# CHAPTER 16

## ETHERS, EPOXIDES, AND SULFIDES

I n contrast to alcohols with their rich chemical reactivity, **ethers** (compounds containing a C—O—C unit) undergo relatively few chemical reactions. As you saw when we discussed Grignard reagents in Chapter 14 and lithium aluminum hydride reductions in Chapter 15, this lack of reactivity of ethers makes them valuable as solvents in a number of synthetically important transformations. In the present chapter you will learn of the conditions in which an ether linkage acts as a functional group, as well as the methods by which ethers are prepared.

Unlike most ethers, **epoxides** (compounds in which the C—O—C unit forms a three-membered ring) are very reactive substances. The principles of nucleophilic substitution are important in understanding the preparation and properties of epoxides.

**Sulfides** (RSR′) are the sulfur analogs of ethers. Just as in the preceding chapter, where we saw that the properties of thiols (RSH) are different from those of alcohols, we will explore differences between sulfides and ethers in this chapter.
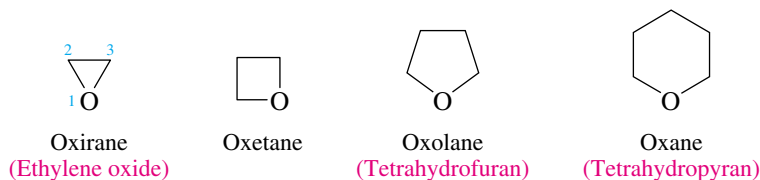
### 16.1 NOMENCLATURE OF ETHERS, EPOXIDES, AND SULFIDES

Ethers are named, in substitutive IUPAC nomenclature, as *alkoxy* derivatives of alkanes. Functional class IUPAC names of ethers are derived by listing the two alkyl groups in the general structure ROR′ in alphabetical order as separate words, and then adding the word "ether" at the end. When both alkyl groups are the same, the prefix *di-* precedes the name of the alkyl group.

|  | $CH_3CH_2OCH_2CH_3$ | $CH_3CH_2OCH_3$ | $CH_3CH_2OCH_2CH_2CH_2Cl$ |
|---|---|---|---|
| **Substitutive IUPAC name:** | Ethoxyethane | Methoxyethane | 1-Chloro-3-ethoxypropane |
| **Functional class IUPAC name:** | Diethyl ether | Ethyl methyl ether | 3-Chloropropyl ethyl ether |

Ethers are described as **symmetrical** or **unsymmetrical** depending on whether the two groups bonded to oxygen are the same or different. Unsymmetrical ethers are also called **mixed ethers.** Diethyl ether is a symmetrical ether; ethyl methyl ether is an unsymmetrical ether.

Cyclic ethers have their oxygen as part of a ring—they are *heterocyclic compounds* (Section 3.15). Several have specific IUPAC names.



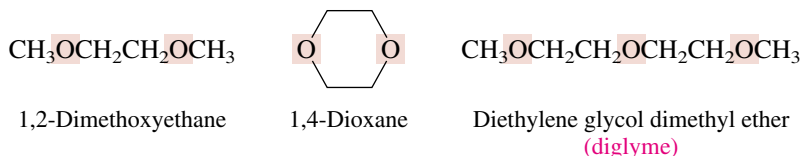| Oxirane | Oxetane | Oxolane | Oxane |
|---|---|---|---|
| (Ethylene oxide) | | (Tetrahydrofuran) | (Tetrahydropyran) |

In each case the ring is numbered starting at the oxygen. The IUPAC rules also permit oxirane (without substituents) to be called *ethylene oxide. Tetrahydrofuran* and *tetrahydropyran* are acceptable synonyms for oxolane and oxane, respectively.

> **Recall from Section 6.18 that epoxides may be named as *-epoxy* derivatives of alkanes in substitutive IUPAC nomenclature.**

> **PROBLEM 16.1** Each of the following ethers has been shown to be or is suspected to be a *mutagen,* which means it can induce mutations in test cells. Write the structure of each of these ethers.
>
> (a) Chloromethyl methyl ether
> (b) 2-(Chloromethyl)oxirane (also known as epichlorohydrin)
> (c) 3,4-Epoxy-1-butene (2-vinyloxirane)
>
> **SAMPLE SOLUTION** (a) Chloromethyl methyl ether has a chloromethyl group (ClCH$_2$—) and a methyl group (CH$_3$—) attached to oxygen. Its structure is ClCH$_2$OCH$_3$.

Many substances have more than one ether linkage. Two such compounds, often used as solvents, are the *diethers* 1,2-dimethoxyethane and 1,4-dioxane. Diglyme, also a commonly used solvent, is a *triether.*



CH$_3$OCH$_2$CH$_2$OCH$_3$        CH$_3$OCH$_2$CH$_2$OCH$_2$CH$_2$OCH$_3$

1,2-Dimethoxyethane     1,4-Dioxane     Diethylene glycol dimethyl ether
                                        (diglyme)

Molecules that contain several ether functions are referred to as *polyethers.* Polyethers have received much recent attention, and some examples of them will appear in Section 16.4.
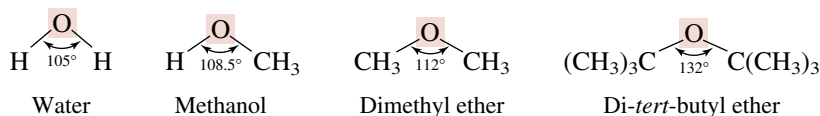
The sulfur analogs (RS—) of alkoxy groups are called *alkylthio* groups. The first two of the following examples illustrate the use of alkylthio prefixes in substitutive nomenclature of sulfides. Functional class IUPAC names of sulfides are derived in exactly the same way as those of ethers but end in the word "sulfide." Sulfur heterocycles have names analogous to their oxygen relatives, except that *ox-* is replaced by *thi-*. Thus the sulfur heterocycles containing three-, four-, five-, and six-membered rings are named *thiirane, thietane, thiolane,* and *thiane,* respectively.
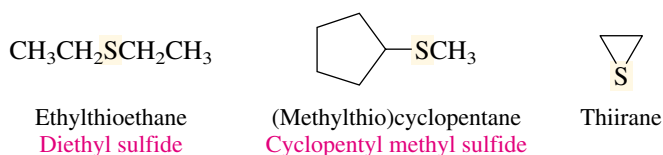
> **Sulfides are sometimes informally referred to as *thioethers,* but this term is not part of systematic IUPAC nomenclature.**



CH$_3$CH$_2$SCH$_2$CH$_3$

| Ethylthioethane | (Methylthio)cyclopentane | Thiirane |
|---|---|---|
| Diethyl sulfide | Cyclopentyl methyl sulfide | |

## 16.2 STRUCTURE AND BONDING IN ETHERS AND EPOXIDES

Bonding in ethers is readily understood by comparing ethers with water and alcohols. Van der Waals strain involving alkyl groups causes the bond angle at oxygen to be larger in ethers than alcohols, and larger in alcohols than in water. An extreme example is di-*tert*-butyl ether, where steric hindrance between the *tert*-butyl groups is responsible for a dramatic increase in the C—O—C bond angle.



| Water | Methanol | Dimethyl ether | Di-*tert*-butyl ether |

Use *Learning By Modeling* to make models of water, methanol, dimethyl ether, and di-*tert*-butyl ether. Minimize their geometries, and examine what happens to the C—O—C bond angle. Compare the C—O bond distances in dimethyl ether and di-*tert*-butyl ether.

Typical carbon–oxygen bond distances in ethers are similar to those of alcohols ($\approx$142 pm) and are shorter than carbon–carbon bond distances in alkanes ($\approx$153 pm).

An ether oxygen affects the conformation of a molecule in much the same way that a $CH_2$ unit does. The most stable conformation of diethyl ether is the all-staggered anti conformation. Tetrahydropyran is most stable in the chair conformation—a fact that has an important bearing on the structures of many carbohydrates.
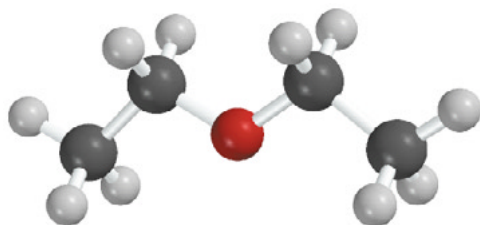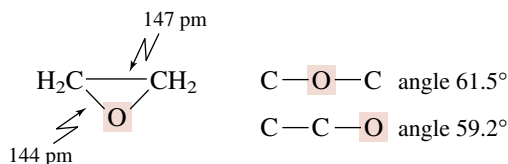


Anti conformation of diethyl ether
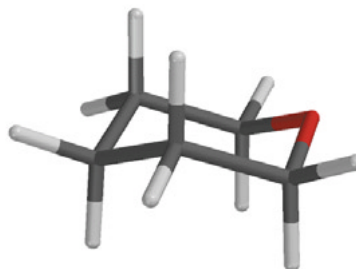


Chair conformation of tetrahydropyran

Incorporating an oxygen atom into a three-membered ring requires its bond angle to be seriously distorted from the normal tetrahedral value. In ethylene oxide, for example, the bond angle at oxygen is 61.5°.



C—O—C angle 61.5°

C—C—O angle 59.2°

Thus epoxides, like cyclopropanes, are strained. They tend to undergo reactions that open the three-membered ring by cleaving one of the carbon–oxygen bonds.

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**PROBLEM 16.2** The heats of combustion of 1,2-epoxybutane (2-ethyloxirane) and tetrahydrofuran have been measured: one is 2499 kJ/mol (597.8 kcal/mol); the other is 2546 kJ/mol (609.1 kcal/mol). Match the heats of combustion with the respective compounds.

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Ethers, like water and alcohols, are polar. Diethyl ether, for example, has a dipole moment of 1.2 D. Cyclic ethers have larger dipole moments; ethylene oxide and tetrahydrofuran have dipole moments in the 1.7- to 1.8-D range—about the same as that of water.

## 16.3   PHYSICAL PROPERTIES OF ETHERS

It is instructive to compare the physical properties of ethers with alkanes and alcohols. With respect to boiling point, ethers resemble alkanes more than alcohols. With respect to solubility in water the reverse is true; ethers resemble alcohols more than alkanes. Why?

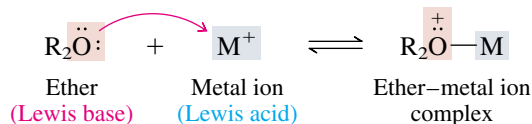|  | $CH_3CH_2OCH_2CH_3$ | $CH_3CH_2CH_2CH_2CH_3$ | $CH_3CH_2CH_2CH_2OH$ |
|---|---|---|---|
|  | Diethyl ether | Pentane | 1-Butanol |
| **Boiling point:** | 35°C | 36°C | 117°C |
| **Solubility in water:** | 7.5 g/100 mL | Insoluble | 9 g/100 mL |

In general, the boiling points of alcohols are unusually high because of hydrogen bonding (Section 4.5). Attractive forces in the liquid phases of ethers and alkanes, which lack —OH groups and cannot form intermolecular hydrogen bonds, are much weaker, and their boiling points lower.

As shown in Figure 16.1, however, the presence of an oxygen atom permits ethers to participate in hydrogen bonds to water molecules. These attractive forces cause ethers to dissolve in water to approximately the same extent as comparably constituted alcohols. Alkanes cannot engage in hydrogen bonding to water.

> **PROBLEM 16.3**   Ethers tend to dissolve in alcohols and vice versa. Represent the hydrogen-bonding interaction between an alcohol molecule and an ether molecule.

## 16.4   CROWN ETHERS

Their polar carbon–oxygen bonds and the presence of unshared electron pairs at oxygen contribute to the ability of ethers to form Lewis acid-Lewis base complexes with metal ions.

$$R_2\ddot{O}: \quad + \quad M^+ \quad \rightleftharpoons \quad R_2\overset{+}{\ddot{O}}\!-\!M$$

| Ether | Metal ion | Ether–metal ion complex |
|---|---|---|
| (Lewis base) | (Lewis acid) | |



**FIGURE 16.1** Hydrogen bonding between diethyl ether and water. The dashed line represents the attractive force between the negatively polarized oxygen of diethyl ether and one of the positively polarized hydrogens of water. The electrostatic potential surfaces illustrate the complementary interaction between the electron-rich (*red*) region of diethyl ether and the electron-poor (*blue*) region of water.
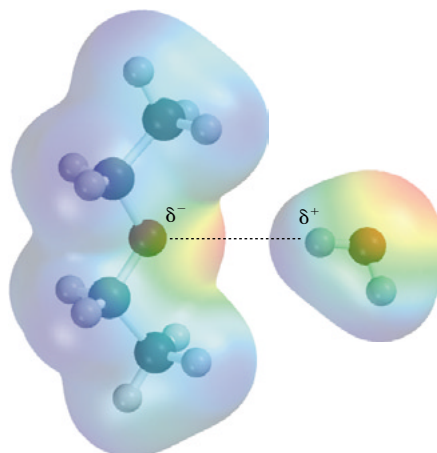
The strength of this bonding depends on the kind of ether. Simple ethers form relatively weak complexes with metal ions. A major advance in the area came in 1967 when Charles J. Pedersen of Du Pont described the preparation and properties of a class of *polyethers* that form much more stable complexes with metal ions than do simple ethers.

Pedersen was a corecipient of the 1987 Nobel Prize in chemistry.

Pedersen prepared a series of *macrocyclic polyethers,* cyclic compounds containing four or more oxygens in a ring of 12 or more atoms. He called these compounds **crown ethers,** because their molecular models resemble crowns. Systematic nomenclature of crown ethers is somewhat cumbersome, and so Pedersen devised a shorthand description whereby the word "crown" is preceded by the total number of atoms in the ring and is followed by the number of oxygen atoms.
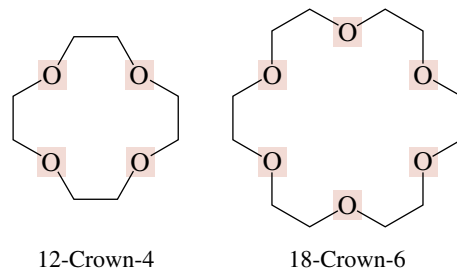
<center>12-Crown-4        18-Crown-6</center>

12-Crown-4 and 18-crown-6 are a cyclic tetramer and hexamer, respectively, of repeating —OCH$_2$CH$_2$— units; they are polyethers based on ethylene glycol (HOCH$_2$CH$_2$OH) as the parent alcohol.

**PROBLEM 16.4**  What organic compound mentioned earlier in this chapter is a cyclic dimer of —OCH$_2$CH$_2$— units?

The metal–ion complexing properties of crown ethers are clearly evident in their effects on the solubility and reactivity of ionic compounds in nonpolar media. Potassium fluoride (KF) is ionic and practically insoluble in benzene alone, but dissolves in it when 18-crown-6 is present. The reason for this has to do with the electron distribution of 18-crown-6 as shown in Figure 16.2*a.* The electrostatic potential surface consists of essentially two regions: an electron-rich interior associated with the oxygens and a hydrocarbon-like exterior associated with the CH$_2$ groups. When KF is added to a solution of 18-crown-6 in benzene, potassium ion (K$^+$) interacts with the oxygens of the crown ether to form a Lewis acid-Lewis base complex. As can be seen in the space-filling model of



(*a*)                                        (*b*)

**FIGURE 16.2** (*a*) An electrostatic potential map of 18-crown-6. The region of highest electron density (*red*) is associated with the negatively polarized oxygens and their lone pairs. The outer periphery of the crown ether (*blue*) is relatively non-polar (hydrocarbon-like) and causes the molecule to be soluble in nonpolar solvents such as benzene. (*b*) A space-filling model of the complex formed between 18-crown-6 and potassium ion (K$^+$). K$^+$ fits into the cavity of the crown ether where it is bound by Lewis acid-Lewis base interaction with the oxygens.
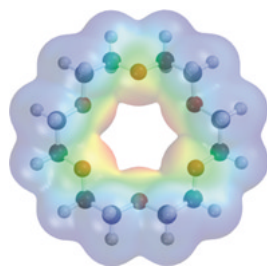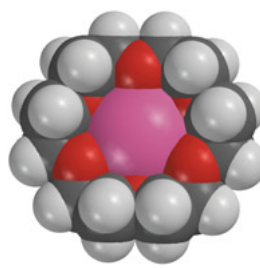
## POLYETHER ANTIBIOTICS

One way in which pharmaceutical companies search for new drugs is by growing colonies of microorganisms in nutrient broths and assaying the substances produced for their biological activity. This method has yielded thousands of antibiotic substances, of which hundreds have been developed into effective drugs. Antibiotics are, by definition, toxic (*anti* = "against"; *bios* = "life"), and the goal is to find substances that are more toxic to infectious organisms than to their human hosts.

