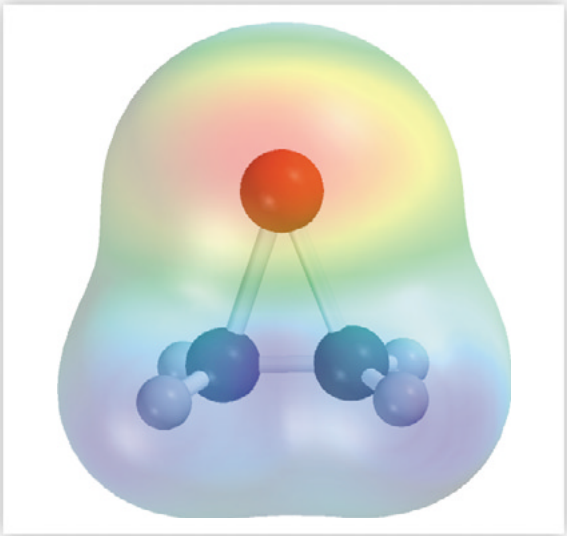
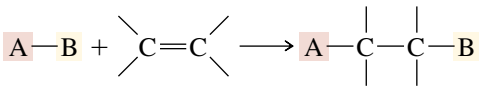


CHAPTER 6

REACTIONS OF ALKENES: ADDITION REACTIONS

Now that we're familiar with the structure and preparation of alkenes, let's look at their chemical reactions. The characteristic reaction of alkenes is **addition** to the double bond according to the general equation:

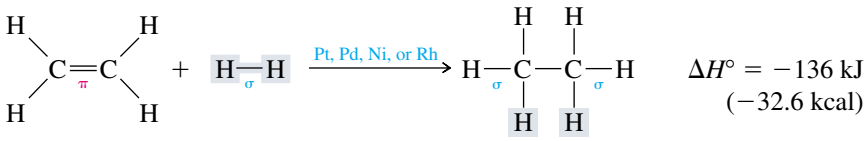


The range of compounds represented as A—B in this equation is quite large, and their variety offers a wealth of opportunity for converting alkenes to a number of other functional group types.

Alkenes are commonly described as **unsaturated hydrocarbons** because they have the capacity to react with substances which add to them. Alkanes, on the other hand, are said to be **saturated** hydrocarbons and are incapable of undergoing addition reactions.

6.1 HYDROGENATION OF ALKENES

The relationship between reactants and products in addition reactions can be illustrated by the *hydrogenation* of alkenes to yield alkanes. **Hydrogenation** is the addition of H_2 to a multiple bond. An example is the reaction of hydrogen with ethylene to form ethane.



Ethylene + Hydrogen → Ethane

$\Delta H^\circ = -136$ kJ (-32.6 kcal)

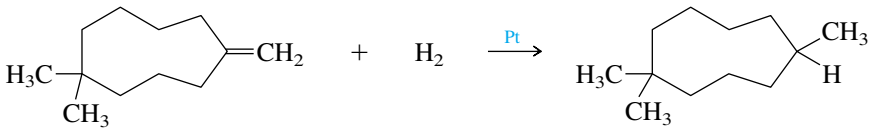
The bonds in the product are stronger than the bonds in the reactants; two C—H σ bonds of an alkane are formed at the expense of the H—H σ bond and the π component of the alkene's double bond. The overall reaction is *exothermic,* and the heat evolved on hydrogenation of one mole of an alkene is its **heat of hydrogenation.** Heat of hydrogenation is a positive quantity equal to $-\Delta H^\circ$ for the reaction.

The uncatalyzed addition of hydrogen to an alkene, although exothermic, is very slow. The rate of hydrogenation increases dramatically, however, in the presence of certain finely divided metal catalysts. *Platinum* is the hydrogenation catalyst most often used, although *palladium, nickel,* and *rhodium* are also effective. Metal-catalyzed addition of hydrogen is normally rapid at room temperature, and the alkane is produced in high yield, usually as the only product.

The French chemist Paul Sabatier received the 1912 Nobel Prize in chemistry for his discovery that finely divided nickel is an effective hydrogenation catalyst.

$$(CH_3)_2C{=}CHCH_3 + H_2 \xrightarrow{Pt} (CH_3)_2CHCH_2CH_3$$

2-Methyl-2-butene Hydrogen 2-Methylbutane (100%)



5,5-Dimethyl(methylene)cyclononane Hydrogen 1,1,5-Trimethylcyclononane (73%)

PROBLEM 6.1 What three alkenes yield 2-methylbutane on catalytic hydrogenation?

The solvent used in catalytic hydrogenation is chosen for its ability to dissolve the alkene and is typically ethanol, hexane, or acetic acid. The metal catalysts are insoluble in these solvents (or, indeed, in any solvent). Two phases, the solution and the metal, are present, and the reaction takes place at the interface between them. Reactions involving a substance in one phase with a different substance in a second phase are called **heterogeneous reactions.**

Catalytic hydrogenation of an alkene is believed to proceed by the series of steps shown in Figure 6.1. As already noted, addition of hydrogen to the alkene is very slow in the absence of a metal catalyst, meaning that any uncatalyzed mechanism must have a very high activation energy. The metal catalyst accelerates the rate of hydrogenation by providing an alternative pathway that involves a sequence of several low activation energy steps.

6.2 HEATS OF HYDROGENATION

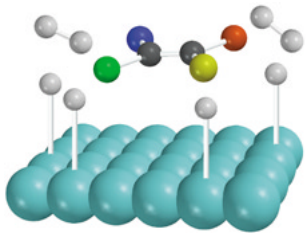
Heats of hydrogenation are used to compare the relative stabilities of alkenes in much the same way as heats of combustion. Both methods measure the differences in the energy of *isomers* by converting them to a product or products common to all. Catalytic hydrogenation of 1-butene, *cis*-2-butene, or *trans*-2-butene yields the same product—butane. As Figure 6.2 shows, the measured heats of hydrogenation reveal that *trans*-2-butene is 4 kJ/mol (1.0 kcal/mol) lower in energy than *cis*-2-butene and that *cis*-2-butene is 7 kJ/mol (1.7 kcal/mol) lower in energy than 1-butene.

Remember that a catalyst affects the rate of a reaction but not the energy relationships between reactants and products. Thus, the heat of hydrogenation of a particular alkene is the same irrespective of what catalyst is used.

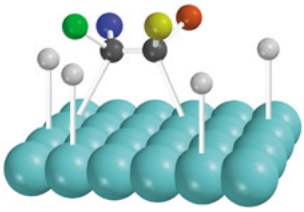
Heats of hydrogenation can be used to *estimate* the stability of double bonds as structural units, even in alkenes that are not isomers. Table 6.1 lists the heats of hydrogenation for a representative collection of alkenes.

FIGURE 6.1 A mechanism for heterogeneous catalysis in the hydrogenation of alkenes.

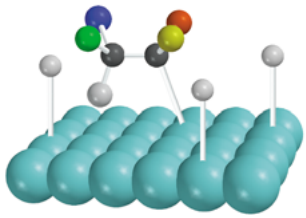
Step 1: Hydrogen molecules react with metal atoms at the catalyst surface. The relatively strong hydrogen–hydrogen σ bond is broken and replaced by two weak metal–hydrogen bonds.



Step 2: The alkene reacts with the metal catalyst. The π component of the double bond between the two carbons is replaced by two relatively weak carbon–metal σ bonds.



Step 3: A hydrogen atom is transferred from the catalyst surface to one of the carbons of the double bond.



Step 4: The second hydrogen atom is transferred, forming the alkane. The sites on the catalyst surface at which the reaction occurred are free to accept additional hydrogen and alkene molecules.

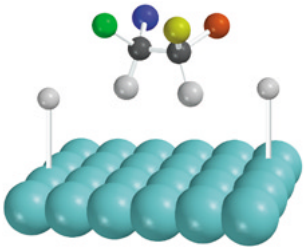


FIGURE 6.2 Heats of hydrogenation of butene isomers plotted on a common scale. All energies are in kilojoules per mole.

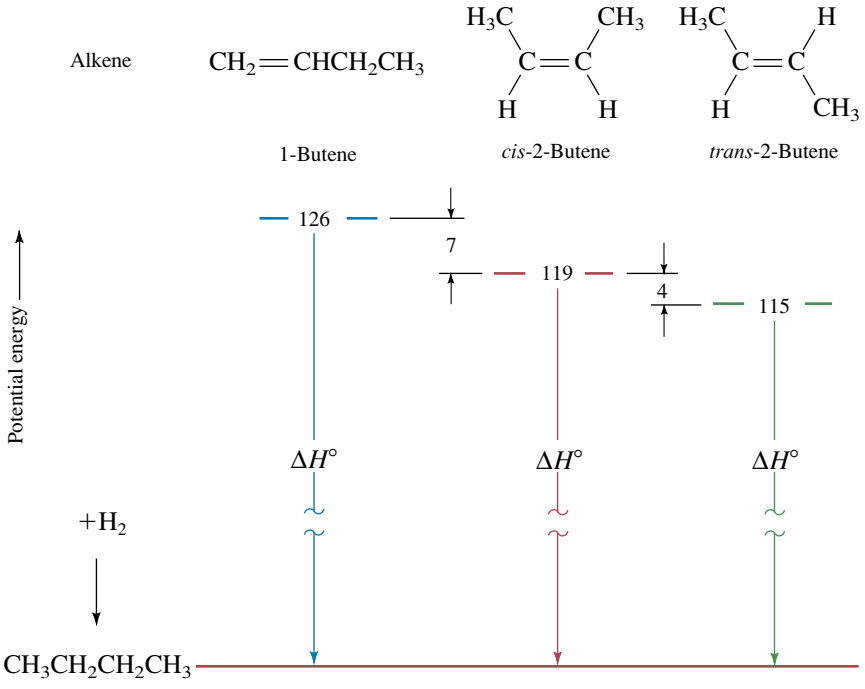
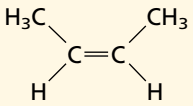
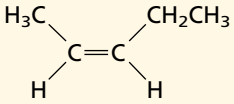
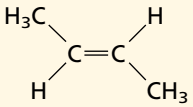
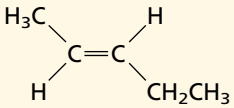
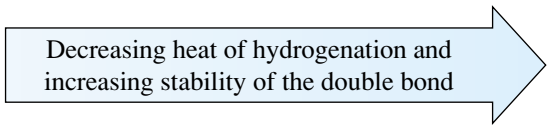


TABLE 6.1 Heats of Hydrogenation of Some Alkenes

Alkene	Structure	Heat of hydrogenation kJ/mol	Heat of hydrogenation kcal/mol
Ethylene	$CH_2{=}CH_2$	136	32.6
Monosubstituted alkenes			
Propene	$CH_2{=}CHCH_3$	125	29.9
1-Butene	$CH_2{=}CHCH_2CH_3$	126	30.1
1-Hexene	$CH_2{=}CHCH_2CH_2CH_2CH_3$	126	30.2
Cis-disubstituted alkenes			
cis-2-Butene		119	28.4
cis-2-Pentene		117	28.1
Trans-disubstituted alkenes			
trans-2-Butene		115	27.4
trans-2-Pentene		114	27.2
Trisubstituted alkenes			
2-Methyl-2-pentene	$(CH_3)_2C{=}CHCH_2CH_3$	112	26.7
Tetrasubstituted alkenes			
2,3-Dimethyl-2-butene	$(CH_3)_2C{=}C(CH_3)_2$	110	26.4

The pattern of alkene stability determined from heats of hydrogenation parallels exactly the pattern deduced from heats of combustion.



$CH_2{=}CH_2$	RCH$=$$CH_2$	RCH$=$CHR	$R_2C{=}CHR$	$R_2C{=}CR_2$
Ethylene	Monosubstituted	Disubstituted	Trisubstituted	Tetrasubstituted

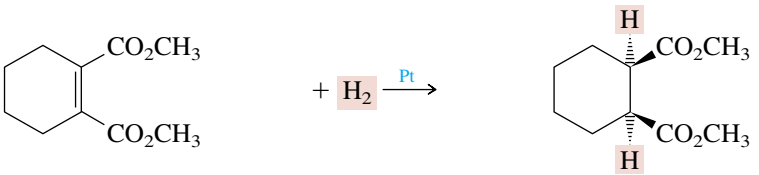
Ethylene, which has no alkyl substituents to stabilize its double bond, has the highest heat of hydrogenation. Alkenes that are similar in structure to one another have similar heats of hydrogenation. For example, the heats of hydrogenation of the monosubstituted (terminal) alkenes propene, 1-butene, and 1-hexene are almost identical. Cis- disubstituted alkenes have lower heats of hydrogenation than monosubstituted alkenes but higher heats of hydrogenation than their more stable trans stereoisomers. Alkenes with trisubstituted double bonds have lower heats of hydrogenation than disubstituted alkenes, and tetrasubstituted alkenes have the lowest heats of hydrogenation.

PROBLEM 6.2 Match each alkene of Problem 6.1 with its correct heat of hydrogenation.

Heats of hydrogenation in kJ/mol (kcal/mol): 112 (26.7); 118 (28.2); 126 (30.2)

6.3 STEREOCHEMISTRY OF ALKENE HYDROGENATION

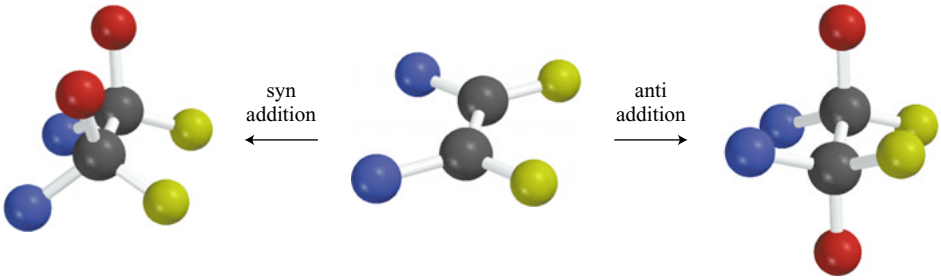
In the mechanism for alkene hydrogenation shown in Figure 6.1, hydrogen atoms are transferred from the catalyst's surface to the alkene. Although the two hydrogens are not transferred simultaneously, it happens that both add to the same face of the double bond, as the following example illustrates.



Dimethyl cyclohexene-1,2-dicarboxylate

Dimethyl cyclohexane-*cis*-1,2-dicarboxylate (100%)

The term **syn addition** describes the stereochemistry of reactions such as catalytic hydrogenation in which two atoms or groups add to the *same face* of a double bond. When atoms or groups add to *opposite faces* of the double bond, the process is called **anti addition.**



Stereoselectivity was defined and introduced in connection with the formation of stereoisomeric alkenes in elimination reactions (Section 5.11).

A second stereochemical aspect of alkene hydrogenation concerns its **stereoselectivity.** A reaction in which a single starting material can give two or more stereoisomeric products but yields one of them in greater amounts than the other (or even to the exclusion of the other) is said to be **stereoselective.** The catalytic hydrogenation of α-pinene (a constituent of turpentine) is an example of a stereoselective reaction. Syn addition of

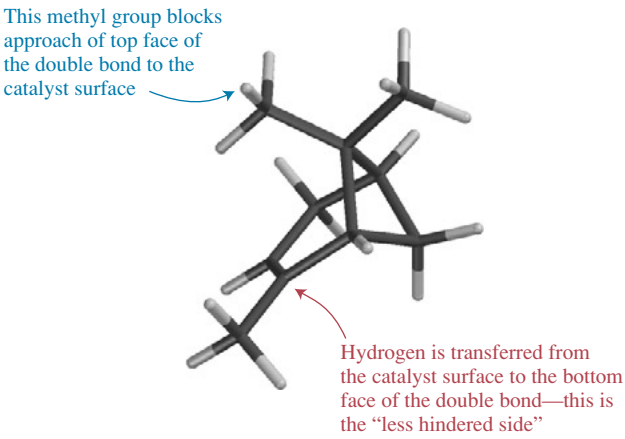
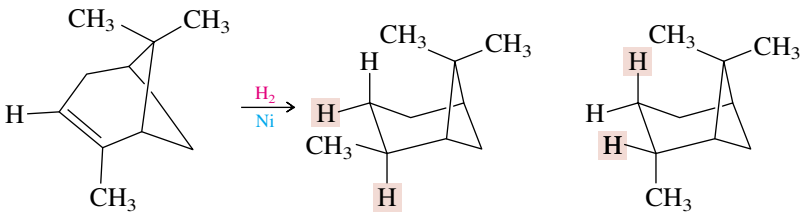


FIGURE 6.3 The methyl group that lies over the double bond of α-pinene shields one face of it, preventing a close approach to the surface of the catalyst. Hydrogenation of α-pinene occurs preferentially from the bottom face of the double bond.

hydrogen can in principle lead to either *cis*-pinane or *trans*-pinane, depending on which face of the double bond accepts the hydrogen atoms (shown in red in the equation).



α-Pinene | *cis*-Pinane (only product) | *trans*-Pinane (not formed)

cis-Pinane and *trans*-pinane are common names that denote the relationship between the pair of methyl groups on the bridge and the third methyl group.

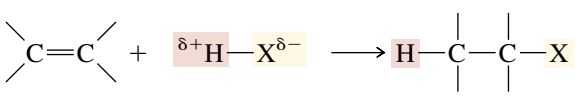
In practice, hydrogenation of α-pinene is observed to be 100% stereoselective. The only product obtained is *cis*-pinane. None of the stereoisomeric *trans*-pinane is formed.

The stereoselectivity of this reaction depends on how the alkene approaches the catalyst surface. As the molecular model in Figure 6.3 shows, one of the methyl groups on the bridge carbon lies directly over the double bond and blocks that face from easy access to the catalyst. The bottom face of the double bond is more exposed, and both hydrogens are transferred from the catalyst surface to that face.

Reactions such as catalytic hydrogenation that take place at the "less hindered" side of a reactant are common in organic chemistry and are examples of steric effects on *reactivity*. We have previously seen steric effects on *structure* and *stability* in the case of *cis* and *trans* stereoisomers and in the preference for equatorial substituents on cyclohexane rings.

6.4 ELECTROPHILIC ADDITION OF HYDROGEN HALIDES TO ALKENES

In many addition reactions the attacking reagent, unlike H_2, is a polar molecule. Hydrogen halides are among the simplest examples of polar substances that add to alkenes.

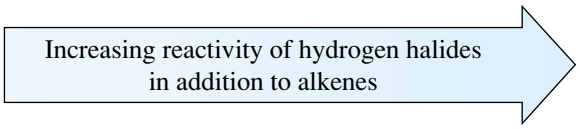


Alkene | Hydrogen halide | Alkyl halide

Addition occurs rapidly in a variety of solvents, including pentane, benzene, dichloromethane, chloroform, and acetic acid.

cis-3-Hexene Hydrogen bromide 3-Bromohexane (76%)

The reactivity of the hydrogen halides reflects their ability to donate a proton. Hydrogen iodide is the strongest acid of the hydrogen halides and reacts with alkenes at the fastest rate.



$$HF << HCl < HBr < HI$$

Slowest rate of addition; least acidic — Fastest rate of addition; most acidic

We can gain a general understanding of the mechanism of hydrogen halide addition to alkenes by extending some of the principles of reaction mechanisms introduced earlier. In Section 5.12 we pointed out that carbocations are the conjugate acids of alkenes. Acid–base reactions are reversible processes. An alkene, therefore, can accept a proton from a hydrogen halide to form a carbocation.

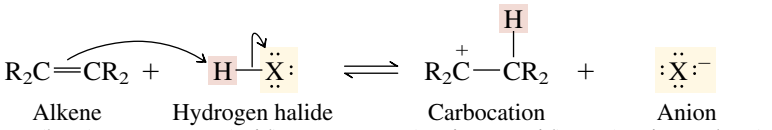
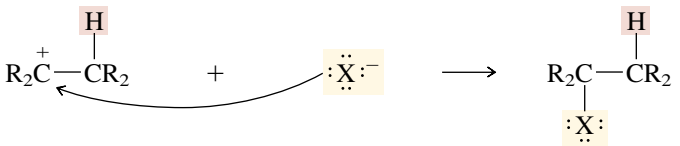


Figure 6.4 shows the complementary nature of the electrostatic potentials of an alkene and a hydrogen halide. We've also seen (Section 4.9) that carbocations, when generated in the presence of halide anions, react with them to form alkyl halides.



Both steps in this general mechanism are based on precedent. It is called **electrophilic addition** because the reaction is triggered by the attack of an electrophile (an acid) on the π electrons of the double bond. Using the two π electrons to form a bond to an electrophile generates a carbocation as a reactive intermediate; normally this is the rate-determining step.

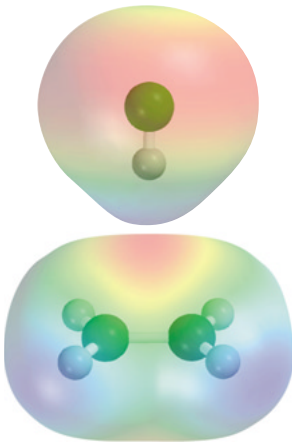
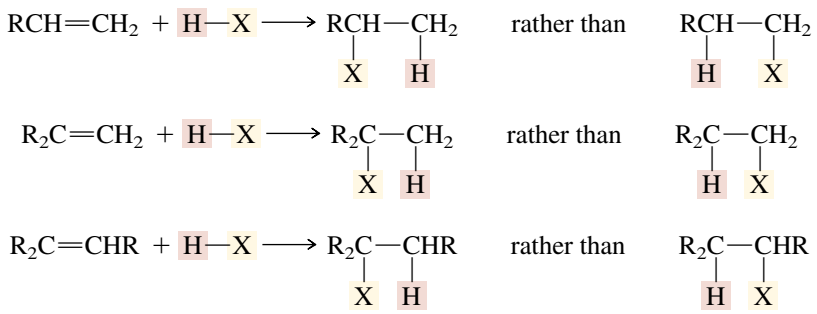


FIGURE 6.4 Electrostatic potential maps of HCl and ethylene. When the two react, the interaction is between the electron-rich site (red) of ethylene and the electron-poor region (blue) of HCl. The electron-rich region of ethylene is associated with the π electrons of the double bond, while H is the electron-poor atom (blue) of HCl.

6.5 REGIOSELECTIVITY OF HYDROGEN HALIDE ADDITION: MARKOVNIKOV'S RULE

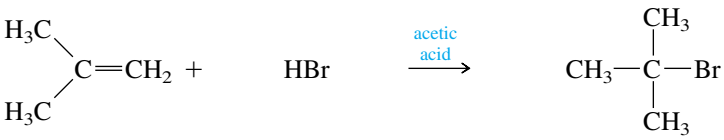
In principle a hydrogen halide can add to an unsymmetrical alkene (an alkene in which the two carbons of the double bond are not equivalently substituted) in either of two directions. In practice, addition is so highly regioselective as to be considered regiospecific.



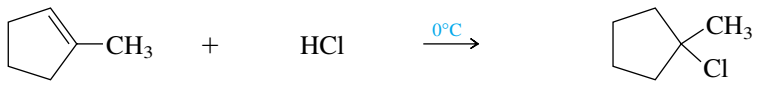
In 1870, Vladimir Markovnikov, a colleague of Alexander Zaitsev at the University of Kazan, noticed a pattern in the hydrogen halide addition to alkenes and assembled his observations into a simple statement. **Markovnikov's rule** states that *when an unsymmetrically substituted alkene reacts with a hydrogen halide, the hydrogen adds to the carbon that has the greater number of hydrogen substituents, and the halogen adds to the carbon having fewer hydrogen substituents.* The preceding general equations illustrate regioselective addition according to Markovnikov's rule, and the equations that follow provide some examples.

An article in the December 1988 issue of the *Journal of Chemical Education* traces the historical development of Markovnikov's rule. In that article Markovnikov's name is spelled *Markownikoff,* which is the way it appeared in his original paper written in German.

1-Butene Hydrogen bromide 2-Bromobutane (80%)

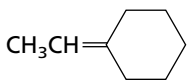


2-Methylpropene Hydrogen bromide 2-Bromo-2-methylpropane (90%)

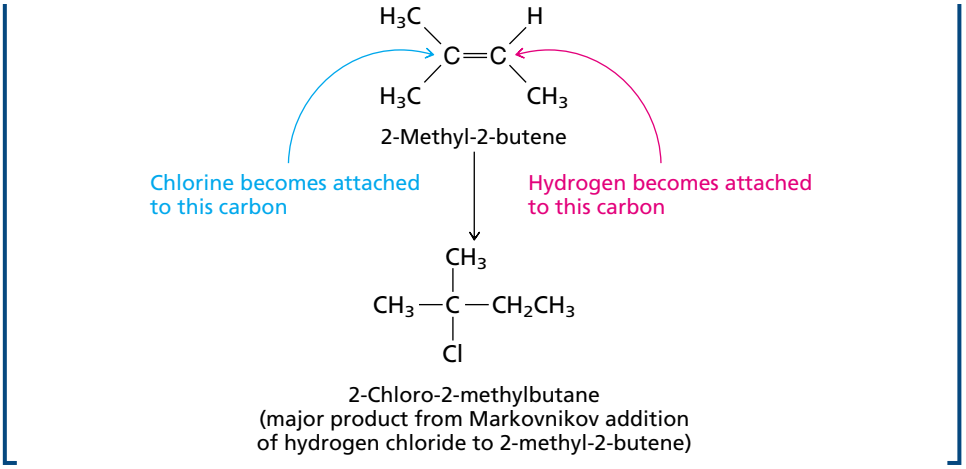


1-Methylcyclopentene Hydrogen chloride 1-Chloro-1-methylcyclopentane (100%)

PROBLEM 6.3 Write the structure of the major organic product formed in the reaction of hydrogen chloride with each of the following:

(a) 2-Methyl-2-butene
(b) 2-Methyl-1-butene
(c) *cis*-2-Butene
(d) 

SAMPLE SOLUTION (a) Hydrogen chloride adds to the double bond of 2-methyl-2-butene in accordance with Markovnikov's rule. The proton adds to the carbon that has one attached hydrogen, chlorine to the carbon that has none.

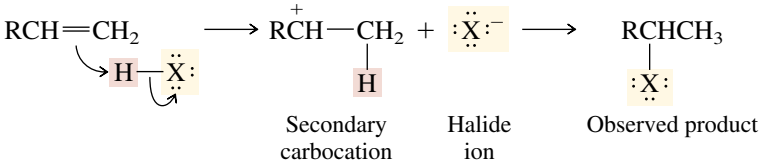


Markovnikov's rule, like Zaitsev's, organizes experimental observations in a form suitable for predicting the major product of a reaction. The reasons why it works appear when we examine the mechanism of electrophilic addition in more detail.

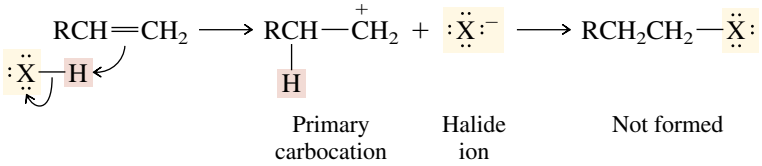
6.6 MECHANISTIC BASIS FOR MARKOVNIKOV'S RULE

Let's compare the carbocation intermediates for addition of a hydrogen halide (HX) to an unsymmetrical alkene of the type $RCH{=}CH_2$ (a) according to Markovnikov's rule and (b) opposite to Markovnikov's rule.

(a) *Addition according to Markovnikov's rule:*



(b) *Addition opposite to Markovnikov's rule:*



The transition state for protonation of the double bond has much of the character of a carbocation, and the activation energy for formation of the more stable carbocation (secondary) is less than that for formation of the less stable (primary) one. Figure 6.5 uses a potential energy diagram to illustrate these two competing modes of addition. Both carbocations are rapidly captured by X^- to give an alkyl halide, with the major product derived from the carbocation that is formed faster. The energy difference between a primary carbocation and a secondary carbocation is so great and their rates of formation are so different that essentially all the product is derived from the secondary carbocation.

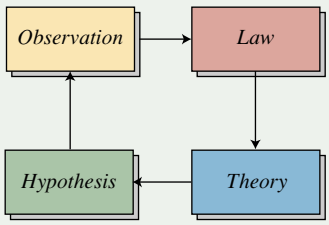
RULES, LAWS, THEORIES, AND THE SCIENTIFIC METHOD

As we have just seen, Markovnikov's rule can be expressed in two ways:

1. When a hydrogen halide adds to an alkene, hydrogen adds to the carbon of the alkene that has the greater number of hydrogens attached to it, and the halogen to the carbon that has the fewer hydrogens.
2. When a hydrogen halide adds to an alkene, protonation of the double bond occurs in the direction that gives the more stable carbocation.

The first of these statements is close to the way Vladimir Markovnikov expressed it in 1870; the second is the way we usually phrase it now. These two statements differ in an important way—a way that is related to the *scientific method.*

Adherence to the scientific method is what defines science. The scientific method has four major elements: observation, law, theory, and hypothesis.



Most *observations* in chemistry come from experiments. If we do enough experiments we may see a pattern running through our observations. A *law* is a mathematical (the law of gravity) or verbal (the law of diminishing returns) description of that pattern. Establishing a law can lead to the framing of a *rule* that lets us predict the results of future experiments. This is what the 1870 version of Markovnikov's rule is: a statement based on experimental observations that has predictive value.

A *theory* is our best present interpretation of why things happen the way they do. The modern version of Markovnikov's rule, which is based on mechanistic reasoning and carbocation stability, recasts the rule in terms of theoretical ideas. Mechanisms, and explanations grounded in them, belong to the theory part of the scientific method.

It is worth remembering that a theory can never be proven correct. It can only be proven incorrect, incomplete, or inadequate. Thus, theories are always being tested and refined. As important as anything else in the scientific method is the *testable hypothesis.* Once a theory is proposed, experiments are designed to test its validity. If the results are consistent with the theory, our belief in its soundness is strengthened. If the results conflict with it, the theory is flawed and must be modified. Section 6.7 describes some observations that support the theory that carbocations are intermediates in the addition of hydrogen halides to alkenes.

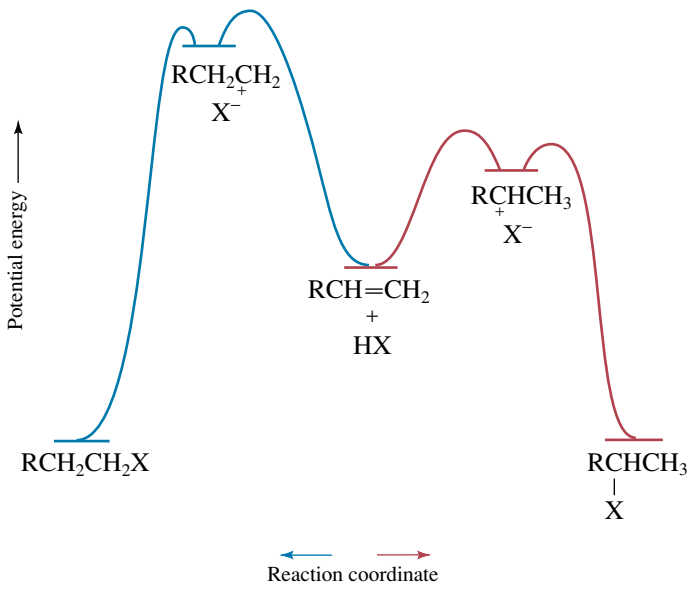
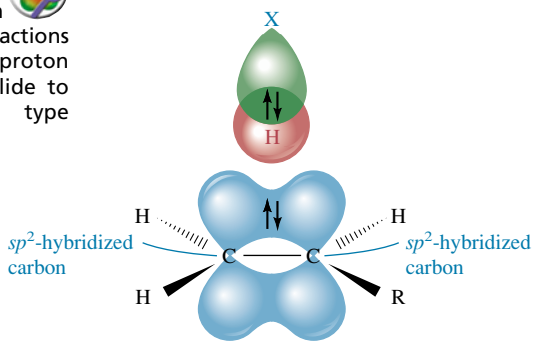
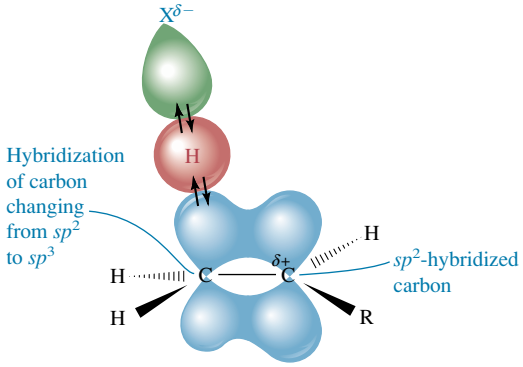


FIGURE 6.5 Energy diagram comparing addition of a hydrogen halide to an alkene according to Markovnikov's rule with addition in the direction opposite to Markovnikov's rule. The alkene and hydrogen halide are shown in the center of the diagram. The lower energy pathway that corresponds to Markovnikov's rule proceeds to the right and is shown in red; the higher energy pathway proceeds to the left and is shown in blue.

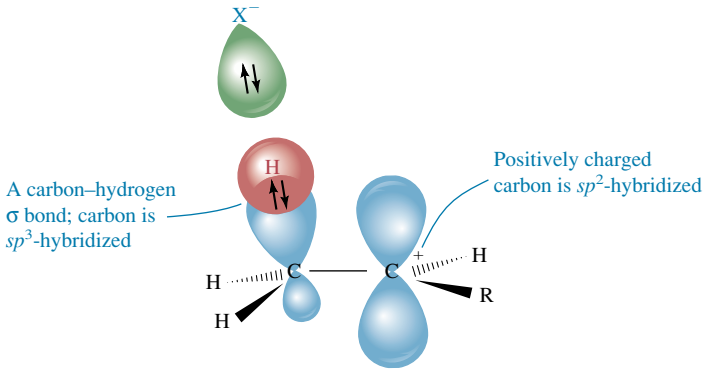
FIGURE 6.6 Electron flow and orbital interactions in the transfer of a proton from a hydrogen halide to an alkene of the type $CH_2{=}CHR$.



(*a*) The hydrogen halide (HX) and the alkene ($CH_2{=}CHR$) approach each other. The electrophile is the hydrogen halide, and the site of electrophilic attack is the orbital containing the σ electrons of the double bond.



(*b*) Electrons flow from the π orbital of the alkene to the hydrogen halide. The π electrons flow in the direction that generates a partial positive charge on the carbon atom that bears the electron-releasing alkyl group (R). The hydrogen–halogen bond is partially broken and a C—H σ bond is partially formed at the transition state.

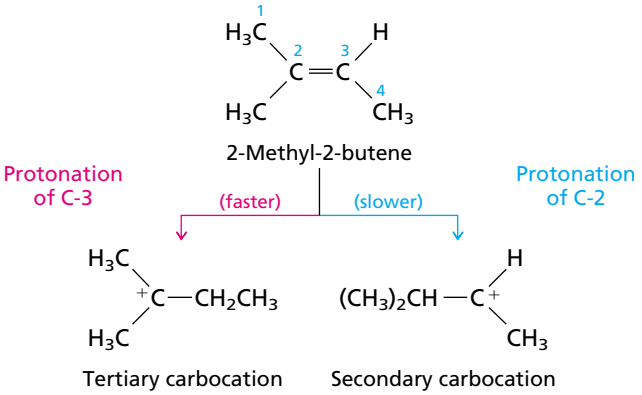


(*c*) Loss of the halide ion (X^-) from the hydrogen halide and C—H σ bond formation complete the formation of the more stable carbocation intermediate $CH_3\overset{+}{C}HR$.

Figure 6.6 focuses on the orbitals involved and shows how the π electrons of the double bond flow in the direction that generates the more stable of the two possible carbocations.

PROBLEM 6.4 Give a structural formula for the carbocation intermediate that leads to the major product in each of the reactions of Problem 6.3 (Section 6.5).

SAMPLE SOLUTION (a) Protonation of the double bond of 2-methyl-2-butene can give a tertiary carbocation or a secondary carbocation.

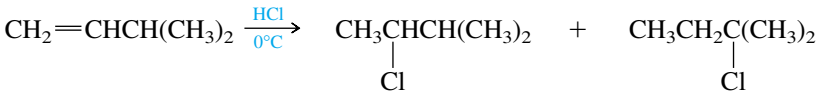


The product of the reaction is derived from the more stable carbocation—in this case, it is a tertiary carbocation that is formed more rapidly than a secondary one.

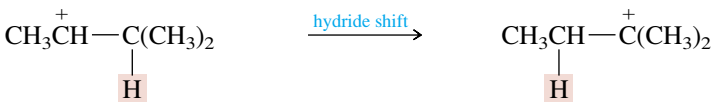
In general, alkyl substituents increase the reactivity of a double bond toward electrophilic addition. Alkyl groups are electron-releasing, and the more *electron-rich* a double bond, the better it can share its π electrons with an electrophile. Along with the observed regioselectivity of addition, this supports the idea that carbocation formation, rather than carbocation capture, is rate-determining.

6.7 CARBOCATION REARRANGEMENTS IN HYDROGEN HALIDE ADDITION TO ALKENES

Our belief that carbocations are intermediates in the addition of hydrogen halides to alkenes is strengthened by the observation that rearrangements sometimes occur. For example, the reaction of hydrogen chloride with 3-methyl-1-butene is expected to produce 2-chloro-3-methylbutane. Instead, a mixture of 2-chloro-3-methylbutane and 2-chloro-2-methylbutane results.



Addition begins in the usual way, by protonation of the double bond to give, in this case, a secondary carbocation. This carbocation can be captured by chloride to give 2-chloro-3-methylbutane (40%) or it can rearrange by way of a hydride shift to give a tertiary carbocation. The tertiary carbocation reacts with chloride ion to give 2-chloro-2-methylbutane (60%).



The similar yields of the two alkyl chloride products indicate that the rate of attack by chloride on the secondary carbocation and the rate of rearrangement must be very similar.

PROBLEM 6.5 Addition of hydrogen chloride to 3,3-dimethyl-1-butene gives a mixture of two isomeric chlorides in approximately equal amounts. Suggest reasonable structures for these two compounds, and offer a mechanistic explanation for their formation.

6.8 FREE-RADICAL ADDITION OF HYDROGEN BROMIDE TO ALKENES

For a long time the regioselectivity of addition of hydrogen bromide to alkenes was unpredictable. Sometimes addition occurred according to Markovnikov's rule, but at other times, seemingly under the same conditions, the opposite regioselectivity *(anti-Markovnikov addition)* was observed. In 1929, Morris S. Kharasch and his students at the University of Chicago began a systematic investigation of this puzzle. After hundreds of experiments, Kharasch concluded that anti-Markovnikov addition occurred when peroxides, that is, organic compounds of the type ROOR, were present in the reaction mixture. He and his colleagues found, for example, that carefully purified 1-butene reacted with hydrogen bromide to give only 2-bromobutane—the product expected on the basis of Markovnikov's rule.

$$\underset{\text{1-Butene}}{CH_2{=}CHCH_2CH_3} + \underset{\text{Hydrogen bromide}}{HBr} \xrightarrow[\text{peroxides}]{\text{no}} \underset{\substack{\text{2-Bromobutane}\\ \text{(only product; 90\% yield)}}}{CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3}$$

On the other hand, when the same reaction was performed in the presence of an added peroxide, only 1-bromobutane was formed.

$$\underset{\text{1-Butene}}{CH_2{=}CHCH_2CH_3} + \underset{\text{Hydrogen bromide}}{HBr} \xrightarrow{\text{peroxides}} \underset{\substack{\text{1-Bromobutane}\\ \text{(only product; 95\% yield)}}}{BrCH_2CH_2CH_2CH_3}$$

Kharasch termed this phenomenon the **peroxide effect** and demonstrated that it could occur even if peroxides were not deliberately added to the reaction mixture. Unless alkenes are protected from atmospheric oxygen, they become contaminated with small amounts of alkyl hydroperoxides, compounds of the type ROOH. These alkyl hydroperoxides act in the same way as deliberately added peroxides to promote addition in the direction opposite to that predicted by Markovnikov's rule.

PROBLEM 6.6 Kharasch's earliest studies in this area were carried out in collaboration with graduate student Frank R. Mayo. Mayo performed over 400 experiments in which allyl bromide (3-bromo-1-propene) was treated with hydrogen bromide under a variety of conditions, and determined the distribution of the "normal" and "abnormal" products formed during the reaction. What two products were formed? Which is the product of addition in accordance with Markovnikov's rule? Which one corresponds to addition opposite to the rule?

Kharasch proposed that hydrogen bromide can add to alkenes by two different mechanisms, both of which are, in modern terminology, regiospecific. The first mechanism is the one we discussed in the preceding section, electrophilic addition, and fol-

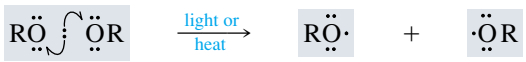
The overall reaction:

1-Butene — Hydrogen bromide — 1-Bromobutane

The mechanism:

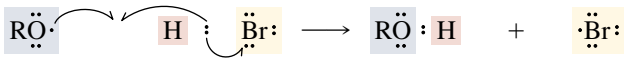
(*a*) Initiation

Step 1: Dissociation of a peroxide into two alkoxy radicals:



Peroxide — Two alkoxy radicals

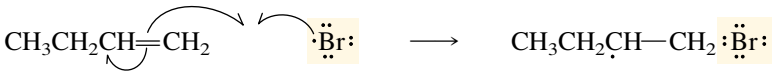
Step 2: Hydrogen atom abstraction from hydrogen bromide by an alkoxy radical:



Alkoxy radical — Hydrogen bromide — Alcohol — Bromine atom

(*b*) Chain propagation

Step 3: Addition of a bromine atom to the alkene:



1-Butene — Bromine atom — (1-Bromomethyl)propyl radical

Step 4: Abstraction of a hydrogen atom from hydrogen bromide by the free radical formed in step 3:

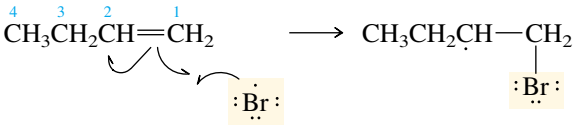
(1-Bromomethyl)propyl radical — Hydrogen bromide — 1-Bromobutane — Bromine atom

FIGURE 6.7 Initiation and propagation steps in the free-radical addition of hydrogen bromide to 1-butene.

lows Markovnikov's rule. It is the mechanism followed when care is taken to ensure that no peroxides are present. The second mechanism is the free-radical chain process, presented in Figure 6.7.

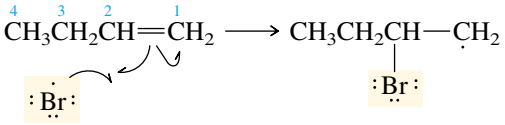
Peroxides are *initiators*; they are not incorporated into the product but act as a source of radicals necessary to get the chain reaction started. The oxygen–oxygen bond of a peroxide is relatively weak, and the free-radical addition of hydrogen bromide to alkenes begins when a peroxide molecule undergoes homolytic cleavage to two alkoxy radicals. This is depicted in step 1 of Figure 6.7. A bromine atom is generated in step 2 when one of these alkoxy radicals abstracts a proton from hydrogen bromide. Once a bromine atom becomes available, the propagation phase of the chain reaction begins. In the propagation phase as shown in step 3, a bromine atom adds to the alkene in the direction that produces the more stable alkyl radical.

Addition of a bromine atom to C-1 gives a secondary alkyl radical.



Secondary alkyl radical

Addition of a bromine atom to C-2 gives a primary alkyl radical.

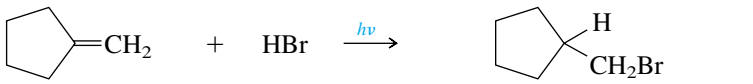


Primary alkyl radical

A secondary alkyl radical is more stable than a primary radical. Bromine therefore adds to C-1 of 1-butene faster than it adds to C-2. Once the bromine atom has added to the double bond, the regioselectivity of addition is set. The alkyl radical then abstracts a hydrogen atom from hydrogen bromide to give the alkyl bromide product as shown in step 4 of Figure 6.7.

The regioselectivity of addition of hydrogen bromide to alkenes under normal (ionic addition) conditions is controlled by the tendency of a *proton* to add to the double bond so as to produce the more stable *carbocation.* Under free-radical conditions the regioselectivity is governed by addition of a *bromine atom* to give the more stable *alkyl radical.*

Free-radical addition of hydrogen bromide to the double bond can also be initiated photochemically, either with or without added peroxides.



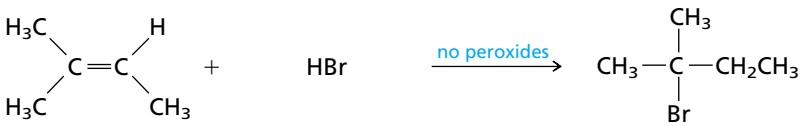
Methylenecyclopentane | Hydrogen bromide | (Bromomethyl)cyclopentane (60%)

Using an sp^2-hybridized carbon for the carbon that has the unpaired electron, make a molecular model of the free-radical intermediate in this reaction.

Among the hydrogen halides, only hydrogen bromide reacts with alkenes by both an ionic and a free-radical mechanism. Hydrogen iodide and hydrogen chloride always add to alkenes by an ionic mechanism and follow Markovnikov's rule. Hydrogen bromide normally reacts by the ionic mechanism, but if peroxides are present or if the reaction is initiated photochemically, the free-radical mechanism is followed.

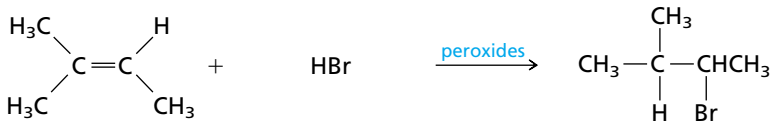
PROBLEM 6.7 Give the major organic product formed when hydrogen bromide reacts with each of the alkenes in Problem 6.3 in the absence of peroxides and in their presence.

SAMPLE SOLUTION (a) The addition of hydrogen bromide in the absence of peroxides exhibits a regioselectivity just like that of hydrogen chloride addition; Markovnikov's rule is followed.



2-Methyl-2-butene | Hydrogen bromide | 2-Bromo-2-methylbutane

Under free-radical conditions in the presence of peroxides, addition takes place with a regioselectivity opposite to that of Markovnikov's rule.

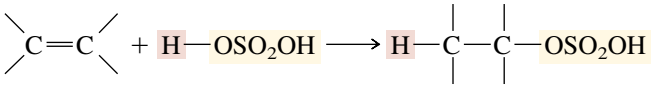


2-Methyl-2-butene Hydrogen bromide 2-Bromo-3-methylbutane

Although the possibility of having two different reaction paths available to an alkene and hydrogen bromide may seem like a complication, it can be an advantage in organic synthesis. From a single alkene one may prepare either of two different alkyl bromides, with control of regioselectivity, simply by choosing reaction conditions that favor ionic addition or free-radical addition of hydrogen bromide.

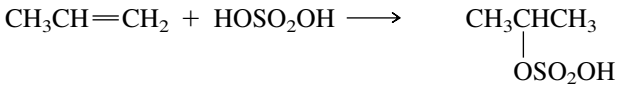
6.9 ADDITION OF SULFURIC ACID TO ALKENES

Acids other than hydrogen halides also add to the carbon–carbon bond of alkenes. Concentrated sulfuric acid, for example, reacts with certain alkenes to form alkyl hydrogen sulfates.



Alkene Sulfuric acid Alkyl hydrogen sulfate

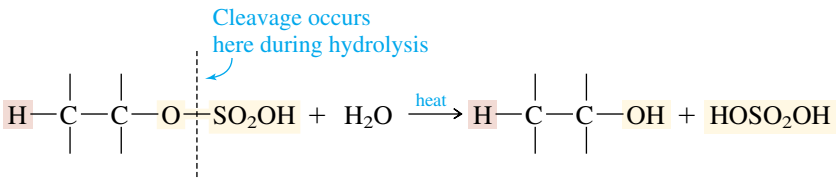
Notice in the following example that a proton adds to the carbon that has the greater number of hydrogens, and the hydrogen sulfate anion ($^-OSO_2OH$) adds to the carbon that has the fewer hydrogens.



Propene Sulfuric acid Isopropyl hydrogen sulfate

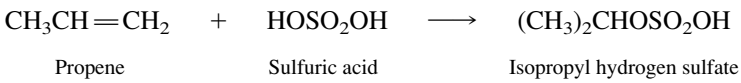
Markovnikov's rule is obeyed because the mechanism of sulfuric acid addition to alkenes, illustrated for the case of propene in Figure 6.8, is analogous to that described earlier for the ionic addition of hydrogen halides.

Alkyl hydrogen sulfates can be converted to alcohols by heating them with water or steam. This is called a **hydrolysis** reaction, because a bond is cleaved by reaction with water. (The suffix *-lysis* indicates cleavage.) It is the oxygen–sulfur bond that is broken when an alkyl hydrogen sulfate undergoes hydrolysis.



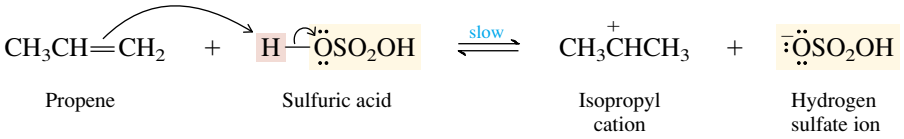
Alkyl hydrogen sulfate Water Alcohol Sulfuric acid

The overall reaction:



The mechanism:

Step 1: Protonation of the carbon–carbon double bond in the direction that leads to the more stable carbocation:



Step 2: Carbocation–anion combination

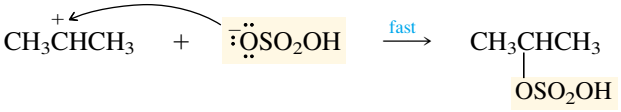
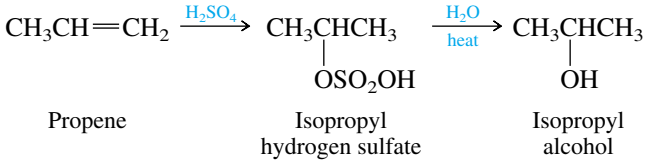


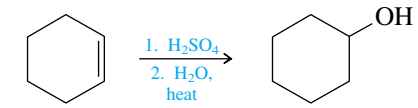
FIGURE 6.8 Mechanism of addition of sulfuric acid to propene.

The combination of sulfuric acid addition to propene, followed by hydrolysis of the resulting isopropyl hydrogen sulfate, is the major method by which over 10^9 lb of isopropyl alcohol is prepared each year in the United States.



It is convenient in synthetic transformations involving more than one step simply to list all the reagents with a single arrow. Individual synthetic steps are indicated by number. Numbering the individual steps is essential so as to avoid the implication that everything is added to the reaction mixture at the same time.

We say that propene has undergone **hydration.** Overall, H and OH have added across the carbon–carbon double bond. In the same manner, cyclohexanol has been prepared by hydration of cyclohexene:



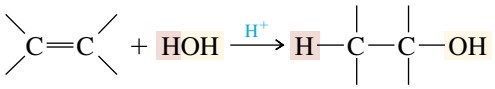
PROBLEM 6.8 Write a structural formula for the compound formed on electrophilic addition of sulfuric acid to cyclohexene (step 1 in the two-step transformation shown in the preceding equation).

Hydration of alkenes by this method, however, is limited to monosubstituted alkenes and disubstituted alkenes of the type RCH=CHR. Disubstituted alkenes of the

type $R_2C{=}CH_2$, along with trisubstituted and tetrasubstituted alkenes, do not form alkyl hydrogen sulfates under these conditions but instead react in a more complicated way with concentrated sulfuric acid (to be discussed in Section 6.21).

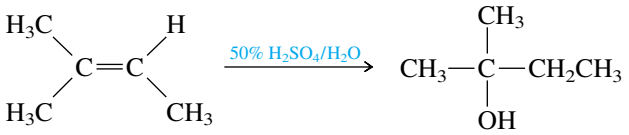
6.10 ACID-CATALYZED HYDRATION OF ALKENES

Another method for the hydration of alkenes is by reaction with water under conditions of acid catalysis.

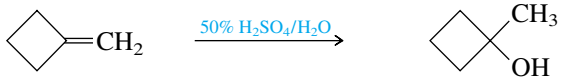


Alkene Water Alcohol

Unlike the addition of concentrated sulfuric acid to form alkyl hydrogen sulfates, this reaction is carried out in a *dilute acid* medium. A 50% water/sulfuric acid solution is often used, yielding the alcohol directly without the necessity of a separate hydrolysis step. Markovnikov's rule is followed:



2-Methyl-2-butene 2-Methyl-2-butanol (90%)



Methylenecyclobutane 1-Methylcyclobutanol (80%)

We can extend the general principles of electrophilic addition to acid-catalyzed hydration. In the first step of the mechanism shown in Figure 6.9, proton transfer to 2-methylpropene forms *tert*-butyl cation. This is followed in step 2 by reaction of the carbocation with a molecule of water acting as a nucleophile. The alkyloxonium ion formed in this step is simply the conjugate acid of *tert*-butyl alcohol. Deprotonation of the alkyloxonium ion in step 3 yields the alcohol and regenerates the acid catalyst.

PROBLEM 6.9 Instead of the three-step mechanism of Figure 6.9, the following two-step mechanism might be considered:

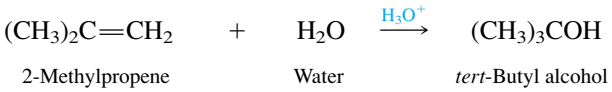
1. $(CH_3)_2C{=}CH_2 + H_3O^+ \xrightarrow{\text{slow}} (CH_3)_3C^+ + H_2O$

2. $(CH_3)_3C^+ + HO^- \xrightarrow{\text{fast}} (CH_3)_3COH$

This mechanism cannot be correct! What is its fundamental flaw?

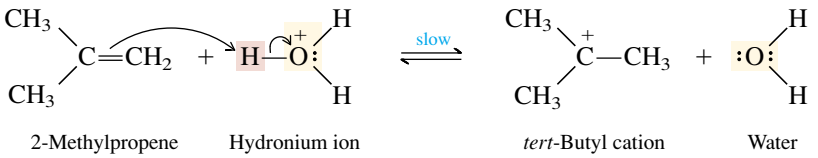
The notion that carbocation formation is rate-determining follows from our previous experience and by observing how the reaction rate is affected by the structure of the alkene. Table 6.2 gives some data showing that alkenes that yield relatively stable carbocations react faster than those that yield less stable carbocations. Protonation of ethylene, the least reactive alkene in the table, yields a primary carbocation; protonation of 2-methylpropene, the most reactive in the table, yields a tertiary carbocation. As we have seen on other occasions, the more stable the carbocation, the faster is its rate of formation.

The overall reaction:

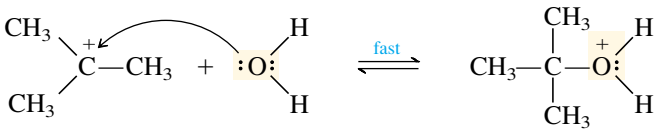


The mechanism:

Step 1: Protonation of the carbon–carbon double bond in the direction that leads to the more stable carbocation:



Step 2: Water acts as a nucleophile to capture *tert*-butyl cation:



Step 3: Deprotonation of *tert*-butyloxonium ion. Water acts as a Brønsted base:

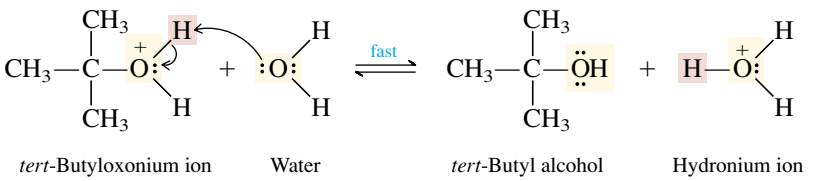


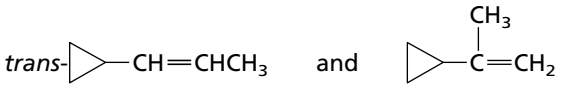
FIGURE 6.9 Mechanism of acid-catalyzed hydration of 2-methylpropene.

TABLE 6.2 Relative Rates of Acid-Catalyzed Hydration of Some Representative Alkenes

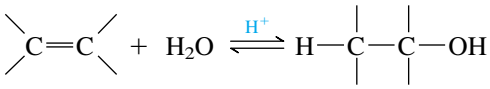
Alkene	Structural formula	Relative rate of acid-catalyzed hydration*
Ethylene	$CH_2{=}CH_2$	1.0
Propene	$CH_3CH{=}CH_2$	1.6×10^6
2-Methylpropene	$(CH_3)_2C{=}CH_2$	2.5×10^{11}

*In water, 25°C.

PROBLEM 6.10 The rates of hydration of the two alkenes shown differ by a factor of over 7000 at 25°C. Which isomer is the more reactive? Why?



You may have noticed that the acid-catalyzed hydration of an alkene and the acid-catalyzed dehydration of an alcohol are the reverse of each other.

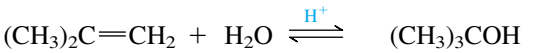


Alkene Water Alcohol

According to **Le Châtelier's principle,** *a system at equilibrium adjusts so as to minimize any stress applied to it.* When the concentration of water is increased, the system responds by consuming water. This means that proportionally more alkene is converted to alcohol; the position of equilibrium shifts to the right. Thus, when we wish to prepare an alcohol from an alkene, we employ a reaction medium in which the molar concentration of water is high—dilute sulfuric acid, for example.

On the other hand, alkene formation is favored when the concentration of water is kept low. The system responds to the absence of water by causing more alcohol molecules to suffer dehydration, and when alcohol molecules dehydrate, they form more alkene. The amount of water in the reaction mixture is kept low by using concentrated strong acids as catalysts. Distilling the reaction mixture is an effective way of removing water as it is formed, causing the equilibrium to shift toward products. If the alkene is low-boiling, it too can be removed by distillation. This offers the additional benefit of protecting the alkene from acid-catalyzed isomerization after it is formed.

In any equilibrium process, the sequence of intermediates and transition states encountered as reactants proceed to products in one direction must also be encountered, and in precisely the reverse order, in the opposite direction. This is called the **principle of microscopic reversibility.** Just as the reaction



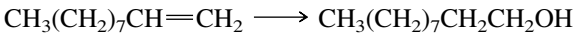
2-Methylpropene Water 2-Methyl-2-propanol

is reversible with respect to reactants and products, so each tiny increment of progress along the reaction coordinate is reversible. Once we know the mechanism for the forward phase of a particular reaction, we also know what the intermediates and transition states must be for the reverse. In particular, the three-step mechanism for the acid-catalyzed hydration of 2-methylpropene in Figure 6.9 is the reverse of that for the acid-catalyzed dehydration of *tert*-butyl alcohol in Figure 5.7.

PROBLEM 6.11 Is the electrophilic addition of hydrogen chloride to 2-methylpropene the reverse of the E1 or the E2 elimination reaction of *tert*-butyl chloride?

6.11 HYDROBORATION–OXIDATION OF ALKENES

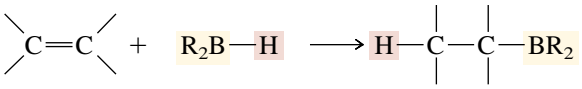
Acid-catalyzed hydration converts alkenes to alcohols with Markovnikov rule regioselectivity. Frequently, however, one needs an alcohol having a structure that corresponds to hydration of an alkene with a regioselectivity apparently opposite to that of Markovnikov's rule. The conversion of 1-decene to 1-decanol is an example of such a transformation.



1-Decene 1-Decanol

The synthetic method used to accomplish this is an indirect one, and is known as **hydroboration–oxidation.** It was developed by Professor Herbert C. Brown and his coworkers at Purdue University in the 1950s as part of a broad program designed to apply boron-containing reagents to organic chemical synthesis. The number of applications is so large (hydroboration–oxidation is just one of them) and the work so novel that Brown was a corecipient of the 1979 Nobel Prize in chemistry.

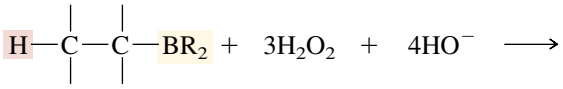
Hydroboration is a reaction in which a boron hydride, a compound of the type R_2BH, adds to a carbon–carbon bond. A new carbon–hydrogen bond and a carbon–boron bond result.



Alkene Boron hydride Organoborane

With sodium hydroxide as the base, boron of the alkylborane is converted to the water-soluble and easily removed sodium salt of boric acid.

Following hydroboration, the organoborane is oxidized by treatment with hydrogen peroxide in aqueous base. This is the **oxidation** stage of the sequence; hydrogen peroxide is the oxidizing agent, and the organoborane is converted to an alcohol.

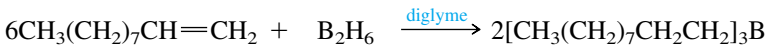


Organoborane Hydrogen peroxide Hydroxide ion

Alcohol Alcohol Borate ion Water

The combination of hydroboration and oxidation leads to the overall hydration of an alkene. Notice, however, that water is not a reactant. The hydrogen that becomes bonded to carbon comes from the organoborane, and the hydroxyl group from hydrogen peroxide.

With this as introduction, let us now look at the individual steps in more detail for the case of hydroboration–oxidation of 1-decene. A boron hydride that is often used is *diborane* (B_2H_6). Diborane adds to 1-decene to give tridecylborane according to the balanced equation:

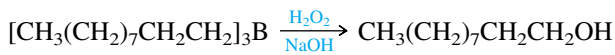


1-Decene Diborane Tridecylborane

Diglyme, shown above the arrow in the equation is the solvent in this example. Diglyme is an acronym for *di*ethylene *gly*col di*m*ethyl *e*ther, and its structure is $CH_3OCH_2CH_2OCH_2CH_2OCH_3$.

There is a pronounced tendency for boron to become bonded to the less substituted carbon of the double bond. Thus, the hydrogen atoms of diborane add to C-2 of 1-decene, and boron to C-1. This is believed to be mainly a steric effect, but the regioselectivity of addition does correspond to Markovnikov's rule in the sense that hydrogen is the negatively polarized atom in a B—H bond and boron the positively polarized one.

Oxidation of tridecylborane gives 1-decanol. The net result is the conversion of an alkene to an alcohol with a regioselectivity opposite to that of acid-catalyzed hydration.



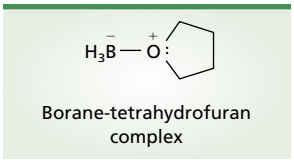
Tridecylborane 1-Decanol

It is customary to combine the two stages, hydroboration and oxidation, in a single equation with the operations numbered sequentially above and below the arrow.

$$CH_3(CH_2)_7CH{=}CH_2 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6,\ \text{diglyme}} CH_3(CH_2)_7CH_2CH_2OH$$

1-Decene — 1-Decanol (93%)

A more convenient hydroborating agent is the borane–tetrahydrofuran complex ($H_3B{\bullet}THF$). It is very reactive, adding to alkenes within minutes at 0°C, and is used in tetrahydrofuran as the solvent.

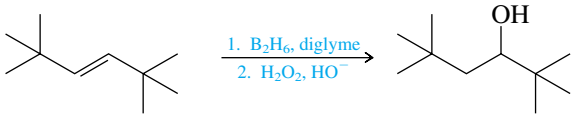


Borane-tetrahydrofuran complex

$$(CH_3)_2C{=}CHCH_3 \xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ H_3B{\cdot}THF} (CH_3)_2CHCHCH_3 \quad (OH)$$

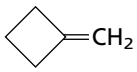
2-Methyl-2-butene — 3-Methyl-2-butanol (98%)

Carbocation intermediates are not involved in hydroboration–oxidation. Hydration of double bonds takes place without rearrangement, even in alkenes as highly branched as the following:



(*E*)-2,2,5,5-Tetramethyl-3-hexene — 2,2,5,5-Tetramethyl-3-hexanol (82%)

PROBLEM 6.12 Write the structure of the major organic product obtained by hydroboration–oxidation of each of the following alkenes:

(a) 2-Methylpropene
(b) *cis*-2-Butene
(c) 
(d) Cyclopentene
(e) 3-Ethyl-2-pentene
(f) 3-Ethyl-1-pentene

SAMPLE SOLUTION (a) In hydroboration–oxidation the elements of water (H and OH) are introduced with a regioselectivity opposite to that of Markovnikov's rule. In the case of 2-methylpropene, this leads to 2-methyl-1-propanol as the product.

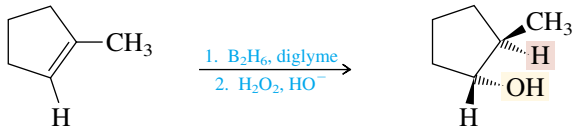
$$(CH_3)_2C{=}CH_2 \xrightarrow[2.\ \text{oxidation}]{1.\ \text{hydroboration}} (CH_3)_2CH{-}CH_2OH$$

2-Methylpropene — 2-Methyl-1-propanol

Hydrogen becomes bonded to the carbon that has the fewer hydrogens, hydroxyl to the carbon that has the greater number of hydrogens.

6.12 STEREOCHEMISTRY OF HYDROBORATION–OXIDATION

A second aspect of hydroboration–oxidation concerns its stereochemistry. As illustrated for the case of 1-methylcyclopentene, H and OH add to the same face of the double bond.



1-Methylcyclopentene

trans-2-Methylcyclopentanol
(only product, 86% yield)

Overall, the reaction leads to syn addition of the elements of water to the double bond. This fact has an important bearing on the mechanism of the process.

PROBLEM 6.13 Hydroboration–oxidation of α-pinene (page 213), like catalytic hydrogenation, is stereoselective. Addition takes place at the less hindered face of the double bond, and a single alcohol is produced in high yield (89%). Suggest a reasonable structure for this alcohol.

6.13 MECHANISM OF HYDROBORATION–OXIDATION

The regioselectivity and syn stereochemistry of hydroboration–oxidation, coupled with a knowledge of the chemical properties of alkenes and boranes, contribute to our understanding of the reaction mechanism.

Borane (BH_3) does not exist as such under normal conditions of temperature and atmospheric pressure. Two molecules of BH_3 combine to give diborane (B_2H_6), which is the more stable form.

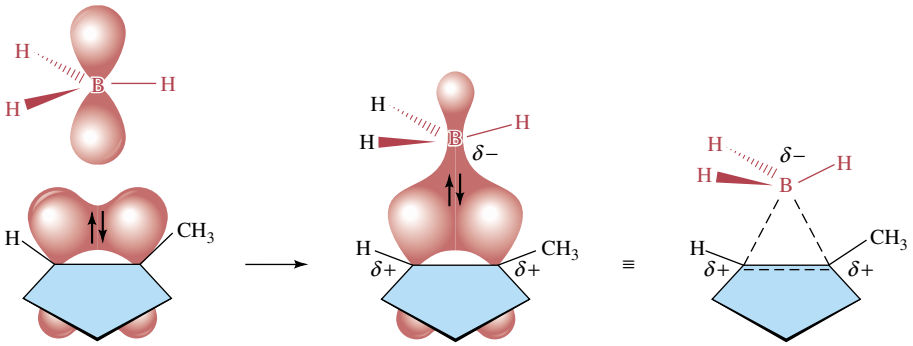
We can consider the hydroboration step as though it involved borane (BH_3). It simplifies our mechanistic analysis and is at variance with reality only in matters of detail. Borane is electrophilic; it has a vacant 2*p* orbital and can accept a pair of electrons into that orbital. The source of this electron pair is the π bond of an alkene. It is believed, as shown in Figure 6.10 for the example of the hydroboration of 1-methylcyclopentene, that the first step produces an unstable intermediate called a *π complex.* In this π complex boron and the two carbon atoms of the double bond are joined by a *three-center two-electron bond,* by which we mean that three atoms share two electrons. Three-center two-electron bonds are frequently encountered in boron chemistry. The π complex is formed by a transfer of electron density from the π orbital of the alkene to the 2*p* orbital of boron. This leaves each carbon of the complex with a small positive charge, while boron is slightly negative. The negative character of boron in this intermediate makes it easy for one of its hydrogen substituents to migrate with a pair of electrons (a hydride shift) from boron to carbon. The transition state for this process is shown in step 2(*a*) of Figure 6.10; completion of the migration in step 2(*b*) yields the alkylborane. According to this mechanism, the carbon–boron bond and the carbon–hydrogen bond are formed on the same side of the alkene. The hydroboration step is a syn addition process.

The regioselectivity of addition is consistent with the electron distribution in the complex. Hydrogen is transferred with a pair of electrons to the carbon atom that can best support a positive charge, namely, the one that bears the methyl group.

Steric effects may be an even more important factor in controlling the regioselectivity of addition. Boron, with its attached substituents, is much larger than a hydrogen atom and becomes bonded to the less crowded carbon of the double bond, whereas hydrogen becomes bonded to the more crowded carbon.

The electrophilic character of boron is again evident when we consider the oxidation of organoboranes. In the oxidation phase of the hydroboration–oxidation sequence, as presented in Figure 6.11, the anion of hydrogen peroxide attacks boron. Hydroperoxide ion is formed in an acid–base reaction in step 1 and attacks boron in step 2. The empty 2*p* orbital of boron makes it electrophilic and permits nucleophilic reagents such as HOO^- to add to it.

