6 Alkenes: Structure and Reactivity

Organic KNOWLEDGE TOOLS

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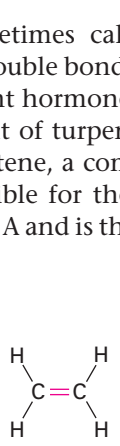
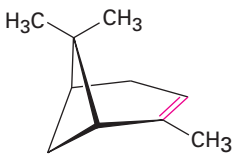
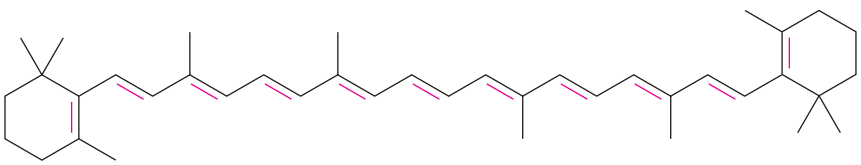
An **alkene**, sometimes called an *olefin*, is a hydrocarbon that contains a carbon–carbon double bond. Alkenes occur abundantly in nature. Ethylene, for instance, is a plant hormone that induces ripening in fruit, and α-pinene is the major component of turpentine. Life itself would be impossible without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



Ethylene



α-Pinene



β-Carotene
(orange pigment and vitamin A precursor)

WHY THIS CHAPTER?

Carbon–carbon double bonds are present in most organic and biological molecules, so a good understanding of their behavior is needed. In this chapter, we'll look at some consequences of alkene stereoisomerism and then focus on the broadest and most general class of alkene reactions, the electrophilic addition reaction.

Sean Duggan

6.1 Industrial Preparation and Use of Alkenes

Ethylene and propylene, the simplest alkenes, are the two most important organic chemicals produced industrially. Approximately 26 million tons of ethylene and 17 million tons of propylene are produced each year in the United States for use in the synthesis of polyethylene, polypropylene, ethylene glycol, acetic acid, acetaldehyde, and a host of other substances (Figure 6.1).

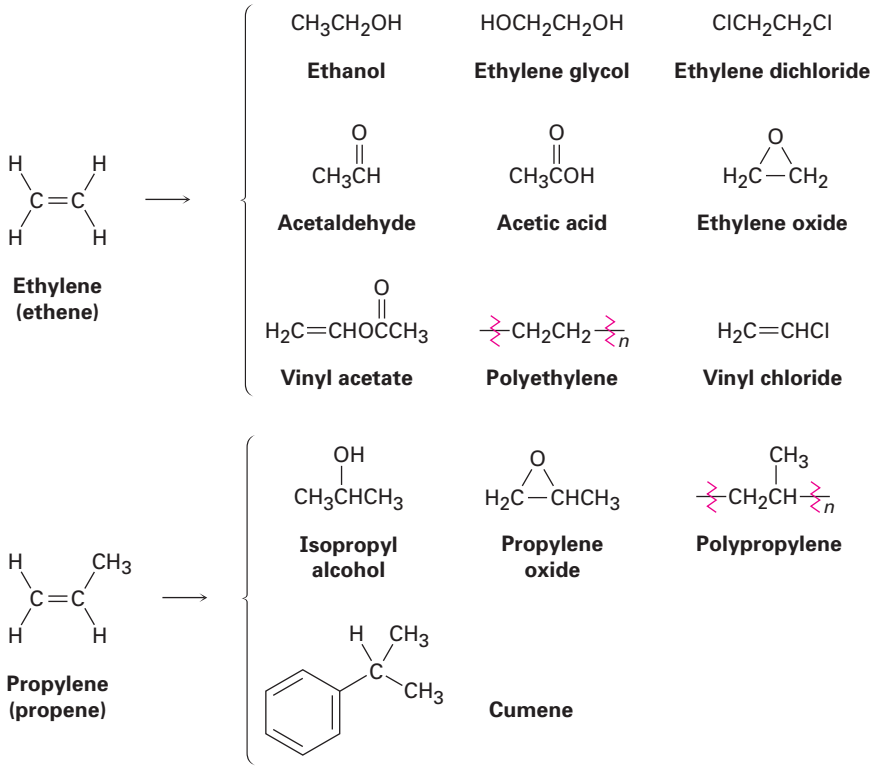


Figure 6.1 Compounds derived industrially from ethylene and propylene.

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

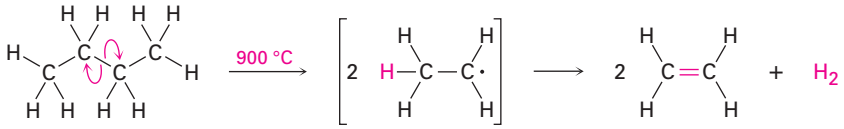
$$CH_3(CH_2)_nCH_3 \quad [n = 0\text{–}6]$$

$$\xrightarrow[\text{steam}]{850\text{–}900\ ^\circ C}$$

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

Thermal cracking takes place without a catalyst at temperatures up to 900 °C. The exact processes are complex, although they undoubtedly involve radical reactions. The high-temperature reaction conditions cause spontaneous homolytic breaking of C−C and C−H bonds, with resultant formation of smaller fragments. We might imagine, for instance, that a molecule of butane

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



Thermal cracking is an example of a reaction whose energetics are dominated by entropy ($\Delta S°$) rather than by enthalpy ($\Delta H°$) in the free-energy equation $\Delta G° = \Delta H° - T\Delta S°$. Although the bond dissociation energy D for a carbon–carbon single bond is relatively high (about 375 kJ/mol) and cracking is highly endothermic, the large positive entropy change resulting from the fragmentation of one large molecule into several smaller pieces, together with the extremely high temperature, makes the $T\Delta S°$ term larger than the $\Delta H°$ term, thereby favoring the cracking reaction.

6.2 Calculating Degree of Unsaturation

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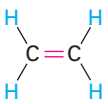
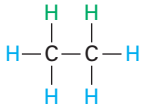
Because of its double bond, an alkene has fewer hydrogens than an alkane with the same number of carbons—C_nH_{2n} for an alkene versus C_nH_{2n+2} for an alkane—and is therefore referred to as **unsaturated**. Ethylene, for example, has the formula C_2H_4, whereas ethane has the formula C_2H_6.



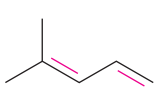
Ethylene: C_2H_4
(fewer hydrogens—*unsaturated*)



Ethane: C_2H_6
(more hydrogens—*saturated*)

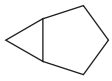
In general, each ring or double bond in a molecule corresponds to a loss of two hydrogens from the alkane formula C_nH_{2n+2}. Knowing this relationship, it's possible to work backward from a molecular formula to calculate a molecule's **degree of unsaturation**—the number of rings and/or multiple bonds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

Let's assume that we want to find the structure of an unknown hydrocarbon. A molecular weight determination on the unknown yields a value of 82, which corresponds to a molecular formula of C_6H_{10}. Since the saturated C_6 alkane (hexane) has the formula C_6H_{14}, the unknown compound has two fewer pairs of hydrogens ($H_{14} - H_{10} = H_4 = 2\ H_2$), and its degree of unsaturation is two. The unknown therefore contains two double bonds, one ring and one double bond, two rings, or one triple bond. There's still a long way to go to establish structure, but the simple calculation has told us a lot about the molecule.



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

Cyclohexene
(one ring, one double bond)



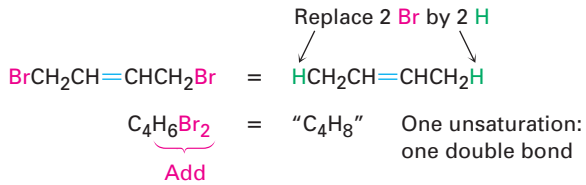
Bicyclo[3.1.0]hexane
(two rings)

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

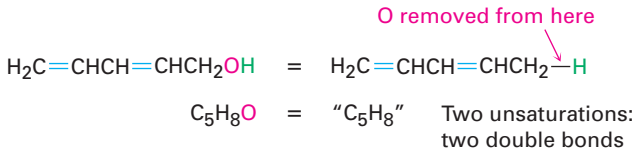
C_6H_{10}

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

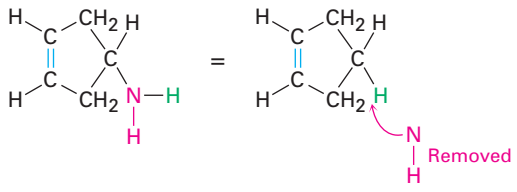
- **Organohalogen compounds (C, H, X, where X = F, Cl, Br, or I)** A halogen substituent acts simply as a replacement for hydrogen in an organic molecule, so we can add the number of halogens and hydrogens to arrive at an equivalent hydrocarbon formula from which the degree of unsaturation can be found. For example, the organohalogen formula $C_4H_6Br_2$ is equivalent to the hydrocarbon formula C_4H_8 and thus has one degree of unsaturation.



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



- **Organonitrogen compounds (C, H, N)** Nitrogen forms three bonds, so an organonitrogen compound has one more hydrogen than a related hydrocarbon; we therefore *subtract* the number of nitrogens from the number of hydrogens to arrive at the equivalent hydrocarbon formula. Again, you can convince yourself of this by seeing what happens when a nitrogen atom is inserted into an alkane bond: C–C becomes C–NH–C or C–H becomes C–NH_2, meaning that one additional hydrogen atom has been added. We must therefore subtract this extra hydrogen atom to arrive at the equivalent hydrocarbon formula. For example, the formula C_5H_9N is equivalent to C_5H_8 and thus has two degrees of unsaturation.



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

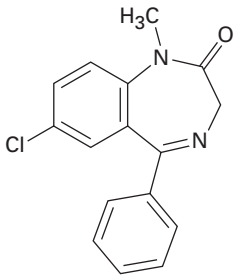
To summarize:

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

Problem 6.1 Calculate the degree of unsaturation in the following formulas, and then draw as many structures as you can for each:
(a) C_4H_8 **(b)** C_4H_6 **(c)** C_3H_4

Problem 6.2 Calculate the degree of unsaturation in the following formulas:
(a) C_6H_5N **(b)** $C_6H_5NO_2$ **(c)** $C_8H_9Cl_3$
(d) $C_9H_{16}Br_2$ **(e)** $C_{10}H_{12}N_2O_3$ **(f)** $C_{20}H_{32}ClN$

Problem 6.3 Diazepam, marketed as an antianxiety medication under the name Valium, has three rings, eight double bonds, and the formula $C_{16}H_?ClN_2O$. How many hydrogens does diazepam have? (Calculate the answer; don't count hydrogens in the structure.)



Diazepam

6.3 Naming Alkenes

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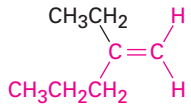
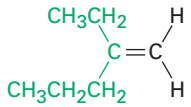
Alkenes are named using a series of rules similar to those for alkanes (Section 3.4), with the suffix *-ene* used instead of *-ane* to identify the family. There are three steps.

Step 1 **Name the parent hydrocarbon.** Find the longest carbon chain containing the double bond, and name the compound accordingly, using the suffix *-ene*:



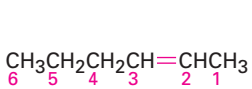
Named as a *pentene*

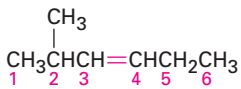
NOT



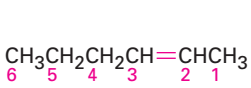
as a hexene, since the double bond is not contained in the six-carbon chain

Step 2 **Number the carbon atoms in the chain.** Begin at the end nearer the double bond or, if the double bond is equidistant from the two ends, begin at the end nearer the first branch point. This rule ensures that the double-bond carbons receive the lowest possible numbers.

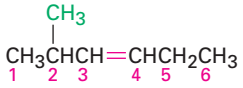




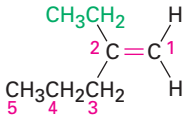
Step 3 **Write the full name.** Number the substituents according to their positions in the chain, and list them alphabetically. Indicate the position of the double bond by giving the number of the first alkene carbon and placing that number directly before the parent name. If more than one double bond is present, indicate the position of each and use one of the suffixes *-diene, -triene*, and so on.



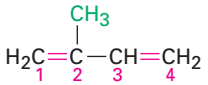
2-Hexene



2-Methyl-3-hexene

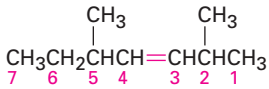


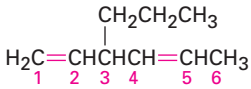
2-Ethyl-1-pentene



2-Methyl-1,3-butadiene

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

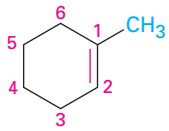




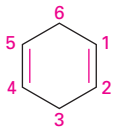
Older naming system: **2,5-Dimethyl-3-heptene** **3-Propyl-1,4-hexadiene**

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

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

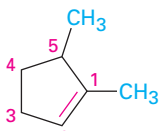


1-Methylcyclohexene



1,4-Cyclohexadiene

(New: Cyclohexa-1,4-diene)



1,5-Dimethylcyclopentene

For historical reasons, there are a few alkenes whose names are firmly entrenched in common usage but don't conform to the rules. For example, the alkene derived from ethane should be called *ethene,* but the name *ethylene* has

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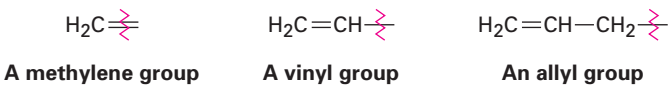
been used so long that it is accepted by IUPAC. Table 6.1 lists several other common names that are often used and are recognized by IUPAC. Note also that a $=CH_2$ substituent is called a **methylene group**, a $H_2C=CH-$ substituent is called a **vinyl group**, and a $H_2C=CHCH_2-$ substituent is called an **allyl group**.



A methylene group **A vinyl group** **An allyl group**

Table 6.1 Common Names of Some Alkenes

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

Problem 6.4 Give IUPAC names for the following compounds:

(a) $H_2C=CHCH(CH_3)C(CH_3)_2$

(b) $CH_3CH_2CH=C(CH_3)CH_2CH_3$

(c) $CH_3CH=CHCH(CH_3)CH=CHCH(CH_3)CH_3$

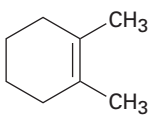
(d) $CH_3CH_2CH_2CH=CHCH(CH_2CH_3)_2$

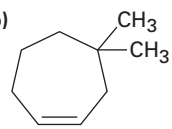
Problem 6.5 Draw structures corresponding to the following IUPAC names:

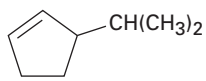
(a) 2-Methyl-1,5-hexadiene **(b)** 3-Ethyl-2,2-dimethyl-3-heptene

(c) 2,3,3-Trimethyl-1,4,6-octatriene **(d)** 3,4-Diisopropyl-2,5-dimethyl-3-hexene

Problem 6.6 Name the following cycloalkenes:

(a) 

(b) 

(c) 

6.4 Cis–Trans Isomerism in Alkenes

We saw in Chapter 1 that the carbon–carbon double bond can be described in two ways. In valence bond language (Section 1.8), the carbons are sp^2-hybridized and have three equivalent hybrid orbitals that lie in a plane at angles of 120° to one another. The carbons form a σ bond by head-on overlap of sp^2 orbitals and a π bond by sideways overlap of unhybridized p orbitals oriented

perpendicular to the sp^2 plane, as shown in Figure 1.14 on page 16. In molecular orbital language (Section 1.11), interaction between the p orbitals leads to one bonding and one antibonding π molecular orbital. The π bonding MO has no node between nuclei and results from a combination of p orbital lobes with the same algebraic sign. The π antibonding MO has a node between nuclei and results from a combination of lobes with different algebraic signs, as shown in Figure 1.18, page 22.

Although essentially free rotation is possible around single bonds (Section 3.6), the same is not true of double bonds. For rotation to occur around a double bond, the π bond must break and re-form (Figure 6.2). Thus, the barrier to double-bond rotation must be at least as great as the strength of the π bond itself, an estimated 350 kJ/mol (84 kcal/mol). Recall that the barrier to bond rotation in ethane is only 12 kJ/mol.

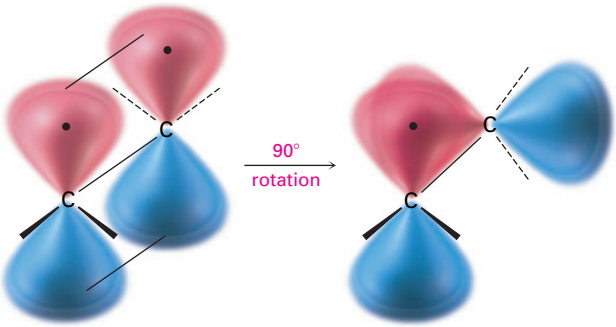
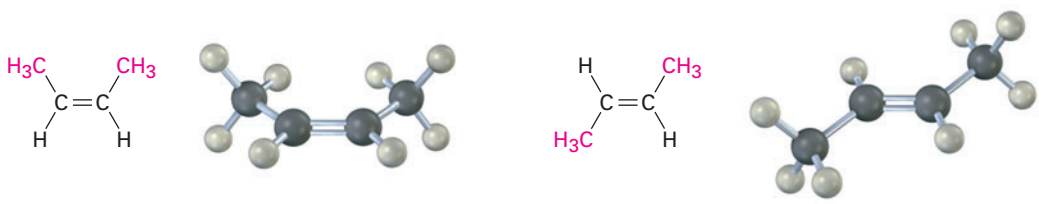


Figure 6.2 The π bond must break for rotation to take place around a carbon–carbon double bond.

The lack of rotation around carbon–carbon double bonds is of more than just theoretical interest; it also has chemical consequences. Imagine the situation for a disubstituted alkene such as 2-butene. (*Disubstituted* means that two substituents other than hydrogen are bonded to the double-bond carbons.) The two methyl groups in 2-butene can be either on the same side of the double bond or on opposite sides, a situation similar to that in disubstituted cycloalkanes (Section 4.2).

Since bond rotation can't occur, the two 2-butenes can't spontaneously interconvert; they are different, isolable compounds. As with disubstituted cycloalkanes, we call such compounds *cis–trans stereoisomers*. The compound with substituents on the same side of the double bond is called *cis*-2-butene, and the isomer with substituents on opposite sides is *trans*-2-butene (Figure 6.3).



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

Figure 6.3 Cis and trans isomers of 2-butene. The cis isomer has the two methyl groups on the same side of the double bond, and the trans isomer has the methyl groups on opposite sides.

Cis–trans isomerism is not limited to *di*substituted alkenes. It can occur whenever both double-bond carbons are attached to two different groups. If one of the double-bond carbons is attached to two identical groups, however, then cis–trans isomerism is not possible (Figure 6.4).

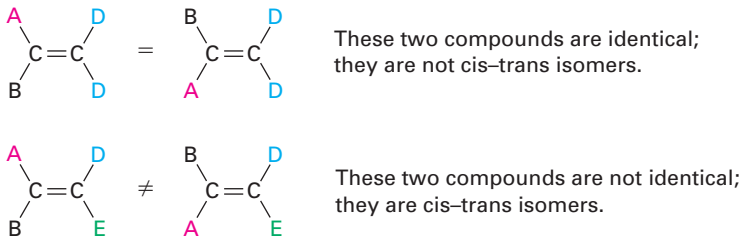
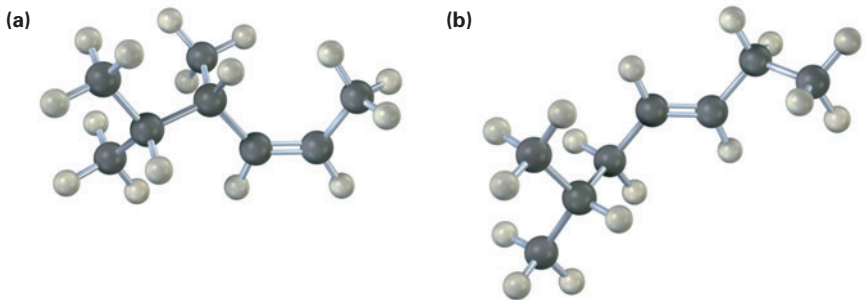


Figure 6.4 The requirement for cis–trans isomerism in alkenes. Compounds that have one of their carbons bonded to two identical groups can't exist as cis–trans isomers. Only when both carbons are bonded to two different groups are cis–trans isomers possible.

Problem 6.7 Which of the following compounds can exist as pairs of cis–trans isomers? Draw each cis–trans pair, and indicate the geometry of each isomer.

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

Problem 6.8 Name the following alkenes, including the cis or trans designation:



6.5 Sequence Rules: The *E,Z* Designation

Key IDEAS

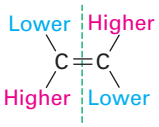
Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

The cis–trans naming system used in the previous section works only with *disubstituted* alkenes—compounds that have two substituents other than hydrogen on the double bond. With trisubstituted and tetrasubstituted double bonds, a more general method is needed for describing double-bond geometry. (*Trisubstituted* means three substituents other than hydrogen on the double bond; *tetrasubstituted* means four substituents other than hydrogen.)

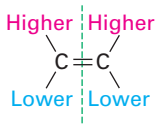
According to the ***E,Z* system** of nomenclature, a set of *sequence rules* is used to assign priorities to the substituent groups on the double-bond carbons. Considering each doubly bonded carbon atom separately, the sequence rules are used to decide which of the two attached groups is higher in priority. If the higher-priority groups on each carbon are on the same side of the double bond, the alkene is designated ***Z***, for the German *zusammen,* meaning "together." If the higher-priority groups are on opposite sides, the alkene is designated ***E***, for

ThomsonNOW™ Click *Organic Interactive* to **practice assigning priorities to groups according to the Cahn–Ingold–Prelog rules.**

the German *entgegen*, meaning "opposite." (A simple way to remember which is which is to note that the groups are on "ze zame zide" in the *Z* isomer.)



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



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

Called the *Cahn–Ingold–Prelog rules* after the chemists who proposed them, the sequence rules are as follows:

Rule 1 **Considering the double-bond carbons separately, look at the two atoms directly attached to each and rank them according to atomic number.** An atom with higher atomic number receives higher priority than an atom with lower atomic number. Thus, the atoms commonly found attached to a double bond are assigned the following order. Note that when different isotopes of the same element are compared, such as deuterium (^{2}H) and protium (^{1}H), the heavier isotope receives priority over the lighter isotope.

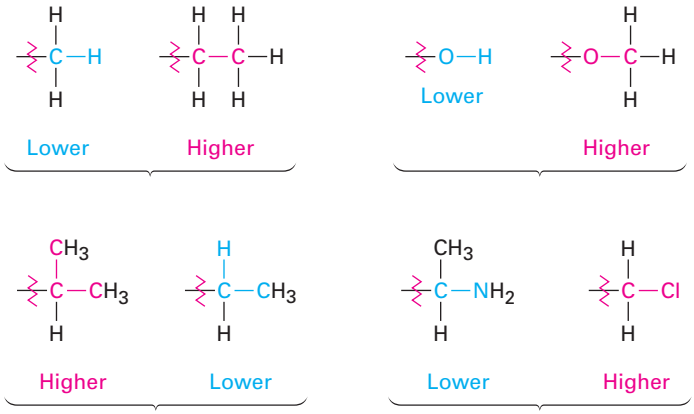
Robert Sidney Cahn	Sir Christopher Kelk Ingold	Vladimir Prelog
Robert Sidney Cahn (1899–1981) was born in England and received a doctoral degree in France. Although not specifically trained as a chemist, he became editor of the British *Journal of the Chemical Society*.	**Sir Christopher Kelk Ingold** (1893–1970) was born in Ilford, England, and received his D.Sc. at the University of London. After 6 years as professor at the University of Leeds, he spent his remaining career at University College, London (1930–1961). Ingold published more than 400 scientific papers and, along with Linus Pauling, was instrumental in developing the theory of resonance.	**Vladimir Prelog** (1906–1998) was born in Sarajevo, Bosnia, where, as a young boy, he was close enough to hear the shots that killed Archduke Ferdinand and ignited World War I. After receiving a Dr.Ing. degree in 1929 at the Institute of Technology in Prague, Czechoslovakia, he taught briefly at the University of Zagreb before becoming professor of chemistry at the Swiss Federal Institute of Technology (ETH) in Zürich (1941–1976). He received the 1975 Nobel Prize in chemistry for his lifetime achievements on the stereochemistry of antibiotics, alkaloids, enzymes, and other naturally occurring molecules.

For example:

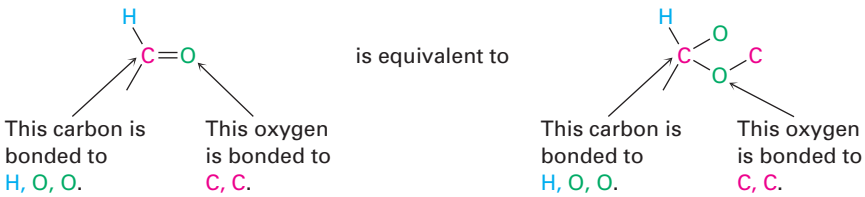
(a) (*E*)-2-Chloro-2-butene **(b) (*Z*)-2-Chloro-2-butene**

Because chlorine has a higher atomic number than carbon, a $-Cl$ substituent receives higher priority than a $-CH_3$ group. Methyl receives higher priority than hydrogen, however, and isomer (a) is assigned *E* geometry because its high-priority groups are on opposite sides of the double bond. Isomer (b) has *Z* geometry because its high-priority groups are on "ze zame zide" of the double bond.

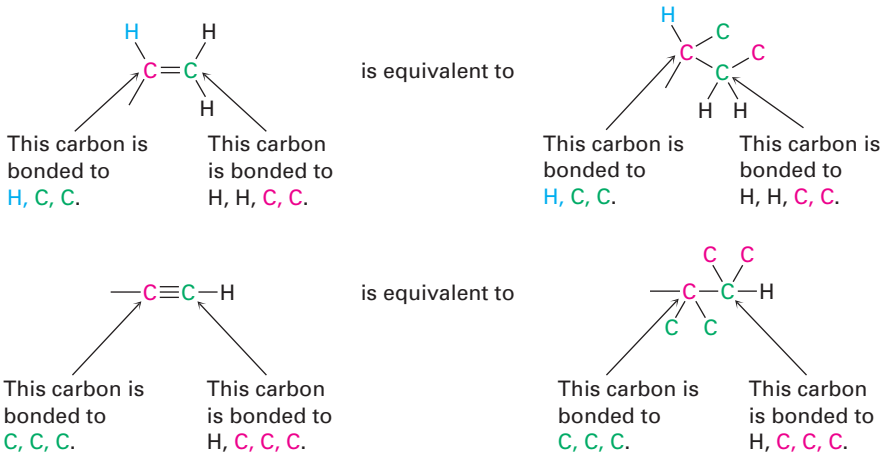
Rule 2 **If a decision can't be reached by ranking the first atoms in the substituent, look at the second, third, or fourth atoms away from the double-bond carbons until the first difference is found.** A $-CH_2CH_3$ substituent and a $-CH_3$ substituent are equivalent by rule 1 because both have carbon as the first atom. By rule 2, however, ethyl receives higher priority than methyl because ethyl has a *carbon* as its highest second atom, while methyl has only *hydrogen* as its second atom. Look at the following examples to see how the rule works:



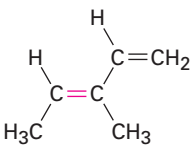
Rule 3 **Multiple-bonded atoms are equivalent to the same number of single-bonded atoms.** For example, an aldehyde substituent ($-CH{=}O$), which has a carbon atom *doubly* bonded to *one* oxygen, is equivalent to a substituent having a carbon atom *singly* bonded to *two* oxygens.



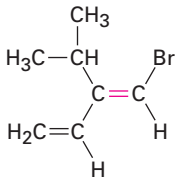
As further examples, the following pairs are equivalent:



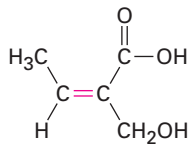
Taking all the sequence rules into account, we can assign the configurations shown in the following examples. Work through each one to convince yourself that the assignments are correct.



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



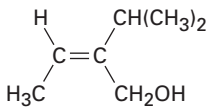
(*E*)-1-Bromo-2-isopropyl-1,3-butadiene



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

WORKED EXAMPLE 6.1 *Assigning E and Z Configurations to Substituted Alkenes*

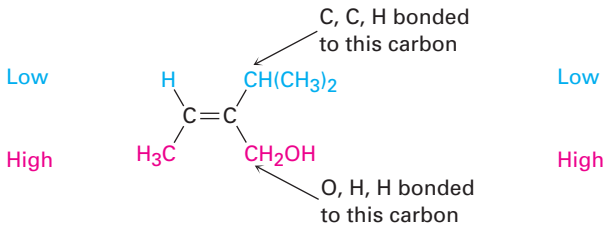
Assign *E* or *Z* configuration to the double bond in the following compound:



Strategy Look at the two substituents connected to each double-bond carbon, and determine their priorities using the Cahn–Ingold–Prelog rules. Then see whether the two high-priority groups are on the same or opposite sides of the double bond.

Solution The left-hand carbon has −H and $-CH_3$ substituents, of which $-CH_3$ receives higher priority by sequence rule 1. The right-hand carbon has $-CH(CH_3)_2$ and $-CH_2OH$ substituents, which are equivalent by rule 1. By rule 2, however, $-CH_2OH$ receives higher priority than $-CH(CH_3)_2$. The substituent $-CH_2OH$ has an *oxygen* as

its highest second atom, but $-CH(CH_3)_2$ has a *carbon* as its highest second atom. The two high-priority groups are on the same side of the double bond, so we assign *Z* configuration.



***Z* configuration**

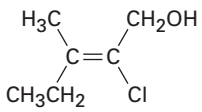
Problem 6.9 Which member in each of the following sets has higher priority?

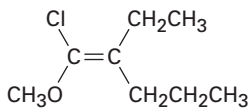
(a) $-H$ or $-Br$ **(b)** $-Cl$ or $-Br$ **(c)** $-CH_3$ or $-CH_2CH_3$
(d) $-NH_2$ or $-OH$ **(e)** $-CH_2OH$ or $-CH_3$ **(f)** $-CH_2OH$ or $-CH{=}O$

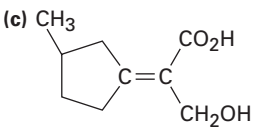
Problem 6.10 Rank the following sets of substituents in order of Cahn–Ingold–Prelog priorities:

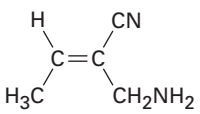
(a) $-CH_3$, $-OH$, $-H$, $-Cl$
(b) $-CH_3$, $-CH_2CH_3$, $-CH{=}CH_2$, $-CH_2OH$
(c) $-CO_2H$, $-CH_2OH$, $-C{\equiv}N$, $-CH_2NH_2$
(d) $-CH_2CH_3$, $-C{\equiv}CH$, $-C{\equiv}N$, $-CH_2OCH_3$

Problem 6.11 Assign *E* or *Z* configuration to the following alkenes:

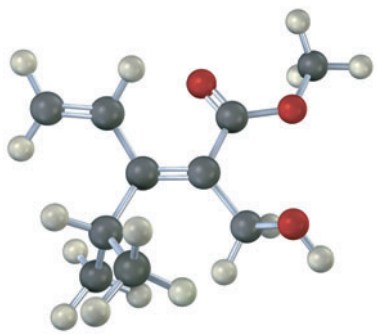
(a)


(b)


(c)


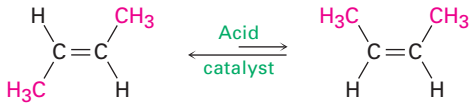
(d)


Problem 6.12 Assign stereochemistry (*E* or *Z*) to the double bond in the following compound, and convert the drawing into a skeletal structure (red = O):



6.6 Stability of Alkenes

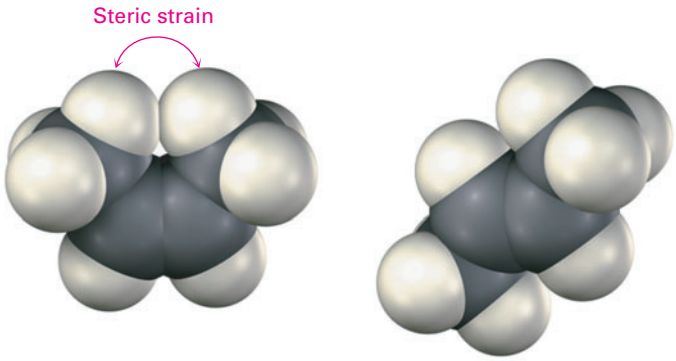
Although the cis–trans interconversion of alkene isomers does not occur spontaneously, it can often be brought about by treating the alkene with a strong acid catalyst. If we interconvert *cis*-2-butene with *trans*-2-butene and allow them to reach equilibrium, we find that they aren't of equal stability. The trans isomer is more stable than the cis isomer by 2.8 kJ/mol (0.66 kcal/mol) at room temperature, leading to a 76:24 ratio.



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

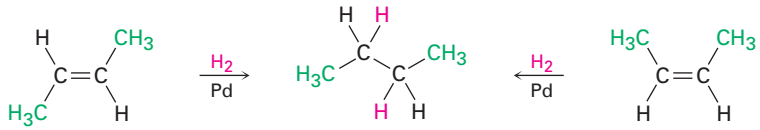
Using the relationship between equilibrium constant and free energy shown previously in Figure 4.12, p. 122, we can calculate that *cis*-2-butene is less stable than *trans*-2-butene by 2.8 kJ/mol (0.66 kcal/mol) at room temperature.

Cis alkenes are less stable than their trans isomers because of steric strain between the two larger substituents on the same side of the double bond. This is the same kind of steric interference that we saw previously in the axial conformation of methylcyclohexane (Section 4.7).



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

Although it's sometimes possible to find relative stabilities of alkene isomers by establishing a cis–trans equilibrium through treatment with strong acid, a more general method is to take advantage of the fact that alkenes undergo a *hydrogenation* reaction to give the corresponding alkane on treatment with H_2 gas in the presence of a catalyst such as palladium or platinum.



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

Energy diagrams for the hydrogenation reactions of *cis*- and *trans*-2-butene are shown in Figure 6.5. Since *cis*-2-butene is less stable than *trans*-2-butene by 2.8 kJ/mol, the energy diagram shows the cis alkene at a higher energy level. After reaction, however, both curves are at the same energy level (butane). It therefore follows that $\Delta G°$ for reaction of the cis isomer must be larger than $\Delta G°$ for reaction of the trans isomer by 2.8 kJ/mol. In other words, more energy is released in the hydrogenation of the cis isomer than the trans isomer because the cis isomer has more energy to begin with.

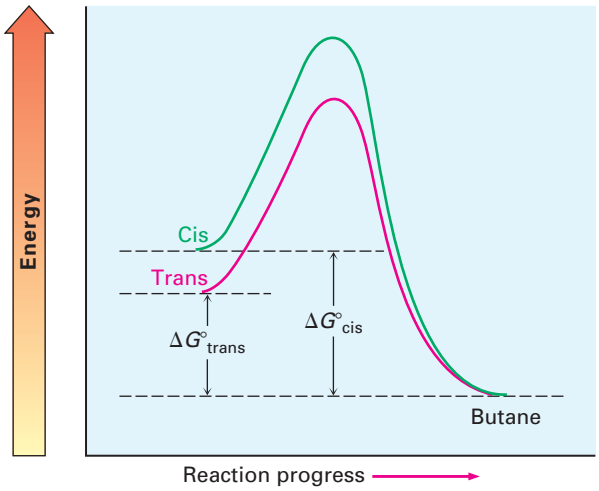
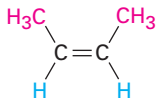
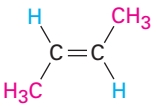


Figure 6.5 Energy diagrams for hydrogenation of *cis*- and *trans*-2-butene. The cis isomer is higher in energy than the trans isomer by about 2.8 kJ/mol and therefore releases more energy in the reaction.

If we were to measure what are called *heats of hydrogenation* ($\Delta H°_{hydrog}$) for the two double-bond isomers and find their difference, we could determine the relative stabilities of cis and trans isomers without having to measure an equilibrium position. In fact, the results bear out our expectation. For *cis*-2-butene, $\Delta H°_{hydrog} = -120$ kJ/mol (−28.6 kcal/mol); for the trans isomer, $\Delta H°_{hydrog} = -116$ kJ/mol (−27.6 kcal/mol).



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



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

The energy difference between the 2-butene isomers as calculated from heats of hydrogenation (4 kJ/mol) agrees reasonably well with the energy difference calculated from equilibrium data (2.8 kJ/mol), but the numbers aren't exactly the same for two reasons. First, there is probably some experimental error, since heats of hydrogenation require skill and specialized equipment to measure accurately. Second, heats of reaction and equilibrium constants don't measure exactly the same thing. Heats of reaction measure enthalpy changes, $\Delta H°$, whereas equilibrium constants measure free-energy changes, $\Delta G°$, so we might expect a slight difference between the two.

Table 6.2 lists some representative data for the hydrogenation of different alkenes, showing that alkenes become more stable with increasing substitution.

For example, ethylene has $\Delta H°_{hydrog} = -137$ kJ/mol (−32.8 kcal/mol), but when one alkyl substituent is attached to the double bond, as in 1-butene, the alkene becomes approximately 10 kJ/mol more stable ($\Delta H°_{hydrog} = -126$ kJ/mol). Further increasing the degree of substitution leads to still further stability. As a general rule, alkenes follow the stability order:

Tetrasubstituted > Trisubstituted > Disubstituted > Monosubstituted

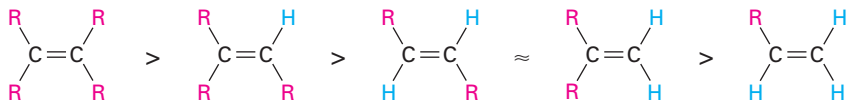


Table 6.2 Heats of Hydrogenation of Some Alkenes

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

The stability order of alkenes is due to a combination of two factors. One is a stabilizing interaction between the C=C π bond and adjacent C−H σ bonds on substituents. In valence-bond language, the interaction is called **hyperconjugation**. In a molecular orbital description, there is a bonding MO that extends over the four-atom C=C−C−H grouping, as shown in Figure 6.6. The more substituents that are present on the double bond, the more hyperconjugation there is and the more stable the alkene.

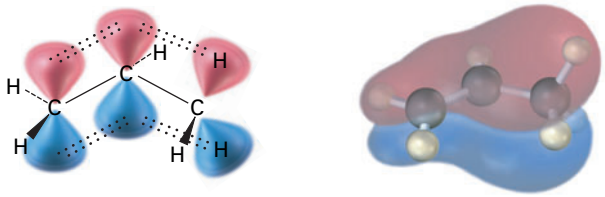


Figure 6.6 Hyperconjugation is a stabilizing interaction between an unfilled π orbital and a neighboring filled C−H σ bond on a substituent. The more substituents there are, the greater the stabilization of the alkene.

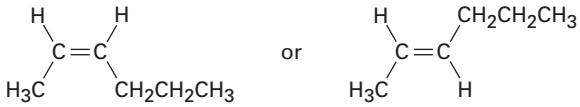
A second factor that contributes to alkene stability involves bond strengths. A bond between an sp^2 carbon and an sp^3 carbon is somewhat stronger than a bond between two sp^3 carbons. Thus, in comparing 1-butene and 2-butene, the monosubstituted isomer has one sp^3–sp^3 bond and one sp^3–sp^2 bond, while

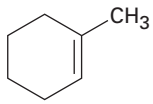
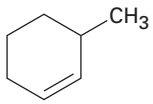
the disubstituted isomer has two sp^3–sp^2 bonds. More highly substituted alkenes always have a higher ratio of sp^3–sp^2 bonds to sp^3–sp^3 bonds than less highly substituted alkenes and are therefore more stable.

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

Problem 6.13 Name the following alkenes, and tell which compound in each pair is more stable:

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

(b)  or

(c)  or 

6.7 Electrophilic Addition Reactions of Alkenes

Before beginning a detailed discussion of alkene reactions, let's review briefly some conclusions from the previous chapter. We said in Section 5.5 that alkenes behave as nucleophiles (Lewis bases) in polar reactions. The carbon–carbon double bond is electron-rich and can donate a pair of electrons to an electrophile (Lewis acid). For example, reaction of 2-methylpropene with HBr yields 2-bromo-2-methylpropane. A careful study of this and similar reactions by Christopher Ingold and others in the 1930s led to the generally accepted mechanism shown in Figure 6.7 for **electrophilic addition reactions**.

The reaction begins with an attack on the electrophile, HBr, by the electrons of the nucleophilic π bond. Two electrons from the π bond form a new σ bond between the entering hydrogen and an alkene carbon, as shown by the curved arrow at the top of Figure 6.7. The carbocation intermediate that results is itself an electrophile, which can accept an electron pair from nucleophilic Br^- ion to form a C–Br bond and yield a neutral addition product.

ThomsonNOW™ Click *Organic Process* to **view an animation of this alkene addition reaction.**

The energy diagram for the overall electrophilic addition reaction (Figure 6.8) has two peaks (transition states) separated by a valley (carbocation intermediate). The energy level of the intermediate is higher than that of the starting alkene, but the reaction as a whole is exergonic (negative $\Delta G°$). The first step, protonation of the alkene to yield the intermediate cation, is relatively slow but, once formed, the cation intermediate rapidly reacts further to yield the final alkyl bromide product. The relative rates of the two steps are indicated in Figure 6.8 by the fact that $\Delta G^{\ddagger}_1$ is larger than $\Delta G^{\ddagger}_2$.

Figure 6.7 MECHANISM: Mechanism of the electrophilic addition of HBr to 2-methylpropene. The reaction occurs in two steps and involves a carbocation intermediate.

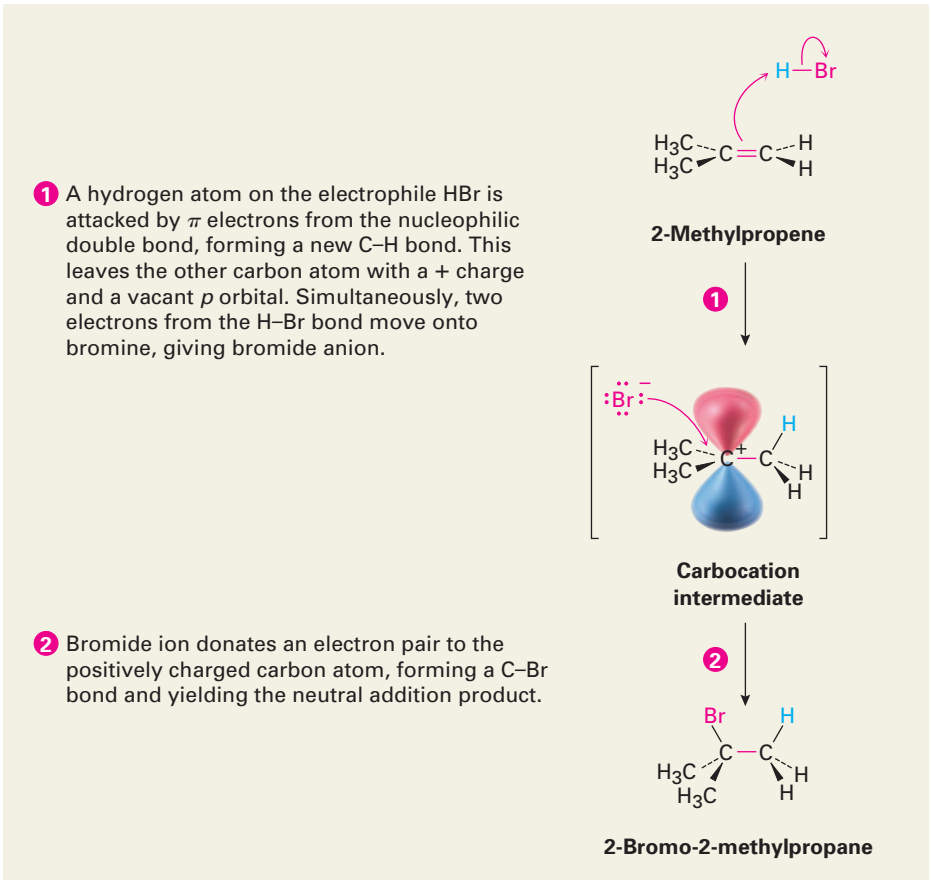
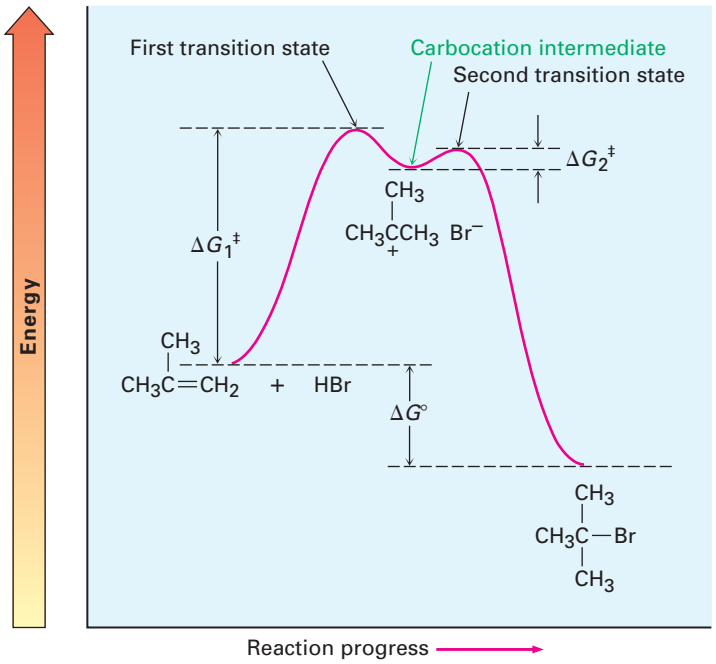
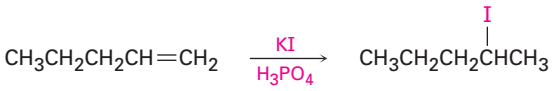


Figure 6.8 Energy diagram for the two-step electrophilic addition of HBr to 2-methylpropene. The first step is slower than the second step.



Electrophilic addition of HX to alkenes is successful not only with HBr but with HCl and HI as well. Note that HI is usually generated in the reaction mixture by treating potassium iodide with phosphoric acid.

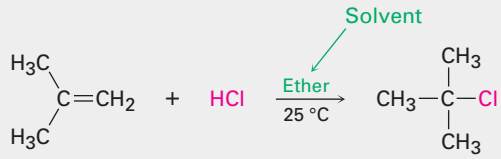
2-Methylpropene **2-Chloro-2-methylpropane (94%)**



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

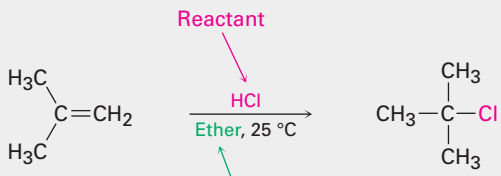
Writing Organic Reactions

This is a good time to mention that organic reaction equations are sometimes written in different ways to emphasize different points. In describing a laboratory process, for example, the reaction of 2-methylpropene with HCl just shown might be written in the format A + B □ C to emphasize that both reactants are equally important for the purposes of the discussion. The solvent and notes about other reaction conditions, such as temperature, are written either above or below the reaction arrow.



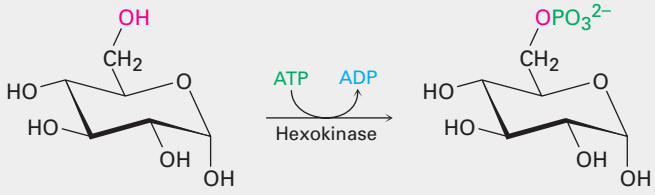
2-Methylpropene **2-Chloro-2-methylpropane**

Alternatively, we might write the same reaction in a format to emphasize that 2-methylpropene is the reactant whose chemistry is of greater interest. The second reactant, HCl, is placed above the reaction arrow together with notes about solvent and reaction conditions.



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

In describing a biological process, the reaction is usually written to show only the structure of the primary reactant and product, while abbreviating the structures of various biological "reagents" and by-products by using a curved arrow that intersects the straight reaction arrow. As discussed in Section 5.11, the reaction of glucose with ATP to give glucose 6-phosphate plus ADP would be written as



Glucose **Glucose 6-phosphate**

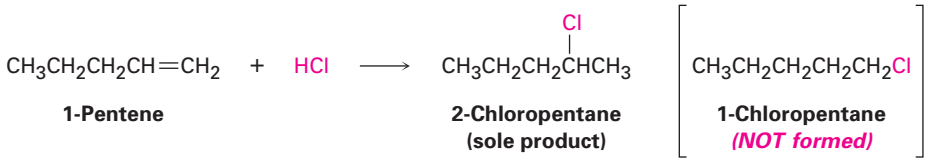
6.8 Orientation of Electrophilic Additions: Markovnikov's Rule

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products from the addition of HX to alkenes.**

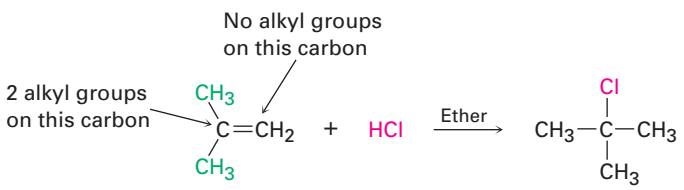
Look carefully at the reactions shown in the previous section. In each case, an unsymmetrically substituted alkene has given a single addition product, rather than the mixture that might have been expected. As another example, 1-pentene *might* react with HCl to give both 1-chloropentane and 2-chloropentane, but it doesn't. Instead, the reaction gives only 2-chloropentane as the sole product. We say that such reactions are **regiospecific** (**ree**-jee-oh-specific) when only one of two possible orientations of addition occurs.



1-Pentene **2-Chloropentane (sole product)** **1-Chloropentane *(NOT formed)***

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

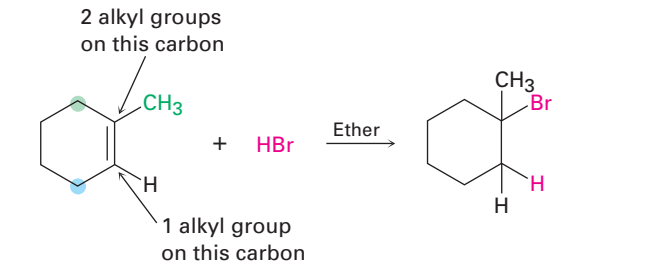
Markovnikov's rule In the addition of HX to an alkene, the H attaches to the carbon with fewer alkyl substituents and the X attaches to the carbon with more alkyl substituents.



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

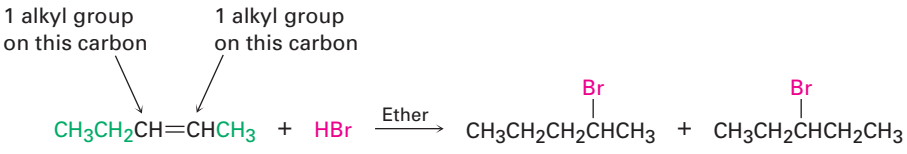
Vladimir Vassilyevich Markovnikov

Vladimir Vassilyevich Markovnikov (1838–1904) was born in Nijni-Novgorod, Russia, and received his Ph.D. working with A. M. Butlerov at the university in Kazan. He was a professor in Kazan (1870), Odessa (1871), and Moscow (1873–1898). In addition to his work on the orientation of addition reactions, he was the first to synthesize a four-membered ring.



1-Methylcyclohexene **1-Bromo-1-methylcyclohexane**

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



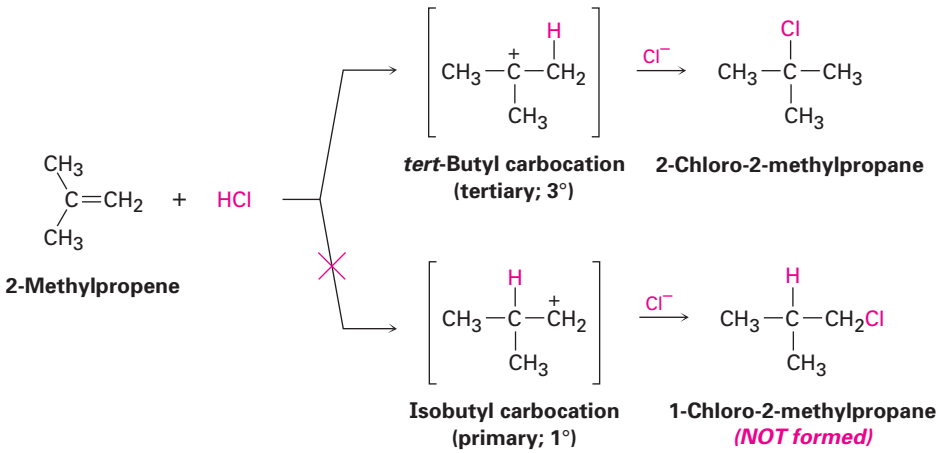
2-Pentene **2-Bromopentane** **3-Bromopentane**

Since carbocations are involved as intermediates in these reactions, Markovnikov's rule can be restated.

Markovnikov's rule (restated)

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

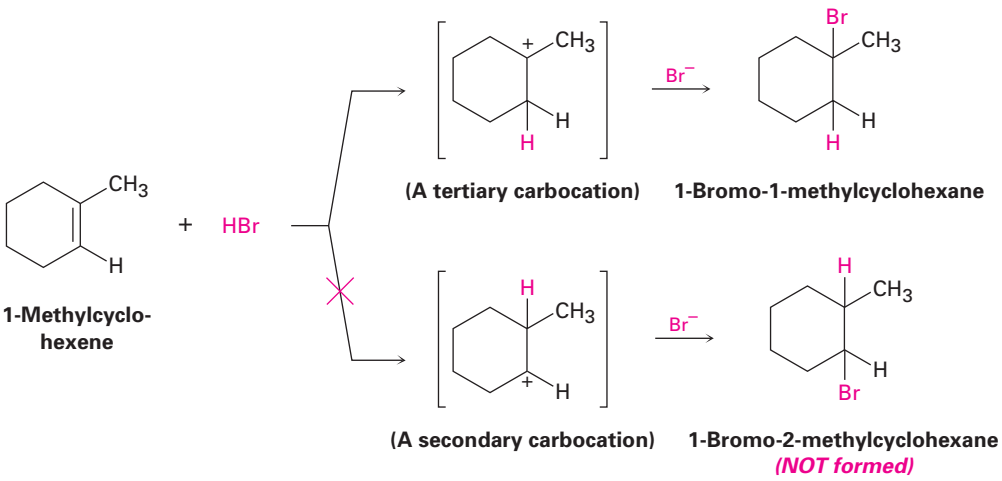
For example, addition of H^+ to 2-methylpropene yields the intermediate *tertiary* carbocation rather than the alternative primary carbocation, and addition to 1-methylcyclohexene yields a tertiary cation rather than a secondary one. Why should this be?



2-Methylpropene

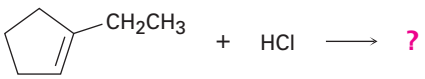
***tert*-Butyl carbocation (tertiary; 3°)** **2-Chloro-2-methylpropane**

Isobutyl carbocation (primary; 1°) **1-Chloro-2-methylpropane *(NOT formed)***



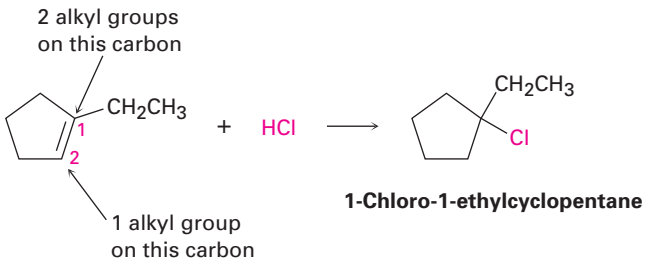
WORKED EXAMPLE 6.2 *Predicting the Product of an Electrophilic Addition Reaction*

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



Strategy When solving a problem that asks you to predict a reaction product, begin by looking at the functional group(s) in the reactants and deciding what kind of reaction is likely to occur. In the present instance, the reactant is an alkene that will probably undergo an electrophilic addition reaction with HCl. Next, recall what you know about electrophilic addition reactions, and use your knowledge to predict the product. You know that electrophilic addition reactions follow Markovnikov's rule, so H^+ will add to the double-bond carbon that has one alkyl group (C2 on the ring) and the Cl will add to the double-bond carbon that has two alkyl groups (C1 on the ring).

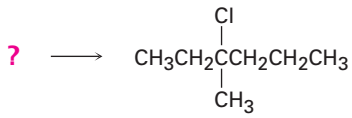
Solution The expected product is 1-chloro-1-ethylcyclopentane.



ThomsonNOW™ Click *Organic Interactive* to **practice predicting products of addition reactions according to Markovnikov's rule.**

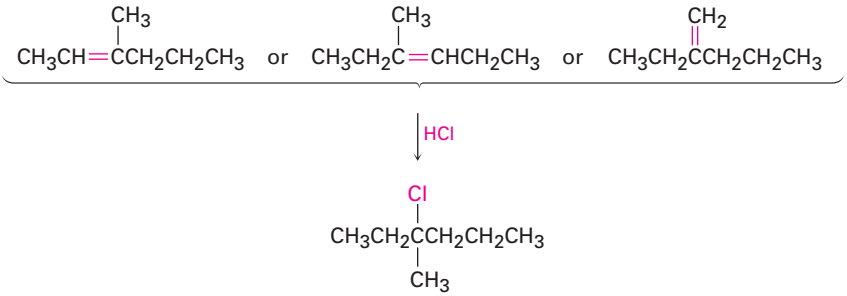
WORKED EXAMPLE 6.3 ***Synthesizing a Specific Compound***

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

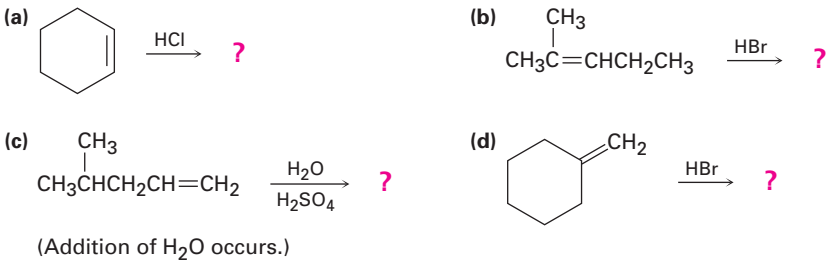


Strategy When solving a problem that asks how to prepare a given product, *always work backward*. Look at the product, identify the functional group(s) it contains, and ask yourself, "How can I prepare that functional group?" In the present instance, the product is a tertiary alkyl chloride, which can be prepared by reaction of an alkene with HCl. The carbon atom bearing the −Cl atom in the product must be one of the double-bond carbons in the reactant. Draw and evaluate all possibilities.

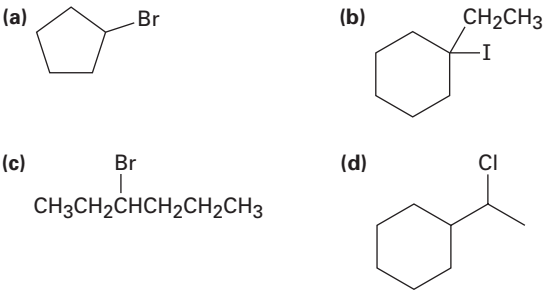
Solution There are three possibilities, any one of which could give the desired product.



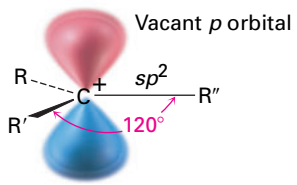
Problem 6.14 Predict the products of the following reactions:



Problem 6.15 What alkenes would you start with to prepare the following alkyl halides?



6.9 Carbocation Structure and Stability



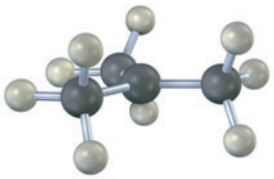
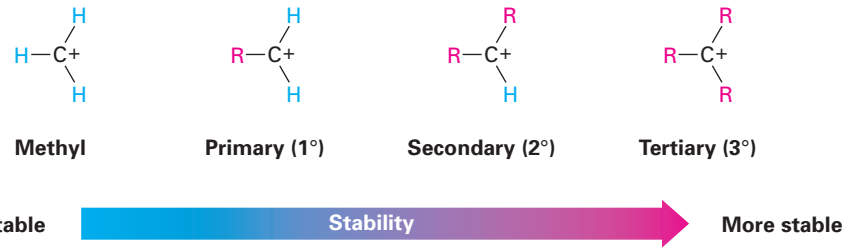


Figure 6.9 The structure of a carbocation. The trivalent carbon is sp^2-hybridized and has a vacant *p* orbital perpendicular to the plane of the carbon and three attached groups.

To understand why Markovnikov's rule works, we need to learn more about the structure and stability of carbocations and about the general nature of reactions and transition states. The first point to explore involves structure.

A great deal of evidence has shown that carbocations are *planar*. The trivalent carbon is sp^2-hybridized, and the three substituents are oriented to the corners of an equilateral triangle, as indicated in Figure 6.9. Because there are only six valence electrons on carbon and all six are used in the three σ bonds, the *p* orbital extending above and below the plane is unoccupied.

