6

Many chemical reactions are like these balanced rocks. They need a shove of energy to get them started moving.

An Overview of Organic Reactions

6.1 Kinds of Organic Reactions
6.2 How Organic Reactions Occur: Mechanisms
6.3 Radical Reactions
6.4 Polar Reactions
6.5 An Example of a Polar Reaction: Addition of HBr to Ethylene
6.6 Using Curved Arrows in Polar Reaction Mechanisms
6.7 Describing a Reaction: Equilibria, Rates, and Energy Changes
6.8 Describing a Reaction: Bond Dissociation Energies
6.9 Describing a Reaction: Energy Diagrams and Transition States
6.10 Describing a Reaction: Intermediates
6.11 A Comparison Between Biological Reactions and Laboratory Reactions
A Deeper Look—Where Do Drugs Come From?

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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.

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 reactions are the same.

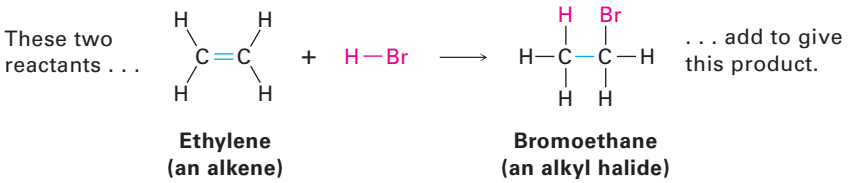
To understand both organic and biological chemistry, it's necessary to know not just *what* occurs but also *why* and *how* chemical reactions take place. In this chapter, we'll start with an overview of the fundamental kinds of organic reactions, we'll see why reactions occur, and we'll see how reactions can be described. Once this background is out of the way, we'll then be ready to begin studying the details of organic chemistry.

6.1 Kinds of Organic Reactions

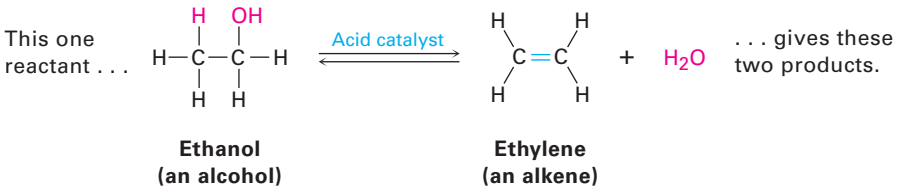
Organic chemical reactions can be organized broadly in two ways—by *what kinds* of reactions occur and by *how* those reactions occur. Let's look first at the kinds of reactions that take place. There are four general types of organic reactions: *additions, eliminations, substitutions,* and *rearrangements*.

* **Addition reactions** occur when two reactants add together to form a single product with no atoms "left over." An example that we'll be

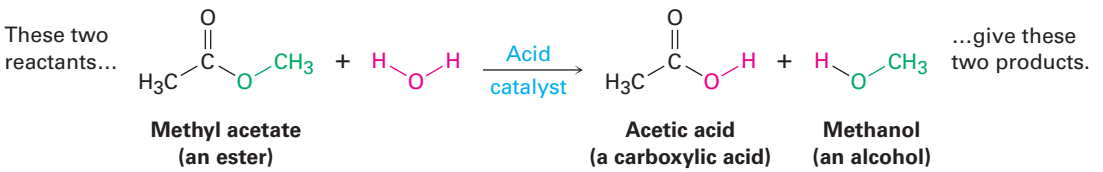
studying soon is the reaction of an alkene, such as ethylene, with HBr to yield an alkyl bromide.



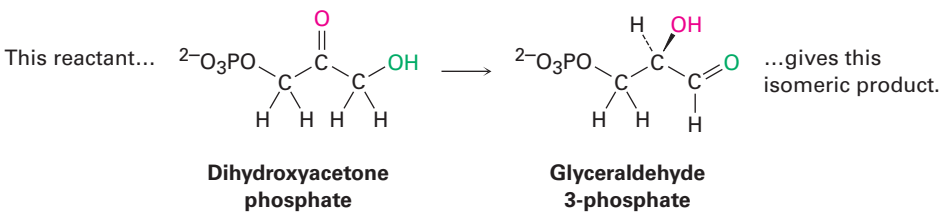
* **Elimination reactions** are, in a sense, the opposite of addition reactions. They occur when a single reactant splits into two products, often with formation of a small molecule such as water or HBr. An example is the acid-catalyzed reaction of an alcohol to yield water and an alkene.



* **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.



Problem 6.1

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

(a) $CH_3Br + KOH \rightarrow CH_3OH + KBr$

(b) $CH_3CH_2Br \rightarrow H_2C{=}CH_2 + HBr$

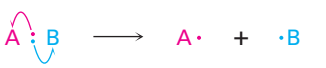
(c) $H_2C{=}CH_2 + H_2 \rightarrow CH_3CH_3$

6.2 How Organic Reactions Occur: Mechanisms

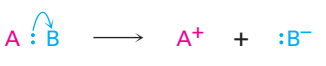
Having looked at the kinds of reactions that take place, let's now see how reactions occur. An overall description of how a reaction occurs is called a **reaction mechanism**. A mechanism describes in detail exactly what takes place at each stage of a chemical transformation—which bonds are broken and in what order, which bonds are formed and in what order, and what the relative rates of the steps are. 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 *symmetrical* way so that one electron remains with each product fragment, or 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. The symmetrical cleavage is said to be *homolytic,* and the unsymmetrical cleavage is said to be *heterolytic*.

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

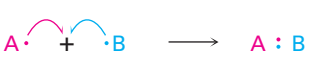


Symmetrical bond-breaking (radical):
one bonding electron stays with each product.



Unsymmetrical bond-breaking (polar):
two bonding electrons stay with one 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 symmetrical way if one electron is donated to the new bond by each reactant or in an unsymmetrical way if both bonding electrons are donated by one reactant.



Symmetrical bond-making (radical):
one bonding electron is donated by each reactant.

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

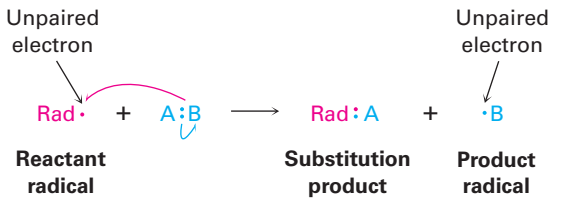
Processes that involve symmetrical bond-breaking and bond-making are called **radical reactions**. A **radical**, often called a "*free radical,*" is a neutral chemical species that contains an odd number of electrons and thus has a single, unpaired electron in one of its orbitals. Processes that involve 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.

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.

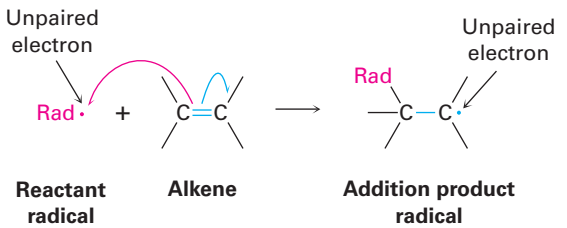
6.3 Radical Reactions

Radical reactions are not as common as polar reactions but are nevertheless important in some industrial processes and biological pathways. Let's see briefly how they occur.

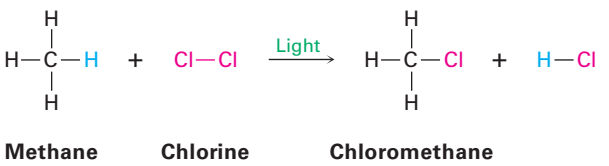
A radical is highly reactive because it contains an atom with an odd number of electrons (usually seven) in its valence shell, rather than a stable, noble-gas octet. A radical can achieve a valence-shell octet in several ways. For example, the radical might abstract an atom and one bonding electron from 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.

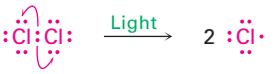


An example of an industrially useful radical reaction is the chlorination of methane to yield chloromethane. This substitution reaction is the first step in the preparation of the solvents dichloromethane (CH_2Cl_2) and chloroform ($CHCl_3$).

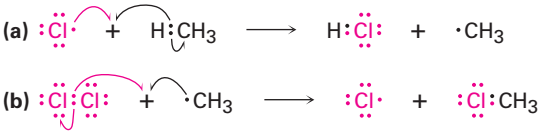


Like many radical reactions in the laboratory, methane chlorination requires three kinds of steps: *initiation, propagation,* and *termination.*

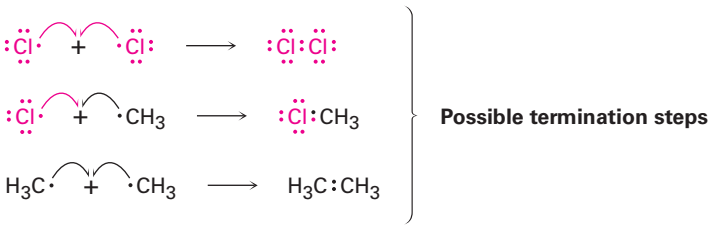
Initiation Irradiation with ultraviolet light begins the reaction by breaking the relatively weak Cl–Cl bond of a small number of Cl_2 molecules to give a few reactive chlorine radicals.



Propagation Once produced, a reactive chlorine radical collides with a methane molecule in a propagation step, abstracting a hydrogen atom to give HCl and a methyl radical ($\cdot CH_3$). This methyl radical reacts further with Cl_2 in a second propagation step to give the product chloromethane plus a new chlorine radical, which cycles back and repeats the first propagation step. Thus, once the sequence has been initiated, it becomes a self-sustaining cycle of repeating steps (a) and (b), making the overall process a *chain reaction.*



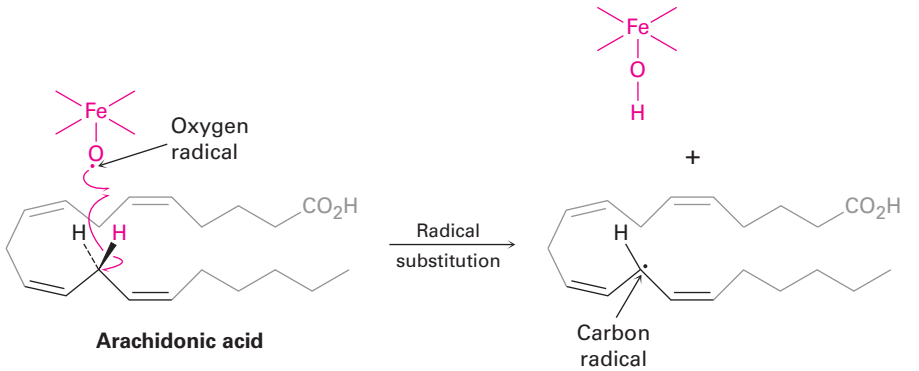
Termination Occasionally, two radicals might collide and combine to form a stable product. When that happens, the reaction cycle is broken and the chain is ended. Such termination steps occur infrequently, however, because the concentration of radicals in the reaction at any given moment is very small. Thus, the likelihood that two radicals will collide is also small.



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.

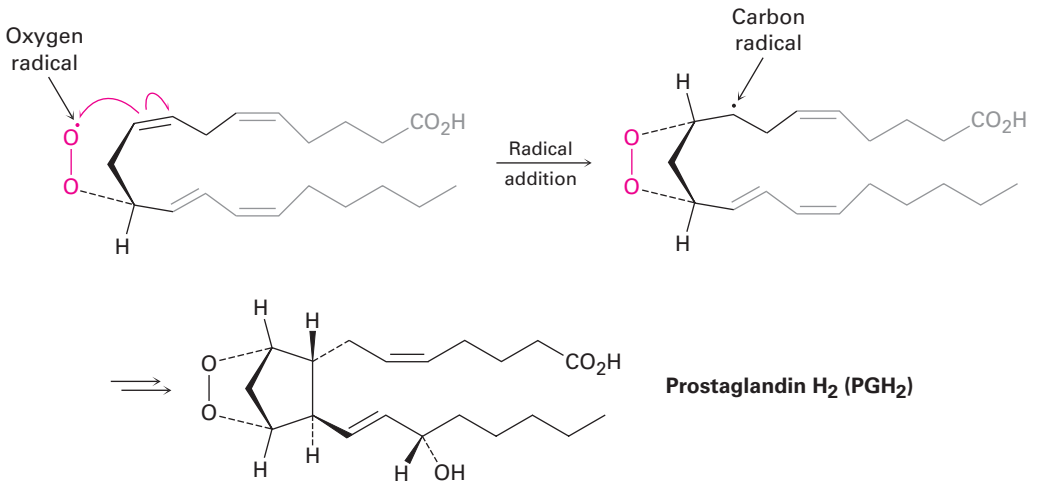
Prostaglandin biosynthesis is initiated by abstraction of a hydrogen atom from arachidonic acid by an iron–oxygen radical, thereby generating a new, carbon radical in a substitution reaction. Don't be intimidated by the size of the molecules; focus on the changes occurring in each step. (To help you 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.



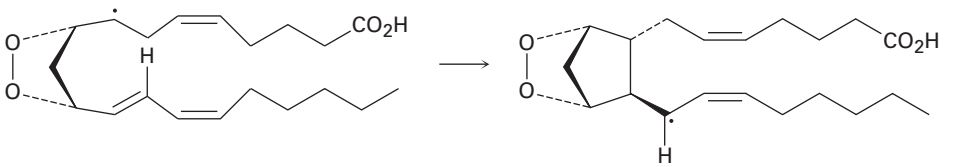
Prostaglandin H_2 (PGH_2)

Problem 6.2

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.

Problem 6.3

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

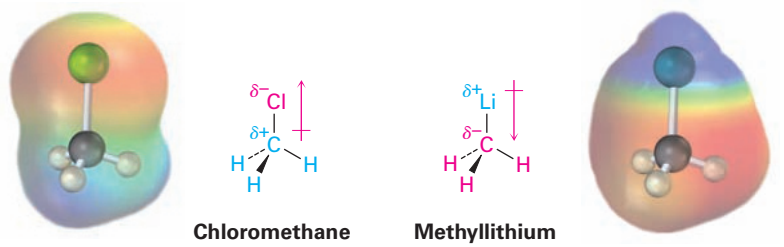


6.4 Polar Reactions

Polar reactions occur because of the electrical attraction between positively polarized and negatively polarized centers on functional groups in molecules. To see how these reactions take place, let's first recall the discussion of polar covalent bonds in **Section 2.1** and then look more deeply into the effects of bond polarity on organic molecules.

Most organic compounds are electrically neutral; they have no net charge, either positive or negative. We saw in **Section 2.1**, however, that certain bonds within a molecule, particularly the bonds in functional groups, are polar. Bond polarity is a consequence of an unsymmetrical electron distribution in a bond and is due to the difference in electronegativity of the bonded atoms.

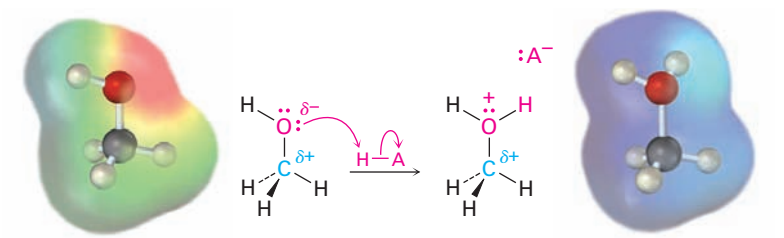
Elements such as oxygen, nitrogen, fluorine, and chlorine are more electronegative than carbon, so a carbon atom bonded to one of these atoms has a partial positive charge ($\delta+$). Conversely, metals are less electronegative than carbon, so a carbon atom bonded to a metal has a partial negative charge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

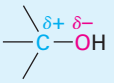
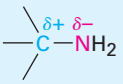
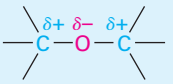
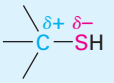
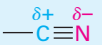
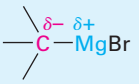
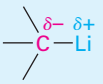
The polarity patterns of some common functional groups are shown in Table 6.1. Note that carbon is always positively polarized except when bonded to a metal.

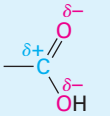
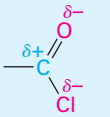
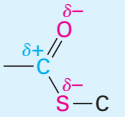
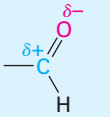
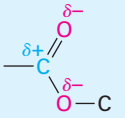
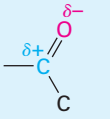
This discussion of bond polarity is oversimplified in that we've considered only bonds that are inherently polar due to differences in electronegativity. Polar bonds can also result from the interaction of functional groups with acids or bases. Take an alcohol such as methanol, for example. In neutral 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 on protonation.



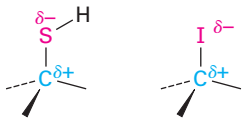
Methanol—weakly electron-poor carbon **Protonated methanol—strongly electron-poor carbon**

Table 6.1 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	

Compound type	Functional group structure
Carbonyl	
Carboxylic acid	
Carboxylic acid chloride	
Thioester	
Aldehyde	
Ester	
Ketone	

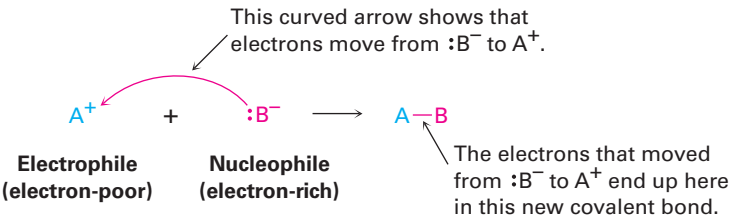
Yet a further consideration is the *polarizability* (as opposed to polarity) of atoms in a molecule. As the electric field around a given atom changes because of changing interactions with solvent or other polar molecules nearby, the electron distribution around that atom also changes. The measure of 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 for sulfur and iodine is that carbon–sulfur and carbon–iodine bonds, although nonpolar according to electronegativity values (Figure 2.2 on page 35), 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 2.11**, chemists indicate the movement of an electron pair during a polar reaction by using a curved, full-headed arrow. A curved arrow shows where electrons move when reactant bonds are broken and product bonds are formed. It means that an electron pair moves *from* the atom (or bond) at the tail of the arrow *to* the atom at the head of the arrow 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 6.1)**.

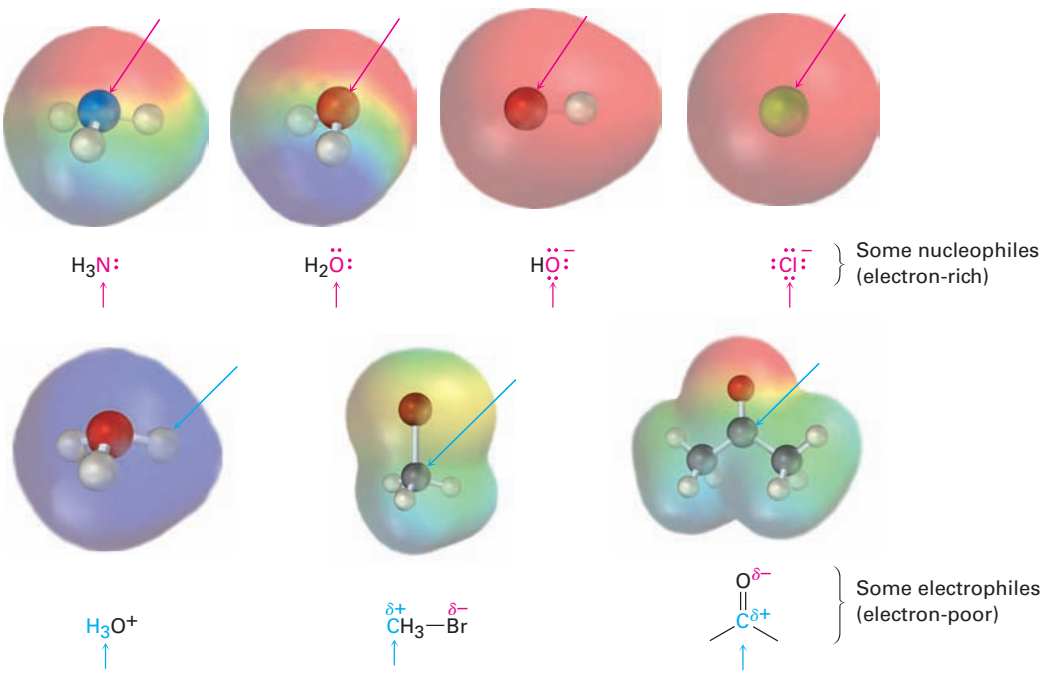


Figure 6.1 Some nucleophiles and electrophiles. Electrostatic potential maps identify the nucleophilic **(negative)** and electrophilic **(positive)** atoms.

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 2.11** 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 bonds to carbon are involved.

Identifying Electrophiles and Nucleophiles

Worked Example 6.1

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.

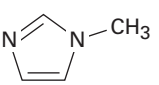
(b) $:C{\equiv}N^-$ (cyanide ion) is likely to be a nucleophile because it is negatively charged.

(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.

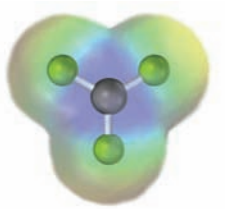
Problem 6.4

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)** 

Problem 6.5

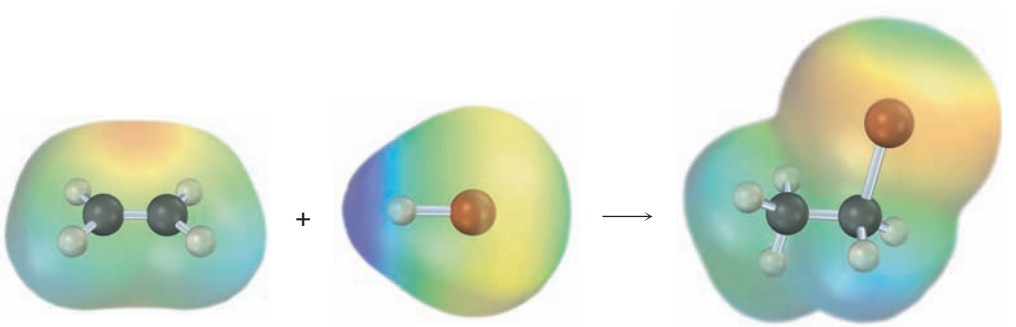
An electrostatic potential map of boron trifluoride is shown. Is BF_3 likely to be a nucleophile or an electrophile? Draw a Lewis structure for BF_3, and explain your answer.

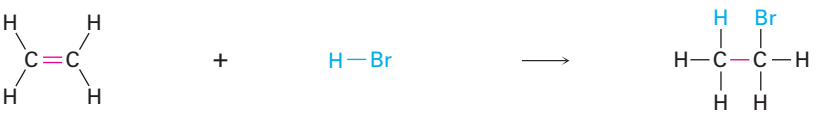


BF_3

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



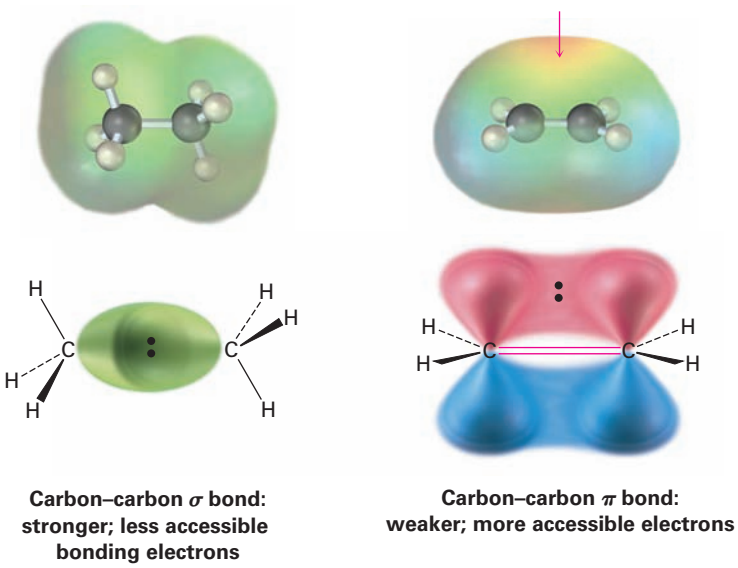


Ethylene (nucleophile) + **Hydrogen bromide** (electrophile) → **Bromoethane**

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 1.8** that a carbon–carbon double bond results from 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 of 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 6.2)**. As a result, the double bond is nucleophilic and the chemistry of alkenes is dominated by reactions with electrophiles.



Carbon–carbon σ bond: stronger; less accessible bonding electrons

Carbon–carbon π bond: weaker; more accessible electrons

Figure 6.2 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.

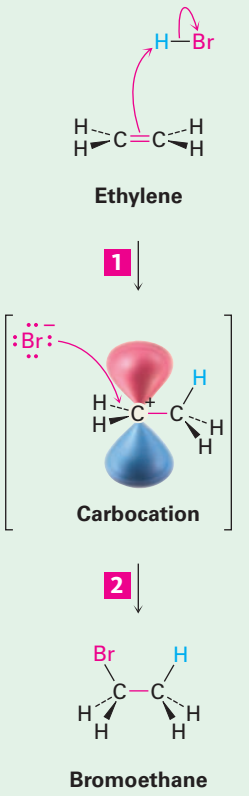
We'll see more details about alkene electrophilic addition reactions shortly, but for the present we can imagine the reaction as taking place by the pathway shown in **Figure 6.3**. The reaction begins when the alkene nucleophile donates a pair of electrons from its C=C bond to HBr to form a new C–H bond plus Br^-, as indicated by the path of the curved arrows in the first step of Figure 6.3. 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 6.3 | MECHANISM

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

1 A hydrogen atom on the electrophile HBr is attacked by π electrons from the nucleophilic double bond, forming a new C–H bond. This leaves the other carbon atom with a + charge and a vacant *p* orbital. Simultaneously, two electrons from the H–Br bond move onto bromine, giving bromide anion.

2 Bromide ion donates an electron pair to the positively charged carbon atom, forming a C–Br bond and yielding the neutral addition product.

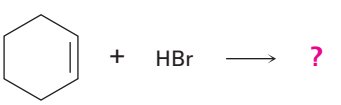


When one of the alkene carbon atoms bonds to the incoming hydrogen, the other carbon atom, having lost its share of the double-bond electrons, now has only six valence electrons and is left with a positive charge. This positively charged species—a carbon-cation, or **carbocation**—is itself an electrophile 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 6.3 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 detail 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.

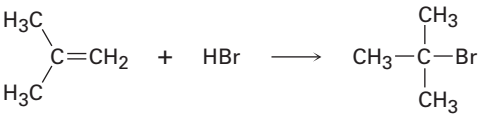
Problem 6.6

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



Problem 6.7

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**

6.6 Using Curved Arrows in Polar Reaction Mechanisms

Key IDEAS

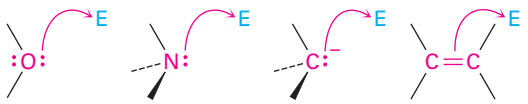
Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

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:

Electrons usually flow *from* one of these nucleophiles.

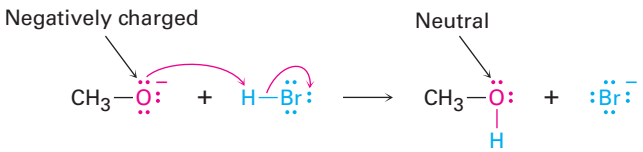


The electrophilic sink must be able to accept an electron pair, usually because it has either a positively charged atom or a positively polarized atom in a functional group. For example:

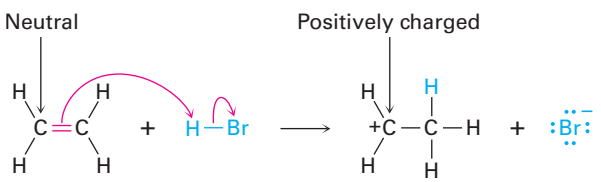
Electrons usually flow *to* one of these electrophiles.

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:

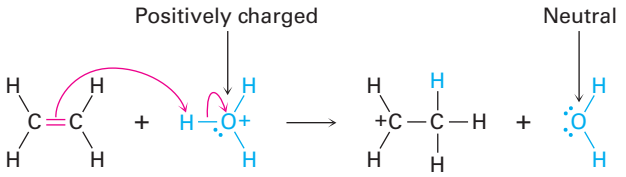


If the nucleophile is neutral, the atom that donates the electron pair acquires a positive charge. For example:

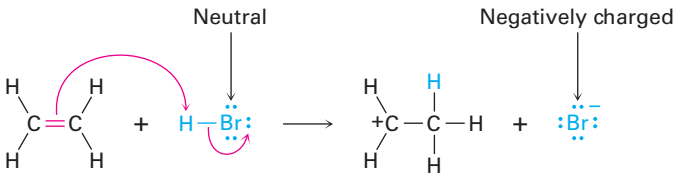


RULE 3

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:



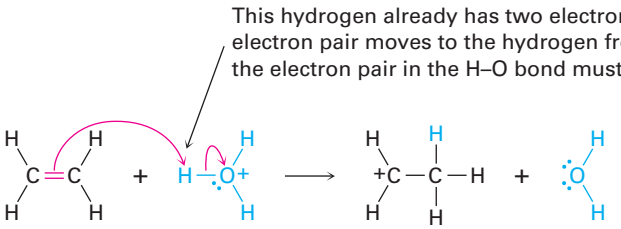
If the electrophile is neutral, the atom that ultimately accepts the electron pair acquires a negative charge. For this to happen, however, the negative charge must be stabilized by being on an electronegative atom such as oxygen, nitrogen, or a halogen. Carbon and hydrogen do not typically stabilize 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 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.

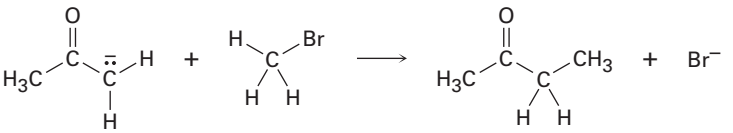


Worked Example 6.2 gives another example of drawing curved arrows.

Using Curved Arrows in Reaction Mechanisms

Worked Example 6.2

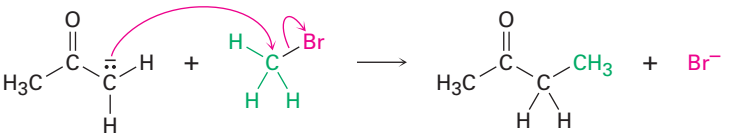
Add curved arrows to the following polar reaction to show the flow of electrons:



Strategy

Look at the reaction, and identify the bonding changes that have occurred. In this case, a C—Br bond has broken and a C—C bond has formed. The formation of the C—C bond involves donation of an electron pair from the nucleophilic carbon atom of the reactant on the left to the electrophilic carbon atom of CH_3Br, so we draw a curved arrow originating from the lone pair on the negatively charged C atom and pointing to the C atom of CH_3Br. At the same time that the C—C bond forms, the C—Br bond must break so that the octet rule is not violated. We therefore draw a second curved arrow from the C—Br bond to Br. The bromine is now a stable Br^- ion.

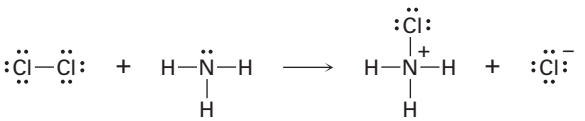
Solution



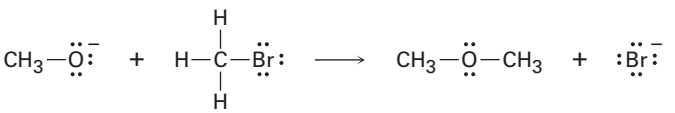
Problem 6.8

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

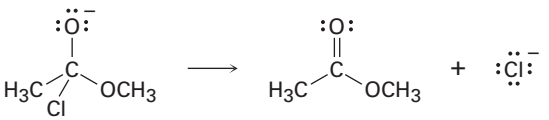
(a)



(b)

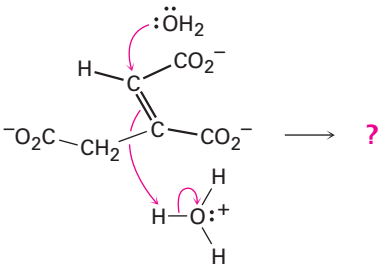


(c)



Problem 6.9

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:



6.7 Describing a Reaction: Equilibria, Rates, and Energy Changes

Every chemical reaction can go in either 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

$$aA + bB \rightleftharpoons cC + dD$$

we have

$$K_{eq} = \frac{[C]^c\ [D]^d}{[A]^a\ [B]^b}$$

The value of the equilibrium constant tells which side of the reaction arrow is energetically favored. If K_{eq} is much larger than 1, then the product concentration term $[C]^c\ [D]^d$ is much larger than the reactant concentration term $[A]^a\ [B]^b$, and the reaction proceeds as written from left to right. If K_{eq} is near 1, appreciable amounts of both reactant and product are present at equilibrium. And if K_{eq} is much smaller than 1, the reaction does not take place as written but instead goes in the reverse direction, from right to left.

In the reaction of ethylene with HBr, for example, we can write the following equilibrium expression and determine experimentally that the equilibrium constant at room temperature is approximately 7.1×10^7:

$$H_2C{=}CH_2 + HBr \rightleftharpoons CH_3CH_2Br$$

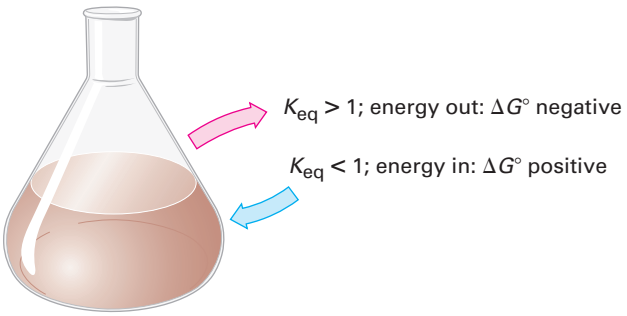
$$K_{eq} = \frac{[CH_3CH_2Br]}{[H_2C{=}CH_2]\,[HBr]} = 7.1 \times 10^7$$

Because K_{eq} is relatively large, the reaction proceeds as written and greater than 99.999 99% 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. The 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: $\Delta G = G_{\text{products}} - G_{\text{reactants}}$. 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 $\Delta G°$, 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 symbolized $\Delta G°'$ 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

$$\Delta G° = -RT \ln K_{eq} \qquad \text{or} \qquad K_{eq} = e^{-\Delta G°/RT}$$

where $R = 8.314$ J/(K · mol) = 1.987 cal/(K · mol)
T = Kelvin temperature
$e = 2.718$
$\ln K_{eq}$ = natural logarithm of K_{eq}

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

$$K_{eq} = 7.1 \times 10^7 \qquad \text{and} \qquad \ln K_{eq} = 18.08$$
$$\Delta G° = -RT \ln K_{eq} = -[8.314 \text{ J/(K · mol)}]\ (298 \text{ K})\ (18.08)$$
$$= -44{,}800 \text{ J/mol} = -44.8 \text{ kJ/mol}$$

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.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

For the reaction of ethylene with HBr at room temperature (298 K), the approximate values are

$H_2C{=}CH_2 + HBr \rightleftharpoons CH_3CH_2Br$

$\Delta G^\circ = -44.8$ kJ/mol
$\Delta H^\circ = -84.1$ kJ/mol
$\Delta S^\circ = -0.132$ kJ/(K · mol)
$K_{eq} = 7.1 \times 10^7$

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 -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

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

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

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

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 $\Delta S^\circ = -0.132$ kJ/(K · mol), is an example. Table 6.2 describes the thermodynamic terms more fully.

Knowing the value of K_{eq} for a reaction is useful, but it's important to realize the 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 undergoes 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?

Table 6.2 Explanation of Thermodynamic Quantities: $\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$

Term	Name	Explanation
ΔG°	Gibbs free-energy change	The energy difference between reactants and products. When ΔG° is negative, the reaction is **exergonic**, has a favorable equilibrium constant, and can occur spontaneously. When ΔG° is positive, the reaction is **endergonic**, has a unfavorable equilibrium constant, and cannot occur spontaneously.
ΔH°	Enthalpy change	The heat of reaction, or difference in strength between the bonds broken in a reaction and the bonds formed. When ΔH° is negative, the reaction releases heat and is **exothermic**. When ΔH° is positive, the reaction absorbs heat and is **endothermic**.
ΔS°	Entropy change	The change in molecular randomness during a reaction. When ΔS° is negative, randomness decreases. When ΔS° is positive, randomness increases.

Problem 6.10

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

Problem 6.11

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

6.8 Describing a Reaction: Bond Dissociation Energies

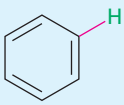
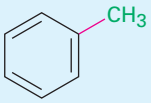
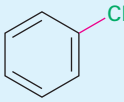
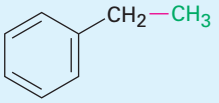
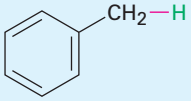
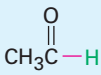
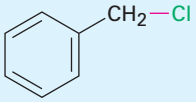
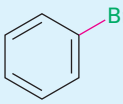
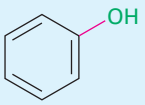
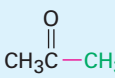
We've just seen that heat is released (negative ΔH) when a bond is formed because the products are more stable and have stronger bonds than the reactants. Conversely, heat is absorbed (positive ΔH) when a bond is broken because the products are less stable and have weaker bonds than the reactants. The amount of energy needed to break a given bond to produce two radical fragments when the molecule is in the gas phase at 25 °C is a quantity called *bond strength*, or **bond dissociation energy (*D*)**.

$$A:B \xrightarrow[\text{energy}]{\text{Bond dissociation}} A\cdot + \cdot B$$

Each specific bond has its own characteristic strength, and extensive tables of 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 6.3 lists some other bond strengths.

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

Table 6.3 Some Bond Dissociation Energies, *D*

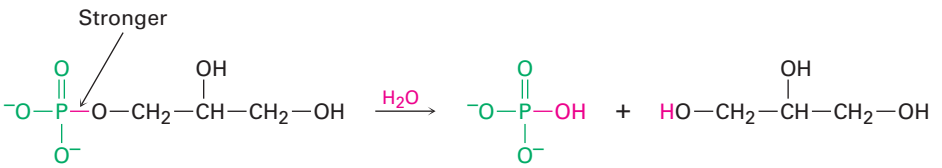
Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)	Bond	*D* (kJ/mol)
H—H	436	$(CH_3)_3C$—I	227	$(CH_3)_2CH$—CH_3	369
H—F	570	H_2C=CH—H	464	$(CH_3)_3C$—CH_3	363
H—Cl	431	H_2C=CH—Cl	396	H_2C=CH—CH_3	426
H—Br	366	H_2C=$CHCH_2$—H	369	H_2C=$CHCH_2$—CH_3	318
H—I	298	H_2C=$CHCH_2$—Cl	298	H_2C=CH_2	728
Cl—Cl	242		472		427
Br—Br	194				
I—I	152				
CH_3—H	439		400		325
CH_3—Cl	350				
CH_3—Br	294				
CH_3—I	239		375		374
CH_3—OH	385				
CH_3—NH_2	386				
C_2H_5—H	421		300	HO—H	497
C_2H_5—Cl	352			HO—OH	211
C_2H_5—Br	293			CH_3O—H	440
C_2H_5—I	233		336	CH_3S—H	366
C_2H_5—OH	391			C_2H_5O—H	441
$(CH_3)_2CH$—H	410		464		352
$(CH_3)_2CH$—Cl	354				
$(CH_3)_2CH$—Br	299				
$(CH_3)_3C$—H	400	HC≡C—H	558	CH_3CH_2O—CH_3	355
$(CH_3)_3C$—Cl	352	CH_3—CH_3	377	NH_2—H	450
$(CH_3)_3C$—Br	293	C_2H_5—CH_3	370	H—CN	528

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 ($\Delta H = -9$ kJ/mol), but when ATP reacts with water, 30 kJ/mol of heat is released ($\Delta H = -30$ kJ/mol). The difference between the two reactions is due to the fact that the bond broken in ATP

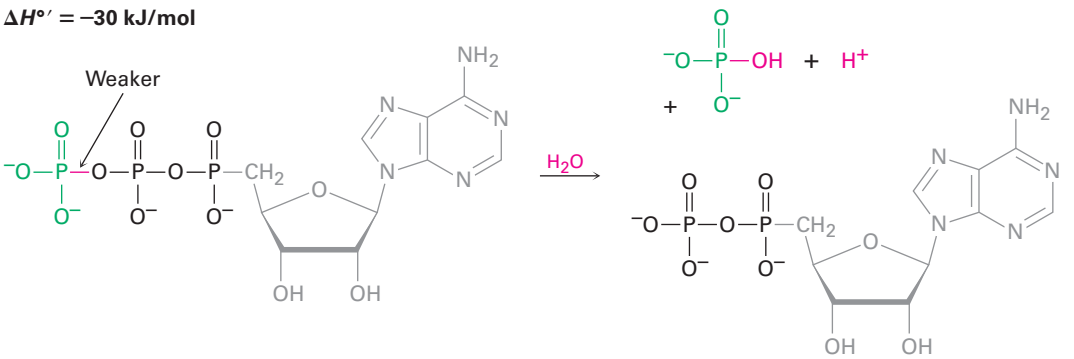
is substantially weaker than the bond broken in glycerol 3-phosphate. We'll see the metabolic importance of this reaction in later chapters.

$\Delta H°' = -9$ kJ/mol



Glycerol 3-phosphate **Glycerol**

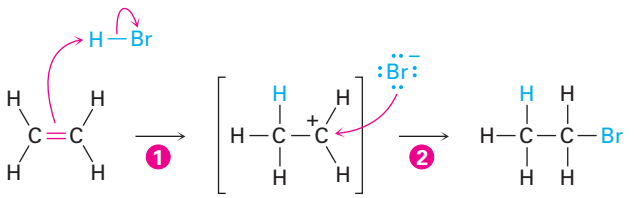
$\Delta H°' = -30$ kJ/mol



Adenosine triphosphate (ATP) **Adenosine diphosphate (ADP)**

6.9 Describing a Reaction: Energy Diagrams and Transition States

For a reaction to take place, reactant molecules must collide and reorganization of atoms and bonds must occur. Let's again look at the addition reaction of HBr and ethylene.



Carbocation

As the reaction proceeds, ethylene and HBr must approach each other, the ethylene π bond and the H–Br bond must break, a new C–H bond must form in step ❶, and a new C–Br bond must form in step ❷.

To depict graphically the energy changes that occur during a reaction, chemists use energy diagrams, such as that shown in **Figure 6.4**. 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.

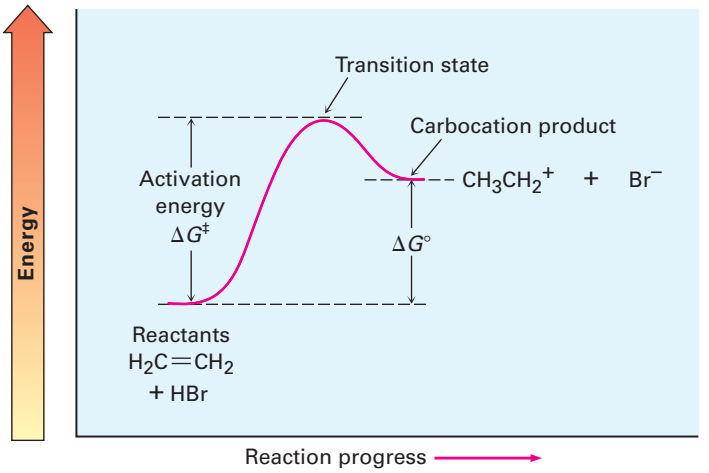


Figure 6.4 An energy diagram for the first step in the reaction of ethylene with HBr. The energy difference between reactants and transition state, $\Delta G^{\ddagger}$, defines the reaction rate. The energy difference between reactants and carbocation product, ΔG°, defines the position of the equilibrium.

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 6.4. 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 nevertheless 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 6.5)**.

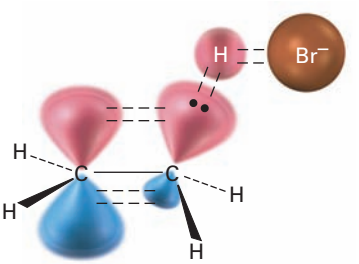


Figure 6.5 A hypothetical transition-state structure for the first step of the reaction of ethylene with HBr. The C=C π bond and H–Br bond are just beginning to break, and the C–H bond is just beginning to form.

The energy difference between reactants and 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 large activation energy results in a slow reaction because few collisions occur with enough energy for the reactants to reach the transition state. A small 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 similar to 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, however, 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 corresponding to the difference between transition state and carbocation product is released. The net energy change for the step, ΔG°, 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 ΔG°, 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 ΔG°, and some have a positive ΔG°. **Figure 6.6** illustrates some different possibilities.

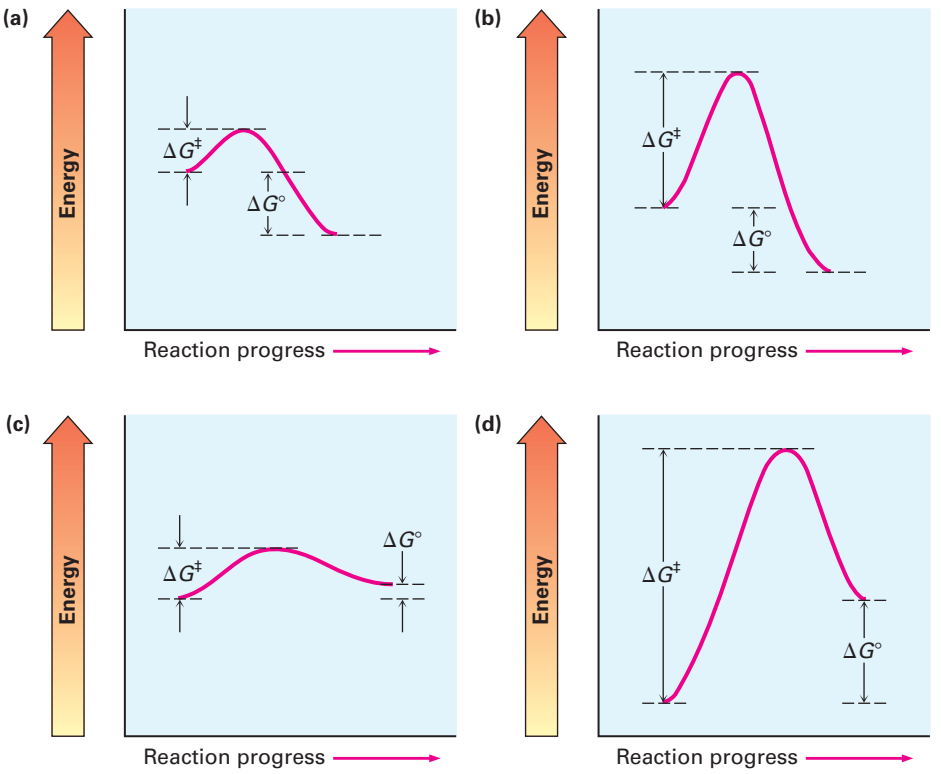


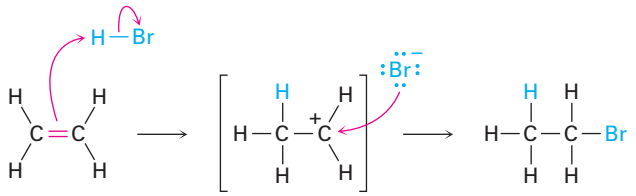
Figure 6.6 Some hypothetical energy diagrams: **(a)** a fast exergonic reaction (small $\Delta G^{\ddagger}$, negative ΔG°); **(b)** a slow exergonic reaction (large $\Delta G^{\ddagger}$, negative ΔG°); **(c)** a fast endergonic reaction (small $\Delta G^{\ddagger}$, small positive ΔG°); **(d)** a slow endergonic reaction (large $\Delta G^{\ddagger}$, positive ΔG°).

Problem 6.12

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

6.10 Describing a Reaction: Intermediates

How can we describe the carbocation formed in the first step of the reaction of ethylene with HBr? The carbocation is clearly different from the reactants, yet it isn't a transition state and it isn't a final product.



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 (ΔG°). 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 6.7**. 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 6.7, 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 the two transition states that neighbor it.

Each step in a multistep process can always be considered separately. Each step has its own $\Delta G^{\ddagger}$ and its own ΔG°. 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 that occurs in. The overall ΔG° of the reaction is the energy difference between reactants and final products.

