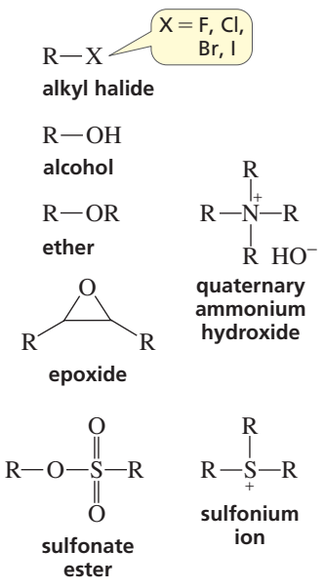
# 10 Reactions of Alcohols, Ethers, Epoxides, Amines, and Sulfur-Containing Compounds

dried coca leaves

*Chemists search the world for plants and berries and the ocean for flora and fauna that might be used as the source of a lead compound for the development of a new drug. In this chapter, we will see how cocaine, which is obtained from the leaves of Erythroxylon coca—a bush native to the highlands of the South American Andes, was used as the source of a lead compound for the development of some common anesthetics (see page 491).*

**Group II**




We saw that alkyl halides, a family of compounds in Group II, undergo substitution and/or elimination reactions because of their electron-withdrawing halogen atoms (Chapter 9). Other families of compounds in Group II also have electron-withdrawing groups, and they too undergo substitution and/or elimination reactions. The relative reactivity of these compounds depends on the electron-withdrawing group—that is, on the leaving group.

## Reactivity Depends on the Basicity of the Leaving Group

- The leaving groups of alcohols and ethers ($HO^-$, $RO^-$) are much stronger bases than the leaving group of an alkyl halide. Because they are stronger bases, they are poorer leaving groups and, therefore, are harder to displace. Consequently, alcohols and ethers are less reactive than alkyl halides in substitution and elimination reactions. We will see that alcohols and ethers must be "activated" before they can undergo a substitution or elimination reaction.
- The leaving group of an amine ($^-NH_2$) is so basic that amines cannot undergo substitution and elimination reactions but they are important bases and nucleophiles.

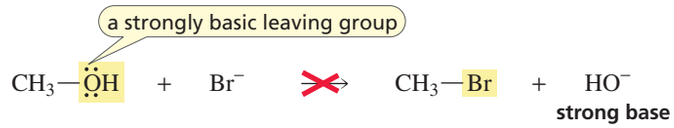
- Tertiary amines, the leaving groups of **quaternary ammonium ions,** not only are less basic than the leaving groups of alcohols and ethers but also have a positive charge that enhances their leaving ability. Therefore, quaternary ammonium ions undergo elimination reactions as long as a strong base is present and the reaction is heated.
- **Sulfonate esters** and **sulfonium ions** have very good leaving groups, the first because of electron delocalization and the second because of its positive charge. Thus, they undergo substitution and/or elimination reactions with ease.

When bases with similar features are compared: the weaker the base, the more easily it is displaced. Recall that the stronger the acid, the weaker its conjugate base.

| | R—X | R—O—H | R—O—R | R—O—S(=O)(=O)—R | R—$NH_2$ | R—$N^+$(R)(R)—R | R—$S^+$(R)—R |
|---|---|---|---|---|---|---|---|
| | alkyl halide X = F, Cl, Br, I | alcohol | ether | sulfonate ester | amine | quaternary ammonium ion | sulfonium ion |
| p$K_a$ of conjugate acid of the leaving group | −10 to 3.2 | ~15 | ~15 | ~ −6 | 40 | ~10 | ~ −6 |

# 10.1 NUCLEOPHILIC SUBSTITUTION REACTIONS OF ALCOHOLS: FORMING ALKYL HALIDES

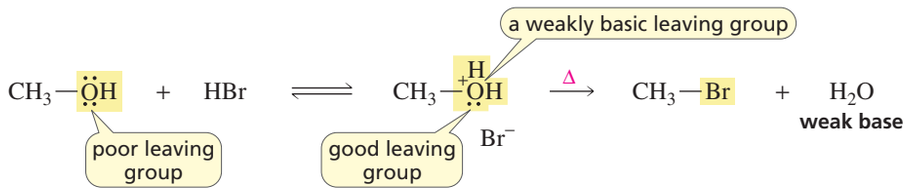
An **alcohol** has a strongly basic leaving group ($HO^-$) that cannot be displaced by a nucleophile. Therefore, an alcohol cannot undergo a nucleophilic substitution reaction.




However, if the alcohol's OH group is converted into a group that is a weaker base (and, therefore, a better leaving group), a nucleophilic substitution reaction can occur.

## Converting an OH Group into a Better Leaving Group

One way to convert an OH group into a weaker base is to protonate it by adding acid to the reaction mixture. Protonation changes the leaving group from $HO^-$ to $H_2O$, which is a weak enough base to be displaced by a nucleophile. The substitution reaction is slow and requires heat (except in the case of tertiary alcohols) if it is to take place at a reasonable rate.

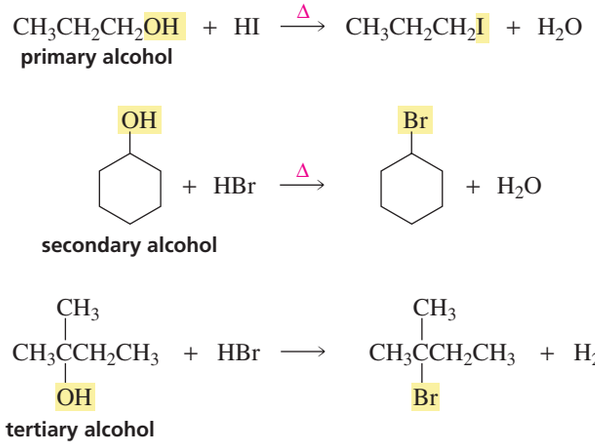



Because the OH group of the alcohol must be protonated before it can be displaced by a nucleophile, only weakly basic nucleophiles ($I^-$, $Br^-$, $Cl^-$) can be used in the substitution reaction. Moderately and strongly basic nucleophiles ($NH_3$, $RNH_2$, and $CH_3O^-$) cannot be used because they too would be protonated in the acidic solution and, once protonated, would no longer be nucleophiles ($^+NH_4$, $RN^+H_3$) or would be poor nucleophiles ($CH_3OH$).

**PROBLEM 1 ♦**

Why are $NH_3$ and $CH_3NH_2$ no longer nucleophiles when they are protonated?

Primary, secondary, and tertiary alcohols all undergo nucleophilic substitution reactions with HI, HBr, and HCl to form alkyl halides.

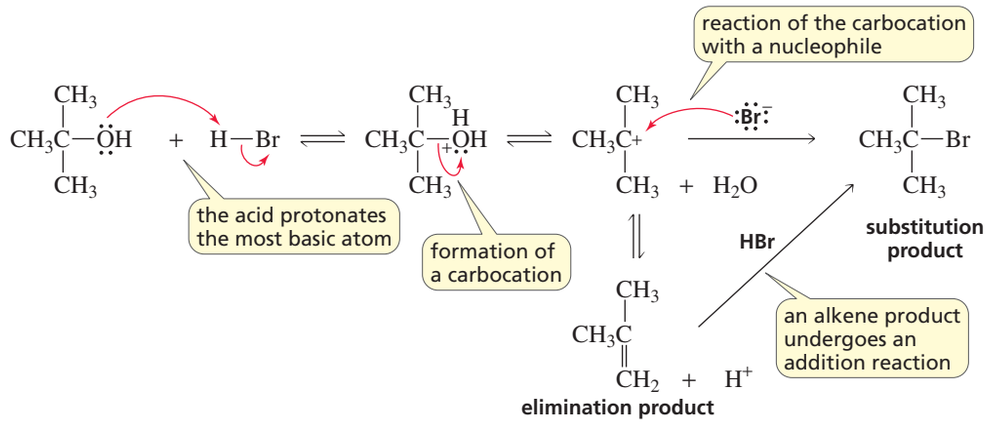



## The $S_N1$ Reaction of Secondary and Tertiary Alcohols

The mechanism of the substitution reaction depends on the structure of the alcohol. Secondary and tertiary alcohols undergo $S_N1$ reactions.

### MECHANISM FOR THE $S_N1$ REACTION OF AN ALCOHOL

An acid protonates the most basic atom in a molecule.




- An acid always reacts with an organic molecule in the same way: it protonates the most basic atom in the molecule.
- Weakly basic water is the leaving group that is expelled, forming a carbocation.
- The carbocation, like the carbocation formed when an alkyl halide dissociates in an $S_N1$ reaction, has two possible fates: it can combine with a nucleophile and form a substitution product, or it can lose a proton and form an elimination product (Section 9.12).

Although the reaction can form both a substitution product and an elimination product, little elimination product is actually obtained because the alkene formed in an elimination reaction can undergo a subsequent electrophilic addition reaction with HBr to form more of the substitution product (Section 6.1).

