18

Ethers and Epoxides; Thiols and Sulfides

Ethers (R—O—R′), like the alcohols we saw in the preceding chapter, are also organic derivatives of water but have two organic groups bonded to the same oxygen atom rather than one. The organic groups might be alkyl, aryl, or vinylic, and the oxygen atom might be in an open chain or a ring. Perhaps the most well-known ether is diethyl ether, which has a long history of medicinal use as an anesthetic and industrial use as a solvent. Other useful ethers include anisole, a pleasant-smelling aromatic ether used in perfumery, and tetrahydrofuran (THF), a cyclic ether often used as a solvent.

CH_3CH_2—O—CH_2CH_3

Diethyl ether

O—CH_3
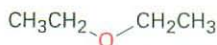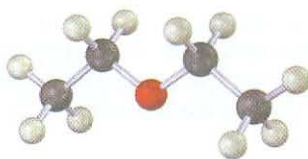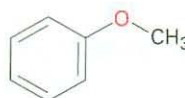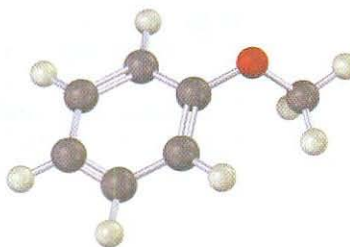
**Anisole**
(methyl phenyl ether)
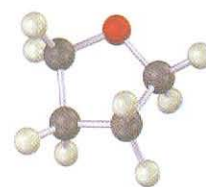
Tetrahydrofuran

Thiols (R—S—H) and **sulfides** (R—S—R′) are sulfur analogs of alcohols and ethers, respectively. Both functional groups are found in various biomolecules, although not as commonly as their oxygen-containing relatives.
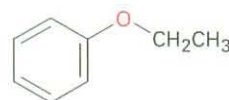
WHY THIS CHAPTER?

This chapter finishes the coverage of functional groups with C—O and C—S single bonds that was begun in Chapter 17. We'll focus primarily on ethers and take only a brief look at thiols and sulfides before going on to an extensive coverage of compounds with C=O bonds in Chapters 19 through 23.

18.1 | Names and Properties of Ethers

Simple ethers with no other functional groups are named by identifying the two organic substituents and adding the word *ether*.
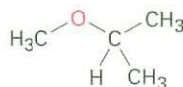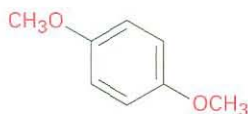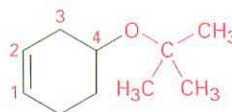
Isopropyl methyl ether   **Ethyl phenyl ether**

If other functional groups are present, the ether part is considered an *alkoxy* substituent. For example:
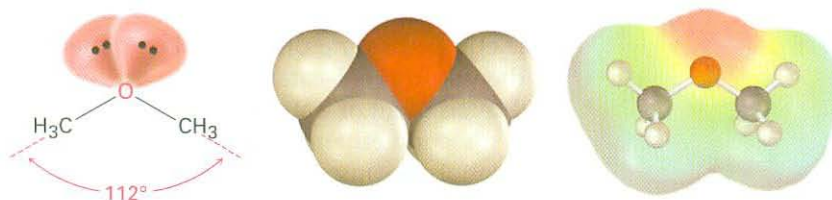
p-Dimethoxybenzene   4-*tert*-Butoxy-1-cyclohexene

ThomsonNOW Click *Organic Interactive* to use a web-based palette to draw ether structures based on their IUPAC names.

Like alcohols, ethers have nearly the same geometry as water. The R—O—R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is *sp*^{3}-hybridized.

The electronegative oxygen atom gives ethers a slight dipole moment, and the boiling points of ethers are often slightly higher than the boiling points of comparable alkanes. Table 18.1 compares the boiling points of some common ethers and the corresponding hydrocarbons.

Ethers are relatively stable and unreactive in many respects, but some ethers react slowly with the oxygen in air to give *peroxides*, compounds that contain an O—O bond. The peroxides from low-molecular-weight ethers such as diisopropyl ether and tetrahydrofuran are explosive and extremely dangerous, even in tiny amounts. Ethers are very useful as solvents in the laboratory, but they must always be used cautiously and should not be stored for long periods of time.

Table 18.1 | **Comparison of Boiling Points of Ethers and Hydrocarbons**

Ether	Boiling point °C	Hydrocarbon	Boiling point °C
CH_3OCH_3	−25	$CH_3CH_2CH_3$	−45
$CH_3CH_2OCH_2CH_3$	34.6	$CH_3CH_2CH_2CH_2CH_3$	36
(tetrahydrofuran structure)	65	(cyclopentane structure)	49
(anisole structure, OCH₃)	158	(ethylbenzene structure, CH₂CH₃)	136

Problem 18.1 | Name the following ethers:

(a)
$$CH_3CHOCHCH_3$$
with CH_3 CH_3 substituents

(b) (cyclopentyl)—$OCH_2CH_2CH_3$

(c) (benzene ring with Br and OCH_3)

(d) (cyclohexene ring with OCH_3)

(e)
$$CH_3CHCH_2OCH_2CH_3$$
with CH_3 substituent

(f) $H_2C{=}CHCH_2OCH{=}CH_2$
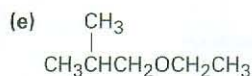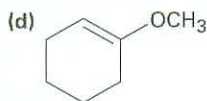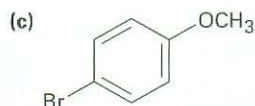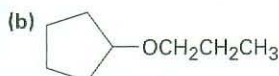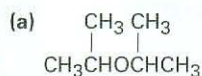
18.2 | Synthesis of Ethers

Diethyl ether and other simple symmetrical ethers are prepared industrially by the sulfuric acid–catalyzed dehydration of alcohols. The reaction occurs by S_N2 displacement of water from a protonated ethanol molecule by the oxygen atom of a second ethanol. Unfortunately, the method is limited to use with primary alcohols because secondary and tertiary alcohols dehydrate by an E1 mechanism to yield alkenes (Section 17.6).

$$CH_3CH_2{-}\ddot{O}H \xrightarrow{\ \ H{-}A\ \ } \left[CH_3CH_2{-}\overset{+}{\ddot{O}}H_2 \xrightarrow[S_N2]{HO{-}CH_2CH_3} CH_3CH_2{-}\overset{+}{\underset{|}{O}}{-}CH_2CH_3 \right]$$

$$CH_3CH_2{-}O{-}CH_2CH_3 \ +\ H_3O^+$$
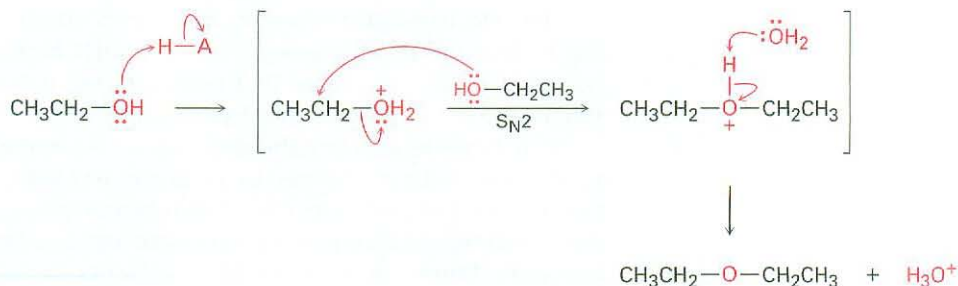
Alexander W. Williamson

Alexander W. Williamson
(1824–1904) was born in London,
England, and received his Ph.D.
at the University of Giessen in
1846. His ability to work in the
laboratory was hampered by a
childhood injury that caused the
loss of an arm. From 1849 until
1887, he was professor of chem-
istry at University College,
London.

The Williamson Ether Synthesis

The most generally useful method of preparing ethers is by the *Williamson ether synthesis,* in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an S_N2 reaction. As 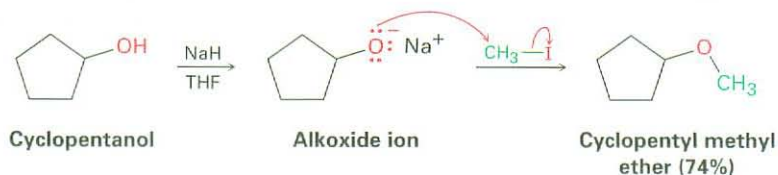we saw earlier in Section 17.2, the alkoxide ion is normally pre-pared by reaction of an alcohol with a strong base such as sodium hydride, NaH.

Cyclopentanol   **Alkoxide ion**   **Cyclopentyl methyl ether (74%)**

A useful variation of the Williamson synthesis involves silver oxide, Ag_2O, as a mild base rather than NaH. Under these conditions, the free alcohol reacts directly with alkyl halide, so there is no need to preform the metal alkoxide inter-mediate. Sugars react particularly well; glucose, for example, reacts with excess iodomethane in the presence of Ag_2O to generate a pentaether in 85% yield.

α-D-Glucose   **α-D-Glucose pentamethyl ether (85%)**
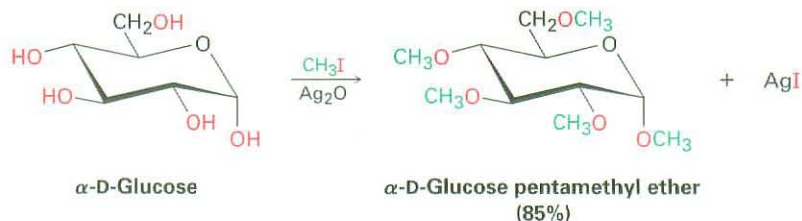
Because the Williamson synthesis is an S_N2 reaction, it is subject to all the usual constraints, as discussed in Section 11.2. Primary halides and tosylates work best because competitive E2 elimination can occur with more hindered substrates. Unsymmetrical ethers should therefore be synthesized by reaction between the more hindered alkoxide partner and less hindered halide partner rather than vice versa. For example, *tert*-butyl methyl ether, a substance used in the 1990s as an octane booster in gasoline, is best prepared by reaction of *tert*-butoxide ion with iodomethane rather than by reaction of methoxide ion with 2-chloro-2-methylpropane.
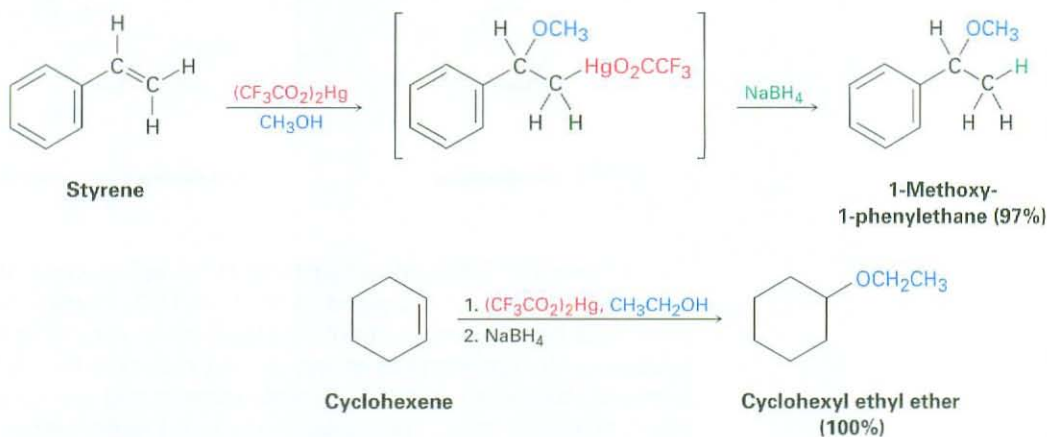

tert-**Butoxide**   **Iodomethane**   *tert*-**Butyl methyl ether**

2-Chloro-2-methylpropane   **2-Methylpropene**
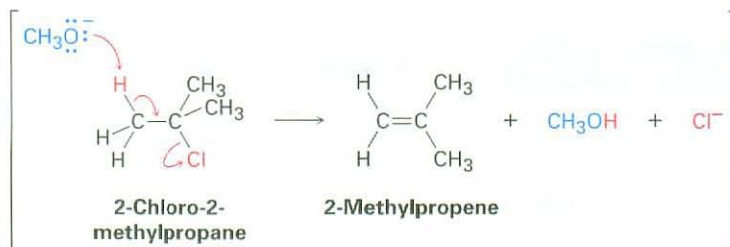
Problem 18.2 | Why do you suppose only symmetrical ethers are prepared by the sulfuric acid–catalyzed dehydration procedure? What product(s) would you expect if ethanol and 1-propanol were allowed to react together? In what ratio would the products be formed if the two alcohols were of equal reactivity?

Problem 18.3 | How would you prepare the following ethers using a Williamson synthesis?
(a) Methyl propyl ether   (b) Anisole (methyl phenyl ether)
(c) Benzyl isopropyl ether   (d) Ethyl 2,2-dimethylpropyl ether

Alkoxymercuration of Alkenes

We saw in Section 7.4 that alkenes react with water in the presence of mercuric acetate to yield a hydroxymercuration product. Subsequent treatment with $NaBH_4$ breaks the C−Hg bond and yields the alcohol. A similar **alkoxymercuration** reaction occurs when an alkene is treated with an *alcohol* in the presence of mercuric acetate or, even better, mercuric trifluoroacetate, $(CF_3CO_2)_2Hg$. Demercuration by reaction with $NaBH_4$ then yields an ether. The net result is Markovnikov addition of the alcohol to the alkene.