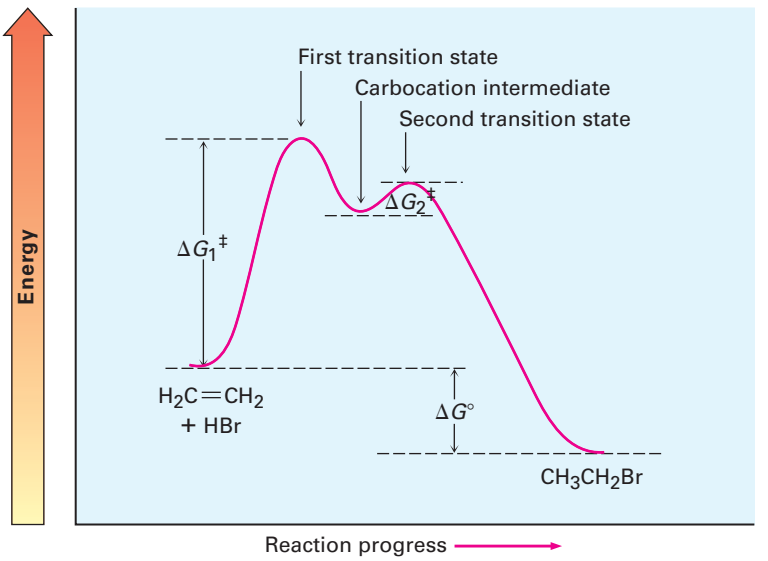


Figure 6.7 An energy diagram for the reaction of ethylene with HBr. Two separate steps are involved, each with its own activation energy ($\Delta G^{\ddagger}$) and free-energy change (ΔG°). The overall $\Delta G^{\ddagger}$ for the complete reaction is the energy difference between reactants and the highest transition state (which corresponds to $\Delta G_1^{\ddagger}$ in this case), and the overall ΔG° for 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 are generally met through the use of large, structurally complex, enzyme catalysts that change the mechanism of a reaction to an alternative pathway that proceeds through a series of small steps rather than one or two large steps. Thus, a typical energy diagram for a biological reaction might look like that in **Figure 6.8**.

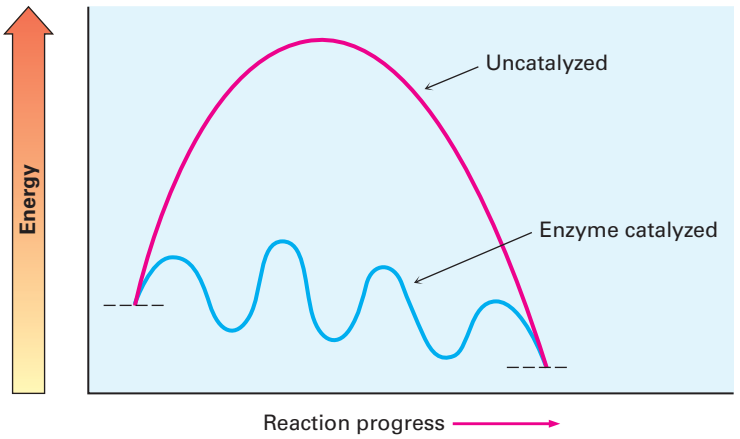


Figure 6.8 An energy diagram for a typical, **enzyme-catalyzed biological reaction** versus an **uncatalyzed laboratory reaction**. The biological reaction involves many steps, each of which has a relatively small activation energy and small energy change. The end result is the same, however.

Drawing an Energy Diagram for a Reaction

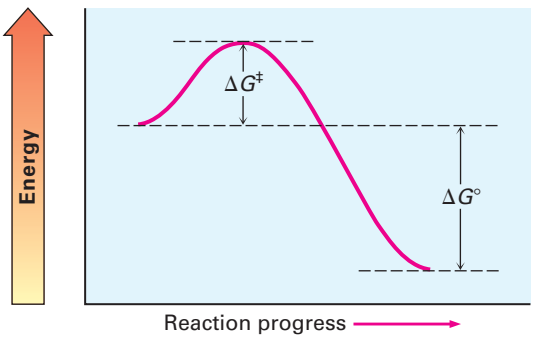
Worked Example 6.3

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



Drawing an Energy Diagram for a Reaction

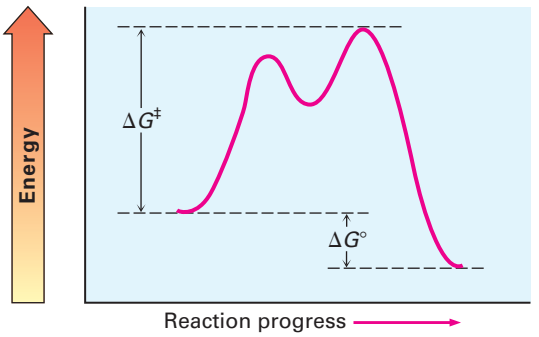
Worked Example 6.4

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



Problem 6.13

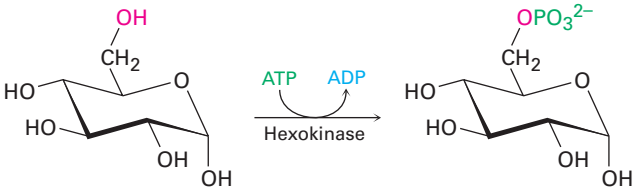
Sketch an energy diagram for a two-step reaction in which both steps are exergonic and in which the second step has a higher-energy transition state than the first. Label the parts of the diagram corresponding to reactant, product, intermediate, overall $\Delta G^{\ddagger}$, and overall $\Delta G°$.

6.11 A Comparison Between Biological Reactions and Laboratory Reactions

Beginning in the next chapter, we'll be seeing a lot of reactions, some that are important in laboratory chemistry yet don't occur in nature and others that have counterparts in biological pathways. In comparing laboratory reactions with biological reactions, several differences are apparent. For one, laboratory reactions are usually carried out in an organic solvent such as diethyl ether or dichloromethane to dissolve the reactants and bring them into contact, whereas biological reactions occur in the aqueous medium inside 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 26.10**, 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 6.9** 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.

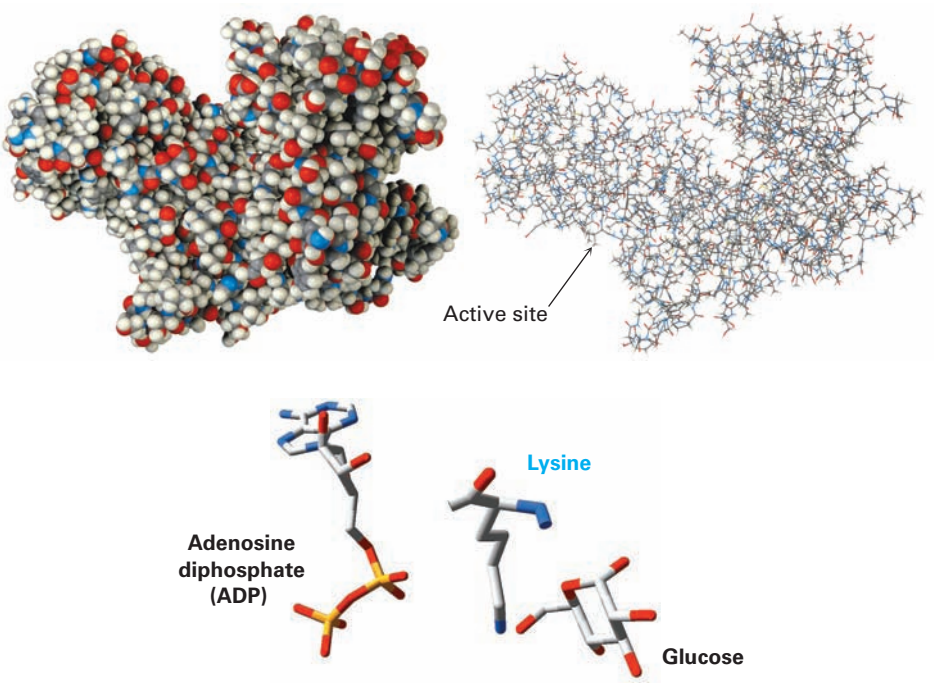
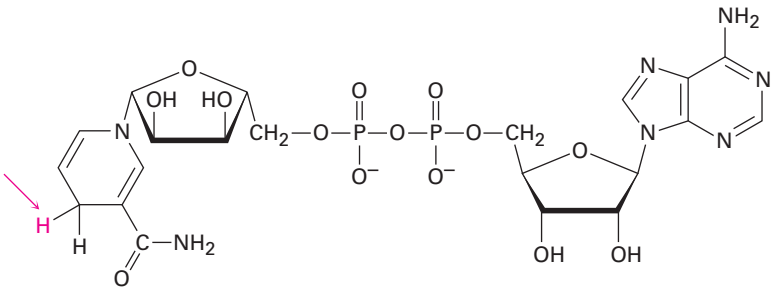


Figure 6.9 Models of hexokinase in space-filling and wire-frame formats, showing the cleft that contains the active site where substrate binding and reaction catalysis occur. At the bottom is an X-ray crystal structure of the enzyme active site, showing the positions of both glucose and ADP as well as a lysine amino acid that acts as a base to deprotonate glucose.

Yet another 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 entire coenzyme, only the one hydrogen atom shown in red is transferred to the double-bond substrate.



Reduced nicotinamide adenine dinucleotide, NADH (a coenzyme)

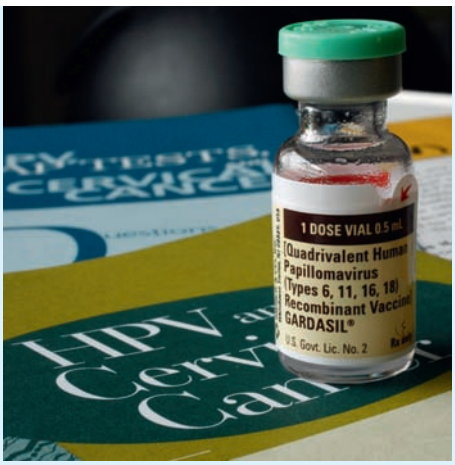
Don't be intimidated by the size of the ATP or NADH molecule; most of the structure is there to provide an overall shape for binding to the enzyme and to provide appropriate solubility behavior. When looking at biological molecules, focus on the small part of the molecule where the chemical change takes 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 6.4 summarizes some of the differences between laboratory and biological reactions.

Table 6.4 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

A DEEPER LOOK Where Do Drugs Come From?



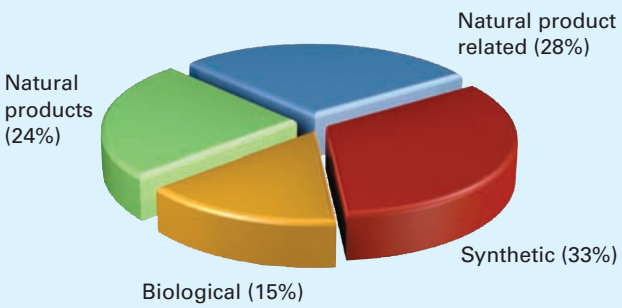
AP Photo/Harry Cabluck

Introduced in June, 2006, Gardasil is the first vaccine ever approved for the prevention of cancer. Where do new drugs like this come from?

It has been estimated that major pharmaceutical companies in the United States spend some $33 billion per year on drug research and development, while government agencies and private foundations spend another $28 billion. What does this money buy? For the period 1981 to 2008, the money resulted in a total of 989 new molecular entities (NMEs)—new biologically active chemical substances approved for sale as drugs by the U.S. Food and Drug Administration (FDA). That's an average of only 35 new drugs each year, spread over all diseases and conditions, and the number is steadily falling. In 2008, only 20 NMEs were approved.

Where do the new drugs come from? According to a study carried out 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, 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%.

Origin of New Drugs 1981–2002



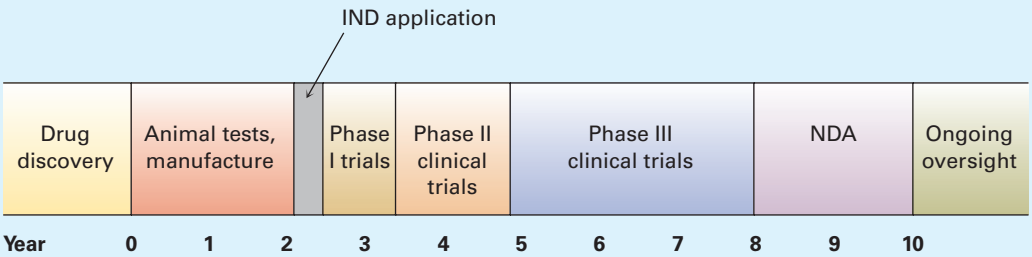
Many years of work go into screening many thousands of substances to identify a single compound that might ultimately gain approval as an NME. But after that single compound has been identified, the work has just begun because it takes an average of 9 to 10 years for a drug to make it through the approval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

Human testing takes 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 for 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

(continued)

(continued)

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.



Summary

Key words

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bond dissociation energy (*D*), 203
carbocation, 196
electrophile, 192
elimination reaction, 185
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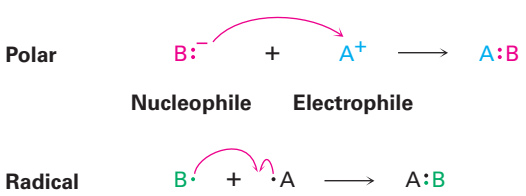
All chemical reactions, whether in the laboratory or in living organisms, follow the same "rules." To understand both organic and biological chemistry, it's necessary to know not just *what* occurs but also *why* and *how* chemical reactions take place. In this chapter, we've taken a brief look at the 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 movement 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 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 reactant 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.

Exercises

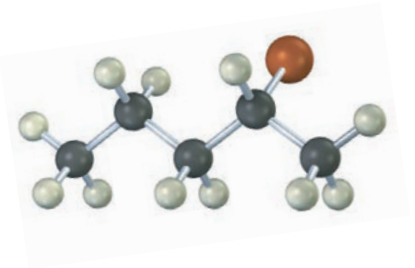
Visualizing Chemistry

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

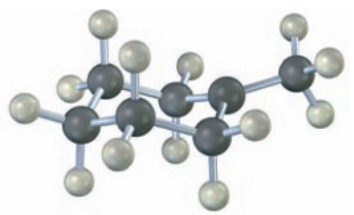
▲ denotes problems linked to the Key Ideas in this chapter.

(Problems 6.1–6.13 appear within the chapter.)

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

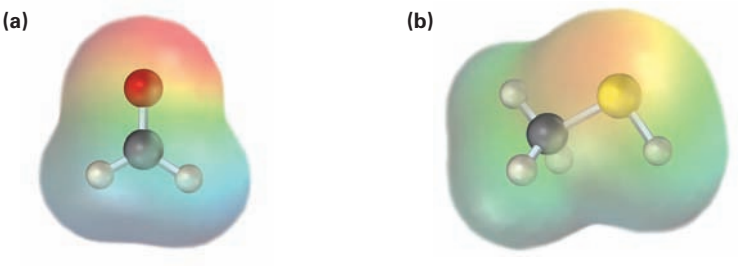


6.15 The following structure represents the carbocation intermediate formed in the addition reaction of HBr to two different alkenes. Draw the structures of both.



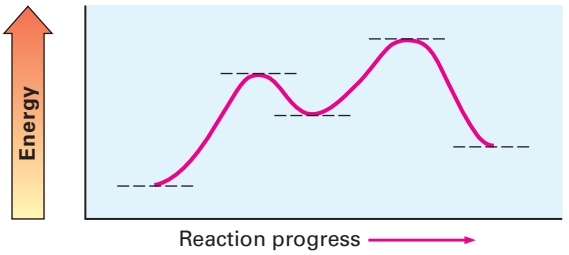
▲ Problems linked to Key Ideas in this chapter

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.



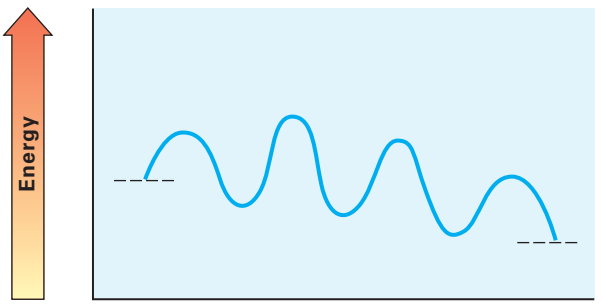
Formaldehyde **Methanethiol**

6.17 Look at the following energy diagram:



(a) Is ΔG° 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.

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 slowest?

▲ Problems linked to Key Ideas in this chapter

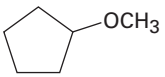
Additional Problems

Polar Reactions

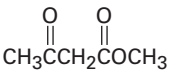
6.19 Identify the functional groups in the following molecules, and show the polarity of each:

(a) $CH_3CH_2C{\equiv}N$

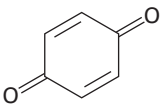
(b)



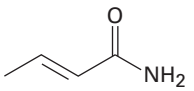
(c)



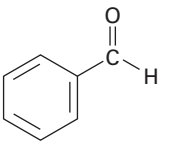
(d)



(e)



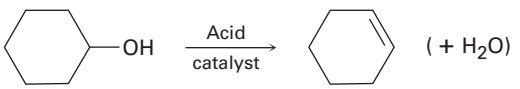
(f)



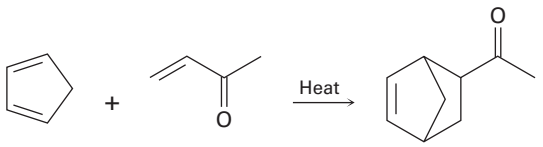
6.20 Identify the following reactions as additions, eliminations, substitutions, or rearrangements:

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

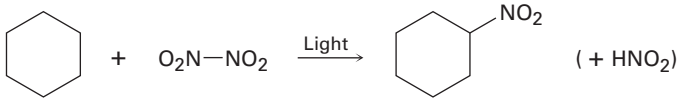
(b)



(c)

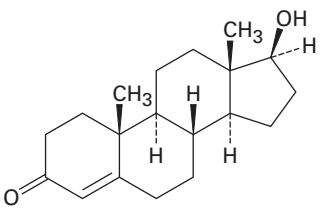


(d)



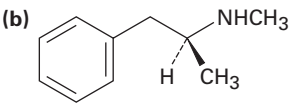
6.21 Identify the likely electrophilic and nucleophilic sites in each of the following molecules:

(a)



Testosterone

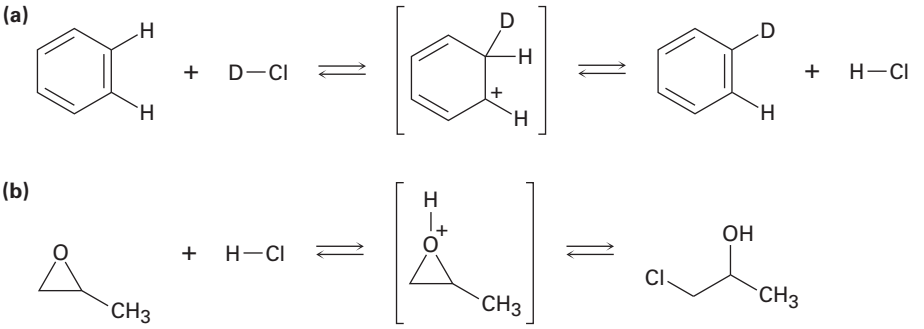
(b)



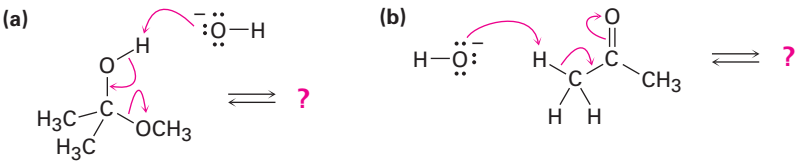
Amphetamine

▲ Problems linked to Key Ideas in this chapter

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



6.23 ▲ Follow the flow of electrons indicated by the curved arrows in each of the following polar reactions, and predict the products that result:



Radical Reactions

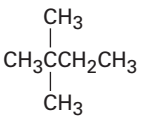
6.24 When a mixture of methane and chlorine is irradiated, reaction commences immediately. When irradiation is stopped, the reaction gradually slows down but does not stop immediately. Explain.

6.25 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.

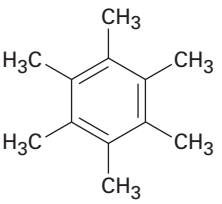
6.26 Despite the limitations of radical chlorination of alkanes, the reaction is still useful for synthesizing certain halogenated compounds. For which of the following compounds does radical chlorination give a single monochloro product?

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

(d)



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



▲ Problems linked to Key Ideas in this chapter

Energy Diagrams and Reaction Mechanisms

6.27 What is the difference between a transition state and an intermediate?

6.28 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?

6.29 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?

6.30 Draw an energy diagram for a two-step exergonic reaction whose second step is faster than its first step.

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

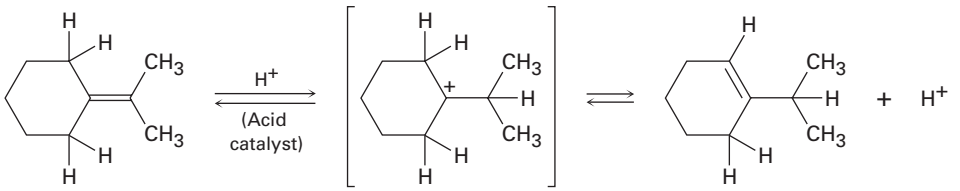
6.32 The addition of water to ethylene to yield ethanol has the following thermodynamic parameters:

$$H_2C{=}CH_2 \quad + \quad H_2O \quad \rightleftharpoons \quad CH_3CH_2OH$$

$\Delta H° = -44$ kJ/mol
$\Delta S° = -0.12$ kJ/(K · mol)
$K_{eq} = 24$

(a) Is the reaction exothermic or endothermic?
(b) Is the reaction favorable (spontaneous) or unfavorable (nonspontaneous) at room temperature (298 K)?

6.33 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.

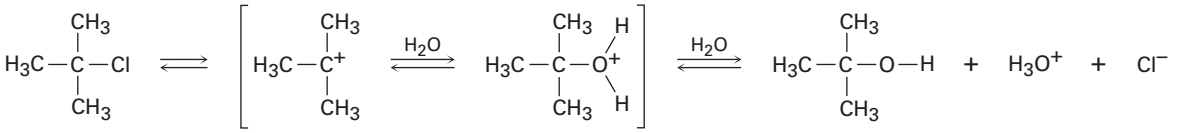
6.34 ▲ Add curved arrows to the mechanism shown in Problem 6.33 to indicate the electron movement in each step.

General Problems

6.35 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

▲ Problems linked to Key Ideas in this chapter

slower than the third. The reaction takes place slowly at room temperature, and the equilibrium constant is near 1.



2-Chloro-2-methylpropane **2-Methyl-2-propanol**

(a) Give approximate values for $\Delta G^{\ddagger}$ and ΔG° that are consistent with the above information.

(b) Draw an energy diagram for the reaction, labeling all points of interest and making sure that the relative energy levels on the diagram are consistent with the information given.

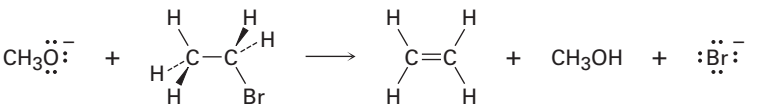
6.36 ▲ Add curved arrows to the mechanism shown in Problem 6.35 to indicate the electron movement in each step.

6.37 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:*

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

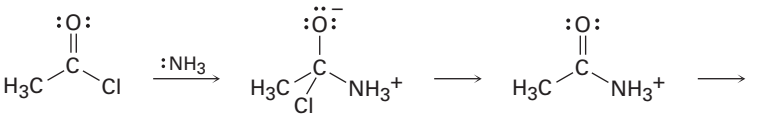
The value of ΔH° for the reaction is -75 kJ/mol, and the value of ΔS° is $+54$ J/(K·mol). What is the value of ΔG° (in kJ/mol) at 298 K? Is the reaction exothermic or endothermic? Is it exergonic or endergonic?

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

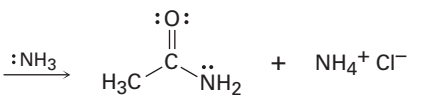


Identify the bonds broken and formed, and draw curved arrows to represent the flow of electrons during the reaction.

6.39 ▲ 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.



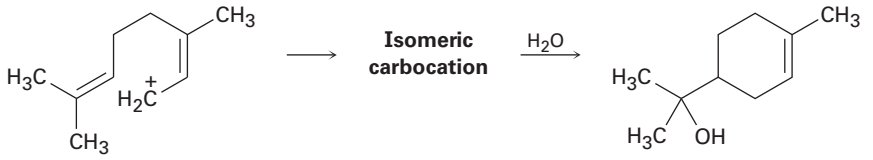
Acetyl chloride



Acetamide

▲ Problems linked to Key Ideas in this chapter

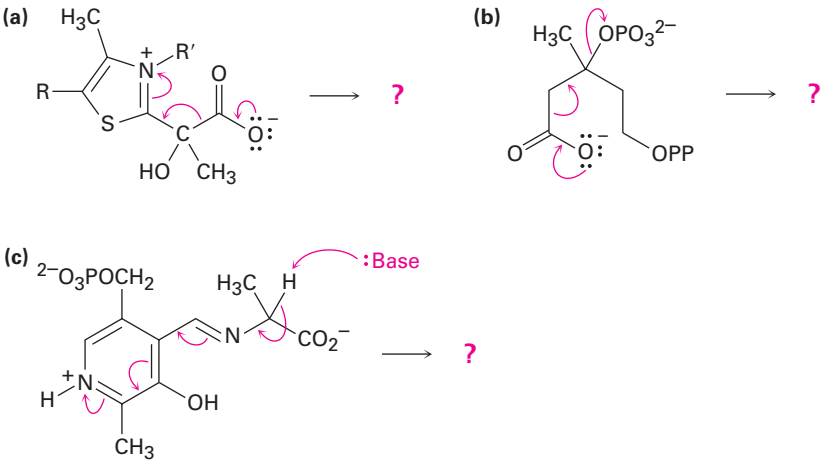
6.40 The naturally occurring molecule α-terpineol is biosynthesized by a route that includes the following step:



Carbocation **α-Terpineol**

(a) Propose a likely structure for the isomeric carbocation intermediate.
(b) Show the mechanism of each step in the biosynthetic pathway, using curved arrows to indicate electron flow.

6.41 Predict the product(s) of each of the following biological reactions by interpreting the flow of electrons as indicated by the curved arrows:



6.42 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.

6.43 Draw the structures of the two carbocation intermediates that might form during the reaction of 2-methylpropene with HBr (Problem 6.42). 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?

▲ Problems linked to Key Ideas in this chapter

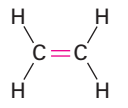
7

The pink color of flamingo feathers is caused by the presence in the bird's diet of β-carotene, a polyalkene.

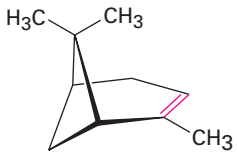
Alkenes: Structure and Reactivity

7.1 Industrial Preparation and Use of Alkenes
7.2 Calculating Degree of Unsaturation
7.3 Naming Alkenes
7.4 Cis–Trans Isomerism in Alkenes
7.5 Alkene Stereochemistry and the *E,Z* Designation
7.6 Stability of Alkenes
7.7 Electrophilic Addition Reactions of Alkenes
7.8 Orientation of Electrophilic Additions: Markovnikov's Rule
7.9 Carbocation Structure and Stability
7.10 The Hammond Postulate
7.11 Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements
A Deeper Look—Bioprospecting: Hunting for Natural Products

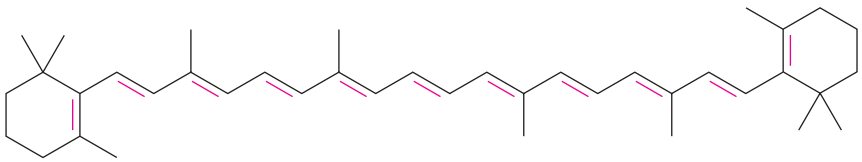
An **alkene**, sometimes called an *olefin,* is a hydrocarbon that contains a carbon–carbon double bond. Alkenes occur abundantly in nature. Ethylene, for instance, is a plant hormone that induces ripening in fruit, and α-pinene is the major component of turpentine. Life itself would be impossible without such alkenes as β-carotene, a compound that contains 11 double bonds. An orange pigment responsible for the color of carrots, β-carotene is an important dietary source of vitamin A and is thought to offer some protection against certain types of cancer.



Ethylene



α-Pinene



β-Carotene
(orange pigment and vitamin A precursor)

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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.

7.1 Industrial Preparation and Use of Alkenes

Ethylene and propylene, the simplest alkenes, are the two most important organic chemicals produced industrially. Approximately 127 million metric tons of ethylene and 54 million metric tons of propylene are produced worldwide each year for use in the synthesis of polyethylene, polypropylene, ethylene glycol, acetic acid, acetaldehyde, and a host of other substances **(Figure 7.1)**.

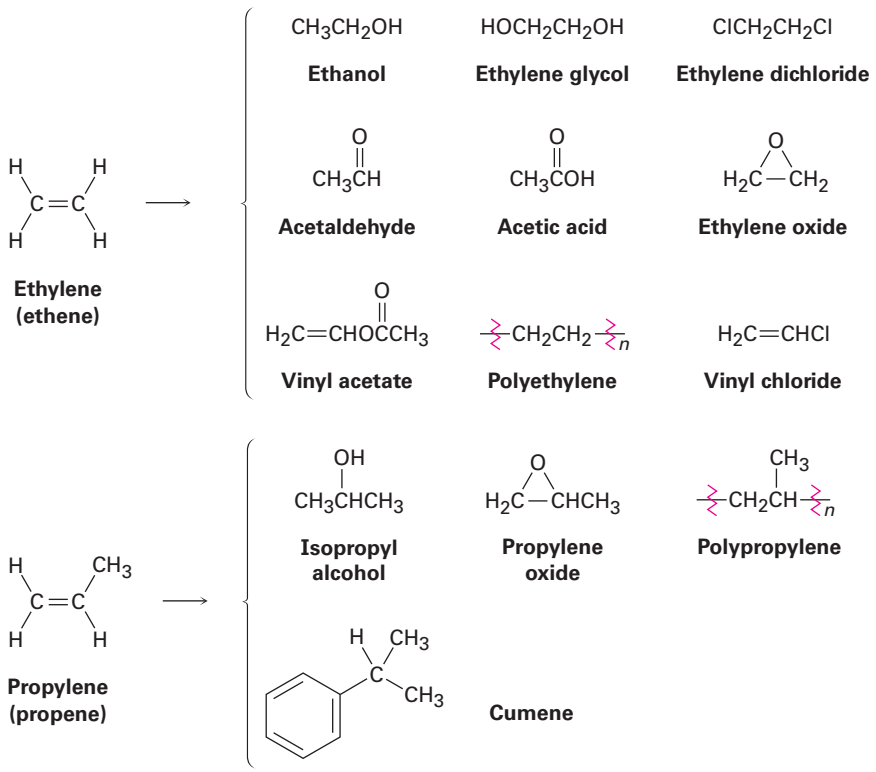


Figure 7.1 Compounds derived industrially from ethylene and propylene.

Ethylene, propylene, and butene are synthesized industrially by steam cracking of light (C_2–C_8) alkanes.

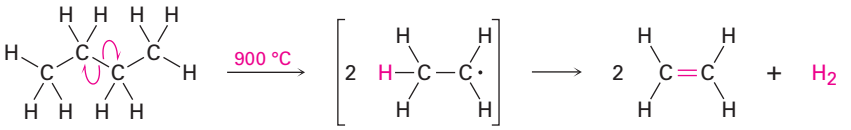
$$CH_3(CH_2)_nCH_3 \quad [n = 0\text{–}6]$$

$$\downarrow \text{ 850–900 °C, steam}$$

$$H_2 + H_2C{=}CH_2 + CH_3CH{=}CH_2 + CH_3CH_2CH{=}CH_2$$

Steam cracking takes place without a catalyst at temperatures up to 900 °C. The process is complex, although it undoubtedly involves radical reactions. The high-temperature reaction conditions cause spontaneous homolytic breaking of C–C and C–H bonds, with resultant formation of smaller fragments. We might imagine, for instance, that a molecule of butane splits into two ethyl

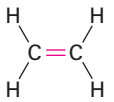
radicals, each of which then loses a hydrogen atom to generate two molecules of ethylene.



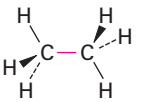
Steam cracking is an example of a reaction whose energetics are dominated by entropy ($\Delta S°$) rather than by enthalpy ($\Delta H°$) in the free-energy equation $\Delta G° = \Delta H° - T\Delta S°$. Although the bond dissociation energy D for a carbon–carbon single bond is relatively high (about 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.

7.2 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.



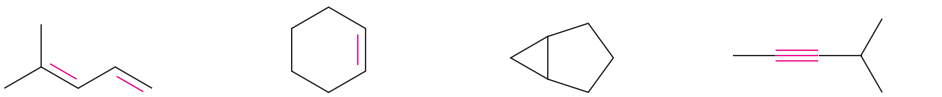
Ethylene: C_2H_4
(Fewer hydrogens—*Unsaturated*)



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 on the unknown 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 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 structure, but the simple calculation has told us a lot about the molecule.



4-Methyl-1,3-pentadiene (two double bonds)

Cyclohexene (one ring, one double bond)

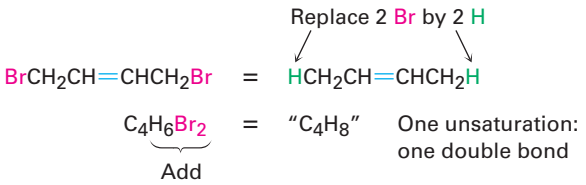
Bicyclo[3.1.0]hexane (two rings)

4-Methyl-2-pentyne (one triple bond)

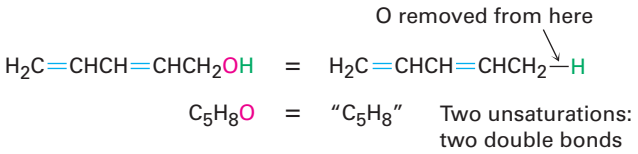
C_6H_{10}

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

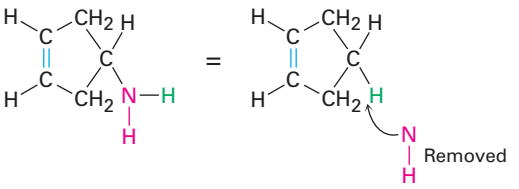
- **Organohalogen compounds (C, H, X, where X = F, Cl, Br, or I)** A halogen substituent acts as a replacement for hydrogen in an organic molecule, so we can add the number of halogens and hydrogens to arrive at an equivalent hydrocarbon formula from which the degree of unsaturation can be found. For 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.

Problem 7.1

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

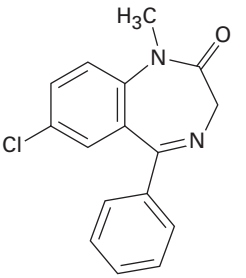
Problem 7.2

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)** $C_{20}H_{32}ClN$

Problem 7.3

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.)



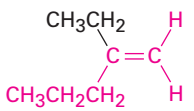
Diazepam

7.3 Naming Alkenes

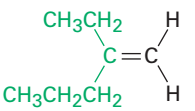
Alkenes are named using a series of rules similar to those for alkanes **(Section 3.4)**, with the suffix *-ene* used instead of *-ane* to identify the functional group. There are three steps.

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*

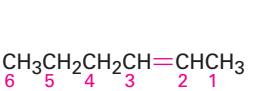


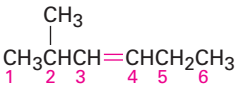
as a hexene, since the double bond is not contained in the six-carbon chain

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

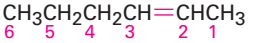
the end nearer the first branch point. This rule ensures that the double-bond carbons receive the lowest possible numbers.



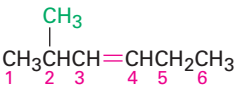


STEP 3

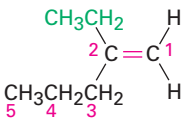
Write the full name. Number the substituents according to their positions in the chain, and list them alphabetically. Indicate the position of the double bond by giving the number of the first alkene carbon and placing that number directly before the parent name. If more than one double bond is present,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



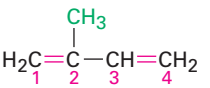
2-Hexene



2-Methyl-3-hexene

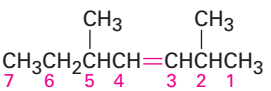


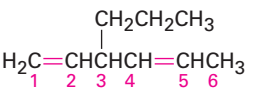
2-Ethyl-1-pentene



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.

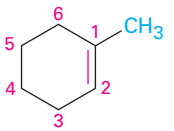




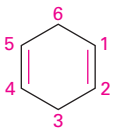
Older naming system:	**2,5-Dimethyl-3-heptene**	**3-Propyl-1,4-hexadiene**
(Newer naming system:	**2,5-Dimethylhept-3-ene**	**3-Propylhexa-1,4-diene)**

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, newer but not yet

widely accepted naming rules place the locant immediately before the suffix in a diene.

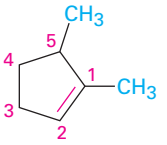


1-Methylcyclohexene



1,4-Cyclohexadiene

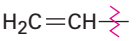
(New: Cyclohexa-1,4-diene)



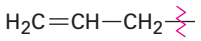
1,5-Dimethylcyclopentene

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 so long that it is accepted by IUPAC. Table 7.1 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

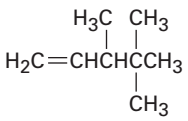
Table 7.1 Common Names of Some Alkenes

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

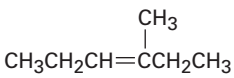
Problem 7.4

Give IUPAC names for the following compounds:

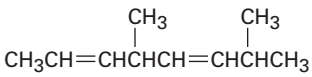
(a)



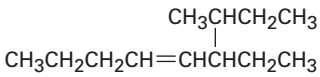
(b)



(c)



(d)



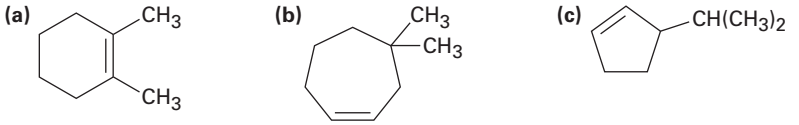
Problem 7.5

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

Problem 7.6

Name the following cycloalkenes:



Problem 7.7

Change the following old names to new, post-1993 names, and draw the structure of each compound:

(a) 2,5,5-Trimethyl-2-hexene **(b)** 2,3-Dimethyl-1,3-cyclohexadiene

7.4 Cis–Trans Isomerism in Alkenes

We saw in Chapter 1 that the carbon–carbon double bond can be described in two ways. In valence bond language **(Section 1.8)**, 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 head-on overlap of sp^2 orbitals and a π bond by sideways overlap of unhybridized p orbitals oriented perpendicular to the sp^2 plane, as shown in Figure 1.14 on page 14.

In molecular orbital language **(Section 1.11)**, 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, as shown in Figure 1.18, page 21.

Although essentially free rotation is possible around single bonds **(Section 3.6)**, 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 7.2)**. 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.

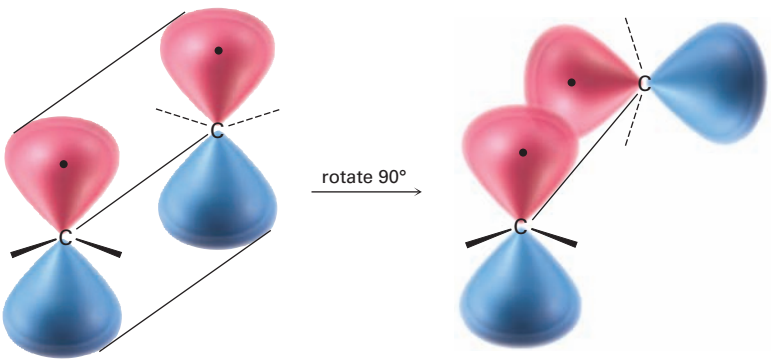
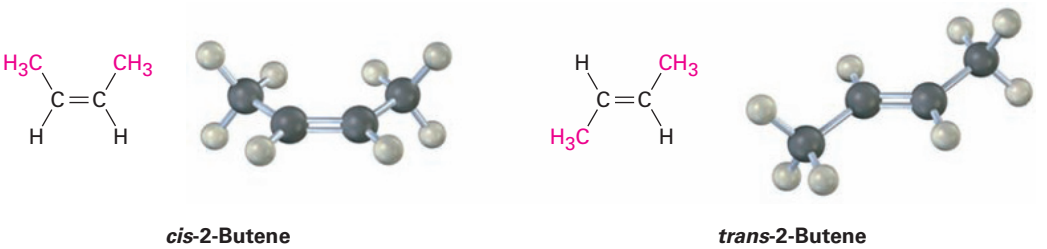


Figure 7.2 The π bond must break for rotation to take place around a carbon–carbon double bond.

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 be either on the same side of the double bond or on opposite sides, a situation similar to that in disubstituted cycloalkanes **(Section 4.2)**.

Since bond rotation can't occur, the two 2-butenes can't spontaneously interconvert; they are different, isolable compounds. As with disubstituted cycloalkanes, we call such compounds *cis–trans stereoisomers*. The compound with substituents on the same side of the double bond is called *cis*-2-butene, and the isomer with substituents on opposite sides is *trans*-2-butene **(Figure 7.3)**.



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

Figure 7.3 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 the 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, then cis–trans isomerism is not possible **(Figure 7.4)**.

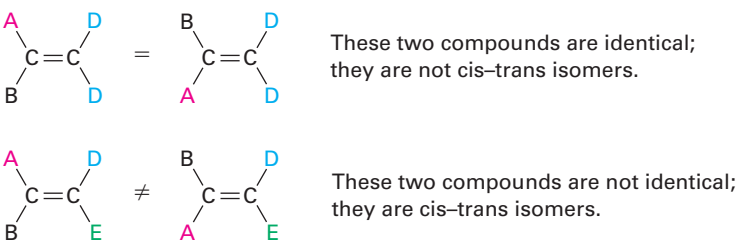


Figure 7.4 The requirement for cis–trans isomerism in alkenes. Compounds that have one of their carbons bonded to two identical groups can't exist as cis–trans isomers. Only when both carbons are bonded to two different groups is cis–trans isomerism possible.

Problem 7.8

The sex attractant of the common housefly is an alkene named *cis*-9-tricosene. Draw its structure. (Tricosane is the straight-chain alkane $C_{23}H_{48}$.)

Problem 7.9

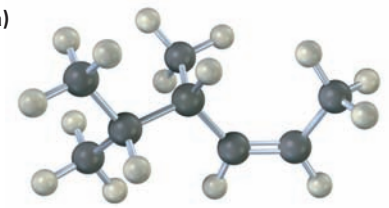
Which of the following compounds can exist as pairs of cis–trans isomers? Draw each cis–trans pair, and indicate the geometry of each isomer.

(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)** $BrCH{=}CHCl$

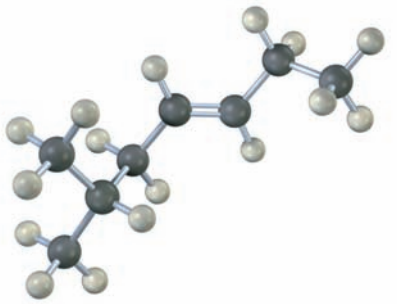
Problem 7.10

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

(a)



(b)



7.5 Alkene Stereochemistry and the *E,Z* Designation

Key IDEAS

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

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 5.5** 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, you should reread **Section 5.5**.

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. An atom with higher atomic number ranks higher than an atom with lower atomic number.

RULE 2

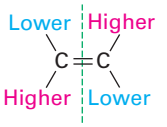
If a decision can't be reached by ranking the first atoms in the two substituents, look at the second, third, or fourth atoms away from the double-bond until the first difference is found.

RULE 3

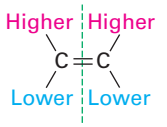
Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.

Once the two groups attached to each doubly bonded carbon atom 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 **Z geometry**, for the German *zusammen,* meaning "together." If the higher-ranked groups are on opposite sides, the alkene has ***E* geometry**, for the German *entgegen,* meaning "opposite." (A simple way to remember which is which to note that the groups are on "ze zame zide" in the *Z* isomer.)

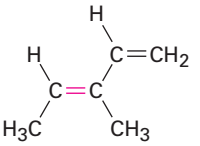


E double bond
(Higher-ranked groups
are on opposite sides.)

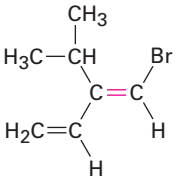


Z double bond
(Higher-ranked groups
are on the same side.)

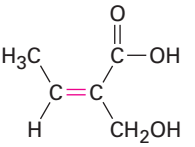
For further practice, work through each of the following examples to convince yourself that the assignments are correct:



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



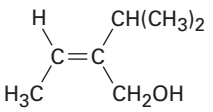
(*E*)-1-Bromo-2-isopropyl-1,3-butadiene



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

Worked Example 7.1 Assigning *E* and *Z* Configurations to Substituted Alkenes

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



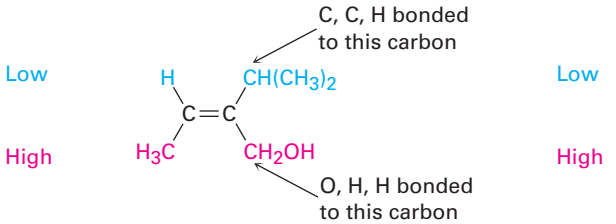
Strategy

Look at the two substituents connected to each double-bond carbon, and determine their ranking using the Cahn–Ingold–Prelog rules. Then see 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 *Z* configuration.



***Z* configuration**

Problem 7.11

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 $-CH=O$

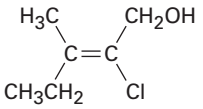
Problem 7.12

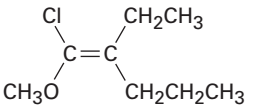
Rank the substituents in each of the following sets according to the sequence rules:

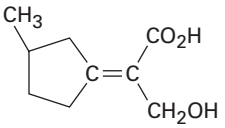
(a) $-CH_3$, $-OH$, $-H$, $-Cl$
(b) $-CH_3$, $-CH_2CH_3$, $-CH=CH_2$, $-CH_2OH$
(c) $-CO_2H$, $-CH_2OH$, $-C\equiv N$, $-CH_2NH_2$
(d) $-CH_2CH_3$, $-C\equiv CH$, $-C\equiv N$, $-CH_2OCH_3$

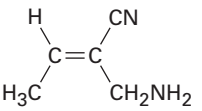
Problem 7.13

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

(a)


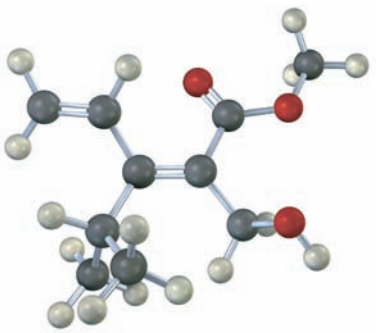
(b)


(c)


(d)


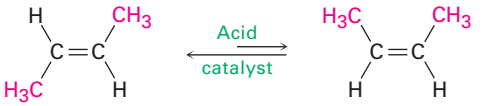
Problem 7.14

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



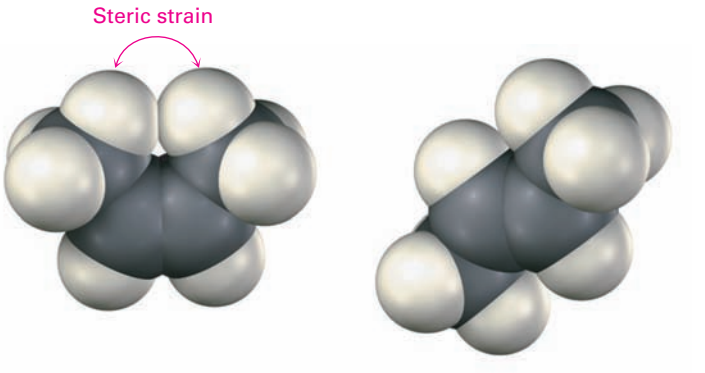
7.6 Stability of Alkenes

Although the cis–trans interconversion of alkene isomers does not occur spontaneously, it can often be brought about 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.