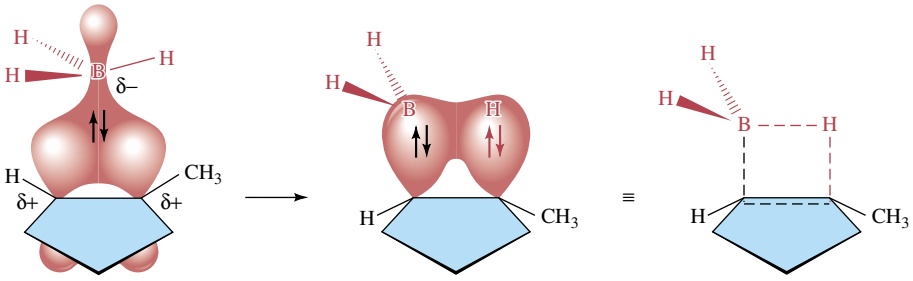
Step 1: A molecule of borane (BH_3) attacks the alkene. Electrons flow from the π orbital of the alkene to the 2*p* orbital of boron. A π complex is formed.



Alternative representations of π-complex intermediate

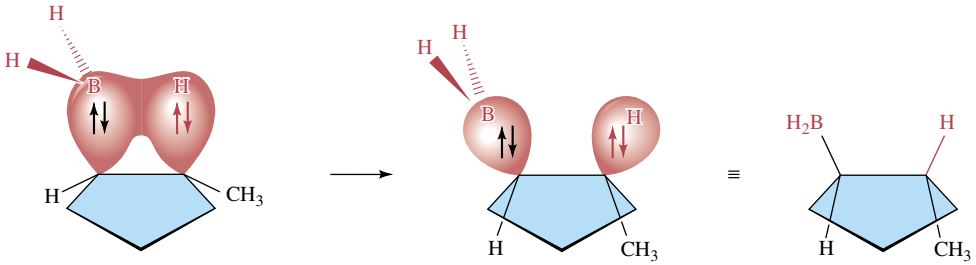
Step 2: The π complex rearranges to an organoborane. Hydrogen migrates from boron to carbon, carrying with it the two electrons in its bond to boron. Development of the transition state for this process is shown in 2(*a*), and its transformation to the organoborane is shown in 2(*b*).

2(*a*)



Representations of transition state for hydride migration in π-complex intermediate

2(*b*)



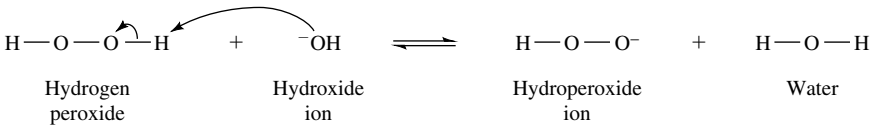
Product of addition of borane (BH_3) to 1-methylcyclopentene

FIGURE 6.10 Orbital interactions and electron redistribution in the hydroboration of 1-methylcyclopentene.

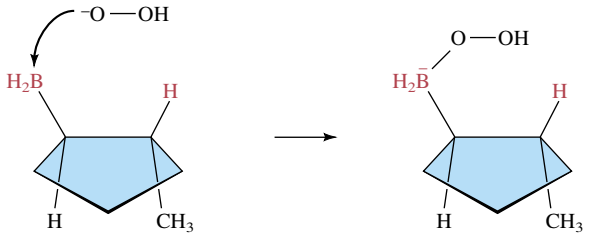
The combination of a negative charge on boron and the weak oxygen–oxygen bond causes an alkyl group to migrate from boron to oxygen in step 3. This alkyl group migration occurs with loss of hydroxide ion and is the step in which the critical carbon–oxygen bond is formed. What is especially significant about this alkyl group migration is that the stereochemical orientation of the new carbon–oxygen bond is the same as that of the original carbon–boron bond. This is crucial to the overall syn stereochemistry of

FIGURE 6.11 The oxidation phase in the hydroboration–oxidation of 1-methylcyclopentene.

Step 1: Hydrogen peroxide is converted to its anion in basic solution:

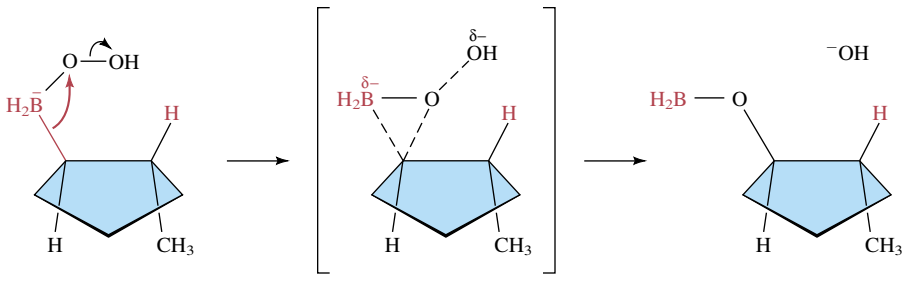


Step 2: Anion of hydrogen peroxide acts as a nucleophile, attacking boron and forming an oxygen–boron bond:



Organoborane intermediate from hydroboration of 1-methylcyclopentene

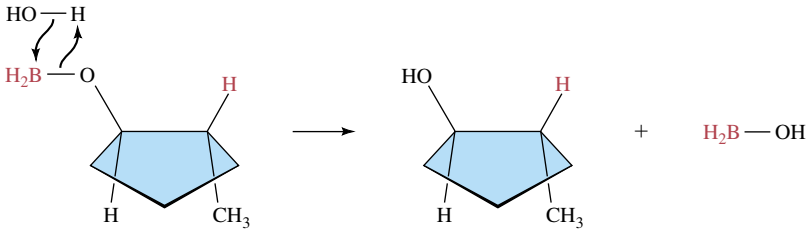
Step 3: Carbon migrates from boron to oxygen, displacing hydroxide ion. Carbon migrates with the pair of electrons in the carbon–boron bond; these become the electrons in the carbon–oxygen bond:



Representation of transition state for migration of carbon from boron to oxygen

Alkoxyborane

Step 4: Hydrolysis cleaves the boron–oxygen bond, yielding the alcohol:



Alkoxyborane

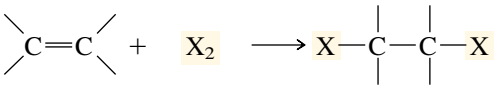
trans-2-Methylcyclopentanol

the hydroboration–oxidation sequence. Migration of the alkyl group from boron to oxygen is said to have occurred with *retention of configuration* at carbon. The alkoxyborane intermediate formed in step 3 undergoes subsequent base-promoted oxygen-boron bond cleavage in step 4 to give the alcohol product.

The mechanistic complexity of hydroboration–oxidation stands in contrast to the simplicity with which these reactions are carried out experimentally. Both the hydroboration and oxidation steps are extremely rapid reactions and are performed at room temperature with conventional laboratory equipment. Ease of operation, along with the fact that hydroboration–oxidation leads to syn hydration of alkenes and occurs with a regioselectivity opposite to Markovnikov's rule, makes this procedure one of great value to the synthetic chemist.

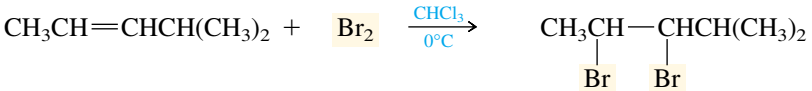
6.14 ADDITION OF HALOGENS TO ALKENES

In contrast to the free-radical substitution observed when halogens react with *alkanes,* halogens normally react with *alkenes* by electrophilic addition.



Alkene Halogen Vicinal dihalide

The products of these reactions are called **vicinal** dihalides. Two substituents, in this case the halogens, are vicinal if they are attached to adjacent carbons. The word is derived from the Latin *vicinalis,* which means "neighboring." The halogen is either chlorine (Cl_2) or bromine (Br_2), and addition takes place rapidly at room temperature and below in a variety of solvents, including acetic acid, carbon tetrachloride, chloroform, and dichloromethane.



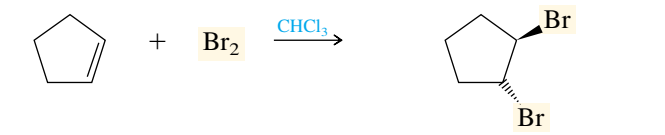
4-Methyl-2-pentene Bromine 2,3-Dibromo-4-methylpentane (100%)

Rearrangements do not normally occur, which can mean either of two things. Either carbocations are not intermediates, or if they are, they are captured by a nucleophile faster than they rearrange. We shall see in Section 6.16 that the first of these is believed to be the case.

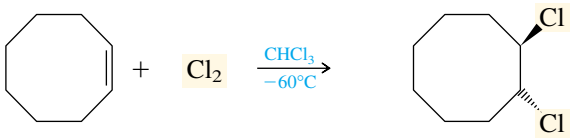
Fluorine addition to alkenes is a violent reaction, difficult to control, and accompanied by substitution of hydrogens by fluorine (Section 4.15). Vicinal diiodides, on the other hand, tend to lose I_2 and revert to alkenes, making them an infrequently encountered class of compounds.

6.15 STEREOCHEMISTRY OF HALOGEN ADDITION

The reaction of chlorine and bromine with cycloalkenes illustrates an important stereochemical feature of halogen addition. Anti addition is observed; the two bromine atoms of Br_2 or the two chlorines of Cl_2 add to opposite faces of the double bond.

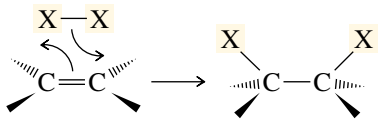


Cyclopentene Bromine *trans*-1,2-Dibromocyclopentane (80% yield; none of the *cis* isomer is formed)



Cyclooctene Chlorine *trans*-1,2-Dichlorocyclooctane (73% yield; none of the *cis* isomer is formed)

These observations must be taken into account when considering the mechanism of halogen addition. They force the conclusion that a simple one-step "bond-switching" process of the following type cannot be correct. A process of this type requires syn addition; it is *not* consistent with the anti addition that we actually see.



PROBLEM 6.14 The mass 82 isotope of bromine (^{82}Br) is radioactive and is used as a tracer to identify the origin and destination of individual atoms in chemical reactions and biological transformations. A sample of 1,1,2-tribromocyclohexane was prepared by adding ^{82}Br—^{82}Br to ordinary (nonradioactive) 1-bromocyclohexene. How many of the bromine atoms in the 1,1,2-tribromocyclohexane produced are radioactive? Which ones are they?

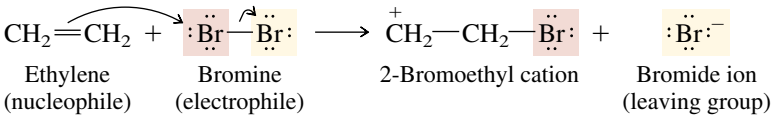
6.16 MECHANISM OF HALOGEN ADDITION TO ALKENES: HALONIUM IONS

Many of the features of the generally accepted mechanism for the addition of halogens to alkenes can be introduced by referring to the reaction of ethylene with bromine:

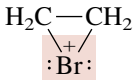
$$\underset{\text{Ethylene}}{CH_2{=}CH_2} + \underset{\text{Bromine}}{Br_2} \longrightarrow \underset{\text{1,2-Dibromoethane}}{BrCH_2CH_2Br}$$

Until it was banned in the United States in 1984, 1,2-dibromoethane (ethylene dibromide, or EDB) was produced on a large scale for use as a pesticide and soil fumigant.

Neither bromine nor ethylene is a polar molecule, but both are *polarizable,* and an induced-dipole/induced-dipole force causes them to be mutually attracted to each other. This induced-dipole/induced-dipole attraction sets the stage for Br_2 to act as an electrophile. Electrons flow from the π system of ethylene to Br_2, causing the weak bromine–bromine bond to break. By analogy to the customary mechanisms for electrophilic addition, we might represent this as the formation of a carbocation in a bimolecular elementary step.



Such a carbocation, however, has been demonstrated to be less stable than an alternative structure called a **cyclic bromonium ion,** in which the positive charge resides on bromine, not carbon.



Ethylenebromonium ion

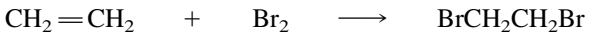
The chief reason why ethylenebromonium ion, in spite of its strained three-membered ring, is more stable than 2-bromoethyl cation is that all its atoms have octets of electrons, whereas carbon has only 6 electrons in the carbocation.

Thus, the mechanism for electrophilic addition of Br_2 to ethylene as presented in Figure 6.12 is characterized by the direct formation of a cyclic bromonium ion as its first elementary step. Step 2 is the conversion of the bromonium ion to 1,2-dibromoethane by reaction with bromide ion (Br^-).

The effect of substituents on the rate of addition of bromine to alkenes (Table 6.3) is substantial and consistent with a rate-determining step in which electrons flow from the alkene to the halogen. Alkyl groups on the carbon–carbon double bond release electrons, stabilize the transition state for bromonium ion formation, and increase the reaction rate.

The graphic on the first page of this chapter is an electrostatic potential map of ethylenebromonium ion.

The overall reaction:



The mechanism:

Step 1: Reaction of ethylene and bromine to form a bromonium ion intermediate:

Step 2: Nucleophilic attack of bromide anion on the bromonium ion:

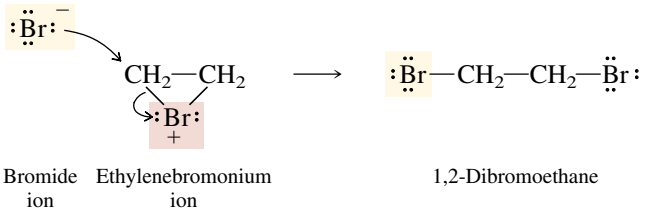


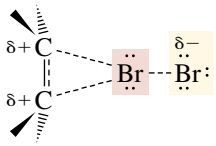
FIGURE 6.12 Mechanism of electrophilic addition of bromine to ethylene.

TABLE 6.3 Relative Rates of Reaction of Some Representative Alkenes with Bromine

Alkene	Structural formula	Relative rate of reaction with bromine*
Ethylene	$CH_2{=}CH_2$	1.0
Propene	$CH_3CH{=}CH_2$	61
2-Methylpropene	$(CH_3)_2C{=}CH_2$	5,400
2,3-Dimethyl-2-butene	$(CH_3)_2C{=}C(CH_3)_2$	920,000

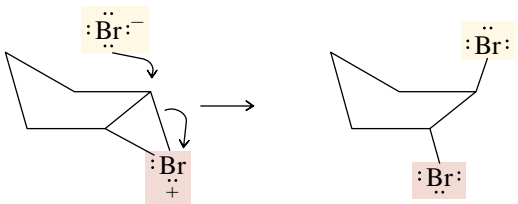
*In methanol, 25°C.

Transition state for bromonium ion formation from an alkene and bromine



PROBLEM 6.15 Arrange the compounds 2-methyl-1-butene, 2-methyl-2-butene, and 3-methyl-1-butene in order of decreasing reactivity toward bromine.

Step 2 of the mechanism in Figure 6.12 is a nucleophilic attack by Br^- at one of the carbons of the cyclic bromonium ion. For reasons that will be explained in Chapter 8, reactions of this type normally take place via a transition state in which the nucleophile approaches carbon from the side opposite the bond that is to be broken. Recalling that the vicinal dibromide formed from cyclopentene is exclusively the trans stereoisomer, we see that attack by Br^- from the side opposite the C—Br bond of the bromonium ion intermediate can give only *trans*-1,2-dibromocyclopentane in accordance with the experimental observations.



Bromonium ion intermediate

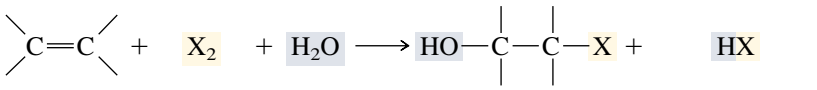
trans-1,2-Dibromocyclopentane

Some supporting evidence is described in the article "The Bromonium Ion," in the August 1963 issue of the *Journal of Chemical Education* (pp. 392–395).

The idea that a cyclic bromonium ion was an intermediate was a novel concept at the time of its proposal in 1937. Much additional evidence, including the isolation of a stable cyclic bromonium ion, has been obtained since then to support it. Similarly, **cyclic chloronium ions** are believed to be involved in the addition of chlorine to alkenes. In the next section we shall see how cyclic chloronium and bromonium ions **(halonium ions)** are intermediates in a second reaction involving alkenes and halogens.

6.17 CONVERSION OF ALKENES TO VICINAL HALOHYDRINS

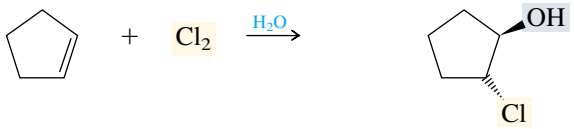
In *aqueous* solution chlorine and bromine react with alkenes to form **vicinal halohydrins,** compounds that have a halogen and a hydroxyl group on adjacent carbons.



Alkene Halogen Water Halohydrin Hydrogen halide

Ethylene Bromine 2-Bromoethanol (70%)

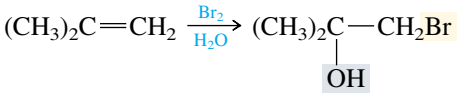
Anti addition occurs. The halogen and the hydroxyl group add to opposite faces of the double bond.



Cyclopentene Chlorine *trans*-2-Chlorocyclopentanol (52–56% yield; cis isomer not formed)

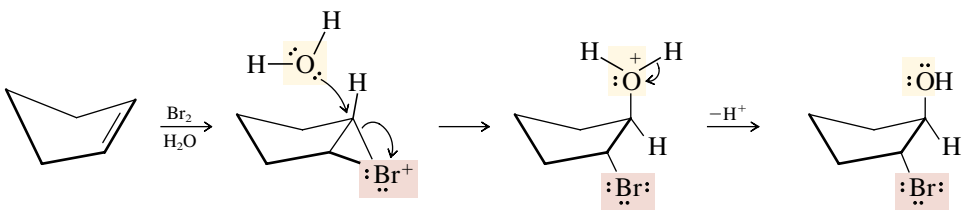
Halohydrin formation, as depicted in Figure 6.13, is mechanistically related to halogen addition to alkenes. A halonium ion intermediate is formed, which is attacked by water in aqueous solution.

The regioselectivity of addition is established when water attacks one of the carbons of the halonium ion. In the reaction shown, the structure of the product tells us that water attacks the more highly substituted carbon.



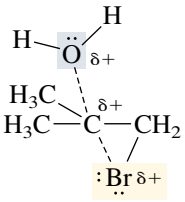
2-Methylpropene 1-Bromo-2-methyl-2-propanol (77%)

This suggests that, as water attacks the bromonium ion, positive charge develops on the carbon from which the bromine departs. The transition state has some of the character of a carbocation. We know that more highly substituted carbocations are more stable than less highly substituted ones; therefore, when the bromonium ion ring opens, it does so by breaking the bond between bromine and the more substituted carbon.

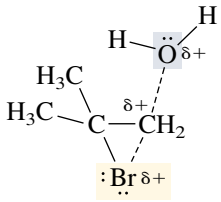


Cyclopentene *trans*-2-Bromocyclopentanol

FIGURE 6.13 Mechanism of bromohydrin formation from cyclopentene. A bridged bromonium ion is formed and is attacked by a water molecule from the side opposite the carbon–bromine bond. The bromine and the hydroxyl group are trans to each other in the product.



More stable transition state; has some of the character of a tertiary carbocation

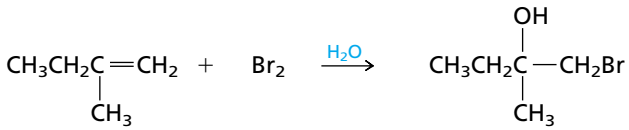


Less stable transition state; has some of the character of a primary carbocation

PROBLEM 6.16 Give the structure of the product formed when each of the following alkenes reacts with bromine in water:

(a) 2-Methyl-1-butene
(b) 2-Methyl-2-butene
(c) 3-Methyl-1-butene
(d) 1-Methylcyclopentene

SAMPLE SOLUTION (a) The hydroxyl group becomes bonded to the more highly substituted carbon of the double bond, and bromine bonds to the less highly substituted one.

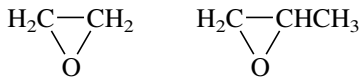


2-Methyl-1-butene Bromine 1-Bromo-2-methyl-2-butanol

6.18 EPOXIDATION OF ALKENES

You have just seen that cyclic halonium ion intermediates are formed when sources of electrophilic halogen attack a double bond. Likewise, three-membered oxygen-containing rings are formed by the reaction of alkenes with sources of electrophilic oxygen.

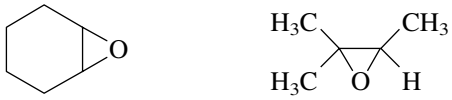
Three-membered rings that contain oxygen are called *epoxides*. At one time, epoxides were named as oxides of alkenes. Ethylene oxide and propylene oxide, for example, are the common names of two industrially important epoxides.



Ethylene oxide Propylene oxide

A second method for naming epoxides in the IUPAC system is described in Section 16.1.

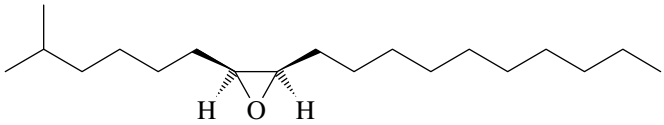
Substitutive IUPAC nomenclature names epoxides as *epoxy* derivatives of alkanes. According to this system, ethylene oxide becomes epoxyethane, and propylene oxide becomes 1,2-epoxypropane. The prefix *epoxy-* always immediately precedes the alkane ending; it is not listed in alphabetical order like other substituents.



1,2-Epoxycyclohexane 2-Methyl-2,3-epoxybutane

Functional group transformations of epoxides rank among the fundamental reactions of organic chemistry, and epoxides are commonplace natural products. The female

gypsy moth, for example, attracts the male by emitting an epoxide known as *disparlure.* On detecting the presence of this pheromone, the male follows the scent to its origin and mates with the female.

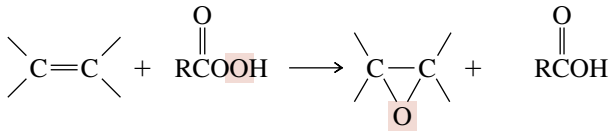


Disparlure

In one strategy designed to control the spread of the gypsy moth, infested areas are sprayed with synthetic disparlure. With the sex attractant everywhere, male gypsy moths become hopelessly confused as to the actual location of individual females. Many otherwise fertile female gypsy moths then live out their lives without producing hungry gypsy moth caterpillars.

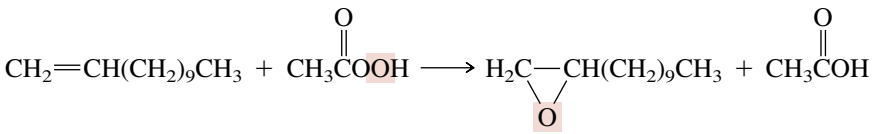
PROBLEM 6.17 Give the substitutive IUPAC name, including stereochemistry, for disparlure.

Epoxides are very easy to prepare via the reaction of an alkene with a peroxy acid. This process is known as **epoxidation.**

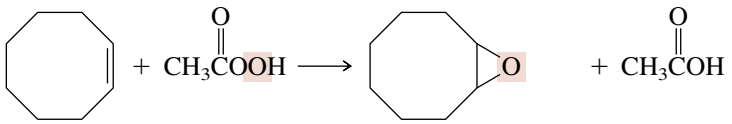


Alkene Peroxy acid Epoxide Carboxylic acid

A commonly used peroxy acid is peroxyacetic acid (CH_3CO_2OH). Peroxyacetic acid is normally used in acetic acid as the solvent, but epoxidation reactions tolerate a variety of solvents and are often carried out in dichloromethane or chloroform.



1-Dodecene Peroxyacetic acid 1,2-Epoxydodecane (52%) Acetic acid



Cyclooctene Peroxyacetic acid 1,2-Epoxycyclooctane (86%) Acetic acid

Epoxidation of alkenes with peroxy acids is a syn addition to the double bond. Substituents that are cis to each other in the alkene remain cis in the epoxide; substituents that are trans in the alkene remain trans in the epoxide.

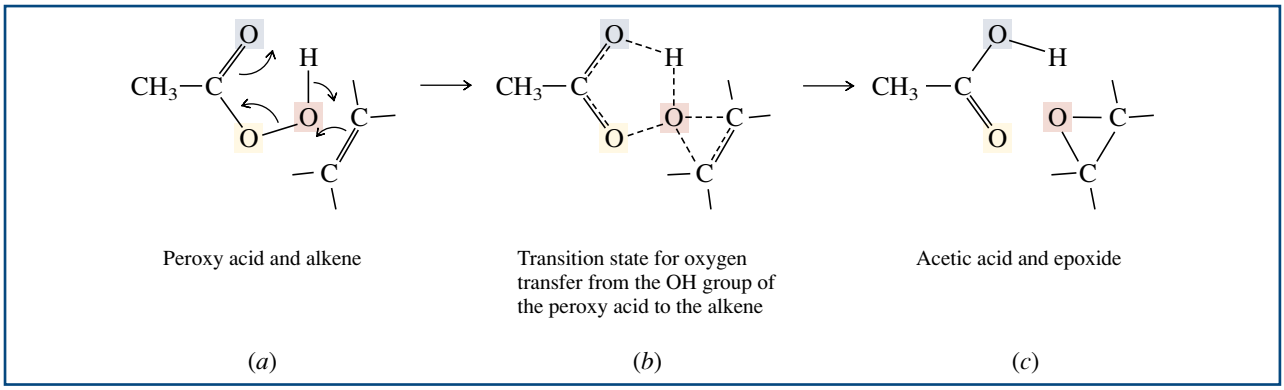


FIGURE 6.14 A one-step mechanism for epoxidation of alkenes by peroxyacetic acid. In (*a*) the starting peroxy acid is shown in a conformation in which the proton of the OH group is hydrogen bonded to the oxygen of the C═O group. (*b*) The weak O—O bond of the peroxy acid breaks, and both C—O bonds of the epoxide form in the same transition state leading to products (*c*).

TABLE 6.4 Relative Rates of Epoxidation of Some Representative Alkenes with Peroxyacetic Acid

Alkene	Structural formula	Relative rate of epoxidation*
Ethylene	$CH_2{=}CH_2$	1.0
Propene	$CH_3CH{=}CH_2$	22
2-Methylpropene	$(CH_3)_2C{=}CH_2$	484
2-Methyl-2-butene	$(CH_3)_2C{=}CHCH_3$	6526

*In acetic acid, 26°C.

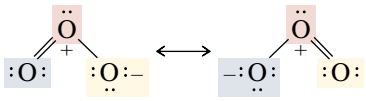
PROBLEM 6.18 Give the structure of the alkene, including stereochemistry, that you would choose as the starting material in a preparation of synthetic disparlure.

As shown in Table 6.4, electron-releasing alkyl groups on the double bond increase the rate of epoxidation. This suggests that the peroxy acid acts as an electrophilic reagent toward the alkene.

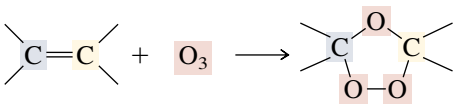
The mechanism of alkene epoxidation is believed to be a concerted process involving a single bimolecular elementary step, as shown in Figure 6.14.

6.19 OZONOLYSIS OF ALKENES

Ozone (O_3) is the triatomic form of oxygen. It is a neutral but polar molecule that can be represented as a hybrid of its two most stable Lewis structures.

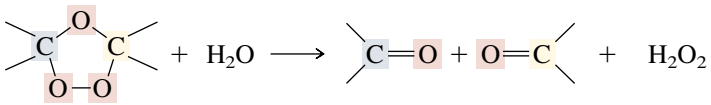


Ozone is a powerful electrophile and undergoes a remarkable reaction with alkenes in which both the σ and π components of the carbon–carbon double bond are cleaved to give a product referred to as an **ozonide.**



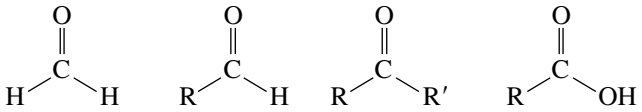
Alkene Ozone Ozonide

Ozonides undergo hydrolysis in water, giving carbonyl compounds.



Ozonide Water Two carbonyl compounds Hydrogen peroxide

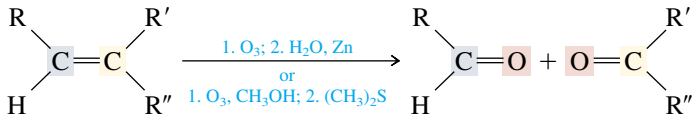
Two aldehydes, two ketones, or one aldehyde and one ketone may be formed. Let's recall the classes of carbonyl compounds from Table 2.2. Aldehydes have at least one hydrogen substituent on the carbonyl group; ketones have two carbon substituents—alkyl groups, for example—on the carbonyl. Carboxylic acids have a hydroxyl substituent attached to the carbonyl group.



Formaldehyde Aldehyde Ketone Carboxylic acid

Aldehydes are easily oxidized to carboxylic acids under conditions of ozonide hydrolysis. When one wishes to isolate the aldehyde itself, a reducing agent such as zinc is included during the hydrolysis step. Zinc reacts with the oxidants present (excess ozone and hydrogen peroxide), preventing them from oxidizing any aldehyde formed. An alternative, more modern technique follows ozone treatment of the alkene in methanol with reduction by dimethyl sulfide (CH_3SCH_3).

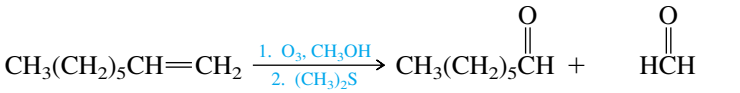
The two-stage reaction sequence is called **ozonolysis** and is represented by the general equation



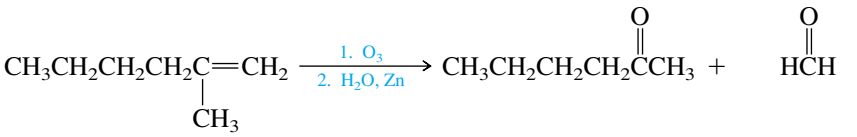
Alkene Aldehyde Ketone

Each carbon of the double bond becomes the carbon of a carbonyl group.

Ozonolysis has both synthetic and analytical applications in organic chemistry. In synthesis, ozonolysis of alkenes provides a method for the preparation of aldehydes and ketones.



1-Octene Heptanal (75%) Formaldehyde



2-Methyl-1-hexene 2-Hexanone (60%) Formaldehyde

When the objective is analytical, the products of ozonolysis are isolated and identified, thereby allowing the structure of the alkene to be deduced. In one such example, an alkene having the molecular formula C_8H_{16} was obtained from a chemical reaction and was then subjected to ozonolysis, giving acetone and 2,2-dimethylpropanal as the products.

Acetone 2,2-Dimethylpropanal

Together, these two products contain all eight carbons of the starting alkene. The two carbonyl carbons correspond to those that were doubly bonded in the original alkene. One of the doubly bonded carbons therefore bears two methyl substituents; the other bears a hydrogen and a *tert*-butyl group. The alkene is identified as 2,4,4-trimethyl-2-pentene, $(CH_3)_2C{=}CHC(CH_3)_3$, as shown in Figure 6.15.

PROBLEM 6.19

The same reaction that gave 2,4,4-trimethyl-2-pentene also yielded an isomeric alkene. This second alkene produced formaldehyde and 4,4-dimethyl-2-pentanone on ozonolysis. Identify this alkene.

4,4-Dimethyl-2-pentanone

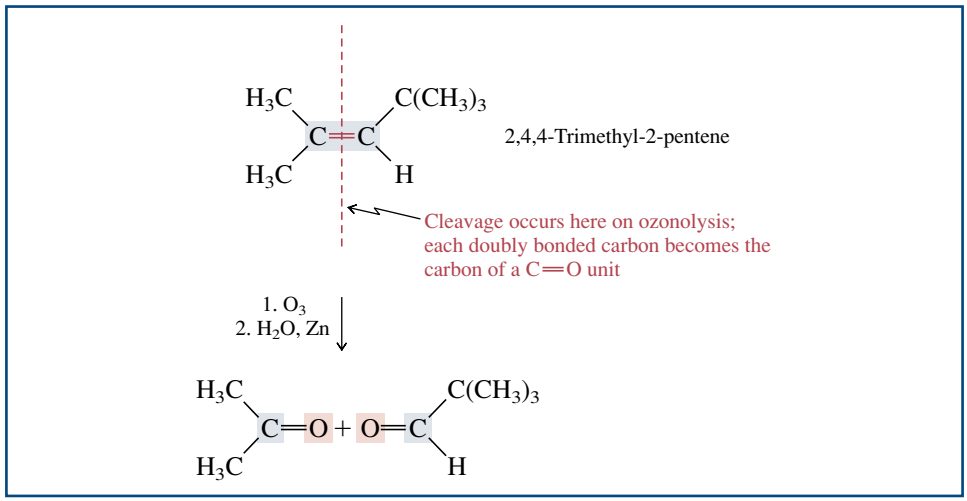


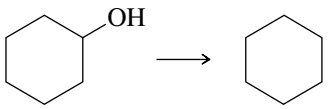
FIGURE 6.15 Ozonolysis of 2,4,4-trimethyl-2-pentene. On cleavage, each of the doubly bonded carbons becomes the carbon of a carbonyl (C=O) group.

6.20 INTRODUCTION TO ORGANIC CHEMICAL SYNTHESIS

An important concern to chemists is *synthesis,* the challenge of preparing a particular compound in an economical way and with confidence that the method chosen will lead to the desired structure. In this section we will introduce the topic of synthesis, emphasizing the need for systematic planning in order to decide what is the best sequence of steps to convert a specified starting material to a desired product (the **target molecule**).

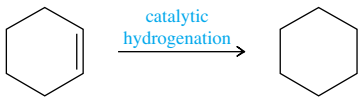
A critical feature of synthetic planning is *to reason backward from the target to the starting material.* A second is to *always use reactions that you know will work.*

Let's begin with a simple example. Suppose you wanted to prepare cyclohexane, given cyclohexanol as the starting material. We haven't encountered any reactions so far that permit us to carry out this conversion in a single step.



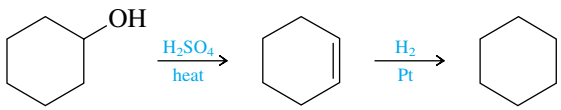
Cyclohexanol Cyclohexane

Reasoning backward, however, we know that we can prepare cyclohexane by hydrogenation of cyclohexene. We'll therefore use this reaction as the last step in our proposed synthesis.



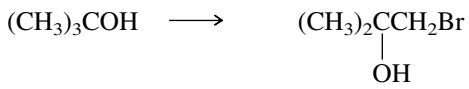
Cyclohexene Cyclohexane

Recognizing that cyclohexene may be prepared by dehydration of cyclohexanol, a practical synthesis of cyclohexane from cyclohexanol becomes apparent.



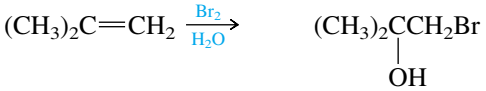
Cyclohexanol Cyclohexene Cyclohexane

As a second example, consider the preparation of 1-bromo-2-methyl-2-propanol from *tert*-butyl alcohol.



tert-Butyl alcohol 1-Bromo-2-methyl-2-propanol

Begin by asking the question, "What kind of compound is the target molecule, and what methods can I use to prepare that kind of compound?" The desired product has a bromine and a hydroxyl on adjacent carbons; it is a *vicinal bromohydrin.* The only method we have learned so far for the preparation of vicinal bromohydrins involves the reaction of alkenes with Br_2 in water. Thus, a reasonable last step is:



2-Methylpropene 1-Bromo-2-methyl-2-propanol

We now have a new problem: Where does the necessary alkene come from? Alkenes are prepared from alcohols by acid-catalyzed dehydration (Section 5.9) or from alkyl halides by E2 elimination (Section 5.14). Because our designated starting material is *tert*-butyl alcohol, we can combine its dehydration with bromohydrin formation to give the correct sequence of steps:

$$(CH_3)_3COH \xrightarrow[\text{heat}]{H_2SO_4} (CH_3)_2C{=}CH_2 \xrightarrow[H_2O]{Br_2} (CH_3)_2\underset{\displaystyle OH}{\overset{\displaystyle |}{C}}CH_2Br$$

tert-Butyl alcohol — 2-Methylpropene — 1-Bromo-2-methyl-2-propanol

PROBLEM 6.20 Write a series of equations describing a synthesis of 1-bromo-2-methyl-2-propanol from *tert*-butyl bromide.

Often more than one synthetic route may be available to prepare a particular compound. Indeed, it is normal to find in the chemical literature that the same compound has been synthesized in a number of different ways. As we proceed through the text and develop a larger inventory of functional group transformations, our ability to evaluate alternative synthetic plans will increase. In most cases the best synthetic plan is the one with the fewest steps.

6.21 REACTIONS OF ALKENES WITH ALKENES: POLYMERIZATION

Whereas 2-methylpropene undergoes acid-catalyzed hydration in dilute sulfuric acid to form *tert*-butyl alcohol (see Section 6.10 and Figure 6.9), an unusual reaction occurs in more concentrated solutions of sulfuric acid. Rather than form the expected alkyl hydrogen sulfate (see Section 6.9), 2-methylpropene is converted to a mixture of two isomeric C_8H_{16} alkenes.

The structures of these two C_8H_{16} alkenes were determined by ozonolysis as described in Section 6.19.

$$2(CH_3)_2C{=}CH_2 \xrightarrow{65\%\ H_2SO_4} CH_2{=}\underset{\displaystyle CH_3}{\overset{\displaystyle |}{C}}CH_2C(CH_3)_3 + (CH_3)_2C{=}CHC(CH_3)_3$$

2-Methylpropene — 2,4,4-Trimethyl-1-pentene — 2,4,4-Trimethyl-2-pentene

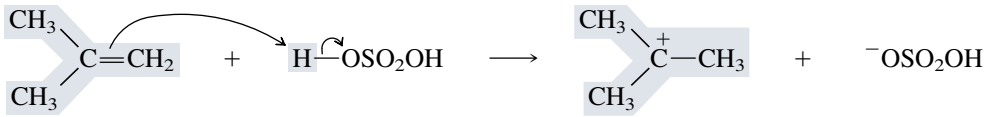
With molecular formulas corresponding to twice that of the starting alkene, the products of this reaction are referred to as **dimers** of 2-methylpropene, which is, in turn, called the **monomer.** The suffix *-mer* is derived from the Greek *meros,* meaning "part." Three monomeric units produce a **trimer,** four a **tetramer,** and so on. A high-molecular-weight material comprising a large number of monomer subunits is called a **polymer.**

PROBLEM 6.21 The two dimers of 2-methylpropene shown in the equation can be converted to 2,2,4-trimethylpentane (known by its common name *isooctane*) for use as a gasoline additive. Can you suggest a method for this conversion?

The two dimers of $(CH_3)_2C{=}CH_2$ are formed by the mechanism shown in Figure 6.16. In step 1 protonation of the double bond generates a small amount of *tert*-butyl cation in equilibrium with the alkene. The carbocation is an electrophile and attacks a second molecule of 2-methylpropene in step 2, forming a new carbon–carbon bond and generating a C_8 carbocation. This new carbocation loses a proton in step 3 to form a mixture of 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene.

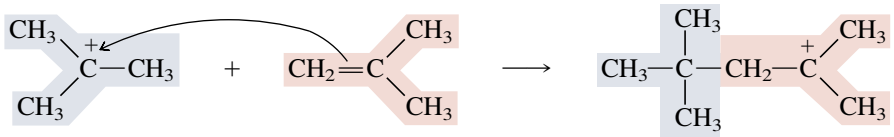
Dimerization in concentrated sulfuric acid occurs mainly with those alkenes that form tertiary carbocations. In some cases reaction conditions can be developed that favor

Step 1: Protonation of the carbon–carbon double bond to form *tert*-butyl cation:



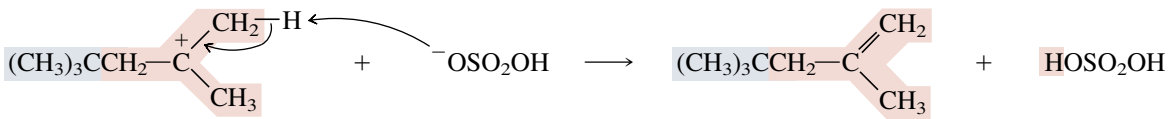
2-Methylpropene | Sulfuric acid | *tert*-Butyl cation | Hydrogen sulfate ion

Step 2: The carbocation acts as an electrophile toward the alkene. A carbon–carbon bond is formed, resulting in a new carbocation—one that has eight carbons:

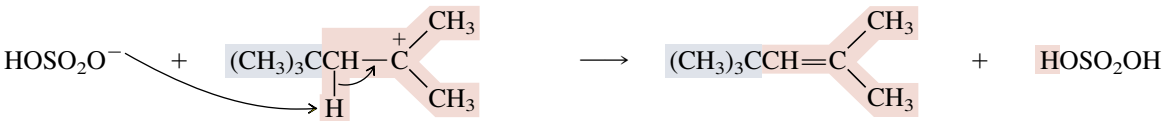


tert-Butyl cation | 2-Methylpropene | 1,1,3,3-Tetramethylbutyl cation

Step 3: Loss of a proton from this carbocation can produce either 2,4,4-trimethyl-1-pentene or 2,4,4-trimethyl-2-pentene:



1,1,3,3-Tetramethylbutyl cation | Hydrogen sulfate ion | 2,4,4-Trimethyl-1-pentene | Sulfuric acid



Hydrogen sulfate ion | 1,1,3,3-Tetramethylbutyl cation | 2,4,4-Trimethyl-2-pentene | Sulfuric acid

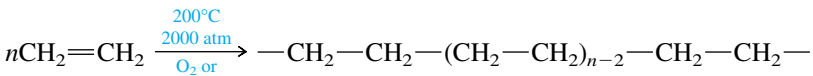
FIGURE 6.16 Mechanism of acid-catalyzed dimerization of 2-methylpropene.

the formation of higher molecular-weight polymers. Because these reactions proceed by way of carbocation intermediates, the process is referred to as **cationic polymerization.**

We made special mention in Section 5.1 of the enormous volume of ethylene and propene production in the petrochemical industry. The accompanying box summarizes the principal uses of these alkenes. Most of the ethylene is converted to **polyethylene,** a high-molecular-weight polymer of ethylene. Polyethylene cannot be prepared by cationic polymerization, but is the simplest example of a polymer that is produced on a large scale by **free-radical polymerization.**

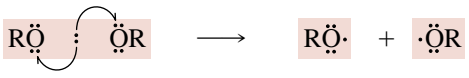
The uses to which ethylene and its relatives are put are summarized in an article entitled "Alkenes and Their Derivatives: The Alchemists' Dream Come True," in the August 1989 issue of the *Journal of Chemical Education* (pp. 670–672).

In the free-radical polymerization of ethylene, ethylene is heated at high pressure in the presence of oxygen or a peroxide.



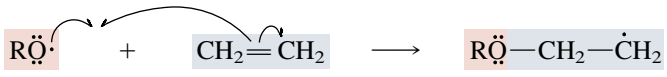
Ethylene | Polyethylene

Step 1: Homolytic dissociation of a peroxide produces alkoxy radicals that serve as free-radical initiators:



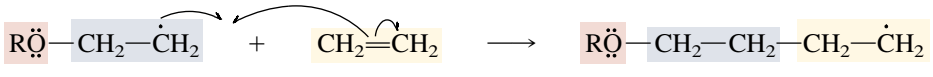
Peroxide — Two alkoxy radicals

Step 2: An alkoxy radical adds to the carbon–carbon double bond:



Alkoxy radical — Ethylene — 2-Alkoxyethyl radical

Step 3: The radical produced in step 2 adds to a second molecule of ethylene:



2-Alkoxyethyl radical — Ethylene — 4-Alkoxybutyl radical

The radical formed in step 3 then adds to a third molecule of ethylene, and the process continues, forming a long chain of methylene groups.

FIGURE 6.17 Mechanism of peroxide-initiated free-radical polymerization of ethylene.

In this reaction *n* can have a value of thousands.

The mechanism of free-radical polymerization of ethylene is outlined in Figure 6.17. Dissociation of a peroxide initiates the process in step 1. The resulting peroxy radical adds to the carbon–carbon double bond in step 2, giving a new radical, which then adds to a second molecule of ethylene in step 3. The carbon–carbon bond-forming process in step 3 can be repeated thousands of times to give long carbon chains.

In spite of the *-ene* ending to its name, polyethylene is much more closely related to alk*anes* than to alk*enes*. It is simply a long chain of CH_2 groups bearing at its ends an alkoxy group (from the initiator) or a carbon–carbon double bond.

A large number of compounds with carbon–carbon double bonds have been polymerized to yield materials having useful properties. Some of the more important or familiar of these are listed in Table 6.5. Not all these monomers are effectively polymerized under free-radical conditions, and much research has been carried out to develop alternative polymerization techniques. One of these, **coordination polymerization,** employs a mixture of titanium tetrachloride, $TiCl_4$, and triethylaluminum, $(CH_3CH_2)_3Al$, as a catalyst. Polyethylene produced by coordination polymerization has a higher density than that produced by free-radical polymerization and somewhat different—in many applications, more desirable—properties. The catalyst system used in coordination polymerization was developed independently by Karl Ziegler in Germany and Giulio Natta in Italy in the early 1950s. They shared the Nobel Prize in chemistry in 1963 for this work. The Ziegler–Natta catalyst system gives a form of **polypropylene** suitable for plastics and fibers. When propene is polymerized under free-radical conditions, the polypropylene has physical properties (such as a low melting point) that make it useless for most applications.

Coordination polymerization is described in more detail in Sections 7.15 and 14.15.

TABLE 6.5 Some Compounds with Carbon–Carbon Double Bonds Used to Prepare Polymers

A. Alkenes of the type $CH_2{=}CH{-}X$ used to form polymers of the type $(-CH_2-\underset{\displaystyle X}{\underset{|}{CH}}-)_n$

Compound	Structure	—X in polymer	Application
Ethylene	$CH_2{=}CH_2$	—H	Polyethylene films as packaging material; "plastic" squeeze bottles are molded from high-density polyethylene.
Propene	$CH_2{=}CH{-}CH_3$	$-CH_3$	Polypropylene fibers for use in carpets and automobile tires; consumer items (luggage, appliances, etc.); packaging material.
Styrene	$CH_2{=}CH-C_6H_5$	$-C_6H_5$	Polystyrene packaging, housewares, luggage, radio and television cabinets.
Vinyl chloride	$CH_2{=}CH{-}Cl$	—Cl	Poly(vinyl chloride) (PVC) has replaced leather in many of its applications; PVC tubes and pipes are often used in place of copper.
Acrylonitrile	$CH_2{=}CH{-}C{\equiv}N$	$-C{\equiv}N$	Wool substitute in sweaters, blankets, etc.

B. Alkenes of the type $CH_2{=}CX_2$ used to form polymers of the type $(-CH_2-CX_2-)_n$

Compound	Structure	X in polymer	Application
1,1-Dichloroethene (vinylidene chloride)	$CH_2{=}CCl_2$	Cl	Saran used as air- and water-tight packaging film.
2-Methylpropene	$CH_2{=}C(CH_3)_2$	CH_3	Polyisobutene is component of "butyl rubber," one of earliest synthetic rubber substitutes.

C. Others

Compound	Structure	Polymer	Application
Tetrafluoroethene	$CF_2{=}CF_2$	$(-CF_2-CF_2-)_n$ (Teflon)	Nonstick coating for cooking utensils; bearings, gaskets, and fittings.
Methyl methacrylate	$CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CO_2CH_3$	$(-CH_2-\underset{\displaystyle CH_3}{\underset{|}{\overset{\displaystyle CO_2CH_3}{\overset{|}{C}}}}-)_n$	When cast in sheets, is transparent; used as glass substitute (Lucite, Plexiglas).
2-Methyl-1,3-butadiene	$CH_2{=}\underset{\displaystyle CH_3}{\underset{|}{C}}CH{=}CH_2$	$(-CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH-CH_2-)_n$ (Polyisoprene)	Synthetic rubber.

Source: R. C. Atkins and F. A. Carey, *Organic Chemistry: A Brief Course,* 2nd ed. McGraw-Hill, New York, 1997, p. 251.

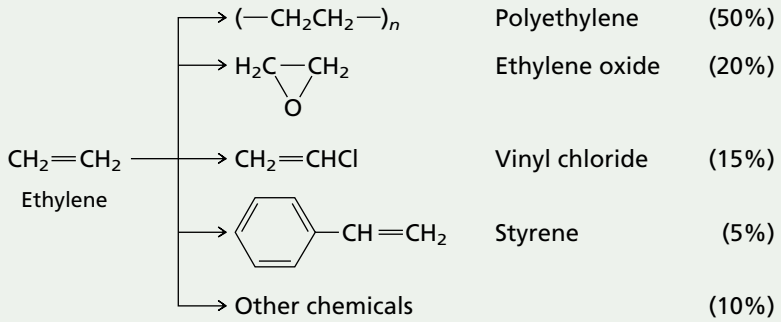
ETHYLENE AND PROPENE: THE MOST IMPORTANT INDUSTRIAL ORGANIC CHEMICALS

Having examined the properties of alkenes and introduced the elements of polymers and polymerization, let's now look at some commercial applications of ethylene and propene.

ETHYLENE We discussed ethylene production in an earlier boxed essay (Section 5.1), where it was pointed out that the output of the U.S. petrochemical industry exceeds 5×10^{10} lb/year. Approximately 90% of this material is used for the preparation of four compounds (polyethylene, ethylene oxide, vinyl chloride, and styrene), with polymerization to polyethylene accounting for half the total. Both vinyl chloride and styrene are polymerized to give poly(vinyl chloride) and polystyrene, respectively (see Table 6.5). Ethylene oxide is a starting material for the preparation of ethylene glycol for use as an antifreeze in automobile radiators and in the production of polyester fibers (see the boxed essay "Condensation Polymers: Polyamides and Polyesters" in Chapter 20).

PROPENE The major use of propene is in the production of polypropylene. Two other propene-derived organic chemicals, acrylonitrile and propylene oxide, are also starting materials for polymer synthesis. Acrylonitrile is used to make acrylic fibers (see Table 6.5), and propylene oxide is one component in the preparation of *polyurethane* polymers. Cumene itself has no direct uses but rather serves as the starting material in a process which yields two valuable industrial chemicals, acetone and phenol.

We have not indicated the reagents employed in the reactions by which ethylene and propene are converted to the compounds shown. Because of patent requirements, different companies often use different processes. Although the processes may be different, they share the common characteristic of being extremely efficient. The industrial chemist faces the challenge of producing valuable materials, at low cost. Thus, success in the industrial environment requires both an understanding of chemistry and an appreciation of the economics associated with alternative procedures. One measure of how successfully these challenges have been met can be seen in the fact that the United States maintains a positive trade balance in chemicals each year. In 1998 that surplus amounted to $13.4 billion in chemicals versus an overall trade deficit of $168.6 billion.



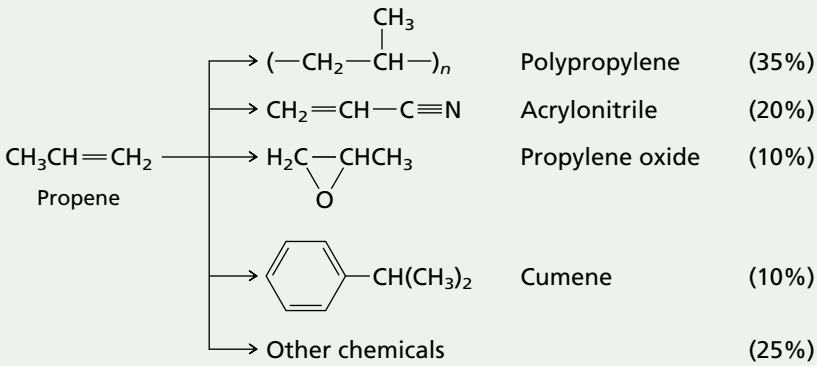
Among the "other chemicals" prepared from ethylene are ethanol and acetaldehyde:

CH_3CH_2OH

Ethanol (industrial solvent; used in preparation of ethyl acetate; unleaded gasoline additive)

CH_3CH (O)

Acetaldehyde (used in preparation of acetic acid)

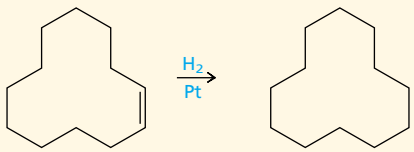
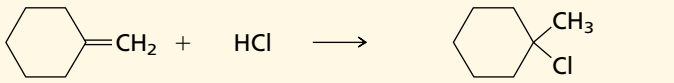


6.22 SUMMARY

Alkenes are **unsaturated hydrocarbons** and react with substances that add to the double bond.

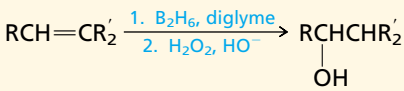
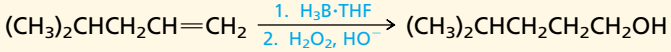
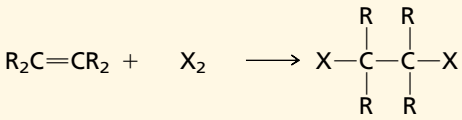
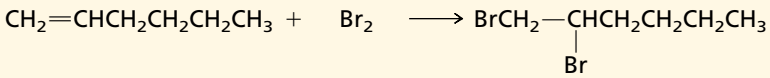
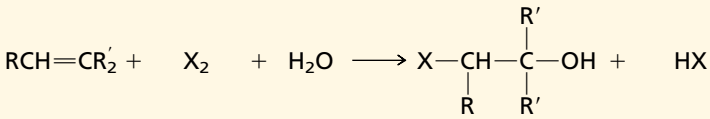
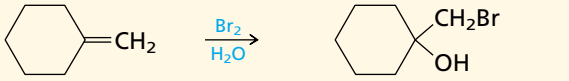
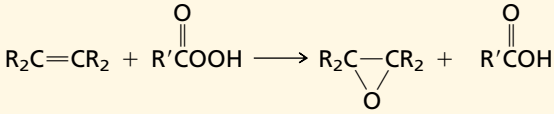
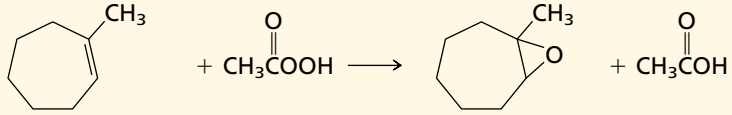
Section 6.1 See Table 6.6.

TABLE 6.6 Addition Reactions of Alkenes

Reaction (section) and comments	General equation and specific example
Catalytic hydrogenation (Sections 6.1–6.3) Alkenes react with hydrogen in the presence of a platinum, palladium, rhodium, or nickel catalyst to form the corresponding alkane.	$R_2C{=}CR_2 + H_2 \xrightarrow{\text{Pt, Pd, Rh, or Ni}} R_2CHCHR_2$ Alkene · Hydrogen · Alkane  *cis*-Cyclododecene · Cyclododecane (100%)
Addition of hydrogen halides (Sections 6.4–6.7) A proton and a halogen add to the double bond of an alkene to yield an alkyl halide. Addition proceeds in accordance with Markovnikov's rule; hydrogen adds to the carbon that has the greater number of hydrogens, halide to the carbon that has the fewer hydrogens.	$RCH{=}CR'_2 + HX \longrightarrow RCH_2{-}CR'_2$ (X) Alkene · Hydrogen halide · Alkyl halide  Methylenecyclohexane · Hydrogen chloride · 1-Chloro-1-methylcyclohexane (75–80%)
Addition of sulfuric acid (Section 6.9) Alkenes react with sulfuric acid to form alkyl hydrogen sulfates. A proton and a hydrogen sulfate ion add across the double bond in accordance with Markovnikov's rule. Alkenes that yield tertiary carbocations on protonation tend to polymerize in concentrated sulfuric acid (Section 6.21).	$RCH{=}CR'_2 + HOSO_2OH \longrightarrow RCH_2{-}CR'_2$ (OSO_2OH) Alkene · Sulfuric acid · Alkyl hydrogen sulfate $CH_2{=}CHCH_2CH_3 + HOSO_2OH \longrightarrow CH_3{-}CHCH_2CH_3$ (OSO_2OH) 1-Butene · Sulfuric acid · *sec*-Butyl hydrogen sulfate
Acid-catalyzed hydration (Section 6.10) Addition of water to the double bond of an alkene takes place in aqueous acid. Addition occurs according to Markovnikov's rule. A carbocation is an intermediate and is captured by a molecule of water acting as a nucleophile.	$RCH{=}CR'_2 + H_2O \xrightarrow{H^+} RCH_2CR'_2$ (OH) Alkene · Water · Alcohol $CH_2{=}C(CH_3)_2 \xrightarrow{50\%\ H_2SO_4/H_2O} (CH_3)_3COH$ 2-Methylpropene · *tert*-Butyl alcohol (55–58%)

(Continued)

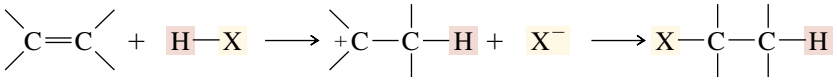
TABLE 6.6 Addition Reactions of Alkenes *(Continued)*

Reaction (section) and comments	General equation and specific example
Hydroboration–oxidation (Sections 6.11–6.13) This two-step sequence achieves hydration of alkenes in a stereospecific syn manner, with a regioselectivity opposite to Markovnikov's rule. An organoborane is formed by electrophilic addition of diborane to an alkene. Oxidation of the organoborane intermediate with hydrogen peroxide completes the process. Rearrangements do not occur.	 Alkene Alcohol  4-Methyl-1-pentene 4-Methyl-1-pentanol (80%)
Addition of halogens (Sections 6.14–6.16) Bromine and chlorine add to alkenes to form vicinal dihalides. A cyclic halonium ion is an intermediate. Stereospecific anti addition is observed.	 Alkene Halogen Vicinal dihalide  1-Hexene Bromine 1,2-Dibromohexane (100%)
Halohydrin formation (Section 6.17) When treated with bromine or chlorine in aqueous solution, alkenes are converted to vicinal halohydrins. A halonium ion is an intermediate. The halogen adds to the carbon that has the greater number of hydrogens. Addition is anti.	 Alkene Halogen Water Vicinal halohydrin Hydrogen halide  Methylenecyclohexane (1-Bromomethyl)cyclohexanol (89%)
Epoxidation (Section 6.18) Peroxy acids transfer oxygen to the double bond of alkenes to yield epoxides. The reaction is a stereospecific syn addition.	 Alkene Peroxy acid Epoxide Carboxylic acid  1-Methylcycloheptene Peroxyacetic acid 1-Methyl-1,2-epoxycycloheptane (65%) Acetic acid

Section 6.2 Hydrogenation of alkenes is exothermic. Heats of hydrogenation can be measured and used to assess the stability of various types of double bonds. The information parallels that obtained from heats of combustion.

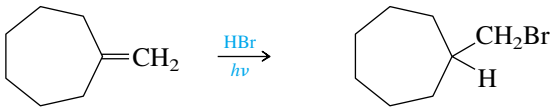
Section 6.3 Hydrogenation of alkenes is a syn addition.

Sections 6.4–6.7 See Table 6.6. Hydrogen halide addition to alkenes proceeds by electrophilic attack of the reagent on the π electrons of the double bond. Carbocations are intermediates.



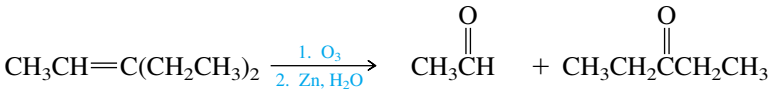
Protonation of the double bond occurs in the direction that gives the more stable of two possible carbocations.

Section 6.8 Hydrogen bromide is unique among the hydrogen halides in that it can add to alkenes either by an ionic mechanism or by a free-radical mechanism. Under photochemical conditions or in the presence of peroxides, free-radical addition is observed, and HBr adds to the double bond with a regioselectivity opposite to that of Markovnikov's rule.



Sections 6.9–6.18 See Table 6.6.

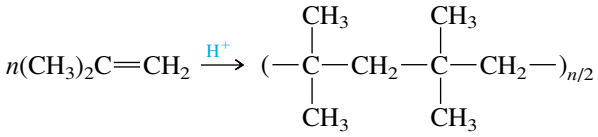
Section 6.19 Alkenes are cleaved to carbonyl compounds by **ozonolysis.** This reaction is useful both for synthesis (preparation of aldehydes, ketones, or carboxylic acids) and analysis. When applied to analysis, the carbonyl compounds are isolated and identified, allowing the substituents attached to the double bond to be deduced.



Section 6.20 The reactions described so far can be carried out sequentially to prepare compounds of prescribed structure from some given starting material. The best way to approach a synthesis is to reason backward from the desired target molecule and to always use reactions that you are sure will work. The 11 exercises that make up Problem 6.32 at the end of this chapter provide some opportunities for practice.

Section 6.21 In their **polymerization,** many individual alkene molecules combine to give a high-molecular-weight product. Among the methods for alkene

polymerization, *cationic polymerization, coordination polymerization,* and *free-radical polymerization* are the most important. An example of cationic polymerization is:



2-Methylpropene Polyisobutylene

PROBLEMS

6.22 Write the structure of the major organic product formed in the reaction of 1-pentene with each of the following:

(a) Hydrogen chloride

(b) Hydrogen bromide

(c) Hydrogen bromide in the presence of peroxides

(d) Hydrogen iodide

(e) Dilute sulfuric acid

(f) Diborane in diglyme, followed by basic hydrogen peroxide

(g) Bromine in carbon tetrachloride

(h) Bromine in water

(i) Peroxyacetic acid

(j) Ozone

(k) Product of part (j) treated with zinc and water

6.23 Repeat Problem 6.22 for 2-methyl-2-butene.

6.24 Repeat Problem 6.22 for 1-methylcyclohexene.

6.25 Match the following alkenes with the appropriate heats of hydrogenation:

(a) 1-Pentene

(b) (*E*)-4,4-Dimethyl-2-pentene

(c) (*Z*)-4-Methyl-2-pentene

(d) (*Z*)-2,2,5,5-Tetramethyl-3-hexene

(e) 2,4-Dimethyl-2-pentene

Heats a hydrogenation in kJ/mol (kcal/mol): 151(36.2); 122(29.3); 114(27.3); 111(26.5); 105(25.1).

6.26 (a) How many alkenes yield 2,2,3,4,4-pentamethylpentane on catalytic hydrogenation?

(b) How many yield 2,3-dimethylbutane?

(c) How many yield methylcyclobutane?

6.27 Two alkenes undergo hydrogenation to yield a mixture of *cis*- and *trans*-1,4-dimethylcyclohexane. A third, however, gives only *cis*-1,4-dimethylcyclohexane. What compound is this?

6.28 Specify reagents suitable for converting 3-ethyl-2-pentene to each of the following:

(a) 2,3-Dibromo-3-ethylpentane

(b) 3-Chloro-3-ethylpentane

(c) 2-Bromo-3-ethylpentane

(d) 3-Ethyl-3-pentanol

(e) 3-Ethyl-2-pentanol

(f) 3-Ethyl-2,3-epoxypentane

(g) 3-Ethylpentane

6.29 (a) Which primary alcohol of molecular formula $C_5H_{12}O$ cannot be prepared from an alkene? Why?

(b) Write equations describing the preparation of three isomeric primary alcohols of molecular formula $C_5H_{12}O$ from alkenes.

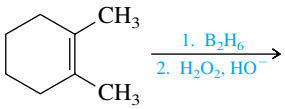
(c) Write equations describing the preparation of the tertiary alcohol of molecular formula $C_5H_{12}O$ from two different alkenes.

6.30 All the following reactions have been reported in the chemical literature. Give the structure of the principal organic product in each case.

(a) $CH_3CH_2CH{=}CHCH_2CH_3 + HBr \xrightarrow{\text{no peroxides}}$

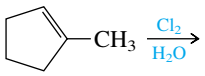
(b) $(CH_3)_2CHCH_2CH_2CH_2CH{=}CH_2 \xrightarrow[\text{peroxides}]{HBr}$

(c) 2-*tert*-Butyl-3,3-dimethyl-1-butene $\xrightarrow[2.\ H_2O_2,\ HO^-]{1.\ B_2H_6}$

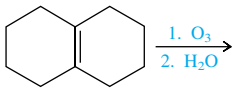
(d) 

(e) $CH_2{=}C(CH_3)CH_2CH_2CH_3 + Br_2 \xrightarrow{CHCl_3}$

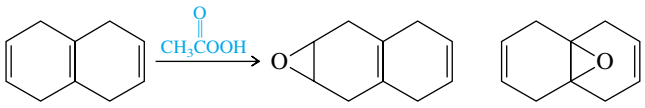
(f) $(CH_3)_2C{=}CHCH_3 + Br_2 \xrightarrow{H_2O}$

(g) 

(h) $(CH_3)_2C{=}C(CH_3)_2 + CH_3\overset{\overset{O}{\|}}{C}OOH \longrightarrow$

(i) 

6.31 A single epoxide was isolated in 79–84% yield in the following reaction. Was this epoxide A or B? Explain your reasoning.



A B

6.32 Suggest a sequence of reactions suitable for preparing each of the following compounds from the indicated starting material. You may use any necessary organic or inorganic reagents.

(a) 1-Propanol from 2-propanol

(b) 1-Bromopropane from 2-bromopropane

(c) 1,2-Dibromopropane from 2-bromopropane

(d) 1-Bromo-2-propanol from 2-propanol

(e) 1,2-Epoxypropane from 2-propanol

(f) *tert*-Butyl alcohol from isobutyl alcohol

(g) *tert*-Butyl iodide from isobutyl iodide

(h) *trans*-2-Chlorocyclohexanol from cyclohexyl chloride

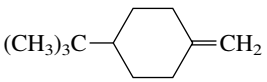
(i) Cyclopentyl iodide from cyclopentane

(j) *trans*-1,2-Dichlorocyclopentane from cyclopentane

(k) $HC(=O)CH_2CH_2CH_2C(=O)H$ from cyclopentanol

6.33 Two different compounds having the molecular formula $C_8H_{15}Br$ are formed when 1,6-dimethylcyclohexene reacts with hydrogen bromide in the dark and in the absence of peroxides. The same two compounds are formed from 1,2-dimethylcyclohexene. What are these two compounds?

6.34 On catalytic hydrogenation over a rhodium catalyst, the compound shown gave a mixture containing *cis*-1-*tert*-butyl-4-methylcyclohexane (88%) and *trans*-1-*tert*-butyl-4-methylcyclohexane (12%).

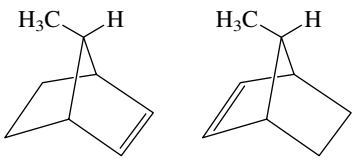


4-*tert*-Butyl(methylene)cyclohexane

(a) What two products are formed in the epoxidation of 4-*tert*-butyl(methylene)cyclohexane? Which one do you think will predominate?

(b) What two products are formed in the hydroboration–oxidation of 4-*tert*-butyl(methylene)cyclohexane? Which one do you think will predominate?

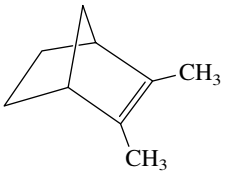
6.35 Compound A undergoes catalytic hydrogenation much faster than does compound B. Why? Making molecular models will help.



A B

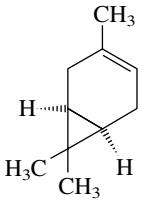
6.36 Catalytic hydrogenation of 1,4-dimethylcyclopentene yields a mixture of two products. Identify them. One of them is formed in much greater amounts than the other (observed ratio = 10:1). Which one is the major product?

6.37 There are two products that can be formed by syn addition of hydrogen to 2,3-dimethylbicyclo[2.2.1]-2-heptene. Write or make molecular models of their structures.



2,3-Dimethylbicyclo[2.2.1]-2-heptene

6.38 Hydrogenation of 3-carene is, in principle, capable of yielding two stereoisomeric products. Write their structures. Only one of them was actually obtained on catalytic hydrogenation over platinum. Which one do you think is formed? Explain your reasoning with the aid of a drawing or a molecular model.



3-Carene

6.39 In a widely used industrial process, the mixture of ethylene and propene that is obtained by dehydrogenation of natural gas is passed into concentrated sulfuric acid. Water is added, and the solution is heated to hydrolyze the alkyl hydrogen sulfate. The product is almost exclusively a single alcohol. Is this alcohol ethanol, 1-propanol, or 2-propanol? Why is this particular one formed almost exclusively?

6.40 On the basis of the mechanism of acid-catalyzed hydration, can you suggest a reason why the reaction

$$CH_2{=}CHCH(CH_3)_2 \xrightarrow[H_2O]{H_2SO_4} CH_3\underset{\displaystyle OH}{\underset{|}{C}}HCH(CH_3)_2$$

would probably *not* be a good method for the synthesis of 3-methyl-2-butanol?

6.41 As a method for the preparation of alkenes, a weakness in the acid-catalyzed dehydration of alcohols is that the initially formed alkene (or mixture of alkenes) sometimes isomerizes under the conditions of its formation. Write a stepwise mechanism showing how 2-methyl-1-butene might isomerize to 2-methyl-2-butene in the presence of sulfuric acid.

