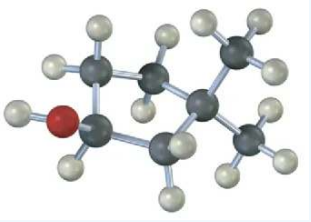
Exercise 8.19.22

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) 

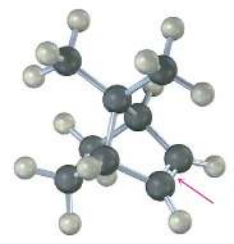
Exercise 8.19.23

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) 

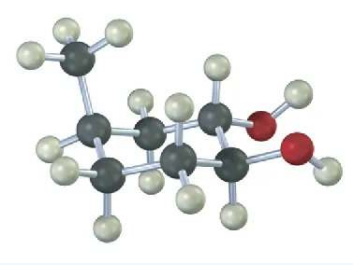
Exercise 8.19.24

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.



Exercise 8.19.25

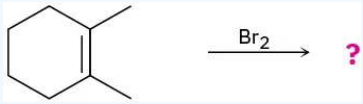
From what alkene was the following 1,2-diol made, and what method was used, epoxide hydrolysis or OsO_4?

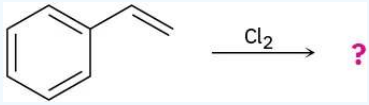


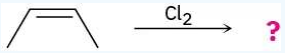
Mechanism Problems

? Exercise 8.19.26

Predict the products for the following reactions, showing the complete mechanism and appropriate stereochemistry:

(a) 

(b) 

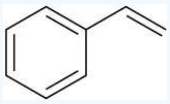
(c) 

? Exercise 8.19.27

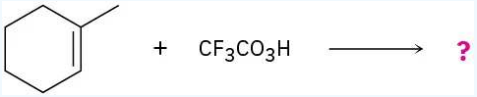
Draw the structures of the organoboranes formed when borane reacts with the following alkenes, including the regiochemistry and stereochemistry as appropriate. Propose a mechanism for each reaction.

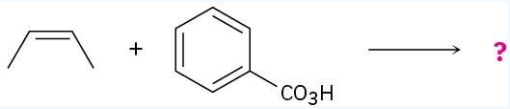
(a) 

(b) 

(c) 

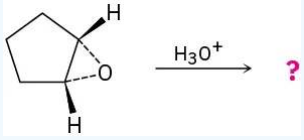
? Exercise 8.19.28

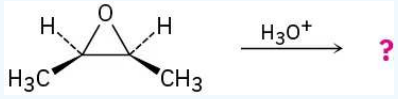
meta-Chlorobenzoic acid is not the only peroxyacid capable of epoxide formation. For each reaction below, predict the products and show the mechanism. (a) 

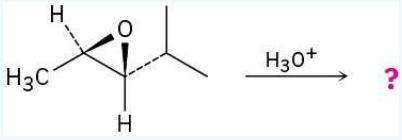
(b) 

? Exercise 8.19.29

Give the mechanism and products for the following acid-catalyzed epoxide-opening reactions, including appropriate stereochemistry.

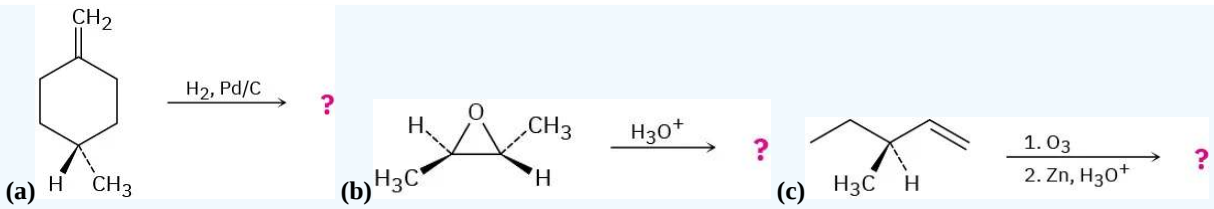
(a) 

(b) 

(c) 

? Exercise 8.19.30

Which of the reactions below would result in a product mixture that would rotate plane-polarized light?



? Exercise 8.19.31

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.

? Exercise 8.19.32

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: $CH_3CH_2CH{=}CH_2 + I{-}N{=}N{=}N \longrightarrow CH_3CH_2\underset{\displaystyle N{=}N{=}N}{\underset{|}{C}}HCH_2I$

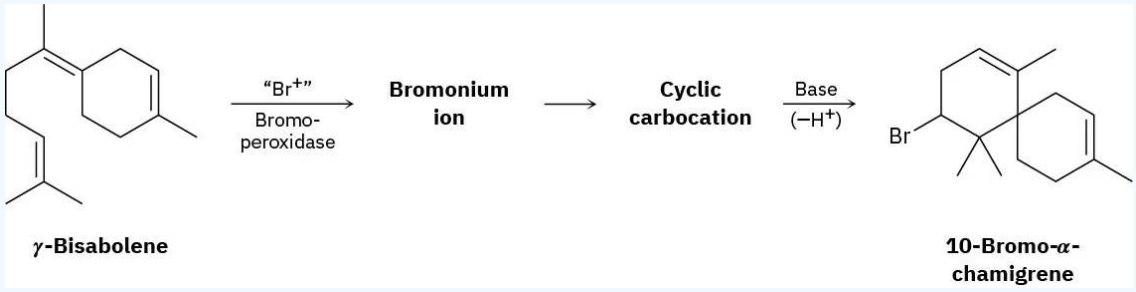
(a) Add lone-pair electrons to the structure shown for IN_3, and draw a second resonance form for the molecule.

(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.

? Exercise 8.19.33

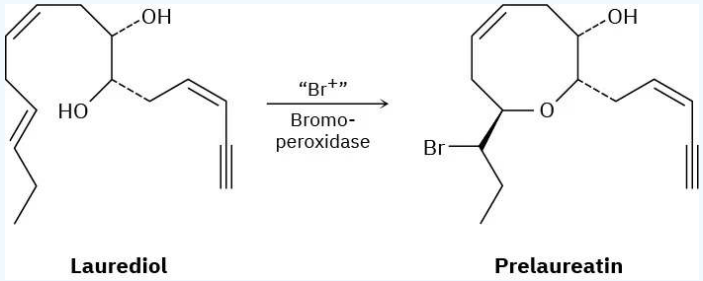
10-Bromo-α-chamigrene, a compound isolated from marine algae, is thought to be biosynthesized from γ-bisabolene by the following route:



Draw the structures of the intermediate bromonium and cyclic carbocation, and propose mechanisms for all three steps.

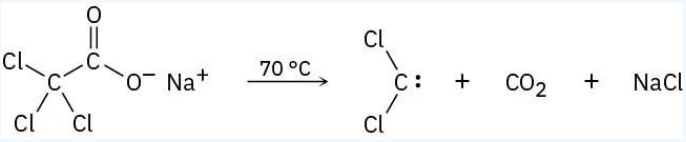
? Exercise 8.19.34

Isolated from marine algae, prelaureatin is thought to be biosynthesized from laurediol by the following route. Propose a mechanism.



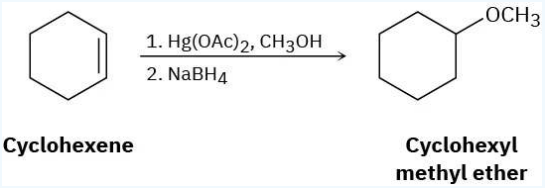
Exercise 8.19.35

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?



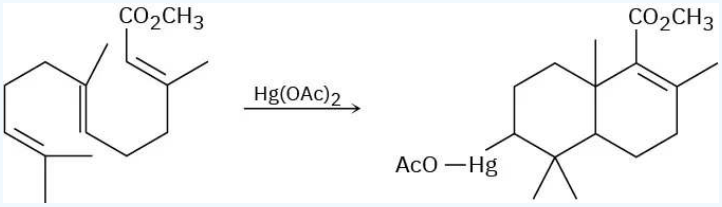
Exercise 8.19.36

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.



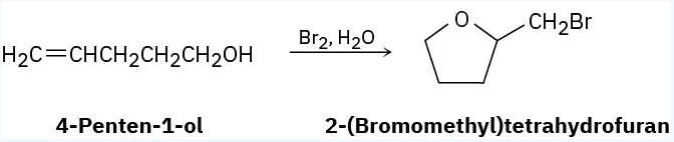
Exercise 8.19.37

Use your general knowledge of alkene chemistry to suggest a mechanism for the following reaction.



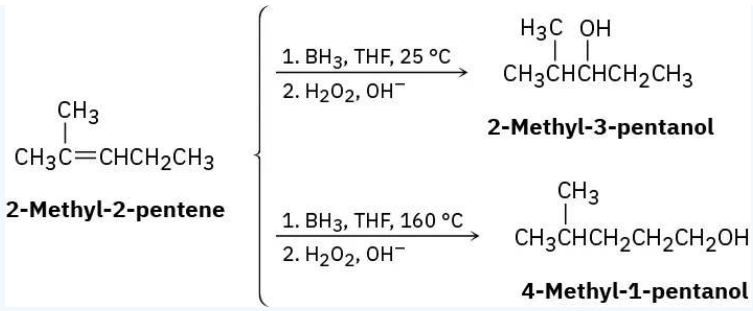
Exercise 8.19.38

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.



Exercise 8.19.39

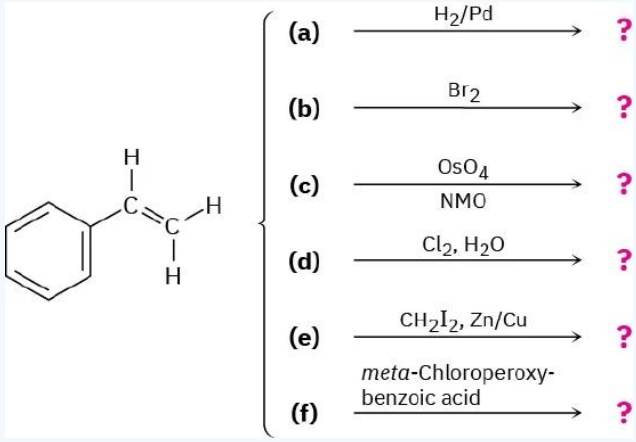
Hydroboration of 2-methyl-2-pentene at 25 °C, followed by oxidation with alkaline H_2O_2, yields 2-methyl-3-pentanol, but hydroboration at 160 °C followed by oxidation yields 4-methyl-1-pentanol. Suggest a mechanism.



Reactions of Alkenes

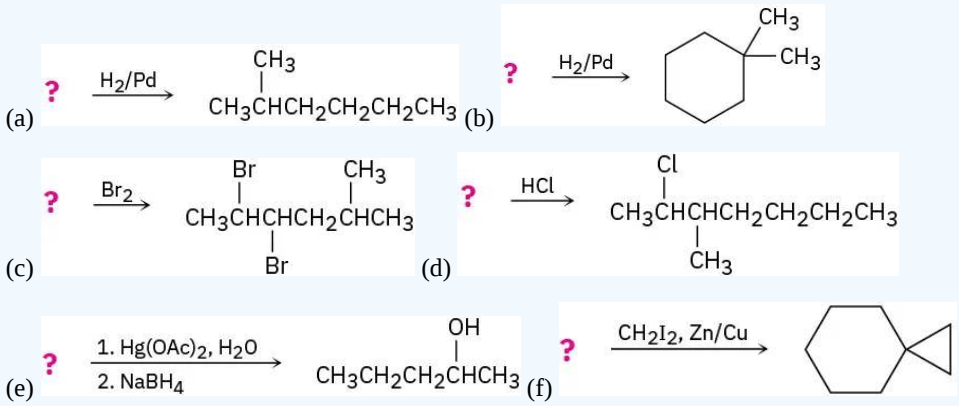
? Exercise 8.19.40

Predict the products of the following reactions (the aromatic ring is unreactive in all cases). Indicate regiochemistry when relevant.



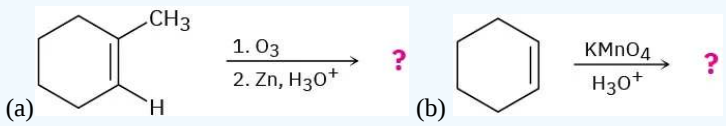
? Exercise 8.19.41

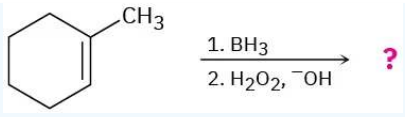
Suggest structures for alkenes that give the following reaction products. There may be more than one answer for some cases.

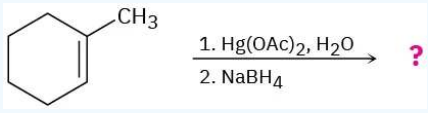


? Exercise 8.19.42

Predict the products of the following reactions, showing both regiochemistry and stereochemistry where appropriate:



(c) 

(d) 

? Exercise 8.19.43

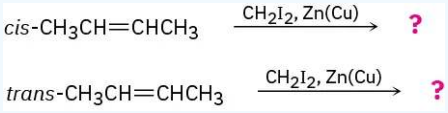
Which reaction would you expect to be faster, addition of HBr to cyclohexene or to 1-methylcyclohexene? Explain.

? Exercise 8.19.44

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.

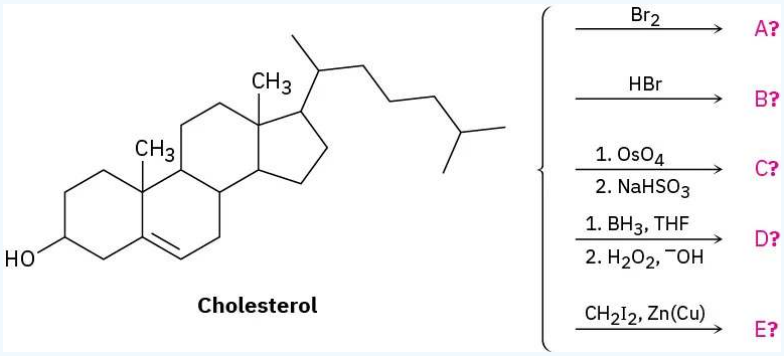
? Exercise 8.19.45

The cis and trans isomers of 2-butene give different cyclopropane products in the Simmons–Smith reaction. Show the structures of both, and explain the difference.



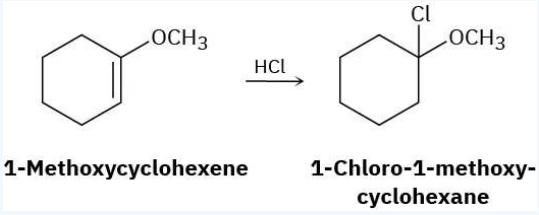
? Exercise 8.19.46

Predict the products of the following reactions. Don't worry about the size of the molecule; concentrate on the functional groups.



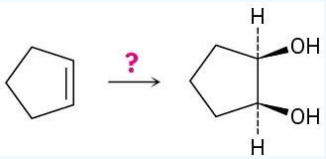
? Exercise 8.19.47

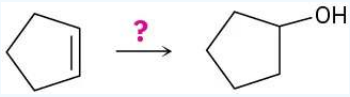
Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as a sole product. Use resonance structures of the carbocation intermediate to explain why none of the alternate regioisomer is formed.

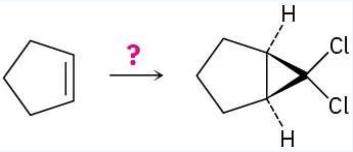


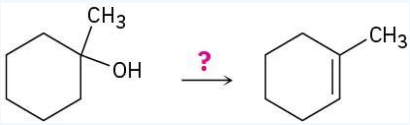
Synthesis Using Alkenes

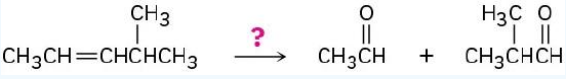
Exercise 8.19.48

(a) 

(b) 

(c) 

(d) 

(e) 

(f) 

Exercise 8.19.49

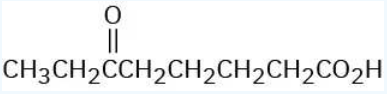
Draw the structure of an alkene that yields only acetone, $(CH_3)_2C{=}O$, on ozonolysis followed by treatment with Zn.

Exercise 8.19.50

(a) $CH_3CH_2CO_2H + CO_2$

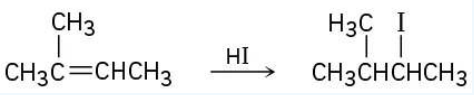
(b) $(CH_3)_2C{=}O + CH_3CH_2CH_2CO_2H$

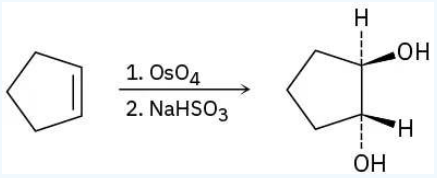
(c) 

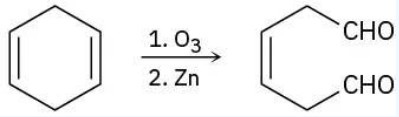
(d) 

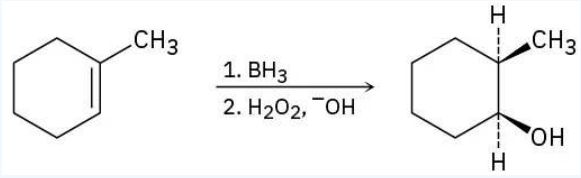
Exercise 8.19.51

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 to them. Explain the potential problems of each.

(a) 

(b) 

(c) 

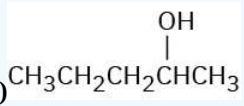
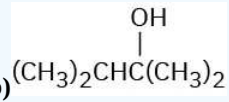
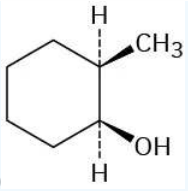
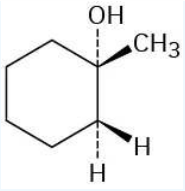
(d) 

Exercise 8.19.52

Problem 8-52

Which of the following alcohols could not be made selectively by hydroboration–oxidation of an alkene? Explain.

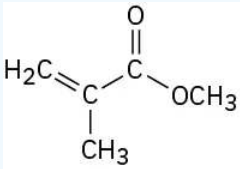
https://chem.libretexts.org/@go/page/564062

(a)  (b)  (c)  (d) 

Polymers

? Exercise 8.19.53

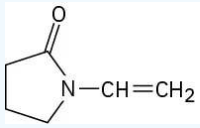
Plexiglas, a clear plastic used to make many molded articles, is made by polymerization of methyl methacrylate. Draw a representative segment of Plexiglas.



Methyl methacrylate

? Exercise 8.19.54

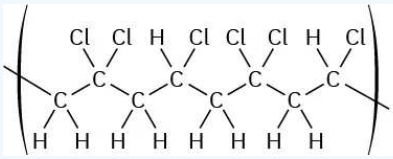
Poly(vinyl pyrrolidone), prepared from *N*-vinylpyrrolidone, is used both in cosmetics and as a component of a synthetic substitute for blood. Draw a representative segment of the polymer.



***N*-Vinylpyrrolidone**

? Exercise 8.19.55

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

? Exercise 8.19.56

$10H_{16}$. 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** ($C_{10}H_{16}O_2$). (a) How many rings does **A** have?

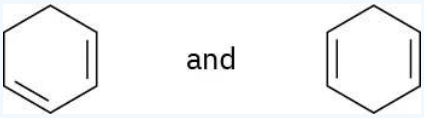
(b) What are the structures of **A** and **B**? (c) Write the reactions.

? Exercise 8.19.57

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.

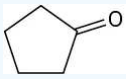
Exercise 8.19.58

Using an oxidative cleavage reaction, explain how you would distinguish between the following two isomeric dienes:



Exercise 8.19.59

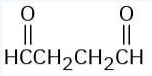
Compound **A**, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 50 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, **B**, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Identify **A** and **B**, and write the reactions.



Cyclopentanone

Exercise 8.19.60

Draw the structure of a hydrocarbon that absorbs 2 molar equivalents of H_2 on catalytic hydrogenation and gives only butanedial on ozonolysis.



Butanedial

Exercise 8.19.61

Simmons–Smith reaction of cyclohexene with diiodomethane gives a single cyclopropane product, but the analogous reaction of cyclohexene with 1,1-diiodoethane gives (in low yield) a mixture of two isomeric methylcyclopropane products. What are the two products, and how do they differ?

Exercise 8.19.62

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.

Exercise 8.19.63

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.

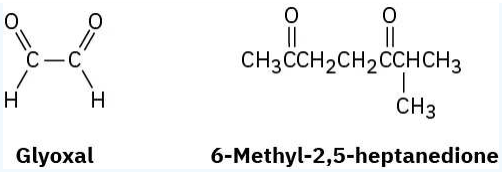
Exercise 8.19.64

(a) Cyclopentene and cyclopentane

(b) 2-Hexene and benzene

Exercise 8.19.65

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.



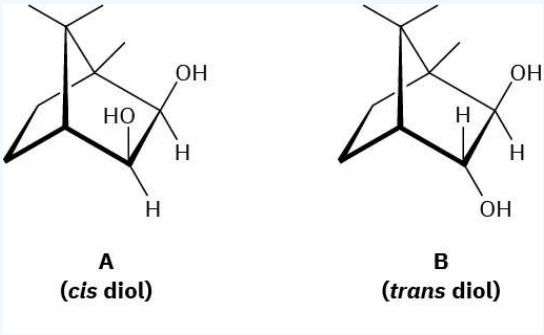
(a) How many degrees of unsaturation does α-terpinene have?

(b) How many double bonds and how many rings does it have?

(c) Propose a structure for α-terpinene.

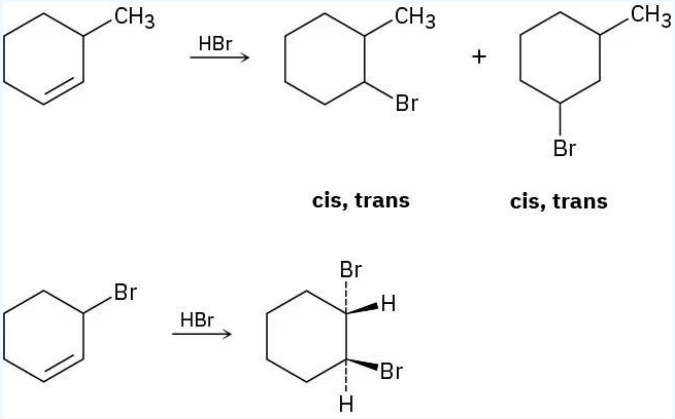
Exercise 8.19.66

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.



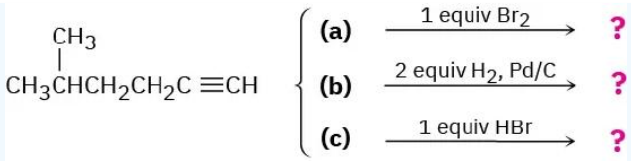
Exercise 8.19.67

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.



Exercise 8.19.68

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?



? Exercise 8.19.69

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.

? Exercise 8.19.70

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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CHAPTER OVERVIEW

9: Alkynes - An Introduction to Organic Synthesis

Learning Objectives

After you have completed Chapter 9, you should be able to

1. fulfillall of the detailed objectives listed under each individual section.
2. solve road-map problems involving any of the reactions introduced to this point.
3. design multistep syntheses using any of the reactions introduced to this point, and determine the viability of a given synthesis.
4. define, and use in context, the key terms introduced.

Addition reactions not only dominate the chemistry of alkenes, they are also the major class of reaction you will encounter. This chapter discusses an important difference between (terminal) alkynes and alkenes, that is, the acidity of the former; it also addresses the problem of devising organic syntheses. Once you have completed this chapter you will have increased the number of organic reactions in your repertoire, and should be able to design much more elaborate multistep syntheses. As you work through Chapter 9, you should notice the many similarities among the reactions described here and those in Chapters 7 and 8.

9.1: Why This Chapter?
9.2: Naming Alkynes
9.3: Preparation of Alkynes - Elimination Reactions of Dihalides
9.4: Reactions of Alkynes - Addition of HX and X_2
9.5: Hydration of Alkynes
9.6: Reduction of Alkynes
9.7: Oxidative Cleavage of Alkynes
9.8: Alkyne Acidity - Formation of Acetylide Anions
9.9: Alkylation of Acetylide Anions
9.10: An Introduction to Organic Synthesis
9.11: Chemistry Matters - The Art of Organic Synthesis
9.12: Key Terms
9.13: Summary
9.14: Summary of Reactions
9.15: Additional Problems

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9.1: Why This Chapter?

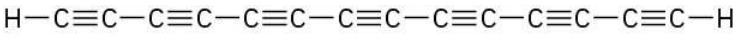
Alkynes are less common than alkenes, both in the laboratory and in living organisms, so we won't cover them in great detail. The real importance of this chapter is that we'll use alkyne chemistry as a vehicle to begin looking at some of the general strategies used in organic synthesis—the construction 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 9.1.1: 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, H–C≡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.



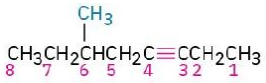
A polyyne detected in interstellar space

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9.2: Naming Alkynes

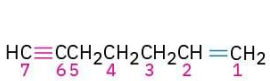
Alkyne nomenclature follows the general rules for hydrocarbons discussed in Section 3.4 and Section 7.3. The suffix *-yne* is used, and the position of the triple bond is indicated by giving the number of the first alkyne carbon in the chain. Numbering the main chain begins at the end nearer the triple bond so that the triple bond receives as low a number as possible.



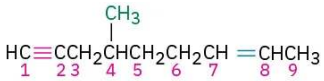
Begin numbering at the end nearer the triple bond.

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:

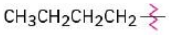


1-Hepten-6-yne
(New: Hept-1-en-6-yne)

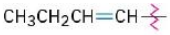


4-Methyl-7-nonen-1-yne
(New: 4-Methylnon-7-en-1-yne)

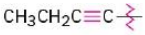
As with alkyl and alkenyl substituents derived from alkanes and alkenes, respectively, alkynyl groups are also possible.



Butyl
(an alkyl group)



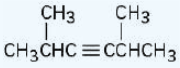
1-Butenyl
(a vinylic group)
(New: But-1-enyl)

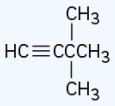


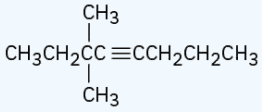
1-Butynyl
(an alkynyl group)
(New: But-1-ynyl)

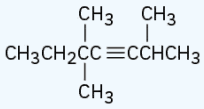
Exercise 9.2.1

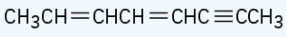
Name the following alkynes:

a. 

b. 

c. 

d. 

e. 

Answer

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 9.2.2

There are seven isomeric alkynes with the formula C_6H_{10}. Draw and name them.

Answer

1-Hexyne, 2-hexyne, 3-hexyne, 3-methyl-1-pentyne, 4-methyl-1-pentyne, 4-methyl-2-pentyne, 3,3-dimethyl-1-butyne

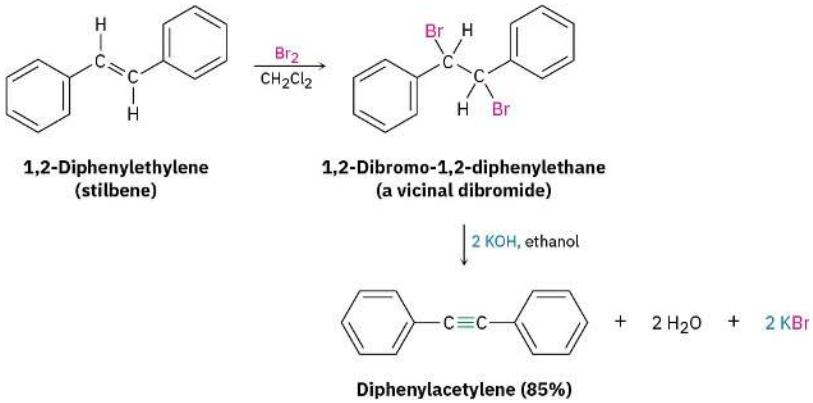
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9.3: Preparation of Alkynes - Elimination Reactions of Dihalides

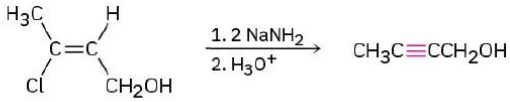
Alkynes can be prepared by the elimination of HX from alkyl halides in a similar manner as alkenes (Section 8.1). Treatment of a 1,2-dihaloalkane (called a *vicinal* dihalide) with an excess amount of a strong base such as KOH or $NaNH_2$ results in a twofold elimination of HX and formation of an alkyne. 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.



1,2-Diphenylethylene (stilbene) → **1,2-Dibromo-1,2-diphenylethane (a vicinal dibromide)** → **Diphenylacetylene (85%)**

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:



(*Z*)-3-Chloro-2-buten-1-ol → **2-Butyn-1-ol**

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9.4: 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 H−C≡C bond angles of 180° (Figure 9.4.1). The length of the C≡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.

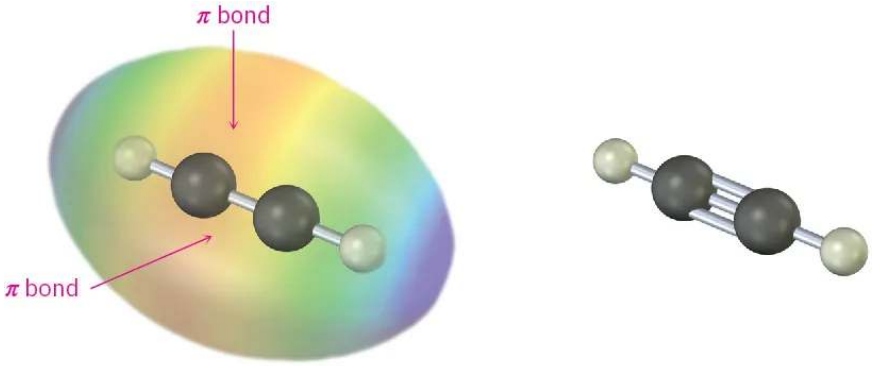
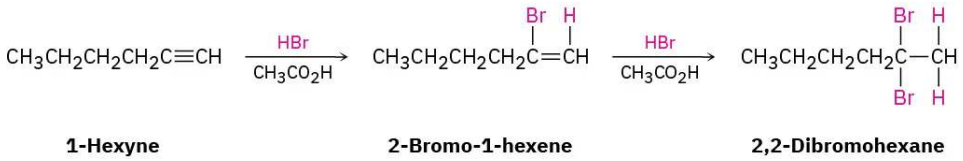


Figure 9.4.1: The structure of acetylene, H−C≡C−H. The H−C≡C bond angles are 180°, and the C≡C bond length is 120 pm. The electrostatic potential map shows that the π bonds create a negative belt around the molecule.

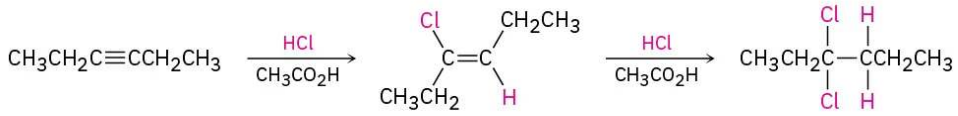
As a general rule, electrophiles undergo addition reactions with alkynes much as they do with alkenes. Take the reaction of alkynes with HX, for instance. The reaction often can be stopped with the addition of 1 equivalent of HX, but reaction with an excess of HX leads to a dihalide product. For example, 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**

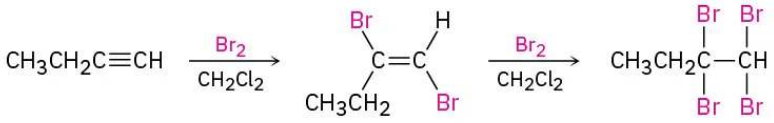
HCl addition



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.

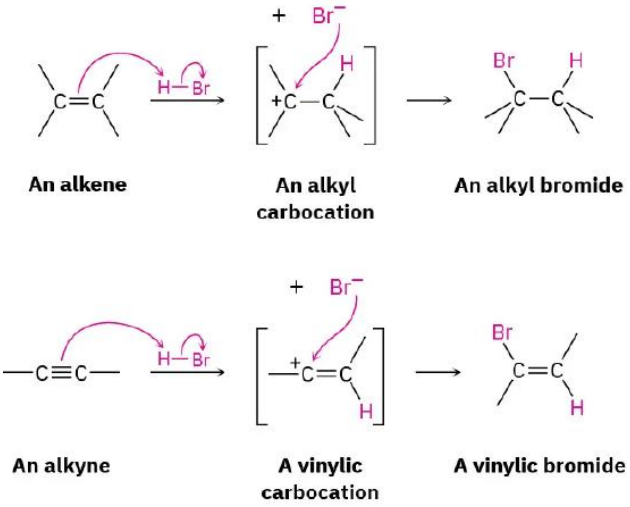
Br_2 addition



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 9.4.2). 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.