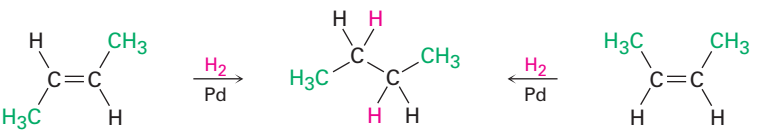
Trans (76%) **Cis (24%)**

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 on treatment 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 7.5**. 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 ΔG° for reaction of the cis isomer must be larger than ΔG° for reaction of the trans isomer by 2.8 kJ/mol. In other words, more energy is released in the hydrogenation of the cis isomer than the trans isomer because the cis isomer has more energy to begin with.

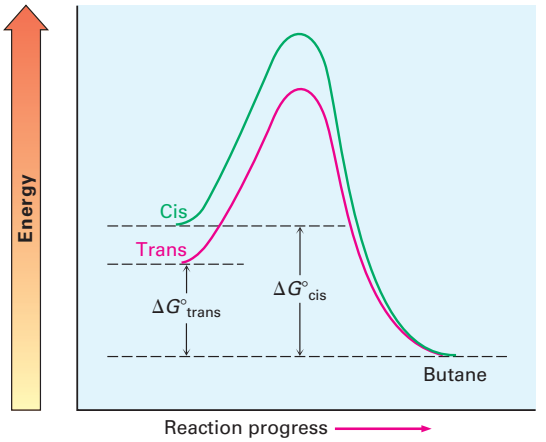
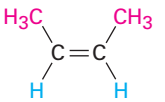
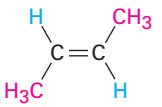


Figure 7.5 Energy diagrams for hydrogenation of *cis*- and *trans*-2-butene. The cis isomer is higher in energy than the trans isomer by about 2.8 kJ/mol and therefore releases more energy in the reaction.

If we were to measure the so-called heats of hydrogenation (ΔH°_{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 $\Delta H^\circ_{hydrog} = -120$ kJ/mol (−28.6 kcal/mol), while *trans*-2-butene has $\Delta H^\circ_{hydrog} = -116$ kJ/mol (−27.6 kcal/mol)—a difference of 4 kJ/mol.



Cis isomer
$\Delta H^\circ_{hydrog} = -120$ kJ/mol

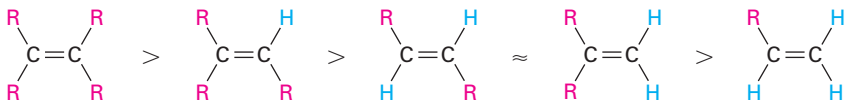


Trans isomer
$\Delta H^\circ_{hydrog} = -116$ kJ/mol

The 4 kJ/mol energy difference between the 2-butene isomers calculated from heats of hydrogenation agrees reasonably well with the 2.8 kcal/mol energy difference calculated from equilibrium data, but the numbers aren't exactly the same for two reasons. First, there is probably some experimental error, since 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, ΔH°, whereas equilibrium constants measure free-energy changes, ΔG°, so we might expect a slight difference between the two.

Table 7.2 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:

Tetrasubstituted > Trisubstituted > Disubstituted > Monosubstituted



The stability order of substituted alkenes is due to a combination of two factors. One is a stabilizing interaction between the C=C π bond 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 7.6**. The more substituents that are present on the double bond, the more hyperconjugation there is and the more stable the alkene.

Table 7.2 Heats of Hydrogenation of Some Alkenes

Substitution	Alkene	$\Delta H°_{hydrog}$ (kJ/mol)	$\Delta H°_{hydrog}$ (kcal/mol)
Ethylene	$H_2C{=}CH_2$	−137	−32.8
Monosubstituted	$CH_3CH{=}CH_2$	−126	−30.1
Disubstituted	$CH_3CH{=}CHCH_3$ (cis)	−120	−28.6
	$CH_3CH{=}CHCH_3$ (trans)	−116	−27.6
	$(CH_3)_2C{=}CH_2$	−119	−28.4
Trisubstituted	$(CH_3)_2C{=}CHCH_3$	−113	−26.9
Tetrasubstituted	$(CH_3)_2C{=}C(CH_3)_2$	−111	−26.6

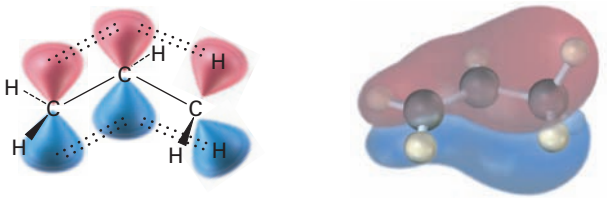


Figure 7.6 Hyperconjugation is a stabilizing interaction between the C=C π bond and adjacent C–H σ bonds on substituents. The more substituents there are, the greater the stabilization of the alkene.

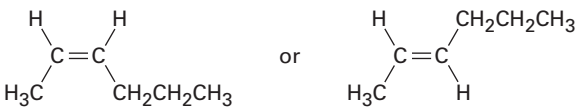
A second factor that contributes to alkene stability involves bond strengths. A bond between an sp^2 carbon and an sp^3 carbon is somewhat stronger than a bond between two sp^3 carbons. Thus, in comparing 1-butene and 2-butene, the monosubstituted isomer has one sp^3–sp^3 bond and one sp^3–sp^2 bond, while the disubstituted isomer has two sp^3–sp^2 bonds. More highly substituted alkenes always have a higher ratio of sp^3–sp^2 bonds to sp^3–sp^3 bonds than less highly substituted alkenes and are therefore more stable.

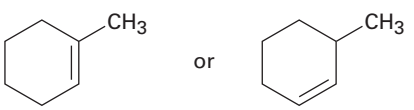
2-Butene (more stable) **1-Butene (less stable)**

Problem 7.15

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

(a) $H_2C{=}CHCH_2CH_3$ or $H_2C{=}C(CH_3)$

(b) 

(c) 

7.7 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 6.5** 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 Christopher Ingold and others in the 1930s led to the generally accepted mechanism shown in **Figure 7.7** for **electrophilic addition reactions**.

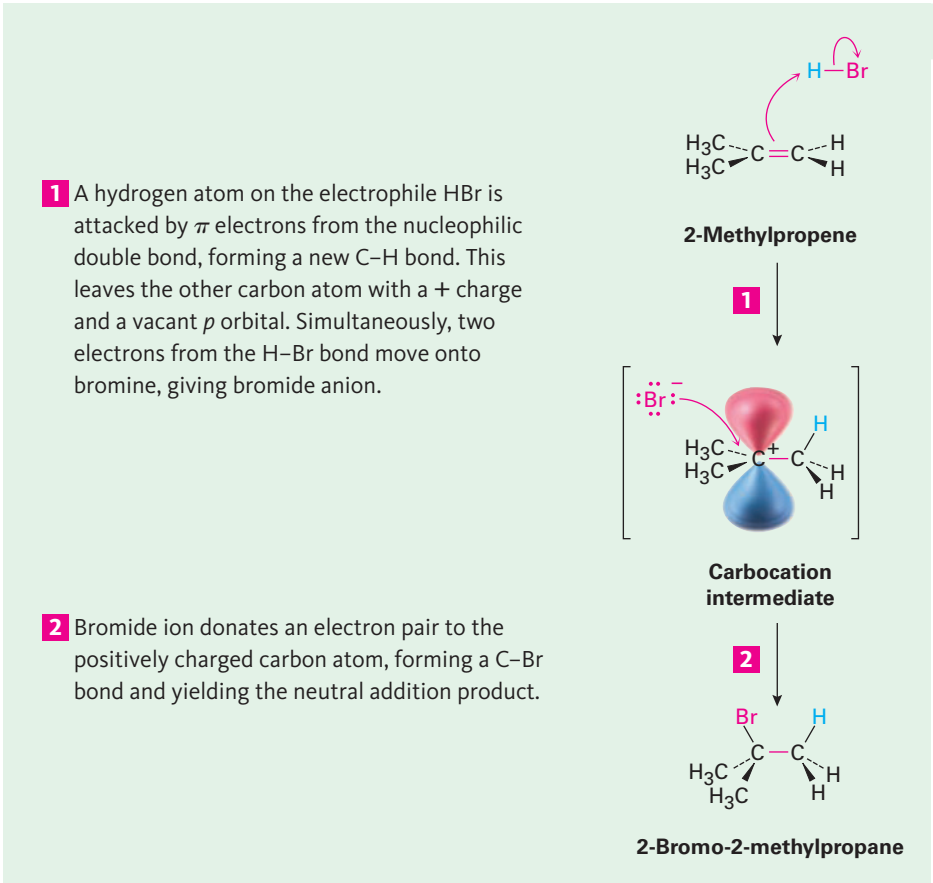


Figure 7.7 | MECHANISM

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 7.7. The carbocation intermediate that results 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)** 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 formed, the cation intermediate rapidly reacts further to yield the final alkyl bromide product. The relative rates of the two steps are indicated in Figure 7.8 by the fact that $\Delta G^{\ddagger}_1$ is larger than $\Delta G^{\ddagger}_2$.

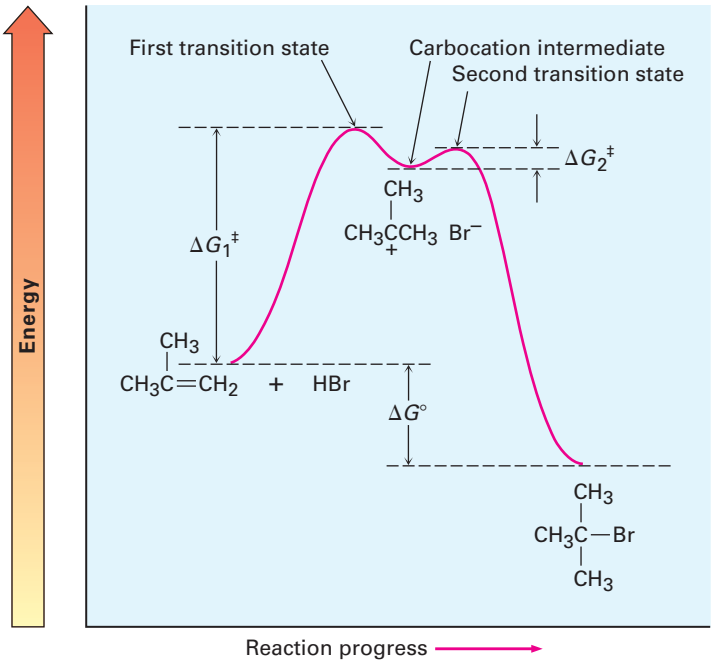
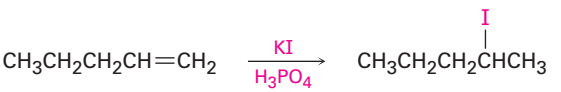


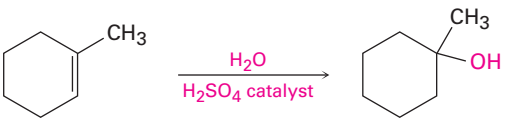
Figure 7.8 Energy diagram for the two-step electrophilic addition of HBr to 2-methylpropene. The first step is slower than the second step.

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%)**



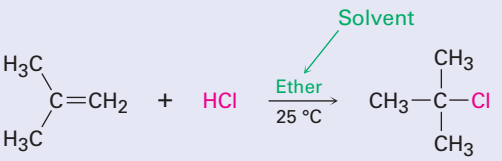
1-Pentene **(HI)** **2-Iodopentane**



1-Methylcyclohexene **1-Methylcyclohexanol**

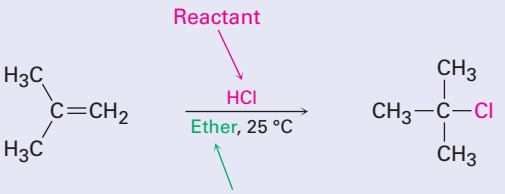
Writing Organic Reactions

This is a good time to mention that organic reaction equations 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.



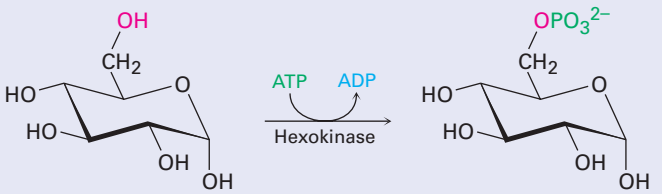
2-Methylpropene **2-Chloro-2-methylpropane**

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-methylpropane**

In describing a biological process, the reaction is usually written to show only the structures of the primary reactant and product, while abbreviating the structures of various biological "reagents" and by-products by using a curved arrow that intersects the straight reaction arrow. As discussed in **Section 6.11**, the reaction of glucose with ATP to give glucose 6-phosphate plus ADP would be written as



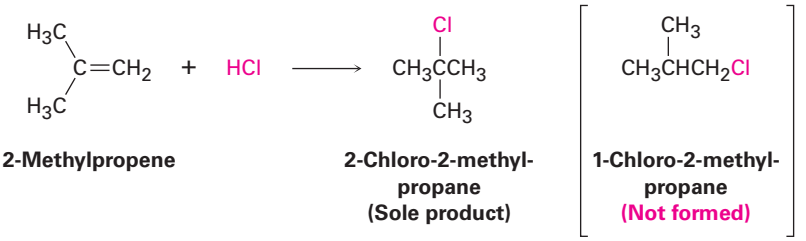
Glucose **Glucose 6-phosphate**

7.8 Orientation of Electrophilic Additions: Markovnikov's Rule

Key IDEAS

Test your knowledge of Key Ideas by answering end-of-chapter exercises marked with ▲.

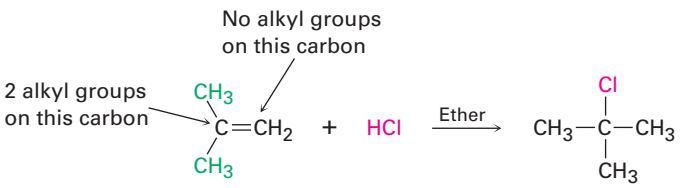
Look carefully at the electrophilic addition reactions shown in the previous section. In each case, an unsymmetrically substituted alkene gives a single addition product rather than the mixture that might be expected. For example, 2-methylpropene *might* react with HCl to give both 2-chloro-2-methylpropane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

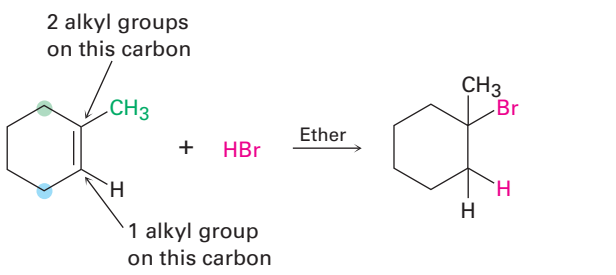


After looking at the results of many such reactions, the Russian chemist Vladimir Markovnikov proposed in 1869 what has become known as **Markovnikov's rule**.

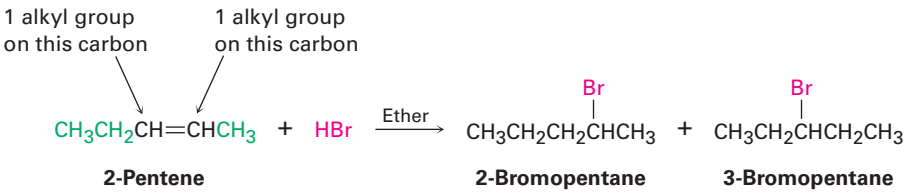
Markovnikov's rule

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.





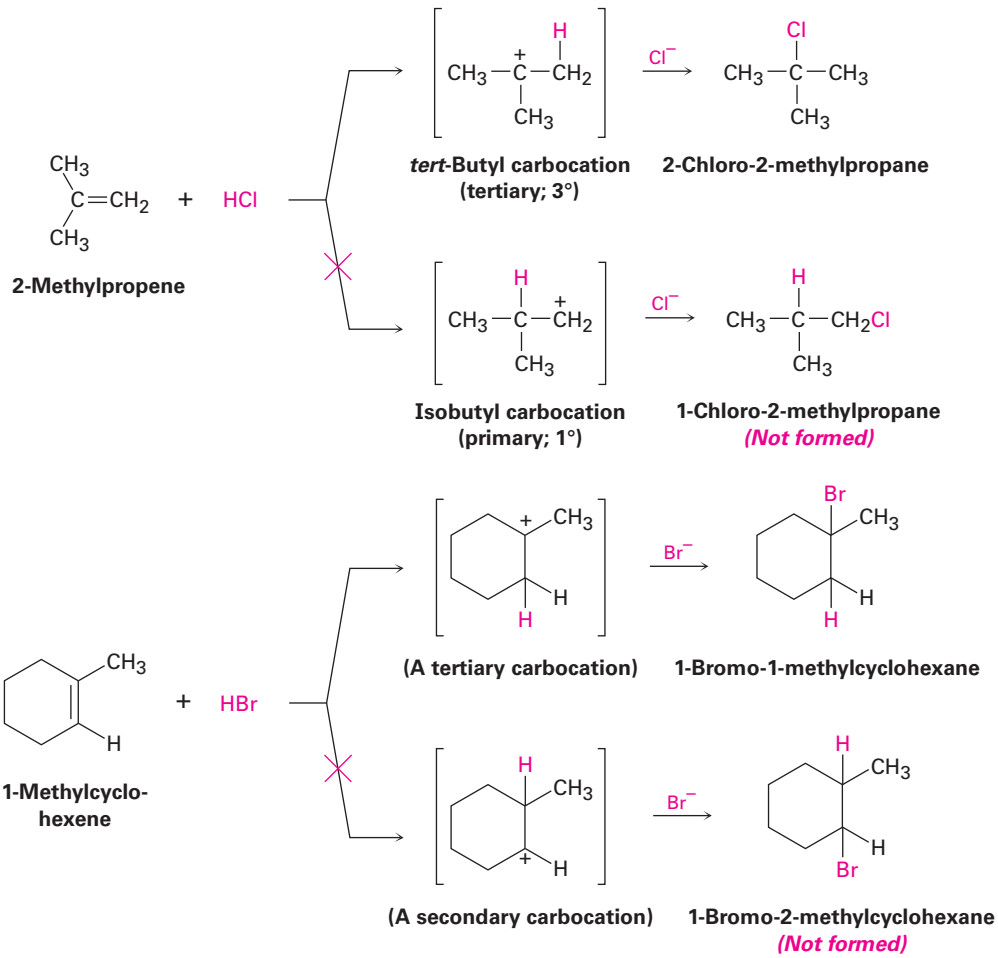
When both double-bond carbon atoms have the same degree of substitution, a mixture of addition products results.



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

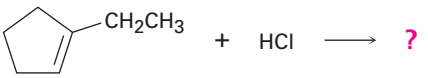
Markovnikov's rule (restated)
In the addition of HX to an alkene, the more highly substituted carbocation is formed as the intermediate rather than the less highly substituted one.

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 7.2 Predicting the Product of an Electrophilic Addition Reaction

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

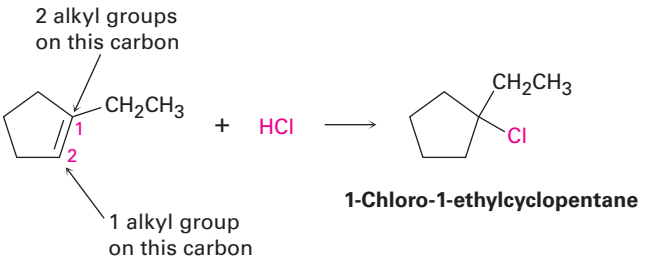


Strategy

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 and use your knowledge 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

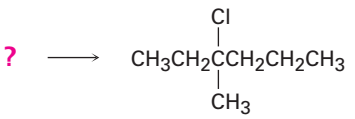
The expected product is 1-chloro-1-ethylcyclopentane.



1-Chloro-1-ethylcyclopentane

Worked Example 7.3 Synthesizing a Specific Compound

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

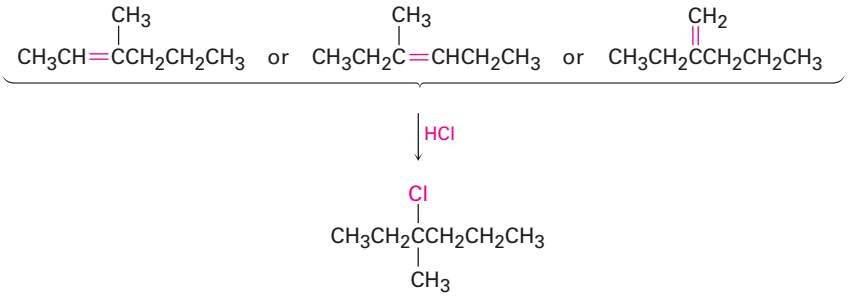


Strategy

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.

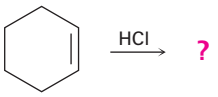
Solution

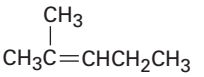
There are three possibilities, any one of which could give the desired product according to Markovnikov's rule.

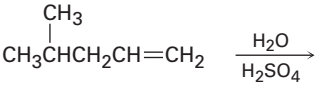


Problem 7.16

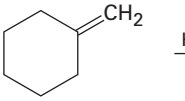
Predict the products of the following reactions:

(a)  HCl → ?

(b)  HBr → ?

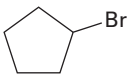
(c)  $\xrightarrow[H_2SO_4]{H_2O}$?

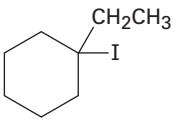
(Addition of H_2O occurs.)

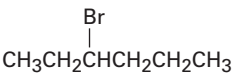
(d)  HBr → ?

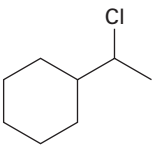
Problem 7.17

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

(a) 

(b) 

(c) 

(d) 

7.9 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 7.9**. 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.

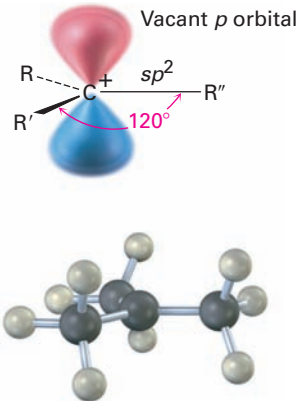
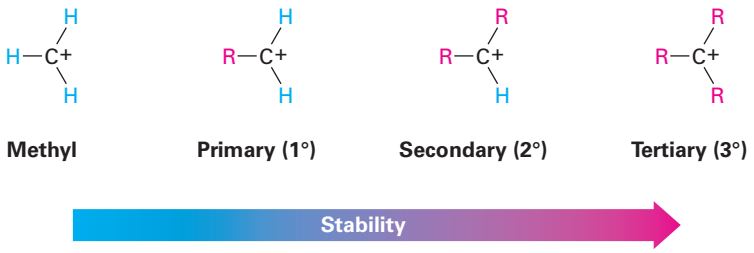


Figure 7.9 The structure of a carbocation. The trivalent carbon is sp^2-hybridized and has a vacant *p* orbital perpendicular to the plane of the carbon and three attached groups.

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 the carbocation by dissociation of the corresponding alkyl halide, $R{-}X \rightarrow R^+ + {:}X^-$. As shown in **Figure 7.10**, 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 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.

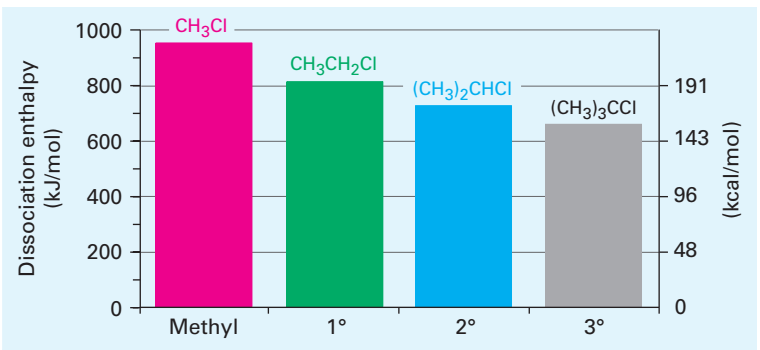


Figure 7.10 A plot of dissociation enthalpy versus substitution pattern for the gas-phase dissociation of alkyl chlorides to yield carbocations. More highly substituted alkyl halides dissociate more easily than less highly substituted ones.

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 2.1** 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 there are attached to the positively charged carbon, the more electron density shifts toward the charge and the more inductive stabilization of the cation occurs **(Figure 7.11)**.

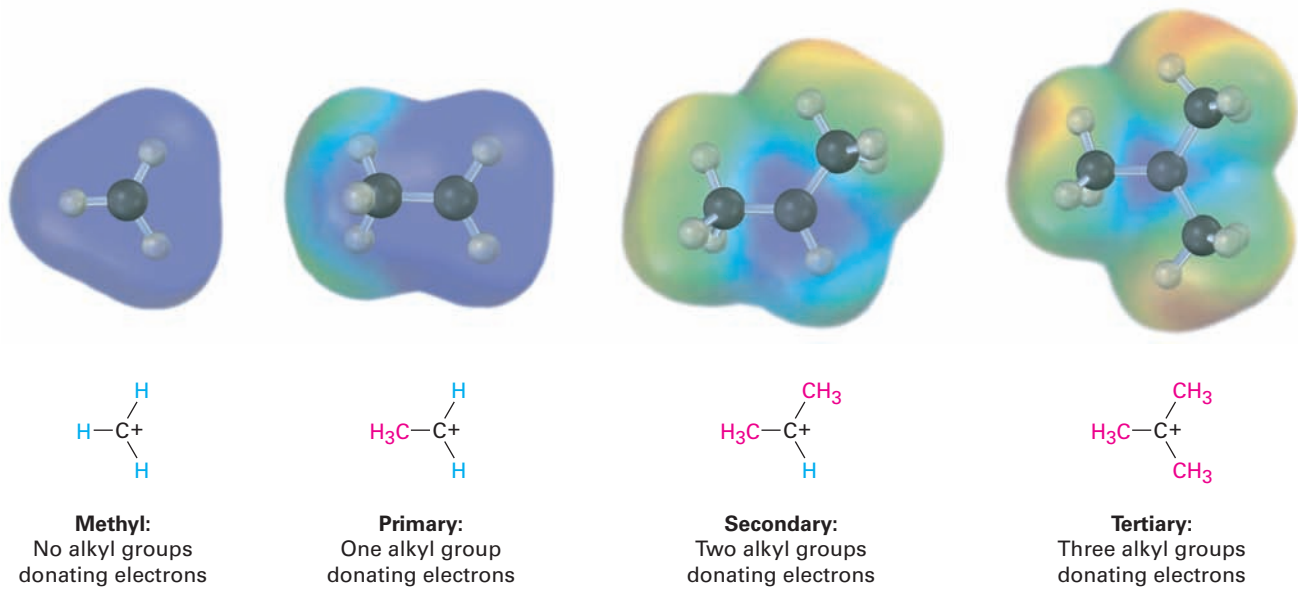


Figure 7.11 A comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups that are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron poor (blue in electrostatic potential maps).

Hyperconjugation, discussed in **Section 7.6** 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 7.12** 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 nearly parallel to the cation *p* orbital. Only the roughly parallel C–H bonds are oriented properly to take part in hyperconjugation.

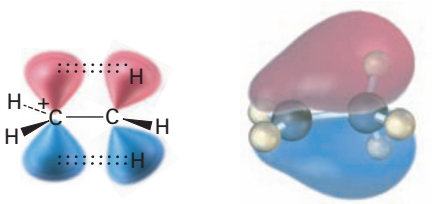
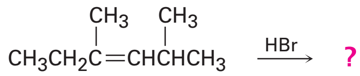


Figure 7.12 Stabilization of the ethyl carbocation, $CH_3CH_2^+$, through hyperconjugation. Interaction of neighboring C–H σ bonds with the vacant *p* orbital stabilizes the cation and lowers its energy. The molecular orbital shows that only the two C–H bonds more nearly parallel to the cation *p* orbital are oriented properly. The C–H bond perpendicular to the cation *p* orbital cannot take part.

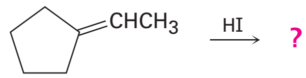
Problem 7.18

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

(a)

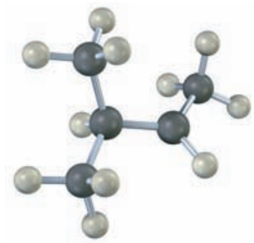


(b)



Problem 7.19

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.



7.10 The Hammond Postulate

Let's summarize our knowledge of electrophilic addition reactions to this point:

- **Electrophilic addition to an unsymmetrically substituted alkene gives the more highly substituted carbocation intermediate.** A more highly substituted carbocation forms faster than a less highly substituted one and, once formed, rapidly goes on to give the final product.
- **A more highly substituted carbocation is more stable than a less highly 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 $\Delta G^{\ddagger}$. 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 7.13**, where the energy profile in part (a) represents the typical situation rather than the profile in part (b). That is, the curves for two similar reactions don't cross one another.

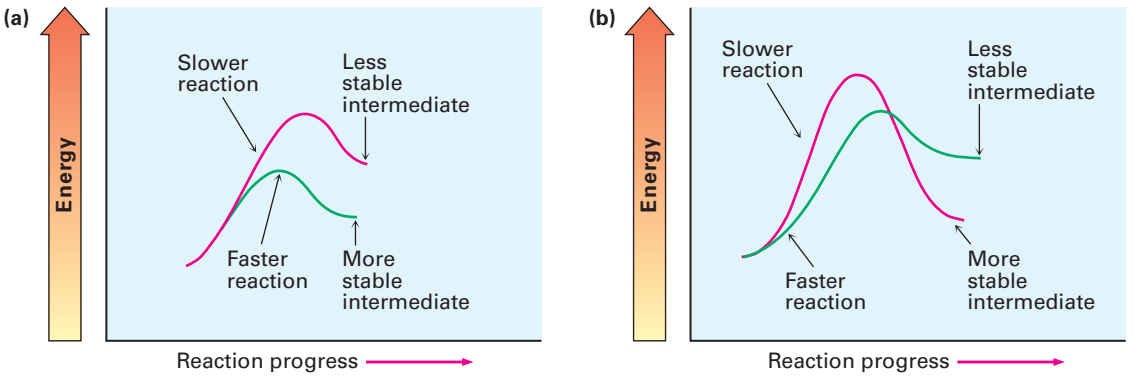


Figure 7.13 Energy diagrams for two similar competing reactions. In **(a)**, the faster reaction yields the more stable intermediate. In **(b)**, the slower reaction yields the more stable intermediate. The curves shown in **(a)** represent the typical situation.

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 7.14**, 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.

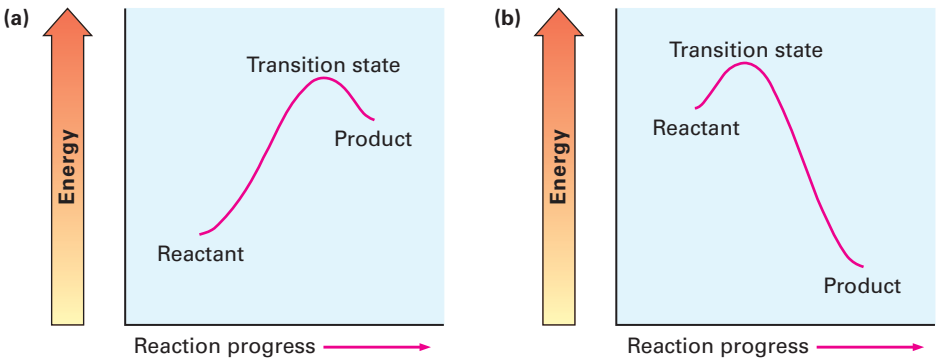


Figure 7.14 Energy diagrams for endergonic and exergonic steps. **(a)** In an endergonic step, the energy levels of transition state and *product* are closer. **(b)** In an exergonic step, the energy levels of transition state and *reactant* are closer.

In an endergonic reaction (Figure 7.14a), the energy level of the transition state is closer to that of the product than to 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 7.14b) 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. More stable carbocations form faster because their greater stability is reflected in the lower-energy transition state leading to them **(Figure 7.15)**.

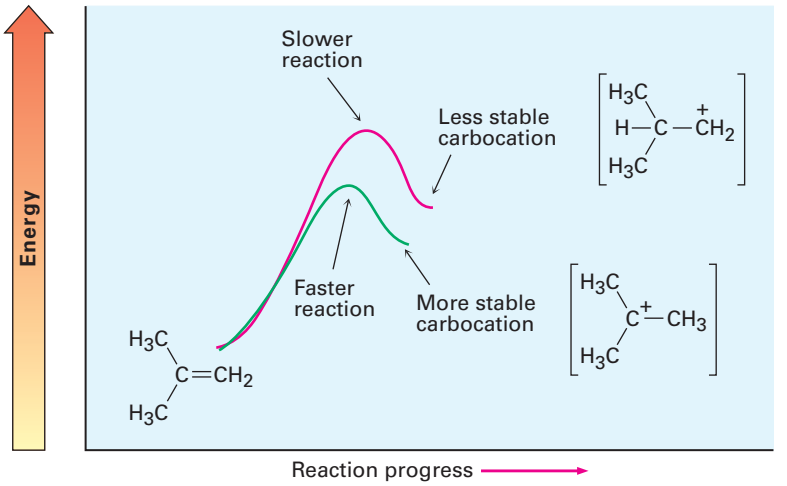


Figure 7.15 Energy diagrams for carbocation formation. The more stable tertiary carbocation is formed faster **(green curve)** because its increased stability lowers the energy of the transition state leading to it.

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 7.16)**. 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.

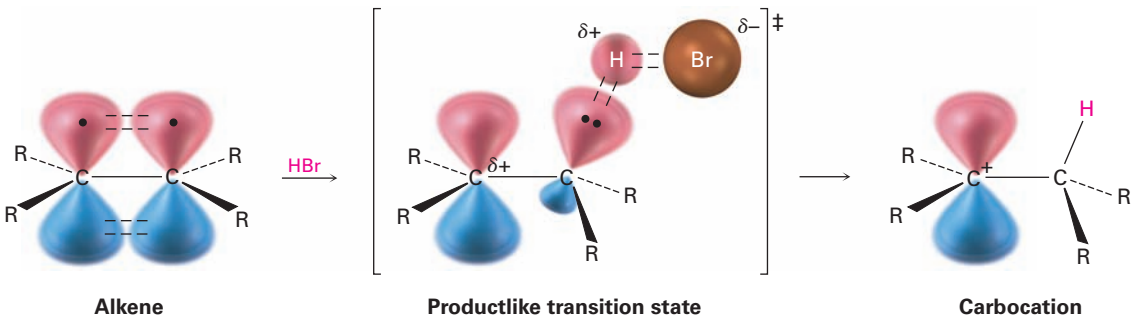


Figure 7.16 The hypothetical structure of a transition state for alkene protonation. The transition state is closer in both energy and structure to the carbocation than to the alkene. Thus, an increase in carbocation stability (lower $\Delta G°$) also causes an increase in transition-state stability (lower $\Delta G^{\ddagger}$), thereby increasing the rate of its formation.

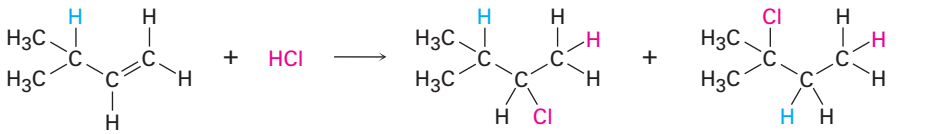
Problem 7.20

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.

7.11 Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements

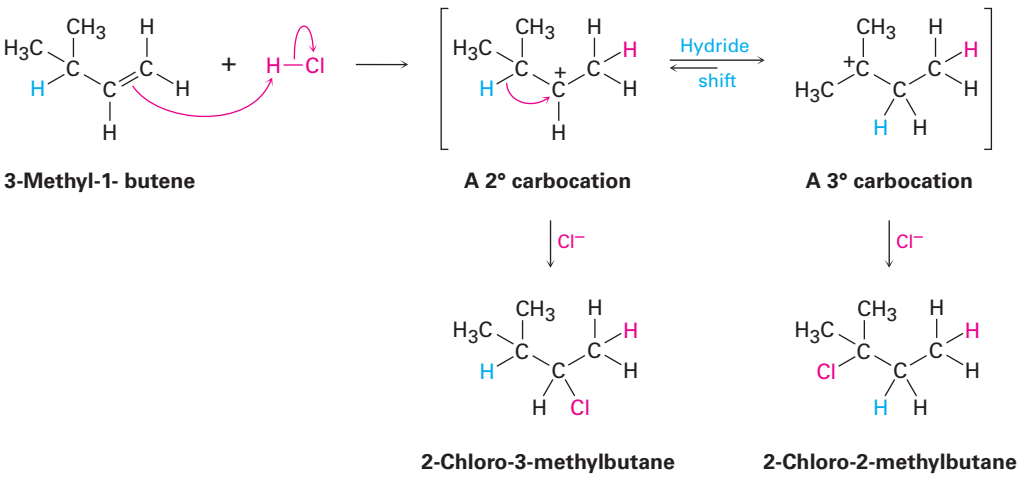
How do we know that the carbocation mechanism for electrophilic addition reactions of alkenes is correct? The answer is that we *don't* know it's correct; at least we don't know with complete certainty. Although an incorrect reaction mechanism can be disproved by demonstrating that it doesn't account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

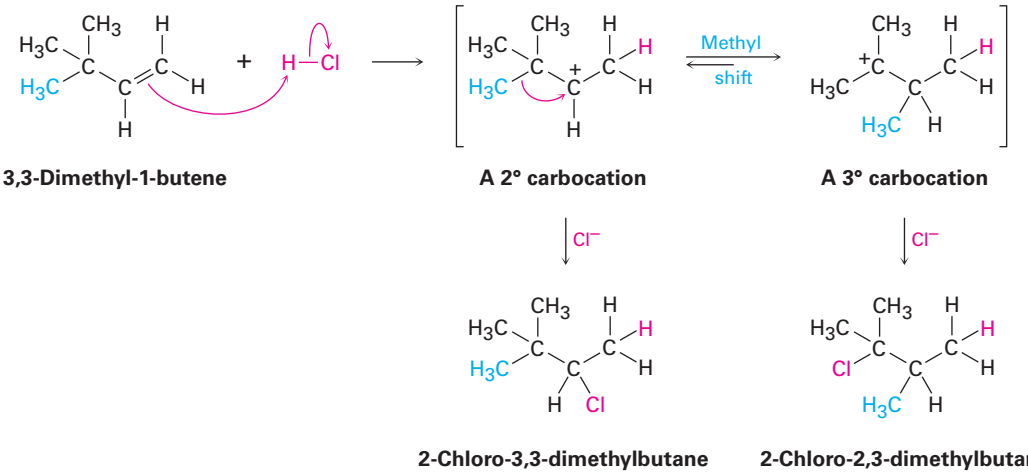
If the reaction takes place in a single step, it would be difficult to account for rearrangement, but if the reaction takes place in several steps, rearrangement is more easily explained. Whitmore suggested that it is a carbocation intermediate that undergoes rearrangement. The secondary carbocation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

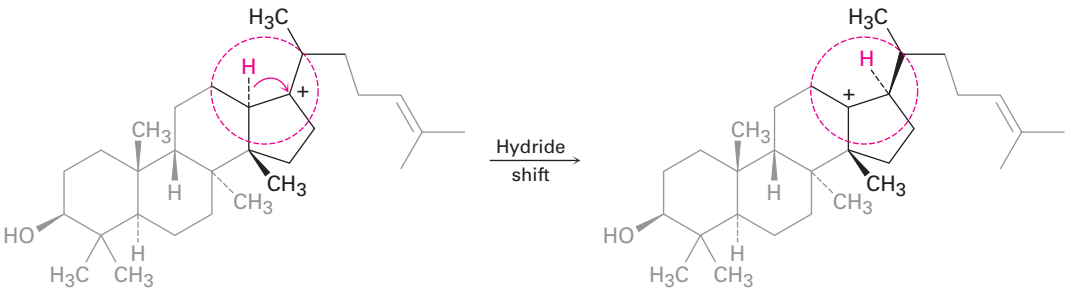
Carbocation rearrangements can also occur by the shift of an alkyl group with its electron pair. For example, reaction of 3,3-dimethyl-1-butene with HCl leads to an equal mixture of unrearranged 2-chloro-3,3-dimethylbutane and rearranged 2-chloro-2,3-dimethylbutane. In this instance, a secondary carbocation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

2-Chloro-3,3-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.

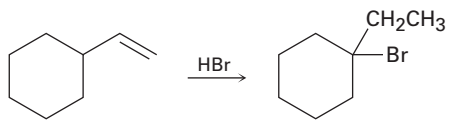


A tertiary carbocation **An isomeric tertiary carbocation**

A word of advice that we've noted before and will repeat on occasion: biological molecules are often larger and more complex in appearance than the molecules chemists work with in the laboratory, but don't be intimidated. When looking at *any* 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.

Problem 7.21

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**

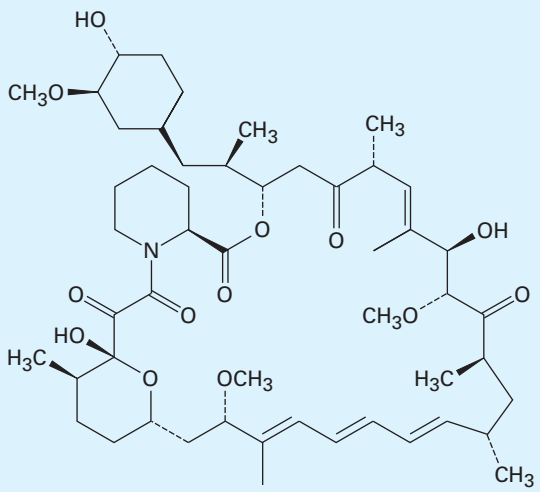
A DEEPER LOOK

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 far 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.

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, an immunosuppressant natural product used during organ transplants, was originally isolated from a soil sample found on Easter Island, or Rapa Nui, an island 2200 miles off the coast of Chile known for its giant Moai statues.



Rapamycin (Sirolimus)

(continued)

(continued)

Where do these natural products come from, and how are they found? Although most chemists and biologists spend most of their 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 *A Deeper Look*, 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 on the previous page, was first isolated from a *Streptomyces hygroscopicus* bacterium found in a soil sample from Easter Island (Rapa Nui), 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. Fortunately, 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.

Summary

Key words

alkene ($R_2C{=}CR_2$), 222
allyl group, 228
degree of unsaturation, 224
***E* geometry, 232**
***E,Z* system, 231**
electrophilic addition reaction, 237
Hammond postulate, 247
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hyperconjugation, 235
Markovnikov's rule, 240
methylene group, 228
regiospecific, 240
unsaturated, 224
vinyl group, 228
***Z* geometry, 232**

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 and most general 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 geometry of a double bond can be specified by application of 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 geometry is ***Z*** (*zusammen,* "together"); if the higher-ranking groups on each carbon are on opposite sides of the double bond, the geometry 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

Tertiary (3°) > Secondary (2°) > Primary (1°) > 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, the 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. The result is isomerization of a less stable carbocation to a more stable one.

Exercises

Visualizing Chemistry

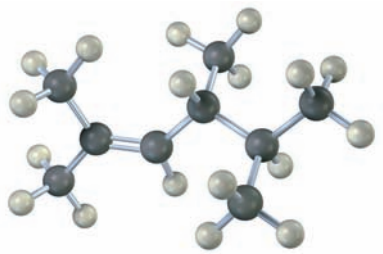
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

▲ denotes problems linked to the Key Ideas in this chapter.

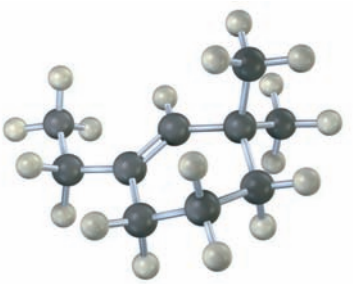
(Problems 7.1–7.21 appear within the chapter.)

7.22 Name the following alkenes, and convert each drawing into a skeletal structure:

(a)

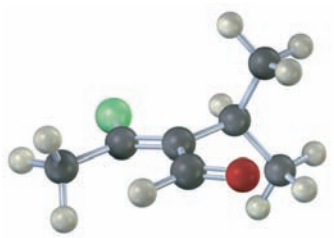


(b)

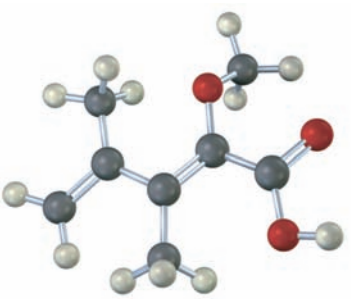


7.23 Assign *E* or *Z* stereochemistry to the double bonds in each of the following alkenes, and convert each drawing into a skeletal structure (red = O, green = Cl):

(a)

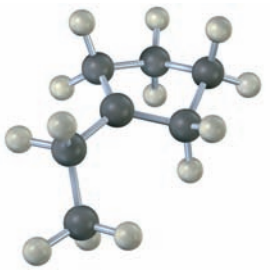


(b)

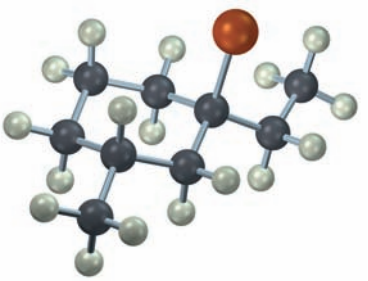


▲ Problems linked to Key Ideas in this chapter

7.24 The following carbocation is an intermediate in the electrophilic addition reaction of HCl with two different alkenes. Identify both, and tell which C–H bonds in the carbocation are aligned for hyperconjugation with the vacant *p* orbital on the positively charged carbon.



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



Additional Problems

Calculating a Degree of Unsaturation

7.26 Calculate the degree of unsaturation in the following formulas, and draw five possible structures for each:

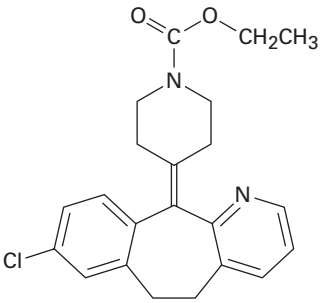
(a) $C_{10}H_{16}$ **(b)** C_8H_8O **(c)** $C_7H_{10}Cl_2$
(d) $C_{10}H_{16}O_2$ **(e)** $C_5H_9NO_2$ **(f)** $C_8H_{10}ClNO$

7.27 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

▲ Problems linked to Key Ideas in this chapter

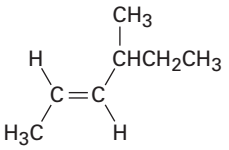
7.28 Loratadine, marketed as an antiallergy medication under the name Claritin, has four rings, eight double bonds, and the formula $C_{22}H_?ClN_2O_2$. How many hydrogens does loratadine have? (Calculate your answer; don't count hydrogens in the structure.)

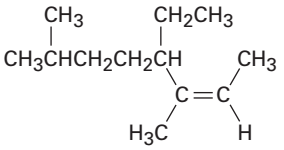


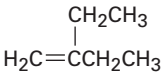
Loratadine

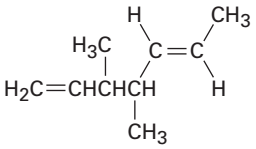
Naming Alkenes

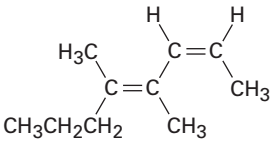
7.29 Name the following alkenes:

(a) 

(b) 

(c) 

(d) 

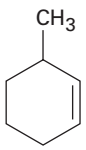
(e) 

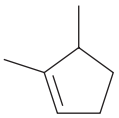
(f) $H_2C{=}C{=}CHCH_3$

7.30 Draw structures corresponding to the following systematic names:

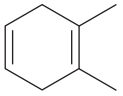
(a) (4*E*)-2,4-Dimethyl-1,4-hexadiene
(b) *cis*-3,3-Dimethyl-4-propyl-1,5-octadiene
(c) 4-Methyl-1,2-pentadiene
(d) (3*E*,5*Z*)-2,6-Dimethyl-1,3,5,7-octatetraene
(e) 3-Butyl-2-heptene
(f) *trans*-2,2,5,5-Tetramethyl-3-hexene

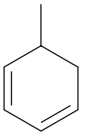
7.31 Name the following cycloalkenes:

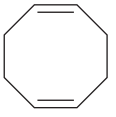
(a) 

(b) 

(c) 

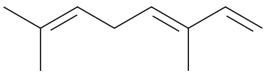
(d) 

(e) 

(f) 

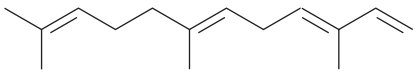
▲ Problems linked to Key Ideas in this chapter

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



Ocimene

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



***α*-Farnesene**

7.34 Menthene, a hydrocarbon found in mint plants, has the systematic name 1-isopropyl-4-methylcyclohexene. Draw its structure.