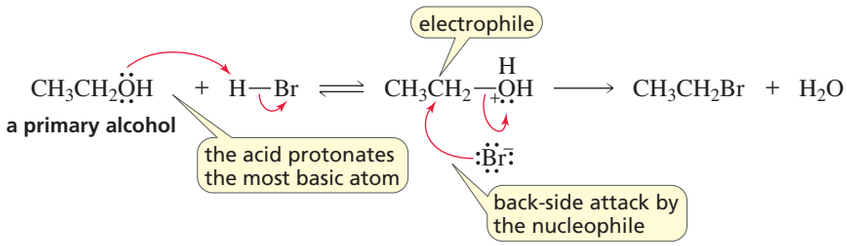
Tertiary alcohols undergo substitution reactions with hydrogen halides faster than secondary alcohols do because tertiary carbocations are more stable and, therefore, are formed more rapidly than secondary carbocations. (Recall that alkyl groups stabilize carbocations by hyperconjugation; Section 6.2) As a result, the reaction of a tertiary alcohol with a hydrogen halide proceeds readily at room temperature, whereas the reaction of a secondary alcohol with a hydrogen halide must be heated to have the reaction occur at a reasonable rate.

## The $S_N2$ Reaction of Primary Alcohols

Primary alcohols cannot undergo $S_N1$ reactions because primary carbocations are too unstable to be formed, even when the reaction is heated (Section 9.3). Therefore, when a primary alcohol reacts with a hydrogen halide, it must do so in an $S_N2$ reaction.

**Carbocation stability: 3° > 2° > 1°**

### MECHANISM FOR THE $S_N2$ REACTION OF AN ALCOHOL



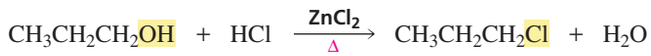

**Secondary and tertiary alcohols undergo $S_N1$ reactions with hydrogen halides.**

**Primary alcohols undergo $S_N2$ reactions with hydrogen halides.**

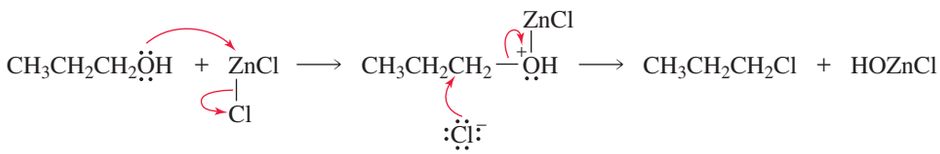
- The acid protonates the most basic atom in the reactant.
- The nucleophile attacks the back side of the carbon and displaces the leaving group.

Only a substitution product is obtained. No elimination product is formed because the halide ion, although a good nucleophile, is a weak base in a reaction mixture that contains alcohol and water (that is, in a polar protic solvent). Recall that a strong base is required to remove a hydrogen from a $\beta$-carbon in an E2 reaction (Section 9.9).

When HCl is used instead of HBr or HI, the $S_N2$ reaction is slower because $Cl^-$ is a poorer nucleophile than $Br^-$ or $I^-$ (Section 9.2). However, the rate of the reaction can be increased if $ZnCl_2$ is used as a catalyst.



$ZnCl_2$ is a Lewis acid that complexes strongly with oxygen's lone-pair electrons. This interaction weakens the C—O bond, thereby creating a better leaving group than water.



### The Lucas Test

Before spectroscopy became available for structural analysis, chemists had to identify compounds by tests that gave visible results. The Lucas test is one such test. It determines whether an alcohol is primary, secondary, or tertiary by taking advantage of the relative rates at which the three classes of alcohols react with HCl/$ZnCl_2$.

To carry out the test, the alcohol is added to a mixture of HCl and $ZnCl_2$ (known as Lucas reagent). Low-molecular-weight alcohols are soluble in Lucas reagent, but the alkyl halide products are not, so they cause the solution to turn cloudy. If the alcohol is tertiary, the solution turns cloudy immediately. If the alcohol is secondary, the solution turns cloudy in approximately one to five minutes. If the alcohol is primary, the solution turns cloudy only if it is heated. Because the test relies on the complete solubility of the alcohol in Lucas reagent, it is limited to alcohols with fewer than six carbons.

**PROBLEM 2 SOLVED**

**LEARN THE STRATEGY**

Using the p$K_a$ values of the conjugate acids of the leaving groups (the p$K_a$ of HBr is −9, and the p$K_a$ of $H_2O$ is 15.7), explain the difference in reactivity between $CH_3Br$ and $CH_3OH$ in a nucleophilic substitution reaction.

**SOLUTION** The conjugate acid of the leaving group of $CH_3Br$ is HBr; the conjugate acid of the leaving group of $CH_3OH$ is $H_2O$. Because HBr is a much stronger acid (p$K_a$ = −9) than $H_2O$ (p$K_a$ = 15.7), $Br^-$ is a much weaker base than $HO^-$. (Recall that the stronger the acid, the weaker its conjugate base.) Therefore, $Br^-$ is a much better leaving group than $HO^-$, causing $CH_3Br$ to be much more reactive than $CH_3OH$ in a nucleophilic substitution reaction.

**USE THE STRATEGY**

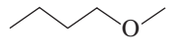
**PROBLEM 3**

Explain the difference in reactivity between $CH_3\overset{+}{O}H_2$ and $CH_3OH$ in a nucleophilic substitution reaction. (The p$K_a$ of $H_3O^+$ is −1.7.)

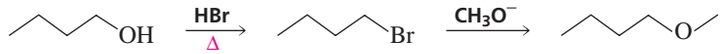
**LEARN THE STRATEGY**

**PROBLEM 4 SOLVED**

Show how 1-butanol can be converted into the following compound:



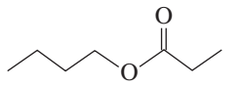
**SOLUTION** Because the OH group of 1-butanol is too basic to allow the alcohol to undergo a nucleophilic substitution reaction with $CH_3O^-$, the alcohol must first be converted into an alkyl halide. The alkyl halide has a leaving group that can be substituted by $CH_3O^-$, the nucleophile required to obtain the desired product.

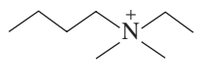


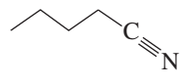

**USE THE STRATEGY**

**PROBLEM 5**

Explain how 1-butanol can be converted into the following compounds:

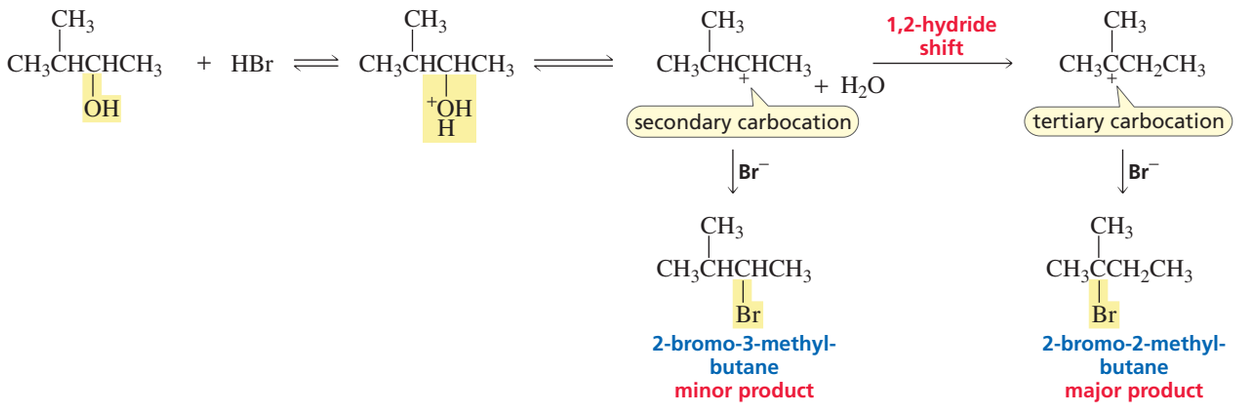
**a.** 


**b.** 


**c.** 


Because the reaction of a secondary alcohol with a hydrogen halide is an $S_N1$ reaction, a carbocation is formed as an intermediate. Therefore, we must check for the possibility of a carbocation rearrangement when determining the product of the substitution reaction. Remember that a carbocation rearrangement will occur if it leads to formation of a more stable carbocation (Section 6.7).

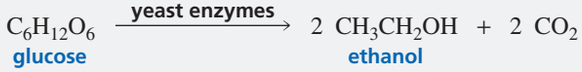
For example, the major product of the following reaction is 2-bromo-2-methylbutane, because a 1,2-hydride shift converts the initially formed secondary carbocation into a more stable tertiary carbocation.




## Grain Alcohol and Wood Alcohol

When ethanol is ingested, it acts on the central nervous system. Moderate amounts affect judgment and lower inhibitions. Higher amounts interfere with motor coordination and cause slurred speech and amnesia. Still higher amounts cause nausea and loss of consciousness. Ingesting very large amounts of ethanol interferes with spontaneous respiration and can be fatal.

The ethanol in alcoholic beverages is produced by the fermentation of glucose, generally obtained from grapes or from grains such as corn, rye, and wheat (which is why ethanol is also known as grain alcohol). Grains are cooked in the presence of malt (sprouted barley) to convert much of their starch into glucose. Yeast enzymes are added to convert the glucose into ethanol and carbon dioxide (Section 24.7).




The kind of beverage produced (white or red wine, beer, scotch, bourbon, champagne) depends on what plant species provides the glucose, whether the $CO_2$ formed in the fermentation is allowed to escape, whether other substances are added, and how the beverage is purified (by sedimentation, for wines; by distillation, for scotch and bourbon).