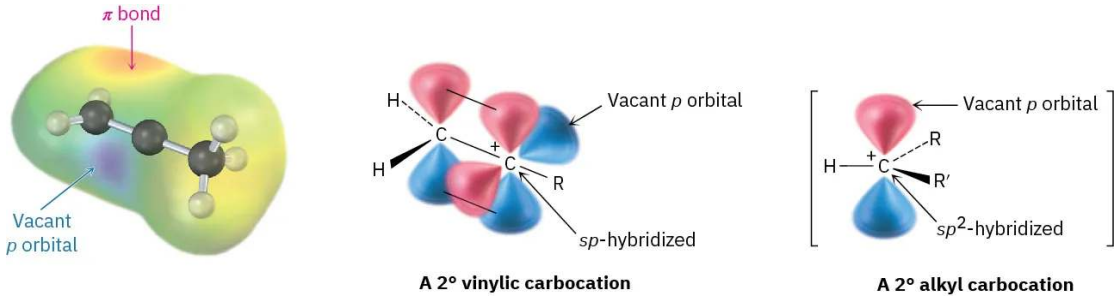
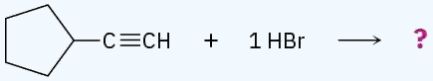


Figure 9.4.2: The structure of a secondary vinylic carbocation. The cationic carbon atom is *sp*-hybridized and has a vacant *p* orbital perpendicular to the plane of the π bond orbitals. Only one R group is attached to the positively charged carbon rather than two, as in a secondary alkyl carbocation. 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 9.4.1

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

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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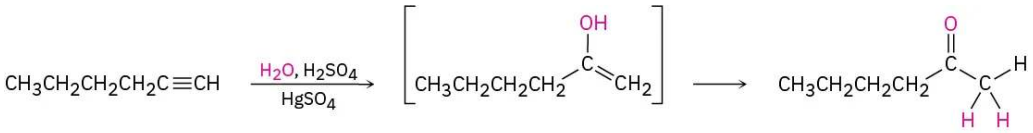
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9.5: Hydration of Alkynes

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.

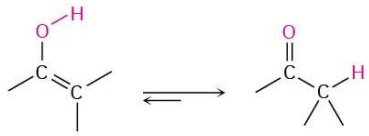
Mercury(II)-Catalyzed Hydration of Alkynes

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 9.5.1, 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.

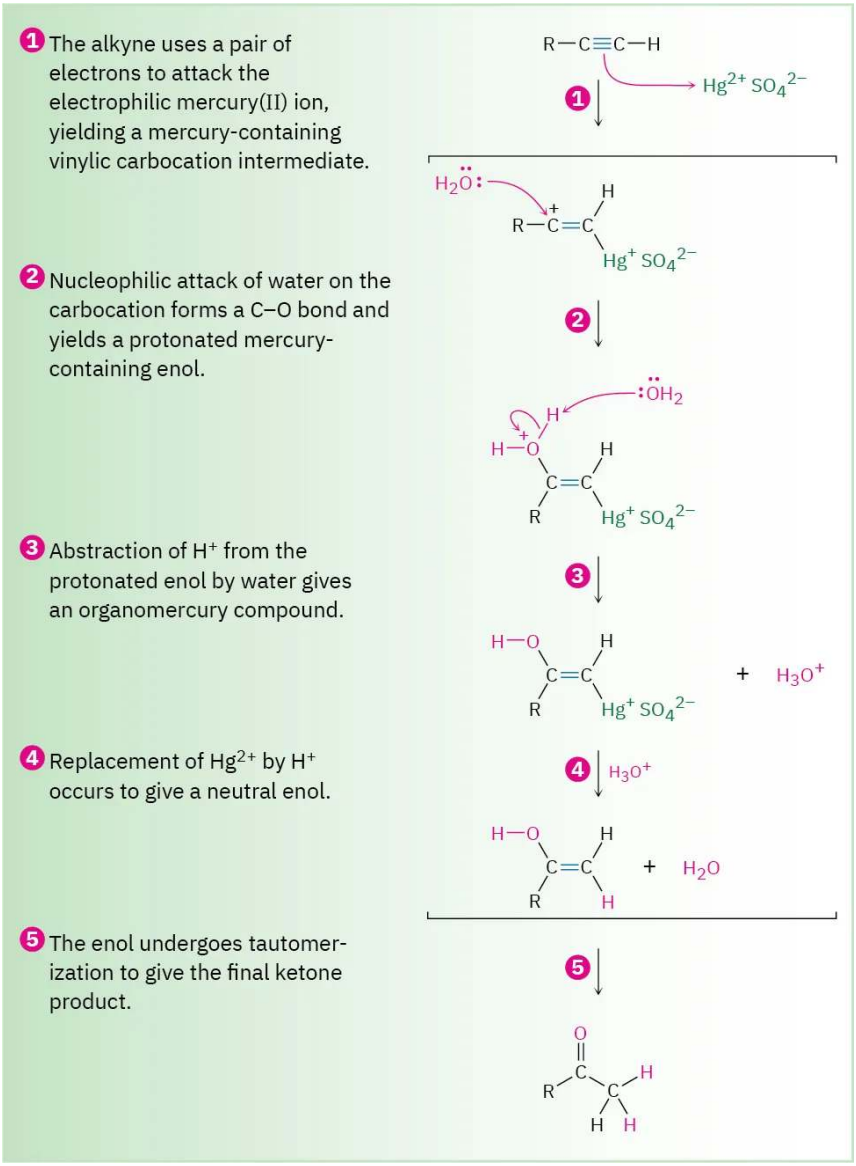
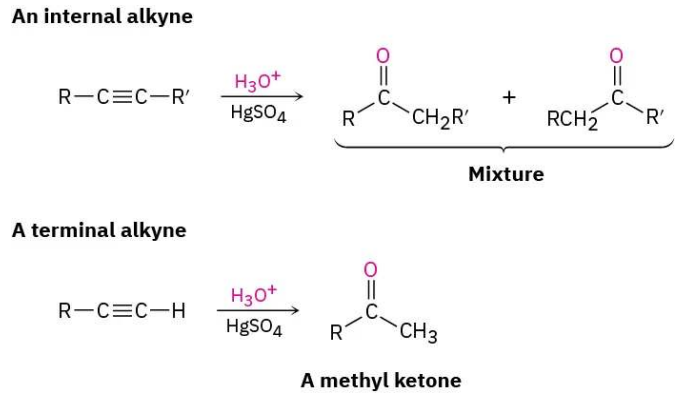


Figure 9.5.1: Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone. The reaction occurs through initial formation of an intermediate enol, which tautomerizes to the ketone.

A mixture of both possible ketones results when an unsymmetrically substituted internal alkyne ($RC{\equiv}CR'RC{\equiv}CR'$ is hydrated. The reaction is therefore most useful when applied to a terminal alkyne ($RC{\equiv}CHRC{\equiv}CH$) because only a methyl ketone is formed.



https://chem.libretexts.org/@go/page/564068

? Exercise 9.5.1

What products would you obtain by mercury-catalyzed hydration of the following alkynes?

a. $CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3$

b. $CH_3CH(CH_3)CH_2C{\equiv}CCH_2CH_2CH_3$

Answer

a. 4-Octanone

b. 2-Methyl-4-octanone and 7-methyl-4-octanone

? Exercise 9.5.2

What alkynes would you start with to prepare the following ketones?

a. $CH_3CH_2CH_2C(=O)CH_3$

b. $CH_3CH_2C(=O)CH_2CH_3$

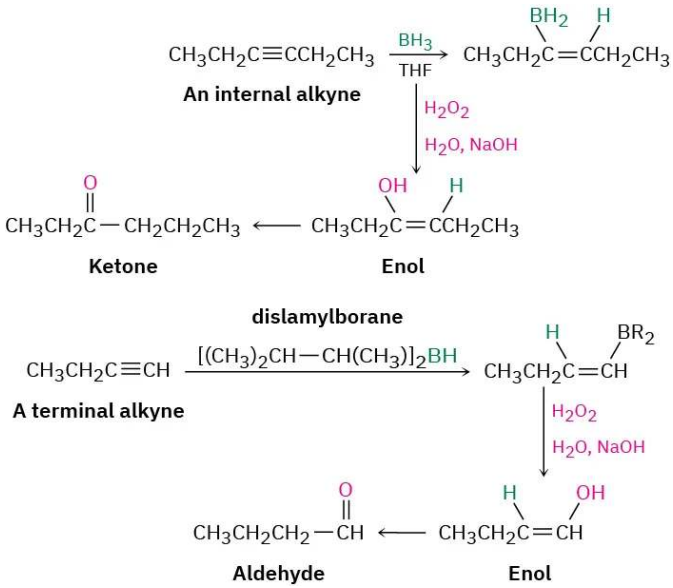
Answer

a. 1-Pentyne

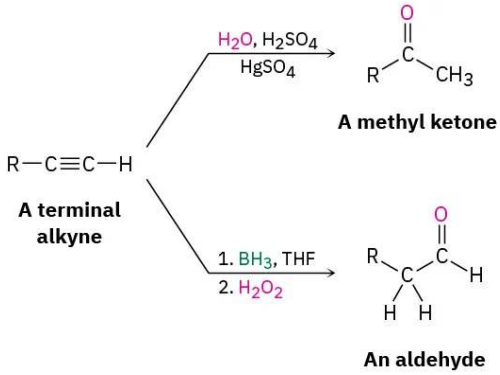
b. 2-Pentyne

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.

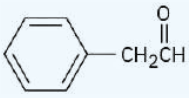


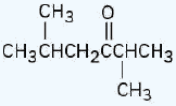
The hydroboration–oxidation sequence is complementary to the direct, mercury(II)-catalyzed hydration reaction of a terminal alkyne because different products result. Direct hydration with aqueous acid and mercury(II) sulfate leads to a methyl ketone, whereas hydroboration–oxidation of the same terminal alkyne leads to an aldehyde.



Exercise 9.5.3

What alkyne would you start with to prepare each of the following compounds by a hydroboration–oxidation reaction?

a. 

b. 

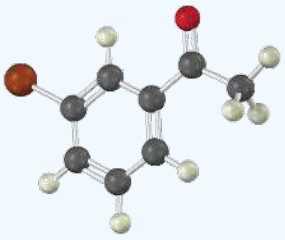
Answer

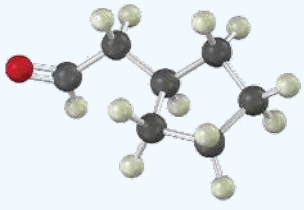
a. $C_6H_5C{\equiv}CH$

b. 2,5-Dimethyl-3-hexyne

Exercise 9.5.4

How would you prepare the following carbonyl compounds starting from an alkyne (reddish brown = Br)?

a. 

b. 

Answer

a. Mercuric sulfate–catalyzed hydration of phenylacetylene

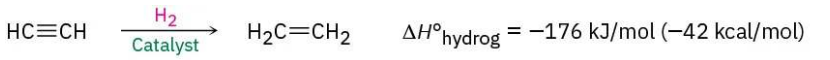
b. Hydroboration/oxidation of cyclopentylacetylene

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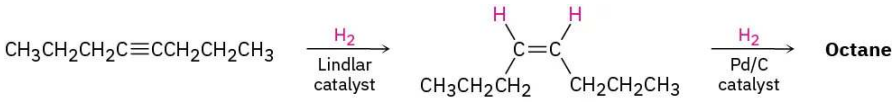
9.6: Reduction of Alkynes

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.

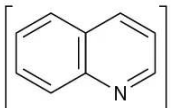




Complete reduction to the alkane occurs when palladium on carbon (Pd/C) is used as catalyst, but hydrogenation can be stopped at the alkene stage if the less active ***Lindlar catalyst*** is used. The Lindlar catalyst is a finely divided palladium metal that has been precipitated onto a calcium carbonate 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.

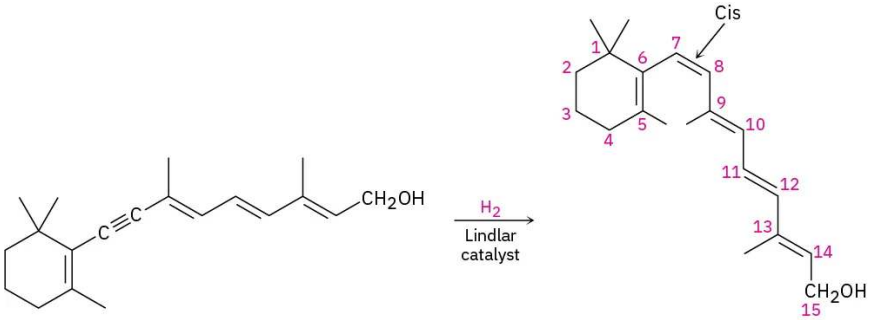


4-Octyne **cis-4-Octene**



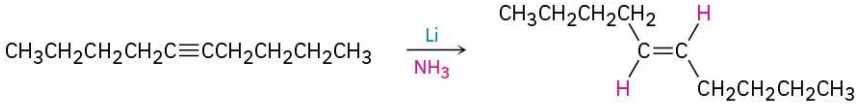
Quinoline

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 9.6.1. 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.

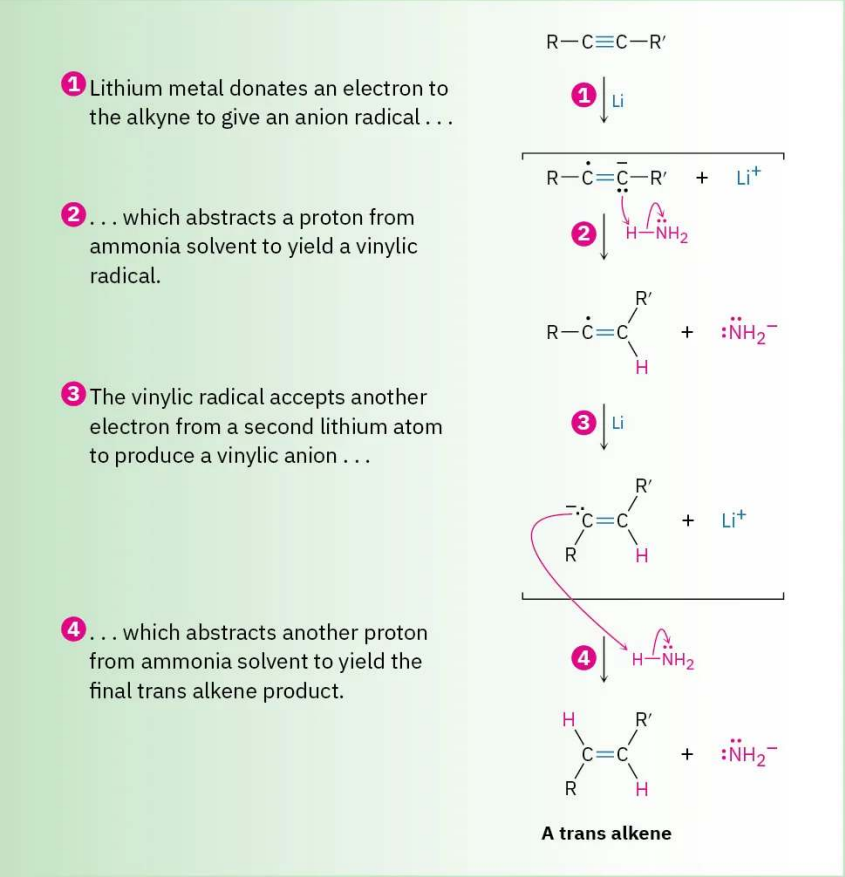


Figure 9.6.1: Mechanism of the lithium/ammonia reduction of an alkyne to produce a trans alkene.

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 9.6.1

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

a. Reduce 2-octyne with Li/NH_3.
b. Reduce 3-heptyne with H_2/Lindlar catalyst.
c. Reduce 3-methyl-1-pentyne.

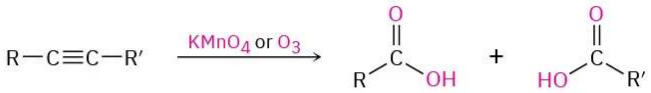
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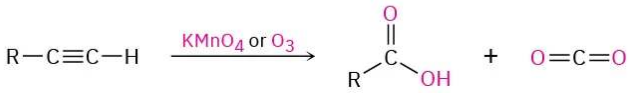
9.7: Oxidative Cleavage of Alkynes

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

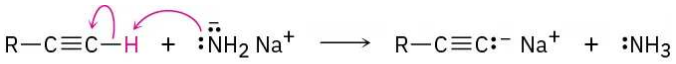


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9.8: Alkyne Acidity - Formation of Acetylide Anions

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.



Acetylide anion

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 9.8.1 show, both methane (p$K_a \approx 60$) and ethylene (p$K_a = 44$) are very weak acids and thus do not react with any of the common bases. Acetylene, however, has p$K_a = 25$ 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 (p$K_a = 35$), is often used to deprotonate terminal alkynes.

Table 9.8.1: 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 9.8.1).

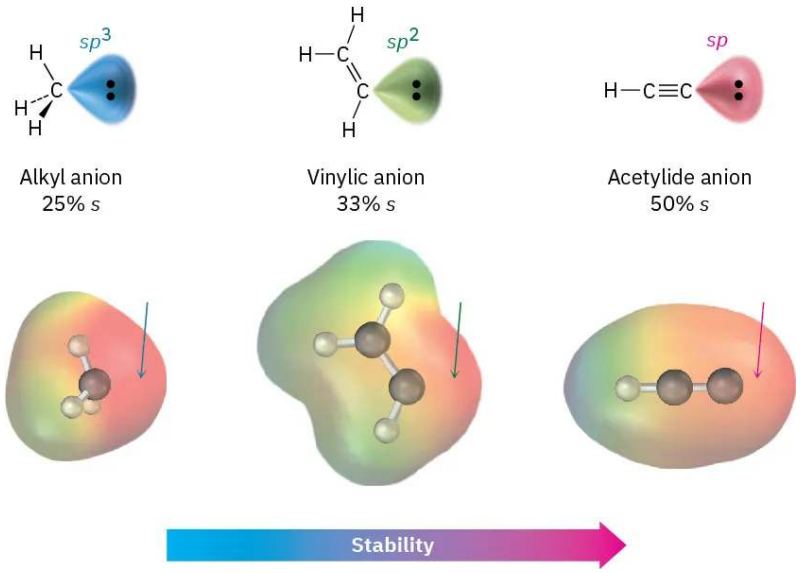


Figure 9.8.1: A comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with *sp* hybridization, has more *s* character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear less negative (red).

? Exercise 9.8.1

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

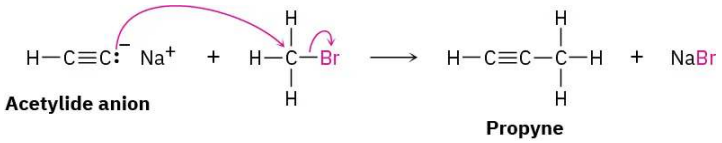
No: (a), (c), (d); yes: (b)

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9.9: 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 9.9.1. 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.

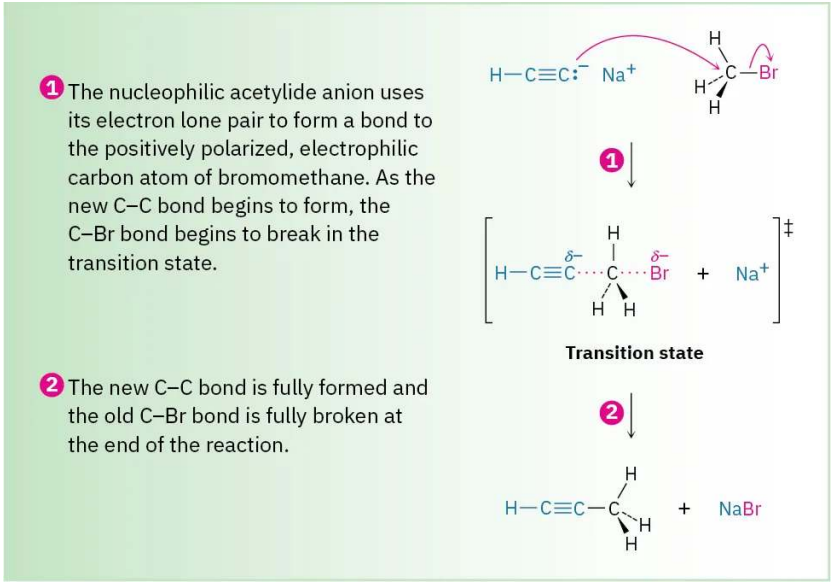
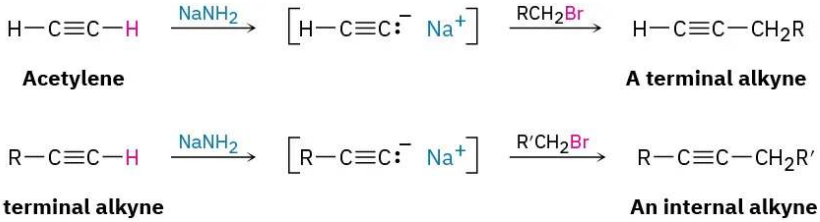


Figure 9.9.1: A mechanism for the alkylation reaction of acetylide anion with bromomethane to give propyne.

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.

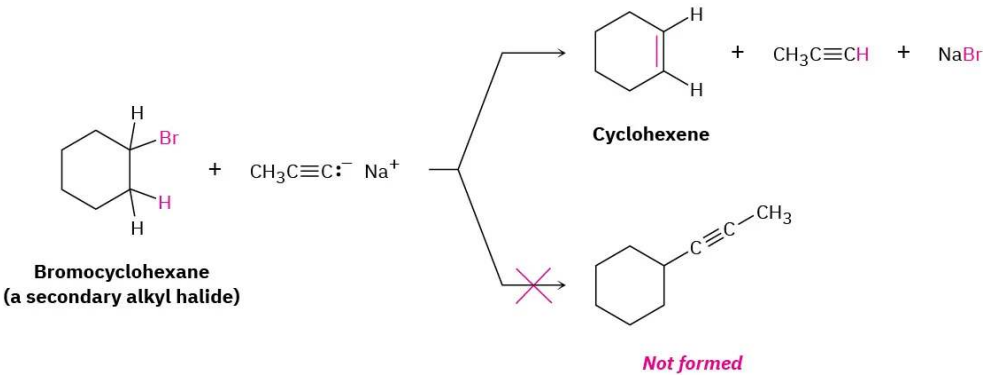


Because of its generality, acetylide alkylation is a good method for preparing substituted alkynes from simpler precursors. A terminal alkyne can be prepared by alkylation of acetylene itself, and an internal alkyne can be prepared by further alkylation of a terminal alkyne.



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.

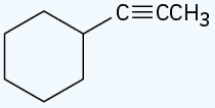


Exercise 9.9.1

Show the terminal alkyne and alkyl halide from which the following products can be obtained. If two routes look feasible, list both.

a. $CH_3CH_2CH_2C{\equiv}CCH_3$

b. $(CH_3)_2CHC{\equiv}CCH_2CH_3$

c. 

Answer

a. 1-Pentyne + CH_3I or propyne + $CH_3CH_2CH_2I$

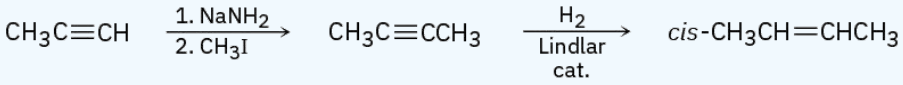
b. 3-Methyl-1-butyne + CH_3CH_2I

c. Cyclohexylacetylene + CH_3I

Exercise 9.9.2

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



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9.10: An Introduction to Organic Synthesis

As mentioned in the introduction, one of the purposes of this chapter is to 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. There are many reasons for carrying out the laboratory synthesis of an organic compound. In the pharmaceutical industry, new molecules are designed and synthesized in the hope that some might be useful new drugs. In the chemical industry, syntheses are done to devise more economical routes to known compounds. In academic laboratories, the synthesis of extremely complex molecules is sometimes done just for the intellectual challenge involved in mastering so difficult a subject. The successful synthesis route is a highly creative work that is sometimes described by such subjective terms as *elegant* or *beautiful*.

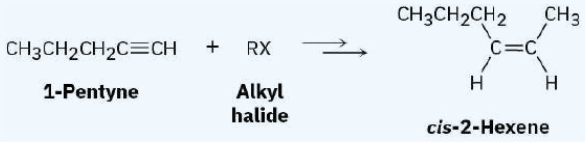
In this book, too, we will often devise syntheses of molecules from simpler precursors, but the purpose here is to learn. The ability to plan a successful multistep synthetic sequence requires a working knowledge of the uses and limitations of many different organic reactions. Furthermore, it requires the practical ability to piece together the steps in a sequence such that each reaction does only what is desired without causing changes elsewhere in the molecule. Planning a synthesis makes you approach a chemical problem in a logical way, draw on your knowledge of chemical reactions, and organize that knowledge into a workable plan—it helps you learn organic chemistry.

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 several examples of increasing complexity.

Worked Example 9.10.1: Devising a Synthesis Route

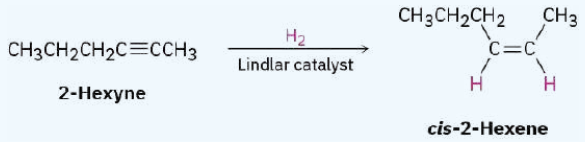
How would you synthesize *cis*-2-hexene from 1-pentyne and an alkyl halide? More than one step is needed.



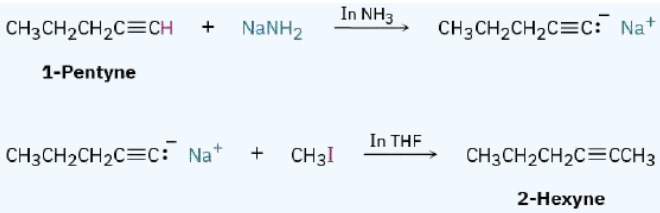
Strategy

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.

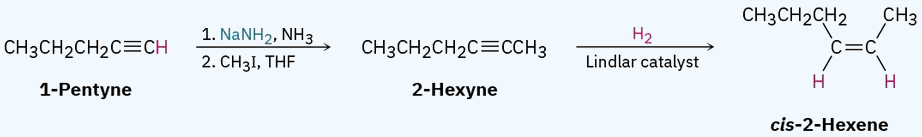


Next ask, "What is an immediate precursor of 2-hexyne?" We've seen that an internal alkyne can be prepared by alkylation of a terminal alkyne anion. In the present instance, we're told to start with 1-pentyne and an alkyl halide. Thus, alkylation of the anion of 1-pentyne with iodomethane should yield 2-hexyne.



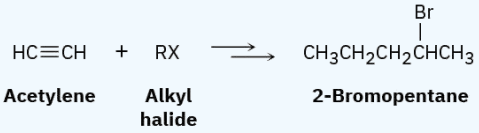
Solution

cis-2-Hexene can be synthesized from the given starting materials in three steps.



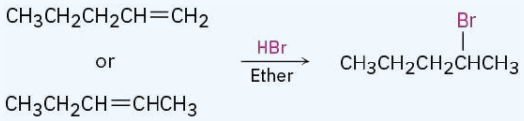
Worked Example 9.10.2: Devising a Synthesis Route

How would you synthesize 2-bromopentane from acetylene and an alkyl halide? More than one step is needed.

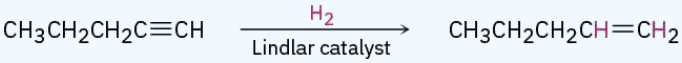


Strategy

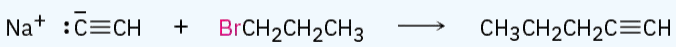
Identify the functional group in the product (an alkyl bromide) and work the problem retrosynthetically. What is an immediate precursor of an alkyl bromide? Perhaps an alkene plus HBr. Of the two possibilities, Markovnikov addition of HBr to 1-pentene looks like a better choice than addition to 2-pentene 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.

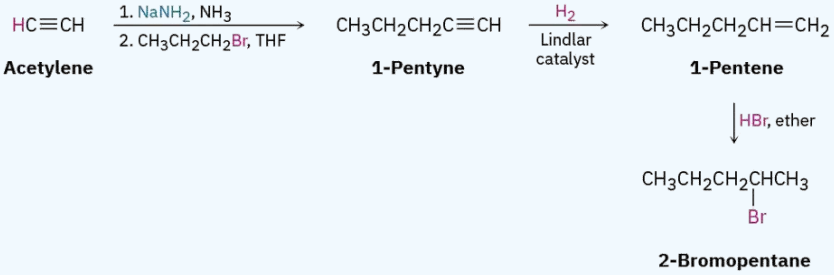


What is an immediate precursor of a terminal alkyne? Perhaps sodium acetylide and an alkyl halide.



Solution

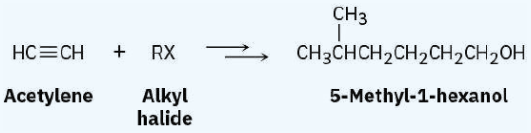
The desired product can be synthesized in four steps from acetylene and 1-bromopropane.



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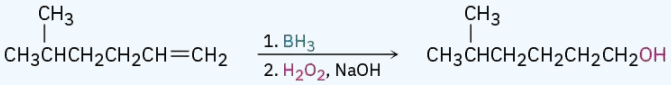
Worked Example 9.10.3: Devising a Synthesis Route

How would you synthesize 5-methyl-1-hexanol (5-methyl-1-hydroxyhexane) from acetylene and an alkyl halide?

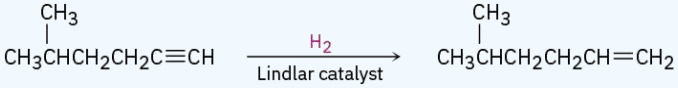


Strategy

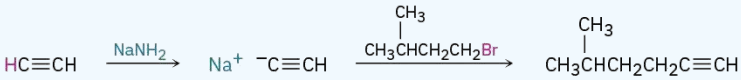
What is an immediate precursor of a primary alcohol? Perhaps a terminal alkene, which could be hydrated with non-Markovnikov regiochemistry by reaction with borane followed by oxidation with H_2O_2.



What is an immediate precursor of a terminal alkene? Perhaps a terminal alkyne, which could be reduced.

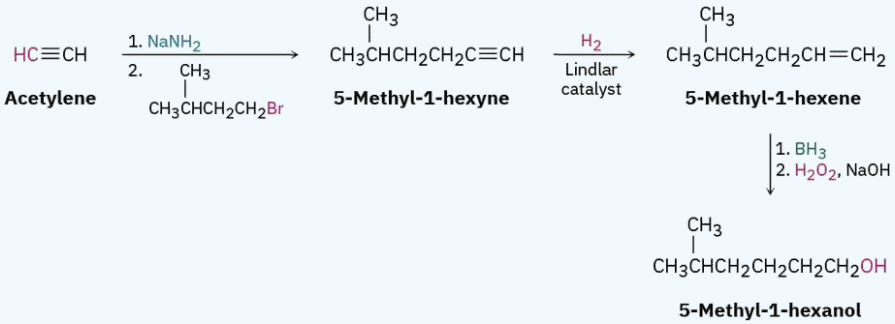


What is an immediate precursor of 5-methyl-1-hexyne? Perhaps acetylene and 1-bromo-3-methylbutane.



Solution

The synthesis can be completed in four steps from acetylene and 1-bromo-3-methylbutane:



Exercise 9.10.1

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

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 9.10.2

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

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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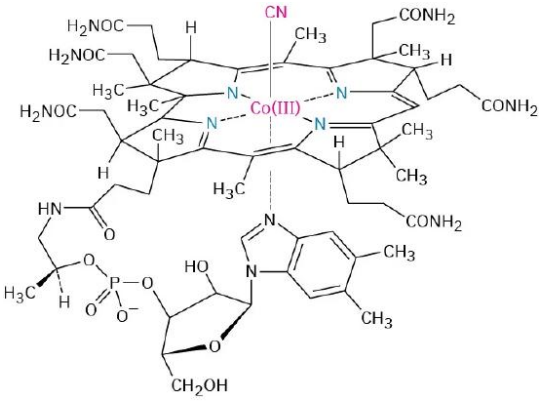
9.11: Chemistry Matters - The Art of Organic Synthesis

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 9.11.1: 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)

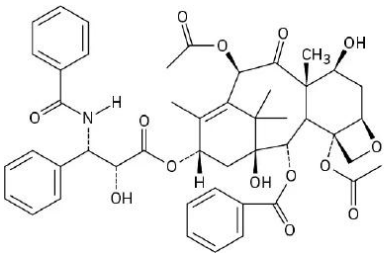
Why put such extraordinary effort into the laboratory synthesis of a molecule so easily obtained from natural sources? There are many reasons. On a basic human level, a chemist might be motivated primarily by the challenge, much as a climber might be challenged by the ascent of a difficult peak. Beyond 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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9.12: Key Terms

- acetylide anion
- alkylation
- alkyne
- enol
- Lindlar Catalyst
- retrosynthetic
- tautomer

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9.13: Summary

Alkynes are less common than alkenes, both in the laboratory and in living organisms, so we haven't covered them in great detail. The real importance of this chapter is that alkyne chemistry is a useful vehicle for looking at the general strategies used in organic synthesis—the construction of complex molecules in the laboratory.

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Alkyne carbon atoms are *sp*-hybridized, and the triple bond consists of one *sp*–*sp* σ bond and two *p*–*p* π bonds. There are relatively few general methods of alkyne synthesis. Two favorable ones are the alkylation of an acetylide anion with a primary alkyl halide and the twofold elimination of HX from a vicinal dihalide.