Styrene   1-Methoxy-
                             1-phenylethane (97%)

Cyclohexene   Cyclohexyl ethyl ether
                             (100%)

The mechanism of the alkoxymercuration reaction is similar to that described in Section 7.4 for hydroxymercuration. The reaction is initiated by electrophilic addition of Hg^{2+} to the alkene, followed by reaction of the intermediate cation with alcohol and reduction of the C−Hg bond by $NaBH_4$. A variety of alcohols and alkenes can be used in the alkoxymercuration reaction. Primary, secondary, and even tertiary alcohols react well, but ditertiary ethers can't be prepared because of steric hindrance to reaction.

WORKED EXAMPLE 18.1 | **Synthesizing an Ether**

How would you prepare ethyl phenyl ether? Use whichever method you think is more appropriate, the Williamson synthesis or the alkoxymercuration reaction.

Strategy | Draw the target ether, identify the two groups attached to oxygen, and recall the limitations of the two methods for preparing ethers. The Williamson synthesis uses an S_N2 reaction and requires that one of the two groups attached to oxygen be either

secondary or (preferably) primary. The alkoxymercuration reaction requires that one of the two groups come from an alkene precursor. Ethyl phenyl ether could be made by either method.

Ethyl phenyl ether

Primary carbon; compatible with Williamson method

Alkene derived; compatible with alkoxymercuration method

Solution

Phenol
1. NaOH
2. CH_3CH_2Br

1. $(CF_3CO_2)_2Hg$, $H_2C=CH_2$
2. $NaBH_4$

Ethyl phenyl ether
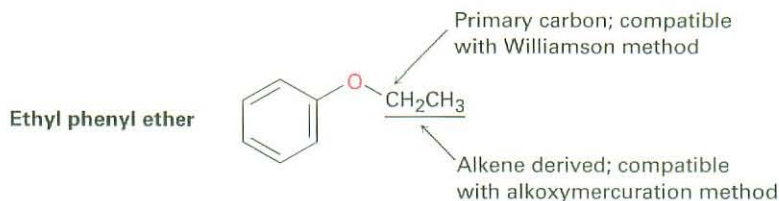
Problem 18.4 Review the mechanism of oxymercuration shown in Figure 7.4 (p. 225), and then write the mechanism of the alkoxymercuration reaction of 1-methylcyclopentene with ethanol. Use curved arrows to show the electron flow in each step.

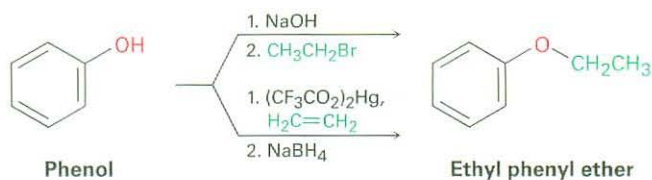**Problem 18.5** How would you prepare the following ethers? Use whichever method you think is more appropriate, the Williamson synthesis or the alkoxymercuration reaction.
(a) Butyl cyclohexyl ether   (b) Benzyl ethyl ether ($C_6H_5CH_2OCH_2CH_3$)
(c) *sec*-Butyl *tert*-butyl ether   (d) Tetrahydrofuran

Problem 18.6 Rank the following halides in order of their reactivity in the Williamson synthesis:
(a) Bromoethane, 2-bromopropane, bromobenzene
(b) Chloroethane, bromoethane, 1-iodopropene

# 18.3 Reactions of Ethers: Acidic Cleavage

Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents. Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers. In fact, ethers undergo only one reaction of general use—they are cleaved by strong acids. Aqueous HBr and HI both work well, but HCl does not cleave ethers.

Ethyl phenyl ether
$\xrightarrow[\text{Reflux}]{\text{HBr, } H_2O}$
Phenol   + CH_3CH_2Br
Bromoethane
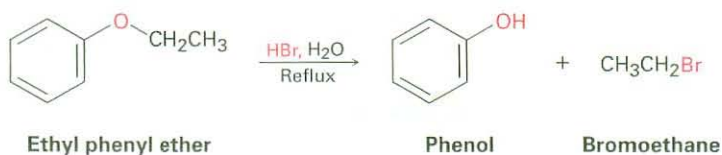
Acidic ether cleavages are typical nucleophilic substitution reactions, either S_N1 or S_N2 depending on the structure of the substrate. Ethers with only primary and secondary alkyl groups react by an S_N2 mechanism, in which I^- or Br^- attacks the protonated ether at the less hindered site. This usually results in a selective cleavage into a single alcohol and a single alkyl halide. For example, ethyl isopropyl ether yields exclusively isopropyl alcohol and iodoethane on cleavage by HI because nucleophilic attack by iodide ion occurs at the less hindered primary site rather than at the more hindered secondary site.
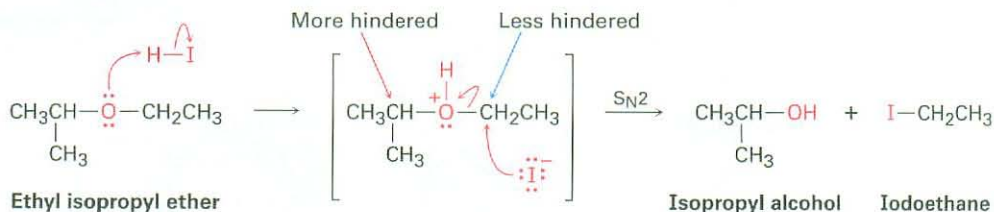

Ethers with a tertiary, benzylic, or allylic group cleave by an S_N1 or E1 mechanism because these substrates can produce stable intermediate carbocations. These reactions are often fast and take place at moderate temperatures. *tert*-Butyl ethers, for example, react by an E1 mechanism on treatment with trifluoroacetic acid at 0 °C. We'll see in Section 26.7 that the reaction is often used in the laboratory synthesis of peptides.
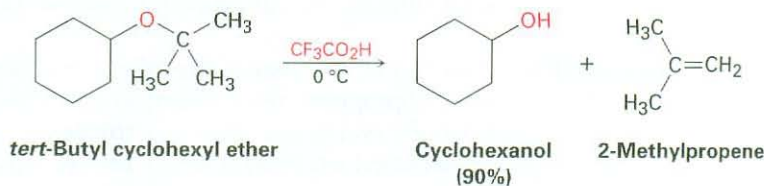

WORKED EXAMPLE 18.2   *Predicting the Product of an Ether Cleavage Reaction*

Predict the products of the following reaction:
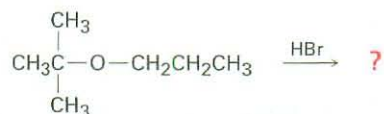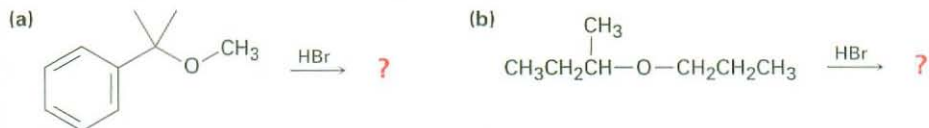

Strategy   Identify the substitution pattern of the two groups attached to oxygen—in this case a tertiary alkyl group and a primary alkyl group. Then recall the guidelines for ether cleavages. An ether with only primary and secondary alkyl groups usually undergoes cleavage by S_N2 attack of a nucleophile on the less hindered alkyl group, but an ether with a tertiary alkyl group usually undergoes cleavage by an S_N1 mechanism. In this case, an S_N1 cleavage of the tertiary C—O bond will occur, giving 1-propanol and a tertiary alkyl bromide.

Solution

tert-**Butyl propyl ether**   **2-Bromo-2-**   **1-Propanol**
                                     methylpropane
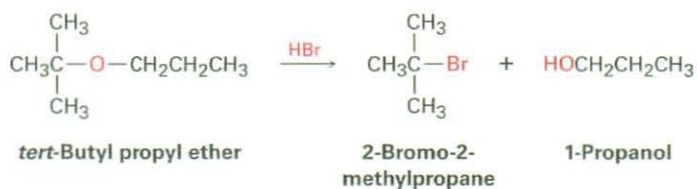
Problem 18.7 | Predict the products of the following reactions:

(a)

(b)

Problem 18.8 | Write the mechanism of the acid-catalyzed cleavage of tert-butyl cyclohexyl ether to yield cyclohexanol and 2-methylpropene.

Problem 18.9 | Why are HI and HBr more effective than HCl in cleaving ethers? (See Section 11.3.)

## 18.4 | Reactions of Ethers: Claisen Rearrangement

Ludwig Claisen

Ludwig Claisen (1851–1930) was born in Cologne, Germany, and received his Ph.D. at the University of Bonn, studying under August Kekulé. He never married, but devoted himself throughout his life to organic chemistry. Among his positions, he was professor at the University of Bonn, Owens College (Manchester), and the universities of Munich, Aachen, Kiel, and Berlin.

Unlike the acid-catalyzed ether cleavage reaction discussed in the previous section, which is general to all ethers, the **Claisen rearrangement** is specific to allyl aryl ethers, $Ar-O-CH_2CH=CH_2$. Treatment of a phenoxide ion with 3-bromopropene (allyl bromide) results in a Williamson ether synthesis and formation of an allyl aryl ether. Heating the allyl aryl ether to 200 to 250 °C then effects Claisen rearrangement, leading to an o-allylphenol. The net result is alkylation of the phenol in an ortho position.

Phenol   **Sodium phenoxide**   **Allyl phenyl ether**

**Allyl phenyl ether**   **o-Allylphenol**
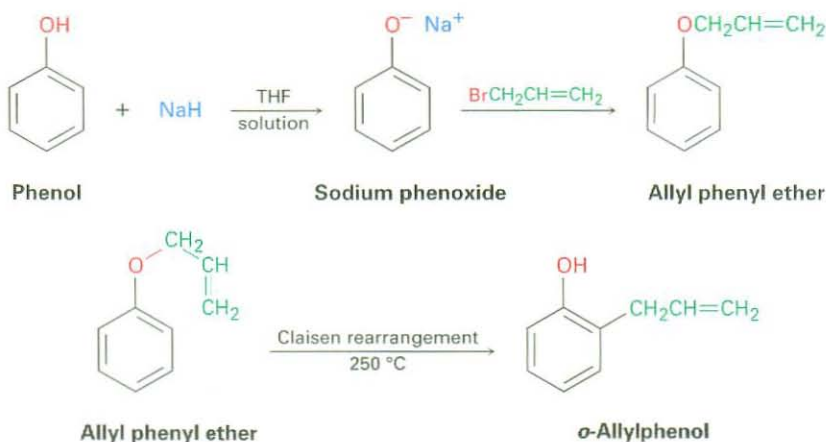
Like the Diels–Alder reaction discussed in Sections 14.4 and 14.5, the Claisen rearrangement reaction takes place through a pericyclic mechanism in which a concerted reorganization of bonding electrons occurs through a six-membered, cyclic transition state. The 6-allyl-2,4-cyclohexadienone intermediate then isomerizes to *o*-allylphenol (Figure 18.1).

| Allyl phenyl ether | Transition state | Intermediate (6-allyl-2,4-cyclohexadienone) | *o*-Allylphenol |
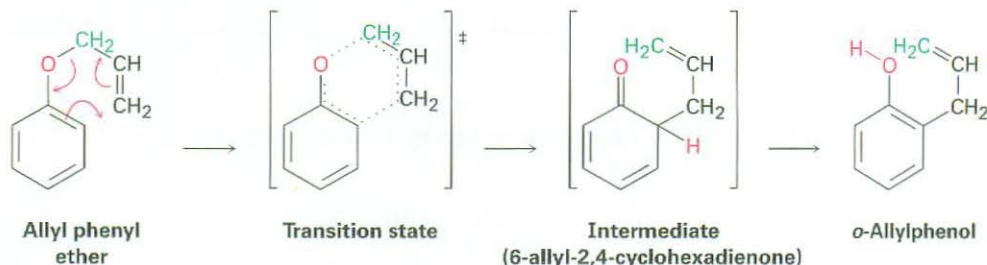
Active Figure 18.1 The mechanism of the Claisen rearrangement. The C−O bond-breaking and C−C bond-making occur simultaneously. *Sign in at* **www.thomsonedu.com** *to see a simulation based on this figure and to take a short quiz.*

Evidence for this mechanism comes from the observation that the rearrangement takes place with an inversion of the allyl group. That is, allyl phenyl ether containing a ^{14}C label on the allyl *ether* carbon atom yields *o*-allylphenol in which the label is on the *terminal* vinylic carbon (green in Figure 18.1). It would be very difficult to explain this result by any mechanism other than a pericyclic one. We'll look at the reaction in more detail in Section 30.8.

Problem 18.10   What product would you expect from Claisen rearrangement of 2-butenyl phenyl ether?



2-Butenyl phenyl ether
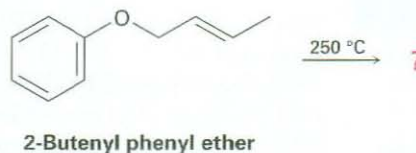
18.5 | Cyclic Ethers: Epoxides

For the most part, cyclic ethers behave like acyclic ethers. The chemistry of the ether functional group is the same, whether it's in an open chain or in a ring. Common cyclic ethers such as tetrahydrofuran and dioxane, for example, are often used as solvents because of their inertness, yet they can be cleaved by strong acids.
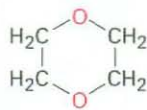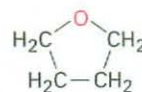

| 1,4-Dioxane | Tetrahydrofuran |

The one group of cyclic ethers that behaves differently from open-chain ethers contains the three-membered-ring compounds called *epoxides,* or *oxiranes,*

which we saw in Section 7.8. The strain of the three-membered ring gives epoxides unique chemical reactivity.