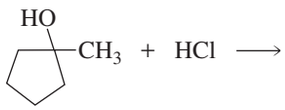
The tax imposed on liquor would make ethanol a prohibitively expensive laboratory reagent. Laboratory alcohol, therefore, is not taxed because ethanol is needed in a wide variety of commercial processes. Although not taxed, it is carefully regulated by the federal government to make certain that it is not used for the preparation of alcoholic beverages. Denatured alcohol—ethanol that has been made undrinkable by the addition of a denaturant such as benzene or methanol—is not taxed, but the added impurities make it unfit for many laboratory uses.

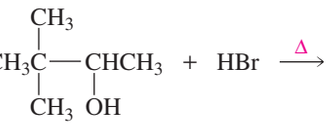
Methanol, also known as wood alcohol (because at one time it was obtained by heating wood in the absence of oxygen), is highly toxic. Ingesting even very small amounts can cause blindness, and ingesting as little as an ounce has been fatal. (See Methanol Poisoning on p. 477.)

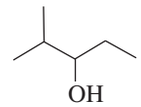
**PROBLEM 6 ♦**

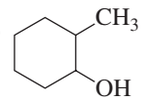
What is the major product of each of the following reactions?

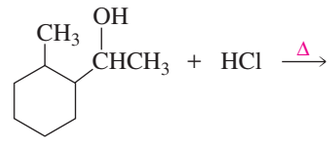
**a.** $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3 + HBr \xrightarrow{\Delta}$

**b.**  $+ HCl \longrightarrow$

**c.** 

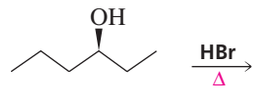
**d.**  $+ HBr \xrightarrow{\Delta}$

**e.**  $+ HCl \xrightarrow{\Delta}$

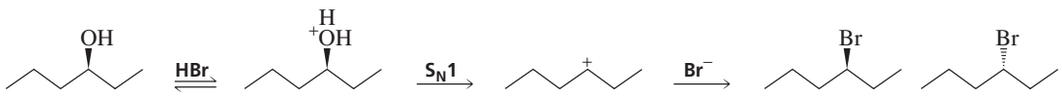
**f.** 

**PROBLEM 7 SOLVED** **LEARN THE STRATEGY**

What stereoisomers does the following reaction form?

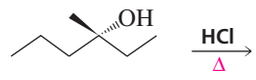


**SOLUTION** This must be an $S_N1$ reaction because the reactant is a secondary alcohol. Therefore, the reaction forms a carbocation intermediate. The bromide ion can attach to the carbocation from either the side from which water left or from the opposite side, so both the *R* and *S* stereoisomers are formed.



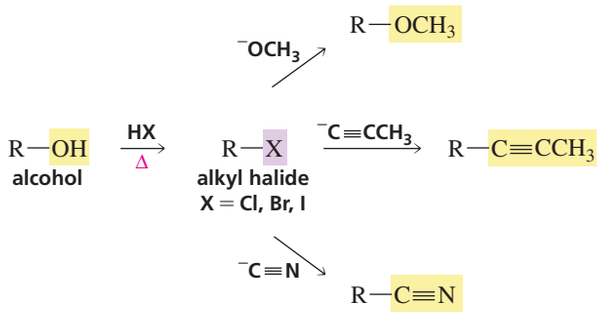
**PROBLEM 8** **USE THE STRATEGY**

What stereoisomer does the following reaction form?



# 10.2 OTHER METHODS USED TO CONVERT ALCOHOLS INTO ALKYL HALIDES

Alcohols are inexpensive and readily available compounds, but they do not undergo nucleophilic substitution because the $HO^-$ group is too basic to be displaced by a nucleophile (Section 10.1). Chemists, therefore, need ways to convert readily available but unreactive alcohols into reactive alkyl halides that can be used as starting materials for the preparation of a wide variety of organic compounds (Section 9.2).




We just saw that an alcohol can be converted to an alkyl halide by treating it with a hydrogen halide. Better yields of the alkyl halide are obtained and carbocation rearrangements can be avoided if a phosphorus trihalide ($PCl_3$ or $PBr_3$) or thionyl chloride ($SOCl_2$) is used instead.

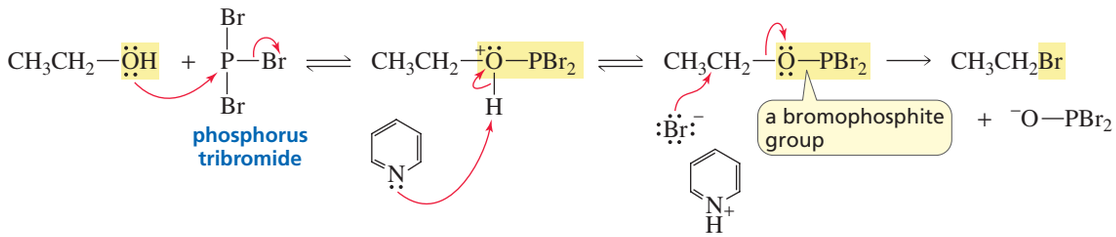
$$CH_3CH_2OH + PBr_3 \xrightarrow[\text{pyridine}]{} CH_3CH_2Br$$

$$CH_3CH_2OH + PCl_3 \xrightarrow[\text{pyridine}]{} CH_3CH_2Cl$$

$$CH_3CH_2OH + SOCl_2 \xrightarrow[\text{pyridine}]{} CH_3CH_2Cl$$

These reagents all act in the same way: they convert the alcohol into an intermediate with a leaving group that is readily displaced by a halide ion.

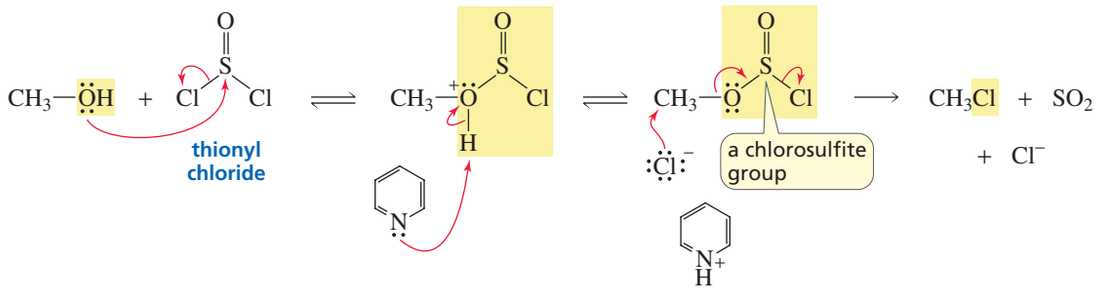
## MECHANISM FOR THE CONVERSION OF AN ALCOHOL TO AN ALKYL BROMIDE (OR ALKYL CHLORIDE) USING $PBr_3$ (OR $PCl_3$)




- The first step is an $S_N2$ reaction on phosphorus.
- Pyridine is generally used as a solvent in these reactions because it is a poor nucleophile. However, it is sufficiently basic to remove a proton from the intermediate, which prevents the intermediate from reverting to starting materials.
- The bromophosphite group is a weaker base than a halide ion, so it is easily displaced by a halide ion.


pyridine

## MECHANISM FOR THE CONVERSION OF AN ALCOHOL TO AN ALKYL CHLORIDE USING $SOCl_2$



- The first step is an $S_N2$ reaction on sulfur.
- Pyridine removes a proton from the intermediate, which prevents the intermediate from reverting to starting materials.
- The chlorosulfite group is a weaker base than a chloride ion, so it is easily displaced by a chloride ion.

The foregoing reactions work well for primary and secondary alcohols, but tertiary alcohols give poor yields because the intermediate formed by a tertiary alcohol is sterically hindered to back-side attack by the halide ion.

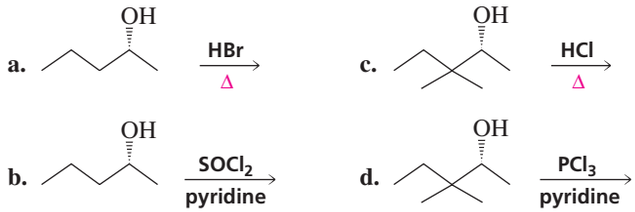
Table 10.1 summarizes some of the methods commonly used to convert alcohols into alkyl halides.

**Table 10.1** Commonly Used Methods for Converting Alcohols into Alkyl Halides

| | | | | |
|---|---|---|---|---|
| ROH | + HBr | $\xrightarrow{\Delta}$ | RBr |
| ROH | + HI | $\xrightarrow{\Delta}$ | RI |
| ROH | + HCl | $\xrightarrow[\Delta]{ZnCl_2}$ | RCl |
| ROH | + $PBr_3$ | $\xrightarrow{\text{pyridine}}$ | RBr |
| ROH | + $PCl_3$ | $\xrightarrow{\text{pyridine}}$ | RCl |
| ROH | + $SOCl_2$ | $\xrightarrow{\text{pyridine}}$ | RCl |

PROBLEM 9

What stereoisomers do the following reactions form?

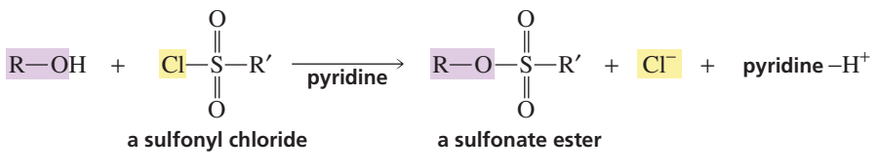



# 10.3 CONVERTING AN ALCOHOL INTO A SULFONATE ESTER

Another way a primary or secondary alcohol can be activated for a subsequent reaction with a nucleophile—instead of converting it into an alkyl halide—is to convert it into a sulfonate ester.