Since 1950, a number of **polyether antibiotics** have been discovered using fermentation technology. They are characterized by the presence of several cyclic ether structural units, as illustrated for the case of *monensin* in Figure 16.3*a*. Monensin and other naturally occurring polyethers are similar to crown ethers in their ability to form stable complexes with metal ions. The structure of the monensin–sodium bromide complex is depicted in Figure 16.3*b*, where it can be seen that four ether oxygens and two hydroxyl groups surround a sodium ion. The alkyl groups are oriented toward the outside of the complex, and the polar oxygens and the metal ion are on the inside. The hydrocarbon-like surface of the complex permits it to carry its sodium ion through the hydrocarbon-like interior of a cell membrane. This disrupts the normal balance of sodium ions within the cell and interferes with important processes of cellular respiration. Small amounts of monensin are added to poultry feed in order to kill parasites that live in the intestines of chickens. Compounds such as monensin and the crown ethers that affect metal ion transport are referred to as **ionophores** ("ion carriers").
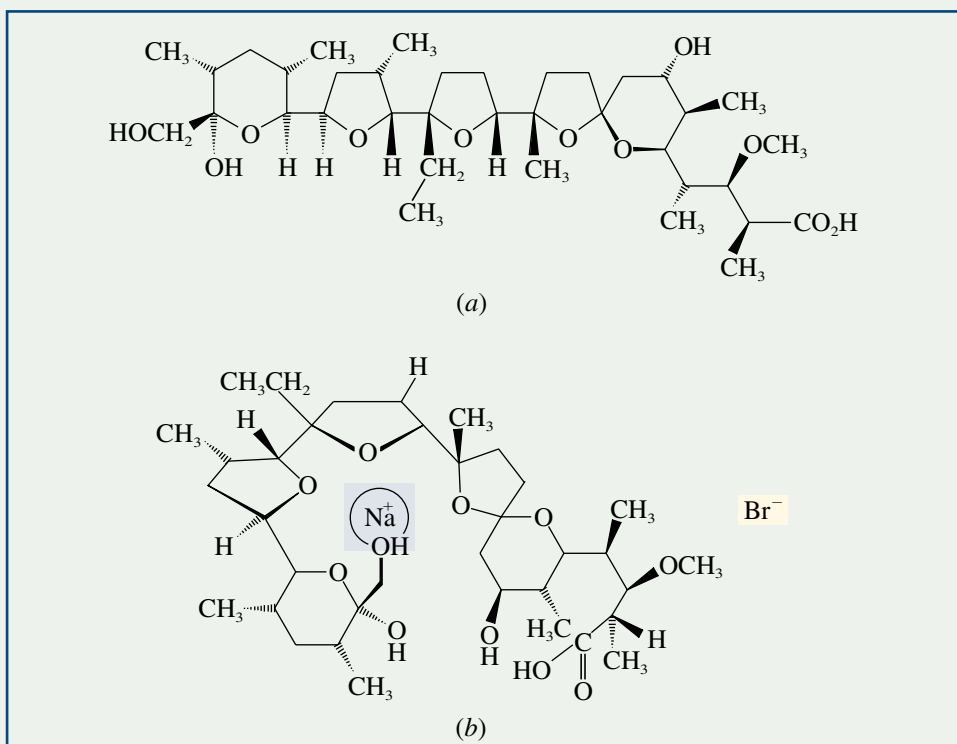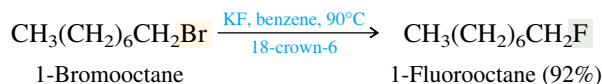


FIGURE 16.3 (*a*) The structure of monensin; (*b*) the structure of the monensin–sodium bromide complex showing coordination of sodium ion by oxygen atoms of monensin.

this complex (Figure 16.2*b*), $K^+$, with an ionic radius of 266 pm, fits comfortably within the 260–320 pm internal cavity of 18-crown-6. Nonpolar $CH_2$ groups dominate the outer surface of the complex, mask its polar interior, and permit the complex to dissolve in nonpolar solvents. Every $K^+$ that is carried into benzene brings a fluoride ion with it, resulting in a solution containing strongly complexed potassium ions and relatively unsolvated fluoride ions.



| 18-Crown-6 | Potassium fluoride (solid) | 18-Crown-6-potassium fluoride complex (in solution) |
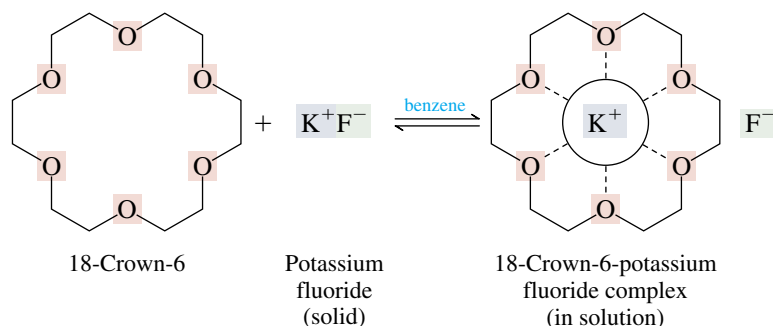
In media such as water and alcohols, fluoride ion is strongly solvated by hydrogen bonding and is neither very basic nor very nucleophilic. On the other hand, the poorly solvated, or "naked," fluoride ions that are present when potassium fluoride dissolves in benzene in the presence of a crown ether are better able to express their anionic reactivity. Thus, alkyl halides react with potassium fluoride in benzene containing 18-crown-6, thereby providing a method for the preparation of otherwise difficultly accessible alkyl fluorides.

$$CH_3(CH_2)_6CH_2Br \xrightarrow[\text{18-crown-6}]{\text{KF, benzene, 90°C}} CH_3(CH_2)_6CH_2F$$

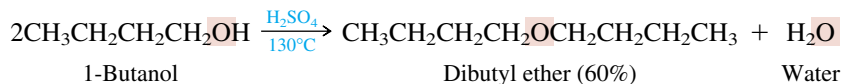| 1-Bromooctane | 1-Fluorooctane (92%) |

The reaction proceeds in the direction indicated because a C—F bond is much stronger than a C—Br bond.

No reaction is observed when the process is carried out under comparable conditions but with the crown ether omitted.

Catalysis by crown ethers has been used to advantage to increase the rate of many organic reactions that involve anions as reactants. Just as important, though, is the increased understanding that studies of crown ether catalysis have brought to our knowledge of biological processes in which metal ions, including $Na^+$ and $K^+$, are transported through the nonpolar interiors of cell membranes.
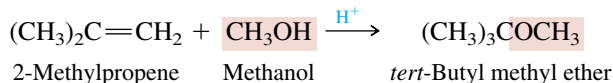
## 16.5  PREPARATION OF ETHERS

Because they are widely used as solvents, many simple dialkyl ethers are commercially available. Diethyl ether and dibutyl ether, for example, are prepared by acid-catalyzed condensation of the corresponding alcohols, as described earlier in Section 15.7.

$$2CH_3CH_2CH_2CH_2OH \xrightarrow[\text{130°C}]{H_2SO_4} CH_3CH_2CH_2CH_2OCH_2CH_2CH_2CH_3 + H_2O$$

| 1-Butanol | Dibutyl ether (60%) | Water |

In general, this method is limited to the preparation of symmetrical ethers in which both alkyl groups are primary. Isopropyl alcohol, however, is readily available at low cost and gives high enough yields of diisopropyl ether to justify making $(CH_3)_2CHOCH(CH_3)_2$ by this method on an industrial scale.

Approximately $4 \times 10^9$ lb of *tert*-butyl methyl ether is prepared in the United States each year by the acid-catalyzed addition of methanol to 2-methylpropene:

$$(CH_3)_2C{=}CH_2 + \underset{\text{Methanol}}{CH_3OH} \xrightarrow{H^+} \underset{\textit{tert}\text{-Butyl methyl ether}}{(CH_3)_3COCH_3}$$

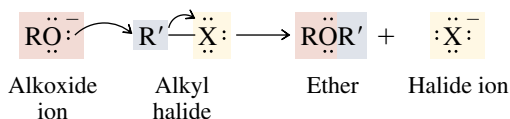$$\underset{\text{2-Methylpropene}}{}$$

Small amounts of *tert*-butyl methyl ether are added to gasoline as an octane booster. The daily consumption of gasoline is so high that the demand for *tert*-butyl methyl ether exceeds our present capacity to produce it.

> *tert*-Butyl methyl ether is often referred to as MTBE, standing for the incorrect name "methyl *tert*-butyl ether." Remember, italicized prefixes are ignored when alphabetizing, and *tert*-butyl precedes methyl.

**PROBLEM 16.5**  Outline a reasonable mechanism for the formation of *tert*-butyl methyl ether according to the preceding equation.
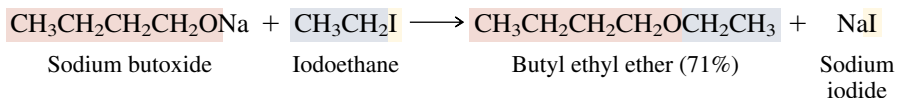
The following section describes a versatile method for preparing either symmetrical or unsymmetrical ethers that is based on the principles of bimolecular nucleophilic substitution.

## 16.6  THE WILLIAMSON ETHER SYNTHESIS

> The reaction is named for Alexander Williamson, a British chemist who used it to prepare diethyl ether in 1850.

A long-standing method for the preparation of ethers is the **Williamson ether synthesis.** Nucleophilic substitution of an alkyl halide by an alkoxide gives the carbon–oxygen bond of an ether:
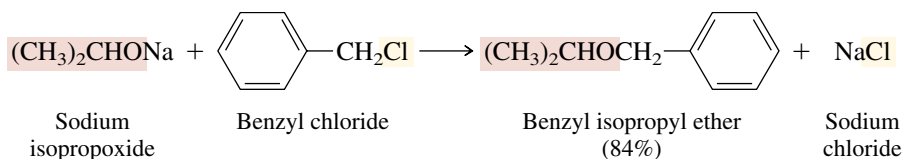
$$\underset{\substack{\text{Alkoxide}\\\text{ion}}}{R\ddot{O}:^-} \quad \underset{\substack{\text{Alkyl}\\\text{halide}}}{R'{-}\ddot{X}:} \longrightarrow \underset{\text{Ether}}{R\ddot{O}R'} + \underset{\text{Halide ion}}{:\ddot{X}:^-}$$

Preparation of ethers by the Williamson ether synthesis is most successful when the alkyl halide is one that is reactive toward $S_N2$ substitution. Methyl halides and primary alkyl halides are the best substrates.

$$\underset{\text{Sodium butoxide}}{CH_3CH_2CH_2CH_2ONa} + \underset{\text{Iodoethane}}{CH_3CH_2I} \longrightarrow \underset{\text{Butyl ethyl ether (71\%)}}{CH_3CH_2CH_2CH_2OCH_2CH_3} + \underset{\substack{\text{Sodium}\\\text{iodide}}}{NaI}$$

**PROBLEM 16.6**  Write equations describing two different ways in which benzyl ethyl ether could be prepared by a Williamson ether synthesis.
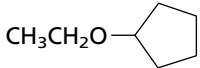
Secondary and tertiary alkyl halides are not suitable, because they tend to react with alkoxide bases by E2 elimination rather than by $S_N2$ substitution. Whether the alkoxide base is primary, secondary, or tertiary is much less important than the nature of the alkyl halide. Thus benzyl isopropyl ether is prepared in high yield from benzyl chloride, a primary chloride that is incapable of undergoing elimination, and sodium isopropoxide:

$$\underset{\substack{\text{Sodium}\\\text{isopropoxide}}}{(CH_3)_2CHONa} + \underset{\text{Benzyl chloride}}{\phantom{xx}CH_2Cl} \longrightarrow \underset{\substack{\text{Benzyl isopropyl ether}\\(84\%)}}{(CH_3)_2CHOCH_2} + \underset{\substack{\text{Sodium}\\\text{chloride}}}{NaCl}$$

The alternative synthetic route using the sodium salt of benzyl alcohol and an isopropyl halide would be much less effective, because of increased competition from elimination as the alkyl halide becomes more sterically hindered.
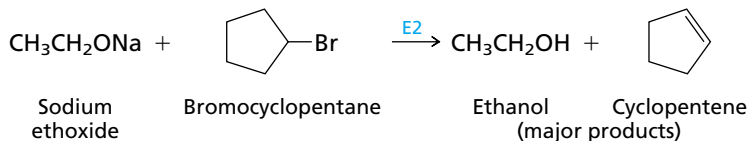
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**PROBLEM 16.7** Only one combination of alkyl halide and alkoxide is appropriate for the preparation of each of the following ethers by the Williamson ether synthesis. What is the correct combination in each case?

(a)

$CH_3CH_2O$—⬠

(c) $(CH_3)_3COCH_2C_6H_5$

(b) $CH_2{=}CHCH_2OCH(CH_3)_2$

**SAMPLE SOLUTION** (a) The ether linkage of cyclopentyl ethyl ether involves a primary carbon and a secondary one. Choose the alkyl halide corresponding to the primary alkyl group, leaving the secondary alkyl group to arise from the alkoxide nucleophile.

⬠—ONa  +  $CH_3CH_2Br$  $\xrightarrow{S_N2}$  ⬠—$OCH_2CH_3$

Sodium cyclopentanolate    Ethyl bromide    Cyclopentyl ethyl ether
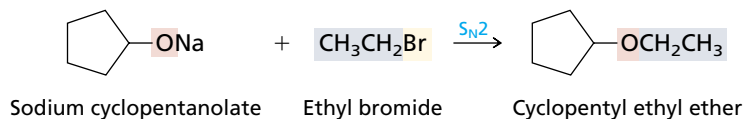
The alternative combination, cyclopentyl bromide and sodium ethoxide, is not appropriate, since elimination will be the major reaction:

$CH_3CH_2ONa$  +  ⬠—Br  $\xrightarrow{E2}$  $CH_3CH_2OH$  +  ⬠

Sodium
ethoxide     Bromocyclopentane        Ethanol      Cyclopentene
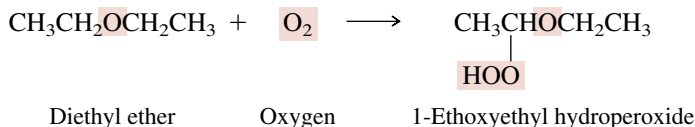                                              (major products)

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Both reactants in the Williamson ether synthesis usually originate in alcohol precursors. Sodium and potassium alkoxides are prepared by reaction of an alcohol with the appropriate metal, and alkyl halides are most commonly made from alcohols by reaction with a hydrogen halide (Section 4.8), thionyl chloride (Section 4.14), or phosphorus tribromide (Section 4.14). Alternatively, alkyl *p*-toluenesulfonates may be used in place of alkyl halides; alkyl *p*-toluenesulfonates are also prepared from alcohols as their immediate precursors (Section 8.14).

## 16.7 REACTIONS OF ETHERS: A REVIEW AND A PREVIEW

Up to this point, we haven't seen any reactions of dialkyl ethers. Indeed, ethers are one of the least reactive of the functional groups we shall study. It is this low level of reactivity, along with an ability to dissolve nonpolar substances, that makes ethers so often used as solvents when carrying out organic reactions. Nevertheless, most ethers are hazardous materials, and precautions must be taken when using them. Diethyl ether is extremely flammable and because of its high volatility can form explosive mixtures in air relatively quickly. Open flames must never be present in laboratories where diethyl ether is being used. Other low-molecular-weight ethers must also be treated as fire hazards.

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**PROBLEM 16.8** Combustion in air is, of course, a chemical property of ethers that is shared by many other organic compounds. Write a balanced chemical equation for the complete combustion (in air) of diethyl ether.
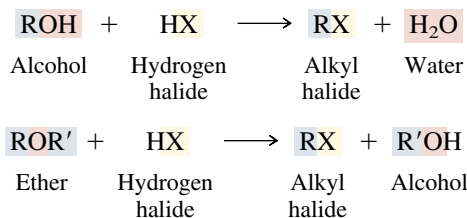
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A second dangerous property of ethers is the ease with which they undergo oxidation in air to form explosive peroxides. Air oxidation of diethyl ether proceeds according to the equation

$$CH_3CH_2OCH_2CH_3 \ + \ O_2 \ \longrightarrow \ CH_3CHOCH_2CH_3$$
$$\underset{HOO}{|}$$

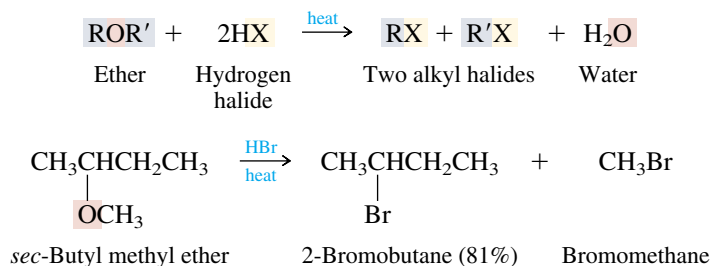Diethyl ether        Oxygen        1-Ethoxyethyl hydroperoxide

The reaction follows a free-radical mechanism and gives a hydroperoxide, a compound of the type ROOH. Hydroperoxides tend to be unstable and shock-sensitive. On standing, they form related peroxidic derivatives, which are also prone to violent decomposition. Air oxidation leads to peroxides within a few days if ethers are even briefly exposed to atmospheric oxygen. For this reason, one should never use old bottles of dialkyl ethers, and extreme care must be exercised in their disposal.