Ethylene oxide, the simplest epoxide, is an intermediate in the manufacture of both ethylene glycol, used for automobile antifreeze, and polyester polymers. More than 4 million tons of ethylene oxide is produced each year in the United States by air oxidation of ethylene over a silver oxide catalyst at 300 °C. This process is not useful for other epoxides, however, and is of little value in the laboratory. Note that the name *ethylene oxide* is not a systematic one because the *-ene* ending implies the presence of a double bond in the molecule. The name is frequently used, however, because ethylene oxide is derived *from* ethylene by addition of an oxygen atom. Other simple epoxides are named similarly. The systematic name for ethylene oxide is 1,2-epoxyethane.

In the laboratory, as we saw in Section 7.8, epoxides are prepared by treatment of an alkene with a peroxyacid (RCO_3H), typically *m*-chloroperoxybenzoic acid.

| Cycloheptene | *meta*-Chloroperoxy-benzoic acid | | 1,2-Epoxy-cycloheptane | *meta*-Chloro-benzoic acid |
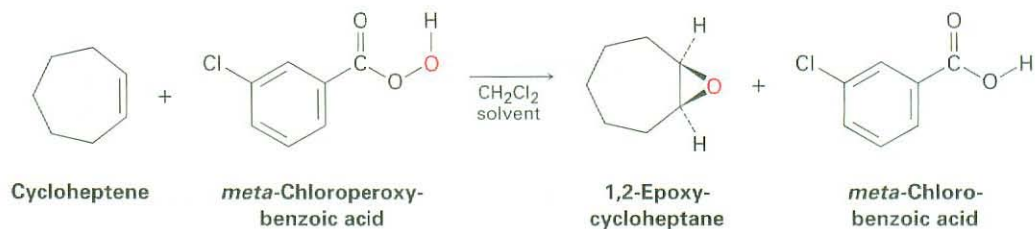
Another method for the synthesis of epoxides is through the use of halohydrins, prepared by electrophilic addition of HO—X to alkenes (Section 7.3). When halohydrins are treated with base, HX is eliminated and an epoxide is produced by an *intramolecular* Williamson ether synthesis. That is, the nucleophilic alkoxide ion and the electrophilic alkyl halide are in the same molecule.
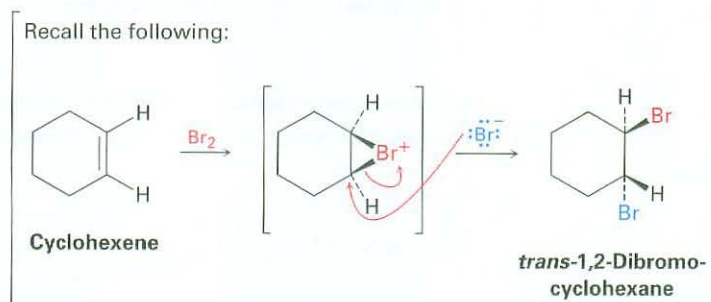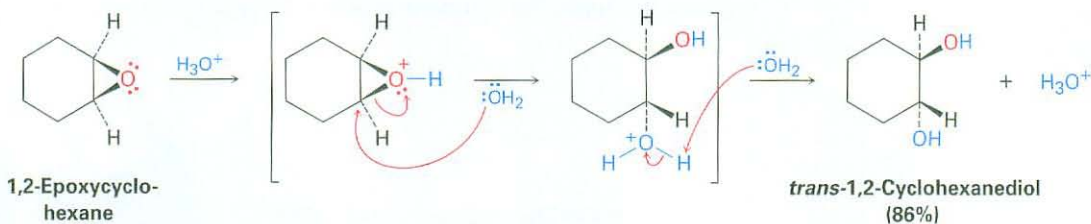

| Cyclohexene | *trans*-2-Chloro-cyclohexanol | | 1,2-Epoxy-cyclohexane |
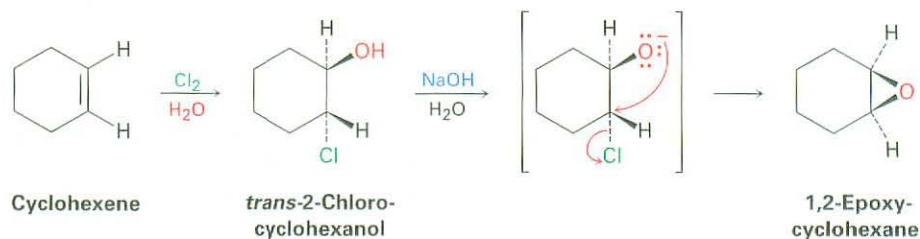
Problem 18.11 | Reaction of *cis*-2-butene with *m*-chloroperoxybenzoic acid yields an epoxide different from that obtained by reaction of the trans isomer. Explain.

18.6 | Reactions of Epoxides: Ring-Opening
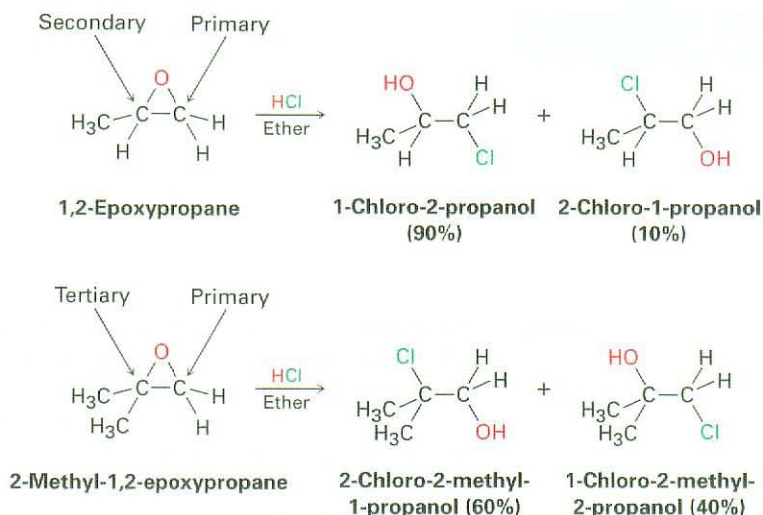
Acid-Catalyzed Epoxide Opening

Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain. As we saw in Section 7.8, dilute aqueous acid at room temperature is sufficient to cause the hydrolysis of epoxides to 1,2-diols, also called *vicinal glycols*. (The word *vicinal* means "adjacent," and a *glycol* is a diol.) The epoxide cleavage takes place by S_N2-like backside attack of a nucleophile on the protonated epoxide, giving a *trans*-1,2-diol as product.

1,2-Epoxycyclo-hexane

trans-1,2-Cyclohexanediol
(86%)

Recall the following:

Cyclohexene

trans-1,2-Dibromo-cyclohexane

Epoxides can also be opened by reaction with acids other than H_3O^+. If anhydrous HX is used, for instance, an epoxide is converted into a trans halohydrin.

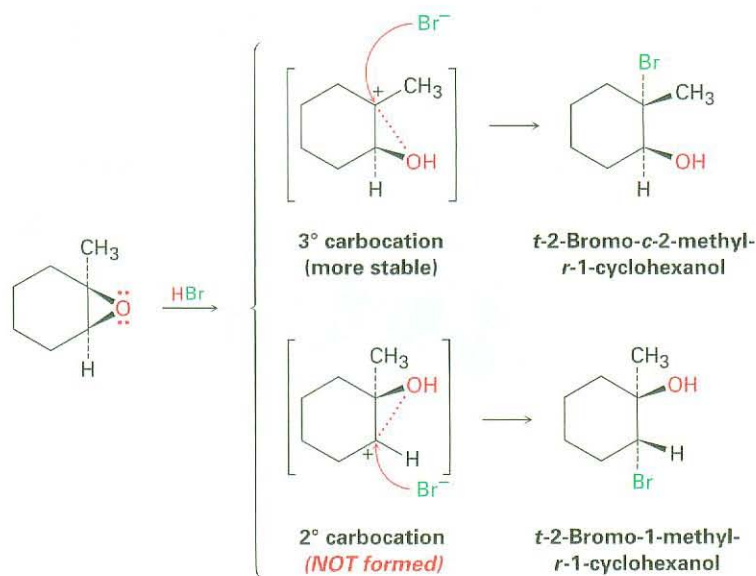**A trans 2-halocyclohexanol**

where   X = F, Br, Cl, or I
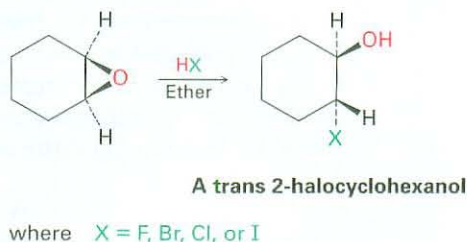
The regiochemistry of acid-catalyzed ring-opening depends on the epoxide's structure, and a mixture of products is often formed. When both epoxide carbon atoms are either primary or secondary, attack of the nucleophile occurs primarily at the *less* highly substituted site—an S_N2-like result. When one of the epoxide carbon atoms is tertiary, however, nucleophilic attack occurs primarily at the *more* highly substituted site—an S_N1-like result. Thus, 1,2-epoxypropane reacts with HCl to give primarily 1-chloro-2-propanol, but 2-methyl-1,2-epoxypropane gives 2-chloro-2-methyl-1-propanol as the major product.

Secondary   Primary

H₃C—C—C—H →(HCl / Ether) 1-Chloro-2-propanol (90%) + 2-Chloro-1-propanol (10%)

1,2-Epoxypropane   **1-Chloro-2-propanol (90%)**   **2-Chloro-1-propanol (10%)**

Tertiary   Primary

2-Methyl-1,2-epoxypropane   **2-Chloro-2-methyl-1-propanol (60%)**   **1-Chloro-2-methyl-2-propanol (40%)**

The mechanisms of these acid-catalyzed epoxide openings are more complex than they at first appear. They seem to be neither purely S_N1 nor S_N2 but instead to be midway between the two extremes and to have characteristics of both. Take the reaction of 1,2-epoxy-1-methylcyclohexane with HBr shown in Figure 18.2, for instance. The reaction yields only a single stereoisomer of 2-bromo-2-methylcyclohexanol in which the −Br and −OH groups are trans, an S_N2-like result caused by backside displacement of the epoxide oxygen. But the fact that Br⁻ attacks the more hindered tertiary side of the epoxide rather than the less hindered secondary side is an S_N1-like result in which the more stable, tertiary carbocation is involved.

Evidently, the transition state for acid-catalyzed epoxide opening has an S_N2-like geometry but also has a large amount of S_N1-like carbocationic character. Since the positive charge in the protonated epoxide is shared by the more highly substituted carbon atom, backside attack of Br⁻ occurs at the more highly substituted site.

Active Figure 18.2 Acid-induced ring-opening of 1,2-epoxy-1-methylcyclohexane with HBr. There is *a high degree* of S_N1-like carbocation character in the transition state, which leads to backside attack of the nucleophile at the tertiary center and to formation of the isomer of 2-bromo-2-methylcyclohexanol that has −Br and −OH groups trans. (Naming of trisubstituted cyclohexanes was explained in Section 7.8.) *Sign in at* www.thomsonedu.com *to see a simulation based on this figure and to take a short quiz.*

3° carbocation (more stable)   *t*-2-Bromo-*c*-2-methyl-*r*-1-cyclohexanol

2° carbocation *(NOT formed)*   *t*-2-Bromo-1-methyl-*r*-1-cyclohexanol

WORKED EXAMPLE 18.3

*Predicting the Product of Epoxide Ring-Opening*

Predict the major product of the following reaction:
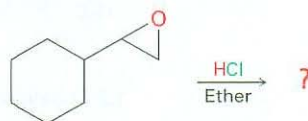

Strategy Identify the substitution pattern of the two epoxide carbon atoms—in this case, one carbon is secondary and one is primary. Then recall the guidelines for epoxide cleavages. An epoxide with only primary and secondary carbons usually undergoes cleavage by S_N2-like attack of a nucleophile on the less hindered carbon, but an epoxide with a tertiary carbon atom usually undergoes cleavage by backside attack on the more hindered carbon. In this case, an S_N2 cleavage of the primary C—O epoxide bond will occur.

Solution
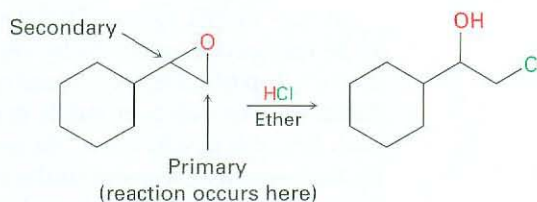
Problem 18.12 Predict the major product of each of the following reactions:

(a)

(b)
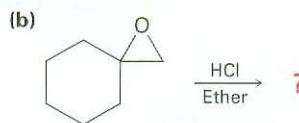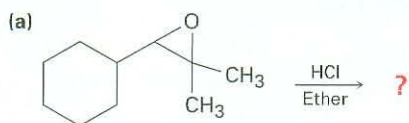
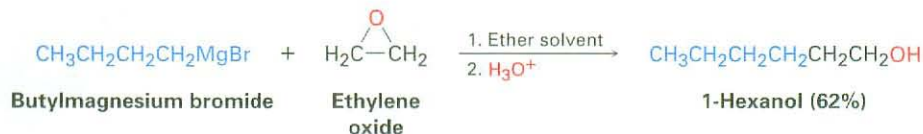**Problem 18.13** How would you prepare the following diols?