The second point to explore involves carbocation stability. 2-Methylpropene might react with H^+ to form a carbocation having three alkyl substituents (a tertiary ion, 3°), or it might react to form a carbocation having one alkyl substituent (a primary ion, 1°). Since the tertiary alkyl chloride, 2-chloro-2-methylpropane, is the only product observed, formation of the tertiary cation is evidently favored over formation of the primary cation. Thermodynamic measurements show that, indeed, the stability of carbocations increases with increasing substitution so that the stability order is tertiary > secondary > primary > methyl.



ThomsonNOW™ Click *Organic Interactive* to **rank the stability of carbocation intermediates.**

One way of determining carbocation stabilities is to measure the amount of energy required to form the carbocation by dissociation of the corresponding alkyl halide, R−X ⇌ $R^+ + :X^-$. As shown in Figure 6.10, tertiary alkyl halides dissociate to give carbocations more easily than secondary or primary ones. As a result, trisubstituted carbocations are more stable than disubstituted ones, which are more stable than monosubstituted ones. The data in Figure 6.10 are taken from measurements made in the gas phase, but a similar stability order is found for carbocations in solution. The dissociation enthalpies are much lower in solution because polar solvents can stabilize the ions, but the order of carbocation stability remains the same.

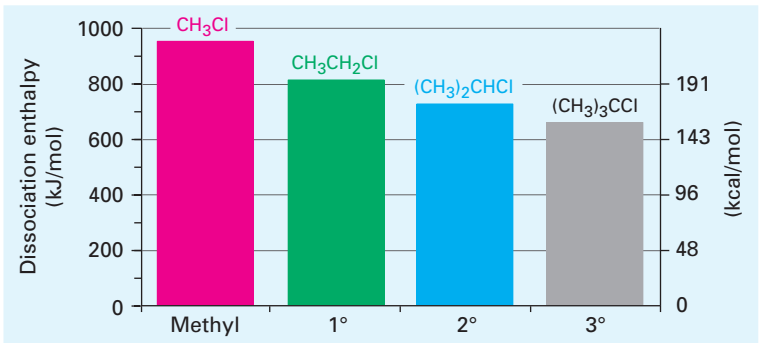


Figure 6.10 A plot of dissociation enthalpy versus substitution pattern for the gas-phase dissociation of alkyl chlorides to yield carbocations. More highly substituted alkyl halides dissociate more easily than less highly substituted ones.

Why are more highly substituted carbocations more stable than less highly substituted ones? There are at least two reasons. Part of the answer has to do with inductive effects, and part has to do with hyperconjugation. Inductive effects, discussed in Section 2.1 in connection with polar covalent bonds, result from the shifting of electrons in a σ bond in response to the electronegativity of nearby atoms. In the present instance, electrons from a relatively larger and more polarizable alkyl group can shift toward a neighboring positive charge more easily than the electron from a hydrogen. Thus, the more alkyl groups there are attached to the positively charged carbon, the more electron density shifts toward the charge and the more inductive stabilization of the cation occurs (Figure 6.11).

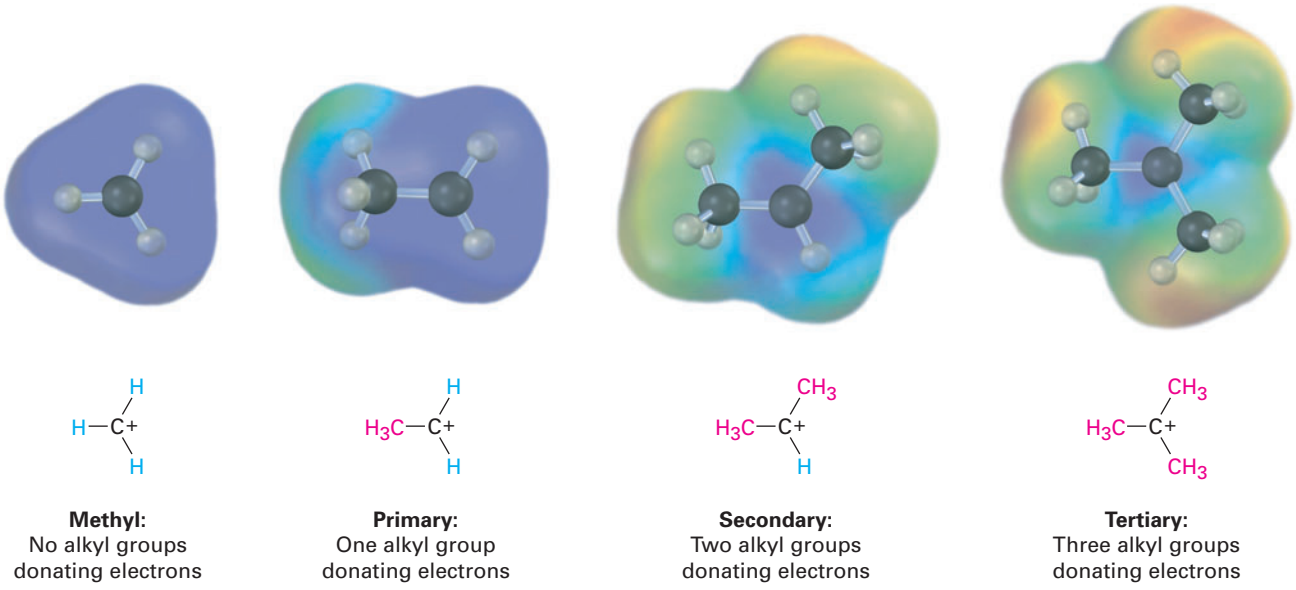


Figure 6.11 A comparison of inductive stabilization for methyl, primary, secondary, and tertiary carbocations. The more alkyl groups there are bonded to the positively charged carbon, the more electron density shifts toward the charge, making the charged carbon less electron-poor (blue in electrostatic potential maps).

Hyperconjugation, discussed in Section 6.6 in connection with the stabilities of substituted alkenes, is the stabilizing interaction between a vacant *p* orbital and properly oriented C–H σ bonds on neighboring carbons. The more alkyl groups there are on the carbocation, the more possibilities there are for hyperconjugation and the more stable the carbocation. Figure 6.12 shows the molecular orbital involved in hyperconjugation for the ethyl carbocation, $CH_3CH_2^+$, and indicates the difference between the C–H bond perpendicular to the cation *p* orbital and the two C–H bonds more nearly parallel to the cation *p* orbital. Only the roughly parallel C–H bonds are oriented properly to take part in hyperconjugation.

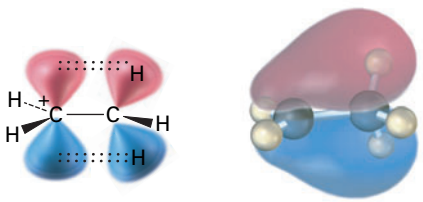
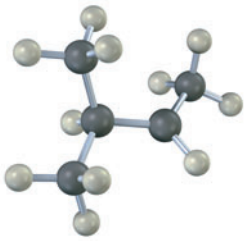


Figure 6.12 Stabilization of the ethyl carbocation, $CH_3CH_2^+$, through hyperconjugation. Interaction of neighboring C–H σ bonds with the vacant *p* orbital stabilizes the cation and lowers its energy. The molecular orbital shows that only the two C–H bonds more nearly parallel to the cation *p* orbital are oriented properly for hyperconjugation. The C–H bond perpendicular to the cation *p* orbital cannot take part.

Problem 6.16 Show the structures of the carbocation intermediates you would expect in the following reactions:

Problem 6.17 Draw a skeletal structure of the following carbocation. Identify it as primary, secondary, or tertiary, and identify the hydrogen atoms that have the proper orientation for hyperconjugation in the conformation shown.



6.10 The Hammond Postulate

Let's summarize our knowledge of electrophilic addition reactions up to this point. We know that:

- **Electrophilic addition to an unsymmetrically substituted alkene gives the more highly substituted carbocation intermediate.** A more highly substituted carbocation forms faster than a less highly substituted one and, once formed, rapidly goes on to give the final product.
- **A more highly substituted carbocation is more stable than a less highly substituted one.** That is, the stability order of carbocations is tertiary > secondary > primary > methyl.

What we have not yet seen is how these two points are related. Why does the *stability* of the carbocation intermediate affect the *rate* at which it's formed and thereby determine the structure of the final product? After all, carbocation stability is determined by the free-energy change $\Delta G°$, but reaction rate is determined by the activation energy $\Delta G^{\ddagger}$. The two quantities aren't directly related.

Although there is no simple quantitative relationship between the stability of a carbocation intermediate and the rate of its formation, there *is* an intuitive relationship. It's generally true when comparing two similar reactions that the more stable intermediate forms faster than the less stable one. The situation is shown graphically in Figure 6.13, where the reaction energy profile in part (a) represents the typical situation rather than the profile in part (b). That is, the curves for two similar reactions don't cross one another.

An explanation of the relationship between reaction rate and intermediate stability was first advanced in 1955. Known as the **Hammond postulate**, the argument goes like this: transition states represent energy maxima. They are high-energy activated complexes that occur transiently during the course of a reaction and immediately go on to a more stable species. Although we can't

George Simms Hammond

George Simms Hammond (1921–2005) was born on Hardscrabble Road in Auburn, Maine, the son of a dairy farmer. He received his Ph.D. at Harvard University in 1947 and served as professor of chemistry at Iowa State University, California Institute of Technology (1958–1972), and the University of California at Santa Cruz (1972–1978). He was known for his exploratory work on organic photochemistry—the use of light to bring about organic reactions.

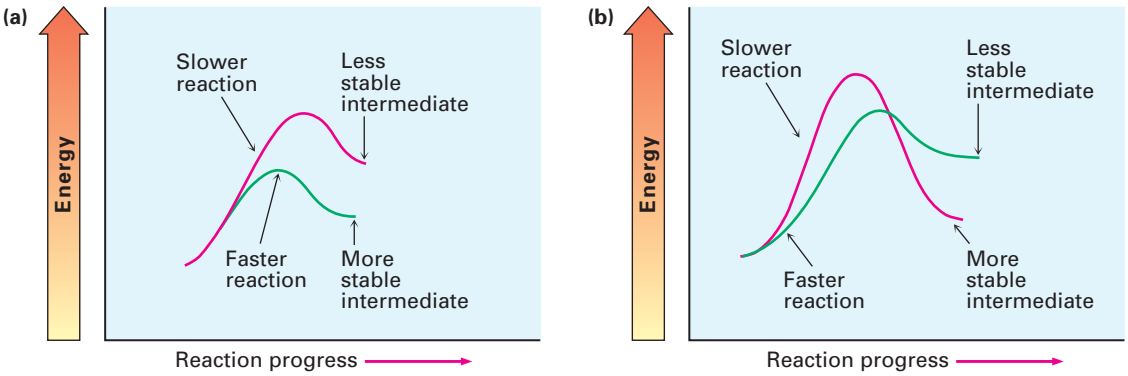


Figure 6.13 Energy diagrams for two similar competing reactions. In **(a)**, the faster reaction yields the more stable intermediate. In **(b)**, the slower reaction yields the more stable intermediate. The curves shown in **(a)** represent the typical situation.

actually observe transition states because they have no finite lifetime, the Hammond postulate says that we can get an idea of a particular transition state's structure by looking at the structure of the nearest stable species. Imagine the two cases shown in Figure 6.14, for example. The reaction profile in part (a) shows the energy curve for an endergonic reaction step, and the profile in part (b) shows the curve for an exergonic step.

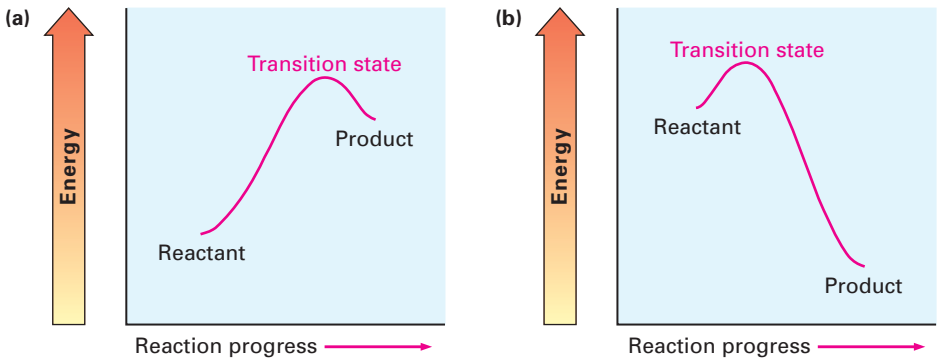


Figure 6.14 Energy diagrams for endergonic and exergonic steps. **(a)** In an endergonic step, the energy levels of transition state and *product* are closer. **(b)** In an exergonic step, the energy levels of transition state and *reactant* are closer.

In an endergonic reaction (Figure 6.14a), the energy level of the transition state is closer to that of the product than to that of the reactant. Since the transition state is closer energetically to the product, we make the natural assumption that it's also closer structurally. In other words, *the transition state for an endergonic reaction step structurally resembles the product of that step.* Conversely, the transition state for an exergonic reaction (Figure 6.14b) is closer energetically, and thus structurally, to the reactant than to the product. We therefore say that *the transition state for an exergonic reaction step structurally resembles the reactant for that step.*

Hammond postulate

The structure of a transition state resembles the structure of the nearest stable species. Transition states for endergonic steps structurally resemble products, and transition states for exergonic steps structurally resemble reactants.

How does the Hammond postulate apply to electrophilic addition reactions? The formation of a carbocation by protonation of an alkene is an endergonic step. Thus, the transition state for alkene protonation structurally resembles the

carbocation intermediate, and any factor that stabilizes the carbocation will stabilize the nearby transition state. Since increasing alkyl substitution stabilizes carbocations, it also stabilizes the transition states leading to those ions, thus resulting in a faster reaction. More stable carbocations form faster because their greater stability is reflected in the lower-energy transition state leading to them (Figure 6.15).

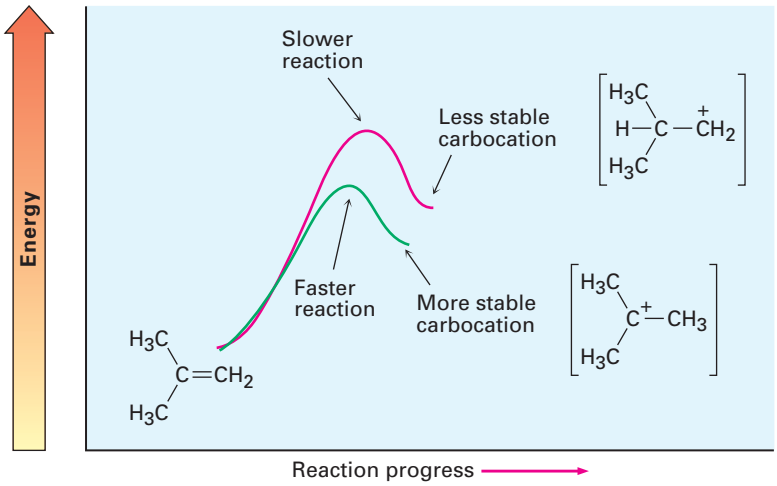


Figure 6.15 Energy diagrams for carbocation formation. The more stable tertiary carbocation is formed faster (green curve) because its increased stability lowers the energy of the transition state leading to it.

We can imagine the transition state for alkene protonation to be a structure in which one of the alkene carbon atoms has almost completely rehybridized from sp^2 to sp^3 and in which the remaining alkene carbon bears much of the positive charge (Figure 6.16). This transition state is stabilized by hyperconjugation and inductive effects in the same way as the product carbocation. The more alkyl groups that are present, the greater the extent of stabilization and the faster the transition state forms.

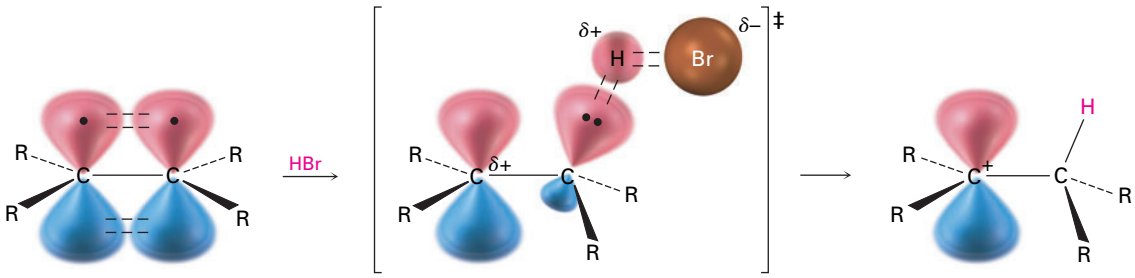


Figure 6.16 The hypothetical structure of a transition state for alkene protonation. The transition state is closer in both energy and structure to the carbocation than to the alkene. Thus, an increase in carbocation stability (lower $\Delta G°$) also causes an increase in transition-state stability (lower $\Delta G^{\ddagger}$), thereby increasing the rate of its formation.

Problem 6.18 What about the second step in the electrophilic addition of HCl to an alkene—the reaction of chloride ion with the carbocation intermediate? Is this step exergonic or endergonic? Does the transition state for this second step resemble the reactant (carbocation) or product (alkyl chloride)? Make a rough drawing of what the transition-state structure might look like.

6.11 Evidence for the Mechanism of Electrophilic Additions: Carbocation Rearrangements

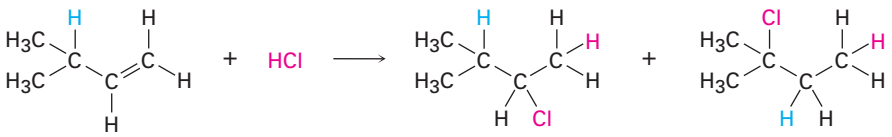
ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products from simple carbocation rearrangements.**

Frank C. Whitmore

Frank C. Whitmore (1887–1947) was born in North Attleboro, Massachusetts, and received his Ph.D. at Harvard working with E. L. Jackson. He was professor of chemistry at Minnesota, Northwestern, and the Pennsylvania State University. Nicknamed "Rocky," he wrote an influential advanced textbook in organic chemistry.

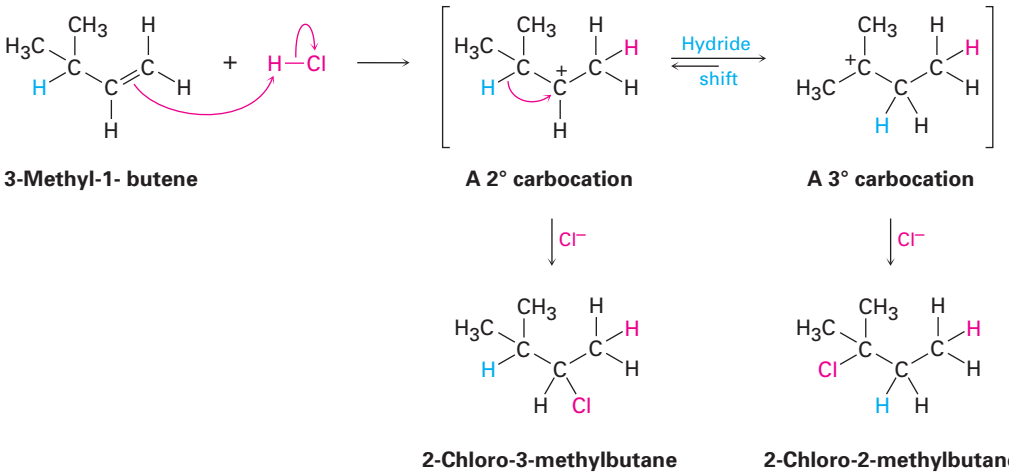
How do we know that the carbocation mechanism for electrophilic addition reactions of alkenes is correct? The answer is that we *don't* know it's correct; at least we don't know with complete certainty. Although an incorrect reaction mechanism can be disproved by demonstrating that it doesn't account for observed data, a correct reaction mechanism can never be entirely proved. The best we can do is to show that a proposed mechanism is consistent with all known facts. If enough facts are accounted for, the mechanism is probably correct.

What evidence is there to support the carbocation mechanism proposed for the electrophilic addition reaction of alkenes? One of the best pieces of evidence was discovered during the 1930s by F. C. Whitmore of the Pennsylvania State University, who found that structural rearrangements often occur during the reaction of HX with an alkene. For example, reaction of HCl with 3-methyl-1-butene yields a substantial amount of 2-chloro-2-methylbutane in addition to the "expected" product, 2-chloro-3-methylbutane.



3-Methyl-1- butene | **2-Chloro-3-methylbutane (approx. 50%)** | **2-Chloro-2-methylbutane (approx. 50%)**

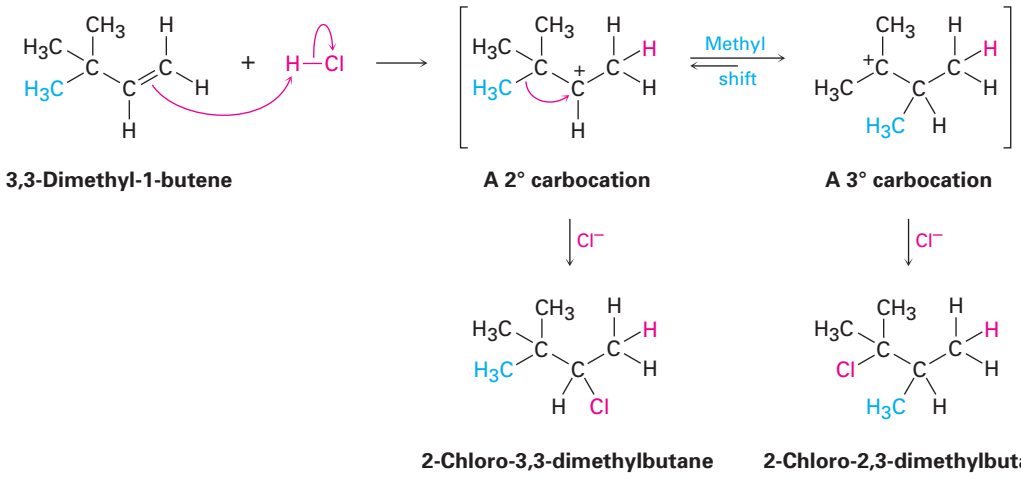
If the reaction takes place in a single step, it would be difficult to account for rearrangement, but if the reaction takes place in several steps, rearrangement is more easily explained. Whitmore suggested that it is a carbocation intermediate that undergoes rearrangement. The secondary carbocation intermediate formed by protonation of 3-methyl-1-butene rearranges to a more stable tertiary carbocation by a **hydride shift**—the shift of a hydrogen atom and its electron pair (a hydride ion, $:H^-$) between neighboring carbons.



3-Methyl-1- butene | **A 2° carbocation** | **A 3° carbocation**

2-Chloro-3-methylbutane | **2-Chloro-2-methylbutane**

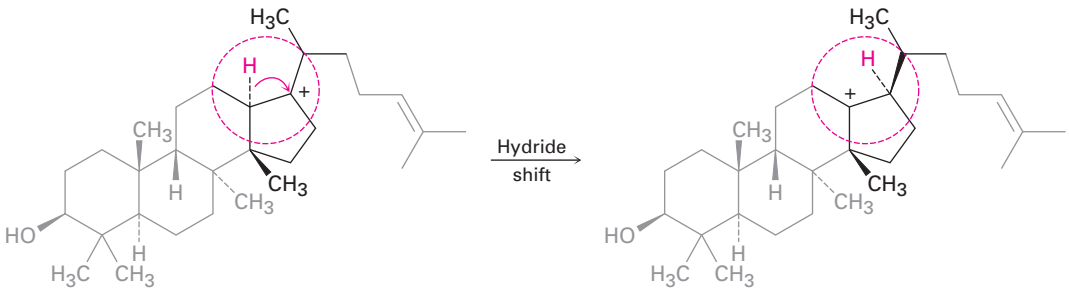
Carbocation rearrangements can also occur by the shift of an alkyl group with its electron pair. For example, reaction of 3,3-dimethyl-1-butene with HCl leads to an equal mixture of unrearranged 2-chloro-3,3-dimethylbutane and rearranged 2-chloro-2,3-dimethylbutane. In this instance, a secondary carbocation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



3,3-Dimethyl-1-butene **A 2° carbocation** **A 3° carbocation**

2-Chloro-3,3-dimethylbutane **2-Chloro-2,3-dimethylbutane**

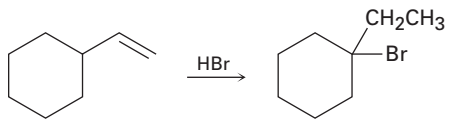
Note the similarities between the two carbocation rearrangements: in both cases, a group ($:H^-$ or $:CH_3^-$) moves to an adjacent positively charged carbon, taking its bonding electron pair with it. Also in both cases, a less stable carbocation rearranges to a more stable ion. Rearrangements of this kind are a common feature of carbocation chemistry and are particularly important in the biological pathways by which steroids and related substances are synthesized. An example is the following hydride shift that occurs during the biosynthesis of cholesterol.



A tertiary carbocation **An isomeric tertiary carbocation**

A word of advice that we'll repeat on occasion: biological molecules are often larger and more complex in appearance than the molecules chemists work with in the laboratory, but don't be intimidated. When looking at *any* chemical transformation, focus only on the part of the molecule where the change is occurring and don't worry about the rest. The tertiary carbocation just pictured looks complicated, but all the chemistry is taking place in the small part of the molecule inside the red circle.

Problem 6.19 On treatment with HBr, vinylcyclohexane undergoes addition and rearrangement to yield 1-bromo-1-ethylcyclohexane. Using curved arrows, propose a mechanism to account for this result.



Vinylcyclohexane **1-Bromo-1-ethylcyclohexane**

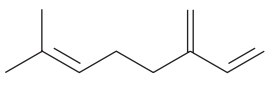
Focus On . . .

Terpenes: Naturally Occurring Alkenes

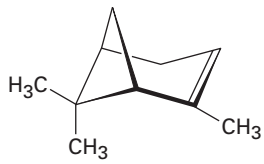
The wonderful fragrance of leaves from the California bay tree is due primarily to myrcene, a simple terpene.

It has been known for centuries that codistillation of many plant materials with steam produces a fragrant mixture of liquids called *essential oils*. For hundreds of years, such plant extracts have been used as medicines, spices, and perfumes. The investigation of essential oils also played a major role in the emergence of organic chemistry as a science during the 19th century.

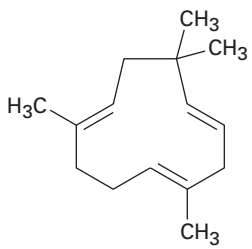
Chemically, plant essential oils consist largely of mixtures of compounds known as *terpenoids*—small organic molecules with an immense diversity of structure. More than 35,000 different terpenoids are known. Some are open-chain molecules, and others contain rings; some are hydrocarbons, and others contain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



Myrcene
(oil of bay)



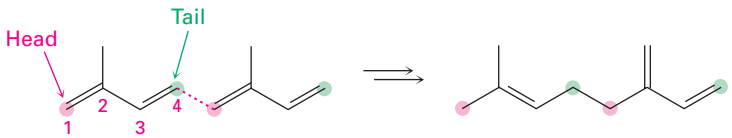
α-Pinene
(turpentine)



Humulene
(oil of hops)

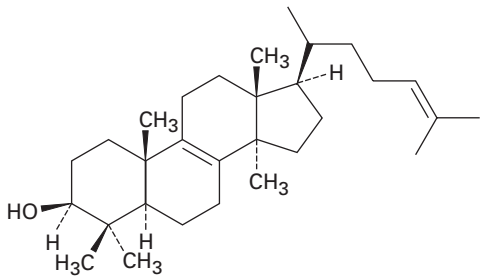
(continued)

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



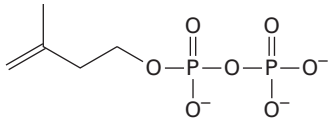
Isoprene **Myrcene**

Terpenes (and terpenoids) are further classified according to the number of 5-carbon units they contain. Thus, *monoterpenes* are 10-carbon substances biosynthesized from two isoprene units, *sesquiterpenes* are 15-carbon molecules from three isoprene units, *diterpenes* are 20-carbon substances from four isoprene units, and so on. Monoterpenes and sesquiterpenes are found primarily in plants, but the higher terpenoids occur in both plants and animals, and many have important biological roles. The triterpenoid lanosterol, for example, is the precursor from which all steroid hormones are made.

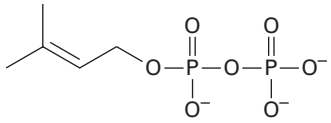


Lanosterol (a triterpene, C_{30})

Isoprene itself is not the true biological precursor of terpenoids. As we'll see in Chapter 27, nature instead uses two "isoprene equivalents"—isopentenyl diphosphate and dimethylallyl diphosphate—which are themselves made by two different routes depending on the organism. Lanosterol, in particular, is biosynthesized from acetic acid by a complex pathway that has been worked out in great detail.



Isopentenyl diphosphate



Dimethylallyl diphosphate

SUMMARY AND KEY WORDS

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

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

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

Tertiary (3°) > Secondary (2°) > Primary (1°) > Methyl

R_3C^+ > R_2CH^+ > RCH_2^+ > CH_3^+

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

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

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

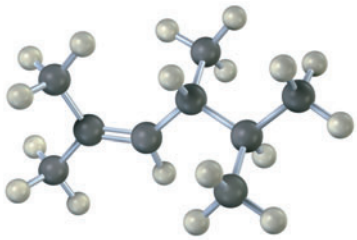
▲ denotes problems linked to Key Ideas of this chapter and testable in ThomsonNOW.

VISUALIZING CHEMISTRY

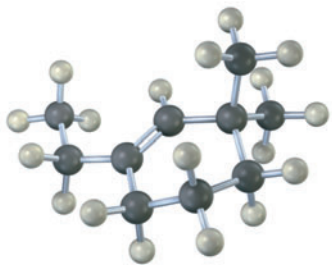
(Problems 6.1–6.19 appear within the chapter.)

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

(a)

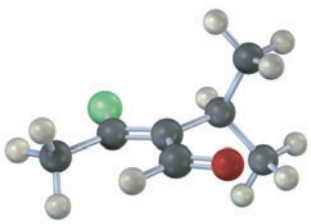


(b)

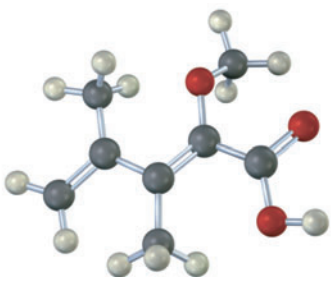


6.21 ■ Assign stereochemistry (*E* or *Z*) to the double bonds in each of the following compounds, and convert each drawing into a skeletal structure (red = O, yellow-green = Cl):

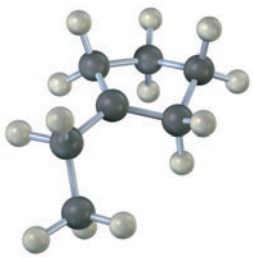
(a)



(b)



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



ADDITIONAL PROBLEMS

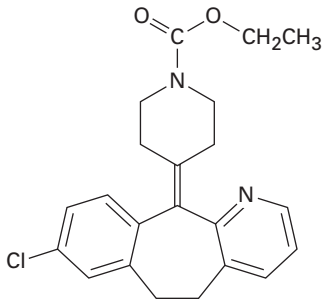
6.23 ■ Calculate the degree of unsaturation in the following formulas, and draw five possible structures for each:

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

6.24 How many hydrogens does each of the following compounds have?

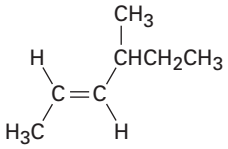
(a) $C_8H_?O_2$, has two rings and one double bond
(b) $C_7H_?N$, has two double bonds
(c) $C_9H_?NO$, has one ring and three double bonds

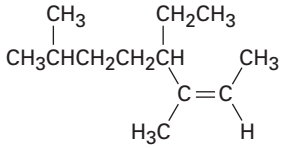
6.25 Loratadine, marketed as an antiallergy medication under the name Claritin, has four rings, eight double bonds, and the formula $C_{22}H_?ClN_2O_2$. How many hydrogens does loratadine have? (Calculate your answer; don't count hydrogens in the structure.)

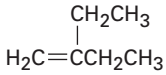


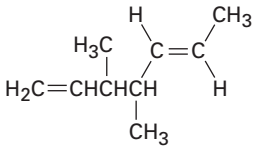
Loratadine

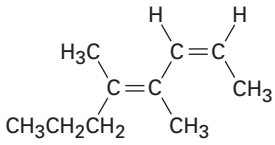
6.26 ■ Name the following alkenes:

(a)


(b)


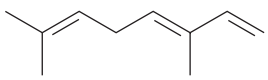
(c)


(d)


(e)


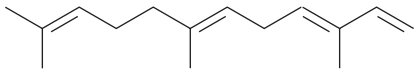
(f) $H_2C{=}C{=}CHCH_3$

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



Ocimene

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



α-Farnesene

■ Assignable in OWL ▲ Key Idea Problems

6.29 ■ Draw structures corresponding to the following systematic names:
(a) (4*E*)-2,4-Dimethyl-1,4-hexadiene
(b) *cis*-3,3-Dimethyl-4-propyl-1,5-octadiene
(c) 4-Methyl-1,2-pentadiene
(d) (3*E*,5*Z*)-2,6-Dimethyl-1,3,5,7-octatetraene
(e) 3-Butyl-2-heptene
(f) *trans*-2,2,5,5-Tetramethyl-3-hexene

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

6.31 Draw and name the 6 pentene isomers, C_5H_{10}, including *E*,*Z* isomers.

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

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

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

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

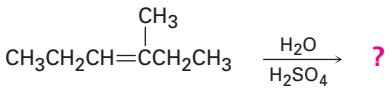
6.36 *trans*-Cyclooctene is less stable than *cis*-cyclooctene by 38.5 kJ/mol, but *trans*-cyclononene is less stable than *cis*-cyclononene by only 12.2 kJ/mol. Explain.

6.37 Allene (1,2-propadiene), $H_2C{=}C{=}CH_2$, has two adjacent double bonds. What kind of hybridization must the central carbon have? Sketch the bonding π orbitals in allene. What shape do you predict for allene?

6.38 The heat of hydrogenation for allene (Problem 6.37) to yield propane is −295 kJ/mol, and the heat of hydrogenation for a typical monosubstituted alkene such as propene is −126 kJ/mol. Is allene more stable or less stable than you might expect for a diene? Explain.

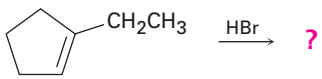
6.39 ■ Predict the major product in each of the following reactions:

(a)

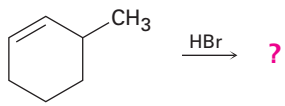


(Addition of H_2O occurs.)

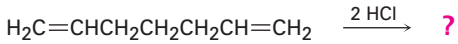
(b)



(c)

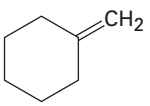


(d)

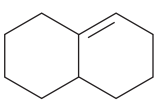


6.40 ■ Predict the major product from addition of HBr to each of the following alkenes:

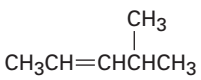
(a)



(b)



(c)



6.41 ■ Rank the following sets of substituents in order of priority according to the Cahn–Ingold–Prelog sequence rules:

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

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

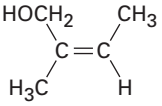
(c) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, $-CH_3$

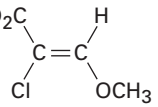
(d) $-CH_3$, $-CH_2CH_3$, $-CH_2CH_2OH$, $-\overset{\overset{O}{\|}}{C}CH_3$

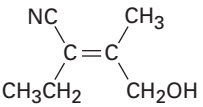
(e) $-CH{=}CH_2$, $-CN$, $-CH_2NH_2$, $-CH_2Br$

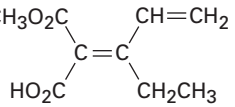
(f) $-CH{=}CH_2$, $-CH_2CH_3$, $-CH_2OCH_3$, $-CH_2OH$

6.42 ▲ Assign *E* or *Z* configuration to each of the following alkenes:

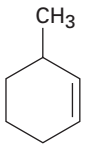
(a) 

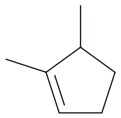
(b) 

(c) 

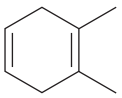
(d) 

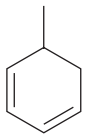
6.43 ■ Name the following cycloalkenes:

(a) 

(b) 

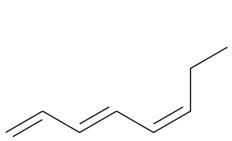
(c) 

(d) 

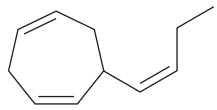
(e) 

(f) 

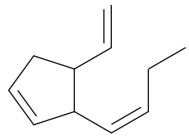
6.44 Fucoserraten, ectocarpen, and multifidene are sex pheromones produced by marine brown algae. What are their systematic names? (The latter two are a bit difficult; make your best guess.)



Fucoserraten



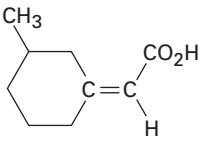
Ectocarpen



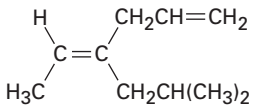
Multifidene

■ Assignable in OWL ▲ Key Idea Problems

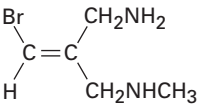
6.45 ▲ Which of the following *E*,*Z* designations are correct, and which are incorrect?

(a) 

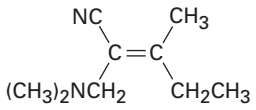
Z

(b) 

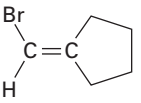
E

(c) 

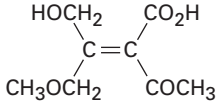
Z

(d) 

E

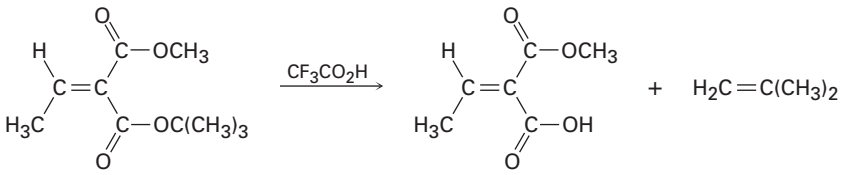
(e) 

Z

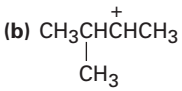
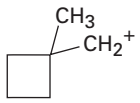
(f) 

E

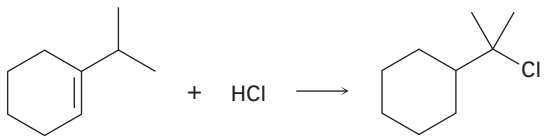
6.46 ▲ *tert*-Butyl esters [$RCO_2C(CH_3)_3$] are converted into carboxylic acids (RCO_2H) by reaction with trifluoroacetic acid, a reaction useful in protein synthesis (Section 26.7). Assign *E*,*Z* designation to the double bonds of both reactant and product in the following scheme, and explain why there is an apparent change of double-bond stereochemistry:



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

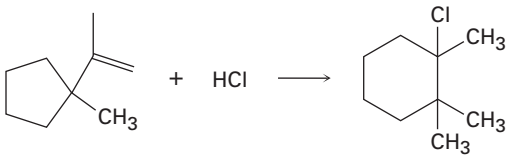
(a) $CH_3CH_2CH_2CH_2^+$ **(b)**  **(c)** 

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

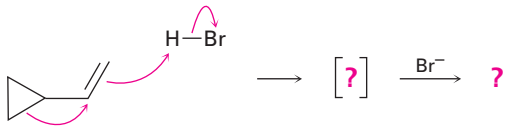


■ Assignable in OWL ▲ Key Idea Problems

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



6.50 Vinylcyclopropane reacts with HBr to yield a rearranged alkyl bromide. Follow the flow of electrons as represented by the curved arrows, show the structure of the carbocation intermediate in brackets, and show the structure of the final product.

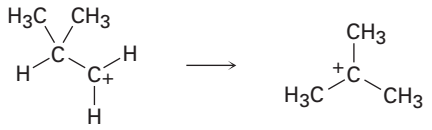


Vinylcyclopropane

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

(a) Cholesterol, $C_{27}H_{46}O$ **(b)** DDT, $C_{14}H_9Cl_5$
(c) Prostaglandin E_1, $C_{20}H_{34}O_5$ **(d)** Caffeine, $C_8H_{10}N_4O_2$
(e) Cortisone, $C_{21}H_{28}O_5$ **(f)** Atropine, $C_{17}H_{23}NO_3$

6.52 The isobutyl cation spontaneously rearranges to the *tert*-butyl cation by a hydride shift. Is the rearrangement exergonic or endergonic? Draw what you think the transition state for the hydride shift might look like according to the Hammond postulate.

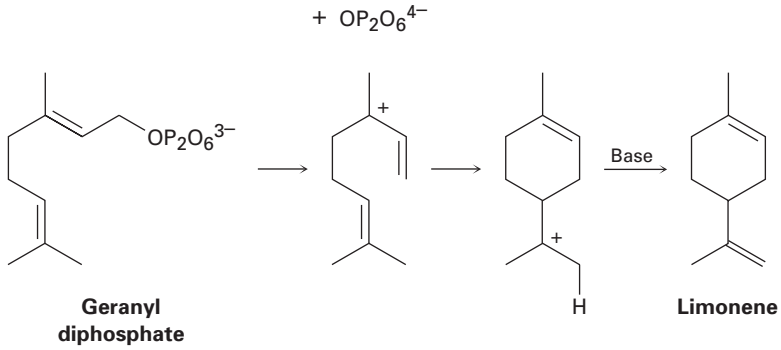


Isobutyl cation ***tert*-Butyl cation**

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

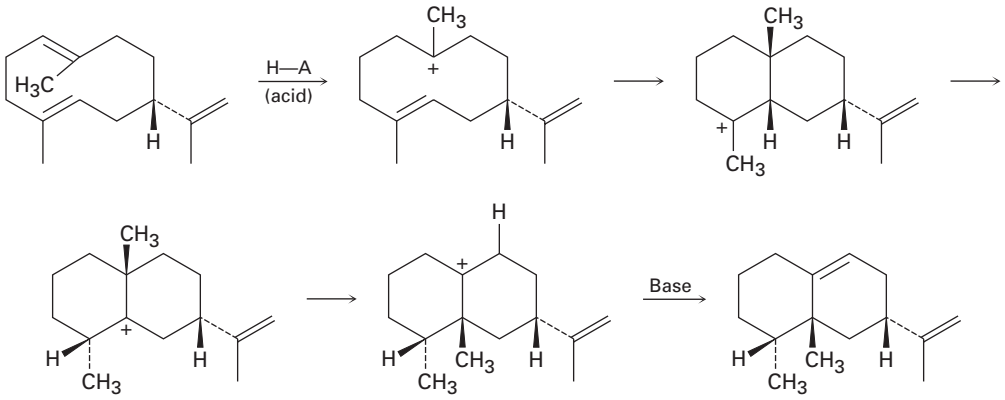
6.54 Make sketches of the transition-state structures involved in the reaction of HBr with 1-pentene (Problem 6.53). Tell whether each structure resembles reactant or product.

6.55 Limonene, a fragrant hydrocarbon found in lemons and oranges, is biosynthesized from geranyl diphosphate by the following pathway. Add curved arrows to show the mechanism of each step. Which step involves an alkene electrophilic addition? (The ion $OP_2O_6^{4-}$ is the diphosphate ion, and "Base" is an unspecified base in the enzyme that catalyzes the reaction.)



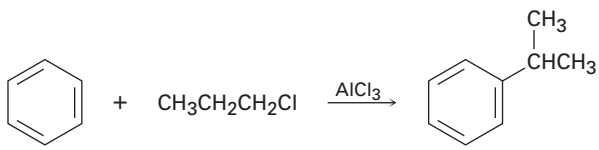
Geranyl diphosphate **Limonene**

6.56 *epi*-Aristolochene, a hydrocarbon found in both pepper and tobacco, is biosynthesized by the following pathway. Add curved arrows to show the mechanism of each step. Which steps involve alkene electrophilic addition(s), and which involve carbocation rearrangement(s)? (The abbreviation H−A stands for an unspecified acid, and "Base" is an unspecified base in the enzyme.)



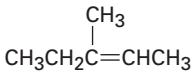
***epi*-Aristolochene**

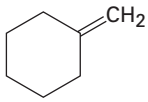
6.57 Aromatic compounds such as benzene react with alkyl chlorides in the presence of $AlCl_3$ catalyst to yield alkylbenzenes. The reaction occurs through a carbocation intermediate, formed by reaction of the alkyl chloride with $AlCl_3$ ($R{-}Cl + AlCl_3 \rightleftharpoons R^+ + AlCl_4^-$). How can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

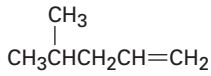


■ Assignable in OWL ▲ Key Idea Problems

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

(a) 

(b) 

(c) 

6.59 Reaction of 2,3-dimethyl-1-butene with HBr leads to an alkyl bromide, $C_6H_{13}Br$. On treatment of this alkyl bromide with KOH in methanol, elimination of HBr to give an alkene occurs and a hydrocarbon that is isomeric with the starting alkene is formed. What is the structure of this hydrocarbon, and how do you think it is formed from the alkyl bromide?

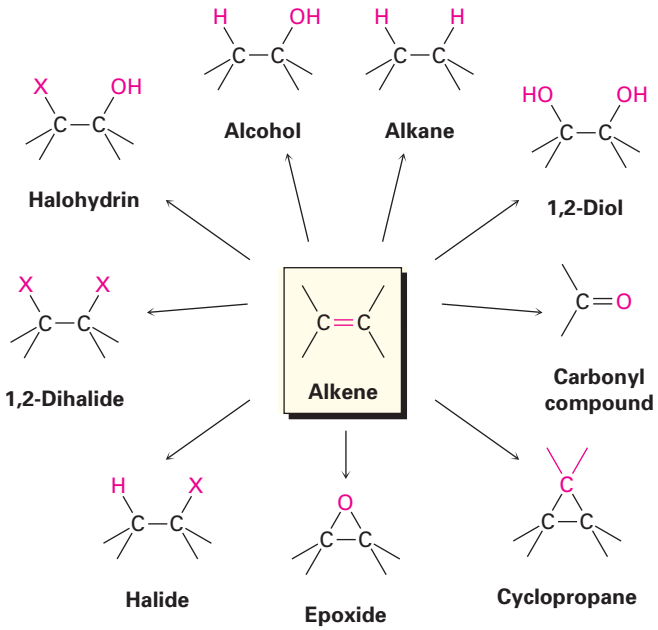
7 Alkenes: Reactions and Synthesis

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at **www.thomsonedu.com** for online self-study and interactive tutorials based on your level of understanding.

Online homework for this chapter may be assigned in Organic OWL.

Alkene addition reactions occur widely, both in the laboratory and in living organisms. Although we've studied only the addition of HX thus far, many closely related reactions also take place. In this chapter, we'll see briefly how alkenes are prepared, we'll discuss many further examples of alkene addition reactions, and we'll see the wide variety of compounds that can be made from alkenes.



WHY THIS CHAPTER?

Much of the background needed to understand organic reactions has now been covered, and it's time to begin a systematic description of the major functional groups. Both in this chapter on alkenes and in future chapters on other

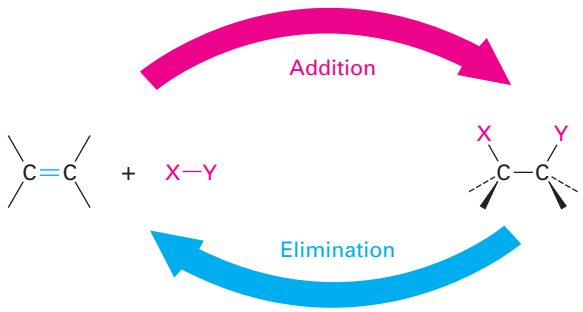
Sean Duggan

functional groups, we'll discuss a variety of reactions but try to focus on the general principles and patterns of reactivity that tie organic chemistry together. There are no shortcuts: you have to know the reactions to understand organic chemistry.

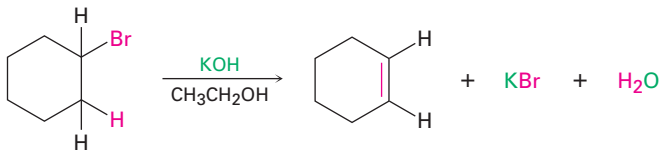
7.1 Preparation of Alkenes: A Preview of Elimination Reactions

Before getting to the main subject of this chapter—the reactions of alkenes—let's take a brief look at how alkenes are prepared. The subject is a bit complex, though, so we'll return in Chapter 11 for a more detailed study. For the present, it's enough to realize that alkenes are readily available from simple precursors—usually alcohols in biological systems and either alcohols or alkyl halides in the laboratory.

Just as the chemistry of alkenes is dominated by addition reactions, the preparation of alkenes is dominated by elimination reactions. Additions and eliminations are, in many respects, two sides of the same coin. That is, an addition reaction might involve the addition of HBr or H_2O to an alkene to form an alkyl halide or alcohol, whereas an elimination reaction might involve the loss of HBr or H_2O from an alkyl halide or alcohol to form an alkene.



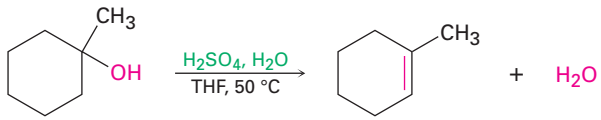
The two most common elimination reactions are *dehydrohalogenation*—the loss of HX from an alkyl halide—and *dehydration*—the loss of water from an alcohol. Dehydrohalogenation usually occurs by reaction of an alkyl halide with strong base such as potassium hydroxide. For example, bromocyclohexane yields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



Bromocyclohexane **Cyclohexene (81%)**

Dehydration is often carried out by treatment of an alcohol with a strong acid. For example, loss of water occurs and 1-methylcyclohexene is formed

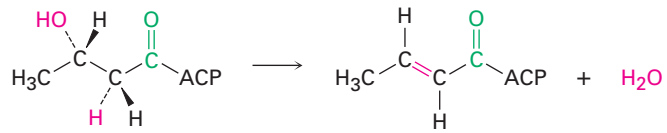
when 1-methylcyclohexanol is warmed with aqueous sulfuric acid in tetrahydrofuran (THF) solvent.



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

Tetrahydrofuran (THF)—a common solvent

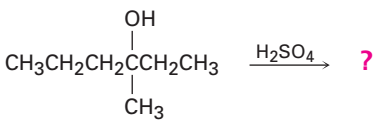
In biological pathways, dehydrations rarely occur with isolated alcohols but instead normally take place on substrates in which the −OH is positioned two carbons away from a carbonyl group. In the biosynthesis of fats, for instance, β-hydroxybutyryl ACP is converted by dehydration to *trans*-crotonyl ACP, where ACP is an abbreviation for *acyl carrier protein*. We'll see the reason for this requirement in Section 11.10.



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

Problem 7.1 One problem with elimination reactions is that mixtures of products are often formed. For example, treatment of 2-bromo-2-methylbutane with KOH in ethanol yields a mixture of two alkene products. What are their likely structures?

Problem 7.2 How many alkene products, including *E*,*Z* isomers, might be obtained by dehydration of 3-methyl-3-hexanol with aqueous sulfuric acid?



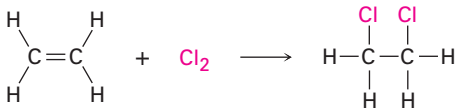
3-Methyl-3-hexanol

7.2 Addition of Halogens to Alkenes

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products of the addition of halogens to alkenes.**

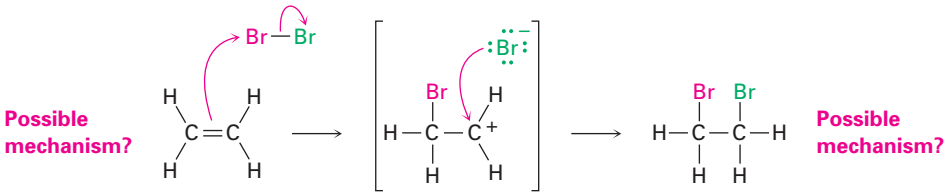
Bromine and chlorine add rapidly to alkenes to yield 1,2-dihalides, a process called *halogenation*. For example, approximately 6 million tons per year of 1,2-dichloroethane (ethylene dichloride) are synthesized industrially by addition

of Cl_2 to ethylene. The product is used both as a solvent and as starting material for the manufacture of poly(vinyl chloride), PVC. Fluorine is too reactive and difficult to control for most laboratory applications, and iodine does not react with most alkenes.



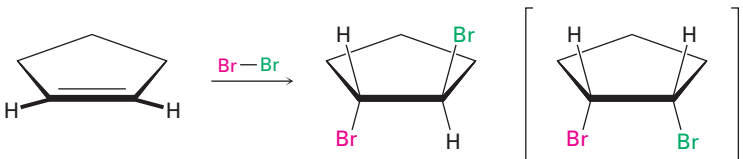
Ethylene **1,2-Dichloroethane (ethylene dichloride)**

Based on what we've seen thus far, a possible mechanism for the reaction of bromine with alkenes might involve electrophilic addition of Br^+ to the alkene, giving a carbocation that could undergo further reaction with Br^- to yield the dibromo addition product.



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

When the halogenation reaction is carried out on a cycloalkene, such as cyclopentene, only the *trans* stereoisomer of the dihalide addition product is formed rather than the mixture of cis and trans isomers that might have been expected if a planar carbocation intermediate were involved. We say that the reaction occurs with **anti stereochemistry**, meaning that the two bromine atoms come from opposite faces of the double bond—one from the top face and one from the bottom face.

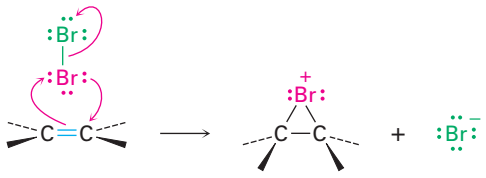


Cyclopentene ***trans*-1,2-Dibromocyclopentane (sole product)** ***cis*-1,2-Dibromocyclopentane *(NOT formed)***

An explanation for the observed anti stereochemistry of addition was suggested in 1937 by George Kimball and Irving Roberts, who proposed that the

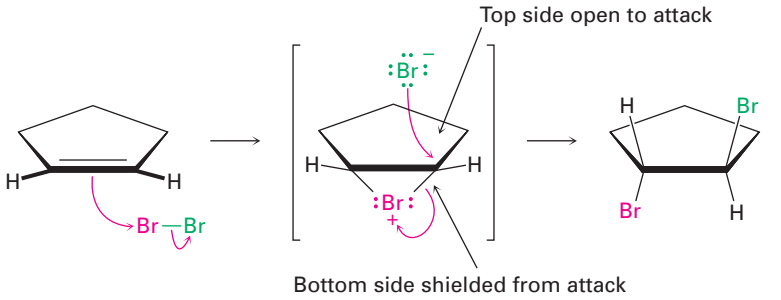
reaction intermediate is not a carbocation but is instead a **bromonium ion**, R_2Br^+, formed by addition of Br^+ to the alkene. (Similarly, a *chloronium ion* contains a positively charged divalent chlorine, R_2Cl^+.) The bromonium ion is formed in a single step by interaction of the alkene with Br_2 and simultaneous loss of Br^-.

ThomsonNOW™ Click *Organic Process* to **view an animation of the bromonium ion intermediate and product formation in this reaction.**



An alkene **A bromonium ion**

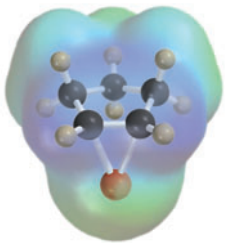
How does the formation of a bromonium ion account for the observed anti stereochemistry of addition to cyclopentene? If a bromonium ion is formed as an intermediate, we can imagine that the large bromine atom might "shield" one side of the molecule. Reaction with Br^- ion in the second step could then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



Cyclopentene **Bromonium ion intermediate** ***trans*-1,2-Dibromocyclopentane**

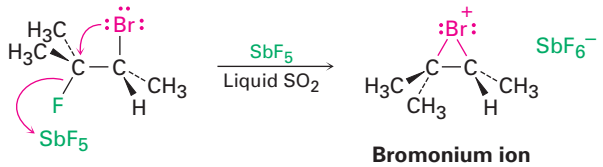
George Andrew Olah

George Andrew Olah (1927–) was born in Budapest, Hungary, and received a doctorate in 1949 at the Technical University of Budapest. During the Hungarian revolution in 1956, he immigrated to Canada and joined the Dow Chemical Company. After moving to the United States, he was professor of chemistry at Case Western Reserve University (1965–1977) and then at the University of Southern California (1977–). He received the 1994 Nobel Prize in chemistry for his work on carbocations.



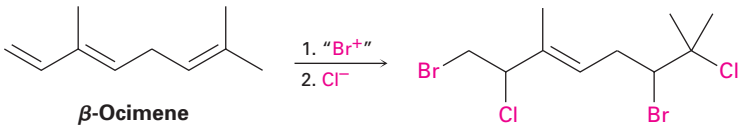
The bromonium ion postulate, made more than 75 years ago to explain the stereochemistry of halogen addition to alkenes, is a remarkable example of deductive logic in chemistry. Arguing from experimental results, chemists were able to make a hypothesis about the intimate mechanistic details of alkene electrophilic reactions. Subsequently, strong evidence supporting the mechanism came from the work of George Olah, who prepared and studied *stable*

solutions of cyclic bromonium ions in liquid SO_2. There's no question that bromonium ions exist.



Bromonium ion (stable in SO_2 solution)

Alkene halogenation reactions occur in nature just as they do in the laboratory but are limited primarily to marine organisms, which live in a halide-rich environment. The reactions are carried out by enzymes called *haloperoxidases,* which use H_2O_2 to oxidize Br^- or Cl^- ions to a biological equivalent of Br^+ or Cl^+. Electrophilic addition to the double bond of a substrate molecule then yields a bromonium or chloronium ion intermediate just as in the laboratory, and reaction with another halide ion completes the process. For example, the following tetrahalide, isolated from the red alga *Plocamium cartilagineum,* is thought to arise from β-ocimene by twofold addition of BrCl through the corresponding bromonium ions.



β-Ocimene

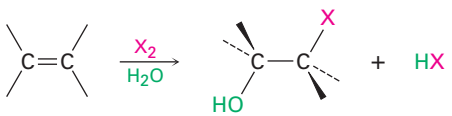
Problem 7.3 What product would you expect to obtain from addition of Cl_2 to 1,2-dimethylcyclohexene? Show the stereochemistry of the product.

Problem 7.4 Addition of HCl to 1,2-dimethylcyclohexene yields a mixture of two products. Show the stereochemistry of each, and explain why a mixture is formed.

7.3 Addition of Hypohalous Acids to Alkenes: Halohydrin Formation

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products of the addition of hypohalous acid to alkenes.**

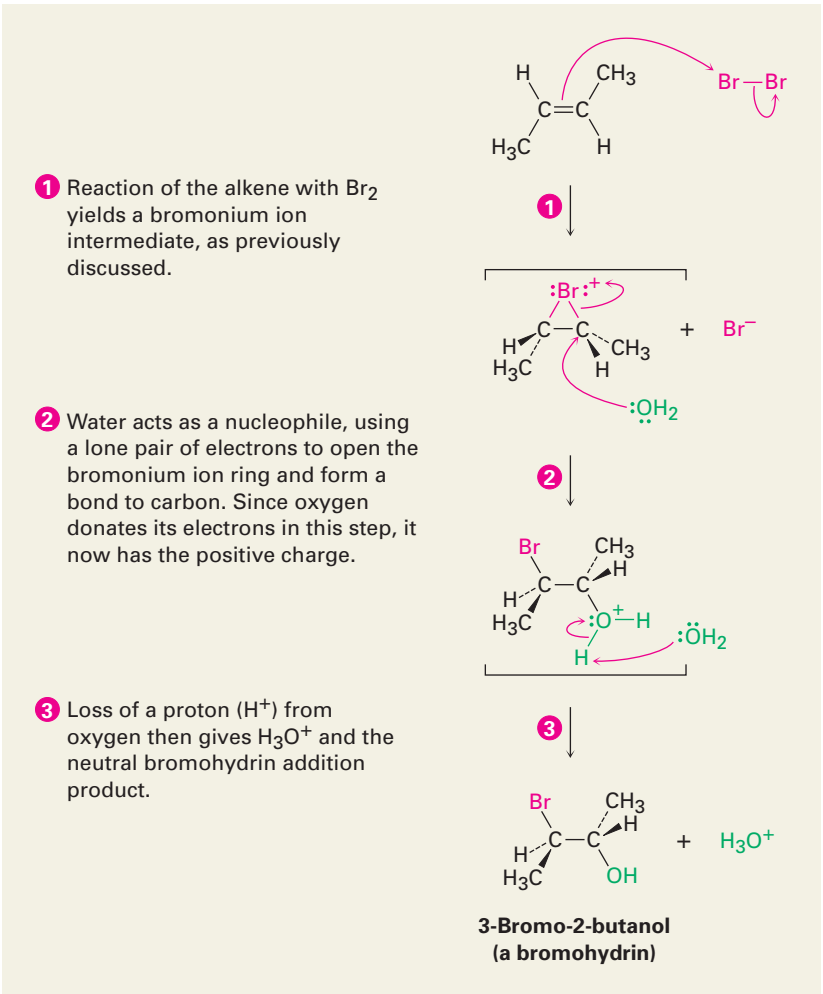
Yet another example of an electrophilic addition is the reaction of alkenes with the hypohalous acids HO−Cl or HO−Br to yield 1,2-halo alcohols, called **halohydrins**. Halohydrin formation doesn't take place by direct reaction of an alkene with HOBr or HOCl, however. Rather, the addition is done indirectly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



An alkene **A halohydrin**

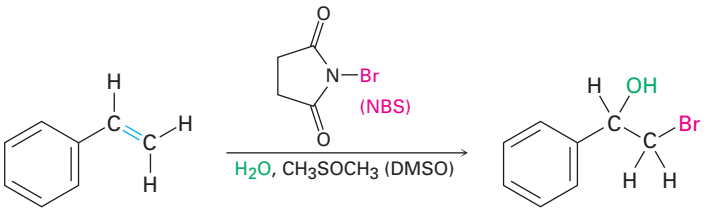
We saw in the previous section that when Br_2 reacts with an alkene, the cyclic bromonium ion intermediate reacts with the only nucleophile present, Br^- ion. If the reaction is carried out in the presence of an additional nucleophile, however, the intermediate bromonium ion can be intercepted by the added nucleophile and diverted to a different product. In the presence of water, for instance, water competes with Br^- ion as nucleophile and reacts with the bromonium ion intermediate to yield a *bromohydrin*. The net effect is addition of HO–Br to the alkene by the pathway shown in Figure 7.1.