## 16.8    ACID-CATALYZED CLEAVAGE OF ETHERS

Just as the carbon–oxygen bond of alcohols is cleaved on reaction with hydrogen halides (Section 4.8), so too is an ether linkage broken:

$$ROH \ + \ HX \ \longrightarrow \ RX \ + \ H_2O$$

Alcohol      Hydrogen        Alkyl      Water
             halide          halide

$$ROR' \ + \ HX \ \longrightarrow \ RX \ + \ R'OH$$

Ether      Hydrogen        Alkyl      Alcohol
           halide          halide

The cleavage of ethers is normally carried out under conditions (excess hydrogen halide, heat) that convert the alcohol formed as one of the original products to an alkyl halide. Thus, the reaction typically leads to two alkyl halide molecules:

$$ROR' \ + \ 2HX \ \xrightarrow{heat} \ RX \ + \ R'X \ + \ H_2O$$

Ether      Hydrogen        Two alkyl halides      Water
           halide

$$CH_3CHCH_2CH_3 \ \xrightarrow[heat]{HBr} \ CH_3CHCH_2CH_3 \ + \ CH_3Br$$
$$\underset{OCH_3}{|} \qquad\qquad\qquad \underset{Br}{|}$$

sec-Butyl methyl ether        2-Bromobutane (81%)        Bromomethane

The order of hydrogen halide reactivity is HI > HBr >> HCl. Hydrogen fluoride is not effective.
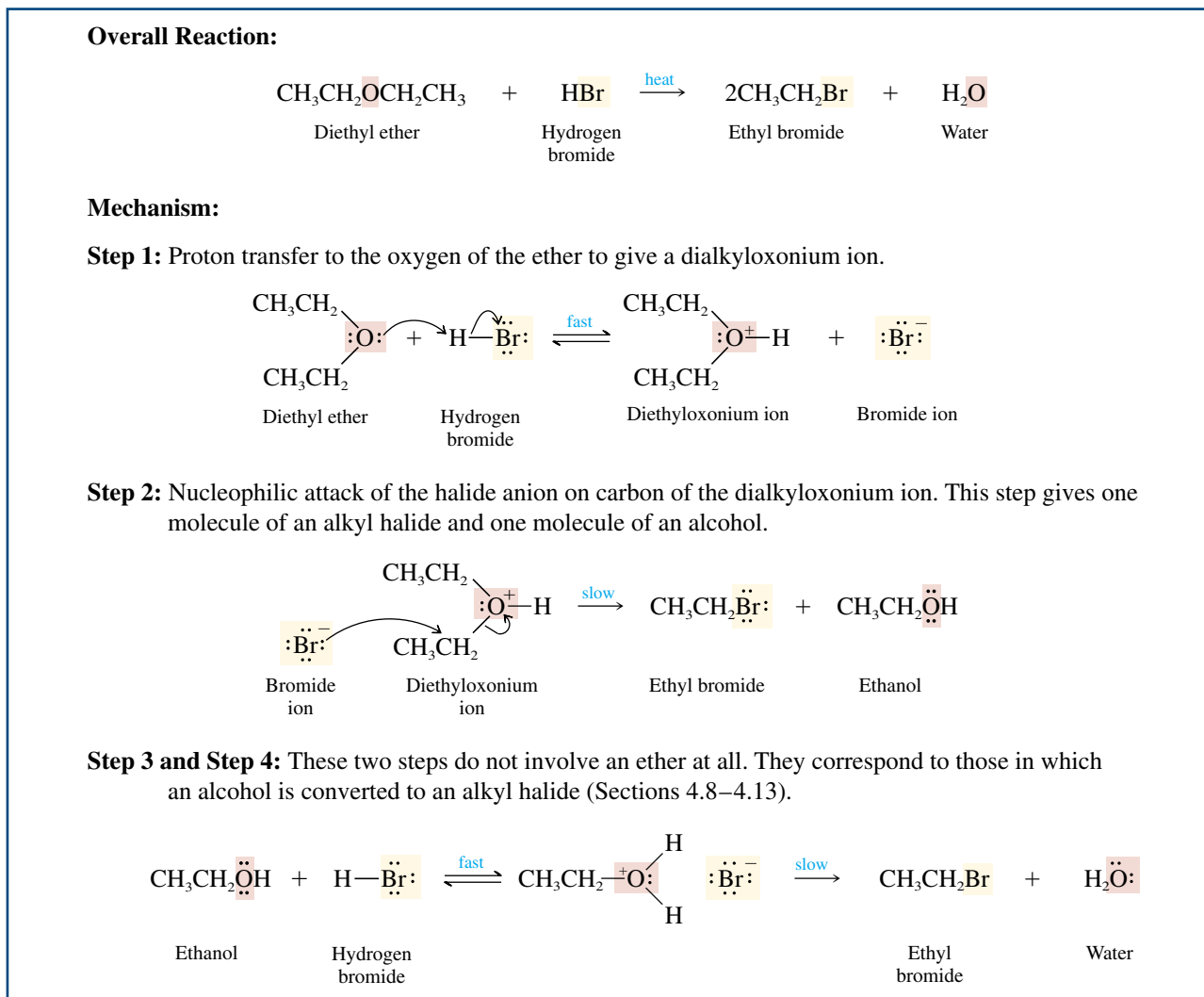
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**PROBLEM 16.9**   A series of dialkyl ethers was allowed to react with excess hydrogen bromide, with the following results. Identify the ether in each case.

   (a) One ether gave a mixture of bromocyclopentane and 1-bromobutane.
   (b) Another ether gave only benzyl bromide.
   (c) A third ether gave one mole of 1,5-dibromopentane per mole of ether.

**SAMPLE SOLUTION** (a) In the reaction of dialkyl ethers with excess hydrogen bromide, each alkyl group of the ether function is cleaved and forms an alkyl bromide. Since bromocyclopentane and 1-bromobutane are the products, the starting ether must be butyl cyclopentyl ether.
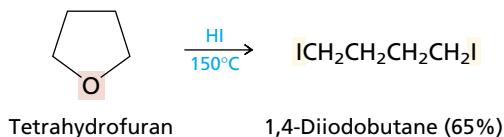


Butyl cyclopentyl ether                    Bromocyclopentane    1-Bromobutane
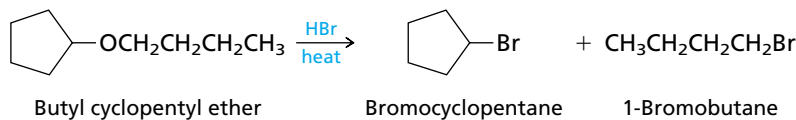
A mechanism for the cleavage of diethyl ether by hydrogen bromide is outlined in Figure 16.4. The key step is an $S_N2$-like attack on a dialkyloxonium ion by bromide (step 2).

**Overall Reaction:**

$$CH_3CH_2OCH_2CH_3 \quad + \quad HBr \xrightarrow{heat} \quad 2CH_3CH_2Br \quad + \quad H_2O$$

Diethyl ether                    Hydrogen          Ethyl bromide          Water
                                 bromide

**Mechanism:**

**Step 1:** Proton transfer to the oxygen of the ether to give a dialkyloxonium ion.



Diethyl ether        Hydrogen          Diethyloxonium ion       Bromide ion
                     bromide

**Step 2:** Nucleophilic attack of the halide anion on carbon of the dialkyloxonium ion. This step gives one molecule of an alkyl halide and one molecule of an alcohol.



Bromide          Diethyloxonium          Ethyl bromide          Ethanol
ion                  ion

**Step 3 and Step 4:** These two steps do not involve an ether at all. They correspond to those in which an alcohol is converted to an alkyl halide (Sections 4.8–4.13).



Ethanol          Hydrogen                                      Ethyl          Water
                 bromide                                       bromide

FIGURE 16.4 The mechanism for the cleavage of ethers by hydrogen halides, using the reaction of diethyl ether with hydrogen bromide as an example.

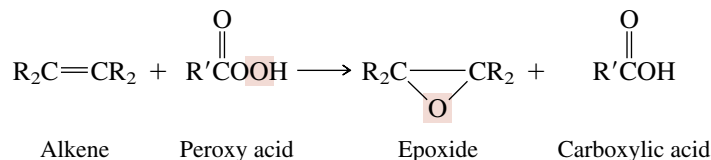**PROBLEM 16.10**   Adapt the mechanism shown in Figure 16.4 to the reaction:

$$\underset{\text{Tetrahydrofuran}}{\text{(cyclic ether with O)}} \xrightarrow[150°C]{\text{HI}} \underset{\text{1,4-Diiodobutane (65\%)}}{\text{ICH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{I}}$$

With mixed ethers of the type ROR′, the question of which carbon–oxygen bond is broken first arises. Although some studies have been carried out on this point of mechanistic detail, it is not one that we need examine at our level of study.

## 16.9   PREPARATION OF EPOXIDES: A REVIEW AND A PREVIEW

There are two main laboratory methods for the preparation of epoxides:

1. Epoxidation of alkenes by reaction with peroxy acids
2. Base-promoted ring closure of vicinal halohydrins

Epoxidation of alkenes was discussed in Section 6.18 and is represented by the general equation

$$\underset{\text{Alkene}}{\text{R}_2\text{C}=\text{CR}_2} + \underset{\text{Peroxy acid}}{\text{R}'\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OOH}} \longrightarrow \underset{\text{Epoxide}}{\text{R}_2\text{C}\underset{\text{O}}{-}\text{CR}_2} + \underset{\text{Carboxylic acid}}{\text{R}'\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OH}}$$

The reaction is easy to carry out, and yields are usually high. Epoxidation is a stereospecific syn addition.

$$\underset{(E)\text{-1,2-Diphenylethene}}{\overset{\text{C}_6\text{H}_5}{\underset{\text{H}}{>}}\text{C}=\text{C}\overset{\text{H}}{\underset{\text{C}_6\text{H}_5}{<}}} + \underset{\substack{\text{Peroxyacetic}\\\text{acid}}}{\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OOH}} \longrightarrow \underset{\substack{trans\text{-2,3-Diphenyloxirane}\\(78\text{–}83\%)}}{\overset{\text{C}_6\text{H}_5}{\underset{\text{H}}{>}}\underset{\text{O}}{\triangle}\overset{\text{H}}{\underset{\text{C}_6\text{H}_5}{<}}} + \underset{\text{Acetic acid}}{\text{CH}_3\overset{\text{O}}{\overset{\|}{\text{C}}}\text{OH}}$$
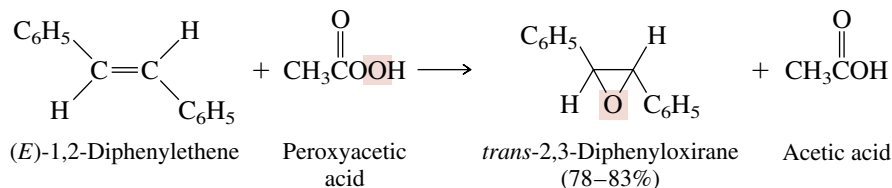
The following section describes the preparation of epoxides by the base-promoted ring closure of vicinal halohydrins. Since vicinal halohydrins are customarily prepared from alkenes (Section 6.17), both methods—epoxidation using peroxy acids and ring closure of halohydrins—are based on alkenes as the starting materials for preparing epoxides.

## 16.10  CONVERSION OF VICINAL HALOHYDRINS TO EPOXIDES

The formation of vicinal halohydrins from alkenes was described in Section 6.17. Halohydrins are readily converted to epoxides on treatment with base:
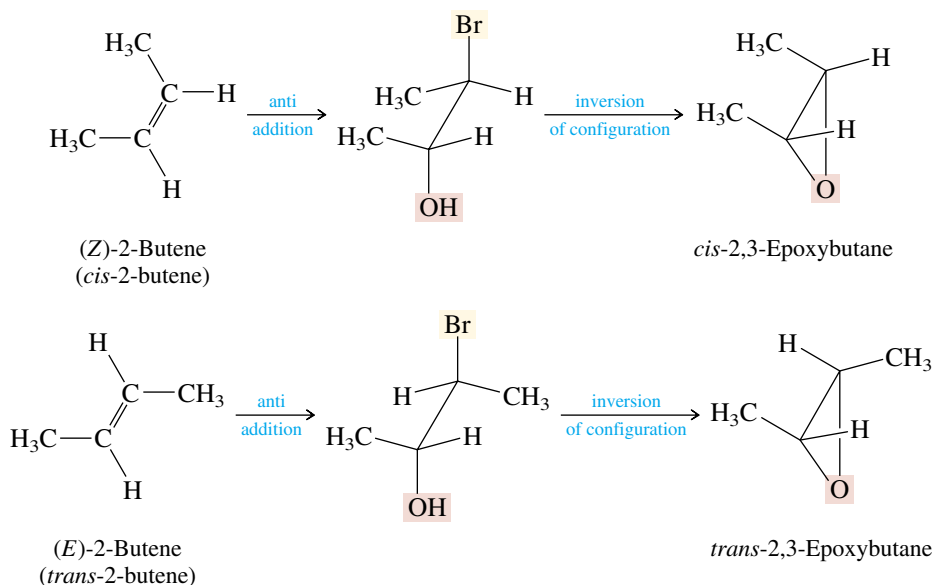
$$\underset{\text{Alkene}}{\text{R}_2\text{C}=\text{CR}_2} \xrightarrow[\text{H}_2\text{O}]{\text{X}_2} \underset{\text{Vicinal halohydrin}}{\underset{\substack{| \quad | \\ \text{HO} \quad \text{X}}}{\text{R}_2\text{C}-\text{CR}_2}} \xrightarrow{\text{HO}^-} \underset{\text{Epoxide}}{\text{R}_2\text{C}\underset{\text{O}}{-}\text{CR}_2}$$
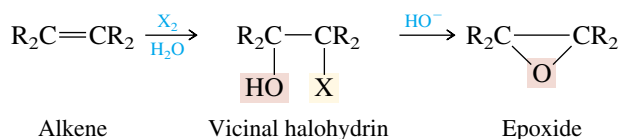
Reaction with base brings the alcohol function of the halohydrin into equilibrium with its corresponding alkoxide:

Vicinal halohydrin
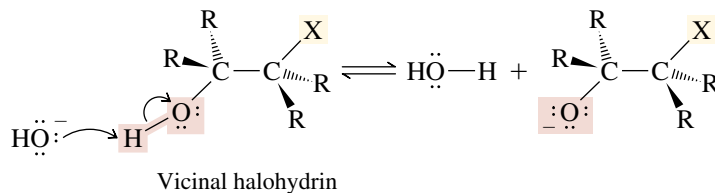
Next, in what amounts to an *intramolecular* Williamson ether synthesis, the alkoxide oxygen attacks the carbon that bears the halide leaving group, giving an epoxide. As in other nucleophilic substitutions, the nucleophile approaches carbon from the side opposite the bond to the leaving group:

Epoxide

NaOH
H₂O

*trans*-2-Bromocyclohexanol          1,2-Epoxycyclohexane (81%)
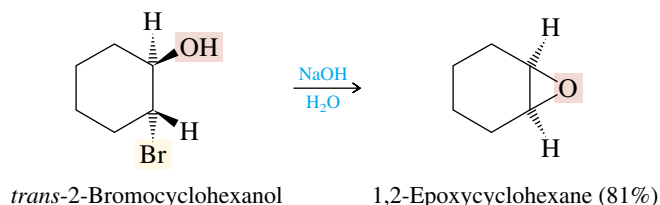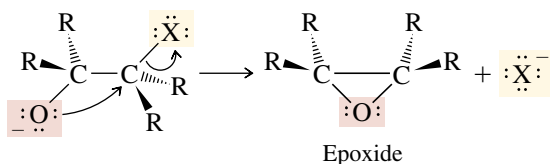
Overall, the stereospecificity of this method is the same as that observed in peroxy acid oxidation of alkenes. Substituents that are cis to each other in the alkene remain cis in the epoxide. This is because formation of the bromohydrin involves anti addition, and the ensuing intramolecular nucleophilic substitution reaction takes place with inversion of configuration at the carbon that bears the halide leaving group.

anti addition → inversion of configuration →

(Z)-2-Butene
(*cis*-2-butene)                                                                *cis*-2,3-Epoxybutane

anti addition → inversion of configuration →

(E)-2-Butene
(*trans*-2-butene)                                                          *trans*-2,3-Epoxybutane

> **PROBLEM 16.11**   Is either of the epoxides formed in the preceding reactions chiral? Is either epoxide optically active when prepared from the alkene by this method?