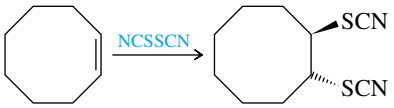
6.42 When bromine is added to a solution of 1-hexene in methanol, the major products of the reaction are as shown:

$$CH_2{=}CHCH_2CH_2CH_2CH_3 \xrightarrow[CH_3OH]{Br_2} BrCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2CH_2CH_3 + BrCH_2\underset{\displaystyle OCH_3}{\underset{|}{C}}HCH_2CH_2CH_2CH_3$$

1-Hexene | 1,2-Dibromohexane | 1-Bromo-2-methoxyhexane

1,2-Dibromohexane is not converted to 1-bromo-2-methoxyhexane under the reaction conditions. Suggest a reasonable mechanism for the formation of 1-bromo-2-methoxyhexane.

6.43 The reaction of thiocyanogen (N≡CS—SC≡N) with *cis*-cyclooctene proceeds by anti addition.



A bridged *sulfonium ion* is presumed to be an intermediate. Write a stepwise mechanism for this reaction.

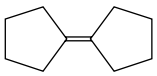
6.44 On the basis of the mechanism of cationic polymerization, predict the alkenes of molecular formula $C_{12}H_{24}$ that can most reasonably be formed when 2-methylpropene [$(CH_3)_2C{=}CH_2$] is treated with sulfuric acid.

6.45 On being heated with a solution of sodium ethoxide in ethanol, compound A ($C_7H_{15}Br$) yielded a mixture of two alkenes B and C, each having the molecular formula C_7H_{14}. Catalytic hydrogenation of the major isomer B or the minor isomer C gave only 3-ethylpentane. Suggest structures for compounds A, B, and C consistent with these observations.

6.46 Compound A ($C_7H_{15}Br$) is not a primary alkyl bromide. It yields a single alkene (compound B) on being heated with sodium ethoxide in ethanol. Hydrogenation of compound B yields 2,4-dimethylpentane. Identify compounds A and B.

6.47 Compounds A and B are isomers of molecular formula $C_9H_{19}Br$. Both yield the same alkene C as the exclusive product of elimination on being treated with potassium *tert*-butoxide in dimethyl sulfoxide. Hydrogenation of alkene C gives 2,3,3,4-tetramethylpentane. What are the structures of compounds A and B and alkene C?

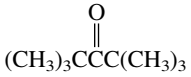
6.48 Alcohol A ($C_{10}H_{18}O$) is converted to a mixture of alkenes B and C on being heated with potassium hydrogen sulfate ($KHSO_4$). Catalytic hydrogenation of B and C yields the same product. Assuming that dehydration of alcohol A proceeds without rearrangement, deduce the structures of alcohol A and alkene C.



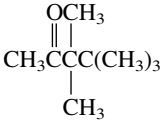
Compound B

6.49 Reaction of 3,3-dimethyl-1-butene with hydrogen iodide yields two compounds A and B, each having the molecular formula $C_6H_{13}I$, in the ratio A:B = 90:10. Compound A, on being heated with potassium hydroxide in *n*-propyl alcohol, gives only 3,3-dimethyl-1-butene. Compound B undergoes elimination under these conditions to give 2,3-dimethyl-2-butene as the major product. Suggest structures for compounds A and B, and write a reasonable mechanism for the formation of each.

6.50 Dehydration of 2,2,3,4,4-pentamethyl-3-pentanol gave two alkenes A and B. Ozonolysis of the lower boiling alkene A gave formaldehyde ($CH_2{=}O$) and 2,2,4,4-tetramethyl-3-pentanone. Ozonolysis of B gave formaldehyde and 3,3,4,4-tetramethyl-2-pentanone. Identify A and B, and suggest an explanation for the formation of B in the dehydration reaction.

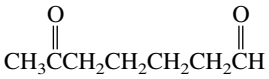


2,2,4,4-Tetramethyl-3-pentanone



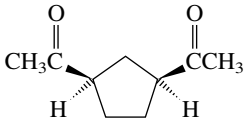
3,3,4,4-Tetramethyl-2-pentanone

6.51 Compound A ($C_7H_{13}Br$) is a tertiary bromide. On treatment with sodium ethoxide in ethanol, A is converted into B (C_7H_{12}). Ozonolysis of B gives C as the only product. Deduce the structures of A and B. What is the symbol for the reaction mechanism by which A is converted to B under the reaction conditions?



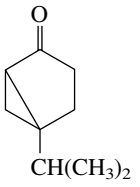
Compound C

6.52 East Indian sandalwood oil contains a hydrocarbon given the name *santene* (C_9H_{14}). Ozonation of santene followed by hydrolysis gives compound A. What is the structure of santene?

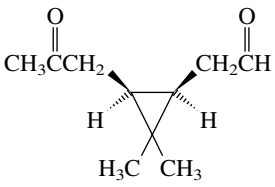


Compound A

6.53 *Sabinene* and Δ^3-*carene* are isomeric natural products with the molecular formula $C_{10}H_{16}$. (a) Ozonolysis of sabinene followed by hydrolysis in the presence of zinc gives compound A. What is the structure of sabinene? What other compound is formed on ozonolysis? (b) Ozonolysis of Δ^3-carene followed by hydrolysis in the presence of zinc gives compound B. What is the structure of Δ^3-carene?

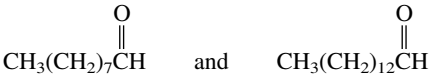


Compound A



Compound B

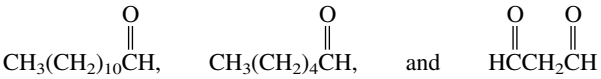
6.54 The sex attractant by which the female housefly attracts the male has the molecular formula $C_{23}H_{46}$. Catalytic hydrogenation yields an alkane of molecular formula $C_{23}H_{48}$. Ozonolysis yields



What is the structure of the housefly sex attractant?

6.55 A certain compound of molecular formula $C_{19}H_{38}$ was isolated from fish oil and from plankton. On hydrogenation it gave 2,6,10,14-tetramethylpentadecane. Ozonolysis gave $(CH_3)_2C{=}O$ and a 16-carbon aldehyde. What is the structure of the natural product? What is the structure of the aldehyde?

6.56 The sex attractant of the female arctiid moth contains, among other components, a compound of molecular formula $C_{21}H_{40}$ that yields

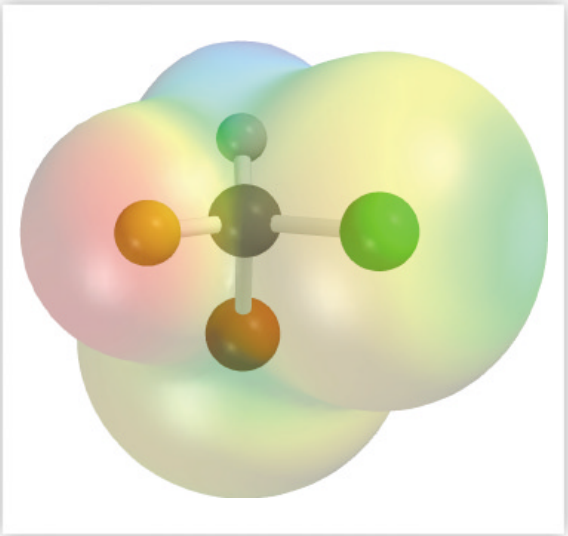


on ozonolysis. What is the constitution of this material?

6.57 Construct a molecular model of the product formed by catalytic hydrogenation of 1,2-dimethylcyclohexene. Assume syn addition occurs.

6.58 Construct a molecular model of the product formed by anti addition of Br_2 to 1,2-dimethylcyclohexene.

6.59 Examine the electrostatic potential map of $H_3B{\cdot}THF$ (borane–tetrahydrofuran complex) on the *Learning By Modeling* CD that accompanies this text. How does the electrostatic potential of the hydrogens bonded to boron differ from the potential of the hydrogens of the tetrahydrofuran ring?



CHAPTER 7

STEREOCHEMISTRY

The Greek word *stereos* means "solid," and *stereochemistry* refers to chemistry in three dimensions. The foundations of organic stereochemistry were laid by Jacobus van't Hoff* and Joseph Achille Le Bel in 1874. Independently of each other, van't Hoff and Le Bel proposed that the four bonds to carbon were directed toward the corners of a tetrahedron. One consequence of a tetrahedral arrangement of bonds to carbon is that two compounds may be different because the arrangement of their atoms in space is different. Isomers that have the same constitution but differ in the spatial arrangement of their atoms are called **stereoisomers.** We have already had considerable experience with certain types of stereoisomers—those involving cis and trans substitution patterns in alkenes and in cycloalkanes.

Our major objectives in this chapter are to develop a feeling for molecules as three-dimensional objects and to become familiar with stereochemical principles, terms, and notation. A full understanding of organic and biological chemistry requires an awareness of the spatial requirements for interactions between molecules; this chapter provides the basis for that understanding.

7.1 MOLECULAR CHIRALITY: ENANTIOMERS

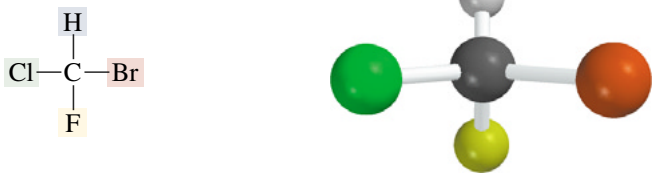
Everything has a mirror image, but not all things are superposable on their mirror images. Mirror-image superposability characterizes many objects we use every day. Cups and saucers, forks and spoons, chairs and beds are all identical with their mirror images. Many other objects though—and this is the more interesting case—are not. Your left hand and your right hand, for example, are mirror images of each other but can't be made to coincide point for point, palm to palm, knuckle to knuckle, in three dimensions. In 1894, William

*Van't Hoff was the recipient of the first Nobel Prize in chemistry in 1901 for his work in chemical dynamics and osmotic pressure—two topics far removed from stereochemistry.

Thomson (Lord Kelvin) coined a word for this property. He defined an object as **chiral** if it is not superposable on its mirror image. Applying Thomson's term to chemistry, we say that a *molecule is chiral if its two mirror-image forms are not superposable in three dimensions.* The work "chiral" is derived from the Greek word *cheir,* meaning "hand," and it is entirely appropriate to speak of the "handedness" of molecules. The opposite of chiral is **achiral.** A molecule that *is* superposable on its mirror image is achiral.

In organic chemistry, chirality most often occurs in molecules that contain a carbon that is attached to four different groups. An example is bromochlorofluoromethane (BrClFCH).

Bromochlorofluoromethane is a known compound, and samples selectively enriched in each enantiomer have been described in the chemical literature. In 1989 two chemists at Polytechnic University (Brooklyn, New York) described a method for the preparation of BrClFCH that is predominantly one enantiomer.



Bromochlorofluoromethane

As shown in Figure 7.1, the two mirror images of bromochlorofluoromethane cannot be superposed on each other. *Since the two mirror images of bromochlorofluoromethane are not superposable, BrClFCH is chiral.*

The two mirror images of bromochlorofluoromethane have the same constitution. That is, the atoms are connected in the same order. But they differ in the arrangement of their atoms in space; they are **stereoisomers.** Stereoisomers that are related as an object and its nonsuperposable mirror image are classified as **enantiomers.** The word "enantiomer" describes a particular relationship between two objects. One cannot look at a single molecule in isolation and ask if it is an enantiomer any more than one can look at an individual human being and ask, "Is that person a cousin?" Furthermore, just as an object has one, and only one, mirror image, a chiral molecule can have one, and only one, enantiomer.

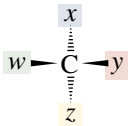
Notice in Figure 7.1*c,* where the two enantiomers of bromochlorofluoromethane are similarly oriented, that the difference between them corresponds to an interchange of the positions of bromine and chlorine. It will generally be true for species of the type C*(w, x, y, z),* where *w, x, y,* and *z* are different atoms or groups, that an exchange of two of them converts a structure to its enantiomer, but an exchange of three returns the original structure, albeit in a different orientation.

Consider next a molecule such as chlorodifluoromethane (ClF_2CH), in which two of the atoms attached to carbon are the same. Figure 7.2 on page 262 shows two molecular models of ClF_2CH drawn so as to be mirror images. As is evident from these drawings, it is a simple matter to merge the two models so that all the atoms match. *Since mirror-image representations of chlorodifluoromethane are superposable on each other, ClF_2CH is achiral.*

The surest test for chirality is a careful examination of mirror-image forms for superposability. Working with models provides the best practice in dealing with molecules as three-dimensional objects and is strongly recommended.

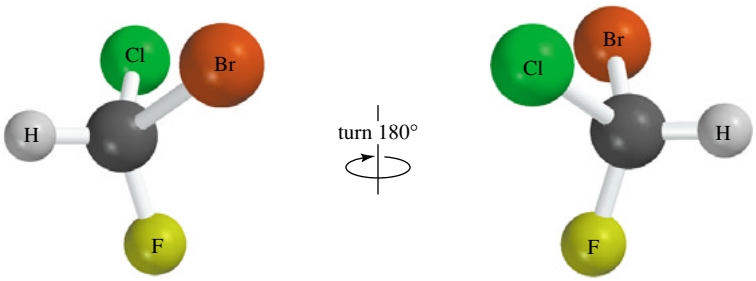
7.2 THE STEREOGENIC CENTER

As we've just seen, molecules of the general type



(*a*) Structures A and B are mirror-image representations of bromochlorofluoromethane (BrClFCH).

(*b*) To test for superposability, reorient B by turning it 180°.



(*c*) Compare A and B. The two do not match. A and B cannot be superposed on each other. Bromochlorofluoromethane is therefore a chiral molecule. The two mirror-image forms are enantiomers of each other.

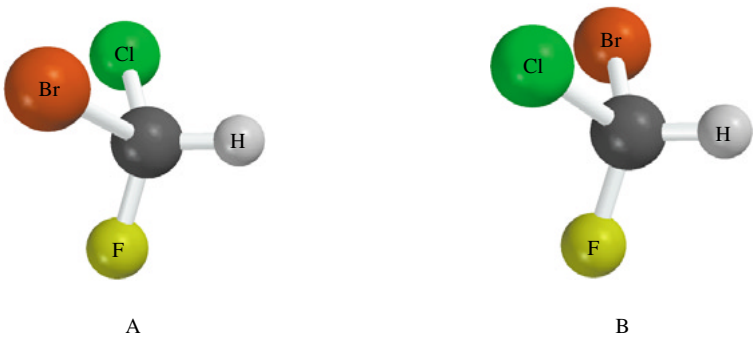


FIGURE 7.1 A molecule with four different groups attached to a single carbon is chiral. Its two mirror-image forms are not superposable.

are chiral when *w, x, y,* and *z* are different substituents. A tetrahedral carbon atom that bears four different substituents is variously referred to as a *chiral center,* a *chiral carbon atom,* an *asymmetric center,* or an *asymmetric carbon atom.* A more modern term is **stereogenic center,** and that is the term that we'll use. (*Stereocenter* is synonymous with *stereogenic center.*)

An article in the December 1987 issue of the *Journal of Chemical Education* gives a thorough discussion of molecular chirality and some of its past and present terminology.

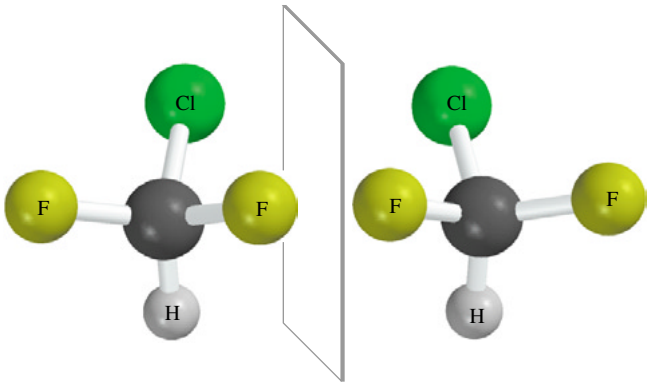
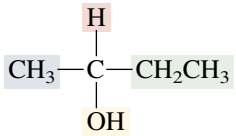
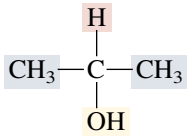


FIGURE 7.2 Mirror-image forms of chlorodifluoromethane are superposable on each other. Chlorodifluoromethane is achiral.

Noting the presence of one (but not more than one) stereogenic center in a molecule is a simple, rapid way to determine that it is chiral. For example, C-2 is a stereogenic center in 2-butanol; it bears a hydrogen atom and methyl, ethyl, and hydroxyl groups as its four different substituents. By way of contrast, none of the carbon atoms bear four different groups in the achiral alcohol 2-propanol.



2-Butanol
Chiral; four different substituents at C-2

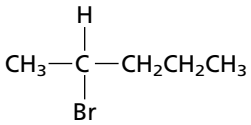


2-Propanol
Achiral; two of the substituents at C-2 are the same

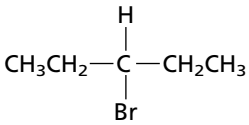
PROBLEM 7.1 Examine the following for stereogenic centers:

(a) 2-Bromopentane
(b) 3-Bromopentane
(c) 1-Bromo-2-methylbutane
(d) 2-Bromo-2-methylbutane

SAMPLE SOLUTION A stereogenic carbon has four different substituents. (a) In 2-bromopentane, C-2 satisfies this requirement. (b) None of the carbons in 3-bromopentane have four different substituents, and so none of its atoms are stereogenic centers.

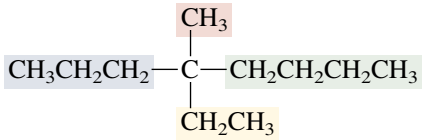


2-Bromopentane

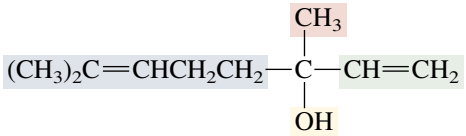


3-Bromopentane

Molecules with stereogenic centers are very common, both as naturally occurring substances and as the products of chemical synthesis. (Carbons that are part of a double bond or a triple bond can't be stereogenic centers.)

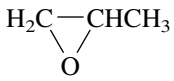


4-Ethyl-4-methyloctane
(a chiral alkane)

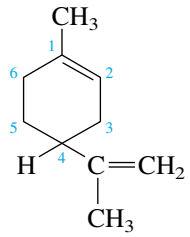


Linalool
(a pleasant-smelling oil obtained from orange flowers)

A carbon atom in a ring can be a stereogenic center if it bears two different substituents and the path traced around the ring from that carbon in one direction is different from that traced in the other. The carbon atom that bears the methyl group in 1,2-epoxypropane, for example, is a stereogenic center. The sequence of groups is O—CH_2 as one proceeds clockwise around the ring from that atom, but is CH_2—O in the anticlockwise direction. Similarly, C-4 is a stereogenic center in limonene.



1-2-Epoxypropane
(product of epoxidation of propene)



Limonene
(a constituent of lemon oil)

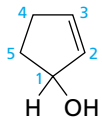
Examine the molecular models of the two enantiomers of 1,2-epoxypropane on *Learning By Modeling* and test them for superposability.

PROBLEM 7.2 Identify the stereogenic centers, if any, in

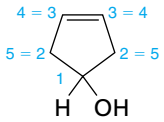
(a) 2-Cyclopenten-1-ol and 3-cyclopenten-1-ol

(b) 1,1,2-Trimethylcyclobutane and 1,1,3-Trimethylcyclobutane

SAMPLE SOLUTION (a) The hydroxyl-bearing carbon in 2-cyclopenten-1-ol is a stereogenic center. There is no stereogenic center in 3-cyclopenten-1-ol, since the sequence of atoms 1 → 2 → 3 → 4 → 5 is equivalent regardless of whether one proceeds clockwise or anticlockwise.

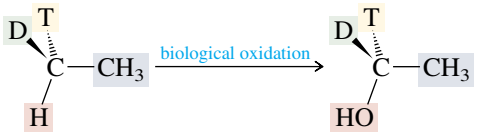


2-Cyclopenten-1-ol



3-Cyclopenten-1-ol
(does not have a stereogenic carbon)

Even isotopes qualify as different substituents at a stereogenic center. The stereochemistry of biological oxidation of a derivative of ethane that is chiral because of deuterium (D = ^{2}H) and tritium (T = ^{3}H) atoms at carbon, has been studied and shown to proceed as follows:



The stereochemical relationship between the reactant and the product, revealed by the isotopic labeling, shows that oxygen becomes bonded to carbon on the same side from which H is lost.

One final, very important point about stereogenic centers. *Everything we have said in this section concerns molecules that have one and only one stereogenic center; molecules with more than one stereogenic center may or may not be chiral.* Molecules that have more than one stereogenic center will be discussed in Sections 7.10 through 7.13.

7.3 SYMMETRY IN ACHIRAL STRUCTURES

Certain structural features can sometimes help us determine by inspection whether a molecule is chiral or achiral. For example, a molecule that has a *plane of symmetry* or a *center of symmetry* is superposable on its mirror image and is achiral.

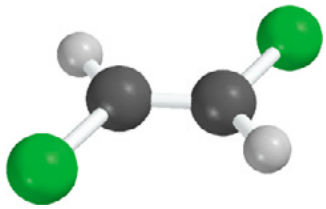
A **plane of symmetry** bisects a molecule so that one half of the molecule is the mirror image of the other half. The achiral molecule chlorodifluoromethane, for example, has the plane of symmetry shown in Figure 7.3.

A point in a molecule is a **center of symmetry** if any line drawn from it to some element of the structure will, when extended an equal distance in the opposite direction, encounter an identical element. The cyclobutane derivative in Figure 7.4 lacks a plane of symmetry, yet is achiral because it possesses a center of symmetry.

PROBLEM 7.3 Locate any planes of symmetry or centers of symmetry in each of the following compounds. Which of the compounds are chiral? Which are achiral?

(a) (*E*)-1,2-Dichloroethene
(b) (*Z*)-1,2,Dichloroethene
(c) *cis*-1,2-Dichlorocyclopropane
(d) *trans*-1,2-Dichlorocyclopropane

SAMPLE SOLUTION (a) (*E*)-1,2-Dichloroethene is planar. The molecular plane is a plane of symmetry.



Furthermore, (*E*)-1,2-dichloroethene has a center of symmetry located at the midpoint of the carbon–carbon double bond. It is achiral.

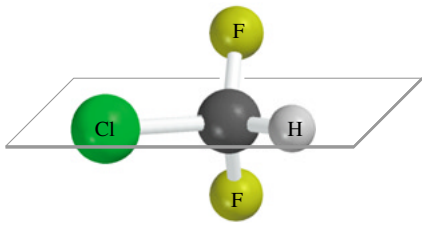


FIGURE 7.3 A plane of symmetry defined by the atoms H—C—Cl divides chlorodifluoromethane into two mirror-image halves.

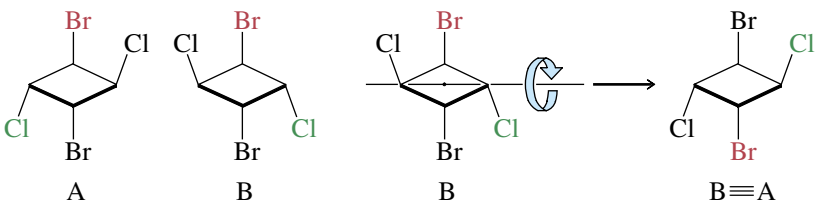


FIGURE 7.4 (*a*) Structural formulas A and B are drawn as mirror images. (*b*) The two mirror images are superposable by rotating form B 180° about an axis passing through the center of the molecule. The center of the molecule is a center of symmetry.

Any molecule with a plane of symmetry or a center of symmetry is achiral, but their absence is not sufficient for a molecule to be chiral. A molecule lacking a center of symmetry or a plane of symmetry is *likely* to be chiral, but the superposability test should be applied to be certain.

7.4 PROPERTIES OF CHIRAL MOLECULES: OPTICAL ACTIVITY

The phenomenon of optical activity was discovered by the French physicist Jean-Baptiste Biot in 1815.

The experimental facts that led van't Hoff and Le Bel to propose that molecules having the same constitution could differ in the arrangement of their atoms in space concerned the physical property of **optical activity.** Optical activity is the ability of a chiral substance to rotate the plane of **plane-polarized light** and is measured using an instrument called a **polarimeter.** (Figure 7.5).

The light used to measure optical activity has two properties: it consists of a single wavelength and it is plane-polarized. The wavelength used most often is 589 nm (called the *D line*), which corresponds to the yellow light produced by a sodium lamp. Except for giving off light of a single wavelength, a sodium lamp is like any other lamp in that its light is unpolarized, meaning that the plane of its electric field vector can have any orientation along the line of travel. A beam of unpolarized light is transformed to plane-polarized light by passing it through a polarizing filter, which removes all the waves except those that have their electric field vector in the same plane. This plane-polarized light now passes through the sample tube containing the substance to be examined, either in the liquid phase or as a solution in a suitable solvent (usually water, ethanol, or chloroform). The sample is "optically active" if it rotates the plane of polarized light. The direction and magnitude of rotation are measured using a second polarizing filter (the "analyzer") and cited as α, the observed rotation.

To be optically active, the sample must contain a chiral substance and one enantiomer must be present in excess of the other. A substance that does not rotate the plane of polarized light is said to be optically inactive. *All achiral substances are optically inactive.*

What causes optical rotation? The plane of polarization of a light wave undergoes a minute rotation when it encounters a chiral molecule. Enantiomeric forms of a chiral molecule cause a rotation of the plane of polarization in exactly equal amounts but in

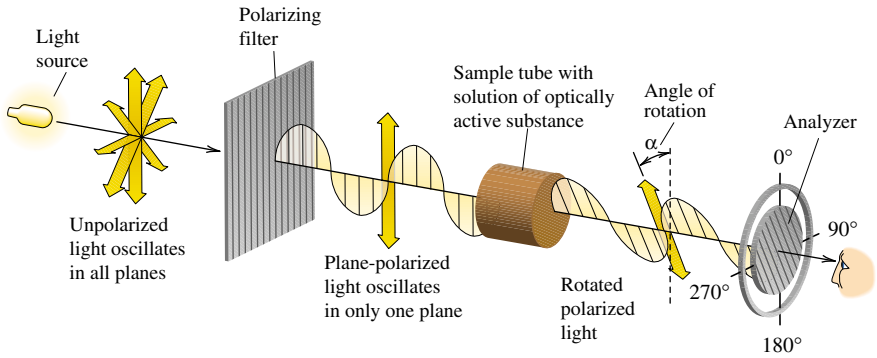


FIGURE 7.5 The sodium lamp emits light moving in all planes. When the light passes through the first polarizing filter, only one plane emerges. The plane-polarized beam enters the sample compartment, which contains a solution enriched in one of the enantiomers of a chiral substance. The plane rotates as it passes through the solution. A second polarizing filter (called the analyzer) is attached to a movable ring calibrated in degrees that is used to measure the angle of rotation α.
(Adapted from M. Silberberg, Chemistry, *2d edition, McGraw-Hill Higher Education, New York, 1992, p. 616.)*

opposite directions. A solution containing equal quantities of enantiomers therefore exhibits no net rotation because all the tiny increments of clockwise rotation produced by molecules of one "handedness" are canceled by an equal number of increments of anticlockwise rotation produced by molecules of the opposite handedness.

Mixtures containing equal quantities of enantiomers are called **racemic mixtures.** Racemic mixtures are optically inactive. Conversely, when one enantiomer is present in excess, a net rotation of the plane of polarization is observed. At the limit, where all the molecules are of the same handedness, we say the substance is **optically pure.** Optical purity, or *percent enantiomeric excess,* is defined as:

$$\begin{aligned}\text{Optical purity} &= \text{percent enantiomeric excess}\\ &= \text{percent of one enantiomer} - \text{percent of other enantiomer}\end{aligned}$$

Thus, a material that is 50% optically pure contains 75% of one enantiomer and 25% of the other.

Rotation of the plane of polarized light in the clockwise sense is taken as positive (+), and rotation in the anticlockwise sense is taken as a negative (−) rotation. The classical terms for positive and negative rotations are *dextrorotatory* and *levorotatory,* from the Latin prefixes *dextro-* ("to the right") and *levo-* ("to the left"), respectively. At one time, the symbols *d* and *l* were used to distinguish between enantiomeric forms of a substance. Thus the dextrorotatory enantiomer of 2-butanol was called *d*-2-butanol, and the levorotatory form *l*-2-butanol; a racemic mixture of the two was referred to as *dl*-2-butanol. Current custom favors using algebraic signs instead, as in (+)-2-butanol, (−)-2-butanol, and (±)-2-butanol, respectively.

The observed rotation α of an optically pure substance depends on how many molecules the light beam encounters. A filled polarimeter tube twice the length of another produces twice the observed rotation, as does a solution twice as concentrated. To account for the effects of path length and concentration, chemists have defined the term **specific rotation,** given the symbol $[\alpha]$. Specific rotation is calculated from the observed rotation according to the expression

$$[\alpha] = \frac{100\alpha}{cl}$$

where c is the concentration of the sample in grams per 100 mL of solution, and l is the length of the polarimeter tube in decimeters. (One decimeter is 10 cm.)

If concentration is expressed as grams per milliliter of solution instead of grams per 100 mL, an equivalent expression is

$$[\alpha] = \frac{\alpha}{cl}$$

Specific rotation is a physical property of a substance, just as melting point, boiling point, density, and solubility are. For example, the lactic acid obtained from milk is exclusively a single enantiomer. We cite its specific rotation in the form $[\alpha]_D^{25} = +3.8°$. The temperature in degrees Celsius and the wavelength of light at which the measurement was made are indicated as superscripts and subscripts, respectively.

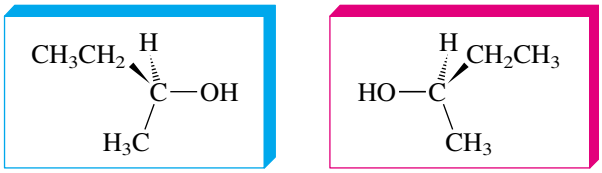
PROBLEM 7.4 Cholesterol, when isolated from natural sources, is obtained as a single enantiomer. The observed rotation α of a 0.3-g sample of cholesterol in 15 mL of chloroform solution contained in a 10-cm polarimeter tube is −0.78°. Calculate the specific rotation of cholesterol.

PROBLEM 7.5 A sample of synthetic cholesterol was prepared consisting entirely of the enantiomer of natural cholesterol. A mixture of natural and synthetic cholesterol has a specific rotation $[\alpha]_D^{20}$ of −13°. What fraction of the mixture is natural cholesterol?

It is convenient to distinguish between enantiomers by prefixing the sign of rotation to the name of the substance. For example, we refer to one of the enantiomers of 2-butanol as (+)-2-butanol and the other as (−)-2-butanol. Optically pure (+)-2-butanol has a specific rotation $[\alpha]_D^{27}$ of +13.5°; optically pure (−)-2-butanol has an exactly opposite specific rotation $[\alpha]_D^{27}$ of −13.5°.

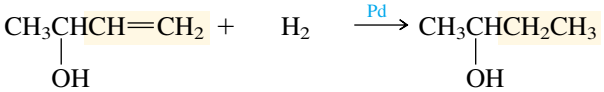
7.5 ABSOLUTE AND RELATIVE CONFIGURATION

The spatial arrangement of substituents at a stereogenic center is its **absolute configuration.** Neither the sign nor the magnitude of rotation by itself can tell us the absolute configuration of a substance. Thus, one of the following structures is (+)-2-butanol and the other is (−)-2-butanol, but without additional information we can't tell which is which.



In several places throughout the chapter we will use red and blue frames to call attention to structures that are enantiomeric.

Although no absolute configuration was known for any substance before 1951, organic chemists had experimentally determined the configurations of thousands of compounds relative to one another (their **relative configurations**) through chemical interconversion. To illustrate, consider (+)-3-buten-2-ol. Hydrogenation of this compound yields (+)-2-butanol.

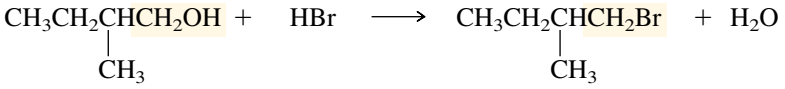


3-Buten-2-ol $[\alpha]_D^{27}$ +33.2° | Hydrogen | 2-Butanol $[\alpha]_D^{27}$ +13.5°

Make a molecular model of one of the enantiomers of 3-buten-2-ol and the 2-butanol formed from it.

Since hydrogenation of the double bond does not involve any of the bonds to the stereogenic center, the spatial arrangement of substituents in (+)-3-buten-2-ol must be the same as that of the substituents in (+)-2-butanol. The fact that these two compounds have the same sign of rotation when they have the same relative configuration is established by the hydrogenation experiment; it could not have been predicted in advance of the experiment.

Sometimes compounds that have the same relative configuration have optical rotations of opposite sign. For example, treatment of (−)-2-methyl-1-butanol with hydrogen bromide converts it to (+)-1-bromo-2-methylbutane.

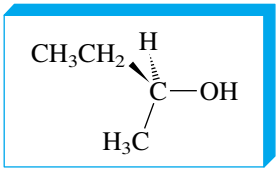


2-Methyl-1-butanol $[\alpha]_D^{25}$ −5.8° | Hydrogen bromide | 1-Bromo-2-methylbutane $[\alpha]_D^{25}$ +4.0° | Water

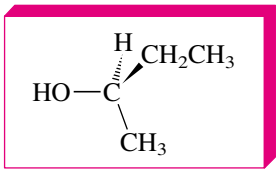
Make a molecular model of one of the enantiomers of 2-methyl-1-1-butanol and the 1-bromo-2-methylbutane formed from it.

This reaction does not involve any of the bonds to the stereogenic center, and so both the starting alcohol (−) and the product bromide (+) have the same relative configuration.

An elaborate network connecting signs of rotation and relative configurations was developed that included the most important compounds of organic and biological chemistry. When, in 1951, the absolute configuration of a salt of (+)-tartaric acid was determined, the absolute configurations of all the compounds whose configurations had been related to (+)-tartaric acid stood revealed as well. Thus, returning to the pair of 2-butanol enantiomers that introduced this section, their absolute configurations are now known to be as shown.

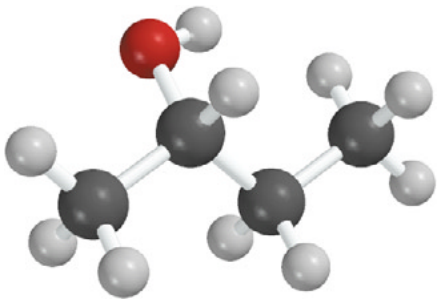


(+)-2-Butanol



(−)-2-Butanol

PROBLEM 7.6 Does the molecular model shown represent (+)-2-butanol or (−)-2-butanol?



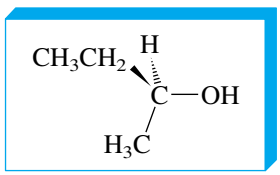
7.6 THE CAHN–INGOLD–PRELOG *R–S* NOTATIONAL SYSTEM

Just as it makes sense to have a nomenclature system by which we can specify the constitution of a molecule in words rather than pictures, so too is it helpful to have one that lets us describe stereochemistry. We have already had some experience with this idea when we distinguished between *E* and *Z* stereoisomers of alkenes.

In the *E–Z* system, substituents are ranked by atomic number according to a set of rules devised by R. S. Cahn, Sir Christopher Ingold, and Vladimir Prelog (Section 5.4). Actually, Cahn, Ingold, and Prelog first developed their ranking system to deal with the problem of the absolute configuration at a stereogenic center, and this is the system's major application. Table 7.1 shows how the Cahn–Ingold–Prelog system, called the **sequence rules,** is used to specify the absolute configuration at the stereogenic center in (+)-2-butanol.

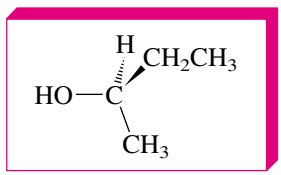
The January 1994 issue of the *Journal of Chemical Education* contains an article that describes how to use your hands to assign *R* and *S* configurations.

As outlined in Table 7.1, (+)-2-butanol has the *S* configuration. Its mirror image is (−)-2-butanol, which has the *R* configuration.



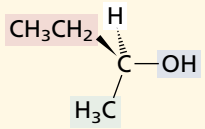
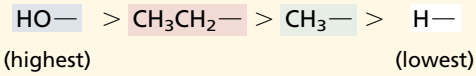
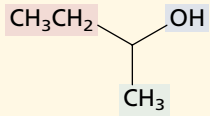
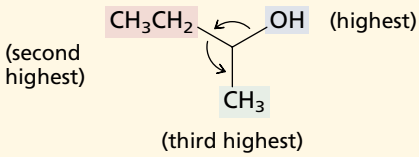
(*S*)-2-Butanol

and



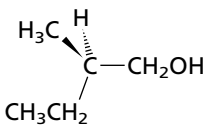
(*R*)-2-Butanol

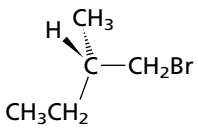
TABLE 7.1 Absolute Configuration According to the Cahn–Ingold–Prelog Notational System

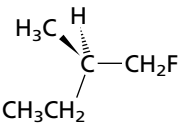
Step number	Example
Given that the absolute configuration of (+)-2-butanol is	 (+)-2-Butanol
1. Identify the substituents at the stereogenic center, and rank them in order of decreasing precedence according to the system described in Section 5.4. Precedence is determined by atomic number, working outward from the point of attachment at the stereogenic center.	In order of decreasing precedence, the four substituents attached to the stereogenic center of 2-butanol are  (highest) (lowest)
2. Orient the molecule so that the lowest ranked substituent points away from you.	As represented in the wedge-and-dash drawing at the top of this table, the molecule is already appropriately oriented. Hydrogen is the lowest ranked substituent attached to the stereogenic center and points away from us.
3. Draw the three highest ranked substituents as they appear to you when the molecule is oriented so that the lowest ranked group points away from you.	
4. If the order of decreasing precedence of the three highest ranked substituents appears in a clockwise sense, the absolute configuration is *R* (Latin *rectus,* "right," "correct"). If the order of decreasing precedence is anticlockwise, the absolute configuration is *S* (Latin *sinister,* "left").	The order of decreasing precedence is *anticlockwise.* The configuration at the stereogenic center is *S.*  (second highest) (highest) (third highest)

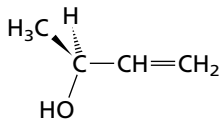
Often, the *R* or *S* configuration and the sign of rotation are incorporated into the name of the compound, as in (*R*)-(−)-2-butanol and (*S*)-(+)-2-butanol.

PROBLEM 7.7 Assign absolute configurations as *R* or *S* to each of the following compounds:

(a)  (+)-2-Methyl-1-butanol

(c)  (+)-1-Bromo-2-methylbutane

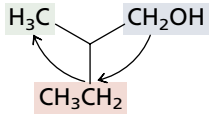
(b)  (+)-1-Fluoro-2-methylbutane

(d)  (+)-3-Buten-2-ol

SAMPLE SOLUTION (a) The highest ranking substituent at the stereogenic center of 2-methyl-1-butanol is CH_2OH; the lowest is H. Of the remaining two, ethyl outranks methyl.

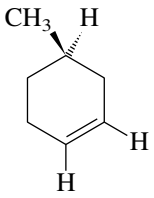
Order of precedence: $CH_2OH > CH_3CH_2 > CH_3 > H$

The lowest ranking substituent (hydrogen) points away from us in the drawing. The three highest ranking groups trace a clockwise path from $CH_2OH \rightarrow CH_3CH_2 \rightarrow CH_3$.



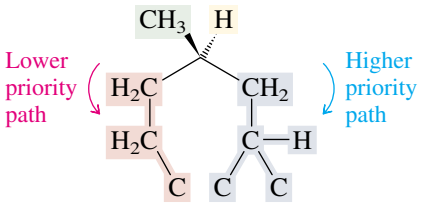
This compound therefore has the *R* configuration. It is (*R*)-(+)-2-methyl-1-butanol.

Compounds in which a stereogenic center is part of a ring are handled in an analogous fashion. To determine, for example, whether the configuration of (+)-4-methylcyclohexene is *R* or *S*, treat the right- and left-hand paths around the ring as if they were independent substituents.



(+)-4-Methylcyclohexene

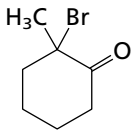
is treated as



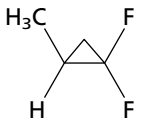
With the lowest ranked substituent (hydrogen) directed away from us, we see that the order of decreasing sequence rule precedence is *clockwise*. The absolute configuration is *R*.

PROBLEM 7.8 Draw three-dimensional representations or make molecular models of

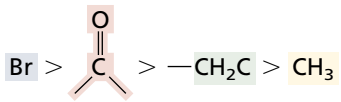
(a) The *R* enantiomer of



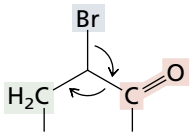
(b) The *S* enantiomer of



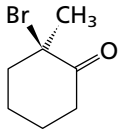
SAMPLE SOLUTION (a) The stereogenic center is the one that bears the bromine. In order of decreasing precedence, the substituents attached to the stereogenic center are



When the lowest ranked substituent (the methyl group) is away from us, the order of decreasing precedence of the remaining groups must appear in a clockwise sense in the *R* enantiomer.



which leads to the structure



(*R*)-2-Bromo-2-methylcyclohexanone

Since its introduction in 1956, the Cahn–Ingold–Prelog system has become the standard method of stereochemical notation.

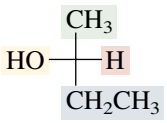
7.7 FISCHER PROJECTIONS

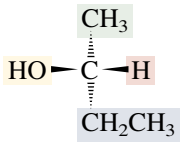
Stereochemistry deals with the three-dimensional arrangement of a molecule's atoms, and we have attempted to show stereochemistry with wedge-and-dash drawings and computer-generated models. It is possible, however, to convey stereochemical information in an abbreviated form using a method devised by the German chemist Emil Fischer.

Fischer was the foremost organic chemist of the late nineteenth century. He won the 1902 Nobel Prize in chemistry for his pioneering work in carbohydrate and protein chemistry.

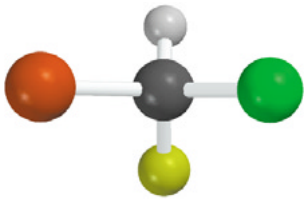
Let's return to bromochlorofluoromethane as a simple example of a chiral molecule. The two enantiomers of BrClFCH are shown as ball-and-stick models, as wedge-and-dash drawings, and as **Fischer projections** in Figure 7.6. Fischer projections are always generated the same way: the molecule is oriented so that the vertical bonds at the stereogenic center are directed away from you and the horizontal bonds point toward you. A projection of the bonds onto the page is a cross. The stereogenic carbon lies at the center of the cross but is not explicitly shown.

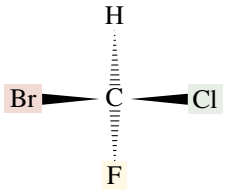
It is customary to orient the molecule so that the carbon chain is vertical with the lowest numbered carbon at the top as shown for the Fischer projection of (*R*)-2-butanol.

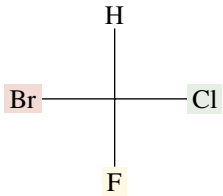
The Fischer projection 

corresponds to 

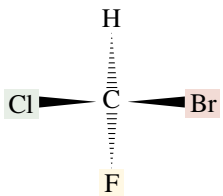
(*R*)-2-Butanol

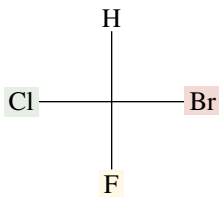






(*R*)-Bromochlorofluoromethane





(*S*)-Bromochlorofluoromethane

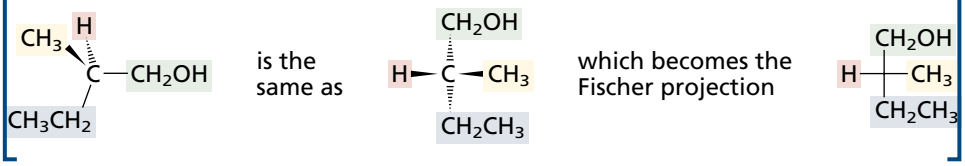
FIGURE 7.6 Ball-and-stick models *(left)*, wedge-and-dash drawings *(center)*, and Fischer projections *(right)* of the *R* and *S* enantiomers of bromochlorofluoromethane.

When specifying a configuration as *R* or *S*, the safest procedure is to convert a Fischer projection to a three-dimensional representation, remembering that the horizontal bonds always point toward you.

Edward Siloac, an undergraduate organic chemistry student at the University of Virginia, published a paper in the June 1999 issue of the *Journal of Chemical Education* (pp. 798–799) that described how to use your hands to translate Fischer projections to *R* and *S* configurations.

PROBLEM 7.9 Write Fischer projections for each of the compounds of Problem 7.7.

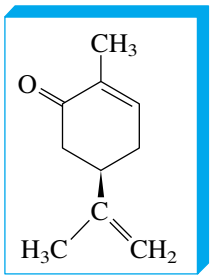
SAMPLE SOLUTION (a) The structure of (*R*)-(+)-2-methyl-1-butanol is shown in the structure that follows at the left. View the structural formula from a position chosen so that the $HOCH_2—C—CH_2CH_3$ segment is aligned vertically, with the vertical bonds pointing away from you. Replace the wedge-and-dash bonds by lines to give the Fischer projection shown at the right.



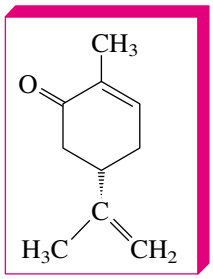
7.8 PHYSICAL PROPERTIES OF ENANTIOMERS

The usual physical properties such as density, melting point, and boiling point are identical within experimental error for both enantiomers of a chiral compound.

Enantiomers can have striking differences, however, in properties that depend on the arrangement of atoms in space. Take, for example, the enantiomeric forms of carvone. (*R*)-(−)-Carvone is the principal component of spearmint oil. Its enantiomer, (*S*)-(+)-carvone, is the principal component of caraway seed oil. The two enantiomers do not smell the same; each has its own characteristic odor.



(*R*)-(−)-Carvone
(from spearmint oil)



(*S*)-(+)-Carvone
(from caraway seed oil)

The difference in odor between (*R*)- and (*S*)-carvone results from their different behavior toward receptor sites in the nose. It is believed that volatile molecules occupy only those odor receptors that have the proper shape to accommodate them. Because the receptor sites are themselves chiral, one enantiomer may fit one kind of receptor while the other enantiomer fits a different kind. An analogy that can be drawn is to hands and gloves. Your left hand and your right hand are enantiomers. You can place your left hand into a left glove but not into a right one. The receptor (the glove) can accommodate one enantiomer of a chiral object (your hand) but not the other.

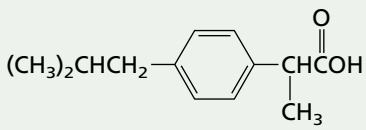
An article entitled "When Drug Molecules Look in the Mirror" in the June 1996 issue of the *Journal of Chemical Education* (pp. 481–484) describes numerous examples of common drugs in which the two enantiomers have different biological properties.

The term "chiral recognition" refers to the process whereby some chiral receptor or reagent interacts selectively with one of the enantiomers of a chiral molecule. Very high levels of chiral recognition are common in biological processes. (−)-Nicotine, for example, is much more toxic than (+)-nicotine, and (+)-adrenaline is more active in the

CHIRAL DRUGS

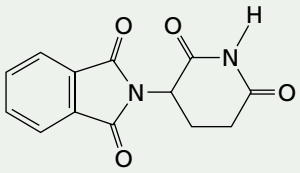
A recent estimate places the number of prescription and over-the-counter drugs marketed throughout the world at about 2000. Approximately one-third of these are either naturally occurring substances themselves or are prepared by chemical modification of natural products. Most of the drugs derived from natural sources are chiral and are almost always obtained as a single enantiomer rather than as a racemic mixture. Not so with the over 500 chiral substances represented among the more than 1300 drugs that are the products of synthetic organic chemistry. Until recently, such substances were, with few exceptions, prepared, sold, and administered as racemic mixtures even though the desired therapeutic activity resided in only one of the enantiomers. Spurred by a number of factors ranging from safety and efficacy to synthetic methodology and economics, this practice is undergoing rapid change as more and more chiral synthetic drugs become available in enantiomerically pure form.

Because of the high degree of chiral recognition inherent in most biological processes (Section 7.8), it is unlikely that both enantiomers of a chiral drug will exhibit the same level, or even the same kind, of effect. At one extreme, one enantiomer has the desired effect, and the other exhibits no biological activity at all. In this case, which is relatively rare, the racemic form is simply a drug that is 50% pure and contains 50% "inert ingredients." Real cases are more complicated. For example, it is the *S* enantiomer that is responsible for the pain-relieving properties of ibuprofen, normally sold as a racemic mixture. The 50% of racemic ibuprofen that is the *R* enantiomer is not completely wasted, however, because enzyme-catalyzed reactions in our body convert much of it to active (*S*)-ibuprofen.



Ibuprofen

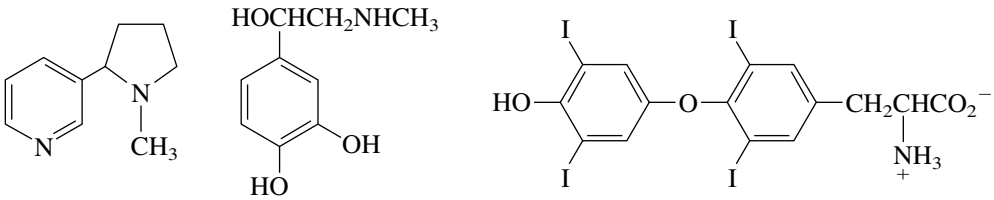
A much more serious drawback to using chiral drugs as racemic mixtures is illustrated by thalidomide, briefly employed as a sedative and antinausea drug in Europe and Great Britain during the period 1959–1962. The desired properties are those of (*R*)-thalidomide. (*S*)-Thalidomide, however, has a very different spectrum of biological activity and was shown to be responsible for over 2000 cases of serious birth defects in children born to women who took it while pregnant.



Thalidomide

Basic research directed toward understanding the factors that control the stereochemistry of chemical reactions has led to new synthetic methods that make it practical to prepare chiral molecules in enantiomerically pure form. Recognizing this, most major pharmaceutical companies are examining their existing drugs to see which ones are the best candidates for synthesis as single enantiomers and, when preparing a new drug, design its synthesis so as to provide only the desired enantiomer. In 1992, the United States Food and Drug Administration (FDA) issued guidelines that encouraged such an approach, but left open the door for approval of new drugs as racemic mixtures when special circumstances warrant. One incentive to developing enantiomerically pure versions of existing drugs is that the novel production methods they require may make them eligible for patent protection separate from that of the original drugs. Thus the temporary monopoly position that patent law views as essential to fostering innovation can be extended by transforming a successful chiral, but racemic, drug into an enantiomerically pure version.

constriction of blood vessels than (−)-adrenaline. (−)-Thyroxine is an amino acid of the thyroid gland, which speeds up metabolism and causes nervousness and loss of weight. Its enantiomer, (+)-thyroxine, exhibits none of these effects but is sometimes given to heart patients to lower their cholesterol levels.

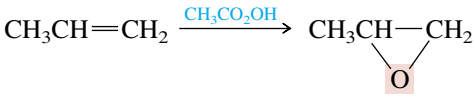


Nicotine Adrenaline Thyroxine

(Can you find the stereogenic center in each of these?)

7.9 REACTIONS THAT CREATE A STEREOGENIC CENTER

Many of the reactions we've already encountered can yield a chiral product from an achiral starting material. Epoxidation of propene, for example, creates a stereogenic center by addition of oxygen to the double bond.



Propene (achiral) 1,2-Epoxypropane (chiral)

In this, as in other reactions in which achiral reactants yield chiral products, the product is formed as a *racemic mixture* and is *optically inactive*. Remember, for a substance to be optically active, not only must it be chiral but one enantiomer must be present in excess of the other.

Figure 7.7 shows why equal amounts of (*R*)- and (*S*)-1,2-epoxypropane are formed in this reaction. The peroxy acid is just as likely to transfer oxygen to one face of the double bond as the other, the rates of formation of the *R* and *S* enantiomers of the product are the same and a racemic mixture of the two results.

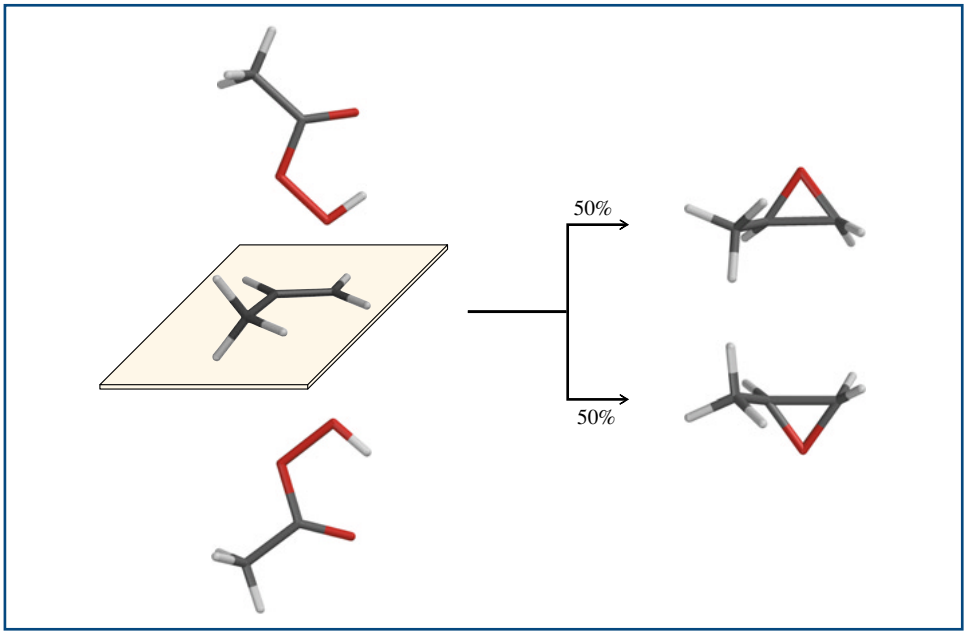


FIGURE 7.7 Epoxidation of propene produces equal amounts of (*R*)- and (*S*)-1,2-epoxypropane.

It is often helpful, especially in a multistep reaction, to focus on the step that creates the stereogenic center. In the ionic addition of hydrogen bromide to 2-butene, for example, the stereogenic center is generated when bromide ion attacks *sec*-butyl cation.

$$CH_3CH{=}CHCH_3 \xrightarrow{HBr} CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_3 \quad \text{via} \quad CH_3\overset{+}{C}HCH_2CH_3$$

(*E*)- or (*Z*)-2-butene (achiral) — 2-Bromobutane (chiral) — *sec*-Butyl cation (achiral)

As seen in Figure 7.8, the bonds to the positively charged carbon are coplanar and define a plane of symmetry in the carbocation, which is achiral. The rates at which bromide ion attacks the carbocation at its two mirror-image faces are equal, and the product, 2-bromobutane, although chiral, is optically inactive because it is formed as a racemic mixture.

It is a general principle that *optically active products cannot be formed when optically inactive substrates react with optically inactive reagents.* This principle holds irrespective of whether the addition is syn or anti, concerted or stepwise. No matter how many steps are involved in a reaction, if the reactants are achiral, formation of one enantiomer is just as likely as the other, and a racemic mixture results.

When a reactant is chiral but optically inactive because it is *racemic,* any products derived from its reactions with optically inactive reagents will be *optically inactive.* For example, 2-butanol is chiral and may be converted with hydrogen bromide to 2-bromobutane, which is also chiral. If racemic 2-butanol is used, each enantiomer will react at the same rate with the achiral reagent. Whatever happens to (*R*)-(−)-2-butanol is mirrored in a corresponding reaction of (*S*)-(+)-2-butanol, and a racemic, optically inactive product results.

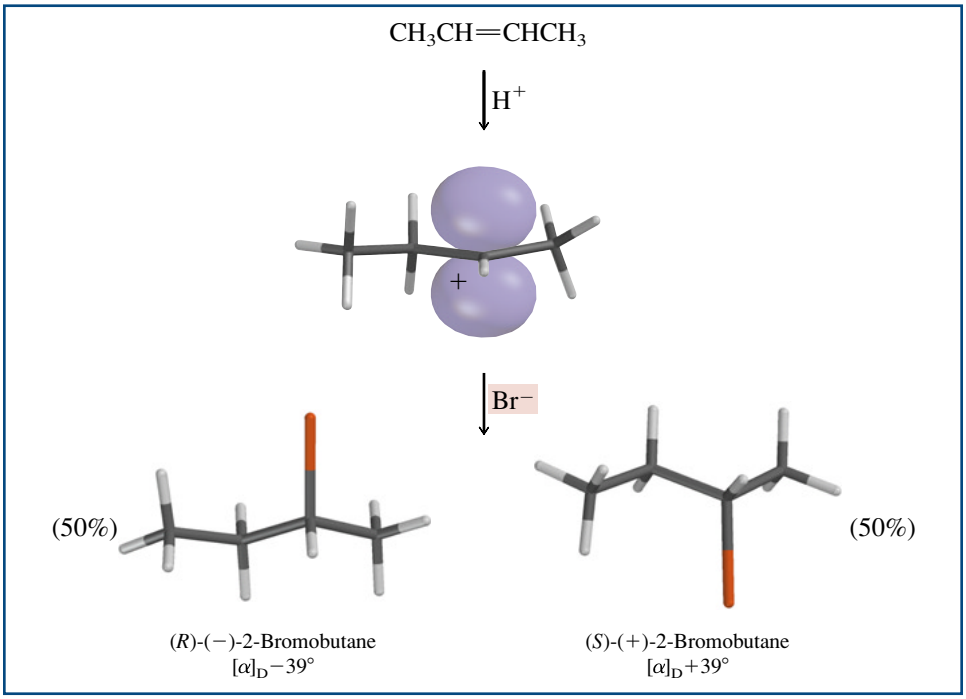
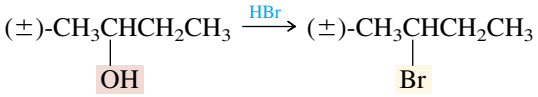
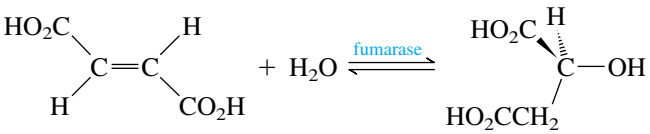


FIGURE 7.8 Electrophilic addition of hydrogen bromide to (*E*) and (*Z*)-2-butene proceeds by way of an achiral carbocation, which leads to equal quantities of (*R*)- and (*S*)-2-bromobutane.



2-Butanol (chiral but racemic) 2-Bromobutane (chiral but racemic)

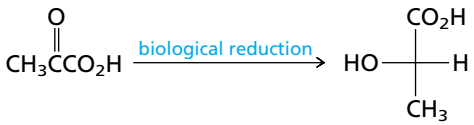
Optically inactive starting materials can give optically active products if they are treated with an optically active reagent or if the reaction is catalyzed by an optically active substance. The best examples are found in biochemical processes. Most biochemical reactions are catalyzed by enzymes. Enzymes are chiral and enantiomerically homogeneous; they provide an asymmetric environment in which chemical reaction can take place. Ordinarily, enzyme-catalyzed reactions occur with such a high level of stereoselectivity that one enantiomer of a substance is formed exclusively even when the substrate is achiral. The enzyme *fumarase,* for example, catalyzes the hydration of fumaric acid to malic acid in apples and other fruits. Only the *S* enantiomer of malic acid is formed in this reaction.



Fumaric acid (*S*)-(−)-Malic acid

The reaction is reversible, and its stereochemical requirements are so pronounced that neither the cis isomer of fumaric acid (maleic acid) nor the *R* enantiomer of malic acid can serve as a substrate for the fumarase-catalyzed hydration–dehydration equilibrium.

PROBLEM 7.10 Biological reduction of pyruvic acid, catalyzed by the enzyme lactate dehydrogenase, gives (+)-lactic acid, represented by the Fischer projection shown. What is the configuration of (+)-lactic acid according to the Cahn–Ingold–Prelog *R*–*S* notational system? Making a molecular model of the Fischer projection will help.

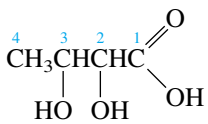


Pyruvic acid (+)-Lactic acid

We'll continue with the three-dimensional details of chemical reactions later in this chapter. First though, we need to develop some additional stereochemical principles concerning structures with more than one stereogenic center.

7.10 CHIRAL MOLECULES WITH TWO STEREOGENIC CENTERS

When a molecule contains two stereogenic centers, as does 2,3-dihydroxybutanoic acid, how many stereoisomers are possible?



2,3-Dihydroxybutanoic acid

We can use straightforward reasoning to come up with the answer. The absolute configuration at C-2 may be *R* or *S*. Likewise, C-3 may have either the *R* or the *S* configuration. The four possible combinations of these two stereogenic centers are

(2*R*,3*R*)	(stereoisomer I)	(2*S*,3*S*)	(stereoisomer II)
(2*R*,3*S*)	(stereoisomer III)	(2*S*,3*R*)	(stereoisomer IV)

Figure 7.9 presents structural formulas for these four stereoisomers. Stereoisomers I and II are enantiomers of each other; the enantiomer of (*R*,*R*) is (*S*,*S*). Likewise stereoisomers III and IV are enantiomers of each other, the enantiomer of (*R*,*S*) being (*S*,*R*).

Stereoisomer I is not a mirror image of III or IV, so is not an enantiomer of either one. Stereoisomers that are not related as an object and its mirror image are called **diastereomers;** *diastereomers are stereoisomers that are not enantiomers.* Thus, stereoisomer I is a diastereomer of III and a diastereomer of IV. Similarly, II is a diastereomer of III and IV.

To convert a molecule with two stereogenic centers to its enantiomer, the configuration at both centers must be changed. Reversing the configuration at only one stereogenic center converts it to a diastereomeric structure.

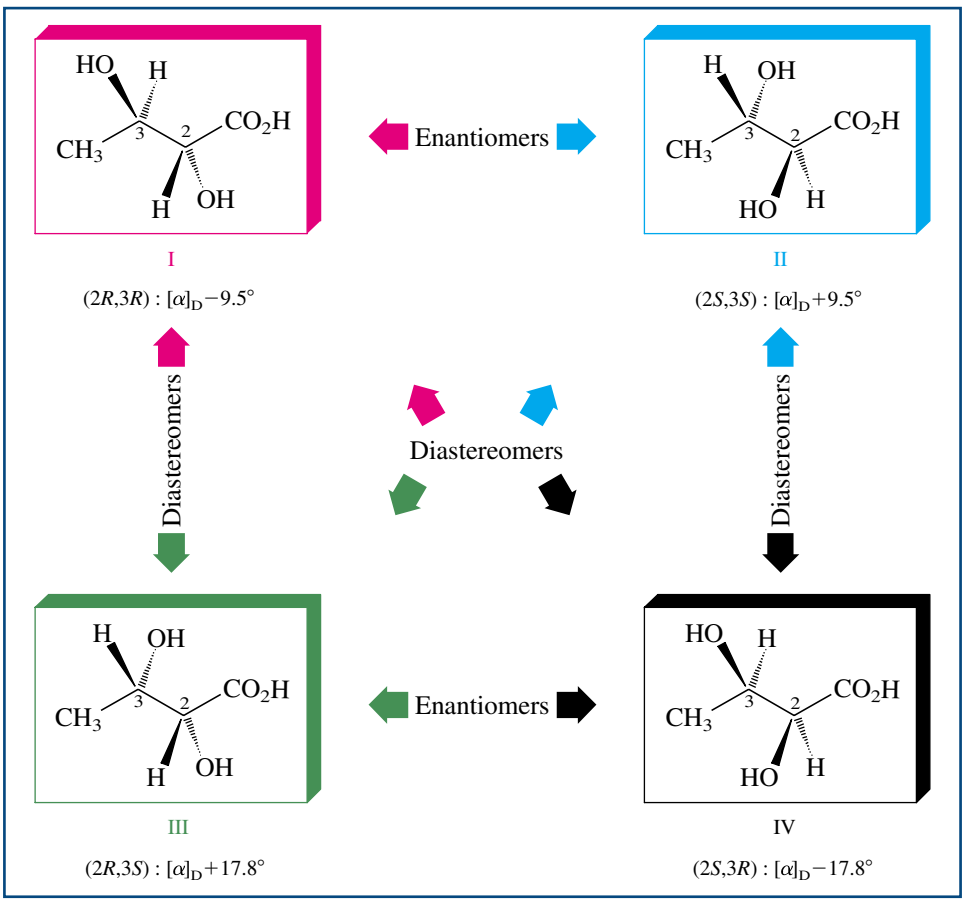


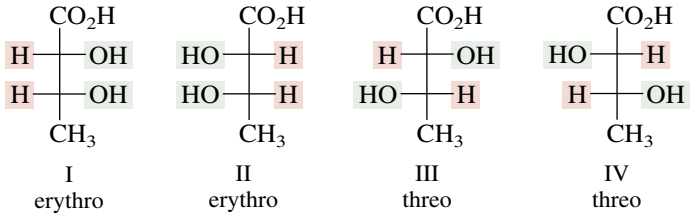
FIGURE 7.9 Stereoisomeric 2,3-dihydroxybutanoic acids. Stereoisomers I and II are enantiomers. Stereoisomers III and IV are enantiomers. All other relationships are diastereomeric (see text).

Enantiomers must have equal and opposite specific rotations. Diastereomeric substances can have different rotations, with respect to both sign and magnitude. Thus, as Figure 7.9 shows, the (2*R*,3*R*) and (2*S*,3*S*) enantiomers (I and II) have specific rotations that are equal in magnitude but opposite in sign. The (2*R*,3*S*) and (2*S*,3*R*) enantiomers (III and IV) likewise have specific rotations that are equal to each other but opposite in sign. The magnitudes of rotation of I and II are different, however, from those of their diastereomers III and IV.

In writing Fischer projections of molecules with two stereogenic centers, the molecule is arranged in an *eclipsed* conformation for projection onto the page, as shown in Figure 7.10. Again, horizontal lines in the projection represent bonds coming toward you; vertical bonds point away.

Organic chemists use an informal nomenclature system based on Fischer projections to distinguish between diastereomers. When the carbon chain is vertical and like substituents are on the same side of the Fischer projection, the molecule is described as the **erythro** diastereomer. When like substituents are on opposite sides of the Fischer projection, the molecule is described as the **threo** diastereomer. Thus, as seen in the Fischer projections of the stereoisomeric 2,3-dihydroxybutanoic acids, compounds I and II are erythro stereoisomers and III and IV are threo.

Erythro and threo describe the *relative configuration* (Section 7.5) of two stereogenic centers within a single molecule.



Because diastereomers are not mirror images of each other, they can have quite different physical and chemical properties. For example, the (2*R*,3*R*) stereoisomer of 3-amino-2-butanol is a liquid, but the (2*R*,3*S*) diastereomer is a crystalline solid.

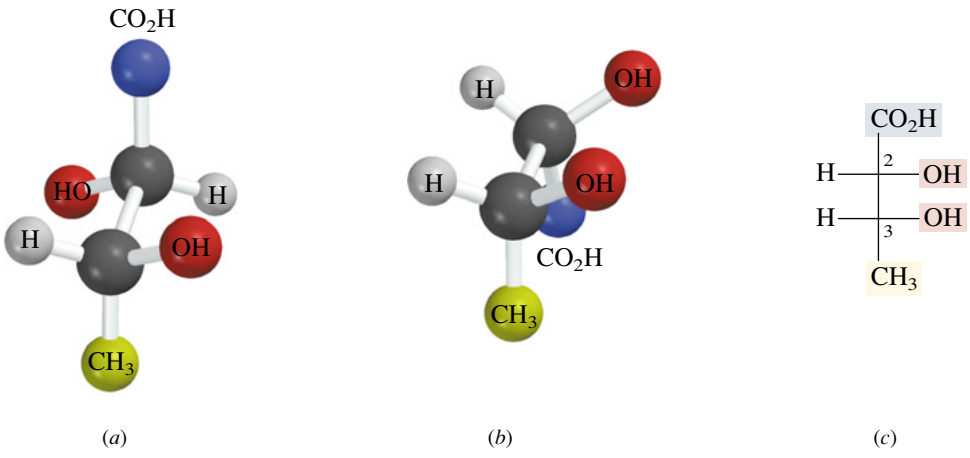
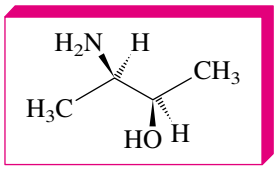
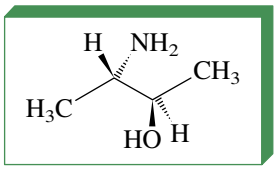


FIGURE 7.10 Representations of (2*R*,3*R*)-dihydroxybutanoic acid. (*a*) The staggered conformation is the most stable but is not properly arranged to show stereochemistry according to the Fischer projection method. (*b*) Rotation about the C-2—C-3 bond gives the eclipsed conformation, and projection of the eclipsed conformation onto the page gives (*c*) a correct Fischer projection.



(2*R*,3*R*)-3-Amino-2-butanol
(liquid)



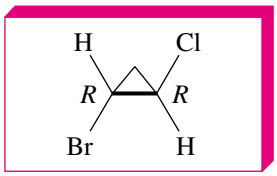
(2*R*,3*S*)-3-Amino-2-butanol
(solid, mp 49°C)

A molecule framed in green is a diastereomer of one framed in red or blue.