7.35 Draw and name the six alkene isomers, C_5H_{10}, including *E,Z* isomers.

7.36 Draw and name the 17 alkene isomers, C_6H_{12}, including *E,Z* isomers.

Alkene Isomers and Their Stability

7.37 Rank the following sets of substituents according to the Cahn–Ingold–Prelog sequence rules:

(a) $-CH_3$, $-Br$, $-H$, $-I$

(b) $-OH$, $-OCH_3$, $-H$, $-CO_2H$

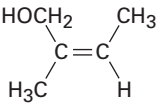
(c) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, $-CH_3$

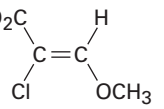
(d) $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-\overset{\overset{O}{\|}}{C}CH_3$

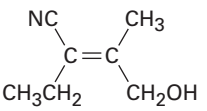
(e) $-CH{=}CH_2$, $-CN$, $-CH_2NH_2$, $-CH_2Br$

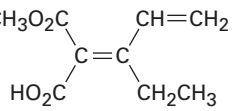
(f) $-CH{=}CH_2$, $-CH_2CH_3$, $-CH_2OCH_3$, $-CH_2OH$

7.38 ▲ Assign *E* or *Z* configuration to each of the following compounds:

(a) 

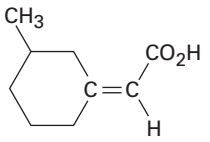
(b) 

(c) 

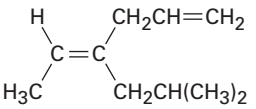
(d) 

▲ Problems linked to Key Ideas in this chapter

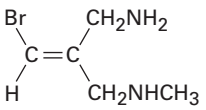
7.39 ▲ Which of the following *E,Z* designations are correct, and which are incorrect?

(a) 

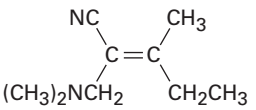
Z

(b) 

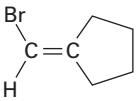
E

(c) 

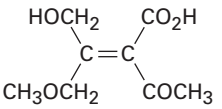
Z

(d) 

E

(e) 

Z

(f) 

E

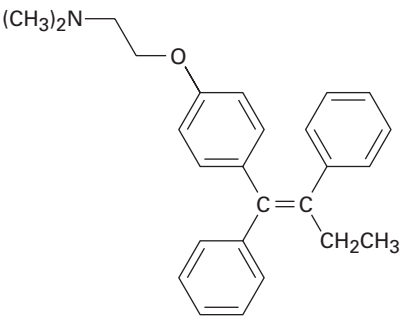
7.40 *trans*-2-Butene is more stable than *cis*-2-butene by only 4 kJ/mol, but *trans*-2,2,5,5-tetramethyl-3-hexene is more stable than its cis isomer by 39 kJ/mol. Explain.

7.41 Cyclodecene can exist in both cis and trans forms, but cyclohexene cannot. Explain. (Making molecular models is helpful.)

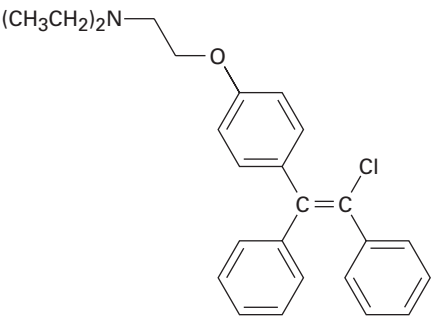
7.42 Normally, a trans alkene is *more* stable than its cis isomer. *trans*-Cyclooctene, however, is *less* stable than *cis*-cyclooctene by 38.5 kJ/mol. Explain.

7.43 *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.

7.44 Tamoxifen, a drug used in the treatment of breast cancer, and clomiphene, a drug used as a fertility treatment, have similar structures but very different effects. Assign *E* or *Z* configuration to the double bonds in both compounds.



Tamoxifen
(anticancer)



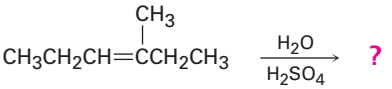
Clomiphene
(fertility treatment)

▲ Problems linked to Key Ideas in this chapter

Carbocations and Electrophilic Addition Reactions

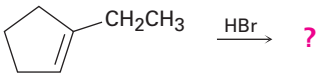
7.45 Predict the major product in each of the following reactions:

(a)

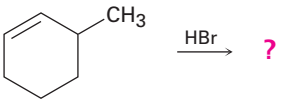


(Addition of H_2O occurs.)

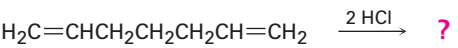
(b)



(c)

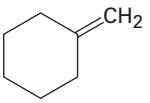


(d)

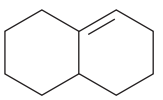


7.46 ▲ Predict the major product from addition of HBr to each of the following alkenes:

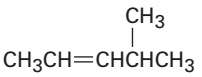
(a)



(b)

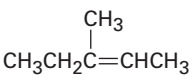


(c)



7.47 ▲ Alkenes can be converted into alcohols by acid-catalyzed addition of water. Assuming that Markovnikov's rule is valid, predict the major alcohol product from each of the following alkenes.

(a)



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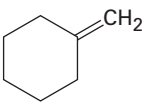

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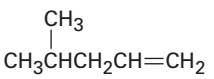
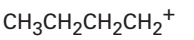
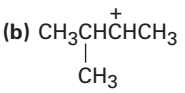


7.48 Each of the following carbocations can rearrange to a more stable ion. Propose structures for the likely rearrangement products.

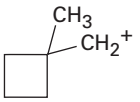
(a)



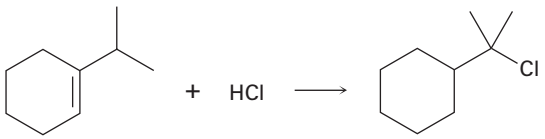
(b)



(c)



7.49 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.



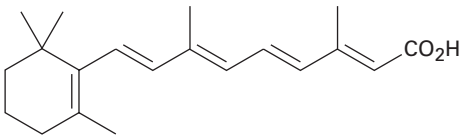
▲ Problems linked to Key Ideas in this chapter

General Problems

7.50 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?

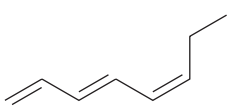
7.51 The heat of hydrogenation for allene (Problem 7.50) to yield propane is −295 kJ/mol, and the heat of hydrogenation for a typical monosubstituted alkene such as propene is −126 kJ/mol. Is allene more stable or less stable than you might expect for a diene? Explain.

7.52 Retin A, or retinoic acid, is a medication commonly used to reduce wrinkles and treat severe acne. How many different isomers arising from double-bond isomerizations are possible?

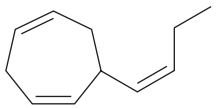


Retin A (retinoic acid)

7.53 Fucoserratene and ectocarpene are sex pheromones produced by marine brown algae. What are their systematic names? (Ectocarpene is a bit difficult; make your best guess, and then check your answer in the *Study Guide and Solutions Manual*.)

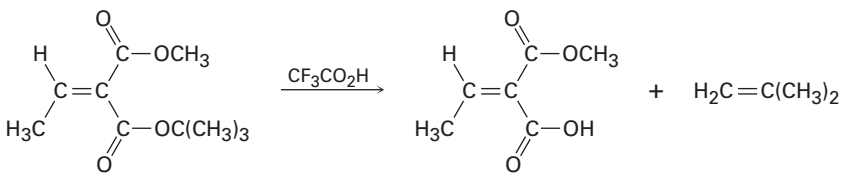


Fucoserratene



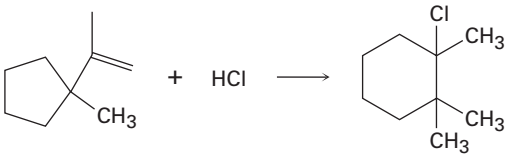
Ectocarpene

7.54 ▲ *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 of double-bond stereochemistry:

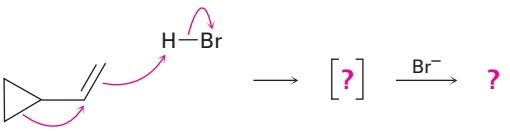


▲ Problems linked to Key Ideas in this chapter

7.55 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.



7.56 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.

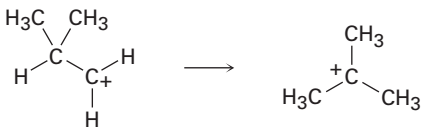


Vinylcyclopropane

7.57 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, $C_{17}H_{23}NO_3$

7.58 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**

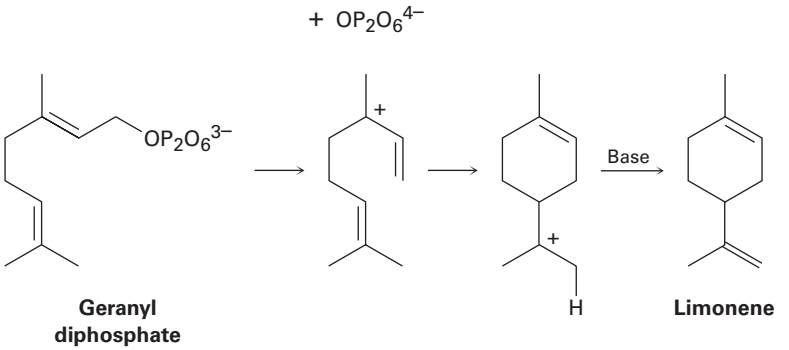
7.59 Draw an energy diagram for the addition of HBr to 1-pentene. Let one curve on your diagram show the formation of 1-bromopentane product and another curve on the same diagram show the formation of 2-bromopentane product. Label the positions for all reactants, intermediates, and products. Which curve has the higher-energy carbocation intermediate? Which curve has the higher-energy first transition state?

7.60 Make sketches of the transition-state structures involved in the reaction of HBr with 1-pentene (Problem 7.59). Tell whether each structure resembles reactant or product.

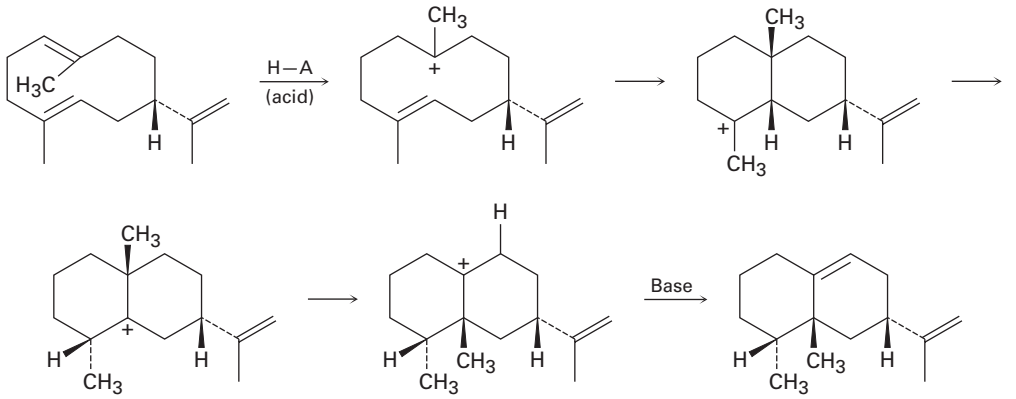
7.61 Limonene, a fragrant hydrocarbon found in lemons and oranges, is biosynthesized from geranyl diphosphate by the following pathway. Add curved arrows to show the mechanism of each step. Which step involves an alkene

▲ Problems linked to Key Ideas in this chapter

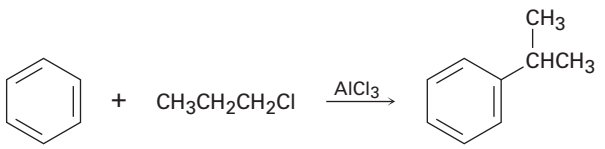
electrophilic addition? (The ion $OP_2O_6^{4-}$ is the diphosphate ion, and "Base" is an unspecified base in the enzyme that catalyzes the reaction.)



7.62 *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.)



7.63 Aromatic compounds such as benzene react with alkyl chlorides in the presence of $AlCl_3$ catalyst to yield alkylbenzenes. The reaction occurs through a carbocation intermediate, formed by reaction of the alkyl chloride with $AlCl_3$ (R–Cl + $AlCl_3 \rightarrow R^+ + AlCl_4^-$). How can you explain the observation that reaction of benzene with 1-chloropropane yields isopropylbenzene as the major product?



7.64 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?

▲ Problems linked to Key Ideas in this chapter

8

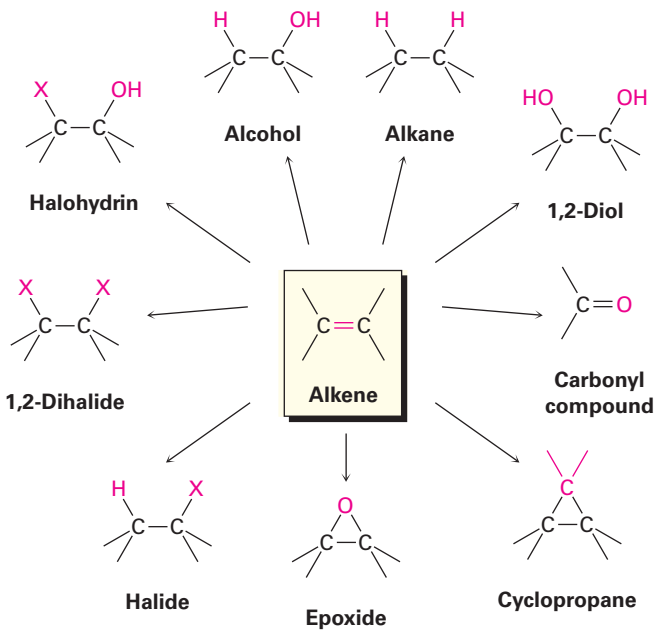
The Spectra fiber used to make the bulletproof vests used by police and military is made of ultra-high-molecular-weight polyethylene, a simple alkene polymer. Ed Darack/Getty Images

Alkenes: Reactions and Synthesis

8.1 Preparing Alkenes: A Preview of Elimination Reactions
8.2 Halogenation of Alkenes: Addition of X_2
8.3 Halohydrins from Alkenes: Addition of HOX
8.4 Hydration of Alkenes: Addition of H_2O by Oxymercuration
8.5 Hydration of Alkenes: Addition of H_2O by Hydroboration
8.6 Reduction of Alkenes: Hydrogenation
8.7 Oxidation of Alkenes: Epoxidation and Hydroxylation
8.8 Oxidation of Alkenes: Cleavage to Carbonyl Compounds
8.9 Addition of Carbenes to Alkenes: Cyclopropane Synthesis
8.10 Radical Additions to Alkenes: Chain-Growth Polymers
8.11 Biological Additions of Radicals to Alkenes
8.12 Reaction Stereochemistry: Addition of H_2O to an Achiral Alkene
8.13 Reaction Stereochemistry: Addition of H_2O to a Chiral Alkene
A Deeper Look—Terpenes: Naturally Occurring Alkenes

OWL Sign in to OWL for Organic Chemistry at **www.cengage.com/owl** to view tutorials and simulations, develop problem-solving skills, and complete online homework assigned by your professor.

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 to give a 1,2-dihalide, addition of a hypohalous acid 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.



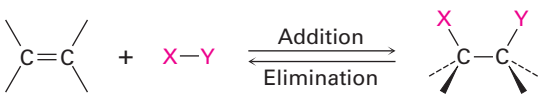
Why This Chapter? Much of the background needed to understand organic reactions has now been covered, and it's time to begin a systematic description of the major functional groups. In this chapter on alkenes and in future chapters on other functional groups, we'll discuss a variety of reactions

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.

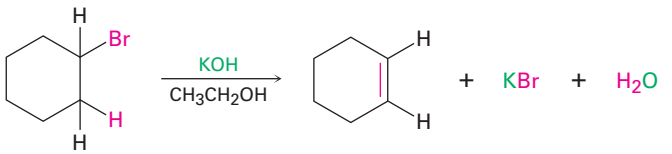
8.1 Preparing Alkenes: A Preview of Elimination Reactions

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 in Chapter 11 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.

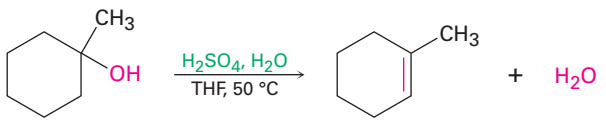


The two most common elimination reactions are *dehydrohalogenation*—the loss of HX from an alkyl halide—and *dehydration*—the loss of water from an alcohol. Dehydrohalogenation usually occurs by reaction of an alkyl halide with strong base such as potassium hydroxide. For example, bromocyclohexane yields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



Bromocyclohexane **Cyclohexene (81%)**

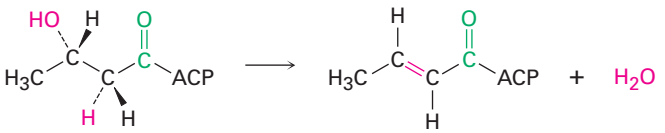
Dehydration is often carried out in the laboratory by treatment of an alcohol with a strong acid. For example, when 1-methylcyclohexanol is warmed with aqueous sulfuric acid in tetrahydrofuran (THF) solvent, loss of water occurs and 1-methylcyclohexene is formed.



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

Tetrahydrofuran (THF)—a common solvent

In biological pathways, dehydrations rarely occur with isolated alcohols. Instead, they normally take place on substrates in which the −OH is positioned two carbons away from a carbonyl 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 11.10**.



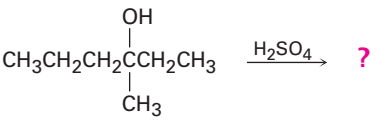
β-Hydroxybutyryl ACP **trans-Crotonyl ACP**

Problem 8.1

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?

Problem 8.2

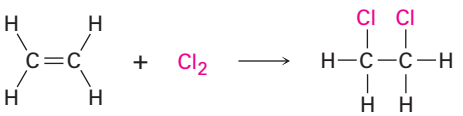
How many alkene products, including *E*,*Z* isomers, might be obtained by dehydration of 3-methyl-3-hexanol with aqueous sulfuric acid?



3-Methyl-3-hexanol

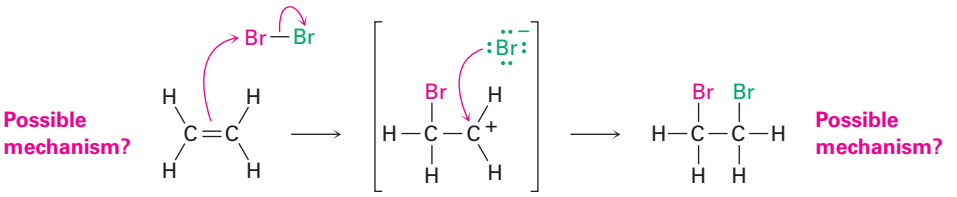
8.2 Halogenation of Alkenes: Addition of X_2

Bromine and chlorine add rapidly to alkenes to yield 1,2-dihalides, a process called *halogenation*. For example, more than 18 million tons 1,2-dichloroethane (ethylene dichloride) is 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. Fluorine is too reactive and difficult to control for most laboratory applications, and iodine does not react with most alkenes.



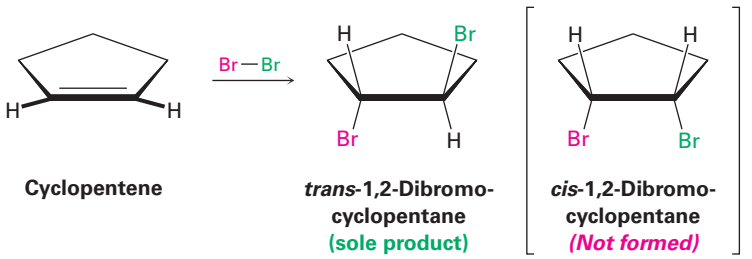
Ethylene **1,2-Dichloroethane (ethylene dichloride)**

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.

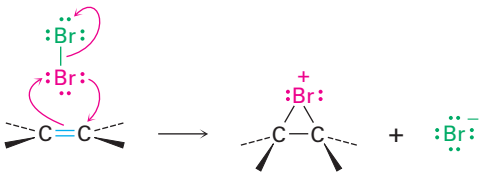


Although this mechanism seems plausible, it's not fully consistent with known facts. In particular, it doesn't explain the *stereochemistry* of the addition reaction. That is, the mechanism doesn't tell which product stereoisomer is formed.

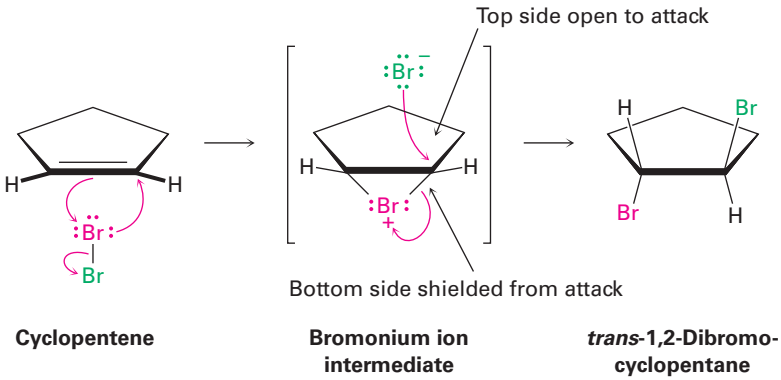
When the halogenation reaction is carried out on a cycloalkene, such as cyclopentene, only the *trans* stereoisomer of the dihalide addition product is formed rather than the mixture of cis and trans isomers that might have been expected if a planar carbocation intermediate were involved. We say that 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.

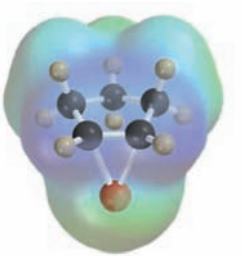


An explanation for the observed stereochemistry of addition was suggested in 1937 by George Kimball and Irving Roberts, who proposed that the reaction intermediate is not a carbocation but is instead a **bromonium ion**, R_2Br^+, formed by electrophilic addition of Br^+ to the alkene. (Similarly, a *chloronium 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 simultaneous loss of Br^-.

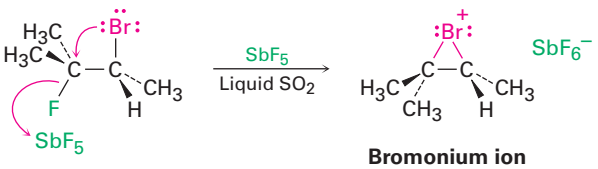


How does the formation of a bromonium ion account for the observed anti stereochemistry of addition to cyclopentene? If a bromonium ion is formed as an intermediate, we can imagine that the large bromine atom might "shield" one side of the molecule. Reaction with Br^- ion in the second step could then occur only from the opposite, unshielded side to give trans product.





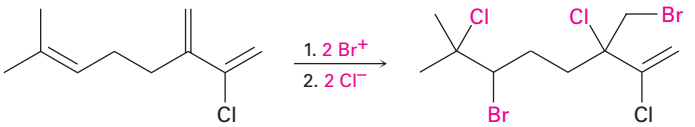
The bromonium ion postulate, made more than 75 years ago to explain the stereochemistry of halogen addition to alkenes, is a remarkable example of deductive logic in chemistry. Arguing from experimental results, chemists were able to make a hypothesis about the intimate mechanistic details of alkene electrophilic reactions. Subsequently, strong evidence supporting the mechanism came from the work of George Olah, who prepared and studied *stable* solutions of cyclic bromonium ions in liquid SO_2. There's no question that bromonium ions exist.



Bromonium ion (stable in SO_2 solution)

Alkene halogenation reactions occur in nature just as they do in the laboratory but are limited primarily to marine organisms, which live in a halide-rich environment. The 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 anticancer pentahalide isolated from red alga, is thought to arise by a route that involves twofold addition of BrCl through the corresponding bromonium ions.



Halomon

Problem 8.3

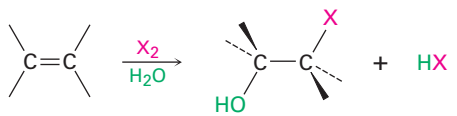
What product would you expect to obtain from addition of Cl_2 to 1,2-dimethylcyclohexene? Show the stereochemistry of the product.

Problem 8.4

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.

8.3 Halohydrins from Alkenes: Addition of HOX

Another example of an electrophilic addition is the reaction of alkenes with the hypohalous acids HO–Cl or HO–Br to yield 1,2-halo alcohols, called **halohydrins**. Halohydrin formation doesn't take place by direct reaction of an alkene with HOBr or HOCl, however. Rather, the addition is done indirectly by reaction of the alkene with either Br_2 or Cl_2 in the presence of water.



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 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 8.1**.

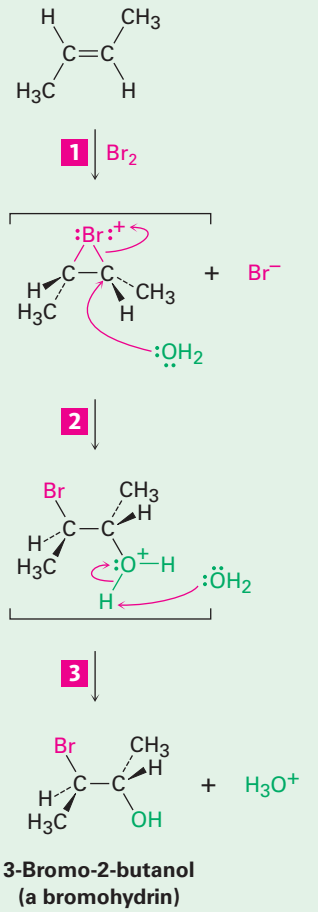
Figure 8.1 | MECHANISM

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.

1 Reaction of the alkene with Br_2 yields a bromonium ion intermediate, as previously discussed.

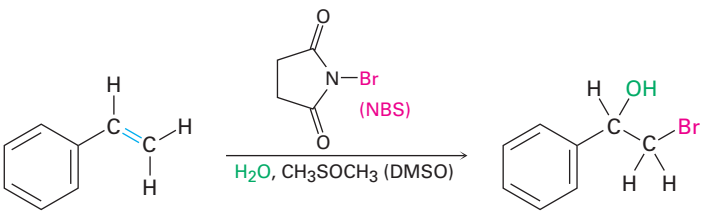
2 Water acts as a nucleophile, using a lone pair of electrons to open the bromonium ion ring and form a bond to carbon. Since oxygen donates its electrons in this step, it now has the positive charge.

3 Loss of a proton (H^+) from oxygen then gives H_3O^+ and the neutral bromohydrin addition product.



3-Bromo-2-butanol (a bromohydrin)

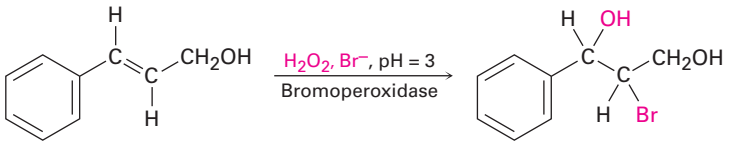
In practice, few alkenes are soluble in water, and bromohydrin formation is often carried out in a solvent such as aqueous dimethyl sulfoxide, CH_3SOCH_3 (DMSO), using a reagent called *N*-bromosuccinimide (NBS) as a source of Br_2. NBS is a stable, easily handled compound that slowly decomposes in water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

Note that the aromatic ring in the above example does not react with Br_2 under the conditions used, even though it appears to contain three carbon–carbon double bonds. As we'll see in Chapter 15, 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 **(Section 8.2)**, halohydrin formation is carried out by haloperoxidases, which function by oxidizing Br^- or Cl^- ions to the corresponding HOBr or HOCl bonded to a metal atom in the enzyme. Electrophilic addition to the double bond of a substrate molecule then yields a bromonium or chloronium ion intermediate, and reaction with water gives the halohydrin. For example:

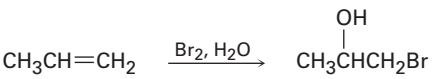


Problem 8.5

What product would you expect from the reaction of cyclopentene with NBS and water? Show the stereochemistry.

Problem 8.6

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.

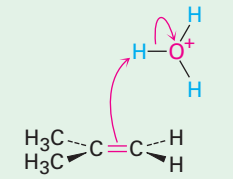


8.4 Hydration of Alkenes: Addition of H_2O by Oxymercuration

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 8.2**, 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 8.2 | MECHANISM

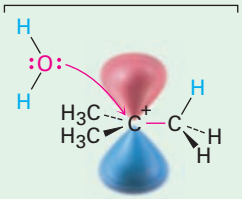
Mechanism of the acid-catalyzed hydration of an alkene to yield an alcohol. Protonation of the alkene gives a carbocation intermediate, which reacts with water. The initial product is then deprotonated.



2-Methylpropene

1 A hydrogen atom on the electrophile H_3O^+ is attacked by π electrons from the nucleophilic double bond, forming a new C–H bond. This leaves the other carbon atom with a + charge and a vacant *p* orbital. Simultaneously, two electrons from the H–O bond move onto oxygen, giving neutral water.

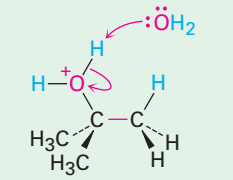
1



Carbocation

2 The nucleophile H_2O donates an electron pair to the positively charged carbon atom, forming a C–O bond and leaving a positive charge on oxygen in the protonated alcohol addition product.

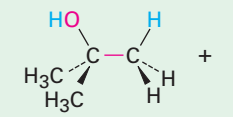
2



Protonated alcohol

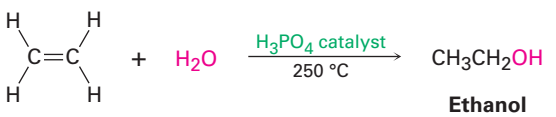
3 Water acts as a base to remove H^+, regenerating H_3O^+ and yielding the neutral alcohol addition product.

3



2-Methyl-2-propanol

Acid-catalyzed alkene hydration is particularly suited to large-scale industrial procedures, and approximately 300,000 tons of ethanol is manufactured each year in the United States by hydration of ethylene. The reaction is of little value in the typical laboratory, however, because it requires high temperatures—250 °C in the case of ethylene—and strongly acidic conditions.

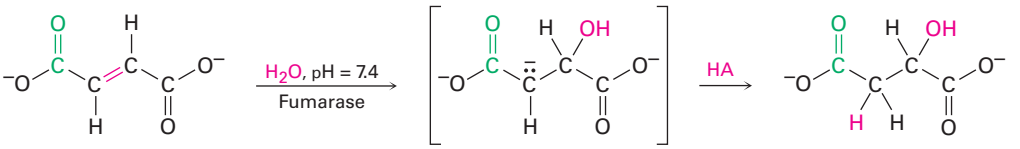


Ethylene

Ethanol

Acid-catalyzed hydration of isolated double bonds, although known, is also uncommon in biological pathways. More frequently, biological hydrations

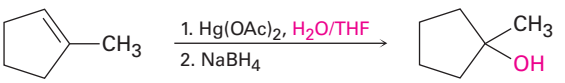
require that the double bond be adjacent to a carbonyl group for reaction to proceed. Fumarate, for instance, is hydrated to give malate as one step in the citric acid cycle of food metabolism. Note that the requirement for an adjacent carbonyl group in the addition of water is the same as that we saw in **Section 8.1** for the elimination of water. We'll see the reason for the requirement in **Section 19.13**, but might 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. Oxymercuration involves electrophilic addition of Hg^{2+} to the alkene on reaction with mercury(II) acetate [$(CH_3CO_2)_2Hg$, often abbreviated $Hg(OAc)_2$] in aqueous tetrahydrofuran (THF) solvent. When the intermediate organomercury compound is then treated with sodium borohydride, $NaBH_4$, 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 8.3)**. Nucleophilic addition of water as in halohydrin formation, followed by loss of a proton, then yields a stable organomercury product. The final step, demercuration of the organomercury compound by reaction with sodium borohydride, is complex and involves radicals. Note that the regiochemistry of the reaction corresponds to Markovnikov addition of water; that is, the −OH group attaches to the more highly substituted carbon atom, and the −H attaches to the less highly substituted carbon. The hydrogen that replaces mercury in the demercuration step can attach from either side of the molecule depending on the exact circumstances.

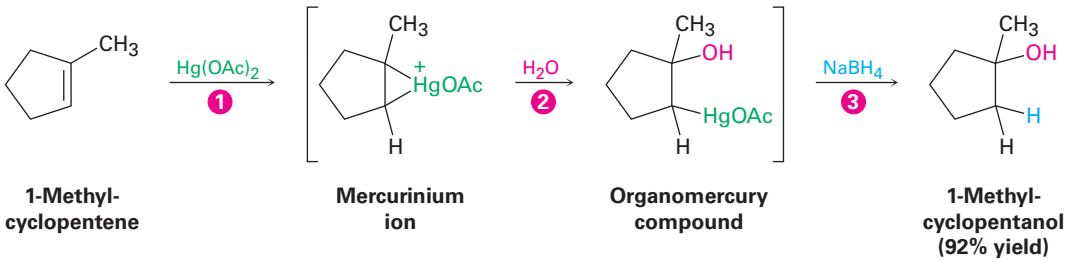


Figure 8.3 Mechanism of the oxymercuration of an alkene to yield an alcohol. (1) Electrophilic addition of Hg^{2+} gives a mercurinium ion, which (2) reacts with water as in halohydrin formation. Loss of a proton gives an organomercury product, and (3) reaction with $NaBH_4$ removes the mercury. The product of the reaction is the more highly substituted alcohol, corresponding to Markovnikov regiochemistry.

Problem 8.7

What products would you expect from oxymercuration–demercuration of the following alkenes?

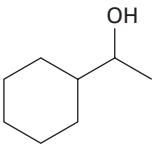
(a) $CH_3CH_2CH_2CH{=}CH_2$

(b) $CH_3C(CH_3){=}CHCH_2CH_3$

Problem 8.8

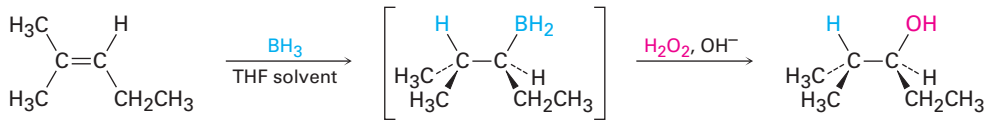
From what alkenes might the following alcohols have been prepared?

(a) $CH_3C(OH)(CH_3)CH_2CH_2CH_2CH_3$

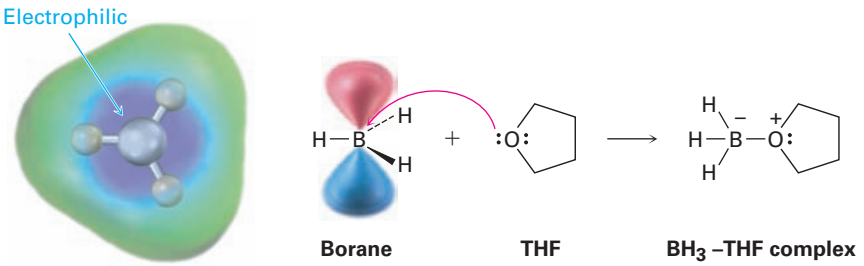
(b) 

8.5 Hydration of Alkenes: Addition of H_2O by Hydroboration

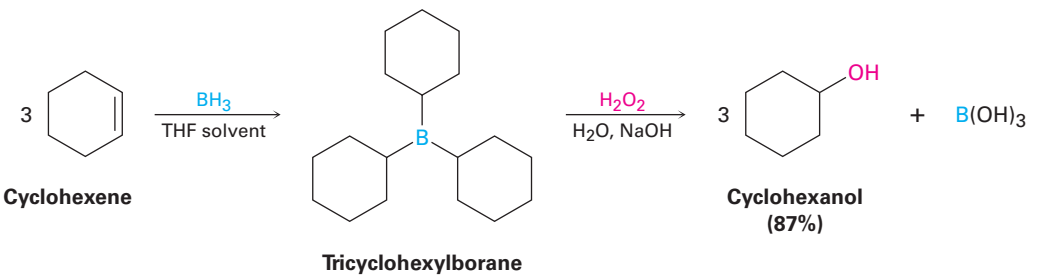
In addition to the oxymercuration–demercuration method, which yields the Markovnikov product, a complementary method that yields the non-Markovnikov product is also useful. Discovered in 1959 by H.C. Brown and called **hydroboration**, the reaction involves addition of a B–H bond of borane, BH_3, to 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:



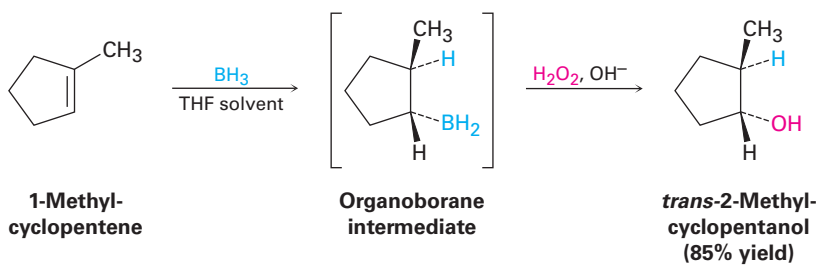
Borane is very reactive as a Lewis acid because the boron atom has only six electrons in its valence shell. In tetrahydrofuran solution, BH_3 accepts an electron pair from a solvent molecule in a Lewis acid–base reaction to complete its octet and form a stable BH_3–THF complex.



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.



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. Boron and hydrogen add to the alkene from the same face of the double bond—that is, with **syn stereochemistry**, the opposite of anti—with boron attaching to the less highly substituted carbon. During the oxidation step, the boron is replaced by an –OH with the same stereochemistry, resulting in an overall syn non-Markovnikov addition of water. This stereochemical result is particularly useful because it is complementary to the Markovnikov regiochemistry observed for oxymercuration–demercuration.



Why does alkene hydroboration take place with syn, non-Markovnikov regiochemistry to yield the less highly substituted alcohol? Hydroboration differs from many other alkene addition reactions in that it occurs in a single step without a carbocation intermediate **(Figure 8.4)**. Because both 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 rather than at the more crowded carbon.

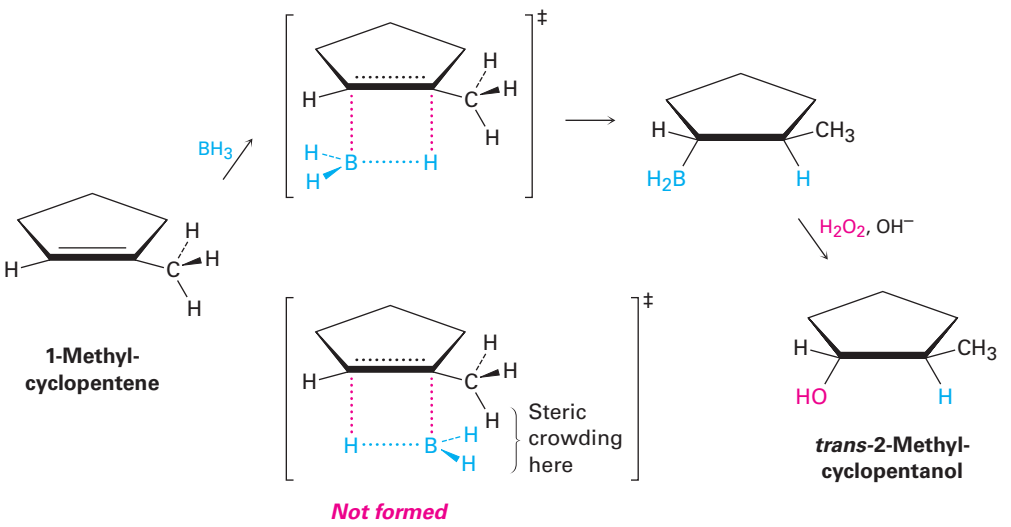


Figure 8.4 Mechanism of alkene hydroboration. The reaction occurs in a single step in which both C–H and C–B bonds form at the same time and on the same face of the double bond. The lower energy, more rapidly formed transition state is the one with less steric crowding, leading to non-Markovnikov regiochemistry.

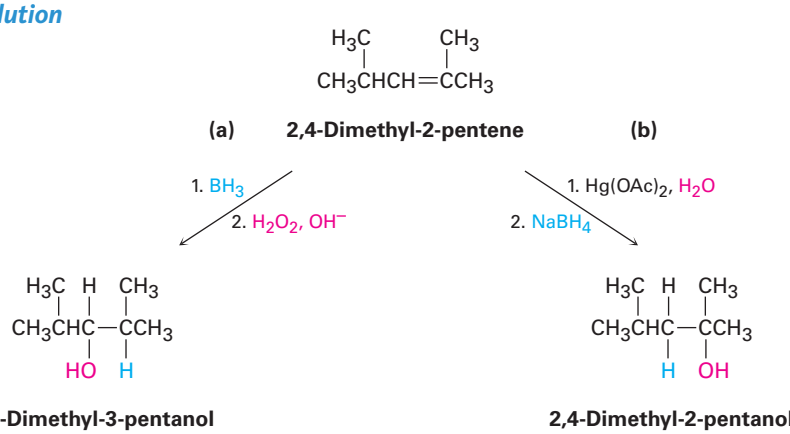
Worked Example 8.1 Predicting the Products Formed in a Reaction

What products would you obtain from reaction of 2,4-dimethyl-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 then 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

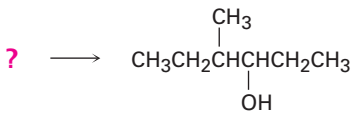


2,4-Dimethyl-3-pentanol **2,4-Dimethyl-2-pentanol**

Synthesizing an Alcohol

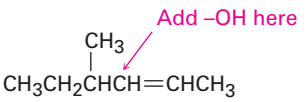
Worked Example 8.2

How might you prepare the following alcohol?

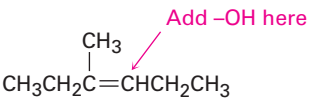


Strategy

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. The —OH bearing carbon in the product must have been a double-bond carbon in the alkene reactant, so there are two possibilities: 4-methyl-2-hexene and 3-methyl-3-hexene.



4-Methyl-2-hexene

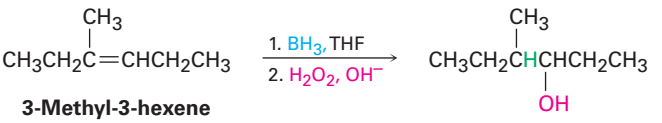


3-Methyl-3-hexene

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.

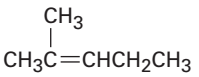
Solution

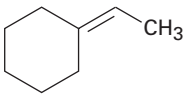


3-Methyl-3-hexene

Problem 8.9

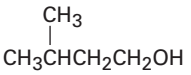
Show the structures of the products you would obtain by hydroboration–oxidation of the following alkenes:

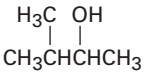
(a) 

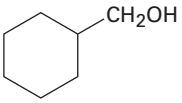
(b) 

Problem 8.10

What alkenes might be used to prepare the following alcohols by hydroboration–oxidation?

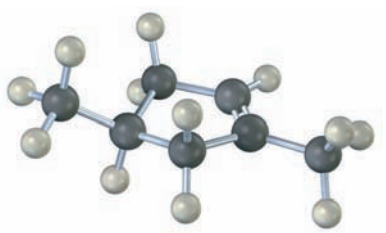
(a) 

(b) 

(c) 

Problem 8.11

The following cycloalkene gives a mixture of two alcohols on hydroboration followed by oxidation. Draw the structures of both, and explain the result.



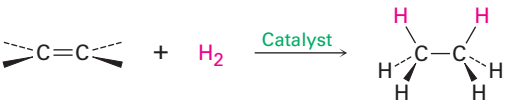
8.6 Reduction of Alkenes: Hydrogenation

Alkenes react with H_2 in the presence of a metal catalyst such as palladium or platinum to yield the corresponding saturated alkane addition products. 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 by 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 the topic in more detail in **Section 10.8**.

Reduction Increases electron density on carbon by:
- forming this: C–H
- or breaking one of these: C–O C–N C–X

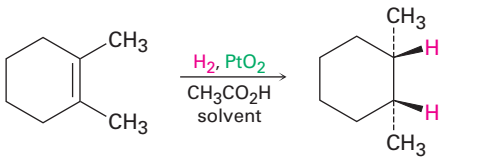
A reduction:



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.

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.

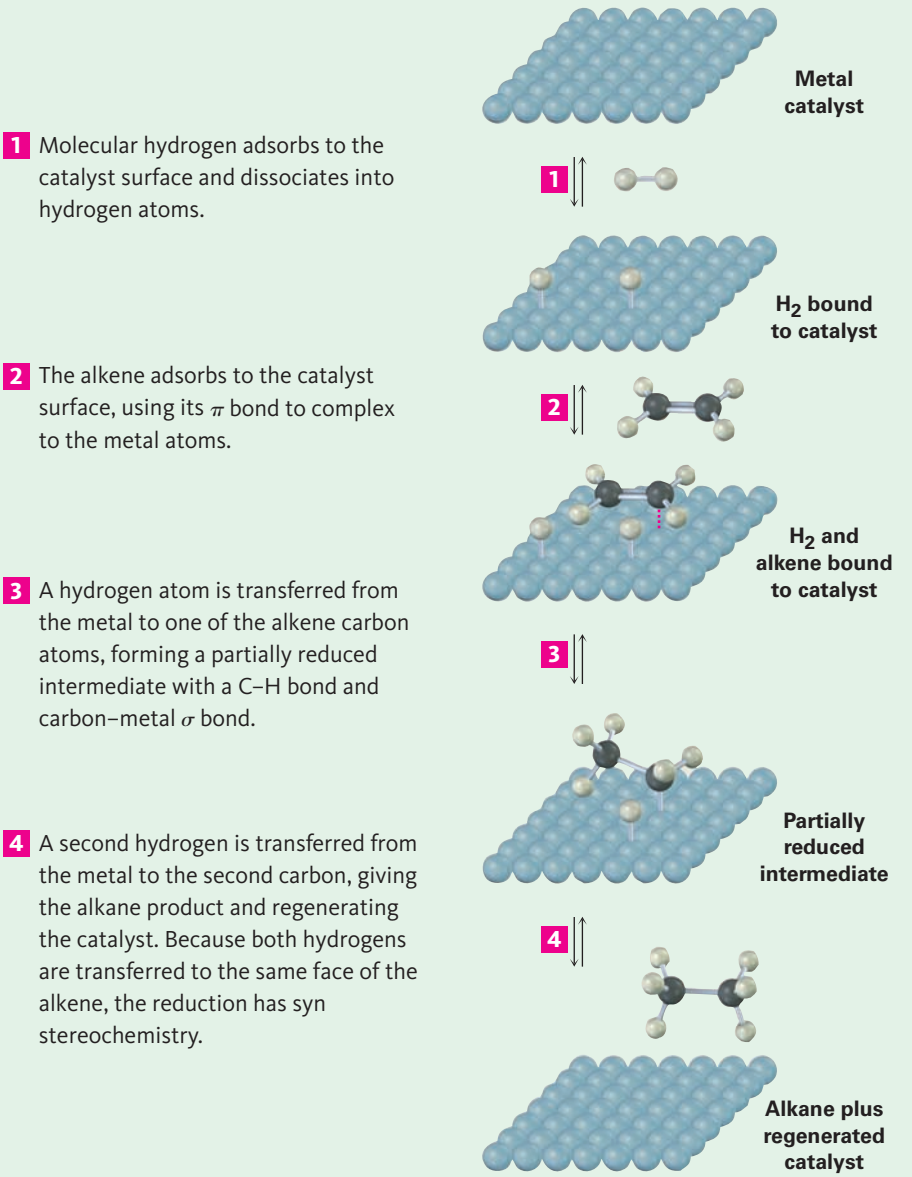


1,2-Dimethylcyclohexene ***cis*-1,2-Dimethylcyclohexane (82%)**

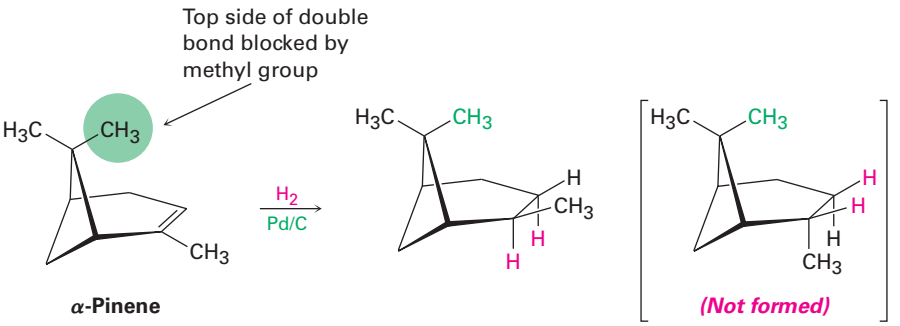
As shown in **Figure 8.5**, hydrogenation begins with adsorption of H_2 onto the catalyst surface. Complexation between catalyst and alkene then occurs as a vacant orbital on the metal interacts with the filled alkene π orbital. In the final steps, hydrogen is inserted into the double bond and the saturated 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 8.5 | MECHANISM

Mechanism of alkene hydrogenation. The reaction takes place with syn stereochemistry on the surface of insoluble catalyst particles.