About $2 \times 10^9$ lb/year of 1,2-epoxypropane is produced in the United States as an intermediate in the preparation of various polymeric materials, including polyurethane plastics and foams and polyester resins. A large fraction of the 1,2-epoxypropane is made from propene by way of its chlorohydrin.

## 16.11 REACTIONS OF EPOXIDES: A REVIEW AND A PREVIEW

*Angle strain is the main source of strain in epoxides, but torsional strain that results from the eclipsing of bonds on adjacent carbons is also present. Both kinds of strain are relieved when a ring-opening reaction occurs.*

The most striking chemical property of epoxides is their far greater reactivity toward nucleophilic reagents compared with that of simple ethers. Epoxides react rapidly with nucleophiles under conditions in which other ethers are inert. This enhanced reactivity results from the ring strain of epoxides. Reactions that lead to ring opening relieve this strain.

We saw an example of nucleophilic ring opening of epoxides in Section 15.4, where the reaction of Grignard reagents with ethylene oxide was described as a synthetic route to primary alcohols:

$$\text{RMgX} \;+\; H_2C\!\!-\!\!CH_2 \xrightarrow[\text{2. } H_3O^+]{\text{1. diethyl ether}} \text{RCH}_2\text{CH}_2\text{OH}$$

| Grignard reagent | Ethylene oxide | | Primary alcohol |
|---|---|---|---|



Benzylmagnesium chloride    Ethylene oxide    3-Phenyl-1-propanol (71%)
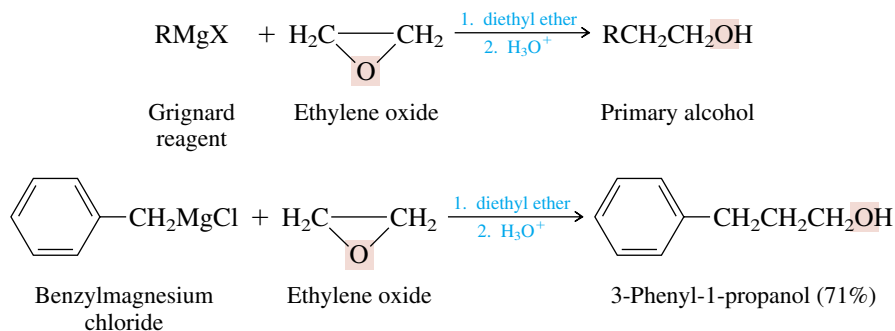
Nucleophiles other than Grignard reagents also open epoxide rings. There are two fundamental ways in which these reactions are carried out. The first (Section 16.12) involves anionic nucleophiles in neutral or basic solution.



Nucleophile    Epoxide    Alkoxide ion    Alcohol
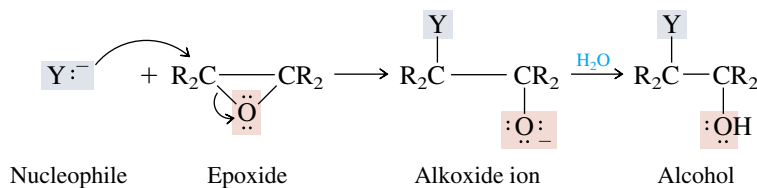
These reactions are usually performed in water or alcohols as solvents, and the alkoxide ion intermediate is rapidly transformed to an alcohol by proton transfer.

Nucleophilic ring-opening reactions of epoxides may also occur under conditions of acid catalysis. Here the nucleophile is not an anion but rather a solvent molecule.



Epoxide    Alcohol
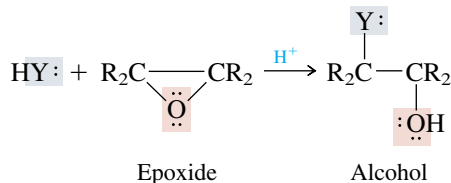
Acid-catalyzed ring opening of epoxides is discussed in Section 16.13.

*There is an important difference in the regiochemistry of ring-opening reactions of epoxides depending on the reaction conditions.* Unsymmetrically substituted epoxides tend to react with anionic nucleophiles at the less hindered carbon of the ring. Under conditions of acid catalysis, however, the more highly substituted carbon is attacked.

Nucleophiles attack here when reaction is catalyzed by acids. → RCH—CH₂ ← Anionic nucleophiles attack here.
$$\text{RCH}\!\!-\!\!\text{CH}_2$$ with O bridging
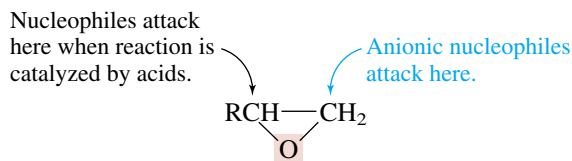
The underlying reasons for this difference in regioselectivity will be explained in Section 16.13.

## 16.12 NUCLEOPHILIC RING-OPENING REACTIONS OF EPOXIDES

Ethylene oxide is a very reactive substance. It reacts rapidly and exothermically with anionic nucleophiles to yield 2-substituted derivatives of ethanol by cleaving the carbon–oxygen bond of the ring:

$$\text{H}_2\text{C}\!\!-\!\!\text{CH}_2 \xrightarrow[\text{ethanol–water, 0°C}]{\text{KSCH}_2\text{CH}_2\text{CH}_2\text{CH}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SCH}_2\text{CH}_2\text{OH}$$

Ethylene oxide (oxirane)    2-(Butylthio)ethanol (99%)

---
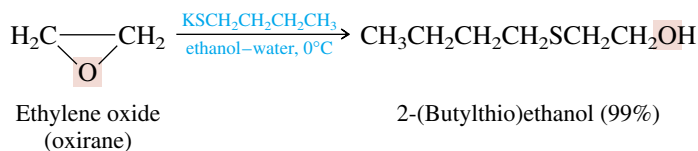
**PROBLEM 16.12**  What is the principal organic product formed in the reaction of ethylene oxide with each of the following?

(a) Sodium cyanide (NaCN) in aqueous ethanol
(b) Sodium azide (NaN₃) in aqueous ethanol
(c) Sodium hydroxide (NaOH) in water
(d) Phenyllithium (C₆H₅Li) in ether, followed by addition of dilute sulfuric acid
(e) 1-Butynylsodium (CH₃CH₂C≡CNa) in liquid ammonia

**SAMPLE SOLUTION**  (a) Sodium cyanide is a source of the nucleophilic cyanide anion. Cyanide ion attacks ethylene oxide, opening the ring and forming 2-cyanoethanol:

$$\text{H}_2\text{C}\!\!-\!\!\text{CH}_2 \xrightarrow[\text{ethanol–water}]{\text{NaCN}} \text{NCCH}_2\text{CH}_2\text{OH}$$

Ethylene oxide    2-Cyanoethanol

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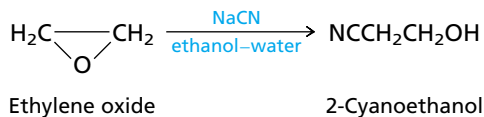
Nucleophilic ring opening of epoxides has many of the features of an S_N2 reaction. Inversion of configuration is observed at the carbon at which substitution occurs.

$$\xrightarrow[\text{CH}_3\text{CH}_2\text{OH}]{\text{NaOCH}_2\text{CH}_3}$$

1,2-Epoxycyclopentane    *trans*-2-Ethoxycyclopentanol (67%)
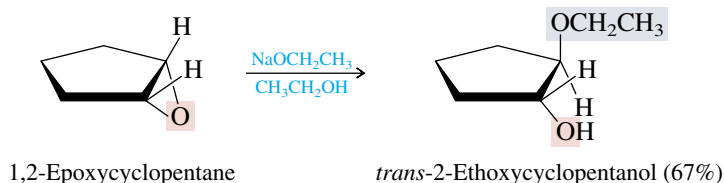
Manipulating models of these compounds can make it easier to follow the stereochemistry.

$$(2R,3R)\text{-2,3-Epoxybutane} \xrightarrow{\text{NH}_3,\ \text{H}_2\text{O}} (2R,3S)\text{-3-Amino-2-butanol (70\%)}$$
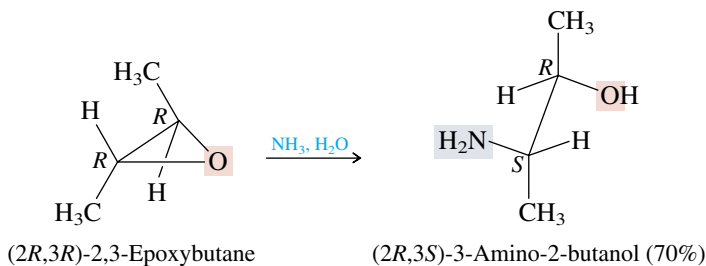
Unsymmetrical epoxides are attacked at the less substituted, less sterically hindered carbon of the ring:

$$2,2,3\text{-Trimethyloxirane} \xrightarrow[\text{CH}_3\text{OH}]{\text{NaOCH}_3} 3\text{-Methoxy-2-methyl-2-butanol (53\%)}$$

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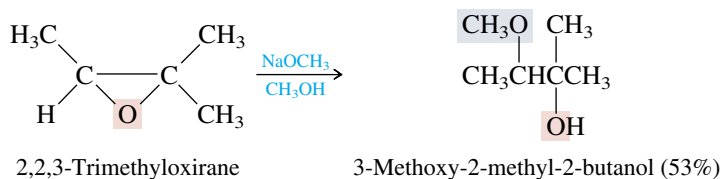
**PROBLEM 16.13** Given the starting material 1-methyl-1,2-epoxycyclopentane, of absolute configuration as shown, decide which one of the compounds A through C correctly represents the product of its reaction with sodium methoxide in methanol.

1-Methyl-1,2-epoxycyclopentane      Compound A      Compound B      Compound C

---
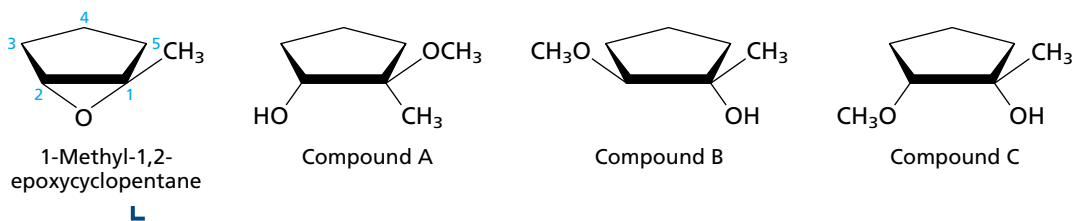
The experimental observations combine with the principles of nucleophilic substitution to give the picture of epoxide ring opening shown in Figure 16.5. The nucleophile attacks the less crowded carbon from the side opposite the carbon–oxygen bond. Bond formation with the nucleophile accompanies carbon–oxygen bond breaking, and a substantial portion of the strain in the three-membered ring is relieved as it begins to open in the transition state. The initial product of nucleophilic substitution is an alkoxide anion, which rapidly abstracts a proton from the solvent to give a β-substituted alcohol as the isolated product.

The reaction of Grignard reagents with epoxides is regioselective in the same sense. Attack occurs at the less substituted carbon of the ring.

**FIGURE 16.5** Nucleophilic ring opening of an epoxide.



Nucleophile      Epoxide          Transition state            Alkoxide ion            β-Substituted alcohol

$$C_6H_5MgBr \quad + \quad H_2C\!\!-\!\!-\!\!-\!\!CHCH_3 \xrightarrow[\text{2. } H_3O^+]{\text{1. diethyl ether}} C_6H_5CH_2CHCH_3$$

Phenylmagnesium bromide          1,2-Epoxypropane          1-Phenyl-2-propanol (60%)
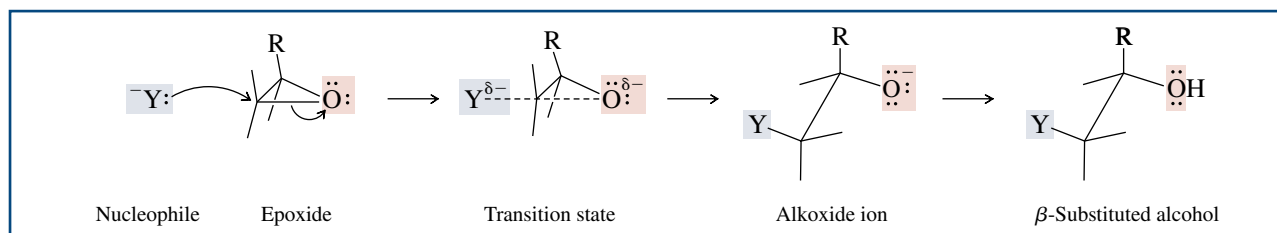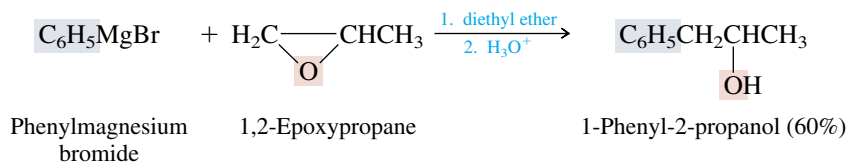
Epoxides are reduced to alcohols on treatment with lithium aluminum hydride. Hydride is transferred to the less crowded carbon.

$$H_2C\!\!-\!\!-\!\!-\!\!CH(CH_2)_7CH_3 \xrightarrow[\text{2. } H_2O]{\text{1. LiAlH}_4} CH_3CH(CH_2)_7CH_3$$

1,2-Epoxydecane          2-Decanol (90%)
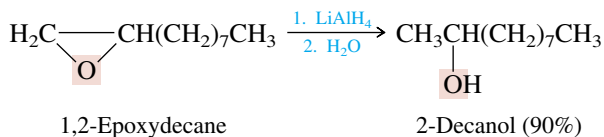
Epoxidation of an alkene, followed by lithium aluminum hydride reduction of the resulting epoxide, gives the same alcohol that would be obtained by acid-catalyzed hydration (Section 6.10) of the alkene.

## 16.13 ACID-CATALYZED RING-OPENING REACTIONS OF EPOXIDES

As we've just seen, nucleophilic ring opening of ethylene oxide yields 2-substituted derivatives of ethanol. Those reactions involved nucleophilic attack on the carbon of the ring under neutral or basic conditions. Other nucleophilic ring-openings of epoxides likewise give 2-substituted derivatives of ethanol but either involve an acid as a reactant or occur under conditions of acid catalysis:

$$H_2C\!\!-\!\!-\!\!-\!\!CH_2 \xrightarrow[\text{10°C}]{\text{HBr}} BrCH_2CH_2OH$$

Ethylene oxide          2-Bromoethanol (87–92%)

$$H_2C\!\!-\!\!-\!\!-\!\!CH_2 \xrightarrow[\text{H}_2\text{SO}_4,\ 25°C]{\text{CH}_3\text{CH}_2\text{OH}} CH_3CH_2OCH_2CH_2OH$$

Ethylene oxide          2-Ethoxyethanol (85%)
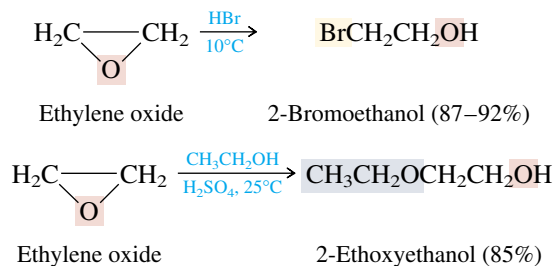
A third example is the industrial preparation of ethylene glycol ($HOCH_2CH_2OH$) by hydrolysis of ethylene oxide in dilute sulfuric acid. This reaction and its mechanism (Figure 16.6) illustrate the difference between the ring openings of epoxides discussed in the preceding section and the acid-catalyzed ones described here. Under conditions of acid catalysis, the species that is attacked by the nucleophile is not the epoxide itself, but rather its conjugate acid. The transition state for ring opening has a fair measure of carbocation character. Breaking of the ring carbon–oxygen bond is more advanced than formation of the bond to the nucleophile.

Transition state for attack by water on conjugate acid of ethylene oxide
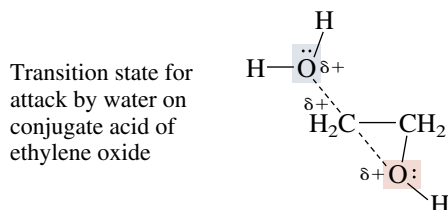
FIGURE 16.6 The mechanism for the acid-catalyzed nucleophilic ring opening of ethylene oxide by water.



**Overall Reaction:**

$H_2C$—$CH_2$ (over O) $+$ $H_2O$ $\xrightarrow{H_3O^+}$ $HOCH_2CH_2OH$

Ethylene oxide     Water     1,2-Ethanediol (ethylene glycol)

**Mechanism:**

**Step 1:** Proton transfer to the oxygen of the epoxide to give an oxonium ion.

Ethylene oxide     Hydronium ion     Ethyleneoxonium ion     Water

**Step 2:** Nucleophilic attack by water on carbon of the oxonium ion. The carbon–oxygen bond of the ring is broken in this step and the ring opens.