PROBLEM 7.11 Draw Fischer projections or make molecular models of the four stereoisomeric 3-amino-2-butanols, and label each erythro or threo as appropriate.

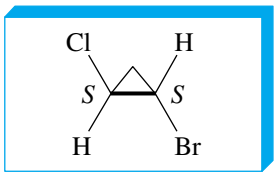
PROBLEM 7.12 One other stereoisomer of 3-amino-2-butanol is a crystalline solid. Which one?

The situation is the same when the two stereogenic centers are present in a ring. There are four stereoisomeric 1-bromo-2-chlorocyclopropanes: a pair of enantiomers in which the halogens are trans and a pair in which they are cis. The cis compounds are diastereomers of the trans.



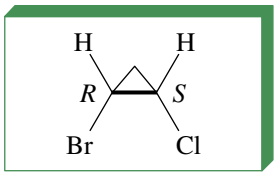
(1*R*,2*R*)-1-Bromo-2-chlorocyclopropane

Enantiomers



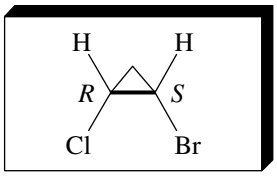
(1*S*,2*S*)-1-Bromo-2-chlorocyclopropane

A molecule framed in black is an enantiomer of a green-framed one. Both are diastereomers of their red or blue-framed stereoisomers.



(1*R*,2*S*)-1-Bromo-2-chlorocyclopropane

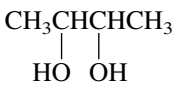
Enantiomers



(1*S*,2*R*)-1-Bromo-2-chlorocyclopropane

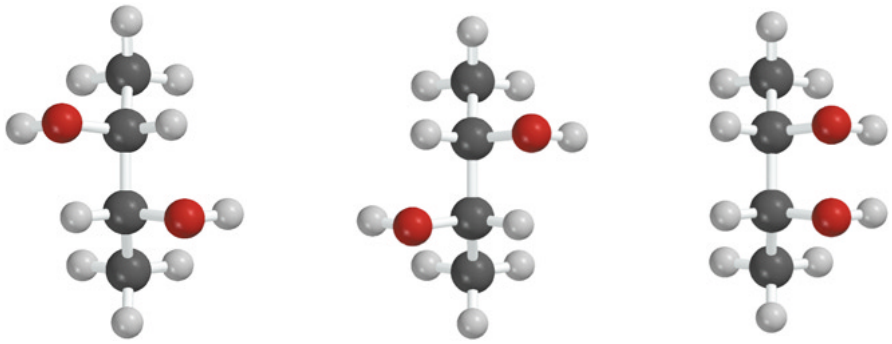
7.11 ACHIRAL MOLECULES WITH TWO STEREOGENIC CENTERS

Now think about a molecule, such as 2,3-butanediol, which has two stereogenic centers that are equivalently substituted.



2,3-Butanediol

Only *three,* not four, stereoisomeric 2,3-butanediols are possible. These three are shown in Figure 7.11. The (2*R*,3*R*) and (2*S*,3*S*) forms are enantiomers of each other and have equal and opposite optical rotations. A third combination of stereogenic centers, (2*R*,3*S*), however, gives an *achiral* structure that is superposable on its (2*S*,3*R*) mirror image. Because it is achiral, this third stereoisomer is *optically inactive.* We call achiral molecules that have stereogenic centers **meso forms.** The meso form in Figure 7.11 is known as *meso*-2,3-butanediol.



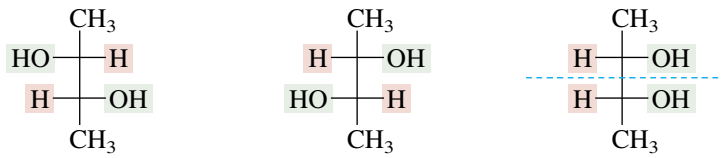
(2*R*,3*R*)-2,3-Butanediol (*a*) (2*S*,3*S*)-2,3-Butanediol (*b*) *meso*-2,3-Butanediol (*c*)

FIGURE 7.11 Stereoisomeric 2,3-butanediols shown in their eclipsed conformations for convenience. Stereoisomers (*a*) and (*b*) are enantiomers of each other. Structure (*c*) is a diastereomer of (*a*) and (*b*), and is achiral. It is called *meso*-2,3-butanediol.

One way to demonstrate that *meso*-2,3-butanediol is achiral is to recognize that its eclipsed conformation has a plane of symmetry that passes through and is perpendicular to the C-2—C-3 bond, as illustrated in Figure 7.12*a*. The anti conformation is achiral as well. As Figure 7.12*b* shows, this conformation is characterized by a center of symmetry at the midpoint of the C-2—C-3 bond.

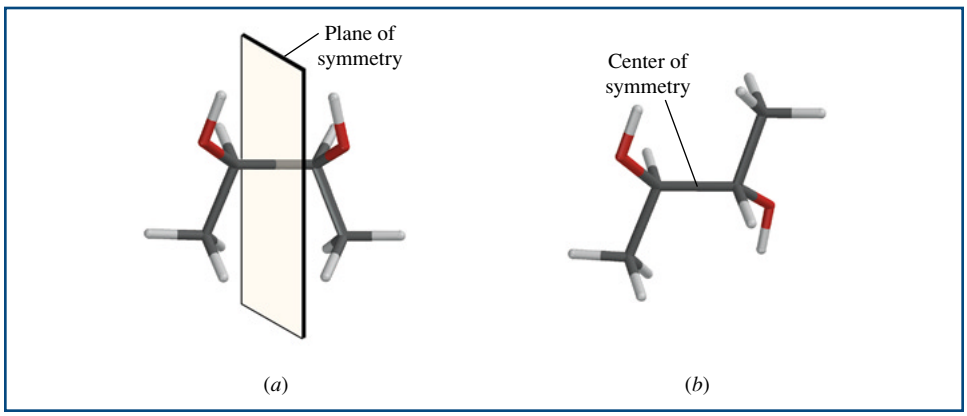
Fischer projection formulas can help us identify meso forms. Of the three stereoisomeric 2,3-butanediols, notice that only in the meso stereoisomer does a dashed line through the center of the Fischer projection divide the molecule into two mirror-image halves.

In the same way that a Fischer formula is a projection of the eclipsed conformation onto the page, the line drawn through its center is a projection of the plane of symmetry which is present in the eclipsed conformation of *meso*-2,3-butanediol.



(2*R*,3*R*)-2,3-Butanediol (2*S*,3*S*)-2,3-Butanediol *meso*-2,3-Butanediol

When using Fischer projections for this purpose, however, be sure to remember what three-dimensional objects they stand for. One should not, for example, test for superposition of the two chiral stereoisomers by a procedure that involves moving any part of a Fischer projection out of the plane of the paper in any step.



(*a*) (*b*)

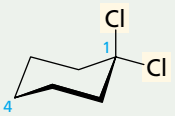
FIGURE 7.12 (*a*) The eclipsed conformation of *meso*-2,3-butanediol has a plane of symmetry. (*b*) The anti conformation of *meso*-2,3-butanediol has a center of symmetry.

CHIRALITY OF DISUBSTITUTED CYCLOHEXANES

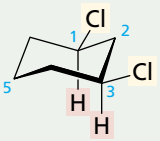
Disubstituted cyclohexanes present us with a challenging exercise in stereochemistry. Consider the seven possible dichlorocyclohexanes: 1,1-; *cis*- and *trans*-1,2-; *cis*- and *trans*-1,3-; and *cis*- and *trans*-1,4-. Which are chiral? Which are achiral?

Four isomers—the ones that are achiral because they have a plane of symmetry—are relatively easy to identify:

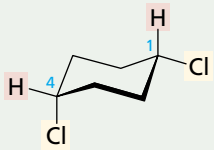
ACHIRAL DICHLOROCYCLOHEXANES



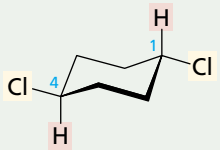
1,1
(plane of symmetry through C-1 and C-4)



cis-1,3
(plane of symmetry through C-2 and C-5)



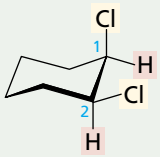
cis-1,4
(plane of symmetry through C-1 and C-4)



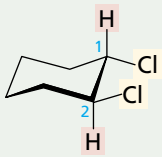
trans-1,4
(plane of symmetry through C-1 and C-4)

The remaining three isomers are chiral:

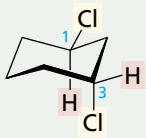
CHIRAL DICHLOROCYCLOHEXANES



cis-1,2

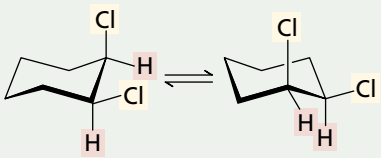


trans-1,2



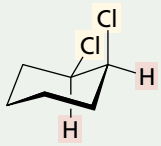
trans-1,3

Among all the isomers, *cis*-1,2-dichlorocyclohexane is unique in that the ring-flipping process typical of cyclohexane derivatives (Section 3.8) converts it to its enantiomer.



A A′

which is equivalent to



A′

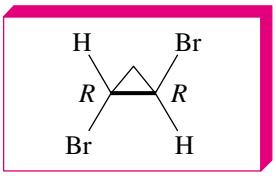
Structures A and A′ are nonsuperposable mirror images of each other. Thus although *cis*-1,2-dichlorocyclohexane is chiral, it is optically inactive when chair–chair interconversion occurs. Such interconversion is rapid at room temperature and converts optically active A to a racemic mixture of A and A′. Since A and A′ are enantiomers interconvertible by a conformational change, they are sometimes referred to as **conformational enantiomers.**

The same kind of spontaneous racemization occurs for any *cis*-1,2 disubstituted cyclohexane in which both substituents are the same. Since such compounds are chiral, it is incorrect to speak of them as meso compounds, which are achiral by definition. Rapid chair–chair interconversion, however, converts them to a 1:1 mixture of enantiomers, and this mixture is optically inactive.

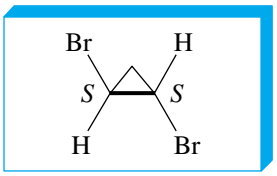
PROBLEM 7.13 A meso stereoisomer is possible for one of the following compounds. Which one?

2,3-Dibromopentane; 2,4-dibromopentane; 3-bromo-2-pentanol; 4-bromo-2-pentanol

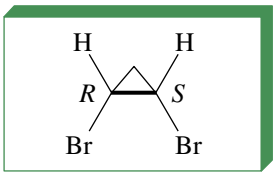
Turning to cyclic compounds, we see that there are three, not four, stereoisomeric 1,2-dibromocyclopropanes. Of these, two are enantiomeric *trans*-1,2-dibromocyclopropanes. The cis diastereomer is a meso form; it has a plane of symmetry.



(1*R*,2*R*)-1,2-Dibromocyclopropane



(1*S*,2*S*)-Dibromocyclopropane



meso-1,2-Dibromocyclopropane

PROBLEM 7.14 One of the stereoisomers of 1,3-dimethylcyclohexane is a meso form. Which one?

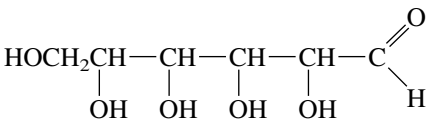
7.12 MOLECULES WITH MULTIPLE STEREOGENIC CENTERS

Many naturally occurring compounds contain several stereogenic centers. By an analysis similar to that described for the case of two stereogenic centers, it can be shown that the maximum number of stereoisomers for a particular constitution is 2^n, where n is equal to the number of stereogenic centers.

PROBLEM 7.15 Using *R* and *S* descriptors, write all the possible combinations for a molecule with three stereogenic centers.

When two or more of a molecule's stereogenic centers are equivalently substituted, meso forms are possible, and the number of stereoisomers is then less than 2^n. Thus, 2^n represents the *maximum* number of stereoisomers for a molecule containing n stereogenic centers.

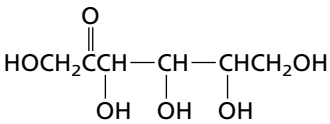
The best examples of substances with multiple stereogenic centers are the *carbohydrates* (Chapter 25). One class of carbohydrates, called *hexoses,* has the constitution



A hexose

Since there are four stereogenic centers and no possibility of meso forms, there are 2^4, or 16, stereoisomeric hexoses. All 16 are known, having been isolated either as natural products or as the products of chemical synthesis.

PROBLEM 7.16 A second category of six-carbon carbohydrates, called *2-hexuloses,* has the constitution shown. How many stereoisomeric 2-hexuloses are possible?



A 2-hexulose

Steroids are another class of natural products with multiple stereogenic centers. One such compound is *cholic acid,* which can be obtained from bile. Its structural formula is given in Figure 7.13. Cholic acid has 11 stereogenic centers, and so there are a total (including cholic acid) of 2^{11}, or 2048, stereoisomers that have this constitution. Of

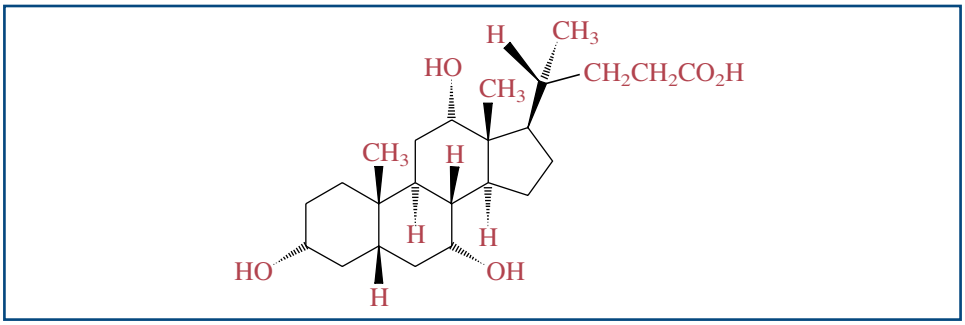
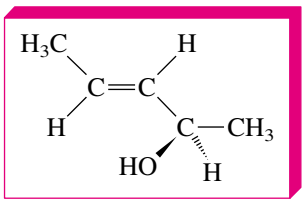


FIGURE 7.13 The structure of cholic acid. Its 11 stereogenic centers are those carbons at which stereochemistry is indicated in the diagram.

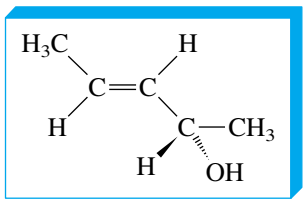
these 2048 stereoisomers, how many are diastereomers of cholic acid? Remember! Diastereomers are stereoisomers that are not enantiomers, and any object can have only one mirror image. Therefore, of the 2048 stereoisomers, one is cholic acid, one is its enantiomer, and the other 2046 are diastereomers of cholic acid. Only a small fraction of these compounds are known, and (+)-cholic acid is the only one ever isolated from natural sources.

Eleven stereogenic centers may seem like a lot, but it is nowhere close to a world record. It is a modest number when compared with the more than 100 stereogenic centers typical for most small proteins and the thousands of stereogenic centers that are present in nucleic acids.

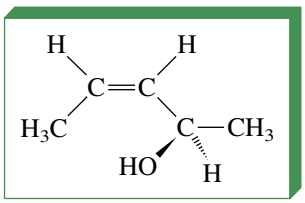
A molecule that contains both stereogenic centers and double bonds has additional opportunities for stereoisomerism. For example, the configuration of the stereogenic center in 3-penten-2-ol may be either *R* or *S,* and the double bond may be either *E* or *Z.* There are therefore four stereoisomers of 3-penten-2-ol even though it has only one stereogenic center.



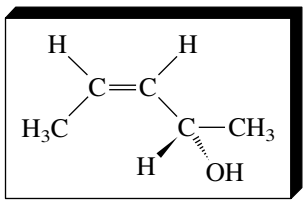
(2*R*,3*E*)-3-Penten-2-ol



(2*S*,3*E*)-3-Penten-2-ol



(2*R*,3*Z*)-3-Penten-2-ol



(2*S*,3*Z*)-3-Penten-2-ol

The relationship of the (2*R*,3*E*) stereoisomer to the others is that it is the enantiomer of (2*S*,3*E*)-3-penten-2-ol and is a diastereomer of the (2*R*,3*Z*) and (2*S*,3*Z*) isomers.

7.13 REACTIONS THAT PRODUCE DIASTEREOMERS

Once we grasp the idea of stereoisomerism in molecules with two or more stereogenic centers, we can explore further details of addition reactions of alkenes.

When bromine adds to (*Z*)- or (*E*)-2-butene, the product 2,3-dibromobutane contains two equivalently substituted stereogenic centers:

$$CH_3CH{=}CHCH_3 \xrightarrow{Br_2} CH_3\underset{\displaystyle Br}{\underset{|}{C}}H\underset{\displaystyle Br}{\underset{|}{C}}HCH_3$$

(*Z*)- or (*E*)-2-butene 2,3-Dibromobutane

Three stereoisomers are possible: a pair of enantiomers and a meso form.

Two factors combine to determine which stereoisomers are actually formed in the reaction.

1. The (*E*)- or (*Z*)-configuration of the starting alkene
2. The anti stereochemistry of addition

Figures 7.14 and 7.15 depict the stereochemical relationships associated with anti addition of bromine to (*E*)- and (*Z*)-2-butene, respectively. The trans alkene (*E*)-2-butene yields only *meso*-2,3-dibromobutane, but the cis alkene (*Z*)-2-butene gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-dibromobutane.

Bromine addition to alkenes is an example of a **stereospecific reaction.** A stereospecific reaction is one in which stereoisomeric starting materials yield products that are stereoisomers of each other. In this case the starting materials, in separate reactions, are the *E* and *Z* stereoisomers of 2-butene. The chiral dibromides from (*Z*)-2-butene are stereoisomers (diastereomers) of the meso dibromide formed from (*E*)-2-butene.

Notice further that, consistent with the principle developed in Section 7.9, optically inactive starting materials (achiral alkenes and bromine) yield optically inactive products (a racemic mixture or a meso structure) in these reactions.

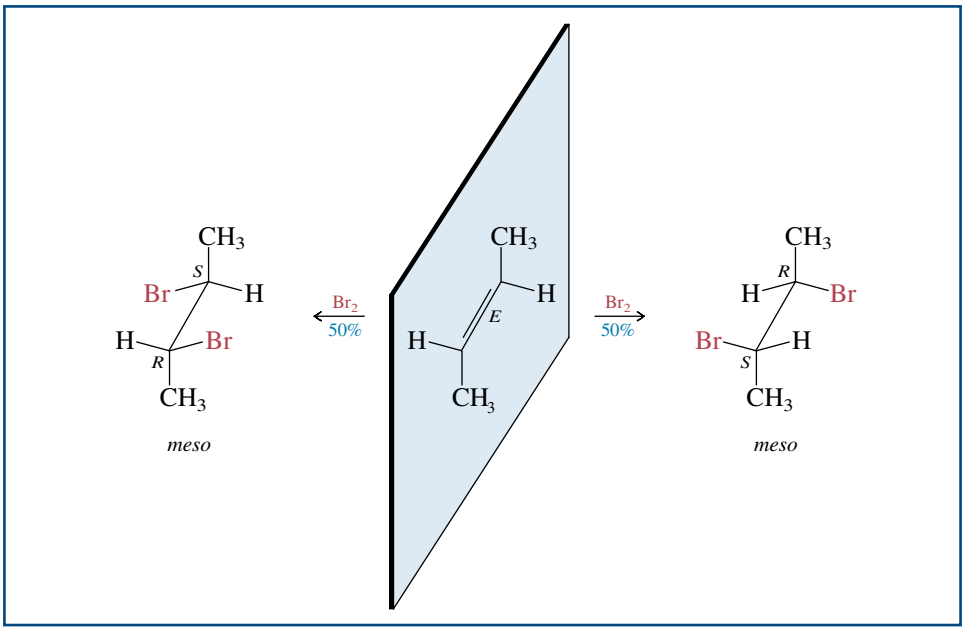


FIGURE 7.14 Anti addition of Br_2 to (*E*)-2-butene gives *meso*-2,3-dibromobutane.

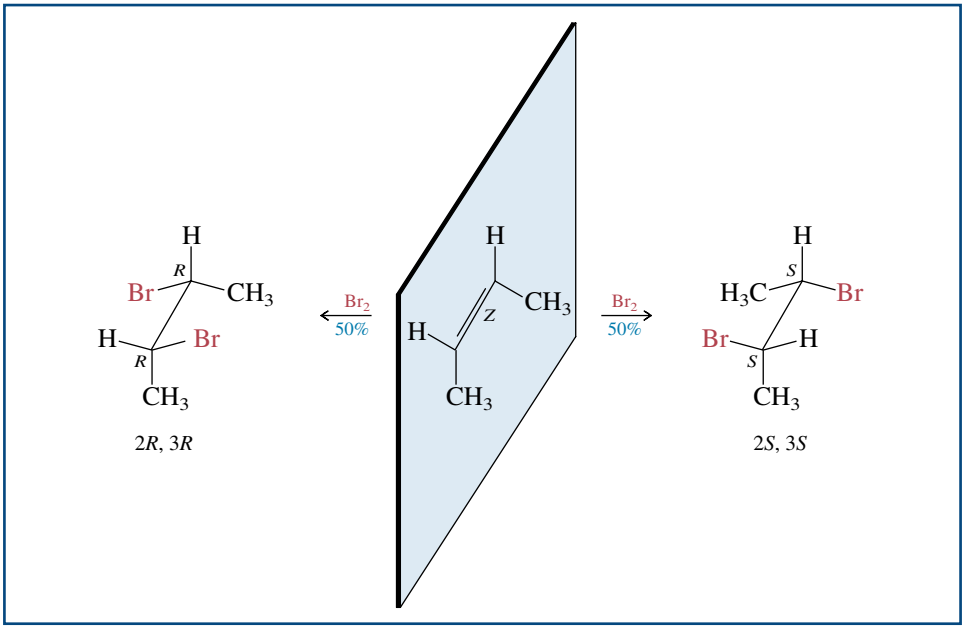
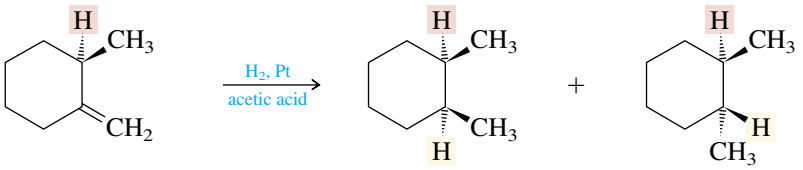


FIGURE 7.15 Anti addition of Br_2 to (*Z*)-2-butene gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-dibromobutane.

PROBLEM 7.17 Epoxidation of alkenes is a stereospecific syn addition. Which stereoisomer of 2-butene reacts with peroxyacetic acid to give *meso*-2,3-epoxybutane? Which one gives a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-epoxybutane?

A reaction that introduces a second stereogenic center into a starting material that already has one need not produce equal quantities of two possible diastereomers. Consider catalytic hydrogenation of 2-methyl(methylene)cyclohexane. As you might expect, both *cis*- and *trans*-1,2-dimethylcyclohexane are formed.



2-Methyl(methylene)cyclohexane

cis-1,2-Dimethylcyclohexane (68%)

trans-1,2-Dimethylcyclohexane (32%)

Make molecular models of the reactant and both products shown in the equation.

The relative amounts of the two products, however, are not equal; more *cis*-1,2-dimethylcyclohexane is formed than *trans*. The reason for this is that it is the less hindered face of the double bond that approaches the catalyst surface and is the face to which hydrogen is transferred. Hydrogenation of 2-methyl(methylene)cyclohexane occurs preferentially at the side of the double bond opposite that of the methyl group and leads to a faster rate of formation of the cis stereoisomer of the product.

PROBLEM 7.18 Could the fact that hydrogenation of 2-methyl(methylene)cyclohexane gives more *cis*-1,2-dimethylcyclohexane than *trans*- be explained on the basis of the relative stabilities of the two stereoisomeric products?

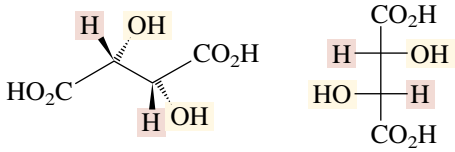
The hydrogenation of 2-methyl(methylene)cyclohexane is an example of a *stereoselective reaction,* meaning one in which stereoisomeric products are formed in unequal amounts from a single starting material (Section 5.11).

A common misconception is that a stereospecific reaction is simply one that is 100% stereoselective. The two terms though have precise definitions that are independent of one another. A stereospecific reaction is one which, when carried out with stereoisomeric starting materials, gives a product from one reactant that is a stereoisomer of the product from the other. A stereoselective reaction is one in which a single starting material gives a predominance of a single stereoisomer when two or more are possible. *Stereospecific* is more closely connected with features of the reaction than with the reactant. Thus terms such as syn *addition* and anti *elimination* describe the stereospecificity of reactions. *Stereoselective* is more closely connected with structural effects in the reactant as expressed in terms such as *addition to the less hindered side.* A stereospecific reaction can also be stereoselective. For example, syn addition describes stereospecificity in the catalytic hydrogenation of alkenes, whereas the preference for addition to the less hindered face of the double bond describes stereoselectivity.

Note that the terms *regioselective* and *regiospecific,* however, are defined in terms of each other. A regiospecific reaction is one that is 100% regioselective.

7.14 RESOLUTION OF ENANTIOMERS

The separation of a racemic mixture into its enantiomeric components is termed **resolution.** The first resolution, that of tartaric acid, was carried out by Louis Pasteur in 1848. Tartaric acid is a byproduct of wine making and is almost always found as its dextrorotatory 2*R*,3*R* stereoisomer, shown here in a perspective drawing and in a Fischer projection.



(2*R*,3*R*)-Tartaric acid (mp 170°C, $[\alpha]_D$ +12°)

PROBLEM 7.19 There are two other stereoisomeric tartaric acids. Write their Fischer projections, and specify the configuration at their stereogenic centers.

A description of Pasteur's work, as part of a broader discussion concerning crystal structure, can be found in the article "Molecules, Crystals, and Chirality" in the July 1997 issue of the *Journal of Chemical Education,* pp. 800–806.

Occasionally, an optically inactive sample of tartaric acid was obtained. Pasteur noticed that the sodium ammonium salt of optically inactive tartaric acid was a mixture of two mirror-image crystal forms. With microscope and tweezers, Pasteur carefully separated the two. He found that one kind of crystal (in aqueous solution) was dextrorotatory, whereas the mirror-image crystals rotated the plane of polarized light an equal amount but were levorotatory.

Although Pasteur was unable to provide a structural explanation—that had to wait for van't Hoff and Le Bel a quarter of a century later—he correctly deduced that the enantiomeric quality of the crystals was the result of enantiomeric molecules. The rare form of tartaric acid was optically inactive because it contained equal amounts of (+)-tartaric acid and (−)-tartaric acid. It had earlier been called *racemic acid* (from Latin *racemus,* "a bunch of grapes"), a name that subsequently gave rise to our present term for an equal mixture of enantiomers.

PROBLEM 7.20 Could the unusual, optically inactive form of tartaric acid studied by Pasteur have been *meso*-tartaric acid?

Pasteur's technique of separating enantiomers not only is laborious but requires that the crystal habits of enantiomers be distinguishable. This happens very rarely.

Consequently, alternative and more general approaches for resolving enantiomers have been developed. Most are based on a strategy of temporarily converting the enantiomers of a racemic mixture to diastereomeric derivatives, separating these diastereomers, then regenerating the enantiomeric starting materials.

Figure 7.16 illustrates this strategy. Say we have a mixture of enantiomers, which, for simplicity, we label as C(+) and C(−). Assume that C(+) and C(−) bear some functional group that can combine with a reagent P to yield adducts C(+)-P and C(−)-P. Now, if reagent P is chiral, and if only a single enantiomer of P, say, P(+), is added to a racemic mixture of C(+) and C(−), as shown in the first step of Figure 7.16, then the products of the reaction are C(+)-P(+) and C(−)-P(+). These products are not mirror images; they are diastereomers. Diastereomers can have different physical properties, which can serve as a means of separating them. The mixture of diastereomers is separated, usually by recrystallization from a suitable solvent. In the last step, an appropriate chemical transformation liberates the enantiomers and restores the resolving agent.

Whenever possible, the chemical reactions involved in the formation of diastereomers and their conversion to separate enantiomers are simple acid–base reactions. For example, naturally occurring (*S*)-(−)-malic acid is often used to resolve amines. One such amine that has been resolved in this way is 1-phenylethylamine. Amines are bases, and malic acid is an acid. Proton transfer from (*S*)-(−)-malic acid to a racemic mixture of (*R*)- and (*S*)-1-phenylethylamine gives a mixture of diastereomeric salts.

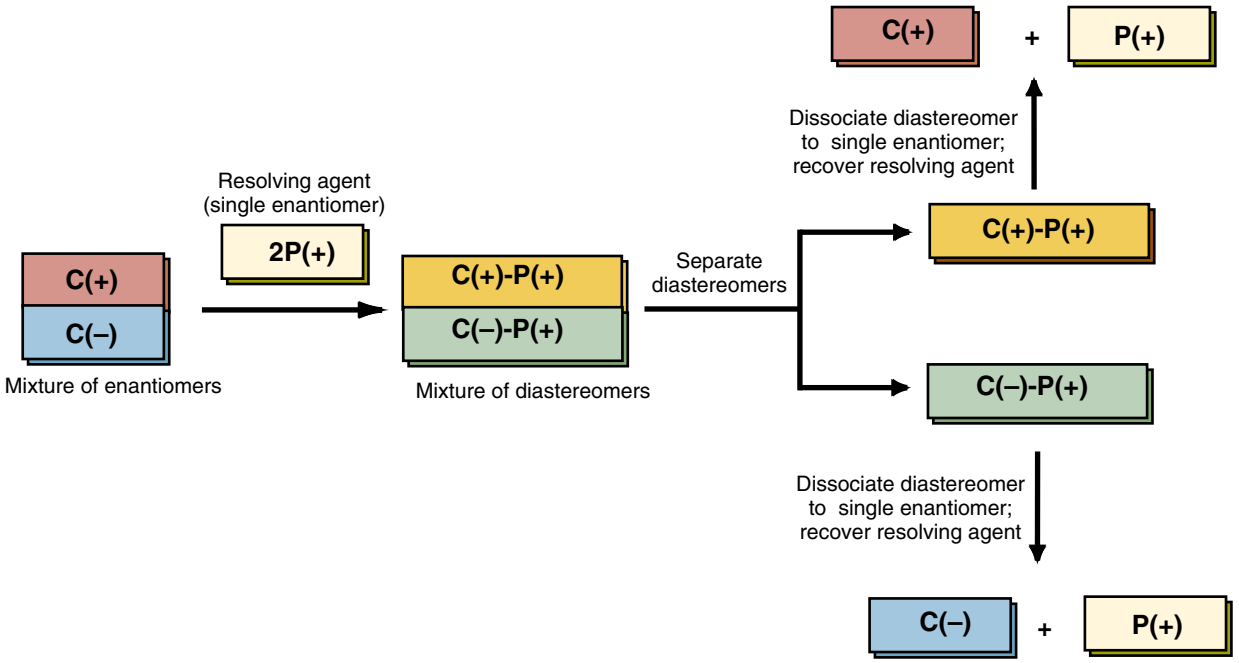
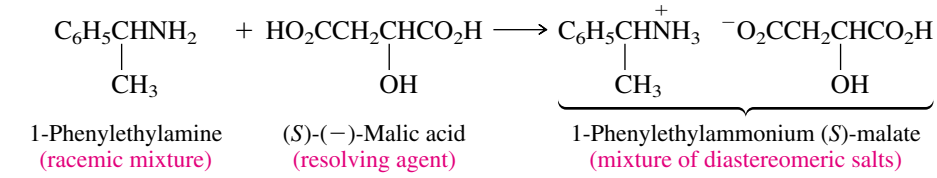
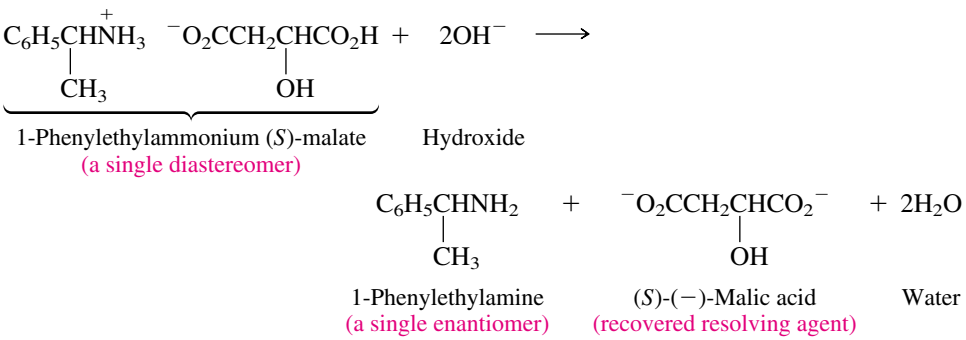


FIGURE 7.16 The general procedure followed in resolving a chiral substance into its enantiomers. Reaction with a single enantiomer of a chiral resolving agent P(+) converts the racemic mixture of enantiomers C(+) and C(−) to a mixture of diastereomers C(+)-P(+) and C(−)-P(+). The mixture of diastereomers is separated—by fractional crystallization, for example. A chemical reaction is then carried out to convert diastereomer C(+)-P(+) to C(+) and the resolving agent P(+). Likewise, diastereomer C(−)-P(+) is converted to C(−) and P(+). C(+) has been separated from C(−), and the resolving agent P(+) can be recovered for further use.



The diastereomeric salts are separated and the individual enantiomers of the amine liberated by treatment with a base:



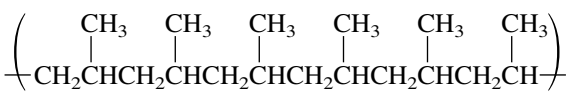
PROBLEM 7.21 In the resolution of 1-phenylethylamine using (−)-malic acid, the compound obtained by recrystallization of the mixture of diastereomeric salts is (*R*)-1-phenylethylammonium (*S*)-malate. The other component of the mixture is more soluble and remains in solution. What is the configuration of the more soluble salt?

This method is widely used for the resolution of chiral amines and carboxylic acids. Analogous methods based on the formation and separation of diastereomers have been developed for other functional groups; the precise approach depends on the kind of chemical reactivity associated with the functional groups present in the molecule.

The rapidly increasing demand for enantiomerically pure starting materials and intermediates in the pharmaceutical industry (see the boxed essay entitled *Chiral Drugs* in this chapter) has increased interest in developing methods for resolving racemic mixtures.

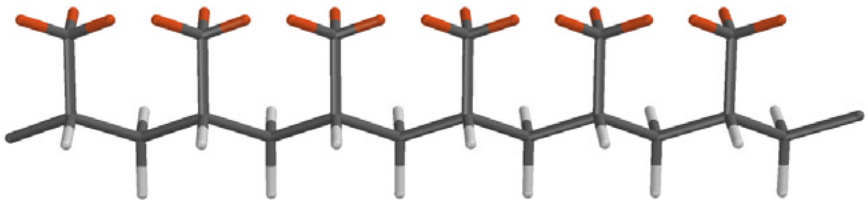
7.15 STEREOREGULAR POLYMERS

Before the development of the Ziegler–Natta catalyst systems (Section 6.21), polymerization of propene was not a reaction of much value. The reason for this has a stereochemical basis. Consider a section of *polypropylene:*



Representation of the polymer chain in an extended zigzag conformation, as shown in Figure 7.17, reveals several distinct structural possibilities differing with respect to the relative configurations of the carbons that bear the methyl groups.

One structure, represented in Figure 7.17*a,* has all the methyl groups oriented in the same direction with respect to the polymer chain. This stereochemical arrangement is said to be **isotactic.** Another form, shown in Figure 7.17*b,* has its methyl groups alternating front and back along the chain. This arrangement is described as **syndiotactic.**



(*a*) Isotactic polypropylene

(*b*) Syndiotactic polypropylene

(*c*) Atactic polypropylene

FIGURE 7.17 Polymers of propene. The main chain is shown in a zigzag conformation. Every other carbon bears a methyl substituent and is a stereogenic center. (*a*) All the methyl groups are on the same side of the carbon chain in isotactic polypropylene. (*b*) Methyl groups alternate from one side to the other in syndiotactic polypropylene. (*c*) The spatial orientation of the methyl groups is random in atactic polypropylene.

Both the isotactic and the syndiotactic forms of polypropylene are known as **stereoregular polymers,** because each is characterized by a precise stereochemistry at the carbon atom that bears the methyl group. There is a third possibility, shown in Figure 7.17*c*, which is described as **atactic.** Atactic polypropylene has a random orientation of its methyl groups; it is not a stereoregular polymer.

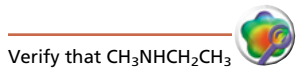
Polypropylene chains associate with one another because of attractive van der Waals forces. The extent of this association is relatively large for isotactic and syndiotactic polymers, because the stereoregularity of the polymer chains permits efficient packing. Atactic polypropylene, on the other hand, does not associate as strongly. It has a lower density and lower melting point than the stereoregular forms. The physical properties of stereoregular polypropylene are more useful for most purposes than those of atactic polypropylene.

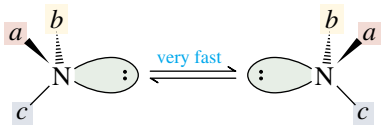
When propene is polymerized under free-radical conditions, the polypropylene that results is atactic. Catalysts of the Ziegler–Natta type, however, permit the preparation of either isotactic or syndiotactic polypropylene. We see here an example of how proper choice of experimental conditions can affect the stereochemical course of a chemical reaction to the extent that entirely new materials with unique properties result.

7.16 STEREOGENIC CENTERS OTHER THAN CARBON

Our discussion to this point has been limited to molecules in which the stereogenic center is carbon. Atoms other than carbon may also be stereogenic centers. Silicon, like carbon, has a tetrahedral arrangement of bonds when it bears four substituents. A large number of organosilicon compounds in which silicon bears four different groups have been resolved into their enantiomers.

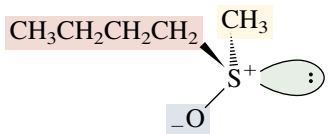
Trigonal pyramidal molecules are chiral if the central atom bears three different groups. If one is to resolve substances of this type, however, the pyramidal inversion that interconverts enantiomers must be slow at room temperature. Pyramidal inversion at nitrogen is so fast that attempts to resolve chiral amines fail because of their rapid racemization.


Verify that $CH_3NHCH_2CH_3$ is chiral by trying to superpose models of both enantiomers.



Phosphorus is in the same group of the periodic table as nitrogen, and tricoordinate phosphorus compounds (phosphines), like amines, are trigonal pyramidal. Phosphines, however, undergo pyramidal inversion much more slowly than amines, and a number of optically active phosphines have been prepared.

Tricoordinate sulfur compounds are chiral when sulfur bears three different substituents. The rate of pyramidal inversion at sulfur is rather slow. The most common compounds in which sulfur is a stereogenic center are sulfoxides such as:



(*S*)-(+)-Butyl methyl sulfoxide

The absolute configuration at sulfur is specified by the Cahn–Ingold–Prelog method with the provision that the unshared electron pair is considered to be the lowest ranking substituent.

A detailed flowchart describing a more finely divided set of subcategories of isomers appears in the February 1990 issue of the *Journal of Chemical Education*.

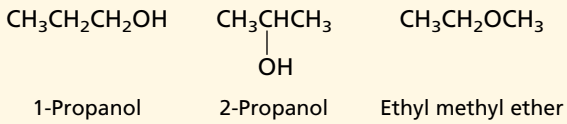
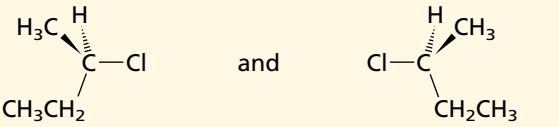
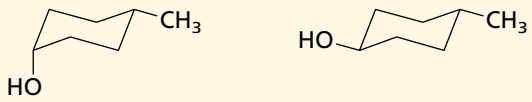
7.17 SUMMARY

Chemistry in three dimensions is known as **stereochemistry.** At its most fundamental level, stereochemistry deals with molecular structure; at another level, it is concerned with chemical reactivity. Table 7.2 summarizes some basic definitions relating to molecular structure and stereochemistry.

Section 7.1 A molecule is **chiral** if it cannot be superposed on its mirror image. *Nonsuperposable mirror images* are **enantiomers** of one another. Molecules in which mirror images are superposable are achiral.

2-Chlorobutane (chiral) 2-Chloropropane (achiral)

TABLE 7.2 Classification of Isomers*

Definition	Example
1. *Constitutional isomers* are isomers that differ in the order in which their atoms are connected.	There are three constitutionally isomeric compounds of molecular formula C_3H_8O:  1-Propanol 2-Propanol Ethyl methyl ether
2. *Stereoisomers* are isomers that have the same constitution but differ in the arrangement of their atoms in space.	
(a) *Enantiomers* are stereoisomers that are related as an object and its nonsuperposable mirror image.	The two enantiomeric forms of 2-chlorobutane are  (*R*)-(−)-2-Chlorobutane (*S*)-(+)-2-Chlorobutane
(b) *Diastereomers* are stereoisomers that are not enantiomers.	The cis and trans isomers of 4-methylcyclohexanol are stereoisomers, but they are not related as an object and its mirror image; they are diastereomers.  *cis*-4-Methylcyclohexanol *trans*-4-Methylcyclohexanol

*Isomers are different compounds that have the same molecular formula. They may be either constitutional isomers or stereoisomers.

Section 7.2 The most common kind of chiral molecule contains a carbon atom that bears four different atoms of groups. Such an atom is called a **stereogenic center.** Table 7.2 shows the enantiomers of 2-chlorobutane. C-2 is a stereogenic center in 2-chlorobutane.

Section 7.3 A molecule that has a plane of symmetry or a center of symmetry is achiral. *cis*-4-Methylcyclohexanol (Table 7.2) has a plane of symmetry that bisects the molecule into two mirror-image halves and is achiral. The same can be said for *trans*-4-methylcyclohexanol.

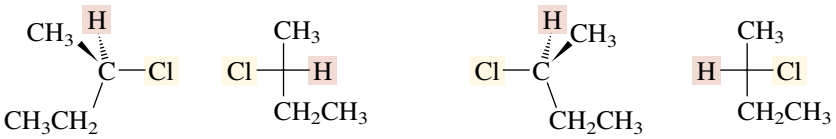
Section 7.4 **Optical activity,** or the degree to which a substance rotates the plane of polarized light, is a physical property used to characterize chiral substances. Enantiomers have equal and opposite **optical rotations.** To be optically active a substance must be chiral, and one enantiomer must be present in excess of the other. A **racemic mixture** is optically inactive and contains equal quantities of enantiomers.

Section 7.5 **Relative configuration** compares the arrangement of atoms in space to some reference. The prefix *cis* in *cis*-4-methylcyclohexanol, for example,

describes relative configuration by referencing the orientation of the CH_3 group to the OH. **Absolute configuration** is an exact description of the arrangement of atoms in space.

Section 7.6 Absolute configuration in chiral molecules is best specified using the prefixes *R* and *S* of the Cahn–Ingold–Prelog notational system. Substituents at a stereogenic center are ranked in order of decreasing precedence. If the three highest ranked substituents trace a clockwise path (highest→second highest→third highest) when the lowest ranked substituent is held away from us, the configuration is *R*. If the path is anticlockwise, the configuration is *S*. Table 7.2 shows the *R* and *S* enantiomers of 2-chlorobutane.

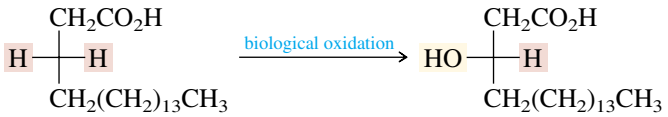
Section 7.7 A **Fischer projection** shows how a molecule would look if its bonds were projected onto a flat surface. Horizontal lines represent bonds coming toward you; vertical bonds point away from you. The projection is normally drawn so that the carbon chain is vertical, with the lowest numbered carbon at the top.



(*R*)-2-Chlorobutane (*S*)-2-Chlorobutane

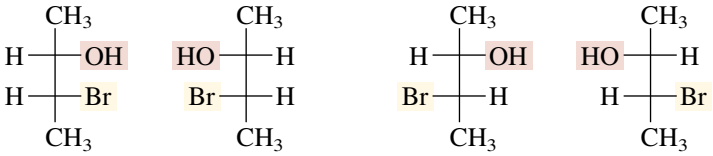
Section 7.8 Both enantiomers of the same substance are identical in most of their physical properties. The most prominent differences are biological ones, such as taste and odor, in which the substance interacts with a chiral receptor site in a living system. Enantiomers also have important consequences in medicine, in which the two enantiomeric forms of a drug can have much different effects on a patient.

Section 7.9 A chemical reaction can convert an achiral substance to a chiral one. If the product contains a single stereogenic center, it is formed as a racemic mixture. Optically active products can be formed from optically inactive starting materials only if some optically active agent is present. The best examples are biological processes in which enzymes catalyze the formation of only a single enantiomer.



Stearic acid (*S*)-3-Hydroxystearic acid

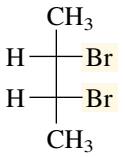
Section 7.10 When a molecule has two stereogenic centers and these two stereogenic centers are not equivalent, four stereoisomers are possible.



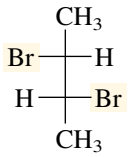
Enantiomers of *erythro*-3-bromo-2-butanol Enantiomers of *threo*-3-bromo-2-butanol

Stereoisomers that are not enantiomers are classified as **diastereomers.** Each enantiomer of *erythro*-3-bromo-2-butanol is a diastereomer of each enantiomer of *threo*-3-bromo-2-butanol.

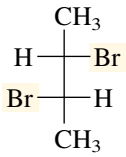
Section 7.11 Achiral molecules that contain stereogenic centers are called **meso forms.** Meso forms typically contain (but are not limited to) two equivalently substituted stereogenic centers. They are optically inactive.



meso-2,3-Dibromobutane



(2*R*,3*R*)-2,3-Dibromobutane



(2*S*,3*S*)-2,3-Dibromobutane

Section 7.12 For a particular constitution, the maximum number of stereoisomers is 2^n, where n is the number of structural units capable of stereochemical variation—usually this is the number of stereogenic centers, but can include *E* and *Z* double bonds as well. The number of stereoisomers is reduced to less than 2^n when there are meso forms.

Section 7.13 Addition reactions of alkenes may generate one (Section 7.9) or two (Section 7.13) stereogenic centers. When two stereogenic centers are produced, their relative stereochemistry depends on the configuration (*E* or *Z*) of the alkene and whether the addition is syn or anti.

Section 7.14 **Resolution** is the separation of a racemic mixture into its enantiomers. It is normally carried out by converting the mixture of enantiomers to a mixture of diastereomers, separating the diastereomers, then regenerating the enantiomers.

Section 7.15 Certain polymers such as polypropylene contain stereogenic centers, and the relative configurations of these centers affect the physical properties of the polymers. Like substituents appear on the same side of a zigzag carbon chain in an **isotactic** polymer, alternate along the chain in a **syndiotactic** polymer, and appear in a random manner in an **atactic** polymer. Isotactic and syndiotactic polymers are referred to as **stereoregular** polymers.

Section 7.16 Atoms other than carbon can be stereogenic centers. Examples include those based on tetracoordinate silicon and tricoordinate sulfur as the stereogenic atom. In principle, tricoordinate nitrogen can be a stereogenic center in compounds of the type N(*x, y, z*), where *x, y,* and *z* are different, but inversion of the nitrogen pyramid is so fast that racemization occurs virtually instantly at room temperature.

PROBLEMS

7.22 Which of the isomeric alcohols having the molecular formula $C_5H_{12}O$ are chiral? Which are achiral?

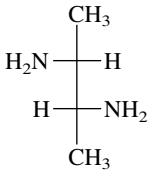
7.23 Write structural formulas or make molecular models for all the compounds that are trichloro derivatives of cyclopropane. (Don't forget to include stereoisomers.) Which are chiral? Which are achiral?

7.24 In each of the following pairs of compounds one is chiral and the other is achiral. Identify each compound as chiral or achiral, as appropriate.

(a) $ClCH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_2OH$ and $HOCH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2OH$

(b) $CH_3CH{=}CHCH_2Br$ and $CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH{=}CH_2$

(c)



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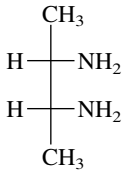
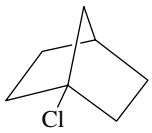


(d)



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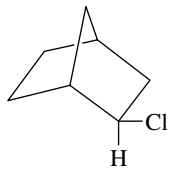
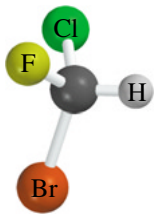
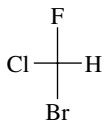
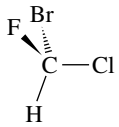


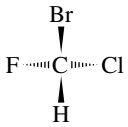
7.25 Compare 2,3-pentanediol and 2,4-pentanediol with respect to the number of stereoisomers possible for each constitution. Which stereoisomers are chiral? Which are achiral?

7.26 In 1996, it was determined that the absolute configuration of (−)-bromochlorofluoromethane is *R*. Which of the following is (are) (−)-BrClFCH?



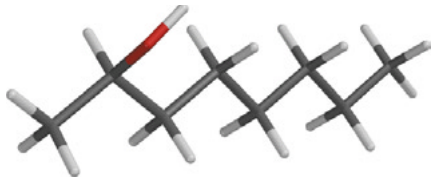




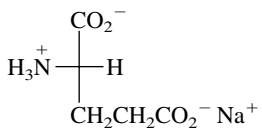


7.27 Specify the configuration at *R* or *S* in each of the following.

(a) (−)-2-Octanol

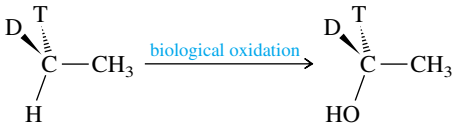


(b) Monosodium L-glutamate (only this stereoisomer is of any value as a flavor-enhancing agent)



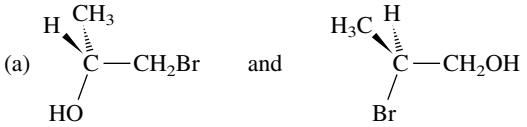
7.28 A subrule of the Cahn–Ingold–Prelog system specifies that higher mass number takes precedence over lower when distinguishing between isotopes.

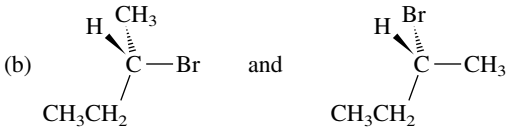
(a) Determine the absolute configurations of the reactant and product in the biological oxidation of isotopically labeled ethane described in Section 7.2.

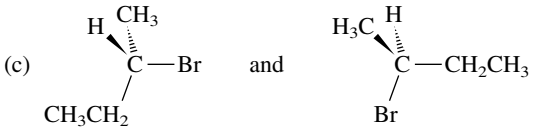


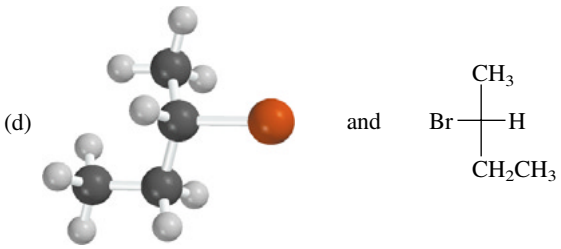
(b) Because OH becomes bonded to carbon at the same side from which H is lost, the oxidation proceeds with retention of configuration (Section 6.13). Compare this fact with the *R* and *S* configurations you determined in part (a) and reconcile any *apparent* conflicts.

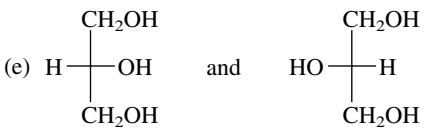
7.29 Identify the relationship in each of the following pairs. Do the drawings represent constitutional isomers or stereoisomers, or are they just different ways of drawing the same compound? If they are stereoisomers, are they enantiomers or diastereomers? (Molecular models may prove useful in this problem.)

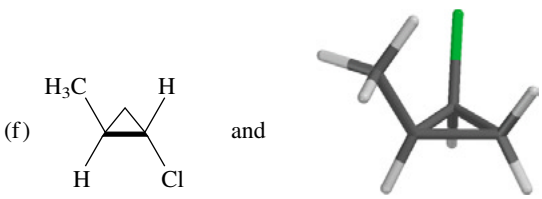


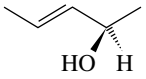
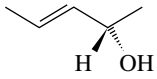


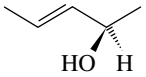
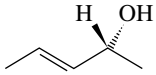


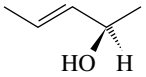
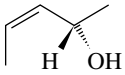


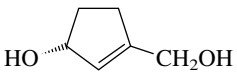
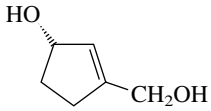


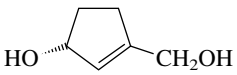
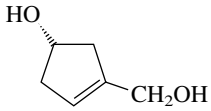


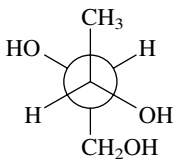
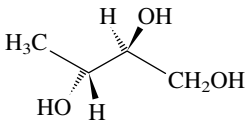
(g)  and 

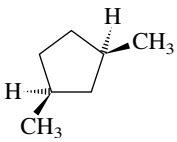
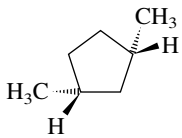
(h)  and 

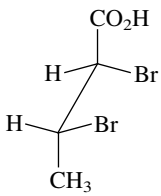
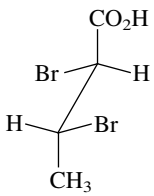
(i)  and 

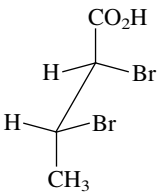
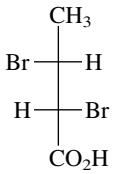
(j)  and 

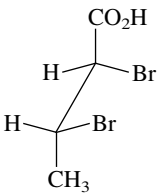
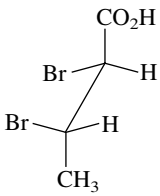
(k)  and 

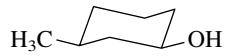
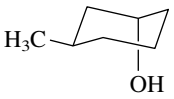
(l)  and 

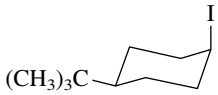
(m)  and 

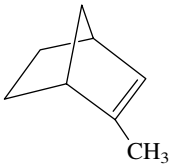
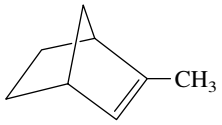
(n)  and 

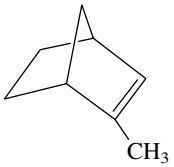
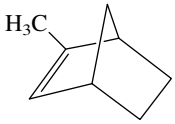
(o)  and 

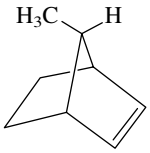
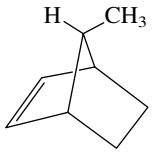
(p)  and 

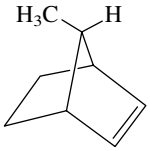
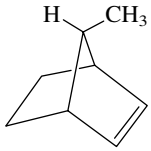
(q)  and 

(r)  and 

(s)  and 

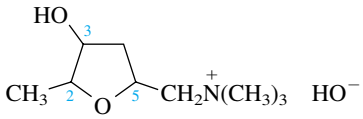
(t)  and 

(u)  and 

(v)  and 

7.30 Chemical degradation of chlorophyll gives a number of substances including *phytol.* The constitution of phytol is given by the name 3,7,11,15-tetramethyl-2-hexadecen-1-ol. How many stereoisomers have this constitution?

7.31 *Muscarine* is a poisonous substance present in the mushroom *Amanita muscaria.* Its structure is represented by the constitution shown.

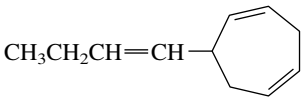


(a) Including muscarine, how many stereoisomers have this constitution?

(b) One of the substituents on the ring of muscarine is trans to the other two. How many of the stereoisomers satisfy this requirement?

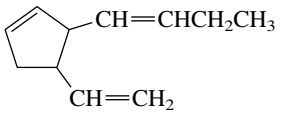
(c) Muscarine has the configuration 2*S*,3*R*,5*S*. Write a structural formula or build a molecular model of muscarine showing its correct stereochemistry.

7.32 *Ectocarpene* is a volatile, sperm cell-attracting material released by the eggs of the seaweed *Ectocarpus siliculosus.* Its constitution is



All the double bonds are cis, and the absolute configuration of the stereogenic center is *S*. Write a stereochemically accurate representation of ectocarpene.

7.33 *Multifidene* is a sperm cell-attracting substance released by the female of a species of brown algae *(Cutleria multifida).* The constitution of multifidene is



(a) How many stereoisomers are represented by this constitution?

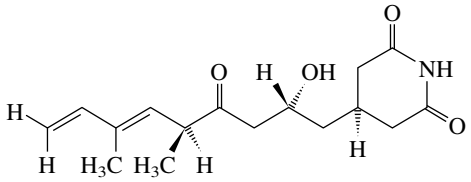
(b) Multifidene has a cis relationship between its alkenyl substituents. Given this information, how many stereoisomers are possible?

(c) The butenyl side chain has the *Z* configuration of its double bond. On the basis of all the data, how many stereoisomers are possible?

(d) Draw stereochemically accurate representations of all the stereoisomers that satisfy the structural requirements of multifidene.

(e) How are these stereoisomeric multifidenes related (enantiomers or diastereomers)?

7.34 *Streptimidone* is an antibiotic and has the structure shown. How many diastereomers of streptimidone are possible? How many enantiomers? Using the *E,Z* and *R,S* descriptors, specify all essential elements of stereochemistry of streptimidone.

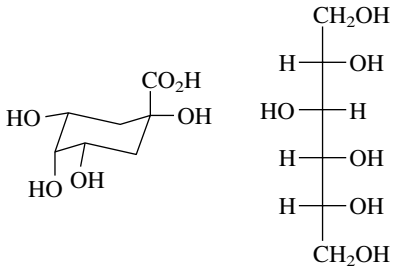


7.35 In Problem 4.26 you were asked to draw the preferred conformation of menthol on the basis of the information that menthol is the most stable stereoisomer of 2-isopropyl-5-methylcyclohexanol. We can now completely describe (−)-menthol structurally by noting that it has the *R* configuration at the hydroxyl-substituted carbon.

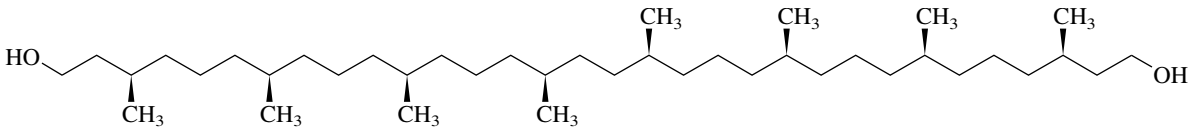
(a) Draw or construct a molecular model of the preferred conformation of (−)-menthol.

(b) (+)-Isomenthol has the same constitution as (−)-menthol. The configurations at C-1 and C-2 of (+)-isomenthol are the opposite of the corresponding stereogenic centers of (−)-menthol. Write the preferred conformation of (+)-isomenthol.

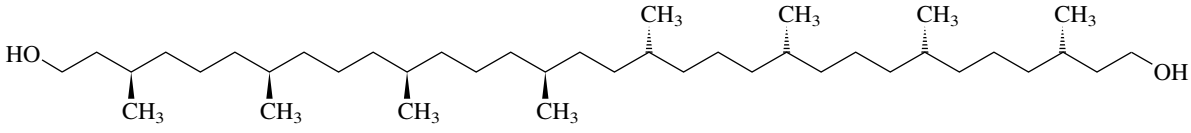
7.36 A certain natural product having $[\alpha]_D$ + 40.3° was isolated. Two structures have been independently proposed for this compound. Which one do you think is more likely to be correct? Why?



7.37 One of the principal substances obtained from archaea (one of the oldest forms of life on earth) is derived from a 40-carbon diol. Given the fact that this diol is optically active, is it compound A or is it compound B?



Compound A



Compound B

7.38 (a) An aqueous solution containing 10 g of optically pure fructose was diluted to 500 mL with water and placed in a polarimeter tube 20 cm long. The measured rotation was −5.20°. Calculate the specific rotation of fructose.

(b) If this solution were mixed with 500 mL of a solution containing 5 g of racemic fructose, what would be the specific rotation of the resulting fructose mixture? What would be its optical purity?

7.39 Write the organic products of each of the following reactions. If two stereoisomers are formed, show both. Label all stereogenic centers *R* or *S* as appropriate.

(a) 1-Butene and hydrogen iodide

(b) (*E*)-2-Pentene and bromine in carbon tetrachloride

(c) (*Z*)-2-Pentene and bromine in carbon tetrachloride

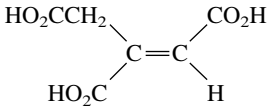
(d) 1-Butene and peroxyacetic acid in dichloromethane

(e) (*Z*)-2-Pentene and peroxyacetic acid in dichloromethane

(f) 1,5,5-Trimethylcyclopentene and hydrogen in the presence of platinum

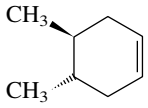
(g) 1,5,5-Trimethylcyclopentene and diborane in tetrahydrofuran followed by oxidation with hydrogen peroxide

7.40 The enzyme *aconitase* catalyzes the hydration of aconitic acid to two products: citric acid and isocitric acid. Isocitric acid is optically active; citric acid is not. What are the respective constitutions of citric acid and isocitric acid?

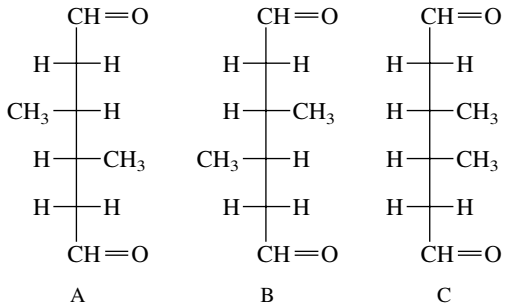


Aconitic acid

7.41 Consider the ozonolysis of *trans*-4,5-dimethylcyclohexene having the configuration shown.



Structures A, B, and C are three stereoisomeric forms of the reaction product.

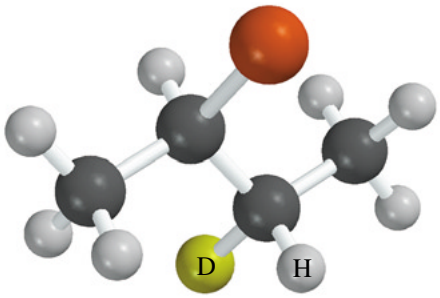


(a) Which, if any, of the compounds A, B, and C are chiral?

(b) What product is formed in the reaction?

(c) What product would be formed if the methyl groups were cis to each other in the starting alkene?

7.42 (a) On being heated with potassium ethoxide in ethanol (70°C), the deuterium-labeled alkyl bromide shown gave a mixture of 1-butene, *cis*-2-butene, and *trans*-2-butene. On the basis of your knowledge of the E2 mechanism, predict which alkene(s), if any, contained deuterium.

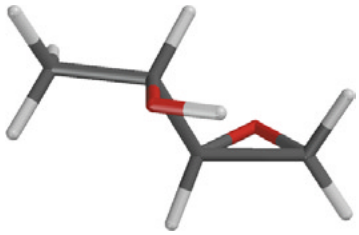


(b) The bromide shown in part (a) is the erythro diastereomer. How would the deuterium content of the alkenes formed by dehydrohalogenation of the threo diastereomer differ from those produced in part (a)?

7.43 A compound (C_6H_{10}) contains a five-membered ring. When Br_2 adds to it, two diastereomeric dibromides are formed. Suggest reasonable structures for the compound and the two dibromides.

7.44 When optically pure 2,3-dimethyl-2-pentanol was subjected to dehydration, a mixture of two alkenes was obtained. Hydrogenation of this alkene mixture gave 2,3-dimethylpentane, which was 50% optically pure. What were the two alkenes formed in the elimination reaction, and what were the relative amounts of each?

7.45 When (*R*)-3-buten-2-ol is treated with a peroxy acid, two stereoisomeric epoxides are formed in a 60:40 ratio. The minor stereoisomer has the structure shown.



(a) Write the structure of the major stereoisomer.

(b) What is the relationship between the two epoxides? Are they enantiomers or diastereomers?

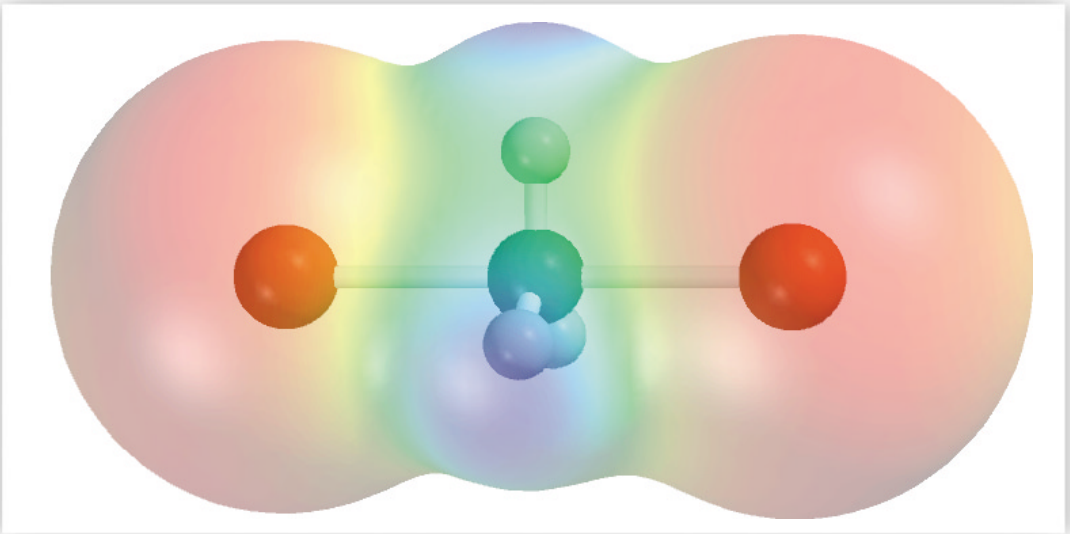
(c) What four stereoisomeric products are formed when racemic 3-buten-2-ol is epoxidized under the same conditions? How much of each stereoisomer is formed?

7.46 Verify that dibromochloromethane is achiral by superposing models of its two mirror image forms. In the same way, verify that bromochlorofluoromethane is chiral.

7.47 Construct a molecular model of (*S*)-3-chlorocyclopentene.

7.48 Construct a molecular model corresponding to the Fischer projection of *meso*-2,3-dibromobutane. Convert this molecular model to a staggered conformation in which the bromines are anti to one another. Are the methyl groups anti or gauche to one another in this staggered conformation?

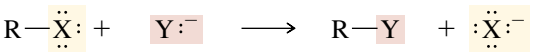
7.49 What alkene gives a racemic mixture of (2*R*,3*S*) and (2*S*,3*R*)-3-bromo-2-butanol on treatment with Br_2 in aqueous solution? (*Hint:* Make a molecular model of one of the enantiomeric 3-bromo-2-butanols, arrange it in a conformation in which the Br and OH groups are anti to one another, then disconnect them.)



CHAPTER 8

NUCLEOPHILIC SUBSTITUTION

When we discussed elimination reactions in Chapter 5, we learned that a Lewis base can react with an alkyl halide to form an alkene. In the present chapter, you will find that the same kinds of reactants can also undergo a different reaction, one in which the Lewis base acts as a **nucleophile** to substitute for the halide substituent on carbon.



Alkyl halide | Lewis base | Product of nucleophilic substitution | Halide anion

We first encountered nucleophilic substitution in Chapter 4, in the reaction of alcohols with hydrogen halides to form alkyl halides. Now we'll see how alkyl halides can themselves be converted to other classes of organic compounds by nucleophilic substitution.

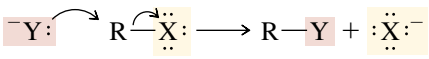
This chapter has a mechanistic emphasis designed to achieve a practical result. By understanding the mechanisms by which alkyl halides undergo nucleophilic substitution, we can choose experimental conditions best suited to carrying out a particular functional group transformation. The difference between a successful reaction that leads cleanly to a desired product and one that fails is often a subtle one. Mechanistic analysis helps us to appreciate these subtleties and use them to our advantage.

8.1 FUNCTIONAL GROUP TRANSFORMATION BY NUCLEOPHILIC SUBSTITUTION

Nucleophilic substitution reactions of alkyl halides are related to elimination reactions in that the halogen acts as a leaving group on carbon and is lost as an anion. The carbon–halogen bond of the alkyl halide is broken **heterolytically:** the pair of electrons in that bond are lost with the leaving group.