Figure 7.1 MECHANISM: Mechanism of bromohydrin formation by reaction of an alkene with Br_2 in the presence of water. Water acts as a nucleophile to react with the intermediate bromonium ion.



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

in the addition reaction, but it is more dangerous and more difficult to handle than NBS.

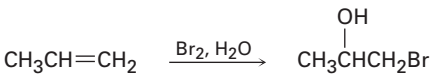


Styrene **2-Bromo-1-phenylethanol (70%)**

Note that the aromatic ring in the preceding example does not react with Br_2 under the conditions used, even though it appears to contain three carbon–carbon double bonds. As we'll see in Chapter 15, aromatic rings are a good deal more stable than might be expected.

Problem 7.5 What product would you expect from the reaction of cyclopentene with NBS and water? Show the stereochemistry.

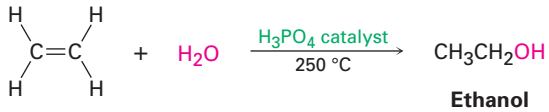
Problem 7.6 When an unsymmetrical alkene such as propene is treated with *N*-bromosuccinimide in aqueous dimethyl sulfoxide, the major product has the bromine atom bonded to the less highly substituted carbon atom. Is this Markovnikov or non-Markovnikov orientation? Explain.



7.4 Addition of Water to Alkenes: Oxymercuration

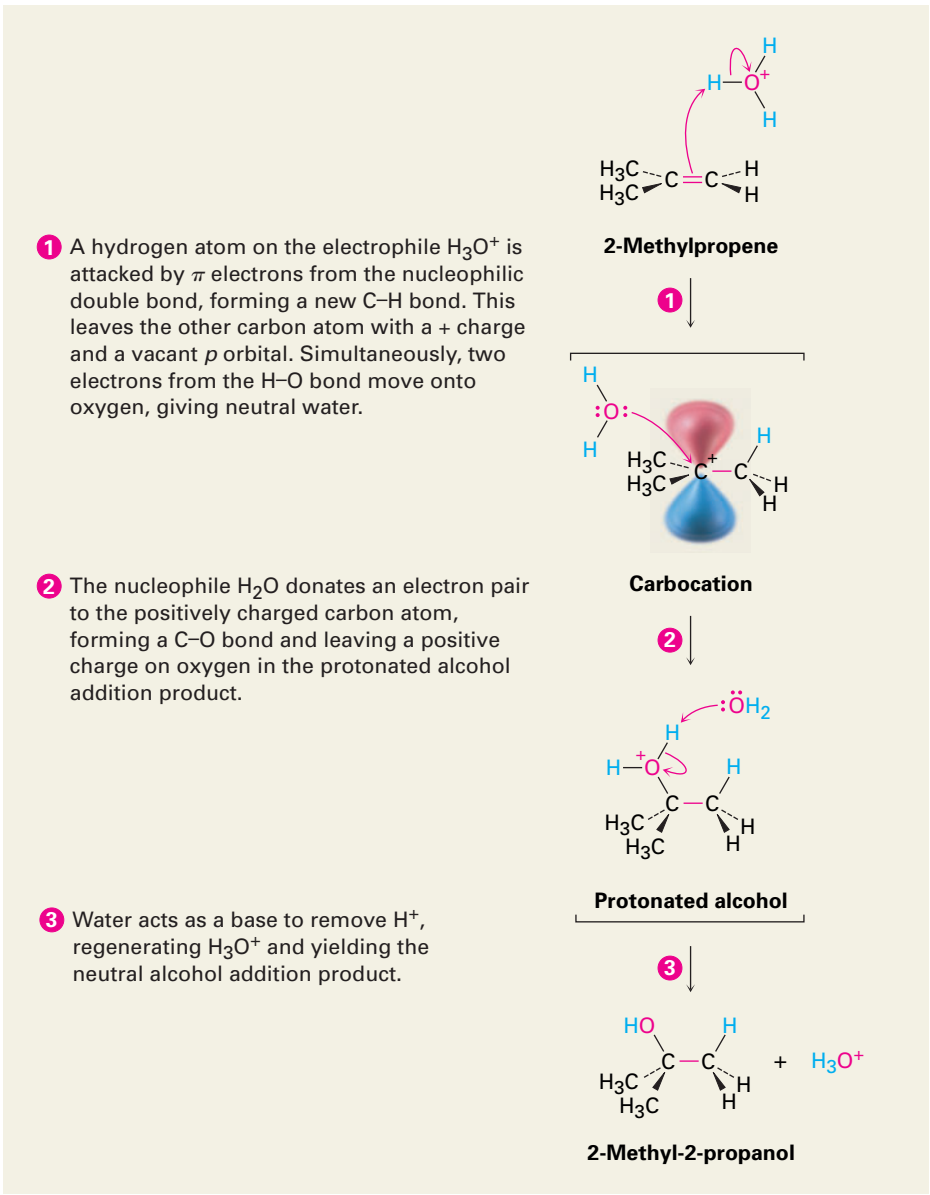
Water adds to alkenes to yield alcohols, a process called *hydration*. The reaction takes place on treatment of the alkene with water and a strong acid catalyst (HA) by a mechanism similar to that of HX addition. Thus, protonation of an alkene double bond yields a carbocation intermediate, which reacts with water to yield a protonated alcohol product (ROH_2^+). Loss of H^+ from this protonated alcohol gives the neutral alcohol and regenerates the acid catalyst (Figure 7.2).

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



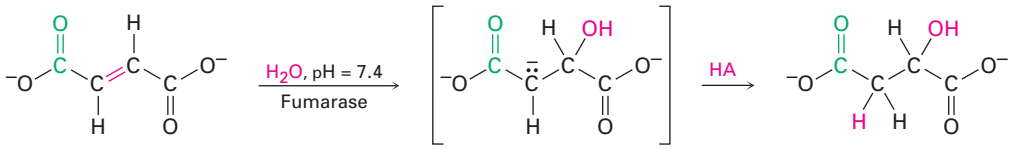
Ethylene **Ethanol**

Figure 7.2 MECHANISM: Mechanism of the acid-catalyzed hydration of an alkene to yield an alcohol. Protonation of the alkene gives a carbocation intermediate that reacts with water.



Acid-catalyzed hydration of isolated double bonds is also uncommon in biological pathways. More frequently, biological hydrations require that the double bond be adjacent to a carbonyl group for reaction to proceed. Fumarate, for instance, is hydrated to give malate as one step in the citric acid cycle of food metabolism. Note that the requirement for an adjacent carbonyl group in the addition of water is the same as that we saw in Section 7.1 for the elimination of water. We'll see the reason for the requirement in Section 19.13, but might note for now that the reaction is not an electrophilic addition but instead occurs

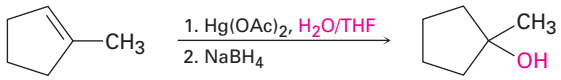
through a mechanism that involves formation of an anion intermediate followed by protonation by an acid HA.



Fumarate **Anion intermediate** **Malate**

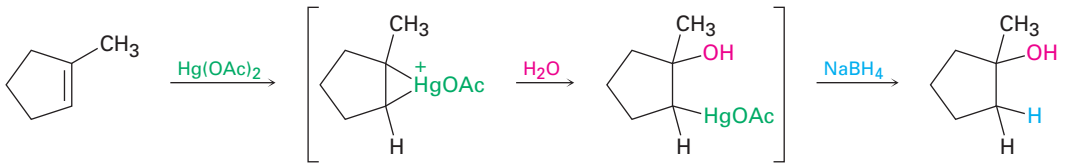
ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products of the oxymercuration of alkenes.**

In the laboratory, alkenes are often hydrated by the **oxymercuration** procedure. When an alkene is treated with mercury(II) acetate [$Hg(O_2CCH_3)_2$, usually abbreviated $Hg(OAc)_2$] in aqueous tetrahydrofuran (THF) solvent, electrophilic addition of Hg^{2+} to the double bond rapidly occurs. The intermediate *organomercury* compound is then treated with sodium borohydride, $NaBH_4$, and an alcohol is produced. For example:



1-Methylcyclopentene **1-Methylcyclopentanol (92%)**

Alkene oxymercuration is closely analogous to halohydrin formation. The reaction is initiated by electrophilic addition of Hg^{2+} (mercuric) ion to the alkene to give an intermediate *mercurinium ion,* whose structure resembles that of a bromonium ion (Figure 7.3). Nucleophilic addition of water as in halohydrin formation, followed by loss of a proton, then yields a stable organomercury product. The final step, reaction of the organomercury compound with sodium borohydride, is complex and appears to involve radicals. Note that the regiochemistry of the reaction corresponds to Markovnikov addition of water; that is, the −OH group attaches to the more highly substituted carbon atom, and the −H attaches to the less highly substituted carbon.



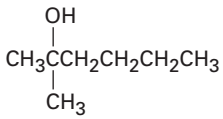
1-Methyl-cyclopentene **Mercurinium ion** **Organomercury compound** **1-Methyl-cyclopentanol (92% yield)**

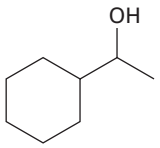
Figure 7.3 Mechanism of the oxymercuration of an alkene to yield an alcohol. The reaction involves a mercurinium ion intermediate and proceeds by a mechanism similar to that of halohydrin formation. The product of the reaction is the more highly substituted alcohol, corresponding to Markovnikov regiochemistry.

Problem 7.7 What products would you expect from oxymercuration of the following alkenes?

(a) $CH_3CH_2CH_2CH{=}CH_2$ **(b)** $CH_3C(CH_3){=}CHCH_2CH_3$

Problem 7.8 What alkenes might the following alcohols have been prepared from?

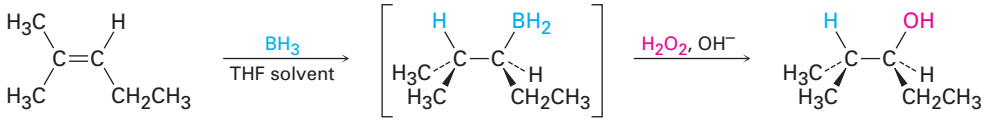
(a) 

(b) 

7.5 Addition of Water to Alkenes: Hydroboration

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products of the hydroboration/oxidation of alkenes.**

In addition to the oxymercuration method, which yields the Markovnikov product, a complementary method that yields the non-Markovnikov product is also useful. Discovered in 1959 by H. C. Brown and called **hydroboration**, the reaction involves addition of a B–H bond of borane, BH_3, to an alkene to yield an organoborane intermediate, RBH_2. Oxidation of the organoborane by reaction with basic hydrogen peroxide, H_2O_2, then gives an alcohol. For example:

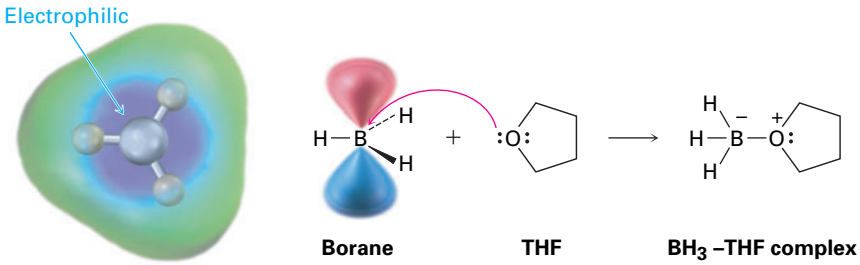


2-Methyl-2-pentene | **Organoborane intermediate** | **2-Methyl-3-pentanol**

Herbert Charles Brown

Herbert Charles Brown (1912–2004) was born in London to Ukrainian parents and brought to the United States in 1914. Brown received his Ph.D. in 1938 from the University of Chicago, taught at Chicago and at Wayne State University, and then became professor of chemistry at Purdue University. The author of more than 1000 scientific papers, he received the 1979 Nobel Prize in chemistry for his work on organoboranes.

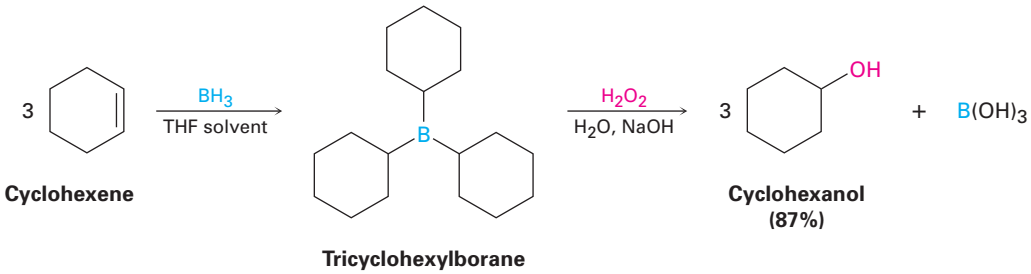
Borane is very reactive because the boron atom has only six electrons in its valence shell. In tetrahydrofuran solution, BH_3 accepts an electron pair from a solvent molecule in a Lewis acid–base reaction to complete its octet and form a stable BH_3–THF complex.



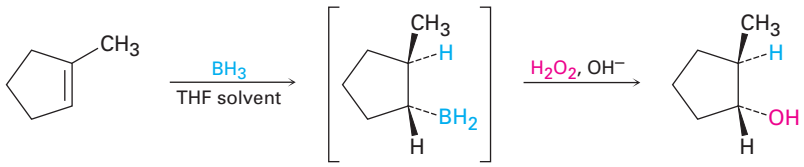
Borane | **THF** | **BH_3 –THF complex**

When an alkene reacts with BH_3 in THF solution, rapid addition to the double bond occurs three times and a *trialkylborane,* R_3B, is formed. For example, 1 molar equivalent of BH_3 adds to 3 molar equivalents of cyclohexene to yield tricyclohexylborane. When tricyclohexylborane is then treated with aqueous hydrogen peroxide (H_2O_2) in basic solution, an oxidation takes place. The three C–B bonds are broken, –OH groups bond to the three carbons, and 3 equivalents of cyclohexanol are produced. The net effect of the

two-step hydroboration/oxidation sequence is hydration of the alkene double bond.



One of the features that makes the hydroboration reaction so useful is the regiochemistry that results when an unsymmetrical alkene is hydroborated. For example, hydroboration/oxidation of 1-methylcyclopentene yields *trans*-2-methylcyclopentanol. Boron and hydrogen both add to the alkene from the same face of the double bond—that is, with **syn stereochemistry**, the opposite of anti—with boron attaching to the less highly substituted carbon. During the oxidation step, the boron is replaced by an −OH with the same stereochemistry, resulting in an overall syn non-Markovnikov addition of water. This stereochemical result is particularly useful because it is complementary to the Markovnikov regiochemistry observed for oxymercuration.

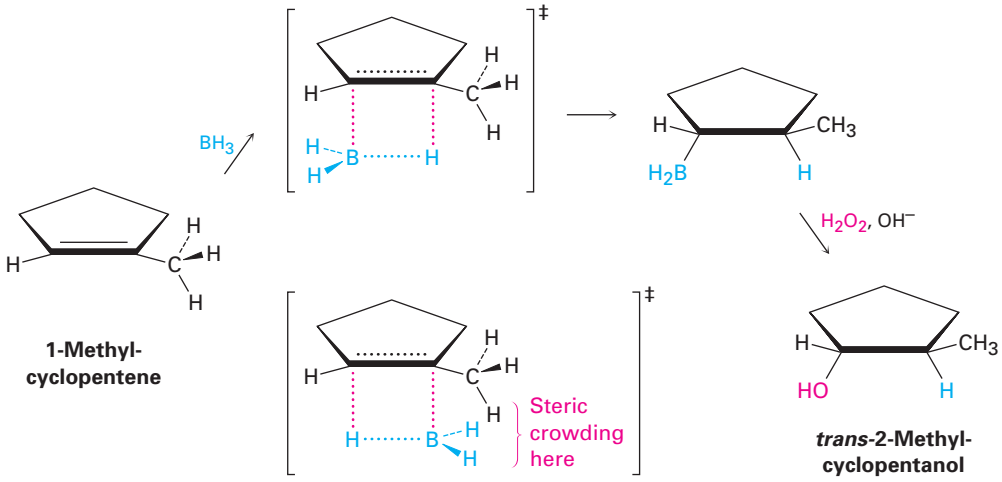


Why does alkene hydroboration take place with non-Markovnikov regiochemistry, yielding the less highly substituted alcohol? Hydroboration differs from many other alkene addition reactions in that it occurs in a single step through a four-center, cyclic transition state without a carbocation intermediate (Figure 7.4). Because both C−H and C−B bonds form at the same time and from the same face of the alkene, syn stereochemistry results. This mechanism accounts not only for the syn stereochemistry of the reaction but also for the regiochemistry. Attachment of boron is favored at the less sterically hindered carbon atom of the alkene, rather than at the more hindered carbon, because there is less steric crowding in the resultant transition state.

WORKED EXAMPLE 7.1 *Predicting the Products Formed in a Reaction*

What products would you obtain from reaction of 2,4-dimethyl-2-pentene with:
(a) BH_3, followed by H_2O_2, OH^- **(b)** $Hg(OAc)_2$, followed by $NaBH_4$

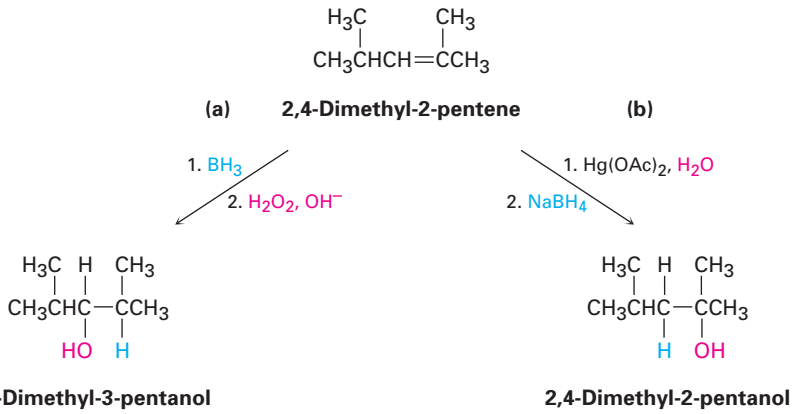
Strategy When predicting the product of a reaction, you have to recall what you know about the kind of reaction being carried out and then apply that knowledge to the specific case you're dealing with. In the present instance, recall that the two methods of



Active Figure 7.4 Mechanism of alkene hydroboration. The reaction occurs in a single step in which both C–H and C–B bonds form at the same time and on the same face of the double bond. The lower energy, more rapidly formed transition state is the one with less steric crowding, leading to non-Markovnikov regiochemistry. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

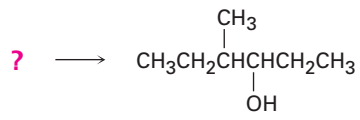
hydration—hydroboration/oxidation and oxymercuration—give complementary products. Hydroboration/oxidation occurs with syn stereochemistry and gives the non-Markovnikov addition product; oxymercuration gives the Markovnikov product.

Solution

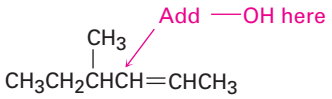


WORKED EXAMPLE 7.2 *Choosing a Reactant to Synthesize a Specific Compound*

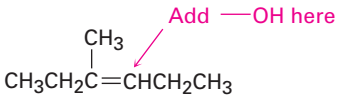
How might you prepare the following alcohol?



Strategy Problems that require the synthesis of a specific target molecule should always be worked backward. Look at the target, identify its functional group(s), and ask yourself "What are the methods for preparing this functional group?" In the present instance, the target molecule is a secondary alcohol (R_2CHOH), and we've seen that alcohols can be prepared from alkenes by either hydroboration/oxidation or oxymercuration. The −OH bearing carbon in the product must have been a double-bond carbon in the alkene reactant, so there are two possibilities: 4-methyl-2-hexene and 3-methyl-3-hexene.



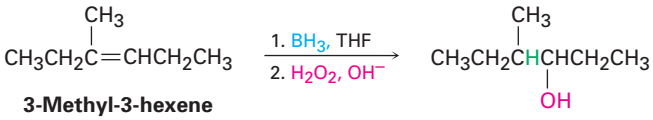
4-Methyl-2-hexene



3-Methyl-3-hexene

4-Methyl-2-hexene has a disubstituted double bond, RCH=CHR′, and would probably give a mixture of two alcohols with either hydration method since Markovnikov's rule does not apply to symmetrically substituted alkenes. 3-Methyl-3-hexene, however, has a trisubstituted double bond, and would give only the desired product on non-Markovnikov hydration using the hydroboration/oxidation method.

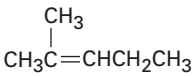
Solution



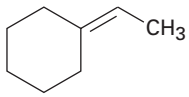
3-Methyl-3-hexene

Problem 7.9 Show the structures of the products you would obtain by hydroboration/oxidation of the following alkenes:

(a)

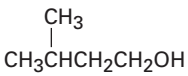


(b)



Problem 7.10 What alkenes might be used to prepare the following alcohols by hydroboration/oxidation?

(a)



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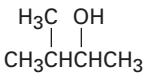
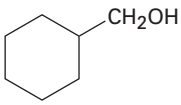
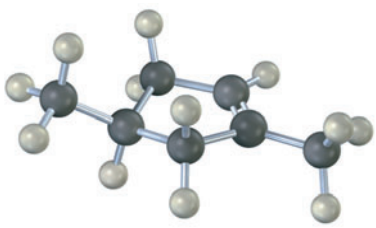


(c)



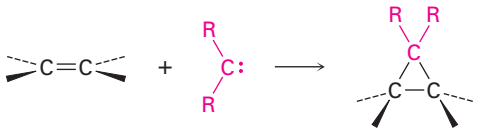
Problem 7.11 The following cycloalkene gives a mixture of two alcohols on hydroboration followed by oxidation. Draw the structures of both, and explain the result.



7.6 Addition of Carbenes to Alkenes: Cyclopropane Synthesis

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products of the addition of various carbenes to alkenes.**

Yet another kind of alkene addition is the reaction of a *carbene* with an alkene to yield a cyclopropane. A **carbene**, $R_2C:$, is a neutral molecule containing a divalent carbon with only six electrons in its valence shell. It is therefore highly reactive and is generated only as a reaction intermediate, rather than as an isolable molecule. Because they're electron-deficient, carbenes behave as electrophiles and react with nucleophilic C=C bonds. The reaction occurs in a single step without intermediates.

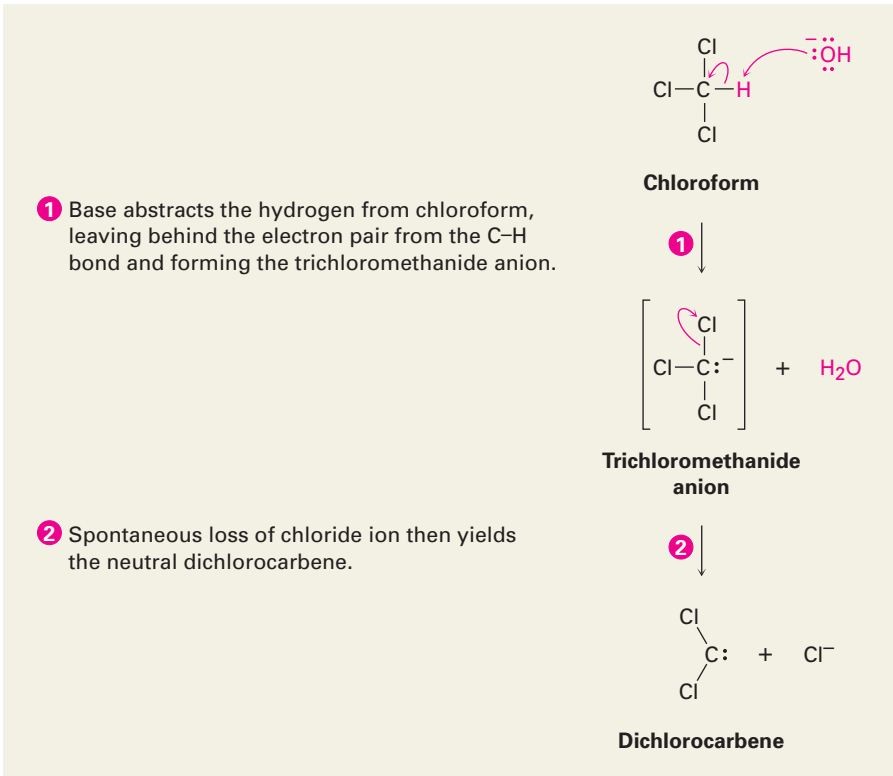


An alkene **A carbene** **A cyclopropane**

One of the simplest methods for generating a substituted carbene is by treatment of chloroform, $CHCl_3$, with a strong base such as KOH. Loss of a proton from $CHCl_3$ gives the trichloromethanide anion, $^-:CCl_3$, which expels a Cl^- ion to yield dichlorocarbene, $:CCl_2$ (Figure 7.5).

Figure 7.5 MECHANISM: Mechanism of the formation of dichlorocarbene by reaction of chloroform with strong base.

ThomsonNOW™ Click *Organic Process* to **view an animation of the mechanism for the addition of dichlorocarbene to alkenes.**



© John McMurry

The dichlorocarbene carbon atom is sp^2-hybridized, with a vacant *p* orbital extending above and below the plane of the three atoms and with an unshared pair of electrons occupying the third sp^2 lobe. Note that this electronic description of dichlorocarbene is similar to that for a carbocation (Section 6.9) with respect to both the sp^2 hybridization of carbon and the vacant *p* orbital. Electrostatic potential maps further show this similarity (Figure 7.6).

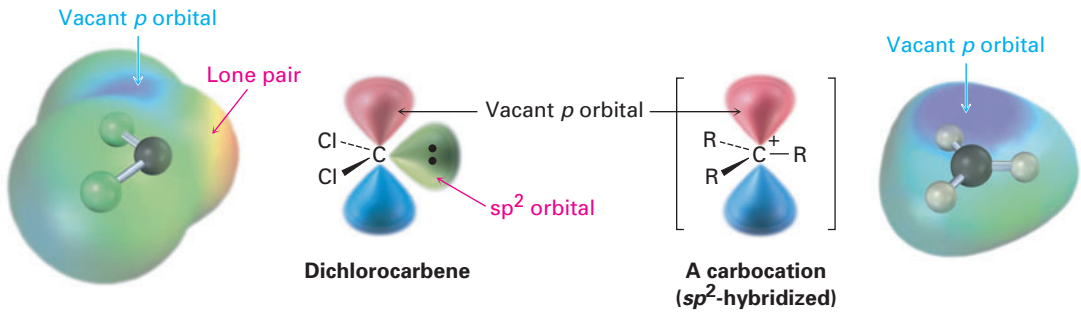
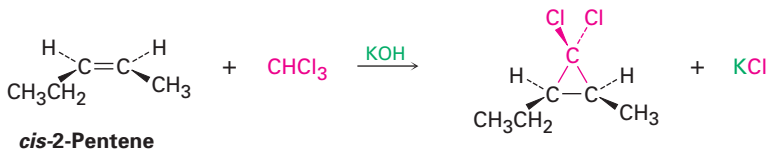
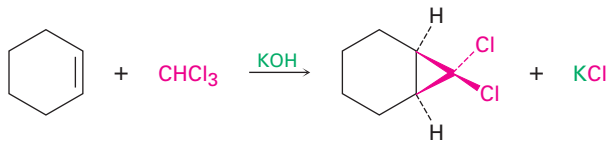


Figure 7.6 The structure of dichlorocarbene. Electrostatic potential maps show how the positive region (blue) coincides with the empty *p* orbital in both dichlorocarbene and a carbocation (CH_3^+). The negative region (red) in the dichlorocarbene map coincides with the lone-pair electrons.

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



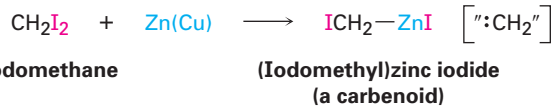
***cis*-2-Pentene**



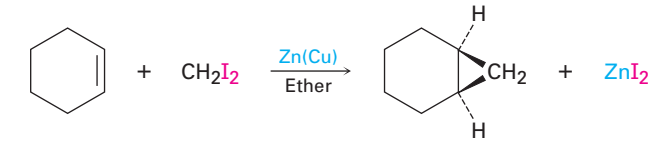
Cyclohexene

The best method for preparing nonhalogenated cyclopropanes is by a process called the **Simmons–Smith reaction**. First investigated at the DuPont company, this reaction does not involve a free carbene. Rather, it utilizes a *carbenoid*—a metal-complexed reagent with carbene-like reactivity. When diiodomethane is treated with a specially prepared zinc–copper mix, (iodomethyl)zinc iodide, ICH_2ZnI, is formed. In the presence of an alkene, (iodomethyl)zinc iodide transfers a CH_2 group to the double bond and yields the cyclopropane. For example, cyclohexene reacts cleanly and in good yield to give the corresponding cyclopropane. Although we won't discuss the mechanistic details, carbene addition to

an alkene is one of a general class of reactions called *cycloadditions*, which we'll study more carefully in Chapter 30.



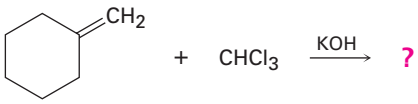
Diiodomethane — **(Iodomethyl)zinc iodide (a carbenoid)**



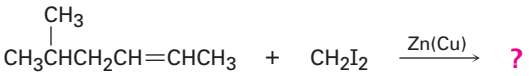
Cyclohexene — **Bicyclo[4.1.0]heptane (92%)**

Problem 7.12 What products would you expect from the following reactions?

(a)



(b)



7.7 Reduction of Alkenes: Hydrogenation

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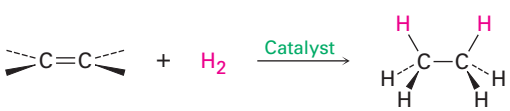
Alkenes react with H_2 in the presence of a metal catalyst to yield the corresponding saturated alkane addition products. We describe the result by saying that the double bond has been **hydrogenated**, or *reduced*. Note that the words *oxidation* and *reduction* are used somewhat differently in organic chemistry from what you might have learned previously. In general chemistry, a reduction is defined as the gain of one or more electrons by an atom. In organic chemistry, however, a **reduction** is a reaction that results in a gain of electron density by carbon, caused either by bond formation between carbon and a less electronegative atom or by bond-breaking between carbon and a more electronegative atom. We'll explore the topic in more detail in Section 10.9.

Reduction Increases electron density on carbon by:

– forming this: C—H

– or breaking one of these: C—O C—N C—X

A reduction:



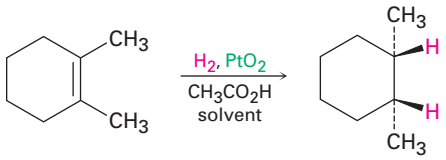
An alkene — **An alkane**

Roger Adams

Roger Adams (1889–1971) was born in Boston, Massachusetts, and received his Ph.D. in 1912 at Harvard. He taught at the University of Illinois from 1916 until his retirement in 1957, during which time he had an enormous influence on the development of organic chemistry in the United States. Among many other accomplishments, he established the structure of tetrahydrocannabinol, the active ingredient in marijuana.

Platinum and palladium are the most common catalysts for alkene hydrogenations. Palladium is normally used as a very fine powder "supported" on an inert material such as charcoal (Pd/C) to maximize surface area. Platinum is normally used as PtO_2, a reagent called *Adams' catalyst* after its discoverer, Roger Adams.

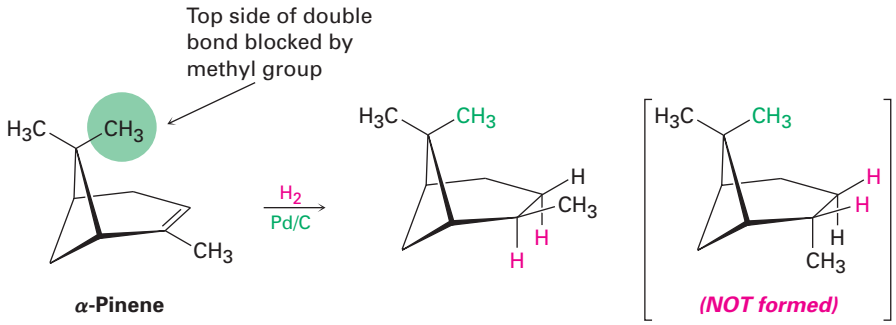
Catalytic hydrogenation, unlike most other organic reactions, is a *heterogeneous* process rather than a homogeneous one. That is, the hydrogenation reaction does not occur in a homogeneous solution but instead takes place on the surface of insoluble catalyst particles. Hydrogenation usually occurs with syn stereochemistry—both hydrogens add to the double bond from the same face.



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

The first step in the reaction is adsorption of H_2 onto the catalyst surface. Complexation between catalyst and alkene then occurs as a vacant orbital on the metal interacts with the filled alkene π orbital. In the final steps, hydrogen is inserted into the double bond and the saturated product diffuses away from the catalyst (Figure 7.7). The stereochemistry of hydrogenation is syn because both hydrogens add to the double bond from the same catalyst surface.

An interesting feature of catalytic hydrogenation is that the reaction is extremely sensitive to the steric environment around the double bond. As a result, the catalyst often approaches only the more accessible face of an alkene, giving rise to a single product. In α-pinene, for example, one of the methyl groups attached to the four-membered ring hangs over the top face of the double bond and blocks approach of the hydrogenation catalyst from that side. Reduction therefore occurs exclusively from the bottom face to yield the product shown.



α-Pinene

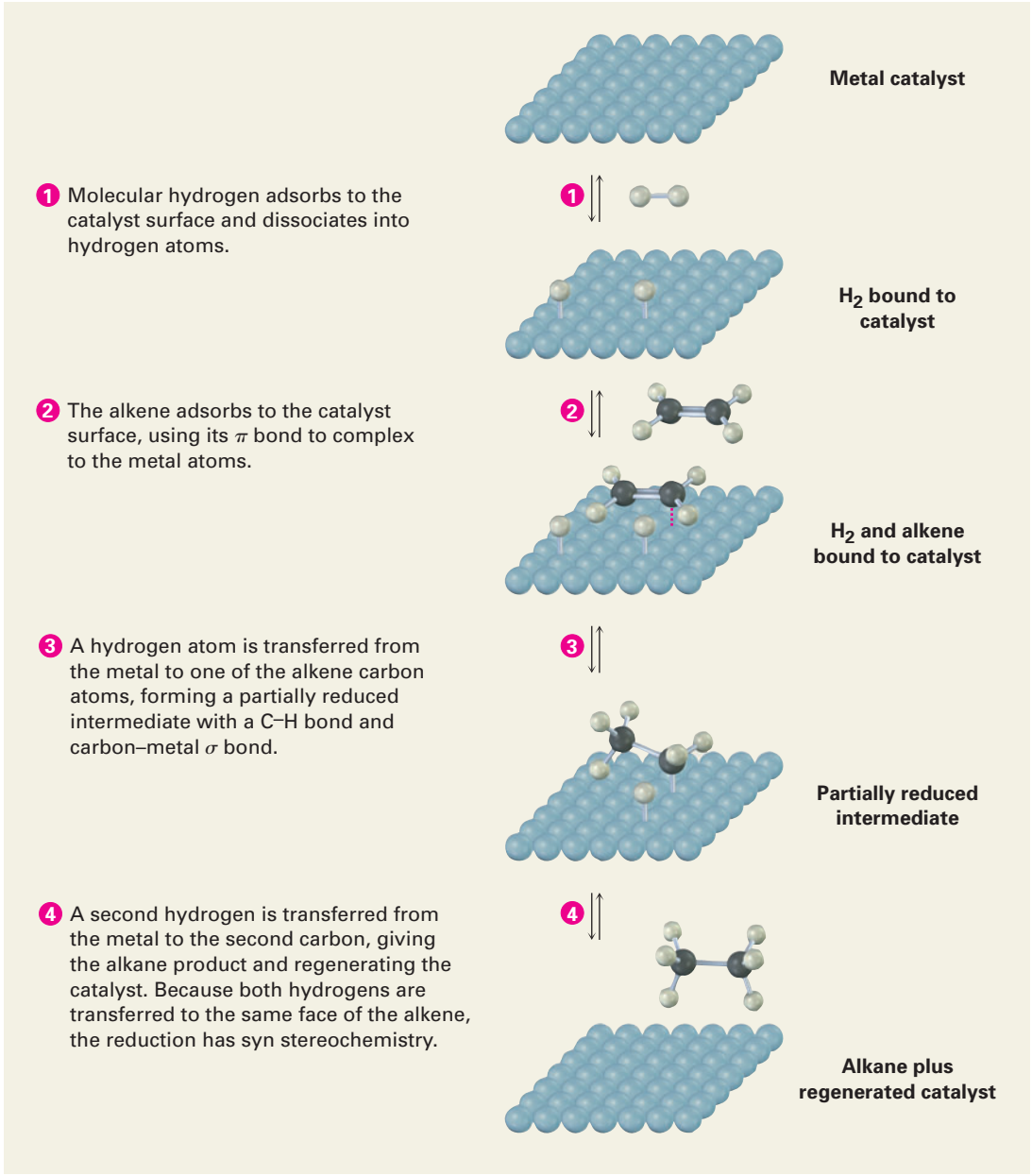
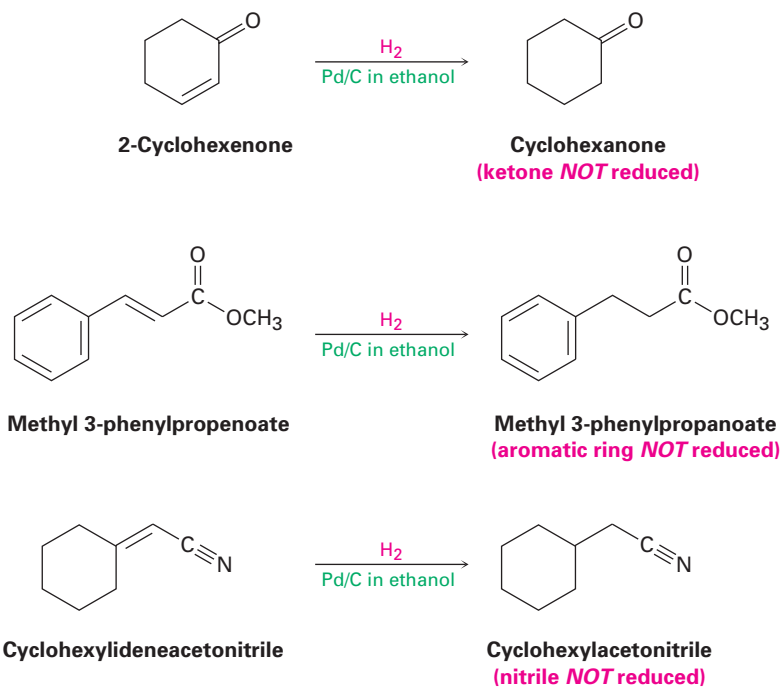


Figure 7.7 MECHANISM: Mechanism of alkene hydrogenation. The reaction takes place with syn stereochemistry on the surface of insoluble catalyst particles.

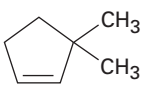
Alkenes are much more reactive than most other unsaturated functional groups toward catalytic hydrogenation, and the reaction is therefore quite selective. Other functional groups such as aldehydes, ketones, esters, and nitriles survive normal alkene hydrogenation conditions unchanged, although reaction with these groups does occur under more vigorous conditions. Note particularly

in the hydrogenation of methyl 3-phenylpropenoate shown below that the aromatic ring is not reduced by hydrogen and palladium even though it contains apparent double bonds.



In addition to its usefulness in the laboratory, catalytic hydrogenation is also important in the food industry, where unsaturated vegetable oils are reduced on a vast scale to produce the saturated fats used in margarine and cooking products (Figure 7.8). As we'll see in Section 27.1, vegetable oils are triesters of glycerol, $HOCH_2CH(OH)CH_2OH$, with three long-chain carboxylic acids called *fatty acids*. The fatty acids are generally polyunsaturated, and their double bonds invariably have cis stereochemistry. Complete hydrogenation yields the corresponding saturated fatty acids, but incomplete hydrogenation often results in partial cis–trans isomerization of a remaining double bond. When eaten and digested, the free trans fatty acids are released, raising blood cholesterol levels and contributing to potential coronary problems.

Problem 7.13 What product would you obtain from catalytic hydrogenation of the following alkenes?

(a) $CH_3CH_3C{=}CHCH_2CH_3$ **(b)** 

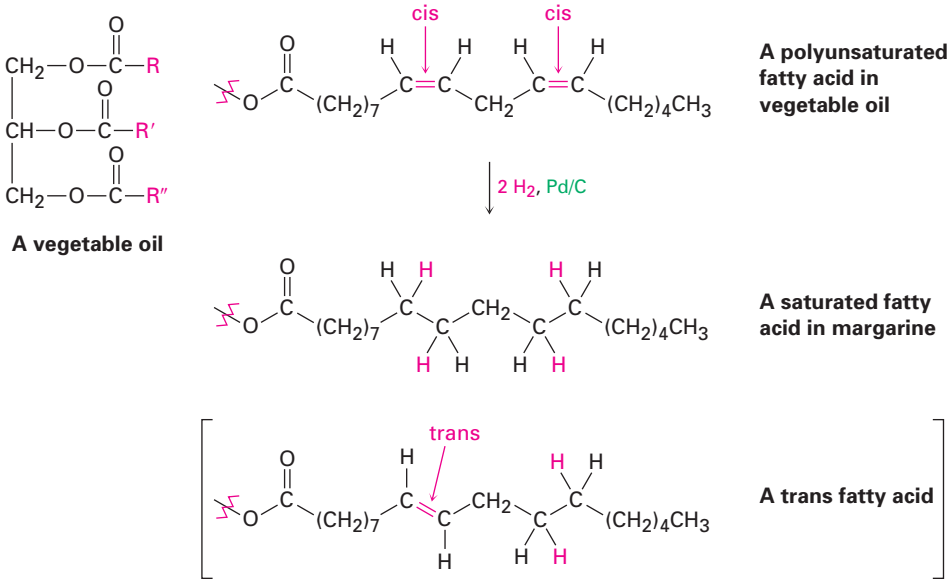


Figure 7.8 Catalytic hydrogenation of polyunsaturated fats leads to saturated products, along with a small amount of isomerized trans fats.

7.8 Oxidation of Alkenes: Epoxidation and Hydroxylation

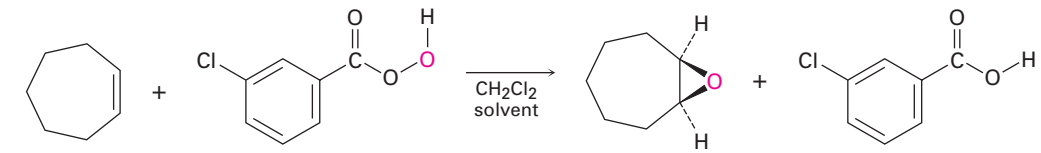
Like the word *reduction* used in the previous section for addition of hydrogen to a double bond, the word *oxidation* has a slightly different meaning in organic chemistry from what you might have previously learned. In general chemistry, an oxidation is defined as the loss of one or more electrons by an atom. In organic chemistry, however, an **oxidation** is a reaction that results in a loss of electron density by carbon, caused either by bond formation between carbon and a more electronegative atom—usually oxygen, nitrogen, or a halogen—or by bond-breaking between carbon and a less electronegative atom—usually hydrogen. Note that an *oxidation* often adds oxygen, while a *reduction* often adds hydrogen.

Oxidation Decreases electron density on carbon by:

– forming one of these: C–O C–N C–X

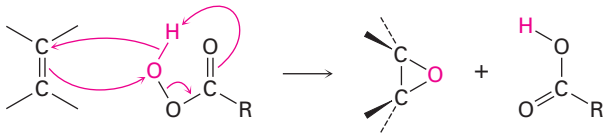
– or breaking this: C–H

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



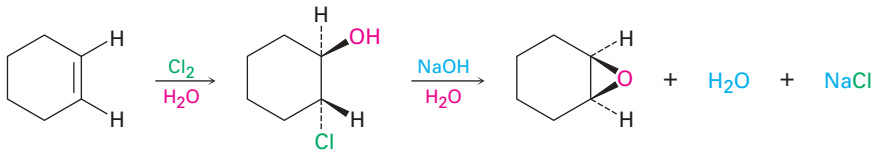
Cycloheptene | ***meta*-Chloroperoxybenzoic acid** | **1,2-Epoxycycloheptane** | ***meta*-Chlorobenzoic acid**

Peroxyacids transfer an oxygen atom to the alkene with syn stereochemistry—both C−O bonds form on the same face of the double bond—through a one-step mechanism without intermediates. The oxygen atom farthest from the carbonyl group is the one transferred.



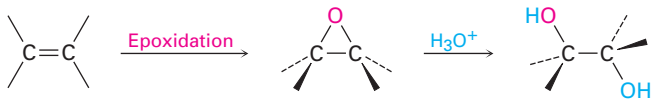
Alkene **Peroxyacid** **Epoxide** **Acid**

Another method for the synthesis of epoxides is through the use of halohydrins, prepared by electrophilic addition of HO−X to alkenes (Section 7.3). When a halohydrin is treated with base, HX is eliminated and an epoxide is produced.



Cyclohexene ***trans*-2-Chlorocyclohexanol** **1,2-Epoxycyclohexane (73%)**

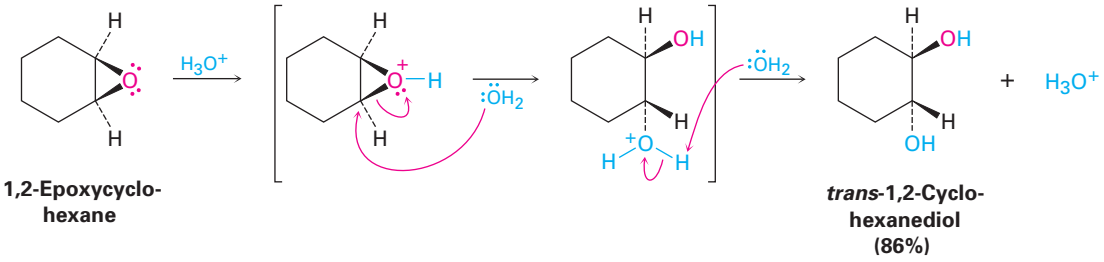
Epoxides undergo an acid-catalyzed ring-opening reaction with water (a *hydrolysis*) to give the corresponding dialcohol *(diol),* also called a **glycol**. Thus, the net result of the two-step alkene epoxidation/hydrolysis is **hydroxylation**—the addition of an −OH group to each of the two double-bond carbons. In fact, more than 3 million tons of ethylene glycol, $HOCH_2CH_2OH$, most of it used for automobile antifreeze, is produced each year in the United States by epoxidation of ethylene followed by hydrolysis.



An alkene **An epoxide** **A 1,2-diol**

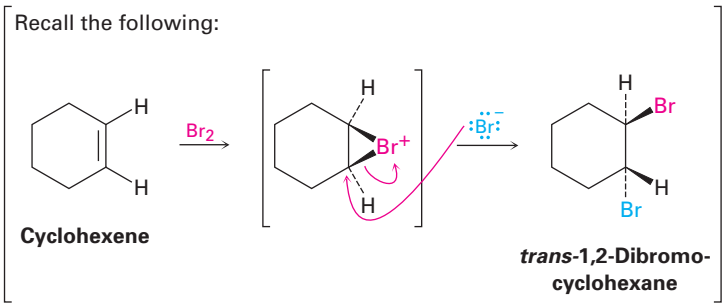
Acid-catalyzed epoxide opening takes place by protonation of the epoxide to increase its reactivity, followed by nucleophilic addition of water. This nucleophilic addition is analogous to the final step of alkene bromination, in which a cyclic bromonium ion is opened by a nucleophile (Section 7.2). That is,

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



1,2-Epoxycyclohexane

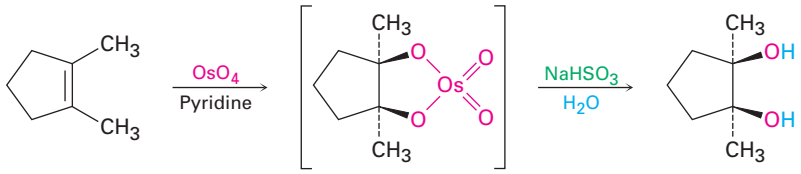
***trans*-1,2-Cyclohexanediol (86%)**



Cyclohexene

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

Hydroxylation can be carried out directly without going through the intermediate epoxide by treating an alkene with osmium tetroxide, OsO_4. The reaction occurs with syn stereochemistry and does not involve a carbocation intermediate. Instead, it takes place through an intermediate cyclic *osmate,* which is formed in a single step by addition of OsO_4 to the alkene. This cyclic osmate is then cleaved using aqueous sodium bisulfite, $NaHSO_3$.



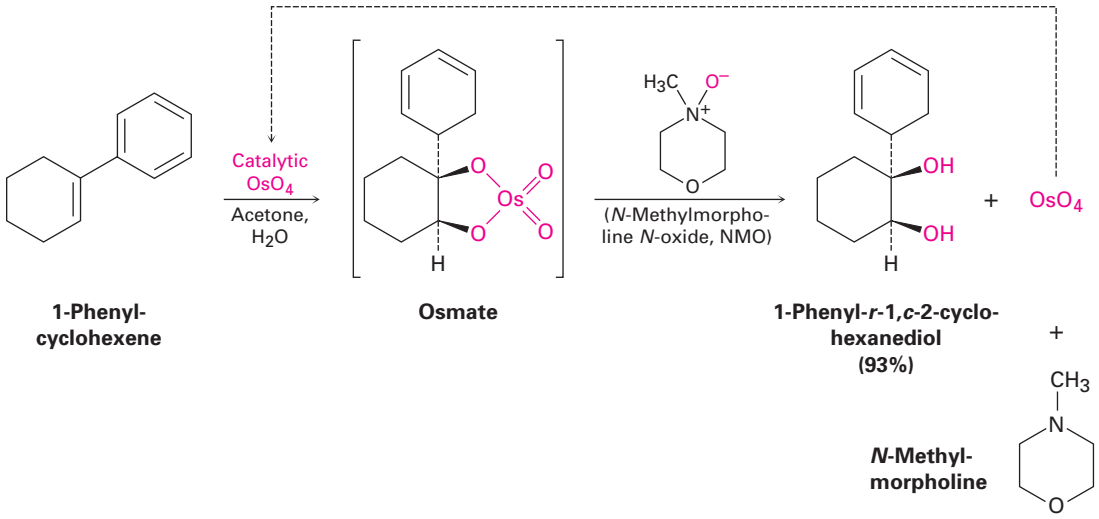
1,2-Dimethylcyclopentene

A cyclic osmate intermediate

***cis*-1,2-Dimethyl-1,2-cyclopentanediol (87%)**

Unfortunately, a serious problem with the osmium tetroxide reaction is that OsO_4 is both very expensive and *very* toxic. As a result, the reaction is usually carried out using only a small, catalytic amount of OsO_4 in the presence of a stoichiometric amount of a safe and inexpensive co-oxidant such as *N*-methylmorpholine *N*-oxide, abbreviated NMO. The initially formed osmate intermediate reacts rapidly with NMO to yield the product diol plus

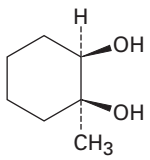
N-methylmorpholine and reoxidized OsO_4. The OsO_4 then reacts with more alkene in a catalytic cycle.

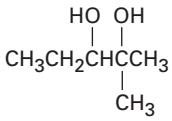


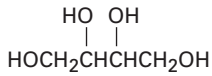
Note that a *cis*- or *trans*- prefix would be ambiguous when naming the diol derived from 1-phenylcyclohexene because the ring has three substituents. In such a case, the substituent with the lowest number is taken as the reference substituent, denoted *r*, and the other substituents are identified as being cis *(c)* or trans *(t)* to that reference. When two substituents share the same lowest number, the one with the highest priority by the Cahn–Ingold–Prelog sequence rules (Section 6.5) is taken as the reference. In the case of 1-phenyl-1,2-cyclohexanediol, the −OH group at C1 is the reference (*r*-1), and the −OH at C2 is either cis (*c*-2) or trans (*t*-2) to that reference. Thus, the diol resulting from cis hydroxylation is named 1-phenyl-*r*-1,*c*-2-cyclohexanediol, and its isomer resulting from trans hydroxylation would be named 1-phenyl-*r*-1,*t*-2-cyclohexanediol.

Problem 7.14 What product would you expect from reaction of *cis*-2-butene with *meta*-chloroperoxybenzoic acid? Show the stereochemistry.

Problem 7.15 How would you prepare each of the following compounds starting with an alkene?

(a) 

(b) 

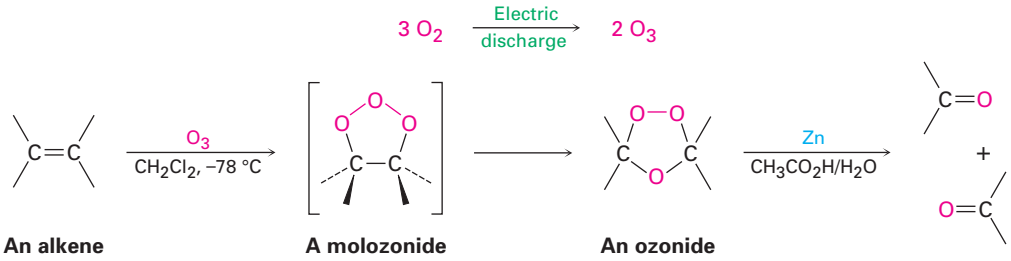
(c) 

7.9 Oxidation of Alkenes: Cleavage to Carbonyl Compounds

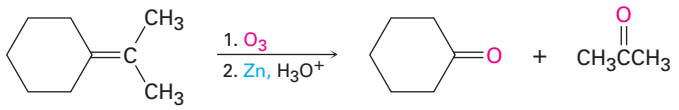
ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to predict products from the oxidation of alkenes.**

In all the alkene addition reactions we've seen thus far, the carbon–carbon double bond has been converted into a single bond but the carbon skeleton has been left intact. There are, however, powerful oxidizing reagents that will cleave C=C bonds and produce two carbonyl-containing fragments.

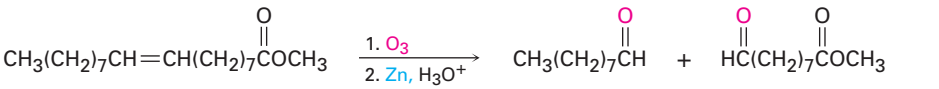
Ozone (O_3) is perhaps the most useful double-bond cleavage reagent. Prepared by passing a stream of oxygen through a high-voltage electrical discharge, ozone adds rapidly to an alkene at low temperature to give a cyclic intermediate called a *molozonide*. Once formed, the molozonide then spontaneously rearranges to form an **ozonide**. Although we won't study the mechanism of this rearrangement in detail, it involves the molozonide coming apart into two fragments that then recombine in a different way.



Low-molecular-weight ozonides are explosive and are therefore not isolated. Instead, the ozonide is immediately treated with a reducing agent such as zinc metal in acetic acid to convert it to carbonyl compounds. The net result of the ozonolysis/reduction sequence is that the C=C bond is cleaved and oxygen becomes doubly bonded to each of the original alkene carbons. If an alkene with a tetrasubstituted double bond is ozonized, two ketone fragments result; if an alkene with a trisubstituted double bond is ozonized, one ketone and one aldehyde result; and so on.

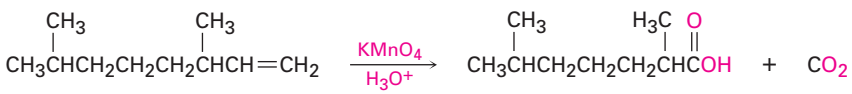


84%; two ketones

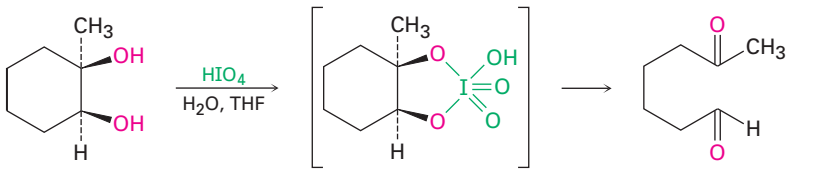


78%; two aldehydes

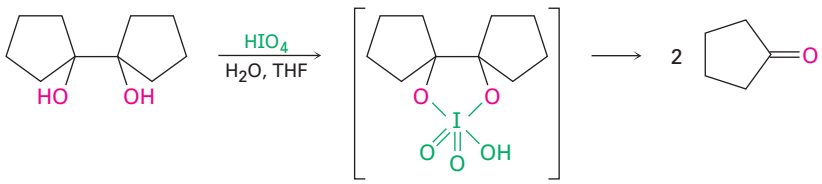
Several oxidizing reagents other than ozone also cause double-bond cleavage. For example, potassium permanganate ($KMnO_4$) in neutral or acidic solution cleaves alkenes to give carbonyl-containing products. If hydrogens are present on the double bond, carboxylic acids are produced; if two hydrogens are present on one carbon, CO_2 is formed.



In addition to direct cleavage with ozone or $KMnO_4$, an alkene can also be cleaved by initial hydroxylation to a 1,2-diol followed by treatment with periodic acid, HIO_4. If the two −OH groups are in an open chain, two carbonyl compounds result. If the two −OH groups are on a ring, a single, open-chain dicarbonyl compound is formed. As indicated in the following examples, the cleavage reaction takes place through a cyclic periodate intermediate.



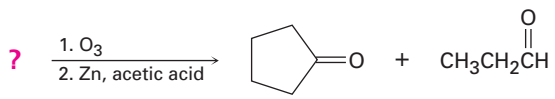
A 1,2-diol **Cyclic periodate intermediate** **6-Oxoheptanal (86%)**



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

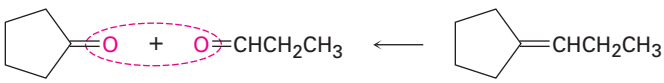
WORKED EXAMPLE 7.3 *Predicting the Reactant in an Ozonolysis Reaction*

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



Strategy Reaction of an alkene with ozone, followed by reduction with zinc, cleaves the carbon–carbon double bond and gives two carbonyl-containing fragments. That is, the C=C bond becomes two C=O bonds. Working backward from the carbonyl-containing products, the alkene precursor can be found by removing the oxygen from each product and joining the two carbon atoms to form a double bond.

Solution



Problem 7.16 What products would you expect from reaction of 1-methylcyclohexene with the following reagents?

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

Problem 7.17 Propose structures for alkenes that yield the following products on reaction with ozone followed by treatment with Zn:

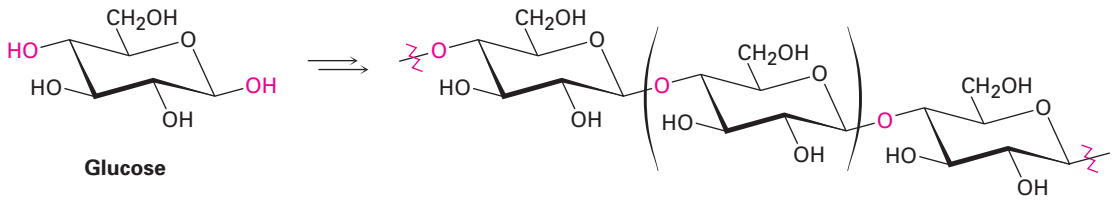
(a) $(CH_3)_2C{=}O + H_2C{=}O$ **(b)** 2 equiv $CH_3CH_2CH{=}O$

7.10 Radical Additions to Alkenes: Polymers

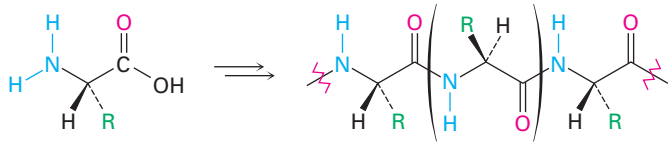
We had a brief introduction to radical reactions in Section 5.3 and said at that time that radicals can add to alkene double bonds, taking one electron from the double bond and leaving one behind to yield a new radical. Let's now look at the process in more detail, focusing on the industrial synthesis of alkene polymers.