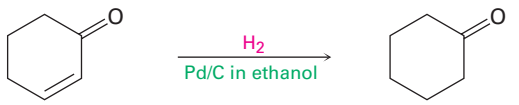


An interesting feature of catalytic hydrogenation is that the reaction is extremely sensitive to the steric environment around the double bond. As a result, the catalyst usually approaches only the more accessible face of an alkene, giving rise to a single product. In α-pinene, for example, one of the 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.

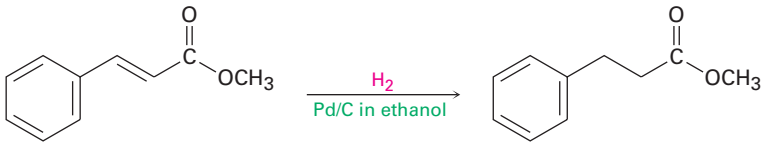


α-Pinene

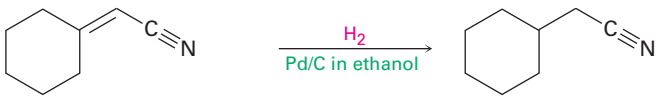
Alkenes are much more reactive than most other unsaturated functional groups toward catalytic hydrogenation, and the reaction is therefore quite selective. Other functional groups, such as aldehydes, ketones, esters, and nitriles, often survive alkene hydrogenation conditions unchanged, although reaction with these groups does occur under more vigorous conditions. Note particularly in the hydrogenation of methyl 3-phenylpropenoate shown below that the aromatic ring is not reduced by hydrogen and palladium even though it contains apparent double bonds.



2-Cyclohexenone — **Cyclohexanone** (ketone not reduced)



Methyl 3-phenylpropenoate — **Methyl 3-phenylpropanoate** (aromatic ring not reduced)



Cyclohexylideneacetonitrile — **Cyclohexylacetonitrile** (nitrile not reduced)

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 8.6)**. As we'll see in **Section 27.1**, 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 contributing to potential coronary problems.

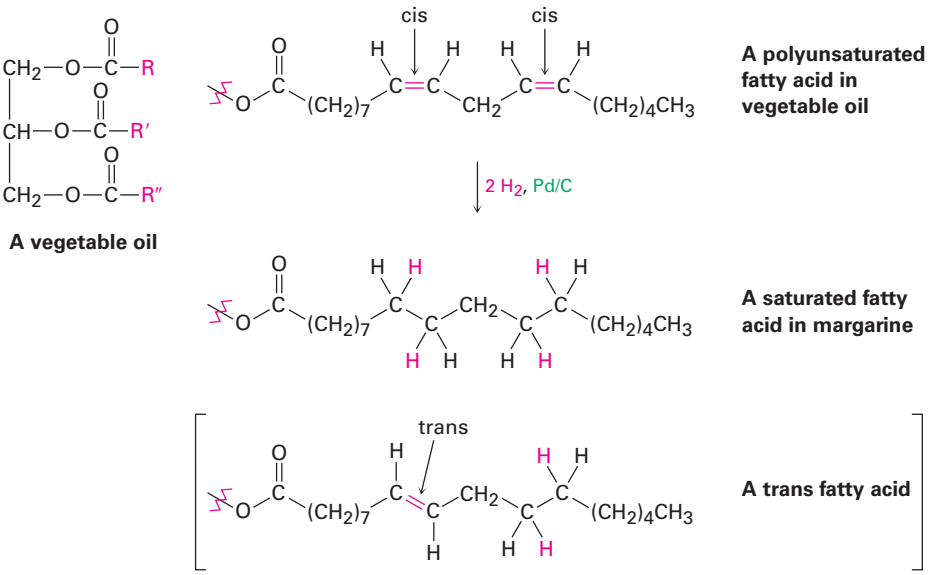
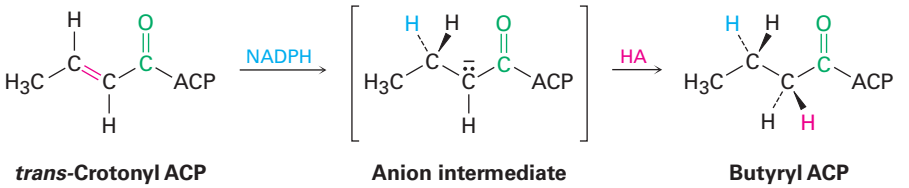


Figure 8.6 Catalytic hydrogenation of polyunsaturated fats leads to saturated products, along with a small amount of isomerized trans fats.

Double-bond reductions are extremely common in biological pathways, although the mechanism of the process is of course different from that of laboratory catalytic hydrogenation over palladium. As with biological hydrations **(Section 8.4)**, 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)**.



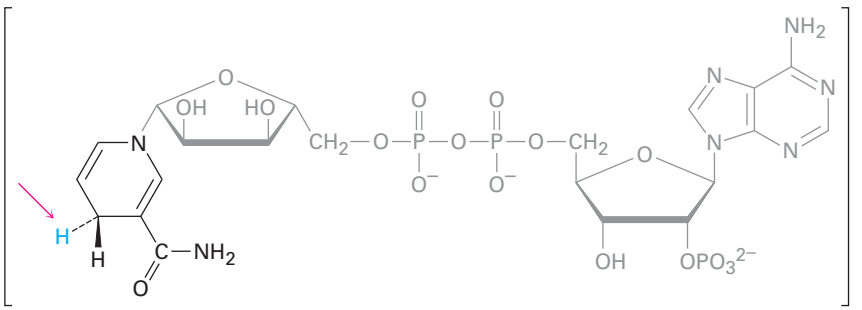
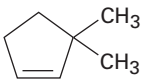
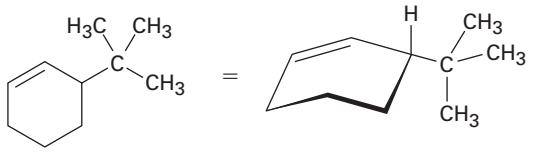


Figure 8.7 Reduction of the carbon–carbon double bond in *trans*-crotonyl ACP, a step in the biosynthesis of fatty acids. **One hydrogen** is delivered from NADPH as a hydride ion, H:⁻; the **other hydrogen** is delivered by protonation of the anion intermediate with an acid, HA.

Problem 8.12

What product would you obtain from catalytic hydrogenation of the following alkenes?

(a) $CH_3CH_2C(CH_3)=CHCH_2CH_3$ **(b)** 

(c) 

8.7 Oxidation of Alkenes: Epoxidation and Hydroxylation

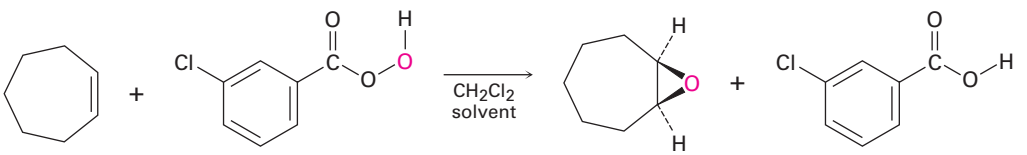
Like the word *reduction* used in the previous section for the addition of hydrogen to a double bond, the word *oxidation* has a slightly different meaning in organic chemistry from what you might have previously learned. In general chemistry, an oxidation is defined as the loss of one or more electrons by an atom. In organic chemistry, however, an **oxidation** is a reaction that results in a loss of electron density by 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

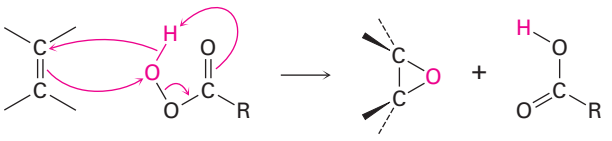
In the laboratory, alkenes are oxidized to give *epoxides* on treatment with a peroxyacid, RCO_3H, such as *meta*-chloroperoxybenzoic acid. An **epoxide**, also called an *oxirane,* is a cyclic ether with an oxygen atom in a three-membered ring. For example:



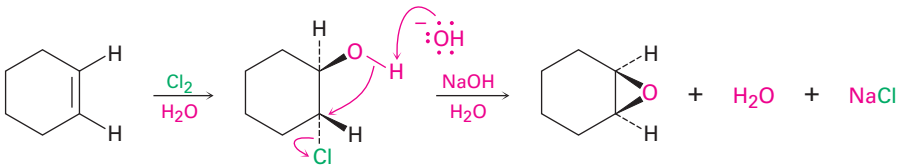
Cycloheptene | ***meta*-Chloroperoxybenzoic acid** | **1,2-Epoxycycloheptane** | ***meta*-Chlorobenzoic acid**

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

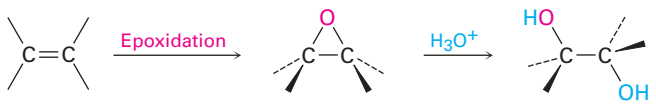
mechanism without intermediates. The oxygen atom farthest from the carbonyl group is the one transferred.



Another method for the synthesis of epoxides is through the use of halohydrins, prepared by electrophilic addition of HO−X to alkenes **(Section 8.3)**. When a halohydrin is treated with base, HX is eliminated and an epoxide is produced.

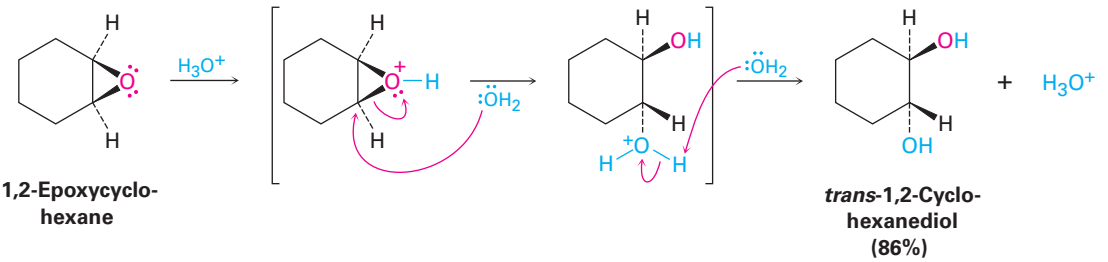


Epoxides undergo an acid-catalyzed ring-opening reaction with water (a *hydrolysis*) to give the corresponding 1,2-dialcohol, or *diol,* also called a **glycol**. Thus, the net result of the two-step alkene epoxidation/hydrolysis is **hydroxylation**—the addition of an −OH group to each of the two double-bond carbons. In fact, approximately 18 million metric tons of ethylene glycol, $HOCH_2CH_2OH$, most of it used for automobile antifreeze, is produced worldwide each year by epoxidation of ethylene followed by hydrolysis.



Acid-catalyzed epoxide opening takes place by 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 8.2)**. That is, a *trans*-1,2-diol results when an epoxycycloalkane is

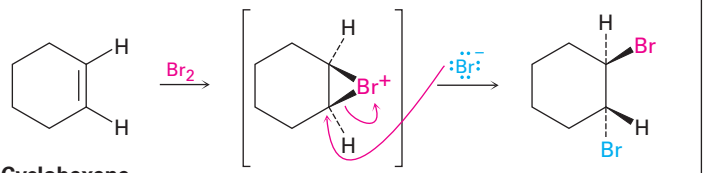
opened by aqueous acid, just as a *trans*-1,2-dibromide results when a cycloalkene is brominated. We'll look at epoxide chemistry in more detail in **Section 18.6**.



1,2-Epoxycyclohexane

***trans*-1,2-Cyclohexanediol (86%)**

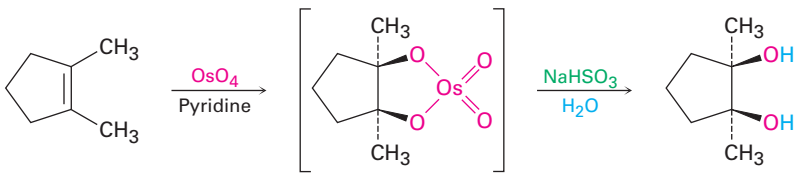
Recall the following:



Cyclohexene

***trans*-1,2-Dibromocyclohexane**

Hydroxylation can 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, $NaHSO_3$.



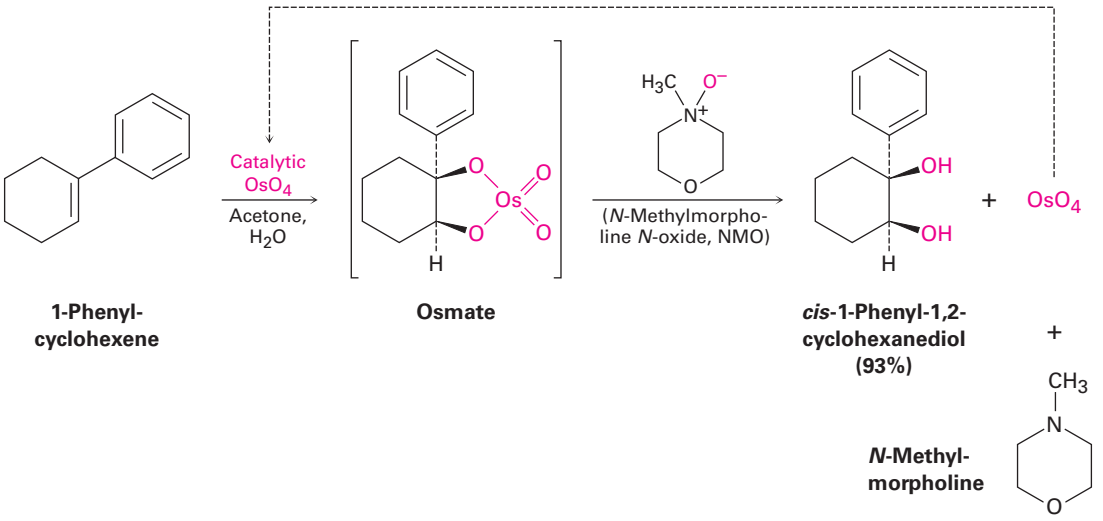
1,2-Dimethylcyclopentene

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.

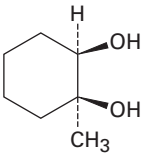


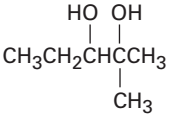
Problem 8.13

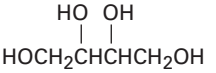
What product would you expect from reaction of *cis*-2-butene with *meta*-chloroperoxybenzoic acid? Show the stereochemistry.

Problem 8.14

How would you prepare each of the following compounds starting with an alkene?

(a) 

(b) 

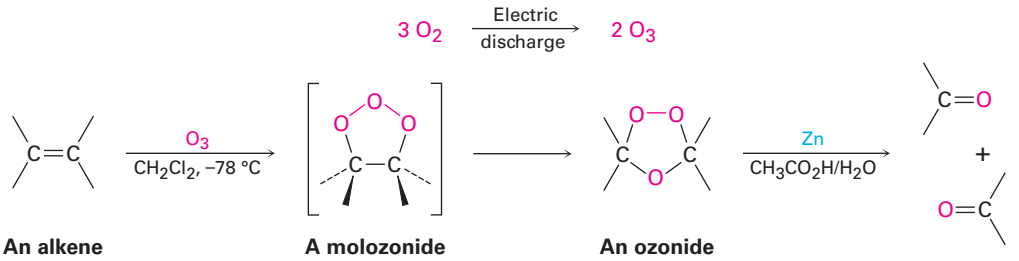
(c) 

8.8 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.

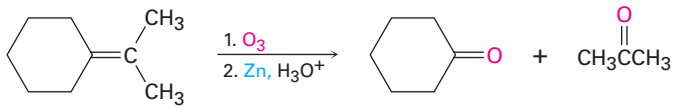
Ozone (O_3) is perhaps the most useful double-bond cleavage reagent. Prepared by passing a stream of oxygen through a high-voltage electrical discharge, ozone adds rapidly to a C=C bond at low temperature to give a cyclic intermediate called a *molozonide*. Once formed, the molozonide spontaneously rearranges 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.



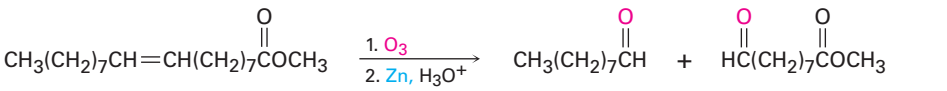
An alkene **A molozonide** **An ozonide**

Low-molecular-weight ozonides are explosive and are therefore not isolated. Instead, the ozonide is immediately treated with a reducing agent such as zinc metal in acetic acid to convert it to 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.



Isopropylidenecyclohexane (tetrasubstituted) **Cyclohexanone** **Acetone**

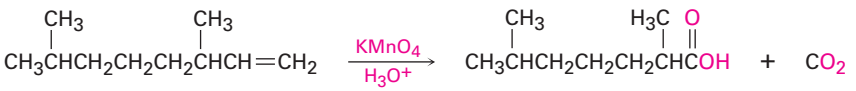
84%; two ketones



Methyl 9-octadecenoate (disubstituted) **Nonanal** **Methyl 9-oxononanoate**

78%; two aldehydes

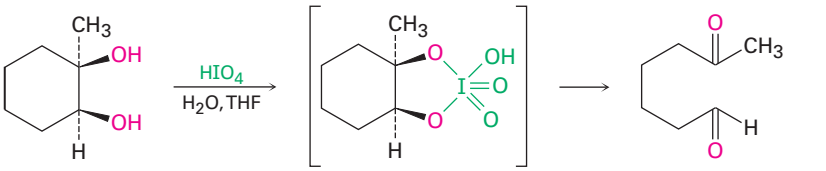
Several oxidizing reagents other than ozone also cause double-bond cleavage, although the reaction is not often used. For example, potassium permanganate ($KMnO_4$) in neutral or acidic solution cleaves alkenes to give carbonyl-containing products. If hydrogens are present on the double bond, carboxylic acids are produced; if two hydrogens are present on one carbon, CO_2 is formed.



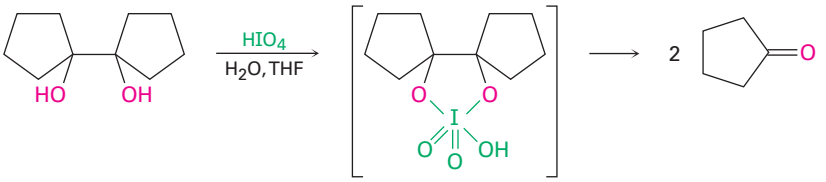
3,7-Dimethyl-1-octene **2,6-Dimethylheptanoic acid (45%)**

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.



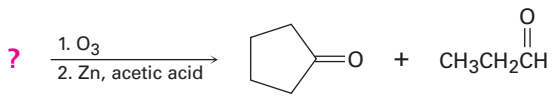
A 1,2-diol **Cyclic periodate intermediate** **6-Oxoheptanal (86%)**



A 1,2-diol **Cyclic periodate intermediate** **Cyclopentanone (81%)**

Worked Example 8.3 Predicting the Reactant in an Ozonolysis Reaction

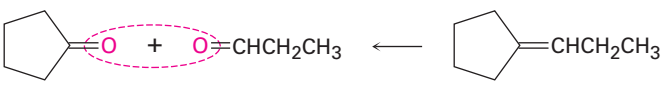
What alkene would yield a mixture of cyclopentanone and propanal on treatment with ozone followed by reduction with zinc?



Strategy

Reaction of an alkene with ozone, followed by reduction with zinc, cleaves the C=C bond and gives two carbonyl-containing fragments. That is, the C=C bond 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 to form a double bond.

Solution



Problem 8.15

What products would you expect from reaction of 1-methylcyclohexene with the following reagents?

(a) Aqueous acidic $KMnO_4$ **(b)** O_3, followed by Zn, CH_3CO_2H

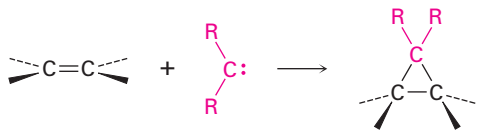
Problem 8.16

Propose structures for alkenes that yield the following products on reaction with ozone followed by treatment with Zn:

(a) $(CH_3)_2C{=}O + H_2C{=}O$ **(b)** 2 equiv $CH_3CH_2CH{=}O$

8.9 Addition of Carbenes to Alkenes: Cyclopropane Synthesis

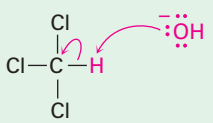
Yet another kind of alkene addition is the reaction with a *carbene* to yield a cyclopropane. A **carbene**, $R_2C:$, is a neutral molecule containing a divalent carbon with only six electrons in its valence shell. It is therefore highly reactive and is generated only as a reaction intermediate, rather 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**

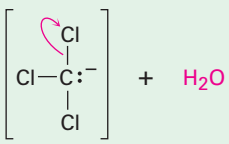
One of the simplest methods for generating a substituted carbene is by treatment of chloroform, $CHCl_3$, with a strong base such as KOH. As shown in **Figure 8.8**, loss of a proton from $CHCl_3$ gives the trichloromethanide anion, $^{-}$**:**CCl_3, which spontaneously expels a Cl^- ion to yield dichlorocarbene, **:**CCl_2.

1 Base abstracts the hydrogen from chloroform, leaving behind the electron pair from the C–H bond and forming the trichloromethanide anion.



Chloroform

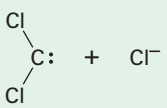
1



Trichloromethanide anion

2 Spontaneous loss of chloride ion then yields the neutral dichlorocarbene.

2



Dichlorocarbene

Figure 8.8 | MECHANISM

Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base. Deprotonation of $CHCl_3$ gives the trichloromethanide anion, $^{-}$**:**CCl_3, which spontaneously expels a Cl^- ion.

The dichlorocarbene carbon atom 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 7.9)** with respect to both the sp^2 hybridization of carbon and the vacant p orbital. Electrostatic potential maps further show this similarity **(Figure 8.9)**.

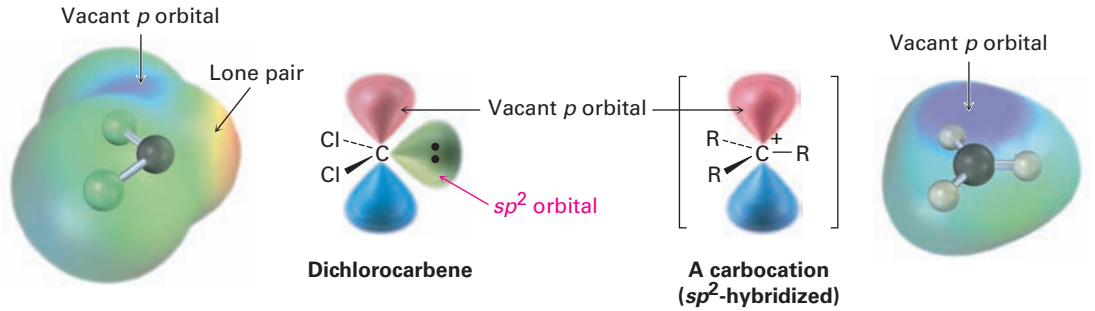
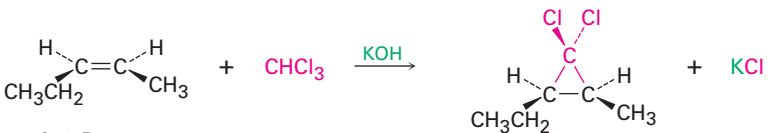
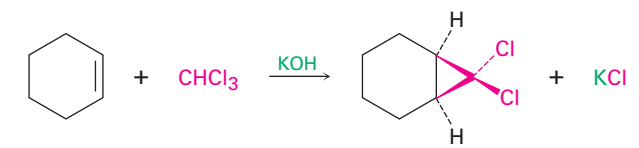


Figure 8.9 The structure of dichlorocarbene. Electrostatic potential maps show how the **positive region** coincides with the empty p orbital in both dichlorocarbene and a carbocation (CH_3^+). The **negative region** in the dichlorocarbene map coincides with the lone-pair electrons.

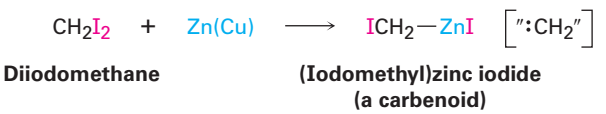
If dichlorocarbene is generated in the presence of an alkene, addition to the double bond occurs and a dichlorocyclopropane is formed. As the reaction of dichlorocarbene with *cis*-2-pentene demonstrates, the addition is **stereospecific**, meaning that only a single stereoisomer is formed as product. Starting from a cis alkene, for instance, only cis-disubstituted cyclopropane is produced; starting from a trans alkene, only trans-disubstituted cyclopropane is produced.



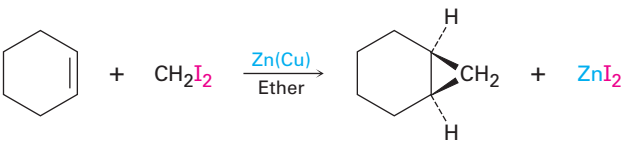


The best method for preparing nonhalogenated cyclopropanes is by a process called the **Simmons–Smith reaction**. First investigated at the DuPont company, this reaction does not involve a free carbene. Rather, it

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, (iodomethyl)zinc iodide transfers a CH_2 group to the double bond and yields the cyclopropane. For example, cyclohexene reacts cleanly and in good yield to give the corresponding cyclopropane. Although we won't discuss the mechanistic details, carbene addition to an alkene is one of a general class of reactions called *cycloadditions*, which we'll study more carefully in Chapter 30.



Diiodomethane **(Iodomethyl)zinc iodide (a carbenoid)**

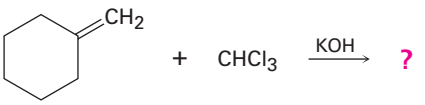


Cyclohexene **Bicyclo[4.1.0]heptane (92%)**

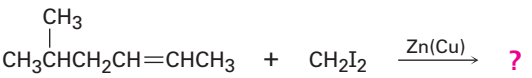
Problem 8.17

What products would you expect from the following reactions?

(a)



(b)



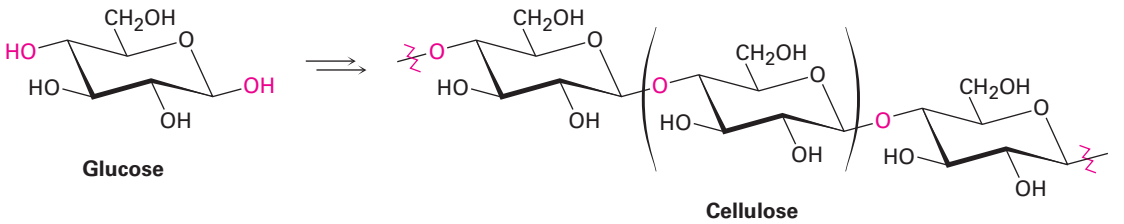
8.10 Radical Additions to Alkenes: Chain-Growth Polymers

In our brief introduction to radical reactions in **Section 6.3**, 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 simply a large—sometimes *very* large—molecule built up by repetitive bonding together of many smaller molecules, called **monomers**.

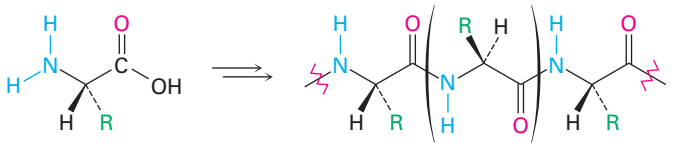
Nature makes wide use of biological polymers. Cellulose, for instance, is a polymer built of repeating glucose monomer units; proteins are polymers built

of repeating amino acid monomers; and nucleic acids are polymers built of repeating nucleotide monomers.

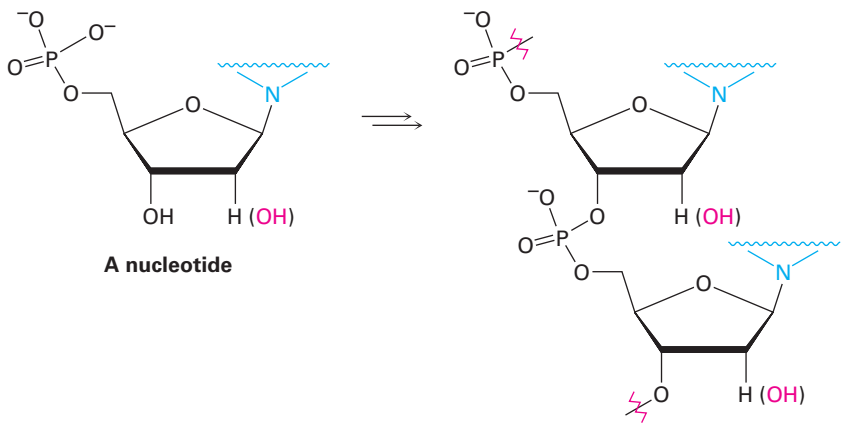
Cellulose—a glucose polymer



Protein—an amino acid polymer



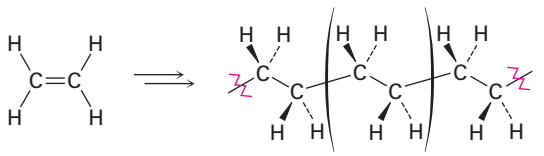
Nucleic acid—a nucleotide polymer



Synthetic polymers, such as polyethylene, are chemically much simpler 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* amu and may contain as many

as 200,000 monomer units incorporated into a gigantic hydrocarbon chain. Worldwide production of polyethylene is approximately 80 million metric tons per year.

Polyethylene—a synthetic alkene polymer

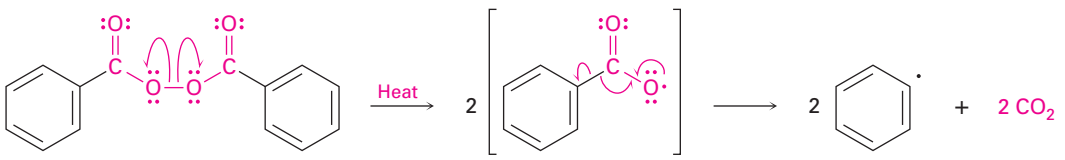


Ethylene **Polyethylene**

Polyethylene and other simple alkene polymers are called **chain-growth polymers** because they are formed in a chain reaction process in which an initiator adds to a carbon–carbon double bond to yield a reactive intermediate. The intermediate then reacts with a second molecule of monomer to yield a new intermediate, which reacts with a third monomer unit, and so on.

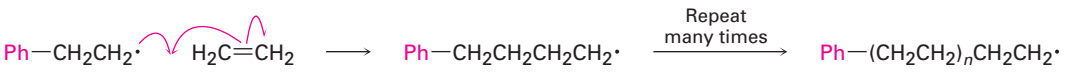
Historically, ethylene polymerization was carried out at high pressure (1000–3000 atm) and high temperature (100–250 °C) in the presence of a radical initiator such as benzoyl peroxide, although other catalysts and reaction conditions are now used. The key step is the addition of a radical to the ethylene double bond, a reaction similar in many respects to what takes place in the addition of an electrophile. In writing the mechanism, recall that a curved half-arrow, or "fishhook" ↶, is used to show the movement of a single electron, as opposed to the full curved arrow used to show the movement of an electron pair in a polar reaction.

- **Initiation** The polymerization reaction is initiated when a few radicals are generated on heating a small amount of benzoyl peroxide catalyst to break the weak O–O bond. The initially formed benzoyloxy radical loses CO_2 and gives a phenyl radical (Ph·), which adds to the C=C bond of ethylene to start the polymerization process. One electron from the ethylene double bond pairs up with the odd electron on the phenyl radical to form a new C–C bond, and the other electron remains on carbon.



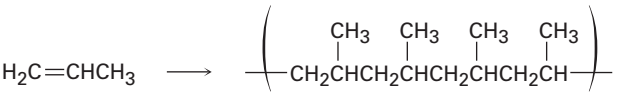
Benzoyl peroxide **Benzoyloxy radical** **Phenyl radical (Ph·)**

- **Propagation** Polymerization occurs when the carbon radical formed in the initiation step adds to another ethylene molecule to yield another radical. Repetition of the process for hundreds or thousands of times builds the polymer chain.

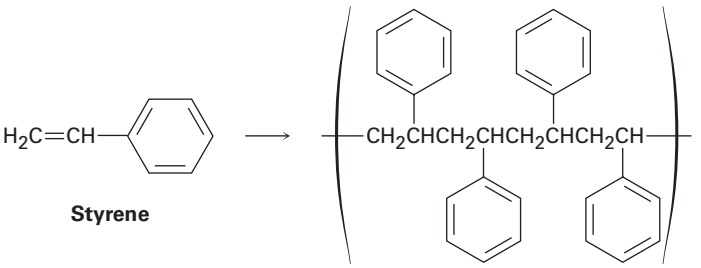


- **Termination** The chain process is eventually ended by a reaction that consumes the radical. Combination of two growing chains is one possible chain-terminating reaction.

Ethylene is not unique in its ability to form a polymer. Many substituted ethylenes, called *vinyl monomers,* also undergo polymerization to yield polymers with substituent groups regularly spaced on alternating carbon atoms along the chain. Propylene, for example, yields polypropylene, and styrene yields polystyrene.

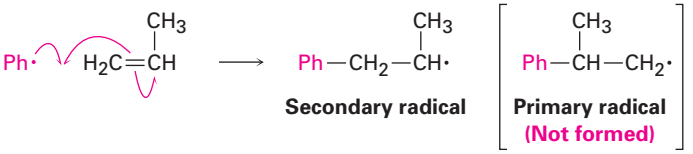


Propylene **Polypropylene**



Styrene **Polystyrene**

When an unsymmetrically substituted vinyl monomer such as propylene or styrene is polymerized, the radical addition steps can take place at either end of the double bond to yield either a primary radical intermediate ($RCH_2\cdot$) 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.



Secondary radical **Primary radical (Not formed)**

Table 8.1 shows some commercially important alkene polymers, their uses, and the vinyl monomers from which they are made.

Table 8.1 Some Alkene Polymers and Their Uses

Monomer	Formula	Trade or common name of polymer	Uses
Ethylene	$H_2C{=}CH_2$	Polyethylene	Packaging, bottles
Propene (propylene)	$H_2C{=}CHCH_3$	Polypropylene	Moldings, rope, carpets
Chloroethylene (vinyl chloride)	$H_2C{=}CHCl$	Poly(vinyl chloride) Tedlar	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

Predicting the Structure of a Polymer

Worked Example 8.4

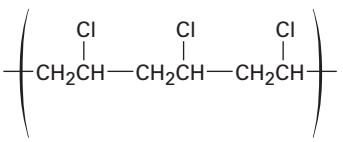
Show the structure of poly(vinyl chloride), a polymer made from $H_2C{=}CHCl$, by drawing several repeating units.

Strategy

Mentally break the carbon–carbon double bond in the monomer unit, and form single bonds by connecting numerous units together.

Solution

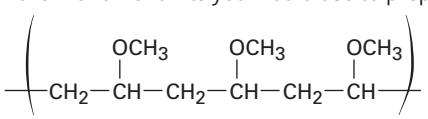
The general structure of poly(vinyl chloride) is



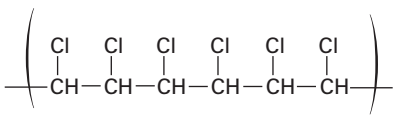
Problem 8.18

Show the monomer units you would use to prepare the following polymers:

(a)



(b)



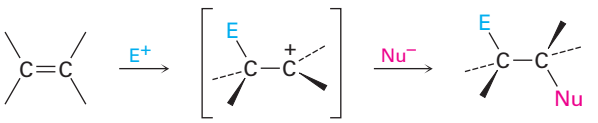
Problem 8.19

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.

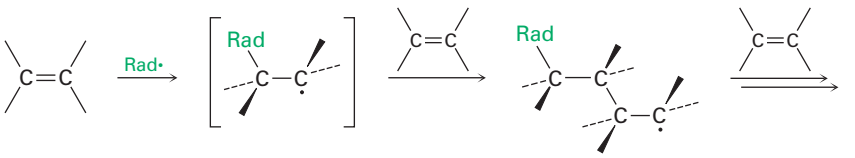
8.11 Biological Additions of Radicals to Alkenes

The same high reactivity of radicals that makes possible 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 the enzyme where reaction takes place, 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. The reaction mechanism was discussed briefly in **Section 6.3**.

As shown in **Figure 8.10**, 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.

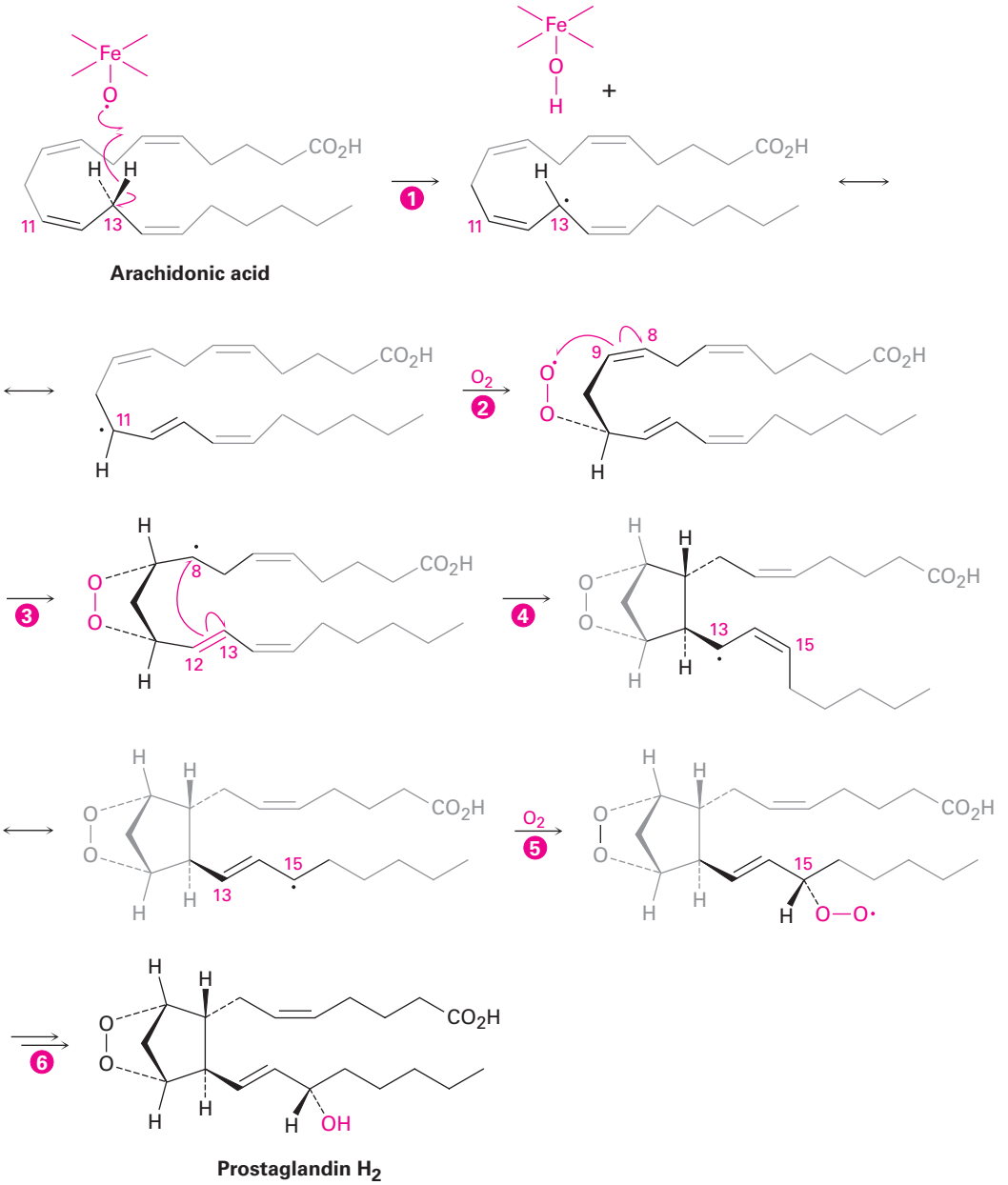
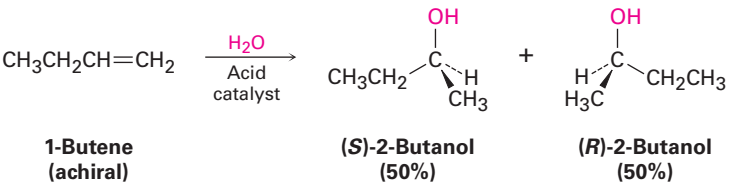


Figure 8.10 Pathway for the biosynthesis of prostaglandins from arachidonic acid. Steps 2 and 5 are radical addition reactions to O_2; steps 3 and 4 are radical additions to carbon–carbon double bonds.

8.12 Reaction Stereochemistry: 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.



1-Butene (achiral) — **(*S*)-2-Butanol (50%)** — **(*R*)-2-Butanol (50%)**

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. Since 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 8.11**, and reaction from the bottom leads to (*R*)-2-butanol through TS 2. *The two transition states are mirror images*. They therefore have identical energies, form at identical rates, and are equally likely to occur.

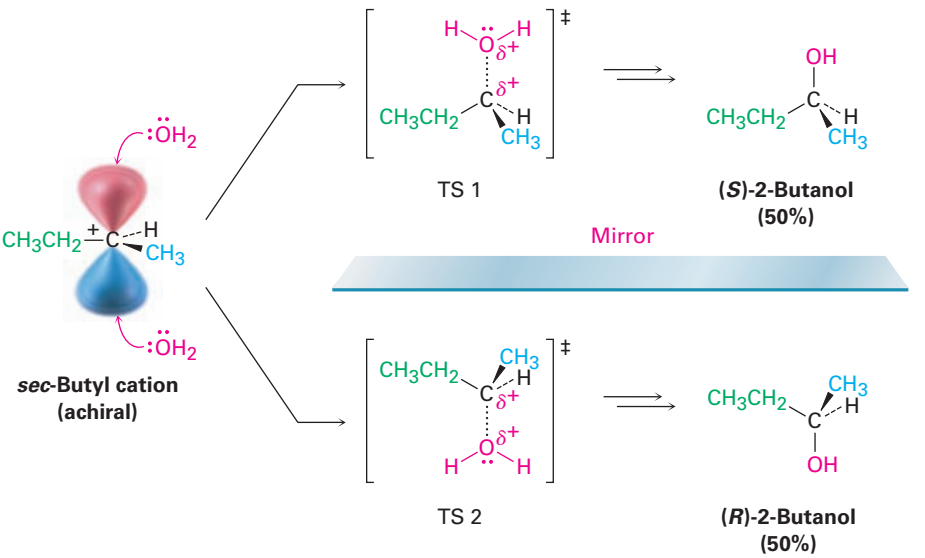
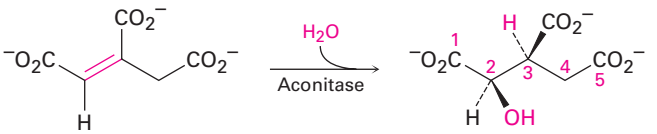


Figure 8.11 Reaction of H_2O with the carbocation resulting from protonation of 1-butene. Reaction from the top leads to *S* product and is the mirror image of reaction from the bottom, which leads to *R* product. Because they are energetically identical, they are equally likely and lead to a racemic 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 reaction of achiral reactants always leads to a racemic mixture of enantiomeric products. Put another way, optical activity can't appear from nowhere; an optically active

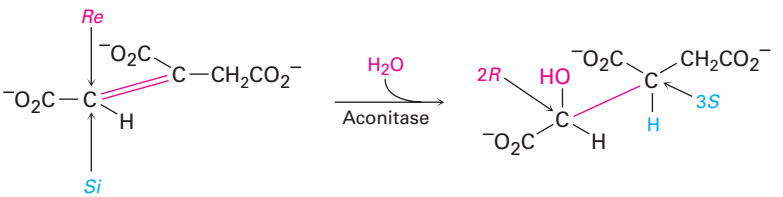
product can only result by starting with an optically active reactant or chiral environment **(Section 5.12)**.

In contrast to laboratory reactions, enzyme-catalyzed biological reactions often give a single enantiomer of a chiral product, even when the substrate is achiral. One step in the citric acid cycle of food metabolism, for instance, is the aconitase-catalyzed addition of water to (*Z*)-aconitate (usually called *cis*-aconitate) to give isocitrate.



***cis*-Aconitate (achiral)** **(2*R*,3*S*)-Isocitrate**

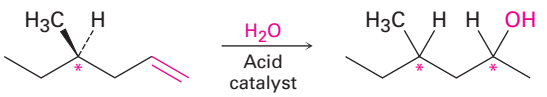
Even though *cis*-aconitate is achiral, only the (2*R*,3*S*) enantiomer of the product is formed. As discussed in **Sections 5.11 and 5.12**, *cis*-aconitate is a prochiral molecule, which is held in a chiral environment by the aconitase enzyme during the reaction. In that chiral environment, the two 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**

8.13 Reaction Stereochemistry: 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 8.12**, the stereochemistry at C2 is established by reaction of H_2O with a carbocation intermediate in the usual manner. *But this carbocation does not have a plane of symmetry;* it is chiral because of the chirality center at C4. Because the carbocation has no plane of symmetry and is chiral, it does not react equally well from top and bottom faces. One of the two faces is likely, for steric reasons, to be a bit more accessible than the other face, 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.

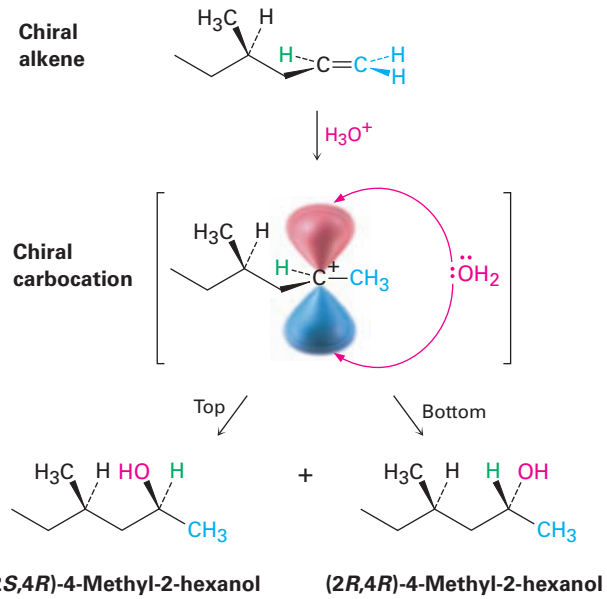


Figure 8.12 Stereochemistry of the acid-catalyzed addition of H_2O to the chiral alkene, (*R*)-4-methyl-1-hexene. A mixture of diastereomeric 2*R*,4*R* and 2*S*,4*R* products is formed in unequal amounts because reaction of the chiral carbocation intermediate is not equally likely from top and bottom. The product mixture is optically active.

As a general rule, the formation of a new chirality center by the reaction of 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.

Problem 8.20

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?

Problem 8.21

What products are formed from hydration of 4-methylcyclopentene? What can you say about the relative amounts of the products?

A DEEPER LOOK

Terpenes: Naturally Occurring Alkenes

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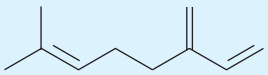
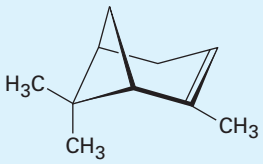
The wonderful fragrance of leaves from the California bay laurel is due primarily to myrcene, a simple terpene.

Ever since its discovery in Persia around 1000 A.D., it has been known that *steam distillation,* the codistillation of plant materials 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.