Water     Ethyleneoxonium ion     2-Hydroxyethyloxonium ion

**Step 3:** Proton transfer to water completes the reaction and regenerates the acid catalyst.

Water     2-Hydroxyethyloxonium ion     Hydronium ion     1,2-Ethanediol

Because *carbocation* character develops at the transition state, substitution is favored at the carbon that can better support a developing positive charge. Thus, in contrast to the reaction of epoxides with relatively basic nucleophiles, in which $S_N2$-like attack is faster at the less crowded carbon of the three-membered ring, acid catalysis promotes substitution at the position that bears the greater number of alkyl groups:

2,2,3-Trimethyloxirane $\xrightarrow[H_2SO_4]{CH_3OH}$ 3-Methoxy-3-methyl-2-butanol (76%)
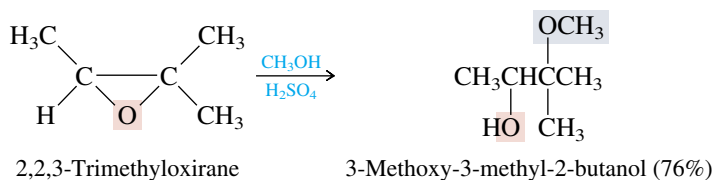
Although nucleophilic participation at the transition state is slight, it is enough to ensure that substitution proceeds with inversion of configuration.



1,2-Epoxycyclohexane          *trans*-2-Bromocyclohexanol (73%)



(2R,3R)-2,3-Epoxybutane       (2R,3S)-3-Methoxy-2-butanol (57%)
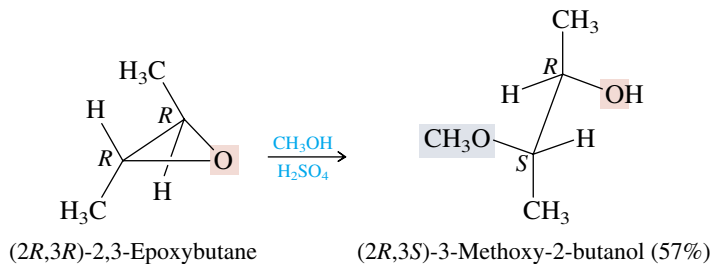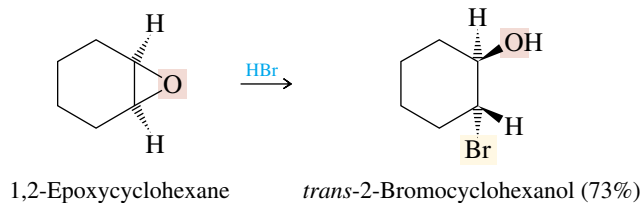
**PROBLEM 16.14**   Which product, compound A, B, or C, would you expect to be formed when 1-methyl-1,2-epoxycyclopentane of the absolute configuration shown is allowed to stand in methanol containing a few drops of sulfuric acid? Compare your answer with that given for Problem 16.13.



1-Methyl-1,2-          Compound A          Compound B          Compound C
epoxycyclopentane
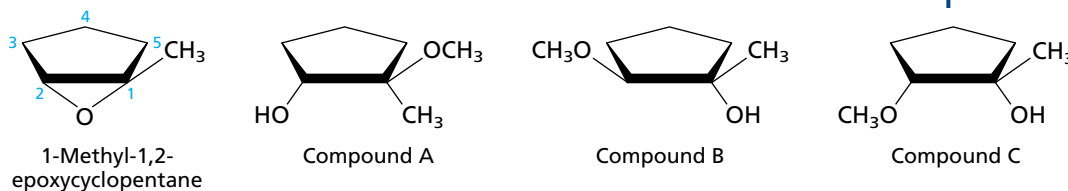
A method for achieving net anti hydroxylation of alkenes combines two stereo-specific processes: epoxidation of the double bond and hydrolysis of the derived epoxide.



Cyclohexene          1,2-Epoxycyclohexane          *trans*-1,2-Cyclohexanediol (80%)
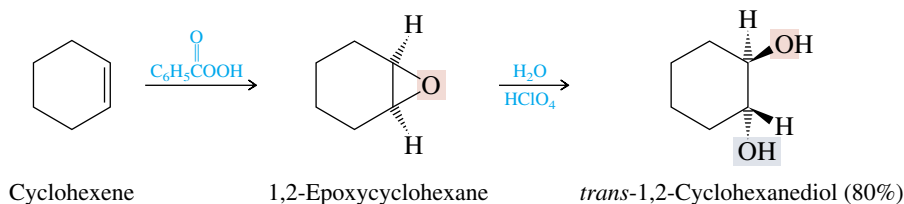
**PROBLEM 16.15**   Which alkene, *cis*-2-butene or *trans*-2-butene, would you choose in order to prepare *meso*-2,3-butanediol by epoxidation followed by acid-catalyzed hydrolysis? Which alkene would yield *meso*-2,3,-butanediol by osmium tetraoxide hydroxylation?

## 16.14  EPOXIDES IN BIOLOGICAL PROCESSES

Many naturally occurring substances are epoxides. You have seen two examples of such compounds already in disparlure, the sex attractant of the gypsy moth (Section 6.18), and in the carcinogenic epoxydiol formed from benzo[a]pyrene (Section 11.8). In most cases, epoxides are biosynthesized by the enzyme-catalyzed transfer of one of the oxygen atoms of an $O_2$ molecule to an alkene. Since only one of the atoms of $O_2$ is

transferred to the substrate, the enzymes that catalyze such transfers are classified as *monooxygenases.* A biological reducing agent, usually the coenzyme NADH (Section 15.11), is required as well.

$$R_2C{=}CR_2 \ + \ O_2 \ + \ H^+ \ + \ NADH \xrightarrow{\text{enzyme}} R_2C\overset{\displaystyle\diagup\diagdown}{\underset{O}{\quad}}CR_2 \ + \ H_2O \ + \ NAD^+$$
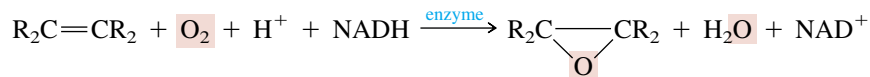
A prominent example of such a reaction is the biological epoxidation of the polyene squalene.



Squalene

$O_2$, NADH, a monooxygenase



Squalene 2,3-epoxide
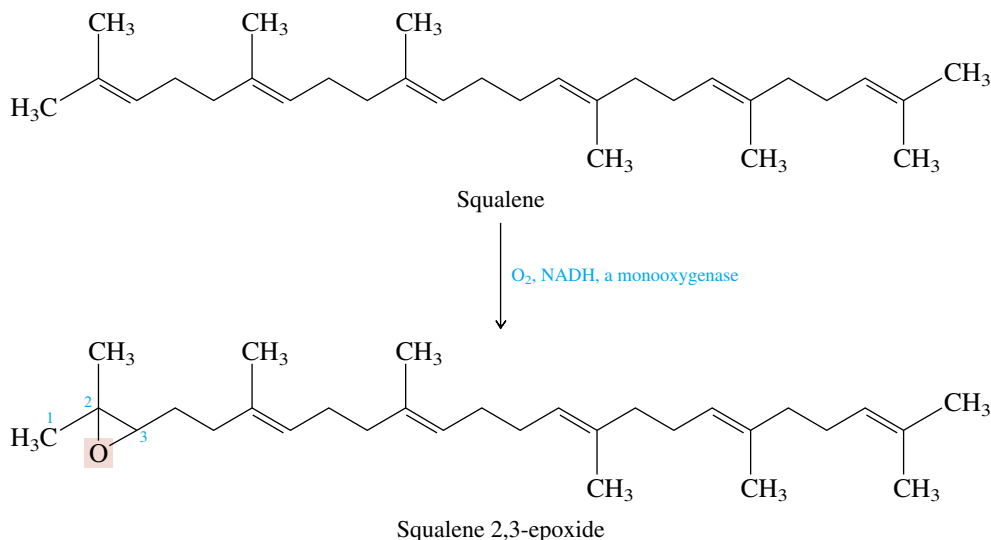
The reactivity of epoxides toward nucleophilic ring opening is responsible for one of the biological roles they play. Squalene 2,3-epoxide, for example, is the biological precursor to cholesterol and the steroid hormones, including testosterone, progesterone, estrone, and cortisone. The pathway from squalene 2,3-epoxide to these compounds is triggered by epoxide ring opening and will be described in Chapter 26.

## 16.15 PREPARATION OF SULFIDES

Sulfides, compounds of the type RSR′, are prepared by nucleophilic substitution reactions. Treatment of a primary or secondary alkyl halide with an alkanethiolate ion (RS⁻) gives a sulfide:



| Sodium alkanethiolate | Alkyl halide | Sulfide | Sodium halide |

$$CH_3CHCH{=}CH_2 \xrightarrow[\text{methanol}]{\text{NaSCH}_3} CH_3CHCH{=}CH_2$$

3-Chloro-1-butene          Methyl 1-methylallyl sulfide (62%)
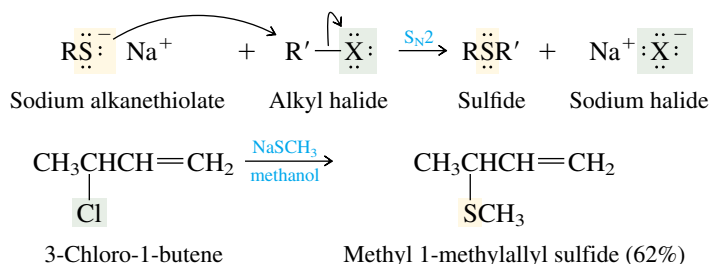
$K_a$ for $CH_3SH$ is $1.8 \times 10^{-11}$ ($pK_a = 10.7$).

It is not necessary to prepare and isolate the sodium alkanethiolate in a separate operation. Because thiols are more acidic than water, they are quantitatively converted to their alkanethiolate anions by sodium hydroxide. Thus, all that is normally done is to add a thiol to sodium hydroxide in a suitable solvent (water or an alcohol) followed by the alkyl halide.

> **PROBLEM 16.16**   The *p*-toluenesulfonate derived from (*R*)-2-octanol and *p*-toluenesulfonyl chloride was allowed to react with sodium benzenethiolate ($C_6H_5SNa$). Give the structure, including stereochemistry and the appropriate *R* or *S* descriptor, of the product.

## 16.16 OXIDATION OF SULFIDES: SULFOXIDES AND SULFONES

We saw in Section 15.14 that thiols differ from alcohols in respect to their behavior toward oxidation. Similarly, sulfides differ from ethers in their behavior toward oxidizing agents. Whereas ethers tend to undergo oxidation at carbon to give hydroperoxides (Section 16.7), sulfides are oxidized at sulfur to give **sulfoxides.** If the oxidizing agent is strong enough and present in excess, oxidation can proceed further to give **sulfones.**



| Sulfide | Sulfoxide | Sulfone |
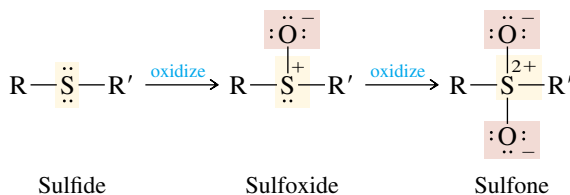
> Third-row elements such as sulfur can expand their valence shell beyond eight electrons, and so sulfur–oxygen bonds in sulfoxides and sulfones are sometimes represented as double bonds.

When the desired product is a sulfoxide, sodium metaperiodate ($NaIO_4$) is an ideal reagent. It oxidizes sulfides to sulfoxides in high yield but shows no tendency to oxidize sulfoxides to sulfones.



| Methyl phenyl sulfide | Sodium metaperiodate | Methyl phenyl sulfoxide (91%) | Sodium iodate |
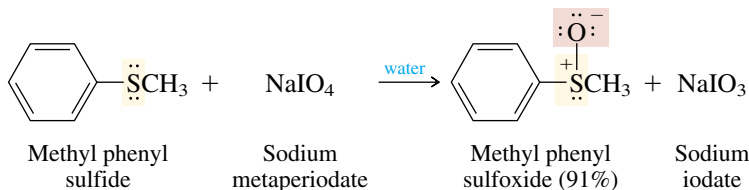
Peroxy acids, usually in dichloromethane as the solvent, are also reliable reagents for converting sulfides to sulfoxides.

One equivalent of a peroxy acid or of hydrogen peroxide converts sulfides to sulfoxides; two equivalents gives the corresponding sulfone.



| Phenyl vinyl sulfide | Hydrogen peroxide | Phenyl vinyl sulfone (74–78%) | Water |
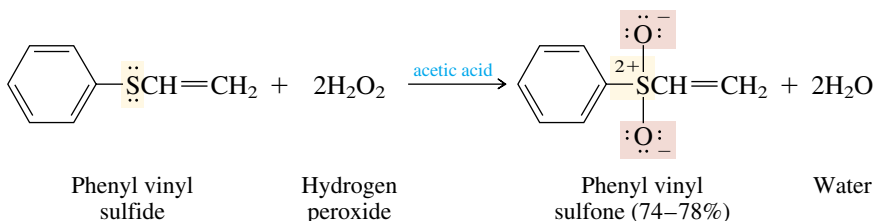
> **PROBLEM 16.17**   Verify, by making molecular models, that the bonds to sulfur are arranged in a trigonal pyramidal geometry in sulfoxides and in a tetrahedral geometry in sulfones. Is phenyl vinyl sulfoxide chiral? What about phenyl vinyl sulfone?

Oxidation of sulfides occurs in living systems as well. Among naturally occurring sulfoxides, one that has received recent attention is *sulforaphane,* which is present in broccoli and other vegetables. Sulforaphane holds promise as a potential anticancer agent because, unlike most anticancer drugs, which act by killing rapidly dividing tumor cells faster than they kill normal cells, sulforaphane is nontoxic and may simply inhibit the formation of tumors.

$$:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:^-$$
$$CH_3\overset{+}{\underset{\cdot\cdot}{S}}CH_2CH_2CH_2CH_2N=C=S$$
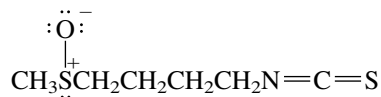
Sulforaphane

## 16.17  ALKYLATION OF SULFIDES: SULFONIUM SALTS

Sulfur is more nucleophilic than oxygen (Section 8.7), and sulfides react with alkyl halides much faster than do ethers. The products of these reactions, called **sulfonium salts,** are also more stable than the corresponding oxygen analogs.



Use *Learning By Modeling* to view the geometry of sulfur in trimethylsulfonium ion.

|   | Sulfide | Alkyl halide | | Sulfonium salt |
|---|---------|--------------|---|----------------|

$$CH_3(CH_2)_{10}CH_2SCH_3 + CH_3I \longrightarrow CH_3(CH_2)_{10}CH_2\overset{CH_3}{\overset{|+}{\underset{\cdot\cdot}{S}}}CH_3 \ I^-$$

Dodecyl methyl sulfide     Methyl iodide     Dodecyldimethylsulfonium iodide

---
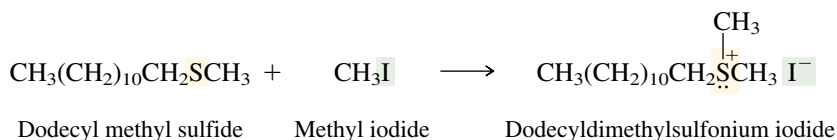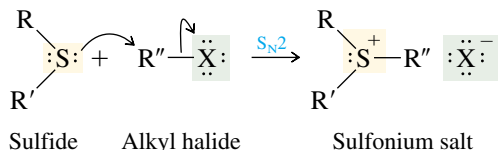
**PROBLEM 16.18**  What other combination of alkyl halide and sulfide will yield the same sulfonium salt shown in the preceding example? Predict which combination will yield the sulfonium salt at the faster rate.

---

The *S* in *S*-adenosylmethionine indicates that the adenosyl group is bonded to sulfur. It does not stand for the Cahn–Ingold–Prelog stereochemical descriptor.

A naturally occurring sulfonium salt, *S-adenosylmethionine (SAM),* is a key substance in certain biological processes. It is formed by a nucleophilic substitution in which the sulfur atom of methionine attacks the primary carbon of adenosine triphosphate, displacing the triphosphate leaving group as shown in Figure 16.7.

*S*-Adenosylmethionine acts as a biological methyl-transfer agent. Nucleophiles, particularly nitrogen atoms of amines, attack the methyl carbon of SAM, breaking the carbon–sulfur bond. The following equation represents the biological formation of *epinephrine* by methylation of *norepinephrine.* Only the methyl group and the sulfur of SAM are shown explicitly in the equation in order to draw attention to the similarity of this reaction, which occurs in living systems, to the more familiar $S_N2$ reactions we have studied.