The chemistry of alkynes is dominated by electrophilic addition reactions, similar to those of alkenes. Alkynes react with HBr and HCl to yield vinylic halides and with Br_2 and Cl_2 to yield 1,2-dihalides (vicinal dihalides). Alkynes can be hydrated by reaction with aqueous sulfuric acid in the presence of mercury(II) catalyst. The reaction leads to an intermediate **enol** that immediately **tautomerizes** to yield a ketone. Because the addition reaction occurs with Markovnikov regiochemistry, a methyl ketone is produced from a terminal alkyne. Alternatively, hydroboration–oxidation of a terminal alkyne yields an aldehyde.

Alkynes can be reduced to yield alkenes and alkanes. Complete reduction of the triple bond over a palladium hydrogenation catalyst yields an alkane; partial reduction by catalytic hydrogenation over a **Lindlar catalyst** yields a cis alkene. Reduction of the alkyne with lithium in ammonia yields a trans alkene.

Terminal alkynes are weakly acidic. The alkyne hydrogen can be removed by a strong base such as $Na^+ {}^-NH_2$ to yield an **acetylide anion**. An acetylide anion acts as a nucleophile and can displace a halide ion from a primary alkyl halide in an **alkylation** reaction. Acetylide anions are more stable than either alkyl anions or vinylic anions because their negative charge is in a hybrid orbital with 50% *s* character, allowing the charge to be closer to the nucleus.

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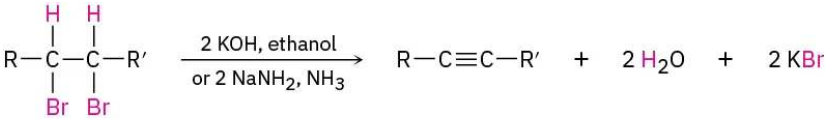
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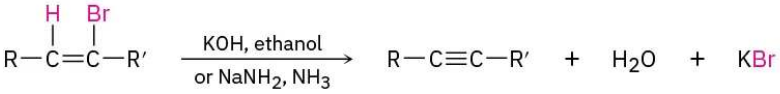
9.14: Summary of Reactions

No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.

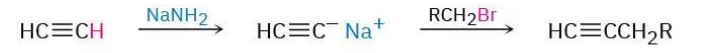
1. Preparation of alkynes

   a. Dehydrohalogenation of vicinal dihalides (Section 9.2)

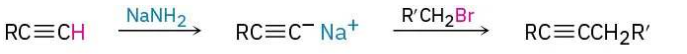




- Alkylation of acetylide anions (Section 9.8)



Acetylene **A terminal alkyne**



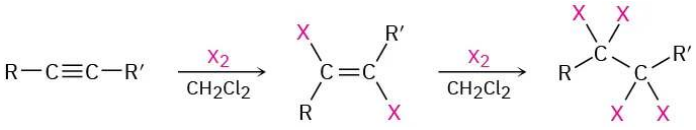
A terminal alkyne **An internal alkyne**

- Reactions of alkynes

   a. Addition of HCl and HBr (Section 9.3)

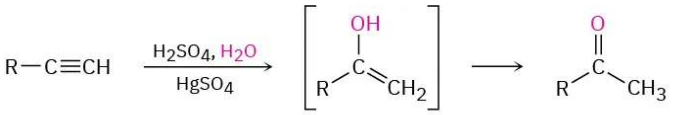


   b. Addition of Cl_2 and Br_2 (Section 9.3)



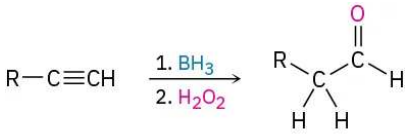
   c. Hydration (Section 9.4)

      (1) Mercuric sulfate catalyzed



An enol **A methyl ketone**

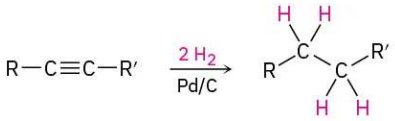
      (2) Hydroboration–oxidation



An aldehyde

   d. Reduction (Section 9.5)

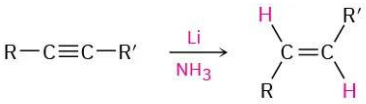
      (1) Catalytic hydrogenation





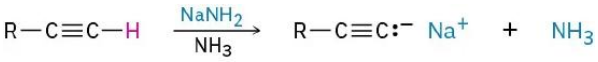
A cis alkene

(2) Lithium in liquid ammonia



A trans alkene

e. Conversion into acetylide anions (Section 9.7)



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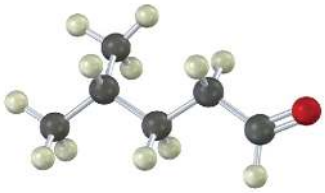
9.15: Additional Problems

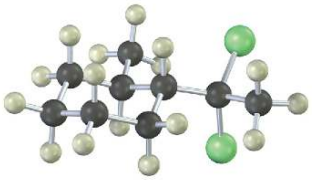
Visualizing Chemistry

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 $HgSO_4$:

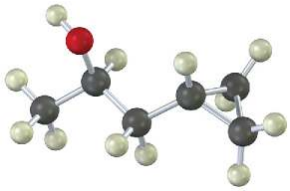
(a)  (b) 

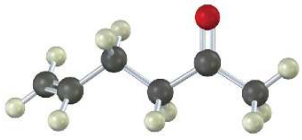
PROBLEM 9.15 From what alkyne might each of the following substances have been made? (Green = Cl.)

a. 

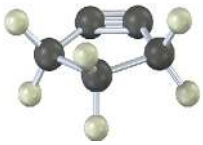
b. 

PROBLEM 9.16 How would you prepare the following substances, starting from any compounds having four carbons or fewer?

a. 

b. 

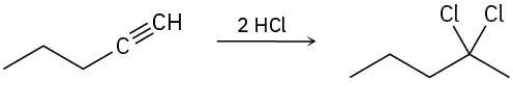
PROBLEM 9.17 The following cycloalkyne is too unstable to exist. Explain.



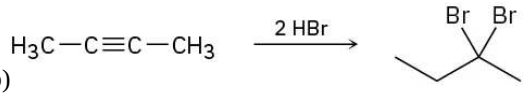
Mechanism Problems

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.

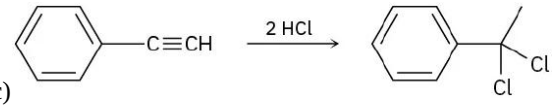
PROBLEM 9.19 Assuming that strong acids add to alkynes in the same manner as they add to alkenes, propose a mechanism for each of the following reactions.

(a) 

(b)

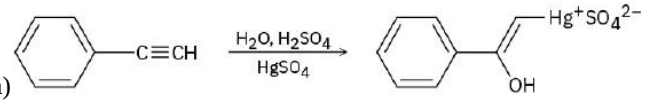


(c)

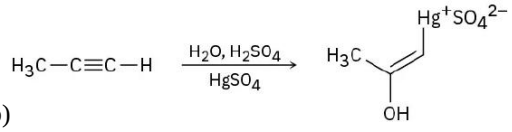


PROBLEM 9.20 The mercury-catalyzed hydration of alkynes involves the formation of an organomercury enol intermediate. Draw the electron-pushing mechanism to show how each of the following intermediates is formed.

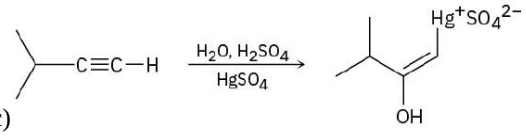
(a)



(b)

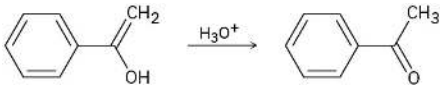


(c)

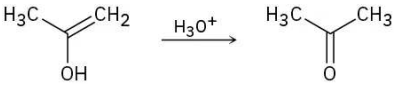


PROBLEM 9.21 The final step in the hydration of an alkyne under acidic conditions is the tautomerization of an enol intermediate to give the corresponding ketone. The mechanism involves a protonation followed by a deprotonation. Show the mechanism for each of the following tautomerizations.

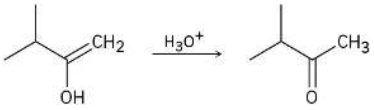
a.



b.

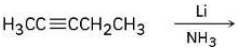


c.

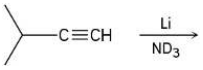


PROBLEM 9.22 Predict the product(s) and show the complete electron-pushing mechanism for each of the following dissolving metal reductions.

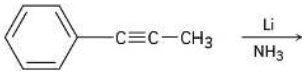
a.



b.

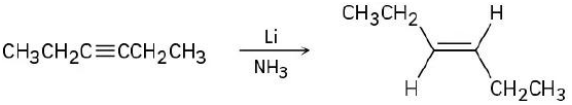


c.

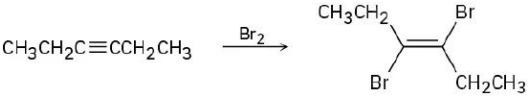


PROBLEM 9.23 Identify the mechanisms for the following reactions as *polar, radical*, or *both*.

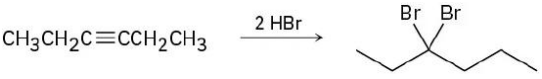
a.



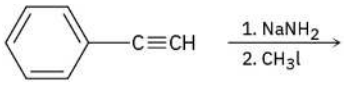
b.

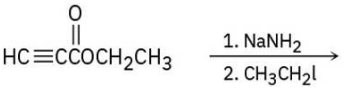


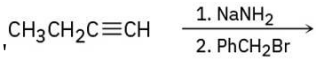
c.



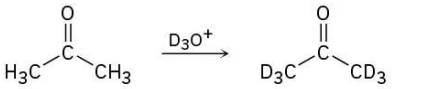
PROBLEM 9.24 Predict the product and provide the complete electron-pushing mechanism for the following two-step synthetic processes.

a. 

b. 

c. 

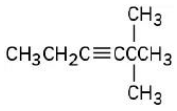
PROBLEM 9.25 Reaction of acetone with D_3O^+ yields hexadeuterioacetone. That is, all the hydrogens in acetone are exchanged for deuterium. Review the mechanism of mercuric-ion-catalyzed alkyne hydration, and then propose a mechanism for this deuterium incorporation.

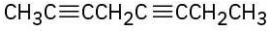


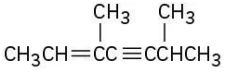
Acetone **Hexadeuterioacetone**

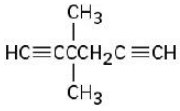
Naming Alkynes

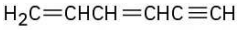
PROBLEM 9.26 Give IUPAC names for the following compounds:

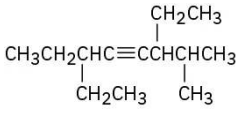
(a) 

(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

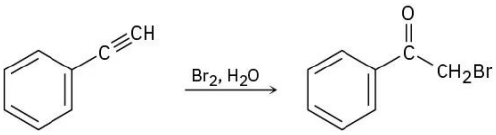
PROBLEM 9.28 The following two hydrocarbons have been isolated from various plants in the sunflower family. Name them according to IUPAC rules.

(a) $CH_3CH{=}CHC{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}CHCH{=}CHCH{=}CH_2$ (all trans)

(b) $CH_3C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}C{\equiv}C\text{-}CH{=}CH_2$

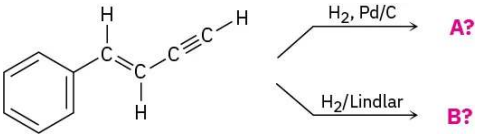
Reactions of Alkynes

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

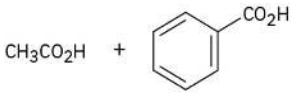
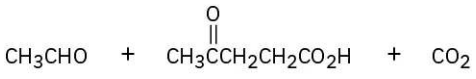
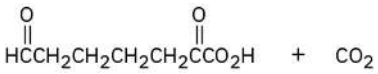
(d) BH_3 in THF, then H_2O_2, OH^- (e) H_2O, H_2SO_4, $HgSO_4$ (f) Excess H_2, Pd/C catalyst

PROBLEM 9.33 Predict the products from reaction of 2-hexyne with the following reagents:

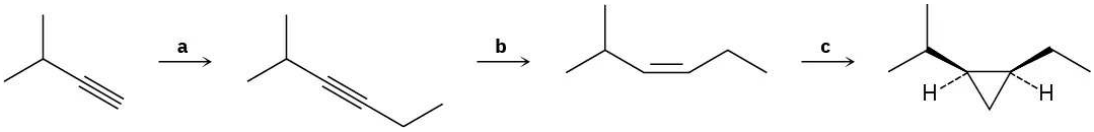
(a) 2 equiv Br_2 (b) 1 equiv HBr (c) Excess HBr

(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:

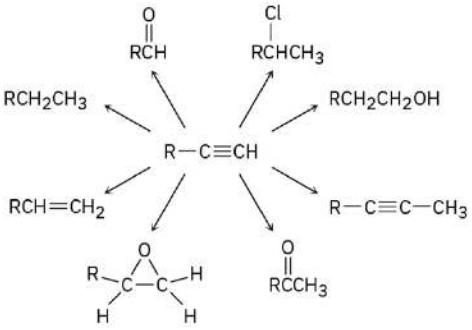
1. $CO_2 + CH_3(CH_2)_5CO_2H$
2. 
3. $HO_2C(CH_2)_8CO_2H$
4. 
5. 

PROBLEM 9.35 Identify the reagents **a–c** in the following scheme:



Organic Synthesis

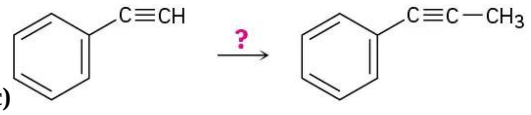
PROBLEM 9.36 How would you carry out the following multistep conversions? More than one step may be needed in some instances.

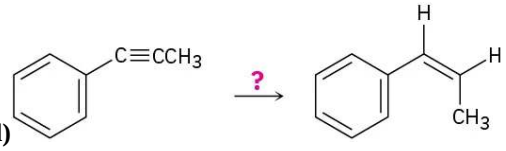


PROBLEM 9.37 How would you carry out the following reactions?

(a) 

(b) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(c) 

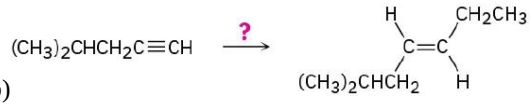
(d) 

(e) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CO_2H$

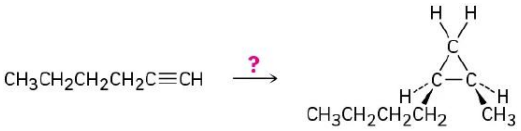
(f) $CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{(2 steps)}]{?} CH_3CH_2CH_2CH_2C{\equiv}CH$

PROBLEM 9.38 Each of the following syntheses requires more than one step. How would you carry them out?

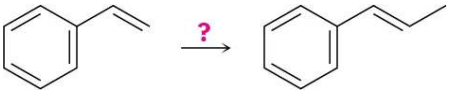
(a) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(b) 

PROBLEM 9.39 How would you carry out the following multistep transformation?



PROBLEM 9.40 How would you carry out the following multistep conversions?



PROBLEM 9.41 Synthesize the following compounds 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

(b) 1,1-Dichloro-2-ethylcyclopropane

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) $CH_3CH_2CH_2C{\equiv}CH$

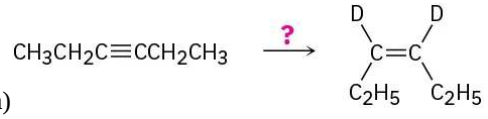
(b) $CH_3CH_2C{\equiv}CCH_2CH_3$

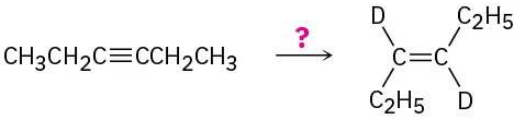
(c) $CH_3CH(CH_3)CH_2CH{=}CH_2$

(d) $CH_3CH_2CH_2C(=O)CH_2CH_2CH_2CH_3$

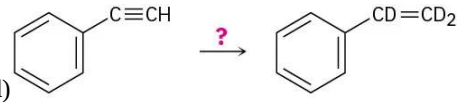
(e) $CH_3CH_2CH_2CH_2CH_2CHO$

PROBLEM 9.43 How would you carry out the following reactions to introduce deuterium into organic molecules?

(a) 

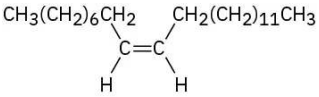
(b) 

(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<sub">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**?

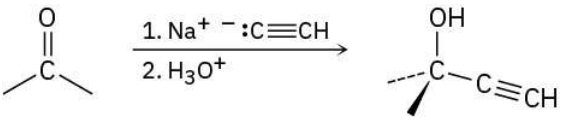
PROBLEM 9.48 Hydrocarbon **A** has the formula $C_{12}H_8$. It absorbs 8 equivalents of H_2 on catalytic reduction over a palladium catalyst. On ozonolysis, only two products are formed: oxalic acid (HO_2CCO_2H) and succinic acid ($HO_2CCH_2CH_2CO_2H$). Write the reactions, and propose a structure for **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 $\xrightarrow{?}$ *cis*-5-Decene

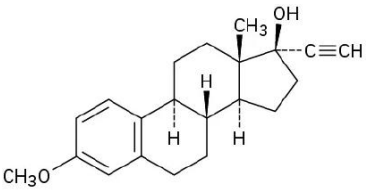
(b) *cis*-5-Decene $\xrightarrow{?}$ *trans*-5-Decene

PROBLEM 9.50 Organometallic reagents such as sodium acetylide undergo an addition reaction with ketones, giving alcohols:



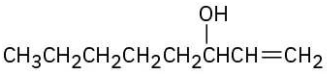
How might you use this reaction to prepare 2-methyl-1,3-butadiene, the starting material used in the manufacture of synthetic rubber?

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

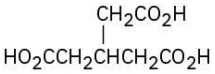
PROBLEM 9.52 1-Octen-3-ol, a potent mosquito attractant commonly used in mosquito traps, can be prepared in two steps from hexanal, $CH_3CH_2CH_2CH_2CH_2CHO$. The first step is an acetylide-addition reaction like that described in Problem 9-50. What is the structure of the product from the first step, and how can it be converted into 1-octen-3-ol?



1-Octen-3-ol

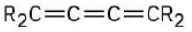
PROBLEM 9.53 Erythrogenic acid, $C_{18}H_{26}O_2$, is an acetylenic fatty acid that turns a vivid red on exposure to light. On catalytic hydrogenation over a palladium catalyst, 5 equivalents of H_2 are absorbed, and stearic acid, $CH_3(CH_2)_{16}CO_2H$, is produced. Ozonolysis of erythrogenic acid gives 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.



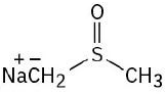
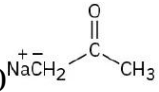
E

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.

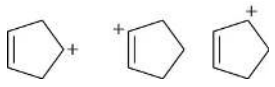


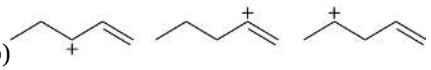
A cumulene

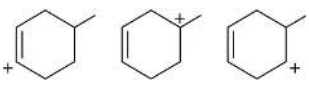
PROBLEM 9.56 Which of the following bases could be used to deprotonate 1-butyne?

(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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CHAPTER OVERVIEW

10: Organohalides

Learning Objectives

After you have completed Chapter 10, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- design a multistep synthesis to prepare a given compound from a given starting material using any of the reactions studied up to this point in the course, including those which involve alkyl halides.
- solve road-map problems requiring a knowledge of any of the reactions or concepts studied up to this point, including those introduced in this chapter.
- define, and use in context, the key terms introduced.

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.

10.1: Why This Chapter?
10.2: Names and Properties of Alkyl Halides
10.3: Preparing Alkyl Halides from Alkanes - Radical Halogenation
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
10.11: Key Terms
10.12: Summary
10.13: Summary of Reactions
10.14: Additional Problems

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10.1: Why This Chapter?

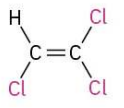
Alkyl halides are encountered less frequently than their oxygen-containing relatives and are not often involved in the biochemical pathways of terrestrial organisms, but some of the kinds of reactions they undergo—nucleophilic substitutions and eliminations—are encountered frequently. Thus, alkyl halide 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.



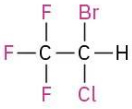
Figure 10.1.1: The gases released during volcanic eruptions contain large amounts of organohalides, including chloromethane, chloroform, dichlorodifluoromethane, and many others. (credit: "Tavurvur volcano" by Taro Taylor, Richard Bartz/Wikimedia Commons, CC BY 2.0)

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.



Trichloroethylene (a solvent)



Halothane (an inhaled anesthetic)

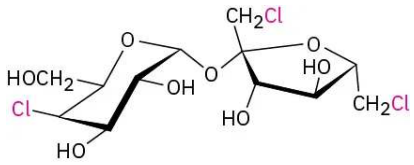


Tetrafluoropropene (a refrigerant)



Bromomethane (a fumigant)

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 (C≡C–X), a vinylic group (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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10.2: Names and Properties of Alkyl Halides

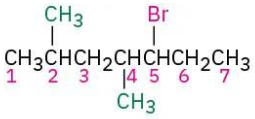
Although commonly called *alkyl halides*, halogen-substituted alkanes are named systematically as *haloalkanes* (Section 3.5), treating the halogen as a substituent on a parent alkane chain. There are three steps:

STEP 1

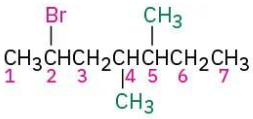
Find the longest chain, and name it as the parent. If a double or triple bond is present, the parent chain must contain it.

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.

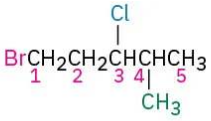


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

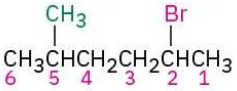
If different halogens are present, number each one and list them in alphabetical order when writing the name.



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.

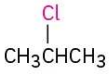


2-Bromo-5-methylhexane
(*Not* 5-bromo-2-methylhexane)

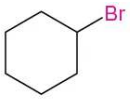
In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.



Iodomethane
(or methyl iodide)



2-Chloropropane
(or isopropyl chloride)



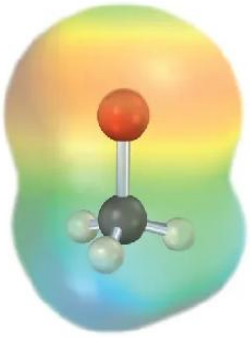
Bromocyclohexane
(or cyclohexyl bromide)

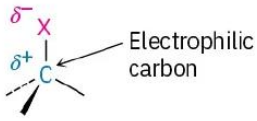
Halogens increase in size going down the periodic table, so the lengths of the corresponding carbon–halogen bonds increase accordingly (Table 10.2.1). In addition, C−X bond strengths decrease going down the periodic table. As we've been doing thus far, we'll continue using an X to represent any of the halogens F, Cl, Br, or I.

Table 10.2.1: 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.

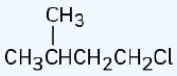


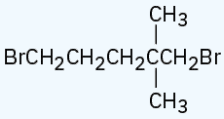


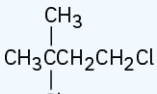
? Exercise 10.2.1

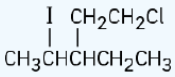
Give IUPAC names for the following alkyl halides:

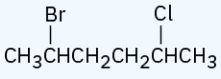
a. $CH_3CH_2CH_2CH_2I$

b. 

c. 

d. 

e. 

f. 

Answer

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

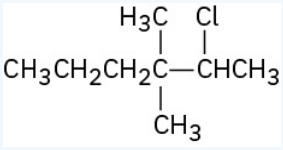
f. 2-Bromo-5-chlorohexane

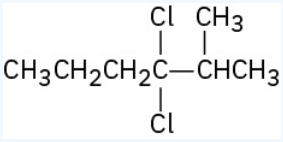
Exercise 10.2.1

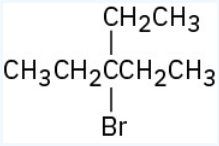
Draw structures corresponding to the following IUPAC names:

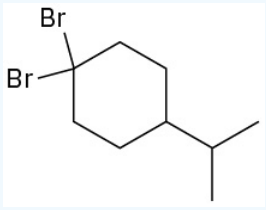
a. 2-Chloro-3,3-dimethylhexane
b. 3,3-Dichloro-2-methylhexane
c. 3-Bromo-3-ethylpentane
d. 1,1-Dibromo-4-isopropylcyclohexane
e. 4-*sec*-Butyl-2-chlorononane
f. 1,1-Dibromo-4-*tert*-butylcyclohexane

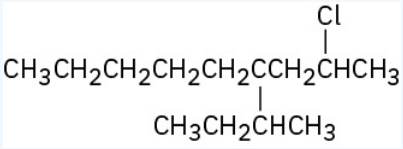
Answer

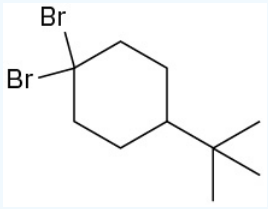
a. 

b. 

c. 

d. 

e. 

f. 

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10.3: Preparing Alkyl Halides from Alkanes - Radical Halogenation

As we saw briefly in Section 6.7, simple alkyl halides can sometimes be prepared by the radical reaction of an alkane with Cl_2 or Br_2 in the presence of ultraviolet light. The detailed mechanism is shown in Figure 10.3.1 for chlorination.

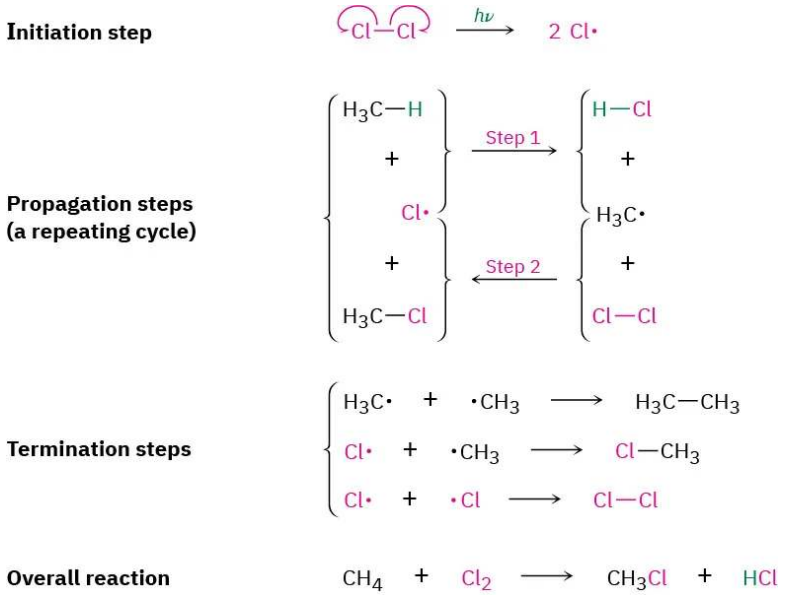
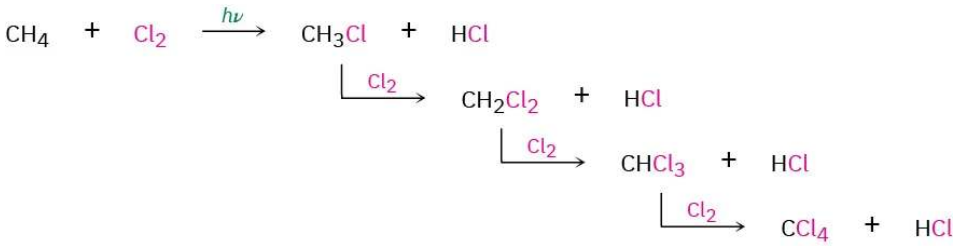


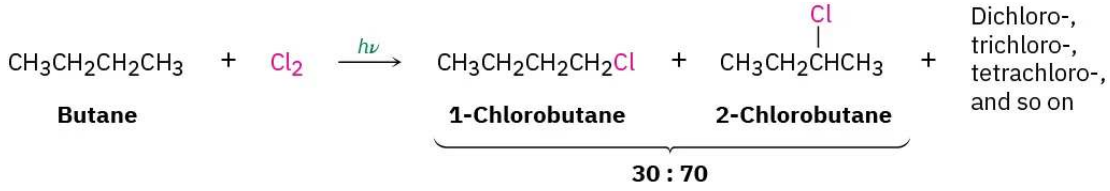
Figure 10.3.1: Mechanism of the radical chlorination of methane. Three kinds of steps are required in radical substitution reactions: initiation, propagation, and termination. The propagation steps are a repeating cycle, with Cl· a reactant in step 1 and a product in step 2, and with ·CH_3 a product in step 1 and a reactant in step 2. The symbol *hν* shown in the initiation step is the standard way of indicating irradiation with light (*ν* is the lowercase Greek letter nu).

Radical substitution reactions require three kinds of steps: *initiation*, *propagation*, and *termination*. Once an initiation step has started the process by producing radicals, the reaction continues in a self-sustaining cycle. The cycle requires two repeating propagation steps in which a radical, the halogen, and the alkane yield alkyl halide product plus more radical to carry on the chain. The chain is occasionally terminated by the combination of two radicals.

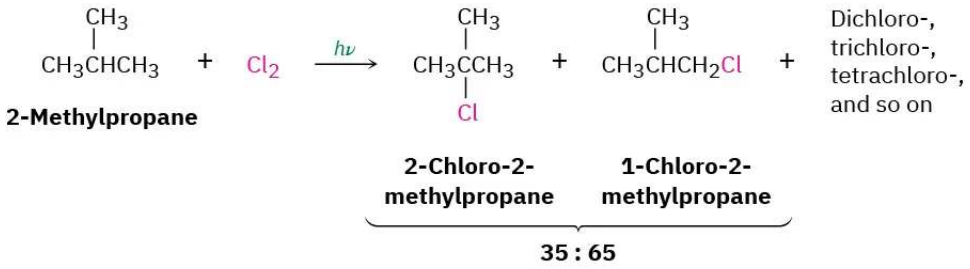
Unfortunately, alkane halogenation is a poor synthetic method for preparing alkyl halides because mixtures of products invariably result. For example, chlorination of methane does not stop cleanly at the monochlorinated stage but continues to give a mixture of dichloro, trichloro, and even tetrachloro products.



The situation is even worse for chlorination of alkanes that have more than one kind of hydrogen. 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.

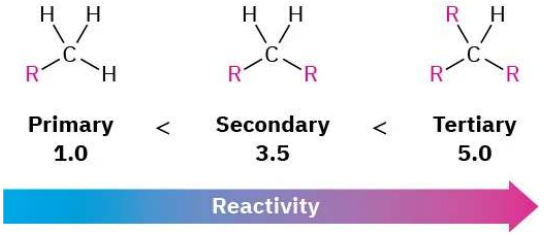


As another example, 2-methylpropane yields 2-chloro-2-methylpropane and 1-chloro-2-methylpropane in a 35 : 65 ratio, along with more highly chlorinated products.

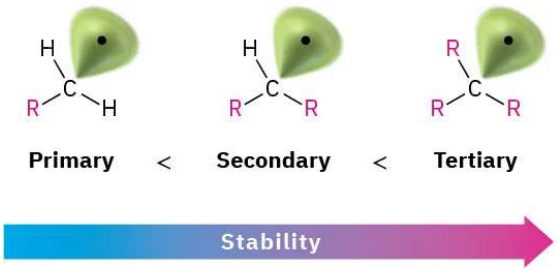


From these and similar reactions, it's possible to calculate a reactivity order toward chlorination for different kinds of hydrogen atoms in a molecule. Take the butane chlorination, for instance. Butane has six equivalent primary hydrogens ($-CH_3$) and four equivalent secondary hydrogens ($-CH_2-$). 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 observed reactivity order of alkane hydrogens toward radical chlorination can be explained by looking at the bond dissociation energies given previously in Table 6.3. The data show that a tertiary C−H bond (400 kJ/mol; 96 kcal/mol) is weaker than a secondary C−H bond (410 kJ/mol; 98 kcal/mol), which is in turn weaker than a primary C−H bond (421 kJ/mol; 101 kcal/mol). Since less energy is needed to break a tertiary C−H bond than to break a primary or secondary C−H bond, the resultant tertiary radical is more stable than a primary or secondary radical.

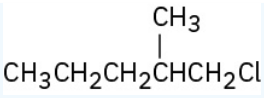


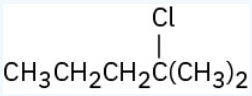
? Exercise 10.3.1

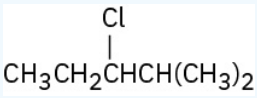
Draw and name all monochloro products you would expect to obtain from radical chlorination of 2-methylpentane. Which, if any, are chiral?