A **polymer** is simply a large—sometimes *very* large—molecule built up by repetitive bonding together of many smaller molecules, called **monomers**. Nature makes wide use of biological polymers. Cellulose, for instance, is a polymer built of repeating glucose monomer units; proteins are polymers built of repeating amino acid monomers; and nucleic acids are polymers built of repeating nucleotide monomers. Synthetic polymers, such as polyethylene, are chemically much simpler than biopolymers, but there is still a great diversity to their structures and properties, depending on the identity of the monomers and on the reaction conditions used for polymerization.

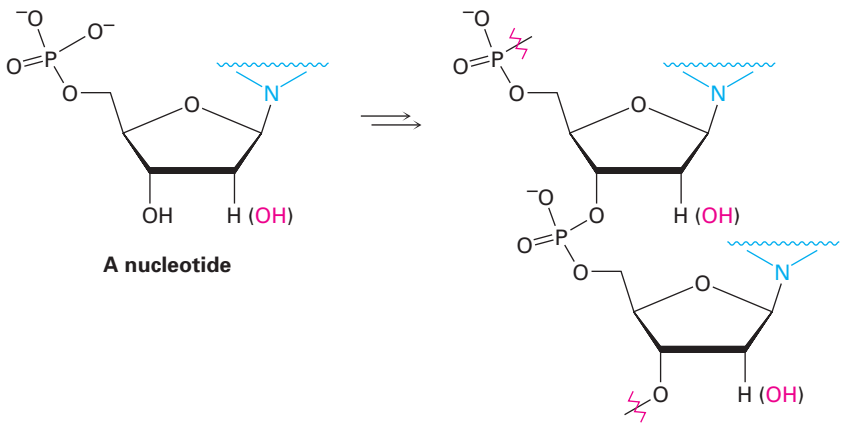
Cellulose—a glucose polymer



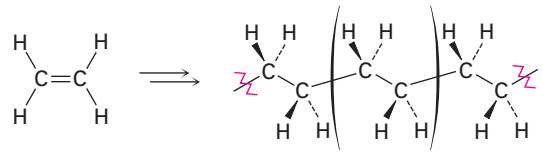
Protein—an amino acid polymer



Nucleic acid—a nucleotide polymer



Polyethylene—a synthetic alkene polymer

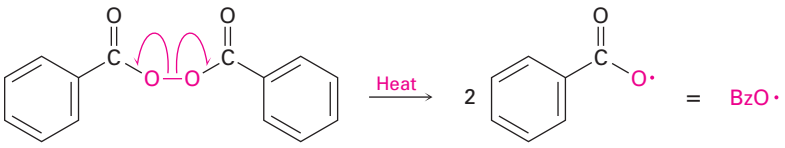


Ethylene **Polyethylene**

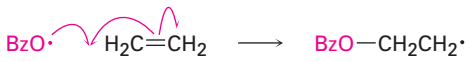
The simplest synthetic polymers are those that result when an alkene is treated with a small amount of a radical as catalyst. Ethylene, for example, yields polyethylene, an enormous alkane that may have up to *200,000* monomer units incorporated into a gigantic hydrocarbon chain. Approximately 14 million tons per year of polyethylene is manufactured in the United States alone.

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

Initiation The polymerization reaction is initiated when a few radicals are generated on heating a small amount of benzoyl peroxide catalyst to break the weak O−O bond. A benzoyloxy radical then adds to the C=C bond of ethylene to generate a carbon radical. One electron from the C=C bond pairs up with the odd electron on the benzoyloxy radical to form a C−O bond, and the other electron remains on carbon.

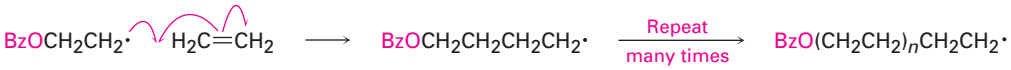


Benzoyl peroxide **Benzoyloxy radical**



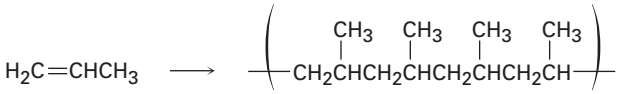
Propagation Polymerization occurs when the carbon radical formed in the initiation step adds to another ethylene molecule to yield another radical.

Repetition of the process for hundreds or thousands of times builds the polymer chain.

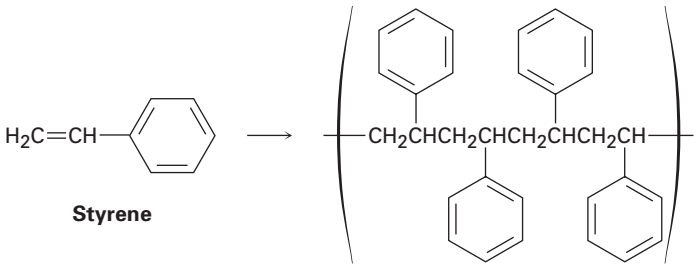


Termination The chain process is eventually ended by a reaction that consumes the radical. Combination of two growing chains is one possible chain-terminating reaction.

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



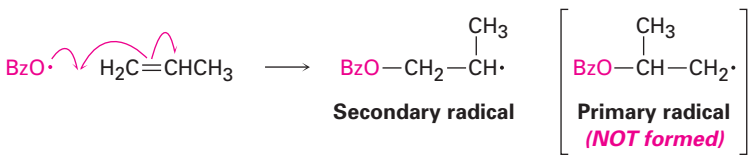
Propylene **Polypropylene**



Styrene

Polystyrene

When an unsymmetrically substituted vinyl monomer such as propylene or styrene is polymerized, the radical addition steps can take place at either end of the double bond to yield either a primary radical intermediate ($RCH_2\cdot$) or a secondary radical ($R_2CH\cdot$). Just as in electrophilic addition reactions, however, we find that only the more highly substituted, secondary radical is formed.



Secondary radical **Primary radical** ***(NOT formed)***

Table 7.1 shows some commercially important alkene polymers, their uses, and the vinyl monomers from which they are made.

Table 7.1 Some Alkene Polymers and Their Uses

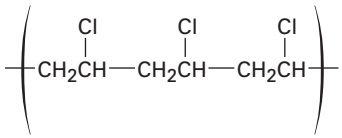
Monomer	Formula	Trade or common name of polymer	Uses
Ethylene	$H_2C{=}CH_2$	Polyethylene	Packaging, bottles
Propene (propylene)	$H_2C{=}CHCH_3$	Polypropylene	Moldings, rope, carpets
Chloroethylene (vinyl chloride)	$H_2C{=}CHCl$	Poly(vinyl chloride) Tedlar	Insulation, films, pipes
Styrene	$H_2C{=}CHC_6H_5$	Polystyrene	Foam, moldings
Tetrafluoroethylene	$F_2C{=}CF_2$	Teflon	Gaskets, nonstick coatings
Acrylonitrile	$H_2C{=}CHCN$	Orlon, Acrilan	Fibers
Methyl methacrylate	$H_2C{=}C(CH_3)CO_2CH_3$	Plexiglas, Lucite	Paint, sheets, moldings
Vinyl acetate	$H_2C{=}CHOCOCH_3$	Poly(vinyl acetate)	Paint, adhesives, foams

WORKED EXAMPLE 7.4 ***Predicting the Structure of a Polymer***

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

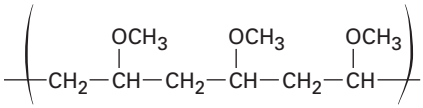
Strategy Mentally break the carbon–carbon double bond in the monomer unit, and form single bonds by connecting numerous units together.

Solution The general structure of poly(vinyl chloride) is

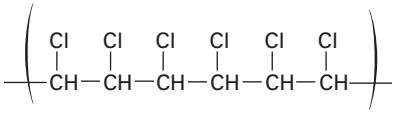


Problem 7.18 Show the monomer units you would use to prepare the following polymers:

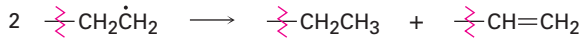
(a)



(b)



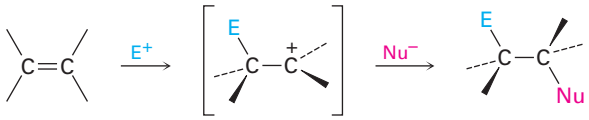
Problem 7.19 One of the chain-termination steps that sometimes occurs to interrupt polymerization is the following reaction between two radicals. Propose a mechanism for the reaction, using fishhook arrows to indicate electron flow.



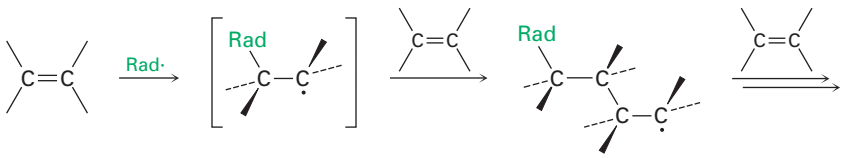
7.11 Biological Additions of Radicals to Alkenes

The same high reactivity of radicals that makes possible the alkene polymerization we saw in the previous section also makes it difficult to carry out controlled radical reactions on complex molecules. As a result, there are severe limitations on the usefulness of radical addition reactions in the laboratory. In contrast to an *electrophilic* addition, where reaction occurs once and the reactive cation intermediate is rapidly quenched in the presence of a nucleophile, the reactive intermediate in a *radical* reaction is not usually quenched, so it reacts again and again in a largely uncontrollable way.

Electrophilic addition
(Intermediate is quenched, so reaction stops.)



Radical addition
(Intermediate is not quenched, so reaction does not stop.)



In biological reactions, the situation is different from that in the laboratory. Only one substrate molecule at a time is present in the active site of the enzyme where reaction takes place, and that molecule is held in a precise position, with coenzymes and other necessary reacting groups nearby. As a result, biological radical reactions are both more controlled and more common than laboratory or industrial radical reactions. A particularly impressive example occurs in the biosynthesis of prostaglandins from arachidonic acid, where a sequence of four radical additions take place. The reaction mechanism was discussed briefly in Section 5.3.

Prostaglandin biosynthesis begins with abstraction of a hydrogen atom from C13 of arachidonic acid by an iron–oxy radical (Figure 7.9, step 1) to give a carbon radical that reacts with O_2 at C11 through a resonance form (step 2). The oxygen radical that results adds to the C8–C9 double bond (step 3) to give

a carbon radical at C8, which then adds to the C12–C13 double bond and gives a carbon radical at C13 (step 4). A resonance form of this carbon radical adds at C15 to a second O_2 molecule (step 5), completing the prostaglandin skeleton, and reduction of the O–O bond then gives prostaglandin H_2 (step 6). The pathway looks complicated, but the entire process is catalyzed with exquisite control by just one enzyme.

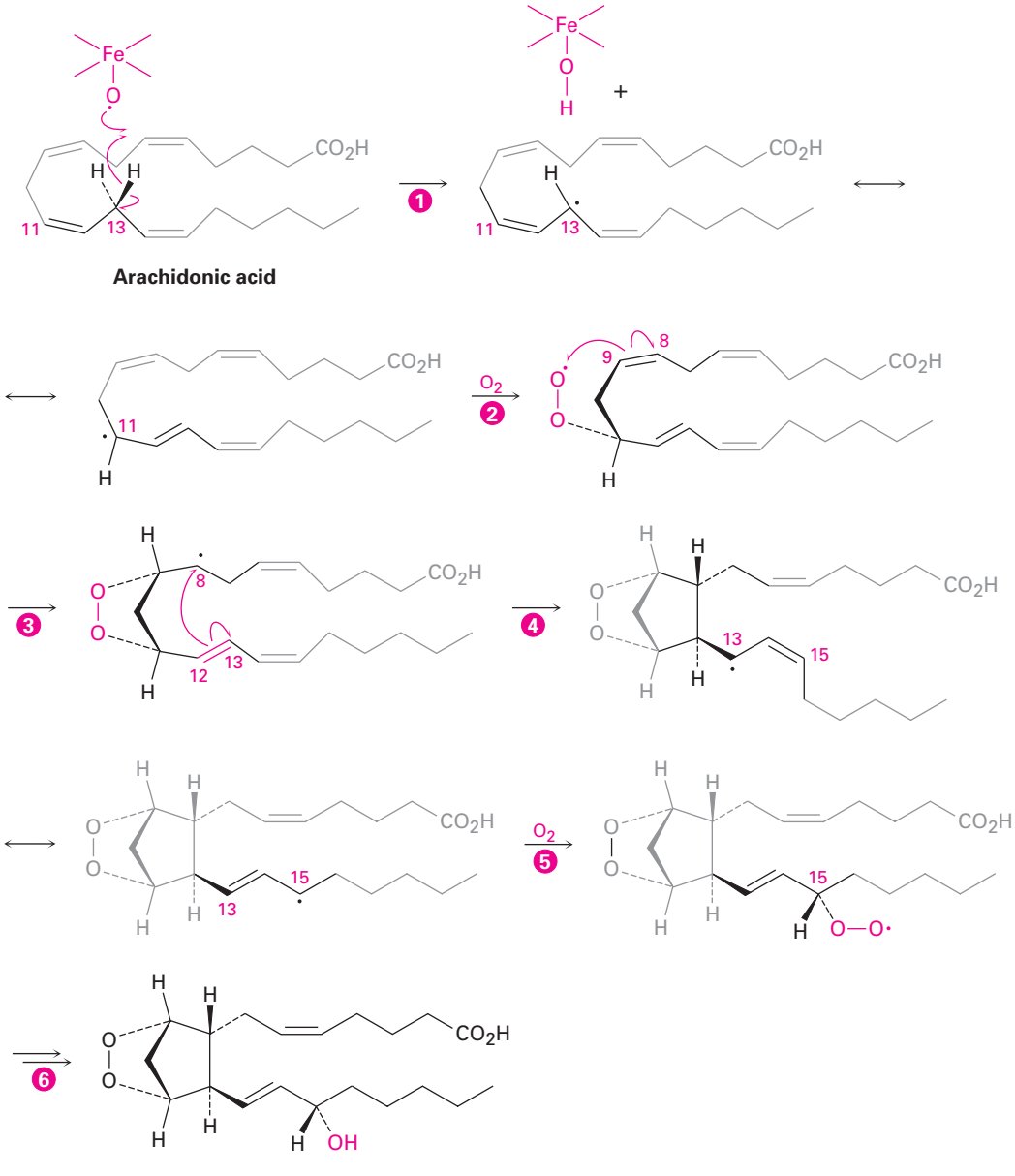


Figure 7.9 Pathway for the biosynthesis of prostaglandins from arachidonic acid. Steps 2 and 5 are radical addition reactions to O_2; steps 3 and 4 are radical additions to carbon–carbon double bonds.

Focus On . . .

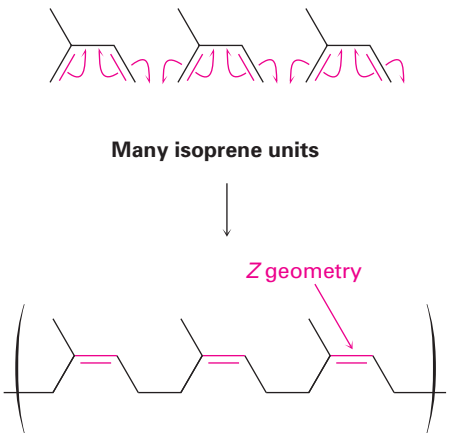
Natural Rubber

© Macduff Everton/Corbis

Natural rubber is obtained from the bark of the rubber tree, *Hevea brasiliensis,* grown on enormous plantations in Southeast Asia.

Rubber—an unusual name for an unusual substance—is a naturally occurring alkene polymer produced by more than 400 different plants. The major source is the so-called rubber tree, *Hevea brasiliensis,* from which the crude material is harvested as it drips from a slice made through the bark. The name *rubber* was coined by Joseph Priestley, the discoverer of oxygen and early researcher of rubber chemistry, for the simple reason that one of rubber's early uses was to rub out pencil marks on paper.

Unlike polyethylene and other simple alkene polymers, natural rubber is a polymer of a *diene,* isoprene (2-methyl-1,3-butadiene). The polymerization takes place by addition of isoprene monomer units to the growing chain, leading to formation of a polymer that still contains double bonds spaced regularly at four-carbon intervals. As the following structure shows, these double bonds have *Z* stereochemistry:



A segment of natural rubber

Crude rubber, called *latex,* is collected from the tree as an aqueous dispersion that is washed, dried, and coagulated by warming in air. The resultant polymer has chains that average about 5000 monomer units in length and have molecular weights of 200,000 to 500,000 amu. This crude coagulate is too soft and tacky to be useful until it is hardened by heating with elemental sulfur, a process called *vulcanization.* By mechanisms that are still not fully understood, vulcanization cross-links the rubber chains together by forming

(continued)

carbon–sulfur bonds between them, thereby hardening and stiffening the polymer. The exact degree of hardening can be varied, yielding material soft enough for automobile tires or hard enough for bowling balls *(ebonite)*.

The remarkable ability of rubber to stretch and then contract to its original shape is due to the irregular shapes of the polymer chains caused by the double bonds. These double bonds introduce bends and kinks into the polymer chains, thereby preventing neighboring chains from nestling together. When stretched, the randomly coiled chains straighten out and orient along the direction of the pull but are kept from sliding over one another by the cross-links. When the stretch is released, the polymer reverts to its original random state.

SUMMARY AND KEY WORDS

Alkenes are generally prepared by an *elimination reaction,* such as *dehydrohalogenation,* the elimination of HX from an alkyl halide, or *dehydration,* the elimination of water from an alcohol.

HCl, HBr, and HI add to alkenes by a two-step electrophilic addition mechanism. Initial reaction of the nucleophilic double bond with H^+ gives a carbocation intermediate, which then reacts with halide ion. Bromine and chlorine add to alkenes via three-membered-ring **bromonium ion** or chloronium ion intermediates to give addition products having **anti stereochemistry**. If water is present during the halogen addition reaction, a **halohydrin** is formed.

Hydration of an alkene—the addition of water—is carried out by either of two procedures, depending on the product desired. **Oxymercuration** involves electrophilic addition of Hg^{2+} to an alkene, followed by trapping of the cation intermediate with water and subsequent treatment with $NaBH_4$. **Hydroboration** involves addition of borane (BH_3) followed by oxidation of the intermediate organoborane with alkaline H_2O_2. The two hydration methods are complementary: oxymercuration gives the product of Markovnikov addition, whereas hydroboration/oxidation gives the product with non-Markovnikov **syn stereochemistry**.

A **carbene**, $R_2C:$, is a neutral molecule containing a divalent carbon with only six valence electrons. Carbenes are highly reactive toward alkenes, adding to give cyclopropanes. Nonhalogenated cyclopropanes are best prepared by treatment of the alkene with CH_2I_2 and zinc–copper, a process called the **Simmons–Smith reaction**.

Alkenes are **reduced** by addition of H_2 in the presence of a catalyst such as platinum or palladium to yield alkanes, a process called **catalytic hydrogenation**. Alkenes are also **oxidized** by reaction with a peroxyacid to give **epoxides**, which can be converted into trans-1,2-diols by acid-catalyzed epoxide hydrolysis. The corresponding cis-1,2-diols can be made directly from alkenes by **hydroxylation** with OsO_4. Alkenes can also be cleaved to produce carbonyl compounds by reaction with ozone, followed by reduction with zinc metal.

Alkene **polymers**—large molecules resulting from repetitive bonding together of many hundreds or thousands of small **monomer** units—are formed by reaction of simple alkenes with a radical initiator at high temperature and

pressure. Polyethylene, polypropylene, and polystyrene are common examples. As a general rule, radical addition reactions are not common in the laboratory but occur much more frequently in biological pathways.

Learning Reactions

What's seven times nine? Sixty-three, of course. You didn't have to stop and figure it out; you knew the answer immediately because you long ago learned the multiplication tables. Learning the reactions of organic chemistry requires the same approach: reactions have to be learned for immediate recall if they are to be useful.

Different people take different approaches to learning reactions. Some people make flash cards; others find studying with friends to be helpful. To help guide your study, most chapters in this book end with a summary of the reactions just presented. In addition, the accompanying *Study Guide and Solutions Manual* has several appendixes that organize organic reactions from other viewpoints. Fundamentally, though, there are no shortcuts. Learning organic chemistry does take effort.

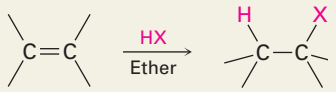
SUMMARY OF REACTIONS

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

1. Addition reactions of alkenes

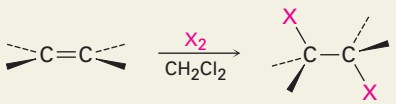
(a) Addition of HCl, HBr, and HI (Sections 6.7 and 6.8)

Markovnikov regiochemistry occurs, with H adding to the less highly substituted alkene carbon and halogen adding to the more highly substituted carbon.



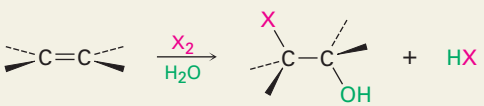
(b) Addition of halogens Cl_2 and Br_2 (Section 7.2)

Anti addition is observed through a halonium ion intermediate.

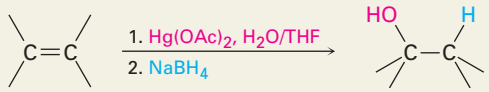


(c) Halohydrin formation (Section 7.3)

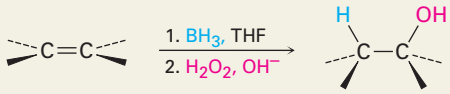
Markovnikov regiochemistry and anti stereochemistry occur.



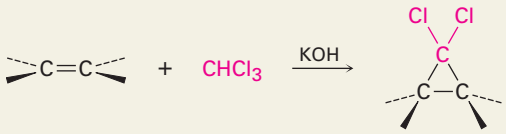
(d) Addition of water by oxymercuration (Section 7.4)
Markovnikov regiochemistry occurs.



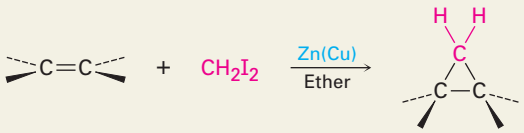
(e) Addition of water by hydroboration/oxidation (Section 7.5)
Non-Markovnikov syn addition occurs.



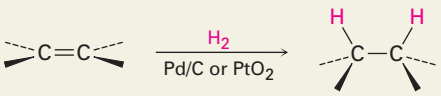
(f) Addition of carbenes to yield cyclopropanes (Section 7.6)
(1) Dichlorocarbene addition



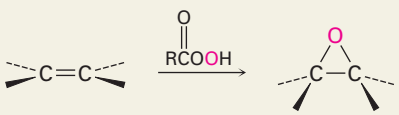
(2) Simmons–Smith reaction



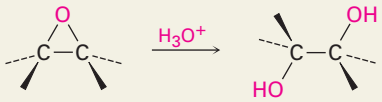
(g) Catalytic hydrogenation (Section 7.7)
Syn addition occurs.



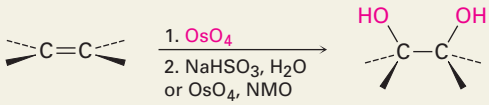
(h) Epoxidation with a peroxyacid (Section 7.8)
Syn addition occurs.



(i) Hydroxylation by acid-catalyzed epoxide hydrolysis (Section 7.8)
Anti stereochemistry occurs.

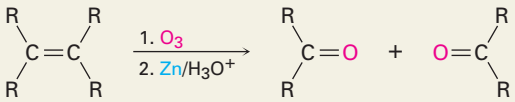


(j) Hydroxylation with OsO_4 (Section 7.8)
Syn addition occurs.

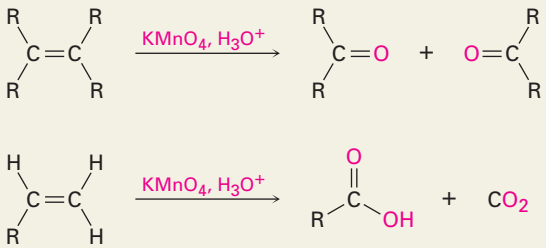


(k) Radical polymerization (Section 7.10)

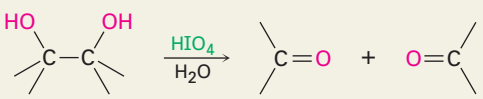
2. Oxidative cleavage of alkenes (Section 7.9)
(a) Reaction with ozone followed by zinc in acetic acid



(b) Reaction with $KMnO_4$ in acidic solution



3. Cleavage of 1,2-diols (Section 7.9)



EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

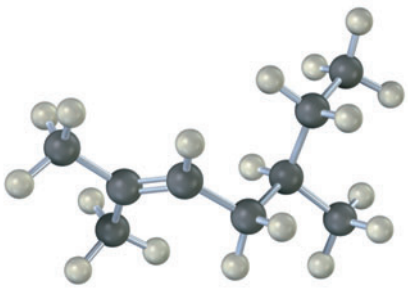
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

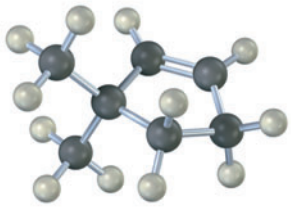
(Problems 7.1–7.19 appear within the chapter.)

7.20 ■ Name the following alkenes, and predict the products of their reaction with (i) *meta*-chloroperoxybenzoic acid, (ii) $KMnO_4$ in aqueous acid, and (iii) O_3, followed by Zn in acetic acid:

(a)

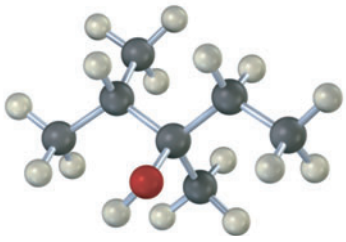


(b)

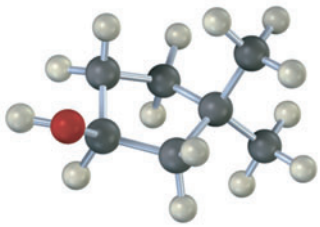


7.21 ■ Draw the structures of alkenes that would yield the following alcohols on hydration (red = O). Tell in each case whether you would use hydroboration/oxidation or oxymercuration.

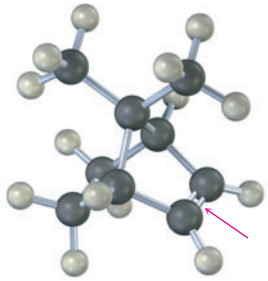
(a)



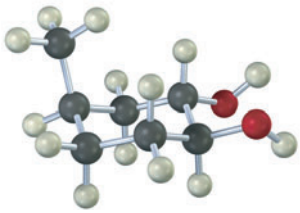
(b)



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



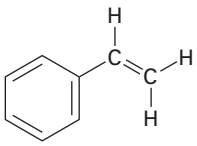
7.23 ■ From what alkene was the following 1,2-diol made, and what method was used, epoxide hydrolysis or OsO_4?



ADDITIONAL PROBLEMS

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to synthesize new functional groups beginning with alkenes**.

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



(a) H_2/Pd → ?

(b) Br_2 → ?

(c) OsO_4, NMO → ?

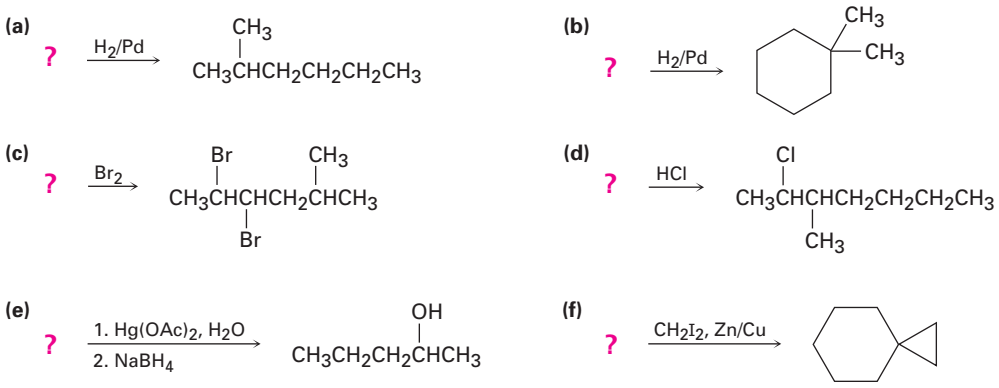
(d) Cl_2, H_2O → ?

(e) CH_2I_2, Zn/Cu → ?

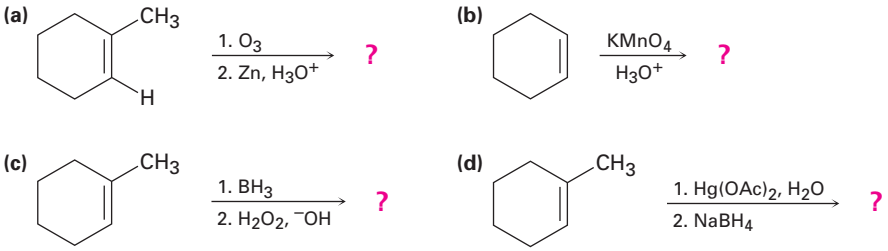
(f) *meta*-Chloroperoxybenzoic acid → ?

■ Assignable in OWL

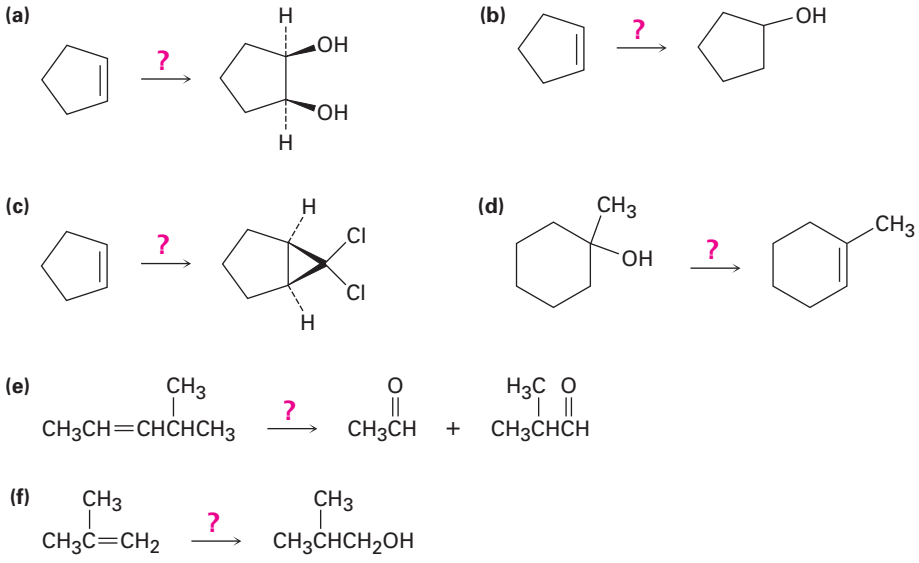
7.25 ■ Suggest structures for alkenes that give the following reaction products. There may be more than one answer for some cases.



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



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



■ Assignable in OWL

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

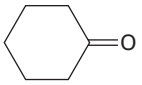
7.29 What product will result from hydroboration/oxidation of 1-methylcyclopentene with deuterated borane, BD_3? Show both the stereochemistry (spatial arrangement) and the regiochemistry (orientation) of the product.

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

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

(a) $CH_3CH_2CO_2H$ + CO_2

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

(c)  + $(CH_3)_2C{=}O$

(d) $CH_3CH_2\overset{\overset{O}{\|}}{C}CH_2CH_2CH_2CH_2CO_2H$

7.32 ■ Compound A has the formula $C_{10}H_{16}$. On catalytic hydrogenation over palladium, it reacts with only 1 molar equivalent of H_2. Compound A also undergoes reaction with ozone, followed by zinc treatment, to yield a symmetrical diketone, B ($C_{10}H_{16}O_2$).

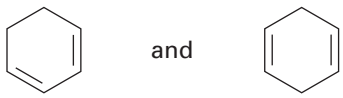
(a) How many rings does A have?

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

(c) Write the reactions.

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

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



7.35 Compound A, $C_{10}H_{18}O$, undergoes reaction with dilute H_2SO_4 at 50 °C to yield a mixture of two alkenes, $C_{10}H_{16}$. The major alkene product, B, gives only cyclopentanone after ozone treatment followed by reduction with zinc in acetic acid. Identify A and B, and write the reactions.

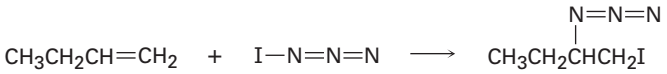
7.36 The cis and trans isomers of 2-butene give different cyclopropane products in the Simmons–Smith reaction. Show the structure of each, and explain the difference.

$$\textit{cis}\text{-}CH_3CH{=}CHCH_3 \xrightarrow{CH_2I_2,\ Zn(Cu)} \ ?$$

$$\textit{trans}\text{-}CH_3CH{=}CHCH_3 \xrightarrow{CH_2I_2,\ Zn(Cu)} \ ?$$

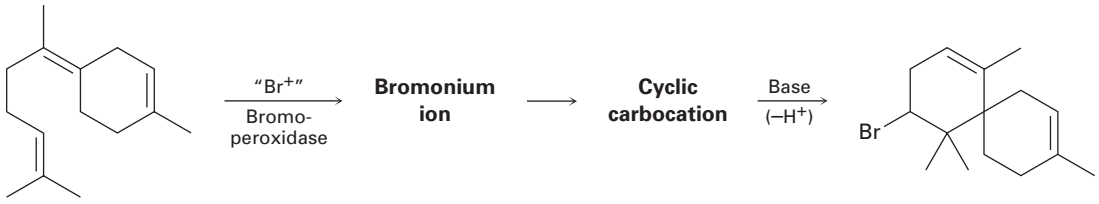
■ Assignable in OWL

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



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

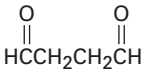
7.38 ■ 10-Bromo-α-chamigrene, a compound isolated from marine algae, is thought to be biosynthesized from γ-bisabolene by the following route:



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

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

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

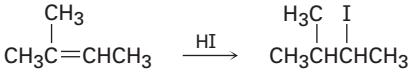


Butanedial

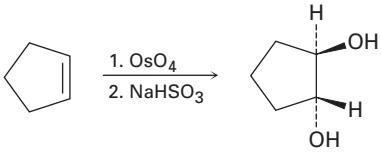
7.40 Simmons–Smith reaction of cyclohexene with diiodomethane gives a single cyclopropane product, but the analogous reaction of cyclohexene with 1,1-diiodoethane gives (in low yield) a mixture of two isomeric methylcyclopropane products. What are the two products, and how do they differ?

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

(a)

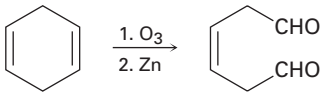


(b)

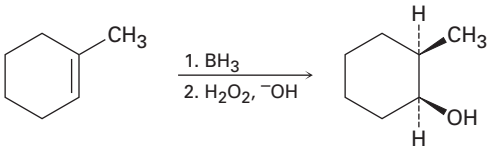


■ Assignable in OWL

(c)



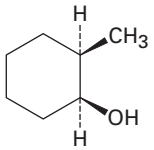
(d)



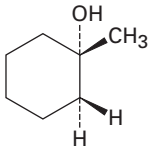
7.42 Which of the following alcohols could *not* be made selectively by hydroboration/oxidation of an alkene? Explain.

(a) $CH_3CH_2CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$ **(b)** $(CH_3)_2\underset{\displaystyle OH}{\underset{|}{C}}HC(CH_3)_2$

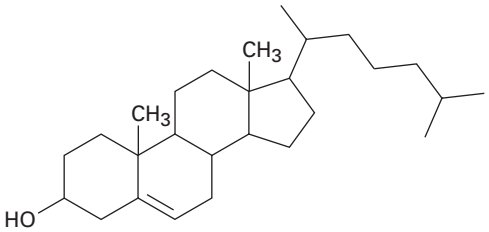
(c)



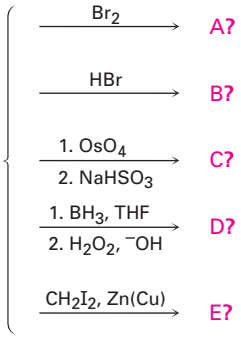
(d)



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



Cholesterol

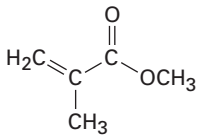


7.44 The sex attractant of the common housefly is a hydrocarbon with the formula $C_{23}H_{46}$. On treatment with aqueous acidic $KMnO_4$, two products are obtained, $CH_3(CH_2)_{12}CO_2H$ and $CH_3(CH_2)_7CO_2H$. Propose a structure.

7.45 Compound A has the formula C_8H_8. It reacts rapidly with $KMnO_4$ to give CO_2 and a carboxylic acid, B ($C_7H_6O_2$), but reacts with only 1 molar equivalent of H_2 on catalytic hydrogenation over a palladium catalyst. On hydrogenation under conditions that reduce aromatic rings, 4 equivalents of H_2 are taken up and hydrocarbon C (C_8H_{16}) is produced. What are the structures of A, B, and C? Write the reactions.

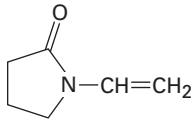
■ Assignable in OWL

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



Methyl methacrylate

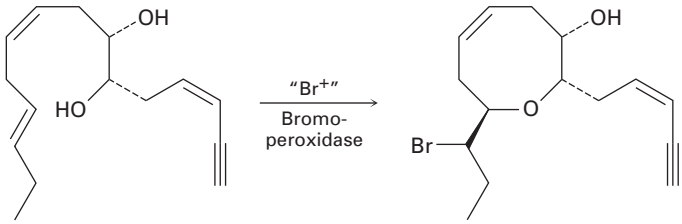
7.47 ■ Poly(vinyl pyrrolidone), prepared from *N*-vinylpyrrolidone, is used both in cosmetics and as a synthetic blood substitute. Draw a representative segment of the polymer.



***N*-Vinylpyrrolidone**

7.48 Reaction of 2-methylpropene with CH_3OH in the presence of H_2SO_4 catalyst yields methyl *tert*-butyl ether, $CH_3OC(CH_3)_3$, by a mechanism analogous to that of acid-catalyzed alkene hydration. Write the mechanism, using curved arrows for each step.

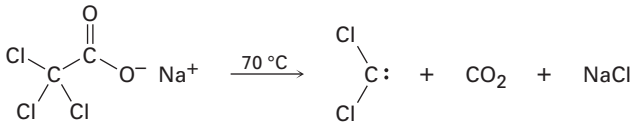
7.49 ■ Isolated from marine algae, prelaureatin is thought to be biosynthesized from laurediol by the following route. Propose a mechanism.



Laurediol **Prelaureatin**

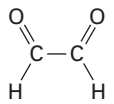
7.50 How would you distinguish between the following pairs of compounds using simple chemical tests? Tell what you would do and what you would see.
(a) Cyclopentene and cyclopentane **(b)** 2-Hexene and benzene

7.51 Dichlorocarbene can be generated by heating sodium trichloroacetate. Propose a mechanism for the reaction, and use curved arrows to indicate the movement of electrons in each step. What relationship does your mechanism bear to the base-induced elimination of HCl from chloroform?

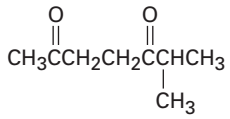


■ Assignable in OWL

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



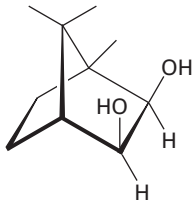
Glyoxal



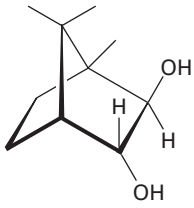
6-Methyl-2,5-heptanedione

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

7.53 Evidence that cleavage of 1,2-diols by HIO_4 occurs through a five-membered cyclic periodate intermediate is based on *kinetic data*—the measurement of reaction rates. When diols A and B were prepared and the rates of their reaction with HIO_4 were measured, it was found that diol A cleaved approximately 1 million times faster than diol B. Make molecular models of A and B and of potential cyclic periodate intermediates, and then explain the kinetic results.

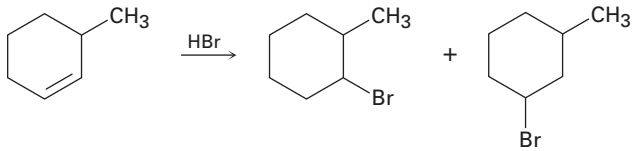


A
(*cis* diol)

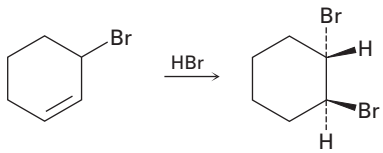


B
(*trans* diol)

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

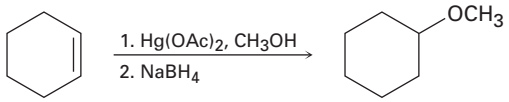


cis, trans **cis, trans**



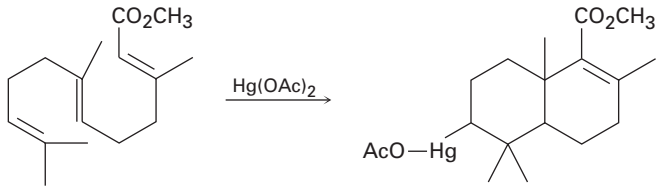
■ Assignable in OWL

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

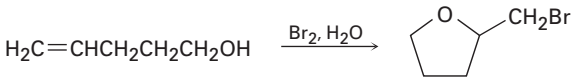


Cyclohexene **Cyclohexyl methyl ether**

7.56 Use your general knowledge of alkene chemistry to suggest a mechanism for the following reaction:

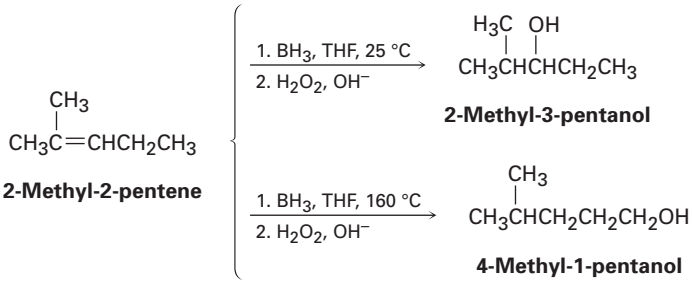


7.57 ■ Treatment of 4-penten-1-ol with aqueous Br_2 yields a cyclic bromo ether rather than the expected bromohydrin. Suggest a mechanism, using curved arrows to show electron movement.



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

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

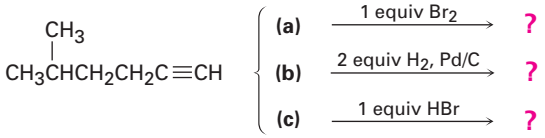


2-Methyl-2-pentene

2-Methyl-3-pentanol

4-Methyl-1-pentanol

7.59 We'll see in the next chapter that alkynes undergo many of the same reactions that alkenes do. What product might you expect from each of the following reactions?



7.60 Hydroxylation of *cis*-2-butene with OsO_4 yields a different product than hydroxylation of *trans*-2-butene. Draw the structure, show the stereochemistry of each product, and explain the difference between them.

■ Assignable in OWL

8 Alkynes: An Introduction to Organic Synthesis

Organic KNOWLEDGE TOOLS

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Online homework for this chapter may be assigned in Organic OWL.

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Acetylene, H—C≡C—H, the simplest alkyne, was once widely used in industry as the starting material for the preparation of acetaldehyde, acetic acid, vinyl chloride, and other high-volume chemicals, but more efficient routes to these substances using ethylene as starting material are now available. Acetylene is still used in the preparation of acrylic polymers but is probably best known as the gas burned in high-temperature oxy–acetylene welding torches.

Much current research is centering on *polyynes*—linear carbon chains of *sp*-hybridized carbon atoms. Polyynes with up to eight triple bonds have been detected in interstellar space, and evidence has been presented for the existence of *carbyne,* an allotrope of carbon consisting of repeating triple bonds in long chains of indefinite length.

H—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—C≡C—H

A polyyne detected in interstellar space

WHY THIS CHAPTER?

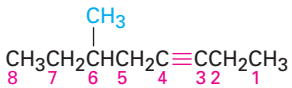
Alkynes are less common than alkenes, both in the laboratory and in living organisms, so we won't cover them in great detail. The real importance of this chapter is that we'll use alkyne chemistry as a vehicle to begin looking at some of the general strategies used in *organic synthesis*—the construction of complex molecules in the laboratory. Without the ability to design and synthesize new molecules in the laboratory, many of the medicines we take for granted would not exist and few new ones would be made.

8.1 Naming Alkynes

Alkyne nomenclature follows the general rules for hydrocarbons discussed in Sections 3.4 and 6.3. The suffix *-yne* is used, and the position of the triple bond is indicated by giving the number of the first alkyne carbon in the

Sean Duggan

chain. Numbering the main chain begins at the end nearer the triple bond so that the triple bond receives as low a number as possible.

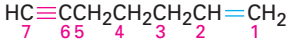


Begin numbering at the end nearer the triple bond.

6-Methyl-3-octyne

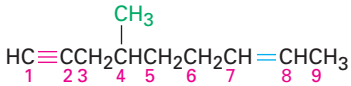
(New: 6-Methyloct-3-yne)

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



1-Hepten-6-yne

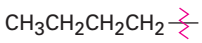
(New: Hept-1-en-6-yne)



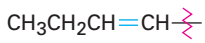
4-Methyl-7-nonen-1-yne

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

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

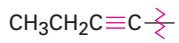


Butyl
(an alkyl group)



1-Butenyl
(a vinylic group)

(New: But-1-enyl)

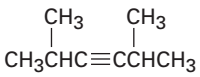


1-Butynyl
(an alkynyl group)

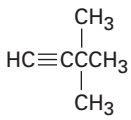
(New: But-1-ynyl)

Problem 8.1 Name the following compounds:

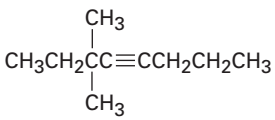
(a)



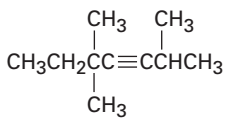
(b)



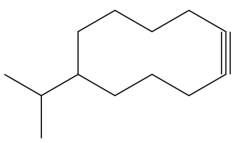
(c)



(d)



(e)



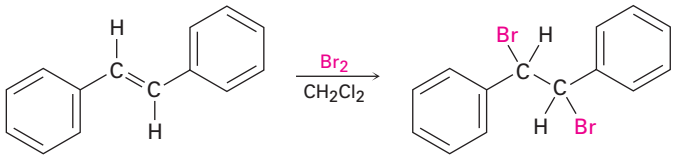
(f) $CH_3CH{=}CHCH{=}CHC{\equiv}CCH_3$

Problem 8.2 There are seven isomeric alkynes with the formula C_6H_{10}. Draw and name them.

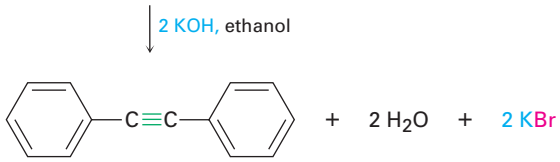
8.2 Preparation of Alkynes: Elimination Reactions of Dihalides

Alkynes can be prepared by the elimination of HX from alkyl halides in much the same manner as alkenes (Section 7.1). Treatment of a 1,2-dihaloalkane (a *vicinal* dihalide) with excess strong base such as KOH or $NaNH_2$ results in a twofold elimination of HX and formation of an alkyne. As with the elimination of HX to form an alkene, we'll defer a discussion of the mechanism until Chapter 11.

The necessary vicinal dihalides are themselves readily available by addition of Br_2 or Cl_2 to alkenes. Thus, the overall halogenation/dehydrohalogenation sequence makes it possible to go from an alkene to an alkyne. For example, diphenylethylene is converted into diphenylacetylene by reaction with Br_2 and subsequent base treatment.

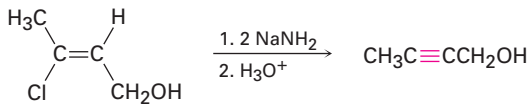


1,2-Diphenylethylene (stilbene) — **1,2-Dibromo-1,2-diphenylethane (a vicinal dibromide)**



Diphenylacetylene (85%)

The twofold dehydrohalogenation takes place through a vinylic halide intermediate, which suggests that vinylic halides themselves should give alkynes when treated with strong base. (*Recall:* A *vinylic* substituent is one that is attached to a double-bond carbon.) This is indeed the case. For example:



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

8.3 Reactions of Alkynes: Addition of HX and X_2

You might recall from Section 1.9 that a carbon–carbon triple bond results from the interaction of two *sp*-hybridized carbon atoms. The two *sp* hybrid orbitals of carbon lie at an angle of 180° to each other along an axis perpendicular to the axes of the two unhybridized $2p_y$ and $2p_z$ orbitals. When two *sp*-hybridized carbons approach each other, one *sp*–*sp* σ bond and two *p*–*p* π bonds are

formed. The two remaining *sp* orbitals form bonds to other atoms at an angle of 180° from the carbon–carbon bond. Thus, acetylene is a linear molecule with H−C≡C bond angles of 180° (Figure 8.1).

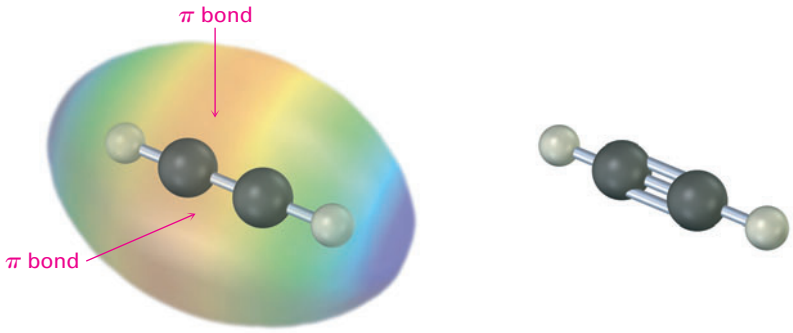


Figure 8.1 The structure of acetylene, H—C≡C—H. The H−C≡C bond angles are 180°, and the C≡C bond length is 120 pm. The electrostatic potential map shows that the π bonds create a negative (red) belt around the molecule.

The length of the carbon–carbon triple bond in acetylene is 120 pm, and the strength is approximately 835 kJ/mol (200 kcal/mol), making it the shortest and strongest known carbon–carbon bond. Measurements show that approximately 318 kJ/mol (76 kcal/mol) is needed to break a π bond in acetylene, a value some 50 kJ/mol larger than the 268 kJ/mol needed to break an alkene π bond.

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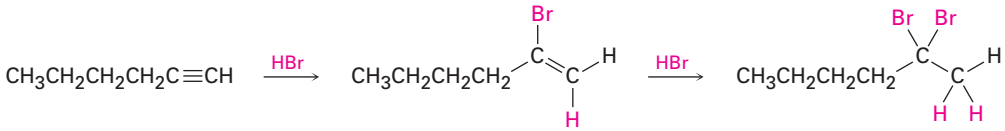
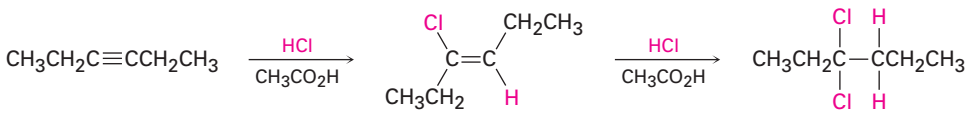
As a general rule, electrophiles undergo addition reactions with alkynes much as they do with alkenes. Take the reaction of alkynes with HX, for instance. The reaction often can be stopped after addition of 1 equivalent of HX, but reaction with an excess of HX leads to a dihalide product. For example, reaction of 1-hexyne with 2 equivalents of HBr yields 2,2-dibromohexane. As the following examples indicate, the regiochemistry of addition follows Markovnikov's rule: halogen adds to the more highly substituted side of the alkyne bond, and hydrogen adds to the less highly substituted side. Trans stereochemistry of H and X normally, although not always, results in the product.

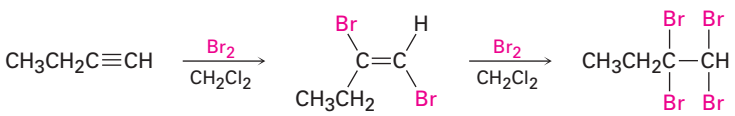


1-Hexyne **2-Bromo-1-hexene** **2,2-Dibromohexane**



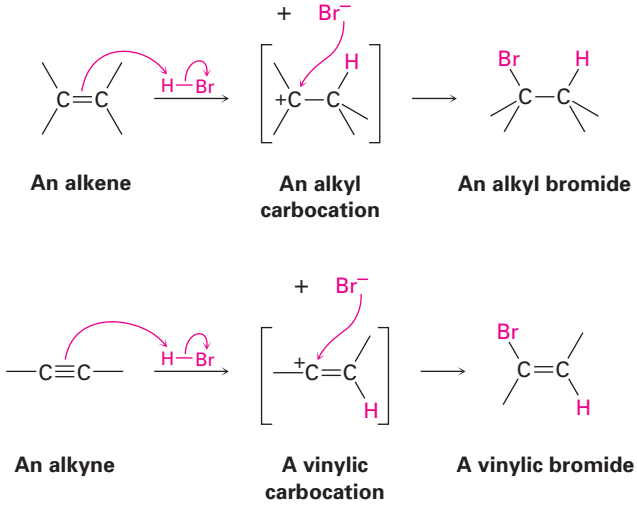
3-Hexyne **(*Z*)-3-Chloro-3-hexene** **3,3-Dichlorohexane**

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



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

The mechanism of alkyne additions is similar but not identical to that of alkene additions. When an electrophile such as HBr adds to an *alkene* (Sections 6.7 and 6.8), the reaction takes place in two steps and involves an *alkyl* carbocation intermediate. If HBr were to add by the same mechanism to an *alkyne,* an analogous *vinylic* carbocation would be formed as the intermediate.



A vinylic carbocation has an *sp*-hybridized carbon and generally forms less readily than an alkyl carbocation (Figure 8.2). As a rule, a *secondary* vinylic carbocation forms about as readily as a *primary* alkyl carbocation, but a *primary* vinylic carbocation is so difficult to form that there is no clear evidence it even exists. Thus, many alkyne additions occur through more complex mechanistic pathways.

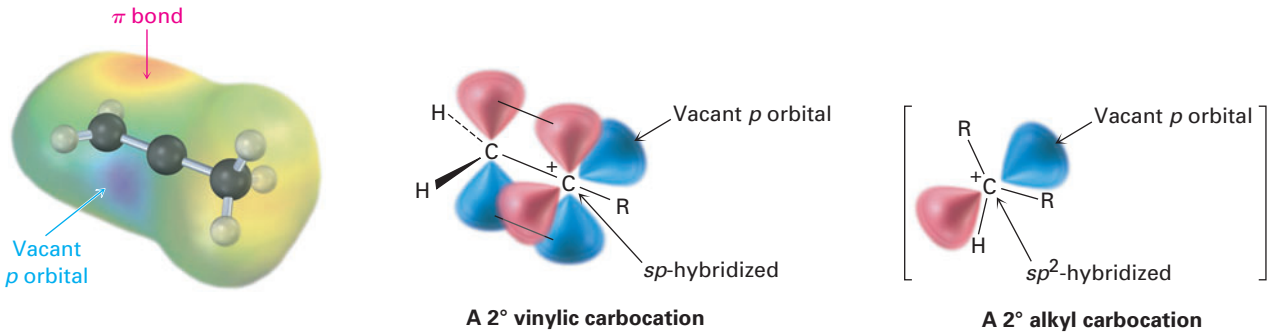
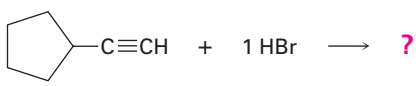


Figure 8.2 The structure of a secondary vinylic carbocation. The cationic carbon atom is *sp*-hybridized and has a vacant *p* orbital perpendicular to the plane of the π bond orbitals. Only one R group is attached to the positively charged carbon rather than two, as in a secondary alkyl carbocation. The electrostatic potential map shows that the most positive (blue) regions coincide with lobes of the vacant *p* orbital and are perpendicular to the most negative (red) regions associated with the π bond.

Problem 8.3 What products would you expect from the following reactions?

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

(b)  + 1 HBr ⟶ ?

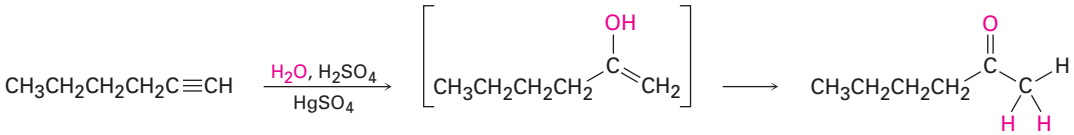
(c) $CH_3CH_2CH_2CH_2C{\equiv}CCH_3 + 1\ HBr \longrightarrow$?

8.4 Hydration of Alkynes

Like alkenes (Sections 7.4 and 7.5), alkynes can be hydrated by either of two methods. Direct addition of water catalyzed by mercury(II) ion yields the Markovnikov product, and indirect addition of water by a hydroboration/oxidation sequence yields the non-Markovnikov product.

Mercury(II)-Catalyzed Hydration of Alkynes

Alkynes don't react directly with aqueous acid but will undergo hydration readily in the presence of mercury(II) sulfate as a Lewis acid catalyst. The reaction occurs with Markovnikov regiochemistry: the −OH group adds to the more highly substituted carbon, and the −H attaches to the less highly substituted one.



1-Hexyne **An enol** **2-Hexanone (78%)**

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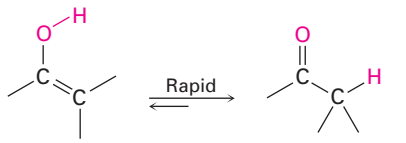
Interestingly, the product actually isolated from alkyne hydration is not the vinylic alcohol, or **enol** (*ene* + *ol*), but is instead a *ketone*. Although the enol is an intermediate in the reaction, it immediately rearranges to a ketone by a process called *keto–enol tautomerism*. The individual keto and enol forms are said to be **tautomers**, a word used to describe constitutional isomers that interconvert rapidly. With few exceptions, the keto–enol tautomeric equilibrium lies on the side of the ketone; enols are almost never isolated. We'll look more closely at this equilibrium in Section 22.1.



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

As shown in Figure 8.3, the mechanism of the mercury(II)-catalyzed alkyne hydration reaction is analogous to the oxymercuration reaction of alkenes (Section 7.4). Electrophilic addition of mercury(II) ion to the alkyne gives a vinylic cation, which reacts with water and loses a proton to yield a mercury-containing enol intermediate. In contrast with alkene oxymercuration, however, no treatment with $NaBH_4$ is necessary to remove the mercury. The acidic reaction conditions alone are sufficient to effect replacement of mercury by hydrogen.

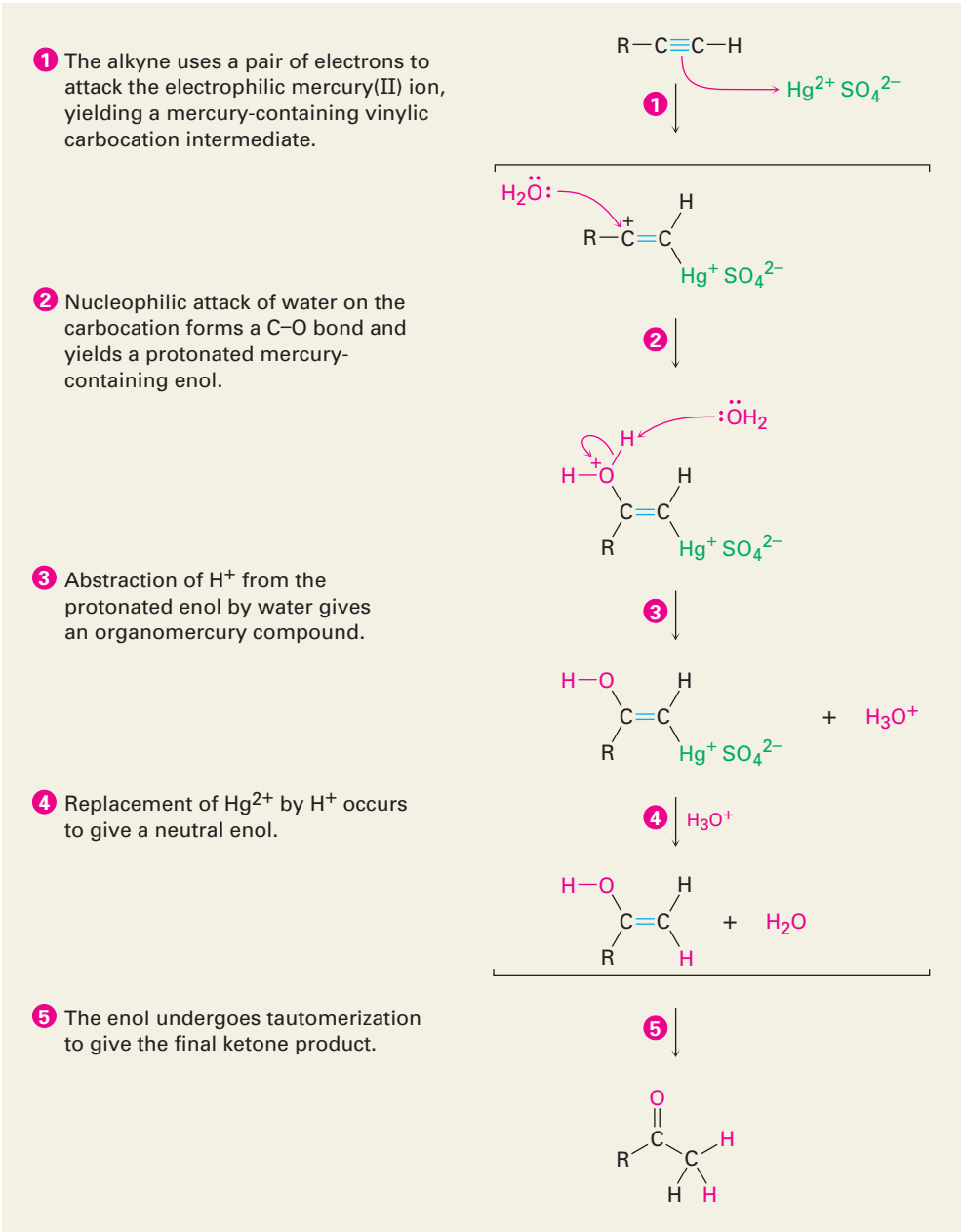


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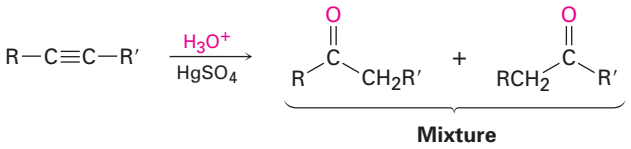
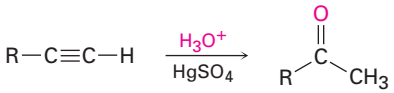
Figure 8.3 MECHANISM: Mechanism of the mercury(II)-catalyzed hydration of an alkyne to yield a ketone. The reaction occurs through initial formation of an intermediate enol, which rapidly tautomerizes to the ketone.