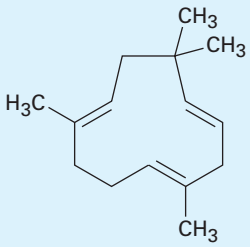
Chemically, plant essential oils consist largely of mixtures of compounds called *terpenoids*—small organic molecules with an immense diversity of structure. More than 35,000 different terpenoids are known. Some are open-chain molecules, and others contain rings; some are hydrocarbons, and others contain oxygen. Hydrocarbon terpenoids, in particular, are known as *terpenes,* and all contain double bonds. For example:



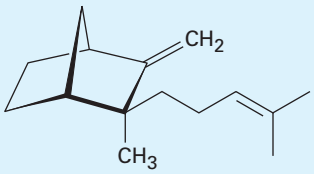
Myrcene
(oil of bay)



α-Pinene
(turpentine)

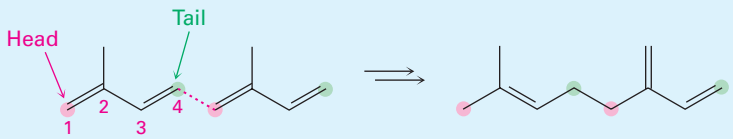


Humulene
(oil of hops)



β-Santalene
(sandalwood oil)

Regardless of their apparent structural differences, all terpenoids are related. According to a formalism called the *isoprene rule,* they can be thought of as arising from head-to-tail joining of 5-carbon isoprene units (2-methyl-1,3-butadiene). Carbon 1 is the head of the isoprene unit, and carbon 4 is the tail. For example, myrcene contains two isoprene units joined head to tail, forming an 8-carbon chain with two 1-carbon branches. α-Pinene similarly contains two isoprene units assembled into a more complex cyclic structure, and humulene contains three isoprene units. See if you can identify the isoprene units in α-pinene, humulene, and β-santalene.

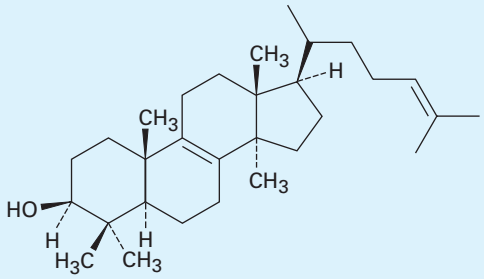


Isoprene **Myrcene**

(continued)

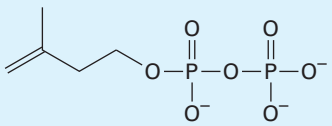
(continued)

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.

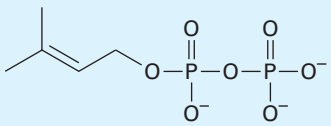


Lanosterol (a triterpene, C_{30})

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 27.5 and 27.7**.



Isopentenyl diphosphate



Dimethylallyl diphosphate

Summary

Key words

anti stereochemistry, 265
bromonium ion, 265
carbene, 287
chain-growth polymer, 291
epoxide, 281
glycol, 282
halohydrin, 267
hydroboration, 272
hydrogenation, 276
hydroxylation, 282
monomer, 289
oxidation, 281
oxymercuration–demercuration, 271
ozonide, 284
polymer, 289

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 flip side of that elimination reaction to prepare alkenes 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 together 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 much more 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.

Key words—cont'd

reduction, 277
Simmons–Smith reaction, 288
stereospecific, 288
syn stereochemistry, 273

Learning Reactions

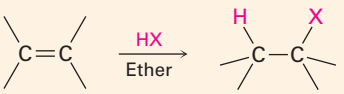
What's seven times nine? Sixty-three, of course. You didn't have to stop and figure it out; you knew the answer immediately because you long ago learned the multiplication tables. Learning the reactions of organic chemistry requires the same approach: reactions have to be learned for immediate recall 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 Solutions Manual* has several appendixes that organize organic reactions from other viewpoints. Fundamentally, though, there are no shortcuts. Learning organic chemistry does take effort.

Summary of Reactions

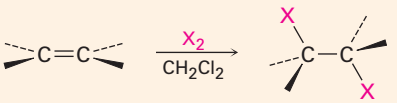
***Note:* No stereochemistry is implied unless specifically indicated with wedged, solid, and dashed lines.**

1. Addition reactions of alkenes
   (a) Addition of HCl, HBr, and HI (Sections 7.7 and 7.8)
   Markovnikov regiochemistry occurs, with H adding to the less highly substituted alkene carbon and halogen adding to the more highly substituted carbon.

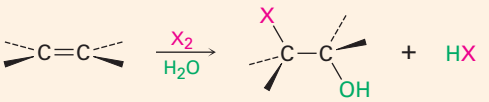


(continued)

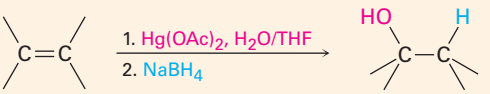
(b) Addition of halogens Cl_2 and Br_2 (Section 8.2)
Anti addition is observed through a halonium ion intermediate.



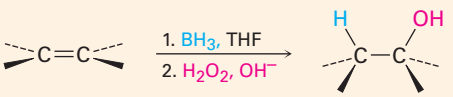
(c) Halohydrin formation (Section 8.3)
Markovnikov regiochemistry and anti stereochemistry occur.



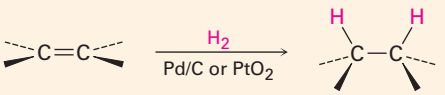
(d) Addition of water by oxymercuration–demercuration (Section 8.4)
Markovnikov regiochemistry occurs.



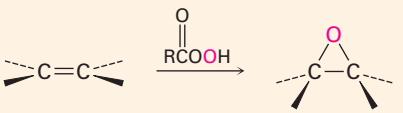
(e) Addition of water by hydroboration–oxidation (Section 8.5)
Non-Markovnikov syn addition occurs.



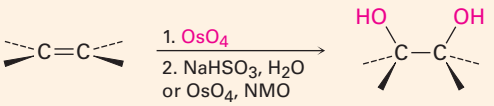
(f) Catalytic hydrogenation (Section 8.6)
Syn addition occurs.



(g) Epoxidation with a peroxyacid (Section 8.7)
Syn addition occurs.

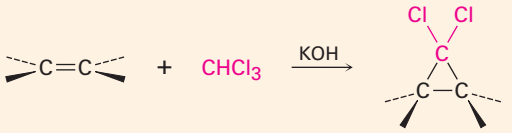


(h) Hydroxylation with OsO_4 (Section 8.7)
Syn addition occurs.

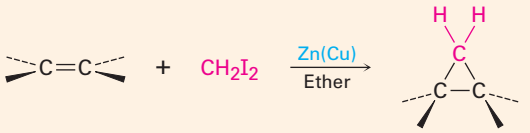


(i) Addition of carbenes to yield cyclopropanes (Section 8.9)

(1) Dichlorocarbene addition

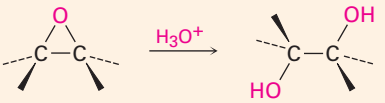


(2) Simmons–Smith reaction



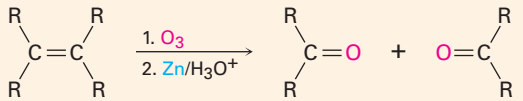
2. Hydroxylation by acid-catalyzed epoxide hydrolysis (Section 8.7)

Anti stereochemistry occurs.

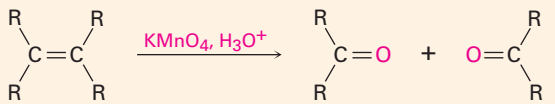


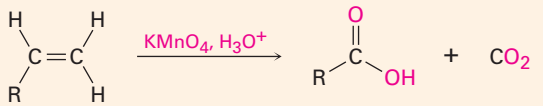
3. Oxidative cleavage of alkenes (Section 8.8)

(a) Reaction with ozone followed by zinc in acetic acid

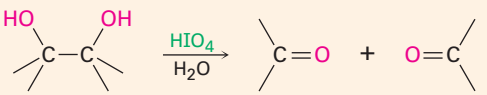


(b) Reaction with $KMnO_4$ in acidic solution





4. Cleavage of 1,2-diols (Section 8.8)



Exercises

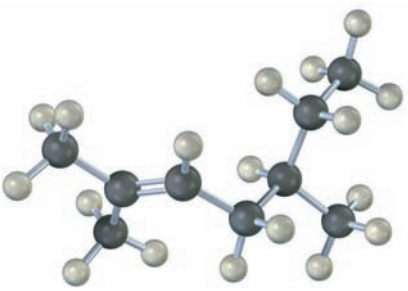
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

Visualizing Chemistry

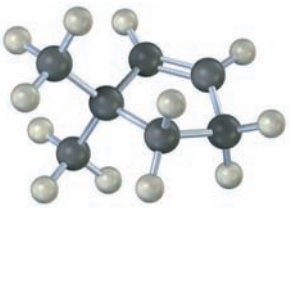
(Problems 8.1–8.21 appear within the chapter.)

8.22 Name the following alkenes, and predict the products of their reaction with (1) *meta*-chloroperoxybenzoic acid, (2) $KMnO_4$ in aqueous acid, and (3) O_3, followed by Zn in acetic acid:

(a)

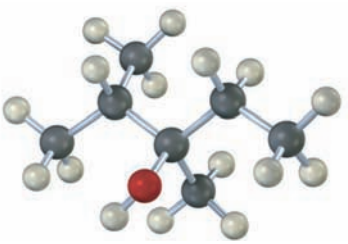


(b)

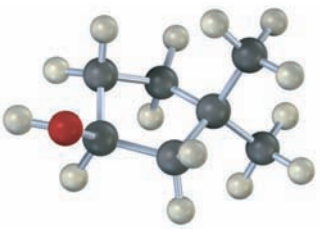


8.23 Draw the structures of alkenes that would yield the following alcohols on hydration (red = O). Tell in each case whether you would use hydroboration–oxidation or oxymercuration–demercuration.

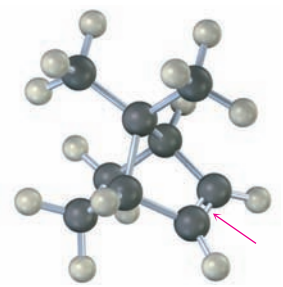
(a)



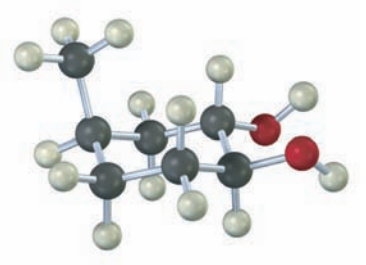
(b)



8.24 The following alkene undergoes hydroboration–oxidation to yield a single product rather than a mixture. Explain the result, and draw the product showing its stereochemistry.



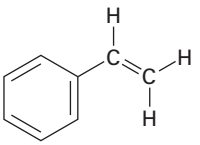
8.25 From what alkene was the following 1,2-diol made, and what method was used, epoxide hydrolysis or OsO_4?



Additional Problems

Reactions of Alkenes

8.26 Predict the products of the following reactions (the aromatic ring is unreactive in all cases). Indicate regiochemistry when relevant.



(a) H_2/Pd → ?

(b) Br_2 → ?

(c) OsO_4, NMO → ?

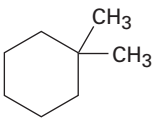
(d) Cl_2, H_2O → ?

(e) CH_2I_2, Zn/Cu → ?

(f) *meta*-Chloroperoxybenzoic acid → ?

8.27 Suggest structures for alkenes that give the following reaction products. There may be more than one answer for some cases.

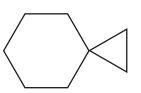
(a) ? $\xrightarrow{H_2/Pd}$ $CH_3CH(CH_3)CH_2CH_2CH_2CH_3$

(b) ? $\xrightarrow{H_2/Pd}$ 

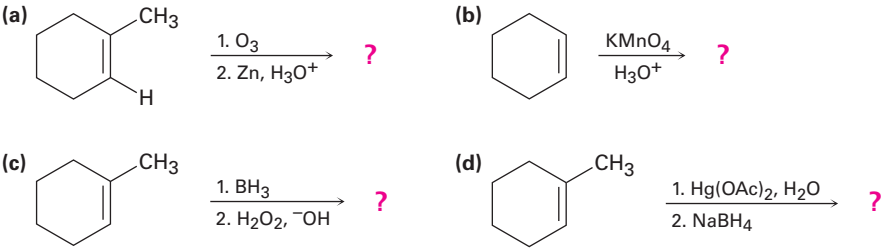
(c) ? $\xrightarrow{Br_2}$ $CH_3CH(Br)CH(Br)CH_2CH(CH_3)CH_3$

(d) ? $\xrightarrow{HCl}$ $CH_3CH(Cl)CH(CH_3)CH_2CH_2CH_2CH_3$

(e) ? $\xrightarrow{1.\ Hg(OAc)_2,\ H_2O}$ $\xrightarrow{2.\ NaBH_4}$ $CH_3CH_2CH_2CH(OH)CH_3$

(f) ? $\xrightarrow{CH_2I_2,\ Zn/Cu}$ 

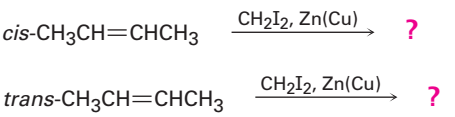
8.28 Predict the products of the following reactions, showing both regiochemistry and stereochemistry where appropriate:



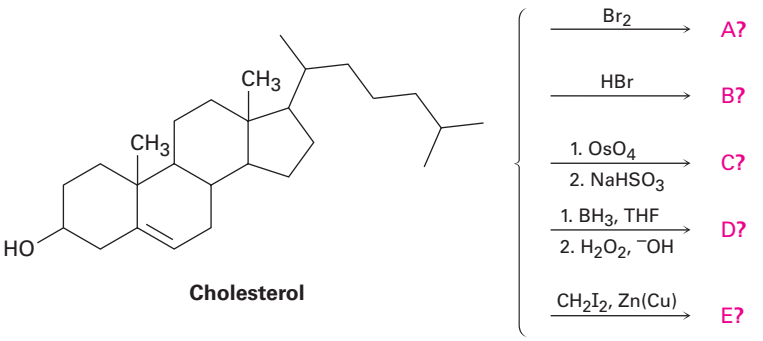
8.29 Which reaction would you expect to be faster, addition of HBr to cyclohexene or to 1-methylcyclohexene? Explain.

8.30 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.

8.31 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.



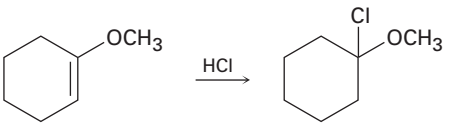
8.32 Predict the products of the following reactions. Don't worry about the size of the molecule; concentrate on the functional groups.



Cholesterol

8.33 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.

8.34 Addition of HCl to 1-methoxycyclohexene yields 1-chloro-1-methoxycyclohexane as the sole product. Use resonance structures of the carbocation intermediate to explain why none of the other regioisomer is formed.

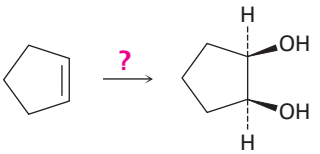


1-Methoxycyclohexene **1-Chloro-1-methoxycyclohexane**

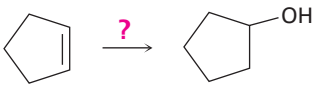
Synthesis Using Alkenes

8.35 How would you carry out the following transformations? Tell the reagents you would use in each case.

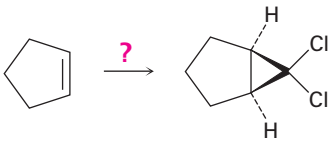
(a)



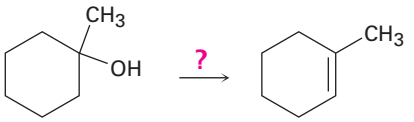
(b)



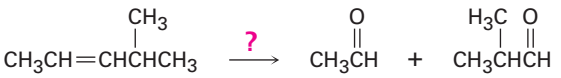
(c)



(d)



(e)



(f)

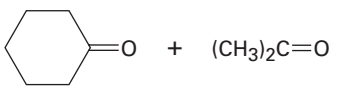
8.36 Draw the structure of an alkene that yields only acetone, $(CH_3)_2C{=}O$, on ozonolysis followed by treatment with Zn.

8.37 Show the structures of alkenes that give the following products on oxidative cleavage with $KMnO_4$ in acidic solution:

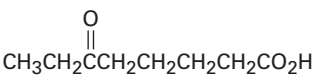
(a) $CH_3CH_2CO_2H$ + CO_2

(b) $(CH_3)_2C{=}O$ + $CH_3CH_2CH_2CO_2H$

(c)

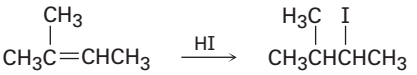


(d)

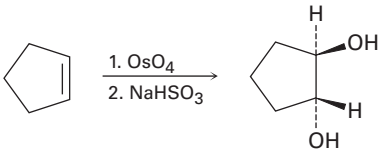


8.38 In planning the synthesis of one compound from another, it's just as important to know what *not* to do as to know what to do. The following reactions all have serious drawbacks to them. Explain the potential problems of each.

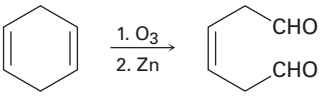
(a)



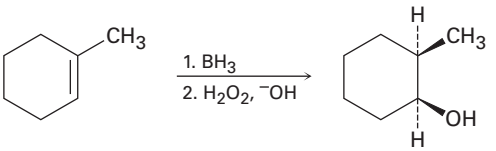
(b)



(c)

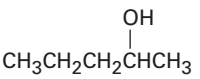


(d)

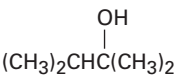


8.39 Which of the following alcohols could *not* be made selectively by hydroboration–oxidation of an alkene? Explain.

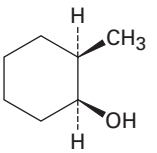
(a)



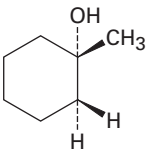
(b)



(c)

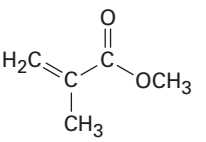


(d)



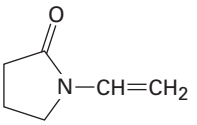
Polymers

8.40 Plexiglas, a clear plastic used to make many molded articles, is made by polymerization of methyl methacrylate. Draw a representative segment of Plexiglas.



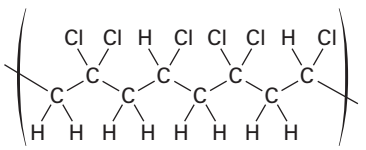
Methyl methacrylate

8.41 Poly(vinyl pyrrolidone), prepared from *N*-vinylpyrrolidone, is used both in cosmetics and as a synthetic blood substitute. Draw a representative segment of the polymer.



***N*-Vinylpyrrolidone**

8.42 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

8.43 Compound **A** has the formula $C_{10}H_{16}$. 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** ($C_{10}H_{16}O_2$).

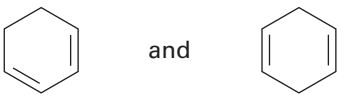
(a) How many rings does **A** have?

(b) What are the structures of **A** and **B**?

(c) Write the reactions.

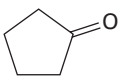
8.44 An unknown hydrocarbon **A** with the formula C_6H_{12} reacts with 1 molar equivalent of H_2 over a palladium catalyst. Hydrocarbon **A** also reacts with OsO_4 to give diol **B**. When oxidized with $KMnO_4$ in acidic solution, **A** gives two fragments. One fragment is propanoic acid, $CH_3CH_2CO_2H$, and the other fragment is ketone **C**. What are the structures of **A**, **B**, and **C**? Write all reactions, and show your reasoning.

8.45 Using an oxidative cleavage reaction, explain how you would distinguish between the following two isomeric dienes:



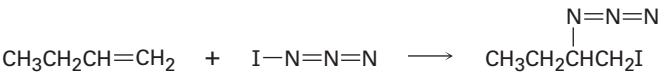
and

8.46 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.



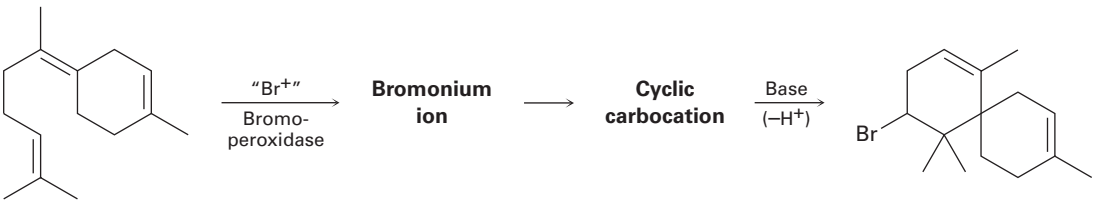
Cyclopentanone

8.47 Iodine azide, IN_3, adds to alkenes by an electrophilic mechanism similar to that of bromine. If a monosubstituted alkene such as 1-butene is used, only one product results:



(a) Add lone-pair electrons to the structure shown for IN_3, and draw a second resonance form for the molecule.
(b) Calculate formal charges for the atoms in both resonance structures you drew for IN_3 in part **(a)**.
(c) In light of the result observed when IN_3 adds to 1-butene, what is the polarity of the $I–N_3$ bond? Propose a mechanism for the reaction using curved arrows to show the electron flow in each step.

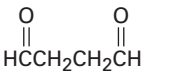
8.48 10-Bromo-α-chamigrene, a compound isolated from marine algae, is thought to be biosynthesized from γ-bisabolene by the following route:



γ-Bisabolene **10-Bromo-α-chamigrene**

Draw the structures of the intermediate bromonium and cyclic carbocation, and propose mechanisms for all three steps.

8.49 Draw the structure of a hydrocarbon that absorbs 2 molar equivalents of H_2 on catalytic hydrogenation and gives only butanedial on ozonolysis.



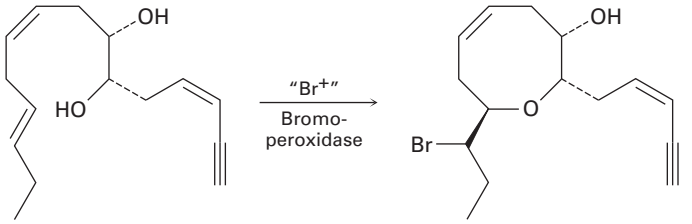
Butanedial

8.50 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?

8.51 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.

8.52 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.

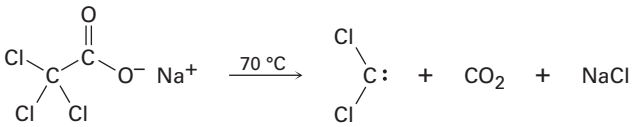
8.53 Isolated from marine algae, prelaureatin is thought to be biosynthesized from laurediol by the following route. Propose a mechanism.



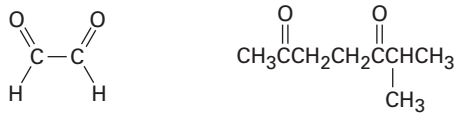
Laurediol **Prelaureatin**

8.54 How would you distinguish between the following pairs of compounds using simple chemical tests? Tell what you would do and what you would see.
(a) Cyclopentene and cyclopentane **(b)** 2-Hexene and benzene

8.55 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?



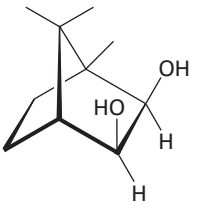
8.56 α-Terpinene, $C_{10}H_{16}$, is a pleasant-smelling hydrocarbon that has been isolated from oil of marjoram. On hydrogenation over a palladium catalyst, α-terpinene reacts with 2 molar equivalents of H_2 to yield a hydrocarbon, $C_{10}H_{20}$. On ozonolysis, followed by reduction with zinc and acetic acid, α-terpinene yields two products, glyoxal and 6-methyl-2,5-heptanedione.



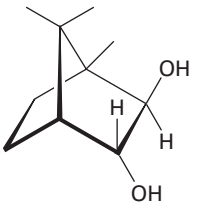
Glyoxal **6-Methyl-2,5-heptanedione**

(a) How many degrees of unsaturation does α-terpinene have?
(b) How many double bonds and how many rings does it have?
(c) Propose a structure for α-terpinene.

8.57 Evidence that cleavage of 1,2-diols by HIO_4 occurs through a five-membered cyclic periodate intermediate is based on *kinetic data*—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 kinetic results.

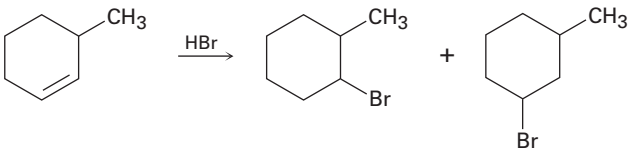


A
(*cis* diol)

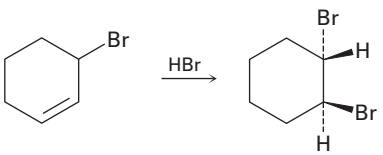


B
(*trans* diol)

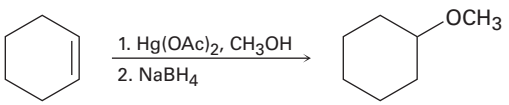
8.58 Reaction of HBr with 3-methylcyclohexene yields a mixture of four products: *cis*- and *trans*-1-bromo-3-methylcyclohexane and *cis*- and *trans*-1-bromo-2-methylcyclohexane. The analogous reaction of HBr with 3-bromocyclohexene yields *trans*-1,2-dibromocyclohexane as the sole product. Draw structures of the possible intermediates, and then explain why only a single product is formed in the reaction of HBr with 3-bromocyclohexene.



cis, trans **cis, trans**

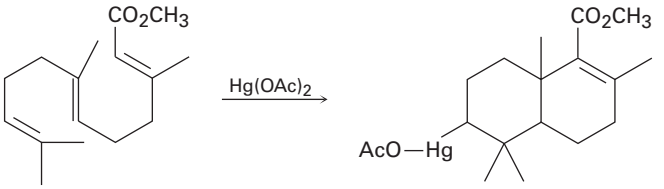


8.59 Reaction of cyclohexene with mercury(II) acetate in CH_3OH rather than H_2O, followed by treatment with $NaBH_4$, yields cyclohexyl methyl ether rather than cyclohexanol. Suggest a mechanism.

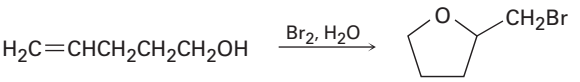


Cyclohexene **Cyclohexyl methyl ether**

8.60 Use your general knowledge of alkene chemistry to suggest a mechanism for the following reaction.

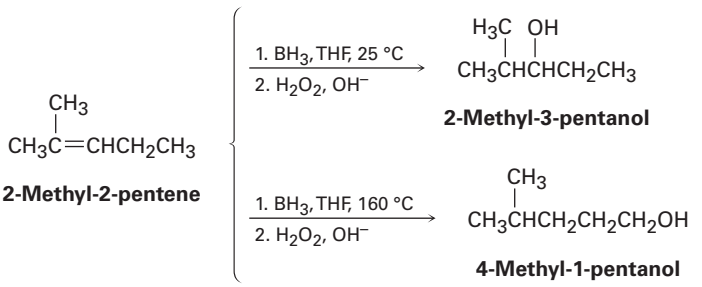


8.61 Treatment of 4-penten-1-ol with aqueous Br_2 yields a cyclic bromo ether rather than the expected bromohydrin, Suggest a mechanism, using curved arrows to show electron movement.



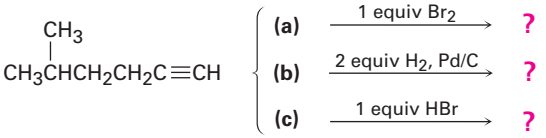
4-Penten-1-ol **2-(Bromomethyl)tetrahydrofuran**

8.62 Hydroboration of 2-methyl-2-pentene at 25 °C followed by oxidation with alkaline H_2O_2 yields 2-methyl-3-pentanol, but hydroboration at 160 °C followed by oxidation yields 4-methyl-1-pentanol. Suggest a mechanism.



2-Methyl-2-pentene **2-Methyl-3-pentanol** **4-Methyl-1-pentanol**

8.63 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?



8.64 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.

8.65 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 produced as 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**.

9

Synthesizing organic compounds is like conducting an orchestra. When in tune, chemists can create highly complex organic compounds. © Olaf Doering/Alamy

Alkynes: An Introduction to Organic Synthesis

9.1 Naming Alkynes
9.2 Preparation of Alkynes: Elimination Reactions of Dihalides
9.3 Reactions of Alkynes: Addition of HX and X_2
9.4 Hydration of Alkynes
9.5 Reduction of Alkynes
9.6 Oxidative Cleavage of Alkynes
9.7 Alkyne Acidity: Formation of Acetylide Anions
9.8 Alkylation of Acetylide Anions
9.9 An Introduction to Organic Synthesis
A Deeper Look—The Art of Organic Synthesis

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 the 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, 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 *sp*-hybridized carbon atoms. Polyynes with up to eight triple bonds have been detected in interstellar space, and evidence has been presented for the existence of *carbyne,* an allotrope of carbon consisting of repeating triple bonds in long chains of indefinite length. The electronic properties of polyynes are being explored for potential use in nanotechnology applications.

H—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—H

A polyyne detected in interstellar space

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.

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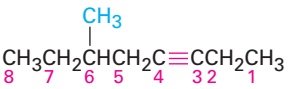
9.1 Naming Alkynes

Alkyne nomenclature follows the general rules for hydrocarbons discussed in **Sections 3.4 and 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.

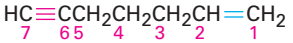


Begin numbering at the end nearer the triple bond.

6-Methyl-3-octyne

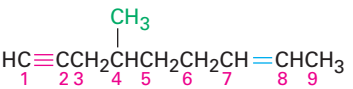
(New: 6-Methyloct-3-yne)

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

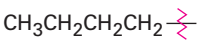
(New: Hept-1-en-6-yne)



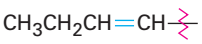
4-Methyl-7-nonen-1-yne

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

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

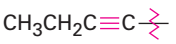


Butyl
(an alkyl group)



1-Butenyl
(a vinylic group)

(New: But-1-enyl)

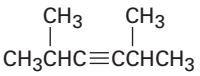


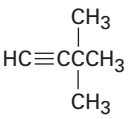
1-Butynyl
(an alkynyl group)

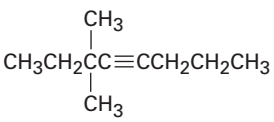
(New: But-1-ynyl)

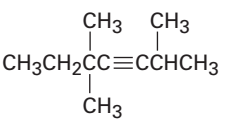
Problem 9.1

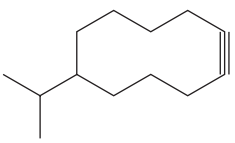
Name the following compounds:

(a) 

(b) 

(c) 

(d) 

(e) 

(f) $CH_3CH{=}CHCH{=}CHC{\equiv}CCH_3$

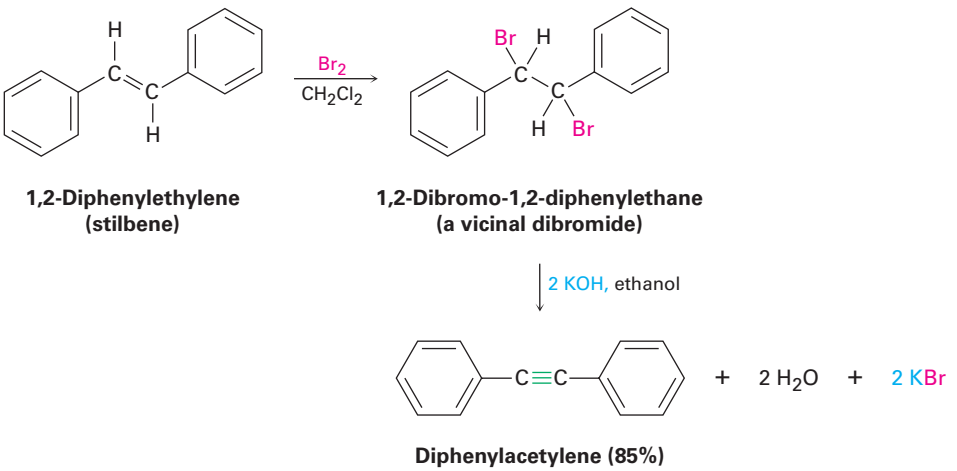
Problem 9.2

There are seven isomeric alkynes with the formula C_6H_{10}. Draw and name them.

9.2 Preparation of Alkynes: Elimination Reactions of Dihalides

Alkynes can be prepared by the elimination of HX from alkyl halides in much the same manner as alkenes **(Section 8.1)**. Treatment of a 1,2-dihaloalkane (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 until 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.

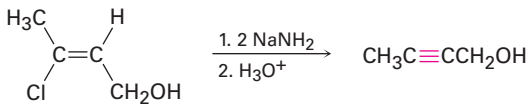


1,2-Diphenylethylene (stilbene)

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. (*Remember:* A *vinylic* substituent is one that is attached to a double-bond carbon.) This is indeed the case. For example:



(*Z*)-3-Chloro-2-buten-1-ol **2-Butyn-1-ol**

9.3 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 9.1)**. 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.

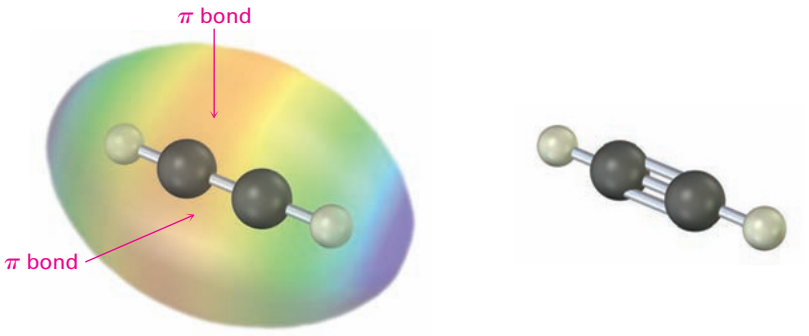
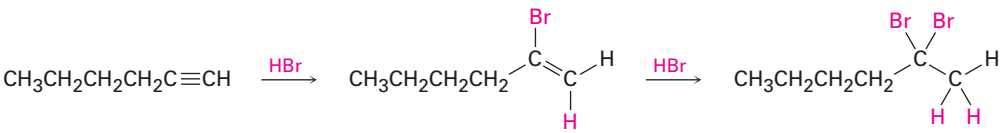
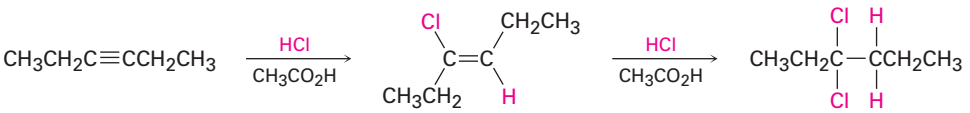


Figure 9.1 The structure of acetylene, H—C≡C—H. The H–C≡C bond angles are 180°, and the C≡C bond length is 120 pm. The electrostatic potential map shows that the π bonds create a **negative belt** around the molecule.

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 after 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, results in the product.

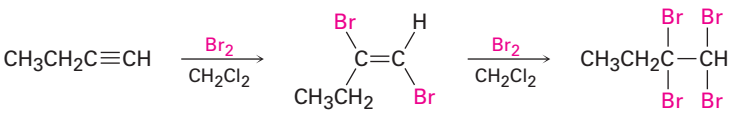


1-Hexyne **2-Bromo-1-hexene** **2,2-Dibromohexane**



3-Hexyne **(*Z*)-3-Chloro-3-hexene** **3,3-Dichlorohexane**

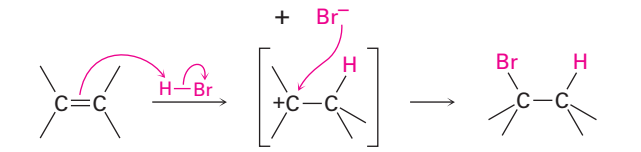
Bromine and chlorine also add to alkynes to give addition products, and trans stereochemistry again results.

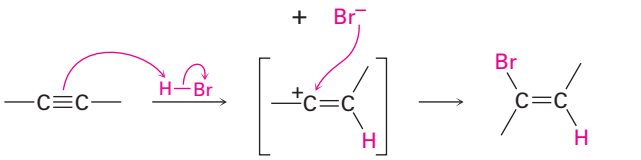


1-Butyne **(*E*)-1,2-Dibromo-1-butene** **1,1,2,2-Tetrabromobutane**

The mechanism of alkyne additions is similar but not identical to that of alkene additions. When an electrophile such as HBr adds to an alkene, the reaction takes place in two steps and involves an alkyl carbocation intermediate

(Sections 7.7 and 7.8). If HBr were to add by the same mechanism to an *alkyne,* an analogous *vinylic* carbocation would be formed as the intermediate.





A vinylic carbocation has an *sp*-hybridized carbon and generally forms less readily than an alkyl carbocation **(Figure 9.2)**. 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.

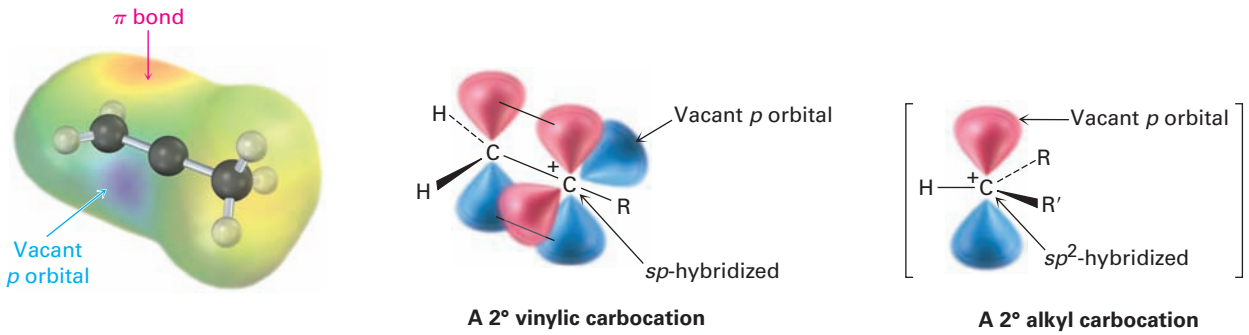
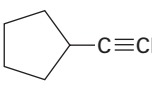


Figure 9.2 The structure of a secondary vinylic carbocation. The cationic carbon atom is *sp*-hybridized and has a vacant *p* orbital perpendicular to the plane of the π bond orbitals. Only one R group is attached to the positively charged carbon rather than two, as in a secondary alkyl carbocation. 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.

Problem 9.3

What products would you expect from the following reactions?

(a) $CH_3CH_2CH_2C{\equiv}CH + 2\ Cl_2 \longrightarrow$?

(b)  + 1 HBr ⟶ ?

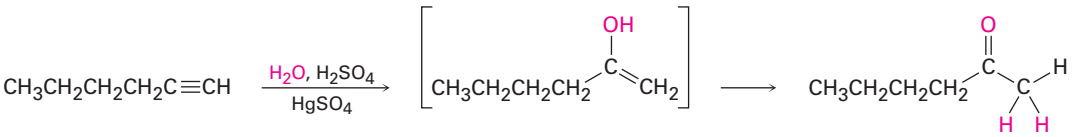
(c) $CH_3CH_2CH_2CH_2C{\equiv}CCH_3 + 1\ HBr \longrightarrow$?

9.4 Hydration of Alkynes

Like alkenes **(Sections 8.4 and 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 product actually isolated from alkyne hydration is not the vinylic alcohol, or **enol** (*ene* + *ol*), but is instead a ketone. Although the enol is an intermediate in the reaction, it immediately rearranges to 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 under spontaneous interconversion accompanied by the change in position of a hydrogen. With few exceptions, the keto–enol tautomeric equilibrium lies on the side of the ketone; enols are almost never isolated. We'll look more closely at this equilibrium in **Section 22.1**.

Enol tautomer (less favored) **Keto tautomer (more favored)**

As shown in **Figure 9.3**, the mechanism of the mercury(II)-catalyzed alkyne hydration reaction is analogous to the oxymercuration reaction of alkenes **(Section 8.4)**. Electrophilic addition of mercury(II) ion to the alkyne gives a vinylic cation, which reacts with water and loses a proton to yield a mercury-containing enol intermediate. In contrast with alkene oxymercuration, however, no treatment with $NaBH_4$ is necessary to remove the mercury. The acidic reaction conditions alone are sufficient to effect replacement of mercury by hydrogen. Tautomerization then gives the ketone.

Figure 9.3 | MECHANISM

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.

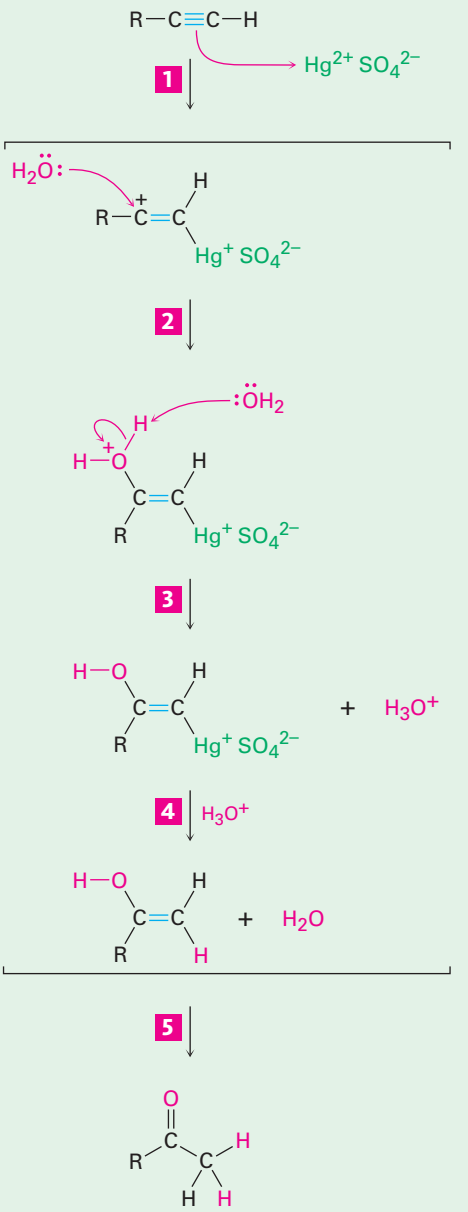
1 The alkyne uses a pair of electrons to attack the electrophilic mercury(II) ion, yielding a mercury-containing vinylic carbocation intermediate.

2 Nucleophilic attack of water on the carbocation forms a C–O bond and yields a protonated mercury-containing enol.

3 Abstraction of H^+ from the protonated enol by water gives an organomercury compound.

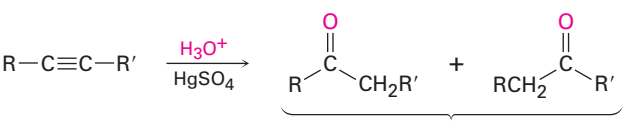
4 Replacement of Hg^{2+} by H^+ occurs to give a neutral enol.

5 The enol undergoes tautomerization to give the final ketone product.

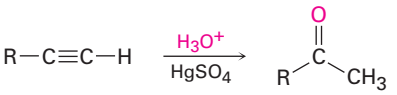


A mixture of both possible ketones results when an unsymmetrically substituted internal alkyne (RC≡CR′) is hydrated. The reaction is therefore most useful when applied to a terminal alkyne (RC≡CH) because only a methyl ketone is formed.

An internal alkyne



A terminal alkyne



A methyl ketone

Problem 9.4

What product would you obtain by hydration of the following alkynes?

(a) $CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3$ **(b)** $CH_3CHCH_2C{\equiv}CCH_2CH_2CH_3$ (CH_3 on the CH)

Problem 9.5

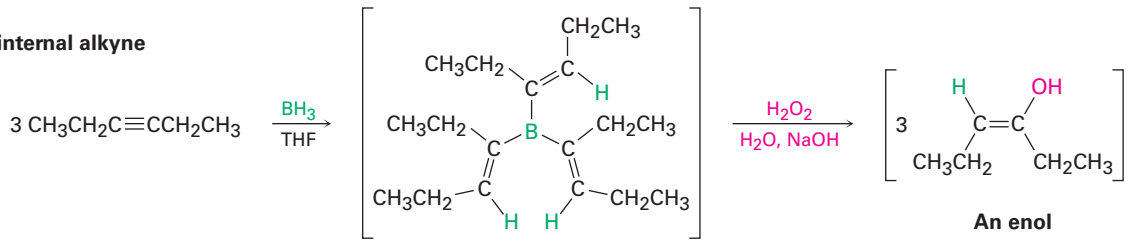
What alkynes would you start with to prepare the following ketones?

(a) $CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ **(b)** $CH_3CH_2\overset{O}{\overset{\|}{C}}CH_2CH_3$

Hydroboration–Oxidation of Alkynes

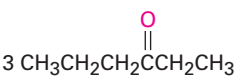
Borane adds rapidly to an alkyne just as it does to an alkene, and the resulting vinylic borane can be oxidized by H_2O_2 to yield an enol. Tautomerization then gives either a ketone or an aldehyde, depending on the structure of the alkyne reactant. Hydroboration–oxidation of an internal alkyne such as 3-hexyne gives a ketone, and hydroboration–oxidation of a terminal alkyne gives an aldehyde. Note that the relatively unhindered terminal alkyne undergoes two additions, giving a doubly hydroborated intermediate. Oxidation with H_2O_2 at pH 8 then replaces both boron atoms by oxygen and generates the aldehyde.

An internal alkyne



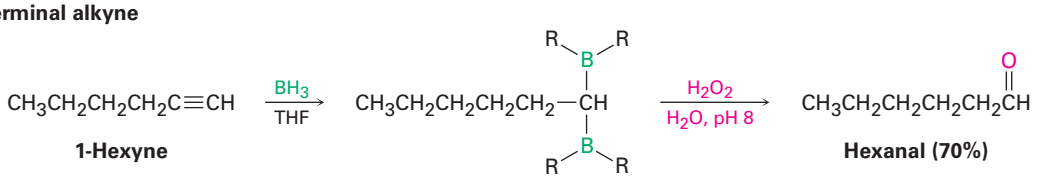
A vinylic borane

An enol



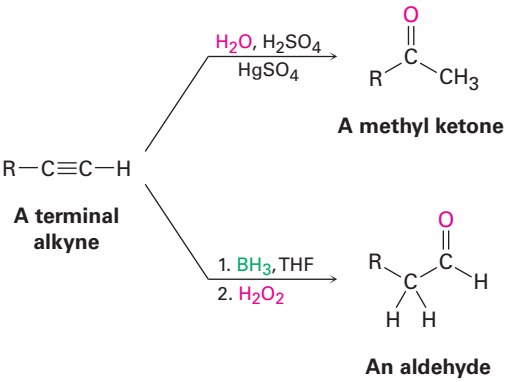
3-Hexanone

A terminal alkyne



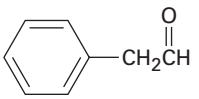
1-Hexyne **Hexanal (70%)**

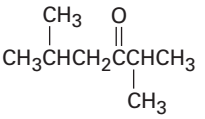
The hydroboration–oxidation sequence is complementary to the direct, mercury(II)-catalyzed hydration reaction of a terminal alkyne because different products result. Direct hydration with aqueous acid and mercury(II) sulfate leads to a methyl ketone, whereas hydroboration–oxidation of the same terminal alkyne leads to an aldehyde.



Problem 9.6

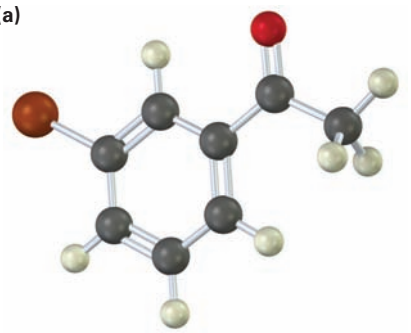
What alkyne would you start with to prepare each of the following compounds by a hydroboration–oxidation reaction?

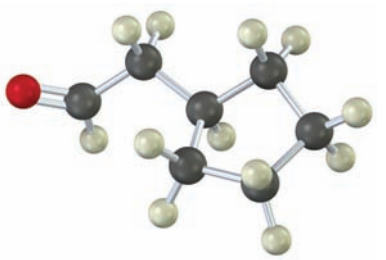
(a) 

(b) 

Problem 9.7

How would you prepare the following carbonyl compounds starting from an alkyne (reddish brown = Br)?