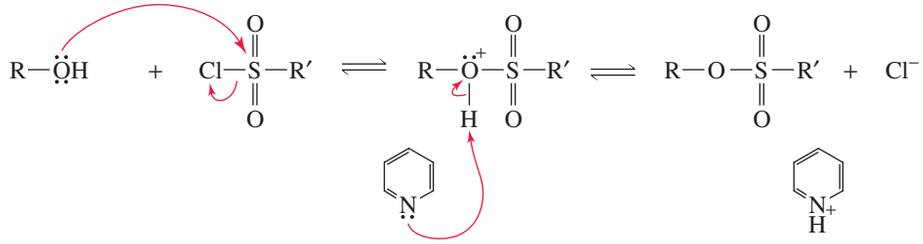
## Forming a Sulfonate Ester

A **sulfonate ester** is formed when an alcohol reacts with a sulfonyl chloride. (Notice that sulfur, which is in the third row of the periodic table, has an expanded valence shell—that is, it is surrounded by 12 electrons.)



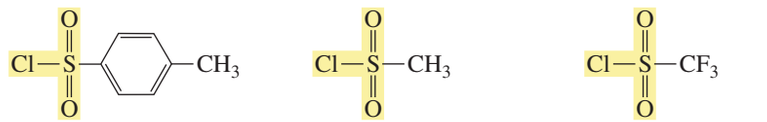

The reaction is a nucleophilic substitution reaction in which the alcohol displaces the chloride ion. Pyridine is the solvent and it is the base that removes a proton from the intermediate.

### MECHANISM FOR THE CONVERSION OF AN ALCOHOL TO A SULFONATE ESTER



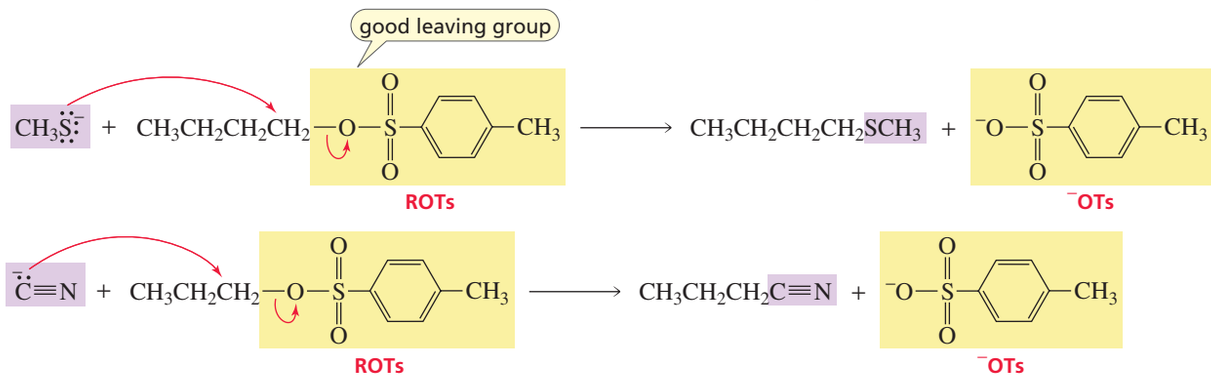
- The first step is an $S_N2$ reaction on sulfur.
- Pyridine removes a proton from the intermediate, which prevents the intermediate from reverting to starting materials.

Several sulfonyl chlorides are available to activate OH groups. The most common one is *para*-toluenesulfonyl chloride (abbreviated as TsCl). The sulfonate ester formed from the reaction of TsCl and an alcohol is called an **alkyl tosylate** (abbreviated as ROTs).



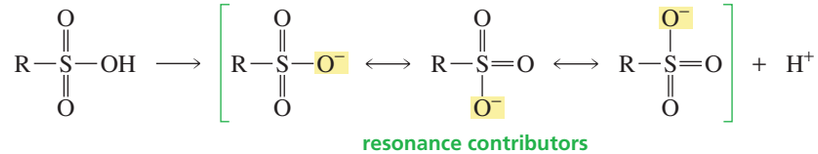

## Sulfonate Esters in Substitution Reactions

Once the alcohol has been activated by being converted into a sulfonate ester, the appropriate nucleophile is added. (Notice that in all cases, the added nucleophile is a *much* better nucleophile than the chloride ion that also is present in the solution, because it was the leaving group in the synthesis of the sulfonate ester.) The reactions are $S_N2$ reactions and take place readily at room temperature because the sulfonate ester has an excellent leaving group. Sulfonate esters react with a wide variety of nucleophiles, so they can be used to synthesize a wide variety of compounds.



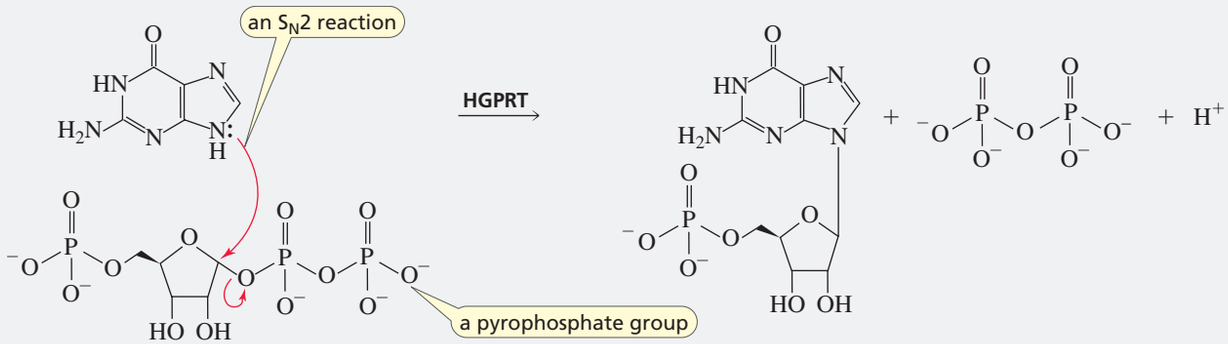

This substitution reaction will not take place if the alcohol that forms the sulfonate ester is tertiary because it would be too sterically hindered to undergo the subsequent $S_N2$ reaction. (Recall that tertiary alkyl halides cannot undergo $S_N2$ reactions; Section 9.2.)

A sulfonate ester has an excellent leaving group. A sulfonic acid is a very strong acid ($pK_a = -6.5$) because its conjugate base is particularly stable (weak) due to delocalization of its negative charge over three oxygens. (Recall from Section 8.6 that electron delocalization stabilizes a species.) As a result, the leaving group of a sulfonate ester is about 100 times better as a leaving group than is chloride ion.



## The Inability to Perform an $S_N2$ Reaction Causes a Severe Clinical Disorder

In the human body, an enzyme called HGPRT catalyzes the nucleophilic substitution reaction shown here. The pyrophosphate group is an excellent leaving group because the electrons released when the group departs, like the electrons released when a sulfonate group departs, are stabilized by electron delocalization.

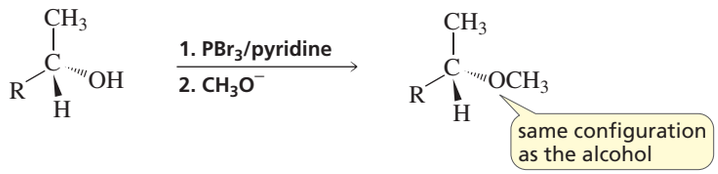


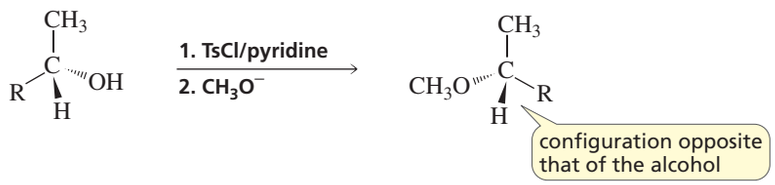

A severe deficiency in HGPRT causes Lesch-Nyhan syndrome. This congenital defect occurs mostly in males and has tragic symptoms—namely, crippling arthritis and severe malfunctions in the nervous system such as mental retardation, highly aggressive and destructive behavior, and self-mutilation. Children with Lesch-Nyhan syndrome have such a compulsive urge to bite their fingers and lips that they must be restrained. Fortunately, HGPRT deficiencies in fetal cells can be detected by amniocentesis. The condition occurs in 1 in 380,000 live births.

**PROBLEM 10 SOLVED**

**LEARN THE STRATEGY**

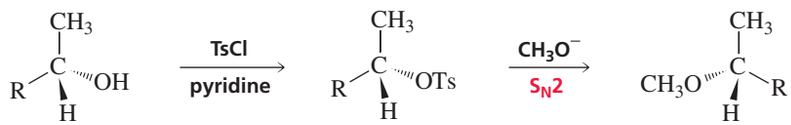
Explain why the ether obtained by treating an optically active alcohol with $PBr_3$ followed by sodium methoxide has the *same* configuration as the alcohol, whereas the ether obtained by treating the alcohol with tosyl chloride followed by sodium methoxide has a configuration *opposite* that of the alcohol.