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

An internal alkyne



A terminal alkyne



A methyl ketone

Problem 8.4 What product would you obtain by hydration of the following alkynes?

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

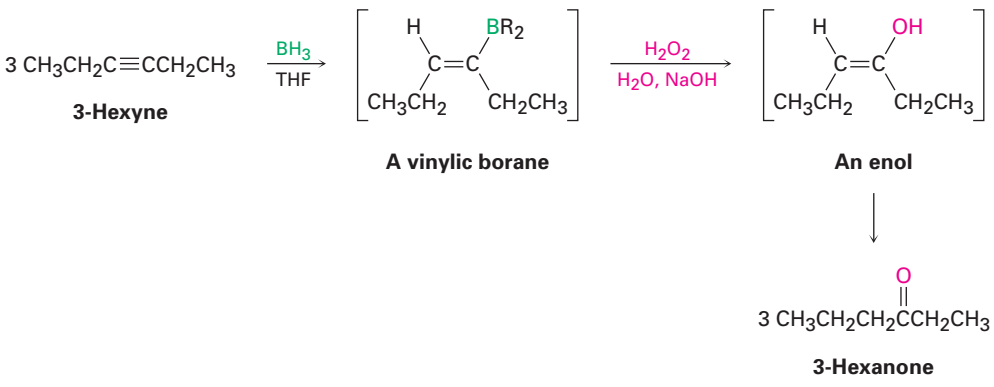
Problem 8.5 What alkynes would you start with to prepare the following ketones?

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

Hydroboration/Oxidation of Alkynes

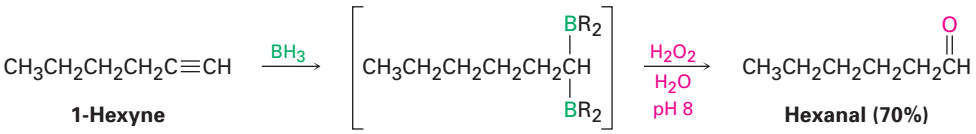
Borane adds rapidly to an alkyne just as it does to an alkene, and the resulting vinylic borane can be oxidized by H_2O_2 to yield an enol. Tautomerization then gives either a ketone or an aldehyde, depending on the structure of the alkyne reactant. Hydroboration/oxidation of an internal alkyne such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

An internal alkyne



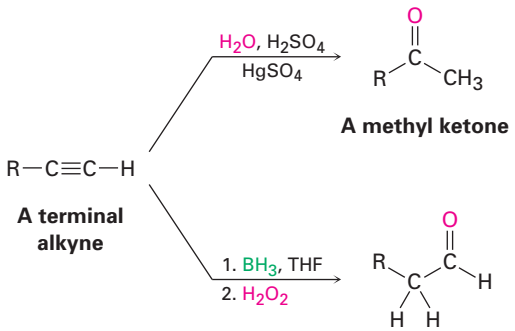
3-Hexyne **A vinylic borane** **An enol** **3-Hexanone**

A terminal alkyne

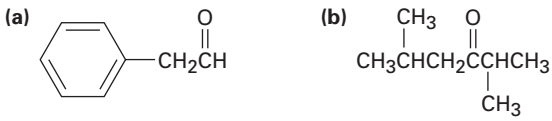


1-Hexyne **Hexanal (70%)**

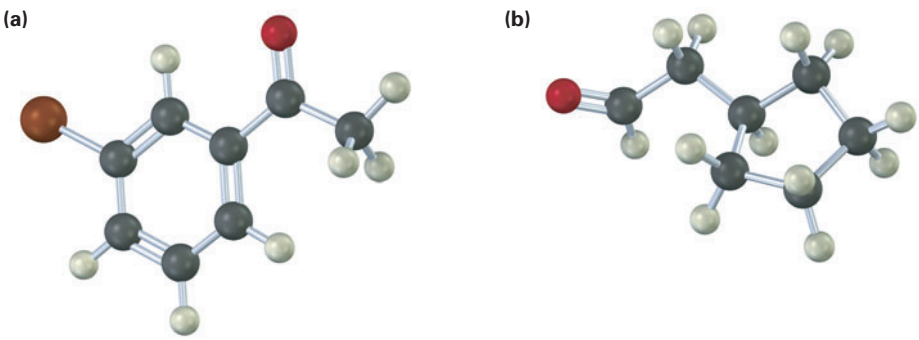
The hydroboration/oxidation sequence is complementary to the direct, mercury(II)-catalyzed hydration reaction of a terminal alkyne because different products result. Direct hydration with aqueous acid and mercury(II) sulfate leads to a methyl ketone, whereas hydroboration/oxidation of the same terminal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



Problem 8.6 What alkyne would you start with to prepare each of the following compounds by a hydroboration/oxidation reaction?



Problem 8.7 How would you prepare the following carbonyl compounds starting from an alkyne (reddish brown = Br)?



8.5 Reduction of Alkynes

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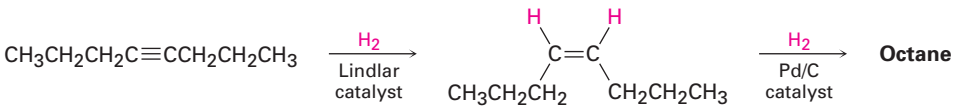
Alkynes are reduced to alkanes by addition of H_2 over a metal catalyst. The reaction occurs in steps through an alkene intermediate, and measurements indicate that the first step in the reaction is more exothermic than the second step.

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

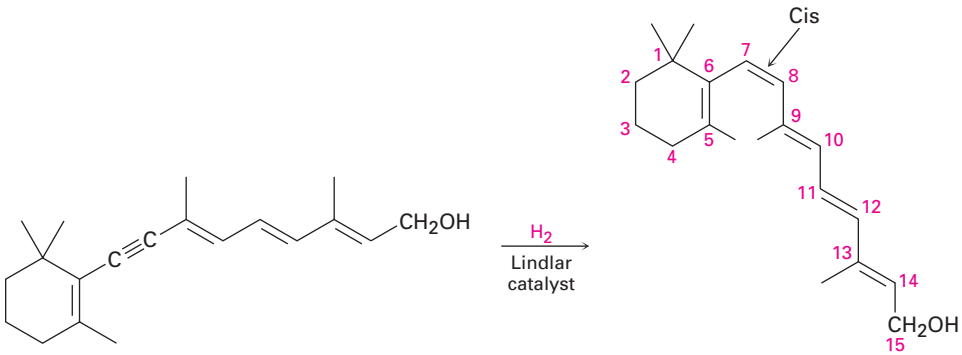
$$H_2C{=}CH_2 \xrightarrow[\text{Catalyst}]{H_2} CH_3{-}CH_3 \qquad \Delta H°_{\text{hydrog}} = -137 \text{ kJ/mol } (-33 \text{ kcal/mol})$$

Complete reduction to the alkane occurs when palladium on carbon (Pd/C) is used as catalyst, but hydrogenation can be stopped at the alkene if the less active *Lindlar catalyst* is used. The Lindlar catalyst is a finely divided palladium metal that has been precipitated onto a calcium carbonate support and then deactivated by treatment with lead acetate and quinoline, an aromatic amine. The hydrogenation occurs with syn stereochemistry (Section 7.5), giving a cis alkene product.



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

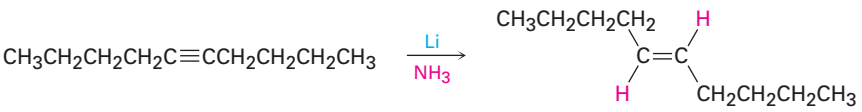
The alkyne hydrogenation reaction has been explored extensively by the Hoffmann–La Roche pharmaceutical company, where it is used in the commercial synthesis of vitamin A. The cis isomer of vitamin A produced on hydrogenation is converted to the trans isomer by heating.



7-*cis*-Retinol
(7-*cis*-vitamin A; vitamin A has a trans double bond at C7)

An alternative method for the conversion of an alkyne to an alkene uses sodium or lithium metal as the reducing agent in liquid ammonia as solvent. This method is complementary to the Lindlar reduction because it produces

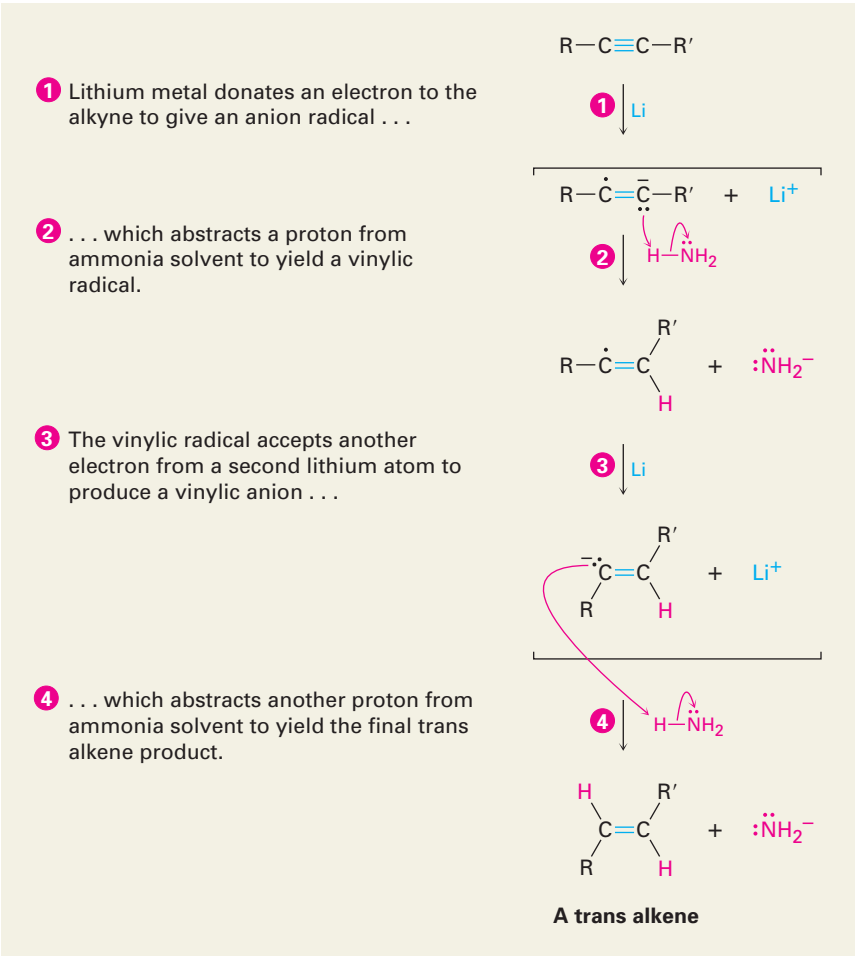
trans rather than cis alkenes. For example, 5-decyne gives *trans*-5-decene on treatment with lithium in liquid ammonia.



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

Alkali metals dissolve in liquid ammonia at −33 °C to produce a deep blue solution containing the metal cation and ammonia-solvated electrons. When an alkyne is then added to the solution, an electron adds to the triple bond to yield an intermediate *anion radical*—a species that is both an anion (has a negative charge) and a radical (has an odd number of electrons). This anion radical is a strong base, which removes H^+ from ammonia to give a vinylic radical. Addition of a second electron to the vinylic radical gives a vinylic anion, which abstracts a second H^+ from ammonia to give trans alkene product. The mechanism is shown in Figure 8.4.

Figure 8.4 MECHANISM: Mechanism of the lithium/ammonia reduction of an alkyne to produce a trans alkene.



Trans stereochemistry of the alkene product is established during the second reduction step when the less hindered trans vinylic anion is formed from the vinylic radical. Vinylic radicals undergo rapid cis–trans equilibration, but vinylic anions equilibrate much less rapidly. Thus, the more stable trans vinylic anion is formed rather than the less stable cis anion and is then protonated without equilibration.

Problem 8.8 Using any alkyne needed, how would you prepare the following alkenes?
(a) *trans*-2-Octene **(b)** *cis*-3-Heptene **(c)** 3-Methyl-1-pentene

8.6 Oxidative Cleavage of Alkynes

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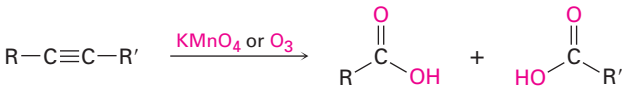
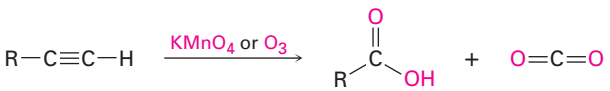
Alkynes, like alkenes, can be cleaved by reaction with powerful oxidizing agents such as ozone or $KMnO_4$, although the reaction is of little value and we mention it only for completeness. A triple bond is generally less reactive than a double bond and yields of cleavage products are sometimes low. The products obtained from cleavage of an internal alkyne are carboxylic acids; from a terminal alkyne, CO_2 is formed as one product.

An internal alkyne

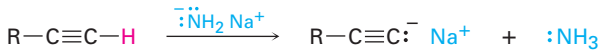


A terminal alkyne



8.7 Alkyne Acidity: Formation of Acetylide Anions

The most striking difference between alkenes and alkynes is that terminal alkynes are weakly acidic. When a terminal alkyne is treated with a strong base, such as sodium amide, $Na^+ {}^-NH_2$, the terminal hydrogen is removed and an **acetylide anion** is formed.



A terminal alkyne **An acetylide anion**

According to the Brønsted–Lowry definition (Section 2.7), an acid is a substance that donates H^+. Although we usually think of oxyacids (H_2SO_4, HNO_3) or halogen acids (HCl, HBr) in this context, any compound containing a hydrogen atom can be an acid under the right circumstances. By measuring dissociation

constants of different acids and expressing the results as pK_a values, an acidity order can be established. Recall from Section 2.8 that a low pK_a corresponds to a strong acid and a high pK_a corresponds to a weak acid.

Where do hydrocarbons lie on the acidity scale? As the data in Table 8.1 show, both methane ($pK_a \approx 60$) and ethylene ($pK_a = 44$) are very weak acids and thus do not react with any of the common bases. Acetylene, however, has $pK_a = 25$ and can be deprotonated by the conjugate base of any acid whose pK_a is greater than 25. Amide ion (NH_2^-), for example, the conjugate base of ammonia ($pK_a = 35$), is often used to deprotonate terminal alkynes.

Table 8.1 Acidity of Simple Hydrocarbons

Family	Example	K_a	pK_a	
Alkyne	$HC{\equiv}CH$	10^{-25}	25	Stronger acid
Alkene	$H_2C{=}CH_2$	10^{-44}	44	
Alkane	CH_4	10^{-60}	60	Weaker acid

Why are terminal alkynes more acidic than alkenes or alkanes? In other words, why are acetylide anions more stable than vinylic or alkyl anions? The simplest explanation involves the hybridization of the negatively charged carbon atom. An acetylide anion has an *sp*-hybridized carbon, so the negative charge resides in an orbital that has 50% "*s* character." A vinylic anion has an sp^2-hybridized carbon with 33% *s* character, and an alkyl anion (sp^3) has only 25% *s* character. Because *s* orbitals are nearer the positive nucleus and lower in energy than *p* orbitals, the negative charge is stabilized to a greater extent in an orbital with higher *s* character (Figure 8.5).

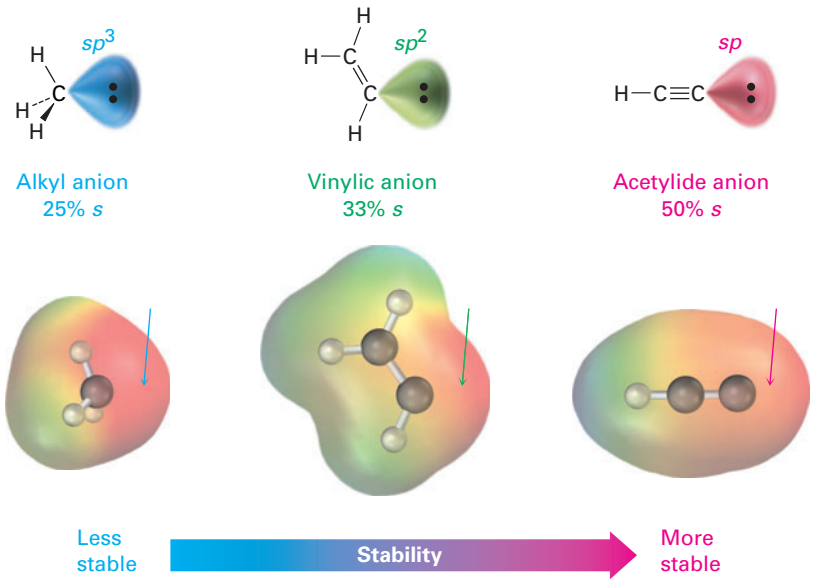


Figure 8.5 A comparison of alkyl, vinylic, and acetylide anions. The acetylide anion, with *sp* hybridization, has more *s* character and is more stable. Electrostatic potential maps show that placing the negative charge closer to the carbon nucleus makes carbon appear less negative (red).

The presence of a negative charge and an unshared electron pair on carbon makes acetylide anions strongly nucleophilic. As a result, they react with many different kinds of electrophiles.

Problem 8.9 The pK_a of acetone, CH_3COCH_3, is 19.3. Which of the following bases is strong enough to deprotonate acetone?

(a) KOH (pK_a of H_2O = 15.7)
(b) $Na^+ {}^-C{\equiv}CH$ (pK_a of C_2H_2 = 25)
(c) $NaHCO_3$ (pK_a of H_2CO_3 = 6.4)
(d) $NaOCH_3$ (pK_a of CH_3OH = 15.6)

8.8 Alkylation of Acetylide Anions

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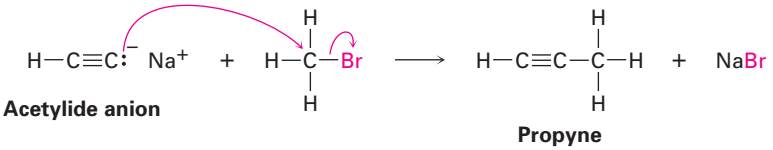
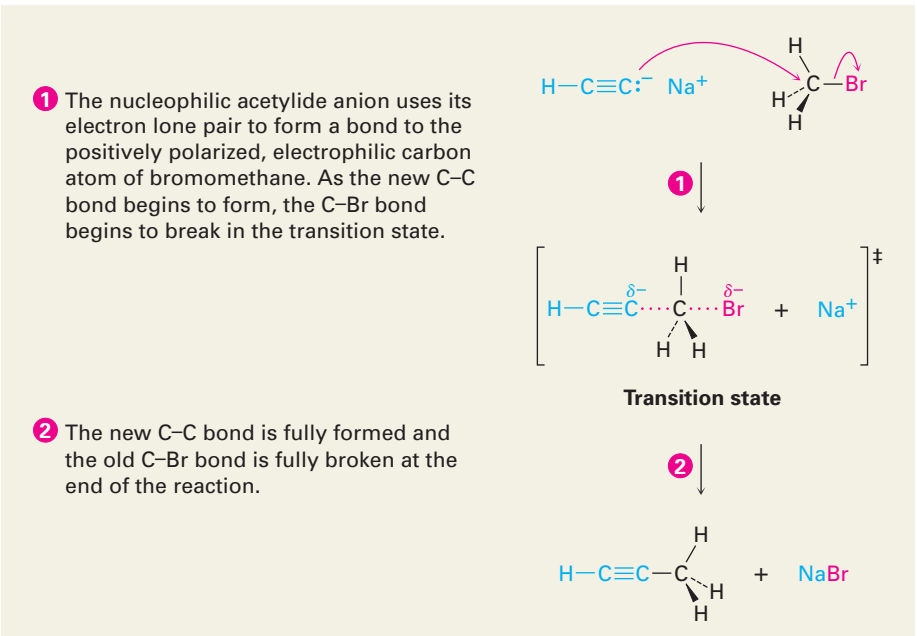
The negative charge and unshared electron pair on carbon make an acetylide anion strongly nucleophilic. As a result, an acetylide anion can react with an alkyl halide such as bromomethane to substitute for the halogen and yield a new alkyne product.



We won't study the details of this substitution reaction until Chapter 11 but for now can picture it as happening by the pathway shown in Figure 8.6. The nucleophilic acetylide ion uses an electron pair to form a bond to the positively polarized, electrophilic carbon atom of bromomethane. As the new C–C bond forms, Br^- departs, taking with it the electron pair from the former C–Br bond and yielding propyne as product. We call such a reaction an **alkylation** because a new alkyl group has become attached to the starting alkyne.

Active Figure 8.6
MECHANISM: A mechanism for the alkylation reaction of acetylide anion with bromomethane to give propyne. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*



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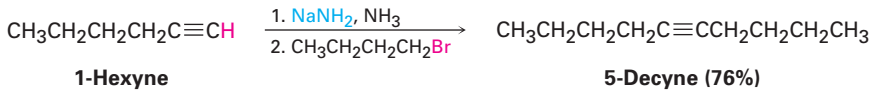
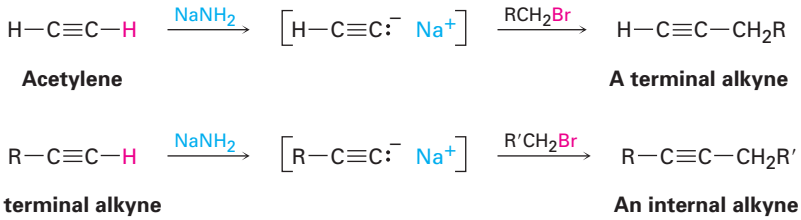
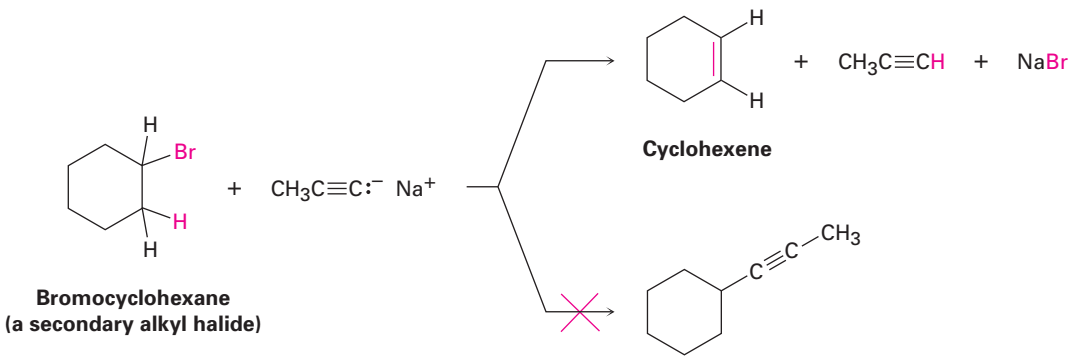
Alkyne alkylation is not limited to acetylene itself. *Any* terminal alkyne can be converted into its corresponding anion and then alkylated by treatment with an alkyl halide, yielding an internal alkyne. For example, conversion of 1-hexyne into its anion, followed by reaction with 1-bromobutane, yields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



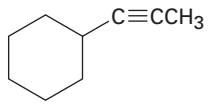
Because of its generality, acetylide alkylation is an excellent method for preparing substituted alkynes from simpler precursors. A terminal alkyne can be prepared by alkylation of acetylene itself, and an internal alkyne can be prepared by further alkylation of a terminal alkyne.



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



Problem 8.10 Show the terminal alkyne and alkyl halide from which the following products can be obtained. If two routes look feasible, list both.

(a) $CH_3CH_2CH_2C{\equiv}CCH_3$ **(b)** $(CH_3)_2CHC{\equiv}CCH_2CH_3$ **(c)** 

Problem 8.11 How would you prepare *cis*-2-butene starting from propyne, an alkyl halide, and any other reagents needed? This problem can't be worked in a single step. You'll have to carry out more than one reaction.

8.9 An Introduction to Organic Synthesis

There are many reasons for carrying out the laboratory synthesis of an organic compound. In the pharmaceutical industry, new organic molecules are designed and synthesized in the hope that some might be useful new drugs. In the chemical industry, syntheses are done to devise more economical routes to known compounds. In academic laboratories, the synthesis of complex molecules is sometimes done purely for the intellectual challenge involved in mastering so difficult a subject. The successful synthesis route is a highly creative work that is sometimes described by such subjective terms as *elegant* or *beautiful*.

In this book, too, we will often devise syntheses of molecules from simpler precursors. Our purpose, however, is pedagogical. The ability to plan a workable synthetic sequence requires knowledge of a variety of organic reactions. Furthermore, it requires the practical ability to fit together the steps in a sequence such that each reaction does only what is desired without causing changes elsewhere in the molecule. Working synthesis problems is an excellent way to learn organic chemistry.

Some of the syntheses we plan may seem trivial. Here's an example:

WORKED EXAMPLE 8.1 ***Devising a Synthesis Route***

Prepare octane from 1-pentyne.

$CH_3CH_2CH_2C{\equiv}CH \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

1-Pentyne **Octane**

Strategy

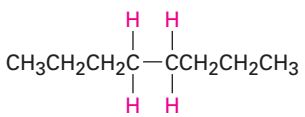
Compare the product with the starting material, and catalog the differences. In this case, we need to add three carbons to the chain and reduce the triple bond. Since the starting material is a terminal alkyne that can be alkylated, we might first prepare the acetylide anion of 1-pentyne, let it react with 1-bromopropane, and then reduce the product using catalytic hydrogenation.

Solution

$$CH_3CH_2CH_2C{\equiv}CH \xrightarrow[2.\ BrCH_2CH_2CH_3,\ THF]{1.\ NaNH_2,\ NH_3} CH_3CH_2CH_2C{\equiv}CCH_2CH_2CH_3$$

1-Pentyne **4-Octyne**

$\downarrow H_2$/Pd in ethanol



Octane

The synthesis route just presented will work perfectly well but has little practical value because you can simply *buy* octane from any of several dozen

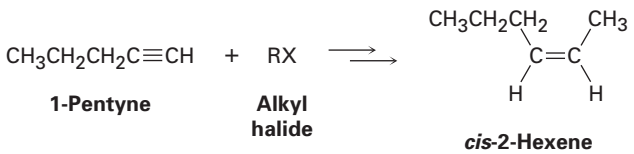
chemical suppliers. The value of working the problem is that it makes you approach a chemical problem in a logical way, draw on your knowledge of chemical reactions, and organize that knowledge into a workable plan—it helps you learn organic chemistry.

There's no secret to planning an organic synthesis: it takes a knowledge of the different reactions, some discipline, and a lot of practice. The only real trick is to work backward in what is often referred to as a **retrosynthetic** direction. Don't look at the starting material and ask yourself what reactions it might undergo. Instead, look at the final product and ask, "What was the immediate precursor of that product?" For example, if the final product is an alkyl halide, the immediate precursor might be an alkene (to which you could add HX). If the final product is a cis alkene, the immediate precursor might be an alkyne (which you could hydrogenate using the Lindlar catalyst). Having found an immediate precursor, work backward again, one step at a time, until you get back to the starting material. You have to keep the starting material in mind, of course, so that you can work back to it, but you don't want that starting material to be your main focus.

Let's work several more examples of increasing complexity.

WORKED EXAMPLE 8.2 *Devising a Synthesis Route*

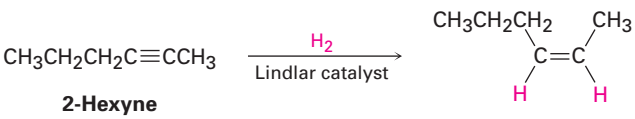
Synthesize *cis*-2-hexene from 1-pentyne and any alkyl halide needed. More than one step is required.



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

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

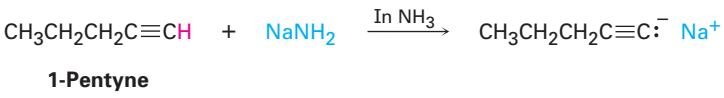
The product in this case is a cis-disubstituted alkene, so the first question is, "What is an immediate precursor of a cis-disubstituted alkene?" We know that an alkene can be prepared from an alkyne by reduction and that the right choice of experimental conditions will allow us to prepare either a trans-disubstituted alkene (using lithium in liquid ammonia) or a cis-disubstituted alkene (using catalytic hydrogenation over the Lindlar catalyst). Thus, reduction of 2-hexyne by catalytic hydrogenation using the Lindlar catalyst should yield *cis*-2-hexene.



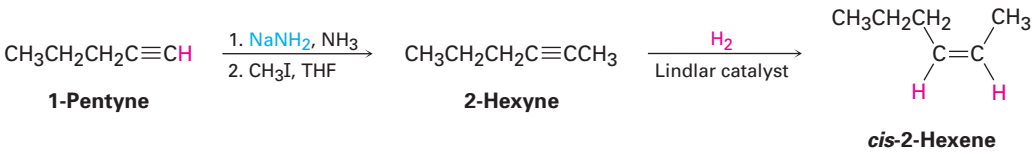
2-Hexyne ***cis*-2-Hexene**

Next ask, "What is an immediate precursor of 2-hexyne?" We've seen that an internal alkyne can be prepared by alkylation of a terminal alkyne anion. In the present

instance, we're told to start with 1-pentyne and an alkyl halide. Thus, alkylation of the anion of 1-pentyne with iodomethane should yield 2-hexyne.

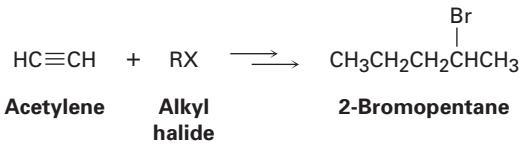


Solution *cis*-2-Hexene can be synthesized from the given starting materials in three steps.

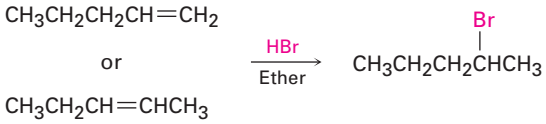


WORKED EXAMPLE 8.3 *Devising a Synthesis Route*

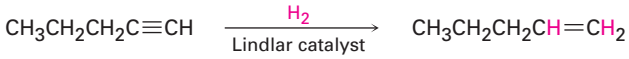
Synthesize 2-bromopentane from acetylene and any alkyl halide needed. More than one step is required.



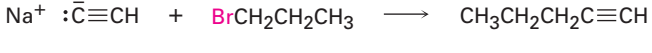
Strategy Identify the functional group in the product (an alkyl bromide) and work the problem retrosynthetically. "What is an immediate precursor of an alkyl bromide?" Perhaps an alkene plus HBr. Of the two possibilities, addition of HBr to 1-pentene looks like a better choice than addition to 2-pentene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



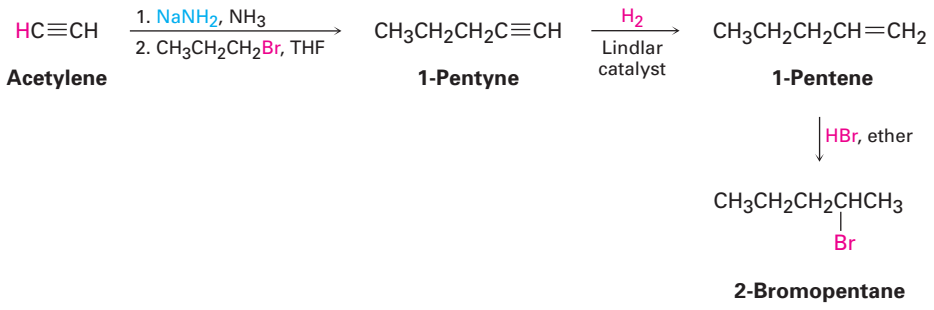
"What is an immediate precursor of an alkene?" Perhaps an alkyne, which could be reduced.



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



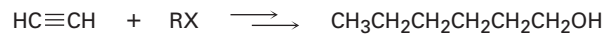
Solution The desired product can be synthesized in four steps from acetylene and 1-bromopropane.



Acetylene **1-Pentyne** **1-Pentene** **2-Bromopentane**

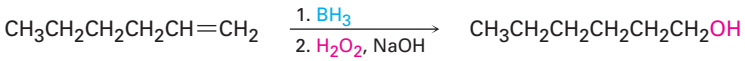
WORKED EXAMPLE 8.4 *Devising a Synthesis Route*

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

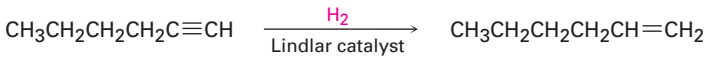


Acetylene **Alkyl halide** **1-Hexanol**

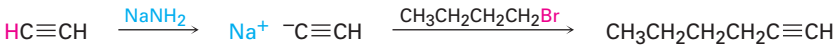
Strategy "What is an immediate precursor of a primary alcohol?" Perhaps a terminal alkene, which could be hydrated with non-Markovnikov regiochemistry by reaction with borane followed by oxidation with H_2O_2.



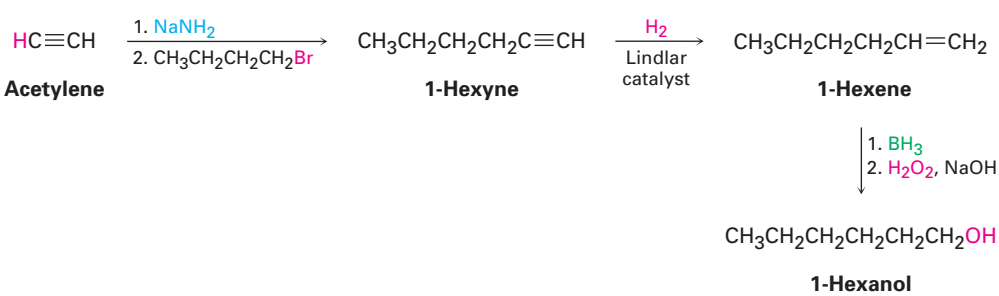
"What is an immediate precursor of a terminal alkene?" Perhaps a terminal alkyne, which could be reduced.



"What is an immediate precursor of 1-hexyne?" Perhaps acetylene and 1-bromobutane.



Solution The synthesis can be completed in four steps from acetylene and 1-bromobutane:



Acetylene **1-Hexyne** **1-Hexene** **1-Hexanol**

Problem 8.12 Beginning with 4-octyne as your only source of carbon, and using any inorganic reagents necessary, how would you synthesize the following compounds?

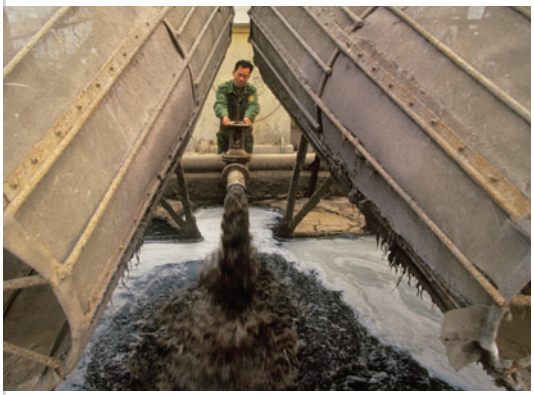
(a) *cis*-4-Octene **(b)** Butanal **(c)** 4-Bromooctane
(d) 4-Octanol **(e)** 4,5-Dichlorooctane **(f)** Butanoic acid

Problem 8.13 Beginning with acetylene and any alkyl halides needed, how would you synthesize the following compounds?

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

Focus On . . .

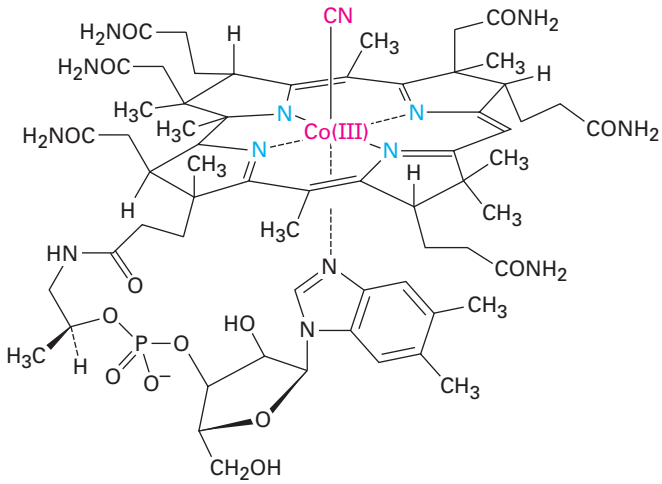
The Art of Organic Synthesis



© Bob Sacha/Corbis

Vitamin B_{12} has been synthesized from scratch in the laboratory, but bacteria growing on sludge from municipal sewage plants do a much better job.

If you think some of the synthesis problems at the end of this chapter are hard, try devising a synthesis of vitamin B_{12} starting only from simple substances you can buy in a chemical catalog. This extraordinary achievement was reported in 1973 as the culmination of a collaborative effort headed by Robert B. Woodward of Harvard University and Albert Eschenmoser of the Swiss Federal Institute of Technology in Zürich. More than 100 graduate students and postdoctoral associates contributed to the work, which took more than a decade.



Vitamin B_{12}

(continued)

Why put such extraordinary effort into the laboratory synthesis of a molecule so easily obtained from natural sources? There are many reasons. On a basic human level, a chemist might be motivated primarily by the challenge, much as a climber might be challenged by the ascent of a difficult peak. Beyond the pure challenge, the completion of a difficult synthesis is also valuable for the way in which it establishes new standards and raises the field to a new level. If vitamin B_{12} can be made, then why can't any molecule found in nature be made? Indeed, the three and a half decades that have passed since the work of Woodward and Eschenmoser have seen the laboratory synthesis of many enormously complex and valuable substances. Sometimes these substances—the anticancer compound Taxol, for instance—are not easily available in nature, so laboratory synthesis is the only method for obtaining larger quantities.

But perhaps the most important reason for undertaking a complex synthesis is that, in so doing, new reactions and new chemistry are discovered. It invariably happens in synthesis that a point is reached at which the planned route fails. At such a time, the only alternatives are to quit or to devise a way around the difficulty. New reactions and new principles come from such situations, and it is in this way that the science of organic chemistry grows richer. In the synthesis of vitamin B_{12}, for example, unexpected findings emerged that led to the understanding of an entire new class of reactions—the *pericyclic* reactions that are the subject of Chapter 30 in this book. From synthesizing vitamin B_{12} to understanding pericyclic reactions—no one could have possibly predicted such a link at the beginning of the synthesis, but that is the way of science.

SUMMARY AND KEY WORDS

acetylide anion, 270
alkylation, 272
alkyne (RC≡CR), 259
enol, 264
retrosynthetic, 275
tautomer, 264

An **alkyne** is a hydrocarbon that contains a carbon–carbon triple bond. Alkyne carbon atoms are *sp*-hybridized, and the triple bond consists of one *sp*–*sp* σ bond and two *p*–*p* π bonds. There are relatively few general methods of alkyne synthesis. Two good ones are the alkylation of an acetylide anion with a primary alkyl halide and the twofold elimination of HX from a vicinal dihalide.

The chemistry of alkynes is dominated by electrophilic addition reactions, similar to those of alkenes. Alkynes react with HBr and HCl to yield *vinylic* halides and with Br_2 and Cl_2 to yield 1,2-dihalides (*vicinal* dihalides). Alkynes can be hydrated by reaction with aqueous sulfuric acid in the presence of mercury(II) catalyst. The reaction leads to an intermediate **enol** that immediately isomerizes to yield a ketone **tautomer**. Since the addition reaction occurs with Markovnikov regiochemistry, a methyl ketone is produced from a terminal alkyne. Alternatively, hydroboration/oxidation of a terminal alkyne yields an aldehyde.

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

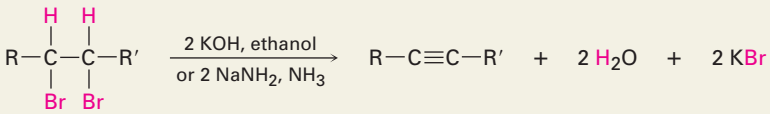
Terminal alkynes are weakly acidic. The alkyne hydrogen can be removed by a strong base such as $Na^+ {}^-NH_2$ to yield an **acetylide anion**. An acetylide

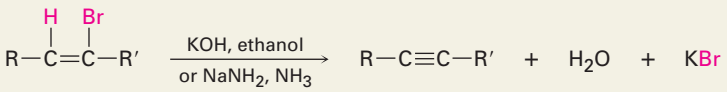
anion acts as a nucleophile and can displace a halide ion from a primary alkyl halide in an **alkylation** reaction. Acetylide anions are more stable than either alkyl anions or vinylic anions because their negative charge is in a hybrid orbital with 50% *s* character, allowing the charge to be closer to the nucleus.

SUMMARY OF REACTIONS

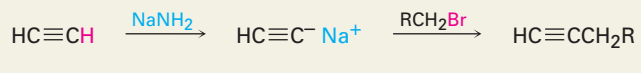
1. Preparation of alkynes

(a) Dehydrohalogenation of vicinal dihalides (Section 8.2)

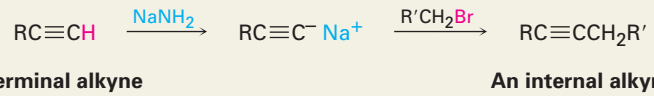




(b) Alkylation of acetylide anions (Section 8.8)



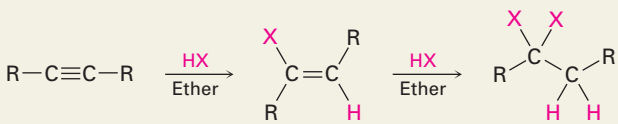
Acetylene **A terminal alkyne**



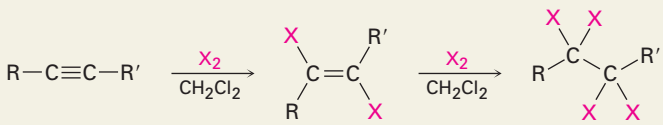
A terminal alkyne **An internal alkyne**

2. Reactions of alkynes

(a) Addition of HCl and HBr (Section 8.3)

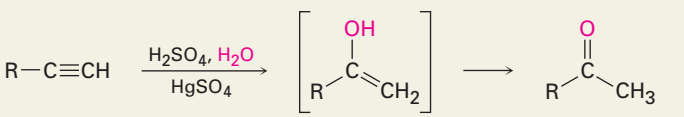


(b) Addition of Cl_2 and Br_2 (Section 8.3)



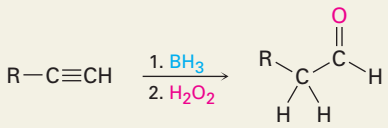
(c) Hydration (Section 8.4)

(1) Mercuric sulfate catalyzed



An enol **A methyl ketone**

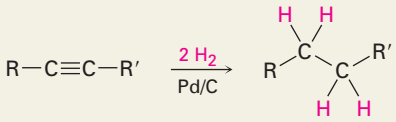
(2) Hydroboration/oxidation

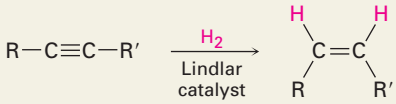


An aldehyde

(d) Reduction (Section 8.5)

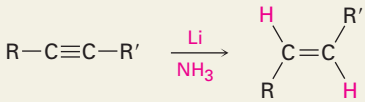
(1) Catalytic hydrogenation





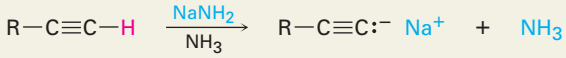
A cis alkene

(2) Lithium in liquid ammonia

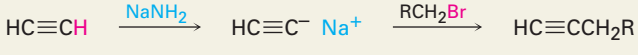


A trans alkene

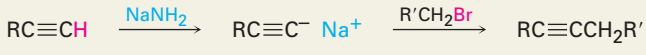
(e) Conversion into acetylide anions (Section 8.7)



(f) Alkylation of acetylide anions (Section 8.8)



Acetylene **A terminal alkyne**



A terminal alkyne **An internal alkyne**

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

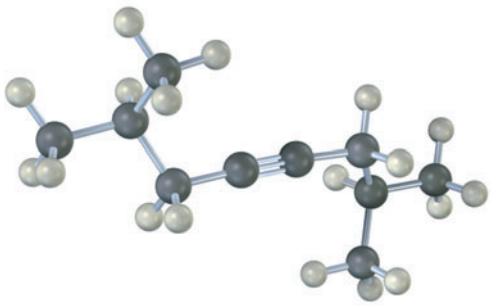
VISUALIZING CHEMISTRY

(Problems 8.1–8.13 appear within the chapter.)

8.14 ■ Name the following alkynes, and predict the products of their reaction with (i) H_2 in the presence of a Lindlar catalyst and (ii) H_3O^+ in the presence of $HgSO_4$:

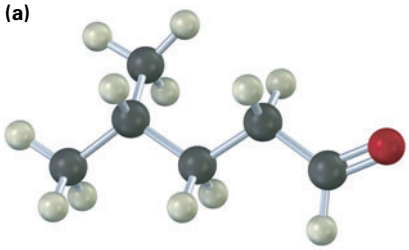
(a)

(b)

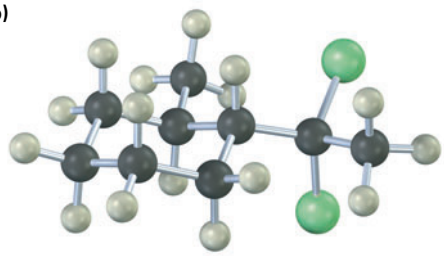


8.15 ■ From what alkyne might each of the following substances have been made? (Yellow-green = Cl.)

(a)

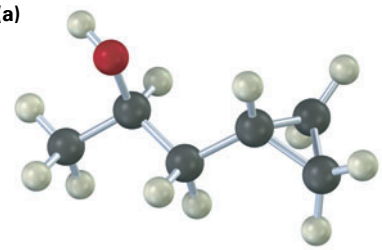


(b)

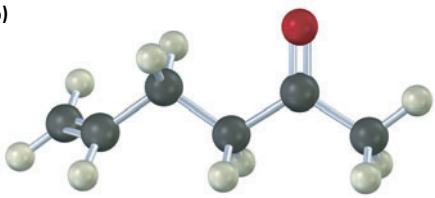


8.16 How would you prepare the following substances, starting from any compounds having four carbons or fewer?

(a)

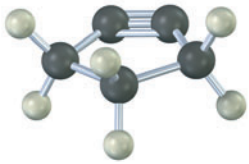


(b)



■ Assignable in OWL

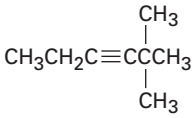
8.17 The following cycloalkyne is too unstable to exist. Explain.



ADDITIONAL PROBLEMS

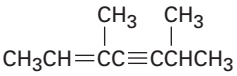
8.18 Give IUPAC names for the following compounds:

(a)

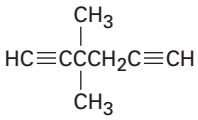


(b) $CH_3C{\equiv}CCH_2C{\equiv}CCH_2CH_3$

(c)

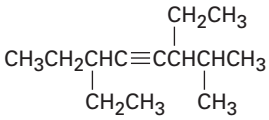


(d)



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

(f)



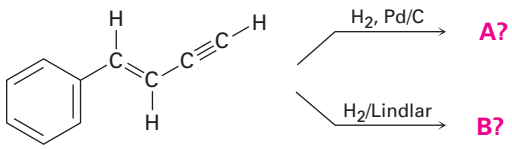
8.19 ■ Draw structures corresponding to the following names:

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

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

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

8.21 ■ Predict the products of the following reactions:



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

(a) How many degrees of unsaturation are present in the unknown?
(b) How many triple bonds are present?
(c) How many double bonds are present?
(d) How many rings are present?
(e) Draw a structure that fits the data.

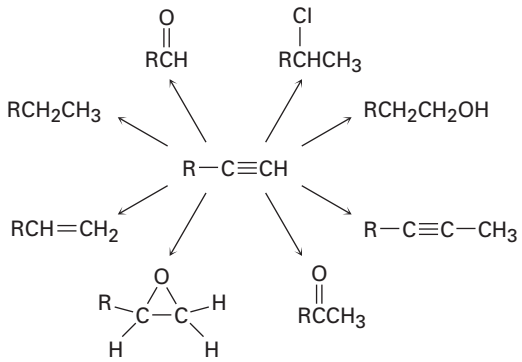
■ Assignable in OWL

8.23 ■ Predict the products from reaction of 1-hexyne with the following reagents:
(a) 1 equiv HBr **(b)** 1 equiv Cl_2
(c) H_2, Lindlar catalyst **(d)** $NaNH_2$ in NH_3, then CH_3Br
(e) H_2O, H_2SO_4, $HgSO_4$ **(f)** 2 equiv HCl

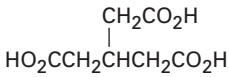
8.24 ■ Predict the products from reaction of 5-decyne with the following reagents:
(a) H_2, Lindlar catalyst **(b)** Li in NH_3
(c) 1 equiv Br_2 **(d)** BH_3 in THF, then H_2O_2, OH^-
(e) H_2O, H_2SO_4, $HgSO_4$ **(f)** Excess H_2, Pd/C catalyst

8.25 ■ Predict the products from reaction of 2-hexyne with the following reagents:
(a) 2 equiv Br_2 **(b)** 1 equiv HBr **(c)** Excess HBr
(d) Li in NH_3 **(e)** H_2O, H_2SO_4, $HgSO_4$

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



8.27 ■ Hydrocarbon A has the formula C_9H_{12} and absorbs 3 equivalents of H_2 to yield B, C_9H_{18}, when hydrogenated over a Pd/C catalyst. On treatment of A with aqueous H_2SO_4 in the presence of mercury(II), two isomeric ketones, C and D, are produced. Oxidation of A with $KMnO_4$ gives a mixture of acetic acid (CH_3CO_2H) and the tricarboxylic acid E. Propose structures for compounds A–D, and write the reactions.



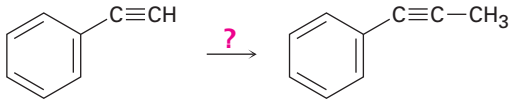
E

8.28 How would you carry out the following reactions?

(a) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2\overset{O}{\overset{\|}{C}}CH_3$

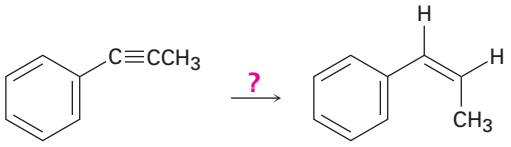
(b) $CH_3CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(c)



■ Assignable in OWL

(d)



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

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

8.29 Occasionally, chemists need to *invert* the stereochemistry of an alkene—that is, to convert a cis alkene to a trans alkene, or vice versa. There is no one-step method for doing an alkene inversion, but the transformation can be carried out by combining several reactions in the proper sequence. How would you carry out the following reactions?

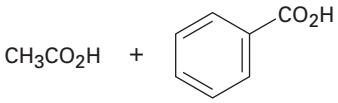
(a) *trans*-5-Decene $\xrightarrow{?}$ *cis*-5-Decene

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

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

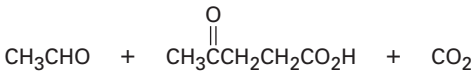
(a) $CO_2 + CH_3(CH_2)_5CO_2H$

(b)

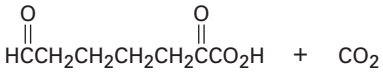


(c) $HO_2C(CH_2)_8CO_2H$

(d)



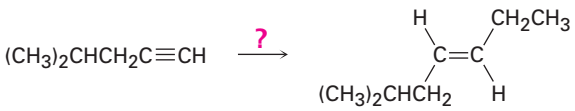
(e)



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

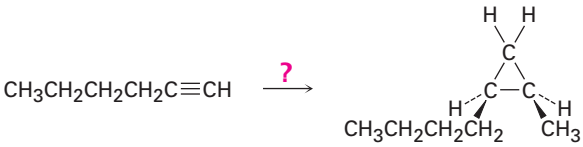
(a) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2CHO$

(b)

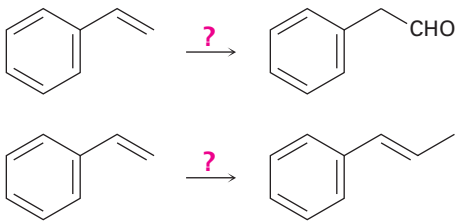


■ Assignable in OWL

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



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



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

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

8.35 ■ How would you synthesize the following compounds from acetylene and any alkyl halides with four or fewer carbons? More than one step may be required.

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

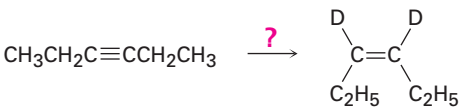
(c) $CH_3CHCH_2CH{=}CH_2$ (with CH_3 on the CH)

(d) $CH_3CH_2CH_2\overset{\displaystyle O}{\overset{\|}{C}}CH_2CH_2CH_2CH_3$

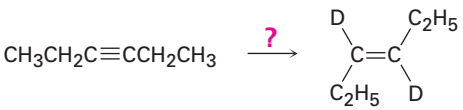
(e) $CH_3CH_2CH_2CH_2CH_2CHO$

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

(a)

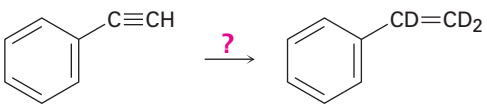


(b)



(c) $CH_3CH_2CH_2C{\equiv}CH \xrightarrow{?} CH_3CH_2CH_2C{\equiv}CD$

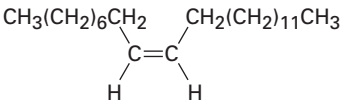
(d)



■ Assignable in OWL

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

8.38 The sex attractant given off by the common housefly is an alkene named *muscalure*. Propose a synthesis of muscalure starting from acetylene and any alkyl halides needed. What is the IUPAC name for muscalure?

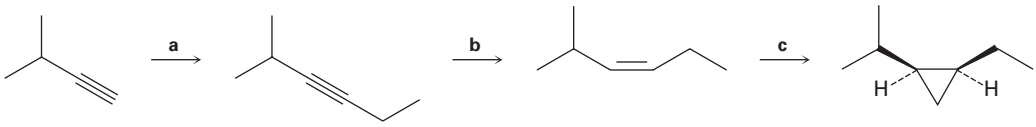


Muscalure

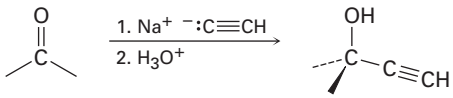
8.39 Compound A (C_9H_{12}) absorbed 3 equivalents of H_2 on catalytic reduction over a palladium catalyst to give B (C_9H_{18}). On ozonolysis, compound A gave, among other things, a ketone that was identified as cyclohexanone. On treatment with $NaNH_2$ in NH_3, followed by addition of iodomethane, compound A gave a new hydrocarbon, C ($C_{10}H_{14}$). What are the structures of A, B, and C?

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

8.41 ■ Identify the reagents a–c in the following scheme:

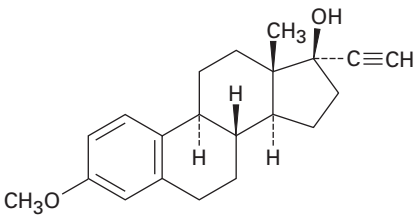


8.42 Organometallic reagents such as sodium acetylide undergo an addition reaction with ketones, giving alcohols:



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

8.43 The oral contraceptive agent Mestranol is synthesized using a carbonyl addition reaction like that shown in Problem 8.42. Draw the structure of the ketone needed.

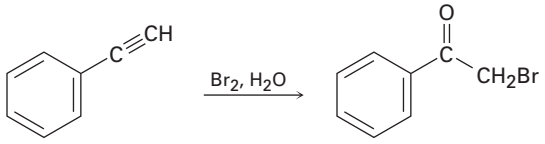


Mestranol

■ Assignable in OWL

8.44 Erythrogenic acid, $C_{18}H_{26}O_2$, is an acetylenic fatty acid that turns a vivid red on exposure to light. On catalytic hydrogenation over a palladium catalyst, 5 equivalents of H_2 is absorbed, and stearic acid, $CH_3(CH_2)_{16}CO_2H$, is produced. Ozonolysis of erythrogenic acid gives four products: formaldehyde, CH_2O; oxalic acid, HO_2CCO_2H; azelaic acid, $HO_2C(CH_2)_7CO_2H$; and the aldehyde acid $OHC(CH_2)_4CO_2H$. Draw two possible structures for erythrogenic acid, and suggest a way to tell them apart by carrying out some simple reactions.

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



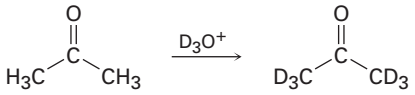
Propose a mechanism for the reaction. To what reaction of alkenes is the process analogous?

8.46 A *cumulene* is a compound with three adjacent double bonds. Draw an orbital picture of a cumulene. What kind of hybridization do the two central carbon atoms have? What is the geometric relationship of the substituents on one end to the substituents on the other end? What kind of isomerism is possible? Make a model to help see the answer.

$$R_2C{=}C{=}C{=}CR_2$$

A cumulene

8.47 Reaction of acetone with D_3O^+ yields hexadeuterioacetone. That is, all the hydrogens in acetone are exchanged for deuterium. Review the mechanism of mercuric ion–catalyzed alkyne hydration, and then propose a mechanism for this deuterium incorporation.



Acetone **Hexadeuterioacetone**

■ Assignable in OWL

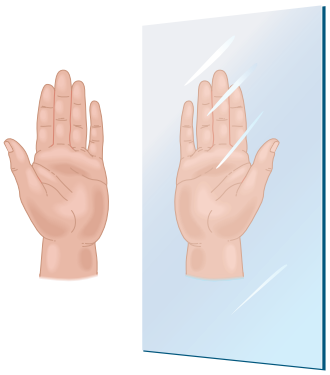
9 Stereochemistry

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at **www.thomsonedu.com** for online self-study and interactive tutorials based on your level of understanding.

Online homework for this chapter may be assigned in Organic OWL.

Are you right-handed or left-handed? You may not spend much time thinking about it, but handedness plays a surprisingly large role in your daily activities. Many musical instruments, such as oboes and clarinets, have a handedness to them; the last available softball glove always fits the wrong hand; left-handed people write in a "funny" way. The fundamental reason for these difficulties is that our hands aren't identical; rather, they're *mirror images*. When you hold a *left* hand up to a mirror, the image you see looks like a *right* hand. Try it.



Left hand **Right hand**

WHY THIS CHAPTER?

Handedness is also important in organic and biological chemistry, where it arises primarily as a consequence of the tetrahedral stereochemistry of sp^3-hybridized carbon atoms. Many drugs and almost all the molecules in our bodies, for instance, are handed. Furthermore, it is molecular handedness that makes possible the specific interactions between enzymes and their substrates that are so crucial to enzyme function. We'll look at handedness and its consequences in this chapter.

Sean Duggan

9.1 Enantiomers and the Tetrahedral Carbon

What causes molecular handedness? Look at generalized molecules of the type CH_3X, CH_2XY, and CHXYZ shown in Figure 9.1. On the left are three molecules, and on the right are their images reflected in a mirror. The CH_3X and CH_2XY molecules are identical to their mirror images and thus are not handed. If you make molecular models of each molecule and its mirror image, you find that you can superimpose one on the other. By contrast, the CHXYZ molecule is *not* identical to its mirror image. You can't superimpose a model of the molecule on a model of its mirror image for the same reason that you can't superimpose a left hand on a right hand. They simply aren't the same.