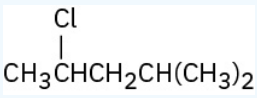
Answer

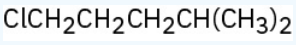
Chiral: 1-chloro-2-methylpentane, 3-chloro-2-methylpentane, 2-chloro-4-methylpentane Achiral: 2-chloro-2-methylpentane, 1-chloro-4-methylpentane











? Exercise 10.3.2

Taking the relative reactivities of primary, secondary, and tertiary hydrogens atoms into account:

a. what product(S) would you expect to obtain from monochloration of 2-methylbutane**?**
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

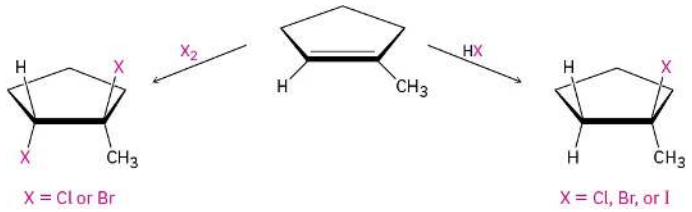
1-Chloro-2-methylbutane (29%), 1-chloro-3-methylbutane (14%), 2-chloro-2-methylbutane (24%), 2-chloro-3-methylbutane (33%)

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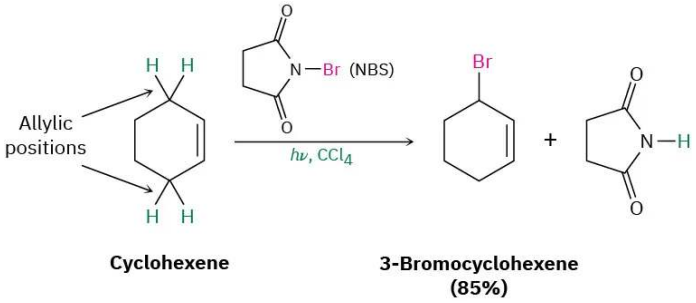
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10.4: Preparing Alkyl Halides from Alkenes - Allylic Bromination

We've already seen several methods for preparing alkyl halides from alkenes, including the reactions of HX and X_2 with alkenes in electrophilic addition reactions (Section 7.8 and Section 8.3). The hydrogen halides HCl, HBr, and HI react with alkenes by a polar mechanism to give the product of Markovnikov addition. Bromine and chlorine undergo anti addition through halonium ion intermediates to give 1,2-dihalogenated products.



Another laboratory method for preparing alkyl halides from alkenes is by reaction with *N*-bromosuccinimide (abbreviated NBS), in the presence of ultraviolet light, to give products resulting from substitution of hydrogen by bromine at the position next to the double bond—the allylic position. Cyclohexene, for example, gives 3-bromocyclohexene.



This allylic bromination with NBS is analogous to the alkane chlorination reaction discussed in the previous section and occurs by a radical chain-reaction pathway (Figure 10.4.1). As in alkane halogenation, a Br· radical abstracts an allylic hydrogen atom, forming an allylic radical plus HBr. The HBr then reacts with NBS to form Br_2, which in turn reacts with the allylic radical to yield the brominated product and a Br· radical that cycles back into the first step and carries on the chain.

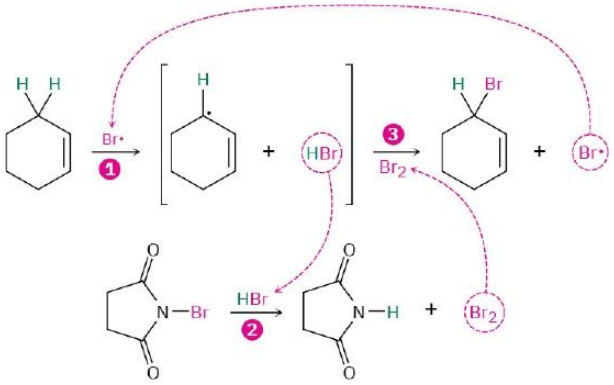
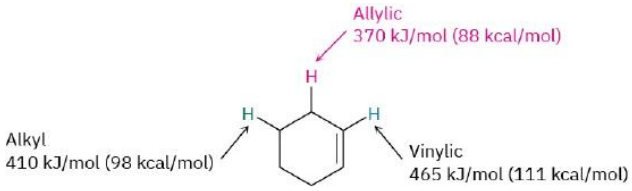
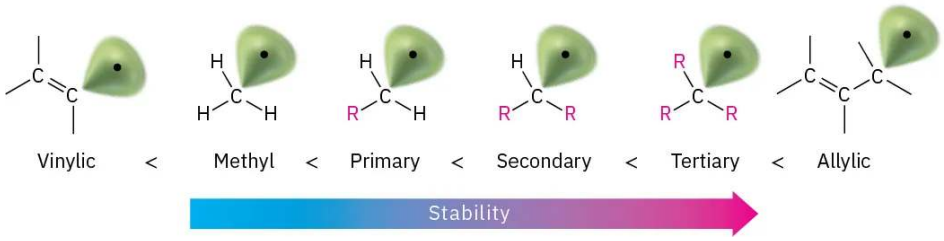


Figure 10.4.1: Mechanism of allylic bromination of an alkene with NBS. The process is a radical chain reaction in which (**1**) a Br· radical abstracts an allylic hydrogen atom of the alkene and gives an allylic radical plus HBr. (**2**) The HBr then reacts with NBS to form Br_2, which (**3**) reacts with the allylic radical to yield the bromoalkene product and a Br· radical that continues the chain.

Why does bromination with NBS occur exclusively at an allylic position rather than elsewhere in the molecule? The answer, once again, is found by looking at bond dissociation energies to see the relative stabilities of various kinds of radicals. Although a typical secondary alkyl C−H bond has a strength of about 410 kJ/mol (98 kcal/mol) and a typical vinylic C−H bond has a strength of 465 kJ/mol (111 kcal/mol), an allylic C−H bond has a strength of only about 370 kJ/mol (88 kcal/mol). An allylic radical is therefore more stable than a typical alkyl radical with the same substitution by about 40 kJ/mol (9 kcal/mol).



We can thus expand the stability ordering to include vinylic and allylic radicals.



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10.5: Stability of the Allyl Radical - Resonance Revisited

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.

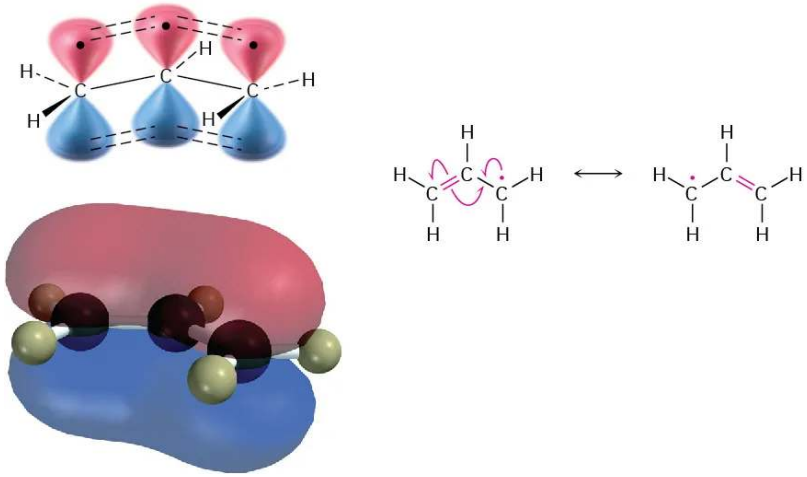


Figure 10.5.1: An orbital view of the allyl radical. The *p* orbital on the central carbon can overlap equally well with a *p* orbital on either neighboring carbon, giving rise to two equivalent resonance structures.

Because the allyl radical is electronically symmetrical, it has two resonance forms—one with the unpaired electron on the left and the double bond on the right and another with the unpaired electron on the right and the double bond on the left. Neither structure is correct by itself; the true structure of the allyl radical is a resonance hybrid of the two. (You might want to review Section 2.5 to Section 2.7 to brush up on resonance.) As noted in Section 2.6, the greater the number of resonance forms, the greater the stability of a compound, because bonding electrons are attracted to more nuclei. An allyl radical, with two resonance forms, is therefore more stable than a typical alkyl radical, which has only a single structure.

In molecular orbital terms, the stability of the allyl radical is due to the fact that the unpaired electron is delocalized, or spread out, over an extended π-orbital network rather than localized at only one site, as shown by the computer-generated MO in Figure 10.5.2. This delocalization is particularly apparent in the so-called spin-density surface in Figure 10.5, which shows the calculated location of the unpaired electron. The two terminal carbons share the unpaired electron equally.

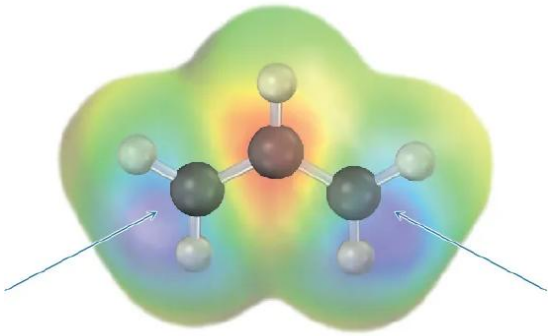
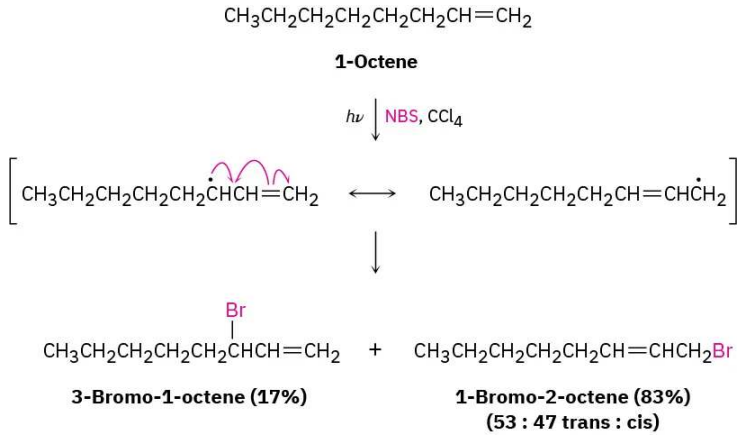


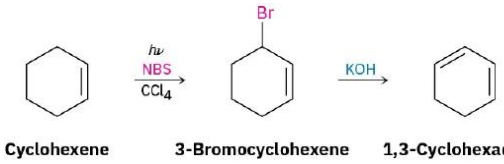
Figure 10.5.2: The spin density surface of the allyl radical locates the position of the unpaired electron and shows that it is equally shared between the two terminal carbons.

In addition to its effect on stability, delocalization of the unpaired electron in the allyl radical has other chemical consequences. Because the unpaired electron is delocalized over both ends of the π orbital system, reaction with Br_2 can occur at either end. As a result, allylic bromination of an unsymmetrical alkene often leads to a mixture of products. For example, bromination of 1-octene gives a mixture of 3-bromo-1-octene and 1-bromo-2-octene. The two products are not formed in equal amounts, however, because

the intermediate allylic radical is not symmetrical and reaction at the two ends is not equally likely. Reaction at the less hindered, primary end is favored.



The products of allylic bromination reactions are useful for conversion into dienes by dehydrohalogenation with base. Cyclohexene can be converted into 1,3-cyclohexadiene, for example.



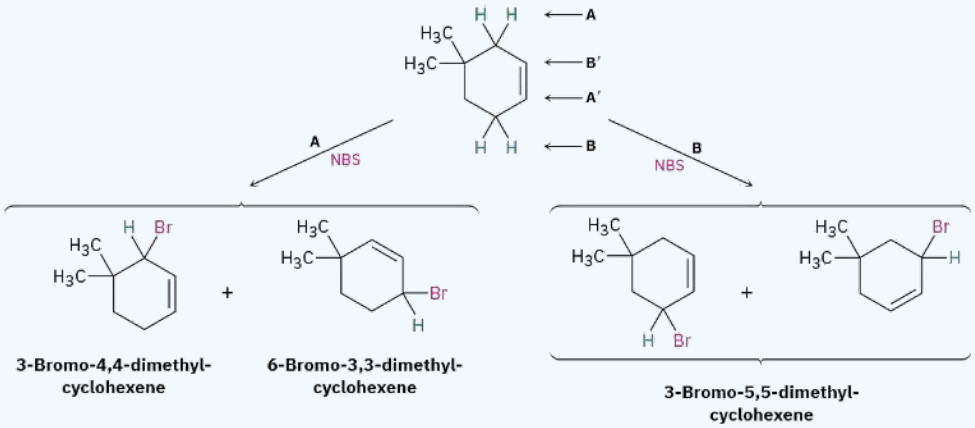
Worked Example 10.5.1: Predicting the Product of an Allylic Bromination Reaction

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



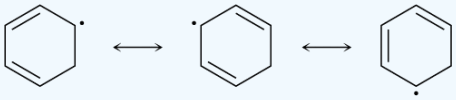
Exercise 10.5.1

Draw three resonance forms for the cyclohexadienyl radical.



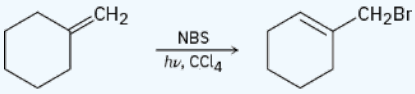
Cyclohexadienyl radical

Answer



Exercise 10.5.2

The major product of the reaction of methylenecyclohexane with *N*-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.



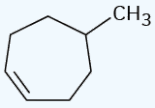
Major product

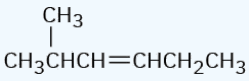
Answer

The intermediate allylic radical reacts at the more accessible site and gives the more highly substituted double bond.

Exercise 10.5.3

What products would you expect from reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

a. 

b. 

Answer

a. 3-Bromo-5-methylcycloheptene and 3-bromo-6-methylcycloheptene

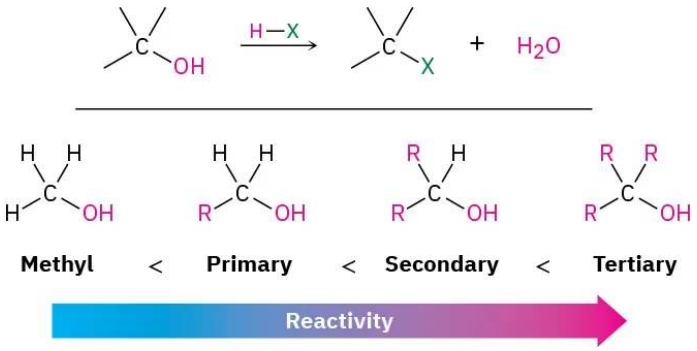
b. Four products

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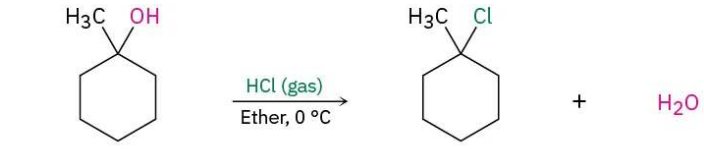
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10.6: Preparing Alkyl Halides from Alcohols

The most generally useful method for preparing alkyl halides is to make them from alcohols, which themselves can be obtained from carbonyl compounds as we'll see in **Sections 17.5** and **17.6**. 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. For reasons that will be discussed in **Section 11.6**, this reaction works best with tertiary alcohols, R_3COH. Primary and secondary alcohols react much more slowly and at higher temperatures.

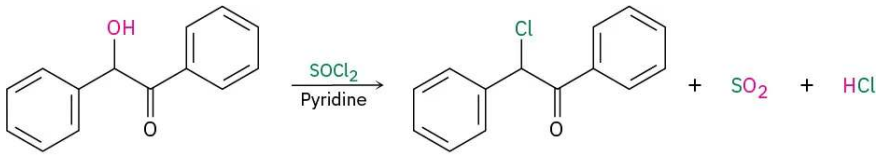


The reaction of HX with a tertiary alcohol is so rapid that it's often carried out simply by bubbling pure HCl or HBr gas into a cold ether solution of the alcohol. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treatment with HCl.

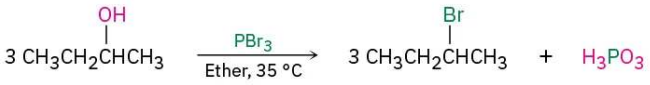


1-Methylcyclohexanol **1-Chloro-1-methylcyclohexane (90%)**

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.



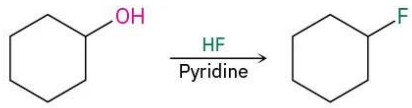
Benzoin **(86%)**



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. We'll look at the mechanisms of these and other related substitution reactions in **Section 11.4**.

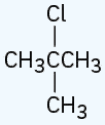
Alkyl fluorides can also be prepared from alcohols. Numerous alternative reagents are used for such reactions, including diethylaminosulfur trifluoride $[(CH_3CH_2)_2NSF_3]$ and HF in pyridine solvent.

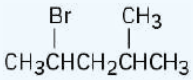


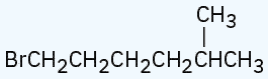
Cyclohexanol **Fluorocyclohexane (99%)**

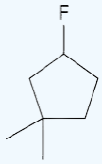
Exercise 10.6.1

How would you prepare the following alkyl halides from the corresponding alcohols?

a. 

b. 

c. 

d. 

Answer

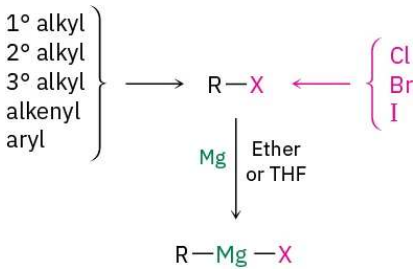
a. 2-Methyl-2-propanol + HCl
b. 4-Methyl-2-pentanol + PBr_3
c. 5-Methyl-1-pentanol + PBr_3
d. 3,3-Dimethyl-cyclopentanol + HF, pyridine

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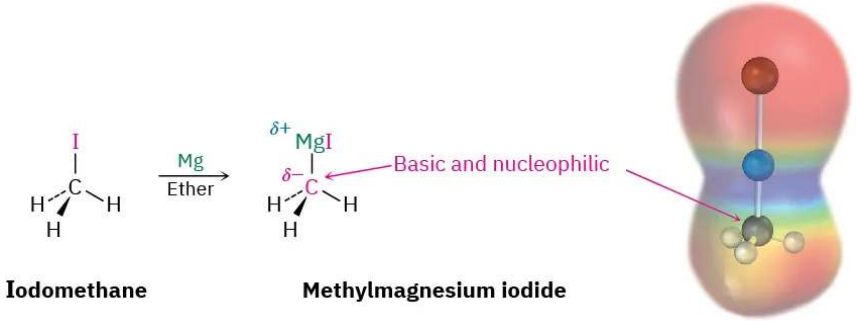
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10.7: Reactions of Alkyl Halides - Grignard Reagents

Alkyl halides, RX, react with magnesium metal in ether or tetrahydrofuran (THF) solvent to yield alkylmagnesium halides, RMgX. The products, called Grignard reagents (RMgX) after their discoverer, Francois Auguste Victor Grignard, who received the 1912 Nobel Prize in Chemistry, are examples of organometallic compounds because they contain a carbon–metal bond. In addition to alkyl halides, Grignard reagents can also be made from alkenyl (vinylic) and aryl (aromatic) halides. The halogen can be Cl, Br, or I, although chlorides are less reactive than bromides and iodides. Organofluorides rarely react with magnesium.



As you might expect from the discussion of electronegativity and bond polarity in Section 6.4, the carbon–magnesium bond is polarized, making the carbon atom of Grignard reagents both nucleophilic and basic. An electrostatic potential map of methylmagnesium iodide, for instance, indicates the electron-rich (red) character of the carbon bonded to magnesium.



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 **pK_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.

$$CH_3CH_2CH_2CH_2CH_2CH_2Br \xrightarrow[\text{Ether}]{Mg} CH_3CH_2CH_2CH_2CH_2CH_2MgBr \xrightarrow{H_2O} CH_3CH_2CH_2CH_2CH_2CH_3$$

1-Bromohexane **1-Hexylmagnesium bromide** **Hexane**

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 Section 17.6. In addition, they act as a simple model for other, more complex carbon-based nucleophiles that *are* important in biological chemistry. We'll see many examples of these in Chapter 29.

? Exercise 10.7.1

How strong a base would you expect a Grignard reagent to be? Look at Table 9.1 and predict whether the following reactions will occur as written. (The pK_a of NH_3 is 35.)

a. $CH_3MgBr + H{-}C{\equiv}C{-}H \longrightarrow CH_4 + H{-}C{\equiv}C{-}MgBr$
b. $CH_3MgBr + NH_3 \longrightarrow CH_4 + H_2N{-}MgBr$

Answer

Both reactions occur.

Exercise 10.7.2

How might you replace a halogen substituent by a deuterium atom if you wanted to prepare a deuterated compound?



Answer

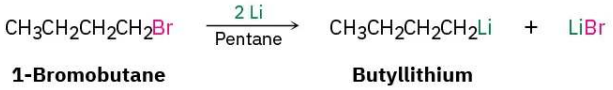
React Grignard reagent with D_2O.

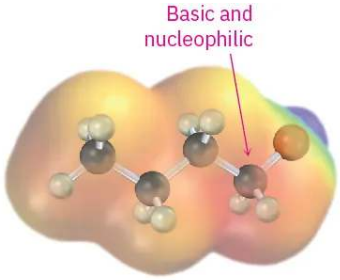
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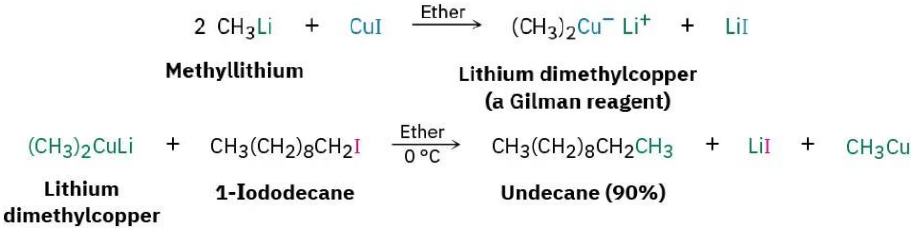
10.8: Organometallic Coupling Reactions

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.

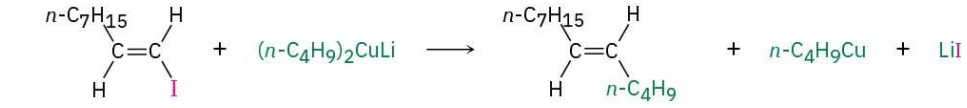


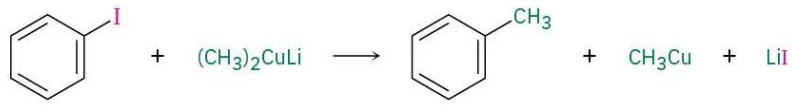


One particularly valuable reaction of alkyllithiums occurs when making lithium diorganocopper compounds, R_2CuLi, by reaction with copper(I) iodide in diethyl ether as solvent. Often called Gilman reagents (LiR_2Cu), lithium diorganocopper compounds are useful because they undergo a *coupling* reaction 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.

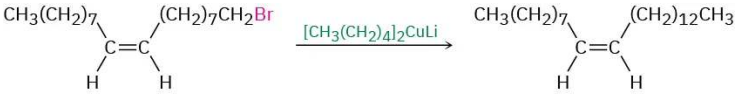


This organometallic coupling reaction is useful in organic synthesis because it forms carbon–carbon bonds, thereby allowing the preparation of larger molecules from smaller ones. As the following examples indicate, the coupling reaction can be carried out on aryl and vinylic halides as well as on alkyl halides.



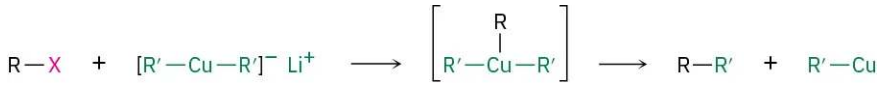


An organocopper coupling reaction is carried out commercially to synthesize muscalure, (9*Z*)-tricosene, the sex attractant secreted by the common housefly. Minute amounts of muscalure greatly increase the lure of insecticide-treated fly bait and provide an effective and species-specific means of insect control.

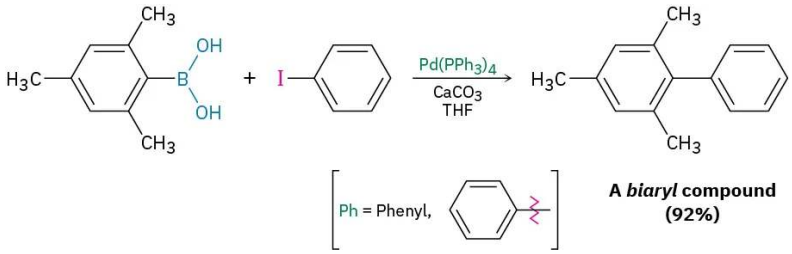


The mechanism of the coupling reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of a mono-organocopper, RCu. The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the

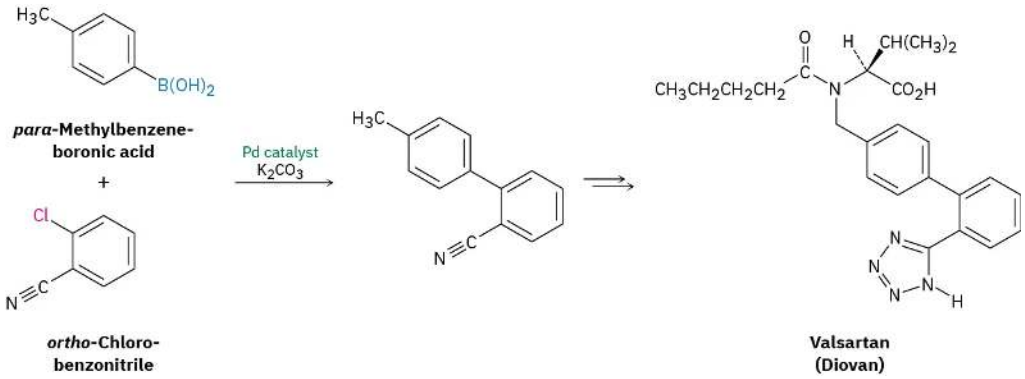
next chapter.



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. 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.



Shown in a simplified form in Figure 10.6, 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.

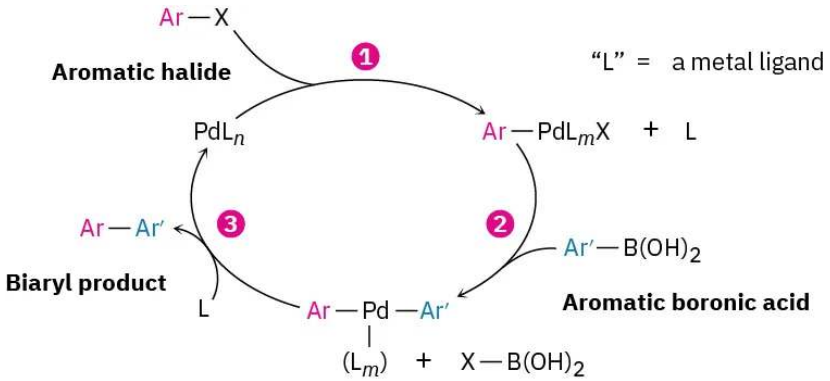
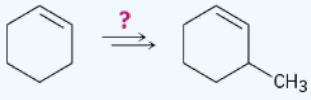


Figure 10.6: Mechanism of the Suzuki–Miyaura coupling reaction of an aromatic boronic acid with an aromatic halide to give a biaryl. The reaction takes place by (**1**) reaction of the aromatic halide, ArX, with the catalyst to form an organopalladium intermediate, followed by (**2**) reaction with the aromatic boronic acid. (**3**) Subsequent decomposition of the diarylpalladium intermediate gives the biaryl product.

Exercise 10.8.1

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

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

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).

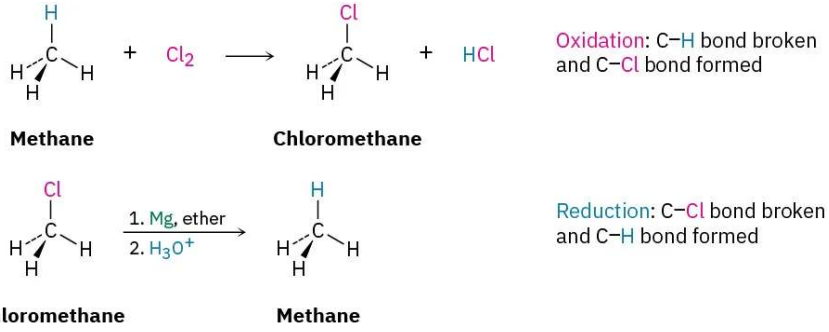
Oxidation: Decreases electron density on carbon by:

- forming one of these: C−O C−N C−X
- or breaking this:C–H

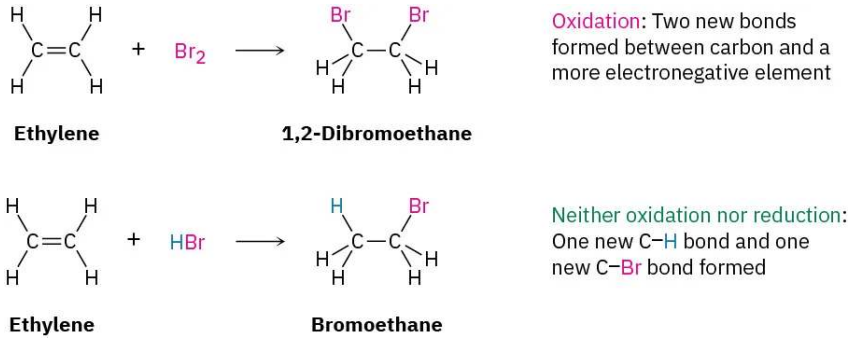
Reduction: Increases electron density on carbon by:

- forming this: C–H
- or breaking one of these: C–O C–N C–X

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.



As other examples, the reaction of an alkene with Br_2 to yield a 1,2-dibromide is an oxidation because two C−Br bonds are formed, but the reaction of an alkene with HBr to yield an alkyl bromide is neither an oxidation nor a reduction because both a C−H and a C−Br bond are formed.



A list of compounds of increasing oxidation level is shown in Figure 10.7. 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.

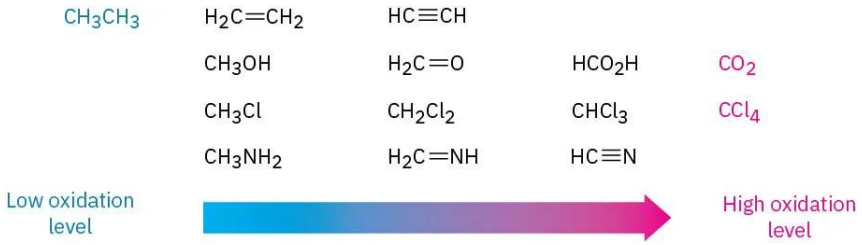
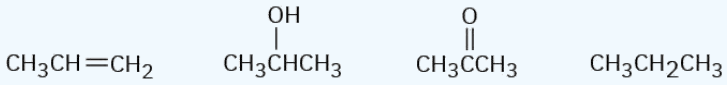


Figure 10.7: Oxidation levels of some common compounds.

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:

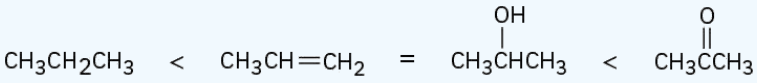


Strategy

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.

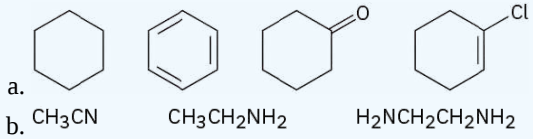
Solution

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

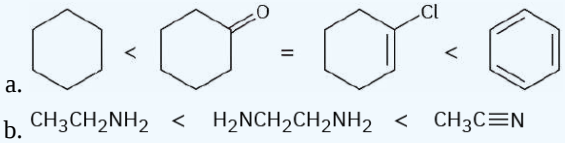


Exercise 10.9.1

Rank both sets of compounds in order of increasing oxidation level:

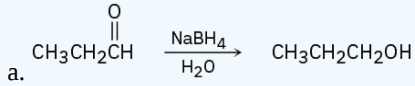


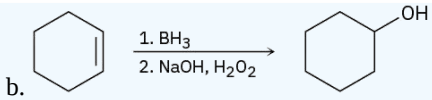
Answer



Exercise 10.9.2

Tell whether each of the following reactions is an oxidation, a reduction, or neither.



b. 

Answer

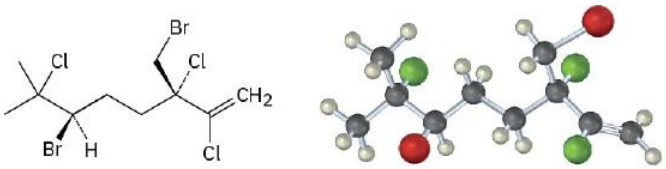
1. Reduction
2. Neither

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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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10.11: Key Terms

- alkyl halide
- allylic
- carbanion
- delocalized
- Gilman reagent (LiR_2Cu)
- Grignard reagent (RMgX)
- organohalide
- organometallic

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10.12: Summary

Alkyl halides are not often found in terrestrial organisms, but the kinds of reactions they undergo are among the most important and well-studied reaction types in organic chemistry. In this chapter, we saw how to name and prepare alkyl halides, and we'll soon make a detailed study of their substitution and elimination reactions.

Simple alkyl halides can be prepared by radical halogenation of alkanes, but mixtures of products usually result. The reactivity order of alkanes toward halogenation is identical to the stability order of radicals: $R_3C\cdot > R_2CH\cdot > RCH_2\cdot$. Alkyl halides can also be prepared from alkenes by reaction with *N*-bromosuccinimide (NBS) to give the product of **allylic** bromination. The NBS bromination of alkenes takes place through an intermediate allylic radical, which is stabilized by resonance.