(a) 

(b) 

9.5 Reduction of Alkynes

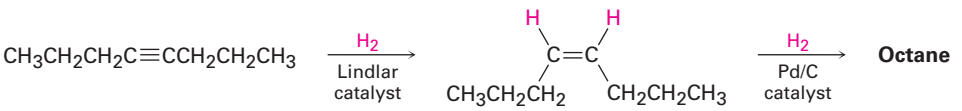
Alkynes are reduced to alkanes by addition of H_2 over a metal catalyst. The reaction occurs in two steps through an alkene intermediate, and

measurements show that the first step in the reaction is more exothermic than the second step.

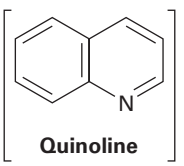
$$HC{\equiv}CH \xrightarrow[\text{Catalyst}]{H_2} H_2C{=}CH_2 \qquad \Delta H°_{\text{hydrog}} = -176 \text{ kJ/mol } (-42 \text{ kcal/mol})$$

$$H_2C{=}CH_2 \xrightarrow[\text{Catalyst}]{H_2} CH_3{-}CH_3 \qquad \Delta H°_{\text{hydrog}} = -137 \text{ kJ/mol } (-33 \text{ kcal/mol})$$

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.

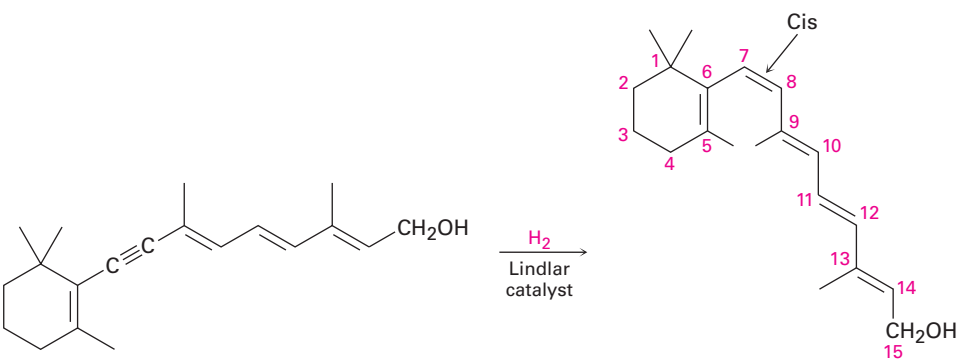


4-Octyne **cis-4-Octene**



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

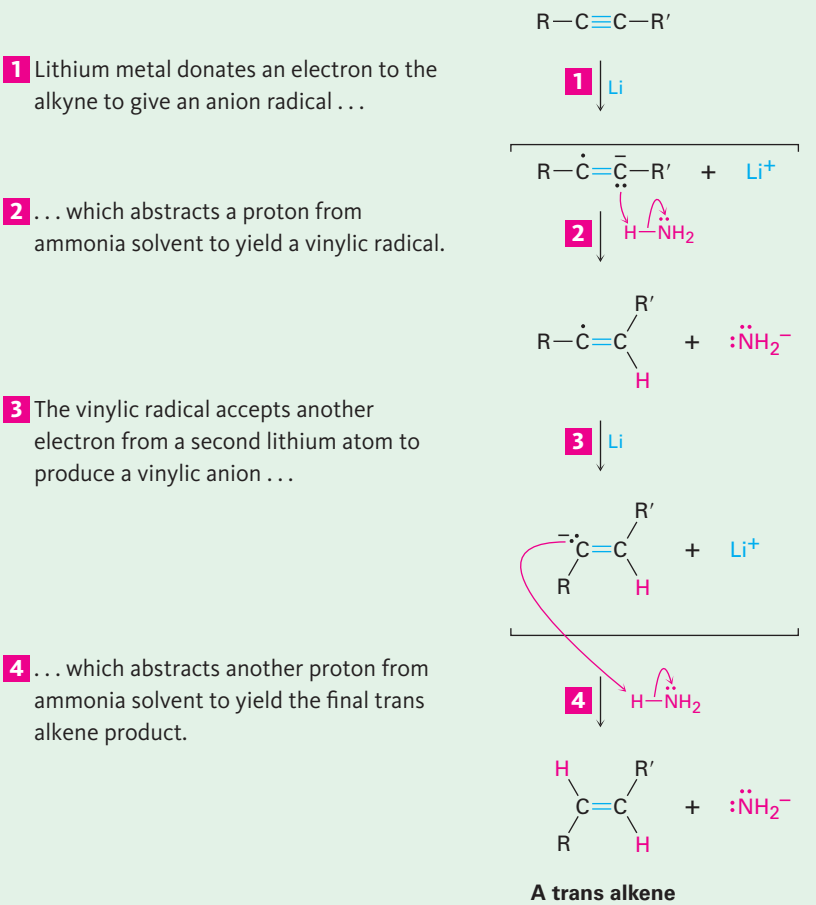
trans rather than cis alkenes. For example, 5-decyne gives *trans*-5-decene on treatment with lithium in liquid ammonia.

5-Decyne ***trans*-5-Decene (78%)**

Alkali metals dissolve in liquid ammonia at −33 °C to produce a deep blue solution containing the metal cation and ammonia-solvated electrons. When an alkyne is then added to the solution, reduction occurs by the mechanism shown in **Figure 9.4**. An electron first adds to the triple bond to yield an intermediate anion radical—a species that is both an anion (has a negative charge) and a radical (has an odd number of electrons). This anion radical is a strong base, able to remove H^+ from ammonia to give a vinylic radical. Addition of a second electron to the vinylic radical gives a vinylic anion, which abstracts a second H^+ from ammonia to give trans alkene product.

Figure 9.4 | MECHANISM

Mechanism of the lithium/ammonia reduction of an alkyne to produce a trans alkene.



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.

Problem 9.8

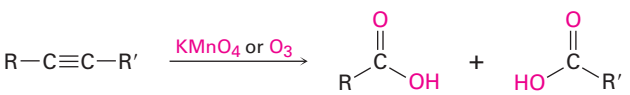
Using any alkyne needed, how would you prepare the following alkenes?

(a) *trans*-2-Octene **(b)** *cis*-3-Heptene **(c)** 3-Methyl-1-pentene

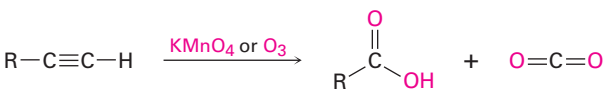
9.6 Oxidative Cleavage of Alkynes

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 we mention it only for completeness. A triple bond is generally less reactive than a double bond, and yields of cleavage products are sometimes 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

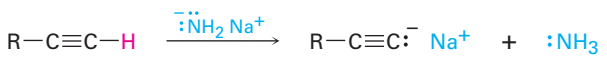


A terminal alkyne



9.7 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 an **acetylide anion** is formed.



A terminal alkyne **An 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 acid.

Where do hydrocarbons lie on the acidity scale? As the data in Table 9.1 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 9.1 Acidity of Simple Hydrocarbons

Family	Example	K_a	pK_a	
Alkyne	HC≡CH	10^{-25}	25	Stronger acid
Alkene	$H_2C{=}CH_2$	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 an sp^2-hybridized carbon with 33% *s* character, and an alkyl anion (sp^3) has only 25% *s* character. Because *s* orbitals are nearer the positive nucleus and lower in energy than *p* orbitals, the negative charge is stabilized to a greater extent in an orbital with higher *s* character **(Figure 9.5)**.

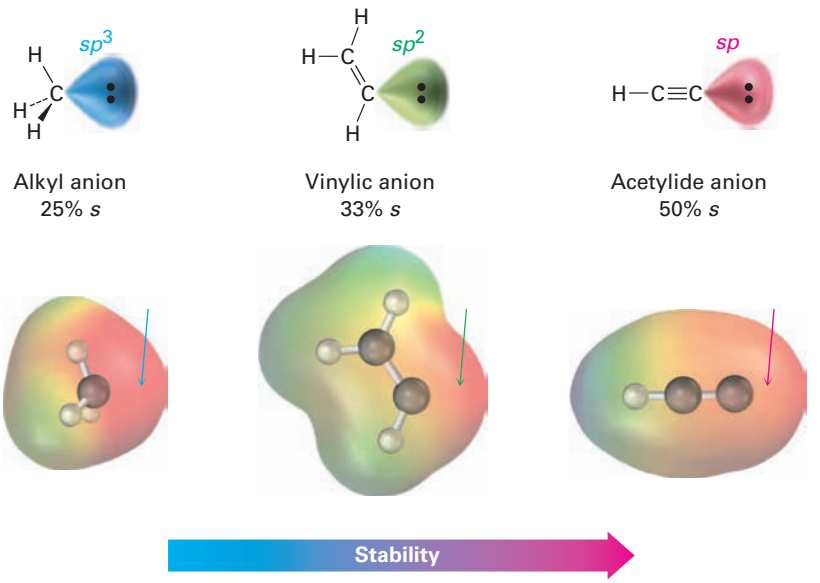


Figure 9.5 A comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with *sp* hybridization, has more *s* character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear less negative (red).

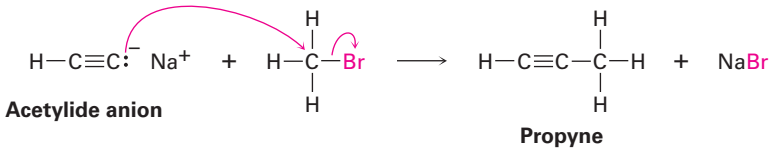
Problem 9.9

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)

9.8 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.



Acetylide anion

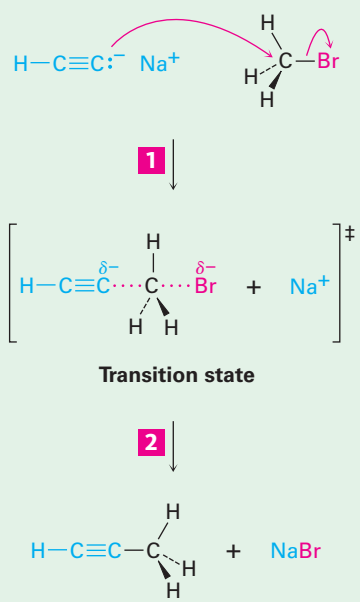
Propyne

We won't study the details of this substitution reaction until Chapter 11 but for now can picture it as happening by the pathway shown in **Figure 9.6**. The nucleophilic acetylide ion uses an electron pair to form a bond to the positively polarized, electrophilic carbon atom of bromomethane. As the new C–C bond forms, Br^- departs, taking with it the electron pair from the former C–Br bond and yielding propyne as product. We call such a reaction an **alkylation** because a new alkyl group has become attached to the starting alkyne.

Figure 9.6 | MECHANISM

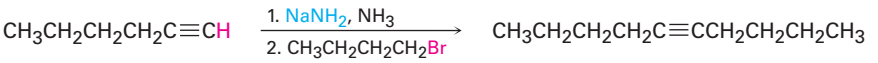
A mechanism for the alkylation reaction of acetylide anion with bromomethane to give propyne.

1 The nucleophilic acetylide anion uses its electron lone pair to form a bond to the positively polarized, electrophilic carbon atom of bromomethane. As the new C–C bond begins to form, the C–Br bond begins to break in the transition state.



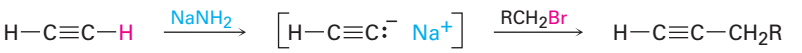
2 The new C–C bond is fully formed and the old C–Br bond is fully broken at the end of the reaction.

Alkyne alkylation is not limited to acetylene itself. Any terminal alkyne can be converted into its corresponding anion and then alkylated by treatment with an alkyl halide, yielding an internal alkyne. For example, conversion of 1-hexyne into its anion, followed by reaction with 1-bromobutane, yields 5-decyne.

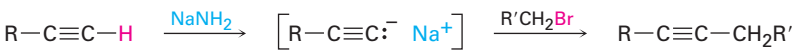


1-Hexyne **5-Decyne (76%)**

Because of its generality, acetylide alkylation is a good method for preparing substituted alkynes from simpler precursors. A terminal alkyne can be prepared by alkylation of acetylene itself, and an internal alkyne can be prepared by further alkylation of a terminal alkyne.

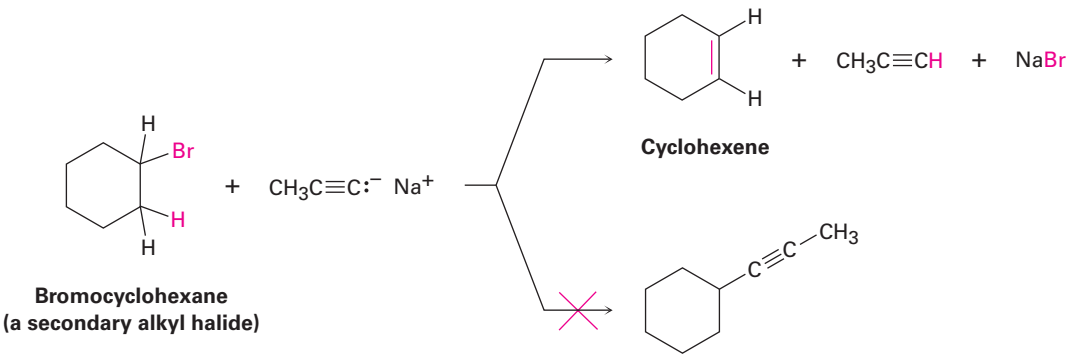


Acetylene **A terminal alkyne**



A terminal alkyne **An internal alkyne**

The alkylation reaction is limited to the use of primary alkyl bromides and alkyl iodides because acetylide ions are sufficiently strong bases to cause elimination instead of substitution when they react with secondary and tertiary alkyl halides. For example, reaction of bromocyclohexane with propyne anion yields the elimination product cyclohexene rather than the substitution product 1-propynylcyclohexane.



Bromocyclohexane (a secondary alkyl halide)

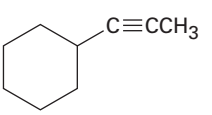
Cyclohexene

Not formed

Problem 9.10

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)**



Problem 9.11

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.

9.9 An Introduction to Organic Synthesis

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 our purpose 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 fit 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.

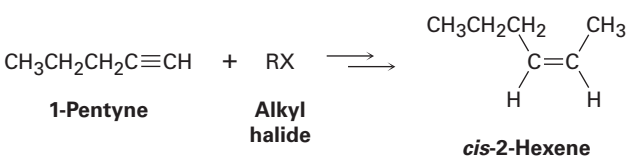
There's no secret to planning an organic synthesis: all it takes is a knowledge of the different reactions and some practice. The only real trick is to *work backward* in what is often called a **retrosynthetic** direction. Don't look at a potential starting material and ask yourself what reactions it 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.

Devising a Synthesis Route

Worked Example 9.1

Synthesize *cis*-2-hexene from 1-pentyne and an alkyl halide. More than one step is needed.

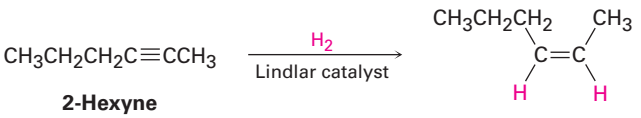


1-Pentyne **Alkyl halide** ***cis*-2-Hexene**

Strategy

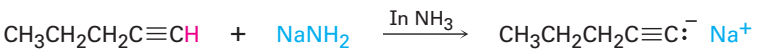
When undertaking any synthesis problem, you should look at the product, identify the functional groups it contains, and then ask yourself how those functional groups can be prepared. Always work retrosynthetically, one step at a time.

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.

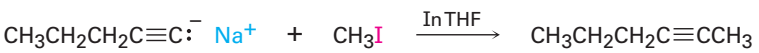


2-Hexyne ***cis*-2-Hexene**

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.



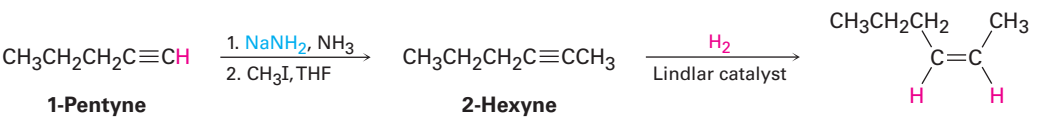
1-Pentyne



2-Hexyne

Solution

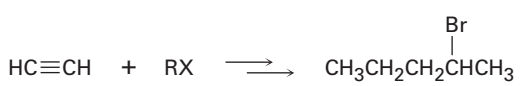
cis-2-Hexene can be synthesized from the given starting materials in three steps.



1-Pentyne **2-Hexyne** ***cis*-2-Hexene**

Worked Example 9.2 Devising a Synthesis Route

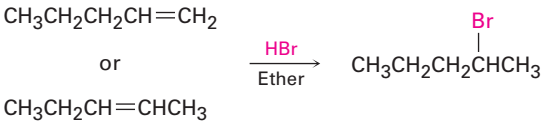
Synthesize 2-bromopentane from acetylene and an alkyl halide. More than one step is needed.



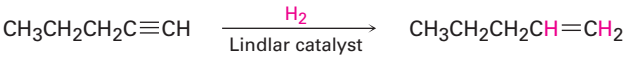
Acetylene **Alkyl halide** **2-Bromopentane**

Strategy

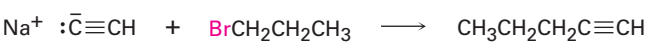
Identify the functional group in the product (an alkyl bromide) and work the problem retrosynthetically. What is an immediate precursor of an alkyl bromide? Perhaps an alkene plus HBr. Of the two possibilities, Markovnikov addition of HBr to 1-pentene looks like a better choice than addition to 2-pentene 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.

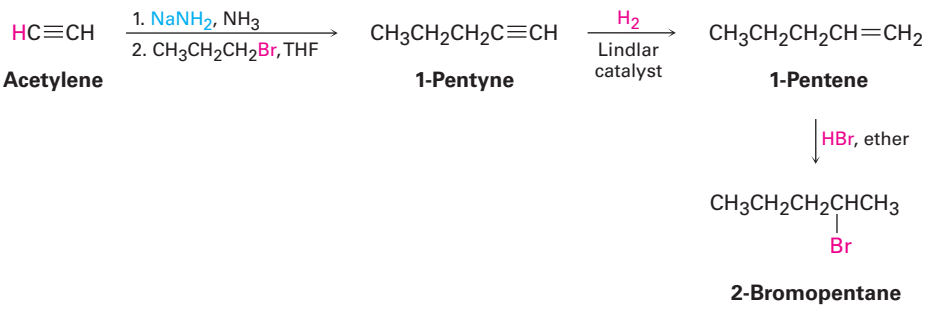


What is an immediate precursor of a terminal alkyne? Perhaps sodium acetylide and an alkyl halide.



Solution

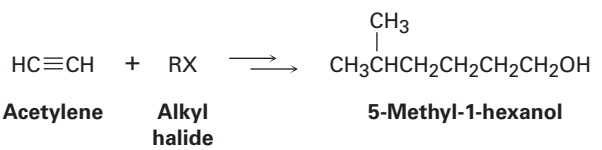
The desired product can be synthesized in four steps from acetylene and 1-bromopropane.



Devising a Synthesis Route

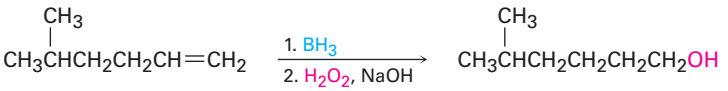
Worked Example 9.3

Synthesize 5-methyl-1-hexanol (5-methyl-1-hydroxyhexane) from acetylene and an alkyl halide.

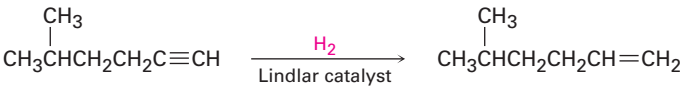


Strategy

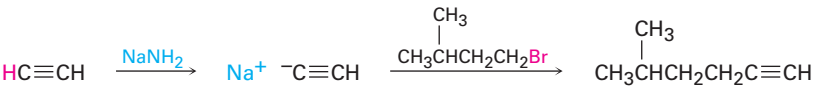
What is an immediate precursor of a primary alcohol? Perhaps a terminal alkene, which could be hydrated with non-Markovnikov regiochemistry by reaction with borane followed by oxidation with H_2O_2.



What is an immediate precursor of a terminal alkene? Perhaps a terminal alkyne, which could be reduced.

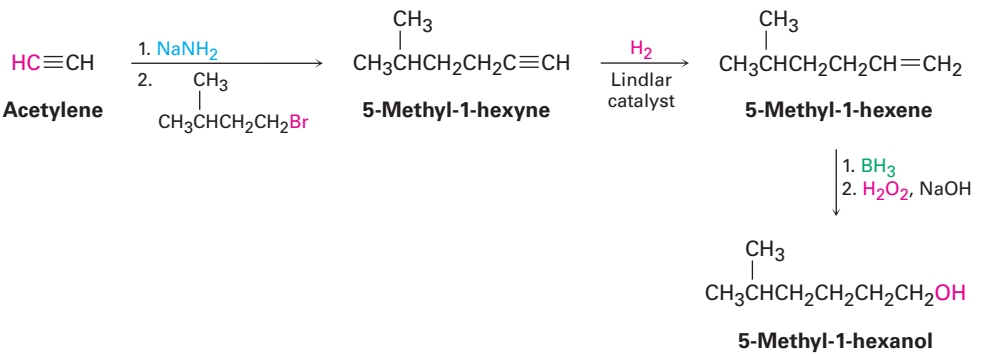


What is an immediate precursor of 5-methyl-1-hexyne? Perhaps acetylene and 1-bromo-3-methylbutane.



Solution

The synthesis can be completed in four steps from acetylene and 1-bromo-3-methylbutane:



Problem 9.12

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

Problem 9.13

Beginning with acetylene and any alkyl halide needed, how would you synthesize the following compounds?

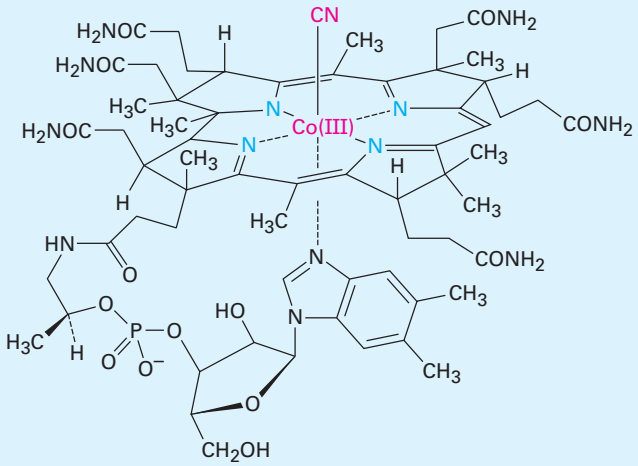
(a) Decane **(b)** 2,2-Dimethylhexane **(c)** Hexanal **(d)** 2-Heptanone

A DEEPER LOOK

The Art of Organic Synthesis

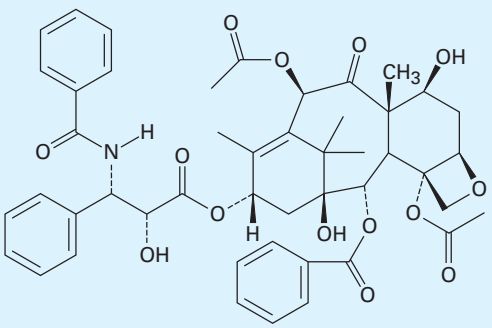
If you think some of the synthesis problems at the end of this chapter are hard, try devising a synthesis of vitamin B_{12} starting only from simple substances you can buy in a chemical catalog. This extraordinary achievement was reported in 1973 as the culmination of a collaborative effort headed by 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.

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.



Vitamin B_{12}

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 for the way in which 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.



Paclitaxel (Taxol)

(continued)

(continued)

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 synthesis that a point is reached at which the planned route fails. At such a time, the only alternatives are 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.

Summary

Key words

acetylide anion, 325
alkylation, 327
alkyne (RC≡CR), 314
enol, 319
retrosynthetic, 329
tautomer, 319

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 to look 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 good ones are the alkylation of an acetylide anion with a primary alkyl halide and the twofold elimination of HX from a vicinal dihalide.

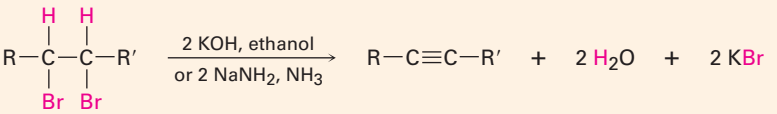
The chemistry of alkynes is dominated by electrophilic addition reactions, similar to those of alkenes. Alkynes react with HBr and HCl to yield vinylic halides and with Br_2 and Cl_2 to yield 1,2-dihalides (vicinal dihalides). Alkynes can be hydrated by reaction with aqueous sulfuric acid in the presence 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.

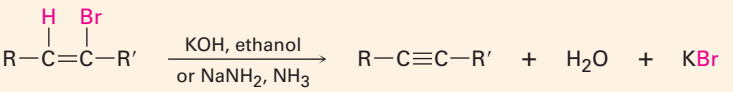
Alkynes can be reduced to yield alkenes and alkanes. Complete reduction of the triple bond over a palladium hydrogenation catalyst yields an alkane; partial reduction by catalytic hydrogenation over a Lindlar catalyst yields a cis alkene. Reduction of the alkyne with lithium in ammonia yields a trans 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.

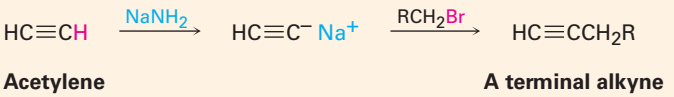
Summary of Reactions

1. Preparation of alkynes
   (a) Dehydrohalogenation of vicinal dihalides (Section 9.2)

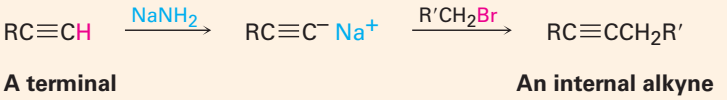




   (b) Alkylation of acetylide anions (Section 9.8)

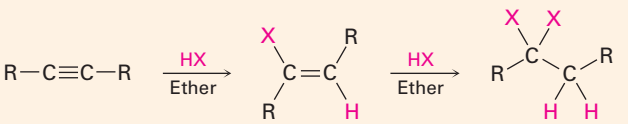


Acetylene **A terminal alkyne**

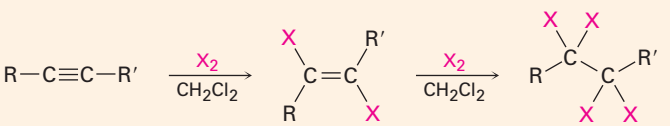


A terminal alkyne **An internal alkyne**

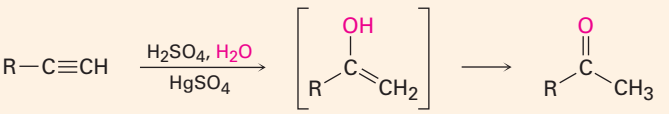
2. Reactions of alkynes
   (a) Addition of HCl and HBr (Section 9.3)



   (b) Addition of Cl_2 and Br_2 (Section 9.3)



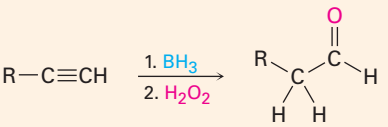
   (c) Hydration (Section 9.4)
      (1) Mercuric sulfate catalyzed



An enol **A methyl ketone**

(continued)

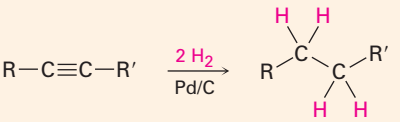
(2) Hydroboration–oxidation

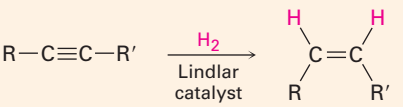


An aldehyde

(d) Reduction (Section 9.5)

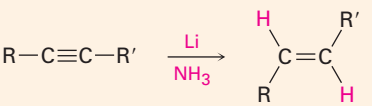
(1) Catalytic hydrogenation





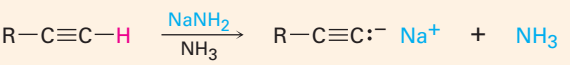
A cis alkene

(2) Lithium in liquid ammonia



A trans alkene

(e) Conversion into acetylide anions (Section 9.7)



Exercises

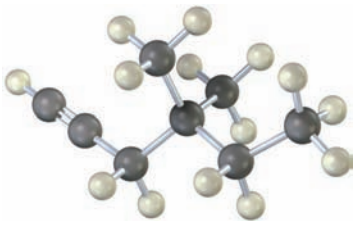
Visualizing Chemistry

OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

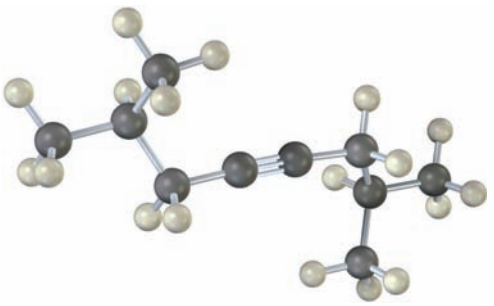
(Problems 9.1–9.13 appear within the chapter.)

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)

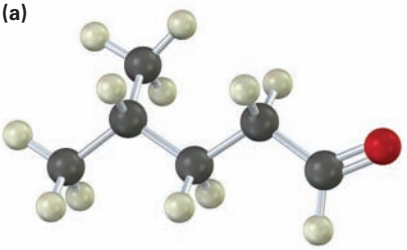


(b)

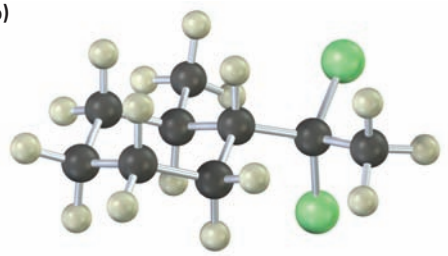


9.15 From what alkyne might each of the following substances have been made? (Green = Cl.)

(a)

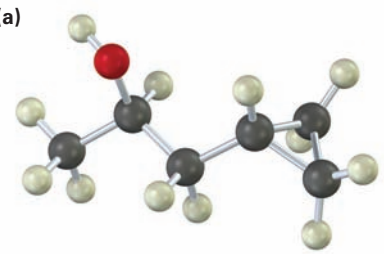


(b)

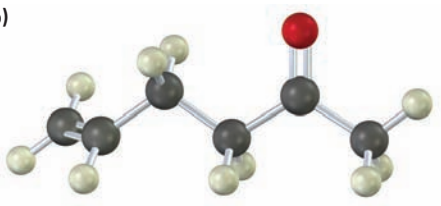


9.16 How would you prepare the following substances, starting from any compounds having four carbons or fewer?

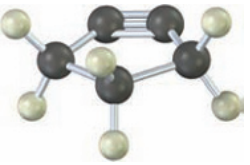
(a)



(b)



9.17 The following cycloalkyne is too unstable to exist. Explain.

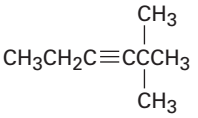


Additional Problems

Naming Alkynes

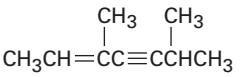
9.18 Give IUPAC names for the following compounds:

(a)

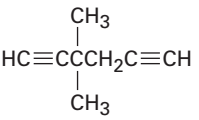


(b) $CH_3C{\equiv}CCH_2C{\equiv}CCH_2CH_3$

(c)

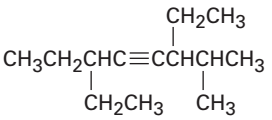


(d)



(e) $H_2C{=}CHCH{=}CHC{\equiv}CH$

(f)



9.19 Draw structures corresponding to the following names:

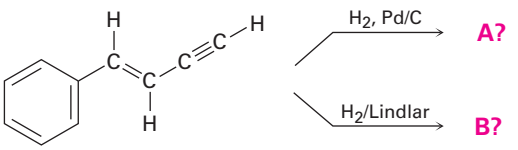
(a) 3,3-Dimethyl-4-octyne
(b) 3-Ethyl-5-methyl-1,6,8-decatriyne
(c) 2,2,5,5-Tetramethyl-3-hexyne
(d) 3,4-Dimethylcyclodecyne
(e) 3,5-Heptadien-1-yne
(f) 3-Chloro-4,4-dimethyl-1-nonen-6-yne
(g) 3-*sec*-Butyl-1-heptyne
(h) 5-*tert*-Butyl-2-methyl-3-octyne

9.20 The following two hydrocarbons have been isolated from various plants in the sunflower family. Name them according to IUPAC rules.

(a) $CH_3CH{=}CHC{\equiv}CC{\equiv}CCH{=}CHCH{=}CHCH{=}CH_2$ (all trans)
(b) $CH_3C{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CC{\equiv}CCH{=}CH_2$

Reactions of Alkynes

9.21 Predict the products of the following reactions:



9.22 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

9.23 Predict the products from reaction of 5-decyne with the following reagents:

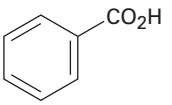
(a) H_2, Lindlar catalyst **(b)** Li in NH_3
(c) 1 equiv Br_2 **(d)** BH_3 in THF, then H_2O_2, OH^-
(e) H_2O, H_2SO_4, $HgSO_4$ **(f)** Excess H_2, Pd/C catalyst

9.24 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, $HgSO_4$

9.25 Propose structures for hydrocarbons that give the following products on oxidative cleavage by $KMnO_4$ or O_3:

(a) CO_2 + $CH_3(CH_2)_5CO_2H$

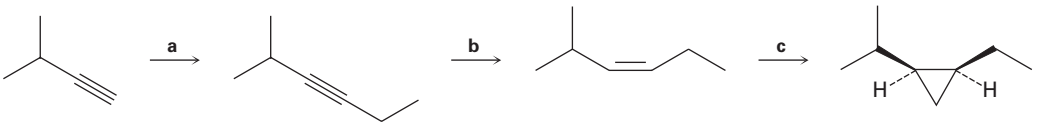
(b) CH_3CO_2H + 

(c) $HO_2C(CH_2)_8CO_2H$

(d) CH_3CHO + $CH_3CCH_2CH_2CO_2H$ + CO_2

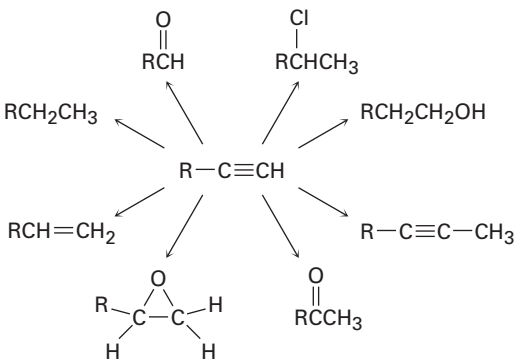
(e) $HCCH_2CH_2CH_2CH_2CCO_2H$ + CO_2

9.26 Identify the reagents **a–c** in the following scheme:



Organic Synthesis

9.27 How would you carry out the following conversions? More than one step may be needed in some instances.

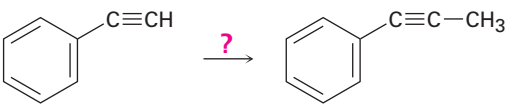


9.28 How would you carry out the following reactions?

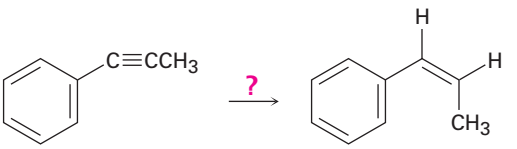
(a)

(b) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(c)



(d)



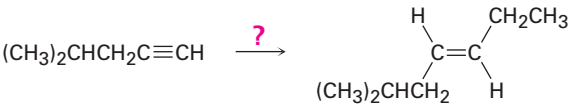
(e) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CO_2H$

(f) $CH_3CH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{(2 steps)}]{?} CH_3CH_2CH_2CH_2C{\equiv}CH$

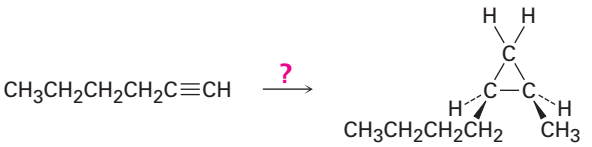
9.29 Each of the following syntheses requires more than one step. How would you carry them out?

(a) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

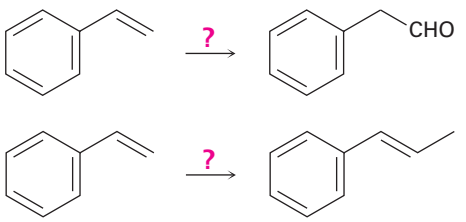
(b)



9.30 How would you carry out the following transformation? More than one step is needed.



9.31 How would you carry out the following conversions? More than one step is needed in each case.

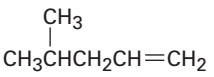


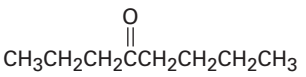
9.32 Synthesize the following compounds using 1-butyne as the only source of carbon, along with any inorganic reagents you need. More than one step may be needed.

(a) 1,1,2,2-Tetrachlorobutane **(b)** 1,1-Dichloro-2-ethylcyclopropane

9.33 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.

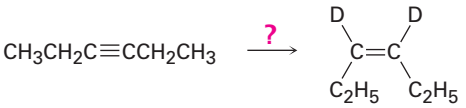
(a) $CH_3CH_2CH_2C{\equiv}CH$ **(b)** $CH_3CH_2C{\equiv}CCH_2CH_3$

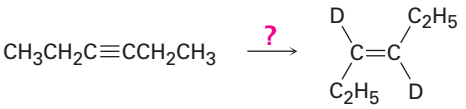
(c)


(d)


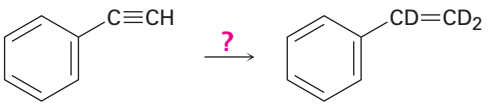
(e) $CH_3CH_2CH_2CH_2CH_2CHO$

9.34 How would you carry out the following reactions to introduce deuterium into organic molecules?

(a)


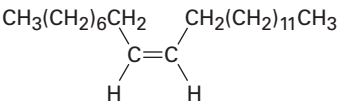
(b)


(c)


(d)


9.35 How would you prepare cyclodecyne starting from acetylene and any alkyl halide needed?

9.36 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

9.37 A hydrocarbon of unknown structure has the formula C_8H_{10}. On catalytic hydrogenation over the Lindlar catalyst, 1 equivalent of H_2 is absorbed. On hydrogenation over a palladium catalyst, 3 equivalents of H_2 are absorbed.

(a) How many degrees of unsaturation are present in the unknown?
(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.

9.38 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**?

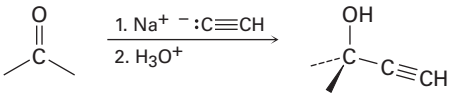
9.39 Hydrocarbon **A** has the formula $C_{12}H_8$. It absorbs 8 equivalents of H_2 on catalytic reduction over a palladium catalyst. On ozonolysis, only two products are formed: oxalic acid (HO_2CCO_2H) and succinic acid ($HO_2CCH_2CH_2CO_2H$). Write the reactions, and propose a structure for **A**.

9.40 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

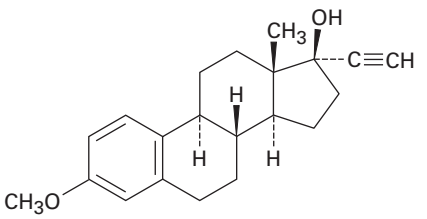
(b) *cis*-5-Decene $\xrightarrow{?}$ *trans*-5-Decene

9.41 Organometallic reagents such as sodium acetylide undergo an addition reaction with ketones, giving alcohols:



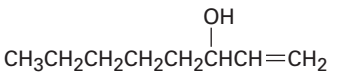
How might you use this reaction to prepare 2-methyl-1,3-butadiene, the starting material used in the manufacture of synthetic rubber?

9.42 The oral contraceptive agent Mestranol is synthesized using a carbonyl addition reaction like that shown in Problem 9.41. Draw the structure of the ketone needed.



Mestranol

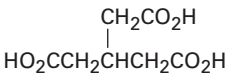
9.43 1-Octen-3-ol, a potent mosquito attractant commonly used in mosquito traps, can be prepared in two steps from hexanal, $CH_3CH_2CH_2CH_2CH_2CHO$. The first step is an acetylide-addition reaction like that described in Problem 9.41. What is the structure of the product from the first step, and how can it be converted into 1-octen-3-ol?



1-Octen-3-ol

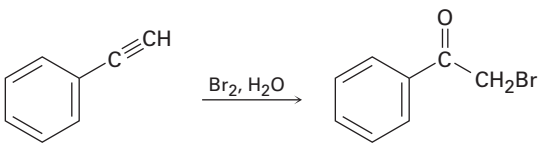
9.44 Erythrogenic acid, $C_{18}H_{26}O_2$, is an acetylenic fatty acid that turns a vivid red on exposure to light. On catalytic hydrogenation over a palladium catalyst, 5 equivalents of H_2 are absorbed, and stearic acid, $CH_3(CH_2)_{16}CO_2H$, is produced. Ozonolysis of erythrogenic acid gives four 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.

9.45 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.



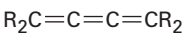
E

9.46 Terminal alkynes react with Br_2 and water to yield bromo ketones. For example:



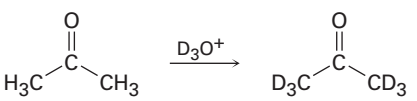
Propose a mechanism for the reaction. To what reaction of alkenes is the process analogous?

9.47 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

9.48 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**

10

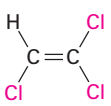
The gases released during volcanic eruptions contain large amounts of organohalides, including chloromethane, chloroform, dichlorodifluoromethane, and many others.

Organohalides

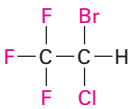
10.1 Names and Properties of Alkyl Halides
10.2 Preparing Alkyl Halides from Alkanes: Radical Halogenation
10.3 Preparing Alkyl Halides from Alkenes: Allylic Bromination
10.4 Stability of the Allyl Radical: Resonance Revisited
10.5 Preparing Alkyl Halides from Alcohols
10.6 Reactions of Alkyl Halides: Grignard Reagents
10.7 Organometallic Coupling Reactions
10.8 Oxidation and Reduction in Organic Chemistry
A Deeper Look—Naturally Occurring Organohalides

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.

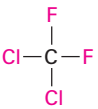
Halogen-substituted organic compounds are widespread in nature, and more than 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for example, is released in large amounts by ocean kelp, as well as by forest fires and volcanoes. Halogen-containing compounds also have a vast array of industrial applications, including their use as solvents, inhaled anesthetics in medicine, refrigerants, and pesticides.



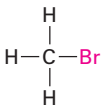
Trichloroethylene (a solvent)



Halothane (an inhaled anesthetic)

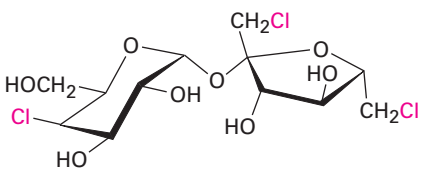


Dichlorodifluoromethane (a refrigerant)



Bromomethane (a fumigant)

Still other halo-substituted compounds are used as medicines and food additives. The nonnutritive sweetener sucralose, marketed as Splenda, contains four 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. We'll be concerned in this chapter, however, primarily with **alkyl halides**, compounds with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

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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 acts as a relatively simple model for many mechanistically similar but structurally more complex reactions found in biomolecules. We'll begin in 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.

10.1 Names and Properties of Alkyl Halides

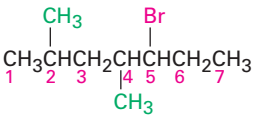
Although commonly called *alkyl halides,* halogen-substituted alkanes are named systematically as *haloalkanes* **(Section 3.4)**, treating the halogen as a substituent on a parent alkane chain. There are three steps:

STEP 1

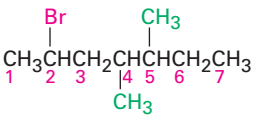
Find the longest chain, and name it as the parent. If a double or triple bond is present, the parent chain must contain it.

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.

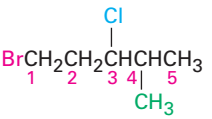


5-Bromo-2,4-dimethylheptane



2-Bromo-4,5-dimethylheptane

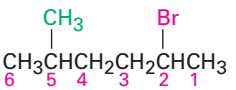
If different halogens are present, number all and list them in alphabetical order when writing the name.



1-Bromo-3-chloro-4-methylpentane

STEP 3

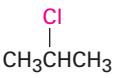
If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.



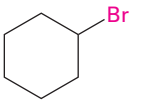
2-Bromo-5-methylhexane
(*Not* 5-bromo-2-methylhexane)

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)



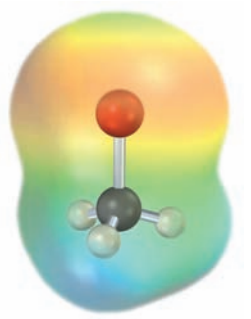
Bromocyclohexane (or cyclohexyl bromide)

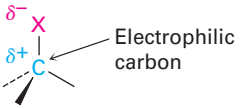
Halogens increase in size going down the periodic table, so the lengths of the corresponding carbon–halogen bonds increase accordingly (Table 10.1). In addition, C–X bond strengths decrease going down the periodic table. As we've been doing thus far, we'll continue to use the abbreviation X to represent any of the halogens F, Cl, Br, or I.

Table 10.1 A Comparison of the Halomethanes

Halomethane	Bond length (pm)	Bond strength (kJ/mol)	Bond strength (kcal/mol)	Dipole moment (*D*)
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 substantial 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.



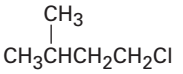


Problem 10.1

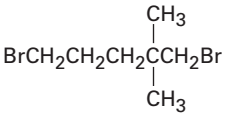
Give IUPAC names for the following alkyl halides:

(a) $CH_3CH_2CH_2CH_2I$

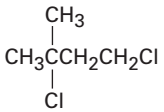
(b)



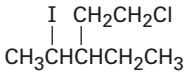
(c)



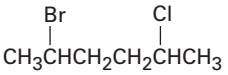
(d)



(e)



(f)



Problem 10.2

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

10.2 Preparing Alkyl Halides from Alkanes: Radical Halogenation

Simple alkyl halides can sometimes be prepared by reaction of an alkane with Cl_2 or Br_2 in the presence of light through a radical chain-reaction pathway **(Section 6.3)**. The mechanism is shown in **Figure 10.1** for chlorination.

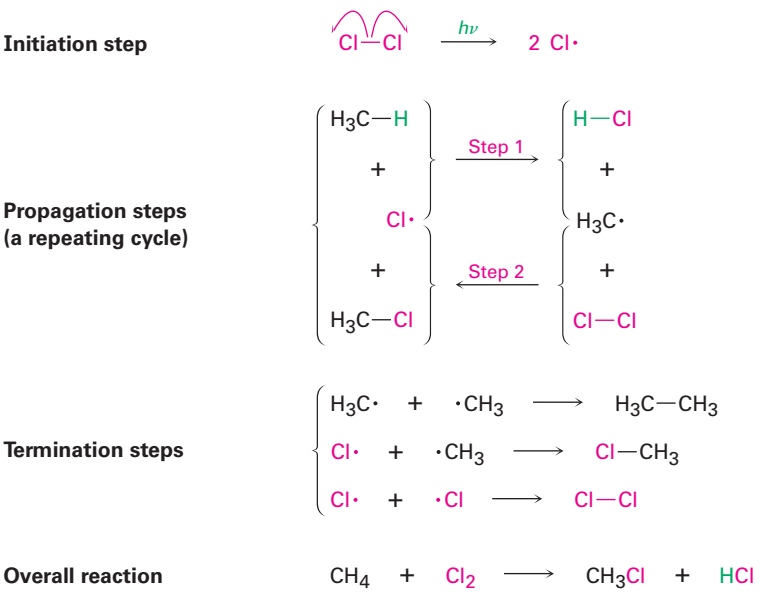
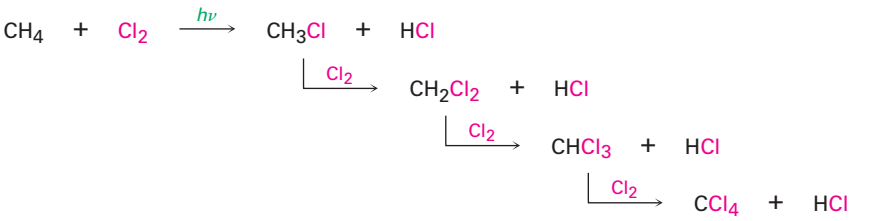


Figure 10.1 Mechanism of the radical chlorination of methane. Three kinds of steps are required: initiation, propagation, and termination. The propagation steps are a repeating cycle, with Cl· a reactant in step 1 and a product in step 2, and with ·CH_3 a product in step 1 and a reactant in step 2. (The symbol *hν* shown in the initiation step is the standard way of indicating irradiation with light.)