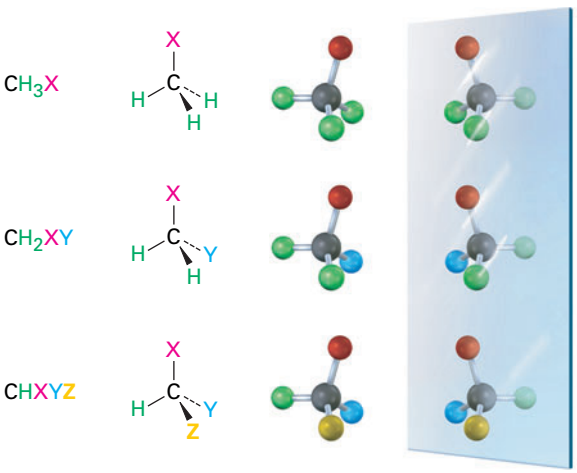
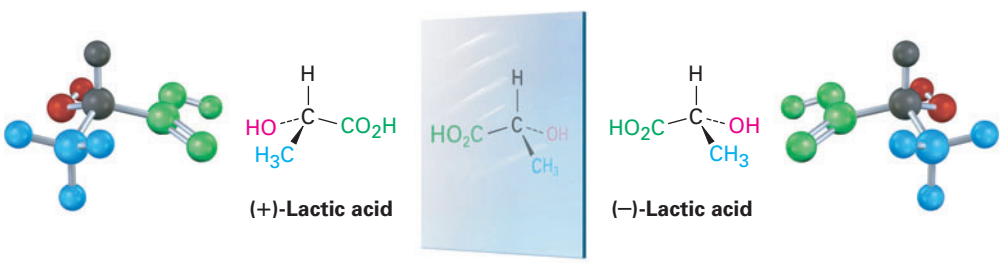


Figure 9.1 Tetrahedral carbon atoms and their mirror images. Molecules of the type CH_3X and CH_2XY are identical to their mirror images, but a molecule of the type CHXYZ is not. A CHXYZ molecule is related to its mirror image in the same way that a right hand is related to a left hand.

Molecules that are not identical to their mirror images are kinds of stereoisomers called **enantiomers** (Greek *enantio,* meaning "opposite"). Enantiomers are related to each other as a right hand is related to a left hand and result whenever a tetrahedral carbon is bonded to four different substituents (one need not be H). For example, lactic acid (2-hydroxypropanoic acid) exists as a pair of enantiomers because there are four different groups (−H, −OH, $-CH_3$, $-CO_2H$) bonded to the central carbon atom. The enantiomers are called (+)-lactic acid and (−)-lactic acid. Both are found in sour milk, but only the (+) enantiomer occurs in muscle tissue.

Lactic acid: a molecule of general formula CHXYZ



No matter how hard you try, you can't superimpose a molecule of (+)-lactic acid on a molecule of (−)-lactic acid; the two simply aren't identical. If any two groups match up, say −H and $-CO_2H$, the remaining two groups don't match (Figure 9.2).

Figure 9.2 Attempts at superimposing the mirror-image forms of lactic acid. **(a)** When the −H and −OH substituents match up, the $-CO_2H$ and $-CH_3$ substituents don't; **(b)** when $-CO_2H$ and $-CH_3$ match up, −H and −OH don't. Regardless of how the molecules are oriented, they aren't identical.

9.2 The Reason for Handedness in Molecules: Chirality

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

Molecules that are not identical to their mirror images, and thus exist in two enantiomeric forms, are said to be **chiral** (**ky**-ral, from the Greek *cheir,* meaning "hand"). You can't take a chiral molecule and its enantiomer and place one on the other so that all atoms coincide.

How can you predict whether a given molecule is or is not chiral? *A molecule is not chiral if it contains a plane of symmetry.* A plane of symmetry is a plane that cuts through the middle of an object (or molecule) in such a way that one half of the object is a mirror image of the other half. A laboratory flask, for example, has a plane of symmetry. If you were to cut the flask in half, one half would be a mirror image of the other half. A hand, however, does not have a plane of symmetry. One "half" of a hand is not a mirror image of the other half (Figure 9.3).

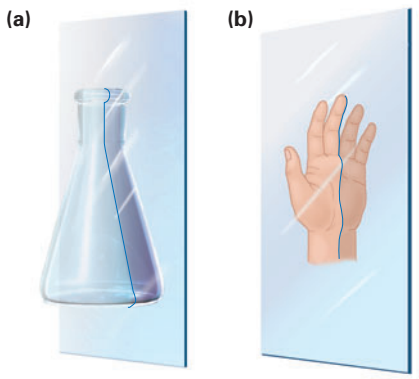


Figure 9.3 The meaning of *symmetry plane.* An object like the flask **(a)** has a symmetry plane cutting through it, making right and left halves mirror images. An object like a hand **(b)** has no symmetry plane; the right "half" of a hand is not a mirror image of the left half.

A molecule that has a plane of symmetry in any of its possible conformations must be identical to its mirror image and hence must be nonchiral, or **achiral**. Thus, propanoic acid, $CH_3CH_2CO_2H$, has a plane of symmetry when lined up as shown in Figure 9.4 and is achiral, while lactic acid, $CH_3CH(OH)CO_2H$, has no plane of symmetry in any conformation and is chiral.

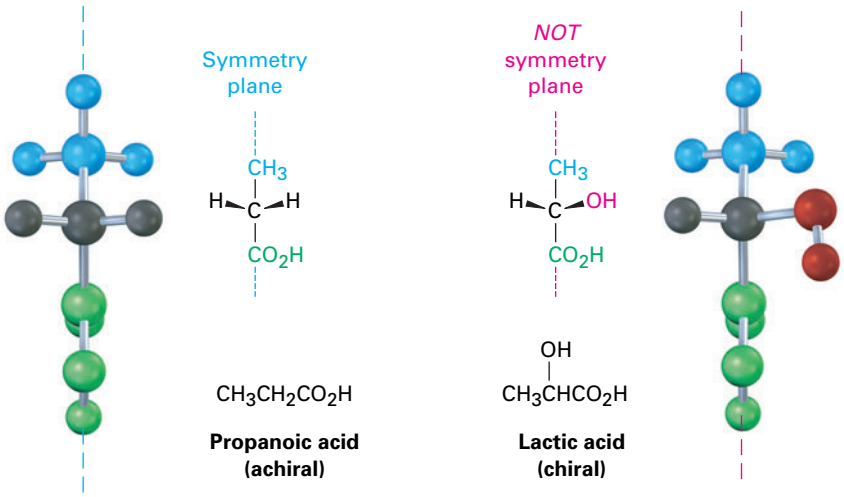
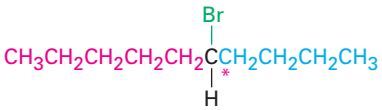


Figure 9.4 The achiral propanoic acid molecule versus the chiral lactic acid molecule. Propanoic acid has a plane of symmetry that makes one side of the molecule a mirror image of the other side. Lactic acid has no such symmetry plane.

ThomsonNOW™ Click *Organic Interactive* to **practice identifying chirality centers in organic molecules**.

The most common, although not the only, cause of chirality in an organic molecule is the presence of a carbon atom bonded to four different groups—for example, the central carbon atom in lactic acid. Such carbons are now referred to as **chirality centers**, although other terms such as *stereocenter, asymmetric center,* and *stereogenic center* have also been used formerly. Note that *chirality* is a property of the entire molecule, whereas a chirality *center* is the *cause* of chirality.

Detecting chirality centers in a complex molecule takes practice because it's not always immediately apparent that four different groups are bonded to a given carbon. The differences don't necessarily appear right next to the chirality center. For example, 5-bromodecane is a chiral molecule because four different groups are bonded to C5, the chirality center (marked with an asterisk). A butyl substituent is similar to a pentyl substituent but it isn't identical. The difference isn't apparent until four carbon atoms away from the chirality center, but there's still a difference.



5-Bromodecane (chiral)

Substituents on carbon 5

—H

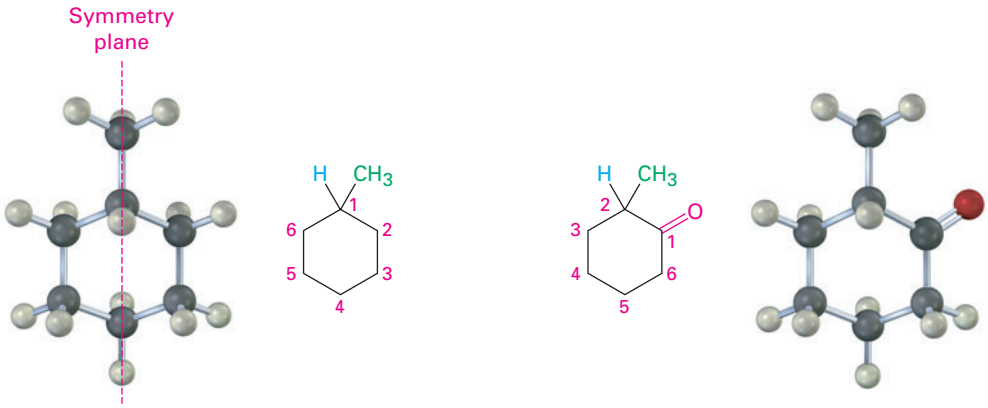
—Br

—$CH_2CH_2CH_2CH_3$ (butyl)

—$CH_2CH_2CH_2CH_2CH_3$ (pentyl)

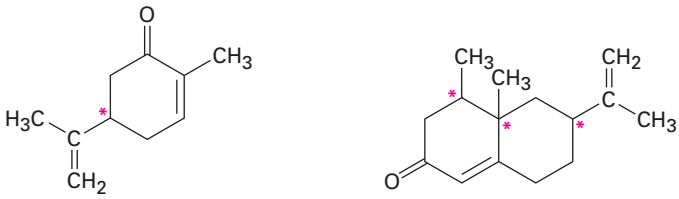
As other possible examples, look at methylcyclohexane and 2-methylcyclohexanone. Methylcyclohexane is achiral because no carbon atom in the molecule is bonded to four different groups. You can immediately eliminate all $-CH_2-$ carbons and the $-CH_3$ carbon from consideration, but what about C1 on the ring? The C1 carbon atom is bonded to a $-CH_3$ group, to an $-H$ atom, and to C2 and C6 of the ring. Carbons 2 and 6 are equivalent, however, as are carbons 3 and 5. Thus, the C6–C5–C4 "substituent" is equivalent to the C2–C3–C4 substituent, and methylcyclohexane is achiral. Another way of reaching the same conclusion is to realize that methylcyclohexane has a symmetry plane, which passes through the methyl group and through C1 and C4 of the ring.

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



Methylcyclohexane (achiral) **2-Methylcyclohexanone (chiral)**

Several more examples of chiral molecules are shown below. Check for yourself that the labeled carbons are chirality centers. You might note that carbons in $-CH_2-$, $-CH_3$, C=O, C=C, and C≡C groups can't be chirality centers. (Why?)



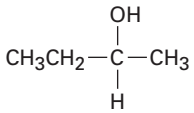
Carvone (spearmint oil) **Nootkatone (grapefruit oil)**

WORKED EXAMPLE 9.1 ***Drawing the Three-Dimensional Structure of a Chiral Molecule***

Draw the structure of a chiral alcohol.

Strategy An alcohol is a compound that contains the $-OH$ functional group. To make an alcohol chiral, we need to have four different groups bonded to a single carbon atom, say $-H$, $-OH$, $-CH_3$, and $-CH_2CH_3$.

Solution

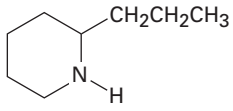


2-Butanol (chiral)

Problem 9.1 Which of the following objects are chiral?
(a) Screwdriver **(b)** Screw **(c)** Beanstalk **(d)** Shoe

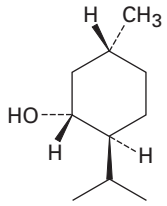
Problem 9.2 Identify the chirality centers in the following molecules. Build molecular models if you need help.

(a)



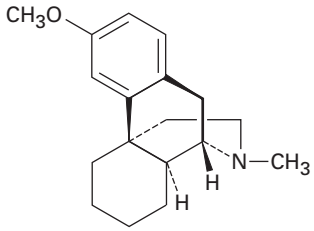
Coniine
(poison hemlock)

(b)



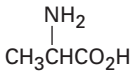
Menthol
(flavoring agent)

(c)



Dextromethorphan
(cough suppressant)

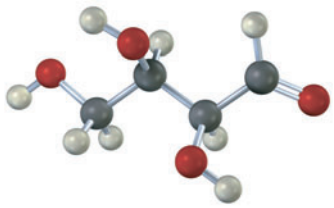
Problem 9.3 Alanine, an amino acid found in proteins, is chiral. Draw the two enantiomers of alanine using the standard convention of solid, wedged, and dashed lines.



Alanine

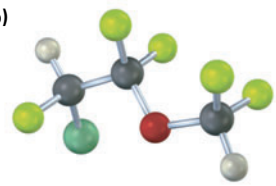
Problem 9.4 Identify the chirality centers in the following molecules (yellow-green = Cl, pale yellow = F):

(a)



Threose
(a sugar)

(b)



Enflurane
(an anesthetic)

9.3 Optical Activity

The study of stereochemistry originated in the early 19th century during investigations by the French physicist Jean-Baptiste Biot into the nature of *plane-polarized light.* A beam of ordinary light consists of electromagnetic waves that oscillate in an infinite number of planes at right angles to the direction of light travel. When a beam of ordinary light is passed through a device called a *polarizer,* however, only the light waves oscillating in a single plane pass through and the light is said to be plane-polarized. Light waves in all other planes are blocked out.

Biot made the remarkable observation that when a beam of plane-polarized light passes through a solution of certain organic molecules, such as sugar or

camphor, the plane of polarization is rotated. Not all organic substances exhibit this property, but those that do are said to be **optically active**.

The amount of rotation can be measured with an instrument called a *polarimeter,* represented in Figure 9.5. A solution of optically active organic molecules is placed in a sample tube, plane-polarized light is passed through the tube, and rotation of the polarization plane occurs. The light then goes through a second polarizer called the *analyzer.* By rotating the analyzer until the light passes through it, we can find the new plane of polarization and can tell to what extent rotation has occurred.

Jean-Baptiste Biot

Jean-Baptiste Biot (1774–1862) was born in Paris, France, and was educated there at the École Polytechnique. In 1800, he was appointed professor of mathematical physics at the College de France. His work on determining the optical rotation of naturally occurring molecules included an experiment on turpentine, which caught fire and nearly burned down the church building he was using for his experiments.

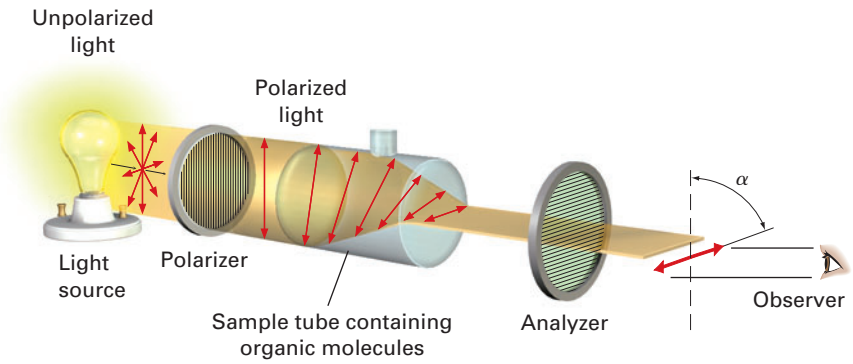


Figure 9.5 Schematic representation of a polarimeter. Plane-polarized light passes through a solution of optically active molecules, which rotate the plane of polarization.

In addition to determining the extent of rotation, we can also find the direction. From the vantage point of the observer looking directly at the analyzer, some optically active molecules rotate polarized light to the left (counterclockwise) and are said to be **levorotatory**, whereas others rotate polarized light to the right (clockwise) and are said to be **dextrorotatory**. By convention, rotation to the left is given a minus sign (−), and rotation to the right is given a plus sign (+). (−)-Morphine, for example, is levorotatory, and (+)-sucrose is dextrorotatory.

ThomsonNOW™ Click *Organic Interactive* to **learn the relationship between observed optical rotation and concentration for optically active compounds.**

The amount of rotation observed in a polarimetry experiment depends on the number of optically active molecules encountered by the light beam. This number, in turn, depends on sample concentration and sample pathlength. If the concentration of sample is doubled, the observed rotation doubles. If the concentration is kept constant but the length of the sample tube is doubled, the observed rotation is doubled. It also happens that the amount of rotation depends on the wavelength of the light used.

To express optical rotations in a meaningful way so that comparisons can be made, we have to choose standard conditions. The **specific rotation**, $[\alpha]_D$, of a compound is defined as the observed rotation when light of 589.6 nanometer (nm; 1 nm = 10^{-9} m) wavelength is used with a sample pathlength l of 1 decimeter (dm; 1 dm = 10 cm) and a sample concentration C of 1 g/mL. (Light of 589.6 nm, the so-called sodium D line, is the yellow light emitted from common sodium lamps.)

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

When optical rotation data are expressed in this standard way, the specific rotation, $[\alpha]_D$, is a physical constant characteristic of a given optically active

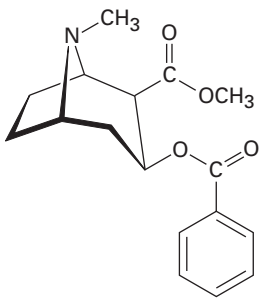
compound. For example, (+)-lactic acid has $[\alpha]_D = +3.82$, and (−)-lactic acid has $[\alpha]_D = -3.82$. That is, the two enantiomers rotate plane-polarized light to exactly the same extent but in opposite directions. Note that specific rotation is generally expressed as a unitless number. Some additional examples are listed in Table 9.1.

Table 9.1 Specific Rotation of Some Organic Molecules

Compound	$[\alpha]_D$	Compound	$[\alpha]_D$
Penicillin V	+233	Cholesterol	−31.5
Sucrose	+66.47	Morphine	−132
Camphor	+44.26	Cocaine	−16
Chloroform	0	Acetic acid	0

WORKED EXAMPLE 9.2 ***Calculating an Optical Rotation***

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



Cocaine

Strategy Observed rotation, α, is equal to specific rotation $[\alpha]_D$ times sample concentration, C, times pathlength, l: $\alpha = [\alpha]_D \times C \times l$, where $[\alpha]_D = -16$, $l = 5.00$ cm $= 0.500$ dm, and $C = 1.20$ g/7.50 mL $= 0.160$ g/mL.

Solution $\alpha = -16 \times 0.500 \times 0.160 = -1.3°$.

Problem 9.5 Is cocaine (Worked Example 9.2) dextrorotatory or levorotatory?

Problem 9.6 A 1.50 g sample of coniine, the toxic extract of poison hemlock, was dissolved in 10.0 mL of ethanol and placed in a sample cell with a 5.00 cm pathlength. The observed rotation at the sodium D line was +1.21°. Calculate $[\alpha]_D$ for coniine.

9.4 Pasteur's Discovery of Enantiomers

Little was done after Biot's discovery of optical activity until 1848, when Louis Pasteur began work on a study of crystalline tartaric acid salts derived from wine. On crystallizing a concentrated solution of sodium ammonium tartrate below

Louis Pasteur

Louis Pasteur (1822–1895) was born at Dôle in the Jura region of France, the son of leather tanners. After receiving his doctorate from the École Normale Supérieure at age 25, his landmark discovery of tartaric acid enantiomers was made only 1 year later. Pasteur is best known for his studies in bacteriology and for his discovery of vaccines for anthrax and rabies.

28 °C, Pasteur made the surprising observation that two distinct kinds of crystals precipitated. Furthermore, the two kinds of crystals were mirror images and were related in the same way that a right hand is related to a left hand.

Working carefully with tweezers, Pasteur was able to separate the crystals into two piles, one of "right-handed" crystals and one of "left-handed" crystals like those shown in Figure 9.6. Although the original sample, a 50:50 mixture of right and left, was optically inactive, solutions of the crystals from each of the sorted piles were optically active, and their specific rotations were equal in amount but opposite in sign.

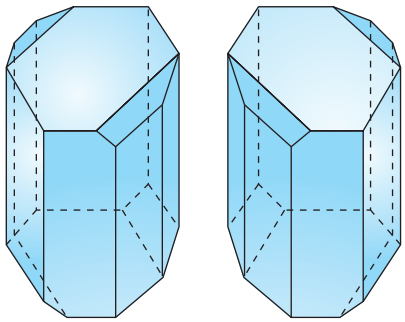
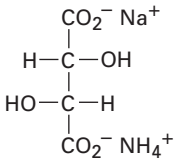


Figure 9.6 Drawings of sodium ammonium tartrate crystals taken from Pasteur's original sketches. One of the crystals is "right-handed" and one is "left-handed."



Sodium ammonium tartrate

Pasteur was far ahead of his time. Although the structural theory of Kekulé had not yet been proposed, Pasteur explained his results by speaking of the molecules themselves, saying, "There is no doubt that [in the *dextro* tartaric acid] there exists an asymmetric arrangement having a nonsuperimposable image. It is no less certain that the atoms of the *levo* acid have precisely the inverse asymmetric arrangement." Pasteur's vision was extraordinary, for it was not until 25 years later that his ideas regarding the asymmetric carbon atom were confirmed.

Today, we would describe Pasteur's work by saying that he had discovered enantiomers. Enantiomers, also called *optical isomers,* have identical physical properties, such as melting point and boiling point, but differ in the direction in which their solutions rotate plane-polarized light.

9.5 Sequence Rules for Specifying Configuration

Key IDEAS

Test your knowledge of Key Ideas by using resources in ThomsonNOW or by answering end-of-chapter problems marked with ▲.

Drawings provide a visual representation of stereochemistry, but a verbal method for indicating the three-dimensional arrangement, or **configuration**, of substituents at a chirality center is also needed. The method used employs the same sequence rules given in Section 6.5 for specifying *E* and *Z* alkene stereochemistry. Let's briefly review the sequence rules and see how they're used to specify the configuration of a chirality center. For a more thorough review, you should reread Section 6.5.

Rule 1 Look at the four atoms directly attached to the chirality center, and assign priorities in order of decreasing atomic number. The atom with the highest atomic number is ranked first; the atom with the lowest atomic number (usually hydrogen) is ranked fourth.

Rule 2 If a decision can't be reached by ranking the first atoms in the substituents, look at the second, third, or fourth atoms outward until a difference is found.

Rule 3 Multiple-bonded atoms are equivalent to the same number of single-bonded atoms. For example:

ThomsonNOW™ Click *Organic Interactive* to **assign absolute configurations using the Cahn–Ingold–Prelog rules.**

Having assigned priorities to the four groups attached to a chiral carbon, we describe the stereochemical configuration around the carbon by orienting the molecule so that the group of lowest priority (4) points directly back, away from us. We then look at the three remaining substituents, which now appear to radiate toward us like the spokes on a steering wheel (Figure 9.7). If a curved arrow drawn from the highest to second-highest to third-highest priority substituent (1 → 2 → 3) is clockwise, we say that the chirality center has the ***R* configuration** (Latin *rectus,* meaning "right"). If an arrow from 1 → 2 → 3 is counterclockwise, the chirality center has the ***S* configuration** (Latin *sinister,* meaning "left"). To remember these assignments, think of a car's steering wheel when making a *R*ight (clockwise) turn.

ThomsonNOW™ Click *Organic Interactive* to **manipulate three-dimensional models and assign *R,S* designations.**

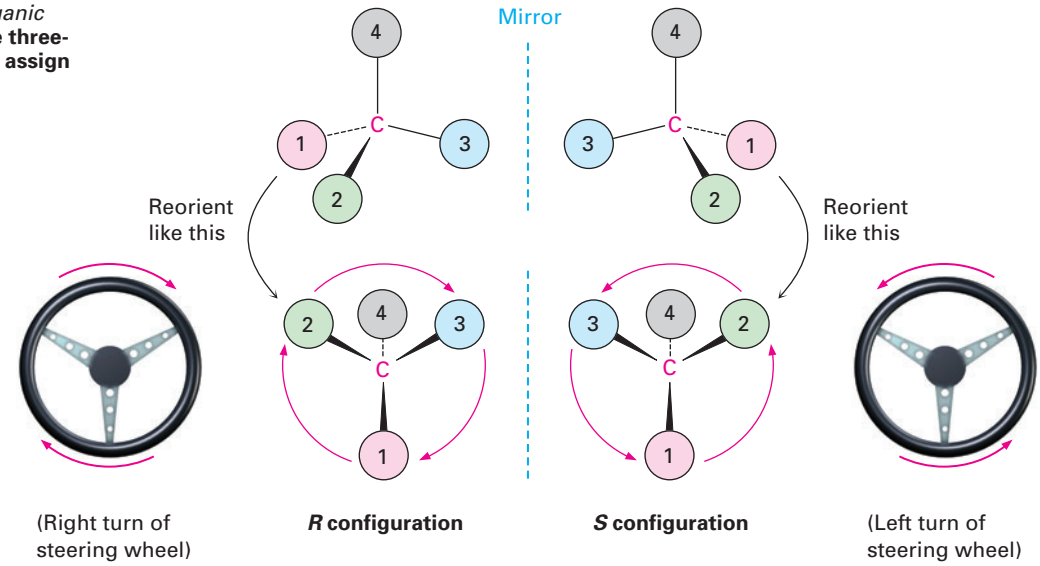


Figure 9.7 Assigning configuration to a chirality center. When the molecule is oriented so that the group of lowest priority (4) is toward the rear, the remaining three groups radiate toward the viewer like the spokes of a steering wheel. If the direction of travel 1 □ 2 □ 3 is clockwise (right turn), the center has the *R* configuration. If the direction of travel 1 □ 2 □ 3 is counterclockwise (left turn), the center is *S*.

Look at (−)-lactic acid in Figure 9.8 for an example of how to assign configuration. Sequence rule 1 says that −OH has priority 1 and −H has priority 4, but it doesn't allow us to distinguish between $-CH_3$ and $-CO_2H$ because

both groups have carbon as their first atom. Sequence rule 2, however, says that $-CO_2H$ is higher priority than $-CH_3$ because O (the second atom in $-CO_2H$) outranks H (the second atom in $-CH_3$). Now, turn the molecule so that the fourth-priority group (−H) is oriented toward the rear, away from the observer. Since a curved arrow from 1 (−OH) to 2 ($-CO_2H$) to 3 ($-CH_3$) is clockwise (right turn of the steering wheel), (−)-lactic acid has the *R* configuration. Applying the same procedure to (+)-lactic acid leads to the opposite assignment.

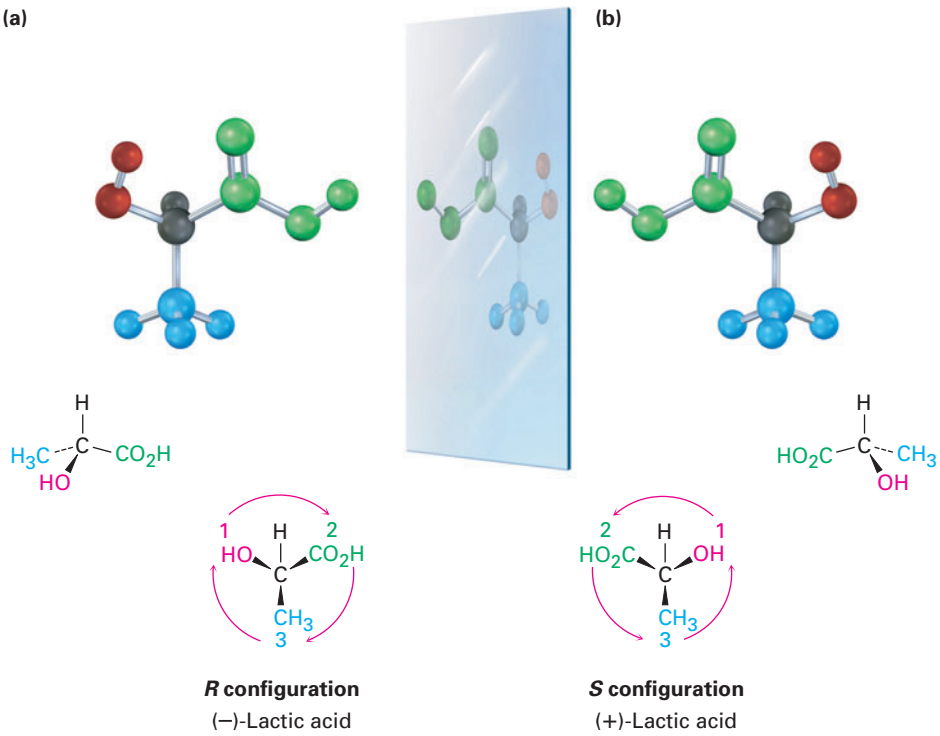


Figure 9.8 Assignment of configuration to **(a)** (*R*)-(−)-lactic acid and **(b)** (*S*)-(+)-lactic acid.

Further examples are provided by naturally occurring (−)-glyceraldehyde and (+)-alanine, which both have the *S* configuration as shown in Figure 9.9. Note that the sign of optical rotation, (+) or (−), is not related to the *R*,*S* designation. (*S*)-Glyceraldehyde happens to be levorotatory (−), and (*S*)-alanine happens to be dextrorotatory (+). There is no simple correlation between *R*,*S* configuration and direction or magnitude of optical rotation.

One further point needs to be mentioned—the matter of **absolute configuration**. How do we know that our assignments of *R*,*S* configuration are correct in an absolute, rather than a relative, sense? Since we can't see the molecules themselves, how do we know that the *R* configuration belongs to the dextrorotatory enantiomer of lactic acid? This difficult question was finally solved in 1951, when J. M. Bijvoet of the University of Utrecht reported an X-ray spectroscopic method for determining the absolute spatial arrangement of atoms in a molecule. Based on his results, we can say with certainty that the *R*,*S* conventions are correct.

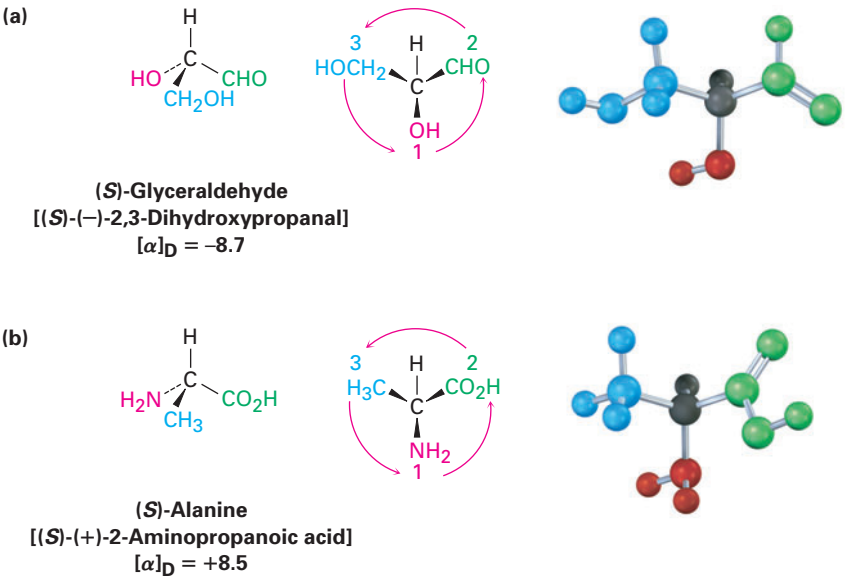
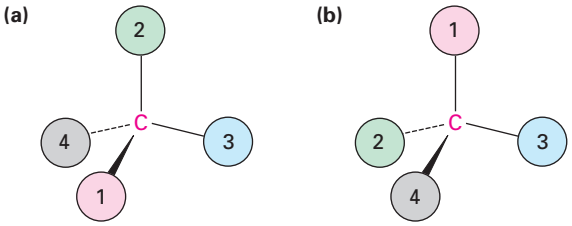


Figure 9.9 Assigning configuration to **(a)** (−)-glyceraldehyde and **(b)** (+)-alanine. Both happen to have the *S* configuration, although one is levorotatory and the other is dextrorotatory.

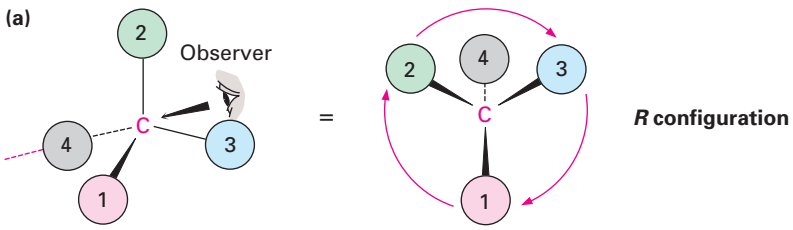
WORKED EXAMPLE 9.3 *Assigning R or S Configuration to Chirality Centers in Molecules*

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

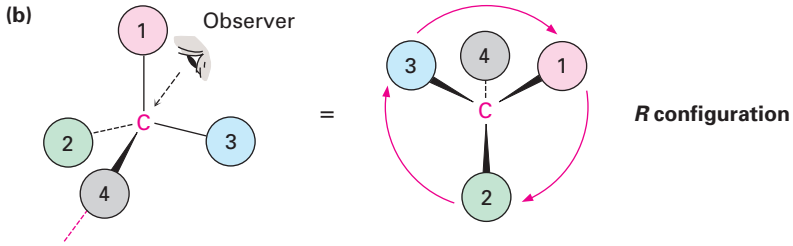


Strategy It takes practice to be able to visualize and orient a molecule in three dimensions. You might start by indicating where the observer must be located—180° opposite the lowest-priority group. Then imagine yourself in the position of the observer, and redraw what you would see.

Solution In **(a)**, you would be located in front of the page toward the top right of the molecule, and you would see group 2 to your left, group 3 to your right, and group 1 below you. This corresponds to an *R* configuration.



In **(b)**, you would be located behind the page toward the top left of the molecule from your point of view, and you would see group 3 to your left, group 1 to your right, and group 2 below you. This also corresponds to an *R* configuration.



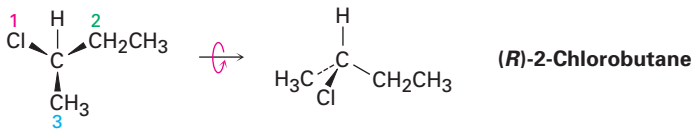
WORKED EXAMPLE 9.4 *Drawing the Three-Dimensional Structure of a Specific Enantiomer*

Draw a tetrahedral representation of (*R*)-2-chlorobutane.

Strategy

Begin by assigning priorities to the four substituents bonded to the chirality center: (1) −Cl, (2) $-CH_2CH_3$, (3) $-CH_3$, (4) −H. To draw a tetrahedral representation of the molecule, orient the lowest-priority −H group away from you and imagine that the other three groups are coming out of the page toward you. Then place the remaining three substituents such that the direction of travel 1 □ 2 □ 3 is clockwise (right turn), and tilt the molecule toward you to bring the rear hydrogen into view. Using molecular models is a great help in working problems of this sort.

Solution



Problem 9.7

Assign priorities to the following sets of substituents:

(a) −H, −OH, $-CH_2CH_3$, $-CH_2CH_2OH$

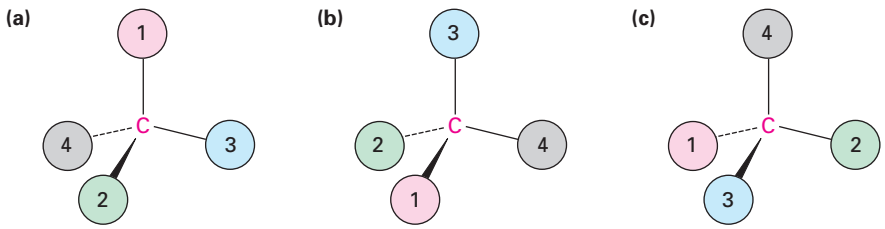
(b) $-CO_2H$, $-CO_2CH_3$, $-CH_2OH$, −OH

(c) −CN, $-CH_2NH_2$, $-CH_2NHCH_3$, $-NH_2$

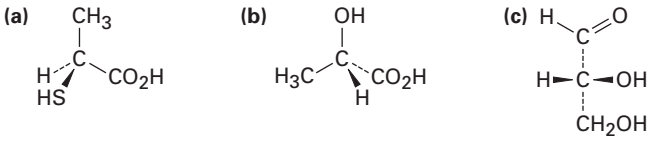
(d) −SH, $-CH_2SCH_3$, $-CH_3$, $-SSCH_3$

Problem 9.8

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

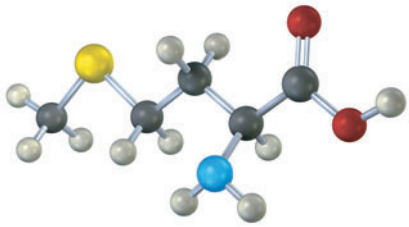


Problem 9.9 Assign *R* or *S* configuration to the chirality center in each of the following molecules:



Problem 9.10 Draw a tetrahedral representation of (*S*)-2-pentanol (2-hydroxypentane).

Problem 9.11 Assign *R* or *S* configuration to the chirality center in the following molecular model of the amino acid methionine (blue = N, yellow = S):



9.6 Diastereomers

Molecules like lactic acid, alanine, and glyceraldehyde are relatively simple because each has only one chirality center and only two stereoisomers. The situation becomes more complex, however, with molecules that have more than one chirality center. As a general rule, a molecule with n chirality centers can have up to 2^n stereoisomers (although it may have fewer, as we'll see shortly). Take the amino acid threonine (2-amino-3-hydroxybutanoic acid), for example. Since threonine has two chirality centers (C2 and C3), there are four possible stereoisomers, as shown in Figure 9.10. Check for yourself that the *R*,*S* configurations are correct.

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to draw stereoisomers.**

The four stereoisomers of 2-amino-3-hydroxybutanoic acid can be grouped into two pairs of enantiomers. The 2*R*,3*R* stereoisomer is the mirror image of 2*S*,3*S*, and the 2*R*,3*S* stereoisomer is the mirror image of 2*S*,3*R*. But what is the relationship between any two molecules that are not mirror images? What, for example, is the relationship between the 2*R*,3*R* isomer and the 2*R*,3*S* isomer? They are stereoisomers, yet they aren't enantiomers. To describe such a relationship, we need a new term—*diastereomer.*

Diastereomers are stereoisomers that are not mirror images. Since we used the right-hand/left-hand analogy to describe the relationship between two enantiomers, we might extend the analogy by saying that the relationship between diastereomers is like that of hands from different people. Your hand and your friend's hand look *similar,* but they aren't identical and they aren't mirror images. The same is true of diastereomers: they're similar, but they aren't identical and they aren't mirror images.

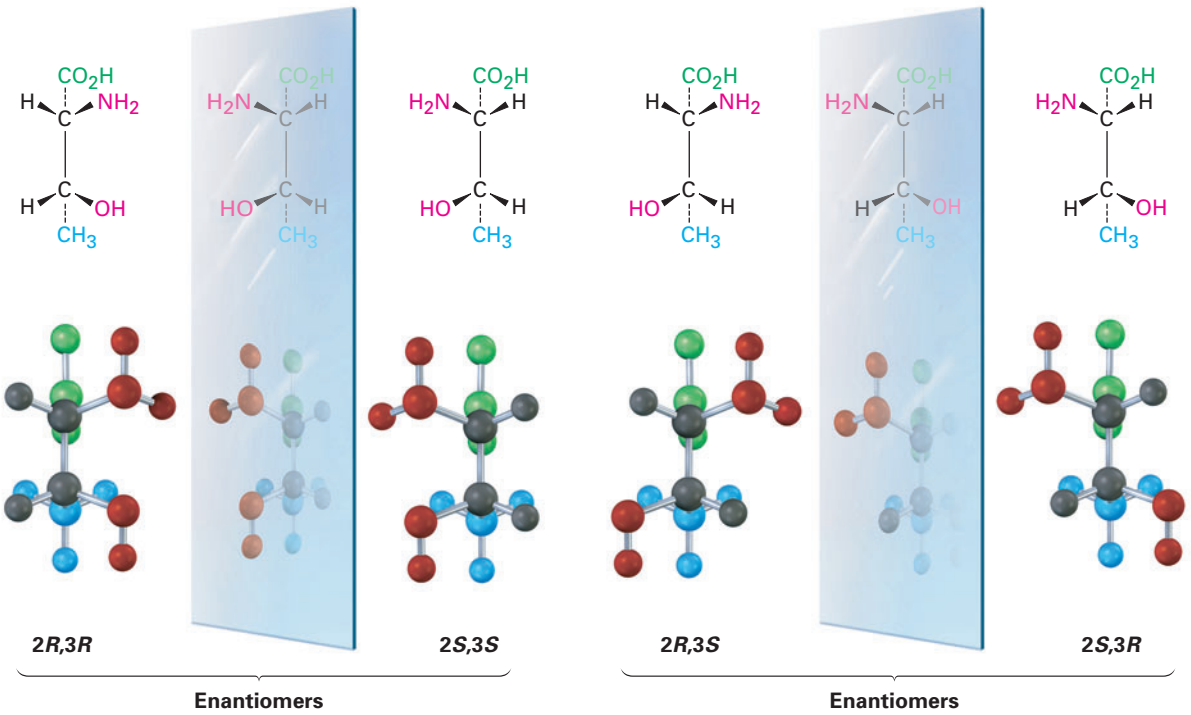


Figure 9.10 The four stereoisomers of 2-amino-3-hydroxybutanoic acid.

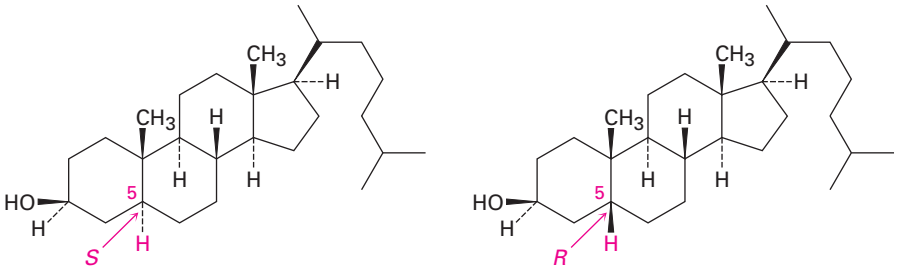
Note carefully the difference between enantiomers and diastereomers. Enantiomers have opposite configurations at *all* chirality centers, whereas diastereomers have opposite configurations at *some* (one or more) chirality centers but the same configuration at others. A full description of the four stereoisomers of threonine is given in Table 9.2. Of the four, only the 2*S*,3*R* isomer, $[\alpha]_D = -28.3$, occurs naturally in plants and animals and is an essential human nutrient. This result is typical: most biological molecules are chiral, and usually only one stereoisomer is found in nature.

Table 9.2 Relationships among the Four Stereoisomers of Threonine

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

In the special case where two diastereomers differ at only one chirality center but are the same at all others, we say that the compounds are **epimers**. Cholestanol and coprostanol, for instance, are both found in human feces and

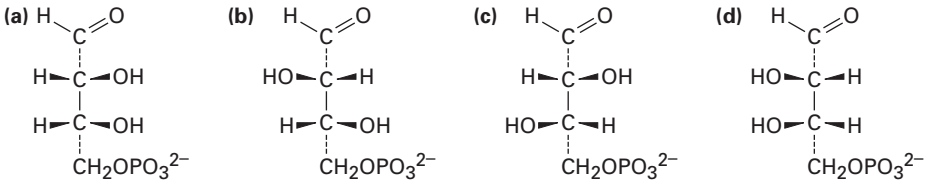
both have nine chirality centers. Eight of the nine are identical, but the one at C5 is different. Thus, cholestanol and coprostanol are *epimeric* at C5.



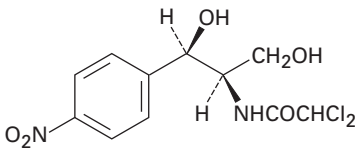
Cholestanol **Coprostanol**

Epimers

Problem 9.12 One of the following molecules **(a)–(d)** is D-erythrose 4-phosphate, an intermediate in the Calvin photosynthetic cycle by which plants incorporate CO_2 into carbohydrates. If D-erythrose 4-phosphate has *R* stereochemistry at both chirality centers, which of the structures is it? Which of the remaining three structures is the enantiomer of D-erythrose 4-phosphate, and which are diastereomers?

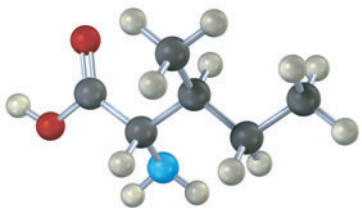


Problem 9.13 Chloramphenicol, a powerful antibiotic isolated in 1949 from the *Streptomyces venezuelae* bacterium, is active against a broad spectrum of bacterial infections and is particularly valuable against typhoid fever. Assign *R,S* configurations to the chirality centers in chloramphenicol.



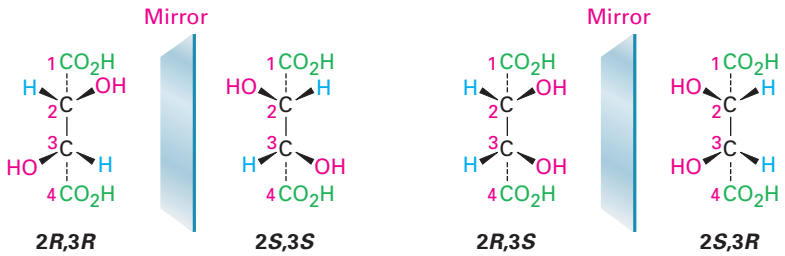
Chloramphenicol

Problem 9.14 Assign *R,S* configuration to each chirality center in the following molecular model of the amino acid isoleucine (blue = N):

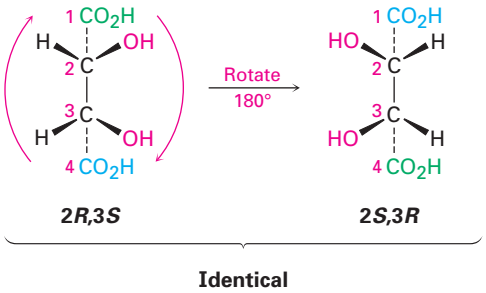


9.7 Meso Compounds

Let's look at one more example of a compound with more than one chirality center, the tartaric acid used by Pasteur. The four stereoisomers can be drawn as follows:



The mirror-image 2*R*,3*R* and 2*S*,3*S* structures are not identical and therefore represent a pair of enantiomers. A close look, however, shows that the 2*R*,3*S* and 2*S*,3*R* structures *are* identical, as can be seen by rotating one structure 180°.



The 2*R*,3*S* and 2*S*,3*R* structures are identical because the molecule has a plane of symmetry and is therefore achiral. The symmetry plane cuts through the C2–C3 bond, making one half of the molecule a mirror image of the other half (Figure 9.11). Because of the plane of symmetry, the molecule is achiral, despite the fact that it has two chirality centers. Compounds that are achiral, yet contain chirality centers, are called **meso** (**me**-zo) **compounds**. Thus, tartaric acid exists in three stereoisomeric forms: two enantiomers and one meso form.

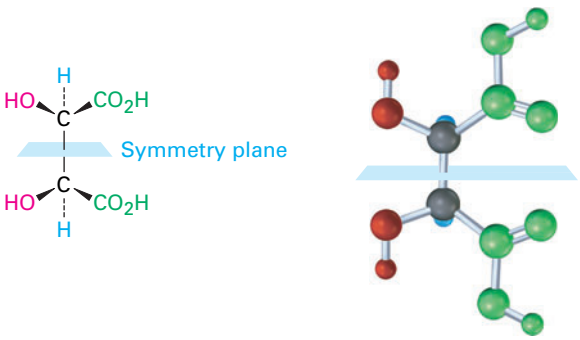


Figure 9.11 A symmetry plane through the C2–C3 bond of *meso*-tartaric acid makes the molecule achiral.

Some physical properties of the three stereoisomers are listed in Table 9.3. The (+)- and (−)-tartaric acids have identical melting points, solubilities, and densities but differ in the sign of their rotation of plane-polarized light. The meso isomer, by contrast, is diastereomeric with the (+) and (−) forms. As such, it has no mirror-image relationship to (+)- and (−)-tartaric acids, is a different compound altogether, and has different physical properties.

Table 9.3 Some Properties of the Stereoisomers of Tartaric Acid

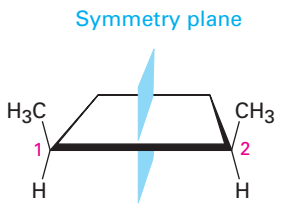
Stereoisomer	Melting point (°C)	$[\alpha]_D$	Density (g/cm^3)	Solubility at 20 °C (g/100 mL H_2O)
(+)	168–170	+12	1.7598	139.0
(−)	168–170	−12	1.7598	139.0
Meso	146–148	0	1.6660	125.0

WORKED EXAMPLE 9.5 ***Distinguishing Chiral Compounds from Meso Compounds***

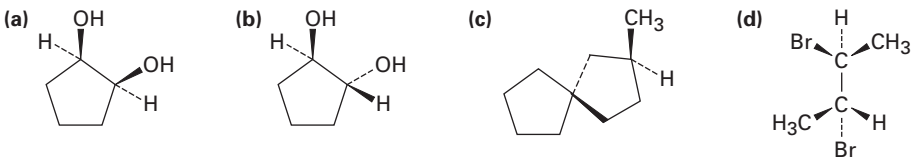
Does *cis*-1,2-dimethylcyclobutane have any chirality centers? Is it chiral?

Strategy To see whether a chirality center is present, look for a carbon atom bonded to four different groups. To see whether the molecule is chiral, look for the presence or absence of a symmetry plane. Not all molecules with chirality centers are chiral overall—meso compounds are an exception.

Solution A look at the structure of *cis*-1,2-dimethylcyclobutane shows that both methyl-bearing ring carbons (C1 and C2) are chirality centers. Overall, though, the compound is achiral because there is a symmetry plane bisecting the ring between C1 and C2. Thus, the molecule is a meso compound.



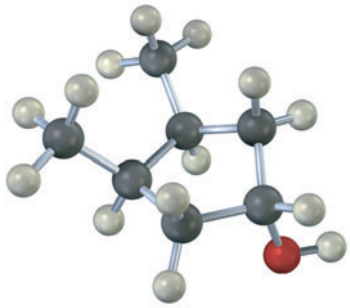
Problem 9.15 Which of the following structures represent meso compounds?



Problem 9.16 Which of the following have a meso form? (Recall that the *-ol* suffix refers to an alcohol, ROH.)

(a) 2,3-Butanediol **(b)** 2,3-Pentanediol **(c)** 2,4-Pentanediol

Problem 9.17 Does the following structure represent a meso compound? If so, indicate the symmetry plane.

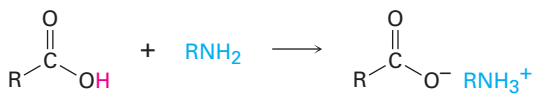


9.8 Racemic Mixtures and the Resolution of Enantiomers

Let's return for a last look at Pasteur's pioneering work. Pasteur took an optically inactive tartaric acid salt and found that he could crystallize from it two optically active forms having what we would now call the 2*R*,3*R* and 2*S*,3*S* configurations. But what was the optically inactive form he started with? It couldn't have been *meso*-tartaric acid, because *meso*-tartaric acid is a different chemical compound and can't interconvert with the two chiral enantiomers without breaking and re-forming chemical bonds.

The answer is that Pasteur started with a 50:50 mixture of the two chiral tartaric acid enantiomers. Such a mixture is called a **racemic** (ray-**see**-mic) **mixture**, or *racemate,* and is denoted either by the symbol (±) or the prefix *d*,*l* to indicate an equal mixture of dextrorotatory and levorotatory forms. Racemic mixtures show no optical rotation because the (+) rotation from one enantiomer exactly cancels the (−) rotation from the other. Through luck, Pasteur was able to separate, or **resolve,** racemic tartaric acid into its (+) and (−) enantiomers. Unfortunately, the fractional crystallization technique he used doesn't work for most racemic mixtures, so other methods are needed.

The most common method of resolution uses an acid–base reaction between a racemic mixture of chiral carboxylic acids (RCO_2H) and an amine base (RNH_2) to yield an ammonium salt.



Carboxylic acid **Amine base** **Ammonium salt**

To understand how this method of resolution works, let's see what happens when a racemic mixture of chiral acids, such as (+)- and (−)-lactic acids, reacts with an achiral amine base, such as methylamine, CH_3NH_2. Stereochemically, the situation is analogous to what happens when left and right hands (chiral) pick up a ball (achiral). Both left and right hands pick up the ball equally well, and the products—ball in right hand versus ball in left hand—are mirror images. In the same way, both (+)- and (−)-lactic acid react with methylamine equally

well, and the product is a racemic mixture of methylammonium (+)-lactate and methylammonium (−)-lactate (Figure 9.12).

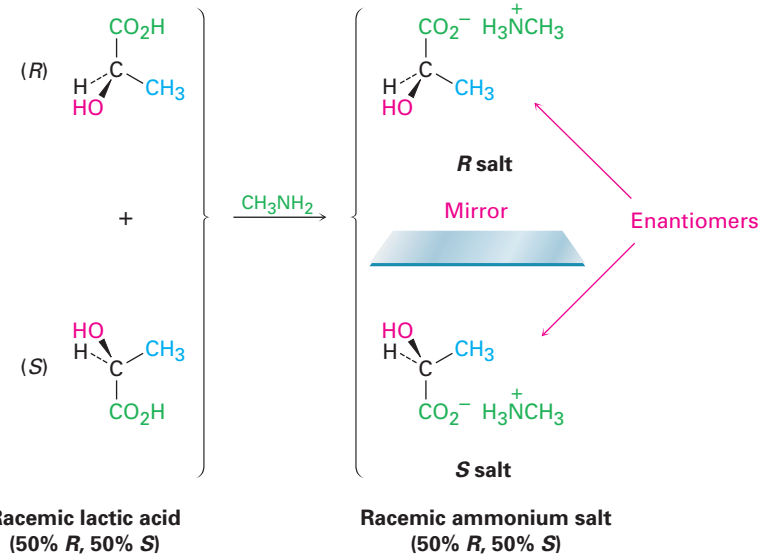


Figure 9.12 Reaction of racemic lactic acid with achiral methylamine leads to a racemic mixture of ammonium salts.

Now let's see what happens when the racemic mixture of (+)- and (−)-lactic acids reacts with a single enantiomer of a chiral amine base, such as (*R*)-1-phenylethylamine. Stereochemically, the situation is analogous to what happens when left and right hands (chiral) put on a right-handed glove (*also chiral*). Left and right hands don't put on the same glove in the same way. The products—right hand in right glove versus left hand in right glove—are not mirror images; they're altogether different.

In the same way, (+)- and (−)-lactic acids react with (*R*)-1-phenylethylamine to give two different products (Figure 9.13). (*R*)-Lactic acid reacts with

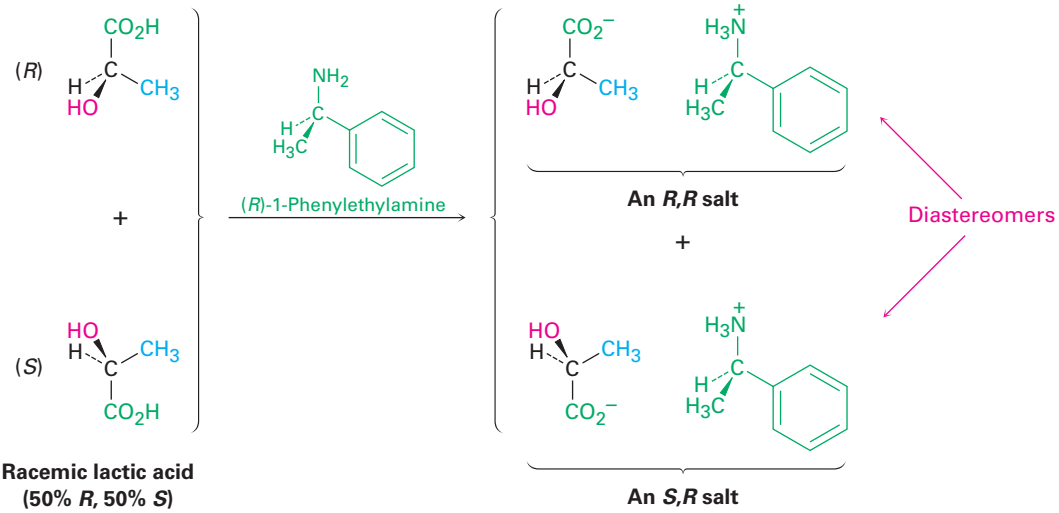
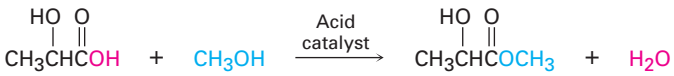


Figure 9.13 Reaction of racemic lactic acid with (*R*)-1-phenylethylamine yields a mixture of diastereomeric ammonium salts.

(*R*)-1-phenylethylamine to give the *R*,*R* salt, and (*S*)-lactic acid reacts with the *R* amine to give the *S*,*R* salt. The two salts are diastereomers; they are different compounds, with different chemical and physical properties. It may therefore be possible to separate them by crystallization or some other means. Once separated, acidification of the two diastereomeric salts with a strong acid then allows us to isolate the two pure enantiomers of lactic acid and to recover the chiral amine for reuse.

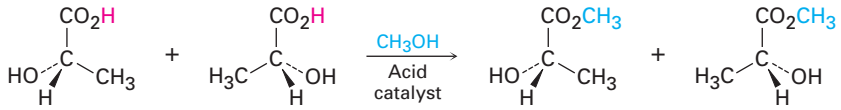
WORKED EXAMPLE 9.6 ***Predicting the Chirality of a Product***

We'll see in Section 21.3 that carboxylic acids (RCO_2H) react with alcohols ($R'OH$) to form esters (RCO_2R'). Suppose that (±)-lactic acid reacts with CH_3OH to form the ester, methyl lactate. What stereochemistry would you expect the product(s) to have? What is the relationship of the products?



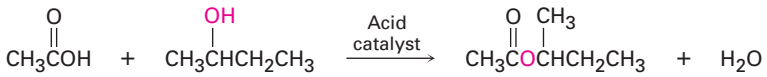
Lactic acid **Methanol** **Methyl lactate**

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



(*S*)-Lactic acid **(*R*)-Lactic acid** **Methyl (*S*)-lactate** **Methyl (*R*)-lactate**

Problem 9.18 Suppose that acetic acid (CH_3CO_2H) reacts with (*S*)-2-butanol to form an ester (see Worked Example 9.6). What stereochemistry would you expect the product(s) to have? What is the relationship of the products?



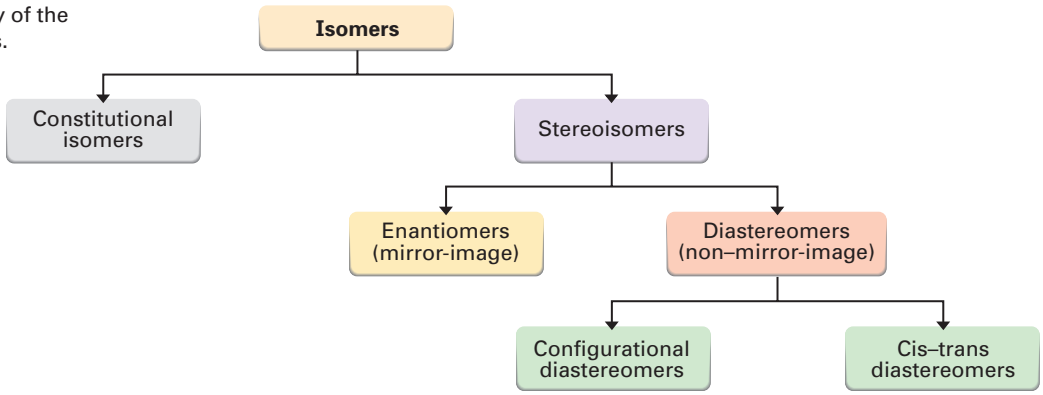
Acetic acid **2-Butanol** ***sec*-Butyl acetate**

Problem 9.19 What stereoisomers would result from reaction of (±)-lactic acid with (*S*)-1-phenylethylamine, and what is the relationship between them?

9.9 A Review of Isomerism

As noted on several previous occasions, isomers are compounds that have the same chemical formula but different structures. We've seen several kinds of isomers in the past few chapters, and it's a good idea at this point to see how they relate to one another (Figure 9.14).

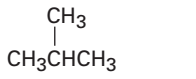
Figure 9.14 A summary of the different kinds of isomers.



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

- **Constitutional isomers** (Section 3.2) are compounds whose atoms are connected differently. Among the kinds of constitutional isomers we've seen are skeletal, functional, and positional isomers.

Different carbon skeletons

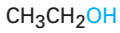


2-Methylpropane

and

Butane

Different functional groups

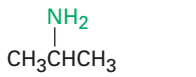


Ethyl alcohol

and

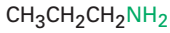
Dimethyl ether

Different position of functional groups



Isopropylamine

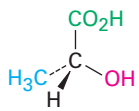
and



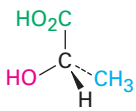
Propylamine

- **Stereoisomers** (Section 4.2) are compounds whose atoms are connected in the same order but with a different geometry. Among the kinds of stereoisomers we've seen are enantiomers, diastereomers, and cis–trans isomers (both in alkenes and in cycloalkanes). Actually, cis–trans isomers are just another kind of diastereomers because they are non–mirror-image stereoisomers.