Alcohols react with HX to form alkyl halides, but the reaction works well only for tertiary alcohols, R_3COH. Primary and secondary alkyl halides are normally prepared from alcohols using either $SOCl_2$, PBr_3, or HF in pyridine. Alkyl halides react with magnesium in ether solution to form organomagnesium halides, called **Grignard reagents (RMgX)**, which are both nucleophilic and strongly basic.

Alkyl halides also react with lithium metal to form organolithium reagents, RLi. In the presence of CuI, these form diorganocoppers, or **Gilman reagents (LiR_2Cu)**. Gilman reagents react with organohalides to yield coupled hydrocarbon products.

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10.13: Summary of Reactions

No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.

1. Preparation of alkyl halides
   a. From alkenes by allylic bromination (Section 10.4)



   b. From alcohols (Section 10.6)
      1. Reaction with HX



Reactivity order: 3° > 2° > 1°

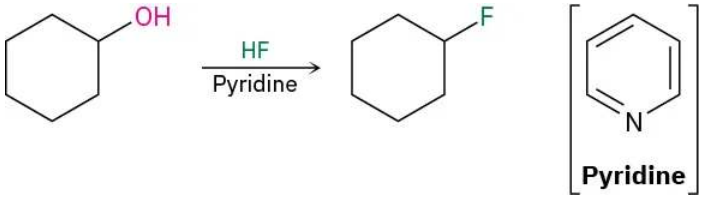
      2. Reaction of 1° and 2° alcohols with $SOCl_2$



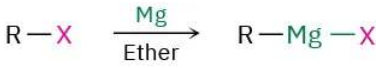
      3. Reaction of 1° and 2° alcohols with PBr_3



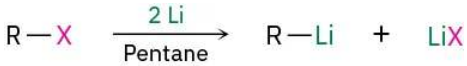
      4. Reaction of 1° and 2° alcohols with HF–pyridine

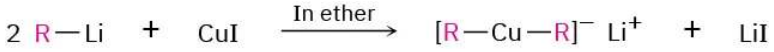


2. Reactions of alkyl halides
   a. Formation of Grignard (organomagnesium) reagents (Section 10.7)

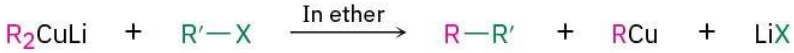


   b. Formation of Gilman (diorganocopper) reagents (Section 10.8)

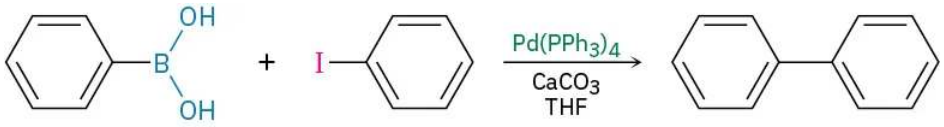




   c. Organometallic coupling (Section 10.8)
      (1) Diorganocopper reaction



      (2) Palladium-catalyzed Suzuki–Miyaura reaction



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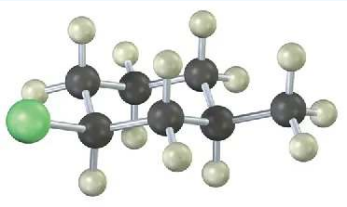
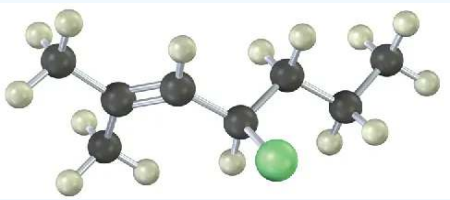
10.14: Additional Problems

10 • Additional Problems

Visualizing Chemistry

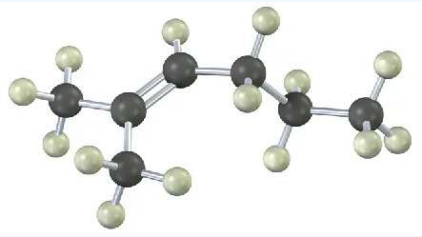
Exercise 10.14.14

Give IUPAC names for the following alkyl halides (green = Cl):

(a)  (b) 

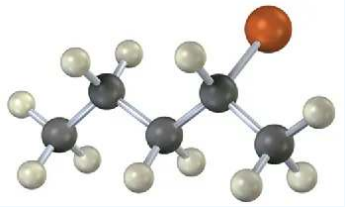
Exercise 10.14.15

Show the product(s) of reaction of the following alkenes with NBS:

(a)  (b) [Image missing]

Exercise 10.14.16

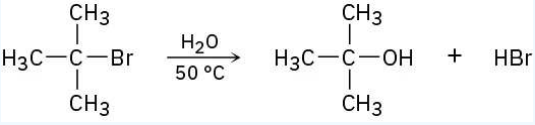
The following alkyl bromide can be prepared by reaction of the alcohol (*S*)-2-pentanol with PBr_3. Name the compound, assign (*R*) or (*S*) stereochemistry, and tell whether the reaction of the alcohol results in the same stereochemistry or a change in stereochemistry (reddish brown = Br).



Mechanism Problems

Exercise 10.14.17

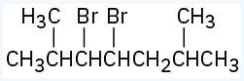
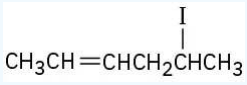
In light of the fact that tertiary alkyl halides undergo spontaneous dissociation to yield a carbocation plus halide ion (see Problem 10-41), propose a mechanism for the following reaction.

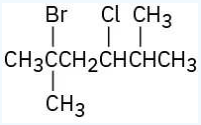
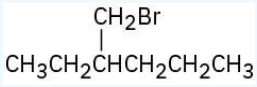


Naming Alkyl Halides

? Exercise 10.14.18

Name the following alkyl halides:

(a)  (b) 

(c)  (d)  (e) $ClCH_2CH_2CH_2C{\equiv}CCH_2Br$

? Exercise 10.14.19

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

? Exercise 10.14.20

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

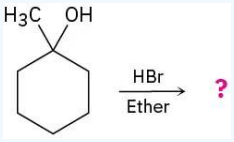
? Exercise 10.14.21

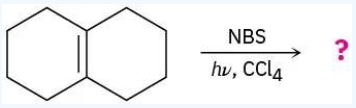
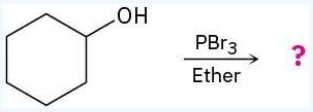
How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

(a) Chlorocyclopentane (b) Methylcyclopentane (c) 3-Bromocyclopentene (d) Cyclopentanol (e) Cyclopentylcyclopentane (f) 1,3-Cyclopentadiene

? Exercise 10.14.22

Predict the product(s) of the following reactions:

(a)  (b) $CH_3CH_2CH_2CH_2OH \xrightarrow{SOCl_2} ?$

(c)  (d) 

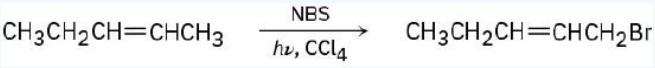
(e) $CH_3CH_2CHBrCH_3 \xrightarrow[Ether]{Mg} A? \xrightarrow{H_2O} B?$

(f) $CH_3CH_2CH_2CH_2Br \xrightarrow[Pentane]{Li} A? \xrightarrow{CuI} B?$

(g) $CH_3CH_2CH_2CH_2Br + (CH_3)_2CuLi \xrightarrow{Ether} ?$

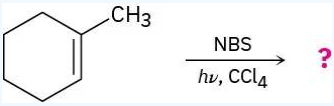
? Exercise 10.14.23

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?



? Exercise 10.14.24

What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?

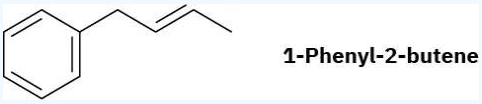


? Exercise 10.14.25

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?

? Exercise 10.14.26

What product would you expect from the reaction of 1-phenyl-2-butene with NBS? Explain.

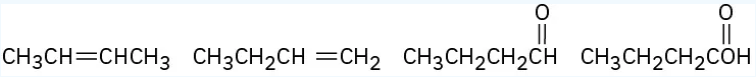


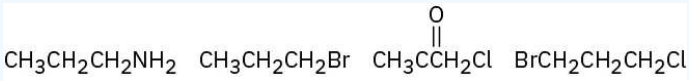
1-Phenyl-2-butene

Oxidation and Reduction

? Exercise 10.14.27

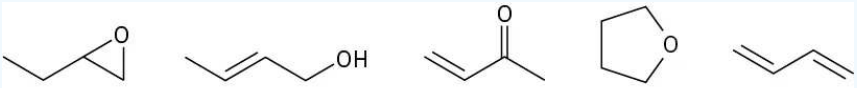
Rank the compounds in each of the following series in order of increasing oxidation level:

(a) 

(b) 

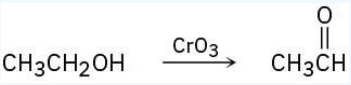
? Exercise 10.14.28

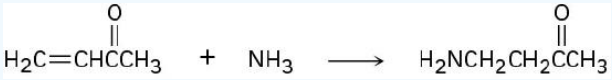
Which of the following compounds have the same oxidation level, and which have different levels?

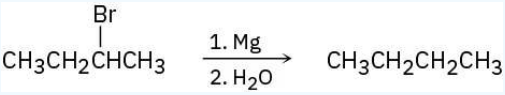


? Exercise 10.14.29

Tell whether each of the following reactions is an oxidation, a reduction, or neither:

(a) 

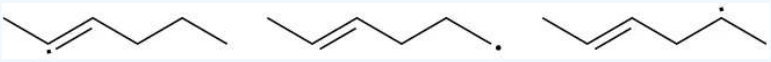
(b) 

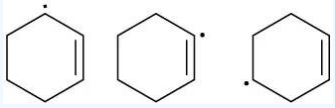
(c) 

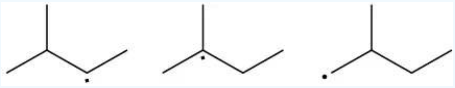
General Problems

? Exercise 10.14.30

Arrange the following radicals from most stable to least stable.

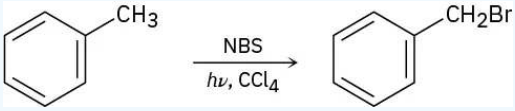
(a) 

(b) 

(c) 

? Exercise 10.14.31

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 in Table 6.3.

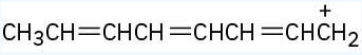


? Exercise 10.14.32

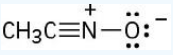
Draw resonance structures for the benzyl radical, $C_6H_5CH_2\cdot$, the intermediate produced in the NBS bromination reaction of toluene (Problem 10-31).

? Exercise 10.14.33

Draw resonance structures for the following species:

(a) 

(b) 

(c) 

? Exercise 10.14.34

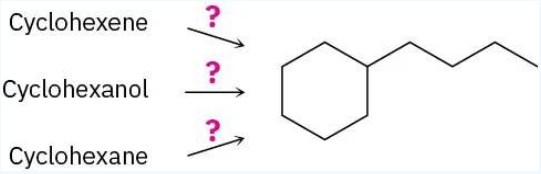
(*S*)-3-Methylhexane undergoes radical bromination to yield optically inactive 3-bromo-3-methylhexane as the major product. Is the product chiral? What conclusions can you draw about the radical intermediate?

? Exercise 10.14.35

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.)

? Exercise 10.14.36

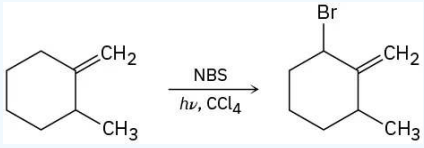
How would you carry out the following syntheses?

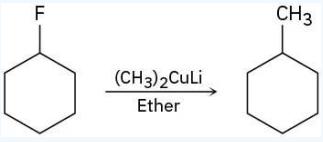


? Exercise 10.14.37

The syntheses shown here are unlikely to occur as written. What is wrong with each?

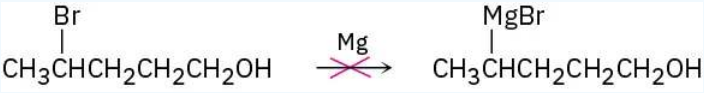
(a) $CH_3CH_2CH_2F \xrightarrow[2.\ H_3O^+]{1.\ Mg} CH_3CH_2CH_3$

(b) 

(c) 

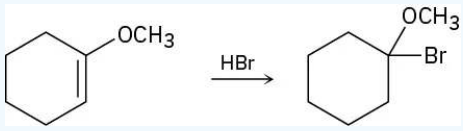
? Exercise 10.14.38

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.



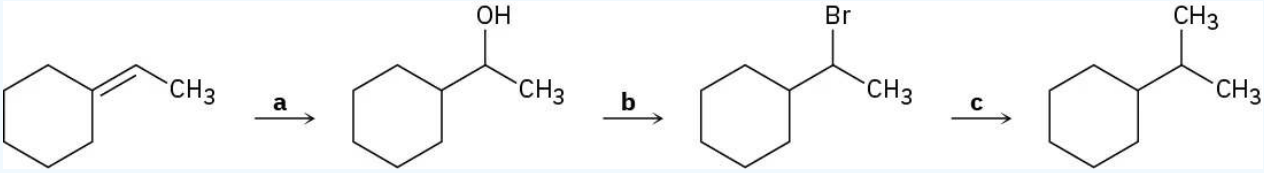
? Exercise 10.14.39

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.



Exercise 10.14.40

Identify the reagents a–c in the following scheme:



Exercise 10.14.41

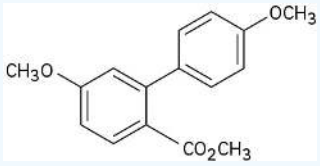
Tertiary alkyl halides, R_3CX, undergo spontaneous dissociation to yield a carbocation, R_3C^+, plus halide ion. Which do you think reacts faster, $(CH_3)_3CBr$ or $H_2C{=}CHC(CH_3)_2Br$? Explain.

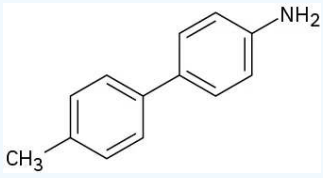
Exercise 10.14.42

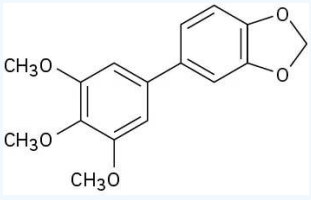
Carboxylic acids (RCO_2H; $pK_a \approx 5$) are approximately 10^{11} times more acidic than alcohols (ROH; $pK_a \approx 16$). In other words, a carboxylate ion (RCO_2^-) is more stable than an alkoxide ion (RO^-). Explain using resonance.

Exercise 10.14.43

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) 

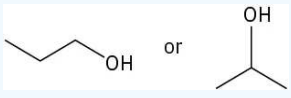
Exercise 10.14.44

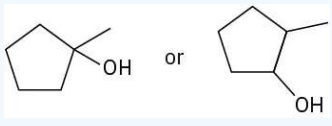
The relative rate of radical bromination is 1 : 82 : 1640 for 1° : 2° : 3° hydrogens, respectively. Draw all of the monobrominated products that you might obtain from the radical bromination of the compounds below. Calculate the relative percentage of each.

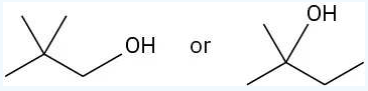
(a) methylcyclobutane (b) 3,3-dimethylpentane (c) 3-methylpentane

Exercise 10.14.45

Choose the alcohol from each pair below that would react faster with HX to form the corresponding alkyl halide.

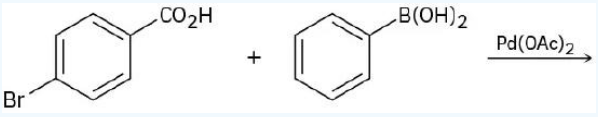
(a) 

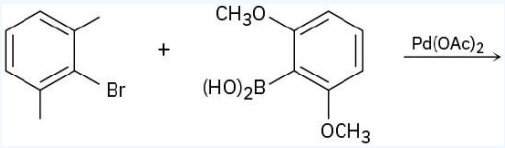
(b) 

(c) 

Exercise 10.14.46

Predict the product and provide the entire catalytic cycle for the following Suzuki–Miyaura reactions.

(a) 

(b) 

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CHAPTER OVERVIEW

11: Reactions of Alkyl Halides- Nucleophilic Substitutions and Eliminations

Learning Objectives

After you have completed Chapter 11, you should be able to

- fulfill all of the detailed objectives listed under each individual section.
- use the reactions studied in this chapter with those from earlier ones when designing multistep syntheses.
- use the reactions and concepts discussed in this chapter to solve road map problems.
- define, and use in context, the key terms introduced.

In this course, you have already seen several examples of nucleophilic substitution reactions; now you will see that these reactions can occur by two different mechanisms. You will study the factors that determine which mechanism will be in operation in a given situation, and examine possible ways for increasing or decreasing the rates at which such reactions occur. The stereochemical consequences of both mechanisms will also be discussed. Elimination reactions often accompany nucleophilic substitution; so these reactions are also examined in this chapter. Again you will see that two different mechanisms are possible, and, as in the case of nucleophilic substitution reactions, chemists have learned a great deal about the factors that determine which mechanism will be observed when a given alkyl halide undergoes such a reaction.

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11.3: The Sn2 Reaction
11.4: Characteristics of the SN2 Reaction
11.5: Characteristics of the SN1 Reaction
11.6: Biological Substitution Reactions
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11.8: The E2 Reaction and the Deuterium Isotope Effect
11.9: The E2 Reaction and Cyclohexane Conformation
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11.11: Biological Elimination Reactions
11.12: A Summary of Reactivity - SN1, SN2, E1, E1cB, and E2
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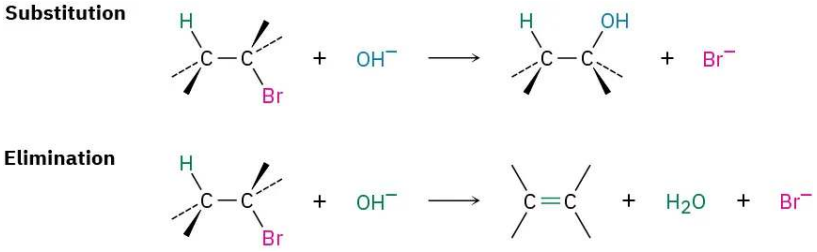
11.1: Why This Chapter?

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 11.1.1: 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.



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11.2: 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 11.2.1.

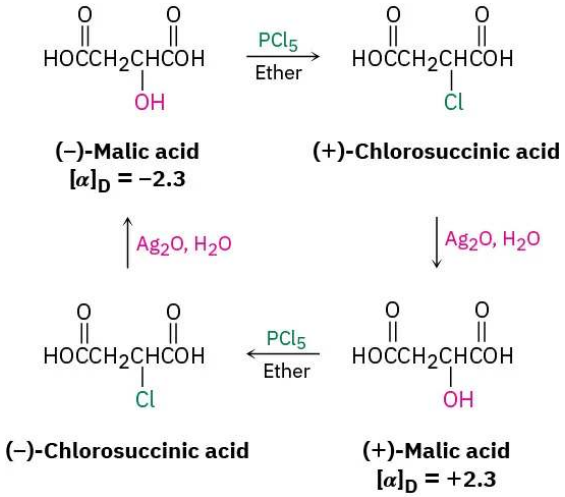


Figure 11.2.1: Walden's cycle of reactions interconverting (+)- and (–)-malic acids.

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 11.2.2). 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.)

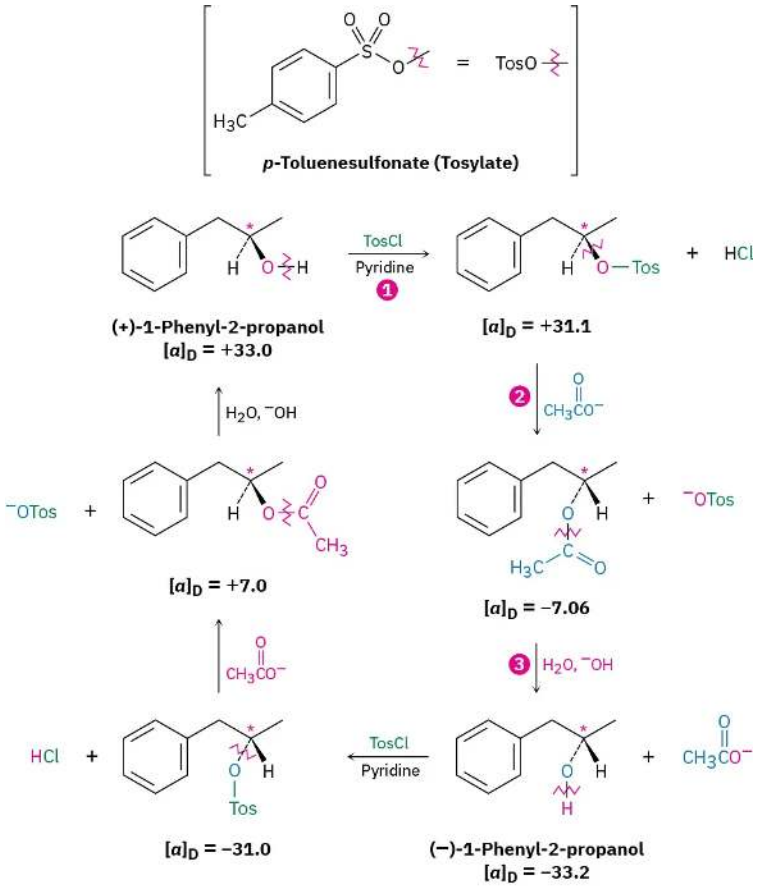
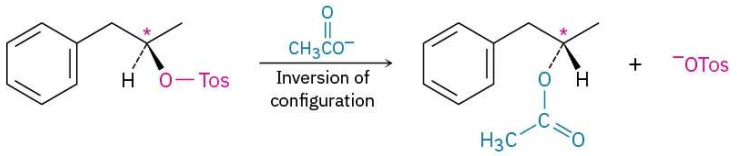


Figure 11.2.2: A Walden cycle interconverting (+) and (–) enantiomers of 1-phenyl-2-propanol. Chirality centers are marked by asterisks, and the bonds broken in each reaction are indicated by red wavy lines. The inversion of chirality occurs in step **2**, where acetate ion substitutes for tosylate ion.

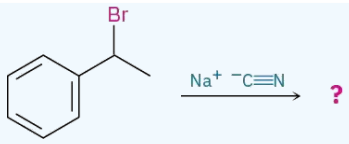
In the three-step reaction sequence shown in Figure 11.2.2, (+)-1-phenyl-2-propanol is interconverted with its (–) enantiomer, so at least one of the three steps must involve an inversion of configuration at the chirality center. Step **1**, formation of a tosylate, occurs by breaking the O–H bond of 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 11.2.1: Predicting the Stereochemistry of a Nucleophilic Substitution Reaction

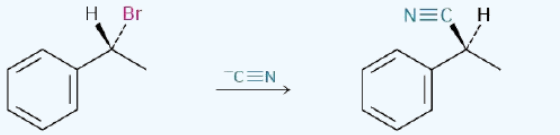
What product would you expect from a nucleophilic substitution reaction of (*R*)-1-bromo-1-phenylethane with cyanide ion, $^{-}C{\equiv}N$, as nucleophile? Show the stereochemistry of both reactant and product, assuming that inversion of configuration occurs.



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 11.2.1

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

(*R*)-1-Methylpentyl acetate, $CH_3CO_2CH(CH_3)CH_2CH_2CH_2CH_3$

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11.3: The Sn2 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 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 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 [RX] or [$^-$OH] changes, the rate of the reaction changes proportionately.

$$\begin{aligned} \text{Reaction rate} &= \text{Rate of disappearance of reactant} \\ &= \text{Rate of appearance of product} \\ &= k \times [\text{RX}] \times [^-\text{OH}] \end{aligned} \tag{11.3.1}$$

where

- [RX] is the CH_3Br concentration in molarity,
- [$^-$OH] is the $^-$OH concentration in molarity, and
- k is a constant value (the rate constant)

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 11.3.1 for the reaction of (*S*)-2-bromobutane with HO^- to give (*R*)-2-butanol.

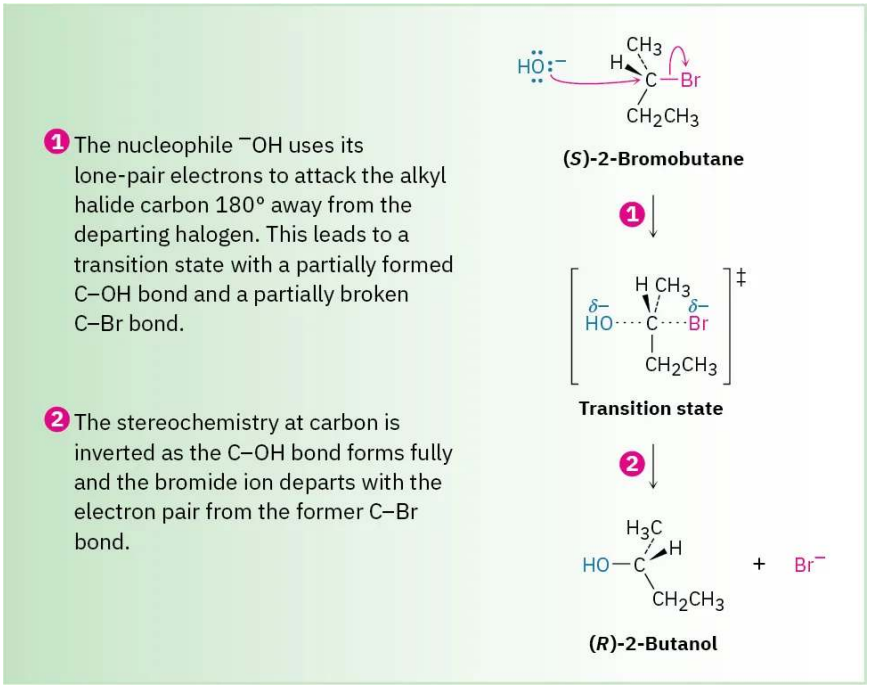


Figure 11.3.1: The mechanism of the S_N2 reaction. The reaction takes place in a single step when the incoming nucleophile approaches from a direction 180° away from the leaving halide ion, thereby inverting the stereochemistry at carbon.

As shown in Figure 11.3.1, 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 11.3.2).

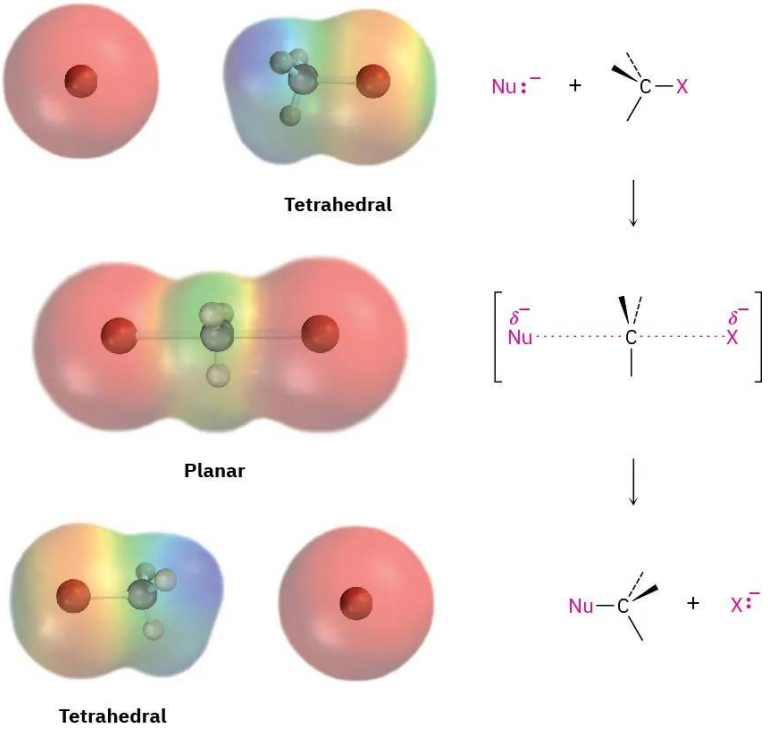


Figure 11.3.2: The transition state of an S_N2 reaction has a planar arrangement of the carbon atom and the remaining three groups. Electrostatic potential maps show that **negative charge** is delocalized in the transition state.

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.

Exercise 11.3.1

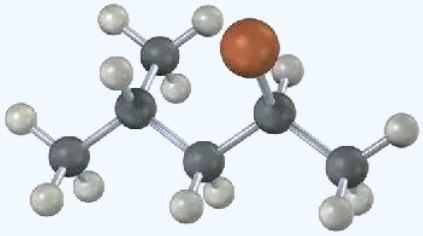
What product would you expect to obtain from S_N2 reaction of OH^- with (*R*)-2-bromobutane? Show the stereochemistry of both the reactant and product.

Answer

(*S*)-2-Butanol

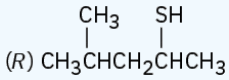
Exercise 11.3.2

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

(*S*)-2-Bromo-4-methylpentane ⟶



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11.4: Characteristics of the SN2 Reaction

Now that we know how S_N2 reactions occur, we need to see how they can be used and what variables affect them. Some S_N2 reactions are fast, and some are slow; some take place in high yield and others in low yield. Understanding the factors involved can be of tremendous value. 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 $\Delta G^{\ddagger}$, the energy difference between reactant ground state and transition state. A change in reaction conditions can affect $\Delta G^{\ddagger}$ either by changing the reactant energy level or by changing the transition-state energy level. Lowering the reactant energy or raising the transition-state energy increases $\Delta G^{\ddagger}$ and decreases the reaction rate; raising the reactant energy or decreasing the transition-state energy decreases $\Delta G^{\ddagger}$ and increases the reaction rate (Figure 11.4.1). We'll see examples of all these effects as we look at S_N2 reaction variables.

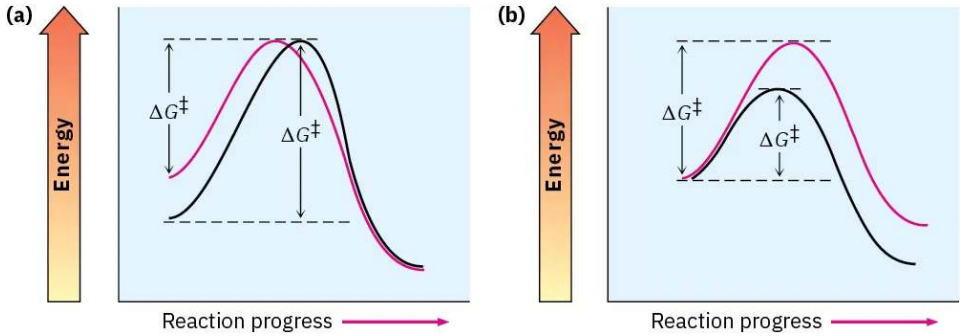


Figure 11.4.1: The effects of changes in reactant and transition-state energy levels on reaction rate. (a) A higher reactant energy level (red curve) corresponds to a faster reaction (smaller $\Delta G^{\ddagger}$). (b) A higher transition-state energy level (red curve) corresponds to a slower reaction (larger $\Delta G^{\ddagger}$).

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. In other words, the transition state for 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 11.4.2).

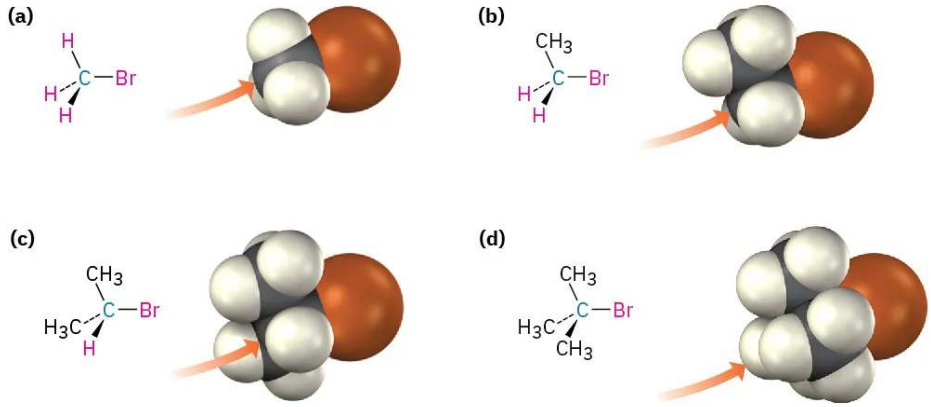
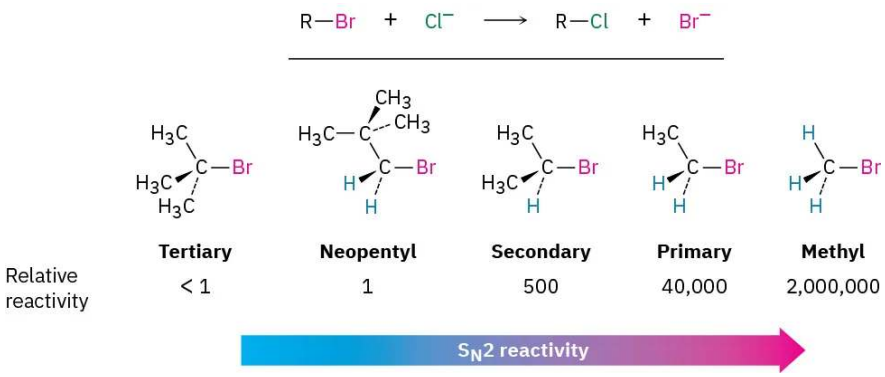


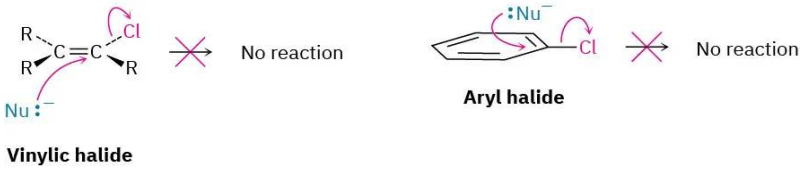
Figure 11.4.2: Steric hindrance to the S_N2 reaction. As the models indicate, the carbon atom in **(a)** bromomethane is readily accessible, resulting in a fast S_N2 reaction. The carbon atoms in **(b)** bromoethane (primary), **(c)** 2-bromopropane (secondary), and **(d)** 2-bromo-2-methylpropane (tertiary) are successively more hindered, resulting in successively slower S_N2 reactions.