(a)

(b)
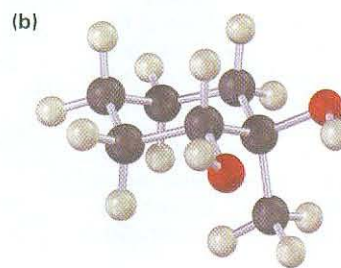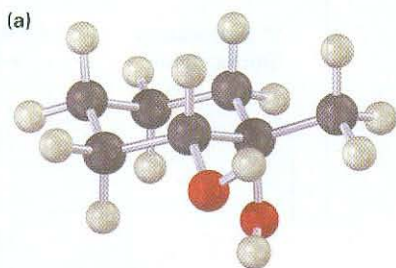
Base-Catalyzed Epoxide Opening

Unlike other ethers, epoxide rings can be cleaved by base as well as by acid. Although an ether oxygen is normally a poor leaving group in an S_N2 reaction (Section 11.3), the strain of the three-membered ring causes epoxides to react with hydroxide ion at elevated temperatures.


Methylenecyclohexane oxide

1-Hydroxymethyl-cyclohexanol (70%)
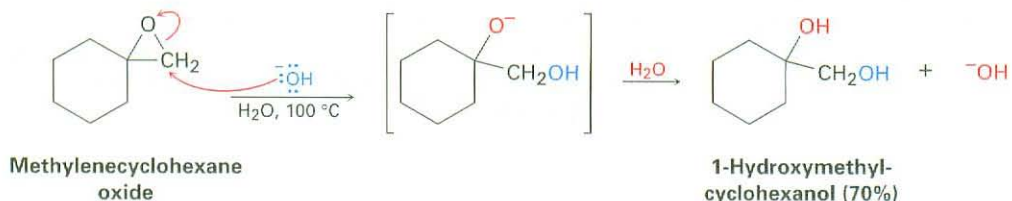
A similar nucleophilic ring-opening occurs when epoxides are treated with Grignard reagents. Ethylene oxide is frequently used, thereby allowing the conversion of a Grignard reagent into a primary alcohol having two more carbons than the starting alkyl halide. 1-Bromobutane, for example, is converted into 1-hexanol by reaction of its Grignard reagent with ethylene oxide.

$$CH_3CH_2CH_2CH_2MgBr \;+\; H_2C-CH_2 \xrightarrow[\text{2. } H_3O^+]{\text{1. Ether solvent}} CH_3CH_2CH_2CH_2CH_2CH_2OH$$

Butylmagnesium bromide   **Ethylene oxide**   **1-Hexanol (62%)**

Base-catalyzed epoxide opening is a typical S_N2 reaction in which attack of the nucleophile takes place at the less hindered epoxide carbon. For example, 1,2-epoxypropane reacts with ethoxide ion exclusively at the less highly substituted, primary, carbon to give 1-ethoxy-2-propanol.

1-Ethoxy-2-propanol (83%)

No attack here (2°)
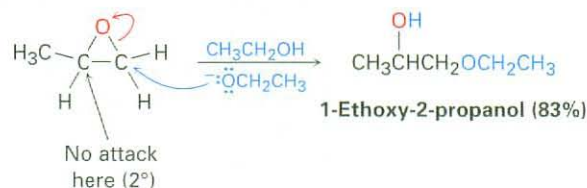
Problem 18.14 | Predict the major product of the following reactions:
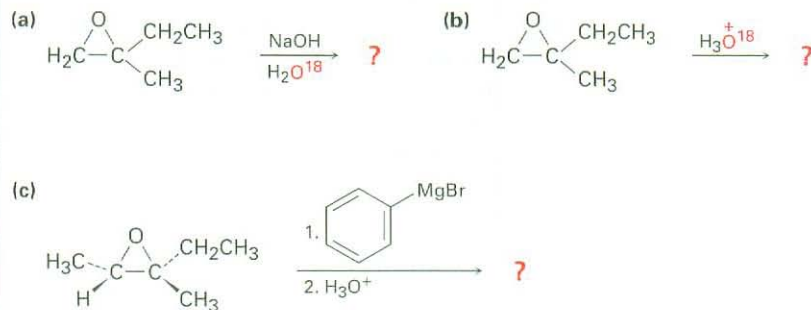
(a)

(b)

(c)

18.7 | Crown Ethers

Crown ethers, discovered in the early 1960s by Charles Pedersen at the DuPont Company, are a relatively recent addition to the ether family. Crown ethers are named according to the general format x-crown-y, where x is the total number of atoms in the ring and y is the number of oxygen atoms. Thus, 18-crown-6 ether is an 18-membered ring containing 6 ether oxygen atoms. Note the size and negative (red) character of the crown ether cavity in the following electrostatic potential map.
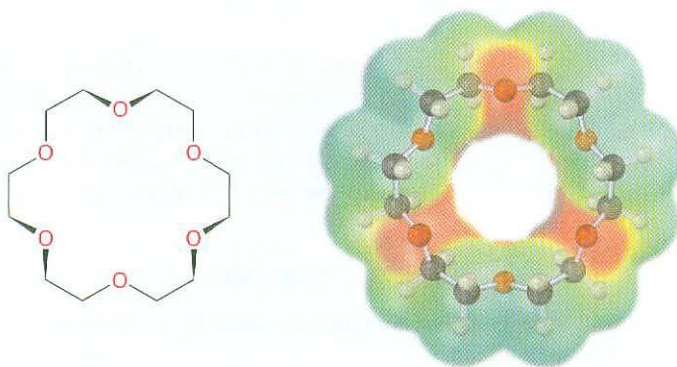
18-Crown-6 ether

The importance of crown ethers derives from their extraordinary ability to solvate metal cations by sequestering the metal in the center of the polyether cavity. For example, 18-crown-6 complexes strongly with potassium ion. Complexes between crown ethers and ionic salts are soluble in nonpolar organic solvents, thus allowing many reactions to be carried out under aprotic conditions that would otherwise have to be carried out in aqueous solution. Potassium permanganate, $KMnO_4$, dissolves in toluene in the presence of 18-crown-6, for instance, and the resulting solution is a valuable reagent for oxidizing alkenes.

Many other inorganic salts, including KF, KCN, and NaN_3, also dissolve in organic solvents with the help of crown ethers. The effect of using a crown ether to dissolve a salt in a hydrocarbon or ether solvent is similar to the effect of dissolving the salt in a polar aprotic solvent such as DMSO, DMF, or HMPA (Section 11.3). In both cases, the metal cation is strongly solvated, leaving the anion bare. Thus, the S_N2 reactivity of an anion is tremendously enhanced in the presence of a crown ether.

Problem 18.15 | 15-Crown-5 and 12-crown-4 ethers complex Na^+ and Li^+, respectively. Make models of these crown ethers, and compare the sizes of the cavities.

18.8 | Thiols and Sulfides

Thiols

Thiols, sometimes called *mercaptans,* are sulfur analogs of alcohols. They are named by the same system used for alcohols, with the suffix *-thiol* used in place of *-ol.* The —SH group itself is referred to as a **mercapto group**.

CH₃CH₂SH

Ethanethiol   **Cyclohexanethiol**   ***m*-Mercaptobenzoic acid**

The most striking characteristic of thiols is their appalling odor. Skunk scent, for instance, is caused primarily by the simple thiols 3-methyl-1-butanethiol and 2-butene-1-thiol. Volatile thiols such as ethanethiol are also added to natural gas and liquefied propane to serve as an easily detectable warning in case of leaks.

Thiols are usually prepared from alkyl halides by S_N2 displacement with a sulfur nucleophile such as hydrosulfide anion, ⁻SH.

$$CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2-Br \ + \ :SH \longrightarrow CH_3CH_2CH_2CH_2CH_2CH_2CH_2CH_2-SH \ + \ Br^-$$

1-Bromooctane   **1-Octanethiol (83%)**

The reaction often works poorly unless an excess of the nucleophile is used because the product thiol can undergo a second S_N2 reaction with alkyl halide to give a sulfide as a by-product. To circumvent this problem, thiourea, $(NH_2)_2C{=}S$, is often used as the nucleophile in the preparation of a thiol from an alkyl halide. The reaction occurs by displacement of the halide ion to yield an intermediate alkyl isothiourea salt, which is hydrolyzed by subsequent reaction with aqueous base.

1-Bromooctane   **Thiourea**

H₂O, NaOH

1-Octanethiol (83%)   **Urea**
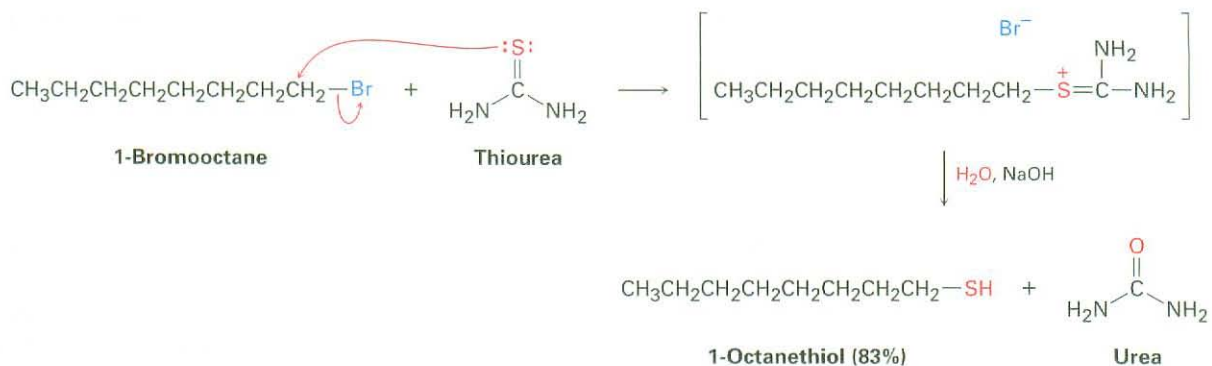
Thiols can be oxidized by Br_2 or I_2 to yield **disulfides (RSSR′)**. The reaction is easily reversed, and a disulfide can be reduced back to a thiol by treatment with zinc and acid.

$$2\ R\!-\!SH \underset{\text{Zn, H}^+}{\overset{I_2}{\rightleftarrows}} R\!-\!S\!-\!S\!-\!R\ +\ 2\ HI$$
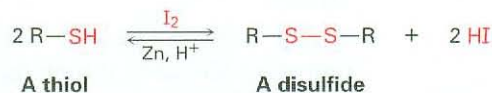
A thiol   **A disulfide**

This thiol–disulfide interconversion is a key part of numerous biological processes. We'll see in Chapter 26, for instance, that disulfide formation is involved in defining the structure and three-dimensional conformations of proteins, where disulfide "bridges" often form cross-links between cysteine amino acid units in the protein chains. Disulfide formation is also involved in the process by which cells protect themselves from oxidative degradation. A cellular component called *glutathione* removes potentially harmful oxidants and is itself oxidized to glutathione disulfide in the process. Reduction back to the thiol requires the coenzyme flavin adenine dinucleotide (reduced), abbreviated $FADH_2$.

Glutathione (GSH)   Glutathione disulfide (GSSG)
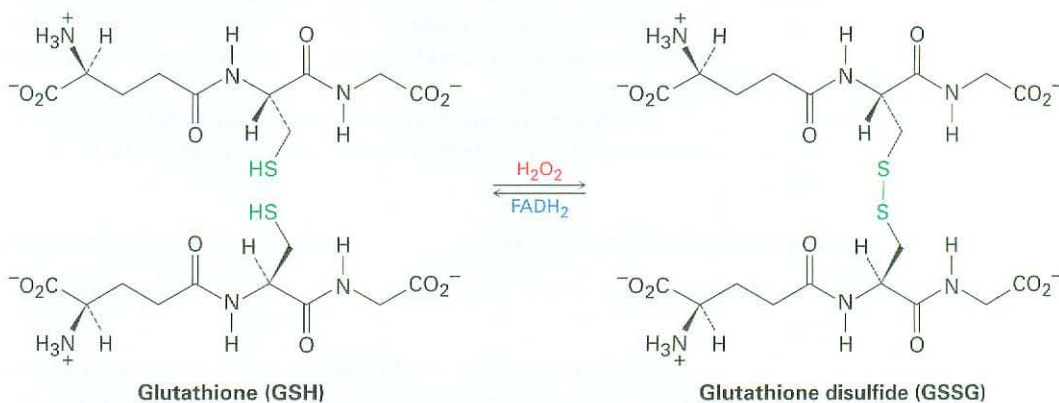
Sulfides

Sulfides are the sulfur analogs of ethers just as thiols are the sulfur analogs of alcohols. Sulfides are named by following the same rules used for ethers, with *sulfide* used in place of *ether* for simple compounds and *alkylthio* used in place of *alkoxy* for more complex substances.

Dimethyl sulfide   **Methyl phenyl sulfide**   **3-(Methylthio)cyclohexene**
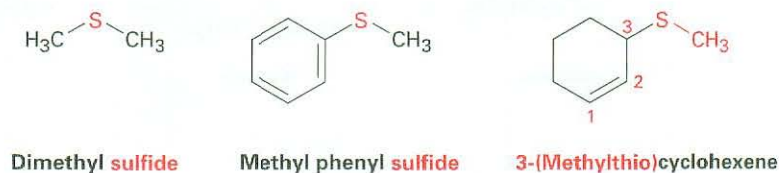
Treatment of a thiol with a base, such as NaH, gives the corresponding **thiolate ion (RS⁻)**, which undergoes reaction with a primary or secondary alkyl halide to give a sulfide. The reaction occurs by an S_N2 mechanism, analogous to the Williamson synthesis of ethers (Section 18.2). Thiolate anions are among

the best nucleophiles known, and product yields are usually high in these S_N2 reactions.