Norepinephrine     SAM
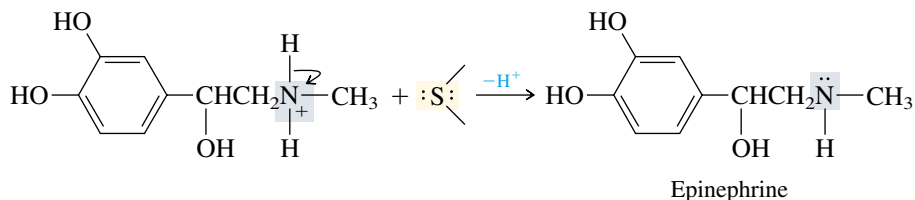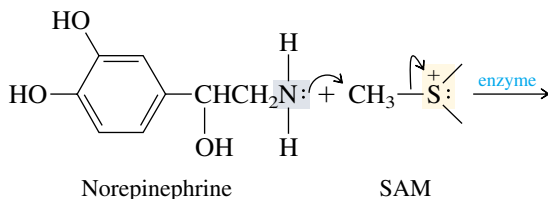
Epinephrine is also known as *adrenaline* and is a hormone with profound physiological effects designed to prepare the body for "fight or flight."



Epinephrine
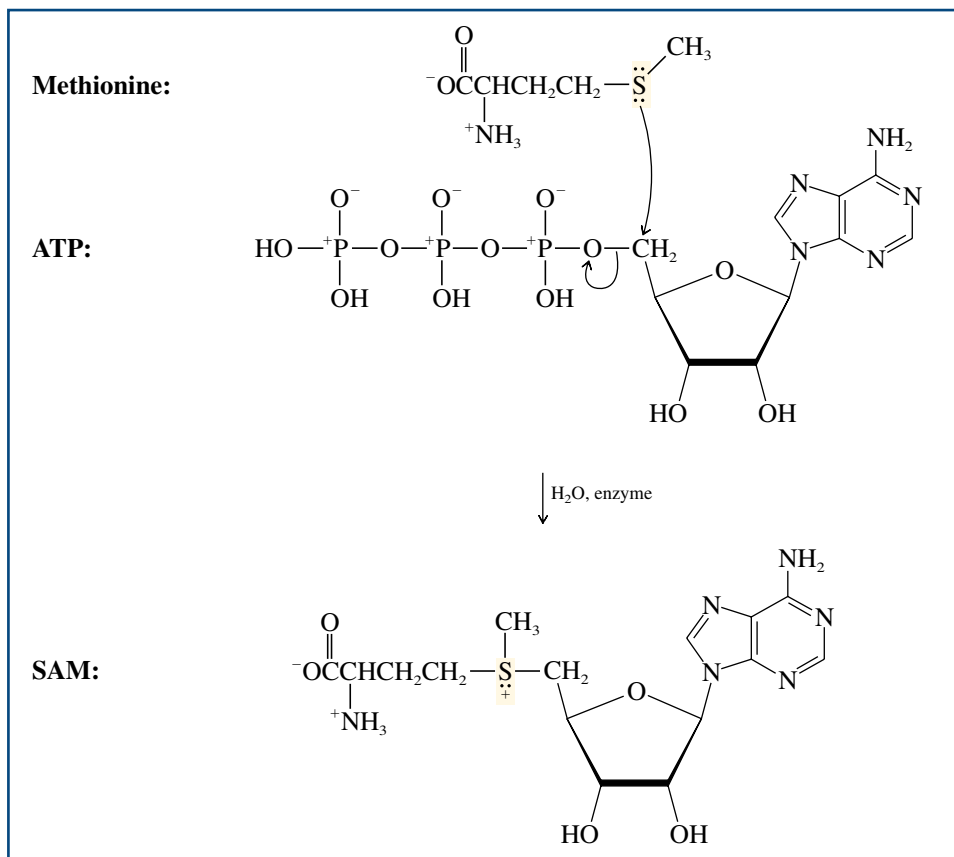
**FIGURE 16.7** Nucleophilic substitution at the primary carbon of adenosine triphosphate (ATP) by the sulfur atom of methionine yields *S*-adenosylmethionine (SAM). The reaction is catalyzed by an enzyme.

## 16.18 SPECTROSCOPIC ANALYSIS OF ETHERS

*Infrared:*   The infrared spectra of ethers are characterized by a strong, rather broad band due to C—O—C stretching between 1070 and 1150 $cm^{-1}$. Dialkyl ethers exhibit this band at near 1100 $cm^{-1}$, as the infrared spectrum of dipropyl ether shows (Figure 16.8).

*$^1H$ NMR:*   The chemical shift of the proton in the **H**—C—O—C unit of an ether is very similar to that of the proton in the **H**—C—OH unit of an alcohol. A range $\delta$ 3.3–4.0 ppm is typical. In the $^1H$ NMR spectrum of dipropyl ether, shown in Figure 16.9, the assignment of signals to the various protons in the molecule is
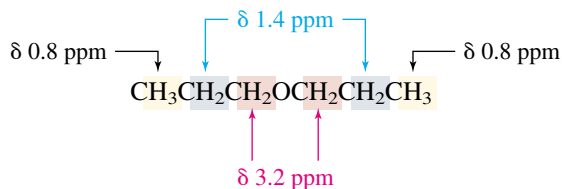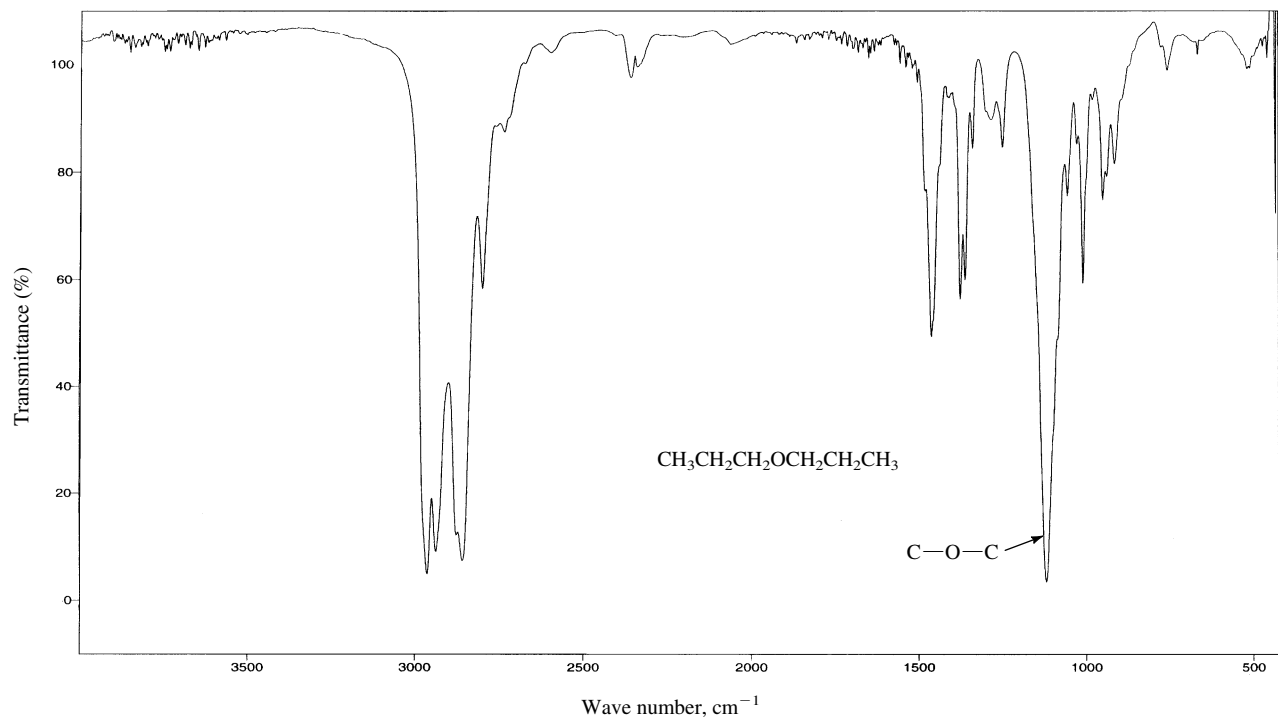
FIGURE 16.8 The infrared spectrum of dipropyl ether ($CH_3CH_2CH_2OCH_2CH_2CH_3$). The strong peak near 1100 cm$^{-1}$ is due to C—O—C stretching.
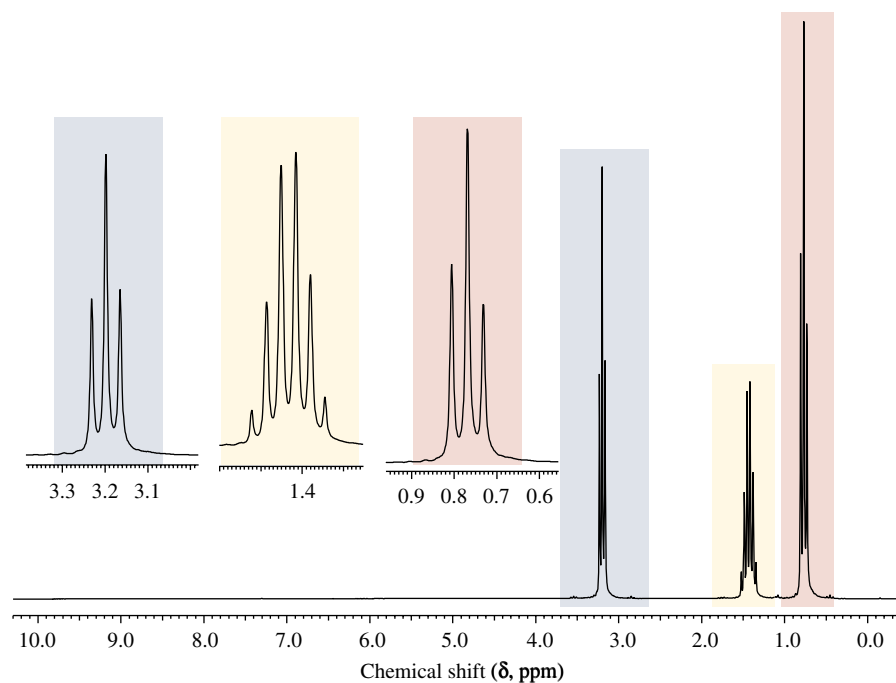


FIGURE 16.9 The 200-MHz $^1$H NMR spectrum of dipropyl ether ($CH_3CH_2CH_2OCH_2CH_2CH_3$).

*13C NMR:* The carbons of an ether function (C—O—C) are about 10 ppm less shielded than those of an alcohol and appear in the range δ 57–87 ppm. The chemical shifts in tetrahydrofuran offer a comparison of C—O—C and C—C—C units.

26.0 ppm

68.0 ppm

O
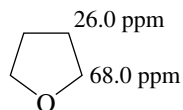
*UV-VIS:* Simple ethers have their absorption maximum at about 185 nm and are transparent to ultraviolet radiation above about 220 nm.

*Mass Spectrometry:* Ethers, like alcohols, lose an alkyl radical from their molecular ion to give an oxygen-stabilized cation. Thus, *m/z* 73 and *m/z* 87 are both more abundant than the molecular ion in the mass spectrum of *sec*-butyl ethyl ether.

$$CH_3CH_2\overset{\cdot\cdot+}{\underset{\cdot\cdot}{O}}—CHCH_2CH_3$$

$$CH_3$$

*m/z* 102

$$CH_3CH_2\overset{+}{\underset{\cdot\cdot}{O}}=CHCH_3 + \cdot CH_2CH_3 \qquad CH_3CH_2\overset{+}{\underset{\cdot\cdot}{O}}=CHCH_2CH_3 + \cdot CH_3$$

*m/z* 73            *m/z* 87
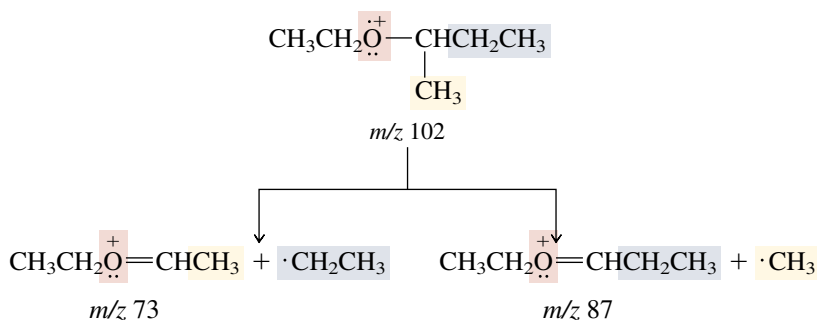
**PROBLEM 16.19** There is another oxygen-stabilized cation of *m/z* 87 capable of being formed by fragmentation of the molecular ion in the mass spectrum of *sec*-butyl ethyl ether. Suggest a reasonable structure for this ion.

## 16.19 SUMMARY

**Section 16.1**    **Ethers** are compounds that contain a C—O—C linkage. In substitutive IUPAC nomenclature, they are named as *alkoxy* derivatives of alkanes. In functional class IUPAC nomenclature, we name each alkyl group as a separate word (in alphabetical order) followed by the word "ether."

$$CH_3OCH_2CH_2CH_2CH_2CH_2CH_3$$

**Substitutive IUPAC name:** 1-Methoxyhexane
**Functional class name:** Hexyl methyl ether

**Epoxides** are normally named as *epoxy* derivatives of alkanes or as substituted *oxiranes.*
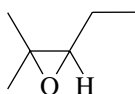
2-Methyl-2,3-epoxypentane
3-Ethyl-2,2-dimethyloxirane

O H

Sulfides are sulfur analogs of ethers: they contain the C—S—C functional group. They are named as *alkylthio* derivatives of alkanes in substitutive IUPAC nomenclature. The functional class IUPAC names of sulfides are derived in the same manner as those of ethers, but the concluding word is "sulfide."

$$CH_3SCH_2CH_2CH_2CH_2CH_2CH_3$$

**Substitutive IUPAC name:** 1-(Methylthio)hexane
**Functional class name:** Hexyl methyl sulfide

**Section 16.2**  The oxygen atom in an ether or epoxide affects the shape of the molecule in much the same way as an $sp^3$-hybridized carbon of an alkane or cycloalkane.
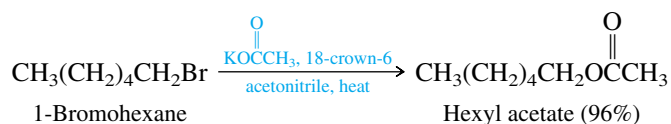


Pentane            Diethyl ether
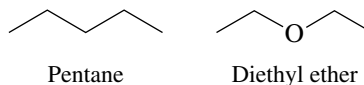
**Section 16.3**  The carbon–oxygen bond of ethers is polar, and ethers can act as proton *acceptors* in hydrogen bonds with water and alcohols.
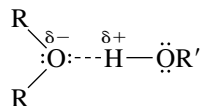


But ethers lack OH groups and cannot act as proton *donors* in forming hydrogen bonds.

**Section 16.4**  Ethers form Lewis acid-Lewis base complexes with metal ions. Certain cyclic polyethers, called **crown ethers,** are particularly effective in coordinating with $Na^+$ and $K^+$, and salts of these cations can be dissolved in nonpolar solvents when crown ethers are present. Under these conditions the rates of many reactions that involve anions are accelerated.

$$CH_3(CH_2)_4CH_2Br \xrightarrow[\text{acetonitrile, heat}]{\text{KOCCH}_3,\ 18\text{-crown-6}} CH_3(CH_2)_4CH_2OCCH_3$$

1-Bromohexane                         Hexyl acetate (96%)

**Sections 16.5 and 16.6**  The two major methods for preparing ethers are summarized in Table 16.1.

| TABLE 16.1 | Preparation of Ethers |
|---|---|
| **Reaction (section) and comments** | **General equation and specific example** |
| **Acid-catalyzed condensation of alcohols (Sections 15.7 and 16.5)** Two molecules of an alcohol condense in the presence of an acid catalyst to yield a dialkyl ether and water. The reaction is limited to the synthesis of symmetrical ethers from primary alcohols. | $2RCH_2OH \xrightarrow{H^+} RCH_2OCH_2R + H_2O$ <br> Alcohol · · · Ether · · · Water <br><br> $CH_3CH_2CH_2OH \xrightarrow[\text{heat}]{H_2SO_4} CH_3CH_2CH_2OCH_2CH_2CH_3$ <br> Propyl alcohol · · · Dipropyl ether |
| **The Williamson ether synthesis (Section 16.6)** An alkoxide ion displaces a halide or similar leaving group in an $S_N2$ reaction. The alkyl halide cannot be one that is prone to elimination, and so this reaction is limited to methyl and primary alkyl halides. There is no limitation on the alkoxide ion that can be used. | $RO^- + R'CH_2X \longrightarrow ROCH_2R' + X^-$ <br> Alkoxide ion · Primary alkyl halide · Ether · Halide ion <br><br> $(CH_3)_2CHCH_2ONa + CH_3CH_2Br \longrightarrow (CH_3)_2CHCH_2OCH_2CH_3 + NaBr$ <br> Sodium isobutoxide · Ethyl bromide · Ethyl isobutyl ether (66%) · Sodium bromide |

Section 16.7    Dialkyl ethers are useful solvents for organic reactions, but dangerous ones due to their tendency to form explosive hydroperoxides by air oxidation in opened bottles.