Enantiomers (nonsuperimposable mirror-image stereoisomers)



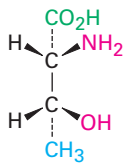
(*R*)-Lactic acid



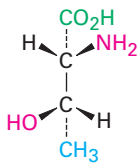
(*S*)-Lactic acid

Diastereomers (nonsuperimposable, non–mirror-image stereoisomers)

Configurational diastereomers

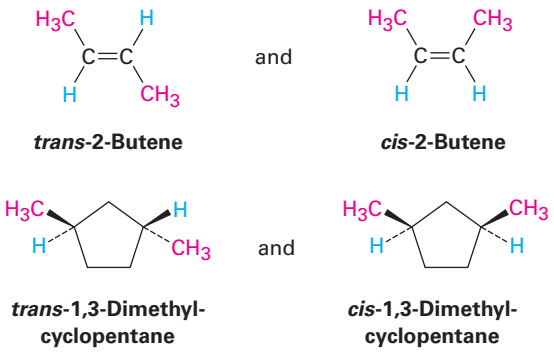


2*R*,3*R*-2-Amino-3-hydroxybutanoic acid



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

Cis–trans diastereomers (substituents on same side or opposite side of double bond or ring)

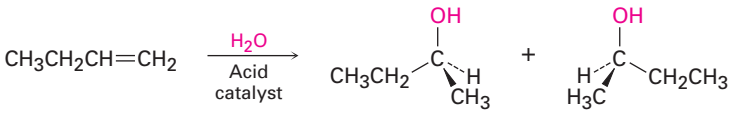


Problem 9.20 What kinds of isomers are the following pairs?
(a) (*S*)-5-Chloro-2-hexene and chlorocyclohexane
(b) (2*R*,3*R*)-Dibromopentane and (2*S*,3*R*)-dibromopentane

9.10 Stereochemistry of Reactions: Addition of H_2O to an Achiral Alkene

ThomsonNOW™ Click *Organic Interactive* to **predict the products and stereochemistry of alkene addition reactions.**

Most of the biochemical reactions that take place in the body, as well as many organic reactions in the laboratory, yield products with chirality centers. For example, acid-catalyzed addition of H_2O to 1-butene in the laboratory yields 2-butanol, a chiral alcohol. What is the stereochemistry of this chiral product? If a single enantiomer is formed, is it *R* or *S*? If a mixture of enantiomers is formed, how much of each? In fact, the 2-butanol produced is a racemic mixture of *R* and *S* enantiomers. Let's see why.



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

To understand why a racemic product results from the reaction of H_2O with 1-butene, think about the reaction mechanism. 1-Butene is first protonated to yield an intermediate secondary (2°) carbocation. Since the trivalent carbon is sp^2-hybridized and planar, the cation has no chirality centers, has a plane of symmetry, and is achiral. As a result, it can react with H_2O equally well from either the top or the bottom. Reaction from the top leads to (*S*)-2-butanol through transition state 1 (TS 1) in Figure 9.15, and reaction from the bottom leads to *R* product through TS 2. *The two transition states are mirror images*. They therefore have identical energies, form at identical rates, and are equally likely to occur.

As a general rule, formation of a new chirality center by reaction between two achiral reactants always leads to a racemic mixture of enantiomeric

products. Put another way, optical activity can't appear from nowhere. An optically active product can only result by starting with an optically active reactant or environment.

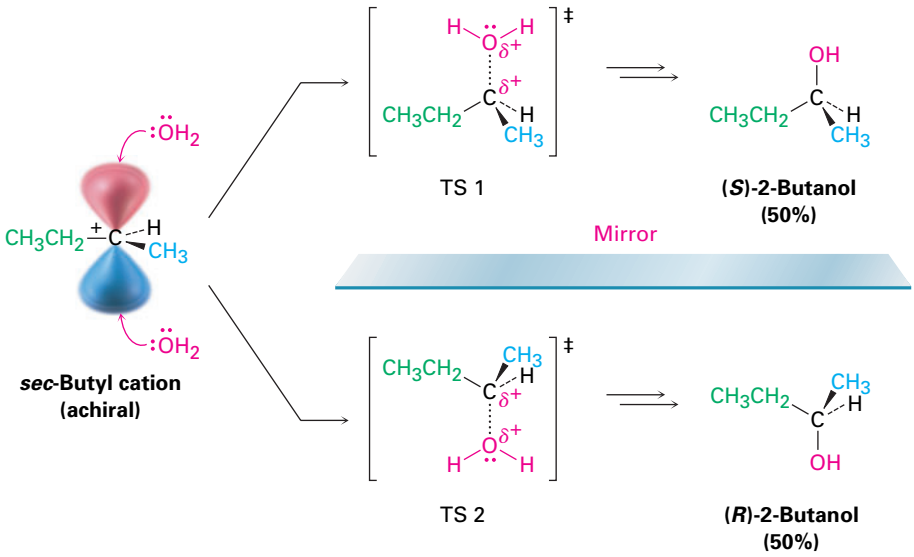
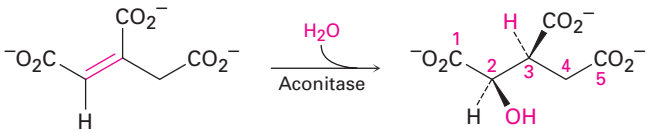


Figure 9.15 Reaction of H_2O with the *sec*-butyl carbocation. Reaction from the top leads to *S* product and is the mirror image of reaction from the bottom, which leads to *R* product. Since both are equally likely, a racemic mixture of products is formed. The dotted C···O bond in the transition state indicates partial bond formation.

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



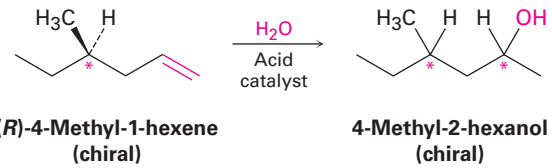
***cis*-Aconitate (achiral)** **(2*R*,3*S*)-Isocitrate**

Even though the *cis*-aconitate substrate is achiral, only the (2*R*,3*S*) enantiomer of the product is formed. We'll look at the reason for this stereospecificity in Section 9.14.

9.11 Stereochemistry of Reactions: Addition of H_2O to a Chiral Alkene

The reaction discussed in the previous section involves addition to an achiral alkene and forms an optically inactive, racemic mixture of the two enantiomeric products. What would happen, though, if we were to carry out the reaction on a *single* enantiomer of a *chiral* reactant? For example, what stereochemical result would be obtained from addition of H_2O to a chiral alkene, such as

(*R*)-4-methyl-1-hexene? The product of the reaction, 4-methyl-2-hexanol, has two chirality centers and so has four possible stereoisomers.



Let's think about the two chirality centers separately. What about the configuration at C4, the methyl-bearing carbon atom? Since C4 has the *R* configuration in the starting material and this chirality center is unaffected by the reaction, its configuration is unchanged. Thus, the configuration at C4 in the product remains *R* (assuming that the relative priorities of the four attached groups are not changed by the reaction).

What about the configuration at C2, the newly formed chirality center? As illustrated in Figure 9.16, the stereochemistry at C2 is established by reaction of H_2O with a carbocation intermediate in the usual manner. But this carbocation does not have a plane of symmetry; it is chiral because of the chirality center at C4. Because the carbocation has no plane of symmetry, it does not react equally well from top and bottom faces. One of the two faces is likely, for steric reasons, to be a bit more accessible than the other face, leading to a mixture of *R* and *S* products in some ratio other than 50:50. Thus, two diastereomeric products, (2*R*,4*R*)-4-methyl-2-hexanol and (2*S*,4*R*)-4-methyl-2-hexanol, are formed in unequal amounts, and the mixture is optically active.

As a general rule, the reaction of a chiral reactant with an achiral reactant leads to unequal amounts of diastereomeric products. If the chiral reactant is optically active because only one enantiomer is used rather than a racemic mixture, then the products are also optically active.

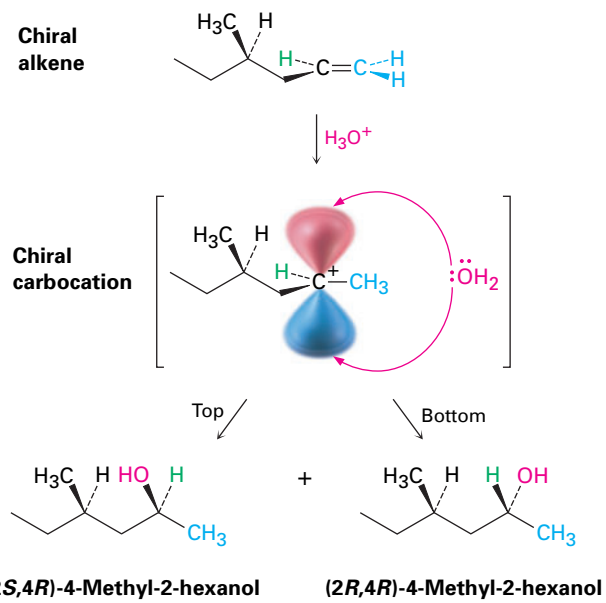


Figure 9.16 Stereochemistry of the addition of H_2O to the chiral alkene, (*R*)-4-methyl-1-hexene. A mixture of diastereomeric 2*R*,4*R* and 2*S*,4*R* products is formed in unequal amounts because reaction of the chiral carbocation intermediate is not equally likely from top and bottom. The product mixture is optically active.

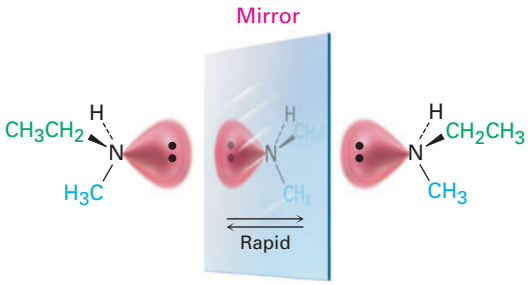
Problem 9.21 What products are formed from acid-catalyzed hydration of racemic (±)-4-methyl-1-hexene? What can you say about the relative amounts of the products? Is the product mixture optically active?

Problem 9.22 What products are formed from hydration of 4-methylcyclopentene? What can you say about the relative amounts of the products?

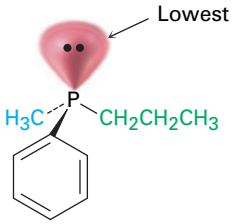
9.12 Chirality at Nitrogen, Phosphorus, and Sulfur

The most common cause of chirality is the presence of four different substituents bonded to a tetrahedral atom, but that atom doesn't necessarily have to be carbon. Nitrogen, phosphorus, and sulfur are all commonly encountered in organic molecules, and all can be chirality centers. We know, for instance, that trivalent nitrogen is tetrahedral, with its lone pair of electrons acting as the fourth "substituent" (Section 1.10). Is trivalent nitrogen chiral? Does a compound such as ethylmethylamine exist as a pair of enantiomers?

The answer is both yes and no. Yes in principle, but no in practice. Trivalent nitrogen compounds undergo a rapid umbrella-like inversion that interconverts enantiomers. We therefore can't isolate individual enantiomers except in special cases.

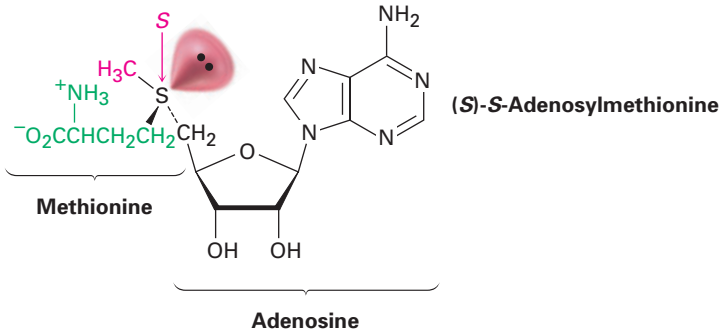


A similar situation occurs in trivalent phosphorus compounds, or *phosphines*. It turns out, though, that inversion at phosphorus is substantially slower than inversion at nitrogen, so stable chiral phosphines *can* be isolated. (*R*)- and (*S*)-methylpropylphenylphosphine, for example, are configurationally stable for several hours at 100 °C. We'll see the importance of phosphine chirality in Section 26.7 in connection with the synthesis of chiral amino acids.



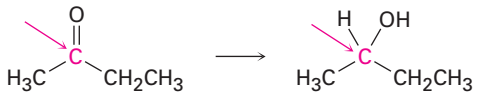
(*R*)-Methylpropylphenylphosphine (configurationally stable)

Divalent sulfur compounds are achiral, but trivalent sulfur compounds called *sulfonium salts* (R_3S^+) can be chiral. Like phosphines, sulfonium salts undergo relatively slow inversion, so chiral sulfonium salts are configurationally stable and can be isolated. The best known example is the coenzyme *S*-adenosylmethionine, the so-called biological methyl donor, which is involved in many metabolic pathways as a source of CH_3 groups. (The "*S*" in the name *S*-adenosylmethionine stands for *sulfur* and means that the adenosyl group is attached to the sulfur atom of methionine.) The molecule has *S* stereochemistry at sulfur and is configurationally stable for several days at room temperature. Its *R* enantiomer is also known but has no biological activity.



9.13 Prochirality

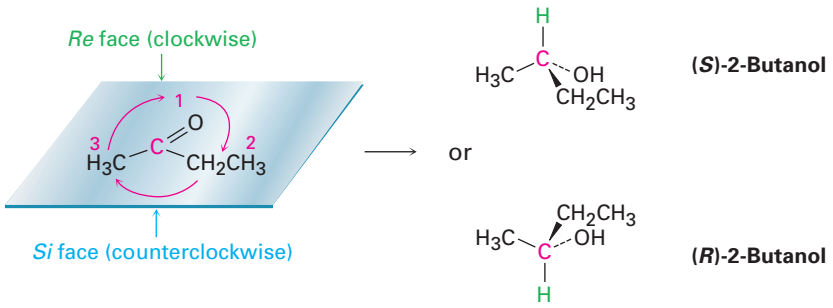
Closely related to the concept of chirality, and particularly important in biological chemistry, is the notion of *prochirality*. A molecule is said to be **prochiral** if can be converted from achiral to chiral in a single chemical step. For instance, an unsymmetrical ketone like 2-butanone is prochiral because it can be converted to the chiral alcohol 2-butanol by addition of hydrogen, as we'll see in Section 17.4.



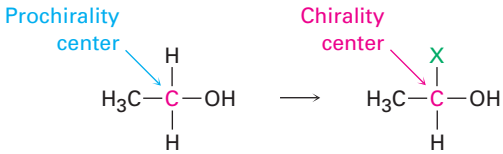
2-Butanone (prochiral) **2-Butanol** (chiral)

Which enantiomer of 2-butanol is produced depends on which face of the planar carbonyl carbon undergoes reaction. To distinguish between the possibilities, we use the stereochemical descriptors *Re* and *Si*. Assign priorities to the three groups attached to the trigonal, sp^2-hybridized carbon, and imagine curved arrows from the highest to second-highest to third-highest priority substituents. The face on which the arrows curve clockwise is designated ***Re*** (similar to *R*), and the face on which the arrows curve counterclockwise is designated ***Si*** (similar to *S*). In this particular example, addition of hydrogen

from the *Re* faces gives (*S*)-2-butanol, and addition from the *Si* face gives (*R*)-2-butanol.

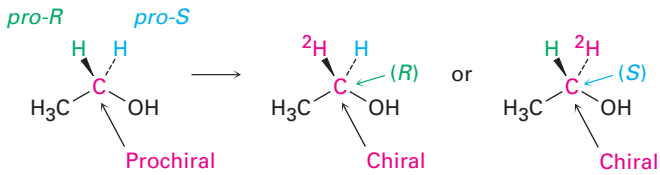


In addition to compounds with planar, sp^2-hybridized carbons, compounds with tetrahedral, sp^3-hybridized atoms can also be prochiral. An sp^3-hybridized atom is said to be a **prochirality center** if, by changing one of its attached groups, it becomes a chirality center. The $-CH_2OH$ carbon atom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



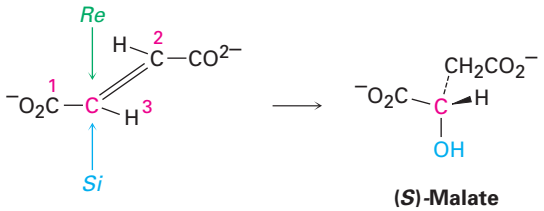
Ethanol

To distinguish between the two identical atoms (or groups of atoms) on a prochirality center, we imagine a change that will raise the priority of one atom over the other without affecting its priority with respect to other attached groups. On the $-CH_2OH$ carbon of ethanol, for instance, we might imagine replacing one of the ^1H atoms (protium) by ^2H (deuterium). The newly introduced ^2H atom is higher in priority than the remaining ^1H atom but remains lower in priority than other groups attached to the carbon. Of the two identical atoms in the original compound, that atom whose replacement leads to an *R* chirality center is said to be ***pro-R*** and that atom whose replacement leads to an *S* chirality center is ***pro-S***.

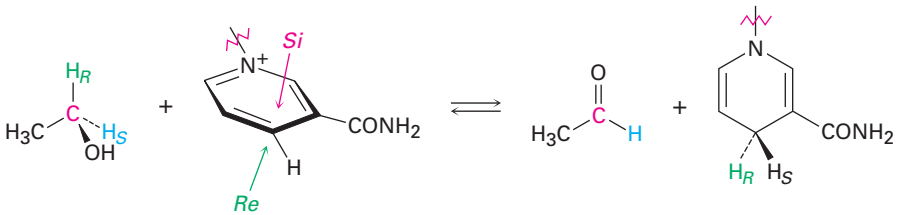


A large number of biological reactions involve prochiral compounds. One of the steps in the citric acid cycle by which food is metabolized, for instance, is

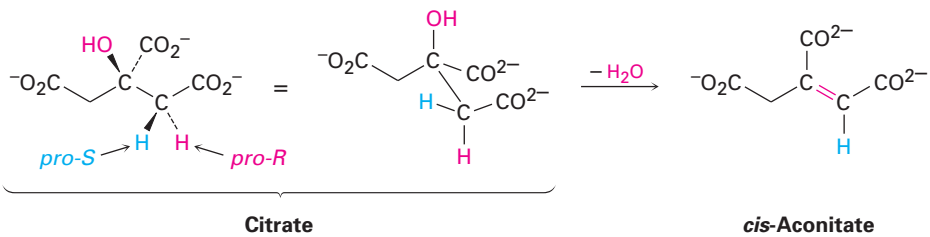
the addition of H_2O to fumarate to give malate. Addition of −OH occurs on the *Si* face of a fumarate carbon and gives (*S*)-malate as product.



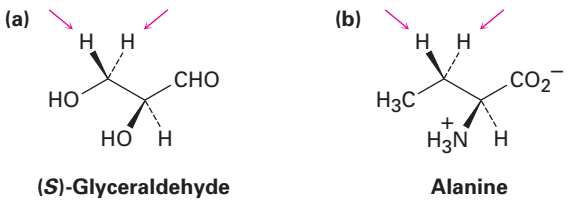
As another example, studies with deuterium-labeled substrates have shown that the reaction of ethanol with the coenzyme NAD^+ catalyzed by yeast alcohol dehydrogenase occurs with exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of NAD^+.



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

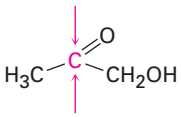


Problem 9.23 Identify the indicated hydrogens in the following molecules as *pro-R* or *pro-S*:



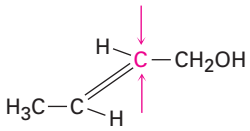
Problem 9.24 Identify the indicated faces of carbon atoms in the following molecules as *Re* or *Si*:

(a)



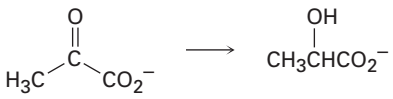
Hydroxyacetone

(b)



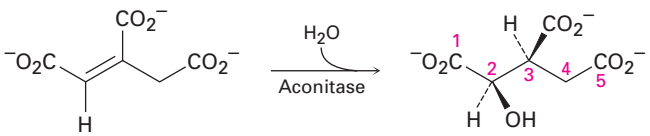
Crotyl alcohol

Problem 9.25 Lactic acid buildup in tired muscles results from reduction of pyruvate. If the reaction occurs from the *Re* face, what is the stereochemistry of the product?



Pyruvate **Lactate**

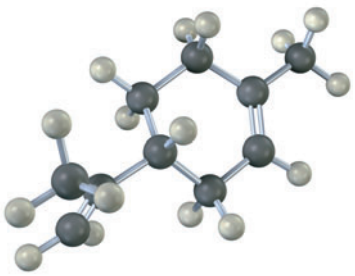
Problem 9.26 The aconitase-catalyzed addition of water to *cis*-aconitate in the citric acid cycle occurs with the following stereochemistry. Does the addition of the OH group occur on the *Re* or the *Si* face of the substrate? What about the addition of the H? Does the reaction have syn or anti stereochemistry?

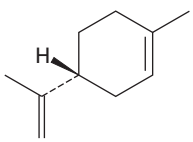


***cis*-Aconitate** **(2*R*,3*S*)-Isocitrate**

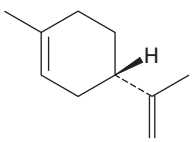
9.14 Chirality in Nature and Chiral Environments

Although the different enantiomers of a chiral molecule have the same physical properties, they usually have different biological properties. For example, the (+) enantiomer of limonene has the odor of oranges, but the (−) enantiomer has the odor of pine trees.

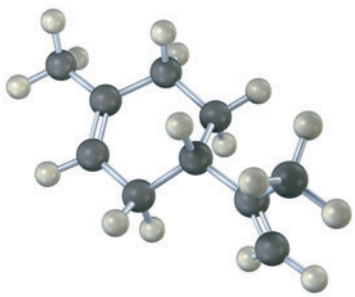




(+)-Limonene (in citrus fruits)

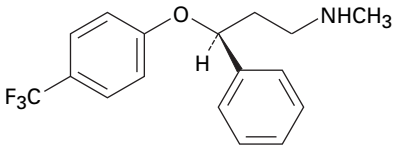


(−)-Limonene (in pine trees)

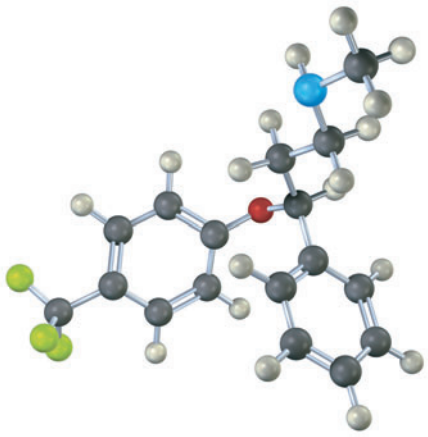


More dramatic examples of how a change in chirality can affect the biological properties of a molecule are found in many drugs, such as fluoxetine, a heavily prescribed medication sold under the trade name Prozac. Racemic fluoxetine is an extraordinarily effective antidepressant but has no activity against

migraine. The pure *S* enantiomer, however, works remarkably well in preventing migraine. The *Focus On* "Chiral Drugs" at the end of this chapter gives other examples.



(*S*)-Fluoxetine
(prevents migraine)



Why do different enantiomers have different biological properties? To have a biological effect, a substance typically must fit into an appropriate receptor that has an exactly complementary shape. But because biological receptors are chiral, only one enantiomer of a chiral substrate can fit in, just as only a right hand will fit into right-handed glove. The mirror-image enantiomer will be a misfit, like a left hand in a right-handed glove. A representation of the interaction between a chiral molecule and a chiral biological receptor is shown in Figure 9.17: one enantiomer fits the receptor perfectly, but the other does not.

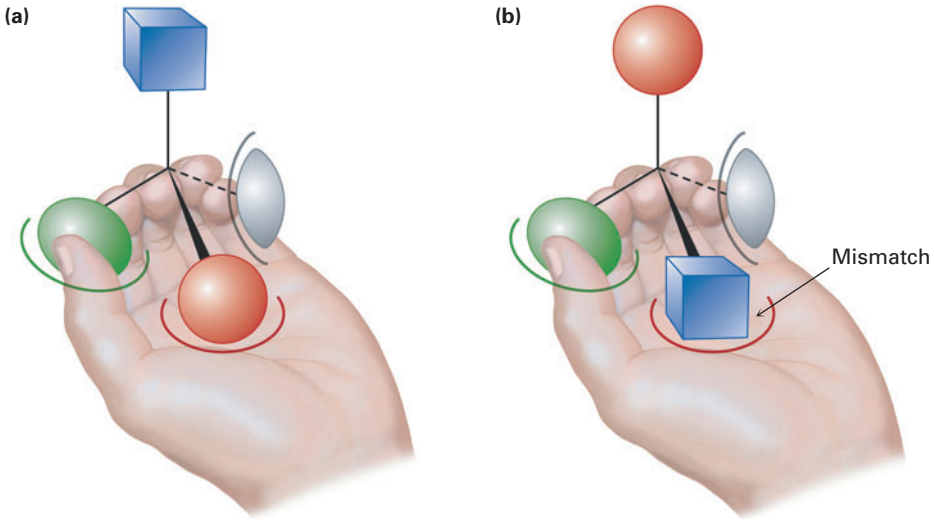


Figure 9.17 Imagine that a left hand interacts with a chiral object, much as a biological receptor interacts with a chiral molecule. **(a)** One enantiomer fits into the hand perfectly: green thumb, red palm, and gray pinkie finger, with the blue substituent exposed. **(b)** The other enantiomer, however, can't fit into the hand. When the green thumb and gray pinkie finger interact appropriately, the palm holds a blue substituent rather than a red one, with the red substituent exposed.

The hand-in-glove fit of a chiral substrate into a chiral receptor is relatively straightforward, but it's less obvious how a prochiral substrate can undergo a selective reaction. Take the reaction of ethanol with NAD^+ catalyzed by yeast alcohol dehydrogenase. As we saw at the end of Section 9.13, the reaction occurs with exclusive removal of the *pro-R* hydrogen from ethanol and with addition only to the *Re* face of the NAD^+ carbon.

We can understand this result by imagining that the chiral enzyme receptor again has three binding sites, as was previously the case in Figure 9.17. When green and gray substituents of a prochiral substrate are held appropriately, however, only one of the two red substituents—say, the *pro-S* one— is also held while the other, *pro-R*, substituent is exposed for reaction.

We describe the situation by saying that the receptor provides a **chiral environment** for the substrate. In the absence of a chiral environment, the two red substituents are chemically identical, but in the presence of the chiral environment, they are chemically distinctive (Figure 9.18a). The situation is similar to what happens when you pick up a coffee mug. By itself, the mug has a plane of symmetry and is achiral. You could, if you wanted, drink from on either side of the handle. When you pick up the mug, however, your hand provides a chiral environment so one side becomes much more accessible and easier to drink from than the other (Figure 9.18b).

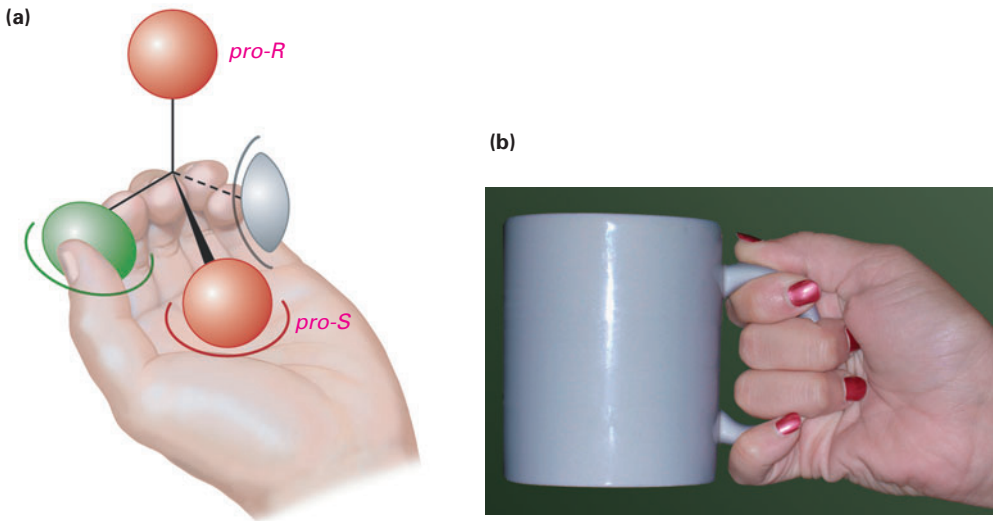


Figure 9.18 **(a)** When a prochiral molecule is held in a chiral environment, the two seemingly identical substituents (red) are distinguishable. **(b)** Similarly, when an achiral coffee mug is held in the chiral environment of your hand, it's much easier to drink from one side than the other because the two sides of the mug are now distinguishable.

Focus On . . .

Chiral Drugs

The hundreds of different pharmaceutical agents approved for use by the U.S. Food and Drug Administration come from many sources (see the Chapter 5 *Focus On*). Many drugs are isolated directly from plants or bacteria, and others are made by chemical modification of naturally occurring compounds, but an

(continued)

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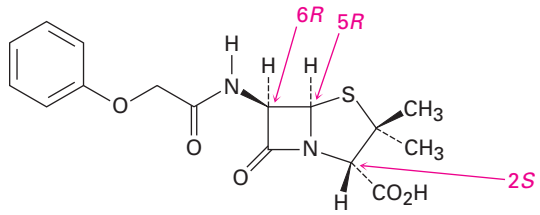
The *S* enantiomer of ibuprofen soothes the aches and pains of athletic injuries much more effectively than the *R* enantiomer.

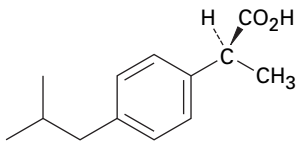
estimated 33% are made entirely in the laboratory and have no relatives in nature.

Those drugs that come from natural sources, either directly or after chemical modification, are usually chiral and are generally found only as a single enantiomer rather than as a racemic mixture. Penicillin V, for example, an antibiotic isolated from the *Penicillium* mold, has the 2*S*,5*R*,6*R* configuration. Its enantiomer, which does not occur naturally but can be made in the laboratory, has no antibiotic activity.

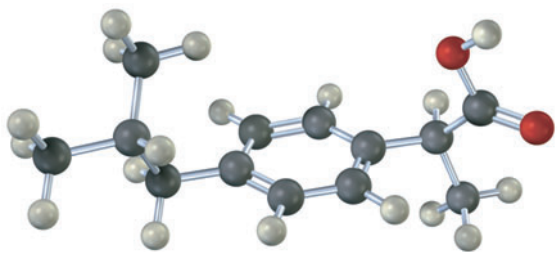


Penicillin V (2*S*,5*R*,6*R* configuration)

In contrast to drugs from natural sources, those drugs that are made entirely in the laboratory are either achiral or, if chiral, are often produced and sold as racemic mixtures. Ibuprofen, for example, has one chirality center and is sold commercially under such trade names as Advil, Nuprin, and Motrin as a racemic mixture of *R* and *S*. It turns out, however, that only the *S* enantiomer is active as an analgesic and anti-inflammatory agent. The *R* enantiomer of ibuprofen is inactive, although it is slowly converted in the body to the active *S* form.



(*S*)-Ibuprofen
(an active analgesic agent)



Not only is it chemically wasteful to synthesize and administer an enantiomer that doesn't serve the intended purpose, many examples are now known where the presence of the "wrong" enantiomer in a racemic mixture

(continued)

either affects the body's ability to utilize the "right" enantiomer or has unintended pharmacological effects of its own. The presence of (*R*)-ibuprofen in the racemic mixture, for instance, slows substantially the rate at which the *S* enantiomer takes effect in the body, from 12 minutes to 38 minutes.

To get around this problem, pharmaceutical companies attempt to devise methods of *enantioselective synthesis,* which allow them to prepare only a single enantiomer rather than a racemic mixture. Viable methods have already been developed for the preparation of (*S*)-ibuprofen, which is now being marketed in Europe. We'll look further into enantioselective synthesis in the Chapter 19 *Focus On.*

SUMMARY AND KEY WORDS

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

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

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

Meso compounds contain chirality centers but are achiral overall because they have a plane of symmetry. **Racemic mixtures**, or *racemates,* are 50:50 mixtures of (+) and (−) enantiomers. Racemic mixtures and individual diastereomers differ in their physical properties, such as solubility, melting point, and boiling point.

Many reactions give chiral products. If the reactants are optically inactive, the products are also optically inactive. If one or both of the reactants is optically active, the product can also be optically active.

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

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

■ indicates problems assignable in Organic OWL.

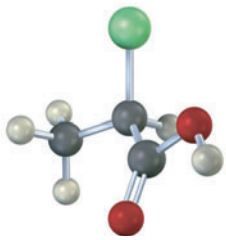
▲ denotes problems linked to Key Ideas of this chapter and testable in ThomsonNOW.

VISUALIZING CHEMISTRY

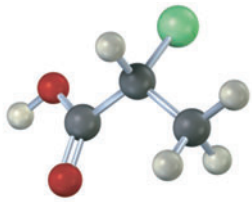
(Problems 9.1–9.26 appear within the chapter.)

9.27 Which of the following structures are identical? (Yellow-green = Cl.)

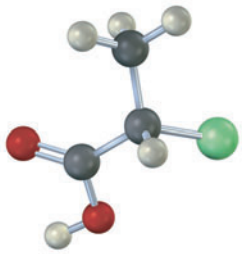
(a)



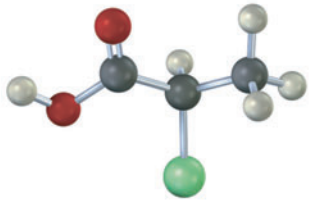
(b)



(c)

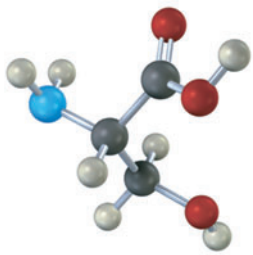


(d)



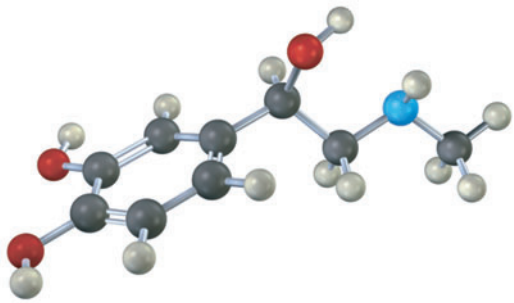
9.28 ■ ▲ Assign *R* or *S* configuration to the chirality centers in the following molecules (blue = N):

(a)



Serine

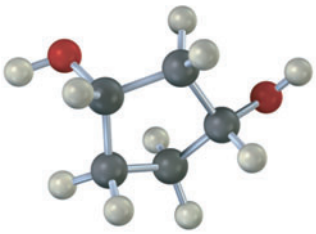
(b)



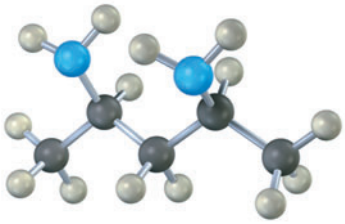
Adrenaline

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

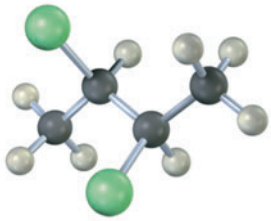
(a)



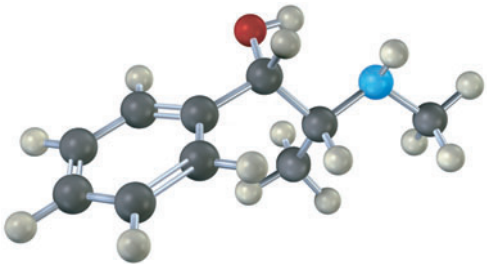
(b)



(c)



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



ADDITIONAL PROBLEMS

9.31 ■ ▲ Which of the following compounds are chiral? Draw them, and label the chirality centers.

(a) 2,4-Dimethylheptane **(b)** 5-Ethyl-3,3-dimethylheptane
(c) *cis*-1,4-Dichlorocyclohexane **(d)** 4,5-Dimethyl-2,6-octadiyne

9.32 ▲ Draw chiral molecules that meet the following descriptions:

(a) A chloroalkane, $C_5H_{11}Cl$ **(b)** An alcohol, $C_6H_{14}O$
(c) An alkene, C_6H_{12} **(d)** An alkane, C_8H_{18}

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

9.34 Draw the nine chiral molecules that have the formula $C_6H_{13}Br$.

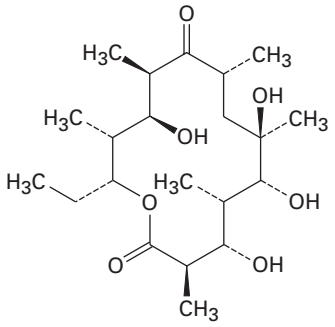
9.35 ■ Draw compounds that fit the following descriptions:

(a) A chiral alcohol with four carbons
(b) A chiral carboxylic acid with the formula $C_5H_{10}O_2$
(c) A compound with two chirality centers
(d) A chiral aldehyde with the formula C_3H_5BrO

9.36 Which of the following objects are chiral?

(a) A basketball **(b)** A fork **(c)** A wine glass
(d) A golf club **(e)** A monkey wrench **(f)** A snowflake

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



Erythronolide B

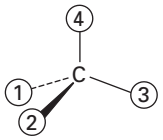
9.38 Draw examples of the following:
(a) A meso compound with the formula C_8H_{18}
(b) A meso compound with the formula C_9H_{20}
(c) A compound with two chirality centers, one *R* and the other *S*

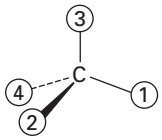
9.39 What is the relationship between the specific rotations of (2*R*,3*R*)-dichloropentane and (2*S*,3*S*)-dichloropentane? Between (2*R*,3*S*)-dichloropentane and (2*R*,3*R*)-dichloropentane?

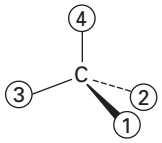
9.40 What is the stereochemical configuration of the enantiomer of (2*S*,4*R*)-2,4-octanediol?

9.41 What are the stereochemical configurations of the two diastereomers of (2*S*,4*R*)-2,4-octanediol?

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

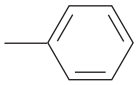
(a) 

(b) 

(c) 

9.43 ■ Assign Cahn–Ingold–Prelog priorities to the following sets of substituents:

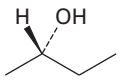
(a) —CH=CH_2, —$CH(CH_3)_2$, —$C(CH_3)_3$, —CH_2CH_3

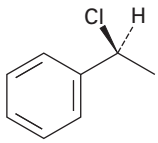
(b) —C≡CH, —CH=CH_2, —$C(CH_3)_3$, 

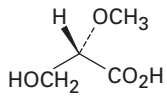
(c) —CO_2CH_3, —$COCH_3$, —CH_2OCH_3, —CH_2CH_3

(d) —C≡N, —CH_2Br, —CH_2CH_2Br, —Br

9.44 ■ Assign *R* or *S* configurations to the chirality centers in the following molecules:

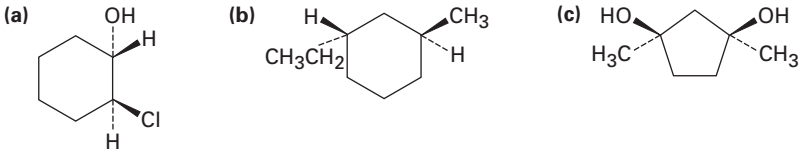
(a) 

(b) 

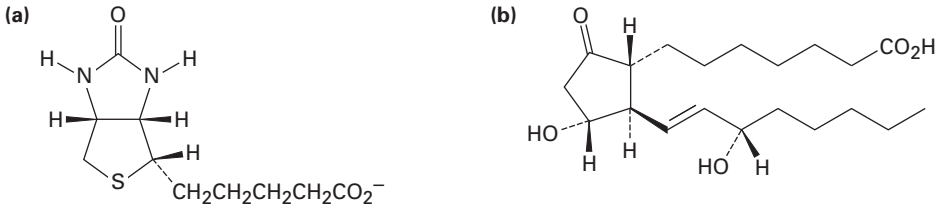
(c) 

■ Assignable in OWL ▲ Key Idea Problems

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



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

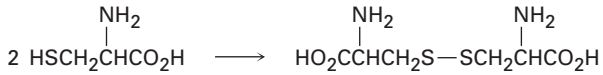


Biotin **Prostaglandin E_1**

9.47 ■ Draw tetrahedral representations of the following molecules:
(a) (*S*)-2-Chlorobutane **(b)** (*R*)-3-Chloro-1-pentene

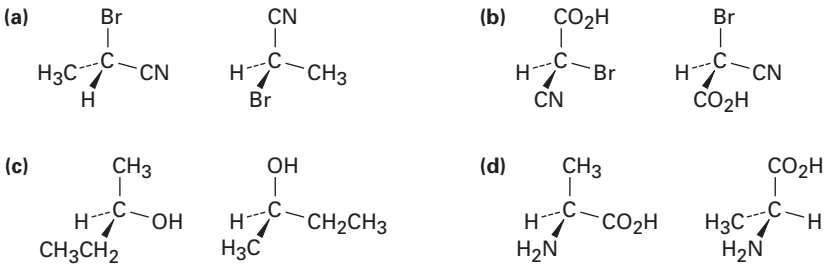
9.48 Draw tetrahedral representations of the two enantiomers of the amino acid cysteine, $HSCH_2CH(NH_2)CO_2H$, and identify each as *R* or *S*.

9.49 The naturally occurring form of the amino acid cysteine (Problem 9.48) has the *S* configuration at its chirality center. On treatment with a mild oxidizing agent, two cysteines join to give cystine, a disulfide. Assuming that the chirality center is not affected by the reaction, is cystine optically active?



Cysteine **Cystine**

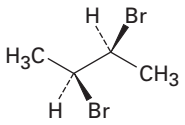
9.50 ■ Which of the following pairs of structures represent the same enantiomer, and which represent different enantiomers?



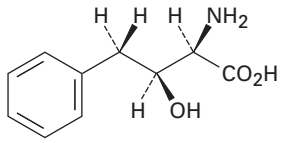
■ Assignable in OWL ▲ Key Idea Problems

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

(a)



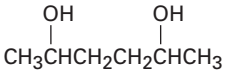
(b)



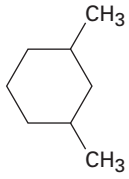
9.52 ■ Draw tetrahedral representations of the following molecules:
(a) The 2*S*,3*R* enantiomer of 2,3-dibromopentane
(b) The meso form of 3,5-heptanediol

9.53 Draw the meso form of each of the following molecules, and indicate the plane of symmetry in each:

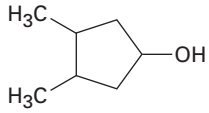
(a)



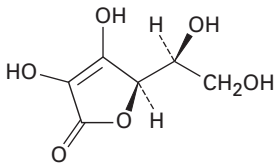
(b)



(c)



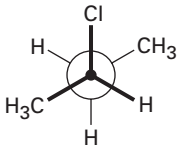
9.54 Assign *R* or *S* configurations to the chirality centers in ascorbic acid (vitamin C).



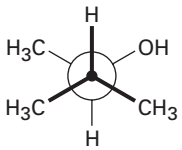
Ascorbic acid

9.55 Assign *R* or *S* stereochemistry to the chirality centers in the following Newman projections:

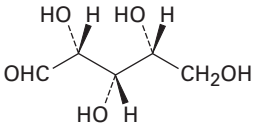
(a)



(b)

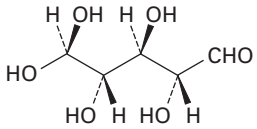


9.56 Xylose is a common sugar found in many types of wood, including maple and cherry. Because it is much less prone to cause tooth decay than sucrose, xylose has been used in candy and chewing gum. Assign *R* or *S* configurations to the chirality centers in xylose.



(+)-Xylose

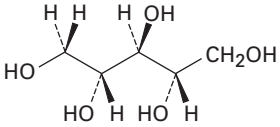
9.57 Ribose, an essential part of ribonucleic acid (RNA), has the following structure:



Ribose

(a) How many chirality centers does ribose have? Identify them.
(b) How many stereoisomers of ribose are there?
(c) Draw the structure of the enantiomer of ribose.
(d) Draw the structure of a diastereomer of ribose.

9.58 On catalytic hydrogenation over a platinum catalyst, ribose (Problem 9.57) is converted into ribitol. Is ribitol optically active or inactive? Explain.

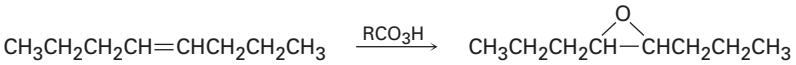


Ribitol

9.59 ■ Hydroxylation of *cis*-2-butene with OsO_4 yields 2,3-butanediol. What stereochemistry do you expect for the product? (Review Section 7.8.)

9.60 Hydroxylation of *trans*-2-butene with OsO_4 also yields 2,3-butanediol. What stereochemistry do you expect for the product?

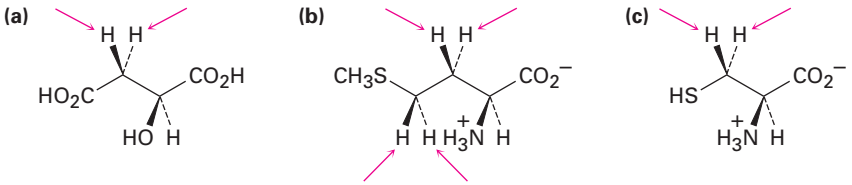
9.61 *cis*-4-Octene reacts with a peroxyacid to yield 4,5-epoxyoctane. Is the product chiral? How many chirality centers does it have? How would you describe it stereochemically? (Review Section 7.8.)



4-Octene **4,5-Epoxyoctane**

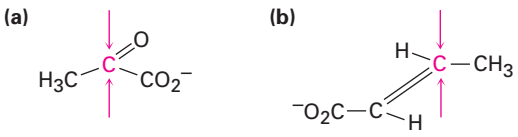
9.62 Answer Problem 9.61 for the epoxidation of *trans*-4-octene.

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



Malic acid **Methionine** **Cysteine**

9.64 ■ Identify the indicated faces in the following molecules as *Re* or *Si*:



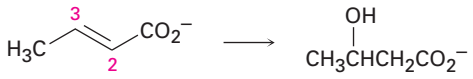
Pyruvate **Crotonate**

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

9.66 Compound A, C_7H_{12}, was found to be optically active. On catalytic reduction over a palladium catalyst, 2 equivalents of hydrogen were absorbed, yielding compound B, C_7H_{16}. On ozonolysis of A, two fragments were obtained. One fragment was identified as acetic acid. The other fragment, compound C, was an optically active carboxylic acid, $C_5H_{10}O_2$. Write the reactions, and draw structures for A, B, and C.

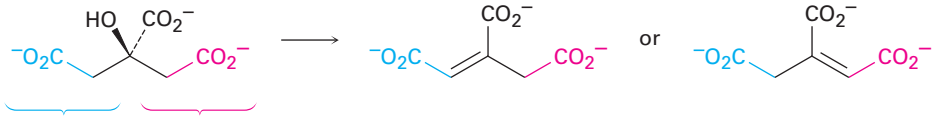
9.67 Compound A, $C_{11}H_{16}O$, was found to be an optically active alcohol. Despite its apparent unsaturation, no hydrogen was absorbed on catalytic reduction over a palladium catalyst. On treatment of A with dilute sulfuric acid, dehydration occurred and an optically inactive alkene B, $C_{11}H_{14}$, was produced as the major product. Alkene B, on ozonolysis, gave two products. One product was identified as propanal, CH_3CH_2CHO. Compound C, the other product, was shown to be a ketone, C_8H_8O. How many degrees of unsaturation does A have? Write the reactions, and identify A, B, and C.

9.68 One of the steps in fat metabolism is the hydration of crotonate to yield 3-hydroxybutyrate. The reaction occurs by addition of −OH to the *Si* face at C3, followed by protonation at C2, also from the *Si* face. Draw the product of the reaction, showing the stereochemistry of each step.



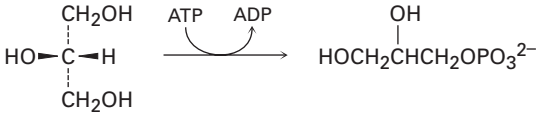
Crotonate **3-Hydroxybutyrate**

9.69 The dehydration of citrate to yield *cis*-aconitate, a step in the citric acid cycle, involves the *pro-R* "arm" of citrate rather than the *pro-S* arm. Which of the following two products is formed?



Citrate ***cis*-Aconitate**

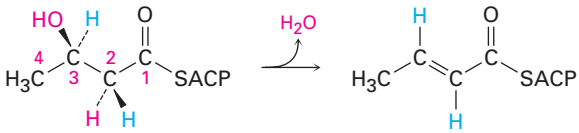
9.70 The first step in the metabolism of glycerol formed by digestion of fats is phosphorylation of the *pro-R* $-CH_2OH$ group by reaction with ATP to give the corresponding glycerol phosphate. Show the stereochemistry of the product.



Glycerol **Glycerol phosphate**

■ Assignable in OWL ▲ Key Idea Problems

9.71 One of the steps in fatty-acid biosynthesis is the dehydration of (*R*)-3-hydroxybutyryl ACP to give *trans*-crotonyl ACP. Does the reaction remove the *pro-R* or the *pro-S* hydrogen from C2?



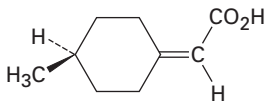
(*R*)-3-Hydroxybutyryl ACP **trans-Crotonyl ACP**

9.72 *Allenes* are compounds with adjacent carbon–carbon double bonds. Many allenes are chiral, even though they don't contain chirality centers. Mycomycin, for example, a naturally occurring antibiotic isolated from the bacterium *Nocardia acidophilus,* is chiral and has $[\alpha]_D = -130$. Explain why mycomycin is chiral. Making a molecular model should be helpful.

$$HC{\equiv}C{-}C{\equiv}C{-}CH{=}C{=}CH{-}CH{=}CH{-}CH{=}CH{-}CH_2CO_2H$$

Mycomycin

9.73 Long before chiral allenes were known (Problem 9.72), the resolution of 4-methylcyclohexylideneacetic acid into two enantiomers had been carried out. Why is it chiral? What geometric similarity does it have to allenes?



4-Methylcyclohexylideneacetic acid

9.74 (*S*)-1-Chloro-2-methylbutane undergoes light-induced reaction with Cl_2 by a radical mechanism to yield a mixture of products, among which are 1,4-dichloro-2-methylbutane and 1,2-dichloro-2-methylbutane.
(a) Write the reaction, showing the correct stereochemistry of the reactant.
(b) One of the two products is optically active, but the other is optically inactive. Which is which?
(c) What can you conclude about the stereochemistry of radical chlorination reactions?

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

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

9.77 Draw both *cis*- and *trans*-1,4-dimethylcyclohexane in their most stable chair conformations.
(a) How many stereoisomers are there of *cis*-1,4-dimethylcyclohexane, and how many of *trans*-1,4-dimethylcyclohexane?
(b) Are any of the structures chiral?
(c) What are the stereochemical relationships among the various stereoisomers of 1,4-dimethylcyclohexane?

■ Assignable in OWL ▲ Key Idea Problems

9.78 Draw both *cis*- and *trans*-1,3-dimethylcyclohexane in their most stable chair conformations.

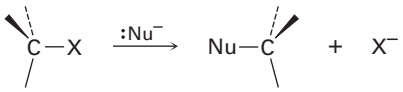
(a) How many stereoisomers are there of *cis*-1,3-dimethylcyclohexane, and how many of *trans*-1,3-dimethylcyclohexane?

(b) Are any of the structures chiral?

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

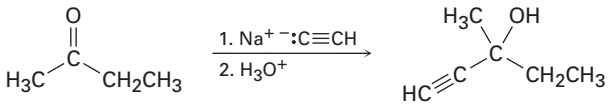
9.79 *cis*-1,2-Dimethylcyclohexane is optically inactive even though it has two chirality centers. Explain.

9.80 We'll see in the next chapter that alkyl halides react with nucleophiles to give substitution products by a mechanism that involves *inversion* of stereochemistry at carbon:



Draw the reaction of (*S*)-2-bromobutane with HS^- ion to yield 2-butanethiol, $CH_3CH_2CH(SH)CH_3$. What is the stereochemistry of the product?

9.81 ■ Ketones react with acetylide ion (Section 8.7) to give alcohols. For example, the reaction of sodium acetylide with 2-butanone yields 3-methyl-1-pentyn-3-ol:

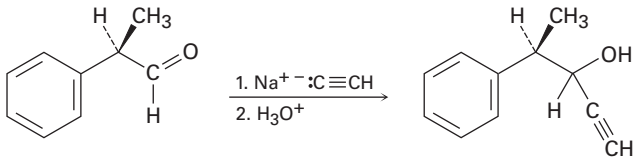


2-Butanone **3-Methyl-1-pentyne-3-ol**

(a) Is the product chiral? Is it optically active?

(b) How many stereoisomers of the product are formed, what are their stereochemical relationships, and what are their relative amounts?

9.82 Imagine that another reaction similar to that in Problem 9.81 is carried out between sodium acetylide and (*R*)-2-phenylpropanal to yield 1-phenyl-3-butyn-2-ol:



(*R*)-2-Phenylpropanal **1-Phenyl-3-butyn-2-ol**

(a) Is the product chiral? Is it optically active?

(b) How many stereoisomers of 1-phenyl-3-butyn-2-ol are formed, what are their stereochemical relationships, and what are their relative amounts?

10 Organohalides

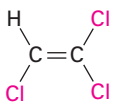
Organic KNOWLEDGE TOOLS

ThomsonNOW™ Throughout this chapter, sign in at **www.thomsonedu.com** for online self-study and interactive tutorials based on your level of understanding.

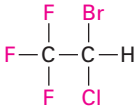
Online homework for this chapter may be assigned in Organic OWL.

Now that we've covered the chemistry of hydrocarbons, it's time to start looking at more complex substances that contain elements in addition to C and H. We'll begin by discussing the chemistry of **organohalides**, compounds that contain one or more halogen atoms.

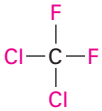
Halogen-substituted organic compounds are widespread throughout nature, and approximately 5000 organohalides have been found in algae and various other marine organisms. Chloromethane, for example, is released in large amounts by oceanic kelp, as well as by forest fires and volcanoes. Halogen-containing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



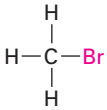
Trichloroethylene (a solvent)



Halothane (an inhaled anesthetic)

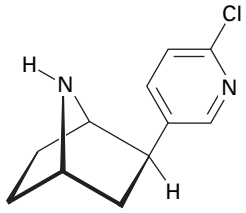


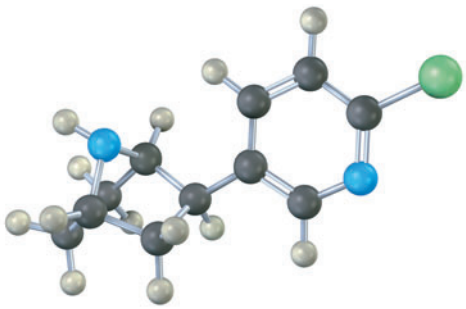
Dichlorodifluoromethane (a refrigerant)



Bromomethane (a fumigant)

Still other halo-substituted compounds are providing important leads to new medicines. The compound epibatidine, for instance, has been isolated from the skin of Ecuadorian frogs and found to be more than 200 times as potent as morphine at blocking pain in animals.





Epibatidine (from the Ecuadorian frog *Epipedobates tricolor*)

Sean Duggan

A large variety of organohalides are known. The halogen might be bonded to an alkynyl group (C≡C−X), a vinylic group (C=C−X), an aromatic ring (Ar−X), or an alkyl group. We'll be concerned in this chapter, however, primarily with **alkyl halides**, compounds with a halogen atom bonded to a saturated, sp^3-hybridized carbon atom.

WHY THIS CHAPTER?

Alkyl halides are encountered less frequently than their oxygen-containing relatives alcohols and ethers, but some of the *kinds* of reactions they undergo—nucleophilic substitutions and eliminations—*are* encountered frequently. Thus, alkyl halide chemistry acts as a relatively simple model for many mechanistically similar but structurally more complex reactions found in biomolecules. We'll begin in this chapter with a look at how to name and prepare alkyl halides, and we'll see several of their reactions. Then in the following chapter, we'll make a detailed study of the substitution and elimination reactions of alkyl halides—two of the most important and well-studied reaction types in organic chemistry.

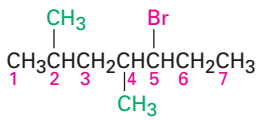
10.1 Naming Alkyl Halides

ThomsonNOW™ Click *Organic Interactive* to **practice assigning IUPAC names to organic halides.**

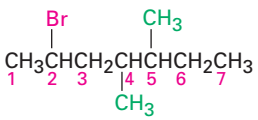
Although members of the class are commonly called *alkyl halides,* they are named systematically as *haloalkanes* (Section 3.4), treating the halogen as a substituent on a parent alkane chain. There are three steps:

Step 1 **Find the longest chain, and name it as the parent.** If a double or triple bond is present, the parent chain must contain it.

Step 2 **Number the carbons of the parent chain beginning at the end nearer the first substituent, whether alkyl or halo.** Assign each substituent a number according to its position on the chain.

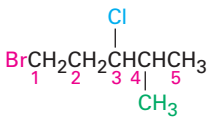


5-Bromo-2,4-dimethylheptane



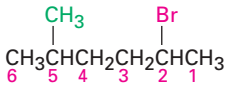
2-Bromo-4,5-dimethylheptane

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



1-Bromo-3-chloro-4-methylpentane

Step 3 **If the parent chain can be properly numbered from either end by step 2, begin at the end nearer the substituent that has alphabetical precedence.**

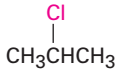


2-Bromo-5-methylhexane
(*NOT* 5-bromo-2-methylhexane)

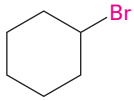
ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to draw structures for alkyl halides, based on their IUPAC names.**

In addition to their systematic names, many simple alkyl halides are also named by identifying first the alkyl group and then the halogen. For example, CH_3I can be called either iodomethane or methyl iodide. Such names are well entrenched in the chemical literature and in daily usage, but they won't be used in this book.

Iodomethane
(or methyl iodide)



2-Chloropropane
(or isopropyl chloride)

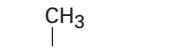


Bromocyclohexane
(or cyclohexyl bromide)

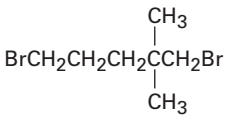
Problem 10.1 Give IUPAC names for the following alkyl halides:

(a) $CH_3CH_2CH_2CH_2I$

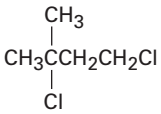
(b)



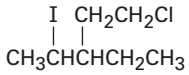
(c)



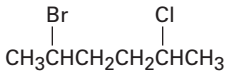
(d)



(e)



(d)



Problem 10.2 Draw structures corresponding to the following IUPAC names:

(a) 2-Chloro-3,3-dimethylhexane
(b) 3,3-Dichloro-2-methylhexane
(c) 3-Bromo-3-ethylpentane
(d) 1,1-Dibromo-4-isopropylcyclohexane
(e) 4-*sec*-Butyl-2-chlorononane
(f) 1,1-Dibromo-4-*tert*-butylcyclohexane

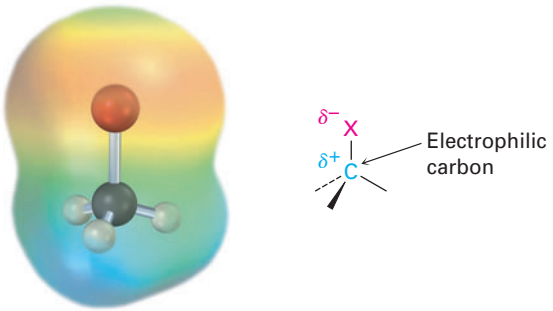
10.2 Structure of Alkyl Halides

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

Table 10.1 A Comparison of the Halomethanes

Halomethane	Bond length (pm)	Bond strength (kJ/mol)	Bond strength (kcal/mol)	Dipole moment (*D*)
CH_3F	139	452	108	1.85
CH_3Cl	178	351	84	1.87
CH_3Br	193	293	70	1.81
CH_3I	214	234	56	1.62

In an earlier discussion of bond polarity in functional groups (Section 5.4), we noted that halogens are more electronegative than carbon. The C−X bond is therefore polar, with the carbon atom bearing a slight positive charge ($\delta+$) and the halogen a slight negative charge ($\delta-$). This polarity results in a substantial dipole moment for all the halomethanes (Table 10.1) and implies that the alkyl halide C−X carbon atom should behave as an electrophile in polar reactions. We'll see in the next chapter that much of the chemistry of alkyl halides is indeed dominated by their electrophilic behavior.



10.3 Preparing Alkyl Halides from Alkanes: Radical Halogenation

Structurally simple alkyl halides can sometimes be prepared by reaction of an alkane with Cl_2 or Br_2 through a radical chain-reaction pathway (Section 5.3). Although inert to most reagents, alkanes react readily with Cl_2 or Br_2 in the presence of light to give alkyl halide substitution products. The reaction occurs by the radical mechanism shown in Figure 10.1 for chlorination.