Sodium benzenethiolate   **Methyl phenyl sulfide**
                                                        (96%)
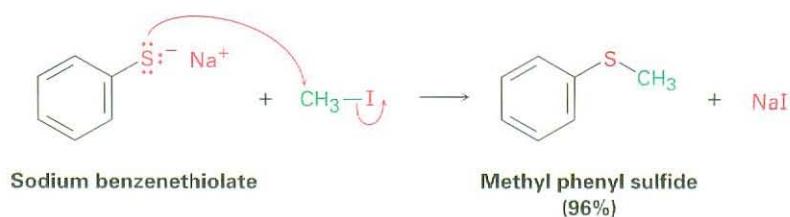
Perhaps surprisingly in light of their close structural similarity, disulfides and ethers differ substantially in their chemistry. Because the valence electrons on sulfur are farther from the nucleus and are less tightly held than those on oxygen (3p electrons versus 2p electrons), sulfur compounds are more nucleophilic than their oxygen analogs. Unlike dialkyl ethers, dialkyl sulfides are good nucleophiles that react rapidly with primary alkyl halides by an S_N2 mechanism to give **sulfonium ions** (R_3S^+).

Dimethyl sulfide   Iodomethane   Trimethylsulfonium iodide
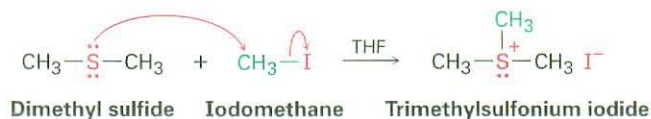
The most common example of this process in living organisms is the reaction of the amino acid methionine with adenosine triphosphate (ATP; Section 5.8) to give S-adenosylmethionine. The reaction is somewhat unusual in that the biological leaving group in this S_N2 process is the *triphosphate* ion rather than the more frequently seen *diphosphate* ion (Section 11.6).

Methionine   **Triphosphate ion**

Adenosine triphosphate (ATP)   *S*-**Adenosylmethionine**
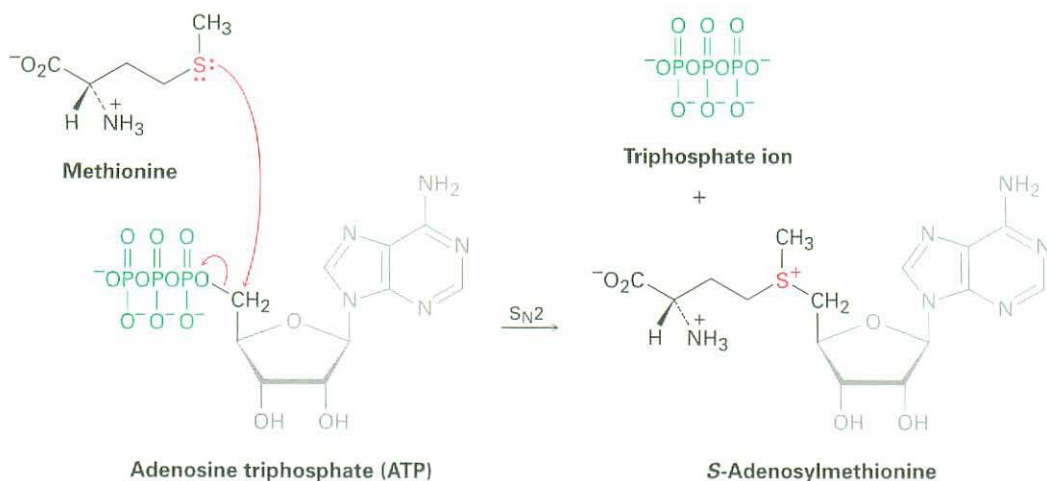
Sulfonium ions are themselves useful alkylating agents because a nucleophile can attack one of the groups bonded to the positively charged sulfur, displacing a neutral sulfide as leaving group. We saw an example in Section 11.6

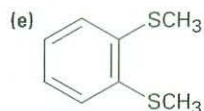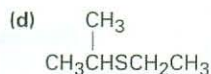(Figure 11.16) in which *S*-adenosylmethionine transferred a methyl group to norepinephrine to give adrenaline.
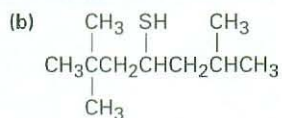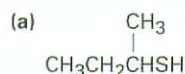
Another difference between sulfides and ethers is that sulfides are easily oxidized. Treatment of a sulfide with hydrogen peroxide, H_2O_2, at room temperature yields the corresponding **sulfoxide (R_2SO)**, and further oxidation of the sulfoxide with a peroxyacid yields a **sulfone (R_2SO_2)**.
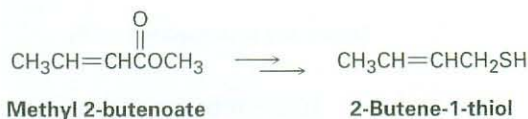

Methyl phenyl sulfide   **Methyl phenyl sulfoxide**   **Methyl phenyl sulfone**
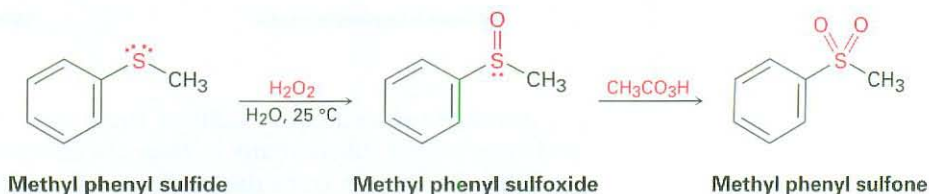
Dimethyl sulfoxide (DMSO) is a particularly well-known sulfoxide that is often used as a polar aprotic solvent. It must be handled with care, however, because it has a remarkable ability to penetrate the skin, carrying along whatever is dissolved in it.

Dimethyl sulfoxide
(a polar aprotic solvent)
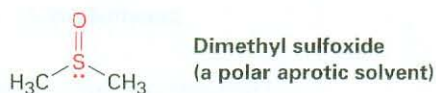
Problem 18.16 | Name the following compounds:

(a)
$$CH_3CH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HSH$$

(b)
$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}CH_2\overset{\overset{\displaystyle SH}{|}}{C}HCH_2\overset{\overset{\displaystyle CH_3}{|}}{C}HCH_3$$
$$|$$
$$CH_3$$

(c)

(d)
$$CH_3\overset{\overset{\displaystyle CH_3}{|}}{C}HSCH_2CH_3$$

(e)

(f)
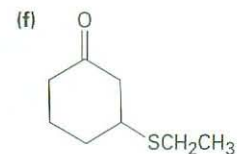
Problem 18.17 | 2-Butene-1-thiol is one component of skunk spray. How would you synthesize this substance from methyl 2-butenoate? From 1,3-butadiene?

$$CH_3CH=CH\overset{\overset{\displaystyle O}{\|}}{C}OCH_3 \longrightarrow CH_3CH=CHCH_2SH$$

Methyl 2-butenoate   **2-Butene-1-thiol**

18.9 | Spectroscopy of Ethers

Infrared Spectroscopy

Ethers are difficult to identify by IR spectroscopy. Although they show an absorption due to C–O single-bond stretching in the range 1050 to 1150 cm^{-1}, many other kinds of absorptions occur in the same range. Figure 18.3 shows the IR spectrum of diethyl ether and identifies the C–O stretch.
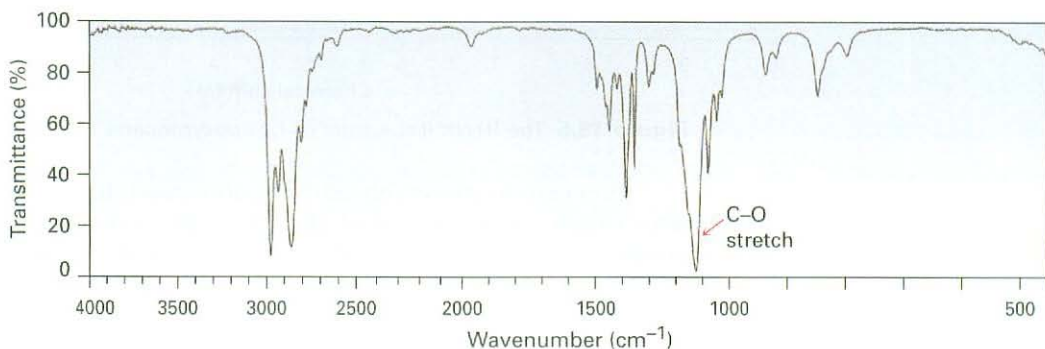
Figure 18.3 The infrared spectrum of diethyl ether, $CH_3CH_2OCH_2CH_3$.

Nuclear Magnetic Resonance Spectroscopy

Hydrogens on carbon next to an ether oxygen are shifted downfield from the normal alkane resonance and show ^1H NMR absorptions in the region 3.4 to 4.5 δ. This downfield shift is clearly seen in the spectrum of dipropyl ether shown in Figure 18.4.
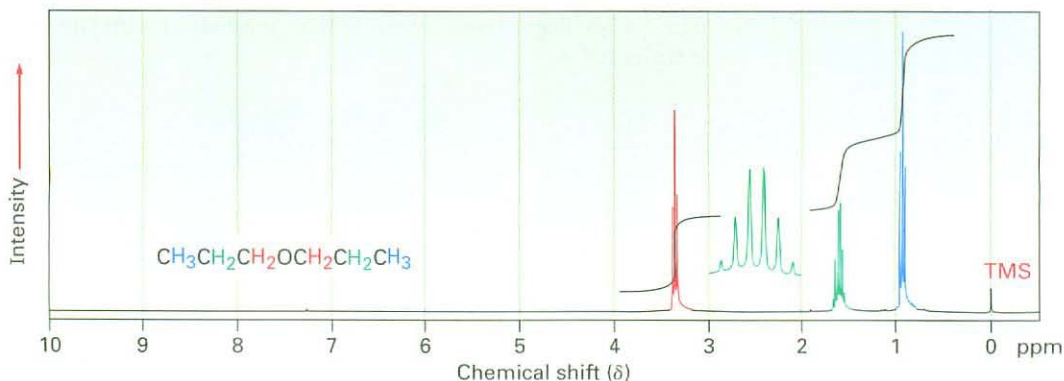
Figure 18.4 The ^1H NMR spectrum of dipropyl ether. Protons on carbon next to oxygen are shifted downfield to 3.4 δ.

Epoxides absorb at a slightly higher field than other ethers and show characteristic resonances at 2.5 to 3.5 δ in their ^1H NMR spectra, as indicated for 1,2-epoxypropane in Figure 18.5.
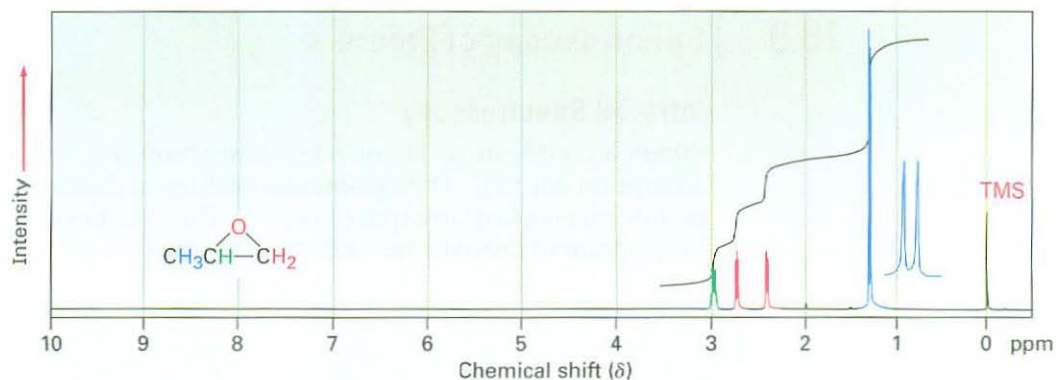
Figure 18.5 The ^1H NMR spectrum of 1,2-epoxypropane.