Section 16.8    The only important reaction of ethers is their cleavage by hydrogen halides.

$$ROR' + 2HX \longrightarrow RX + R'X + H_2O$$

| Ether | Hydrogen halide | Alkyl halide | Alkyl halide | Water |

The order of hydrogen halide reactivity is $HI > HBr > HCl$.



Benzyl ethyl ether        Benzyl bromide        Ethyl bromide
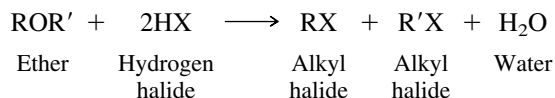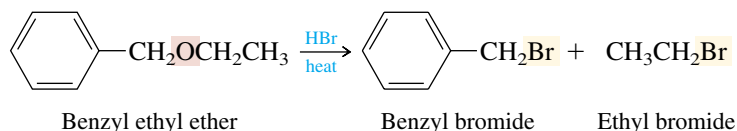
Sections 16.9 and 16.10    Epoxides are prepared by the methods listed in Table 16.2.

Section 16.11    Epoxides are much more reactive than ethers, especially in reactions that lead to cleavage of their three-membered ring.

| TABLE 16.2 | Preparation of Epoxides |
| --- | --- |
| **Reaction (section) and comments** | **General equation and specific example** |
| **Peroxy acid oxidation of alkenes (Sections 6.18 and 16.9)** Peroxy acids transfer oxygen to alkenes to yield epoxides. Stereospecific syn addition is observed. |  |
| **Base-promoted cyclization of vicinal halohydrins (Section 16.10)** This reaction is an intramolecular version of the Williamson ether synthesis. The alcohol function of a vicinal halohydrin is converted to its conjugate base, which then displaces halide from the adjacent carbon to give an epoxide. |  |

**Section 16.12**  Anionic nucleophiles usually attack the less substituted carbon of the epoxide in an $S_N2$-like fashion.

$$RCH{-}CR_2 \;+\; Y^- \;\longrightarrow\; \overset{\displaystyle Y}{RCH{-}CR_2} \;\longrightarrow\; \overset{\displaystyle Y}{RCH{-}CR_2}$$
$$\underset{O}{}\qquad\qquad\qquad\qquad \underset{O_-}{}\qquad\qquad \underset{OH}{}$$

Epoxide        Nucleophile                              β-substituted alcohol



Nucleophile attacks this carbon.

2,2,3-Trimethyloxirane    $\xrightarrow[\text{CH}_3\text{OH}]{\text{NaOCH}_3}$

$$\overset{CH_3O \;\; CH_3}{CH_3CHCCH_3}$$
$$\underset{OH}{}$$

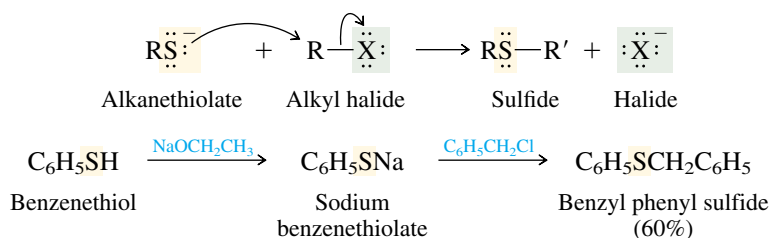3-Methoxy-2-methyl-2-butanol (53%)
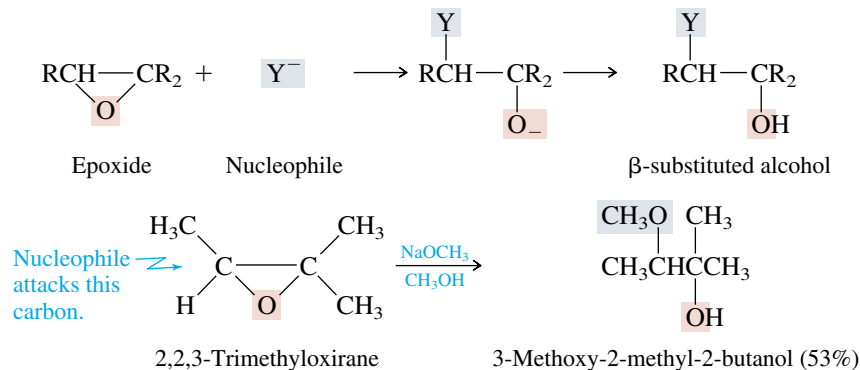
**Section 16.13**  Under conditions of acid catalysis, nucleophiles attack the carbon that can better support a positive charge. Carbocation character is developed in the transition state

$$RCH{-}CR_2 + H^+ \;\rightleftharpoons\; \overset{+}{RCH{-}CR_2} \xrightarrow{HY} \overset{\overset{+}{YH}}{RCH{-}CR_2} \xrightarrow{-H^+} \overset{Y}{RCHCR_2}$$

Epoxide                                                                 β-substituted alcohol



Nucleophile attacks this carbon.

2,2,3-Trimethyloxirane    $\xrightarrow[\text{H}_2\text{SO}_4]{\text{CH}_3\text{OH}}$

$$\overset{OCH_3}{CH_3CHCCH_3}$$
$$\underset{HO \;\; CH_3}{}$$

3-Methoxy-3-methyl-2-butanol (76%)
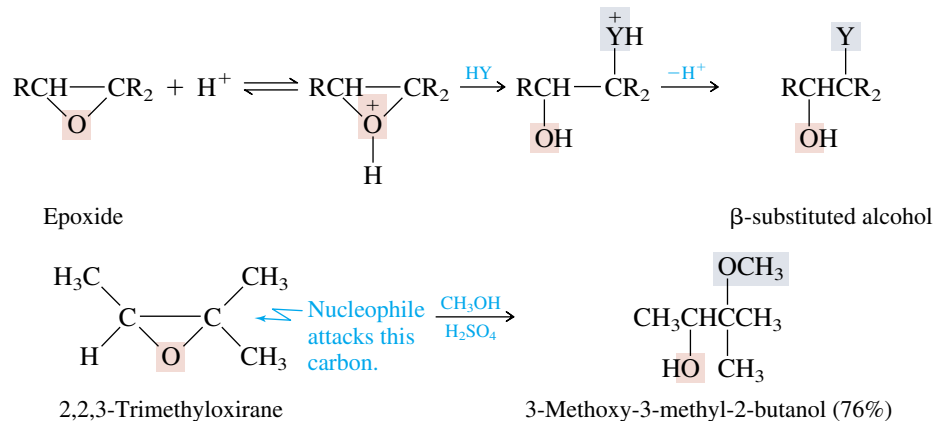
Inversion of configuration is observed at the carbon that is attacked by the nucleophile, irrespective of whether the reaction takes place in acidic or basic solution.
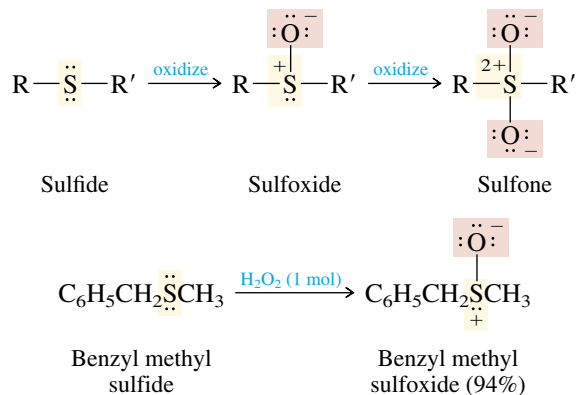
**Section 16.14**  Epoxide functions are present in a great many natural products, and epoxide ring opening is sometimes a key step in the biosynthesis of other substances.

**Section 16.15**  Sulfides are prepared by nucleophilic substitution ($S_N2$) in which an alkanethiolate ion attacks an alkyl halide.

$$R\ddot{S}:^- \;+\; R{-}\ddot{X}: \;\longrightarrow\; R\ddot{S}{-}R' \;+\; :\ddot{X}:^-$$

Alkanethiolate    Alkyl halide              Sulfide        Halide

$$C_6H_5SH \xrightarrow{\text{NaOCH}_2\text{CH}_3} C_6H_5SNa \xrightarrow{\text{C}_6\text{H}_5\text{CH}_2\text{Cl}} C_6H_5SCH_2C_6H_5$$

Benzenethiol            Sodium                Benzyl phenyl sulfide
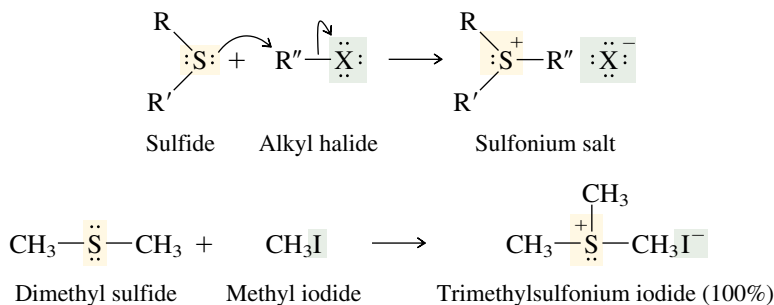                     benzenethiolate                (60%)

**Section 16.16**  Oxidation of sulfides yields sulfoxides, then sulfones. Sodium metaperiodate is specific for the oxidation of sulfides to sulfoxides, and no further.

Hydrogen peroxide or peroxy acids can yield sulfoxides (1 mol of oxidant per mole of sulfide) or sulfone (2 mol of oxidant) per mole of sulfide.



Sulfide        Sulfoxide        Sulfone



Benzyl methyl
sulfide

Benzyl methyl
sulfoxide (94%)

Section 16.17  Sulfides react with alkyl halides to give sulfonium salts.



Sulfide      Alkyl halide      Sulfonium salt



Dimethyl sulfide     Methyl iodide     Trimethylsulfonium iodide (100%)

Section 16.18  An H—C—O—C structural unit in an ether resembles an H—C—O—H unit of an alcohol with respect to the C—O stretching frequency in its infrared spectrum and the H—C chemical shift in its $^1$H NMR spectrum.

## PROBLEMS

**16.20** Write the structures of all the constitutionally isomeric ethers of molecular formula $C_5H_{12}O$, and give an acceptable name for each.

**16.21** Many ethers, including diethyl ether, are effective as general anesthetics. Because simple ethers are quite flammable, their place in medical practice has been taken by highly halogenated nonflammable ethers. Two such general anesthetic agents are *isoflurane* and *enflurane*. These compounds are isomeric; isoflurane is 1-chloro-2,2,2-trifluoroethyl difluoromethyl ether; enflurane is 2-chloro-1,1,2-trifluoroethyl difluoromethyl ether. Write the structural formulas of isoflurane and enflurane.

**16.22** Although epoxides are always considered to have their oxygen atom as part of a three-membered ring, the prefix *epoxy* in the IUPAC system of nomenclature can be used to denote a cyclic ether of various sizes. Thus

$$\underset{O}{\underset{1}{H_2C}}\overset{\overset{\displaystyle CH_3}{\underset{2}{|}}}{\underset{}{CH}}\overset{3}{CH}\overset{4}{CH_2}\overset{5}{CH_2}\overset{6}{CH_3}$$
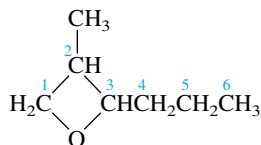
may be named 2-methyl-1,3-epoxyhexane. Using the epoxy prefix in this way, name each of the following compounds:

(a)

(c)

(b) $H_3C$ — $C$ — $O$ — $CH_2CH_2CH_3$, $H_3C$

(d)
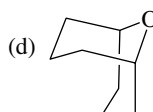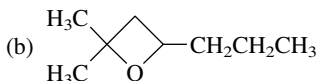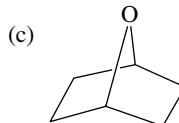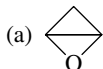
**16.23** The name of the parent six-membered sulfur-containing heterocycle is *thiane*. It is numbered beginning at sulfur. Multiple incorporation of sulfur in the ring is indicated by the prefixes *di-*, *tri-*, and so on.

  (a) How many methyl-substituted thianes are there? Which ones are chiral?

  (b) Write structural formulas for 1,4-dithiane and 1,3,5-trithiane.

  (c) Which dithiane isomer is a disulfide?

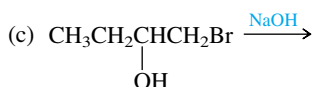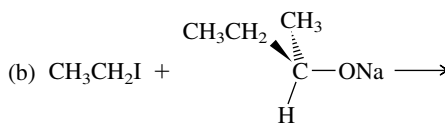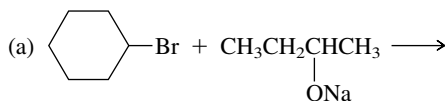  (d) Draw the two most stable conformations of the sulfoxide derived from thiane.

**16.24** The most stable conformation of 1,3-dioxan-5-ol is the chair form that has its hydroxyl group in an axial orientation. Suggest a reasonable explanation for this fact. Building a molecular model is helpful.
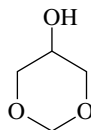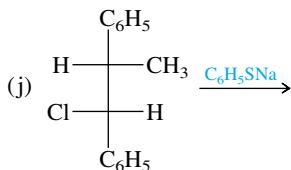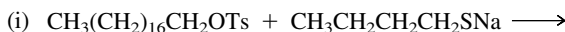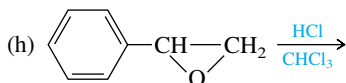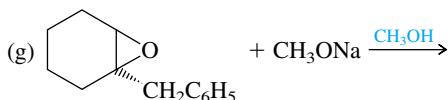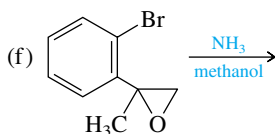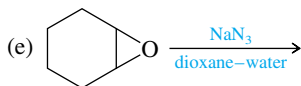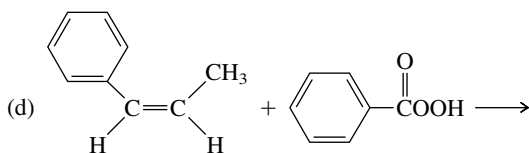
1,3-Dioxan-5-ol

**16.25** Outline the steps in the preparation of each of the constitutionally isomeric ethers of molecular formula $C_4H_{10}O$, starting with the appropriate alcohols. Use the Williamson ether synthesis as your key reaction.

**16.26** Predict the principal organic product of each of the following reactions. Specify stereochemistry where appropriate.

(a) ⬡—Br + $CH_3CH_2CHCH_3$ ⟶
                        |
                       ONa

(b) $CH_3CH_2I$ +

$CH_3CH_2$  $CH_3$
        \  /
         C—ONa ⟶
         |
         H

(c) $CH_3CH_2CHCH_2Br$ $\xrightarrow{\text{NaOH}}$
              |
              OH

(d)



$$\text{(phenyl)C}=\text{C(CH}_3\text{)(H), H} \quad + \quad \text{C}_6\text{H}_5\text{COOH} \longrightarrow$$

(e)



$$\xrightarrow[\text{dioxane}-\text{water}]{\text{NaN}_3}$$

(f)



$$\xrightarrow[\text{methanol}]{\text{NH}_3}$$

(g)



$$+ \text{CH}_3\text{ONa} \xrightarrow{\text{CH}_3\text{OH}}$$

(h)



$$\xrightarrow[\text{CHCl}_3]{\text{HCl}}$$

(i)  $\text{CH}_3(\text{CH}_2)_{16}\text{CH}_2\text{OTs} + \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{SNa} \longrightarrow$

(j)



$$\xrightarrow{\text{C}_6\text{H}_5\text{SNa}}$$

**16.27** Oxidation of 4-*tert*-butylthiane (see Problem 16.23 for the structure of thiane) with sodium metaperiodate gives a mixture of two compounds of molecular formula $C_9H_{18}OS$. Both products give the same sulfone on further oxidation with hydrogen peroxide. What is the relationship between the two compounds?
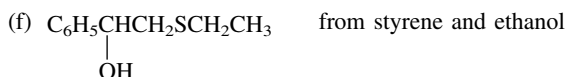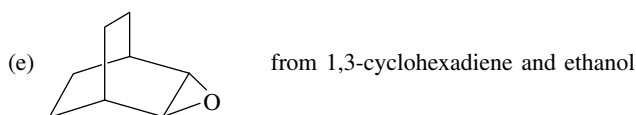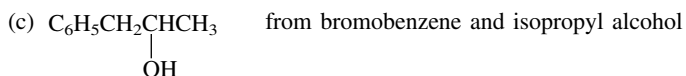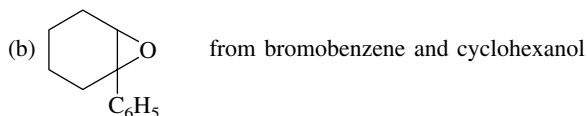
**16.28** When $(R)$-$(+)$-2-phenyl-2-butanol is allowed to stand in methanol containing a few drops of sulfuric acid, racemic 2-methoxy-2-phenylbutane is formed. Suggest a reasonable mechanism for this reaction.