As Figure 11.4.2 shows, the difficulty of 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:

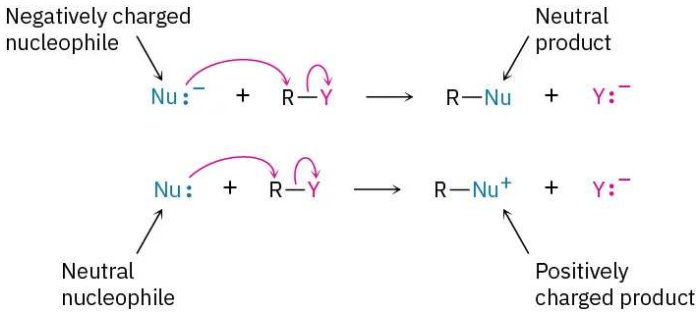


Vinylic halides (\(\ce{R2C=CR}\)) and aryl halides are not shown on this reactivity list because they are unreactive toward S_N2 displacement. This lack of reactivity is due to steric factors: the incoming nucleophile would have to approach in the plane of the carbon–carbon double bond and burrow through part of the molecule to carry out a backside displacement.

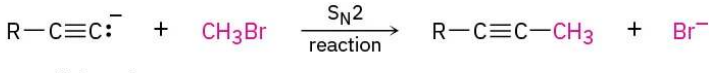


The Nucleophile

Another variable that has a major effect on the S_N2 reaction is the nature of the nucleophile. Any species, either neutral or negatively charged, can act as a nucleophile as long as it has an unshared pair of electrons; that is, as long as it is a Lewis base. If the nucleophile is negatively charged, the product is neutral; if the nucleophile is neutral, the product is positively charged.



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

Table 11.4.1 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.

$$\mathrm{Nu:^- + CH_3Br \longrightarrow CH_3Nu + Br^-}$$

There are large differences in the rates at which various nucleophiles react.

Table 11.4.1: 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
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 11.4.1? 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 nucleophilicities aren't always simple, but some trends can be detected from the data of Table 11.4.1.

- **Nucleophilicity roughly parallels basicity** when comparing nucleophiles that have the same reacting 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 11.4.1

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

a. 1-Iodobutane
b. 1-Butanol
c. 1-Hexyne
d. Butylammonium bromide

? Exercise 11.4.2

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

a. $(CH_3)_2N^-$
b. $(CH_3)_3N$
c. H_2S

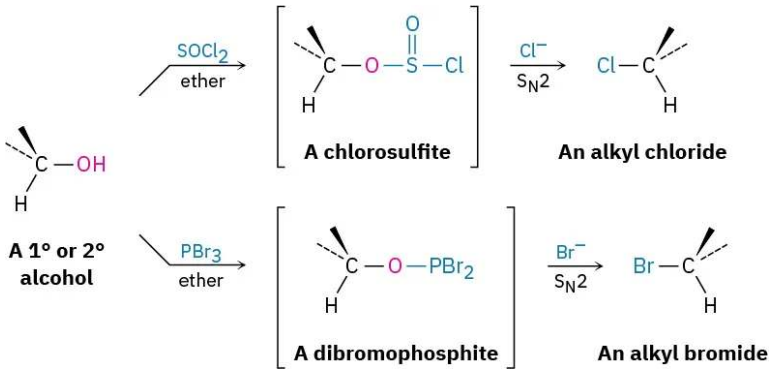
The Leaving Group

Still another variable that can affect the S_N2 reaction is the nature of the group displaced by the incoming nucleophile, the leaving group. 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 energy of the transition state 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.

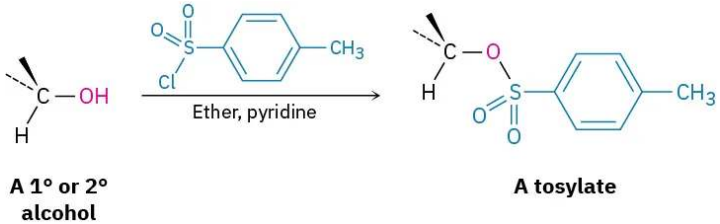
	OH^-, NH_2^-, OR^-	F^-	Cl^-	Br^-	I^-	$TosO^-$
Relative reactivity	<<1	1	200	10,000	30,000	60,000

Leaving group reactivity

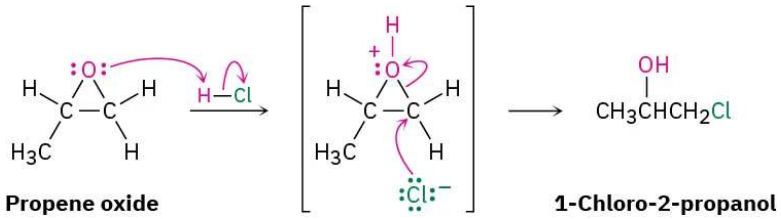
It's just as important to know which are poor leaving groups as to know which are good, and the preceding data clearly indicate that F^-, HO^-, RO^-, and H_2N^- are not displaced by nucleophiles. In other words, alkyl fluorides, alcohols, ethers, and amines do not typically undergo S_N2 reactions. To 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.



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. We'll look at the process in more detail in **Section 18.5**.



? Exercise 11.4.2

Rank the following compounds in order of their expected reactivity toward S_N2 reaction:

CH_3Br, CH_3OTos, $(CH_3)_3CCl$, $(CH_3)_2CHCl$

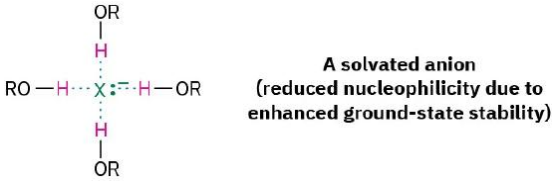
Answer

$CH_3OTos > CH_3Br > (CH_3)_2CHCl > (CH_3)_3CCl$

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. 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.



Solvent	CH_3OH	H_2O	DMSO	DMF	CH_3CN	HMPA
Relative reactivity	1	7	1300	2800	5000	200,000

Solvent reactivity

? Exercise 11.4.4

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

Similar to protic solvents

A Summary of S_N2 Reaction Characteristics

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 11.4.3:

- **Substrate** Steric hindrance raises the energy of the S_N2 transition state, increasing $\Delta G^{\ddagger}$ and decreasing the reaction rate (Figure 11.4.3*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 11.4.3*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 11.4.3*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 11.4.3*d*).

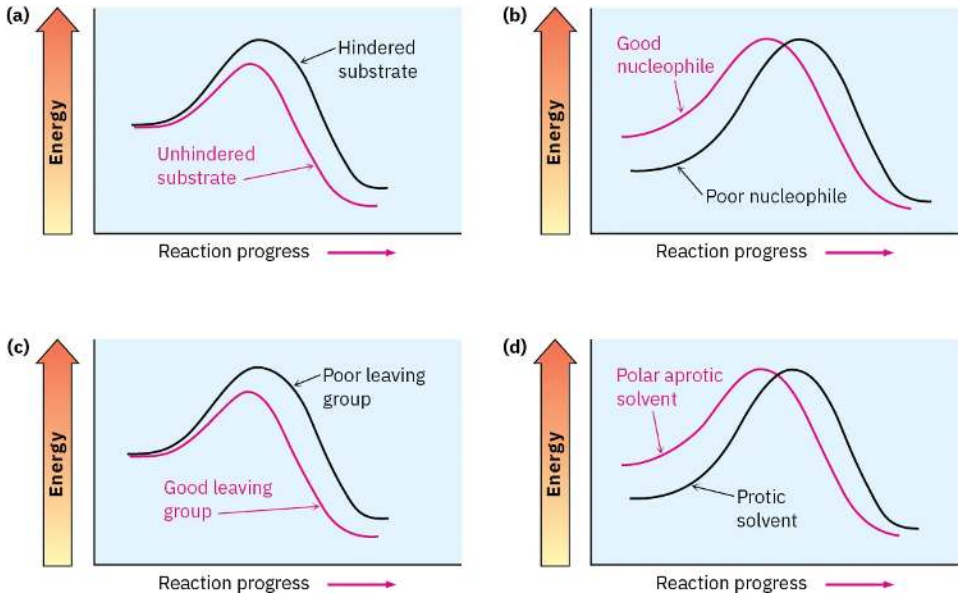


Figure 11.4.3: Energy diagrams showing the effects of (a) substrate, (b) nucleophile, (c) leaving group, and (d) solvent on S_N2 reaction rates. Substrate and leaving group effects are felt primarily in the transition state. Nucleophile and solvent effects are felt primarily in the reactant ground state.

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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.

The Substrate

According to the Hammond postulate (Section 7.10), 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. The more stable the carbocation intermediate, the faster the S_N1 reaction.

We saw in Section 7.9 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 11.5.1 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.

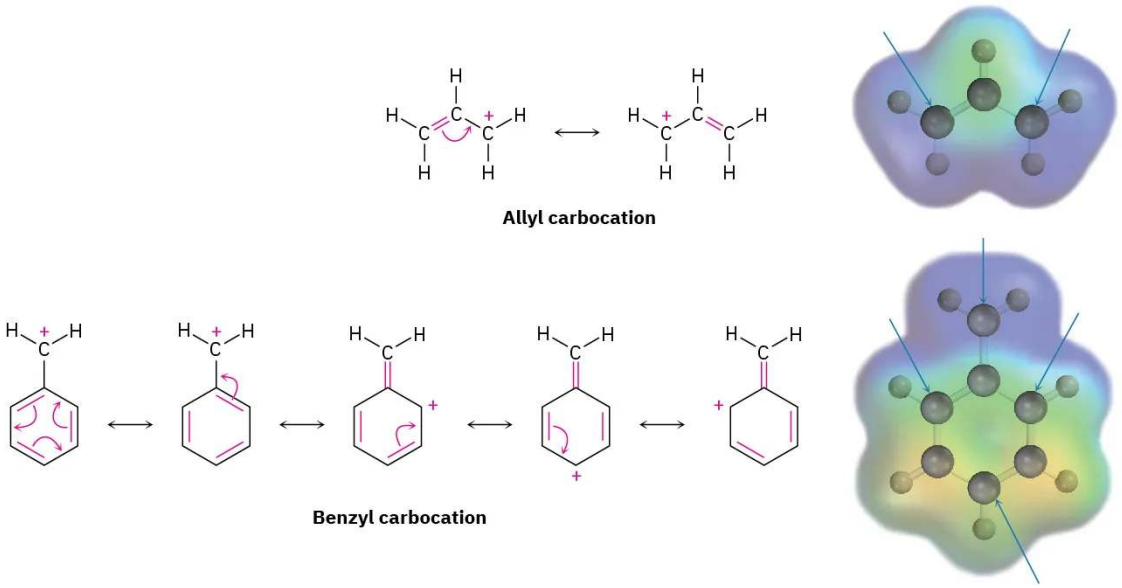
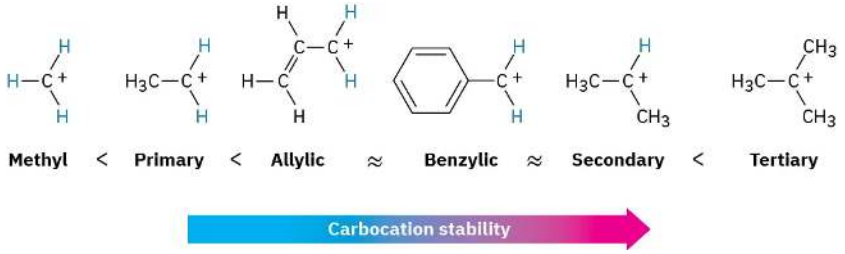


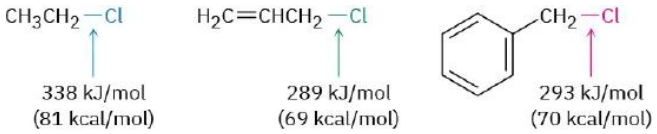
Figure 11.5.1: Resonance forms of allylic and benzylic carbocations. The positive charge is delocalized over the π system in both. **Electron-poor atoms** are indicated by blue arrows.

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.



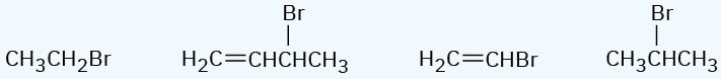
We should also note parenthetically that primary allylic and benzylic substrates are particularly reactive in S_N2 reactions as well as in S_N1 reactions. Allylic and benzylic C–X bonds are about 50 kJ/mol (12 kcal/mol) weaker than the corresponding saturated bonds

and are therefore more easily broken.



? Exercise 11.5.1

Rank the following substances in order of their expected S_N1 reactivity:



Answer

$H_2C{=}CHCH(Br)CH_3 > CH_3CH(Br)CH_3 > CH_3CH_2Br > H_2C{=}CHBr$

? Exercise 11.5.2

3-Bromo-1-butene and 1-bromo-2-butene undergo S_N1 reaction at nearly the same rate, even though one is a secondary halide and the other is primary. Explain.

Answer

The same allylic carbocation intermediate is formed.

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



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 10.5). As shown in Figure 11.5.2, the alcohol is first protonated and then spontaneously loses H_2O to generate a carbocation, which reacts with halide ion to give the alkyl halide. 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.

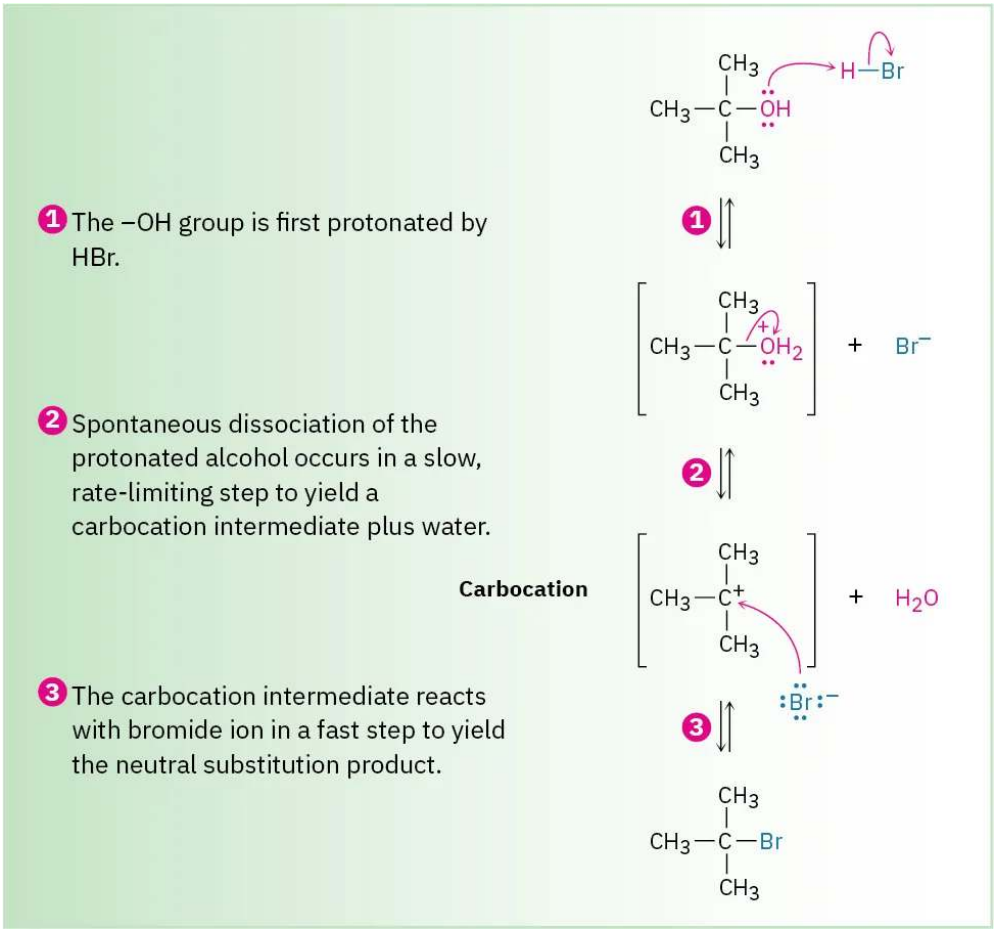
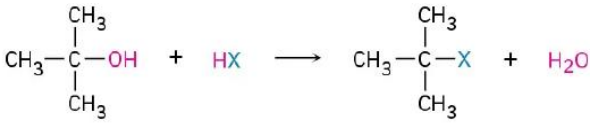


Figure 11.5.2: The mechanism of the S_N1 reaction of a tertiary alcohol with HBr to yield an alkyl halide. Neutral water is the leaving group (step **2**)

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.



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.

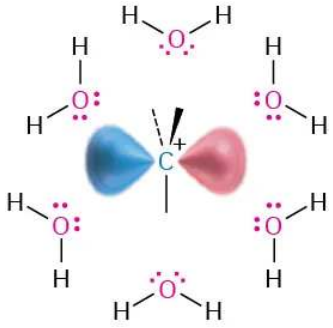
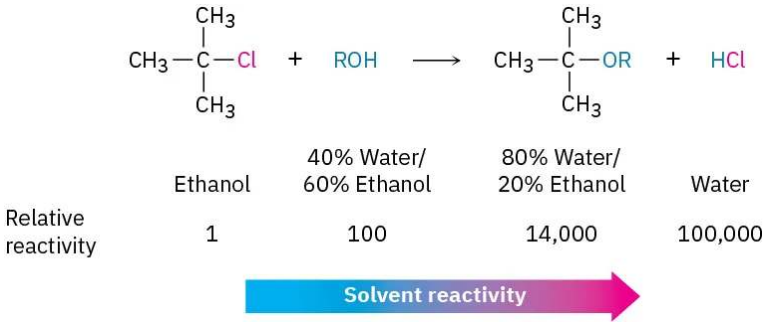


Figure 11.5.3: Solvation of a carbocation by water. The electron-rich oxygen atoms of solvent molecules orient around the positively charged carbocation and thereby stabilize it.

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. 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 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.

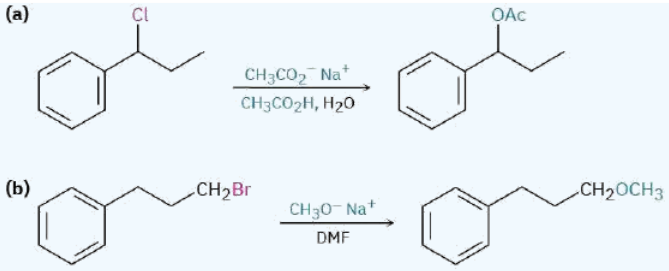
A Summary of S_N1 Reaction Characteristics

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 stabilize the carbocation intermediate by solvation, thereby increasing the reaction rate.

✔ Worked Example 11.5.1: 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.

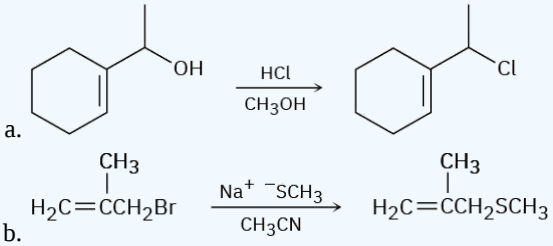
Solution

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 11.5.3

Predict whether each of the following substitution reactions is likely to be S_N1 or S_N2: (a)



Answer

a. S_N1

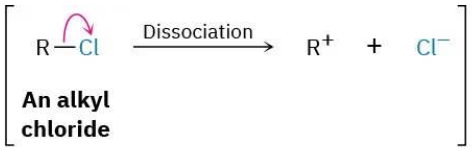
b. S_N2

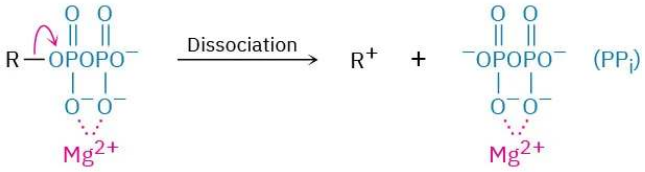
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11.6: Biological Substitution Reactions

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 the Chapter 8 *Chemistry Matters* and will discuss in **Section 27.5**. 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 11.6.1). 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.

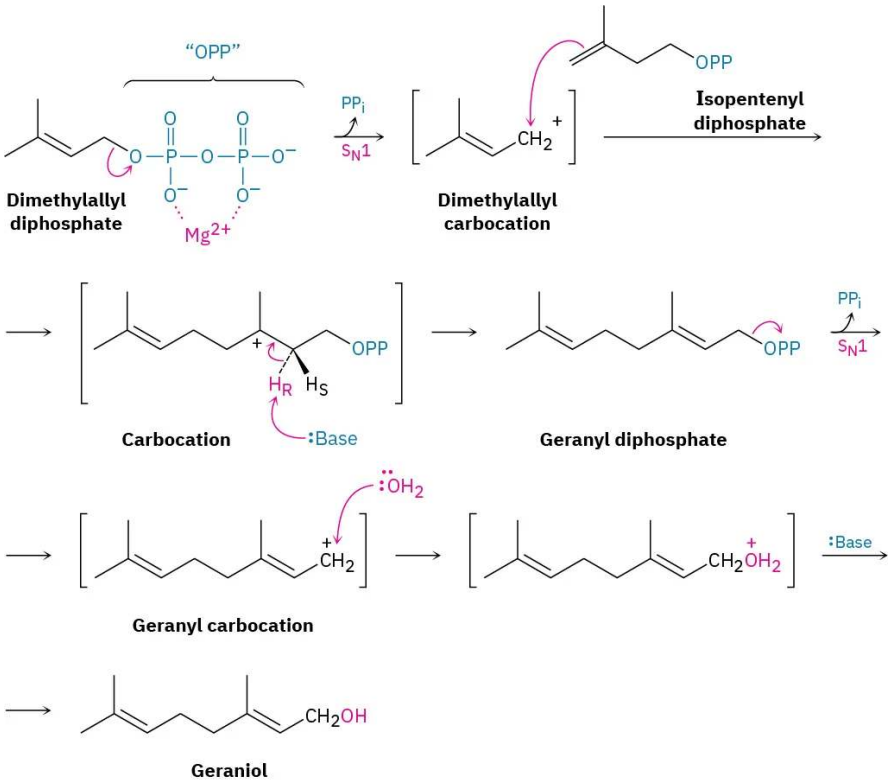


Figure 11.6.1: Biosynthesis of geraniol from dimethylallyl diphosphate. Two S_N1 reactions occur, both with diphosphate ion as the leaving group.

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 11.6.2). In effect, *S*-adenosylmethionine is simply a biological equivalent of CH_3Cl.

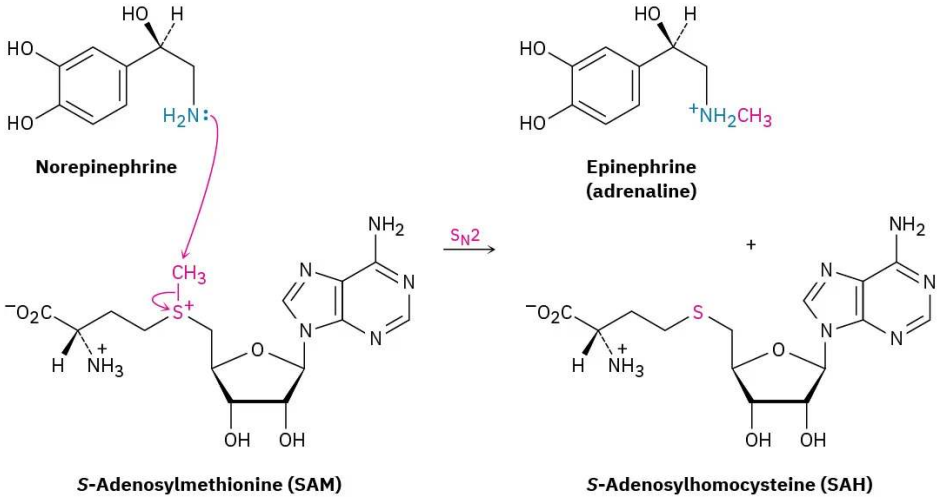
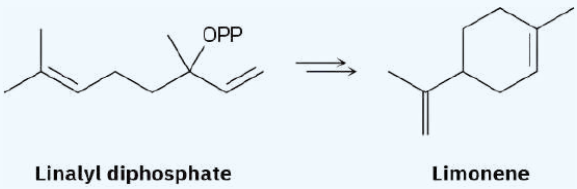


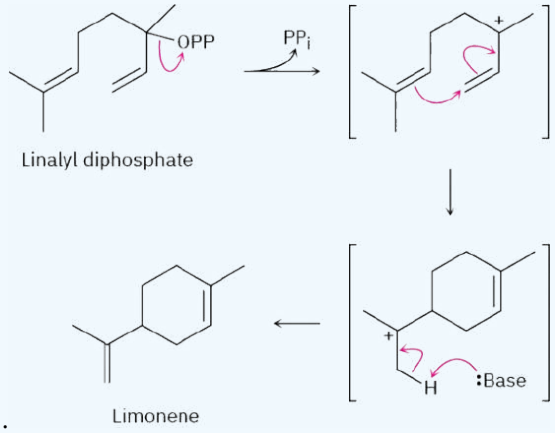
Figure 11.6.2: The biosynthesis of epinephrine from norepinephrine occurs by an S_N2 reaction with *S*-adenosylmethionine.

Exercise 11.6.1

Review the mechanism of geraniol biosynthesis shown in Figure 11.6.1, and propose a mechanism for the biosynthesis of limonene from linalyl diphosphate.



Answer



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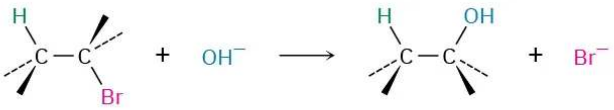
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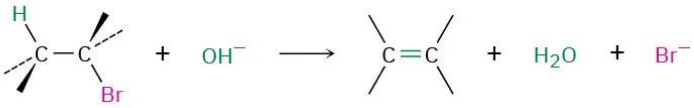
11.7: Elimination Reactions- Zaitsev's Rule

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:

Substitution



Elimination

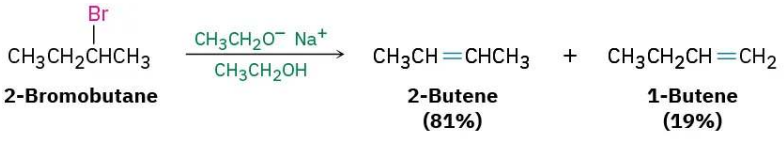


Elimination reactions are more complex than substitution reactions for several reasons. One is the problem of regiochemistry. What product results by loss of HX from an unsymmetrical halide? In fact, elimination reactions almost always give mixtures of alkene products, and the best we can usually do is to predict which will be the major product.

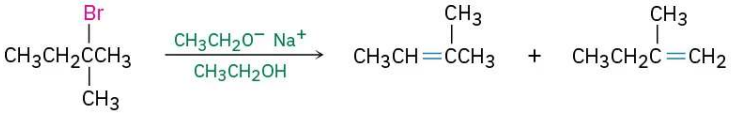
According to Zaitsev's rule, formulated in 1875 by the Russian chemist Alexander Zaitsev, base-induced elimination reactions generally (although not always) give the more stable alkene product—that is, the alkene with more alkyl substituents on the double-bond carbons. In the following two cases, for example, the more highly substituted alkene product predominates.

ZAITSEV'S RULE

In the elimination of HX from an alkyl halide, the more highly substituted alkene product predominates.



2-Bromobutane — **2-Butene (81%)** + **1-Butene (19%)**

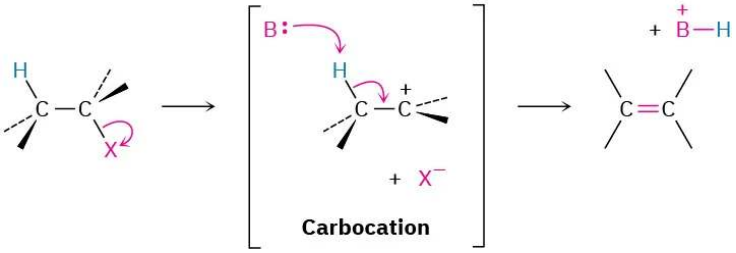


2-Bromo-2-methylbutane — **2-Methyl-2-butene (70%)** + **2-Methyl-1-butene (30%)**

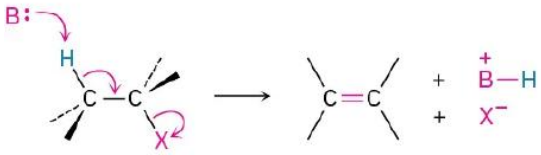
Another factor that complicates a study of elimination reactions is that they can take place by different mechanisms, just as substitutions can. We'll consider three of the most common mechanisms—the E1, E2, and E1cB reactions—which differ in the timing of C–H and C–X bond-breaking.

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.

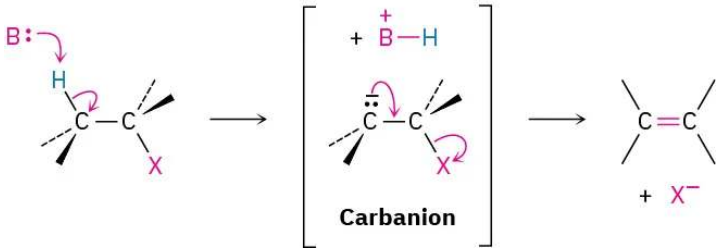
E1 Reaction: C–X bond breaks first to give a carbocation intermediate, followed by base removal of a proton to yield the alkene.



E2 Reaction: C–H and C–X bonds break simultaneously, giving the alkene in a single step without intermediates.

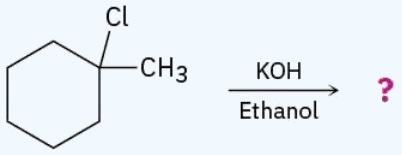


E1cB Reaction: C–H bond breaks first, giving a carbanion intermediate that loses X^- to form the alkene.



Worked Example 11.7.1: Predicting the Product of an Elimination Reaction

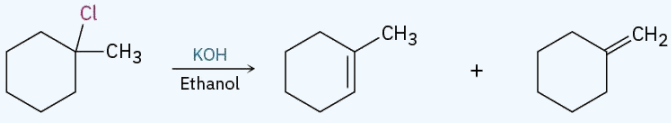
What product would you expect from reaction of 1-chloro-1-methylcyclohexane with KOH in ethanol?



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.

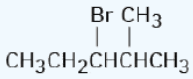
Solution

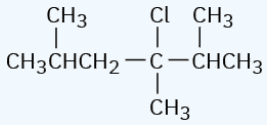


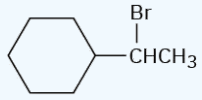
1-Chloro-1-methyl-cyclohexane | **1-Methylcyclohexene (major)** | **Methylenecyclohexane (minor)**

Exercise 11.7.1

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. 

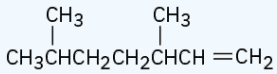
c. 

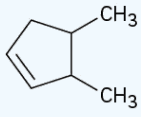
Answer

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 11.7.2

What alkyl halides might the following alkenes have been made from?

a. 

b. 

Answer

a. 1-Bromo-3,6-dimethylheptane
b. 4-Bromo-1,2-dimethylcyclopentane

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11.8: The E2 Reaction and the Deuterium Isotope Effect

The E2 reaction (for *elimination, bimolecular*) occurs when an alkyl halide is treated with a strong base, such as hydroxide ion or alkoxide ion (RO^-). It is the most commonly occurring pathway for elimination and can be formulated as shown in Figure 11.8.1.