Ether carbon atoms also exhibit a downfield shift in the ^{13}C NMR spectrum, where they usually absorb in the 50 to 80 δ range. For example, the carbon atoms next to oxygen in methyl propyl ether absorb at 58.5 and 74.8 δ. Similarly, the methyl carbon in anisole absorbs at 54.8 δ.
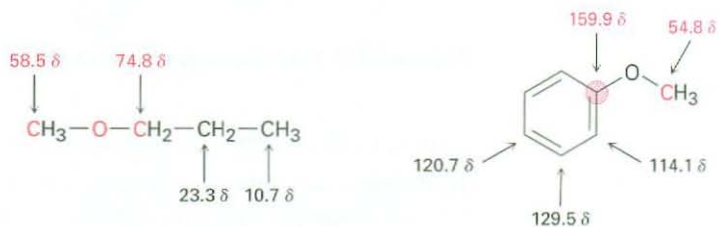
Problem 18.18 | The ^1H NMR spectrum shown is that of an ether with the formula C_4H_8O. Propose a structure.
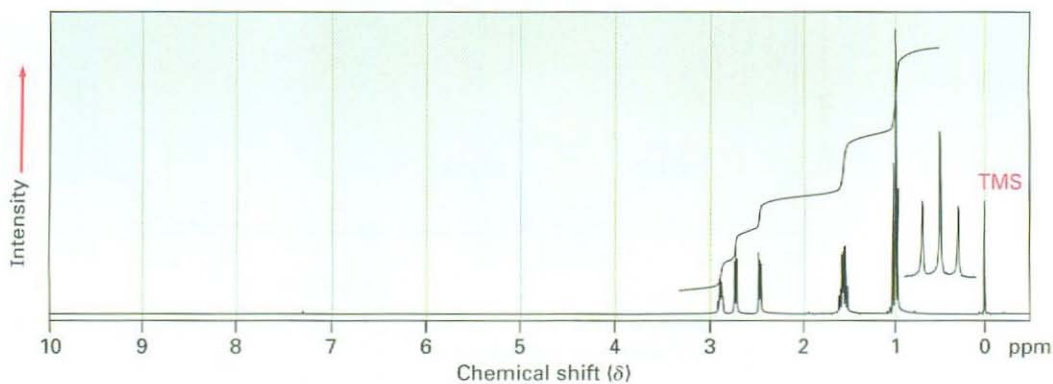
Focus On . . .

Epoxy Resins and Adhesives

Kayaks are often made of a high-strength polymer coated with epoxy resin.

Few nonchemists know exactly what an epoxide is, but practically everyone has used an "epoxy glue" for household repairs or an epoxy resin for a protective coating. Epoxy resins and adhesives generally consist of two components that are mixed just prior to use. One component is a liquid "prepolymer," and the second is a "curing agent" that reacts with the prepolymer and causes it to solidify.

The most widely used epoxy resins and adhesives are based on a prepolymer made from bisphenol A and epichlorohydrin. On treatment with base, bisphenol A is converted into its anion, which acts as a nucleophile in an S_N2 reaction with epichlorohydrin. Each epichlorohydrin molecule can react with two molecules of bisphenol A, once by S_N2 displacement of chloride ion and once by nucleophilic opening of the epoxide ring. At the same time, each bisphenol A molecule can react with two epichlorohydrins, leading to a long polymer chain. Each end of a prepolymer chain has an unreacted epoxy group, and each chain has numerous secondary alcohol groups spaced regularly along its midsection.

Bisphenol A   **Epichlorohydrin**
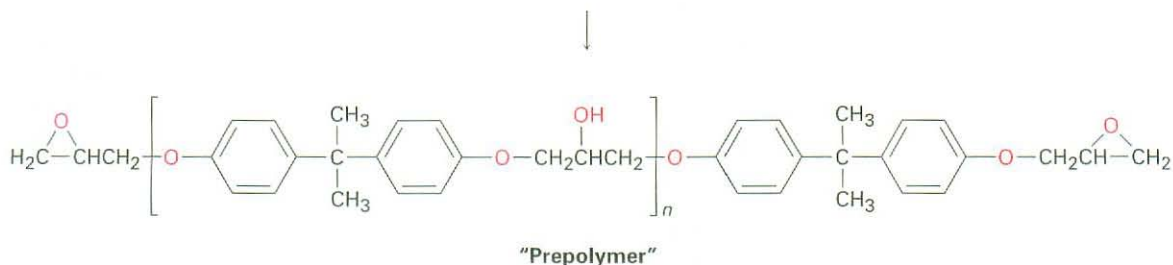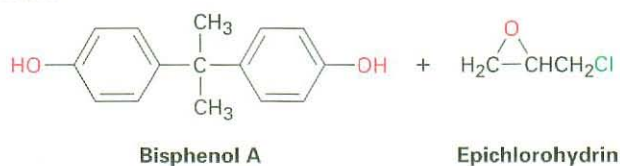
"Prepolymer"

When the epoxide is to be used, a basic curing agent such as a tertiary amine, R_3N, is added to cause the individual prepolymer chains to link together. This "cross-linking" of chains is simply a base-catalyzed epoxide

ring-opening of an −OH group in the middle of one chain with an epoxide group on the end of another chain. The result of such cross-linking is formation of a vast, three-dimensional tangle that has enormous strength and chemical resistance.
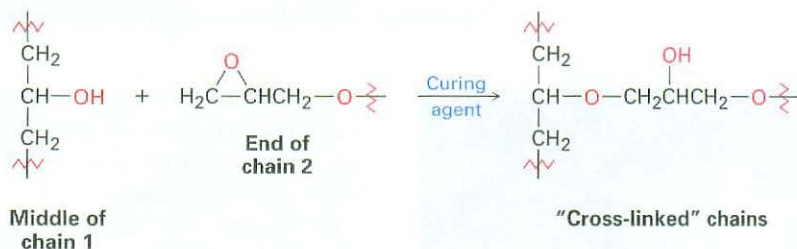
SUMMARY AND KEY WORDS

Ethers are compounds that have two organic groups bonded to the same oxygen atom, ROR'. The organic groups can be alkyl, vinylic, or aryl, and the oxygen atom can be in a ring or in an open chain. Ethers are prepared by either the Williamson ether synthesis, which involves S$_N$2 reaction of an alkoxide ion with a primary alkyl halide, or the **alkoxymercuration** reaction, which involves Markovnikov addition of an alcohol to an alkene.

Ethers are inert to most reagents but react with strong acids to give cleavage products. Both HI and HBr are often used. The cleavage reaction takes place by an S$_N$2 mechanism at the less highly substituted site if only primary and secondary alkyl groups are bonded to the ether oxygen, but by an S$_N$1 or E1 mechanism if one of the alkyl groups bonded to oxygen is tertiary. Aryl allyl ethers undergo **Claisen rearrangement** to give o-allylphenols.

Epoxides are cyclic ethers with a three-membered, oxygen-containing ring. Because of the strain in the ring, epoxides undergo a cleavage reaction with both acids and bases. Acid-induced ring-opening occurs with a regiochemistry that depends on the structure of the epoxide. Cleavage of the C−O bond at the less highly substituted site occurs if both epoxide carbons are primary or secondary, but cleavage of the C−O bond to the more highly substituted site occurs if one of the epoxide carbons is tertiary. Base-catalyzed epoxide ring-opening occurs by S$_N$2 reaction of a nucleophile at the less hindered epoxide carbon.

Thiols, the sulfur analogs of alcohols, are usually prepared by S$_N$2 reaction of an alkyl halide with thiourea. Mild oxidation of a thiol yields a **disulfide**, and mild reduction of a disulfide gives back the thiol. **Sulfides**, the sulfur analogs of ethers, are prepared by an S$_N$2 reaction between a thiolate anion and a primary or secondary alkyl halide. Sulfides are much more nucleophilic than ethers and can be oxidized to **sulfoxides** and to **sulfones**. Sulfides can also be alkylated by reaction with a primary alkyl halide to yield **sulfonium ions**.

SUMMARY OF REACTIONS

1. Synthesis of ethers (Section 18.2)

   (a) Williamson ether synthesis

$$RO^- \ + \ R'CH_2X \ \longrightarrow \ ROCH_2R' \ + \ X^-$$

   (b) Alkoxymercuration/demercuration

$$\text{C=C} \xrightarrow[\text{2. NaBH}_4]{\text{1. ROH, (CF}_3\text{CO}_2)_2\text{Hg}} \text{C}-\text{C}$$
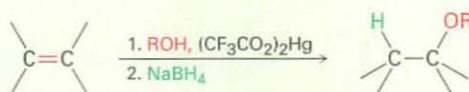
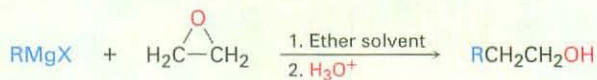2. Reactions of ethers

   (a) Cleavage by HBr or HI (Section 18.3)

$$R-O-R' \xrightarrow[\text{H}_2\text{O}]{\text{HX}} RX \ + \ R'OH$$
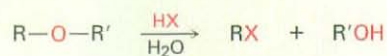
   (b) Claisen rearrangement (Section 18.4)
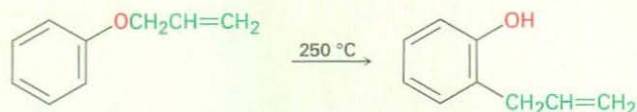
$$\xrightarrow{250\ °C}$$

   (c) Acid-catalyzed epoxide opening (Section 18.6)

$$\xrightarrow{\text{H}_3\text{O}^+}$$

$$\xrightarrow{\text{HBr}}$$

   (d) Base-catalyzed epoxide opening (Section 18.6)

$$\xrightarrow{\text{RO}^-,\ \text{ROH}}$$

$$RMgX \ + \ H_2C-CH_2 \xrightarrow[\text{2. H}_3\text{O}^+]{\text{1. Ether solvent}} RCH_2CH_2OH$$
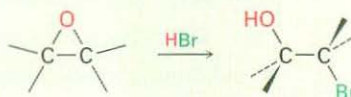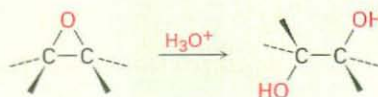
3. Synthesis of thiols (Section 18.8)

$$RCH_2Br \xrightarrow[\text{2. } H_2O, \text{ NaOH}]{\text{1. } (H_2N)_2C=S} RCH_2SH$$
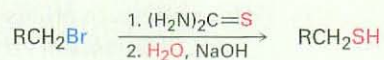
4. Oxidation of thiols to disulfides (Section 18.8)

$$2\,RSH \xrightarrow{I_2,\ H_2O} RS-SR$$
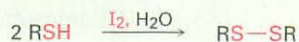
5. Synthesis of sulfides (Section 18.8)

$$RS^- + R'CH_2Br \longrightarrow RSCH_2R' + Br^-$$

6. Oxidation of sulfides to sulfoxides and sulfones (Section 18.8)
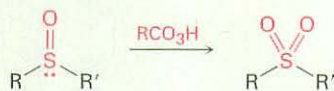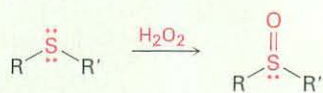
EXERCISES

Organic KNOWLEDGE TOOLS

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

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

■ indicates problems assignable in Organic OWL.

VISUALIZING CHEMISTRY

(Problems 18.1–18.18 appear within the chapter)

18.19 ■ Give IUPAC names for the following compounds (reddish brown = Br):

(a)

(b)

(c)

■ Assignable in OWL
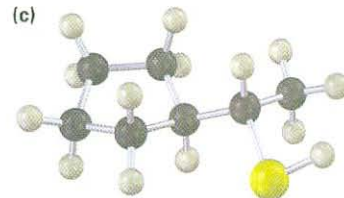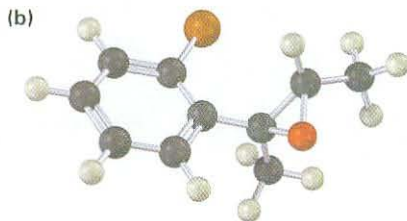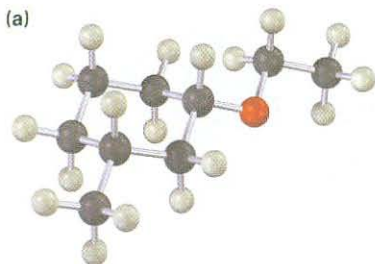
18.20 ■ Show the product, including stereochemistry, that would result from reaction of the following epoxide with HBr:
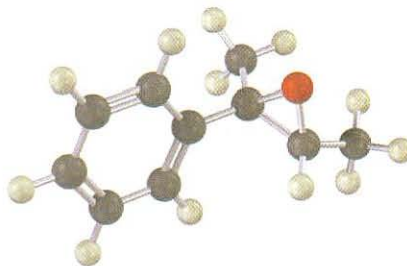
**18.21** ■ Show the product, including stereochemistry, of the following reaction:


1. CH₃MgBr, ether
2. H₃O⁺
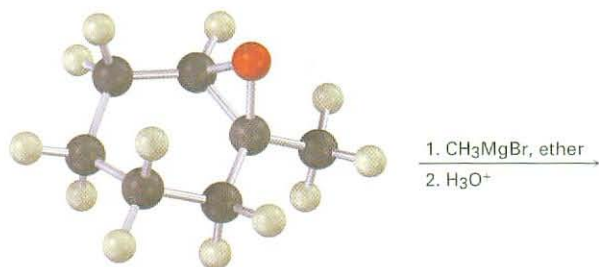
18.22 Treatment of the following alkene with a peroxyacid yields an epoxide different from that obtained by reaction with aqueous Br₂ followed by base treatment. Propose structures for the two epoxides, and explain the result.
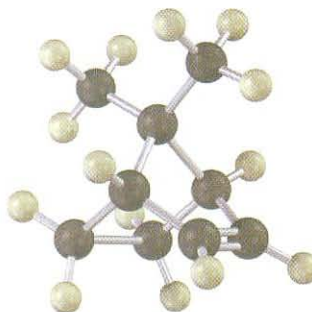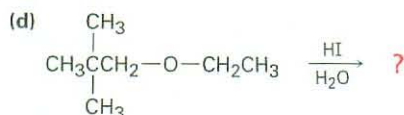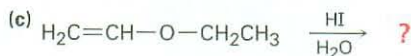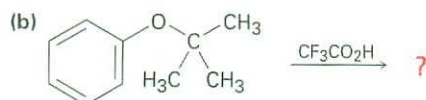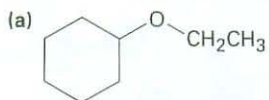