**16.29** Select reaction conditions that would allow you to carry out each of the following stereo-specific transformations:

(a)



$$\longrightarrow (R)\text{-1,2-propanediol}$$

(b)



$$\longrightarrow (S)\text{-1,2-propanediol}$$
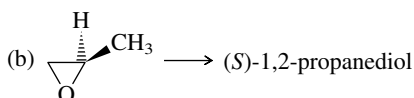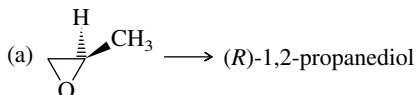
**16.30** The last step in the synthesis of divinyl ether (used as an anesthetic under the name *Vinethene*) involves heating $ClCH_2CH_2OCH_2CH_2Cl$ with potassium hydroxide. Show how you could prepare the necessary starting material $ClCH_2CH_2OCH_2CH_2Cl$ from ethylene.

**16.31** Suggest short, efficient reaction sequences suitable for preparing each of the following compounds from the given starting materials and any necessary organic or inorganic reagents:
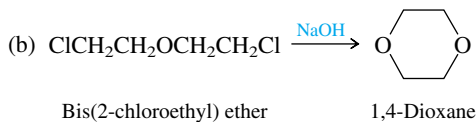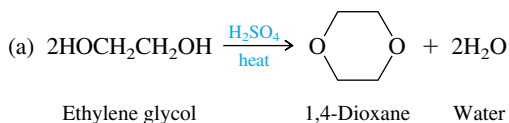
(a) $C_6H_5$—$CH_2OCH_3$    from    $C_6H_5$—$\overset{\overset{\displaystyle O}{\|}}{C}OCH_3$

(b) (structure: epoxide-fused cyclohexane with $C_6H_5$)    from bromobenzene and cyclohexanol

(c) $C_6H_5CH_2\underset{\underset{\displaystyle OH}{|}}{C}HCH_3$    from bromobenzene and isopropyl alcohol

(d) $C_6H_5CH_2CH_2CH_2OCH_2CH_3$    from benzyl alcohol and ethanol

(e) (bicyclic structure with O)    from 1,3-cyclohexadiene and ethanol

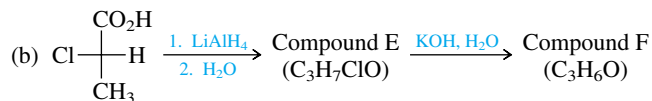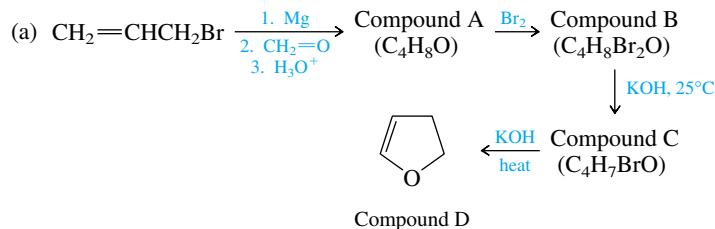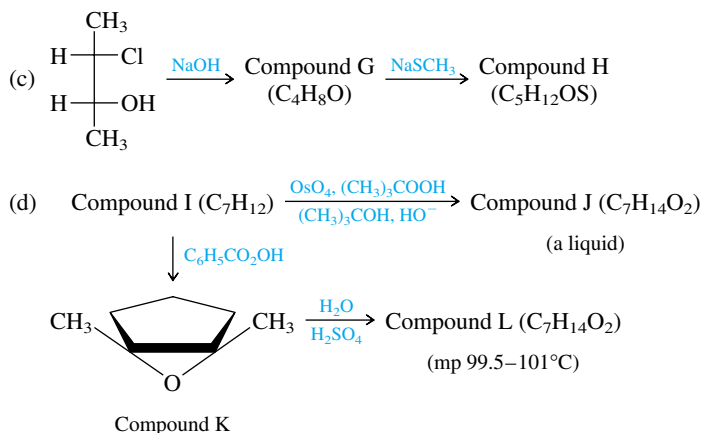(f) $C_6H_5\underset{\underset{\displaystyle OH}{|}}{C}HCH_2SCH_2CH_3$    from styrene and ethanol
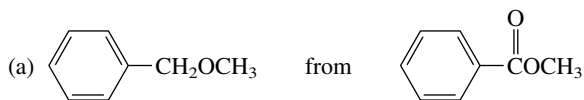
**16.32** Among the ways in which 1,4-dioxane may be prepared are the methods expressed in the equations shown:

(a) $2HOCH_2CH_2OH \xrightarrow[\text{heat}]{H_2SO_4}$ (1,4-dioxane ring) $+ 2H_2O$

   Ethylene glycol          1,4-Dioxane      Water

(b) $ClCH_2CH_2OCH_2CH_2Cl \xrightarrow{NaOH}$ (1,4-dioxane ring)

   Bis(2-chloroethyl) ether          1,4-Dioxane

Suggest reasonable mechanisms for each of these reactions.

**16.33** Deduce the identity of the missing compounds in the following reaction sequences. Show stereochemistry in parts (b) through (d).

(a) $CH_2$=$CHCH_2Br \xrightarrow[\substack{\text{2. } CH_2=O \\ \text{3. } H_3O^+}]{\text{1. Mg}}$ Compound A $(C_4H_8O)$ $\xrightarrow{Br_2}$ Compound B $(C_4H_8Br_2O)$

$\Bigg\downarrow$ KOH, 25°C

(furan-type ring structure) Compound D $\xleftarrow[\text{heat}]{\text{KOH}}$ Compound C $(C_4H_7BrO)$

(b) $Cl\overset{\overset{\displaystyle CO_2H}{|}}{\underset{\underset{\displaystyle CH_3}{|}}{C}}H \xrightarrow[\text{2. } H_2O]{\text{1. LiAlH}_4}$ Compound E $(C_3H_7ClO)$ $\xrightarrow{KOH, H_2O}$ Compound F $(C_3H_6O)$

(c)

$$\overset{CH_3}{\underset{CH_3}{\overset{|}{\underset{|}{\text{H}-\overset{|}{\underset{|}{\text{C}}}-\text{Cl}}}}}$$ (with H—OH below)

$\xrightarrow{\text{NaOH}}$ Compound G $\xrightarrow{\text{NaSCH}_3}$ Compound H
$(C_4H_8O)$    $(C_5H_{12}OS)$

(d) Compound I $(C_7H_{12})$ $\xrightarrow[\text{(CH}_3)_3\text{COH, HO}^-]{\text{OsO}_4, \text{(CH}_3)_3\text{COOH}}$ Compound J $(C_7H_{14}O_2)$
(a liquid)

$\downarrow$ $C_6H_5CO_2OH$

$CH_3$ [epoxide ring structure] $CH_3$ $\xrightarrow[\text{H}_2\text{SO}_4]{\text{H}_2\text{O}}$ Compound L $(C_7H_{14}O_2)$
O
(mp 99.5–101°C)

Compound K

**16.34** Cineole is the chief component of eucalyptus oil; it has the molecular formula $C_{10}H_{18}O$ and contains no double or triple bonds. It reacts with hydrochloric acid to give the dichloride shown:

$$\text{Cineole} \xrightarrow{\text{HCl}}$$

[structure of dichloride:]
Cl
CH₃—C—CH₃
(attached to cyclohexane ring with Cl and CH₃ at opposite position)
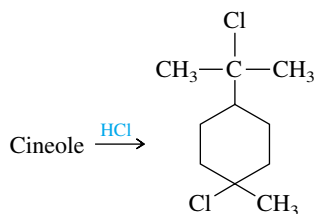
Deduce the structure of cineole.

**16.35** The *p*-toluenesulfonate shown undergoes an intramolecular Williamson reaction on treatment with base to give a spirocyclic ether. Demonstrate your understanding of the terminology used in the preceding sentence by writing the structure, including stereochemistry, of the product.

[structure:]
OH
(cyclohexane ring) —CH₂CH₂CH₂OTs $\xrightarrow{\text{base}}$ $C_{15}H_{20}O$
—C₆H₅
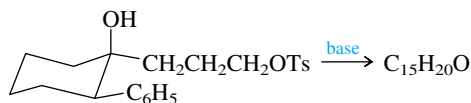
**16.36** All the following questions pertain to $^1$H NMR spectra of isomeric ethers having the molecular formula $C_5H_{12}O$.

(a) Which one has only singlets in its $^1$H NMR spectrum?

(b) Along with other signals, this ether has a coupled doublet–septet pattern. None of the protons responsible for this pattern are coupled to protons anywhere else in the molecule. Identify this ether.

(c) In addition to other signals in its $^1$H NMR spectrum, this ether exhibits two signals at relatively low field. One is a singlet; the other is a doublet. What is the structure of this ether?

(d) In addition to other signals in its $^1$H NMR spectrum, this ether exhibits two signals at relatively low field. One is a triplet; the other is a quartet. Which ether is this?

**16.37** The $^1$H NMR spectrum of compound A $(C_8H_8O)$ consists of two singlets of equal area at δ 5.1 (sharp) and 7.2 ppm (broad). On treatment with excess hydrogen bromide, compound A is converted to a single dibromide $(C_8H_8Br_2)$. The $^1$H NMR spectrum of the dibromide is similar to that of A in that it exhibits two singlets of equal area at δ 4.7 (sharp) and 7.3 ppm (broad). Suggest reasonable structures for compound A and the dibromide derived from it.
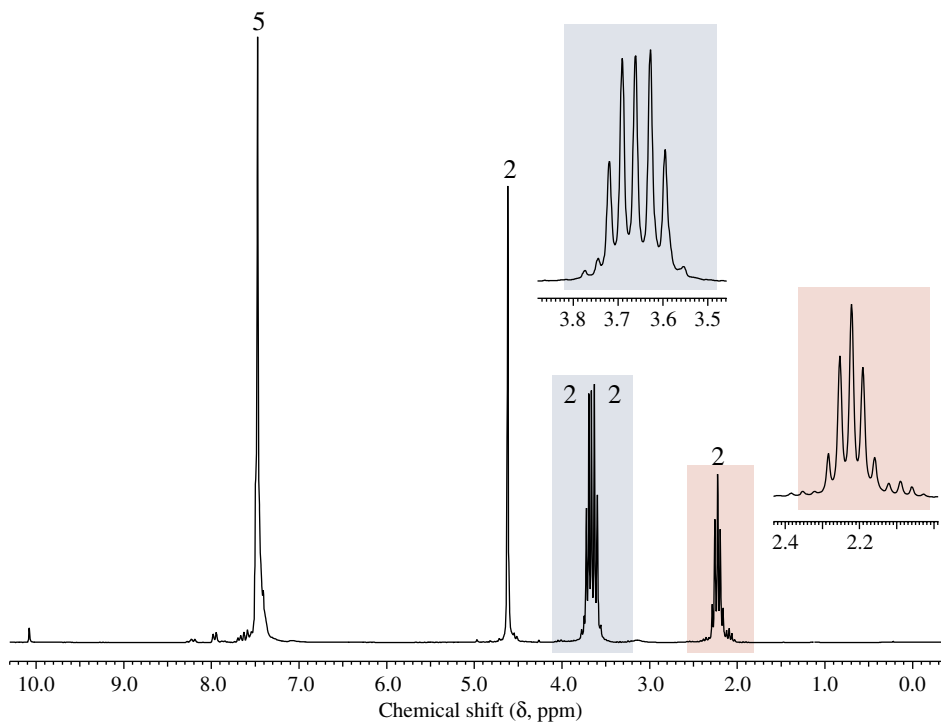
**FIGURE 16.10** The 200-MHz $^1$H NMR spectrum of a compound, $C_{10}H_{13}BrO$ (Problem 16.38). The integral ratios of the signals reading from left to right (low to high field) are 5:2:2:2:2. The signals centered at 3.6 and 3.7 ppm are two overlapping triplets.
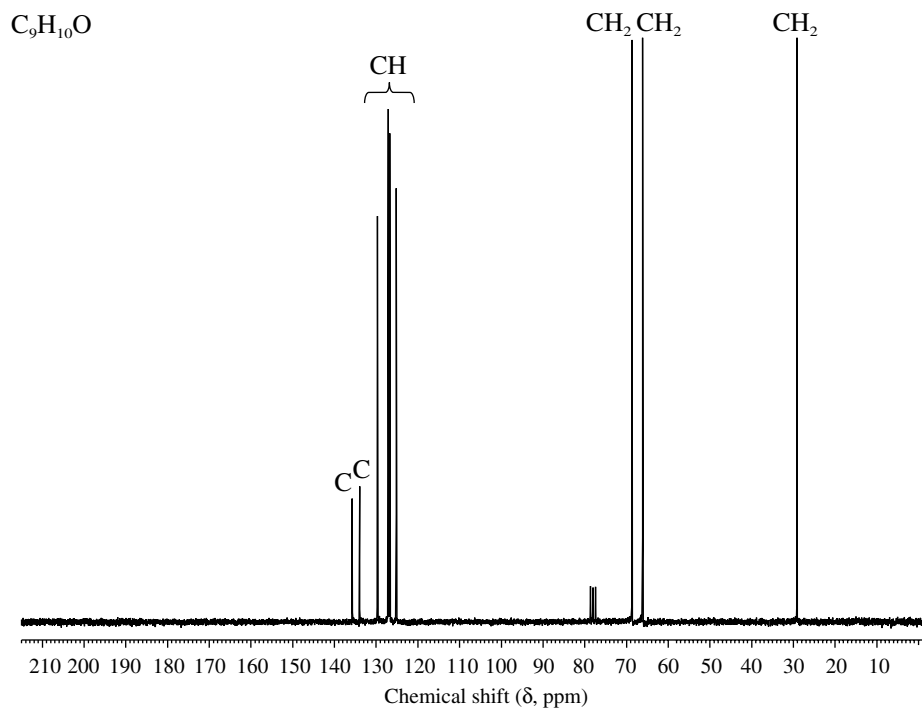


**FIGURE 16.11** The $^{13}$C NMR spectrum of a compound, $C_9H_{10}O$ (Problem 16.39).

**16.38** The $^1$H NMR spectrum of a compound ($C_{10}H_{13}BrO$) is shown in Figure 16.10. The compound gives benzyl bromide, along with a second compound $C_3H_6Br_2$, when heated with HBr. What is the first compound?

**16.39** A compound is a cyclic ether of molecular formula $C_9H_{10}O$. Its $^{13}$C NMR spectrum is shown in Figure 16.11. Oxidation of the compound with sodium dichromate and sulfuric acid gave 1,2-benzenedicarboxylic acid. What is the compound?

**16.40** Make a molecular model of dimethyl sulfide. How does its bond angle at sulfur compare with the C—O—C bond angle in dimethyl ether?

**16.41** View molecular models of dimethyl ether and ethylene oxide on *Learning By Modeling*. Which one has the greater dipole moment? Do the calculated dipole moments bear any relationship to the observed boiling points (ethylene oxide: $+10°C$; dimethyl ether: $-25°C$)?

**16.42** Find the molecular model of 18-crown-6 (Figure 16.2) on *Learning By Modeling,* and examine its electrostatic potential surface. View the surface in various modes (dots, contours, and as a transparent surface). Does 18-crown-6 have a dipole moment? Are vicinal oxygens anti or gauche to one another?

**16.43** Find the model of dimethyl sulfoxide [$(CH_3)_2S{=}O$] on *Learning By Modeling,* and examine its electrostatic potential surface. To which atom (S or O) would you expect a proton to bond?

**16.44** Construct a molecular model of *trans*-2-bromocyclohexanol in its most stable conformation. This conformation is ill-suited to undergo epoxide formation on treatment with base. Why? What must happen in order to produce 1,2-epoxycyclohexane from *trans*-2-bromocyclohexanol?

**16.45** Construct a molecular model of *threo*-3-bromo-2-butanol. What is the stereochemistry (cis or trans) of the 2,3-epoxybutane formed on treatment of *threo*-3-bromo-2-butanol with base? Repeat the exercise for *erythro*-3-bromo-2-butanol.