**SOLUTION** Conversion of the alcohol to the ether by way of an alkyl halide requires two successive $S_N2$ reactions: (1) attack of $Br^-$ on the bromophosphite intermediate and (2) attack of $CH_3O^-$ on the alkyl halide. Each $S_N2$ reaction takes place with inversion of configuration, so the final product has the same configuration as the starting material.

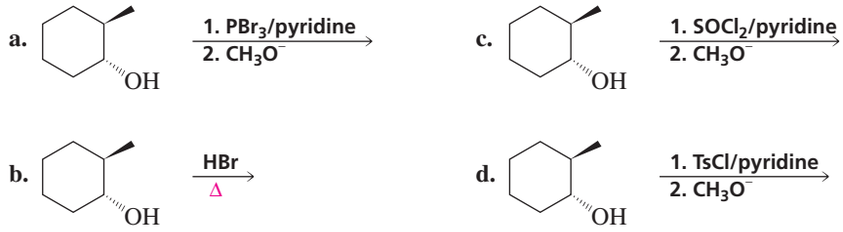

In contrast, conversion of the alcohol to the ether by way of an alkyl tosylate requires only one $S_N2$ reaction (attack of $CH_3O^-$ on the alkyl tosylate), so the final product and the starting material have opposite configurations.



USE THE STRATEGY

**PROBLEM 11**

What stereoisomers do the following reactions form?




**PROBLEM 12**

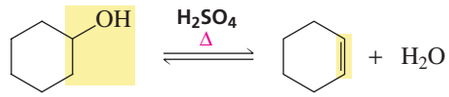
Show how 1-propanol can be converted into the following compounds by means of a sulfonate ester:

**a.** $CH_3CH_2CH_2SCH_2CH_3$ **b.** $CH_3CH_2CH_2OCH_2\underset{\displaystyle CH_3}{\underset{|}{C}}HCH_3$

# 10.4 ELIMINATION REACTIONS OF ALCOHOLS: DEHYDRATION

An alcohol can undergo an elimination reaction by losing an OH from one carbon and an H from an adjacent carbon. The product of the reaction is an alkene. Overall, this amounts to the elimination of a molecule of water. Loss of water from a molecule is called **dehydration.**

Dehydration of an alcohol requires an acid catalyst and heat. Sulfuric acid ($H_2SO_4$) is the most commonly used acid catalyst. Recall that a catalyst increases the rate of a reaction but is not consumed during the course of a reaction (Section 5.13).

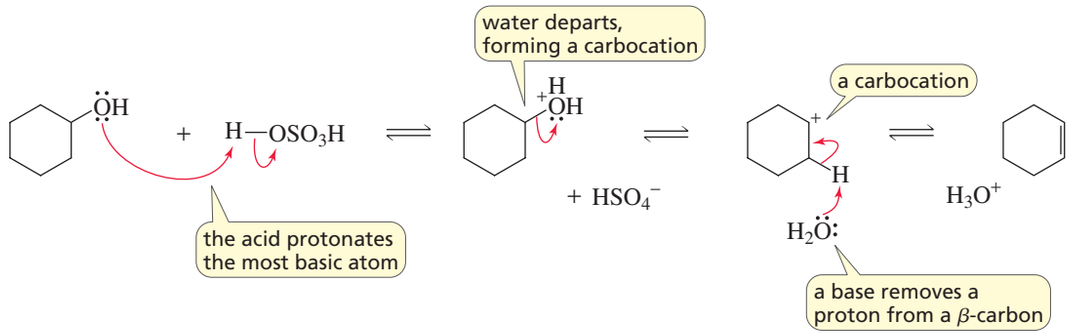



## The E1 Dehydration of Secondary and Tertiary Alcohols

The mechanism for acid-catalyzed dehydration depends on the structure of the alcohol; dehydrations of secondary and tertiary alcohols are E1 reactions.

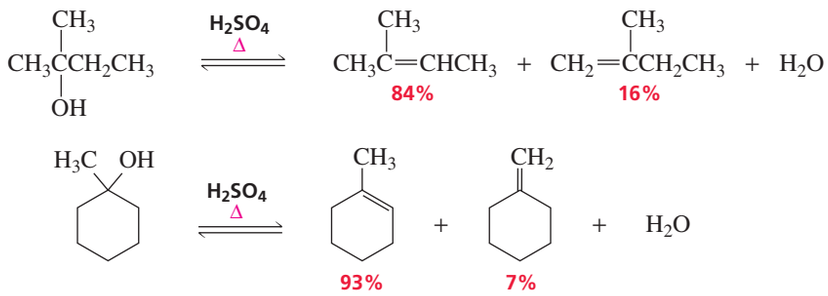
### MECHANISM FOR THE E1 DEHYDRATION OF AN ALCOHOL

Dehydration of secondary and tertiary alcohols are E1 reactions.

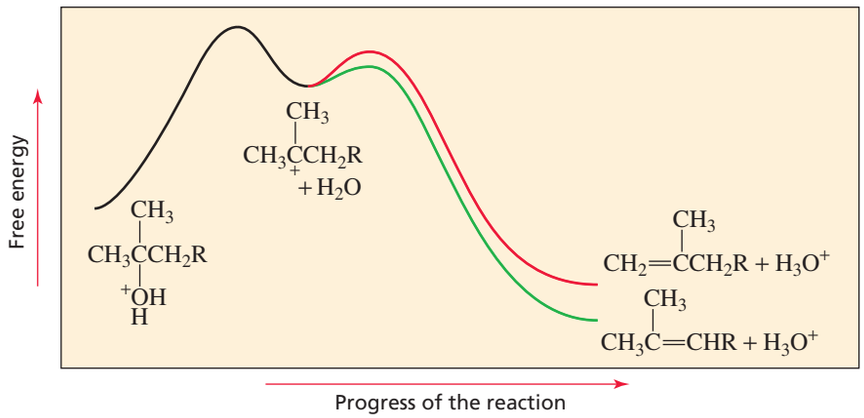



- The acid protonates the most basic atom in the reactant. As we saw earlier, protonation converts the very poor leaving group ($HO^-$) into a good leaving group ($H_2O$).
- Water departs, leaving behind a carbocation.
- A base in the reaction mixture (water is the base that is present in the highest concentration) removes a proton from a $\beta$-carbon (a carbon adjacent to the positively charged carbon), forming an alkene and regenerating the acid catalyst. Notice that the dehydration reaction is an E1 reaction of a protonated alcohol.

When acid-catalyzed dehydration leads to more than one elimination product, the major product is the more stable alkene—that is, the one obtained by removing a proton from the $\beta$-carbon bonded to the fewest hydrogens (Section 9.7).

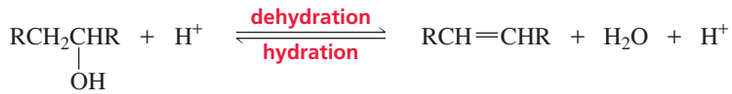



The more stable alkene is the major product because it has the more stable transition state leading to its formation (Figure 10.1).




◀ **Figure 10.1**
**The more stable alkene is the major product obtained from the dehydration of an alcohol because the transition state leading to its formation is more stable (indicated by the green line), allowing it to be formed more rapidly.**

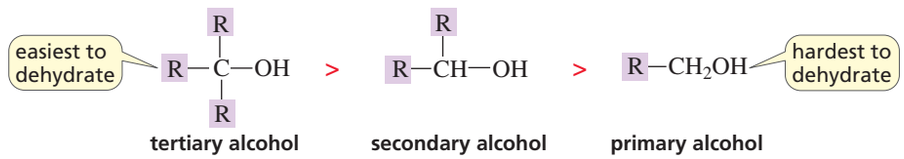
Notice that the acid-catalyzed dehydration of an alcohol is the reverse of the acid-catalyzed addition of water to an alkene (Section 6.5).



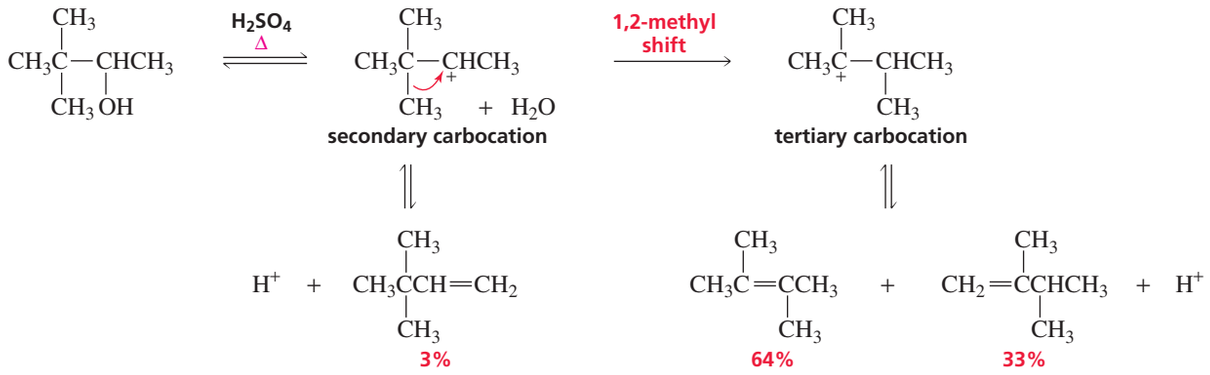

To prevent the alkene formed in the dehydration reaction from adding water and reforming the alcohol, the alkene is removed by distillation as it is formed because it has a lower boiling point than the alcohol (Section 3.9). Removing a product displaces the reaction to the right according to Le Châtelier's principle (Section 5.7).