ADDITIONAL PROBLEMS

18.23 ■ Draw structures corresponding to the following IUPAC names:
   (a) Ethyl 1-ethylpropyl ether   (b) Di(p-chlorophenyl) ether
   (c) 3,4-Dimethoxybenzoic acid   (d) Cyclopentyloxycyclohexane
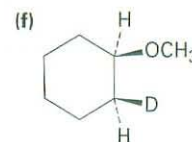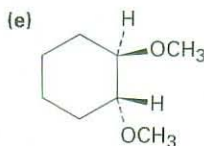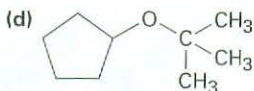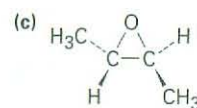   (e) 4-Allyl-2-methoxyphenol (eugenol; from oil of cloves)

18.24 ■ Give IUPAC names for the following structures:

(a)

(b)

(c)

(d)

(e)

(f)

(g)

(h)

(i)
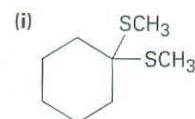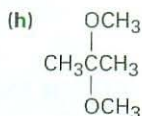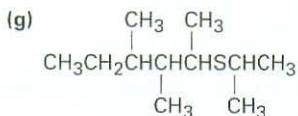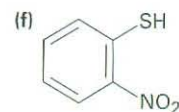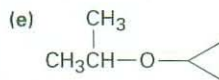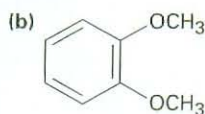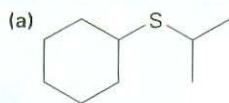
18.25 ■ Predict the products of the following ether cleavage reactions:

(a)

$$\xrightarrow[\text{H}_2\text{O}]{\text{HI}} \ ?$$

(b)

$$\xrightarrow{\text{CF}_3\text{CO}_2\text{H}} \ ?$$

(c) $\text{H}_2\text{C}=\text{CH}-\text{O}-\text{CH}_2\text{CH}_3 \xrightarrow[\text{H}_2\text{O}]{\text{HI}} \ ?$

(d)

$$\xrightarrow[\text{H}_2\text{O}]{\text{HI}} \ ?$$

18.26 ■ How would you prepare the following ethers?

(a)

(b)

(c)

(d)

(e)

(f)
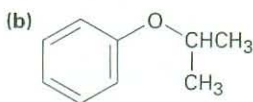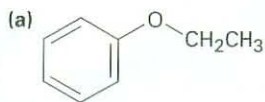
18.27 ■ How would you prepare the following compounds from 1-phenylethanol?
  (a) Methyl 1-phenylethyl ether   (b) Phenylepoxyethane
  (c) *tert*-Butyl 1-phenylethyl ether   (d) 1-Phenylethanethiol

18.28 ■ Predict the products of the following reactions:

(a)

$$\text{OCH}_2\overset{\overset{\displaystyle CH_3}{|}}{\text{CH}}\text{CH}_3 \quad \xrightarrow{\text{HBr}} \quad ?$$
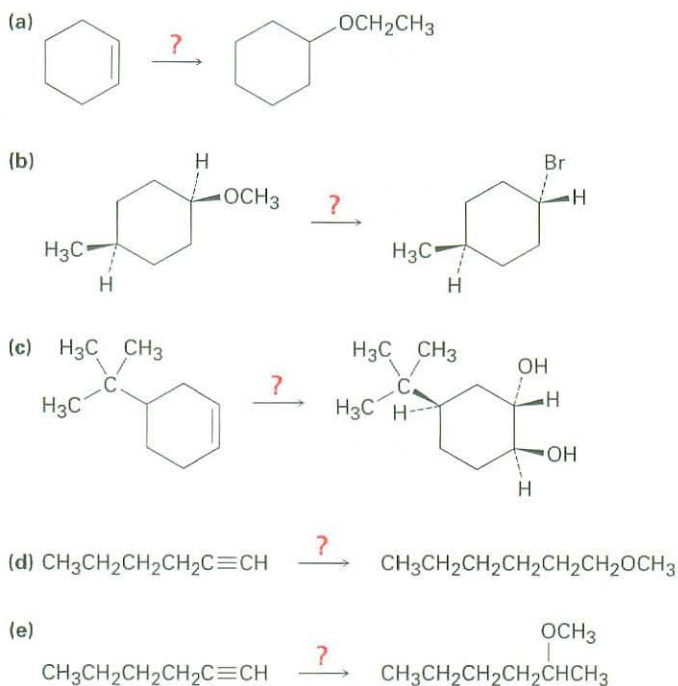
(b)

$$\text{CH}_3\overset{\overset{\displaystyle CH_3}{|}}{\text{CH}}\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \quad \xrightarrow[\text{2. NaOH, H}_2\text{O}]{\text{1. (NH}_2)_2\text{C}=\text{S}} \quad ?$$

(c)

 $\xrightarrow{\text{Br}_2}$?

(d)

 $\xrightarrow{\text{H}_2\text{O}_2, \text{ H}_2\text{O}}$?
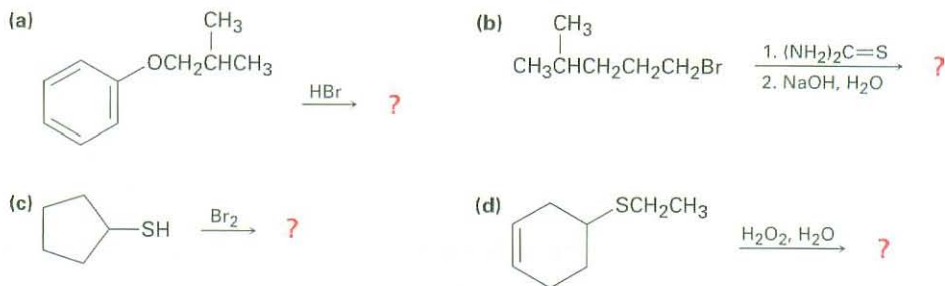
18.29 ■ How would you carry out the following transformations? More than one step may be required.

(a)

(b)

(c)

(d) $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH} \xrightarrow{?} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_3$

(e)

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C}\equiv\text{CH} \xrightarrow{?} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\overset{\overset{\displaystyle OCH_3}{|}}{\text{CH}}\text{CH}_3$$

18.30 What product would you expect from cleavage of tetrahydrofuran with HI?

18.31 How could you prepare benzyl phenyl ether from benzene and phenol? More than one step is required.

18.32 ■ When 2-methyl-2,5-pentanediol is treated with sulfuric acid, dehydration occurs and 2,2-dimethyltetrahydrofuran is formed. Suggest a mechanism for this reaction. Which of the two oxygen atoms is most likely to be eliminated, and why?
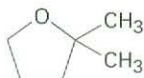

2,2-Dimethyltetrahydrofuran

18.33 ■ Write the mechanism of the hydrolysis of *cis*-5,6-epoxydecane by reaction with aqueous acid. What is the stereochemistry of the product, assuming normal backside S_N2 attack?

18.34 What is the stereochemistry of the product from acid-catalyzed hydrolysis of *trans*-5,6-epoxydecane? How does the product differ from that formed in Problem 18.33?

18.35 Methyl aryl ethers, such as anisole, are cleaved to iodomethane and a phenoxide ion by treatment with LiI in hot DMF. Propose a mechanism for this reaction.

18.36 ■ *tert*-Butyl ethers can be prepared by the reaction of an alcohol with 2-methylpropene in the presence of an acid catalyst. Propose a mechanism for this reaction.

18.37 *Meerwein's reagent,* triethyloxonium tetrafluoroborate, is a powerful ethylating agent that converts alcohols into ethyl ethers at neutral pH. Show the reaction of Meerwein's reagent with cyclohexanol, and account for the fact that trialkyloxonium salts are much more reactive alkylating agents than alkyl iodides.

$$(CH_3CH_2)_3O^+ \ BF_4^- \qquad \textbf{Meerwein's reagent}$$

18.38 Safrole, a substance isolated from oil of sassafras, is used as a perfumery agent. Propose a synthesis of safrole from catechol (1,2-benzenediol).

Safrole
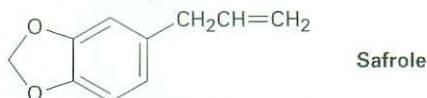
18.39 Epoxides are reduced by treatment with lithium aluminum hydride to yield alcohols. Propose a mechanism for this reaction.
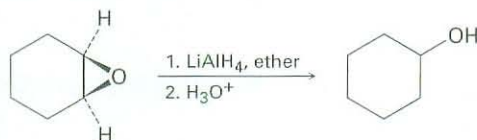

18.40 Show the structure and stereochemistry of the alcohol that would result if 1,2-epoxycyclohexane (Problem 18.39) were reduced with lithium aluminum deuteride, $LiAlD_4$.

18.41 Acid-catalyzed hydrolysis of a 1,2-epoxycyclohexane produces a trans-diaxial 1,2-diol. What product would you expect to obtain from acidic hydrolysis of *cis*-3-*tert*-butyl-1,2-epoxycyclohexane? (Recall that the bulky *tert*-butyl group locks the cyclohexane ring into a specific conformation.)

18.42 Grignard reagents react with oxetane, a four-membered cyclic ether, to yield primary alcohols, but the reaction is much slower than the corresponding reaction with ethylene oxide. Suggest a reason for the difference in reactivity between oxetane and ethylene oxide.
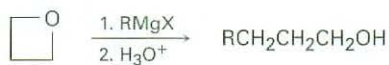

Oxetane

18.43 Treatment of *trans*-2-chlorocyclohexanol with NaOH yields 1,2-epoxycyclo-hexane, but reaction of the cis isomer under the same conditions yields cyclo-hexanone. Propose mechanisms for both reactions, and explain why the different results are obtained.
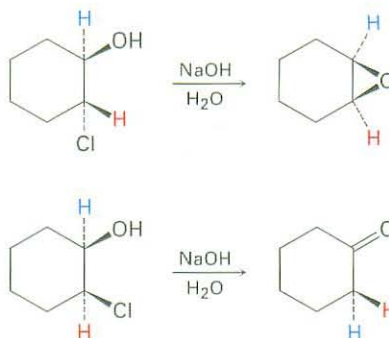

18.44 Ethers undergo an acid-catalyzed cleavage reaction when treated with the Lewis acid BBr$_3$ at room temperature. Propose a mechanism for the reaction.
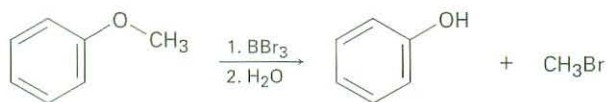

18.45 The *Zeisel method* is an analytical procedure for determining the number of methoxyl groups in a compound. A weighed amount of the compound is heated with concentrated HI, ether cleavage occurs, and the iodomethane product is distilled off and passed into an alcohol solution of AgNO$_3$, where it reacts to form a precipitate of silver iodide. The AgI is then collected and weighed, and the percentage of methoxyl groups in the sample is thereby determined. For example, 1.06 g of vanillin, the material responsible for the characteristic odor of vanilla, yields 1.60 g of AgI. If vanillin has a molecular weight of 152, how many methoxyl groups does it contain?

18.46 Disparlure, C$_{19}$H$_{38}$O, is a sex attractant released by the female gypsy moth, *Lymantria dispar*. The ^{1}H NMR spectrum of disparlure shows a large absorption in the alkane region, 1 to 2 δ, and a triplet at 2.8 δ. Treatment of disparlure, first with aqueous acid and then with KMnO$_4$, yields two carboxylic acids identified as undecanoic acid and 6-methylheptanoic acid. (KMnO$_4$ cleaves 1,2-diols to yield carboxylic acids.) Neglecting stereochemistry, propose a structure for disparlure. The actual compound is a chiral molecule with 7*R*,8*S* stereochemistry. Draw disparlure, showing the correct stereochemistry.

18.47 How would you synthesize racemic disparlure (Problem 18.46) from com-pounds having ten or fewer carbons?

18.48 ■ Treatment of 1,1-diphenyl-1,2-epoxyethane with aqueous acid yields diphenylacetaldehyde as the major product. Propose a mechanism for the reaction.
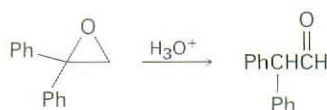
18.49 How would you prepare *o*-hydroxyphenylacetaldehyde from phenol? More than one step is required.
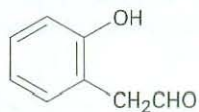
*o*-**Hydroxyphenylacetaldehyde**

18.50 ■ Imagine that you have treated (2*R*,3*R*)-2,3-epoxy-3-methylpentane with aqueous acid to carry out a ring-opening reaction.
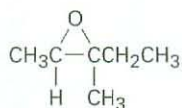
2,3-Epoxy-3-methylpentane
(no stereochemistry implied)

(a) Draw the epoxide, showing stereochemistry.
(b) Draw and name the product, showing stereochemistry.
(c) Is the product chiral? Explain.
(d) Is the product optically active? Explain.