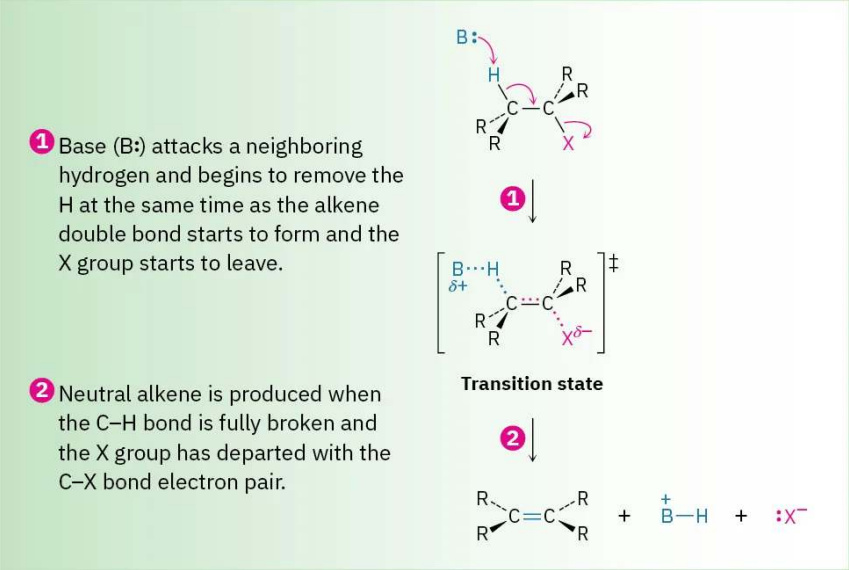
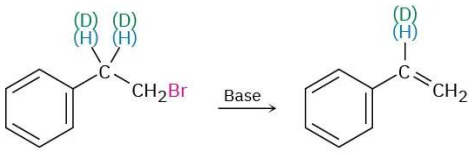


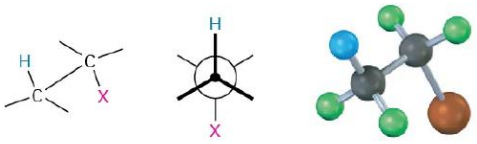
Figure 11.8.1: Mechanism of the E2 reaction of an alkyl halide. The reaction takes place in a single step through a transition state in which the double bond begins to form at the same time the H and X groups are leaving.

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. 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.

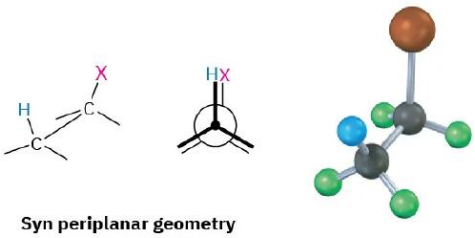
A second piece of evidence in support of the E2 mechanism is provided by a phenomenon known as the deuterium isotope effect. For reasons that we won't go into, a carbon–hydrogen bond is weaker by about 5 kJ/mol (1.2 kcal/mol) than the corresponding carbon–deuterium bond. Thus, a C–H bond is more easily broken than an equivalent C–D bond, and the rate of C–H bond cleavage is faster. For instance, the base-induced elimination of HBr from 1-bromo-2-phenylethane proceeds 7.11 times faster than the corresponding elimination of DBr from 1-bromo-2, 2-dideuterio-2-phenylethane. This result tells us that the C–H (or C–D) bond is broken in the rate-limiting step, consistent with our picture of the E2 reaction as a one-step process. If it were otherwise, we wouldn't observe a rate difference.



Yet a third 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.

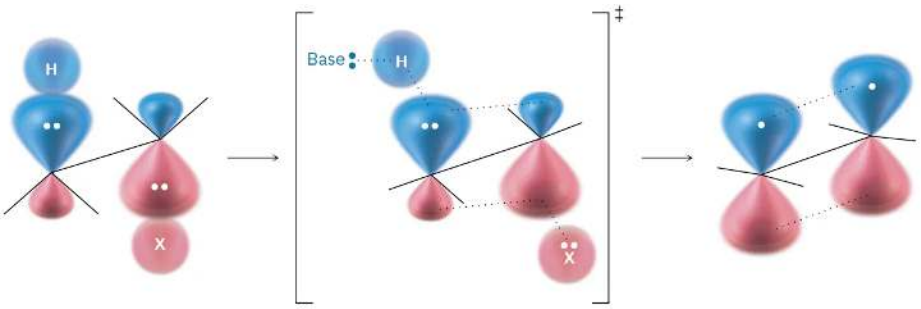


Anti periplanar geometry
(staggered, lower energy)



Syn periplanar geometry
(eclipsed, higher energy)

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).



Anti periplanar reactant | Anti transition state | Alkene product

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.

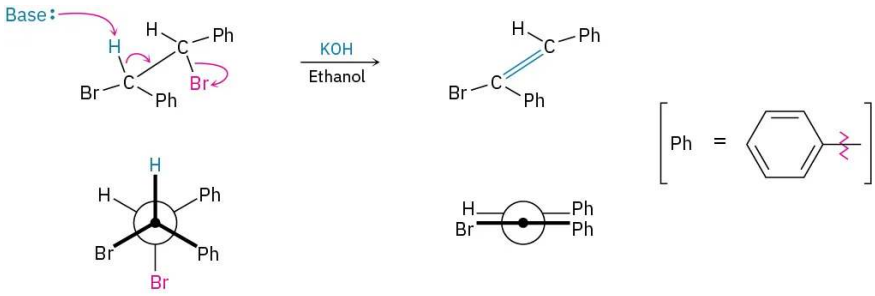
You can think of E2 elimination reactions with periplanar geometry as being similar to S_N2 reactions with 180° geometry. In an S_N2 reaction, an electron pair from the incoming nucleophile pushes out the leaving group on the opposite side of the molecule. In an E2 reaction, an electron pair from a neighboring C–H bond also pushes out the leaving group on the opposite side of the molecule.



S_N2 reaction
(backside attack)

E2 reaction
(anti periplanar)

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

✔ Worked Example 11.8.1: Predicting the Double-Bond Stereochemistry of the Product in an E2 Reaction

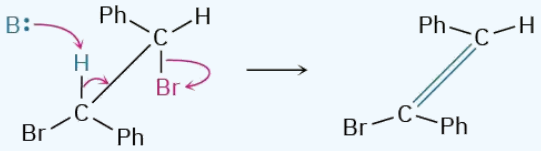
What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*S*,2*S*)-1,2-dibromo-1,2-diphenylethane?

Strategy

Draw (1*S*,2*S*)-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.



? Exercise 11.8.1

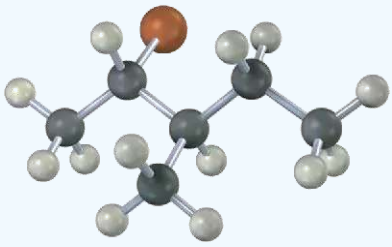
What stereochemistry do you expect for the alkene obtained by E2 elimination of (1*R*,2*R*)-1,2-dibromo-1,2-diphenylethane? Draw a Newman projection of the reacting conformation.

Answer

(*Z*)-1-Bromo-1,2-diphenylethylene

? 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

(*Z*)-3-Methyl-2-pentene

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11.9: The E2 Reaction and Cyclohexane Conformation

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.

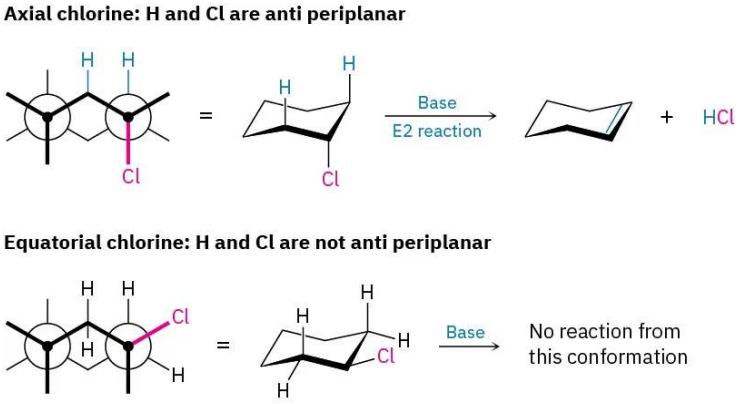


Figure 11.9.1: The geometric requirement for an E2 reaction in a substituted cyclohexane. The leaving group and the hydrogen must both be axial for anti periplanar elimination to occur.

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-menthene as the major alkene product, whereas menthyl chloride yields 2-menthene.

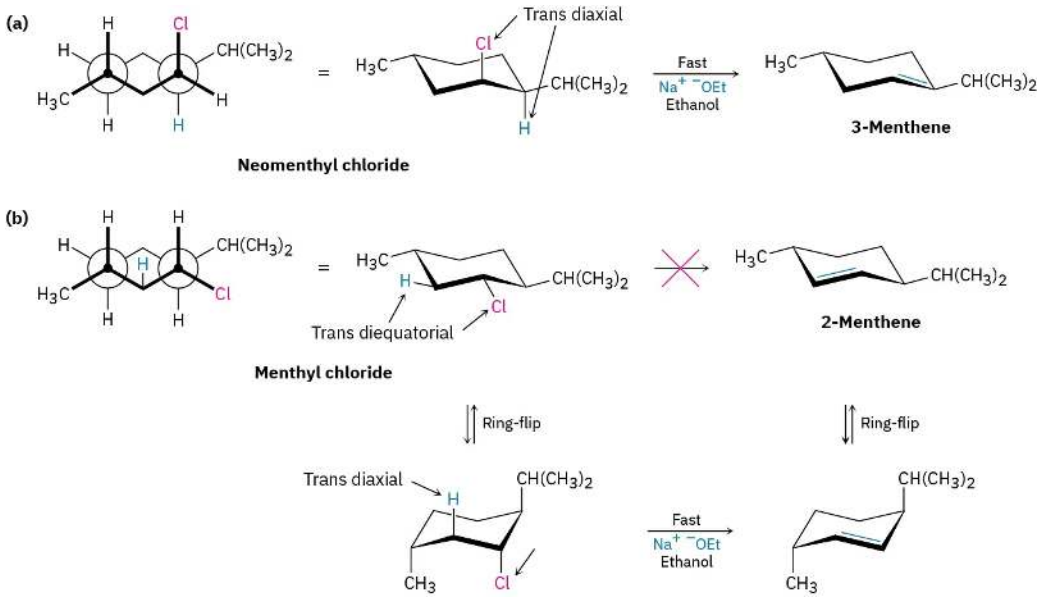


Figure 11.9.2: Dehydrochlorination of menthyl and neomenthyl chlorides. (a) Neomenthyl chloride loses HCl directly from its more stable conformation, but (b) menthyl chloride must first ring-flip to a higher energy conformation before HCl loss can occur. The abbreviation "Et" represents an ethyl group.

The difference in reactivity between the isomeric menthyl 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.

? Exercise 11.9.1

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

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.

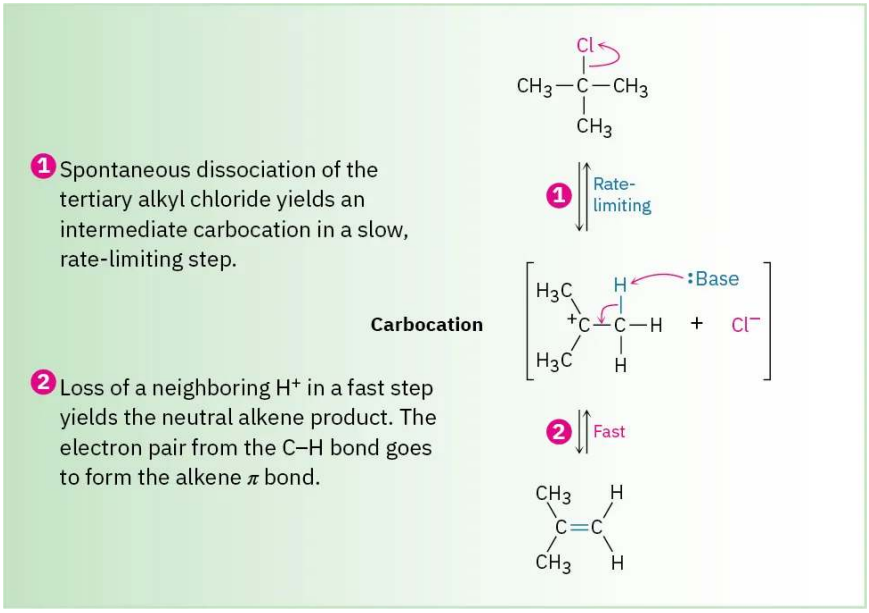
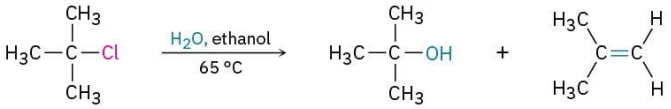


Figure 11.10.1: Mechanism of the E1 reaction. Two steps are involved, the first of which is rate-limiting, and a carbocation intermediate is present.

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).

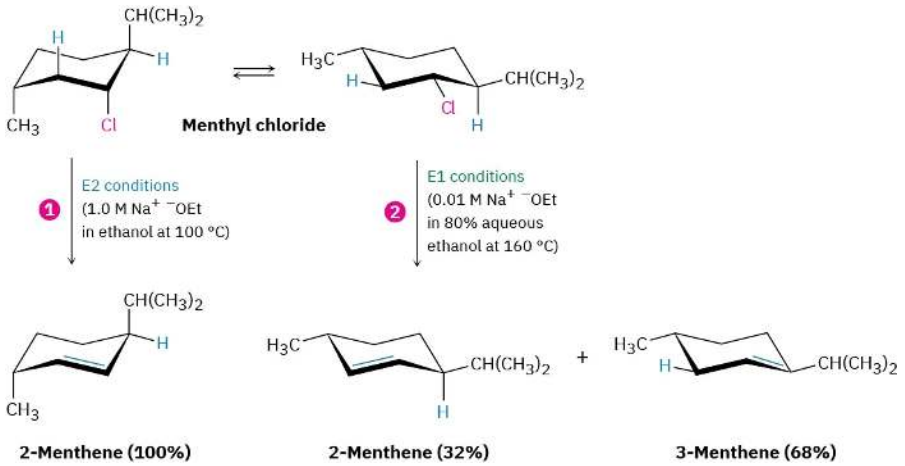
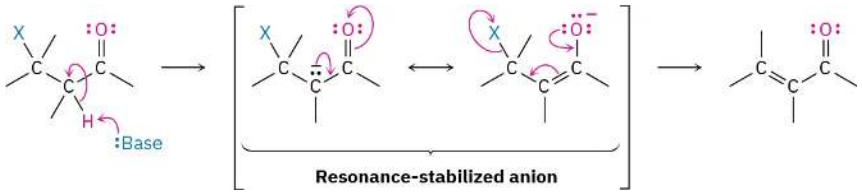


Figure 11.10.2: Elimination reactions of menthyl chloride. E2 conditions (**1**, strong base in 100% ethanol) lead to 2-menthene through an anti periplanar elimination, whereas E1 conditions (**2**, dilute base in 80% aqueous ethanol) lead to a mixture of 2-menthene and 3-menthene.

The E1cB Reaction

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. 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═. 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 **Section 22.5**.

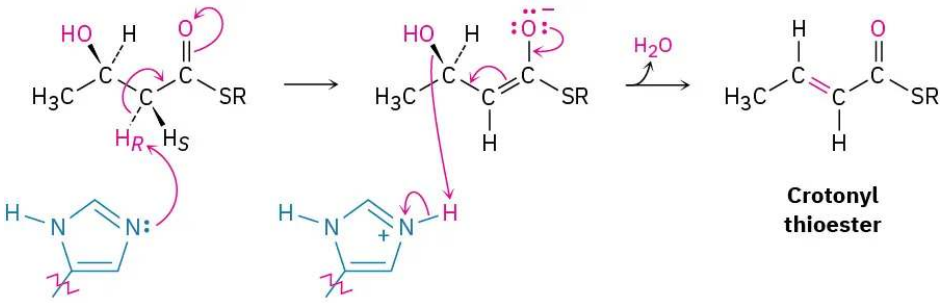


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11.11: Biological Elimination Reactions

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.



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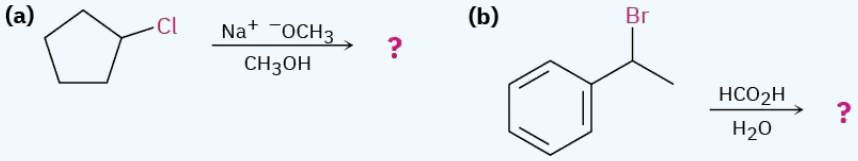
11.12: A Summary of Reactivity - SN1, SN2, E1, E1cB, and E2

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 alkyl halides:** 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.
- **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:

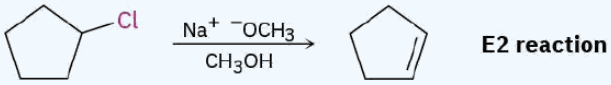


Strategy

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.

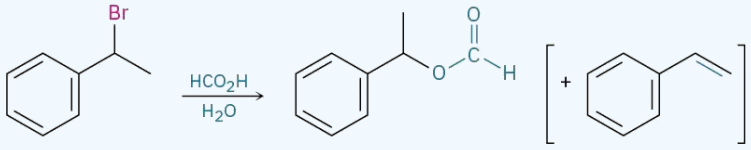
Solution

(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.



E2 reaction

(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.



S_N1 **E1**

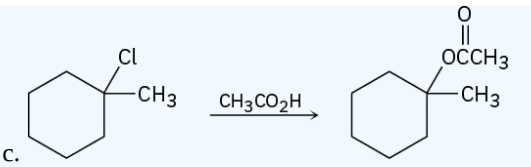
Exercise 11.12.1

Tell whether each of the following reactions is likely to be S_N1, S_N2, E1, E1cB, or E2:

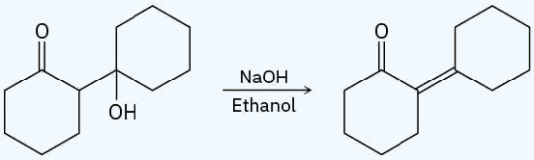
a. $CH_3CH_2CH_2CH_2Br \xrightarrow[THF]{NaN_3} CH_3CH_2CH_2CH_2N{=}N{=}N$

b. $CH_3CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[Ethanol]{KOH} CH_3CH_2CH{=}CHCH_3$

c.



d.



Answer

a. S_N2
b. E2
c. S_N1
d. E1cB

Problem 11-20

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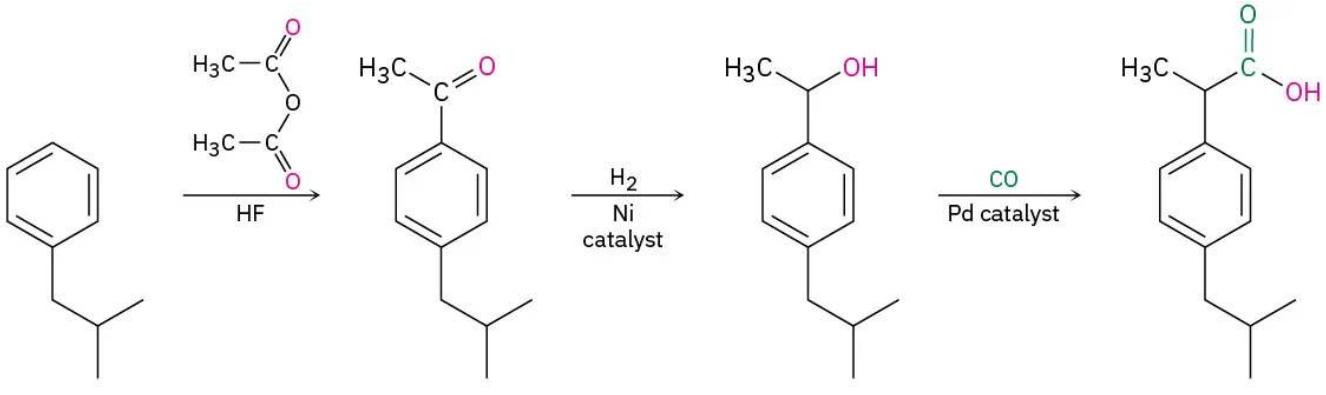
11.13: Chemistry Matters—Green Chemistry

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.



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11.14: Key Terms

- anti periplanar
- benzylic
- bimolecular
- deuterium isotope effect
- E1 reaction
- E1cB reaction
- E2 reaction
- first-order reaction
- ion pair
- kinetics
- leaving group
- nucleophilic substitution reaction
- periplanar
- rate-determining step
- rate-limiting step
- second-order reaction
- S_N1 reaction
- S_N2 reaction
- solvation
- syn periplanar
- tosylate
- unimolecular
- Zaitsev's rule

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11.15: Summary

The reaction of an alkyl halide or tosylate with a nucleophile/base results either in *substitution* or in *elimination*. The resultant nucleophilic substitution and base-induced elimination reactions are two of the most widely occurring and versatile reaction types in organic chemistry, both in the laboratory and in biological pathways.

Nucleophilic substitutions are of two types: **S_N2 reactions** and **S_N1 reactions**. In the S_N2 reaction, the entering nucleophile approaches the halide from a direction 180° away from the leaving group, resulting in an umbrella-like inversion of configuration at the carbon atom. The reaction is kinetically **second-order** and is strongly inhibited by increasing steric bulk of the reactants. Thus, S_N2 reactions are favored for primary and secondary substrates.

In the S_N1 reaction, the substrate spontaneously dissociates to a carbocation in a slow **rate-limiting step**, followed by a rapid reaction with the nucleophile. As a result, S_N1 reactions are kinetically **first-order** and take place with substantial racemization of configuration at the carbon atom. They are most favored for tertiary substrates. Both S_N1 and S_N2 reactions occur in biological pathways, although the leaving group is typically a diphosphate ion rather than a halide.

Eliminations of alkyl halides to yield alkenes occur by three mechanisms: **E2 reactions**, **E1 reactions**, and **E1cB reactions**, which differ in the timing of C–H and C–X bond-breaking. In the E2 reaction, C–H and C–X bond-breaking occur simultaneously when a base abstracts H^+ from one carbon while the leaving group departs from the neighboring carbon. The reaction takes place preferentially through an **anti periplanar** transition state in which the four reacting atoms—hydrogen, two carbons, and leaving group—are in the same plane. The reaction shows **second-order kinetics** and a **deuterium isotope effect**, and occurs when a secondary or tertiary substrate is treated with a strong base. These elimination reactions usually give a mixture of alkene products in which the more highly substituted alkene predominates (**Zaitsev's rule**).

In the E1 reaction, C–X bond-breaking occurs first. The substrate dissociates to yield a carbocation in the slow rate-limiting step before losing H^+ from an adjacent carbon in a second step. The reaction shows **first-order kinetics** and no deuterium isotope effect and occurs when a tertiary substrate reacts in polar, nonbasic solution.

In the E1cB reaction, C–H bond-breaking occurs first. A base abstracts a proton to give a carbanion, followed by loss of the leaving group from the adjacent carbon in a second step. The reaction is favored when the leaving group is two carbons removed from a carbonyl, which stabilizes the intermediate anion by resonance. Biological elimination reactions typically occur by this E1cB mechanism.

In general, substrates react in the following way:

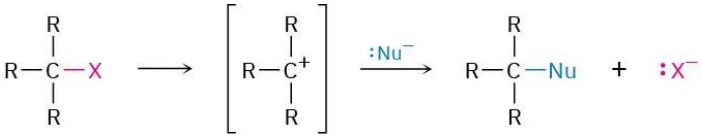
RCH_2X (primary)	⟶	Mostly S_N2 substitution
R_2CHX (secondary)	⟶	S_N2 substitution with nonbasic nucleophiles E2 elimination with strong bases
R_3CX (tertiary)	⟶	Mostly E2 elimination (S_N1 substitution and E1 elimination in nonbasic solvents)

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11.16: Summary of Reactions

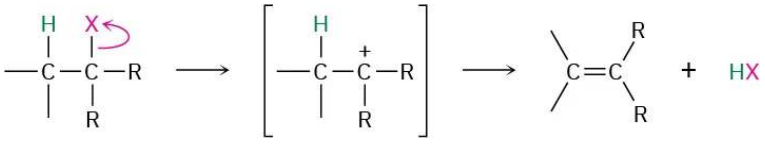
1. Nucleophilic substitutions
    a. S_N1 reaction of 3°, allylic, and benzylic halides (Section 11.4 and Section 11.5)



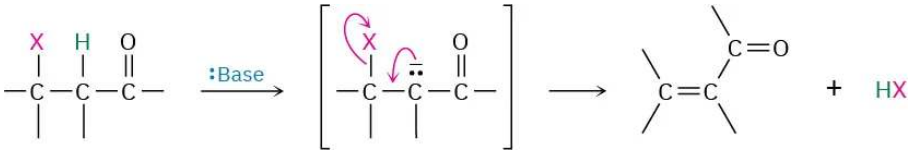
- S_N2 reaction of 1° and simple 2° halides (Section 11.2 and Section 11.3)



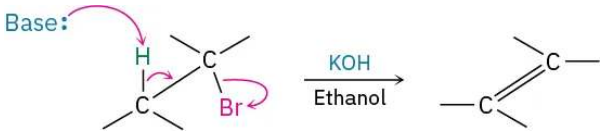
- Eliminations
    a. E1 reaction (Section 11.10)



- E1cB reaction (Section 11.10)



- E2 reaction (Section 11.8)



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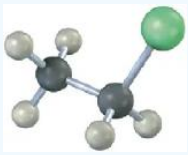
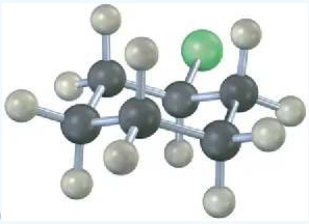
11.17: Additional Problems

11 • Additional Problems

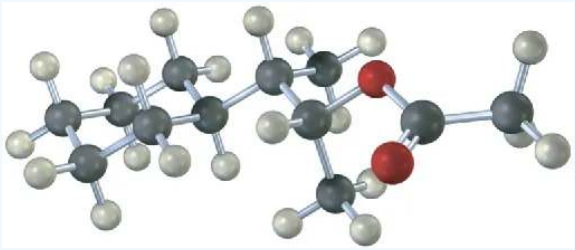
Visualizing Chemistry

Exercise 11.17.21

Write the product you would expect from reaction of each of the following alkyl halides with (1) $Na^+ {}^-SCH_3$ and (2) $Na^+ {}^-OH$ (green = Cl):

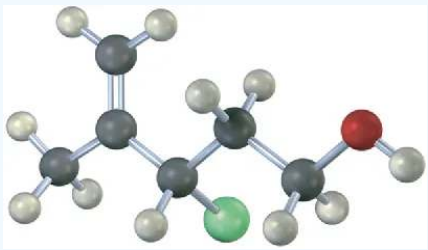
(a)  (b)  (c) 

Exercise 11.17.22

From what alkyl bromide was the following alkyl acetate made by S_N2 reaction? Write the reaction, showing all stereochemistry. 

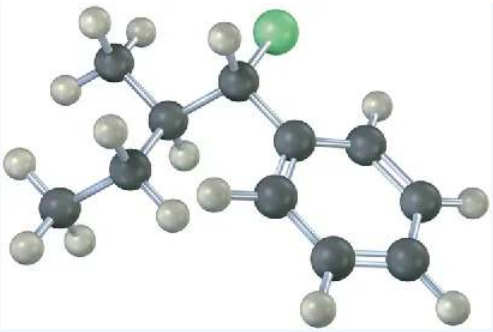
Exercise 11.17.23

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):



Exercise 11.17.24

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):

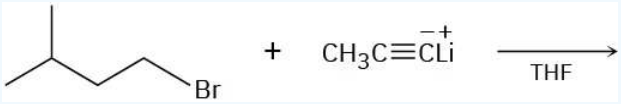


Mechanism Problems

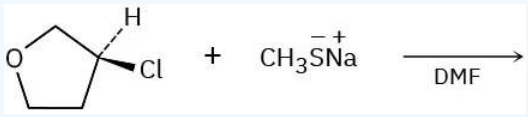
Exercise 11.17.25

Predict the product(s) and show the mechanism for each of the following reactions. What do the mechanisms have in common? Why?

(a) $CH_3CH_2CH_2OTos + NaBr \xrightarrow{DMF}$

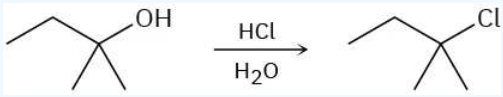
(b) 

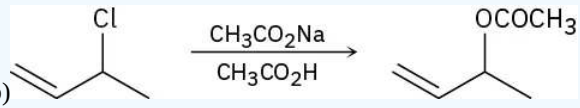
(c) 

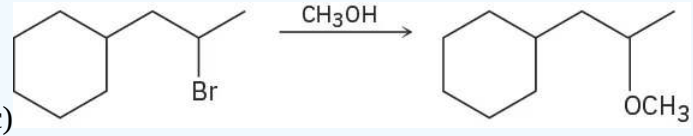
(d) 

Exercise 11.17.26

Show the mechanism for each of the following reactions. What do the mechanisms have in common? Why?

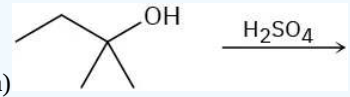
(a) 

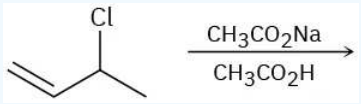
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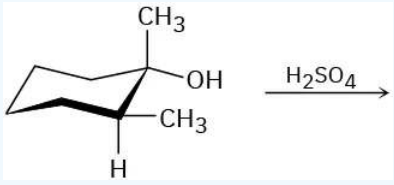
(c) 

Exercise 11.17.27

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?

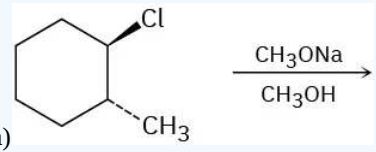
(a) 

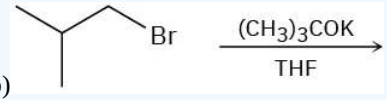
(b) 

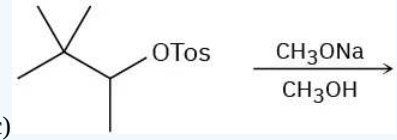
(c) 

Exercise 11.17.28

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?

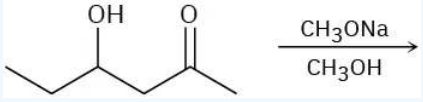
(a) 

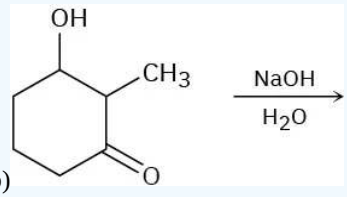
(b) 

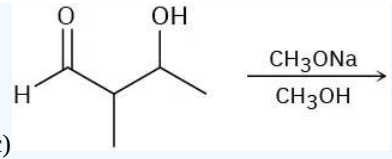
(c) 

Exercise 11.17.29

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?

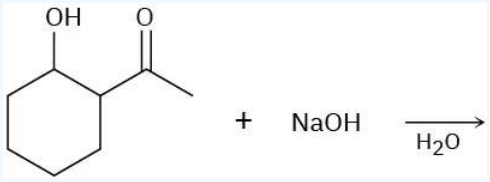
(a) 

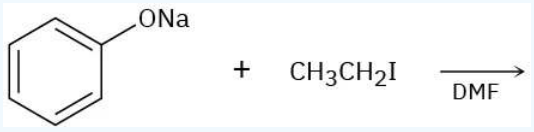
(b) 

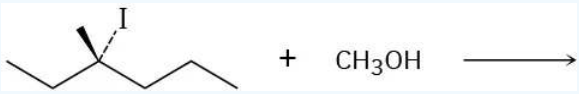
(c) 

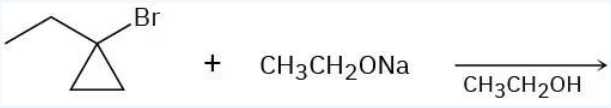
Exercise 11.17.30

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.

(a) 

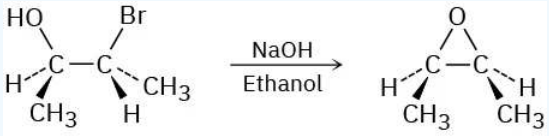
(b) 

(c) 

(d) 

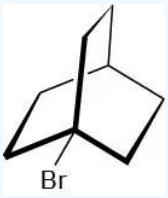
Exercise 11.17.31

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.



Exercise 11.17.32

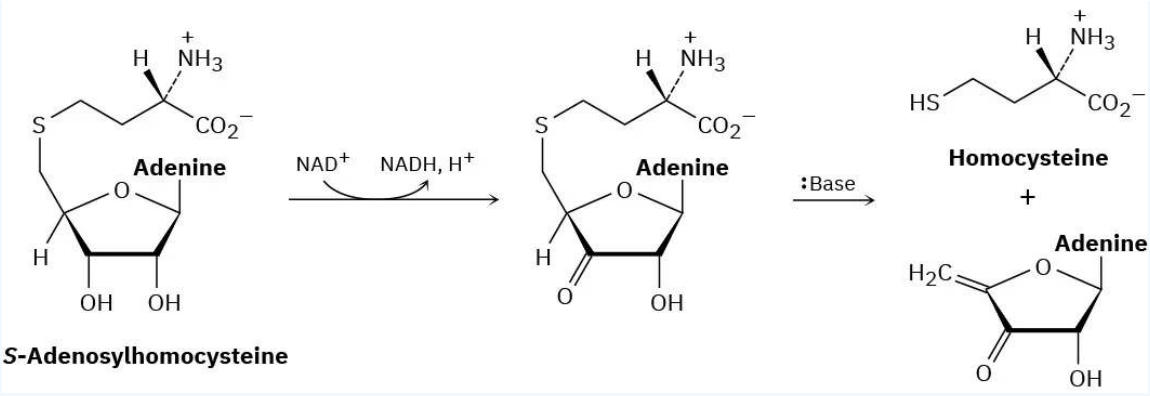
The following tertiary alkyl bromide does not undergo a nucleophilic substitution reaction by either S_N1 or S_N2 mechanisms. Explain.