The carbon–halogen bond in an alkyl halide is polar

and is cleaved on attack by a nucleophile so that the two electrons in the bond are retained by the halogen



The most frequently encountered nucleophiles in functional group transformations are anions, which are used as their lithium, sodium, or potassium salts. If we use M to represent lithium, sodium, or potassium, some representative nucleophilic reagents are

MOR (a metal *alkoxide,* a source of the nucleophilic anion $RO:^-$)

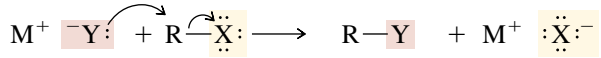
MOCR (a metal *carboxylate,* a source of the nucleophilic anion $RC(=O)O:^-$)

MSH (a metal *hydrogen sulfide,* a source of the nucleophilic anion $HS:^-$)

MCN (a metal *cyanide,* a source of the nucleophilic anion $:C\equiv N:^-$)

MN_3 (a metal *azide,* a source of the nucleophilic anion $:N^-=N^+=N:^-$)

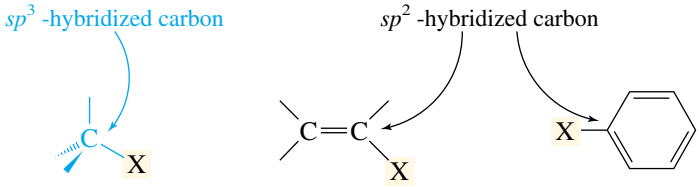
Table 8.1 illustrates an application of each of these to a functional group transformation. The anionic portion of the salt substitutes for the halogen of an alkyl halide. The metal cation portion becomes a lithium, sodium, or potassium halide.



Nucleophilic reagent	Alkyl halide	Product of nucleophilic substitution	Metal halide

Notice that all the examples in Table 8.1 involve **alkyl halides,** that is, compounds in which the halogen is attached to an sp^3-hybridized carbon. **Alkenyl halides** and **aryl halides,** compounds in which the halogen is attached to sp^2-hybridized carbons, are essentially unreactive under these conditions, and the principles to be developed in this chapter do not apply to them.

Alkenyl halides are also referred to as *vinylic halides.*

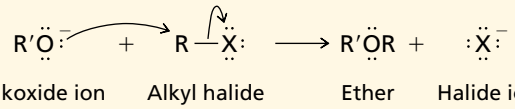
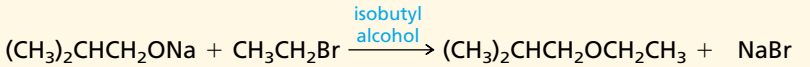
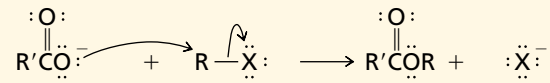
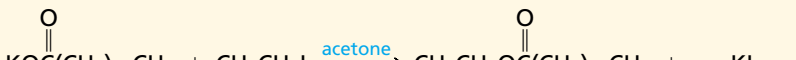
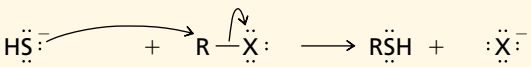
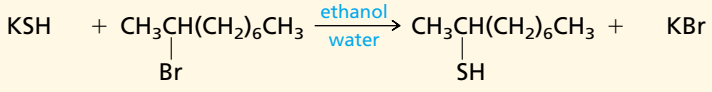
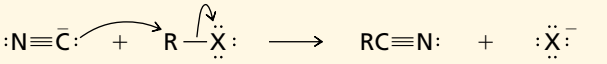
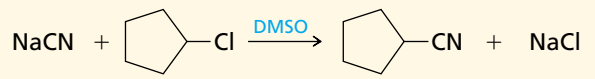
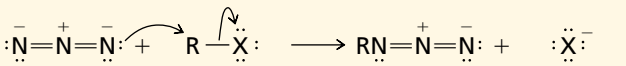
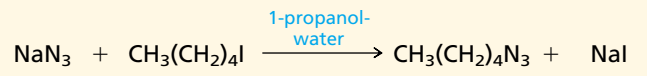


Alkyl halide Alkenyl halide Aryl halide

To ensure that reaction occurs in homogeneous solution, solvents are chosen that dissolve both the alkyl halide and the ionic salt. The alkyl halide substrates are soluble in organic solvents, but the salts often are not. Inorganic salts are soluble in water, but alkyl halides are not. Mixed solvents such as ethanol–water mixtures that can dissolve enough of both the substrate and the nucleophile to give fairly concentrated solutions are frequently used. Many salts, as well as most alkyl halides, possess significant solubility in dimethyl sulfoxide (DMSO), which makes this a good medium for carrying out nucleophilic substitution reactions.

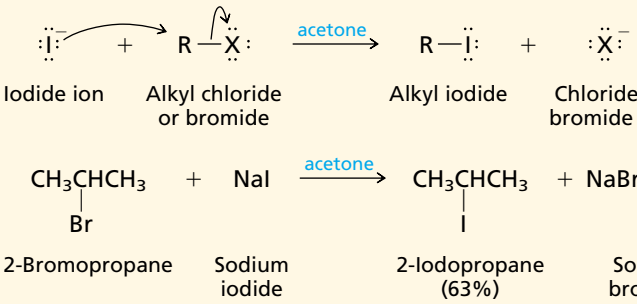
The use of DMSO as a solvent in *dehydrohalogenation* reactions was mentioned earlier, in Section 5.14.

TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides

Nucleophile and comments	General equation and specific example
Alkoxide ion ($RO:^-$) The oxygen atom of a metal alkoxide acts as a nucleophile to replace the halogen of an alkyl halide. The product is an *ether.*	 Alkoxide ion · Alkyl halide · Ether · Halide ion  Sodium isobutoxide · Ethyl bromide · Ethyl isobutyl ether (66%) · Sodium bromide
Carboxylate ion (RCO_2^-) An *ester* is formed when the negatively charged oxygen of a carboxylate replaces the halogen of an alkyl halide.	 Carboxylate ion · Alkyl halide · Ester · Halide ion  Potassium octadecanoate · Ethyl iodide · Ethyl octadecanoate (95%) · Potassium iodide
Hydrogen sulfide ion (HS^-) Use of hydrogen sulfide as a nucleophile permits the conversion of alkyl halides to compounds of the type RSH. These compounds are the sulfur analogs of alcohols and are known as *thiols.*	 Hydrogen sulfide ion · Alkyl halide · Thiol · Halide ion  Potassium hydrogen sulfide · 2-Bromononane · 2-Nonanethiol (74%) · Potassium bromide
Cyanide ion ($:C\equiv N:^-$) The negatively charged carbon atom of cyanide ion is usually the site of its nucleophilic character. Use of cyanide ion as a nucleophile permits the extension of a carbon chain by carbon–carbon bond formation. The product is an *alkyl cyanide,* or *nitrile.*	 Cyanide ion · Alkyl halide · Alkyl cyanide · Halide ion  Sodium cyanide · Cyclopentyl chloride · Cyclopentyl cyanide (70%) · Sodium chloride
Azide ion ($:N=N^+=N:^-$) Sodium azide is a reagent used for carbon–nitrogen bond formation. The product is an *alkyl azide.*	 Azide ion · Alkyl halide · Alkyl azide · Halide ion  Sodium azide · Pentyl iodide · Pentyl azide (52%) · Sodium iodide

(Continued)

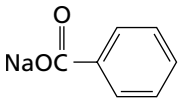
TABLE 8.1 Representative Functional Group Transformations by Nucleophilic Substitution Reactions of Alkyl Halides *(Continued)*

Nucleophile and comments	General equation and specific example
Iodide ion ($:\ddot{I}:^-$) Alkyl chlorides and bromides are converted to *alkyl iodides* by treatment with sodium iodide in acetone. NaI is soluble in acetone, but NaCl and NaBr are insoluble and crystallize from the reaction mixture, driving the reaction to completion.	

PROBLEM 8.1 Write a structural formula for the principal organic product formed in the reaction of methyl bromide with each of the following compounds:

(a) NaOH (sodium hydroxide)

(b) $KOCH_2CH_3$ (potassium ethoxide)

(c)  (sodium benzoate)

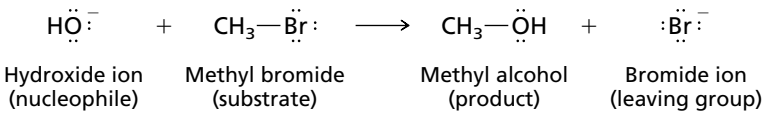
(d) LiN_3 (lithium azide)

(e) KCN (potassium cyanide)

(f) NaSH (sodium hydrogen sulfide)

(g) NaI (sodium iodide)

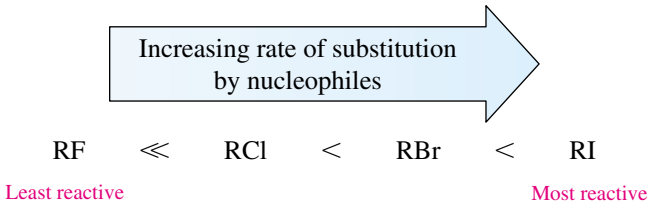
SAMPLE SOLUTION (a) The nucleophile in sodium hydroxide is the negatively charged hydroxide ion. The reaction that occurs is nucleophilic substitution of bromide by hydroxide. The product is methyl alcohol.



With this as background, you can begin to see how useful alkyl halides are in synthetic organic chemistry. Alkyl halides may be prepared from alcohols by nucleophilic substitution, from alkanes by free-radical halogenation, and from alkenes by addition of hydrogen halides. They then become available as starting materials for the preparation of other functionally substituted organic compounds by replacement of the halide leaving group with a nucleophile. The range of compounds that can be prepared by nucleophilic substitution reactions of alkyl halides is quite large; the examples shown in Table 8.1 illustrate only a few of them. Numerous other examples will be added to the list in this and subsequent chapters.

8.2 RELATIVE REACTIVITY OF HALIDE LEAVING GROUPS

Among alkyl halides, alkyl iodides undergo nucleophilic substitution at the fastest rate, alkyl fluorides the slowest.



The order of alkyl halide reactivity in nucleophilic substitutions is the same as their order in eliminations. Iodine has the weakest bond to carbon, and iodide is the best leaving group. Alkyl iodides are several times more reactive than alkyl bromides and from 50 to 100 times more reactive than alkyl chlorides. Fluorine has the strongest bond to carbon, and fluoride is the poorest leaving group. Alkyl fluorides are rarely used as substrates in nucleophilic substitution because they are several thousand times less reactive than alkyl chlorides.

PROBLEM 8.2 A single organic product was obtained when 1-bromo-3-chloropropane was allowed to react with one molar equivalent of sodium cyanide in aqueous ethanol. What was this product?

The relationship between leaving group ability and basicity is explored in more detail in Section 8.14.

Leaving-group ability is also related to basicity. A strongly basic anion is usually a poorer leaving group than a weakly basic one. Fluoride is the most basic and the poorest leaving group among the halide anions, iodide the least basic and the best leaving group.

8.3 THE S_N2 MECHANISM OF NUCLEOPHILIC SUBSTITUTION

The mechanisms by which nucleophilic substitution takes place have been the subject of much study. Extensive research by Sir Christopher Ingold and Edward D. Hughes and their associates at University College, London, during the 1930s emphasized kinetic and stereochemical measurements to probe the mechanisms of these reactions.

Recall that the term "kinetics" refers to how the rate of a reaction varies with changes in concentration. Consider the nucleophilic substitution in which sodium hydroxide reacts with methyl bromide to form methyl alcohol and sodium bromide:

$$\underset{\text{Methyl bromide}}{CH_3Br} + \underset{\text{Hydroxide ion}}{HO^-} \longrightarrow \underset{\text{Methyl alcohol}}{CH_3OH} + \underset{\text{Bromide ion}}{Br^-}$$

The rate of this reaction is observed to be directly proportional to the concentration of both methyl bromide and sodium hydroxide. It is first-order in each reactant, or *second-order* overall.

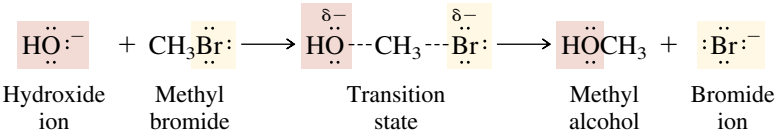
$$\text{Rate} = k[CH_3Br][HO^-]$$

Hughes and Ingold interpreted second-order kinetic behavior to mean that the rate-determining step is *bimolecular,* that is, that both hydroxide ion and methyl bromide are involved at the transition state. The symbol given to the detailed description of the mechanism that they developed is S_N2, standing for **substitution nucleophilic bimolecular.**

The S_N2 mechanism was introduced earlier in Section 4.13.

The Hughes and Ingold S_N2 mechanism is a single-step process in which both the alkyl halide and the nucleophile are involved at the transition state. Cleavage of the bond between carbon and the leaving group is assisted by formation of a bond between carbon and the nucleophile. In effect, the nucleophile "pushes off" the leaving group from

its point of attachment to carbon. For this reason, the S_N2 mechanism is sometimes referred to as a **direct displacement** process. The S_N2 mechanism for the hydrolysis of methyl bromide may be represented by a single elementary step:



Carbon is partially bonded to both the incoming nucleophile and the departing halide at the transition state. Progress is made toward the transition state as the nucleophile begins to share a pair of its electrons with carbon and the halide ion leaves, taking with it the pair of electrons in its bond to carbon.

PROBLEM 8.3 Is the two-step sequence depicted in the following equations consistent with the second-order kinetic behavior observed for the hydrolysis of methyl bromide?

$$CH_3Br \xrightarrow{\text{slow}} CH_3^+ + Br^-$$

$$CH_3^+ + HO^- \xrightarrow{\text{fast}} CH_3OH$$

The S_N2 mechanism is believed to describe most substitutions in which simple primary and secondary alkyl halides react with anionic nucleophiles. All the examples cited in Table 8.1 proceed by the S_N2 mechanism (or a mechanism very much like S_N2—remember, mechanisms can never be established with certainty but represent only our best present explanations of experimental observations). We'll examine the S_N2 mechanism, particularly the structure of the transition state, in more detail in Section 8.5 after first looking at some stereochemical studies carried out by Hughes and Ingold.

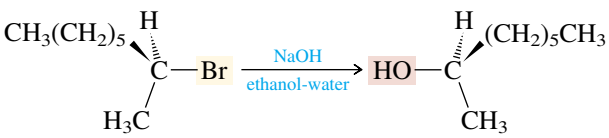
8.4 STEREOCHEMISTRY OF S_N2 REACTIONS

What is the structure of the transition state in an S_N2 reaction? In particular, what is the spatial arrangement of the nucleophile in relation to the leaving group as reactants pass through the transition state on their way to products?

Two stereochemical possibilities present themselves. In the pathway shown in Figure 8.1*a,* the nucleophile simply assumes the position occupied by the leaving group. It attacks the substrate at the same face from which the leaving group departs. This is called "front-side displacement," or substitution with **retention of configuration.**

In a second possibility, illustrated in Figure 8.1*b,* the nucleophile attacks the substrate from the side opposite the bond to the leaving group. This is called "back-side displacement," or substitution with **inversion of configuration.**

Which of these two opposite stereochemical possibilities operates was determined in experiments with optically active alkyl halides. In one such experiment, Hughes and Ingold determined that the reaction of 2-bromooctane with hydroxide ion gave 2-octanol having a configuration opposite that of the starting alkyl halide.



(*S*)-(+)-2-Bromooctane (*R*)-(−)-2-Octanol

Although the alkyl halide and alcohol given in this example have opposite configurations when they have opposite signs of rotation, it cannot be assumed that this will be true for all alkyl halide/alcohol pairs. (See Section 7.5)

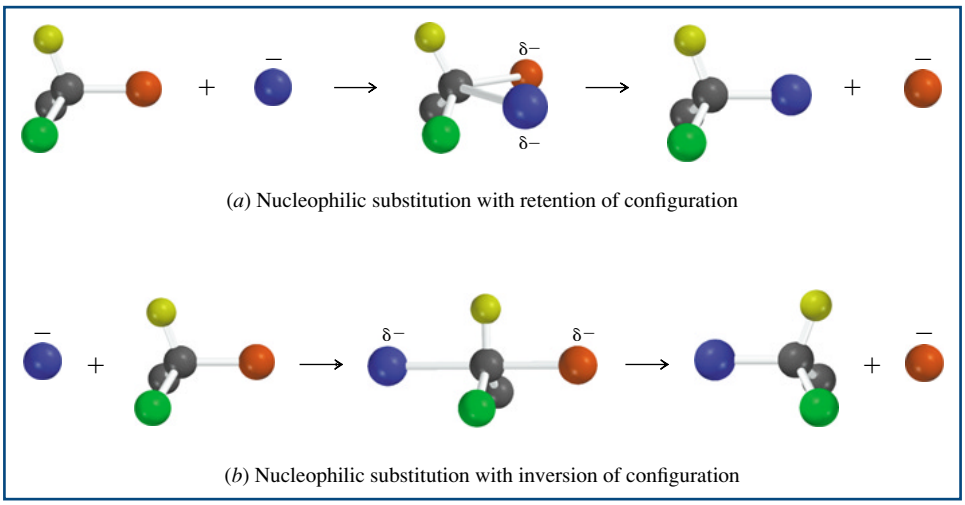
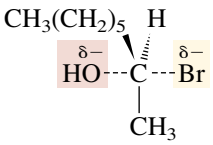


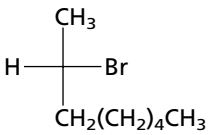
FIGURE 8.1 Two contrasting stereochemical pathways for substitution of a leaving group (red) by a nucleophile (blue). In (*a*) the nucleophile attacks carbon at the same side from which the leaving group departs. In (*b*) nucleophilic attack occurs at the side opposite the bond to the leaving group.

Nucleophilic substitution had occurred with inversion of configuration, consistent with the following transition state:



For a change of pace, try doing Problem 8.4 with molecular models instead of making structural drawings.

PROBLEM 8.4 The Fischer projection formula for (+)-2-bromooctane is shown. Write the Fischer projection of the (−)-2-octanol formed from it by nucleophilic substitution with inversion of configuration.



PROBLEM 8.5 Would you expect the 2-octanol formed by S_N2 hydrolysis of (−)-2-bromooctane to be optically active? If so, what will be its absolute configuration and sign of rotation? What about the 2-octanol formed by hydrolysis of racemic 2-bromooctane?

The first example of a stereoelectronic effect in this text concerned anti elimination in E2 reactions of alkyl halides (Section 5.16).

Numerous similar experiments have demonstrated the generality of this observation. Substitution by the S_N2 mechanism is stereospecific and proceeds with inversion of configuration at the carbon that bears the leaving group. *There is a stereoelectronic requirement for the nucleophile to approach carbon from the side opposite the bond to the leaving group.* Organic chemists often speak of this as a **Walden inversion,** after the German chemist Paul Walden, who described the earliest experiments in this area in the 1890s.

8.5 HOW S_N2 REACTIONS OCCUR

When we consider the overall reaction stereochemistry along with the kinetic data, a fairly complete picture of the bonding changes that take place during S_N2 reactions emerges. The potential energy diagram of Figure 8.2 for the hydrolysis of *(S)*-(+)-2-bromooctane is one that is consistent with the experimental observations.

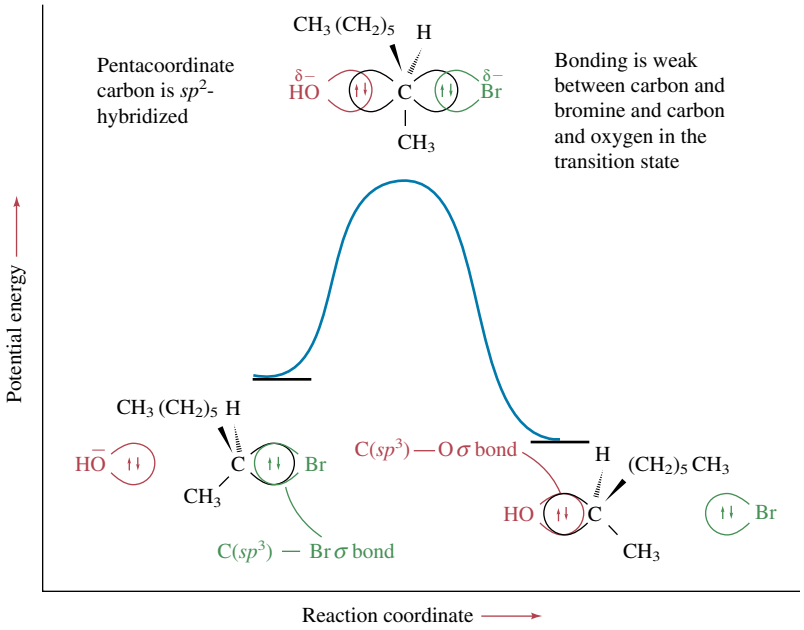


FIGURE 8.2 Hybrid orbital description of the bonding changes that take place at carbon during nucleophilic substitution by the S_N2 mechanism.

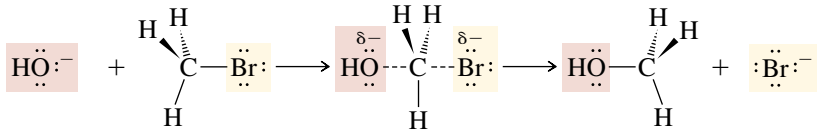
Hydroxide ion acts as a nucleophile, using an unshared electron pair to attack carbon from the side opposite the bond to the leaving group. The hybridization of the carbon at which substitution occurs changes from sp^3 in the alkyl halide to sp^2 in the transition state. Both the nucleophile (hydroxide) and the leaving group (bromide) are partially bonded to this carbon in the transition state. We say that the S_N2 transition state is *pentacoordinate;* carbon is fully bonded to three substituents and partially bonded to both the leaving group and the incoming nucleophile. The bonds to the nucleophile and the leaving group are relatively long and weak at the transition state.

Once past the transition state, the leaving group is expelled and carbon becomes tetracoordinate, its hybridization returning to sp^3.

During the passage of starting materials to products, three interdependent and synchronous changes take place:

1. Stretching, then breaking, of the bond to the leaving group
2. Formation of a bond to the nucleophile from the opposite side of the bond that is broken
3. Stereochemical inversion of the tetrahedral arrangement of bonds to the carbon at which substitution occurs

Although this mechanistic picture developed from experiments involving optically active alkyl halides, chemists speak even of methyl bromide as undergoing nucleophilic substitution with *inversion.* By this they mean that tetrahedral inversion of the bonds to carbon occurs as the reactant proceeds to the product.



For an animation of this S_N2 reaction, see *Learning By Modeling.*

We saw in Section 8.2 that the rate of nucleophilic substitution depends strongly on the leaving group—alkyl iodides are the most reactive, alkyl fluorides the least. In the next section, we'll see that the structure of the alkyl group can have an even greater effect.

8.6 STERIC EFFECTS IN S_N2 REACTIONS

There are very large differences in the rates at which the various kinds of alkyl halides—methyl, primary, secondary, or tertiary—undergo nucleophilic substitution. As Table 8.2 shows for the reaction of a series of alkyl bromides:

$$\underset{\text{Alkyl bromide}}{RBr} + \underset{\text{Lithium iodide}}{LiI} \xrightarrow{\text{acetone}} \underset{\text{Alkyl iodide}}{RI} + \underset{\text{Lithium bromide}}{LiBr}$$

the rates of nucleophilic substitution of a series of alkyl bromides differ by a factor of over 10^6 when comparing the most reactive member of the group (methyl bromide) and the least reactive member (*tert*-butyl bromide).

The large rate difference between methyl, ethyl, isopropyl, and *tert*-butyl bromides reflects the **steric hindrance** each offers to nucleophilic attack. The nucleophile must approach the alkyl halide from the side opposite the bond to the leaving group, and, as illustrated in Figure 8.3, this approach is hindered by alkyl substituents on the carbon that is being attacked. The three hydrogens of methyl bromide offer little resistance to approach of the nucleophile, and a rapid reaction occurs. Replacing one of the hydrogens by a methyl group somewhat shields the carbon from attack by the nucleophile and causes ethyl bromide to be less reactive than methyl bromide. Replacing all three hydrogen substituents by methyl groups almost completely blocks back-side approach to the tertiary carbon of $(CH_3)_3CBr$ and shuts down bimolecular nucleophilic substitution.

In general, S_N2 reactions exhibit the following dependence of rate on substrate structure:

Increasing rate of substitution by the S_N2 mechanism

R_3CX	<	R_2CHX	<	RCH_2X	<	CH_3X
Tertiary		Secondary		Primary		Methyl
Least reactive, most crowded						Most reactive, least crowded

TABLE 8.2 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N2 Mechanism*

Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	221,000
Ethyl bromide	CH_3CH_2Br	Primary	1,350
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	1
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	Too small to measure

*Substitution of bromide by lithium iodide in acetone.
†Ratio of second-order rate constant k for indicated alkyl bromide to k for isopropyl bromide at 25°C.

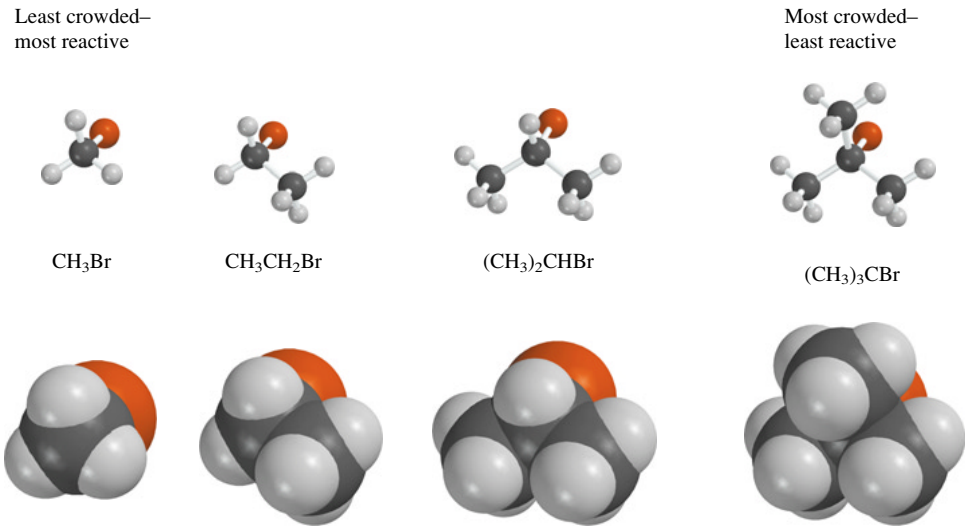
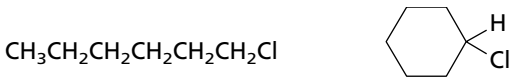


FIGURE 8.3 Ball-and-spoke and space-filling models of alkyl bromides, showing how substituents shield the carbon atom that bears the leaving group from attack by a nucleophile. The nucleophile must attack from the side opposite the bond to the leaving group.

PROBLEM 8.6 Identify the compound in each of the following pairs that reacts with sodium iodide in acetone at the faster rate:

(a) 1-Chlorohexane or cyclohexyl chloride
(b) 1-Bromopentane or 3-bromopentane
(c) 2-Chloropentane or 2-fluoropentane
(d) 2-Bromo-2-methylhexane or 2-bromo-5-methylhexane
(e) 2-Bromopropane or 1-bromodecane

SAMPLE SOLUTION (a) Compare the structures of the two chlorides. 1-Chlorohexane is a primary alkyl chloride; cyclohexyl chloride is secondary. Primary alkyl halides are less crowded at the site of substitution than secondary ones and react faster in substitution by the S_N2 mechanism. 1-Chlorohexane is more reactive.



1-Chlorohexane
(primary, more reactive)

Cyclohexyl chloride
(secondary, less reactive)

Alkyl groups at the carbon atom *adjacent* to the point of nucleophilic attack also decrease the rate of the S_N2 reaction. Compare the rates of nucleophilic substitution in the series of primary alkyl bromides shown in Table 8.3. Taking ethyl bromide as the standard and successively replacing its C-2 hydrogens by methyl groups, we see that each additional methyl group decreases the rate of displacement of bromide by iodide. The effect is slightly smaller than for alkyl groups that are attached directly to the carbon that bears the leaving group, but it is still substantial. When C-2 is completely substituted by methyl groups, as it is in neopentyl bromide [$(CH_3)_3CCH_2Br$], we see the unusual case of a primary alkyl halide that is practically inert to substitution by the S_N2 mechanism because of steric hindrance.

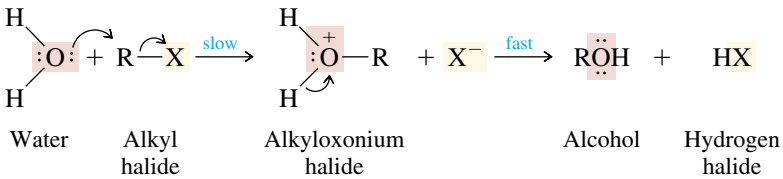
TABLE 8.3 Effect of Chain Branching on Reactivity of Primary Alkyl Bromides Toward Substitution Under S_N2 Conditions*

Alkyl bromide	Structure	Relative rate†
Ethyl bromide	CH_3CH_2Br	1.0
Propyl bromide	$CH_3CH_2CH_2Br$	0.8
Isobutyl bromide	$(CH_3)_2CHCH_2Br$	0.036
Neopentyl bromide	$(CH_3)_3CCH_2Br$	0.00002

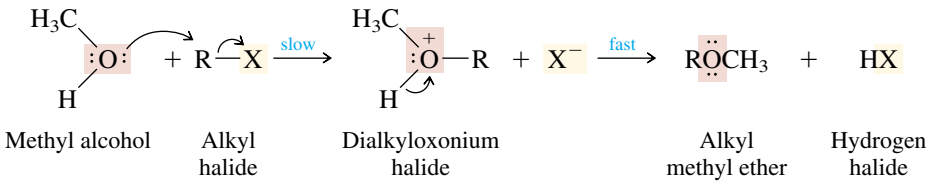
*Substitution of bromide by lithium iodide in acetone.
†Ratio of second-order rate constant *k* for indicated alkyl bromide to *k* for ethyl bromide at 25°C.

8.7 NUCLEOPHILES AND NUCLEOPHILICITY

The Lewis base that acts as the nucleophile often is, but need not always be, an anion. Neutral Lewis bases can also serve as nucleophiles. Common examples of substitutions involving neutral nucleophiles include *solvolysis* reactions. **Solvolysis** reactions are substitutions in which the nucleophile is the solvent in which the reaction is carried out. Solvolysis in *water* converts an alkyl halide to an *alcohol.*



Solvolysis in *methyl alcohol* converts an alkyl halide to an *alkyl methyl ether.*



In these and related solvolyses, the first stage is the one in which nucleophilic substitution takes place and is rate-determining. The proton-transfer step that follows it is much faster.

Since, as we have seen, the nucleophile attacks the substrate in the rate-determining step of the S_N2 mechanism, it follows that the rate at which substitution occurs may vary from nucleophile to nucleophile. Just as some alkyl halides are more reactive than others, some nucleophiles are more reactive than others. Nucleophilic strength, or **nucleophilicity,** is a measure of how fast a Lewis base displaces a leaving group from a suitable substrate. By measuring the rate at which various Lewis bases react with methyl iodide in methanol, a list of their nucleophilicities relative to methanol as the standard nucleophile has been compiled. It is presented in Table 8.4.

Neutral Lewis bases such as water, alcohols, and carboxylic acids are much weaker nucleophiles than their conjugate bases. When comparing species that have the same nucleophilic atom, a negatively charged nucleophile is more reactive than a neutral one.

TABLE 8.4 Nucleophilicity of Some Common Nucleophiles

Reactivity class	Nucleophile	Relative reactivity*
Very good nucleophiles	I^-, HS^-, RS^-	$>10^5$
Good nucleophiles	Br^-, HO^-, RO^-, CN^-, N_3^-	10^4
Fair nucleophiles	NH_3, Cl^-, F^-, RCO_2^-	10^3
Weak nucleophiles	H_2O, ROH	1
Very weak nucleophiles	RCO_2H	10^{-2}

*Relative reactivity is k(nucleophile)/k(methanol) for typical S_N2 reactions and is approximate. Data pertain to methanol as the solvent.

RO^- (Alkoxide ion) is more nucleophilic than ROH (Alcohol)

RCO^- (Carboxylate ion) is more nucleophilic than RCOH (Carboxylic acid)

As long as the nucleophilic atom is the same, the more basic the nucleophile, the more reactive it is. An alkoxide ion (RO^-) is more basic and more nucleophilic than a carboxylate ion (RCO_2^-).

RO^- (Stronger base; Conjugate acid is ROH: $K_a = 10^{-16}$ ($pK_a = 16$)) is more nucleophilic than RCO^- (Weaker base; Conjugate acid is RCO_2H: $K_a = 10^{-5}$ ($pK_a = 5$))

The connection between basicity and nucleophilicity holds when comparing atoms in the *same row* of the periodic table. Thus, HO^- is more basic and more nucleophilic than F^-, and H_3N is more basic and more nucleophilic than H_2O. *It does not hold when proceeding down a column in the periodic table.* For example, I^- is the least basic of the halide ions but is the most nucleophilic. F^- is the most basic halide ion but the least nucleophilic. The factor that seems most responsible for the inverse relationship between basicity and nucleophilicity among the halide ions is the degree to which they are *solvated* by hydrogen bonds of the type illustrated in Figure 8.4. Smaller anions, because of their high charge-to-size ratio, are more strongly solvated than larger ones. In order to act as a nucleophile, the halide must shed some of the solvent molecules that surround it. Among the halide anions, F^- forms the strongest hydrogen bonds to water and alcohols, and I^- the weakest. Thus, the nucleophilicity of F^- is suppressed more than that of Cl^-, Cl^- more than Br^-, and Br^- more than I^-. Similarly, HO^- is smaller, more solvated, and less nucleophilic than HS^-.

Nucleophilicity is also related to polarizability, or the ease of distortion of the electron "cloud" surrounding the nucleophile. The partial bond between the nucleophile and the alkyl halide that characterizes the S_N2 transition state is more fully developed at a longer distance when the nucleophile is very polarizable than when it is not. An increased degree of bonding to the nucleophile lowers the energy of the transition state and

A descriptive term applied to a highly polarizable species is *soft*. Iodide is a very soft nucleophile. Conversely, fluoride ion is not very polarizable and is said to be a *hard* nucleophile.

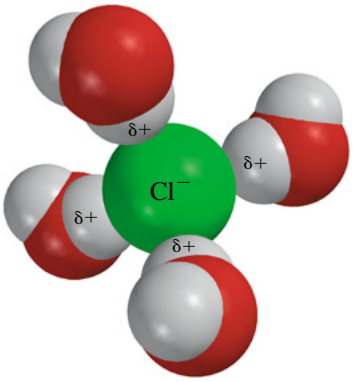


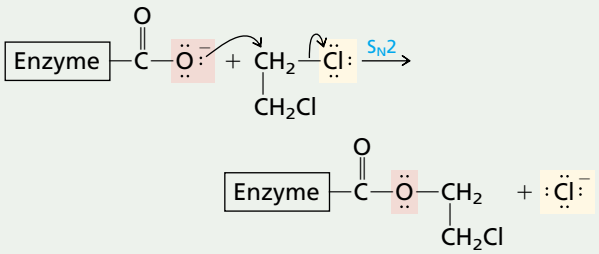
FIGURE 8.4 Solvation of a chloride by ion–dipole attractive forces with water. The negatively charged chloride ion interacts with the positively polarized hydrogens of water.

AN ENZYME-CATALYZED NUCLEOPHILIC SUBSTITUTION OF AN ALKYL HALIDE

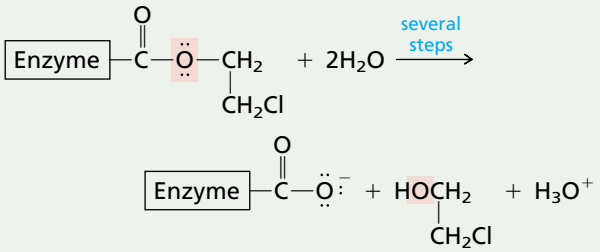
Nucleophilic substitution is one of a variety of mechanisms by which living systems detoxify halogenated organic compounds introduced into the environment. Enzymes that catalyze these reactions are known as *haloalkane dehalogenases.* The hydrolysis of 1,2-dichloroethane to 2-chloroethanol, for example, is a biological nucleophilic substitution catalyzed by a dehalogenase.

$$\underset{\text{1,2-Dichloroethane}}{ClCH_2CH_2Cl} + \underset{\text{Water}}{2H_2O} \xrightarrow[\text{enzyme}]{\text{dehalogenase}} \underset{\text{2-Chloroethanol}}{ClCH_2CH_2OH} + \underset{\text{Hydronium ion}}{H_3O^+} + \underset{\text{Chloride ion}}{Cl^-}$$

The haloalkane dehydrogenase is believed to act by using one of its side-chain carboxylates to displace chloride by an S_N2 mechanism. (Recall the reaction of carboxylate ions with alkyl halides from Table 8.1.)



The product of this nucleophilic substitution then reacts with water, restoring the enzyme to its original state and giving the observed products of the reaction.



This stage of the reaction proceeds by a mechanism that will be discussed in Chapter 20. Both stages are faster than the reaction of 1,2-dichloroethane with water in the absence of the enzyme.

Some of the most common biological S_N2 reactions involve attack at methyl groups, especially a methyl group of *S-adenosylmethionine.* Examples of these will be given in Chapter 16.

increases the rate of substitution. Among related atoms, polarizability increases with increasing size. Thus iodide is the most polarizable and most nucleophilic halide ion, fluoride the least.

PROBLEM 8.7 Sodium nitrite ($NaNO_2$) reacted with 2-iodooctane to give a mixture of two constitutionally isomeric compounds of molecular formula $C_8H_{17}NO_2$ in a combined yield of 88%. Suggest reasonable structures for these two isomers.

8.8 THE S_N1 MECHANISM OF NUCLEOPHILIC SUBSTITUTION

Having just learned that tertiary alkyl halides are practically inert to substitution by the S_N2 mechanism because of steric hindrance, we might wonder whether they undergo nucleophilic substitution at all. We'll see in this section that they do, but by a mechanism different from S_N2.

Hughes and Ingold observed that the hydrolysis of *tert*-butyl bromide, which occurs readily, is characterized by a *first-order* rate law:

$$\underset{\text{tert-Butyl bromide}}{(CH_3)_3CBr} + \underset{\text{Water}}{H_2O} \longrightarrow \underset{\text{tert-Butyl alcohol}}{(CH_3)_3COH} + \underset{\text{Hydrogen bromide}}{HBr}$$

$$\text{Rate} = k[(CH_3)_3CBr]$$

They found that the rate of hydrolysis depends only on the concentration of *tert*-butyl bromide. Adding the stronger nucleophile hydroxide ion, moreover, causes no change in the rate of substitution, nor does this rate depend on the concentration of hydroxide. Just as second-order kinetics was interpreted as indicating a bimolecular rate-determining step, first-order kinetics was interpreted as evidence for a *unimolecular* rate-determining step—a step that involves only the alkyl halide.

The proposed mechanism is outlined in Figure 8.5 and is called S_N1, standing for **substitution nucleophilic unimolecular.** The first step, a unimolecular dissociation of the alkyl halide to form a carbocation as the key intermediate, is rate-determining. An energy diagram for the process is shown in Figure 8.6.

The S_N1 mechanism was earlier introduced in Section 4.11.

PROBLEM 8.8 Suggest a structure for the product of nucleophilic substitution obtained on solvolysis of *tert*-butyl bromide in methanol, and outline a reasonable mechanism for its formation.

The S_N1 mechanism is an *ionization* mechanism. The nucleophile does not participate until after the rate-determining step has taken place. Thus, the effects of nucleophile and alkyl halide structure are expected to be different from those observed for reactions proceeding by the S_N2 pathway. How the structure of the alkyl halide affects the rate of S_N1 reactions is the topic of the next section.

8.9 CARBOCATION STABILITY AND S_N1 REACTION RATES

In order to compare S_N1 substitution rates in a range of alkyl halides, experimental conditions are chosen in which competing substitution by the S_N2 route is very slow. One such set of conditions is solvolysis in aqueous formic acid (HCO_2H):

$$\underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O} \xrightarrow[\text{acid}]{\text{formic}} \underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX}$$

FIGURE 8.5 The S_N1 mechanism for hydrolysis of *tert*-butyl bromide.

The Overall Reaction:

$$(CH_3)_3CBr + 2H_2O \longrightarrow (CH_3)_3COH + H_3O^+ + Br^-$$

tert-Butyl bromide; Water; *tert*-Butyl alcohol; Hydronium ion; Bromide ion

Step 1: The alkyl halide dissociates to a carbocation and a halide ion.

$$(CH_3)_3C{-}\ddot{Br}: \xrightarrow{\text{slow}} (CH_3)_3C^+ + :\ddot{Br}:^-$$

tert-Butyl bromide; *tert*-Butyl cation; Bromide ion

Step 2: The carbocation formed in step 1 reacts rapidly with a water molecule. Water is a nucleophile. This step completes the nucleophilic substitution stage of the mechanism and yields an alkyloxonium ion.

$$(CH_3)_3C^+ + :O(H)H \xrightarrow{\text{fast}} (CH_3)_3C{-}\overset{+}{O}(H)H$$

tert-Butyl cation; Water; *tert*-Butyloxonium ion

Step 3: This step is a fast acid-base reaction that follows the nucleophilic substitution. Water acts as a base to remove a proton from the alkyloxonium ion to give the observed product of the reaction, *tert*-butyl alcohol.

$$(CH_3)_3C{-}\overset{+}{O}(H)H + :O(H)H \xrightarrow{\text{fast}} (CH_3)_3C{-}\ddot{O}:H + H{-}\overset{+}{O}(H)H$$

tert-Butyloxonium ion; Water; *tert*-Butyl alcohol; Hydronium ion

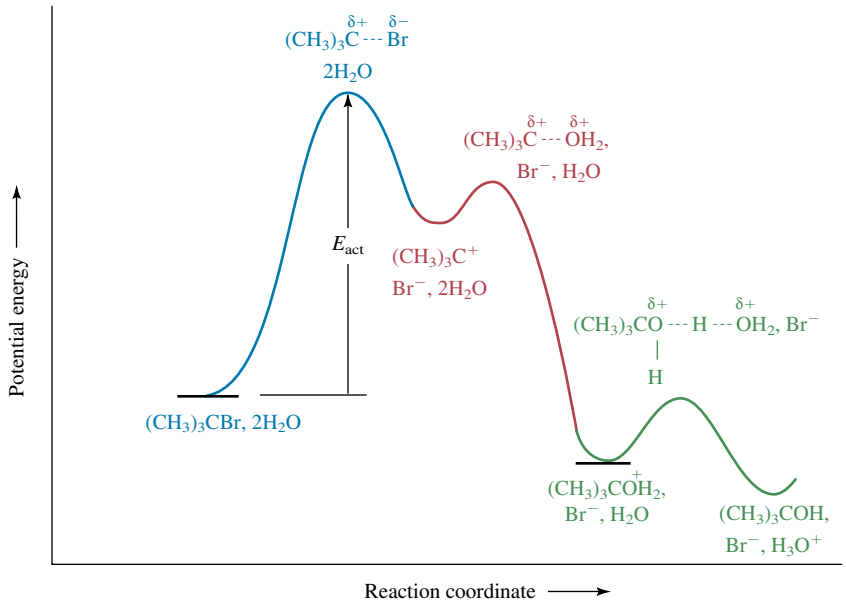


FIGURE 8.6 Energy diagram illustrating the S_N1 mechanism for hydrolysis of *tert*-butyl bromide.

Neither formic acid nor water is very nucleophilic, and so S_N2 substitution is suppressed. The relative rates of hydrolysis of a group of alkyl bromides under these conditions are presented in Table 8.5.

The relative rate order in S_N1 reactions is exactly the opposite of that seen in S_N2 reactions:

S_N1 reactivity: methyl < primary < secondary < tertiary
S_N2 reactivity: tertiary < secondary < primary < methyl

Clearly, the steric crowding that influences reaction rates in S_N2 processes plays no role in S_N1 reactions. The order of alkyl halide reactivity in S_N1 reactions is the same as the order of carbocation stability: the more stable the carbocation, the more reactive the alkyl halide. We have seen this situation before in the reaction of alcohols with hydrogen halides (Section 4.12), in the acid-catalyzed dehydration of alcohols (Section 5.9), and in the conversion of alkyl halides to alkenes by the E1 mechanism (Section 5.17). As in these other reactions, an electronic effect, specifically, the stabilization of the carbocation intermediate by alkyl substituents, is the decisive factor.

PROBLEM 8.9 Identify the compound in each of the following pairs that reacts at the faster rate in an S_N1 reaction:

(a) Isopropyl bromide or isobutyl bromide
(b) Cyclopentyl iodide or 1-methylcyclopentyl iodide
(c) Cyclopentyl bromide or 1-bromo-2,2-dimethylpropane
(d) *tert*-Butyl chloride or *tert*-butyl iodide

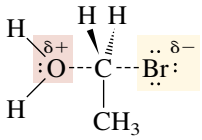
SAMPLE SOLUTION (a) Isopropyl bromide, $(CH_3)_2CHBr$, is a secondary alkyl halide, whereas isobutyl bromide, $(CH_3)_2CHCH_2Br$, is primary. Since the rate-determining step in an S_N1 reaction is carbocation formation and since secondary carbocations are more stable than primary carbocations, isopropyl bromide is more reactive than isobutyl bromide in nucleophilic substitution by the S_N1 mechanism.

Primary carbocations are so high in energy that their intermediacy in nucleophilic substitution reactions is unlikely. When ethyl bromide undergoes hydrolysis in aqueous formic acid, substitution probably takes place by a direct displacement of bromide by water in an S_N2-like process.

TABLE 8.5 Reactivity of Some Alkyl Bromides Toward Substitution by the S_N1 Mechanism*

Alkyl bromide	Structure	Class	Relative rate†
Methyl bromide	CH_3Br	Unsubstituted	1
Ethyl bromide	CH_3CH_2Br	Primary	2
Isopropyl bromide	$(CH_3)_2CHBr$	Secondary	43
tert-Butyl bromide	$(CH_3)_3CBr$	Tertiary	100,000,000

*Solvolysis in aqueous formic acid.
†Ratio of rate constant *k* for indicated alkyl bromide to *k* for methyl bromide at 25°C.

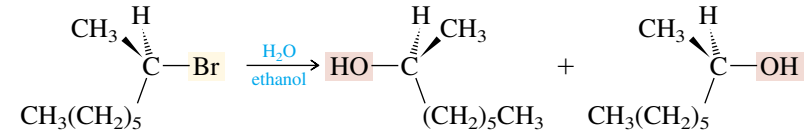


Bimolecular transition state
for hydrolysis of ethyl bromide

8.10 STEREOCHEMISTRY OF S_N1 REACTIONS

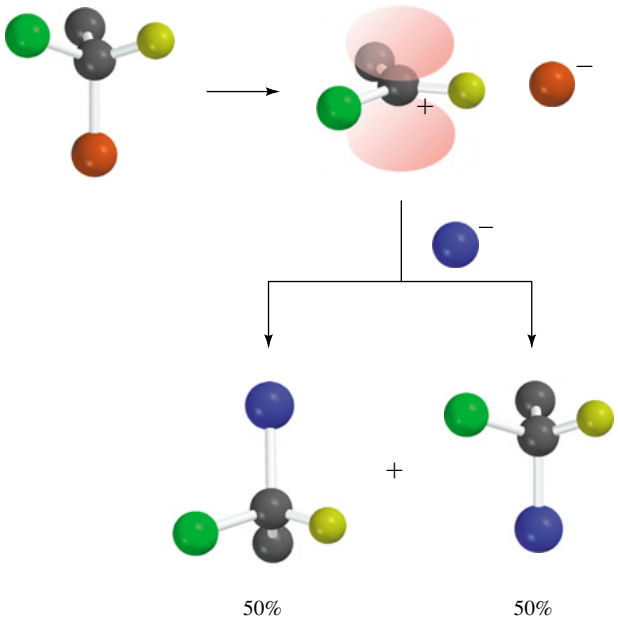
Although S_N2 reactions are stereospecific and proceed with inversion of configuration at carbon, the situation is not as clear-cut for S_N1 reactions. When the leaving group is attached to the stereogenic center of an optically active halide, ionization gives a carbocation intermediate that is achiral. It is achiral because the three bonds to the positively charged carbon lie in the same plane, and this plane is a plane of symmetry for the carbocation. As shown in Figure 8.7, such a carbocation should react with a nucleophile at the same rate at either of its two faces. We expect the product of substitution by the S_N1 mechanism to be racemic and optically inactive. This outcome is rarely observed in practice, however. Normally, the product is formed with predominant, but not complete, inversion of configuration.

For example, the hydrolysis of optically active 2-bromooctane in the absence of added base follows a first-order rate law, but the resulting 2-octanol is formed with 66% inversion of configuration.



(*R*)-(−)-2-Bromooctane (*S*)-(+)-2-Octanol (*R*)-(−)-2-Octanol

66% net inversion corresponds
to 83% *S*, 17% *R*



50% 50%

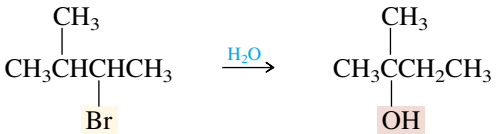
FIGURE 8.7 Formation of a racemic product by nucleophilic substitution via a carbocation intermediate.

Partial but not complete loss of optical activity in S_N1 reactions probably results from the carbocation not being completely "free" when it is attacked by the nucleophile. Ionization of the alkyl halide gives a carbocation–halide ion pair, as depicted in Figure 8.8. The halide ion shields one side of the carbocation, and the nucleophile captures the carbocation faster from the opposite side. More product of inverted configuration is formed than product of retained configuration. In spite of the observation that the products of S_N1 reactions are only partially racemic, the fact that these reactions are not stereospecific is more consistent with a carbocation intermediate than a concerted bimolecular mechanism.

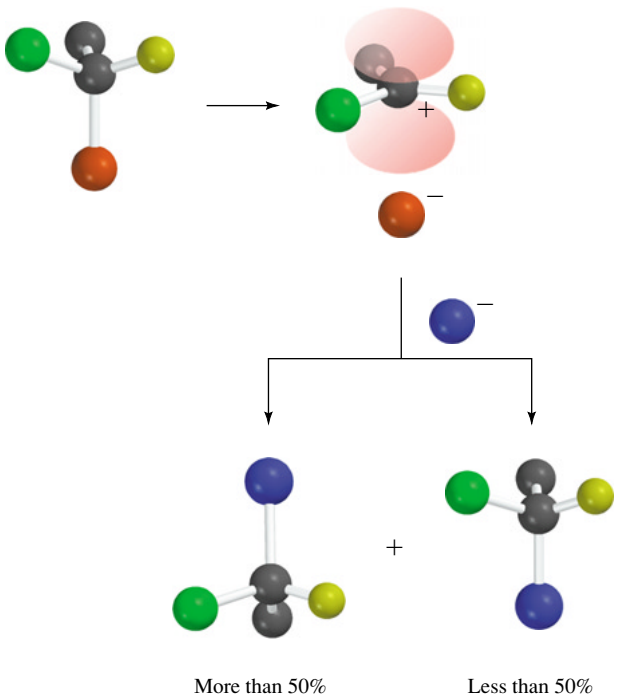
PROBLEM 8.10 What two stereoisomeric substitution products would you expect to isolate from the hydrolysis of *cis*-1,4-dimethylcyclohexyl bromide? From hydrolysis of *trans*-1,4-dimethylcyclohexyl bromide?

8.11 CARBOCATION REARRANGEMENTS IN S_N1 REACTIONS

Additional evidence for carbocation intermediates in certain nucleophilic substitutions comes from observing rearrangements of the kind normally associated with such species. For example, hydrolysis of the secondary alkyl bromide 2-bromo-3-methylbutane yields the rearranged tertiary alcohol 2-methyl-2-butanol as the only substitution product.



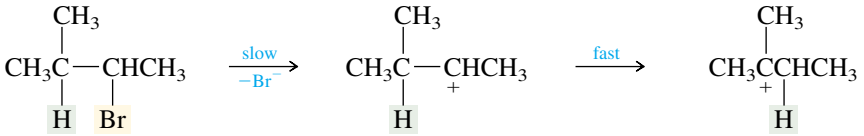
2-Bromo-3-methylbutane 2-Methyl-2-butanol (93%)



More than 50% Less than 50%

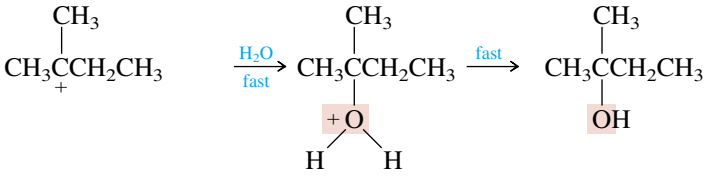
FIGURE 8.8 Inversion of configuration predominates in S_N1 reactions because one face of the carbocation is shielded by the leaving group (red).

A reasonable mechanism for this observation assumes rate-determining ionization of the substrate as the first step followed by a hydride shift that converts the secondary carbocation to a more stable tertiary one.



2-Bromo-3-methylbutane | 1,2-Dimethylpropyl cation (a secondary carbocation) | 1,1-Dimethylpropyl cation (a tertiary carbocation)

The tertiary carbocation then reacts with water to yield the observed product.



1,1-Dimethylpropyl cation | 2-Methyl-2-butanol

PROBLEM 8.11 Why does the carbocation intermediate in the hydrolysis of 2-bromo-3-methylbutane rearrange by way of a hydride shift rather than a methyl shift?

Rearrangements, when they do occur, are taken as evidence for carbocation intermediates and point to the S_N1 mechanism as the reaction pathway. Rearrangements are never observed in S_N2 reactions.

8.12 EFFECT OF SOLVENT ON THE RATE OF NUCLEOPHILIC SUBSTITUTION

The major effect of the solvent is on the *rate* of nucleophilic substitution, not on what the products are. Thus we need to consider two related questions:

1. What properties of the *solvent* influence the rate most?
2. How does the rate-determining step of the *mechanism* respond to this property of the solvent?

Because the S_N1 and S_N2 mechanisms are so different from each other, let's examine each one separately.

Solvent Effects on the Rate of Substitution by the S_N1 Mechanism. Table 8.6 lists the relative rate of solvolysis of *tert*-butyl chloride in several media in order of increasing **dielectric constant** (ϵ). Dielectric constant is a measure of the ability of a material, in this case the solvent, to moderate the force of attraction between oppositely charged particles compared with that of a standard. The standard dielectric is a vacuum, which is assigned a value ϵ of exactly 1. The higher the dielectric constant ϵ, the better the medium is able to support separated positively and negatively charged species. Solvents with high dielectric constants are classified as *polar solvents.* As Table 8.6 illustrates, the rate of solvolysis of *tert*-butyl chloride (which is equal to its rate of ionization) increases dramatically as the dielectric constant of the solvent increases.

TABLE 8.6 Relative Rate of S_N1 Solvolysis of *tert*-Butyl Chloride as a Function of Solvent Polarity*

Solvent	Dielectric constant ϵ	Relative rate
Acetic acid	6	1
Methanol	33	4
Formic acid	58	5,000
Water	78	150,000

*Ratio of first-order rate constant for solvolysis in indicated solvent to that for solvolysis in acetic acid at 25°C.

According to the S_N1 mechanism, a molecule of an alkyl halide ionizes to a positively charged carbocation and a negatively charged halide ion in the rate-determining step. As the alkyl halide approaches the transition state for this step, a partial positive charge develops on carbon and a partial negative charge on the halogen. Figure 8.9 contrasts the behavior of a nonpolar and a polar solvent on the energy of the transition state. Polar and nonpolar solvents are similar in their interaction with the starting alkyl halide, but differ markedly in how they affect the transition state. A solvent with a low dielectric constant has little effect on the energy of the transition state, whereas one with a high dielectric constant stabilizes the charge-separated transition state, lowers the activation energy, and increases the rate of reaction.

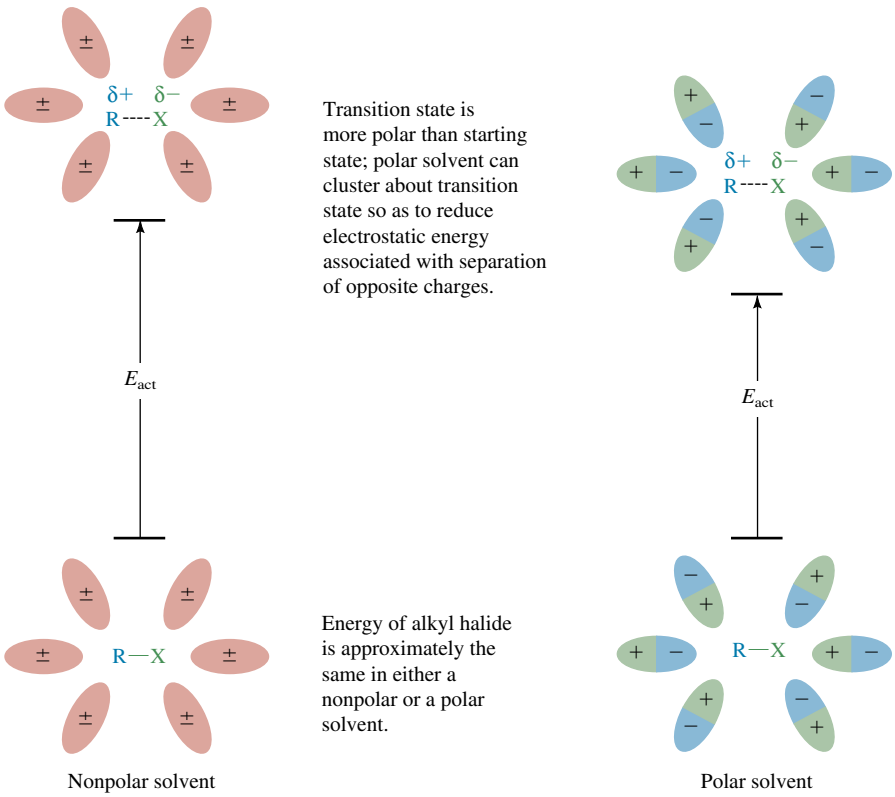


FIGURE 8.9 A polar solvent stabilizes the transition state of an S_N1 reaction and increases its rate.

Solvent Effects on the Rate of Substitution by the S_N2 Mechanism. Polar solvents are required in typical bimolecular substitutions because ionic substances, such as the sodium and potassium salts cited earlier in Table 8.1, are not sufficiently soluble in nonpolar solvents to give a high enough concentration of the nucleophile to allow the reaction to occur at a rapid rate. Other than the requirement that the solvent be polar enough to dissolve ionic compounds, however, the effect of solvent polarity on the rate of S_N2 reactions is small. What is most important is whether or not the polar solvent is **protic** or **aprotic.**

Water (HOH), alcohols (ROH), and carboxylic acids (RCO_2H) are classified as *polar protic solvents;* they all have OH groups that allow them to form hydrogen bonds to anionic nucleophiles as shown in Figure 8.10. Solvation forces such as these stabilize the anion and suppress its nucleophilicity. *Aprotic solvents,* on the other hand, lack OH groups and do not solvate anions very strongly, leaving them much more able to express their nucleophilic character. Table 8.7 compares the second-order rate constants k for S_N2 substitution of 1-bromobutane by azide ion (a good nucleophile) in some common polar aprotic solvents with the corresponding k's for the much slower reactions observed in the polar protic solvents methanol and water.

$$\underset{\text{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{Azide ion}}{N_3^-} \longrightarrow \underset{\text{1-Azidobutane}}{CH_3CH_2CH_2CH_2N_3} + \underset{\text{Bromide ion}}{Br^-}$$

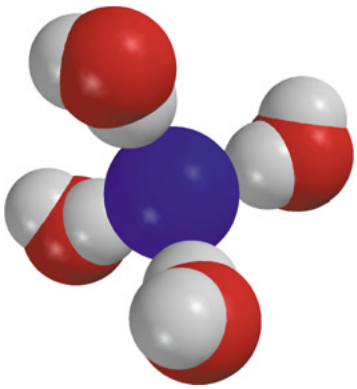


FIGURE 8.10 Hydrogen bonding of the solvent to the nucleophile stabilizes the nucleophile and makes it less reactive.

TABLE 8.7 Relative Rate of S_N2 Displacement of 1-Bromobutane by Azide in Various Solvents*

Solvent	Structural formula	Dielectric constant ϵ	Type of solvent	Relative rate
Methanol	CH_3OH	32.6	Polar protic	1
Water	H_2O	78.5	Polar protic	7
Dimethyl sulfoxide	$(CH_3)_2S{=}O$	48.9	Polar aprotic	1300
N,N-Dimethylformamide	$(CH_3)_2NCH{=}O$	36.7	Polar aprotic	2800
Acetonitrile	$CH_3C{\equiv}N$	37.5	Polar aprotic	5000

*Ratio of second-order rate constant for substitution in indicated solvent to that for substitution in methanol at 25°C.

The large rate enhancements observed for bimolecular nucleophilic substitutions in polar aprotic solvents are used to advantage in synthetic applications. An example can be seen in the preparation of alkyl cyanides (nitriles) by the reaction of sodium cyanide with alkyl halides:

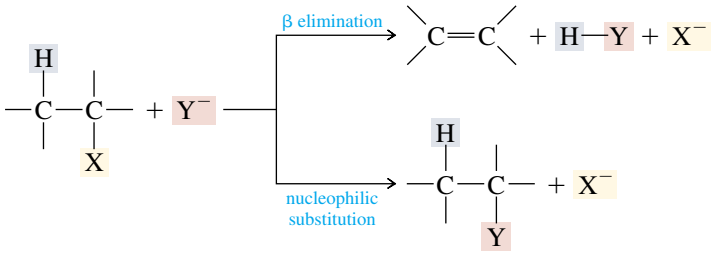
$$\underset{\text{Hexyl halide}}{CH_3(CH_2)_4CH_2X} + \underset{\text{Sodium cyanide}}{NaCN} \longrightarrow \underset{\text{Hexyl cyanide}}{CH_3(CH_2)_4CH_2CN} + \underset{\text{Sodium halide}}{NaX}$$

When the reaction was carried out in aqueous methanol as the solvent, hexyl bromide was converted to hexyl cyanide in 71% yield by heating with sodium cyanide. Although this is a perfectly acceptable synthetic reaction, a period of over *20 hours* was required. Changing the solvent to dimethyl sulfoxide brought about an increase in the reaction rate sufficient to allow the less reactive substrate hexyl chloride to be used instead, and the reaction was complete (91% yield) in only *20 minutes.*

The *rate* at which reactions occur can be important in the laboratory, and understanding how solvents affect rate is of practical value. As we proceed through the text, however, and see how nucleophilic substitution is applied to a variety of functional group transformations, be aware that it is the nature of the substrate and the nucleophile that, more than anything else, determines what *product* is formed.

8.13 SUBSTITUTION AND ELIMINATION AS COMPETING REACTIONS

We have seen that an alkyl halide and a Lewis base can react together in either a substitution or an elimination reaction.



Substitution can take place by the S_N1 or the S_N2 mechanism, elimination by E1 or E2.

How can we predict whether substitution or elimination will be the principal reaction observed with a particular combination of reactants? The two most important factors are the *structure of the alkyl halide* and the *basicity of the anion.* It is useful to approach the question from the premise that the characteristic reaction of alkyl halides with Lewis bases is *elimination,* and that substitution predominates only under certain special circumstances. In a typical reaction, a typical secondary alkyl halide such as isopropyl bromide reacts with a typical nucleophile such as sodium ethoxide mainly by elimination:

$$\underset{\text{Isopropyl bromide}}{CH_3\underset{\displaystyle Br}{\underset{|}{C}}HCH_3} \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} \underset{\text{Propene (87\%)}}{CH_3CH{=}CH_2} + \underset{\text{Ethyl isopropyl ether (13\%)}}{CH_3\underset{\displaystyle OCH_2CH_3}{\underset{|}{C}}HCH_3}$$

Figure 8.11 illustrates the close relationship between the E2 and S_N2 pathways for this case, and the results cited in the preceding equation clearly show that E2 is faster than S_N2 when the alkyl halide is secondary and the nucleophile is a strong base.

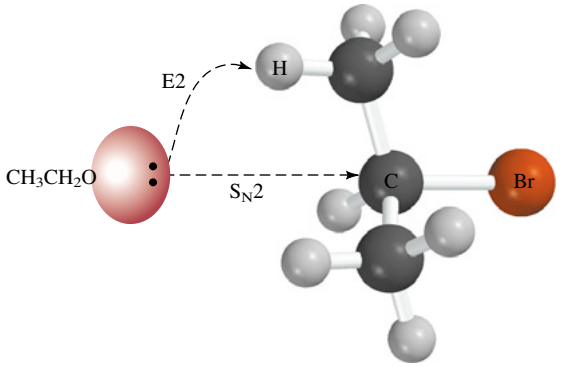


FIGURE 8.11 When a Lewis base reacts with an alkyl halide, either substitution or elimination can occur. Substitution (S_N2) occurs when the nucleophile attacks carbon to displace bromide. Elimination occurs when the Lewis base abstracts a proton from the β carbon. The alkyl halide shown is isopropyl bromide. The carbon atom that bears the leaving group is somewhat sterically hindered, and elimination (E2) predominates over substitution with alkoxide bases.

As crowding at the carbon that bears the leaving group decreases, the rate of nucleophilic attack by the Lewis base increases. A low level of steric hindrance to approach of the nucleophile is one of the special circumstances that permit substitution to predominate, and primary alkyl halides react with alkoxide bases by an S_N2 mechanism in preference to E2:

$$\underset{\text{Propyl bromide}}{CH_3CH_2CH_2Br} \xrightarrow[CH_3CH_2OH,\ 55°C]{NaOCH_2CH_3} \underset{\text{Propene (9\%)}}{CH_3CH{=}CH_2} + \underset{\text{Ethyl propyl ether (91\%)}}{CH_3CH_2CH_2OCH_2CH_3}$$

If, however, the base itself is a crowded one, such as potassium *tert*-butoxide, even primary alkyl halides undergo elimination rather than substitution:

$$\underset{\text{1-Bromooctadecane}}{CH_3(CH_2)_{15}CH_2CH_2Br} \xrightarrow[(CH_3)_3COH,\ 40°C]{KOC(CH_3)_3} \underset{\text{1-Octadecene (87\%)}}{CH_3(CH_2)_{15}CH{=}CH_2} + \underset{\textit{tert}\text{-Butyl octadecyl ether (13\%)}}{CH_3(CH_2)_{15}CH_2CH_2OC(CH_3)_3}$$

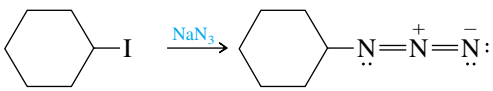
A second factor that can tip the balance in favor of substitution is weak basicity of the nucleophile. Nucleophiles that are less basic than hydroxide react with both primary and secondary alkyl halides to give the product of nucleophilic substitution in high yield. To illustrate, cyanide ion is much less basic than hydroxide and reacts with 2-chlorooctane to give the corresponding alkyl cyanide as the major product.

Cyanide is a weaker base than hydroxide because its conjugate acid HCN (pK_a 9.1) is a stronger acid than water (pK_a15.7).

$$\underset{\text{2-Chlorooctane}}{CH_3\underset{\displaystyle Cl}{\underset{|}{C}}H(CH_2)_5CH_3} \xrightarrow[DMSO]{KCN} \underset{\text{2-Cyanooctane (70\%)}}{CH_3\underset{\displaystyle CN}{\underset{|}{C}}H(CH_2)_5CH_3}$$

The conjugate acid of azide ion is called *hydrazoic acid* (HN_3). It has a pK_a of 4.6, and so is similar to acetic acid in its acidity.

Azide ion ($:\ddot{\overset{-}{N}}{=}\overset{+}{N}{=}\ddot{\overset{-}{N}}:$) is a good nucleophile and an even weaker base than cyanide. It reacts with secondary alkyl halides mainly by substitution:

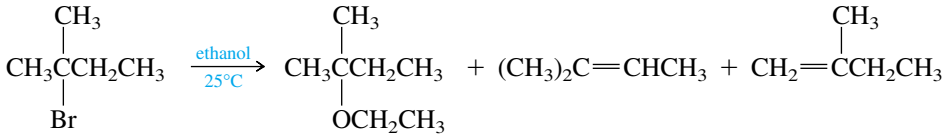


Cyclohexyl iodide Cyclohexyl azide (75%)

Hydrogen sulfide ion HS^-, and anions of the type RS^-, are substantially less basic than hydroxide ion and react with both primary and secondary alkyl halides to give mainly substitution products.

Hydrogen sulfide (pK_a 7.0) is a stronger acid than water (pK_a 15.7). Therefore HS^- is a much weaker base than HO^-.

Tertiary alkyl halides are so sterically hindered to nucleophilic attack that the presence of any anionic Lewis base favors elimination. Usually substitution predominates over elimination in tertiary alkyl halides only when anionic Lewis bases are absent. In the solvolysis of the tertiary bromide 2-bromo-2-methylbutane, for example, the ratio of substitution to elimination is 64:36 in pure ethanol but falls to 1:99 in the presence of 2 M sodium ethoxide.