Because the rate-determining step in the dehydration of a secondary or tertiary alcohol is formation of a carbocation intermediate, the rate of dehydration reflects the ease with which the carbocation is formed: tertiary alcohols are the easiest to dehydrate because tertiary carbocations are more stable and are, therefore, more easily formed than secondary and primary carbocations (Section 6.2).

**relative ease of dehydration**

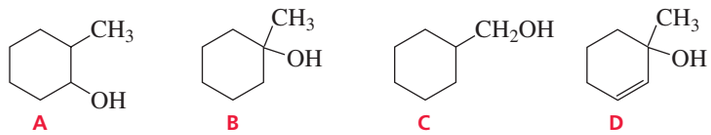



Be sure to check the structure of the carbocation formed in a dehydration reaction for the possibility of rearrangement. Remember that a carbocation will rearrange if rearrangement produces a more stable carbocation (Section 6.7). For example, the secondary carbocation formed initially in the following reaction rearranges to a more stable tertiary carbocation:




**PROBLEM 13 ♦**

Which of the following alcohols dehydrates the fastest when heated with acid?

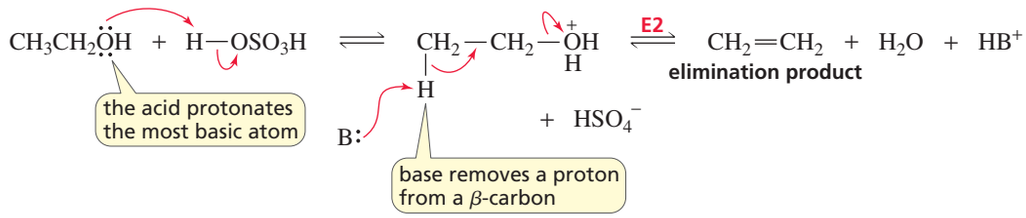


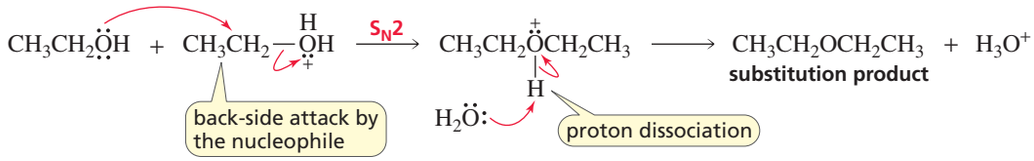

## The E2 Dehydration of Primary Alcohols

While the dehydration of a secondary or a tertiary alcohol is an E1 reaction, the dehydration of a primary alcohol is an E2 reaction, because primary carbocations are too unstable to form. Any base (B:) in the reaction mixture (ROH, ROR, $H_2O$, or $HSO_4^-$) can remove the proton in the elimination reaction.

### MECHANISM FOR THE E2 DEHYDRATION OF A PRIMARY ALCOHOL AND FOR THE COMPETING $S_N2$ REACTION

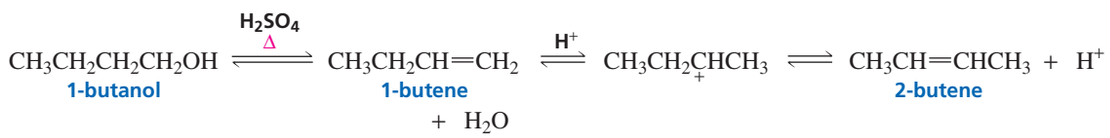
**Dehydration of a primary alcohol is an E2 reaction.**




The reaction also forms an ether in a competing $S_N2$ reaction, because primary alcohols are the ones most likely to form substitution products under $S_N2$/E2 conditions. However, the elimination reaction is favored because of the high temperature required for the dehydration reaction (Section 9.12).

Because the dehydration of a primary alcohol is an E2 reaction, we expect 1-butene to be the product of the E2 dehydration of 1-butanol. The product, however, is actually 2-butene.



2-Butene is the final product because after 1-butene forms, a proton from the acidic solution adds to the double bond (adding to the $sp^2$ carbon bonded to the most hydrogens in accordance with the rule that governs electrophilic addition reactions), thereby forming a carbocation (Section 6.4). Loss of a proton from the $\beta$-carbon bonded to the fewest hydrogens (Zaitsev's rule) forms 2-butene (Section 9.8).

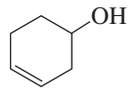
**PROBLEM 14**

What is the major product obtained when each of the following alcohols is heated in the presence of $H_2SO_4$?

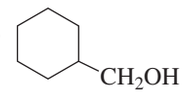
**a.** $CH_3CH_2C(OH)(CH_3)CHCH_3$ (CH$_3$ branch)

**c.** $CH_3CH_2CH(OH)C(CH_3)_2$

**e.** $CH_2{=}CHCH_2CH_2OH$

**b.** 

**d.** $CH_3CH_2CH_2CH_2CH_2OH$

**f.** 

**Alcohols undergo $S_N1$/E1 reactions unless they must form a primary carbocation, in which case they undergo $S_N2$/E2 reactions.**

**PROBLEM 15**

Heating an alcohol with sulfuric acid is a good way to prepare a symmetrical ether such as diethyl ether.

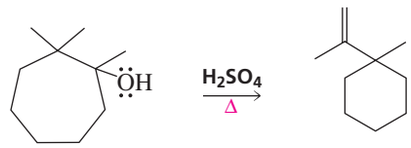
**a.** Explain why it is not a good way to prepare an unsymmetrical ether such as ethyl propyl ether.
**b.** How would you synthesize ethyl propyl ether?

## PROBLEM-SOLVING STRATEGY

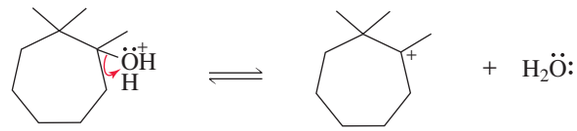
**LEARN THE STRATEGY**

### Proposing a Mechanism

Propose a mechanism for the following reaction:

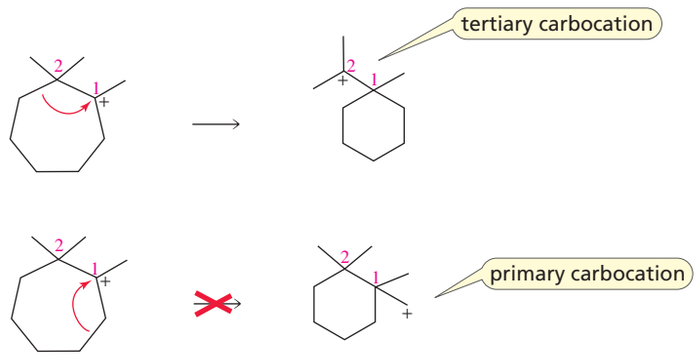



Even the most complicated-looking mechanism can be reasoned out if you proceed one step at a time, always keeping in mind the structure of the final product. Recall that when an acid is added to a reactant, it protonates the most basic atom in the reactant. Oxygen is the only basic atom, so that is where protonation occurs. Loss of water forms a tertiary carbocation.

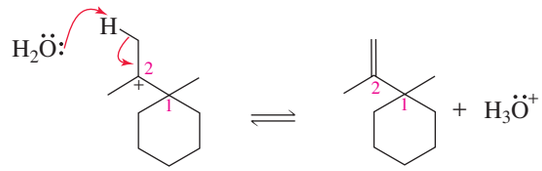



Because the reactant contains a seven-membered ring and the final product has a six-membered ring, a ring-contraction rearrangement must occur to relieve the strain in the seven-membered ring. When doing a *ring-contraction* or a *ring-expansion rearrangement* (Problem 70), you may find it helpful to label the equivalent carbons in the reactant and product, as shown here. Of the two possible pathways for ring contraction, one leads to a tertiary carbocation and the other leads to a primary carbocation. The correct pathway must be the one that leads to the tertiary carbocation, because only that carbocation has the same arrangement of atoms as the product and the primary carbocation would be too unstable to form.

<Au/Ed: Problem number revised due to reordering of problems.>



The final product is obtained by removing a proton from a $\beta$-carbon of the rearranged carbocation.

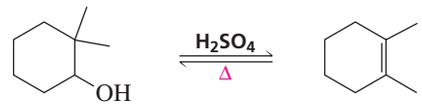


USE THE STRATEGY

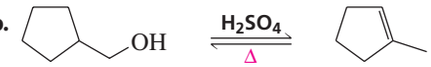
**PROBLEM 16**

Propose a mechanism for each of the following reactions:

**a.**



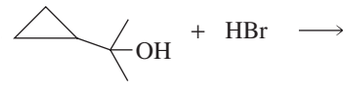
**b.**



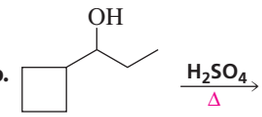
**PROBLEM 17**

Draw the product of each of the following reactions:

**a.**

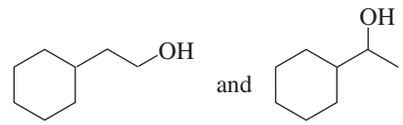


**b.**



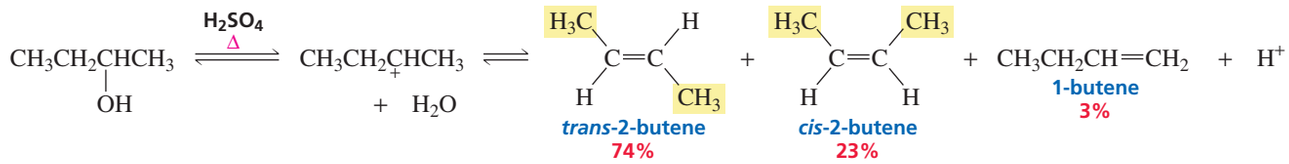
**PROBLEM 18**

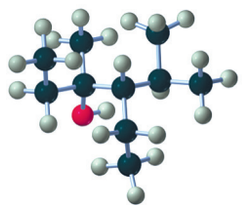
Explain why the following alcohols, when heated with acid, form the same alkene.