Exercise 11.17.33

Metabolism of *S*-adenosylhomocysteine (Section 11.6) involves the following sequence. Propose a mechanism for the second step.

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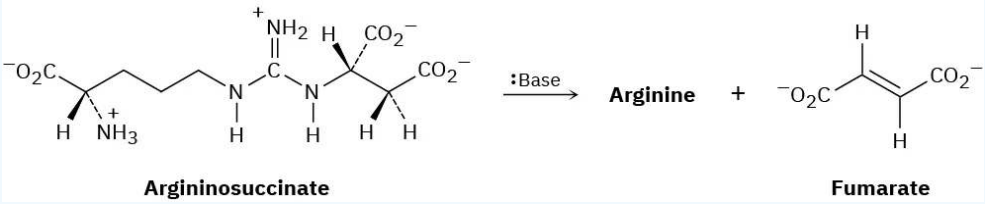


Exercise 11.17.34

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.

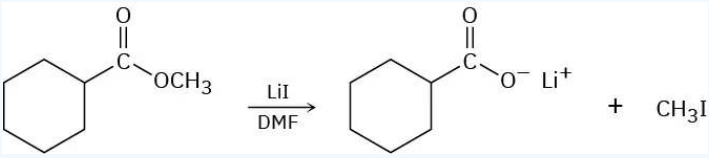
Exercise 11.17.35

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.



Exercise 11.17.36

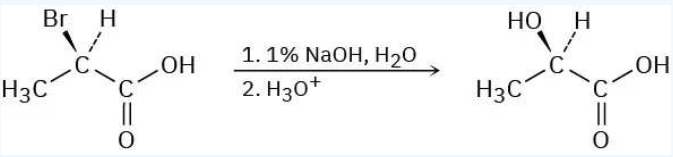
Methyl esters (RCO_2CH_3) undergo a cleavage reaction to yield carboxylate ions plus iodomethane on heating with LiI in dimethylformamide:



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?

Exercise 11.17.37

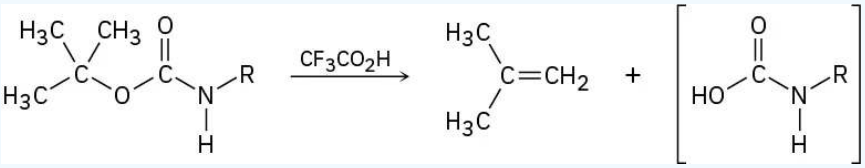
S_N2 reactions take place with inversion of configuration, and S_N1 reactions take place with racemization. The following substitution reaction, however, occurs with complete *retention* of configuration. Propose a mechanism. (Hint: two inversions = retention.)



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Exercise 11.17.38

Propose a mechanism for the following reaction, an important step in the laboratory synthesis of proteins:



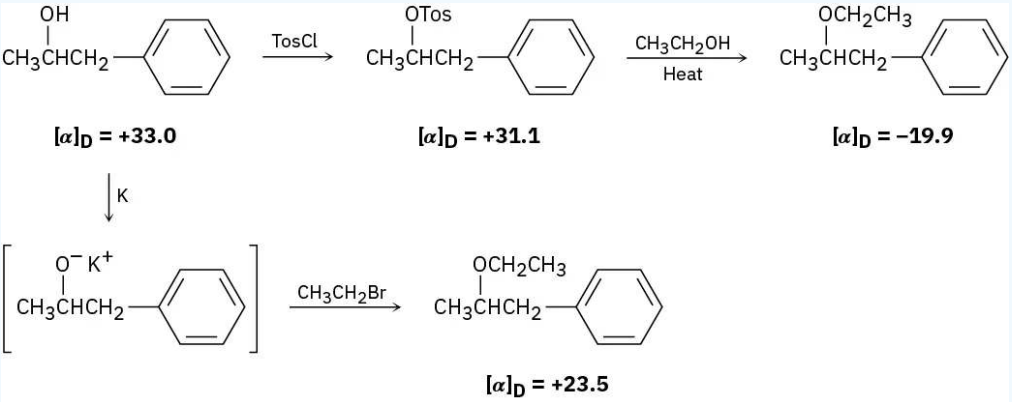
Nucleophilic Substitution Reactions

Exercise 11.17.39

Draw all isomers of C_4H_9Br, name them, and arrange them in order of decreasing reactivity in the S_N2 reaction.

Exercise 11.17.40

The following Walden cycle has been carried out: Explain the results, and indicate where inversion occurs.



Exercise 11.17.41

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 $CH_2C{=}CHCH_2Br$

Exercise 11.17.42

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 $^-OCH_3$

Exercise 11.17.43

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.

Exercise 11.17.44

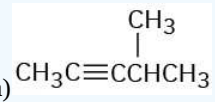
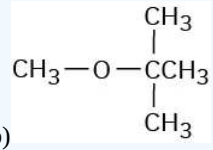
What effect would you expect the following changes to have on the rate of the reaction of ethanol with 2-iodo-2-methylbutane?

(a) The concentration of the halide is tripled.

(b) The concentration of the ethanol is halved by adding diethyl ether as an inert solvent.

Exercise 11.17.45

How might you prepare each of the following using a nucleophilic substitution reaction at some step?

(a)  (b)  (c) $CH_3CH_2CH_2CH_2CN$ (d) $CH_3CH_2CH_2NH_2$

Exercise 11.17.46

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

Exercise 11.17.47

Predict the product and give the stereochemistry resulting from reaction of each of the following nucleophiles with (*R*)-2-bromooctane:

(a) ^-CN

(b) $CH_3CO_2^-$

(c) CH_3S^-

Exercise 11.17.48

(*R*)-2-Bromooctane undergoes racemization to give (±)-2-bromooctane when treated with NaBr in dimethyl sulfoxide. Explain.

Elimination Reactions

Exercise 11.17.49

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

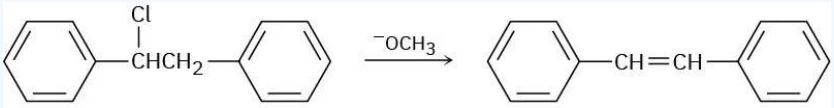
? Exercise 11.17.50

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≡CH (f) Mg, then H_2O

? Exercise 11.17.51

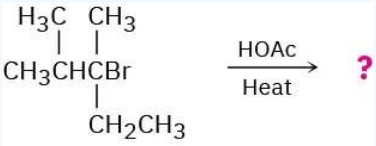
1-Chloro-1,2-diphenylethane can undergo E2 elimination to give either *cis*- or *trans*-1,2-diphenylethylene (stilbene). Draw Newman projections of the reactive conformations leading to both possible products, and suggest a reason why the *trans* alkene is the major product.



1-Chloro-1,2-diphenylethane **trans-1,2-Diphenylethylene**

? Exercise 11.17.52

Predict the major alkene product of the following E1 reaction:



? Exercise 11.17.53

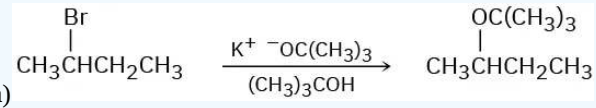
There are eight diastereomers of 1,2,3,4,5,6-hexachlorocyclohexane. Draw each in its more stable chair conformation. One isomer loses HCl in an E2 reaction nearly 1000 times more slowly than the others. Which isomer reacts so slowly, and why?

General Problems

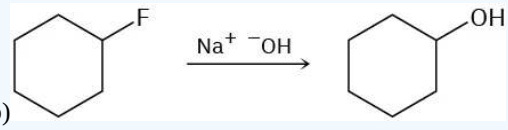
? Exercise 11.17.54

The following reactions are unlikely to occur as written. Tell what is wrong with each, and predict the actual product.

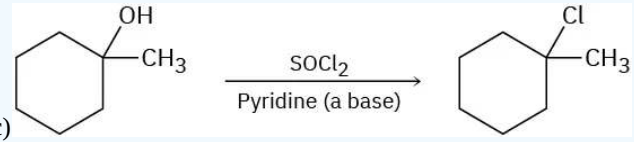
(a)



(b)

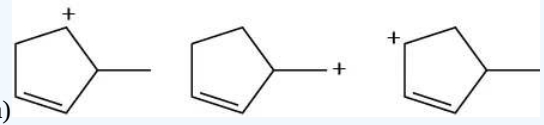


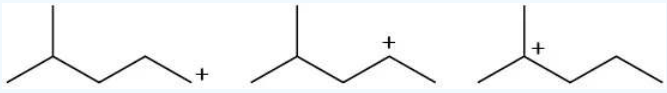
(c)

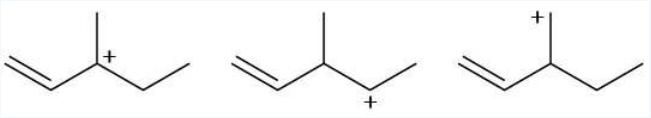


? Exercise 11.17.55

Arrange the following carbocations in order of increasing stability.

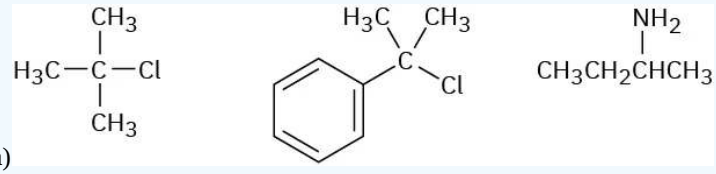
(a) 

(b) 

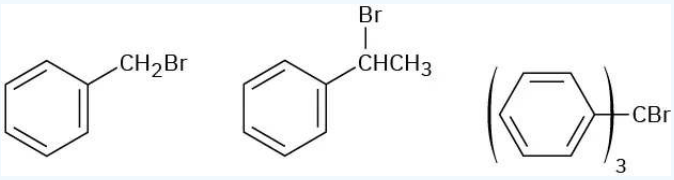
(c) 

Exercise 11.17.56

Order each of the following sets of compounds with respect to S_N1 reactivity:

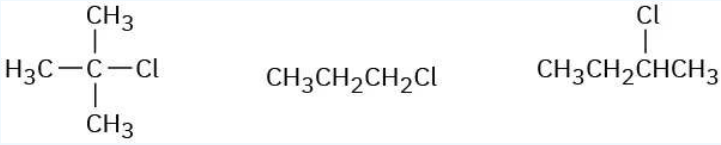
(a) 

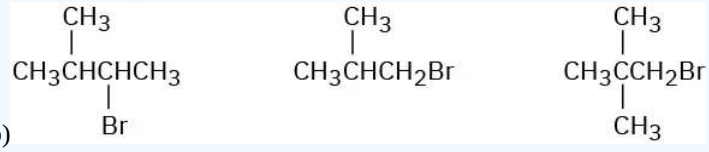
(b) $(CH_3)_3CCl$ $(CH_3)_3CBr$ $(CH_3)_3COH$

(c) 

Exercise 11.17.57

Order each of the following sets of compounds with respect to S_N2 reactivity:

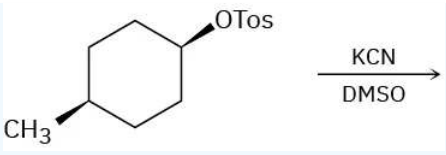
(a) 

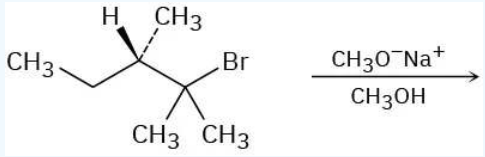
(b) 

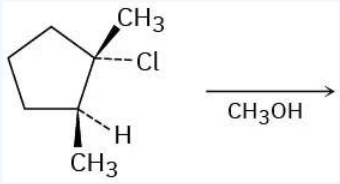
(c) $CH_3CH_2CH_2OCH_3$ $CH_3CH_2CH_2OTos$ $CH_3CH_2CH_2Br$

Exercise 11.17.58

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.

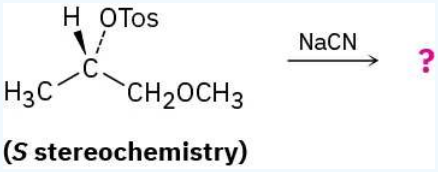
(a) 

(b) 

(c) 

Exercise 11.17.59

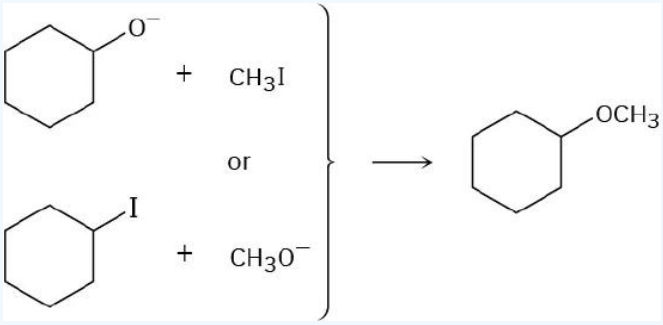
Reaction of the following *S* tosylate with cyanide ion yields a nitrile product that also has *S* stereochemistry. Explain.



(*S* stereochemistry)

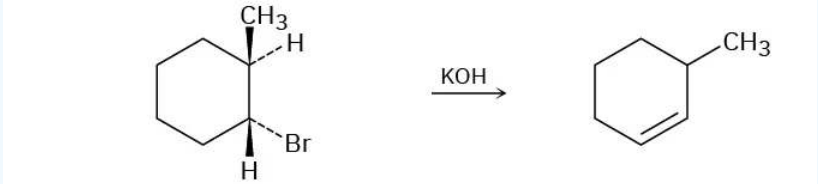
Exercise 11.17.60

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.



Exercise 11.17.61

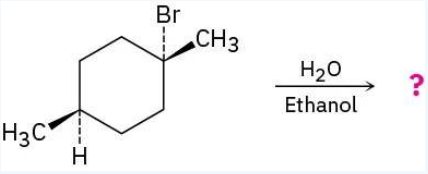
How can you explain the fact that *trans*-1-bromo-2-methylcyclohexane yields the non-Zaitsev elimination product 3-methylcyclohexene on treatment with base?



***trans*-1-Bromo-2-methylcyclohexane** **3-Methylcyclohexene**

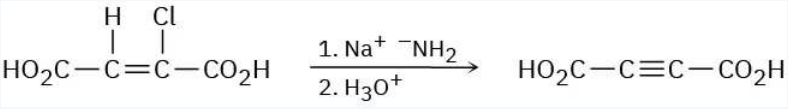
Exercise 11.17.62

Predict the product(s) of the following reaction, indicating stereochemistry where necessary:



Exercise 11.17.63

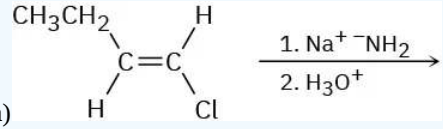
Alkynes can be made by dehydrohalogenation of vinylic halides in a reaction that is essentially an E2 process. In studying the stereochemistry of this elimination, it was found that (*Z*)-2-chloro-2-butenedioic acid reacts 50 times as fast as the corresponding *E* isomer. What conclusion can you draw about the stereochemistry of eliminations in vinylic halides? How does this result compare with eliminations of alkyl halides?



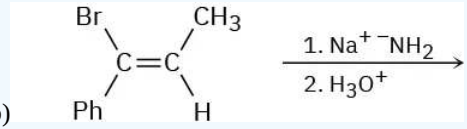
Exercise 11.17.64

Based on your answer to Problem 11-63, predict the product(s) and show the mechanism for each of the following reactions.

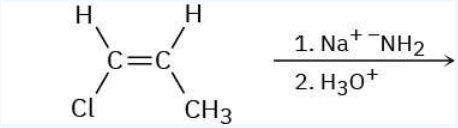
(a)



(b)

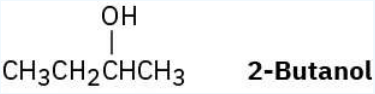


(c)



Exercise 11.17.65

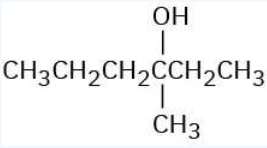
(*S*)-2-Butanol slowly racemizes on standing in dilute sulfuric acid. Explain.



2-Butanol

Exercise 11.17.66

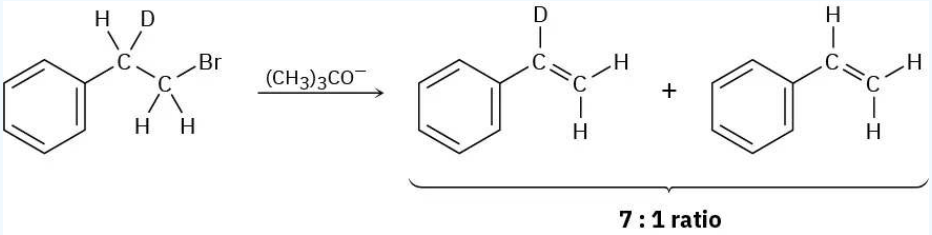
The reaction of HBr with (*R*)-3-methyl-3-hexanol leads to racemic 3-bromo-3-methylhexane. Explain.



3-Methyl-3-hexanol

Exercise 11.17.67

Treatment of 1-bromo-2-deuterio-2-phenylethane with strong base leads to a mixture of deuterated and nondeuterated phenylethylenes in an approximately 7 : 1 ratio. Explain.

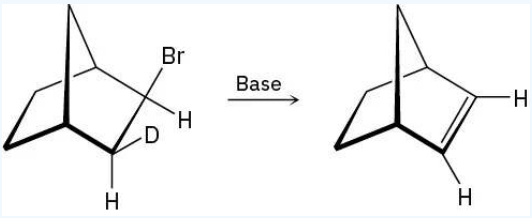


Exercise 11.17.68

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.

Exercise 11.17.69

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.



Exercise 11.17.70

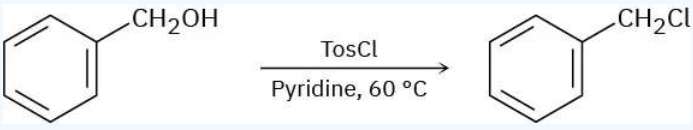
The reaction of 1-chlorooctane with $CH_3CO_2^-$ to give octyl acetate is greatly accelerated by adding a small quantity of iodide ion. Explain.

Exercise 11.17.71

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?

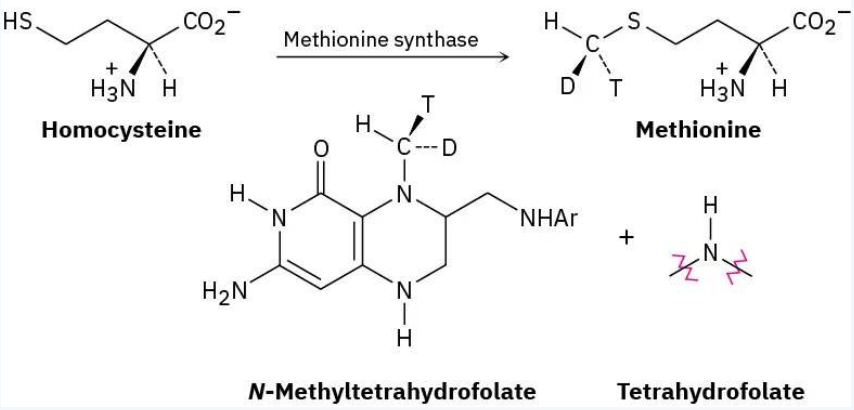
Exercise 11.17.72

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 higher temperature, an alkyl chloride is often formed. Explain.



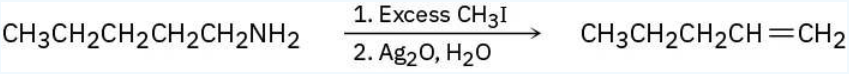
Exercise 11.17.73

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?



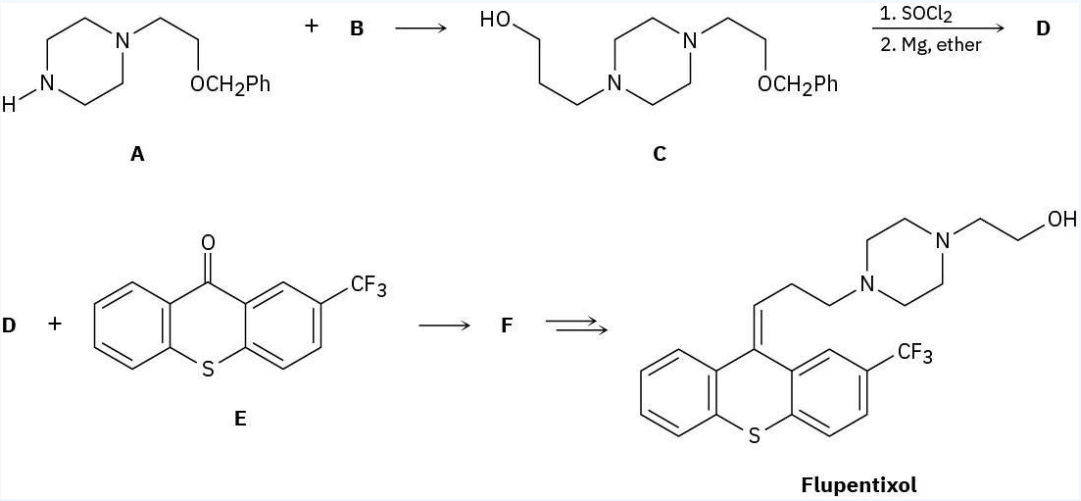
Exercise 11.17.74

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 base. Pentylamine, for example, yields 1-pentene. Propose a structure for the intermediate, and explain why it readily undergoes elimination.



Exercise 11.17.75

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 Section 19.7 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.

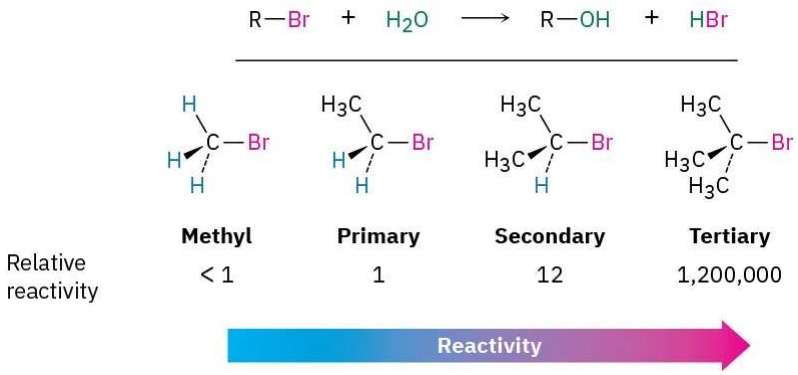
(d) Two stereoisomers of flupentixol are subsequently formed from F, but only one is shown. Draw the other isomer, and identify the type of stereoisomerism.

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11.18: 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.

$$\begin{aligned}\text{Reaction rate} &= \text{Rate of disappearance of alkyl halide}\\ &= \text{Rate of appearance of product}\\ &= k \times [\text{RX}]\end{aligned}$$

To explain this result, we need to know more about kinetics 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. 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 mechanism shown in Figure 11.18.1 accounts for these observations.

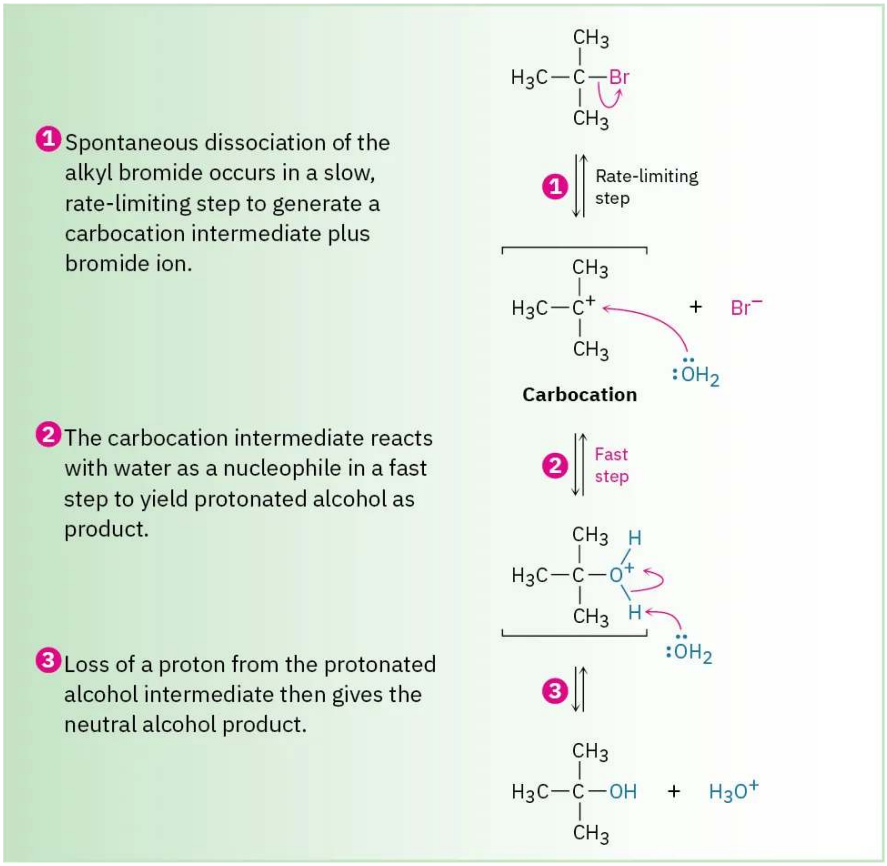


Figure 11.18.1: The mechanism of the S_N1 reaction of 2-bromo-2-methylpropane with H_2O involves three steps. Step 1—the spontaneous, unimolecular dissociation of the alkyl bromide to yield a carbocation—is rate-limiting.

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 energy diagram is shown in Figure 11.18.2.

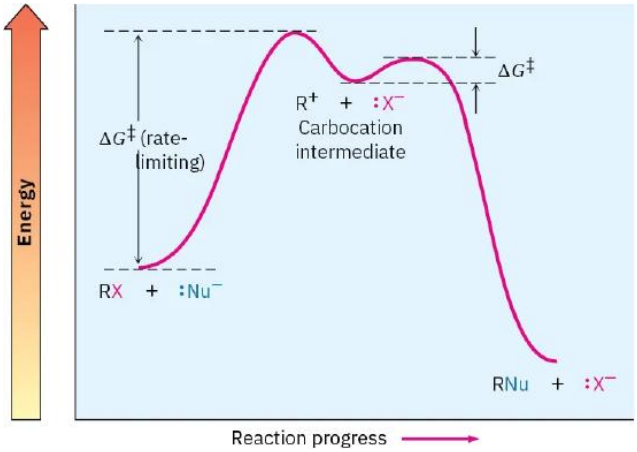


Figure 11.18.2: An energy diagram for an S_N1 reaction. The rate-limiting step is the spontaneous dissociation of the alkyl halide to give a carbocation intermediate. Reaction of the carbocation with a nucleophile then occurs in a second, faster step.

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 symmetrical intermediate carbocation can react with a nucleophile equally well from either side, leading to a racemic, 50 : 50 mixture of enantiomers (Figure 11.18.3).

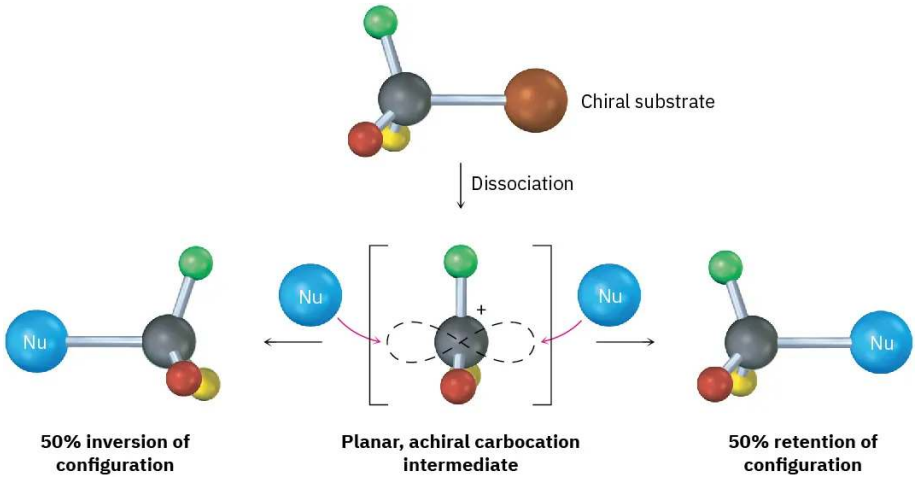
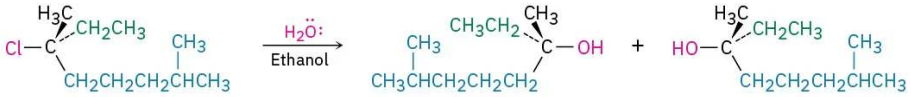


Figure 11.18.3: Stereochemistry of the S_N1 reaction. Because the reaction goes through an achiral intermediate, an enantiomerically pure reactant gives an optically inactive racemic product.

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, first proposed by Saul Winstein at UCLA, 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 11.18.4).

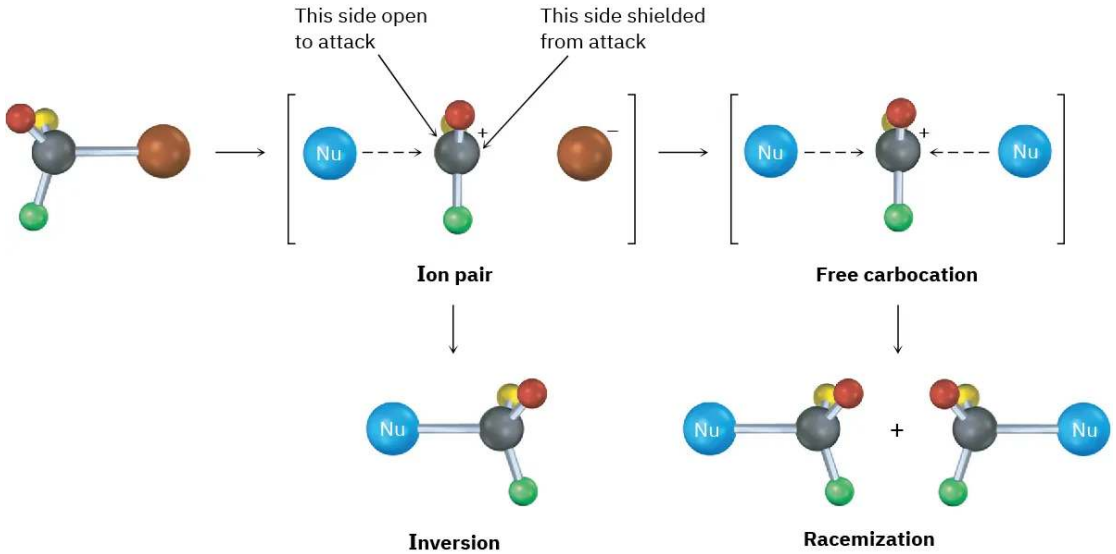


Figure 11.18.4: Ion pairs in an S_N1 reaction. The leaving group shields one side of the carbocation intermediate from reaction with the nucleophile, thereby leading to some inversion of configuration rather than complete racemization.

Exercise 11.18.1

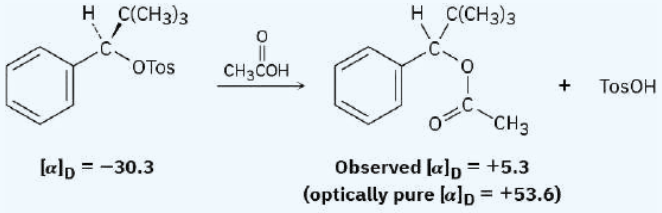
What product(s) would you expect from reaction of (*S*)-3-chloro-3-methyloctane with acetic acid? Show the stereochemistry of both reactant and product.

Answer

Racemic 1-ethyl-1-methylhexyl acetate

Exercise 11.18.2

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?

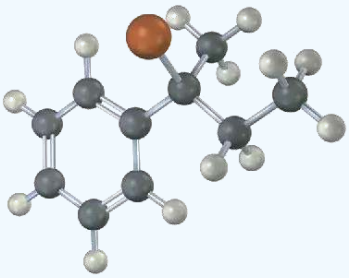


Answer

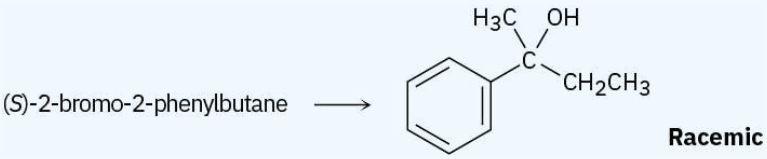
90.1% racemization, 9.9% inversion

Exercise 11.18.3

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



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