2-Bromo-2-methylbutane

2-Ethoxy-2-methylbutane (Major product in absence of sodium ethoxide)

2-Methyl-2-butene

2-Methyl-1-butene

(Alkene mixture is major product in presence of sodium ethoxide)

PROBLEM 8.12 Predict the major organic product of each of the following reactions:

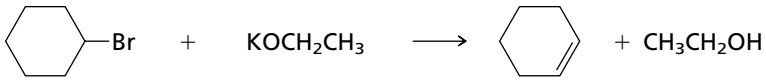
(a) Cyclohexyl bromide and potassium ethoxide

(b) Ethyl bromide and potassium cyclohexanolate

(c) *sec*-Butyl bromide solvolysis in methanol

(d) *sec*-Butyl bromide solvolysis in methanol containing 2 M sodium methoxide

SAMPLE SOLUTION (a) Cyclohexyl bromide is a secondary halide and reacts with alkoxide bases by elimination rather than substitution. The major organic products are cyclohexene and ethanol.



Cyclohexyl bromide Potassium ethoxide Cyclohexene Ethanol

Regardless of the alkyl halide, raising the temperature causes both the rate of substitution and the rate of elimination to increase. The rate of elimination, however, usually increases faster than the rate of substitution, so that at higher temperatures the proportion of elimination products increases at the expense of substitution products.

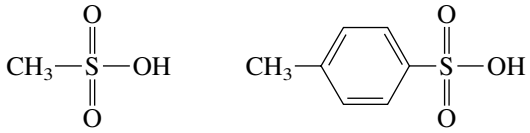
As a practical matter, elimination can always be made to occur quantitatively. Strong bases, especially bulky ones such as *tert*-butoxide ion, react even with primary alkyl halides by an E2 process at elevated temperatures. The more difficult task is to find the set of conditions that promote substitution. In general, the best approach is to choose conditions that favor the S_N2 mechanism—an unhindered substrate, a good nucleophile that is not strongly basic, and the lowest practical temperature consistent with reasonable reaction rates.

Functional group transformations that rely on substitution by the S_N1 mechanism are not as generally applicable as those of the S_N2 type. Hindered substrates are prone to elimination, and there is the possibility of rearrangement when carbocation intermediates are involved. Only in cases in which elimination is impossible are S_N1 reactions used for functional group transformations.

8.14 SULFONATE ESTERS AS SUBSTRATES IN NUCLEOPHILIC SUBSTITUTION

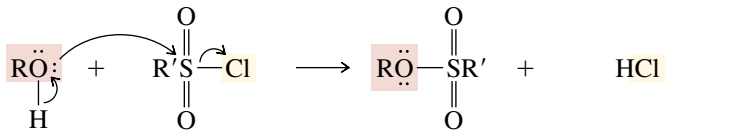
Two kinds of starting materials have been examined in nucleophilic substitution reactions to this point. In Chapter 4 we saw alcohols can be converted to alkyl halides by reaction with hydrogen halides and pointed out that this process is a nucleophilic substitution taking place on the protonated form of the alcohol, with water serving as the leaving group. In the present chapter the substrates have been alkyl halides, and halide ions have been the leaving groups. A few other classes of organic compounds undergo nucleophilic substitution reactions analogous to those of alkyl halides, the most important of these being alkyl esters of sulfonic acids.

Sulfonic acids such as methanesulfonic acid and *p*-toluenesulfonic acid are strong acids, comparable in acidity with sulfuric acid.



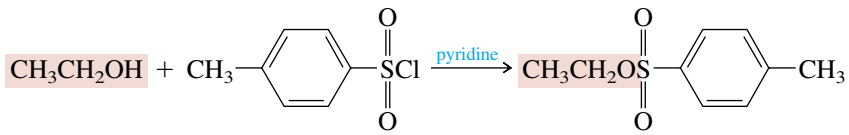
Methanesulfonic acid *p*-Toluenesulfonic acid

Alkyl sulfonates are derivatives of sulfonic acids in which the proton of the hydroxyl group is replaced by an alkyl group. They are prepared by treating an alcohol with the appropriate sulfonyl chloride.



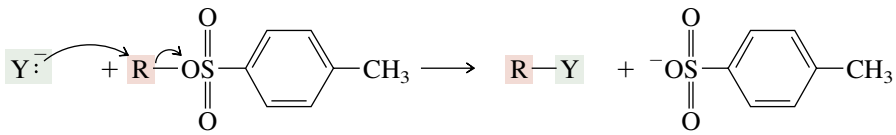
Alcohol Sulfonyl chloride Sulfonate ester Hydrogen chloride

These reactions are usually carried out in the presence of pyridine.



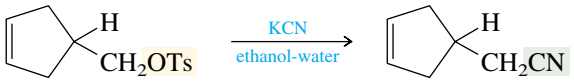
Ethanol *p*-Toluenesulfonyl chloride Ethyl *p*-toluenesulfonate (72%)

Alkyl sulfonate esters resemble alkyl halides in their ability to undergo elimination and nucleophilic substitution.



Nucleophile *p*-Toluenesulfonate ester Product of nucleophilic substitution *p*-Toluenesulfonate anion

The sulfonate esters used most frequently are the *p*-toluenesulfonates. They are commonly known as *tosylates* and given the abbreviated formula ROTs.



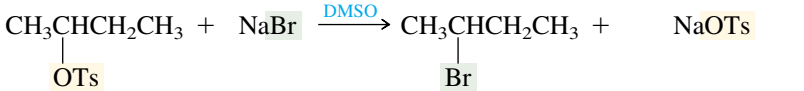
(3-Cyclopentenyl)methyl *p*-toluenesulfonate — 4-(Cyanomethyl)cyclopentene (86%)

p-Toluenesulfonate (TsO^-) is a very good leaving group. As Table 8.8 reveals, alkyl *p*-toluenesulfonates undergo nucleophilic substitution at rates that are even faster than those of alkyl iodides. A correlation of leaving-group abilities with carbon–halogen bond strengths was noted earlier, in Section 8.2. Note also the correlation with the basicity of the leaving group. Iodide is the weakest base among the halide anions and is the best leaving group, fluoride the strongest base and the poorest leaving group. A similar correlation with basicity is seen among oxygen-containing leaving groups. The weaker the base, the better the leaving group. Trifluoromethanesulfonic acid (CF_3SO_2OH) is a much stronger acid than *p*-toluenesulfonic acid, and therefore trifluoromethanesulfonate is a much weaker base than *p*-toluenesulfonate and a much better leaving group.

Trifluoromethanesulfonate esters are called *triflates*.

Notice too that strongly basic leaving groups are absent from Table 8.8. In general, any species that has a K_a less than 1 for its conjugate acid cannot be a leaving group in a nucleophilic substitution. Thus, hydroxide (HO^-) is far too strong a base to be displaced from an alcohol (ROH), and alcohols do not undergo nucleophilic substitution. In strongly acidic media, alcohols are protonated to give alkyloxonium ions, and these do undergo nucleophilic substitution, because the leaving group is a weakly basic water molecule.

Since halides are poorer leaving groups than *p*-toluenesulfonate, alkyl *p*-toluenesulfonates can be converted to alkyl halides by S_N2 reactions involving chloride, bromide, or iodide as the nucleophile.



sec-Butyl *p*-toluenesulfonate — Sodium bromide — *sec*-Butyl bromide (82%) — Sodium *p*-toluenesulfonate

TABLE 8.8 Approximate Relative Leaving-Group Abilities*

Leaving group	Relative rate	Conjugate acid of leaving group	K_a of conjugate acid	pK_a
F^-	10^{-5}	HF	3.5×10^{-4}	3.5
Cl^-	10^0	HCl	10^7	−7
Br^-	10^1	HBr	10^9	−9
I^-	10^2	HI	10^{10}	−10
H_2O	10^1	H_3O^+	55	−1.7
TsO^-	10^5	TsOH	6×10^2	−2.8
$CF_3SO_2O^-$	10^8	CF_3SO_2OH	10^6	−6

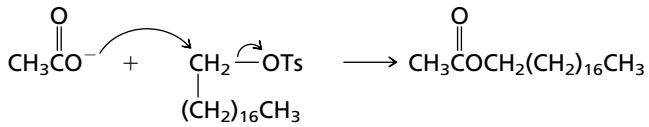
*Values are approximate and vary according to substrate.

PROBLEM 8.13 Write a chemical equation showing the preparation of octadecyl *p*-toluenesulfonate.

PROBLEM 8.14 Write equations showing the reaction of octadecyl *p*-toluenesulfonate with each of the following reagents:

(a) Potassium acetate ($KOCCH_3$, with O double-bonded to C)
(b) Potassium iodide (KI)
(c) Potassium cyanide (KCN)
(d) Potassium hydrogen sulfide (KSH)
(e) Sodium butanethiolate ($NaSCH_2CH_2CH_2CH_3$)

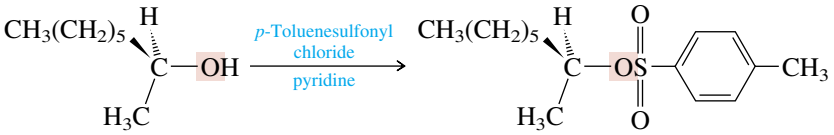
SAMPLE SOLUTION All these reactions of octadecyl *p*-toluenesulfonate have been reported in the chemical literature, and all proceed in synthetically useful yield. You should begin by identifying the nucleophile in each of the parts to this problem. The nucleophile replaces the *p*-toluenesulfonate leaving group in an S_N2 reaction. In part (a) the nucleophile is acetate ion, and the product of nucleophilic substitution is octadecyl acetate.



Acetate ion Octadecyl tosylate Octadecyl acetate

Sulfonate esters are subject to the same limitations as alkyl halides. Competition from elimination needs to be considered when planning a functional group transformation that requires an anionic nucleophile, because tosylates undergo elimination reactions, just as alkyl halides do.

An advantage that sulfonate esters have over alkyl halides is that their preparation from alcohols does not involve any of the bonds to carbon. The alcohol oxygen becomes the oxygen that connects the alkyl group to the sulfonyl group. Thus, the configuration of a sulfonate ester is exactly the same as that of the alcohol from which it was prepared. If we wish to study the stereochemistry of nucleophilic substitution in an optically active substrate, for example, we know that a tosylate ester will have the same configuration and the same optical purity as the alcohol from which it was prepared.



(*S*)-(+)-2-Octanol
$[\alpha]_D^{25}$ +9.9°
(optically pure)

(*S*)-(+)-1-Methylheptyl p-toluenesulfonate
$[\alpha]_D^{25}$ +7.9°
(optically pure)

The same cannot be said about reactions with alkyl halides as substrates. The conversion of optically active 2-octanol to the corresponding halide *does* involve a bond to the stereogenic center, and so the optical purity and absolute configuration of the alkyl halide need to be independently established.

The mechanisms by which sulfonate esters undergo nucleophilic substitution are the same as those of alkyl halides. Inversion of configuration is observed in S_N2 reactions of alkyl sulfonates and predominant inversion accompanied by racemization in S_N1 processes.

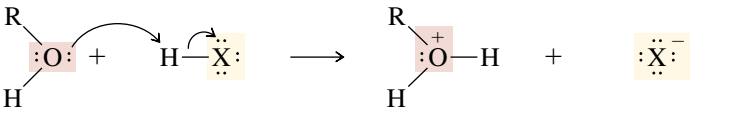
PROBLEM 8.15 The hydrolysis of sulfonate esters of 2-octanol is a stereospecific reaction and proceeds with complete inversion of configuration. Write a structural formula that shows the stereochemistry of the 2-octanol formed by hydrolysis of an optically pure sample of (S)-(+)-1-methylheptyl *p*-toluenesulfonate, identify the product as *R* or *S*, and deduce its specific rotation.

8.15 LOOKING BACK: REACTIONS OF ALCOHOLS WITH HYDROGEN HALIDES

The principles developed in this chapter can be applied to a more detailed examination of the reaction of alcohols with hydrogen halides than was possible when this reaction was first introduced in Chapter 4.

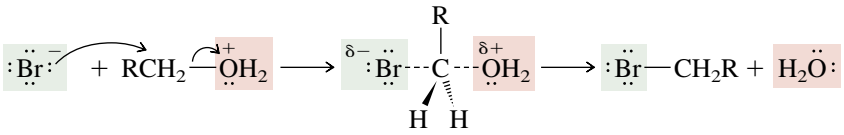
$$\underset{\text{Alcohol}}{ROH} + \underset{\text{Hydrogen halide}}{HX} \longrightarrow \underset{\text{Alkyl halide}}{RX} + \underset{\text{Water}}{H_2O}$$

As pointed out in Chapter 4, the first step in the reaction is proton transfer to the alcohol from the hydrogen halide to yield an alkyloxonium ion. This is an acid-base reaction.



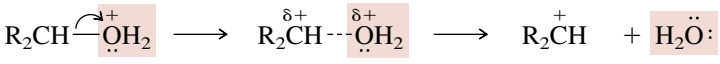
Alcohol (base) | Hydrogen halide (acid) | Alkyloxonium ion (conjugate acid) | Halide ion (conjugate base)

With primary alcohols, the next stage is an S_N2 reaction in which the halide ion, bromide, for example, displays a molecule of water from the alkyloxonium ion.



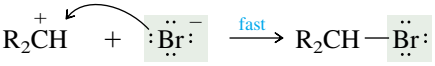
Bromide ion | Primary alkyloxonium ion | S_N2 transition state | Primary alkyl bromide | Water

With secondary and tertiary alcohols, this stage is an S_N1 reaction in which the alkyloxonium ion dissociates to a carbocation and water.



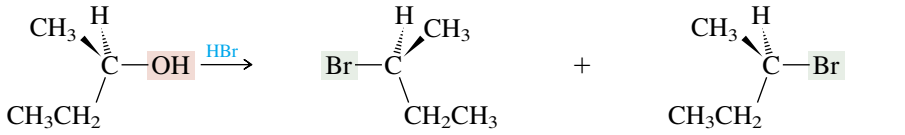
Secondary alkyloxonium ion | S_N1 transition state | Secondary carbocation | Water

Following its formation, the carbocation is captured by halide.



Secondary carbocation | Bromide ion | Secondary alkyl bromide

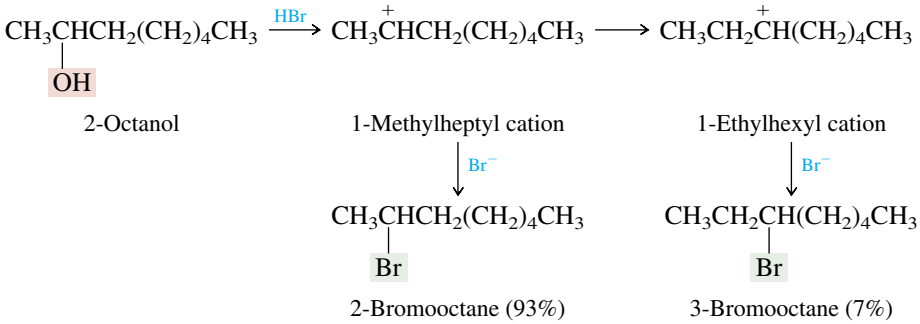
With optically active secondary alcohols the reaction proceeds with predominant, but incomplete, inversion of configuration.



(*R*)-(−)-2-Butanol (*S*)-(+)-2-Bromobutane (87%) (*R*)-(−)-2-Bromobutane (13%)

The few studies that have been carried out with optically active tertiary alcohols indicate that almost complete racemization attends the preparation of tertiary alkyl halides by this method.

Rearrangement can occur, and the desired alkyl halide is sometimes accompanied by an isomeric halide. An example is seen in the case of the secondary alcohol 2-octanol, which yields a mixture of 2- and 3-bromooctane:



PROBLEM 8.16 Treatment of 3-methyl-2-butanol with hydrogen chloride yielded only a trace of 2-chloro-3-methylbutane. An isomeric chloride was isolated in 97% yield. Suggest a reasonable structure for this product.

Unbranched primary alcohols and tertiary alcohols tend to react with hydrogen halides without rearrangement. The alkyloxonium ions from primary alcohols react rapidly with bromide ion, for example, in an S_N2 process without significant development of positive charge at carbon. Tertiary alcohols give tertiary alkyl halides because tertiary carbocations are stable and show little tendency to rearrange.

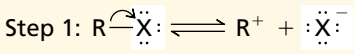
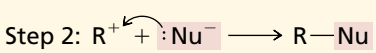
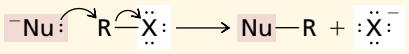
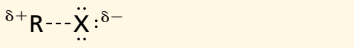
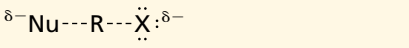
When it is necessary to prepare secondary alkyl halides with assurance that no trace of rearrangement accompanies their formation, the corresponding alcohol is first converted to its *p*-toluenesulfonate ester and this ester is then allowed to react with sodium chloride, bromide, or iodide, as described in Section 8.14.

8.16 SUMMARY

Section 8.1 Nucleophilic substitution is an important reaction type in synthetic organic chemistry because it is one of the main methods for functional group transformations. Examples of synthetically useful nucleophilic substitutions were given in Table 8.1. It is a good idea to return to that table and review its entries now that the details of nucleophilic substitution have been covered.

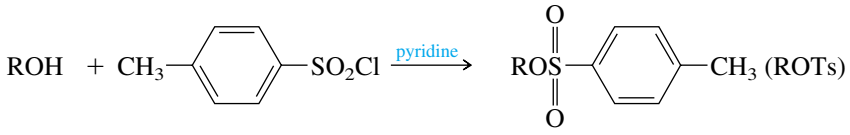
Sections 8.2–8.12 These sections show how a variety of experimental observations led to the proposal of the S_N1 and the S_N2 mechanisms for nucleophilic substitution. Summary Table 8.9 integrates the material in these sections.

TABLE 8.9 Comparison of S_N1 and S_N2 Mechanisms of Nucleophilic Substitution in Alkyl Halides

	S_N1	S_N2
Characteristics of mechanism	Two elementary steps: Step 1:  Step 2:  Ionization of alkyl halide (step 1) is rate-determining. (Section 8.8)	Single step:  Nucleophile displaces leaving group; bonding to the incoming nucleophile accompanies cleavage of the bond to the leaving group. (Sections 8.3 and 8.5)
Rate-determining transition state	 (Section 8.8)	 (Sections 8.3 and 8.5)
Molecularity	Unimolecular (Section 8.8)	Bimolecular (Section 8.3)
Kinetics and rate law	First order: Rate = k[alkyl halide] (Section 8.8)	Second order: Rate = k[alkyl halide][nucleophile] (Section 8.3)
Relative reactivity of halide leaving groups	RI > RBr > RCl ≫ RF (Section 8.2)	RI > RBr > RCl ≫ RF (Section 8.2)
Effect of structure on rate	$R_3CX > R_2CHX > RCH_2X > CH_3X$ Rate is governed by stability of carbocation that is formed in ionization step. Tertiary alkyl halides can react only by the S_N1 mechanism; they never react by the S_N2 mechanism. (Section 8.9)	$CH_3X > RCH_2X > R_2CHX > R_3CX$ Rate is governed by steric effects (crowding in transition state). Methyl and primary alkyl halides can react only by the S_N2 mechanism; they never react by the S_N1 mechanism. (Section 8.6)
Effect of nucleophile on rate	Rate of substitution is independent of both concentration and nature of nucleophile. Nucleophile does not participate until after rate-determining step. (Section 8.8)	Rate depends on both nature of nucleophile and its concentration. (Sections 8.3 and 8.7)
Effect of solvent on rate	Rate increases with increasing polarity of solvent as measured by its dielectric constant ϵ. (Section 8.12)	Polar aprotic solvents give fastest rates of substitution; solvation of $Nu:^-$ is minimal and nucleophilicity is greatest. (Section 8.12)
Stereochemistry	Not stereospecific: racemization accompanies inversion when leaving group is located at a stereogenic center. (Section 8.10)	Stereospecific: 100% inversion of configuration at reaction site. Nucleophile attacks carbon from side opposite bond to leaving group. (Section 8.4)
Potential for rearrangements	Carbocation intermediate capable of rearrangement. (Section 8.11)	No carbocation intermediate; no rearrangement.

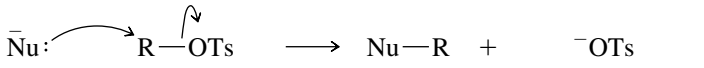
Section 8.13 When nucleophilic substitution is used for synthesis, the competition between substitution and elimination must be favorable. However, *the normal reaction of a secondary alkyl halide with a base as strong or stronger than hydroxide is elimination (E2).* Substitution by the S_N2 mechanism predominates only when the base is weaker than hydroxide or the alkyl halide is primary. Elimination predominates when tertiary alkyl halides react with any anion.

Section 8.14 Nucleophilic substitution can occur with leaving groups other than halide. Alkyl *p*-toluenesulfonates *(tosylates),* which are prepared from alcohols by reaction with *p*-toulenesulfonyl chloride, are often used.



Alcohol *p*-Toluenesulfonyl chloride Alkyl *p*-toluenesulfonate (alkyl tosylate)

Section 8.15 In its ability to act as a leaving group, *p*-toluenesulfonate is comparable to iodide.



Nucleophile Alkyl *p*-toluenesulfonate Substitution product *p*-Toluenesulfonate ion

The reactions of alcohols with hydrogen halides to give alkyl halides (Chapter 4) are nucleophilic substitution reactions of alkyloxonium ions in which water is the leaving group. Primary alcohols react by an S_N2-like displacement of water from the alkyloxonium ion by halide. Secondary and tertiary alcohols give alkyloxonium ions which form carbocations in an S_N1-like process. Rearrangements are possible with secondary alcohols, and substitution takes place with predominant, but not complete, inversion of configuration.

PROBLEMS

8.17 Write the structure of the principal organic product to be expected from the reaction of 1-bromopropane with each of the following:

(a) Sodium iodide in acetone

(b) Sodium acetate ($CH_3\overset{\overset{O}{\|}}{C}ONa$) in acetic acid

(c) Sodium ethoxide in ethanol

(d) Sodium cyanide in dimethyl sulfoxide

(e) Sodium azide in aqueous ethanol

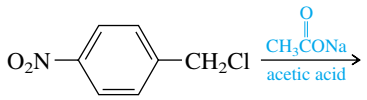
(f) Sodium hydrogen sulfide in ethanol

(g) Sodium methanethiolate ($NaSCH_3$) in ethanol

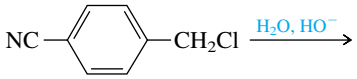
8.18 All the reactions of 1-bromopropane in the preceding problem give the product of nucleophilic substitution in high yield. High yields of substitution products are also obtained in all but one of the analogous reactions using 2-bromopropane as the substrate. In one case, however, 2-bromopropane is converted to propene, especially when the reaction is carried out at elevated temperature (about 55°C). Which reactant is most effective in converting 2-bromopropane to propene?

8.19 Each of the following nucleophilic substitution reactions has been reported in the chemical literature. Many of them involve reactants that are somewhat more complex than those we have dealt with to this point. Nevertheless, you should be able to predict the product by analogy to what you know about nucleophilic substitution in simple systems.

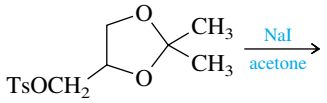
(a) $BrCH_2\overset{\displaystyle O}{\overset{\|}{C}}OCH_2CH_3 \xrightarrow[\text{acetone}]{\text{NaI}}$

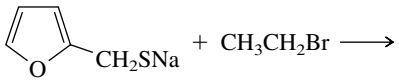
(b) 

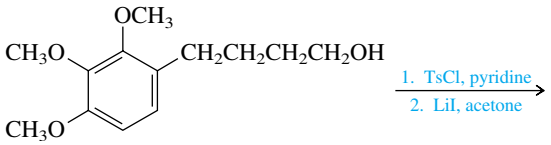
(c) $CH_3CH_2OCH_2CH_2Br \xrightarrow[\text{ethanol–water}]{\text{NaCN}}$

(d) 

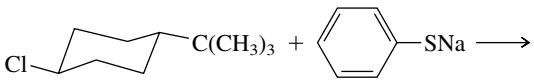
(e) $ClCH_2\overset{\displaystyle O}{\overset{\|}{C}}OC(CH_3)_3 \xrightarrow[\text{acetone–water}]{\text{NaN}_3}$

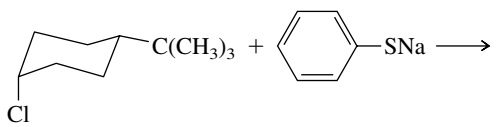
(f) 

(g) 

(h) 

8.20 Each of the reactions shown involves nucleophilic substitution. The product of reaction (a) is an isomer of the product of reaction (b). What kind of isomer? By what mechanism does nucleophilic substitution occur? Write the structural formula of the product of each reaction.

(a) 

(b) 

8.21 Arrange the isomers of molecular formula C_4H_9Cl in order of decreasing rate of reaction with sodium iodide in acetone.

8.22 There is an overall 29-fold difference in reactivity of 1-chlorohexane, 2-chlorohexane, and 3-chlorohexane toward potassium iodide in acetone.

(a) Which one is the most reactive? Why?

(b) Two of the isomers differ by only a factor of 2 in reactivity. Which two are these? Which one is the more reactive? Why?

8.23 In each of the following indicate which reaction will occur faster. Explain your reasoning.

(a) $CH_3CH_2CH_2CH_2Br$ or $CH_3CH_2CH_2CH_2I$ with sodium cyanide in dimethyl sulfoxide

(b) 1-Chloro-2-methylbutane or 1-chloropentane with sodium iodide in acetone

(c) Hexyl chloride or cyclohexyl chloride with sodium azide in aqueous ethanol

(d) Solvolysis of 1-bromo-2,2-dimethylpropane or *tert*-butyl bromide in ethanol

(e) Solvolysis of isobutyl bromide or *sec*-butyl bromide in aqueous formic acid

(f) Reaction of 1-chlorobutane with sodium acetate in acetic acid or with sodium methoxide in methanol

(g) Reaction of 1-chlorobutane with sodium azide or sodium *p*-toluenesulfonate in aqueous ethanol

8.24 Under conditions of photochemical chlorination, $(CH_3)_3CCH_2C(CH_3)_3$ gave a mixture of two monochlorides in a 4:1 ratio. The structures of these two products were assigned on the basis of their S_N1 hydrolysis rates in aqueous ethanol. The major product (compound A) underwent hydrolysis much more slowly than the minor one (compound B). Deduce the structures of compounds A and B.

8.25 The compound KSCN is a source of *thiocyanate* ion.

(a) Write the two most stable Lewis structures for thiocyanate ion and identify the atom in each that bears a formal charge of -1.

(b) Two constitutionally isomeric products of molecular formula C_5H_9NS were isolated in a combined yield of 87% in the reaction shown. (*DMF* stands for *N,N*-dimethylformamide, a polar aprotic solvent.) Suggest reasonable structures for these two compounds.

$$CH_3CH_2CH_2CH_2Br \xrightarrow[DMF]{KSCN}$$

(c) The major product of the reaction cited in (b) constituted 99% of the mixture of isomers. Its structure corresponds to attack by the most polarizable atom of thiocyanate ion on 1-bromobutane. What is this product?

8.26 Reaction of ethyl iodide with triethylamine $[(CH_3CH_2)_3N{:}]$ yields a crystalline compound $C_8H_{20}NI$ in high yield. This compound is soluble in polar solvents such as water but insoluble in nonpolar ones such as diethyl ether. It does not melt below about 200°C. Suggest a reasonable structure for this product.

8.27 Write an equation, clearly showing the stereochemistry of the starting material and the product, for the reaction of (*S*)-1-bromo-2-methylbutane with sodium iodide in acetone. What is the configuration (*R* or *S*) of the product?

8.28 Identify the product in each of the following reactions:

(a) $ClCH_2CH_2\underset{\displaystyle Cl}{\underset{|}{C}}HCH_2CH_3 \xrightarrow[acetone]{NaI\ (1.0\ equiv)} C_5H_{10}ClI$

(b) $BrCH_2CH_2Br + NaSCH_2CH_2SNa \longrightarrow C_4H_8S_2$

(c) $ClCH_2CH_2CH_2CH_2Cl + Na_2S \longrightarrow C_4H_8S$

8.29 Give the mechanistic symbols (S_N1, S_N2, E1, E2) that are most consistent with each of the following statements:

(a) Methyl halides react with sodium ethoxide in ethanol only by this mechanism.

(b) Unhindered primary halides react with sodium ethoxide in ethanol mainly by this mechanism.

(c) When cyclohexyl bromide is treated with sodium ethoxide in ethanol, the major product is formed by this mechanism.

(d) The substitution product obtained by solvolysis of *tert*-butyl bromide in ethanol arises by this mechanism.

(e) In ethanol that contains sodium ethoxide, *tert*-butyl bromide reacts mainly by this mechanism.

(f) These reaction mechanisms represent concerted processes.

(g) Reactions proceeding by these mechanisms are stereospecific.

(h) These reaction mechanisms involve carbocation intermediates.

(i) These reaction mechanisms are the ones most likely to have been involved when the products are found to have a different carbon skeleton from the substrate.

(j) Alkyl iodides react faster than alkyl bromides in reactions that proceed by these mechanisms.

8.30 Outline an efficient synthesis of each of the following compounds from the indicated starting material and any necessary organic or inorganic reagents:

(a) Cyclopentyl cyanide from cyclopentane

(b) Cyclopentyl cyanide from cyclopentene

(c) Cyclopentyl cyanide from cyclopentanol

(d) $NCCH_2CH_2CN$ from ethyl alcohol

(e) Isobutyl iodide from isobutyl chloride

(f) Isobutyl iodide from *tert*-butyl chloride

(g) Isopropyl azide from isopropyl alcohol

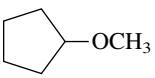
(h) Isopropyl azide from 1-propanol

(i) (*S*)-*sec*-Butyl azide from (*R*)-*sec*-butyl alcohol

(j) (*S*)-$CH_3CH_2\underset{\displaystyle SH}{\underset{|}{C}}HCH_3$ from (*R*)-*sec*-butyl alcohol

8.31 Select the combination of alkyl bromide and potassium alkoxide that would be the most effective in the syntheses of the following ethers:

(a) $CH_3OC(CH_3)_3$

(b) 

(c) $(CH_3)_3CCH_2OCH_2CH_3$

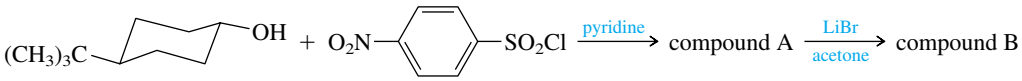
8.32 (*Note to the student:* This problem previews an important aspect of Chapter 9 and is well worth attempting in order to get a head start on the material presented there.)

Alkynes of the type $RC{\equiv}CH$ may be prepared by nucleophilic substitution reactions in which one of the starting materials is sodium acetylide ($Na^+ :\bar{C}{\equiv}CH$).

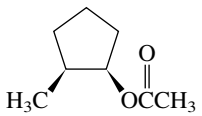
(a) Devise a method for the preparation of $CH_3CH_2C{\equiv}CH$ from sodium acetylide and any necessary organic or inorganic reagents.

(b) Given the information that K_a for acetylene ($HC{\equiv}CH$) is 10^{-26} (pK_a 26), comment on the scope of this preparative procedure with respect to R in $RC{\equiv}CH$. Could you prepare $(CH_3)_2CHC{\equiv}CH$ or $(CH_3)_3CC{\equiv}CH$ in good yield by this method?

8.33 Give the structures, including stereochemistry, of compounds A and B in the following sequence of reactions:



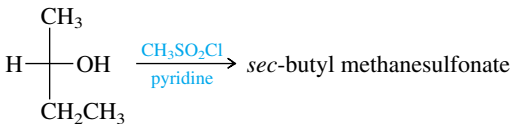
8.34 (a) Suggest a reasonable series of synthetic transformations for converting *trans*-2-methylcyclopentanol to *cis*-2-methylcyclopentyl acetate.



cis-2-Methylcyclopentyl acetate

(b) How could you prepare *cis*-2-methylcyclopentyl acetate from 1-methylcyclopentanol?

8.35 Optically pure (*S*)-(+)-2-butanol was converted to its methanesulfonate ester according to the reaction shown.



(a) Write the Fischer projection of the *sec*-butyl methanesulfonate formed in this reaction.

(b) The *sec*-butyl methanesulfonate in part (a) was treated with $NaSCH_2CH_3$ to give a product having an optical rotation α_D of $-25°$. Write the Fischer projection of this product. By what mechanism is it formed? What is its absolute configuration (*R* or *S*)?

(c) When treated with PBr_3 , optically pure (*S*)-(+)-2-butanol gave 2-bromobutane having an optical rotation $\alpha_D = -38°$. This bromide was then allowed to react with $NaSCH_2CH_3$ to give a product having an optical rotation α_D of $+23°$. Write the Fischer projection for (−)-2-bromobutane and specify its configuration as *R* or *S*. Does the reaction of 2-butanol with PBr_3 proceed with predominant inversion or retention of configuration?

(d) What is the optical rotation of optically pure 2-bromobutane?

8.36 In a classic experiment, Edward Hughes (a colleague of Ingold's at University College, London) studied the rate of racemization of 2-iodooctane by sodium iodide in acetone and compared it with the rate of incorporation of radioactive iodine into 2-iodooctane.

$$RI + [I^*]^- \longrightarrow RI^* + I^-$$

(I* = radioactive iodine)

How will the rate of racemization compare with the rate of incorporation of radioactivity if

(a) Each act of exchange proceeds stereospecifically with retention of configuration?

(b) Each act of exchange proceeds stereospecifically with inversion of configuration?

(c) Each act of exchange proceeds in a stereorandom manner, in which retention and inversion of configuration are equally likely?

8.37 The ratio of elimination to substitution is exactly the same (26% elimination) for 2-bromo-2-methylbutane and 2-iodo-2-methylbutane in 80% ethanol/20% water at 25°C.

(a) By what mechanism does substitution most likely occur in these compounds under these conditions?

(b) By what mechanism does elimination most likely occur in these compounds under these conditions?

(c) Which substrate undergoes substitution faster?

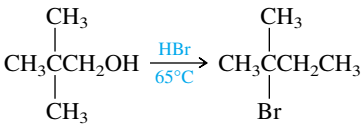
(d) Which substrate undergoes elimination faster?

(e) What two substitution products are formed from each substrate?

(f) What two elimination products are formed from each substrate?

(g) Why do you suppose the ratio of elimination to substitution is the same for the two substrates?

8.38 The reaction of 2,2-dimethyl-1-propanol with HBr is very slow and gives 2-bromo-2-methylpropane as the major product.



Give a mechanistic explanation for these observations.

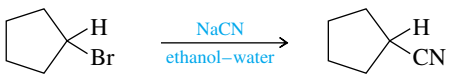
8.39 Solvolysis of 2-bromo-2-methylbutane in acetic acid containing potassium acetate gave three products. Identify them.

8.40 Solvolysis of 1,2-dimethylpropyl *p*-toluenesulfonate in acetic acid (75°C) yields five different products: three are alkenes and two are substitution products. Suggest reasonable structures for these five products.

8.41 Solution A was prepared by dissolving potassium acetate in methanol. Solution B was prepared by adding potassium methoxide to acetic acid. Reaction of methyl iodide either with solution A or with solution B gave the same major product. Why? What was this product?

8.42 If the temperature is not kept below 25°C during the reaction of primary alcohols with *p*-toluenesulfonyl chloride in pyridine, it is sometimes observed that the isolated product is not the desired alkyl *p*-toluenesulfonate but is instead the corresponding alkyl chloride. Suggest a mechanistic explanation for this observation.

8.43 The reaction of cyclopentyl bromide with sodium cyanide to give cyclopentyl cyanide



Cyclopentyl bromide Cyclopentyl cyanide

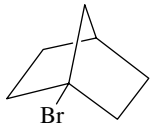
proceeds faster if a small amount of sodium iodide is added to the reaction mixture. Can you suggest a reasonable mechanism to explain the catalytic function of sodium iodide?

8.44 Illustrate the stereochemistry associated with unimolecular nucleophilic substitution by constructing molecular models of *cis*-4-*tert*-butylcyclohexyl bromide, its derived carbocation, and the alcohols formed from it by hydrolysis under S_N1 conditions.

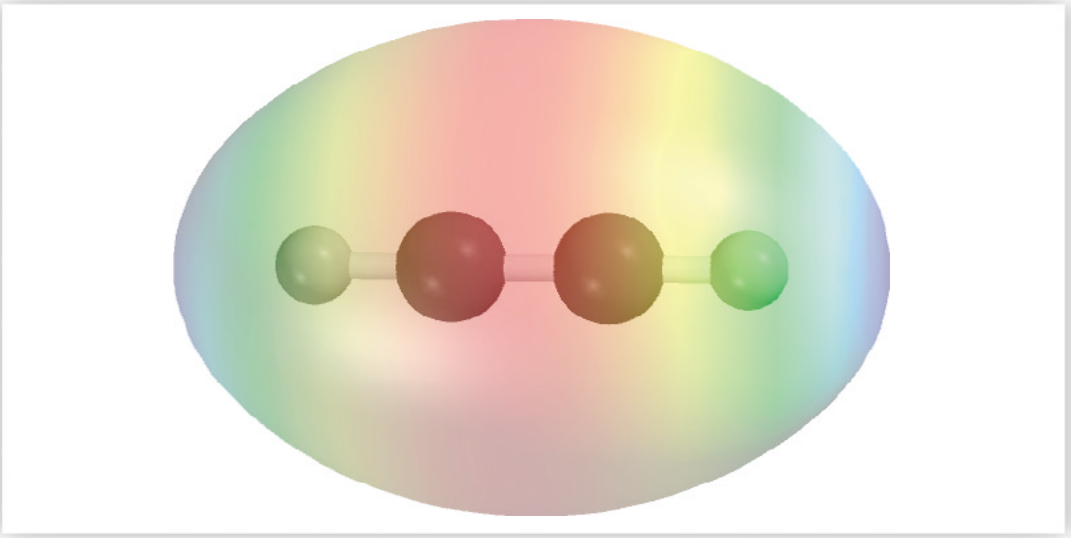
8.45 Given the molecular formula $C_6H_{11}Br$, construct a molecular model of the isomer that is a primary alkyl bromide yet relatively unreactive toward bimolecular nucleophilic substitution.

8.46 Cyclohexyl bromide is less reactive than noncyclic secondary alkyl halides toward S_N2 substitution. Construct a molecular model of cyclohexyl bromide and suggest a reason for its low reactivity.

8.47 1-Bromobicyclo[2.2.1]heptane (the structure of which is shown) is exceedingly unreactive toward nucleophilic substitution by either the S_N1 or S_N2 mechanism. Use molecular models to help you understand why.



1-Bromobicyclo[2.2.1]heptane



CHAPTER 9

ALKYNES

Hydrocarbons that contain a carbon–carbon triple bond are called **alkynes.** Noncyclic alkynes have the molecular formula C_nH_{2n-2}. *Acetylene* (HC≡CH) is the simplest alkyne. We call compounds that have their triple bond at the end of a carbon chain (RC≡CH) *monosubstituted,* or *terminal, alkynes.* Disubstituted alkynes (RC≡CR′) are said to have *internal* triple bonds. You will see in this chapter that a carbon–carbon triple bond is a functional group, reacting with many of the same reagents that react with the double bonds of alkenes.

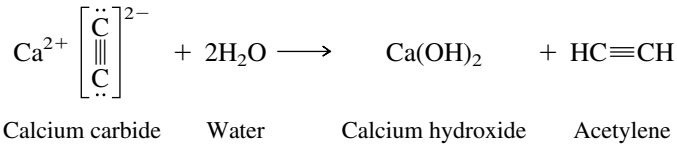
The most distinctive aspect of the chemistry of acetylene and terminal alkynes is their acidity. As a class, compounds of the type RC≡CH are the most acidic of all simple hydrocarbons. The structural reasons for this property, as well as the ways in which it is used to advantage in chemical synthesis, are important elements of this chapter.

9.1 SOURCES OF ALKYNES

Acetylene was first characterized by the French chemist P. E. M. Berthelot in 1862 and did not command much attention until its large-scale preparation from calcium carbide in the last decade of the nineteenth century stimulated interest in industrial applications. In the first stage of that synthesis, limestone and coke, a material rich in elemental carbon obtained from coal, are heated in an electric furnace to form calcium carbide.

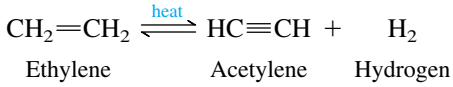
$$\underset{\substack{\text{Calcium oxide}\\ \text{(from limestone)}}}{CaO} + \underset{\substack{\text{Carbon}\\ \text{(from coke)}}}{3C} \xrightarrow{1800\text{–}2100^\circ C} \underset{\text{Calcium carbide}}{CaC_2} + \underset{\text{Carbon monoxide}}{CO}$$

Calcium carbide is the calcium salt of the doubly negative carbide ion ($:\bar{C}\equiv\bar{C}:$). Carbide dianion is strongly basic and reacts with water to form acetylene:



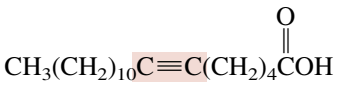
PROBLEM 9.1 Use curved arrows to show how calcium carbide reacts with water to give acetylene.

Beginning in the middle of the twentieth century, alternative methods of acetylene production became practical. One of these is based on the dehydrogenation of ethylene.

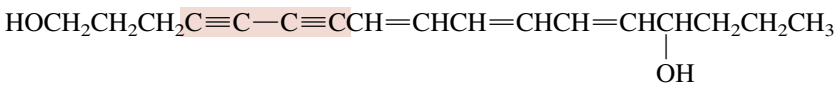


The reaction is endothermic, and the equilibrium favors ethylene at low temperatures but shifts to favor acetylene above 1150°C. Indeed, at very high temperatures most hydrocarbons, even methane, are converted to acetylene. Acetylene has value not only by itself but is also the starting material from which higher alkynes are prepared.

Natural products that contain carbon–carbon triple bonds are numerous. Two examples are *tariric acid,* from the seed fat of a Guatemalan plant, and *cicutoxin,* a poisonous substance isolated from water hemlock.



Tariric acid



Cicutoxin

Diacetylene (HC≡C—C≡CH) has been identified as a component of the hydrocarbon-rich atmospheres of Uranus, Neptune, and Pluto. It is also present in the atmospheres of Titan and Triton, satellites of Saturn and Neptune, respectively.

9.2 NOMENCLATURE

In naming alkynes the usual IUPAC rules for hydrocarbons are followed, and the suffix *-ane* is replaced by *-yne.* Both acetylene and ethyne are acceptable IUPAC names for HC≡CH. The position of the triple bond along the chain is specified by number in a manner analogous to alkene nomenclature.

PROBLEM 9.2 Write structural formulas and give the IUPAC names for all the alkynes of molecular formula C_5H_8.

When the —C≡CH group is named as a substituent, it is designated as an *ethynyl* group.

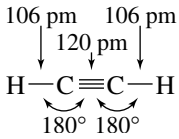
9.3 PHYSICAL PROPERTIES OF ALKYNES

Alkynes resemble alkanes and alkenes in their physical properties. They share with these other hydrocarbons the properties of low density and low water-solubility. They are slightly more polar and generally have slightly higher boiling points than the corresponding alkanes and alkenes.

Examples of physical properties of alkynes are given in Appendix 1.

9.4 STRUCTURE AND BONDING IN ALKYNES: *sp* HYBRIDIZATION

Acetylene is linear, with a carbon–carbon bond distance of 120 pm and carbon–hydrogen bond distances of 106 pm.

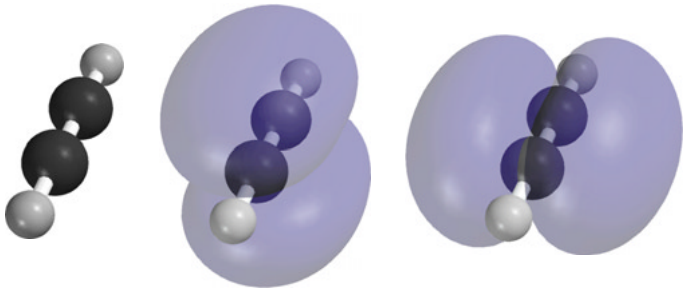


Linear geometries characterize the H—C≡C—C and C—C≡C—C units of terminal and internal triple bonds, respectively as well. This linear geometry is responsible for the relatively small number of known *cycloalkynes*. Figure 9.1 shows a molecular model for cyclononyne in which the bending of the C—C≡C—C unit is clearly evident. Angle strain destabilizes cycloalkynes to the extent that cyclononyne is the smallest one that is stable enough to be stored for long periods. The next smaller one, cyclooctyne, has been isolated, but is relatively reactive and polymerizes on standing.

In spite of the fact that few cycloalkynes occur naturally, they gained recent attention when it was discovered that some of them hold promise as anticancer drugs. (See the boxed essay *Natural and "Designed" Enediyne Antibiotics* following this section.)

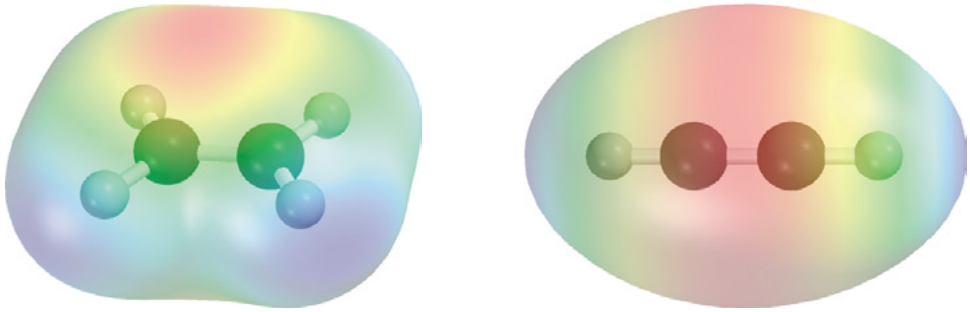
An *sp* hybridization model for the carbon–carbon triple bond was developed in Section 1.18 and is reviewed for acetylene in Figure 9.2. Figure 9.3 maps the electrostatic potential in ethylene and acetylene and shows how the second π bond in acetylene causes a band of high electron density to encircle the molecule.

FIGURE 9.1 Molecular model of cyclononyne, showing bending of bond angles associated with triply bonded carbons. This model represents the structure obtained when the strain energy is minimized according to molecular mechanics and closely matches the structure determined experimentally. Notice too the degree to which the staggering of bonds on adjacent atoms governs the overall shape of the ring.



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

FIGURE 9.2 The carbon atoms of acetylene are connected by a σ + π + π triple bond. Both carbon atoms are *sp*-hybridized, and each is bonded to a hydrogen by an *sp*–1*s* σ bond. The σ component of the triple bond arises by *sp*–*sp* overlap. Each carbon has two *p* orbitals, the axes of which are perpendicular to each other. One π bond is formed by overlap of the *p* orbitals shown in (*b*), the other by overlap of the *p* orbitals shown in (*c*). Each π bond contains two electrons.



Ethylene Acetylene

FIGURE 9.3 Electrostatic potential maps of ethylene and acetylene. The region of highest negative charge (red) is associated with the π bonds and lies between the two carbons in both. This electron-rich region is above and below the plane of the molecule in ethylene. Because acetylene has two π bonds, its band of high electron density encircles the molecule.

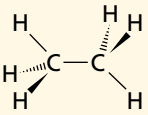
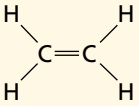
At this point, it's useful to compare some structural features of alkanes, alkenes, and alkynes. Table 9.1 gives some of the most fundamental ones. To summarize, as we progress through the series in the order ethane → ethylene → acetylene:

1. The geometry at carbon changes from tetrahedral → trigonal planar → linear.
2. The C—C and C—H bonds become shorter and stronger.
3. The acidity of the C—H bonds increases.

All of these trends can be accommodated by the orbital hybridization model. The bond angles are characteristic for the sp^3, sp^2, and *sp* hybridization states of carbon and don't require additional comment. The bond distances, bond strengths, and acidities are related to the *s* character in the orbitals used for bonding. *s* Character is a simple concept, being nothing more than the percentage of the hybrid orbital contributed by an *s* orbital. Thus, an sp^3 orbital has one quarter *s* character and three quarters *p,* an sp^2 orbital has one third *s* and two thirds *p,* and an *sp* orbital one half *s* and one half *p.* We then use this information to analyze how various qualities of the hybrid orbital reflect those of its *s* and *p* contributors.

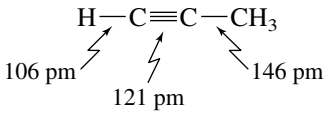
Take C—H bond distance and bond strength, for example. Recalling that an electron in a 2*s* orbital is, on average, closer to the nucleus and more strongly held than an

TABLE 9.1 Structural Features of Ethane, Ethylene, and Acetylene

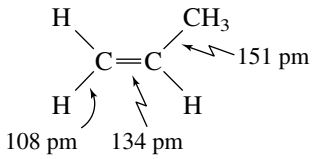
Feature	Ethane	Ethylene	Acetylene
Systematic name	Ethane	Ethene	Ethyne
Molecular formula	C_2H_6	C_2H_4	C_2H_2
Structural formula			H—C≡C—H
C—C bond distance, pm	153	134	120
C—H bond distance, pm	111	110	106
H—C—C bond angles	111.0°	121.4°	180°
C—C bond dissociation energy, kJ/mol (kcal/mol)	368 (88)	611 (146)	820 (196)
C—H bond dissociation energy, kJ/mol (kcal/mol)	410 (98)	452 (108)	536 (128)
Hybridization of carbon	sp^3	sp^2	*sp*
s character in C—H bonds	25%	33%	50%
Approximate acidity as measured by K_a (pK_a)	10^{-62} (62)	10^{-45} (45)	10^{-26} (26)

electron in a 2*p* orbital, it follows that an electron in an orbital with more *s* character will be closer to the nucleus and more strongly held than an electron in an orbital with less *s* character. Thus, when an *sp* orbital of carbon overlaps with a hydrogen 1*s* orbital to give a C—H σ bond, the electrons are held more strongly and the bond is stronger and shorter than electrons in a bond between hydrogen and sp^2-hybridized carbon. Similar reasoning holds for the shorter C—C bond distance of acetylene compared to ethylene, although here the additional π bond in acetylene is also a factor.

The pattern is repeated in higher alkynes as shown when comparing propyne and propene. The bonds to the *sp*-hybridized carbons of propyne are shorter than the corresponding bonds to the sp^2 hybridized carbons of propene.



Propyne



Propene


How do the bond distances of molecular models of propene and propyne compare with the experimental values?

An easy way to keep track of the effect of the *s* character of carbon is to associate it with electronegativity. As the *s* character of carbon increases, so does that carbon's apparent electronegativity (the electrons in the bond involving that orbital are closer to carbon). The hydrogens in C—H bonds behave as if they are attached to an increasingly more electronegative carbon in the series ethane → ethylene → acetylene.

PROBLEM 9.3 How do bond distances and bond strengths change with electronegativity in the series NH_3, H_2O, and HF?

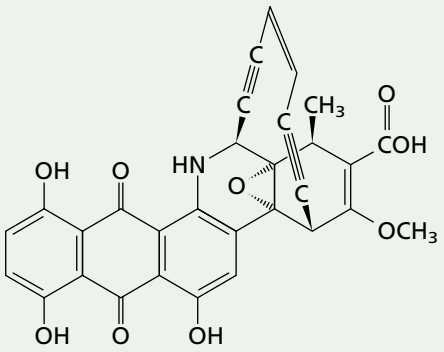
The property that most separates acetylene from ethane and ethylene is its acidity. It, too, can be explained on the basis of the greater electronegativity of *sp*-hybridized carbon compared with sp^3 *and* sp^2.

NATURAL AND "DESIGNED" ENEDIYNE ANTIBIOTICS

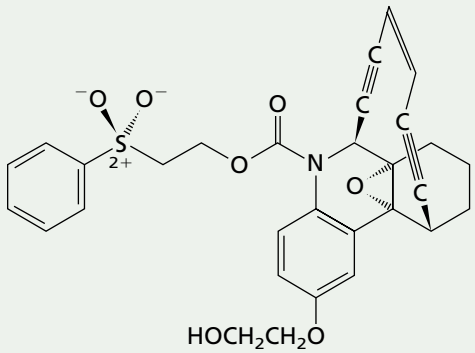
Beginning in the 1980s, research directed toward the isolation of new drugs derived from natural sources identified a family of tumor-inhibitory antibiotic substances characterized by novel structures containing a C≡C—C═C—C≡C unit as part of a 9- or 10-membered ring. With one double bond and two triple bonds (*-ene* + *di-* + *-yne*), these compounds soon became known as *enediyne* antibiotics. The simplest member of the class is *dynemicin A*;* most of the other enediynes have even more complicated structures.

Enediynes hold substantial promise as anticancer drugs because of their potency and selectivity. Not only do they inhibit cell growth, they have a greater tendency to kill cancer cells than they do normal cells. The mechanism by which enediynes act involves novel chemistry unique to the C≡C—C═C—C≡C unit, which leads to a species that cleaves DNA and halts tumor growth.

The history of drug development has long been based on naturally occurring substances. Often, however, compounds that might be effective drugs are produced by plants and microorganisms in such small amounts that their isolation from natural sources is not practical. If the structure is relatively simple, chemical synthesis provides an alternative source of the drug, making it more available at a lower price. Equally important, chemical synthesis, modification, or both can improve the effectiveness of a drug. Building on the enediyne core of dynemicin A, for example, Professor Kyriacos C. Nicolaou and his associates at the Scripps Research Institute and the University of California at San Diego have prepared a simpler analog that is both more potent and more selective than dynemicin A. It is a "designed enediyne" in that its structure was conceived on the basis of chemical reasoning so as to carry out its biochemical task. The designed enediyne offers the additional advantage of being more amenable to large-scale synthesis.



Dynemicin A

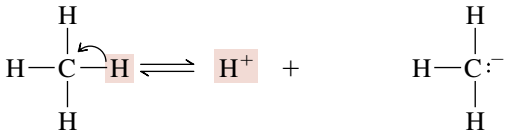


"Designed" enediyne

**Learning By Modeling* contains a model of dynemicin A, which shows that the C≡C—C═C—C≡C unit can be incorporated into the molecule without much angle strain.

9.5 ACIDITY OF ACETYLENE AND TERMINAL ALKYNES

The C—H bonds of hydrocarbons show little tendency to ionize, and alkanes, alkenes, and alkynes are all very weak acids. The ionization constant K_a for methane, for example, is too small to be measured directly but is estimated to be about 10^{-60} (pK_a 60).



Methane Proton Methide anion (a *carbanion*)

The conjugate base of a hydrocarbon is called a **carbanion.** It is an anion in which the negative charge is borne by carbon. Since it is derived from a very weak acid, a carbanion such as $^{-}{:}CH_3$ is an exceptionally strong base.

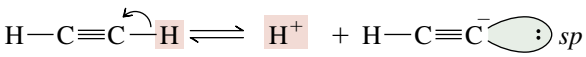
In general, the ability of an atom to bear a negative charge is related to its electronegativity. Both the electronegativity of an atom X and the acidity of H—X increase across a row in the periodic table.

CH_4	<	NH_3	<	H_2O	<	HF
Methane		Ammonia		Water		Hydrogen fluoride
$K_a \approx 10^{-60}$		$\approx 10^{-36}$		1.8×10^{-16}		3.5×10^{-4}
$pK_a \approx 60$		≈ 36		15.7		3.2
(weakest acid)						(strongest acid)

Using the relationship from the preceding section that the effective electronegativity of carbon in a C—H bond increases with its *s* character ($sp^3 < sp^2 < sp$), the order of hydrocarbon acidity behaves much like the preceding methane, ammonia, water, hydrogen fluoride series.

CH_3CH_3	<	$CH_2{=}CH_2$	<	$HC{\equiv}CH$
Ethane		Ethylene		Acetylene
$K_a \approx 10^{-62}$		$\approx 10^{-45}$		$= 10^{-26}$
$pK_a \approx 62$		≈ 45		$= 26$
(weakest acid)				(strongest acid)

The acidity increases as carbon becomes more electronegative. Ionization of acetylene gives an anion in which the unshared electron pair occupies an orbital with 50% *s* character.



Acetylene Proton Acetylide ion

In the corresponding ionizations of ethylene and ethane, the unshared pair occupies an orbital with 33% (sp^2) and 25% (sp^3) *s* character, respectively.

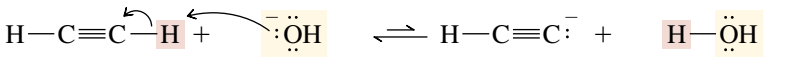
Terminal alkynes (RC≡CH) resemble acetylene in acidity.

$(CH_3)_3CC{\equiv}CH$ $\qquad K_a = 3 \times 10^{-26}$ $(pK_a = 25.5)$

3,3-Dimethyl-1-butyne

The electrostatic potential map of $(CH_3)_3CC{\equiv}CH$ on *Learning By Modeling* clearly shows the greater positive character of the acetylenic hydrogen relative to the methyl hydrogens.

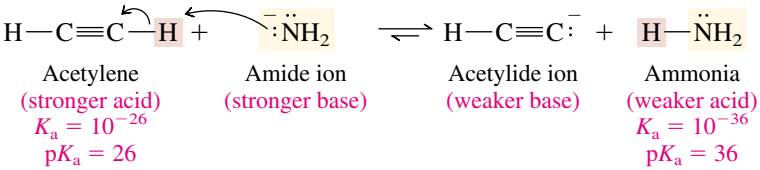
Although acetylene and terminal alkynes are far stronger acids than other hydrocarbons, we must remember that they are, nevertheless, very weak acids—much weaker than water and alcohols, for example. Hydroxide ion is too weak a base to convert acetylene to its anion in meaningful amounts. The position of the equilibrium described by the following equation lies overwhelmingly to the left:



Acetylene	Hydroxide ion	Acetylide ion	Water
(weaker acid)	(weaker base)	(stronger base)	(stronger acid)
$K_a = 10^{-26}$			$K_a = 1.8 \times 10^{-16}$
$pK_a = 26$			$pK_a = 15.7$

Because acetylene is a far weaker acid than water and alcohols, these substances are not suitable solvents for reactions involving acetylide ions. Acetylide is instantly converted to acetylene by proton transfer from compounds that contain hydroxyl groups.

Amide ion is a much stronger base than acetylide ion and converts acetylene to its conjugate base quantitatively.



Solutions of sodium acetylide (HC≡CNa) may be prepared by adding *sodium amide* ($NaNH_2$) to acetylene in liquid ammonia as the solvent. Terminal alkynes react similarly to give species of the type RC≡CNa.

PROBLEM 9.4 Complete each of the following equations to show the conjugate acid and the conjugate base formed by proton transfer between the indicated species. Use curved arrows to show the flow of electrons, and specify whether the position of equilibrium lies to the side of reactants or products.

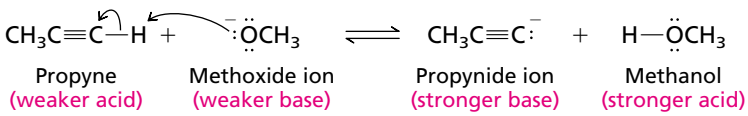
(a) $CH_3C{\equiv}CH + {}^{-}:\ddot{O}CH_3 \rightleftharpoons$

(b) $HC{\equiv}CH + H_2\ddot{C}CH_3 \rightleftharpoons$

(c) $CH_2{=}CH_2 + {}^{-}:\ddot{N}H_2 \rightleftharpoons$

(d) $CH_3C{\equiv}CCH_2OH + {}^{-}:\ddot{N}H_2 \rightleftharpoons$

SAMPLE SOLUTION (a) The equation representing the acid–base reaction between propyne and methoxide ion is:



Alcohols are stronger acids than acetylene, and so the position of equilibrium lies to the left. Methoxide ion is not a strong enough base to remove a proton from acetylene.

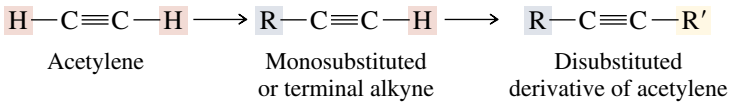
Anions of acetylene and terminal alkynes are nucleophilic and react with methyl and primary alkyl halides to form carbon–carbon bonds by nucleophilic substitution. Some useful applications of this reaction will be discussed in the following section.

9.6 PREPARATION OF ALKYNES BY ALKYLATION OF ACETYLENE AND TERMINAL ALKYNES

Organic synthesis makes use of two major reaction types:

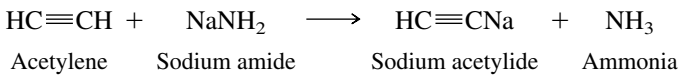
1. Functional group transformations
2. Carbon–carbon bond-forming reactions

Both strategies are applied to the preparation of alkynes. In this section we shall see how to prepare alkynes while building longer carbon chains. By attaching alkyl groups to acetylene, more complex alkynes can be prepared.

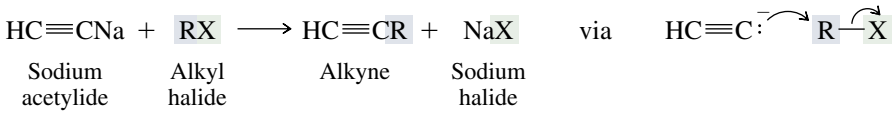


Reactions that attach alkyl groups to molecular fragments are called **alkylation** reactions. One way in which alkynes are prepared is by alkylation of acetylene.

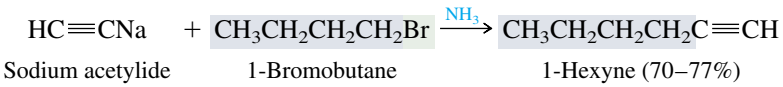
Alkylation of acetylene involves a sequence of two separate operations. In the first one, acetylene is converted to its conjugate base by treatment with sodium amide.



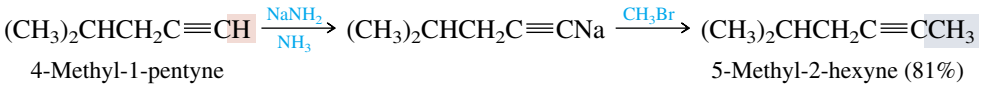
Next, an alkyl halide (the *alkylating agent*) is added to the solution of sodium acetylide. Acetylide ion acts as a nucleophile, displacing halide from carbon and forming a new carbon–carbon bond. Substitution occurs by an S_N2 mechanism.



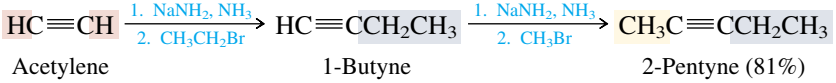
The synthetic sequence is usually carried out in liquid ammonia as the solvent. Alternatively, diethyl ether or tetrahydrofuran may be used.



An analogous sequence using terminal alkynes as starting materials yields alkynes of the type RC≡CR′.



Dialkylation of acetylene can be achieved by carrying out the sequence twice.



As in other nucleophilic substitution reactions, alkyl *p*-toluenesulfonates may be used in place of alkyl halides.

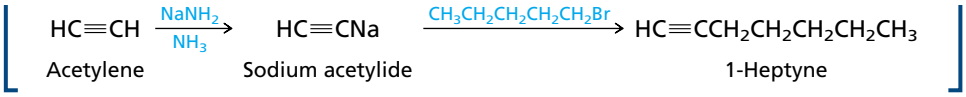
PROBLEM 9.5 Outline efficient syntheses of each of the following alkynes from acetylene and any necessary organic or inorganic reagents:

(a) 1-Heptyne

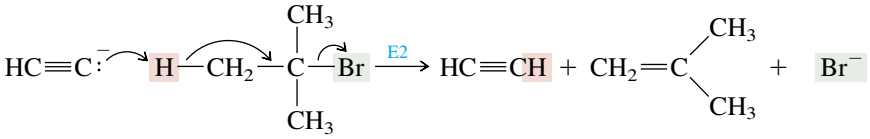
(b) 2-Heptyne

(c) 3-Heptyne

SAMPLE SOLUTION (a) An examination of the structural formula of 1-heptyne reveals it to have a pentyl group attached to an acetylene unit. Alkylation of acetylene, by way of its anion, with a pentyl halide is a suitable synthetic route to 1-heptyne.



The major limitation to this reaction is that synthetically acceptable yields are obtained only with methyl halides and primary alkyl halides. Acetylide anions are very basic, much more basic than hydroxide, for example, and react with secondary and tertiary alkyl halides by elimination.



The desired S_N2 substitution pathway is observed only with methyl and primary alkyl halides.

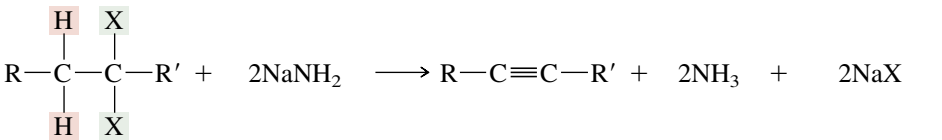
PROBLEM 9.6 Which of the alkynes of molecular formula C_5H_8 can be prepared in good yield by alkylation or dialkylation of acetylene? Explain why the preparation of the other C_5H_8 isomers would not be practical.

A second strategy for alkyne synthesis, involving functional group transformation reactions, is described in the following section.

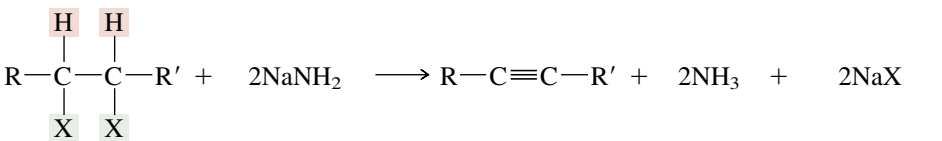
9.7 PREPARATION OF ALKYNES BY ELIMINATION REACTIONS

Just as it is possible to prepare alkenes by dehydrohalogenation of alkyl halides, so may alkynes be prepared by a *double dehydrohalogenation* of dihaloalkanes. The dihalide may be a **geminal dihalide,** one in which both halogens are on the same carbon, or it may be a **vicinal dihalide,** one in which the halogens are on adjacent carbons.

Double dehydrohalogenation of a geminal dihalide



Double dehydrohalogenation of a vicinal dihalide



The most frequent applications of these procedures are in the preparation of terminal alkynes. Since the terminal alkyne product is acidic enough to transfer a proton to amide anion, one equivalent of base in addition to the two equivalents required for double

dehydrohalogenation is needed. Adding water or acid after the reaction is complete converts the sodium salt to the corresponding alkyne.

Double dehydrohalogenation of a geminal dihalide

$$(CH_3)_3CCH_2CHCl_2 \xrightarrow[NH_3]{3NaNH_2} (CH_3)_3CC{\equiv}CNa \xrightarrow{H_2O} (CH_3)_3CC{\equiv}CH$$

1,1-Dichloro-3,3-dimethylbutane — Sodium salt of alkyne product (not isolated) — 3,3-Dimethyl-1-butyne (56–60%)

Double dehydrohalogenation of a vicinal dihalide

$$CH_3(CH_2)_7CHCH_2Br \xrightarrow[NH_3]{3NaNH_2} CH_3(CH_2)_7C{\equiv}CNa \xrightarrow{H_2O} CH_3(CH_2)_7C{\equiv}CH$$

(Br on the CH)

1,2-Dibromodecane — Sodium salt of alkyne product (not isolated) — 1-Decyne (54%)

Double dehydrohalogenation to form terminal alkynes may also be carried out by heating geminal and vicinal dihalides with potassium *tert*-butoxide in dimethyl sulfoxide.

PROBLEM 9.7 Give the structures of three isomeric dibromides that could be used as starting materials for the preparation of 3,3-dimethyl-1-butyne.

Since vicinal dihalides are prepared by addition of chlorine or bromine to alkenes (Section 6.14), alkenes, especially terminal alkenes, can serve as starting materials for the preparation of alkynes as shown in the following example:

$$(CH_3)_2CHCH{=}CH_2 \xrightarrow{Br_2} (CH_3)_2CHCHCH_2Br \xrightarrow[2.\ H_2O]{1.\ NaNH_2,\ NH_3} (CH_3)_2CHC{\equiv}CH$$

(Br on the CH)

3-Methyl-1-butene — 1,2-Dibromo-3-methylbutane — 3-Methyl-1-butyne (52%)

PROBLEM 9.8 Show, by writing an appropriate series of equations, how you could prepare propyne from each of the following compounds as starting materials. You may use any necessary organic or inorganic reagents.

(a) 2-Propanol
(b) 1-Propanol
(c) Isopropyl bromide
(d) 1,1-Dichloroethane
(e) Ethyl alcohol

SAMPLE SOLUTION (a) Since we know that we can convert propene to propyne by the sequence of reactions

$$CH_3CH{=}CH_2 \xrightarrow{Br_2} CH_3CHCH_2Br \xrightarrow[2.\ H_2O]{1.\ NaNH_2,\ NH_3} CH_3C{\equiv}CH$$

(Br on the CH)

Propene — 1,2-Dibromopropane — Propyne

all that remains to completely describe the synthesis is to show the preparation of propene from 2-propanol. Acid-catalyzed dehydration is suitable.

$$(CH_3)_2CHOH \xrightarrow[heat]{H^+} CH_3CH{=}CH_2$$

2-Propanol — Propene

9.8 REACTIONS OF ALKYNES

We have already discussed one important chemical property of alkynes, the acidity of acetylene and terminal alkynes. In the remaining sections of this chapter several other reactions of alkynes will be explored. Most of them will be similar to reactions of alkenes. Like alkenes, alkynes undergo addition reactions. We'll begin with a reaction familiar to us from our study of alkenes, namely, catalytic hydrogenation.