## The Stereochemistry of the Dehydration Reaction

The stereochemical outcome of the E1 dehydration of an alcohol is identical to the stereochemical outcome of the E1 dehydrohalogenation of an alkyl halide. That is, both the *E* and *Z* stereoisomers are obtained as products, and the major product is the stereoisomer in which the larger group on each of the $sp^2$ carbons are on opposite sides of the double bond. Because that stereoisomer is more stable, it is formed more rapidly (Section 9.10).



**PROBLEM 19 ♦**

What stereoisomers are formed in the following reactions? Which stereoisomer is the major product?

**a.** the acid-catalyzed dehydration of 1-pentanol to 2-pentene
**b.** the acid-catalyzed dehydration of 3,4-dimethyl-3-hexanol to 3,4-dimethyl-3-hexene

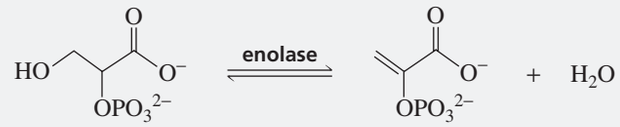
**PROBLEM 20 ♦**

If the compound shown in the margin is heated in the presence of $H_2SO_4$,

**a.** what constitutional isomer would be formed in greatest yield?
**b.** what stereoisomer would be formed in greater yield?

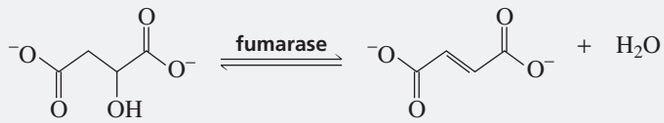
## Biological Dehydrations

Dehydration reactions occur in cells. Instead of being catalyzed by strong acids, which would not be available to a cell, they are catalyzed by enzymes. Enolase, for example, catalyzes the dehydration of 2-phosphoglycerate in glycolysis. Glycolysis is a series of reactions that prepare glucose for entry into the citric acid cycle (Section 24.6).




2-phosphoglycerate phosphoenolpyruvate

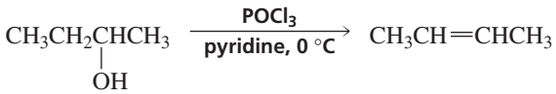
Fumarase is the enzyme that catalyzes the dehydration of malate in the citric acid cycle. The citric acid cycle is a series of reactions that oxidize compounds derived from carbohydrates, fatty acids, and amino acids (Section 24.9).



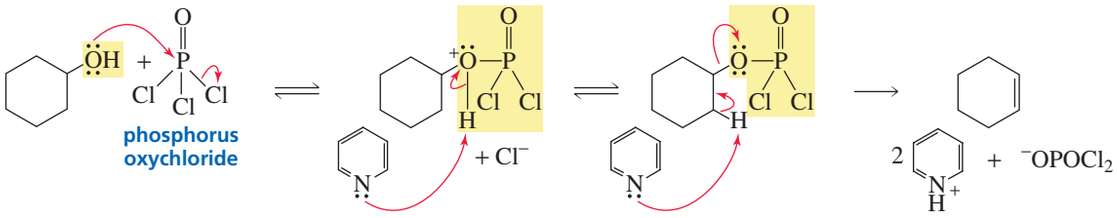

malate fumarate

## Changing an E1 Dehydration into an E2 Dehydration

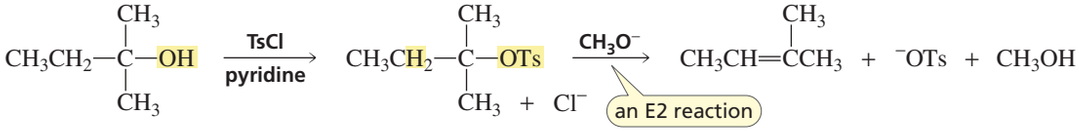
The relatively harsh conditions (acid and heat) required for alcohol dehydration and the structural changes resulting from carbocation rearrangements in the E1 reaction may result in low yields of the desired alkene. Dehydration, however, can be carried out under milder conditions that favor E2 reactions by replacing the OH group with a good leaving group.




For example, reaction with phosphorus oxychloride ($POCl_3$) converts the OH group of the alcohol into $OPOCl_2$, which is a good leaving group. The reaction conditions (pyridine is the solvent so it is present at a high concentration) favor an E2 reaction and carbocations are not formed in E2 reactions, so carbocation rearrangements do not occur. Pyridine removes a proton in order to prevent the intermediate from reverting to starting materials and is the base employed in the E2 reaction. Pyridine also prevents the buildup of HCl, which would add to the alkene.

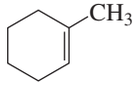
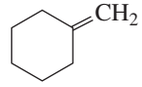



Sulfonate esters also have good leaving groups. So dehydration *via* an E2 reaction can be achieved by converting the alcohol to a sulfonate ester and then adding a strong base to carry out the E2 reaction. This reaction works well only with tertiary alcohols because there is no competing $S_N2$ reaction.



**PROBLEM 21 ♦**

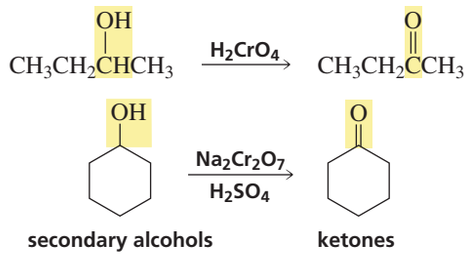
What alcohol would you treat with phosphorus oxychloride and pyridine to form each of the following alkenes?

**a.** $CH_3CH_2\overset{\displaystyle CH_3}{\overset{|}{C}}{=}CH_2$ **b.**  **c.** $CH_3CH{=}CHCH_2CH_3$ **d.** 

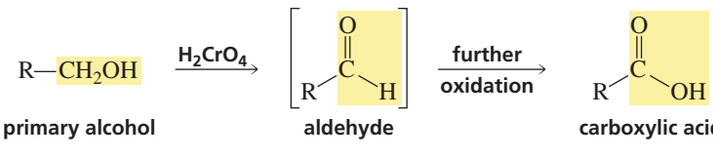
# 10.5 OXIDATION OF ALCOHOLS

## Chromium-Based Oxidizing Agents

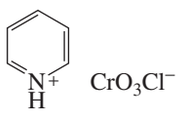
A variety of reagents are available that oxidize alcohols. For many years, a commonly used reagent was chromic acid ($H_2CrO_4$), which is formed when sodium dichromate ($Na_2Cr_2O_7$) is dissolved in aqueous acid. Notice that *secondary alcohols* are oxidized to *ketones*.



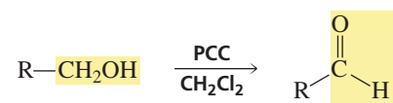

*Primary alcohols* are initially oxidized to *aldehydes* by chromic acid. The reaction, however, does not stop at the aldehyde. Instead, the aldehyde is further oxidized to a *carboxylic acid*. These reactions are easily recognized as oxidations because the number of C—H bonds in the reactant decreases and the number of C—O bonds increases (Section 6.8).



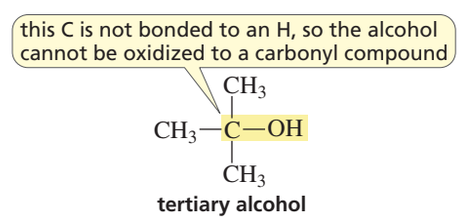

Pyridinium chlorochromate (PCC) is a gentler oxidizing agent. It also oxidizes secondary alcohols to ketones, but it stops the reaction at the aldehyde when it oxidizes primary alcohols. PCC must be used in an anhydrous solvent such as $CH_2Cl_2$ because if water is present, the aldehyde will be further oxidized to a carboxylic acid.



pyridinium chlorochromate
PCC

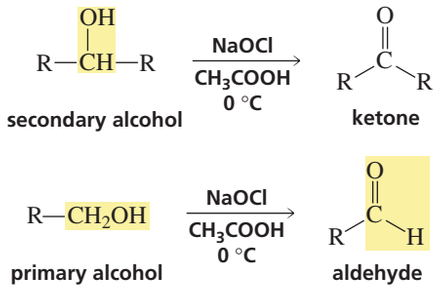



Notice that in the oxidation of both primary and secondary alcohols, a hydrogen is removed from the carbon to which the OH is attached. The carbon bearing the OH group in a tertiary alcohol is not bonded to a hydrogen, so its OH group cannot be oxidized to a carbonyl (C=O) group.