Recall from Section 5.3 that radical substitution reactions require three kinds of steps: *initiation, propagation,* and *termination*. Once an initiation step has started the process by producing radicals, the reaction continues in a self-sustaining cycle. The cycle requires two repeating propagation steps in which a radical, the halogen, and the alkane yield alkyl halide product plus more radical to carry on the chain. The chain is occasionally terminated by the combination of two radicals.

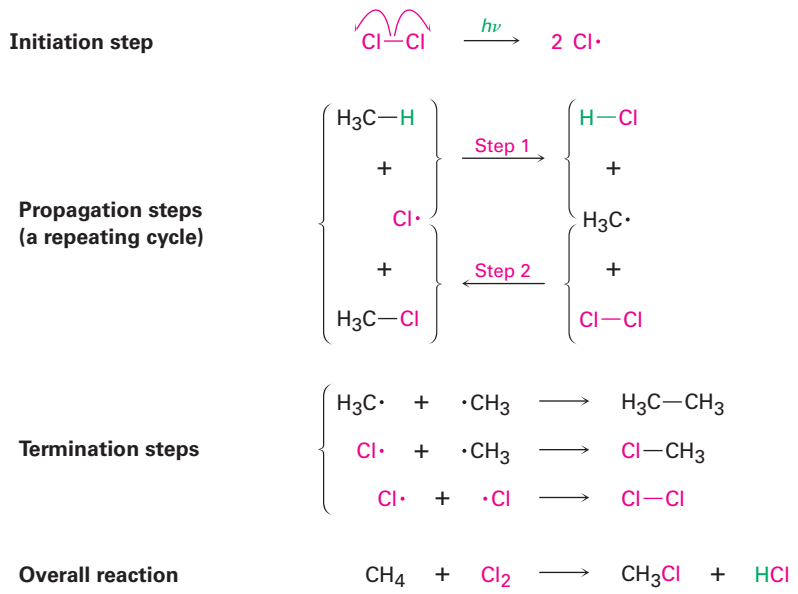
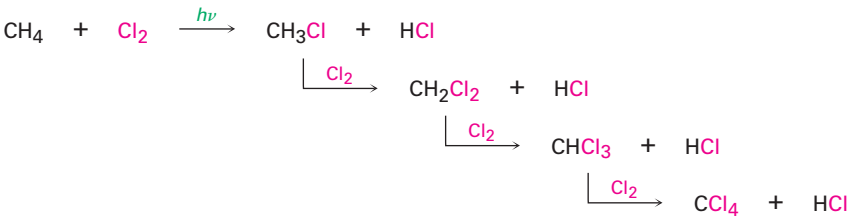
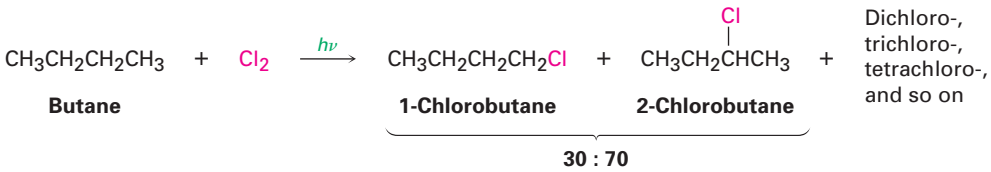


Figure 10.1 Mechanism of the radical chlorination of methane. Three kinds of steps are required: initiation, propagation, and termination. The propagation steps are a repeating cycle, with Cl· a reactant in step 1 and a product in step 2, and with $\cdot CH_3$ a product in step 1 and a reactant in step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

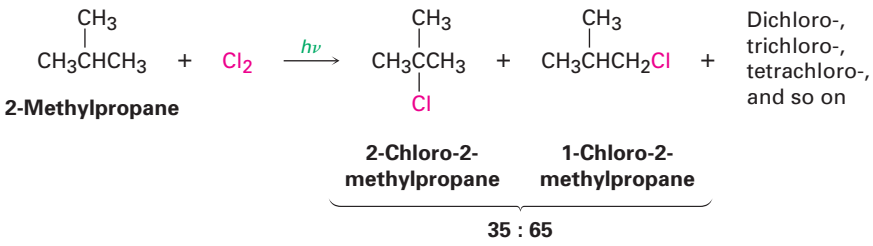
Although interesting from a mechanistic point of view, alkane halogenation is a poor synthetic method for preparing alkyl halides because mixtures of products invariably result. For example, chlorination of methane does not stop cleanly at the monochlorinated stage but continues to give a mixture of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



The situation is even worse for chlorination of alkanes that have more than one sort of hydrogen. For example, chlorination of butane gives two monochlorinated products in addition to dichlorobutane, trichlorobutane, and so on. Thirty percent of the monochloro product is 1-chlorobutane, and seventy percent is 2-chlorobutane.

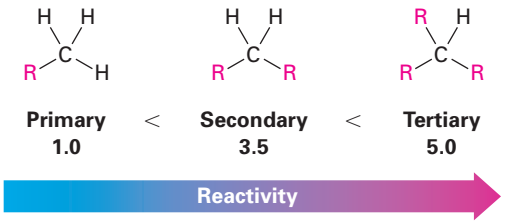


As another example, 2-methylpropane yields 2-chloro-2-methylpropane and 1-chloro-2-methylpropane in the ratio 35 : 65, along with more highly chlorinated products.

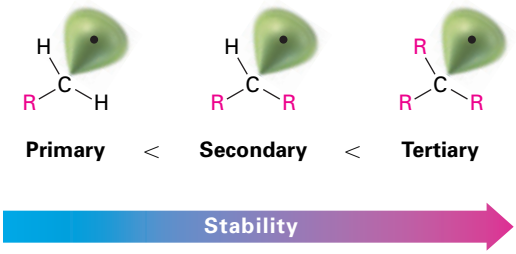


From these and similar reactions, it's possible to calculate a reactivity order toward chlorination for different sorts of hydrogen atoms in a molecule. Take the butane chlorination, for instance. Butane has six equivalent primary hydrogens ($-CH_3$) and four equivalent secondary hydrogens ($-CH_2-$). The fact that butane yields 30% of 1-chlorobutane product means that *each one* of the six primary hydrogens is responsible for 30% ÷ 6 = 5% of the product. Similarly, the fact that 70% of 2-chlorobutane is formed means that each of the four secondary hydrogens is responsible for 70% ÷ 4 = 17.5% of the product. Thus, reaction of a secondary hydrogen happens 17.5% ÷ 5% = 3.5 times as often as reaction of a primary hydrogen.

A similar calculation for the chlorination of 2-methylpropane indicates that each of the nine primary hydrogens accounts for 65% ÷ 9 = 7.2% of the product, while the single tertiary hydrogen (R_3CH) accounts for 35% of the product. Thus, a tertiary hydrogen is 35 ÷ 7.2 = 5 times as reactive as a primary hydrogen toward chlorination.



What are the reasons for the observed reactivity order of alkane hydrogens toward radical chlorination? A look at the bond dissociation energies given previously in Table 5.3 on page 156 hints at the answer. The data in Table 5.3 indicate that a tertiary C–H bond (390 kJ/mol; 93 kcal/mol) is weaker than a secondary C–H bond (401 kJ/mol; 96 kcal/mol), which is in turn weaker than a primary C–H bond (420 kJ/mol; 100 kcal/mol). Since less energy is needed to break a tertiary C–H bond than to break a primary or secondary C–H bond, the resultant tertiary radical is more stable than a primary or secondary radical.



An explanation of the relationship between reactivity and bond strength in radical chlorination reactions relies on the Hammond postulate, discussed in Section 6.10 to explain why more stable carbocations form faster than less stable ones in alkene electrophilic addition reactions. An energy diagram for the formation of an alkyl radical during alkane chlorination is shown in Figure 10.2. Although the hydrogen abstraction step is slightly exergonic, there is nevertheless a certain amount of developing radical character in the transition state. Since the increasing alkyl substitution that stabilizes the radical intermediate also stabilizes the transition state leading to that intermediate, the more stable radical forms faster than the less stable one.

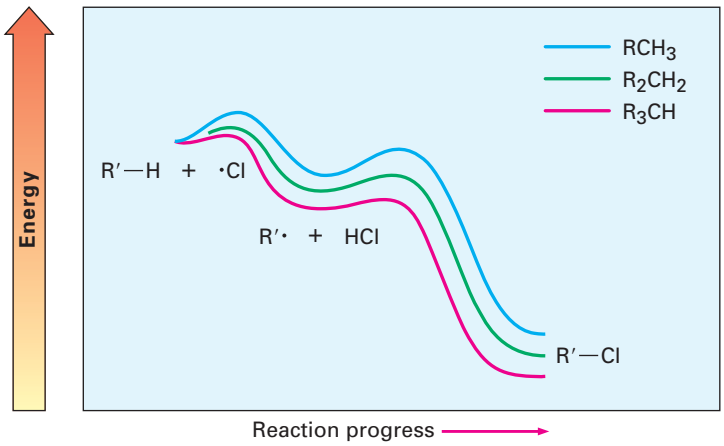
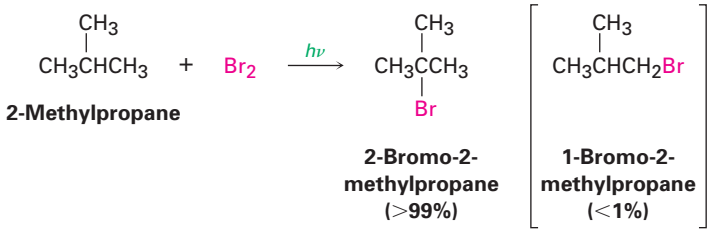
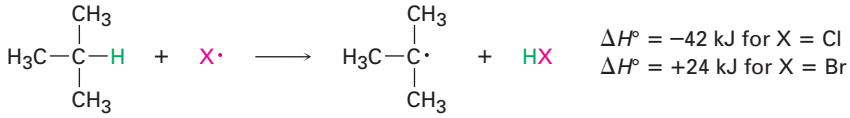


Figure 10.2 Energy diagram for alkane chlorination. The relative rates of formation of tertiary, secondary, and primary radicals are the same as their stability order.

In contrast with alkane chlorination, alkane bromination is usually much more selective. In its reaction with 2-methylpropane, for example, bromine abstracts the tertiary hydrogen with greater than 99% selectivity, as opposed to the 35:65 mixture observed in the corresponding chlorination.



The enhanced selectivity of alkane bromination over chlorination can be explained by turning once again to the Hammond postulate. In comparing the abstractions of an alkane hydrogen by Cl· and Br· radicals, reaction with Br· is less exergonic. As a result, the transition state for bromination resembles the alkyl radical more closely than does the transition state for chlorination, and the stability of that radical is therefore more important for bromination than for chlorination.



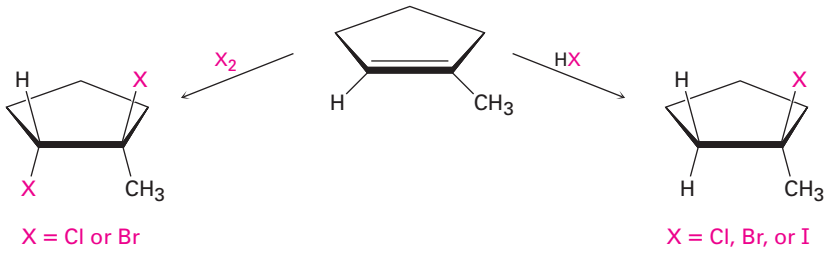
2-Methylpropane

Problem 10.3 Draw and name all monochloro products you would expect to obtain from radical chlorination of 2-methylpentane. Which, if any, are chiral?

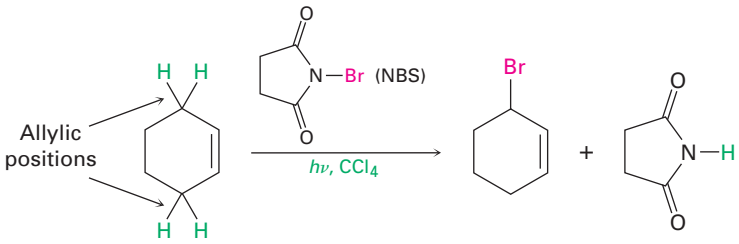
Problem 10.4 Taking the relative reactivities of 1°, 2°, and 3° hydrogen atoms into account, what product(s) would you expect to obtain from monochlorination of 2-methylbutane? What would the approximate percentage of each product be? (Don't forget to take into account the number of each sort of hydrogen.)

10.4 Preparing Alkyl Halides from Alkenes: Allylic Bromination

We've already seen several methods for preparing alkyl halides from alkenes, including the reactions of HX and X_2 with alkenes in electrophilic addition reactions (Sections 6.7 and 7.2). The hydrogen halides HCl, HBr, and HI react with alkenes by a polar mechanism to give the product of Markovnikov addition. Bromine and chlorine undergo anti addition through halonium ion intermediates to give 1,2-dihalogenated products.

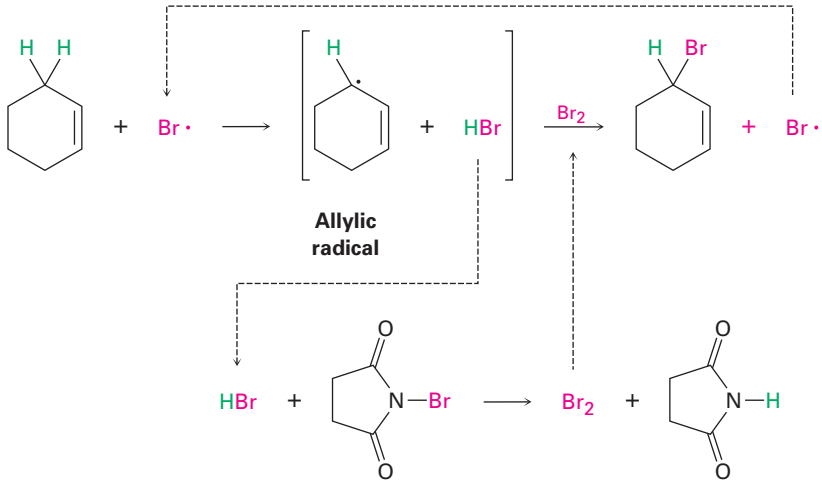


Another method for preparing alkyl halides from alkenes is by reaction with *N*-bromosuccinimide (abbreviated NBS) in the presence of light to give products resulting from substitution of hydrogen by bromine at the **allylic** position—the position *next to* the double bond. Cyclohexene, for example, gives 3-bromocyclohexene.



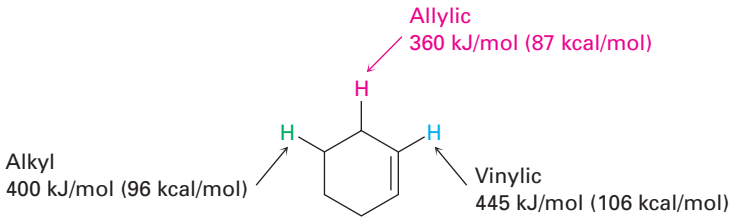
This allylic bromination with NBS is analogous to the alkane halogenation reaction discussed in the previous section and occurs by a radical chain reaction pathway. As in alkane halogenation, Br· radical abstracts an allylic hydrogen atom of the alkene, thereby forming an allylic radical plus HBr. This allylic radical then reacts with Br_2 to yield the product and a Br· radical, which cycles back

into the first step and carries on the chain. The Br_2 results from reaction of NBS with the HBr formed in the first step.

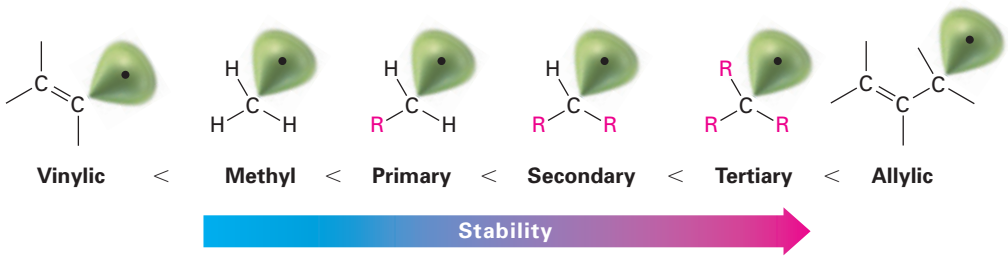


Why does bromination with NBS occur exclusively at an allylic position rather than elsewhere in the molecule? The answer, once again, is found by looking at bond dissociation energies to see the relative stabilities of various kinds of radicals.

There are three sorts of C–H bonds in cyclohexene, and Table 5.3 gives an estimate of their relative strengths. Although a typical secondary alkyl C–H bond has a strength of about 400 kJ/mol (96 kcal/mol) and a typical vinylic C–H bond has a strength of 445 kJ/mol (106 kcal/mol), an *allylic* C–H bond has a strength of only about 360 kJ/mol (87 kcal/mol). An allylic radical is therefore more stable than a typical alkyl radical with the same substitution by about 40 kJ/mol (9 kcal/mol).



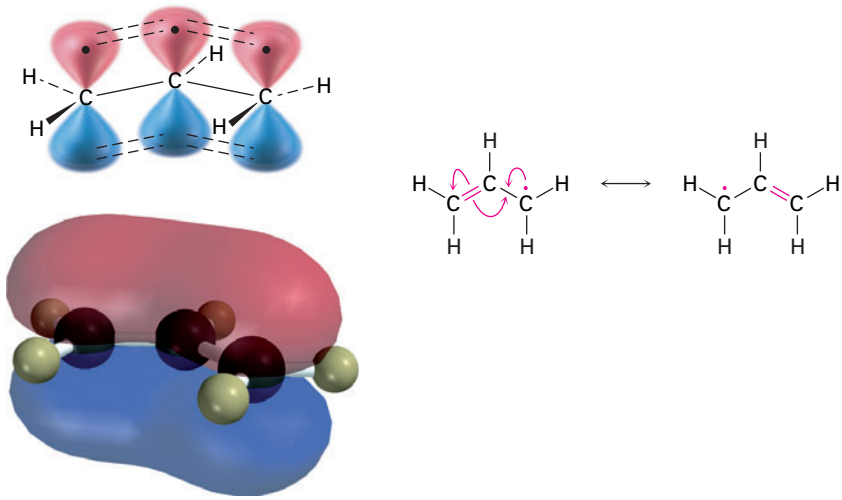
We can thus expand the stability ordering to include vinylic and allylic radicals.



10.5 Stability of the Allyl Radical: Resonance Revisited

To see why allylic radicals are so stable, look at the orbital picture in Figure 10.3. The radical carbon atom with an unpaired electron can adopt sp^2 hybridization, placing the unpaired electron in a *p* orbital and giving a structure that is electronically symmetrical. The *p* orbital on the central carbon can therefore overlap equally well with a *p* orbital on *either* of the two neighboring carbons.

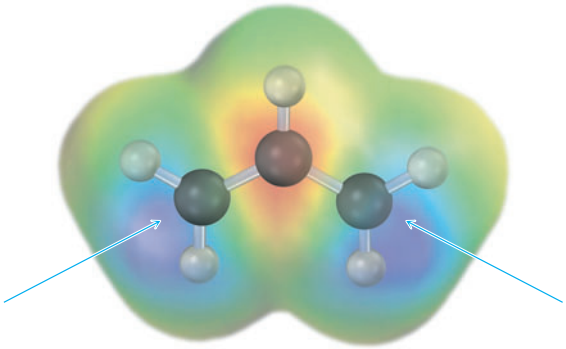
Because the allyl radical is electronically symmetrical, it can be drawn in either of two resonance forms—with the unpaired electron on the left and the double bond on the right or with the unpaired electron on the right and the double bond on the left. Neither structure is correct by itself; the true structure of the allyl radical is a resonance hybrid of the two. (You might want to review Sections 2.4–2.6 to brush up on resonance.) As noted in Section 2.5, the greater the number of resonance forms, the greater the stability of a compound because bonding electrons are attracted to more nuclei. An allyl radical, with two resonance forms, is therefore more stable than a typical alkyl radical, which has only a single structure.



Active Figure 10.3 An orbital view of the allyl radical. The *p* orbital on the central carbon can overlap equally well with a *p* orbital on either neighboring carbon, giving rise to two equivalent resonance structures. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

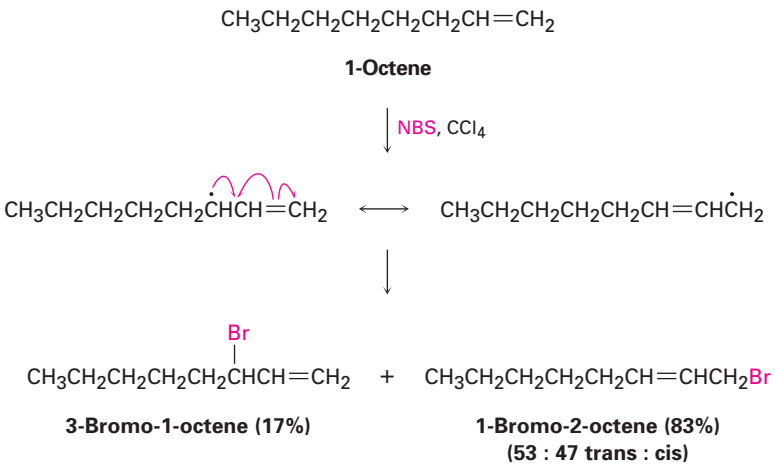
In molecular orbital terms, the stability of the allyl radical is due to the fact that the unpaired electron is **delocalized**, or spread out, over an extended π orbital network rather than localized at only one site, as shown by the computer-generated MO in Fig 10.3. This delocalization is particularly apparent in the so-called spin density surface in Figure 10.4, which shows the calculated location of the unpaired electron. The two terminal carbons share the unpaired electron equally.

In addition to its effect on stability, delocalization of the unpaired electron in the allyl radical has other chemical consequences. Because the unpaired electron is delocalized over both ends of the π orbital system, reaction with Br_2 can occur at either end. As a result, allylic bromination of an unsymmetrical alkene often leads to a mixture of products. For example, bromination of 1-octene gives a mixture of 3-bromo-1-octene and 1-bromo-2-octene. The two products are not formed in equal amounts, however, because the intermediate allylic radical is

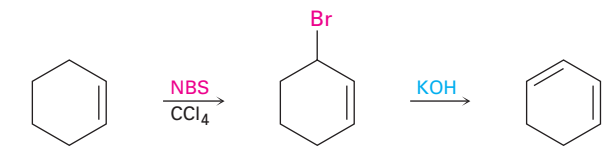


Active Figure 10.4 The spin density surface of the allyl radical locates the position of the unpaired electron (blue) and shows that it is equally shared between the two terminal carbons. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

not symmetrical and reaction at the two ends is not equally likely. Reaction at the less hindered, primary end is favored.



The products of allylic bromination reactions are useful for conversion into dienes by dehydrohalogenation with base. Cyclohexene can be converted into 1,3-cyclohexadiene, for example.



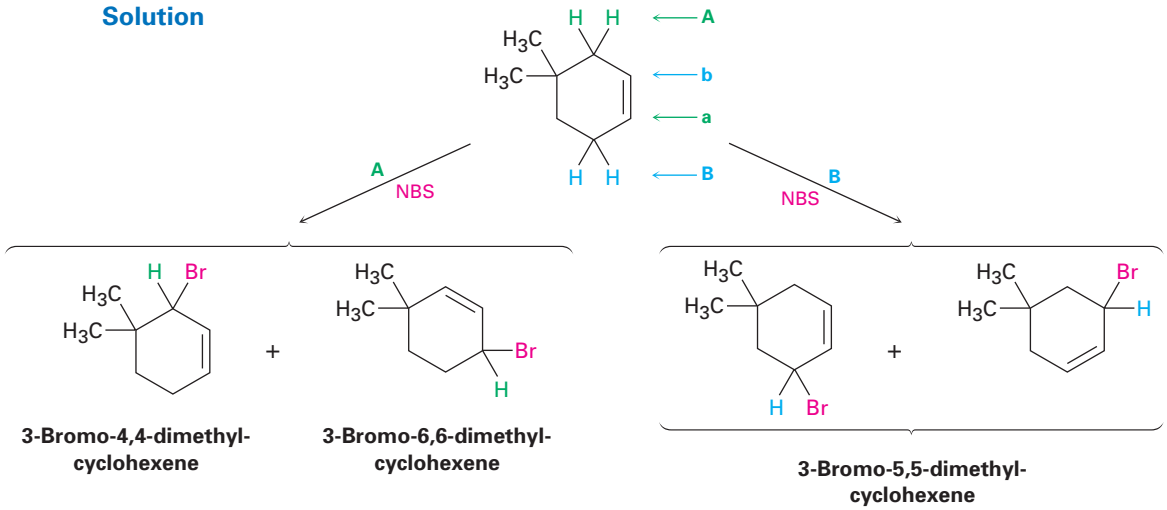
WORKED EXAMPLE 10.1 *Predicting the Product of an Allylic Bromination Reaction*

What products would you expect from reaction of 4,4-dimethylcyclohexene with NBS?

Strategy Draw the alkene reactant, and identify the allylic positions. In this case, there are two different allylic positions; we'll label them **A** and **B**. Now abstract an allylic hydrogen

from each position to generate the two corresponding allylic radicals. Each of the two allylic radicals can add a Br atom at either end (**A** or **a**; **B** or **b**) to give a mixture of up to four products. Draw and name the products. In the present instance, the "two" products from reaction at position **B** are identical, so a total of only three products are formed in this reaction.

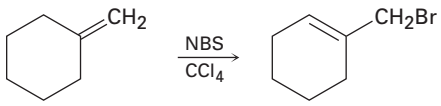
Solution



Problem 10.5 Draw three resonance forms for the cyclohexadienyl radical.

Cyclohexadienyl radical

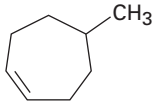
Problem 10.6 The major product of the reaction of methylenecyclohexane with *N*-bromosuccinimide is 1-(bromomethyl)cyclohexene. Explain.



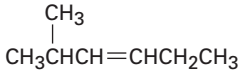
Major product

Problem 10.7 What products would you expect from reaction of the following alkenes with NBS? If more than one product is formed, show the structures of all.

(a)



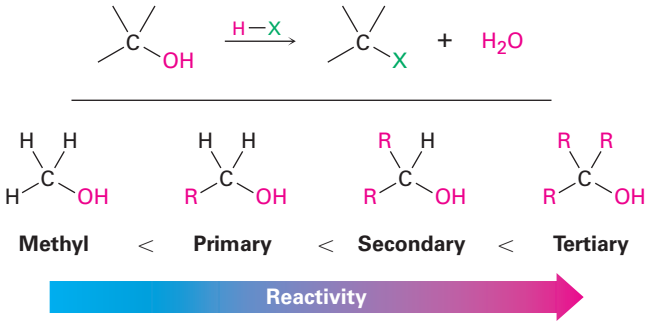
(b)



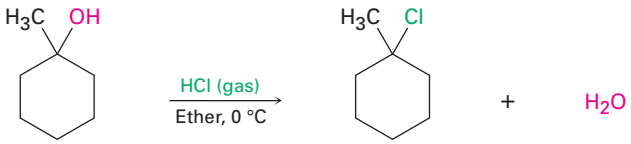
10.6 Preparing Alkyl Halides from Alcohols

ThomsonNOW™ Click *Organic Interactive* to **use a web-based palette to design a synthesis of alkyl halides, beginning with alcohols.**

The most generally useful method for preparing alkyl halides is to make them from alcohols, which themselves can be obtained from carbonyl compounds, as we'll see in Sections 17.4 and 17.5. Because of the importance of the process, many different methods have been developed to transform alcohols into alkyl halides. The simplest method is to treat the alcohol with HCl, HBr, or HI. For reasons that will be discussed in Section 11.5, the reaction works best with tertiary alcohols, R_3COH. Primary and secondary alcohols react much more slowly and at higher temperatures.

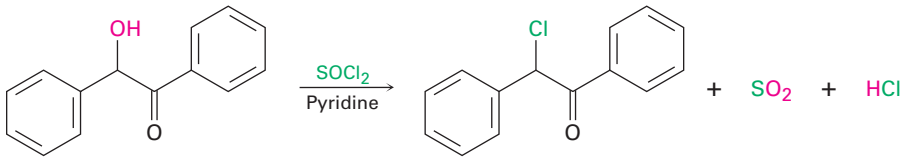


The reaction of HX with a tertiary alcohol is so rapid that it's often carried out simply by bubbling the pure HCl or HBr gas into a cold ether solution of the alcohol. 1-Methylcyclohexanol, for example, is converted into 1-chloro-1-methylcyclohexane by treating with HCl.

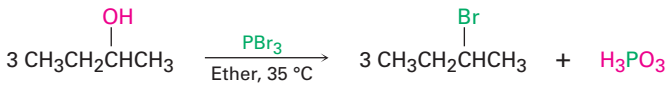


1-Methylcyclohexanol **1-Chloro-1-methylcyclohexane (90%)**

Primary and secondary alcohols are best converted into alkyl halides by treatment with either thionyl chloride ($SOCl_2$) or phosphorus tribromide (PBr_3). These reactions, which normally take place readily under mild conditions, are less acidic and less likely to cause acid-catalyzed rearrangements than the HX method.



Benzoin **(86%)**



2-Butanol **2-Bromobutane (86%)**

As the preceding examples indicate, the yields of these $SOCl_2$ and PBr_3 reactions are generally high, and other functional groups such as ethers, carbonyls, and aromatic rings don't usually interfere. We'll look at the mechanisms of these substitution reactions in the next chapter.

Problem 10.8 How would you prepare the following alkyl halides from the corresponding alcohols?

(a) CH_3CCH_3 (Cl on the central C, CH_3 below)

(b) $CH_3CHCH_2CHCH_3$ (Br on the second C, CH_3 on the fourth C)

(c) $BrCH_2CH_2CH_2CH_2CHCH_3$ (CH_3 on the last C)

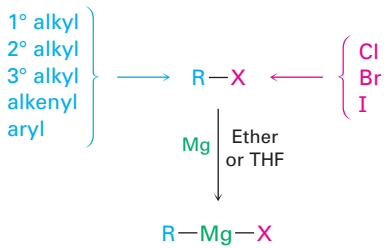
(d) $CH_3CH_2CHCH_2CCH_3$ (CH_3 on the third C, Cl on the fourth C, CH_3 below the fourth C)

10.7 Reactions of Alkyl Halides: Grignard Reagents

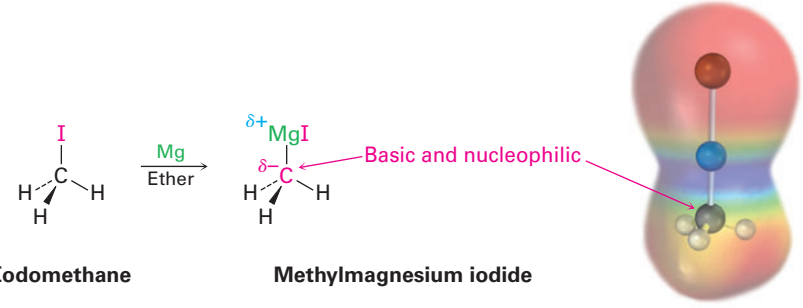
François Auguste Victor Grignard

François Auguste Victor Grignard (1871–1935) was born in Cherbourg, France, and received his Ph.D. at the University of Lyon in 1901. During his doctoral work under Philippe Barbier, Grignard discovered the preparation and usefulness of organomagnesium reagents. He became professor of chemistry at Nancy and at Lyon, and he won the Nobel Prize in chemistry in 1912. During World War I, he was drafted into the French army as a Corporal (a Nobel Prize–winning Corporal!), where he developed a method for detecting German war gases.

Alkyl halides, RX, react with magnesium metal in ether or tetrahydrofuran (THF) solvent to yield alkylmagnesium halides, RMgX. The products, called **Grignard reagents** after their discoverer, Victor Grignard, are examples of *organometallic* compounds because they contain a carbon–metal bond. In addition to alkyl halides, Grignard reagents can also be made from alkenyl (vinylic) and aryl (aromatic) halides. The halogen can be Cl, Br, or I, although chlorides are less reactive than bromides and iodides. Organofluorides rarely react with magnesium.



As you might expect from the discussion of electronegativity and bond polarity in Section 5.4, the carbon–magnesium bond is polarized, making the carbon atom of Grignard reagents both nucleophilic and basic. An electrostatic potential map of methylmagnesium iodide, for instance, indicates the electron-rich (red) character of the carbon bonded to magnesium.



Iodomethane **Methylmagnesium iodide**

In a formal sense, a Grignard reagent is the magnesium salt, $R_3C^-\ ^+MgX$, of a carbon acid, $R_3C{-}H$. But because hydrocarbons are such weak acids, with pK_a's in the range of 44 to 60 (Section 8.7), carbon anions are very strong bases. Grignard reagents therefore react with such weak acids as H_2O, ROH, RCO_2H, and RNH_2 to abstract a proton and yield hydrocarbons. Thus, an organic halide can be reduced to a hydrocarbon by converting it to a Grignard reagent followed by protonation, $R{-}X \rightarrow R{-}MgX \rightarrow R{-}H$.

$$\underset{\textbf{1-Bromohexane}}{CH_3CH_2CH_2CH_2CH_2CH_2Br} \xrightarrow[\text{Ether}]{Mg} \underset{\textbf{1-Hexylmagnesium bromide}}{CH_3CH_2CH_2CH_2CH_2CH_2MgBr} \xrightarrow{H_2O} \underset{\textbf{Hexane (85\%)}}{CH_3CH_2CH_2CH_2CH_2CH_3}$$

We'll see many more uses of Grignard reagents as sources for carbon nucleophiles in later chapters.

Problem 10.9 How strong a base would you expect a Grignard reagent to be? Look at Table 8.1 on page 271, and then predict whether the following reactions will occur as written. (The pK_a of NH_3 is 35.)

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

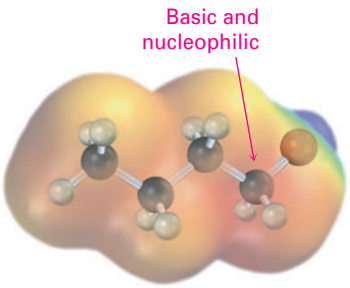
(b) $CH_3MgBr + NH_3 \rightarrow CH_4 + H_2N{-}MgBr$

Problem 10.10 How might you replace a halogen substituent by a deuterium atom if you wanted to prepare a deuterated compound?

10.8 Organometallic Coupling Reactions

Many other kinds of organometallic compounds can be prepared in a manner similar to that of Grignard reagents. For instance, alkyllithium reagents, RLi, can be prepared by the reaction of an alkyl halide with lithium metal. Alkyllithiums are both nucleophiles and strong bases, and their chemistry is similar in many respects to that of alkylmagnesium halides.

$$\underset{\textbf{1-Bromobutane}}{CH_3CH_2CH_2CH_2Br} \xrightarrow[\text{Pentane}]{2\ Li} \underset{\textbf{Butyllithium}}{CH_3CH_2CH_2CH_2Li} + LiBr$$



One particularly valuable reaction of alkyllithiums is in making lithium diorganocopper compounds, LiR_2Cu, by reaction with copper(I) iodide in

Henry Gilman

Henry Gilman (1893–1986) was born in Boston, Massachusetts, and received his Ph.D. in 1918 at Harvard. He then became professor of chemistry at Iowa State University (1919–1962), where he remained active until his death at age 93. An extremely prolific researcher, Gilman published more than 1000 scientific papers during his career. Remarkably, he lost much of his eyesight at age 53 but still went on to accomplish some of his finest work in later years.

diethyl ether as solvent. Called **Gilman reagents**, lithium diorganocopper compounds are useful because they undergo a *coupling* reaction with organochlorides, organobromides, and organoiodides (but not fluorides). One of the alkyl groups from the Gilman reagent replaces the halogen of the organohalide, forming a new carbon–carbon bond and yielding a hydrocarbon product. Lithium dimethylcopper, for example, reacts with 1-iododecane to give undecane in 90% yield.

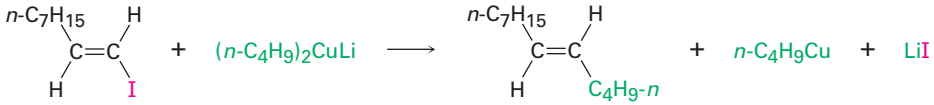
$$2\ CH_3Li + CuI \xrightarrow{\text{Ether}} (CH_3)_2Cu^-\ Li^+ + LiI$$

Methyllithium — **Lithium dimethylcopper (a Gilman reagent)**

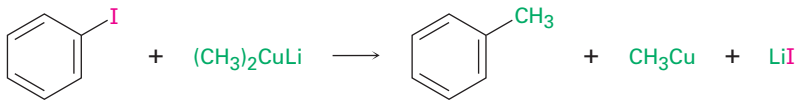
$$(CH_3)_2CuLi + CH_3(CH_2)_8CH_2I \xrightarrow[0\ ^\circ C]{\text{Ether}} CH_3(CH_2)_8CH_2CH_3 + LiI + CH_3Cu$$

Lithium dimethylcopper — **1-Iododecane** — **Undecane (90%)**

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

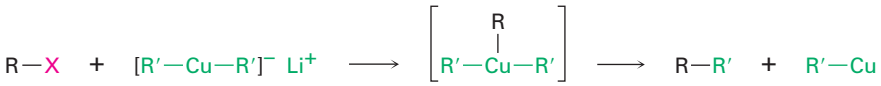


***trans*-1-Iodo-1-nonene** — ***trans*-5-Tridecene (71%)**



Iodobenzene — **Toluene (91%)**

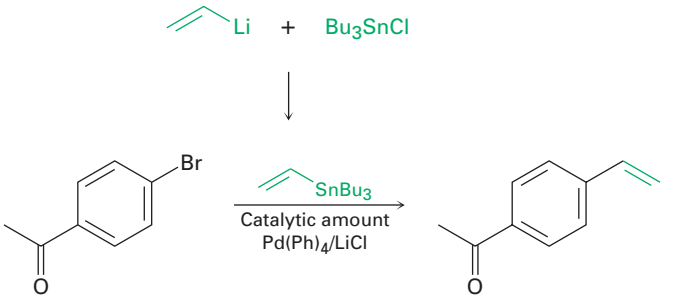
The mechanism of the reaction involves initial formation of a triorganocopper intermediate, followed by coupling and loss of RCu. The coupling is not a typical polar nucleophilic substitution reaction of the sort considered in the next chapter.



ThomsonNOW™ Click *Organic Interactive* to **learn more about the preparation of organometallics and their use in coupling reactions.**

In addition to the coupling reaction of diorganocopper reagents with organohalides, related processes also occur with other organometallics, particularly organopalladium compounds. One of the more commonly used procedures is the palladium-catalyzed reaction of an aryl or vinyl substituted organotin reagent with an organohalide. The organotin is itself usually formed

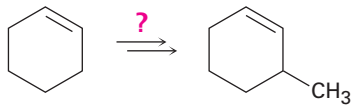
by reaction of an organolithium such as vinyllithium with tributyltin chloride, Bu_3SnCl. For example:



***para*-Bromoacetophenone** ***para*-Vinylacetophenone**

Problem 10.11 How would you carry out the following transformations using an organocopper coupling reaction? More than one step is required in each case.

(a)



(b) $CH_3CH_2CH_2CH_2Br \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

(c) $CH_3CH_2CH_2CH{=}CH_2 \xrightarrow{?} CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_2CH_3$

10.9 Oxidation and Reduction in Organic Chemistry

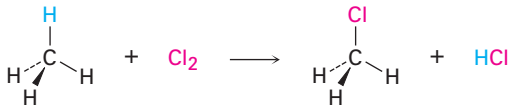
We've pointed out on several occasions that some of the reactions discussed in this and earlier chapters are either *oxidations* or *reductions*. As noted in Sections 7.7 and 7.8, an organic oxidation results in a loss of electron density by carbon, caused either by bond formation between carbon and a more electronegative atom (usually O, N, or a halogen) or by bond-breaking between carbon and a less electronegative atom (usually H). Conversely, an organic reduction results in a gain of electron density by carbon, caused either by bond formation between carbon and a less electronegative atom or by bond-breaking between carbon and a more electronegative atom.

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

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

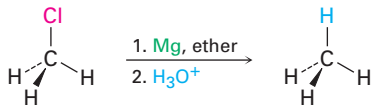
Based on these definitions, the chlorination reaction of methane to yield chloromethane is an oxidation because a C–H bond is broken and a C–Cl bond

is formed. The conversion of an alkyl chloride to an alkane via a Grignard reagent followed by protonation is a reduction, however, because a C–Cl bond is broken and a C–H bond is formed.



Methane **Chloromethane**

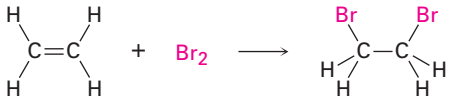
Oxidation: C–H bond broken and C–Cl bond formed



Chloromethane **Methane**

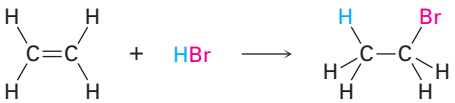
Reduction: C–Cl bond broken and C–H bond formed

As other examples, the reaction of an alkene with Br_2 to yield a 1,2-dibromide is an oxidation because two C–Br bonds are formed, but the reaction of an alkene with HBr to yield an alkyl bromide is neither an oxidation nor a reduction because both a C–H and a C–Br bond are formed.



Ethylene **1,2-Dibromoethane**

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



Ethylene **Bromoethane**

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

A list of compounds of increasing oxidation level is shown in Figure 10.5. Alkanes are at the lowest oxidation level because they have the maximum possible number of C–H bonds per carbon, and CO_2 is at the highest level because it has the maximum possible number of C–O bonds per carbon. Any reaction that converts a compound from a lower level to a higher level is an oxidation, any reaction that converts a compound from a higher level to a lower level is a reduction, and any reaction that doesn't change the level is neither an oxidation nor a reduction.

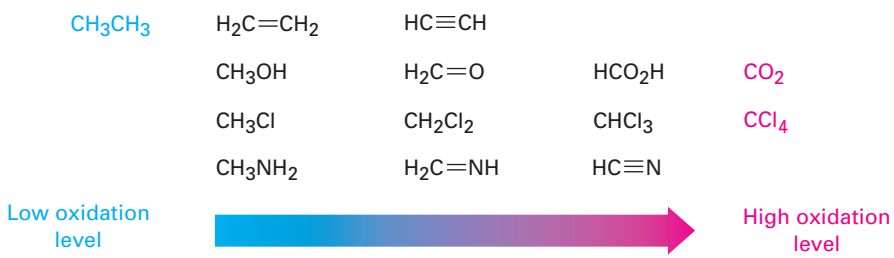
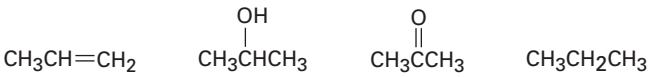


Figure 10.5 Oxidation levels of some common types of compounds.

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

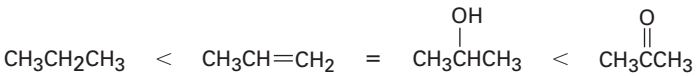
WORKED EXAMPLE 10.2 *Comparing Oxidation Levels of Compounds*

Rank the following compounds in order of increasing oxidation level:



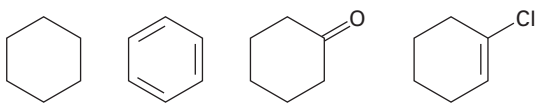
Strategy Compounds that have the same number of carbon atoms can be compared by adding the number of C−O, C−N, and C−X bonds in each and then subtracting the number of C−H bonds. The larger the resultant value, the higher the oxidation level.

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



Problem 10.12 Rank each of the following series of compounds in order of increasing oxidation level:

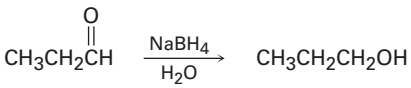
(a)



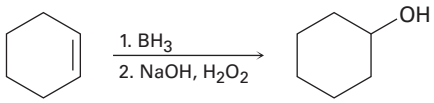
(b) CH_3CN $CH_3CH_2NH_2$ $H_2NCH_2CH_2NH_2$

Problem 10.13 Tell whether each of the following reactions is an oxidation, a reduction, or neither.

(a)



(b)



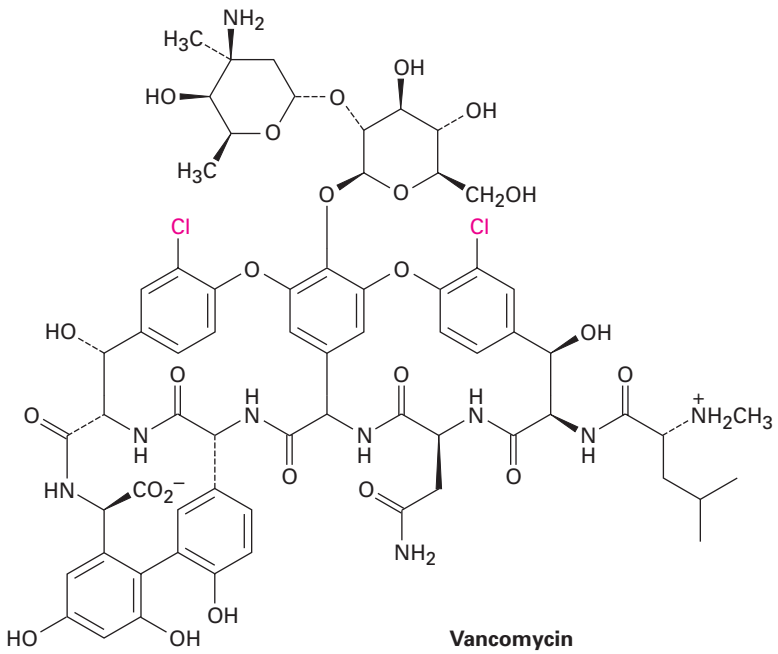
Focus On . . .

Naturally Occurring Organohalides

© Stuart Westmorland/Corbis

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

As recently as 1970, only about 30 naturally occurring organohalogen compounds were known. It was simply assumed that chloroform, halogenated phenols, chlorinated aromatic compounds called PCBs, and other such substances found in the environment were industrial pollutants. Now, only a third of a century later, the situation is quite different. More than 5000 organohalogen compounds have been found to occur naturally, and tens of thousands more surely exist. From a simple compound like chloromethane to an extremely complex one like vancomycin, a remarkably diverse range of organohalogen compounds exists in plants, bacteria, and animals. Many even have valuable physiological activity. Vancomycin, for instance, is a powerful antibiotic produced by the bacterium *Amycolatopsis orientalis* and used clinically to treat methicillin-resistant *Staphylococcus aureus* (MRSA).



Vancomycin

Some naturally occurring organohalogen compounds are produced in massive quantities. Forest fires, volcanoes, and marine kelp release up to *5 million tons* of CH_3Cl per year, for example, while annual industrial emissions

(continued)

total about 26,000 tons. Termites are thought to release as much as 10^8 kg of chloroform per year. A detailed examination of the Okinawan acorn worm *Ptychodera flava* found that the 64 million worms living in a 1 km^2 study area excreted nearly 8000 pounds per year of bromophenols and bromoindoles, compounds previously thought to be nonnatural pollutants.

Why do organisms produce organohalogen compounds, many of which are undoubtedly toxic? The answer seems to be that many organisms use organohalogen compounds for self-defense, either as feeding deterrents, as irritants to predators, or as natural pesticides. Marine sponges, coral, and sea hares, for example, release foul-tasting organohalogen compounds that deter fish, starfish, and other predators from eating them. Even humans appear to produce halogenated compounds as part of their defense against infection. The human immune system contains a peroxidase enzyme capable of carrying out halogenation reactions on fungi and bacteria, thereby killing the pathogen. And most remarkable of all, even free chlorine—Cl_2—has been found to be present in humans.

Much remains to be learned—only a few hundred of the more than 500,000 known species of marine organisms have been examined—but it is clear that organohalogen compounds are an integral part of the world around us.

SUMMARY AND KEY WORDS

Alkyl halides contain a halogen bonded to a saturated, sp^3-hybridized carbon atom. The C−X bond is polar, and alkyl halides can therefore behave as electrophiles.

Simple alkyl halides can be prepared by radical halogenation of alkanes, but mixtures of products usually result. The reactivity order of alkanes toward halogenation is identical to the stability order of radicals: $R_3C\cdot > R_2CH\cdot > RCH_2\cdot$. Alkyl halides can also be prepared from alkenes by reaction with *N*-bromosuccinimide (NBS) to give the product of **allylic** bromination. The NBS bromination of alkenes takes place through an intermediate allylic radical, which is stabilized by resonance.

Alcohols react with HX to form alkyl halides, but the reaction works well only for tertiary alcohols, R_3COH. Primary and secondary alkyl halides are normally prepared from alcohols using either $SOCl_2$ or PBr_3. Alkyl halides react with magnesium in ether solution to form organomagnesium halides, called **Grignard reagents (RMgX)**. Because Grignard reagents are both nucleophilic and basic, they react with acids to yield hydrocarbons. The overall result of Grignard formation and protonation is the conversion of an alkyl halide into an alkane (RX → RMgX → RH).

Alkyl halides also react with lithium metal to form organolithium reagents, RLi. In the presence of CuI, these form diorganocoppers, or **Gilman reagents (LiR_2Cu)**. Gilman reagents react with alkyl halides to yield coupled hydrocarbon products.

In organic chemistry, an *oxidation* is a reaction that causes a decrease in electron density on carbon, either by bond formation between carbon and a more electronegative atom (usually oxygen, nitrogen, or a halogen) or by bond-breaking

between carbon and a less electronegative atom (usually hydrogen). Conversely, a *reduction* causes an increase of electron density on carbon, either by bond-breaking between carbon and a more electronegative atom or by bond formation between carbon and a less electronegative atom. Thus, the halogenation of an alkane to yield an alkyl halide is an oxidation, while the conversion of an alkyl halide to an alkane by protonation of a Grignard reagent is a reduction.

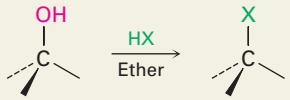
SUMMARY OF REACTIONS

1. Preparation of alkyl halides

(a) From alkenes by allylic bromination (Section 10.4)

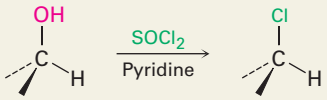
(b) From alcohols (Section 10.6)

(1) Reaction with HX

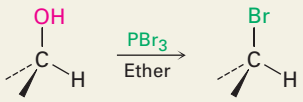


Reactivity order: 3° > 2° > 1°

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

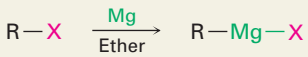


(3) Reaction of 1° and 2° alcohols with PBr_3

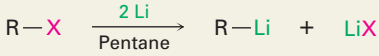


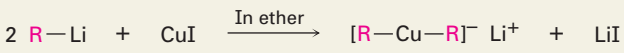
2. Reactions of alkyl halides

(a) Formation of Grignard (organomagnesium) reagents (Section 10.7)



(b) Formation of Gilman (diorganocopper) reagents (Section 10.8)





(c) Organometallic coupling (Section 10.8)

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

(d) Reduction of alkyl halides to alkanes (Section 10.7)

$$R-X \xrightarrow[\text{Ether}]{Mg} R-Mg-X \xrightarrow{H_3O^+} R-H + HOMgX$$

EXERCISES

Organic KNOWLEDGE TOOLS

ThomsonNOW™ Sign in at **www.thomsonedu.com** to assess your knowledge of this chapter's topics by taking a pre-test. The pre-test will link you to interactive organic chemistry resources based on your score in each concept area.

Online homework for this chapter may be assigned in Organic OWL.

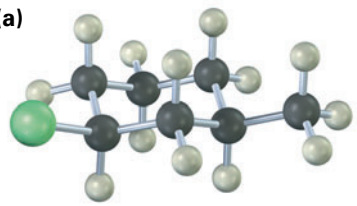
■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

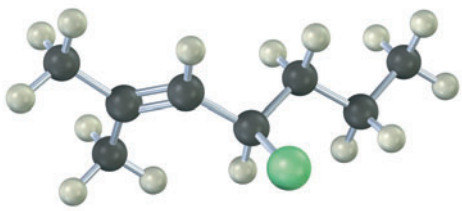
(Problems 10.1–10.13 appear within the chapter.)

10.14 ■ Give a IUPAC name for each of the following alkyl halides (yellow-green = Cl):

(a)

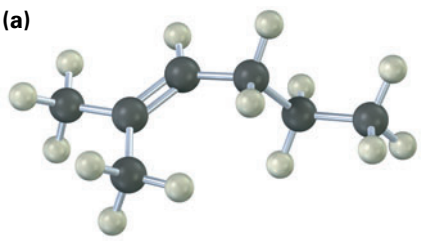


(b)

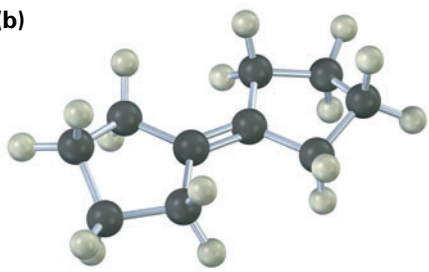


10.15 ■ Show the product(s) of reaction of the following alkenes with NBS:

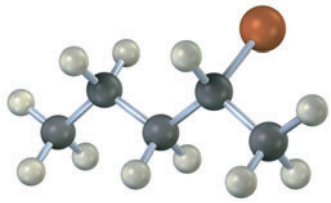
(a)



(b)



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



ADDITIONAL PROBLEMS

10.17 ■ Name the following alkyl halides:

(a) $CH_3CHCHCHCH_2CHCH_3$ (Br, Br, CH_3)

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

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

(d) $CH_3CH_2CHCH_2CH_2CH_3$ (CH_2Br)

(e) $ClCH_2CH_2CH_2C{\equiv}CCH_2Br$

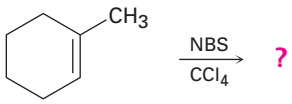
10.18 ■ Draw structures corresponding to the following IUPAC names:
(a) 2,3-Dichloro-4-methylhexane
(b) 4-Bromo-4-ethyl-2-methylhexane
(c) 3-Iodo-2,2,4,4-tetramethylpentane
(d) *cis*-1-Bromo-2-ethylcyclopentane

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

10.20 A chemist requires a large amount of 1-bromo-2-pentene as starting material for a synthesis and decides to carry out an NBS allylic bromination reaction. What is wrong with the following synthesis plan? What side products would form in addition to the desired product?

$$CH_3CH_2CH{=}CHCH_3 \xrightarrow[CCl_4]{NBS} CH_3CH_2CH{=}CHCH_2Br$$

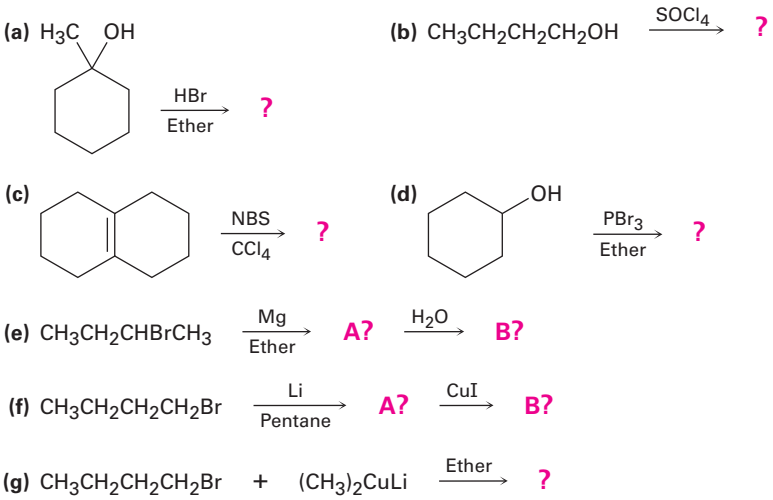
10.21 What product(s) would you expect from the reaction of 1-methylcyclohexene with NBS? Would you use this reaction as part of a synthesis?



10.22 ■ How would you prepare the following compounds, starting with cyclopentene and any other reagents needed?
(a) Chlorocyclopentane
(b) Methylcyclopentane
(c) 3-Bromocyclopentene
(d) Cyclopentanol
(e) Cyclopentylcyclopentane
(f) 1,3-Cyclopentadiene

■ Assignable in OWL

10.23 ■ Predict the product(s) of the following reactions:

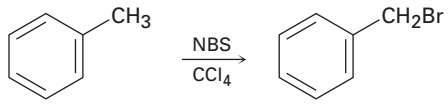


10.24 (*S*)-3-Methylhexane undergoes radical bromination to yield optically inactive 3-bromo-3-methylhexane as the major product. Is the product chiral? What conclusions can you draw about the radical intermediate?

10.25 Assume that you have carried out a radical chlorination reaction on (*R*)-2-chloropentane and have isolated (in low yield) 2,4-dichloropentane. How many stereoisomers of the product are formed and in what ratio? Are any of the isomers optically active? (See Problem 10.24.)

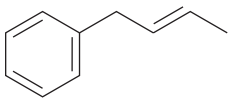
10.26 What product(s) would you expect from the reaction of 1,4-hexadiene with NBS? What is the structure of the most stable radical intermediate?

10.27 Alkylbenzenes such as toluene (methylbenzene) react with NBS to give products in which bromine substitution has occurred at the position next to the aromatic ring (the *benzylic* position). Explain, based on the bond dissociation energies in Table 5.3 on page 156.



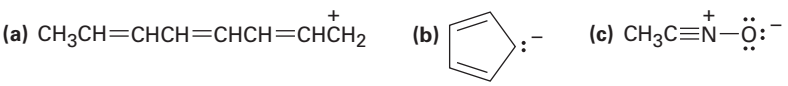
10.28 Draw resonance structures for the benzyl radical, $C_6H_5CH_2\cdot$, the intermediate produced in the NBS bromination reaction of toluene (Problem 10.27).

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



1-Phenyl-2-butene

10.30 ■ Draw resonance structures for the following species:



■ Assignable in OWL

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

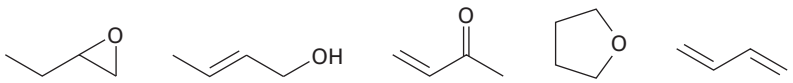
(a)

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

(b)

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

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



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

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

(a)

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

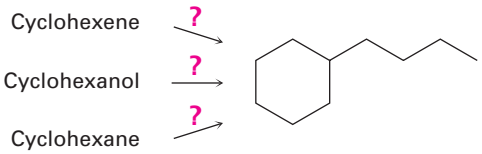
(b)

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

(c)

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

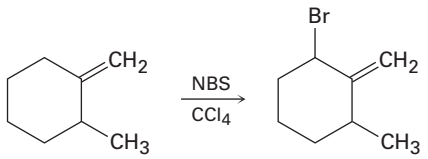
10.34 ■ How would you carry out the following syntheses?



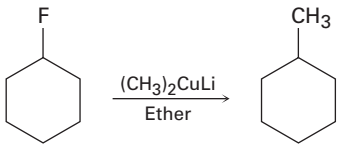
10.35 The syntheses shown here are unlikely to occur as written. What is wrong with each?

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

(b)

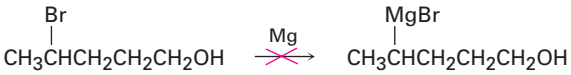


(c)

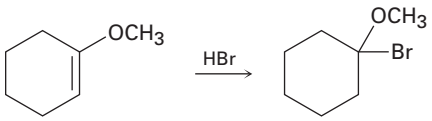


■ Assignable in OWL

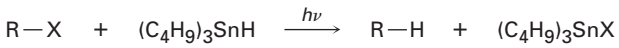
10.36 Why do you suppose it's not possible to prepare a Grignard reagent from a bromo alcohol such as 4-bromo-1-pentanol? Give another example of a molecule that is unlikely to form a Grignard reagent.



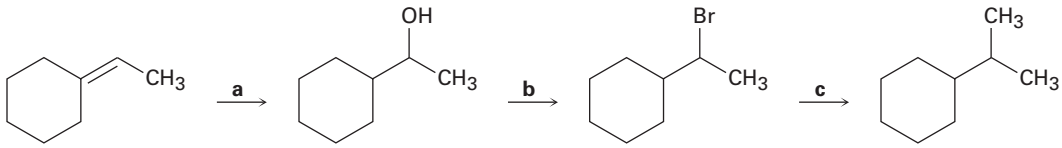
10.37 ■ Addition of HBr to a double bond with an ether (−OR) substitute occurs regiospecifically to give a product in which the −Br and −OR are bonded to the same carbon. Draw the two possible carbocation intermediates in this electrophilic addition reaction, and explain using resonance why the observed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



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

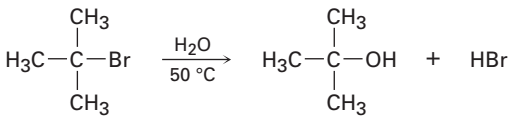


10.39 Identify the reagents a–c in the following scheme:



10.40 Tertiary alkyl halides, R_3CX, undergo spontaneous dissociation to yield a carbocation, R_3C^+, plus halide ion. Which do you think reacts faster, $(CH_3)_3CBr$ or $H_2C{=}CHC(CH_3)_2Br$? Explain.

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



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

■ Assignable in OWL