9.9 HYDROGENATION OF ALKYNES

The conditions for hydrogenation of alkynes are similar to those employed for alkenes. In the presence of finely divided platinum, palladium, nickel, or rhodium, two molar equivalents of hydrogen add to the triple bond of an alkyne to yield an alkane.

$$\underset{\text{Alkyne}}{RC{\equiv}CR'} + \underset{\text{Hydrogen}}{2H_2} \xrightarrow{\text{Pt, Pd, Ni, or Rh}} \underset{\text{Alkane}}{RCH_2CH_2R'}$$

$$\underset{\text{4-Methyl-1-hexyne}}{CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2C{\equiv}CH} + \underset{\text{Hydrogen}}{2H_2} \xrightarrow{\text{Ni}} \underset{\text{3-Methylhexane (77\%)}}{CH_3CH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2CH_2CH_3}$$

PROBLEM 9.9 Write a series of equations showing how you could prepare octane from acetylene and any necessary organic and inorganic reagents.

Substituents affect the heats of hydrogenation of alkynes in the same way they affect alkenes. Alkyl groups release electrons to *sp*-hybridized carbon, stabilizing the alkyne and decreasing the heat of hydrogenation.

	$CH_3CH_2C{\equiv}CH$	$CH_3C{\equiv}CCH_3$
	1-Butyne	2-Butyne
$-\Delta H°$ (hydrogenation)	292 kJ/mol (69.9 kcal/mol)	275 kJ/mol (65.6 kcal/mol)

Alkenes are intermediates in the hydrogenation of alkynes to alkanes.

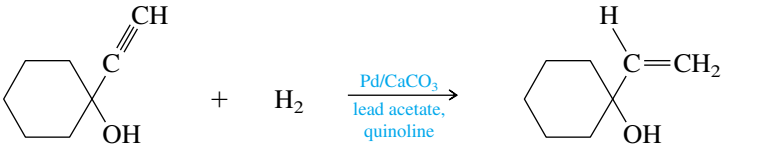
$$\underset{\text{Alkyne}}{RC{\equiv}CR'} \xrightarrow[\text{catalyst}]{H_2} \underset{\text{Alkene}}{RCH{=}CHR'} \xrightarrow[\text{catalyst}]{H_2} \underset{\text{Alkane}}{RCH_2CH_2R'}$$

The heat of hydrogenation of an alkyne is greater than twice the heat of hydrogenation of the derived alkene. The first hydrogenation step of an alkyne is therefore more exothermic than the second.

Noting that alkenes are intermediates in the hydrogenation of alkynes leads us to consider the possibility of halting hydrogenation at the alkene stage. If partial hydrogenation of an alkyne could be achieved, it would provide a useful synthesis of alkenes. In practice it is a simple matter to convert alkynes to alkenes by hydrogenation in the presence of specially developed catalysts. The one most frequently used is the **Lindlar catalyst,** a palladium on calcium carbonate combination to which lead acetate and quinoline have been added. Lead acetate and quinoline partially deactivate ("poison") the catalyst, making it a poor catalyst for alkene hydrogenation while retaining its ability to catalyze the addition of hydrogen to alkynes.

The high energy of acetylene is released when it is mixed with oxygen and burned in an *oxyacetylene torch.* The temperature of the flame (about 3000°C) exceeds that of any other hydrocarbon fuel and is higher than the melting point of iron (1535°C).

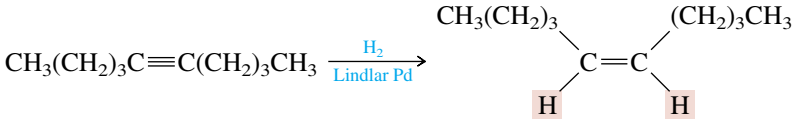
The structure of quinoline is shown on page 430.



1-Ethynylcyclohexanol Hydrogen 1-Vinylcyclohexanol (90–95%)

In subsequent equations, we will not specify the components of the Lindlar palladium catalyst in detail but will simply write "Lindlar Pd" over the reaction arrow.

Hydrogenation of alkynes to alkenes yields the cis (or *Z*) alkene by syn addition to the triple bond.

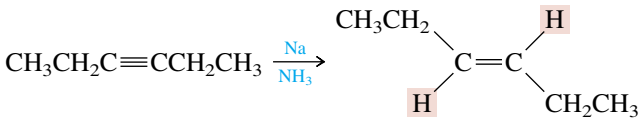


5-Decyne (*Z*)-5-Decene (87%)

PROBLEM 9.10 Oleic acid and stearic acid are naturally occurring compounds, which can be isolated from various fats and oils. In the laboratory, each can be prepared by hydrogenation of a compound known as *stearolic acid,* which has the formula $CH_3(CH_2)_7C{\equiv}C(CH_2)_7CO_2H$. Oleic acid is obtained by hydrogenation of stearolic acid over Lindlar palladium; stearic acid is obtained by hydrogenation over platinum. What are the structures of oleic acid and stearic acid?

9.10 METAL–AMMONIA REDUCTION OF ALKYNES

A useful alternative to catalytic partial hydrogenation for converting alkynes to alkenes is reduction by a Group I metal (lithium, sodium, or potassium) in liquid ammonia. The unique feature of metal–ammonia reduction is that it converts alkynes to trans (or *E*) alkenes whereas catalytic hydrogenation yields cis (or *Z*) alkenes. Thus, from the same alkyne one can prepare either a cis or a trans alkene by choosing the appropriate reaction conditions.



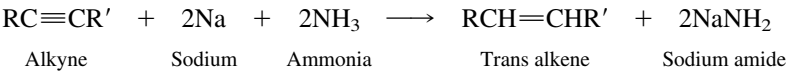
3-Hexyne (*E*)-3-Hexene (82%)

PROBLEM 9.11 Sodium–ammonia reduction of stearolic acid (see Problem 9.10) yields a compound known as *elaidic acid.* What is the structure of elaidic acid?

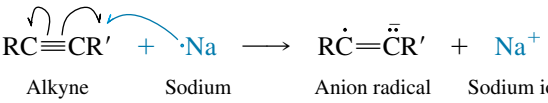
PROBLEM 9.12 Suggest efficient syntheses of (*E*)- and (*Z*)-2-heptene from propyne and any necessary organic or inorganic reagents.

The stereochemistry of metal–ammonia reduction of alkynes differs from that of catalytic hydrogenation because the mechanisms of the two reactions are different. The mechanism of hydrogenation of alkynes is similar to that of catalytic hydrogenation of alkenes (Sections 6.1 and 6.3). A mechanism for metal–ammonia reduction of alkynes is outlined in Figure 9.4.

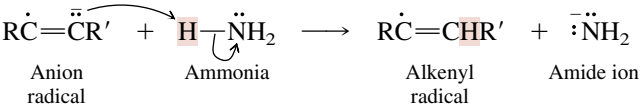
Overall Reaction:



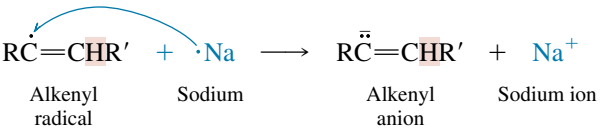
Step 1: Electron transfer from sodium to the alkyne. The product is an anion radical.



Step 2: The anion radical is a strong base and abstracts a proton from ammonia.



Step 3: Electron transfer to the alkenyl radical.



Step 4: Proton transfer from ammonia converts the alkenyl anion to an alkene.

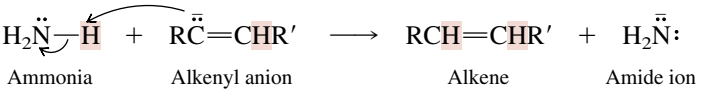
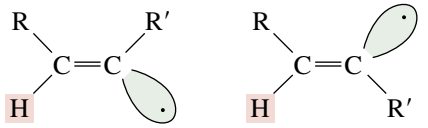


FIGURE 9.4 Mechanism of the sodium–ammonia reduction of an alkyne.

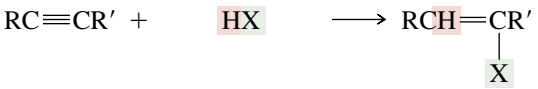
The mechanism includes two single-electron transfers (steps 1 and 3) and two proton transfers (steps 2 and 4). Experimental evidence indicates that step 2 is rate-determining, and it is believed that the observed trans stereochemistry reflects the distribution of the two stereoisomeric alkenyl radical intermediates formed in this step.



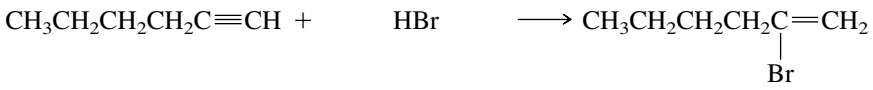
The more stable (*E*)-alkenyl radical, in which the alkyl groups R and R′ are trans to each other, is formed faster than its *Z* stereoisomer. Steps 3 and 4, which follow, are fast, and the product distribution is determined by the *E*–*Z* ratio of radicals produced in step 2.

9.11 ADDITION OF HYDROGEN HALIDES TO ALKYNES

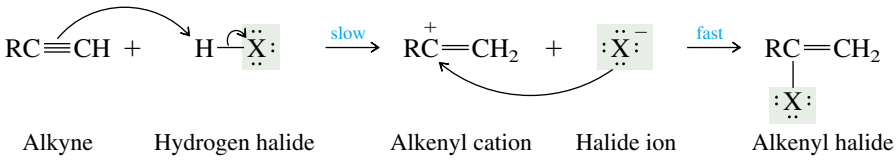
Alkynes react with many of the same electrophilic reagents that add to the carbon–carbon double bond of alkenes. Hydrogen halides, for example, add to alkynes to form alkenyl halides.



The regioselectivity of addition follows Markovnikov's rule. A proton adds to the carbon that has the greater number of hydrogens, and halide adds to the carbon with the fewer hydrogens.



When formulating a mechanism for the reaction of alkynes with hydrogen halides, we could propose a process analogous to that of electrophilic addition to alkenes in which the first step is formation of a carbocation and is rate-determining. The second step according to such a mechanism would be nucleophilic capture of the carbocation by a halide ion.



Evidence from a variety of sources, however, indicates that alkenyl cations (also called *vinylic cations*) are much less stable than simple alkyl cations, and their involvement in these additions has been questioned. For example, although electrophilic addition of hydrogen halides to alkynes occurs more slowly than the corresponding additions to alkenes, the difference is not nearly as great as the difference in carbocation stabilities would suggest.

Furthermore, kinetic studies reveal that electrophilic addition of hydrogen halides to alkynes follows a rate law that is third-order overall and second-order in hydrogen halide.

$$\text{Rate} = k[\text{alkyne}][\text{HX}]^2$$

This third-order rate dependence suggests a termolecular transition state, one that involves two molecules of the hydrogen halide. Figure 9.5 depicts such a termolecular process using curved arrow notation to show the flow of electrons, and dashed-line notation to

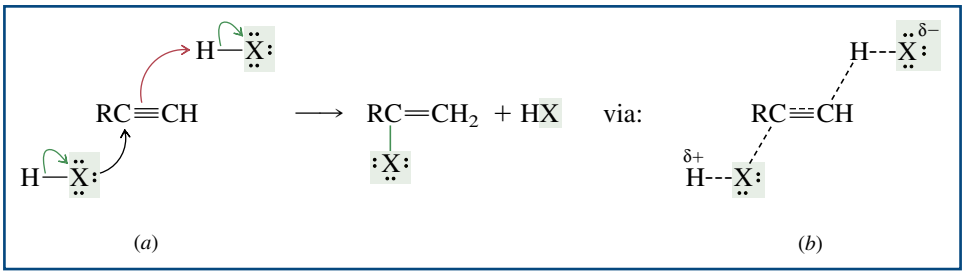
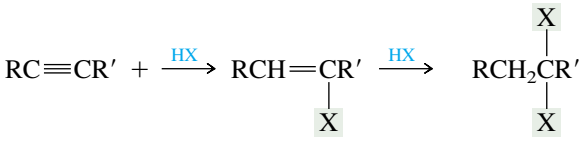


FIGURE 9.5 (*a*), Curved arrow notation and (*b*) transition-state representation for electrophilic addition of a hydrogen halide HX to an alkyne.

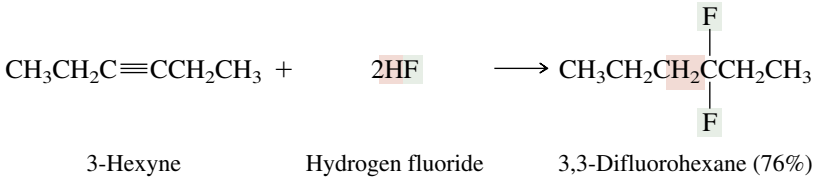
For further discussion of this topic, see the article "The Electrophilic Addition to Alkynes" in the November 1993 edition of the *Journal of Chemical Education* (p. 873). Additional commentary appeared in the November 1996 issue.

indicate the bonds being made and broken at the transition state. This mechanism, called Ad_E3 for *addition-electrophilic-termolecular,* avoids the formation of a very unstable alkenyl cation intermediate by invoking nucleophilic participation by the halogen at an early stage. Nevertheless, since Markovnikov's rule is observed, it seems likely that some degree of positive character develops at carbon and controls the regioselectivity of addition.

In the presence of excess hydrogen halide, geminal dihalides are formed by sequential addition of two molecules of hydrogen halide to the carbon–carbon triple bond.



The hydrogen halide adds to the initially formed alkenyl halide in accordance with Markovnikov's rule. Overall, both protons become bonded to the same carbon and both halogens to the adjacent carbon.



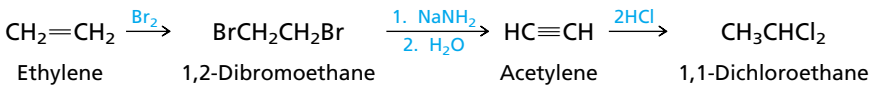
PROBLEM 9.13 Write a series of equations showing how you could prepare 1,1-dichloroethane from

(a) Ethylene

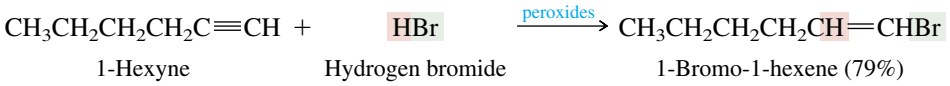
(b) Vinyl chloride (CH_2=CHCl)

(c) 1,1-Dibromoethane

SAMPLE SOLUTION (a) Reasoning backward, we recognize 1,1-dichloroethane as the product of addition of two molecules of hydrogen chloride to acetylene. Thus, the synthesis requires converting ethylene to acetylene as a key feature. As described in Section 9.7, this may be accomplished by conversion of ethylene to a vicinal dihalide, followed by double dehydrohalogenation. A suitable synthesis based on this analysis is as shown:

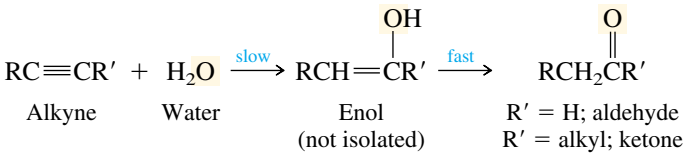


Hydrogen bromide (but not hydrogen chloride or hydrogen iodide) adds to alkynes by a free-radical mechanism when peroxides are present in the reaction mixture. As in the free-radical addition of hydrogen bromide to alkenes (Section 6.8), a regioselectivity opposite to Markovnikov's rule is observed.



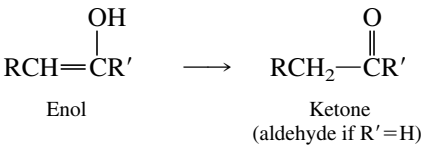
9.12 HYDRATION OF ALKYNES

By analogy to the hydration of alkenes, hydration of an alkyne is expected to yield an alcohol. The kind of alcohol, however, would be of a special kind, one in which the hydroxyl group is a substituent on a carbon–carbon double bond. This type of alcohol is called an **enol** (the double bond suffix *-ene* plus the alcohol suffix *-ol*). An important property of enols is their rapid isomerization to aldehydes or ketones under the conditions of their formation.

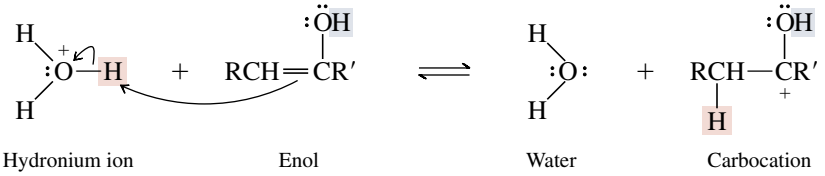


The process by which enols are converted to aldehydes or ketones is called *keto–enol isomerism* (or *keto–enol tautomerism*) and proceeds by the sequence of proton transfers shown in Figure 9.6. Proton transfer to the double bond of an enol occurs readily because the carbocation that is produced is a very stable one. The positive charge on carbon is stabilized by electron release from oxygen and may be represented in resonance terms as shown on the following page.

Overall Reaction:



Step 1: The enol is formed in aqueous acidic solution. The first step of its transformation to a ketone is proton transfer to the carbon–carbon double bond.



Step 2: The carbocation transfers a proton from oxygen to a water molecule, yielding a ketone

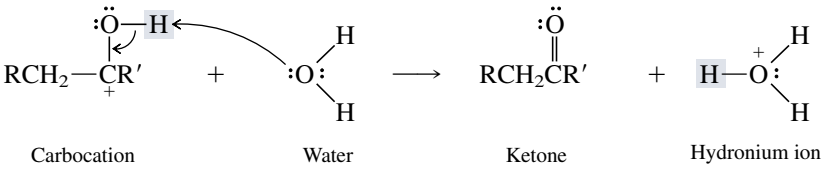
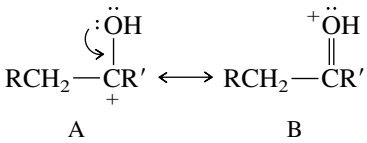


FIGURE 9.6 Conversion of an enol to a ketone takes place by way of two solvent-mediated proton transfers. A proton is transferred to carbon in the first step, then removed from oxygen in the second.



A B

Delocalization of an oxygen lone pair stabilizes the cation. All the atoms in B have octets of electrons, making it a more stable structure than A. Only six electrons are associated with the positively charged carbon in A.

PROBLEM 9.14 Give the structure of the enol formed by hydration of 2-butyne, and write a series of equations showing its conversion to its corresponding ketone isomer.

In general, ketones are more stable than their enol precursors and are the products actually isolated when alkynes undergo acid-catalyzed hydration. The standard method for alkyne hydration employs aqueous sulfuric acid as the reaction medium and mercury(II) sulfate or mercury(II) oxide as a catalyst.

Mercury(II) sulfate and mercury(II) oxide are also known as *mercuric* sulfate and oxide, respectively.

4-Octyne 4-Octanone (89%)

Hydration of alkynes follows Markovnikov's rule; terminal alkynes yield methyl-substituted ketones.

1-Octyne 2-Octanone (91%)

PROBLEM 9.15 Show by a series of equations how you could prepare 2-octanone from acetylene and any necessary organic or inorganic reagents. How could you prepare 4-octanone?

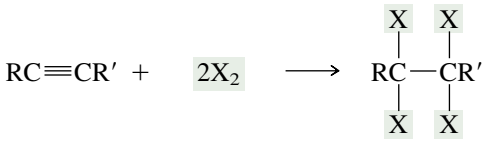
Because of the regioselectivity of alkyne hydration, acetylene is the only alkyne structurally capable of yielding an aldehyde under these conditions.

Acetylene Water Vinyl alcohol (not isolated) Acetaldehyde

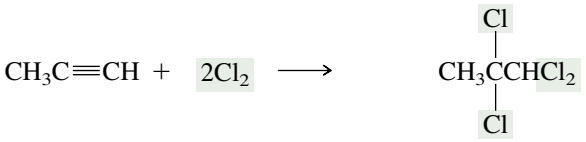
At one time acetaldehyde was prepared on an industrial scale by this method. Modern methods involve direct oxidation of ethylene and are more economical.

9.13 ADDITION OF HALOGENS TO ALKYNES

Alkynes react with chlorine and bromine to yield tetrahaloalkanes. Two molecules of the halogen add to the triple bond.

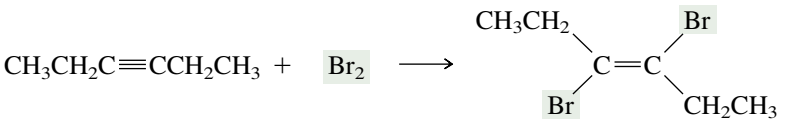


Alkyne | Halogen (chlorine or bromine) | Tetrahaloalkane



Propyne | Chlorine | 1,1,2,2-Tetrachloropropane (63%)

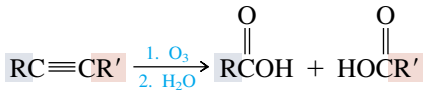
A dihaloalkene is an intermediate and is the isolated product when the alkyne and the halogen are present in equimolar amounts. The stereochemistry of addition is anti.

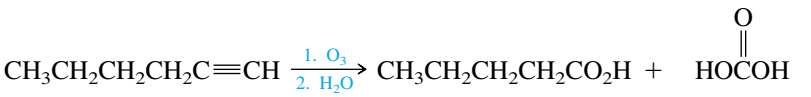


3-Hexyne | Bromine | (*E*)-3,4-Dibromo-3-hexene (90%)

9.14 OZONOLYSIS OF ALKYNES

Carboxylic acids are produced when alkynes are subjected to ozonolysis.





1-Hexyne | Pentanoic acid (51%) | Carbonic acid

Recall that when carbonic acid is formed as a reaction product, it dissociates to carbon dioxide and water.

Ozonolysis is sometimes used as a tool in structure determination. By identifying the carboxylic acids produced, we can deduce the structure of the alkyne. As with many other chemical methods of structure determination, however, it has been superseded by spectroscopic methods.

PROBLEM 9.16 A certain hydrocarbon had the molecular formula $C_{16}H_{26}$ and contained two triple bonds. Ozonolysis gave $CH_3(CH_2)_4CO_2H$ and $HO_2CCH_2CH_2CO_2H$ as the only products. Suggest a reasonable structure for this hydrocarbon.

9.15 SUMMARY

Section 9.1 **Alkynes** are hydrocarbons that contain a carbon–carbon *triple bond*. Simple alkynes having no other functional groups or rings have the general formula C_nH_{2n-2}. Acetylene is the simplest alkyne.

Section 9.2 Alkynes are named in much the same way as alkenes, using the suffix *-yne* instead of *-ene*.

4,4-Dimethyl-2-pentyne

Section 9.3 The physical properties (boiling point, solubility in water, dipole moment) of alkynes resemble those of alkanes and alkenes.

Section 9.4 Acetylene is linear and alkynes have a linear geometry of their X—C≡C—Y units. The carbon–carbon triple bond in alkynes is composed of a σ and two π components. The triply bonded carbons are *sp*-hybridized. The σ component of the triple bond contains two electrons in an orbital generated by the overlap of *sp*-hybridized orbitals on adjacent carbons. Each to these carbons also has two 2*p* orbitals, which overlap in pairs so as to give two π orbitals, each of which contains two electrons.

Section 9.5 Acetylene and terminal alkynes are more *acidic* than other hydrocarbons. They have a K_a's for ionization of approximately 10^{-26}, compared with about 10^{-45} for alkenes and about 10^{-60} for alkanes. Sodium amide is a strong enough base to remove a proton from acetylene or a terminal alkyne, but sodium hydroxide is not.

$$\underset{\text{1-Butyne}}{CH_3CH_2C{\equiv}CH} + \underset{\text{Sodium amide}}{NaNH_2} \longrightarrow \underset{\text{Sodium 1-butynide}}{CH_3CH_2C{\equiv}CNa} + \underset{\text{Ammonia}}{NH_3}$$

Sections 9.6–9.7 Table 9.2 summarizes the methods for preparing alkynes.

Section 9.8 Like alkenes, alkynes undergo addition reactions.

Sections 9.9–9.10 Table 9.3 summarizes reactions that reduce alkynes to alkenes and alkanes.

Sections 9.11–9.13 Table 9.4 summarizes electrophilic addition to alkynes.

Section 9.14 Carbon–carbon triple bonds can be cleaved by ozonolysis. The cleavage products are carboxylic acids.

$$\underset{\text{2-Hexyne}}{CH_3CH_2CH_2C{\equiv}CCH_3} \xrightarrow[2.\ H_2O]{1.\ O_3} \underset{\text{Butanoic acid}}{CH_3CH_2CH_2\overset{\overset{O}{\|}}{C}OH} + \underset{\text{Acetic acid}}{HO\overset{\overset{O}{\|}}{C}CH_3}$$

PROBLEMS

9.17 Write structural formulas and give the IUPAC names for all the alkynes of molecular formula C_6H_{10}.

9.18 Provide the IUPAC name for each of the following alkynes:

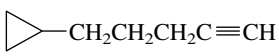
(a) $CH_3CH_2CH_2C{\equiv}CH$

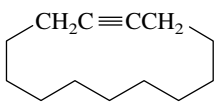
(b) $CH_3CH_2C{\equiv}CCH_3$

(c) $CH_3C{\equiv}C\underset{\displaystyle CH_3}{\underset{|}{C}}HCH(CH_3)_2$

TABLE 9.2 Preparation of Alkynes

Reaction (section) and comments	General equation and specific example
Alkylation of acetylene and terminal alkynes (Section 9.6) The acidity of acetylene and terminal alkynes permits them to be converted to their conjugate bases on treatment with sodium amide. These anions are good nucleophiles and react with methyl and primary alkyl halides to form carbon–carbon bonds. Secondary and tertiary alkyl halides cannot be used, because they yield only elimination products under these conditions.	$RC{\equiv}CH + NaNH_2 \longrightarrow RC{\equiv}CNa + NH_3$ Alkyne; Sodium amide; Sodium alkynide; Ammonia $RC{\equiv}CNa + R'CH_2X \longrightarrow RC{\equiv}CCH_2R' + NaX$ Sodium alkynide; Primary alkyl halide; Alkyne; Sodium halide $(CH_3)_3CC{\equiv}CH \xrightarrow[2.\ CH_3I]{1.\ NaNH_2,\ NH_3} (CH_3)_3CC{\equiv}CCH_3$ 3,3-Dimethyl-1-butyne; 4,4-Dimethyl-2-pentyne (96%)
Double dehydrohalogenation of geminal dihalides (Section 9.7) An E2 elimination reaction of a geminal dihalide yields an alkenyl halide. If a strong enough base is used, sodium amide, for example, a second elimination step follows the first and the alkenyl halide is converted to an alkyne.	$RCH(X)CHR'(X) + 2NaNH_2 \longrightarrow RC{\equiv}CR' + 2NaX$ Geminal dihalide; Sodium amide; Alkyne; Sodium halide $(CH_3)_3CCH_2CHCl_2 \xrightarrow[2.\ H_2O]{1.\ 3NaNH_2,\ NH_3} (CH_3)_3CC{\equiv}CH$ 1,1-Dichloro-3,3-dimethylbutane; 3,3-Dimethyl-1-butyne (56–60%)
Double dehydrohalogenation of vicinal dihalides (Section 9.7) Dihalides in which the halogens are on adjacent carbons undergo two elimination processes analogous to those of geminal dihalides.	$RCH(X)CHR'(X) + 2NaNH_2 \longrightarrow RC{\equiv}CR' + 2NaX$ Vicinal dihalide; Sodium amide; Alkyne; Sodium halide $CH_3CH_2CH(Br)CH_2Br \xrightarrow[2.\ H_2O]{1.\ 3NaNH_2,\ NH_3} CH_3CH_2C{\equiv}CH$ 1,2-Dibromobutane; 1-Butyne (78–85%)

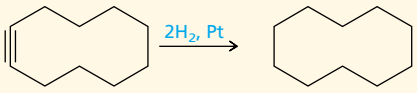
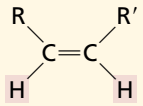
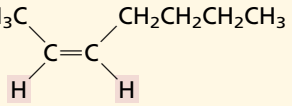
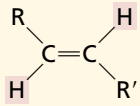
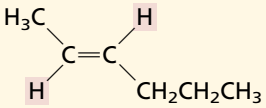
(d) 

(e) 

(f) $CH_3CH_2CH_2CH_2CH(C{\equiv}CCH_3)CH_2CH_2CH_2CH_2CH_3$

(g) $(CH_3)_3CC{\equiv}CC(CH_3)_3$

TABLE 9.3 Conversion of Alkynes to Alkenes and Alkanes

Reaction (section) and comments	General equation and specific example
Hydrogenation of alkynes to alkanes (Section 9.9) Alkynes are completely hydrogenated, yielding alkanes, in the presence of the customary metal hydrogenation catalysts.	$RC{\equiv}CR' + 2H_2 \xrightarrow{\text{metal catalyst}} RCH_2CH_2R'$ Alkyne — Hydrogen — Alkane  $2H_2$, Pt Cyclodecyne — Cyclodecane (71%)
Hydrogenation of alkynes to alkenes (Section 9.9) Hydrogenation of alkynes may be halted at the alkene stage by using special catalysts. Lindlar palladium is the metal catalyst employed most often. Hydrogenation occurs with syn stereochemistry and yields a cis alkene.	$RC{\equiv}CR' + H_2 \xrightarrow{\text{Lindlar Pd}}$  Alkyne — Hydrogen — Cis alkene $CH_3C{\equiv}CCH_2CH_2CH_2CH_3 \xrightarrow[\text{Lindlar Pd}]{H_2}$  2-Heptyne — *cis*-2-Heptene (59%)
Metal–ammonia reduction (Section 9.10) Group I metals—sodium is the one usually employed—in liquid ammonia as the solvent convert alkynes to trans alkenes. The reaction proceeds by a four-step sequence in which electron-transfer and proton-transfer steps alternate.	$RC{\equiv}CR' + 2Na + 2NH_3 \longrightarrow$  $+ 2NaNH_2$ Alkyne — Sodium — Ammonia — Trans alkene — Sodium amide $CH_3C{\equiv}CCH_2CH_2CH_3 \xrightarrow[NH_3]{Na}$  2-Hexyne — *trans*-2-Hexene (69%)

9.19 Write a structural formula or build a molecular model of each of the following:

(a) 1-Octyne

(b) 2-Octyne

(c) 3-Octyne

(d) 4-Octyne

(e) 2,5-Dimethyl-3-hexyne

(f) 4-Ethyl-1-hexyne

(g) Ethynylcyclohexane

(h) 3-Ethyl-3-methyl-1-pentyne

9.20 All the compounds in Problem 9.19 are isomers except one. Which one?

9.21 Write structural formulas for all the alkynes of molecular formula C_8H_{14} that yield 3-ethylhexane on catalytic hydrogenation.

TABLE 9.4 Electrophilic Addition to Alkynes

Reaction (section) and comments	General equation and specific example
Addition of hydrogen halides (Section 9.11) Hydrogen halides add to alkynes in accordance with Markovnikov's rule to give alkenyl halides. In the presence of 2 eq of hydrogen halide, a second addition occurs to give a geminal dihalide.	$RC{\equiv}CR' \xrightarrow{HX} RCH{=}CR' \xrightarrow{HX} RCH_2CR'$ (X on alkenyl halide; X, X on geminal dihalide) Alkyne — Alkenyl halide — Geminal dihalide $CH_3C{\equiv}CH + 2HBr \longrightarrow CH_3CCH_3$ (Br, Br) Propyne — Hydrogen bromide — 2,2-Dibromopropane (100%)
Acid-catalyzed hydration (Section 9.12) Water adds to the triple bond of alkynes to yield ketones by way of an unstable enol intermediate. The enol arises by Markovnikov hydration of the alkyne. Enol formation is followed by rapid isomerization of the enol to a ketone.	$RC{\equiv}CR' + H_2O \xrightarrow[Hg^{2+}]{H_2SO_4} RCH_2CR'$ (O) Alkyne — Water — Ketone $HC{\equiv}CCH_2CH_2CH_2CH_3 + H_2O \xrightarrow[HgSO_4]{H_2SO_4} CH_3CCH_2CH_2CH_2CH_3$ (O) 1-Hexyne — Water — 2-Hexanone (80%)
Halogenation (Section 9.13) Addition of 1 equivalent of chlorine or bromine to an alkyne yields a trans dihaloalkene. A tetrahalide is formed on addition of a second equivalent of the halogen.	$RC{\equiv}CR' \xrightarrow{X_2}$ (R, X; X, R') $\xrightarrow{X_2}$ (X, X; X, X) Alkyne — Dihaloalkene — Tetrahaloalkane $CH_3C{\equiv}CH + 2Cl_2 \longrightarrow CH_3CCHCl_2$ (Cl, Cl) Propyne — Chlorine — 1,1,2,2-Tetrachloropropane (63%)

9.22 An unknown acetylenic amino acid obtained from the seed of a tropical fruit has the molecular formula $C_7H_{11}NO_2$. On catalytic hydrogenation over platinum this amino acid yielded homoleucine (an amino acid of known structure shown here) as the only product. What is the structure of the unknown amino acid?

$CH_3CH_2CHCH_2CHCO^-$ (O; CH_3; $^+NH_3$)

Homoleucine

9.23 Show by writing appropriate chemical equations how each of the following compounds could be converted to 1-hexyne:

(a) 1,1-Dichlorohexane
(b) 1-Hexene
(c) Acetylene
(d) 1-Iodohexane

9.24 Show by writing appropriate chemical equations how each of the following compounds could be converted to 3-hexyne:

(a) 1-Butene
(b) 1,1-Dichlorobutane
(c) Acetylene

9.25 When 1,2-dibromodecane was treated with potassium hydroxide in aqueous ethanol, it yielded a mixture of three isomeric compounds of molecular formula $C_{10}H_{19}Br$. Each of these compounds was converted to 1-decyne on reaction with sodium amide in dimethyl sulfoxide. Identify these three compounds.

9.26 Write the structure of the major organic product isolated from the reaction of 1-hexyne with

(a) Hydrogen (2 mol), platinum
(b) Hydrogen (1 mol), Lindlar palladium
(c) Lithium in liquid ammonia
(d) Sodium amide in liquid ammonia
(e) Product in part (d) treated with 1-bromobutane
(f) Product in part (d) treated with *tert*-butyl bromide
(g) Hydrogen chloride (1 mol)
(h) Hydrogen chloride (2 mol)
(i) Chlorine (1 mol)
(j) Chlorine (2 mol)
(k) Aqueous sulfuric acid, mercury(II) sulfate
(l) Ozone followed by hydrolysis

9.27 Write the structure of the major organic product isolated from the reaction of 3-hexyne with

(a) Hydrogen (2 mol), platinum
(b) Hydrogen (1 mol), Lindlar palladium
(c) Lithium in liquid ammonia
(d) Hydrogen chloride (1 mol)
(e) Hydrogen chloride (2 mol)
(f) Chlorine (1 mol)
(g) Chlorine (2 mol)
(h) Aqueous sulfuric acid, mercury(II) sulfate
(i) Ozone followed by hydrolysis

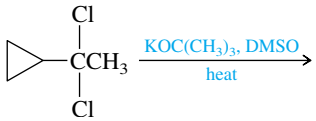
9.28 When 2-heptyne was treated with aqueous sulfuric acid containing mercury(II) sulfate, two products, each having the molecular formula $C_7H_{14}O$, were obtained in approximately equal amounts. What are these two compounds?

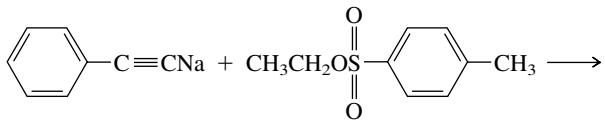
9.29 The alkane formed by hydrogenation of (*S*)-4-methyl-1-hexyne is optically active, but the one formed by hydrogenation of (*S*)-3-methyl-1-pentyne is not. Explain. Would you expect the products of hydrogenation of these two compounds in the presence of Lindlar palladium to be optically active?

9.30 All the following reactions have been described in the chemical literature and proceed in good yield. In some cases the reactants are more complicated than those we have so far encountered. Nevertheless, on the basis of what you have already learned, you should be able to predict the principal product in each case.

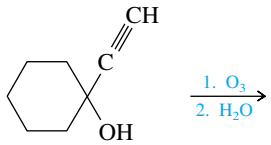
(a) $NaC{\equiv}CH + ClCH_2CH_2CH_2CH_2CH_2CH_2I \longrightarrow$

(b) $BrCH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_2Br \xrightarrow[2.\ H_2O]{1.\ \text{excess } NaNH_2,\ NH_3}$

(c) 

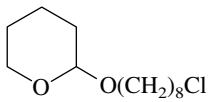
(d) 

(e) Cyclodecyne $\xrightarrow[2.\ H_2O]{1.\ O_3}$

(f) 

(g) $CH_3\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}(OH){\equiv}CH \xrightarrow[HgO]{H_2O,\ H_2SO_4}$

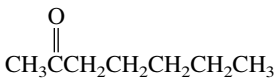
(h) $(Z)\text{-}CH_3CH_2CH_2CH_2CH{=}CHCH_2(CH_2)_7C{\equiv}CCH_2CH_2OH \xrightarrow[2.\ H_2O]{1.\ Na,\ NH_3}$

(i) 

$+ NaC{\equiv}CCH_2CH_2CH_2CH_3 \longrightarrow$

(j) Product of part (i) $\xrightarrow[\text{Lindlar Pd}]{H_2}$

9.31 The ketone 2-heptanone has been identified as contributing to the odor of a number of dairy products, including condensed milk and cheddar cheese. Describe a synthesis of 2-heptanone from acetylene and any necessary organic or inorganic reagents.



2-Heptanone

9.32 (Z)-9-Tricosene $[(Z)\text{-}CH_3(CH_2)_7CH{=}CH(CH_2)_{12}CH_3]$ is the sex pheromone of the female housefly. Synthetic (Z)-9-tricosene is used as bait to lure male flies to traps that contain insecticide. Using acetylene and alcohols of your choice as starting materials, along with any necessary inorganic reagents, show how you could prepare (Z)-9-tricosene.

9.33 Show by writing a suitable series of equations how you could prepare each of the following compounds from the designated starting materials and any necessary organic or inorganic reagents:

(a) 2,2-Dibromopropane from 1,1-dibromopropane

(b) 2,2-Dibromopropane from 1,2-dibromopropane

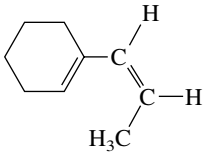
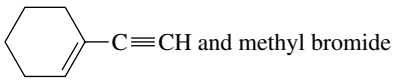
(c) 1,1,2,2-Tetrachloropropane from 1,2-dichloropropane

(d) 2,2-Diiodobutane from acetylene and ethyl bromide

(e) 1-Hexene from 1-butene and acetylene

(f) Decane from 1-butene and acetylene

(g) Cyclopentadecyne from cyclopentadecene

(h)  from  and methyl bromide

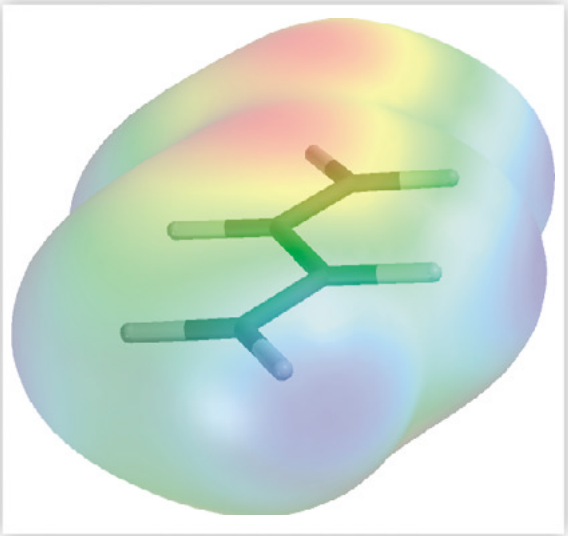
(i) *meso*-2,3-Dibromobutane from 2-butyne

9.34 Assume that you need to prepare 4-methyl-2-pentyne and discover that the only alkynes on hand are acetylene and propyne. You also have available methyl iodide, isopropyl bromide, and 1,1-dichloro-3-methylbutane. Which of these compounds would you choose in order to perform your synthesis, and how would you carry it out?

9.35 Compound A has the molecular formula $C_{14}H_{25}Br$ and was obtained by reaction of sodium acetylide with 1,12-dibromododecane. On treatment of compound A with sodium amide, it was converted to compound B ($C_{14}H_{24}$). Ozonolysis of compound B gave the diacid $HO_2C(CH_2)_{12}CO_2H$. Catalytic hydrogenation of compound B over Lindlar palladium gave compound C ($C_{14}H_{26}$), and hydrogenation over platinum gave compound D ($C_{14}H_{28}$). Sodium–ammonia reduction of compound B gave compound E ($C_{14}H_{26}$). Both C and E yielded $O{=}CH(CH_2)_{12}CH{=}O$ on ozonolysis. Assign structures to compounds A through E so as to be consistent with the observed transformations.

9.36 Use molecular models to compare $-C{\equiv}CH$, $-CH{=}CH_2$, and $-CH_2CH_3$ with respect to their preference for an equatorial orientation when attached to a cyclohexane ring. One of these groups is very much different from the other two. Which one? Why?

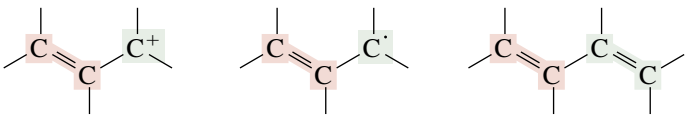
9.37 Try making a model of a hydrocarbon that contains three carbons, only one of which is *sp*-hybridized. What is its molecular formula? Is it an alkyne? What must be the hybridization state of the other two carbons? (You will learn more about compounds of this type in Chapter 10.)



CHAPTER 10

CONJUGATION IN ALKADIENES AND ALLYLIC SYSTEMS

Not all the properties of alkenes are revealed by focusing exclusively on the functional group behavior of the double bond. A double bond can affect the properties of a second functional unit to which it is directly attached. It can be a substituent, for example, on a positively charged carbon in an **allylic carbocation,** or on a carbon that bears an unpaired electron in an **allylic free radical,** or it can be a substituent on a second double bond in a **conjugated diene.**



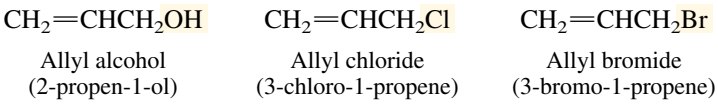
Allylic carbocation | Allylic free radical | Conjugated diene

Conjugare is a Latin verb meaning "to link or yoke together," and allylic carbocations, allylic free radicals, and conjugated dienes are all examples of **conjugated systems.** In this chapter we'll see how conjugation permits two functional units within a molecule to display a kind of reactivity that is qualitatively different from that of either unit alone.

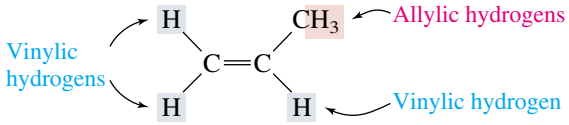
10.1 THE ALLYL GROUP

The group $CH_2{=}CHCH_2{-}$ is known as **allyl*,** which is both a common name and a permissible IUPAC name. It is most often encountered in functionally substituted derivatives, and the following compounds containing this group are much better known by their functional class IUPAC names than by their substitutive ones:

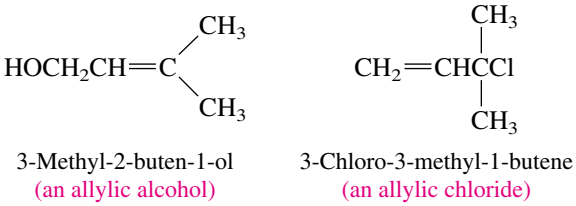
*"Allyl" is derived from the botanical name for garlic (*Allium sativum*). It was found in 1892 that the major component obtained by distilling garlic oil is $CH_2{=}CHCH_2SSCH_2CH{=}CH_2$, and the word "allyl" was coined for the $CH_2{=}CHCH_2{-}$ group on the basis of this origin.



The term "allylic" refers to a C=C—C unit. Its sp^3-hybridized carbon is called the **allylic carbon,** and an **allylic substituent** is one that is attached to an allylic carbon. Conversely, the sp^2-hybridized carbons of a carbon–carbon double bond are called **vinylic carbons,** and substituents attached to either one of them are referred to as **vinylic substituents.**



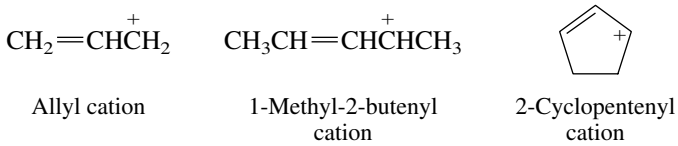
"Allylic" is often used as a general term for molecules that have a functional group at an allylic position. Thus, the following compounds represent an *allylic alcohol* and an *allylic chloride,* respectively.



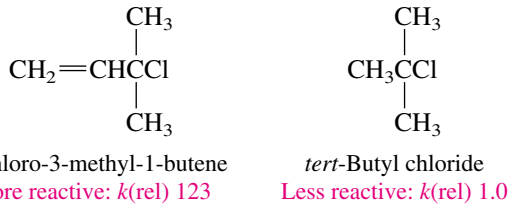
10.2 ALLYLIC CARBOCATIONS

Allylic carbocations are carbocations in which the positive charge is on an allylic carbon. Allyl cation is the simplest allylic carbocation.

Representative allylic carbocations

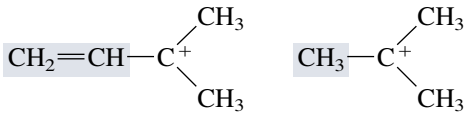


A substantial body of evidence indicates that allylic carbocations are more stable than simple alkyl cations. For example, the rate of solvolysis of a chloride that is both tertiary and allylic is much faster than that of a typical tertiary alkyl chloride.



The first-order rate constant for ethanolysis of the allylic chloride 3-chloro-3-methyl-1-butene is over 100 times greater than that of *tert*-butyl chloride at the same temperature.

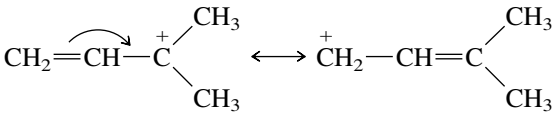
Both compounds react by an S_N1 mechanism, and their relative rates reflect their activation energies for carbocation formation. Since the allylic chloride is more reactive, we reason that it ionizes more rapidly because it forms a more stable carbocation. Structurally, the two carbocations differ in that the allylic carbocation has a vinyl substituent on its positively charged carbon in place of one of the methyl groups of *tert*-butyl cation.



1,1-Dimethylallyl cation (more stable) | *tert*-Butyl cation (less stable)

A vinyl group stabilizes a carbocation more than does a methyl group. Why?

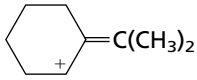
A vinyl group is an extremely effective electron-releasing substituent. A resonance interaction of the type shown permits the π electrons of the double bond to be delocalized and disperses the positive charge.



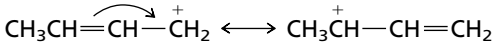
A rule of thumb is that a C=C substituent stabilizes a carbocation about as well as two alkyl groups. Although allyl cation ($CH_2{=}CHCH_2^+$) is a primary carbocation, it is about as stable as a typical secondary carbocation such as isopropyl cation, $(CH_3)_2CH^+$.

It's important to recognize that the positive charge is shared by the two end carbons in the C=C—C$^+$ unit; the center carbon does not bear a positive charge in either of the resonance structures that we just wrote. Keep that fact in mind as you answer Problem 10.1.

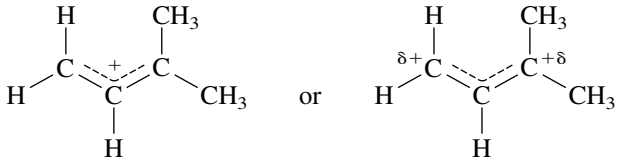
PROBLEM 10.1 Write a second resonance structure for each of the following carbocations:

(a) $CH_3CH{=}CHCH_2^+$ (b)  (c) 

SAMPLE SOLUTION (a) When writing resonance forms of carbocations, electrons are moved in pairs from sites of high electron density toward the positively charged carbon.

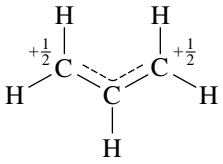


Electron delocalization in allylic carbocations can be indicated using a dashed line to show the sharing of a pair of π electrons by the three carbons. The structural formula is completed by placing a positive charge above the dashed line or by adding partial positive charges to the carbons at the end of the allylic system.



Two dashed-line representations of 1,1-dimethylallyl cation

In the case of the parent cation $CH_2{=}CH{-}CH_2^+$ both the terminal carbons are equivalently substituted, and so each bears exactly half of a unit positive charge.



Allyl cation

This same sharing of positive charge between the first and third carbons in $CH_2{=}CH{-}CH_2^+$ is shown by the use of colors in an electrostatic potential map (Figure 10.1).

An orbital overlap description of electron delocalization in 1,1-dimethylallyl cation $CH_2{=}CH{-}\overset{+}{C}(CH_3)_2$ is given in Figure 10.2. Figure 10.2*a* shows the π bond and the vacant *p* orbital as independent units. Figure 10.2*b* shows how the units can overlap to give an extended π orbital that encompasses all three carbons. This permits the two π electrons to be delocalized over three carbons and disperses the positive charge.

Since the positive charge in an allylic carbocation is shared by two carbons, there are two potential sites for attack by a nucleophile. Thus, hydrolysis of 3-chloro-3-methyl-1-butene gives a mixture of two allylic alcohols:

$$(CH_3)_2\underset{\displaystyle Cl}{\underset{|}{C}}CH{=}CH_2 \xrightarrow[Na_2CO_3]{H_2O} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}CH{=}CH_2 \;+\; (CH_3)_2C{=}CHCH_2OH$$

3-Chloro-3-methyl-1-butene

2-Methyl-3-buten-2-ol (85%)

3-Methyl-2-buten-1-ol (15%)

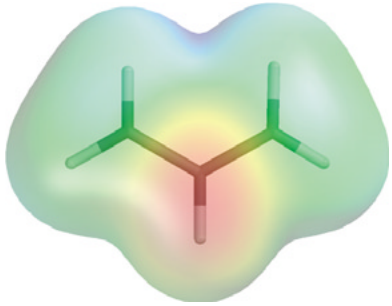
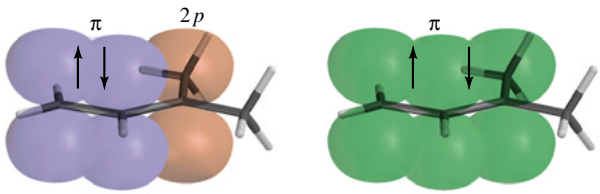


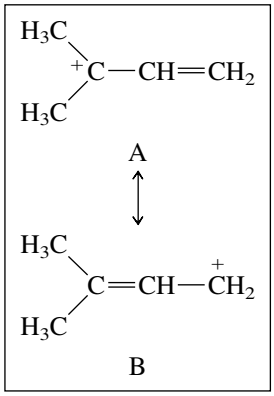
FIGURE 10.1 An electrostatic potential map for allyl cation. The middle carbon (red region) has the least positive charge of the three carbons; the end carbons (blue regions) have the most positive charge.



(*a*) (*b*)

FIGURE 10.2 Electron delocalization in an allylic carbocation. (*a*) The π orbital of the double bond, and the vacant 2*p* orbital of the positively charged carbon. (*b*) Overlap of the π orbital and the 2*p* orbital gives an extended π orbital that encompasses all three carbons. The two electrons in the π bond are delocalized over two carbons in (*a*) and over three carbons in (*b*).

Both alcohols are formed from the same carbocation. Water may react with the carbocation to give either a primary alcohol or a tertiary alcohol.



$$\xrightarrow{H_2O} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}CH{=}CH_2 \;+\; (CH_3)_2C{=}CHCH_2OH$$

2-Methyl-3-buten-2-ol (85%) 3-Methyl-2-buten-1-ol (15%)

Use *Learning By Modeling* to view the carbocation represented by resonance structures A and B. How is the positive charge distributed among its carbons?

It must be emphasized that we are not dealing with an equilibrium between two isomeric carbocations. *There is only one carbocation.* Its structure is not adequately represented by either of the individual resonance forms but is a hybrid having qualities of both of them. The carbocation has more of the character of A than B because resonance structure A is more stable than B. Water attacks faster at the tertiary carbon because it bears more of the positive charge.

The same two alcohols are formed in the hydrolysis of 1-chloro-3-methyl-2-butene:

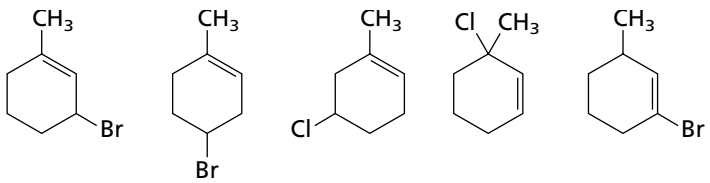
$$(CH_3)_2C{=}CHCH_2Cl \xrightarrow[Na_2CO_3]{H_2O} (CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}CH{=}CH_2 \;+\; (CH_3)_2C{=}CHCH_2OH$$

1-Chloro-3-methyl-2-butene 2-Methyl-3-buten-2-ol (85%) 3-Methyl-2-buten-1-ol (15%)

The carbocation formed on ionization of 1-chloro-3-methyl-2-butene is the same allylic carbocation as the one formed on ionization of 3-chloro-3-methyl-1-butene and gives the same mixture of products.

Reactions of allylic systems that yield products in which double-bond migration has occurred are said to have proceeded with **allylic rearrangement,** or by way of an **allylic shift.**

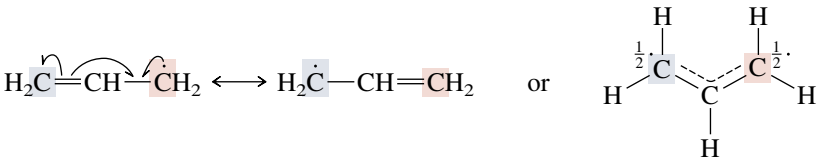
PROBLEM 10.2 From among the following compounds, choose the two that yield the same carbocation on ionization.



Later in this chapter we'll see how allylic carbocations are involved in electrophilic addition to dienes and how the principles developed in this section apply there as well.

10.3 ALLYLIC FREE RADICALS

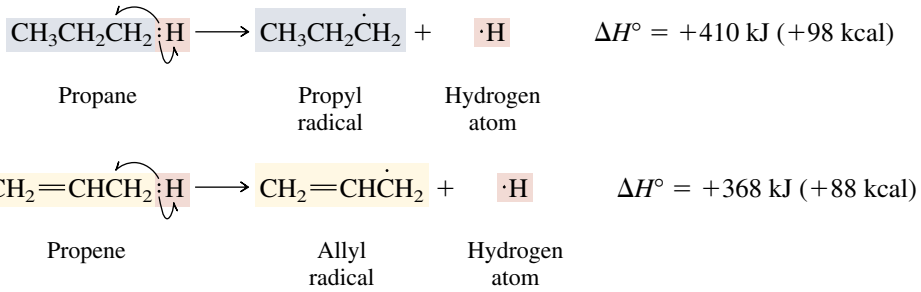
Just as allyl cation is stabilized by electron delocalization, so is allyl radical:



Allyl radical

Allyl radical is a conjugated system in which three electrons are delocalized over three carbons. The unpaired electron has an equal probability of being found at C-1 or C-3.

Reactions that generate allylic radicals occur more readily than those involving simple alkyl radicals. Compare the bond dissociation energies of the primary C—H bonds of propane and propene:

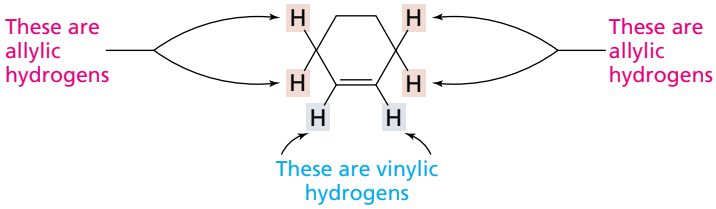


It requires less energy, by 42 kJ/mol (10 kcal/mol), to break a bond to a primary hydrogen atom in propene than in propane. The free radical produced from propene is allylic and stabilized by electron delocalization; the one from propane is not.

PROBLEM 10.3 Identify the allylic hydrogens in

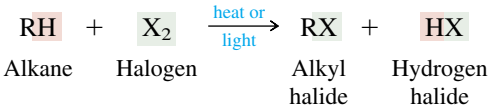
(a) Cyclohexene
(b) 1-Methylcyclohexene
(c) 2,3,3-Trimethyl-1-butene
(d) 1-Octene

SAMPLE SOLUTION (a) Allylic hydrogens are bonded to an allylic carbon. An allylic carbon is an sp^3-hybridized carbon that is attached directly to an sp^2-hybridized carbon of an alkene. Cyclohexene has four allylic hydrogens.

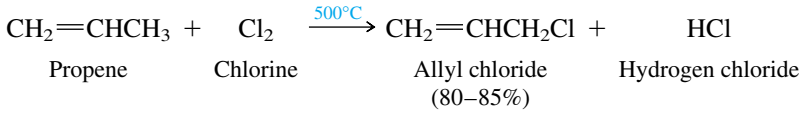


10.4 ALLYLIC HALOGENATION

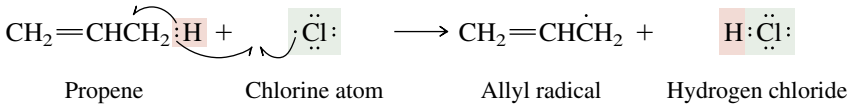
Of the reactions that involve carbon radicals, the most familiar are the chlorination and bromination of alkanes (Sections 4.15 through 4.19):

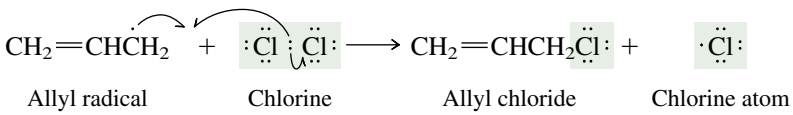


Although alkenes typically react with chlorine and bromine by *addition* at room temperature and below (Section 6.14), *substitution* becomes competitive at higher temperatures, especially when the concentration of the halogen is low. When substitution does occur, it is highly selective for the allylic position. This forms the basis of an industrial preparation of allyl chloride:



The reaction proceeds by a free-radical chain mechanism, involving the following propagation steps:

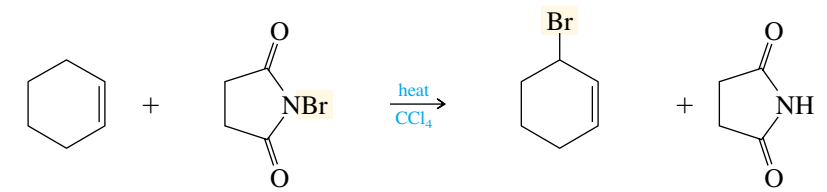




Allyl chloride is quite reactive toward nucleophilic substitutions, especially those that proceed by the S_N2 mechanism, and is used as a starting material in the synthesis of a variety of drugs and agricultural and industrial chemicals.

Allylic brominations are normally carried out using one of a number of specialized reagents developed for that purpose. *N*-Bromosuccinimide (NBS) is the most frequently used of these reagents. An alkene is dissolved in carbon tetrachloride, *N*-bromosuccinimide is added, and the reaction mixture is heated, illuminated with a sunlamp, or both. The products are an allylic halide and succinimide.

N-Bromosuccinimide will be seen again as a reagent for selective bromination in Section 11.12.



N-Bromosuccinimide provides a low concentration of molecular bromine, which reacts with alkenes by a mechanism analogous to that of other free-radical halogenations.

PROBLEM 10.4 Assume that *N*-bromosuccinimide serves as a source of Br_2, and write equations for the propagation steps in the formation of 3-bromocyclohexene by allylic bromination of cyclohexene.

Although allylic brominations and chlorinations offer a method for attaching a reactive functional group to a hydrocarbon framework, we need to be aware of two important limitations. For allylic halogenation to be effective in a particular synthesis:

1. All the allylic hydrogens in the starting alkene must be equivalent.
2. Both resonance forms of the allylic radical must be equivalent.

In the two examples cited so far, the chlorination of propene and the bromination of cyclohexene, both criteria are met.

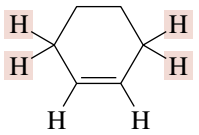
All the allylic hydrogens of propene are equivalent.

$$CH_2{=}CH{-}CH_3$$

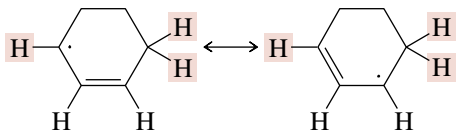
The two resonance forms of allyl radical are equivalent.

$$CH_2{=}CH{-}\dot{C}H_2 \longleftrightarrow \dot{C}H_2{-}CH{=}CH_2$$

All the allylic hydrogens of cyclohexene are equivalent.



The two resonance forms of 2-cyclohexenyl radical are equivalent.



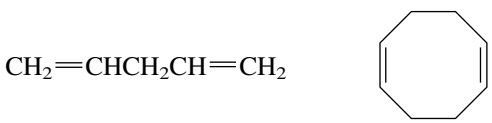
Unless both criteria are met, mixtures of constitutionally isomeric allylic halides result.

PROBLEM 10.5 The two alkenes 2,3,3-trimethyl-1-butene and 1-octene were each subjected to allylic halogenation with *N*-bromosuccinimide. One of these alkenes yielded a single allylic bromide, whereas the other gave a mixture of two constitutionally isomeric allylic bromides. Match the chemical behavior to the correct alkene and give the structure of the allylic bromide(s) formed from each.

10.5 CLASSES OF DIENES

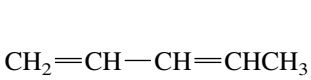
Allylic carbocations and allylic radicals are conjugated systems involved as reactive intermediates in chemical reactions. The third type of conjugated system that we will examine, **conjugated dienes,** consists of stable molecules.

A hydrocarbon that contains two double bonds is called an **alkadiene,** and the relationship between the double bonds may be described as *isolated, conjugated,* or *cumulated.* **Isolated diene** units are those in which two carbon–carbon double bond units are separated from each other by one or more sp^3-hybridized carbon atoms. 1,4-Pentadiene and 1,5-cyclooctadiene have isolated double bonds:

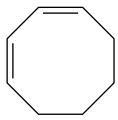


1,4-Pentadiene 1,5-Cyclooctadiene

Conjugated dienes are those in which two carbon–carbon double bond units are directly connected to each other by a single bond. 1,3-Pentadiene and 1,3-cyclooctadiene contain conjugated double bonds:



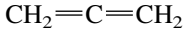
1,3-Pentadiene



1,3-Cyclooctadiene

Cumulated dienes are those in which one carbon atom is common to two carbon–carbon double bonds. The simplest cumulated diene is 1,2-propadiene, also called *allene*, and compounds of this class are generally referred to as *allenes*.

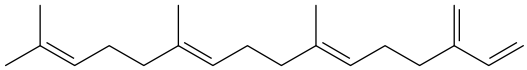
Allene is an acceptable IUPAC name for 1,2-propadiene.



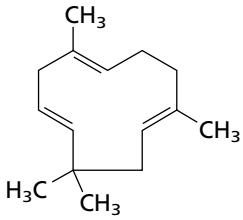
1,2-Propadiene

PROBLEM 10.6 Many naturally occurring substances contain several carbon–carbon double bonds: some isolated, some conjugated, and some cumulated. Identify the types of carbon–carbon double bonds found in each of the following substances:

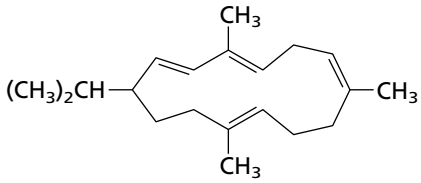
(a) β-Springene (a scent substance from the dorsal gland of springboks)



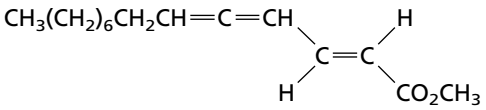
(b) Humulene (found in hops and oil of cloves)



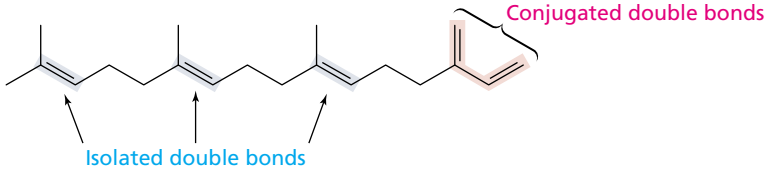
(c) Cembrene (occurs in pine resin)



(d) The sex attractant of the male dried-bean beetle



SAMPLE SOLUTION (a) β-Springene has three isolated double bonds and a pair of conjugated double bonds:



Isolated double bonds are separated from other double bonds by at least one sp^3-hybridized carbon. Conjugated double bonds are joined by a single bond.

Alkadienes are named according to the IUPAC rules by replacing the *-ane* ending of an alkane with *-adiene* and locating the position of each double bond by number. Compounds with three carbon–carbon double bonds are called *alkatrienes* and named accordingly, those with four double bonds are *alkatetraenes,* and so on.

10.6 RELATIVE STABILITIES OF DIENES

Which is the most stable arrangement of double bonds in an alkadiene—isolated, conjugated, or cumulated?

As we saw in Chapter 6, the stabilities of alkenes may be assessed by comparing their heats of hydrogenation. Figure 10.3 depicts the heats of hydrogenation of an isolated diene (1,4-pentadiene) and a conjugated diene (1,3-pentadiene), along with the alkenes 1-pentene and (*E*)-2-pentene. The figure shows that an isolated pair of double bonds behaves much like two independent alkene units. The measured heat of hydrogenation of the two double bonds in 1,4-pentadiene is 252 kJ/mol (60.2 kcal/mol), exactly twice the heat of hydrogenation of 1-pentene. Furthermore, the heat evolved on hydrogenation of each double bond must be 126 kJ/mol (30.1 kcal/mol), since 1-pentene is an intermediate in the hydrogenation of 1,4-pentadiene to pentane.

By the same reasoning, hydrogenation of the terminal double bond in the conjugated diene (*E*)-1,3-pentadiene releases only 111 kJ/mol (26.5 kcal/mol) when it is hydrogenated to (*E*)-2-pentene. Hydrogenation of the terminal double bond in the conjugated diene evolves 15 kJ/mol (3.6 kcal/mol) less heat than hydrogenation of a terminal double bond in the diene with isolated double bonds. *A conjugated double bond is 15 kJ/mol (3.6 kcal/mol) more stable than a simple double bond.* We call this increased stability due to conjugation the **delocalization energy, resonance energy,** or **conjugation energy.**

The cumulated double bonds of an allenic system are of relatively high energy. The heat of hydrogenation of allene is more than twice that of propene.

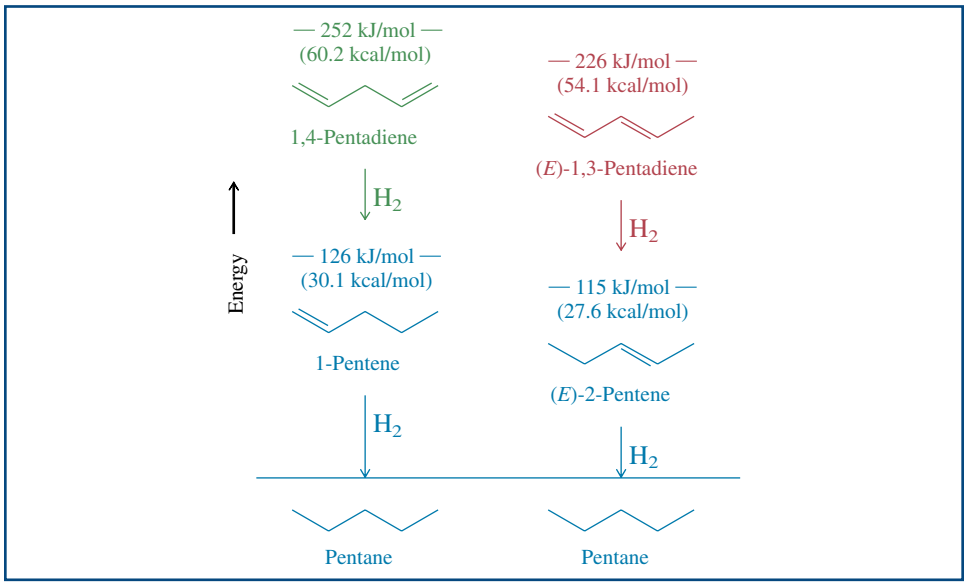


FIGURE 10.3 Heats of hydrogenation of some C_5H_{10} alkenes and C_5H_8 alkadienes.

$$\underset{\text{Allene}}{CH_2{=}C{=}CH_2} + \underset{\text{Hydrogen}}{2H_2} \longrightarrow \underset{\text{Propane}}{CH_3CH_2CH_3} \qquad \Delta H^\circ = -295 \text{ kJ } (-70.5 \text{ kcal})$$

$$\underset{\text{Propene}}{CH_3CH{=}CH_2} + \underset{\text{Hydrogen}}{H_2} \longrightarrow \underset{\text{Propane}}{CH_3CH_2CH_3} \qquad \Delta H^\circ = -125 \text{ kJ } (-29.9 \text{ kcal})$$

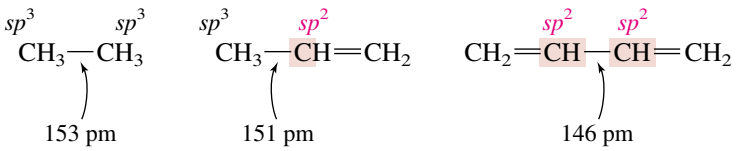
PROBLEM 10.7 Another way in which energies of isomers may be compared is by their heats of combustion. Match the heat of combustion with the appropriate diene.