**18.51** Identify the reagents **a–e** in the following scheme:
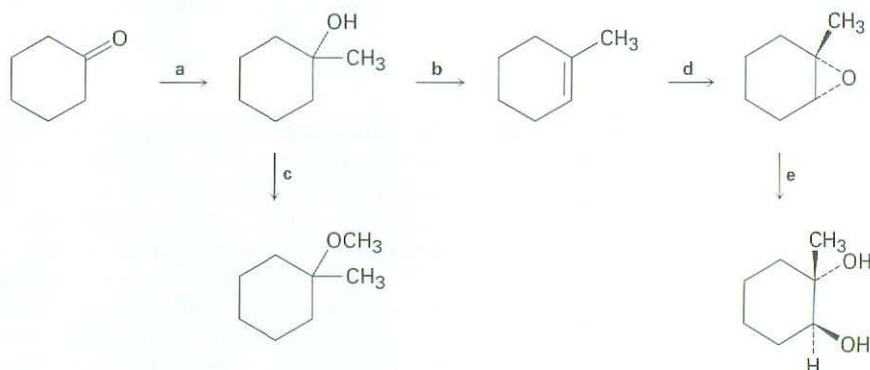
18.52 Fluoxetine, a heavily prescribed antidepressant marketed under the name Prozac, can be prepared by a route that begins with reaction between a phenol and an alkyl chloride.
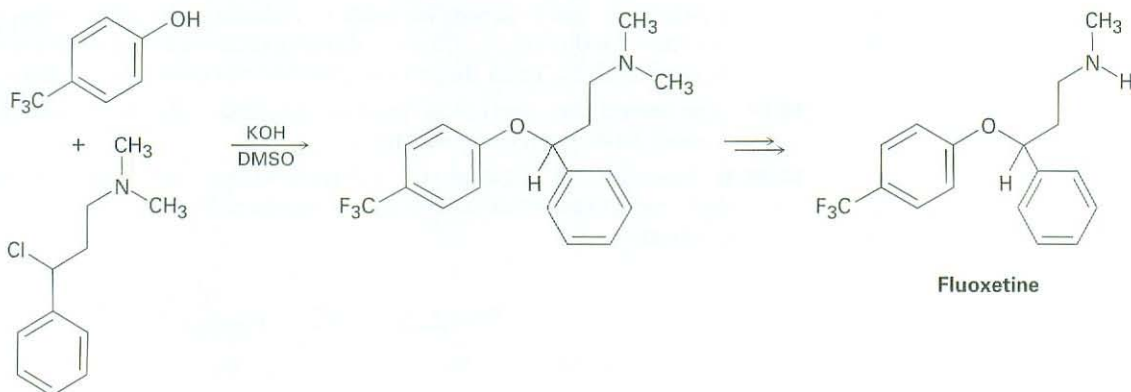
Fluoxetine

(a) The rate of the reaction depends on both phenol and alkyl halide. Is this an S_N1 or an S_N2 reaction? Show the mechanism.

(b) The physiologically active enantiomer of fluoxetine has (S) stereochemistry. Based on your answer in part (a), draw the structure of the alkyl chloride you would need, showing the correct stereochemistry.

18.53 The herbicide acifluorfen can be prepared by a route that begins with reaction between a phenol and an aryl fluoride. Propose a mechanism.


Acifluorfen
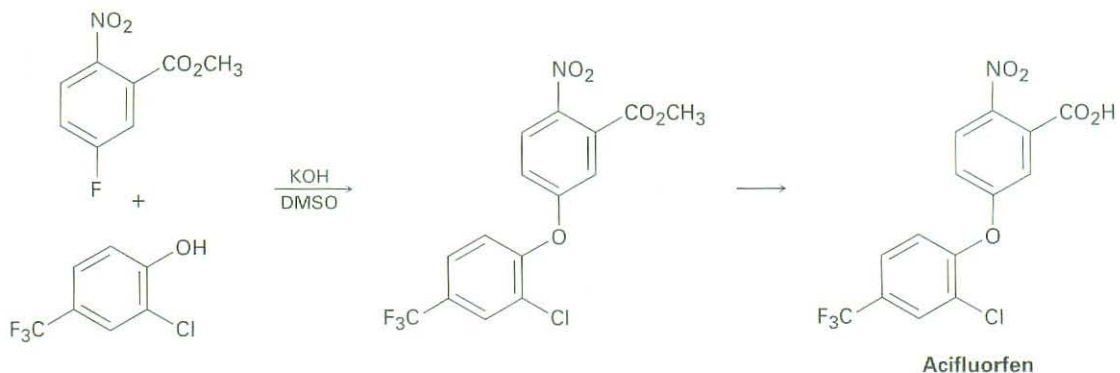
18.54 ■ The red fox *(Vulpes vulpes)* uses a chemical communication system based on scent marks in urine. Recent work has shown one component of fox urine to be a sulfide. Mass spectral analysis of the pure scent-mark component shows $M^+ = 116$. IR spectroscopy shows an intense band at 890 cm^{-1}, and ^{1}H NMR spectroscopy reveals the following peaks:

1.74 δ (3 H, singlet); 2.11 δ (3 H, singlet); 2.27 δ (2 H, triplet, J = 4.2 Hz); 2.57 δ (2 H, triplet, J = 4.2 Hz); 4.73 δ (2 H, broad)

Propose a structure consistent with these data. [Note: $(CH_3)_2S$ absorbs at 2.1 δ.]

18.55 ■ Anethole, $C_{10}H_{12}O$, a major constituent of the oil of anise, has the ^{1}H NMR spectrum shown. On oxidation with $Na_2Cr_2O_7$, anethole yields *p*-methoxybenzoic acid. What is the structure of anethole? Assign all peaks in the NMR spectrum, and account for the observed splitting patterns.
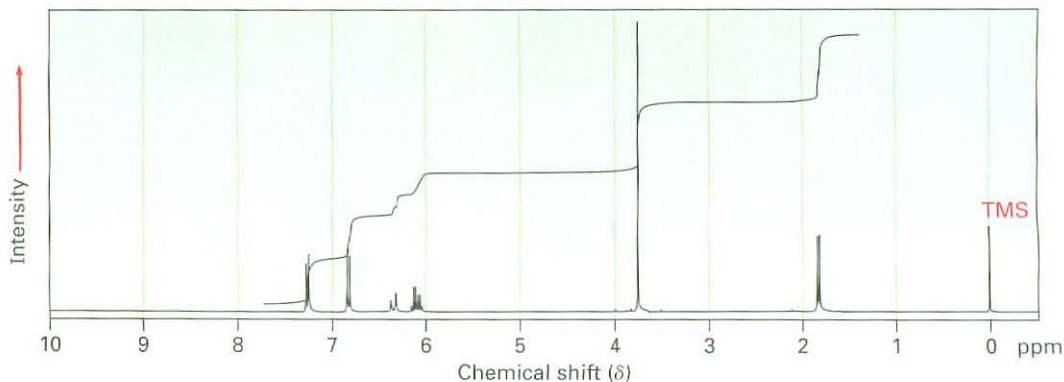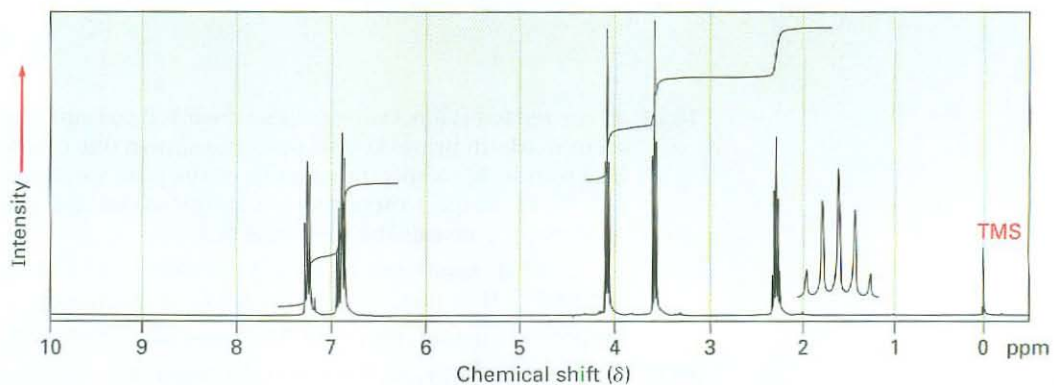

18.56 How would you synthesize anethole (Problem 18.55) from phenol?

18.57 ■ Propose structures for compounds that have the following ^{1}H NMR spectra:
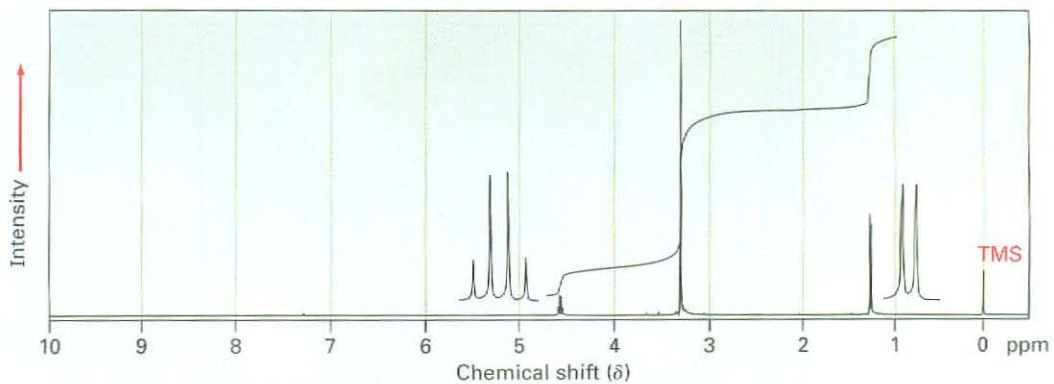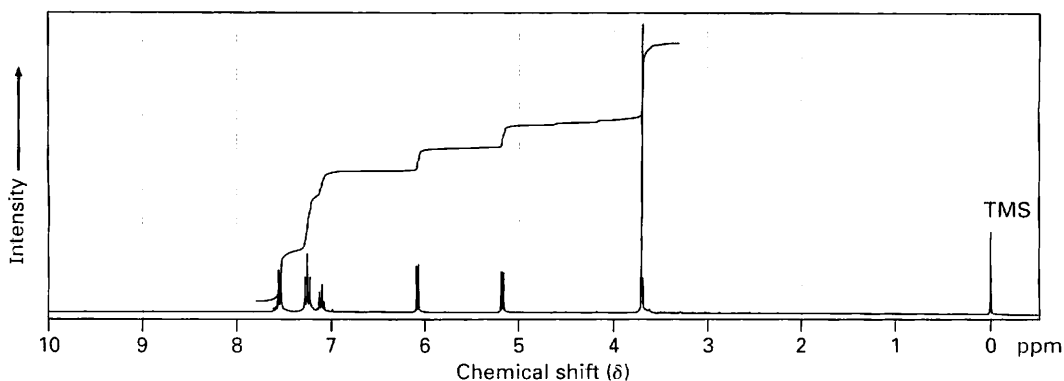
(a) $C_5H_{12}S$
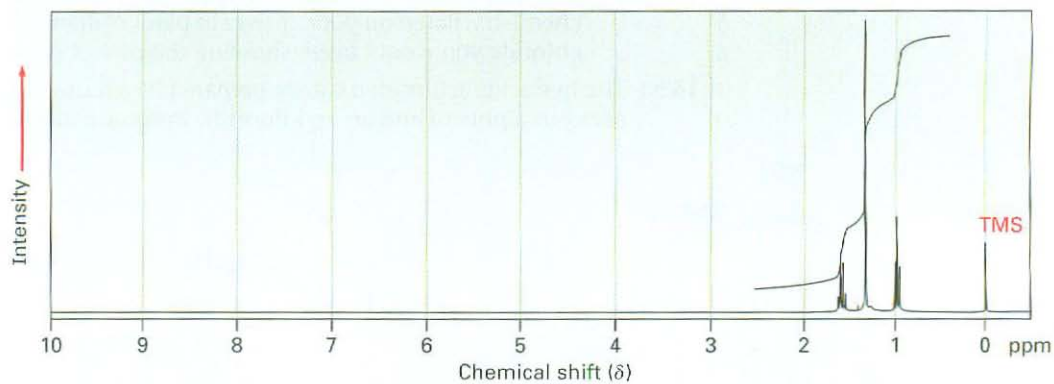
(b) $C_9H_{11}BrO$

(c) $C_4H_{10}O_2$

(d) $C_9H_{10}O$

18.58 Aldehydes and ketones undergo acid-catalyzed reaction with alcohols to yield *hemiacetals,* compounds that have one alcohol-like oxygen and one ether-like oxygen bonded to the same carbon. Further reaction of a hemiacetal with alcohol then yields an *acetal,* a compound that has two ether-like oxygens bonded to the same carbon.

A hemiacetal   **An acetal**
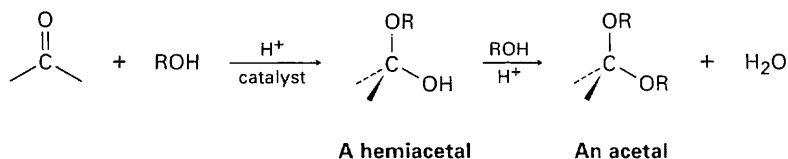
(a) Show the structures of the hemiacetal and acetal you would obtain by reaction of cyclohexanone with ethanol.

(b) Propose a mechanism for the conversion of a hemiacetal into an acetal.

18.59 We saw in Section 17.4 that ketones react with $NaBH_4$ to yield alcohols. We'll also see in Section 22.3 that ketones react with Br_2 to yield α-bromo ketones. Perhaps surprisingly, treatment with $NaBH_4$ of the α-bromo ketone from acetophenone yields an epoxide rather than a bromo alcohol. Show the structure of the epoxide, and explain its formation.

Acetophenone   **An α-bromo ketone**