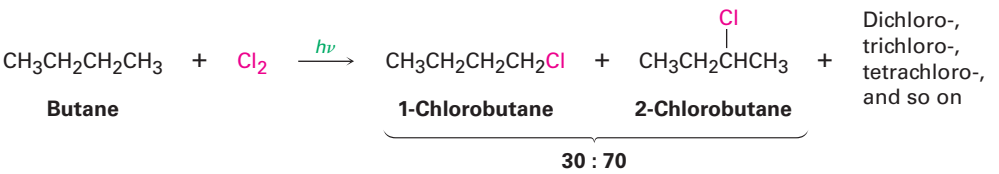
Recall from **Section 6.3** that radical substitution reactions require three kinds of steps: *initiation, propagation,* and *termination.* Once an initiation step has started the process by producing radicals, the reaction continues in a self-sustaining cycle. The cycle requires two repeating propagation 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.

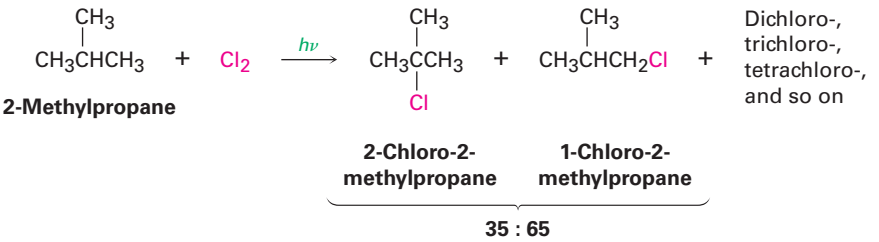
Although interesting from a mechanistic point of view, alkane halogenation is a poor synthetic method for preparing alkyl halides because mixtures of products invariably result. For example, chlorination of methane does not stop cleanly at the monochlorinated stage but continues to give a mixture of dichloro, trichloro, and even tetrachloro products.



The situation is even worse for chlorination of alkanes that have more than one sort of hydrogen. For example, chlorination of butane gives two monochlorinated products in a 30:70 ratio in addition to dichlorobutane, trichlorobutane, and so on.

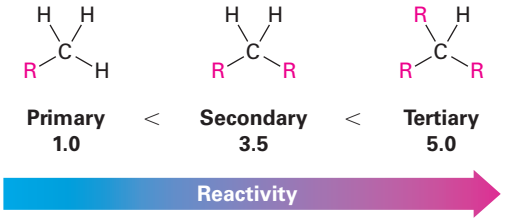


As another example, 2-methylpropane yields 2-chloro-2-methylpropane and 1-chloro-2-methylpropane in a 35:65 ratio, along with more highly chlorinated products.

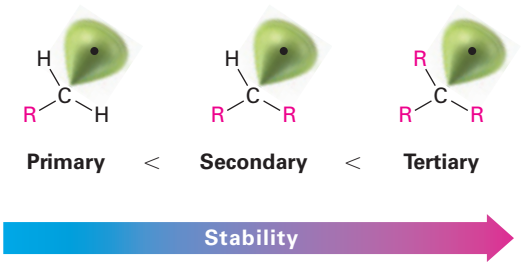


From these and similar reactions, it's possible to calculate a reactivity order toward chlorination for different sorts of hydrogen atoms in a molecule. Take the butane chlorination, for instance. Butane has six equivalent primary hydrogens ($-CH_3$) and four equivalent secondary hydrogens ($-CH_2-$). 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 on page 204. 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.



Problem 10.3

Draw and name all monochloro products you would expect to obtain from radical chlorination of 2-methylpentane. Which, if any, are chiral?

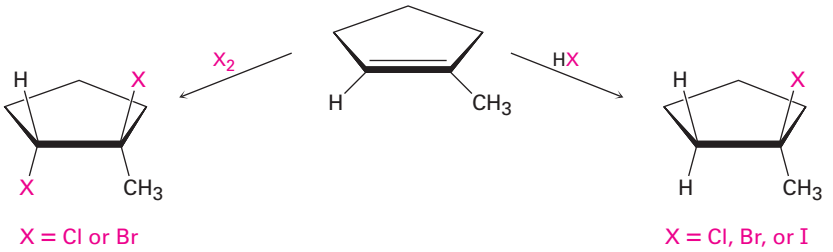
Problem 10.4

Taking the relative reactivities of 1°, 2°, and 3° hydrogen atoms into account, what product(s) would you expect to obtain from monochlorination of 2-methylbutane? What would the approximate percentage of each product be? (Don't forget to take into account the number of each sort of hydrogen.)

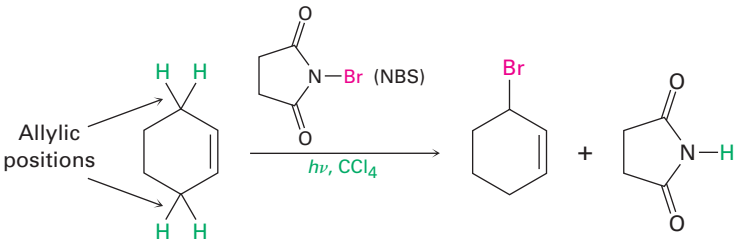
10.3 Preparing Alkyl Halides from Alkenes: Allylic Bromination

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 **(Sections 7.7 and 8.2)**. 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 method for preparing alkyl halides from alkenes is by reaction with *N*-bromosuccinimide (abbreviated NBS) in the presence of 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 10.2)**. 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.

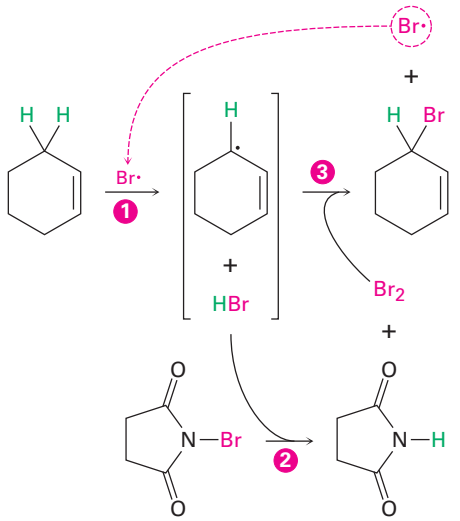
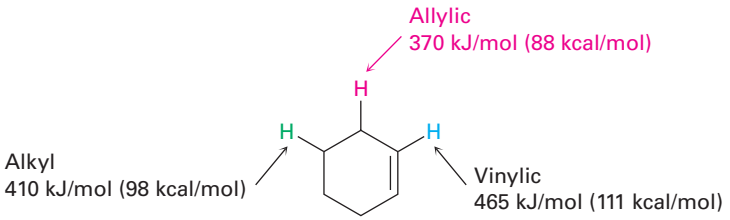


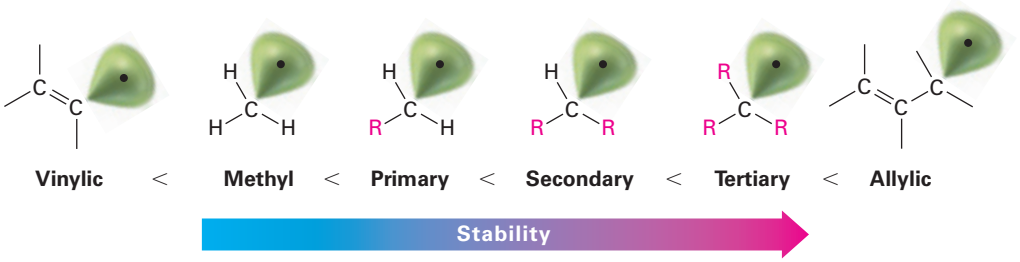
Figure 10.2 Mechanism of allylic bromination of an alkene with NBS. The process is a radical chain reaction in which (1) a Br• radical abstracts an allylic hydrogen atom of the alkene and gives an allylic radical plus HBr. (2) The HBr then reacts with NBS to form Br_2, which (3) reacts with the allylic radical to yield the bromoalkene product and a Br• radical that carries on 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.



10.4 Stability of the Allyl Radical: Resonance Revisited

To see why an allylic radical is so stable, look at the orbital picture in **Figure 10.3**. 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.

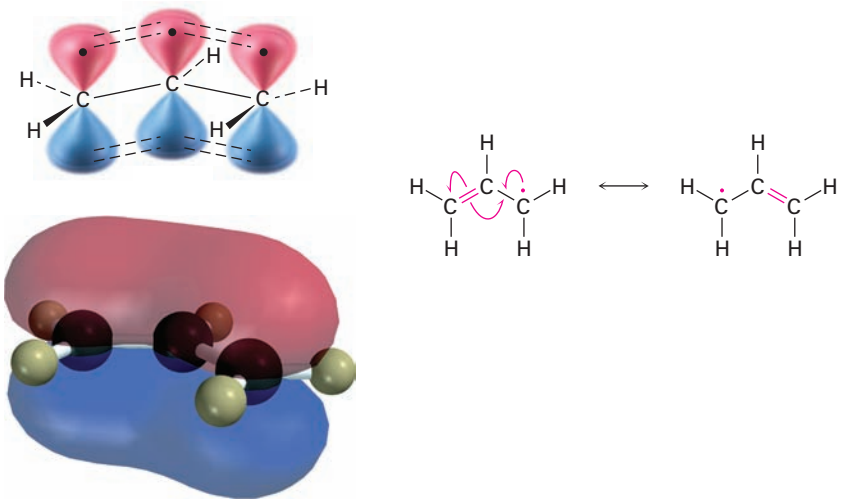


Figure 10.3 An orbital view of the allyl radical. The *p* orbital on the central carbon can overlap equally well with a *p* orbital on either neighboring carbon, giving rise to two equivalent resonance structures.

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 **Sections 2.4–2.6** to brush up on resonance.) As noted in **Section 2.5**, 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 10.3. This delocalization is particularly apparent in the so-called spin density surface in **Figure 10.4**, which shows the calculated location of the unpaired electron. The two terminal carbons share the unpaired electron equally.

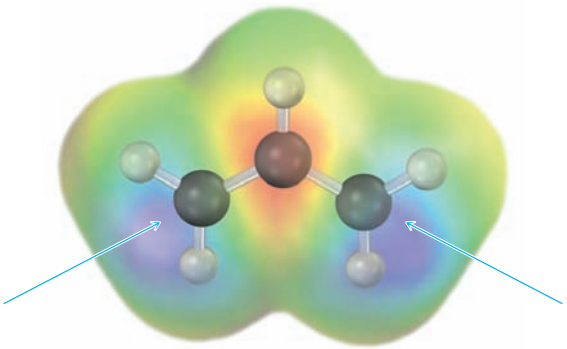
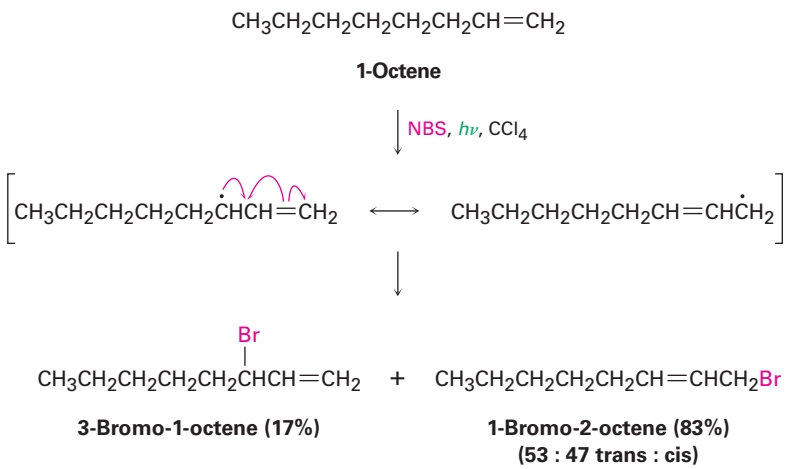
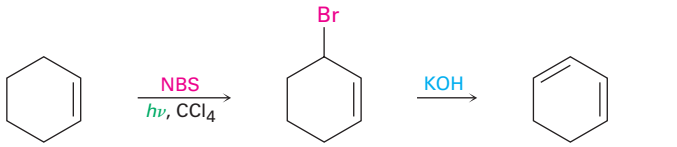


Figure 10.4 The spin density surface of the allyl radical locates the position of the **unpaired electron** and shows that it is equally shared between the two terminal carbons.

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.



Cyclohexene **3-Bromocyclohexene** **1,3-Cyclohexadiene**

Predicting the Product of an Allylic Bromination Reaction

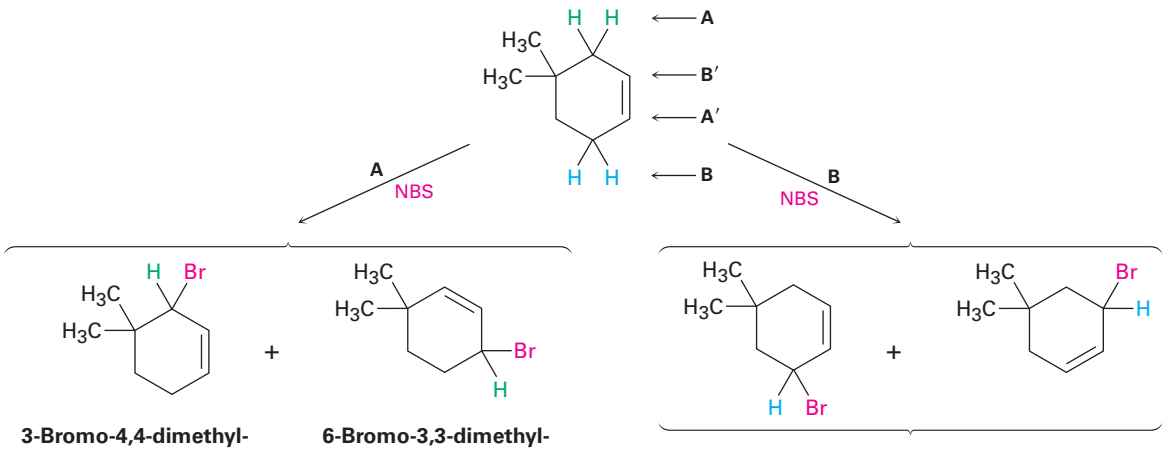
Worked Example 10.1

What products would you expect from 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.

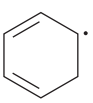
Solution



3-Bromo-4,4-dimethylcyclohexene **6-Bromo-3,3-dimethylcyclohexene** **3-Bromo-5,5-dimethylcyclohexene**

Problem 10.5

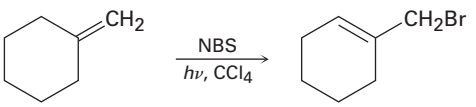
Draw three resonance forms for the cyclohexadienyl radical.



Cyclohexadienyl radical

Problem 10.6

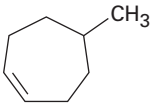
The major product of the reaction of methylenecyclohexane with *N*-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.

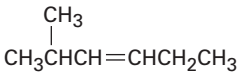


Major product

Problem 10.7

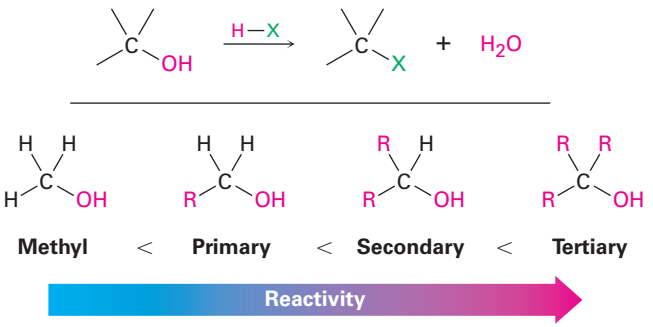
What products would you expect from reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

(a) 

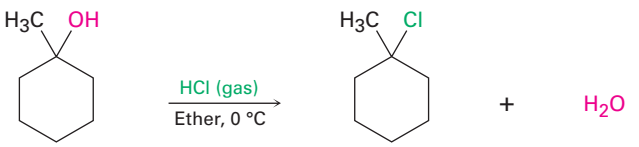
(b) 

10.5 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 17.4 and 17.5**. Because of the importance of the 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 11.5**, the reaction works best with tertiary alcohols, R_3COH. Primary and secondary alcohols react much more slowly and at higher temperatures.

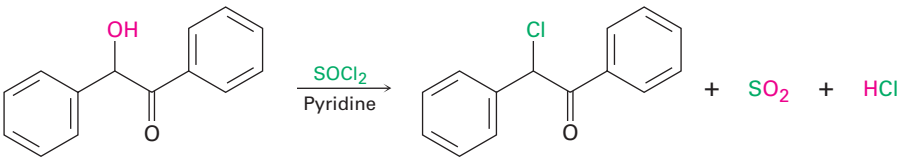


The reaction of HX with a tertiary alcohol is so rapid that it's often carried out simply by bubbling the pure HCl or HBr gas into a cold ether solution of the alcohol. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treating with HCl.

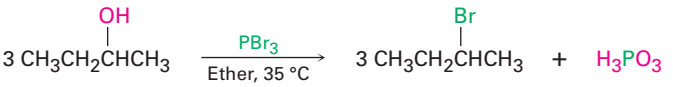


1-Methylcyclohexanol **1-Chloro-1-methylcyclohexane (90%)**

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.



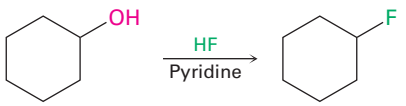
Benzoin **(86%)**



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 11.3**.

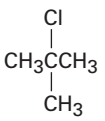
Alkyl fluorides can also be prepared from alcohols. Numerous alternative reagents are used for the reaction, including diethylaminosulfur trifluoride [$(CH_3CH_2)_2NSF_3$] and HF in pyridine solvent.

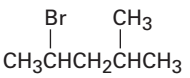


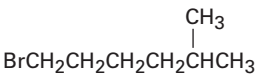
Cyclohexanol **Fluorocyclohexane (99%)**

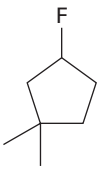
Problem 10.8

How would you prepare the following alkyl halides from the corresponding alcohols?

(a) 

(b) 

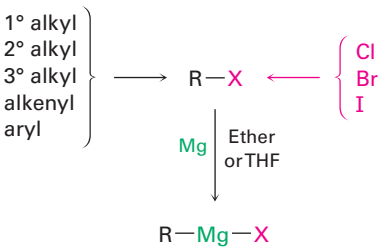
(c) 

(d) 

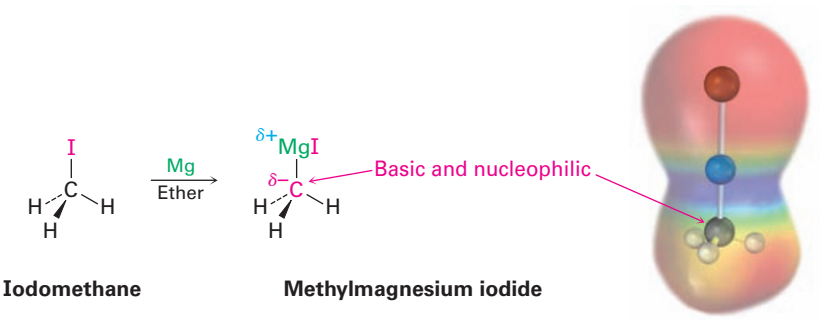
10.6 Reactions of Alkyl Halides: Grignard Reagents

Alkyl halides, RX, react with magnesium metal in ether or tetrahydrofuran (THF) solvent to yield alkylmagnesium halides, RMgX. The products, called **Grignard reagents** after their discoverer, Victor Grignard, are examples of

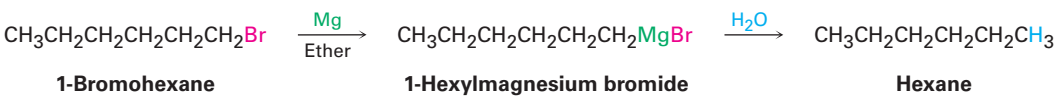
organometallic compounds because they contain a carbon–metal bond. In addition to alkyl halides, Grignard reagents can also be made from alkenyl (vinylic) and aryl (aromatic) halides. The halogen can be Cl, Br, or I, although chlorides are less reactive than bromides and iodides. Organofluorides rarely 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 9.7)**, carbon anions are very strong bases. Grignard reagents must therefore be protected from atmospheric moisture to prevent their being protonated and destroyed in an acid–base reaction: $R—Mg—X + H_2O \rightarrow R—H + HO—Mg—X$.



Grignard reagents themselves don't occur in living organisms, but they are useful carbon-based nucleophiles in several important laboratory reactions, which we'll look at in detail in Chapter 17. 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 in Chapter 29.

Problem 10.9

How strong a base would you expect a Grignard reagent to be? Look at Table 9.1 on page 326, and predict whether the following reactions will occur as written. (The pK_a of NH_3 is 35.)

(a) $CH_3MgBr + H{-}C{\equiv}C{-}H \rightarrow CH_4 + H{-}C{\equiv}C{-}MgBr$

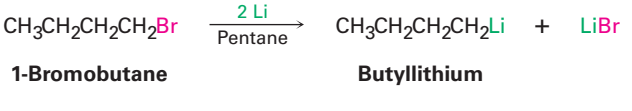
(b) $CH_3MgBr + NH_3 \rightarrow CH_4 + H_2N{-}MgBr$

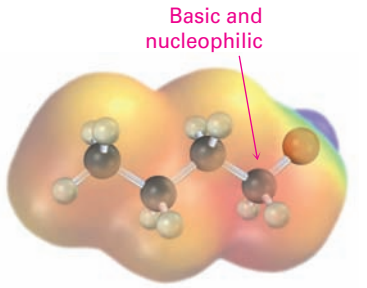
Problem 10.10

How might you replace a halogen substituent by a deuterium atom if you wanted to prepare a deuterated compound?

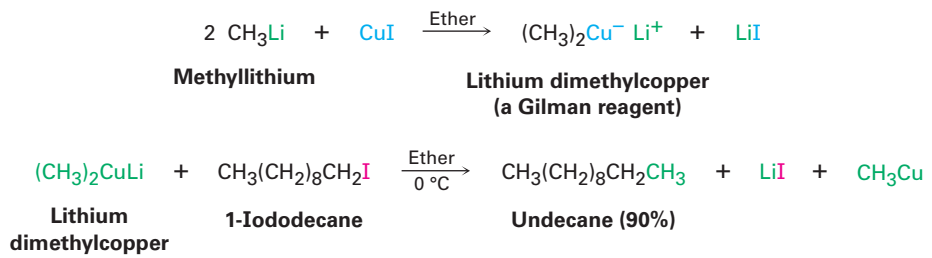
10.7 Organometallic Coupling Reactions

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.

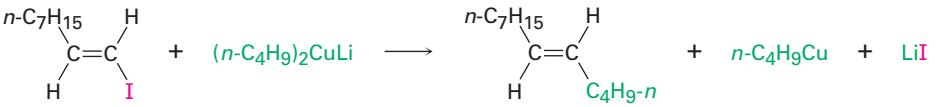




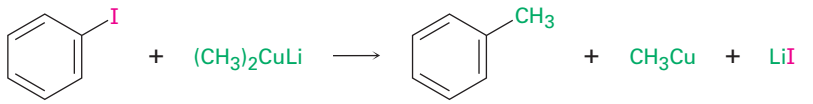
One particularly valuable reaction of alkyllithiums is in making lithium diorganocopper compounds, R_2CuLi, by reaction with copper(I) iodide in diethyl ether as solvent. Called **Gilman reagents**, lithium diorganocopper compounds are useful because they undergo a *coupling* reaction with organochlorides, bromides, and iodides (but not fluorides). One of the alkyl groups from the Gilman 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 90% yield.



This organometallic coupling reaction is useful in organic synthesis because it forms carbon–carbon bonds, thereby making possible the preparation of larger molecules from smaller ones. As the following examples indicate, the coupling reaction can be carried out on aryl and vinylic halides as well as on alkyl halides.

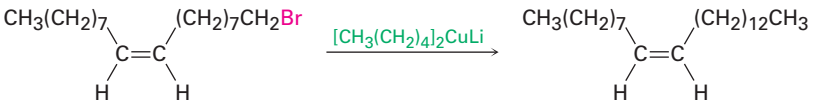


***trans*-1-Iodo-1-nonene** ***trans*-5-Tridecene (71%)**



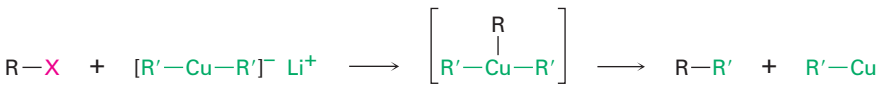
Iodobenzene **Toluene (91%)**

An organocopper coupling reaction is carried out commercially to synthesize muscalure, (9*Z*)-tricosene, the sex attractant secreted by the common housefly. Minute amounts of muscalure greatly increase the lure of insecticide-treated fly bait and provide an effective and species-specific means of insect control.



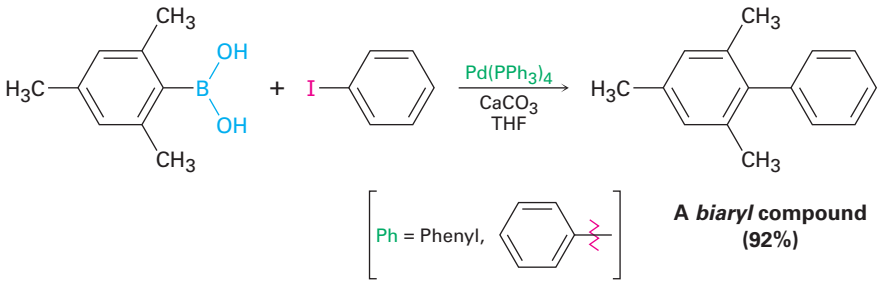
***cis*-1-Bromo-9-octadecene** **Muscalure (9*Z*-tricosene)**

The mechanism of the coupling reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of RCu. The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the next chapter.

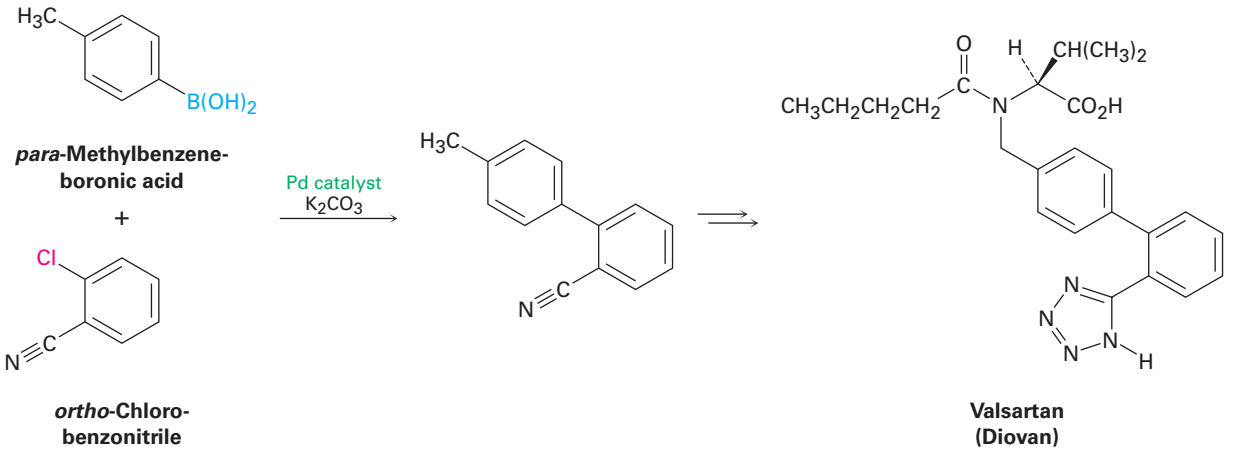


In addition to the coupling reaction of diorganocopper reagents with organohalides, related processes also occur with other organometallic reagents, particularly organopalladium compounds. One of the most commonly used procedures is the coupling reaction of an aromatic or vinyl substituted boronic acid [R—$B(OH)_2$] with an aromatic or vinyl substituted organohalide in the presence of a base and a palladium catalyst. The reaction is less general than the diorganocopper reaction because it does not 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,* the process is particularly useful for preparing so-called biaryl compounds, which have two aromatic rings joined together. 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 a widely prescribed antihypertensive agent whose synthesis begins with a Suzuki–Miyaura coupling of *ortho*-chlorobenzonitrile with *para*-methylbenzeneboronic acid.



Shown in a simplified form in **Figure 10.5**, 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.

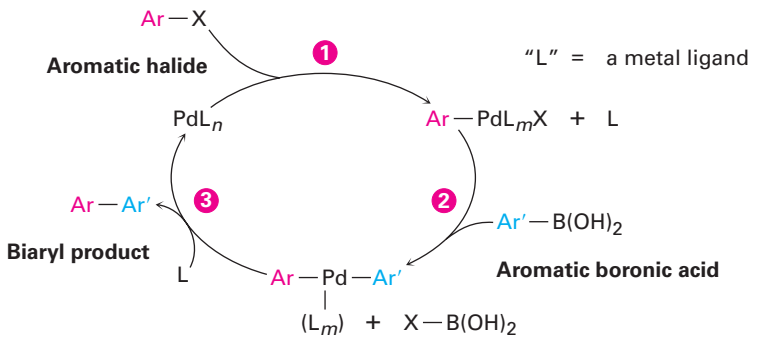
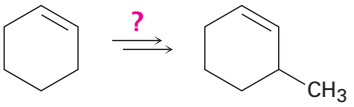


Figure 10.5 Mechanism of the Suzuki–Miyaura coupling reaction of an aromatic boronic acid with an aromatic halide to give a biaryl. The reaction takes place by (1) reaction of the aromatic halide, ArX, with the catalyst to form an organopalladium intermediate, followed by (2) reaction with the aromatic boronic acid. (3) Subsequent decomposition of the diarylpalladium intermediate gives the biaryl product.

Problem 10.11

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) $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

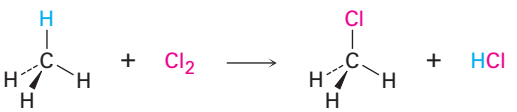
10.8 Oxidation and Reduction in Organic Chemistry

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 8.7**, 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 8.6)**.

Oxidation Decreases electron density on carbon by:
- forming one of these: C–O C–N C–X
- or breaking this: C–H

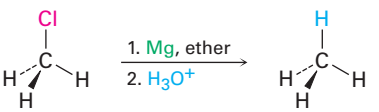
Reduction Increases electron density on carbon by:
- forming this: C–H
- or breaking one of these: C–O C–N C–X

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.



Methane **Chloromethane**

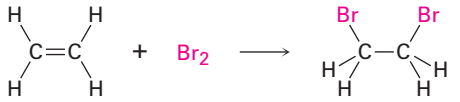
Oxidation: C–H bond broken and C–Cl bond formed



Chloromethane **Methane**

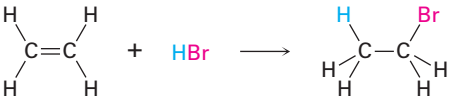
Reduction: C–Cl bond broken and C–H bond formed

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.



Ethylene **1,2-Dibromoethane**

Oxidation: Two new bonds formed between carbon and a more electronegative element



Ethylene **Bromoethane**

Neither oxidation nor reduction: One new C–H bond and one new C–Br bond formed

A list of compounds of increasing oxidation level is shown in **Figure 10.6**. 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.

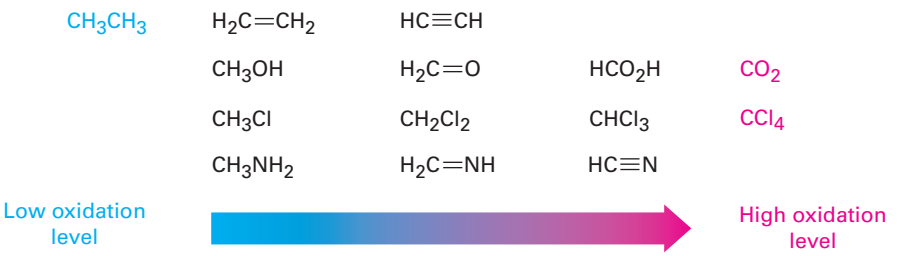


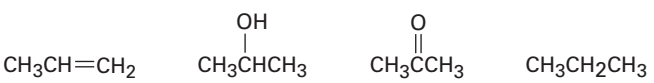
Figure 10.6 Oxidation levels of some common types of compounds.

Worked Example 10.2 shows how to compare the oxidation levels of different compounds with the same number of carbon atoms.

Comparing Oxidation Levels

Worked Example 10.2

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

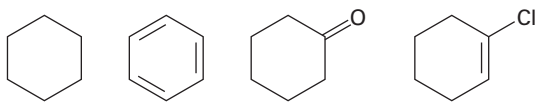
The first compound (propene) has six C—H bonds, giving an oxidation level of −6; the second (2-propanol) has one C—O bond and seven C—H bonds, giving an oxidation level of −6; the third (acetone) has two C—O bonds and six C—H bonds, giving an oxidation level of −4; and the fourth (propane) has eight C—H bonds, giving an oxidation level of −8. Thus, the order of increasing oxidation level is

$$CH_3CH_2CH_3 \;<\; CH_3CH{=}CH_2 \;=\; CH_3\overset{\displaystyle OH}{\overset{|}{C}}HCH_3 \;<\; CH_3\overset{\displaystyle O}{\overset{\|}{C}}CH_3$$

Problem 10.12

Rank each of the following series of compounds in order of increasing oxidation level:

(a)

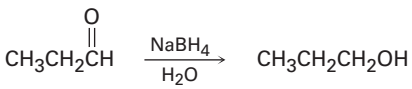


(b) CH_3CN $CH_3CH_2NH_2$ $H_2NCH_2CH_2NH_2$

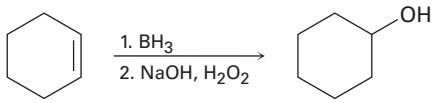
Problem 10.13

Tell whether each of the following reactions is an oxidation, a reduction, or neither.

(a)



(b)



Marine corals secrete organohalogen compounds that act as a feeding deterrent to fish.

Naturally Occurring Organohalides

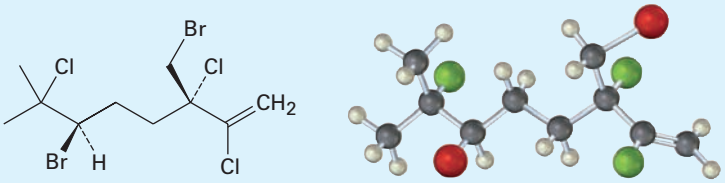
A DEEPER LOOK

As recently as 1970, 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, a bit more than a third of 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

(continued)

(continued)

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, volcanoes, 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 nonnatural 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, as irritants to predators, or as natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalides that deter fish, starfish, and other predators from eating them. 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.

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 is clear that organohalides are an integral part of the world around us.

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

Key words

alkyl halide, 344
allylic, 350
carbanion, 356
delocalized, 352
Gilman reagent (LiR_2Cu), 357
Grignard reagent (RMgX), 355
organohalide, 344

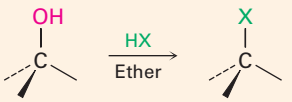
prepared from alcohols using either $SOCl_2$, PBr_3, or HF in pyridine. Alkyl halides react with magnesium in ether solution to form organomagnesium halides, called **Grignard reagents (RMgX)**, which are both nucleophilic and strongly basic.

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.

Summary of Reactions

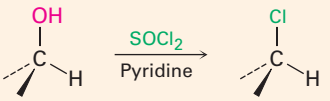
1. Preparation of alkyl halides
   (a) From alkenes by allylic bromination (Section 10.3)

   (b) From alcohols (Section 10.5)
      (1) Reaction with HX

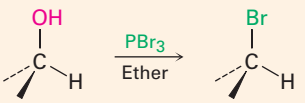


Reactivity order: 3° > 2° > 1°

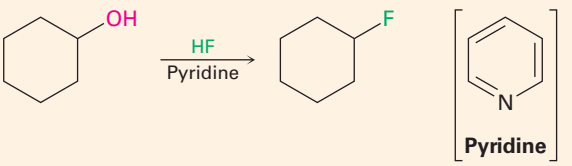
      (2) Reaction of 1° and 2° alcohols with $SOCl_2$



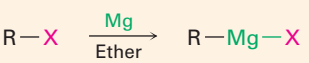
      (3) Reaction of 1° and 2° alcohols with PBr_3



      (4) Reaction of 1° and 2° alcohols with HF–pyridine



2. Reactions of alkyl halides
   (a) Formation of Grignard (organomagnesium) reagents (Section 10.6)



(continued)

(b) Formation of Gilman (diorganocopper) reagents (Section 10.7)

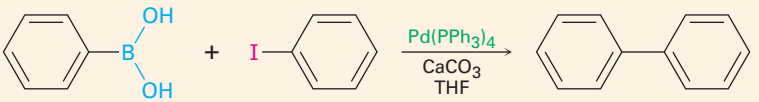
$$R{-}X \xrightarrow[\text{Pentane}]{2\ Li} R{-}Li + LiX$$

$$2\ R{-}Li + CuI \xrightarrow{\text{In ether}} [R{-}Cu{-}R]^{-}\ Li^{+} + LiI$$

(c) Organometallic coupling (Section 10.7)
(1) Diorganocopper reaction

$$R_2CuLi + R'{-}X \xrightarrow{\text{In ether}} R{-}R' + RCu + LiX$$

(2) Palladium-catalyzed Suzuki–Miyaura reaction



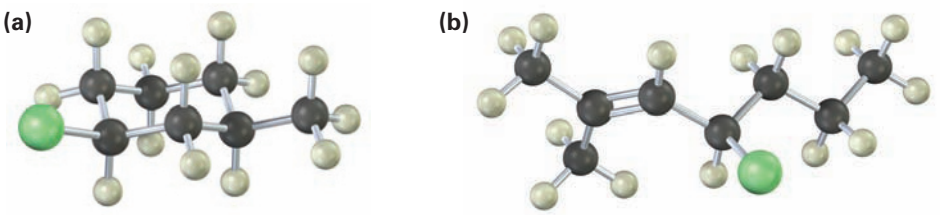
Exercises

Visualizing Chemistry

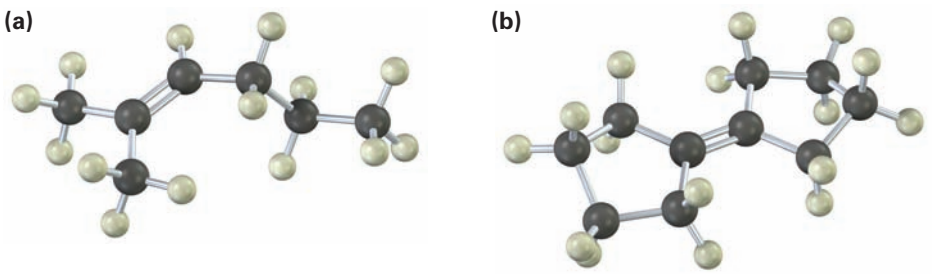
OWL Interactive versions of these problems are assignable in OWL for Organic Chemistry.

(Problems 10.1–10.13 appear within the chapter.)

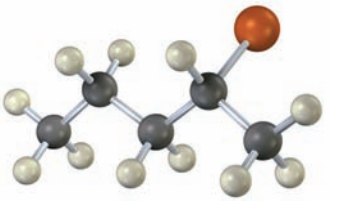
10.14 Give IUPAC names for the following alkyl halides (green = Cl):



10.15 Show the product(s) of reaction of the following alkenes with NBS:



10.16 The following alkyl bromide can be prepared by reaction of the alcohol (*S*)-2-pentanol with PBr_3. Name the compound, assign (*R*) or (*S*) stereochemistry, and tell whether the reaction of the alcohol occurs with retention of the same stereochemistry or with a change in stereochemistry (reddish brown = Br).



Additional Problems

Naming Alkyl Halides

10.17 Name the following alkyl halides:

(a) $CH_3CHCHCHCH_2CHCH_3$ (with H_3C, Br, Br, CH_3 substituents)

(b) $CH_3CH{=}CHCH_2CHCH_3$ (with I substituent)

(c) $CH_3CCH_2CHCHCH_3$ (with Br, Cl, CH_3, CH_3 substituents)

(d) $CH_3CH_2CHCH_2CH_2CH_3$ (with CH_2Br substituent)

(e) $ClCH_2CH_2CH_2C{\equiv}CCH_2Br$

10.18 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

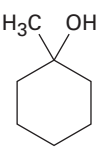
10.19 Draw and name the monochlorination products you might obtain by radical chlorination of 2-methylbutane. Which of the products are chiral? Are any of the products optically active?

Synthesizing Alkyl Halides

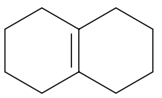
10.20 How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?

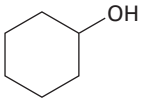
(a) Chlorocyclopentane
(b) Methylcyclopentane
(c) 3-Bromocyclopentene
(d) Cyclopentanol
(e) Cyclopentylcyclopentane
(f) 1,3-Cyclopentadiene

10.21 Predict the product(s) of the following reactions:

(a)  $\xrightarrow[\text{Ether}]{\text{HBr}}$ **?**

(b) $CH_3CH_2CH_2CH_2OH \xrightarrow{SOCl_2}$ **?**

(c)  $\xrightarrow[h\nu,\ CCl_4]{\text{NBS}}$ **?**

(d)  $\xrightarrow[\text{Ether}]{PBr_3}$ **?**

(e) $CH_3CH_2CHBrCH_3 \xrightarrow[\text{Ether}]{\text{Mg}}$ **A?** $\xrightarrow{H_2O}$ **B?**

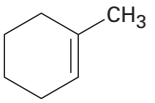
(f) $CH_3CH_2CH_2CH_2Br \xrightarrow[\text{Pentane}]{\text{Li}}$ **A?** $\xrightarrow{\text{CuI}}$ **B?**

(g) $CH_3CH_2CH_2CH_2Br + (CH_3)_2CuLi \xrightarrow{\text{Ether}}$ **?**

10.22 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?

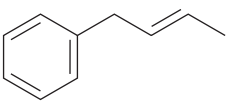
$$CH_3CH_2CH{=}CHCH_3 \xrightarrow[h\nu,\ CCl_4]{\text{NBS}} CH_3CH_2CH{=}CHCH_2Br$$

10.23 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?

 $\xrightarrow[h\nu,\ CCl_4]{\text{NBS}}$ **?**

10.24 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?

10.25 What product would you expect from the reaction of 1-phenyl-2-butene with NBS? Explain.



1-Phenyl-2-butene

Oxidation and Reduction

10.26 Rank the compounds in each of the following series in order of increasing oxidation level:

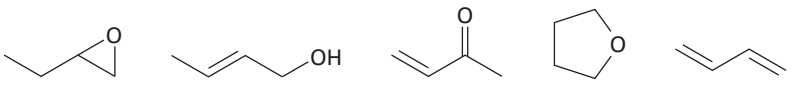
(a)

$CH_3CH{=}CHCH_3$ $CH_3CH_2CH{=}CH_2$ $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}H$ $CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH$

(b)

$CH_3CH_2CH_2NH_2$ $CH_3CH_2CH_2Br$ $CH_3\overset{\overset{O}{\|}}{C}CH_2Cl$ $BrCH_2CH_2CH_2Cl$

10.27 Which of the following compounds have the same oxidation level, and which have different levels?



1 **2** **3** **4** **5**

10.28 Tell whether each of the following reactions is an oxidation, a reduction, or neither:

(a)

$CH_3CH_2OH \xrightarrow{CrO_3} CH_3\overset{\overset{O}{\|}}{C}H$

(b)

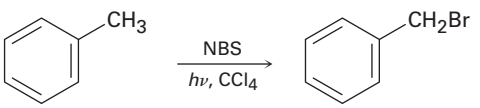
$H_2C{=}CH\overset{\overset{O}{\|}}{C}CH_3 + NH_3 \longrightarrow H_2NCH_2CH_2\overset{\overset{O}{\|}}{C}CH_3$

(c)

$CH_3CH_2\overset{\overset{Br}{|}}{C}HCH_3 \xrightarrow[2.\ H_2O]{1.\ Mg} CH_3CH_2CH_2CH_3$

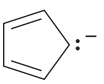
General Problems

10.29 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 on page 204.



10.30 Draw resonance structures for the benzyl radical, $C_6H_5CH_2\cdot$, the intermediate produced in the NBS bromination reaction of toluene (Problem 10.29).

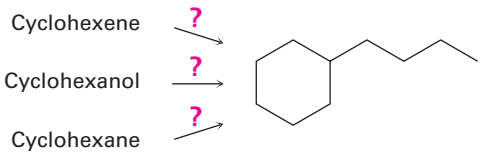
10.31 Draw resonance structures for the following species:

(a) $CH_3CH{=}CHCH{=}CHCH{=}\overset{+}{C}HCH_2$ **(b)**  **(c)** $CH_3C{\equiv}\overset{+}{N}{-}\ddot{O}:^{-}$

10.32 (*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?

10.33 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 10.32.)

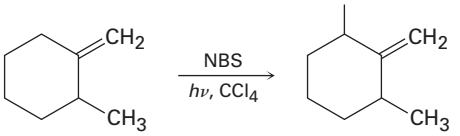
10.34 How would you carry out the following syntheses?



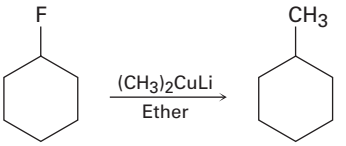
10.35 The syntheses shown here are unlikely to occur as written. What is wrong with each?

(a) $CH_3CH_2CH_2F \xrightarrow[2.\ H_3O^+]{1.\ Mg} CH_3CH_2CH_3$

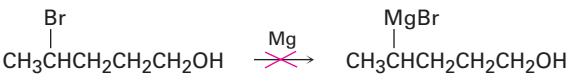
(b)



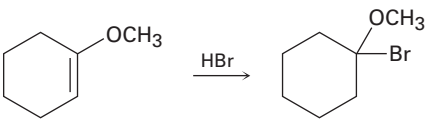
(c)



10.36 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.



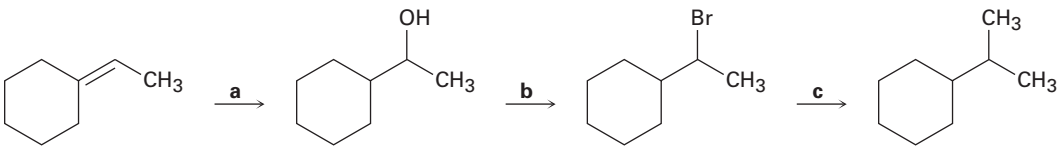
10.37 Addition of HBr to a double bond with an ether (−OR) substituent occurs regiospecifically to give a product in which the −Br and −OR are bonded to the same carbon. Draw the two possible carbocation intermediates in this electrophilic addition reaction, and explain using resonance why the observed product is formed.



10.38 Alkyl halides can be reduced to alkanes by a radical reaction with tributyltin hydride, $(C_4H_9)_3SnH$, in the presence of light ($h\nu$). Propose a radical chain mechanism by which the reaction might occur. The initiation step is the light-induced homolytic cleavage of the Sn–H bond to yield a tributyltin radical.

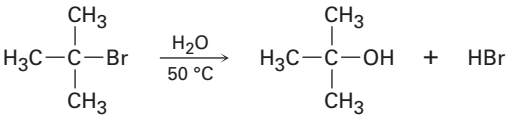
$$R{-}X \quad + \quad (C_4H_9)_3SnH \xrightarrow{h\nu} \quad R{-}H \quad + \quad (C_4H_9)_3SnX$$

10.39 Identify the reagents **a–c** in the following scheme:



10.40 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.

10.41 In light of the fact that tertiary alkyl halides undergo spontaneous dissociation to yield a carbocation plus halide ion (Problem 10.40), propose a mechanism for the following reaction.



10.42 Carboxylic acids (RCO_2H; $pK_a \approx 5$) are approximately 10^{11} times more acidic than alcohols (ROH; $pK_a \approx 16$). In other words, a carboxylate ion (RCO_2^-) is more stable than an alkoxide ion (RO^-). Explain, using resonance.

10.43 How might you use a Suzuki–Miyaura coupling to prepare the following biaryl compound? Show the two potential reaction partners.