Dienes:	1,2-Pentadiene, (*E*)-1,3-pentadiene, 1,4-pentadiene
Heats of combustion:	3186 kJ/mol, 3217 kJ/mol, 3251 kJ/mol 761.6 kcal/mol, 768.9 kcal/mol, 777.1 kcal/mol

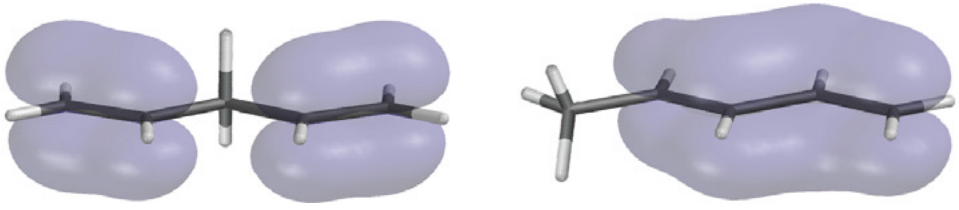
Thus, the order of alkadiene stability decreases in the order: conjugated diene (most stable) → isolated diene → cumulated diene (least stable). To understand this ranking, we need to look at structure and bonding in alkadienes in more detail.

10.7 BONDING IN CONJUGATED DIENES

At 146 pm the C-2—C-3 distance in 1,3-butadiene is relatively short for a carbon–carbon single bond. This is most reasonably seen as a hybridization effect. In ethane both carbons are sp^3-hybridized and are separated by a distance of 153 pm. The carbon–carbon single bond in propene unites sp^3- and sp^2-hybridized carbons and is shorter than that of ethane. Both C-2 and C-3 are sp^2-hybridized in 1,3-butadiene, and a decrease in bond distance between them reflects the tendency of carbon to attract electrons more strongly as its *s* character increases.



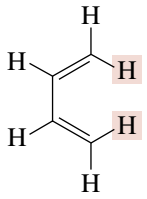
The factor most responsible for the increased stability of conjugated double bonds is the greater delocalization of their π electrons compared with the π electrons of isolated double bonds. As shown in Figure 10.4*a,* the π electrons of an isolated diene system occupy, in pairs, two noninteracting π orbitals. Each of these π orbitals encompasses two carbon atoms. An sp^3-hybridized carbon isolates the two π orbitals from each other, preventing the exchange of electrons between them. In a conjugated diene, however, mutual overlap of the two π orbitals, represented in Figure 10.4*b,* gives an orbital system in which each π electron is delocalized over four carbon atoms. Delocalization of electrons lowers their energy and gives a more stable molecule.



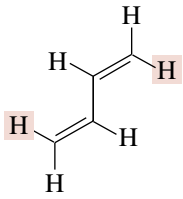
(*a*) Isolated double bonds (*b*) Conjugated double bonds

FIGURE 10.4 (*a*) Isolated double bonds are separated from each other by one or more sp^3-hybridized carbons and cannot overlap to give an extended π orbital. (*b*) In a conjugated diene, overlap of two π orbitals gives an extended π system encompassing four carbon atoms.

Additional evidence for electron delocalization in 1,3-butadiene can be obtained by considering its conformations. Overlap of the two π electron systems is optimal when the four carbon atoms are coplanar. Two conformations allow this coplanarity: they are called the *s*-cis and *s*-trans conformations.



s-Cis conformation of 1,3-butadiene



s-Trans conformation of 1,3-butadiene

The letter *s* in *s*-cis and *s*-trans refers to conformations around the C—C single bond in the diene. The *s*-trans conformation of 1,3-butadiene is 12 kJ/mol (2.8 kcal/mol) more

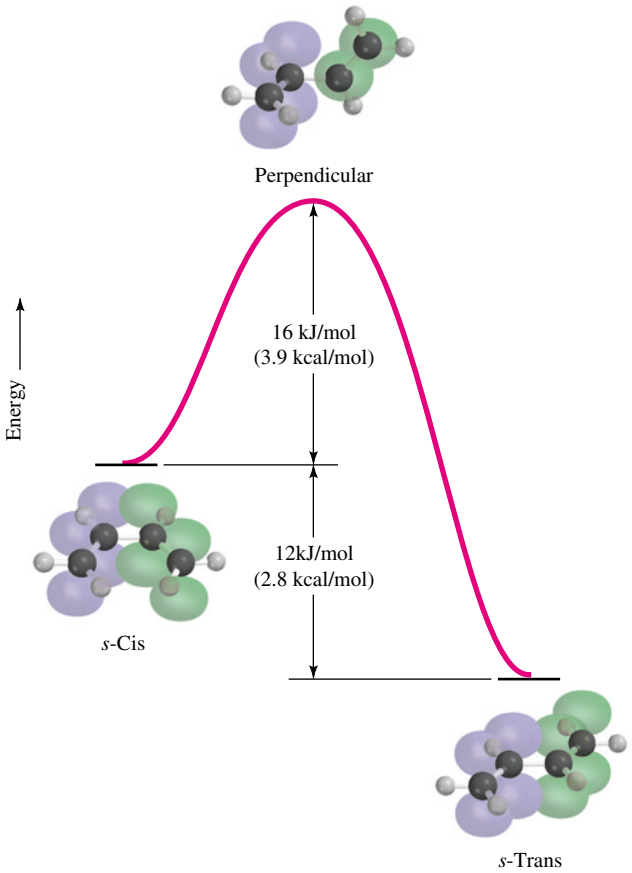


FIGURE 10.5 Conformations and electron delocalization in 1,3-butadiene. The *s*-cis and the *s*-trans conformations permit the 2*p* orbitals to be aligned parallel to one another for maximum π electron delocalization. The *s*-trans conformation is more stable than the *s*-cis. Stabilization resulting from π electron delocalization is least in the perpendicular conformation, which is a transition state for rotation about the C-2—C-3 single bond.

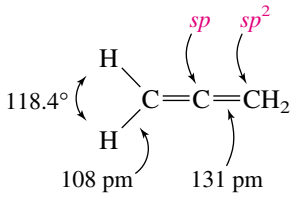
stable than the *s*-cis, which is destabilized by van der Waals strain between the hydrogens at C-1 and C-4.

The *s*-cis and *s*-trans conformations of 1,3-butadiene interconvert by rotation around the C-2—C-3 bond, as illustrated in Figure 10.5. The conformation at the midpoint of this rotation, the *perpendicular conformation,* has its 2*p* orbitals in a geometry that prevents extended conjugation. It has localized double bonds. The main contributor to the energy of activation for rotation about the single bond in 1,3-butadiene is the decrease in electron delocalization that attends conversion of the *s*-cis or *s*-trans conformation to the perpendicular conformation.

Return to the models of 1,3-butadiene in Figure 10.5 on *Learning By Modeling* and compare space-filling models of the *s*-cis and *s*-trans conformation.

10.8 BONDING IN ALLENES

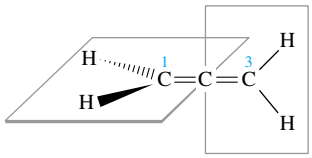
The three carbons of allene lie in a straight line, with relatively short carbon–carbon bond distances of 131 pm. The central carbon, since it bears only two substituents, is *sp*-hybridized. The terminal carbons of allene are sp^2-hybridized.



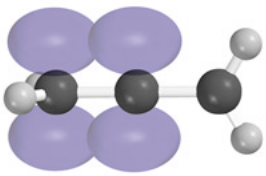
Allene

Structural studies show allene to be nonplanar. As Figure 10.6 illustrates, the plane of one HCH unit is perpendicular to the plane of the other. Figure 10.6 also portrays the

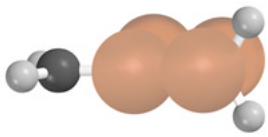
(*a*) Planes defined by H(C-1)H and H(C-3)H are mutually perpendicular.



(*b*) The *p* orbital of C-1 and one of the *p* orbitals of C-2 can overlap so as to participate in π bonding.



(*c*) The *p* orbital of C-3 and one of the *p* orbitals of C-2 can overlap so as to participate in a second π orbital perpendicular to the one in (*b*).



(*d*) Allene is a nonplanar molecule characterized by a linear carbon chain and two mutually perpendicular π bonds.

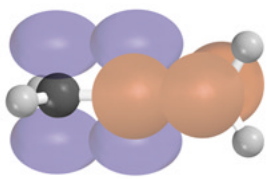


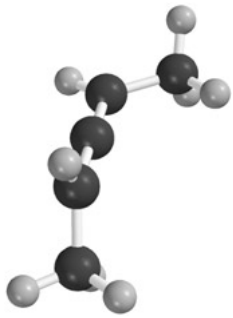
FIGURE 10.6 Bonding and geometry in 1,2-propadiene (allene).

reason for the molecular geometry of allene. The 2*p* orbital of each of the terminal carbons overlaps with a different 2*p* orbital of the central carbon. Since the 2*p* orbitals of the central carbon are perpendicular to each other, the perpendicular nature of the two HCH units follows naturally.

The nonplanarity of allenes has an interesting stereochemical consequence. 1,3-Disubstituted allenes are chiral; they are not superposable on their mirror images. Even an allene as simple as 2,3-pentadiene ($CH_3CH{=}C{=}CHCH_3$) has been obtained as separate enantiomers.

Examine models of both enantiomers of 2,3-pentadiene to verify that they are nonsuperposable.

(+)-2,3-Pentadiene



(−)-2,3-Pentadiene

The enantiomers shown are related as a right-hand and left-hand screw, respectively.

Chiral allenes are examples of a small group of molecules that are chiral, but don't have a stereogenic center. What they do have is a **stereogenic axis,** also called a **chiral axis,** which in the case of 2,3-pentadiene is a line passing through the three carbons of the allene unit (carbons 2, 3, and 4).

The Cahn–Ingold–Prelog *R,S* notation has been extended to chiral allenes and other molecules that have a stereogenic axis. Such compounds are so infrequently encountered, however, we will not cover the rules for specifying their stereochemistry in this text.

PROBLEM 10.8 Is 2-methyl-2,3-pentadiene chiral? What about 2-chloro-2,3-pentadiene?

Because of the linear geometry required of cumulated dienes, cyclic allenes, like cycloalkynes, are strained unless the rings are fairly large. 1,2-Cyclononadiene is the smallest cyclic allene that is sufficiently stable to be isolated and stored conveniently.

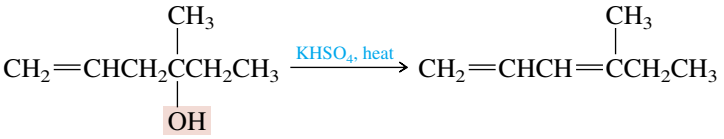
10.9 PREPARATION OF DIENES

The use of 1,3-butadiene in the preparation of synthetic rubber is discussed in the boxed essay "Diene Polymers" that appears later in this chapter.

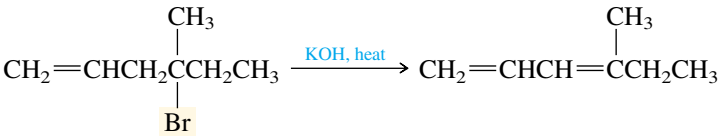
The conjugated diene 1,3-butadiene is used in the manufacture of synthetic rubber and is prepared on an industrial scale in vast quantities. Production in the United States is currently 4×10^9 lb/year. One industrial process is similar to that used for the preparation of ethylene: in the presence of a suitable catalyst, butane undergoes thermal dehydrogenation to yield 1,3-butadiene.

$$CH_3CH_2CH_2CH_3 \xrightarrow[\text{chromia–alumina}]{590\text{–}675^\circ C} CH_2{=}CHCH{=}CH_2 + 2H_2$$

Laboratory syntheses of conjugated dienes can be achieved by elimination reactions of unsaturated alcohols and alkyl halides. In the two examples that follow, the conjugated diene is produced in high yield even though an isolated diene is also possible.



3-Methyl-5-hexen-3-ol 4-Methyl-1,3-hexadiene (88%)

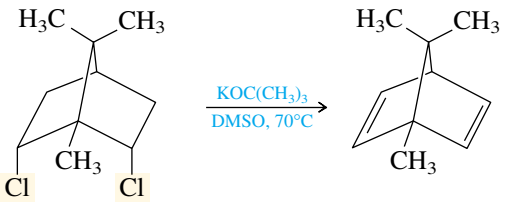


4-Bromo-4-methyl-1-hexene 4-Methyl-1,3-hexadiene (78%)

As we saw earlier, dehydrations and dehydrohalogenations are typically regioselective in the direction that leads to the most stable double bond. Conjugated dienes are more stable than isolated dienes and are formed faster via a lower energy transition state.

PROBLEM 10.9 What dienes containing isolated double bonds are capable of being formed, but are not observed, in the two preceding equations describing elimination in 3-methyl-5-hexen-3-ol and 4-bromo-4-methyl-1-hexene?

Dienes with isolated double bonds can be formed when the structure of the substrate doesn't permit the formation of a conjugated diene.



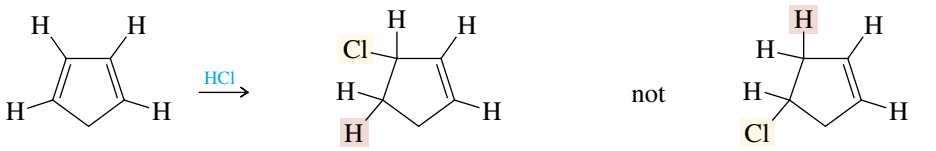
2,6-Dichlorocamphane Bornadiene (83%)

We will not discuss the preparation of cumulated dienes. They are prepared less readily than isolated or conjugated dienes and require special methods.

10.10 ADDITION OF HYDROGEN HALIDES TO CONJUGATED DIENES

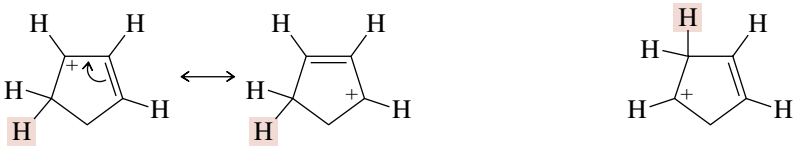
Our discussion of chemical reactions of alkadienes will be limited to those of conjugated dienes. The reactions of isolated dienes are essentially the same as those of individual alkenes. The reactions of cumulated dienes are—like their preparation—so specialized that their treatment is better suited to an advanced course in organic chemistry.

Electrophilic addition is the characteristic chemical reaction of alkenes, and conjugated dienes undergo addition reactions with the same electrophiles that react with alkenes, and by similar mechanisms. As we saw in the reaction of hydrogen halides with alkenes (Section 6.5), the regioselectivity of electrophilic addition is governed by protonation of the double bond in the direction that gives the more stable of two possible carbocations. With conjugated dienes it is one of the terminal carbons that is protonated, because the species that results is an allylic carbocation which is stabilized by electron delocalization. Thus, when 1,3-cyclopentadiene reacts with hydrogen chloride, the product is 3-chlorocyclopentene.



1,3-Cyclopentadiene 3-Chlorocyclopentene (70–90%) 4-Chlorocyclopentene

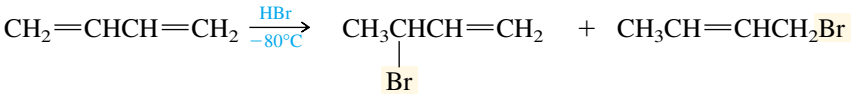
The carbocation that leads to the observed product is secondary and allylic; the other is secondary but not allylic.



Protonation at end of diene unit gives a carbocation that is both secondary and allylic; product is formed from this carbocation.

Protonation at C-2 gives a carbocation that is secondary but not allylic; less stable carbocation; not formed as rapidly.

Both resonance forms of the allylic carbocation from 1,3-cyclopentadiene are equivalent, and so attack at either of the carbons that share the positive charge gives the same product, 3-chlorocyclopentene. This is not the case with 1,3-butadiene, and so hydrogen halides add to 1,3-butadiene to give a mixture of two regioisomeric allylic halides. For the case of electrophilic addition of hydrogen bromide,

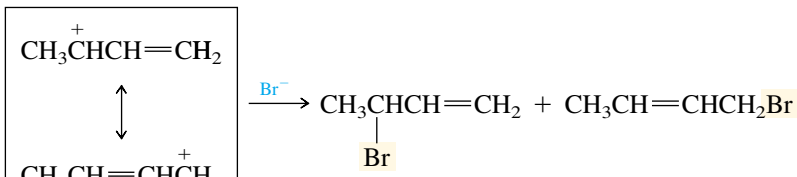


1,3-Butadiene 3-Bromo-1-butene (81%) 1-Bromo-2-butene (19%)

The major product corresponds to addition of a proton at C-1 and bromide at C-2. This mode of addition is called **1,2 addition,** or **direct addition.** The minor product has its proton and bromide at C-1 and C-4, respectively, of the original diene system. This mode of addition is called **1,4 addition,** or **conjugate addition.** The double bond that was between C-3 and C-4 in the starting material remains there in the product from 1,2 addition but migrates to a position between C-2 and C-3 in the product from 1,4 addition.

Both the 1,2-addition product and the 1,4-addition product are derived from the same allylic carbocation.

Use *Learning By Modeling* to view the charge distribution in the allylic carbocation shown in the equation.



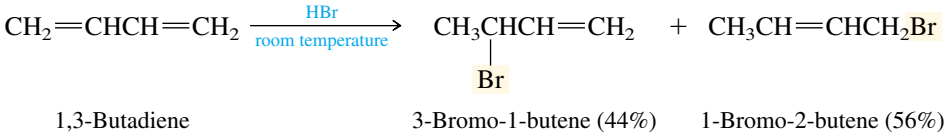
3-Bromo-1-butene (major) 1-Bromo-2-butene (minor)

The secondary carbon bears more of the positive charge than does the primary carbon, and attack by the nucleophilic bromide ion is faster there. Hence, the major product is the secondary bromide.

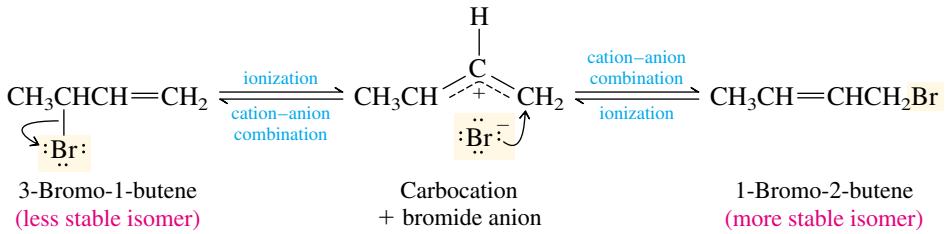
When the major product of a reaction is the one that is formed at the fastest rate, we say that the reaction is governed by **kinetic control.** Most organic reactions fall into

this category, and the electrophilic addition of hydrogen bromide to 1,3-butadiene at low temperature is a kinetically controlled reaction.

When, however, the ionic addition of hydrogen bromide to 1,3-butadiene is carried out at room temperature, the ratio of isomeric allylic bromides observed is different from that which is formed at −80°C. At room temperature, the 1,4-addition product predominates.



Clearly, the temperature at which the reaction occurs exerts a major influence on the product composition. To understand why, an important fact must be added. The 1,2- and 1,4-addition products *interconvert rapidly* by allylic rearrangement at elevated temperature in the presence of hydrogen bromide. Heating the product mixture to 45°C in the presence of hydrogen bromide leads to a mixture in which the ratio of 3-bromo-1-butene to 1-bromo-2-butene is 15:85.



The product of 1,4 addition, 1-bromo-2-butene, contains an internal double bond and so is *more stable* than the product of 1,2 addition, 3-bromo-l-butene, which has a terminal double bond.

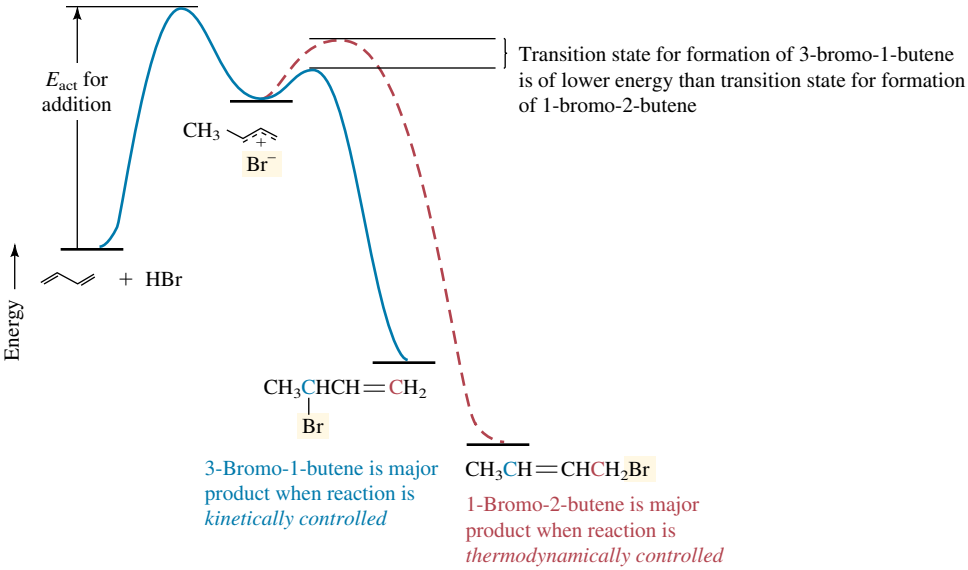


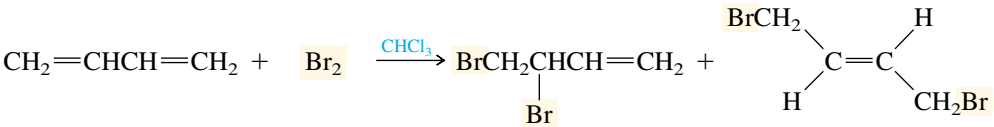
FIGURE 10.7 Energy diagram showing relationship of kinetic control to thermodynamic control in addition of hydrogen bromide to 1,3-butadiene.

When addition occurs under conditions in which the products can equilibrate, the composition of the reaction mixture no longer reflects the relative rates of formation of the products but tends to reflect their *relative stabilities.* Reactions of this type are said to be governed by **thermodynamic control.** One way to illustrate kinetic and thermodynamic control in the addition of hydrogen bromide to 1,3-butadiene is by way of the energy diagram of Figure 10.7. At low temperature, addition takes place irreversibly. Isomerization is slow because insufficient thermal energy is available to permit the products to surmount the energy barrier for ionization. At higher temperatures isomerization is possible, and the more stable product predominates.

PROBLEM 10.10 Addition of hydrogen chloride to 2-methyl-1,3-butadiene is a kinetically controlled reaction and gives one product in much greater amounts than any isomers. What is this product?

10.11 HALOGEN ADDITION TO DIENES

Mixtures of 1,2- and 1,4-addition products are obtained when 1,3-butadiene reacts with chlorine or bromine.



1,3-Butadiene | Bromine | 3,4-Dibromo-1-butene (37%) | (*E*)-1,4-Dibromo-2-butene (63%)

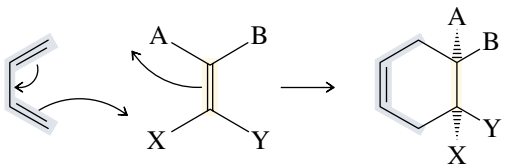
The tendency for conjugate addition is pronounced, and *E* double bonds are generated almost exclusively.

PROBLEM 10.11 Exclusive of stereoisomers, how many products are possible in the electrophilic addition of 1 eq of bromine to 2-methyl-1,3-butadiene?

10.12 THE DIELS–ALDER REACTION

A particular kind of conjugate addition reaction earned the Nobel Prize in chemistry for Otto Diels and Kurt Alder of the University of Kiel (Germany) in 1950. The Diels–Alder reaction is the *conjugate addition of an alkene to a diene.* Using 1,3-butadiene as a typical diene, the Diels–Alder reaction may be represented by the general equation:

For an animation of this reaction, see *Learning By Modeling.*



1,3-Butadiene | Dienophile | Diels–Alder adduct

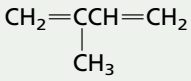
Epoxidation of alkenes (Section 6.18) is another example of a cycloaddition.

The alkene that adds to the diene is called the **dienophile.** Because the Diels–Alder reaction leads to the formation of a ring, it is termed a **cycloaddition** reaction. The product contains a cyclohexene ring as a structural unit.

The Diels–Alder cycloaddition is one example of a **pericyclic reaction.** A pericyclic reaction is a one-step reaction that proceeds through a cyclic transition state. Bond

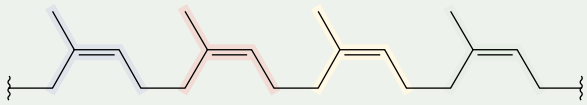
DIENE POLYMERS

Some 500 years ago during Columbus's second voyage to what are now the Americas, he and his crew saw children playing with balls made from the latex of trees that grew there. Later, Joseph Priestley called this material "rubber" to describe its ability to erase pencil marks by rubbing, and in 1823 Charles Macintosh demonstrated how rubber could be used to make waterproof coats and shoes. Shortly thereafter Michael Faraday determined an empirical formula of C_5H_8 for rubber. It was eventually determined that rubber is a polymer of 2-methyl-1,3-butadiene.



2-Methyl-1,3-butadiene (common name: *isoprene*)

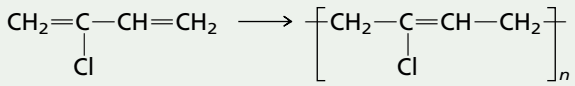
The structure of rubber corresponds to 1,4 addition of several thousand isoprene units to one another:



All the double bonds in rubber have the *Z* (or cis) configuration. A different polymer of isoprene, called *gutta-percha,* has shorter polymer chains and *E* (or trans) double bonds. Gutta-percha is a tough, horn-like substance once used as a material for golf ball covers.*

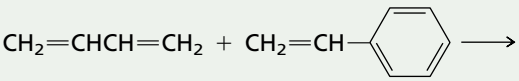
In natural rubber the attractive forces between neighboring polymer chains are relatively weak, and there is little overall structural order. The chains slide easily past one another when stretched and return, in time, to their disordered state when the distorting force is removed. The ability of a substance to recover its original shape after distortion is its *elasticity.* The elasticity of natural rubber is satisfactory only within a limited temperature range; it is too rigid when cold and too sticky when warm to be very useful. Rubber's elasticity is improved by *vulcanization,* a process discovered by Charles Goodyear in 1839. When natural rubber is heated with sulfur, a chemical reaction occurs in which neighboring polyisoprene chains become connected through covalent bonds to sulfur. Although these sulfur "bridges" permit only limited movement of one chain with respect to another, their presence ensures that the rubber will snap back to its original shape once the distorting force is removed.

As the demand for rubber increased, so did the chemical industry's efforts to prepare a synthetic substitute. One of the first **elastomers** (a synthetic polymer that possesses elasticity) to find a commercial niche was *neoprene,* discovered by chemists at Du Pont in 1931. Neoprene is produced by free-radical polymerization of 2-chloro-1,3-butadiene and has the greatest variety of applications of any elastomer. Some uses include electrical insulation, conveyer belts, hoses, and weather balloons.

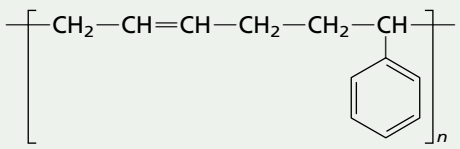


2-Chloro-1,3-butadiene Neoprene

The elastomer produced in greatest amount is *styrene-butadiene rubber* (SBR). Annually, just under 10^9 lb of SBR is produced in the United States, and almost all of it is used in automobile tires. As its name suggests, SBR is prepared from styrene and 1,3-butadiene. It is an example of a **copolymer,** a polymer assembled from two or more different monomers. Free-radical polymerization of a mixture of styrene and 1,3-butadiene gives SBR.



1,3-Butadiene Styrene

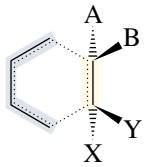


Styrene-butadiene rubber

Coordination polymerization of isoprene using Ziegler–Natta catalyst systems (Section 6.21) gives a material similar in properties to natural rubber, as does polymerization of 1,3-butadiene. Poly(1,3-butadiene) is produced in about two thirds the quantity of SBR each year. It, too, finds its principal use in tires.

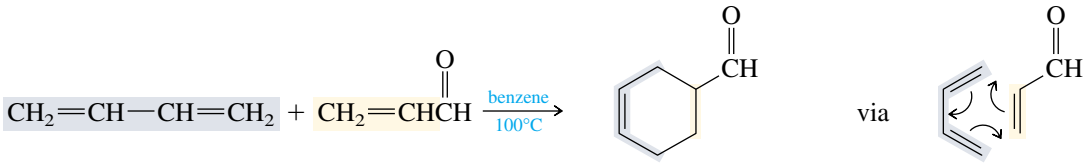
* A detailed discussion of the history, structure, and applications of natural rubber appears in the May 1990 issue of the *Journal of Chemical Education.*

formation occurs at both ends of the diene system, and the Diels–Alder transition state involves a cyclic array of six carbons and six π electrons. The diene must adopt the *s*-cis conformation in the transition state.



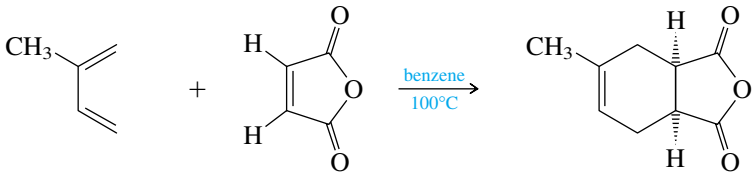
Transition state for
Diels–Alder cycloaddition

The simplest of all Diels–Alder reactions, cycloaddition of ethylene to 1,3-butadiene, does not proceed readily. It has a high activation energy and a low reaction rate. Substituents such as C═O or C≡N, however, when *directly* attached to the double bond of the dienophile, increase its reactivity, and compounds of this type give high yields of Diels–Alder adducts at modest temperatures.



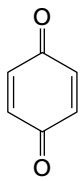
1,3-Butadiene Acrolein Cyclohexene-4-carboxaldehyde (100%)

The product of a Diels–Alder cycloaddition always contains one more ring than was present in the reactants. The dienophile *maleic anhydride* contains one ring, so the product of its addition to a diene contains two.



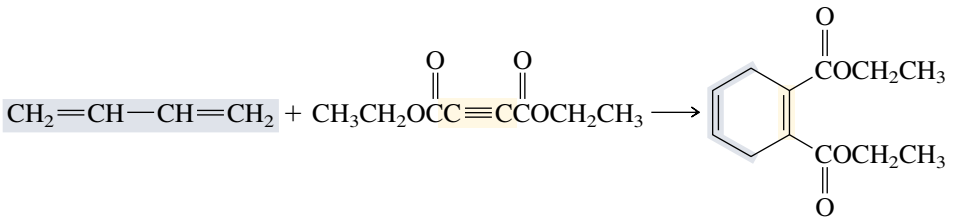
2-Methyl-1,3-butadiene Maleic anhydride 1-Methylcyclohexene-4,5-dicarboxylic anhydride (100%)

PROBLEM 10.12 Benzoquinone is a very reactive dienophile. It reacts with 2-chloro-1,3-butadiene to give a single product, $C_{10}H_9ClO_2$, in 95% yield. Write a structural formula for this product.



Benzoquinone

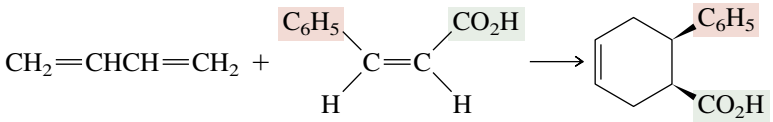
Acetylene, like ethylene, is a poor dienophile, but alkynes that bear C═O or C≡N substituents react readily with dienes. A cyclohexadiene derivative is the product.



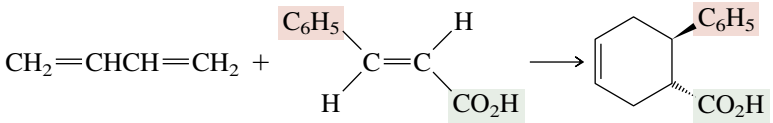
1,3-Butadiene | Diethyl acetylenedicarboxylate | Diethyl 1,4-cyclohexadiene-1,2-dicarboxylate (98%)

The Diels–Alder reaction is stereospecific. Substituents that are cis in the dienophile remain cis in the product; substituents that are trans in the dienophile remain trans in the product.

Recall from Section 7.13 that a stereospecific reaction is one in which each stereoisomer of a particular starting material yields a different stereoisomeric form of the reaction product. In the examples shown, the product from Diels–Alder cycloaddition of 1,3-butadiene to *cis*-cinnamic acid is a stereoisomer of the product from *trans*-cinnamic acid. Each product, although chiral, is formed as a racemic mixture.

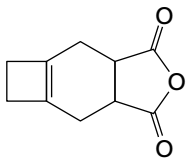


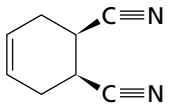
1,3-Butadiene | *cis*-Cinnamic acid | Only product

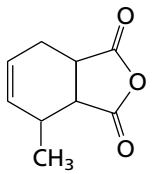


1,3-Butadiene | *trans*-Cinnamic acid | Only product

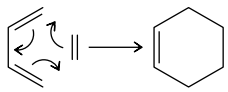
PROBLEM 10.13 What combination of diene and dienophile would you choose in order to prepare each of the following compounds?

(a) 

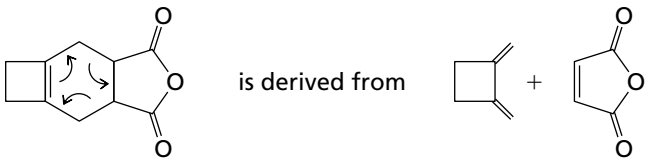
(b) 

(c) 

SAMPLE SOLUTION (a) Using curved arrows, we represent a Diels–Alder reaction as

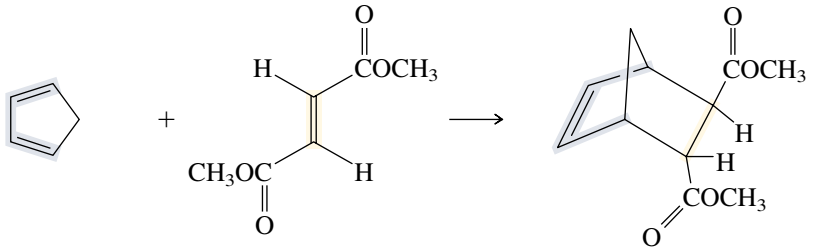


To deduce the identity of the diene and dienophile that lead to a particular Diels–Alder adduct, we use curved arrows in the reverse fashion to "undo" the cyclohexene derivative. Start with the π component of the double bond in the six-membered ring, and move electrons in pairs.



Diels–Alder adduct | is derived from | Diene | Dienophile

Cyclic dienes yield bridged bicyclic Diels–Alder adducts.



1,3-Cyclopentadiene Dimethyl fumarate Dimethylbicyclo[2.2.1]hept-2-ene-*trans*-5,6-dicarboxylate

PROBLEM 10.14 The Diels–Alder reaction of 1,3-cyclopentadiene with methyl acrylate ($H_2C{=}CHCOCH_3$) gives a mixture of two diastereomers. Write their structural formulas.

The importance of the Diels–Alder reaction is in synthesis. It gives us a method to form *two* new carbon–carbon bonds in a single operation and requires no reagents, such as acids or bases, that might affect other functional groups in the molecule.

The mechanism of the Diels–Alder reaction is best understood on the basis of a molecular orbital approach. To understand this approach we need to take a more detailed look at the π orbitals of alkenes and dienes.

10.13 THE π MOLECULAR ORBITALS OF ETHYLENE AND 1,3-BUTADIENE

The valence bond approach has served us well to this point as a tool to probe structure and reactivity in organic chemistry. An appreciation for the delocalization of π electrons through a system of overlapping *p* orbitals has given us insights into conjugated systems that are richer in detail than those obtained by examining Lewis formulas. An even deeper understanding can be gained by applying qualitative molecular orbital theory to these π electron systems. We shall see that useful information can be gained by directing attention to what are called the **frontier orbitals** of molecules. The frontier orbitals are the *highest occupied molecular orbital* (the *HOMO*) and the *lowest unoccupied molecular orbital* (the *LUMO*). When electrons are transferred *from* a molecule, it is the electrons in the HOMO that are involved, because they are the most weakly held. When electrons are transferred *to* a molecule, they go into the LUMO, because that is the lowest energy orbital available.

Ethylene. Let's begin by examining the π molecular orbitals of ethylene. Recall from Section 1.14 that the number of molecular orbitals is equal to the number of atomic orbitals that combine to form them. We saw that the 1*s* orbitals of two hydrogen atoms overlap to give both a bonding (σ) and an antibonding (σ*) orbital. The same principle applies to π orbitals. As Figure 10.8 illustrates for the case of ethylene, the 2*p* orbitals of adjacent carbons overlap to give both a bonding (π) and an antibonding (π*) orbital. Notice that the σ electrons are not explicitly considered in Figure 10.8. These electrons are strongly held, and the collection of σ bonds can be thought of as an inert framework that supports the valence electrons of the π orbital.

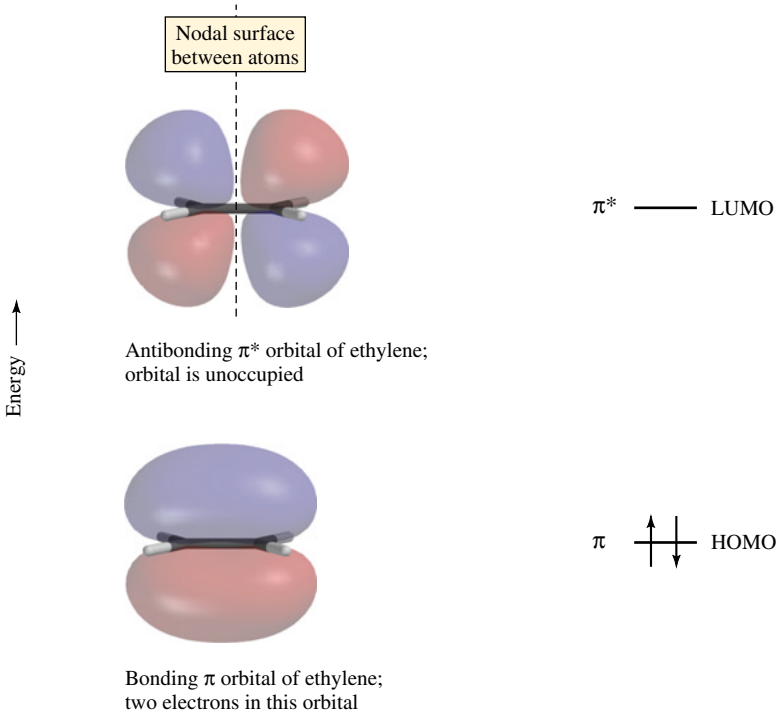


FIGURE 10.8 The bonding (π) and antibonding (π*) molecular orbitals of ethylene. The wave function changes sign (red to blue) on passing through a nodal surface. The plane of the molecule is a nodal surface in both orbitals; the antibonding orbital has an additional nodal surface perpendicular to the plane of the molecule.

Both the π and π* molecular orbitals of ethylene are *antisymmetric* with respect to the plane of the molecule. By this we mean that the wave function changes sign on passing through the molecular plane. It's convenient to designate the signs of *p* orbital wave functions by shading one lobe of a *p* orbital in red and the other in blue instead of using plus (+) and minus (−) signs that might be confused with electronic charges. The plane of the molecule corresponds to a nodal plane where the probability of finding the π electrons is zero. The bonding π orbital has no nodes other than this plane, whereas the antibonding π* orbital has a nodal plane between the two carbons. The more nodes an orbital has, the higher is its energy.

As is true for all orbitals, a π orbital may contain a maximum of two electrons. Ethylene has two π electrons, and these occupy the bonding π molecular orbital, which is the HOMO. The antibonding π* molecular orbital is vacant, and is the LUMO.

PROBLEM 10.15 Which molecular orbital of ethylene (π or π*) is the most important one to look at in a reaction in which ethylene is attacked by an electrophile?

1,3-Butadiene. The π molecular orbitals of 1,3-butadiene are shown in Figure 10.9. The four sp^2-hybridized carbons contribute four 2*p* atomic orbitals, and their overlap leads to four π molecular orbitals. Two are bonding (π_1 and π_2) and two are antibonding (π_3^* and π_4^*). Each π molecular orbital encompasses all four carbons of the diene. There are four π electrons, and these are distributed in pairs between the two orbitals of lowest energy (π_1 and π_2). Both bonding orbitals are occupied; π_2 is the HOMO. Both antibonding orbitals are vacant; π_3^* is the LUMO.

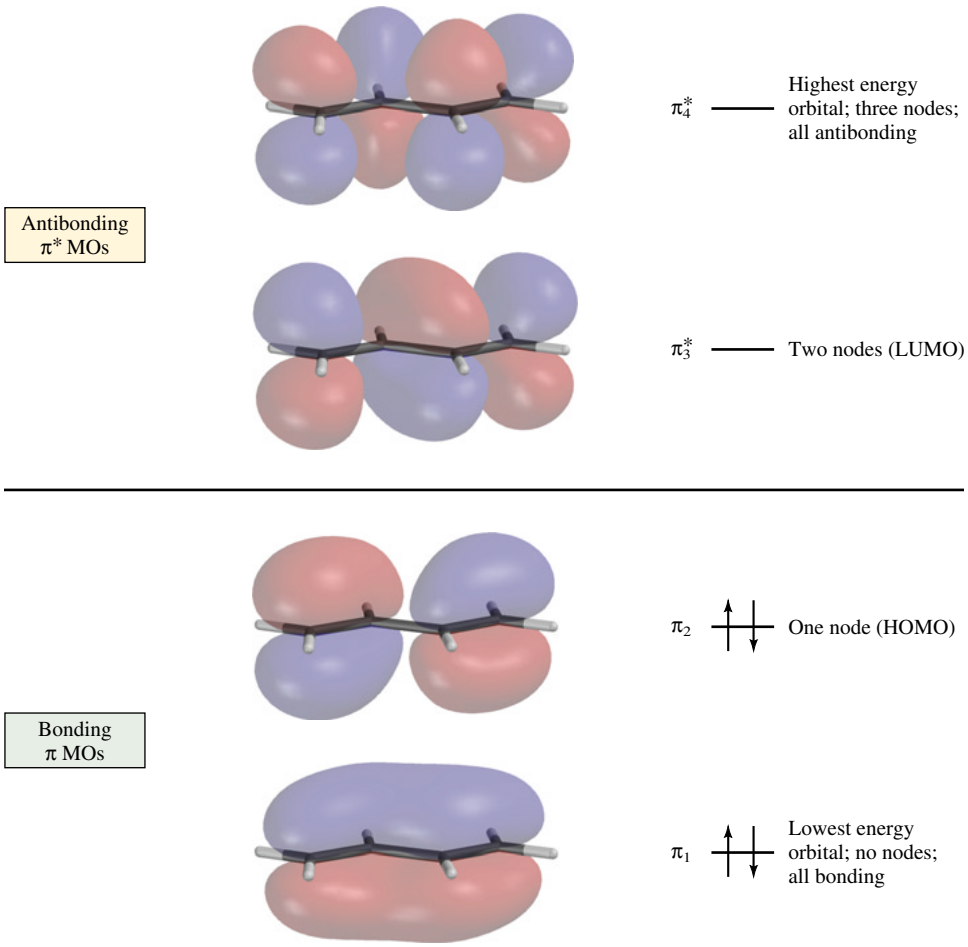


FIGURE 10.9 The π molecular orbitals of 1,3-butadiene.

10.14 A π MOLECULAR ORBITAL ANALYSIS OF THE DIELS–ALDER REACTION

Let us now examine the Diels–Alder cycloaddition from a molecular orbital perspective. Chemical experience, such as the observation that the substituents that increase the reactivity of a dienophile tend to be those that attract electrons, suggests that electrons flow from the diene to the dienophile during the reaction. Thus, the orbitals to be considered are the HOMO of the diene and the LUMO of the dienophile. As shown in Figure 10.10 for the case of ethylene and 1,3-butadiene, the symmetry properties of the HOMO of the diene and the LUMO of the dienophile permit bond formation between the ends of the diene system and the two carbons of the dienophile double bond because the necessary orbitals overlap "in phase" with each other. Cycloaddition of a diene and an alkene is said to be a **symmetry-allowed** reaction.

Contrast the Diels–Alder reaction with a cycloaddition reaction that looks superficially similar, the combination of two ethylene molecules to give cyclobutane.

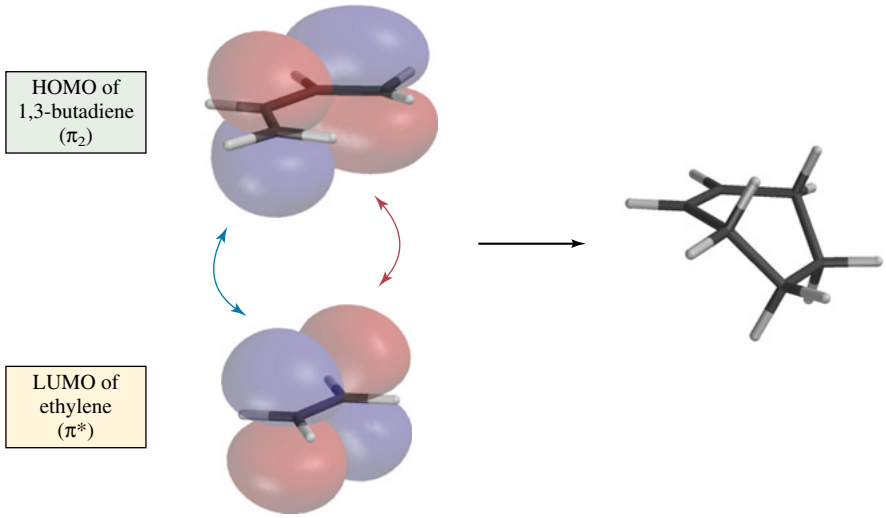
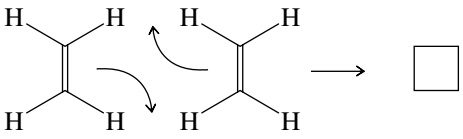


FIGURE 10.10 The HOMO of 1,3-butadiene and the LUMO of ethylene have the proper symmetry to allow σ bond formation to occur at both ends of the diene chain in the same transition state.



Reactions of this type are rather rare and seem to proceed in a stepwise fashion rather than by way of a concerted mechanism involving a single transition state.

Figure 10.11 shows the interaction between the HOMO of one ethylene molecule and the LUMO of another. In particular, notice that two of the carbons that are to become

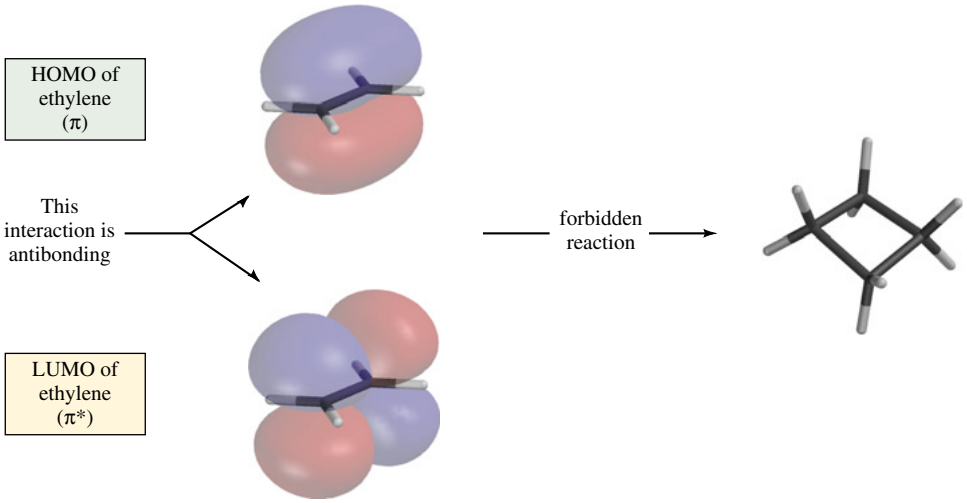
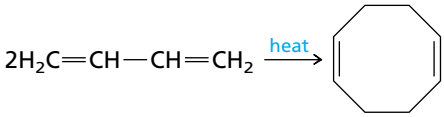


FIGURE 10.11 The HOMO of one ethylene molecule and the LUMO of another do not have the proper symmetry to permit two σ bonds to be formed in the same transition state for concerted cycloaddition.

σ-bonded to each other in the product experience an antibonding interaction during the cycloaddition process. This raises the activation energy for cycloaddition and leads the reaction to be classified as a **symmetry-forbidden** reaction. Reaction, were it to occur, would take place slowly and by a mechanism in which the two new σ bonds are formed in separate steps rather than by way of a concerted process involving a single transition state.

PROBLEM 10.16 Use frontier orbital analysis to decide whether the dimerization of 1,3-butadiene shown here is allowed or forbidden.

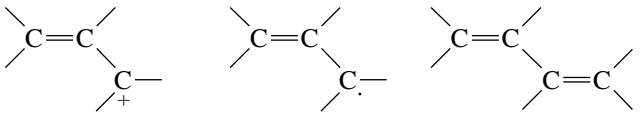


Frontier orbital analysis is a powerful theory that aids our understanding of a great number of organic reactions. Its early development is attributed to Professor Kenichi Fukui of Kyoto University, Japan. The application of frontier orbital methods to Diels–Alder reactions represents one part of what organic chemists refer to as the *Woodward–Hoffmann rules,* a beautifully simple analysis of organic reactions by Professor R. B. Woodward of Harvard University and Professor Roald Hoffmann of Cornell University. Professors Fukui and Hoffmann were corecipients of the 1981 Nobel Prize in chemistry for their work.

Woodward's death in 1979 prevented his being considered for a share of the 1981 prize with Fukui and Hoffmann. Woodward had earlier won a Nobel Prize (1965) for his achievements in organic synthesis.

10.15 SUMMARY

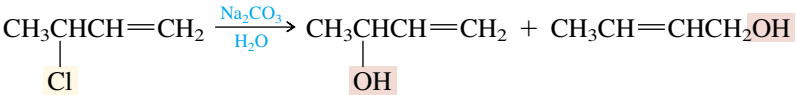
This chapter focused on the effect of a carbon–carbon double bond as a stabilizing substituent on a positively charged carbon in an **allylic carbocation,** on a carbon bearing an odd electron in an **allylic free radical,** and on a second double bond as in a **conjugated diene.**



Allylic carbocation Allylic radical Conjugated diene

Section 10.1 **Allyl** is the common name of the parent group $CH_2{=}CHCH_2{-}$ and is an acceptable name in IUPAC nomenclature.

Section 10.2 The carbocations formed as intermediates when allylic halides undergo S_N1 reactions have their positive charge shared by the two end carbons of the allylic system and may be attacked by nucleophiles at either site. Products may be formed with the same pattern of bonds as the starting allylic halide or with *allylic rearrangement.*

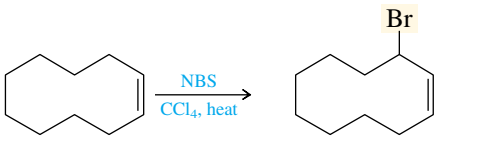


3-Chloro-1-butene 3-Buten-2-ol (65%) 2-Buten-1-ol (35%)

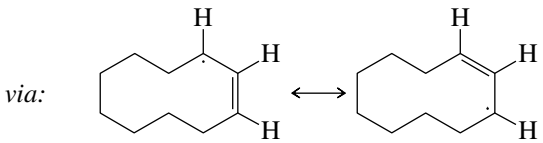
via: $CH_3\overset{+}{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3CH{=}CH{-}\overset{+}{C}H_2$

Sections 10.3–10.4

Alkenes react with *N*-bromosuccinimide (NBS) to give allylic bromides. NBS serves as a source of Br_2, and substitution occurs by a free-radical mechanism. The reaction is used for synthetic purposes only when the two resonance forms of the allylic radical are equivalent. Otherwise a mixture of isomeric allylic bromides is produced.

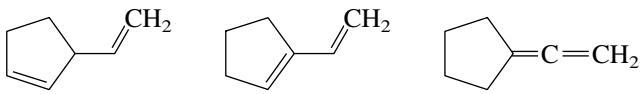


Cyclodecene 3-Bromocyclodecene (56%)



Section 10.5

Dienes are classified as having **isolated, conjugated,** or **cumulated** double bonds.



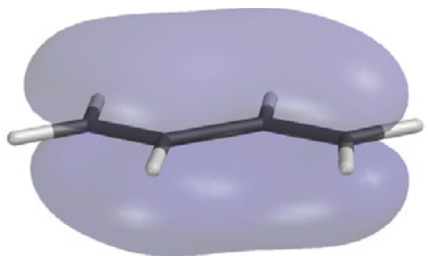
Isolated Conjugated Cumulated

Section 10.6

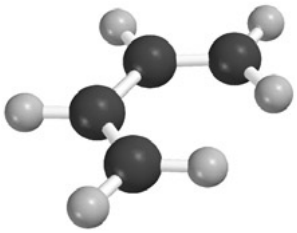
Conjugated dienes are more stable than isolated dienes, and cumulated dienes are the least stable of all.

Section 10.7

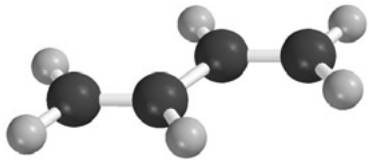
Conjugated dienes are stabilized by electron delocalization to the extent of 12–16 kJ/mol (3–4 kcal/mol). Overlap of the *p* orbitals of four adjacent sp^2-hybridized carbons in a conjugated diene gives an extended π system through which the electrons are delocalized.



The two most stable conformations of conjugated dienes are the *s*-cis and *s*-trans. The *s*-trans conformation is normally more stable than the *s*-cis. Both conformations are planar, which allows the *p* orbitals to overlap to give an extended π system.



s-cis



s-trans

Section 10.8 1,2-Propadiene ($CH_2{=}C{=}CH_2$), also called **allene,** is the simplest cumulated diene. The two π bonds in an allene share an *sp*-hybridized carbon and are at right angles to each other. Certain allenes such as 2,3-pentadiene ($CH_3CH{=}C{=}CHCH_3$) possess a *stereogenic axis* and are chiral.

Section 10.9 1,3-Butadiene is an industrial chemical and is prepared by dehydrogenation of butane. Elimination reactions such as dehydration and dehydrohalogenation are common routes to alkadienes.

$$CH_2{=}CHCH_2\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2CH_3 \xrightarrow[\text{heat}]{KHSO_4} CH_2{=}CHCH{=}\overset{\displaystyle CH_3}{\overset{|}{C}}CH_2CH_3$$

$\overset{|}{OH}$

3-Methyl-5-hexen-3-ol 4-Methyl-1,3-hexadiene (88%)

Elimination is typically regioselective and gives a conjugated diene rather than an isolated or cumulated diene system of double bonds.

Section 10.10 Protonation at the terminal carbon of a conjugated diene system gives an allylic carbocation that can be captured by the halide nucleophile at either of the two sites that share the positive charge. Nucleophilic attack at the carbon adjacent to the one that is protonated gives the product of *direct addition* (*1,2 addition*). Capture at the other site gives the product of *conjugate addition* (*1,4 addition*).

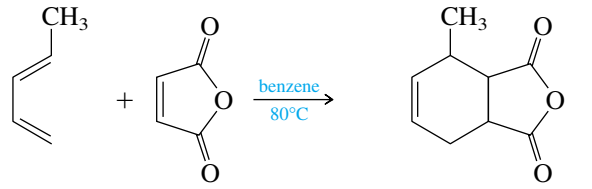
$$CH_2{=}CHCH{=}CH_2 \xrightarrow{HCl} CH_3\overset{\displaystyle Cl}{\overset{|}{C}}HCH{=}CH_2 + CH_3CH{=}CHCH_2Cl$$

1,3-Butadiene 3-Chloro-1-butene (78%) 1-Chloro-2-butene (22%)

via: $CH_3\overset{+}{C}H{-}CH{=}CH_2 \longleftrightarrow CH_3CH{=}CH{-}\overset{+}{C}H_2$

Section 10.11 1,4-Addition predominates when Cl_2 and Br_2 add to conjugated dienes.

Section 10.12 Conjugate addition of an alkene (the *dienophile*) to a conjugated diene gives a cyclohexene derivative in a process called the *Diels–Alder reaction.* It is concerted and stereospecific; substituents that are cis to each other on the dienophile remain cis in the product.



trans-1,3-Pentadiene + Maleic anhydride → 3-Methylcyclohexene-4,5-dicarboxylic anhydride (81%)

Sections 10.13–10.14 The Diels–Alder reaction is believed to proceed in a single step. A deeper level of understanding of the bonding changes in the transition state can be obtained by examining the nodal properties of the highest occupied molecular orbital (HOMO) of the diene and the lowest unoccupied molecular orbital (LUMO) of the dienophile.

PROBLEMS

10.17 Write structural formulas for each of the following:

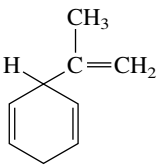
(a) 3,4-Octadiene
(b) (*E, E*)-3,5-Octadiene
(c) (*Z, Z*)-1,3-Cyclooctadiene
(d) (*Z, Z*)-1,4-Cyclooctadiene
(e) (*E, E*)-1,5-Cyclooctadiene
(f) (2*E*,4*Z*,6*E*)-2,4,6-Octatriene
(g) 5-Allyl-1,3-cyclopentadiene
(h) *trans*-1,2-Divinylcyclopropane
(i) 2,4-Dimethyl-1,3-pentadiene

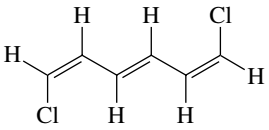
10.18 Give the IUPAC names for each of the following compounds:

(a) $CH_2{=}CH(CH_2)_5CH{=}CH_2$

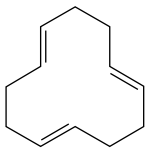
(b) $(CH_3)_2C{=}C(CH_3){-}C(CH_3){=}C(CH_3)_2$

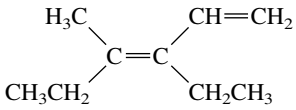
(c) $(CH_2{=}CH)_3CH$

(d) 

(e) 

(f) $CH_2{=}C{=}CHCH{=}CHCH_3$

(g) 

(h) 

10.19 (a) What compound of molecular formula C_6H_{10} gives 2,3-dimethylbutane on catalytic hydrogenation over platinum?

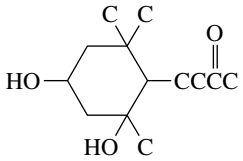
(b) What two compounds of molecular formula $C_{11}H_{20}$ give 2,2,6,6-tetramethylheptane on catalytic hydrogenation over platinum?

10.20 Write structural formulas for all the

(a) Conjugated dienes (b) Isolated dienes (c) Cumulated dienes

that give 2,4-dimethylpentane on catalytic hydrogenation.

10.21 A certain species of grasshopper secretes an allenic substance of molecular formula $C_{13}H_{20}O_3$ that acts as an ant repellent. The carbon skeleton and location of various substituents in this substance are indicated in the partial structure shown. Complete the structure, adding double bonds where appropriate.

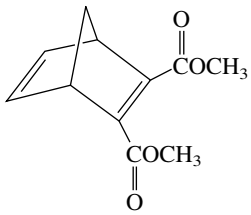


10.22 Show how you could prepare each of the following compounds from propene and any necessary organic or inorganic reagents:

(a) Allyl bromide
(b) 1,2-Dibromopropane
(c) 1,3-Dibromopropane
(d) 1-Bromo-2-chloropropane
(e) 1,2,3-Tribromopropane
(f) Allyl alcohol
(g) 1-Penten-4-yne ($CH_2{=}CHCH_2C{\equiv}CH$)
(h) 1,4-Pentadiene

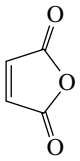
10.23 Show, by writing a suitable sequence of chemical equations, how you could prepare each of the following compounds from cyclopentene and any necessary organic or inorganic reagents:

(a) 2-Cyclopenten-1-ol
(b) 3-Iodocyclopentene
(c) 3-Cyanocyclopentene
(d) 1,3-Cyclopentadiene
(e)



10.24 Give the structure, exclusive of stereochemistry, of the principal organic product formed on reaction of 2,3-dimethyl-1,3-butadiene with each of the following:

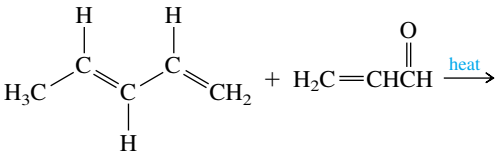
(a) 2 mol H_2, platinum catalyst
(b) 1 mol HCl (product of direct addition)
(c) 1 mol HCl (product of conjugate addition)
(d) 1 mol Br_2 (product of direct addition)
(e) 1 mol Br_2 (product of conjugate addition)
(f) 2 mol Br_2
(g)



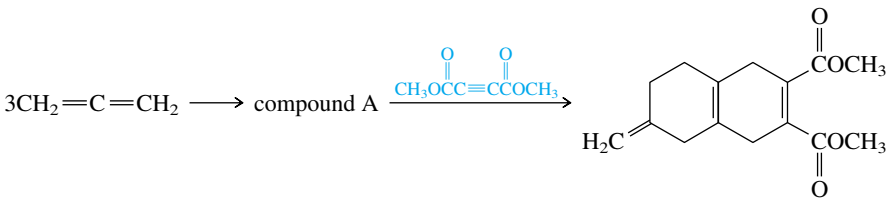
10.25 Repeat the previous problem for the reactions of 1,3-cyclohexadiene.

10.26 Give the structure of the Diels–Alder adduct of 1,3-cyclohexadiene and dimethyl acetylenedicarboxylate. ($CH_3OCC{\equiv}CCOCH_3$)

10.27 Two constitutional isomers of molecular formula $C_8H_{12}O$ are formed in the following reaction. Ignoring stereochemistry suggest reasonable structures for these Diels–Alder adducts.

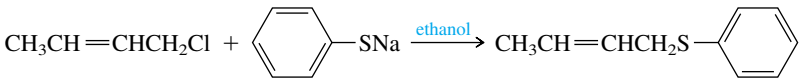


10.28 Allene can be converted to a trimer (compound A) of molecular formula C_9H_{12}. Compound A reacts with dimethyl acetylenedicarboxylate to give compound B. Deduce the structure of compound A.



Compound B

10.29 The following reaction gives only the product indicated. By what mechanism does this reaction most likely occur?



10.30 Suggest reasonable explanations for each of the following observations:

(a) The first-order rate constant for the solvolysis of $(CH_3)_2C{=}CHCH_2Cl$ in ethanol is over 6000 times greater than that of allyl chloride (25°C).

(b) After a solution of 3-buten-2-ol in aqueous sulfuric acid had been allowed to stand for 1 week, it was found to contain both 3-buten-2-ol and 2-buten-1-ol.

(c) Treatment of $CH_3CH{=}CHCH_2OH$ with hydrogen bromide gave a mixture of 1-bromo-2-butene and 3-bromo-1-butene.

(d) Treatment of 3-buten-2-ol with hydrogen bromide gave the same mixture of bromides as in part (c).

(e) The major product in parts (c) and (d) was 1-bromo-2-butene.

10.31 2-Chloro-1,3-butadiene (chloroprene) is the monomer from which the elastomer *neoprene* is prepared. 2-Chloro-1,3-butadiene is the thermodynamically controlled product formed by addition of hydrogen chloride to vinylacetylene ($CH_2{=}CHC{\equiv}CH$). The principal product under conditions of kinetic control is the allenic chloride 4-chloro-1,2-butadiene. Suggest a mechanism to account for the formation of each product.

10.32 (a) Write equations expressing the *s*-trans $\rightleftharpoons$ *s*-cis conformational equilibrium for (*E*)-1,3-pentadiene and for (*Z*)-1,3-pentadiene.

(b) For which stereoisomer will the equilibrium favor the *s*-trans conformation more strongly? Why? Support your prediction by making molecular models.

10.33 Which of the following are chiral?

(a) 2-Methyl-2,3-hexadiene

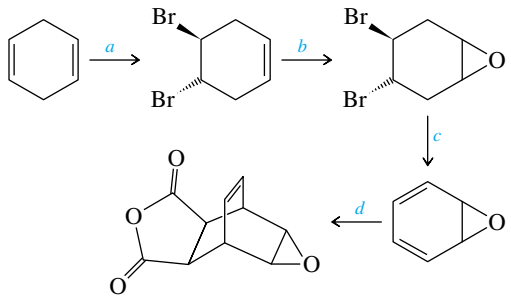
(b) 4-Methyl-2,3-hexadiene

(c) 2,4-Dimethyl-2,3-pentadiene

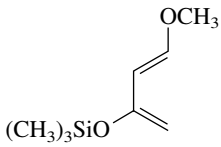
10.34 (a) Describe the molecular geometry expected for 1,2,3-butatriene ($CH_2{=}C{=}C{=}CH_2$).

(b) Two stereoisomers are expected for 2,3,4-hexatriene ($CH_3CH{=}C{=}C{=}CHCH_3$). What should be the relationship between these two stereoisomers?

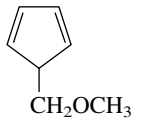
10.35 Suggest reagents suitable for carrying out each step in the following synthetic sequence:



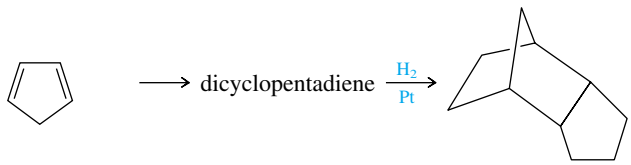
10.36 A very large number of Diels–Alder reactions are recorded in the chemical literature, many of which involve relatively complicated dienes, dienophiles, or both. On the basis of your knowledge of Diels–Alder reactions, predict the constitution of the Diels–Alder adduct that you would expect to be formed from the following combinations of dienes and dienophiles:

(a)  + $CH_3O_2CC{\equiv}CCO_2CH_3$

(b)  + $CH_3O_2CC{\equiv}CCO_2CH_3$

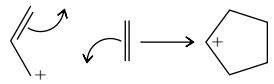
(c)  + $CH_2{=}CHNO_2$

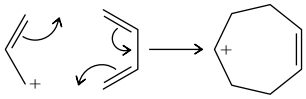
10.37 On standing, 1,3-cyclopentadiene is transformed into a new compound called *dicyclopentadiene,* having the molecular formula $C_{10}H_{12}$. Hydrogenation of dicyclopentadiene gives the compound shown. Suggest a structure for dicyclopentadiene. What kind of reaction is occurring in its formation?



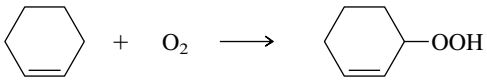
1,3-Cyclopentadiene $C_{10}H_{12}$ $C_{10}H_{16}$

10.38 Refer to the molecular orbital diagrams of allyl cation (Figure 10.12) and those presented earlier in this chapter for ethylene and 1,3-butadiene (Figures 10.8 and 10.9) to decide which of the following cycloaddition reactions are allowed and which are forbidden according to the Woodward–Hoffmann rules.

(a) 

(b) 

10.39 Alkenes slowly undergo a reaction in air called *autoxidation* in which allylic hydroperoxides are formed.



Cyclohexene Oxygen 3-Hydroperoxycyclohexene

Keeping in mind that oxygen has two unpaired electrons ($\cdot\ddot{O}:\ddot{O}\cdot$), suggest a reasonable mechanism for this reaction.

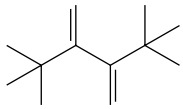
10.40 Make molecular models of:

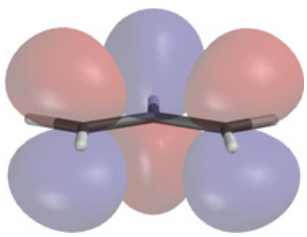
(a) 1,2-Pentadiene (c) 1,4-Pentadiene

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

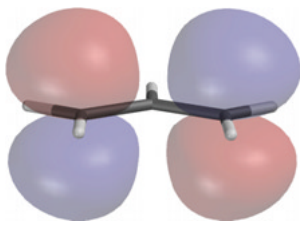
Examine the C—C bond distances in these substances. Is there a correlation with the hybridization states of the bonded carbons?

10.41 The compound shown is quite unreactive in Diels–Alder reactions. Make a space-filling model of it in the conformation required for the Diels–Alder reaction to see why.

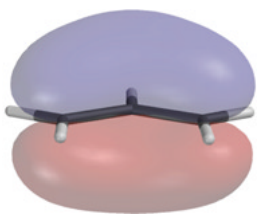




π_3^* ——



π_2 ——



π_2 

FIGURE 10.12 The π molecular orbitals of allyl cation. Allyl cation has two π electrons, and they are in the orbital marked π_1.