## Hypochlorous Acid as the Oxidizing Reagent

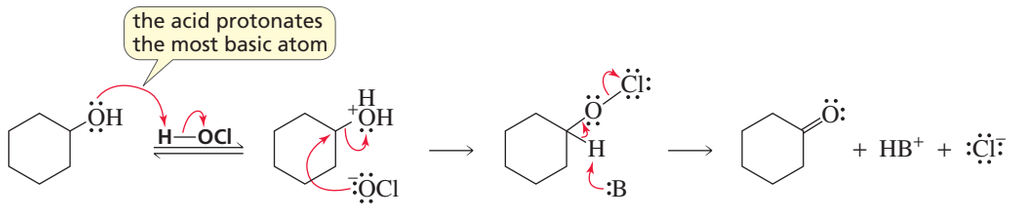
Because of the toxicity of chromium-based reagents, other reagents for the oxidation of alcohols have been developed. One of the more common is hypochlorous acid (HOCl). Because HOCl is unstable, it is generated in the reaction mixture by an acid–base reaction between $H^+$ and $^-OCl$ (using $CH_3COOH$ and NaOCl). Secondary alcohols are oxidized to ketones, and primary alcohols are oxidized to aldehydes.




Primary alcohols are oxidized to aldehydes by HOCl.

Secondary alcohols are oxidized to ketones.

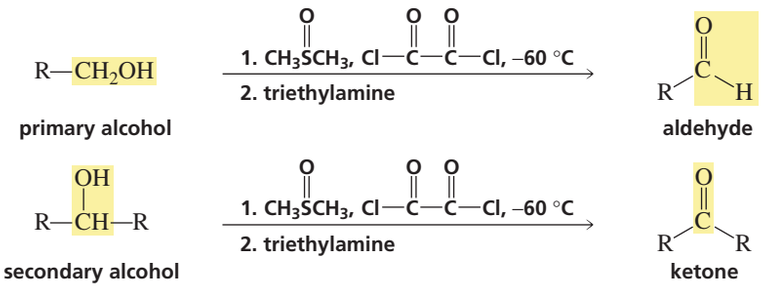
### MECHANISM FOR THE OXIDATION OF AN ALCOHOL BY HOCl



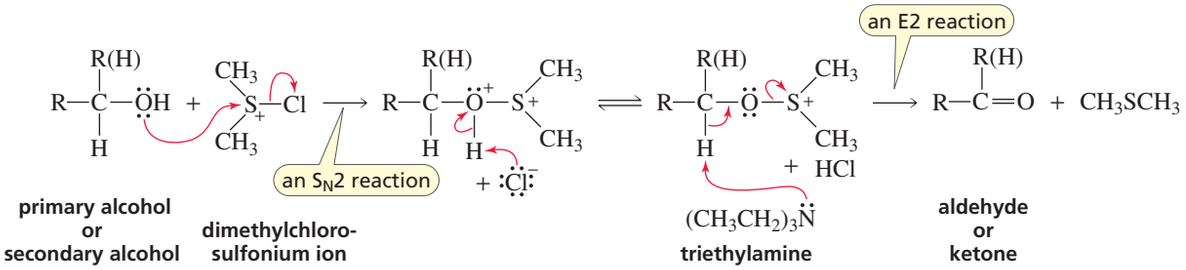

- The acid protonates the oxygen, the most basic atom in the alcohol.
- Because the reaction is not heated, water does not leave spontaneously but must be kicked out by hypochlorite ion in an $S_N2$ reaction.
- A base in the reaction mixture removes a proton from the carbon bonded to the O—Cl group, and the very weak O—Cl bond breaks.

## The Swern Oxidation

The Swern oxidation also uses nontoxic reagents—dimethyl sulfoxide [$(CH_3)_2SO$], oxalyl chloride [$(COCl)_2$], and triethylamine. Primary alcohols are oxidized to aldehydes, and secondary alcohols are oxidized to ketones.

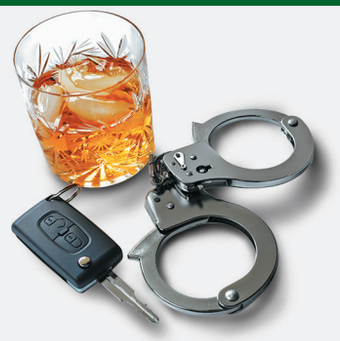



The actual oxidizing agent is the dimethylchlorosulfonium ion. (See Chapter 16, Problem 80.)



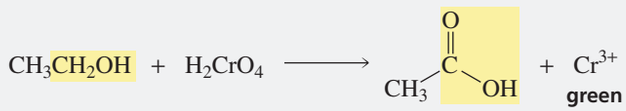
- The alcohol displaces the chloride ion in an $S_N2$ reaction.
- The intermediate loses a proton.
- A base removes a proton in an E2 reaction to form the aldehyde (or ketone).

## Blood Alcohol Concentration



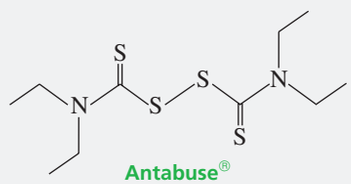
As blood passes through the arteries in our lungs, an equilibrium is established between the alcohol in our blood and the alcohol in our breath. Therefore, if the concentration of one is known, then the concentration of the other can be determined.

The test that law enforcement agencies use to determine a person's blood alcohol level is based on the oxidation of breath ethanol. In this test, a person blows into a device called a breathalyzer and a measured volume of breath passes through a solution of chromic acid, an oxidizing agent. When ethanol is oxidized, the oxidizing agent is reduced to green chromic ion. The breathalyzer contains a spectrophotometer that quantitatively measures the amount of visible light absorbed by the green chromic ion—the greater the absorbance, the greater the concentration of chromic ion and, therefore, the greater the concentration of breath ethanol (Section 13.21).



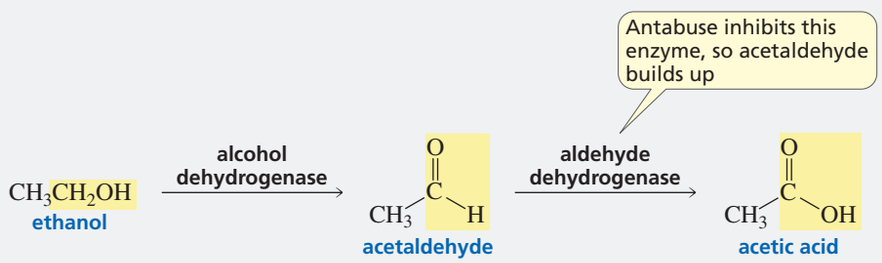

## Treating Alcoholism with Antabuse

Disulfiram, most commonly known as Antabuse, is used to treat alcoholism. It causes violently unpleasant effects if ethanol is consumed within two days after taking the drug.




Antabuse®

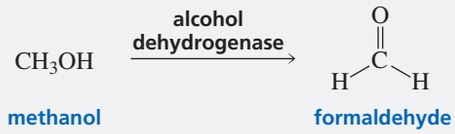
Antabuse works by inhibiting aldehyde dehydrogenase, the enzyme responsible for oxidizing acetaldehyde (a product of ethanol metabolism) to acetic acid. This causes a buildup of acetaldehyde. It is acetaldehyde that causes the unpleasant physiological effects of intoxication: intense flushing, nausea, dizziness, sweating, throbbing headaches, decreased blood pressure, and, ultimately, shock. Consequently, Antabuse should be taken only under strict medical supervision. In Chapter 23, we will see what can be done to prevent a hangover.




In some people, aldehyde dehydrogenase does not function properly even under normal circumstances. Their symptoms in response to ingesting alcohol are nearly the same as those of individuals who are medicated with Antabuse.

## Methanol Poisoning

In addition to oxidizing ethanol to acetaldehyde, alcohol dehydrogenase can oxidize methanol to formaldehyde. Formaldehyde is damaging to many tissues, and because eye tissue is particularly sensitive, methanol ingestion can cause blindness.




If methanol is ingested, the patient is given ethanol intravenously for several hours. Ethanol competes with methanol for binding at the active site of the enzyme. Binding ethanol minimizes the amount of methanol that can be bound, which minimizes the amount of formaldehyde that can be formed. So ethanol is given to the patient until all the ingested methanol has been excreted in the urine.

**PROBLEM 22 ♦**

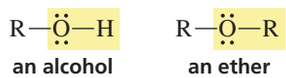
What product is obtained from the reaction of each of the following alcohols with

**a.** $H_2CrO_4$? **b.** HOCl? **c.** the regents required for a Swern oxidation?

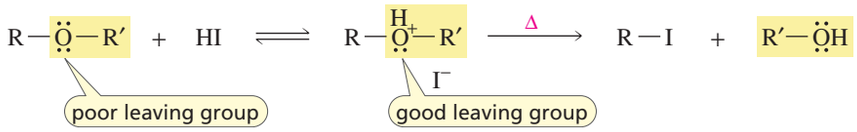
**1.** 3-pentanol **3.** 2-methyl-2-pentanol **5.** cyclohexanol
**2.** 1-pentanol **4.** 2,4-hexanediol **6.** 1,4-butanediol

# 10.6 NUCLEOPHILIC SUBSTITUTION REACTIONS OF ETHERS

The OR group of an **ether** and the OH group of an alcohol have nearly the same basicity because the conjugate acids of these two groups have similar p$K_a$ values. (The p$K_a$ of $CH_3OH$ is 15.5, and the p$K_a$ of $H_2O$ is 15.7.) Both groups are strong bases, so both are very poor leaving groups. Consequently, ethers, like alcohols, need to be activated before they undergo a nucleophilic substitution reaction.

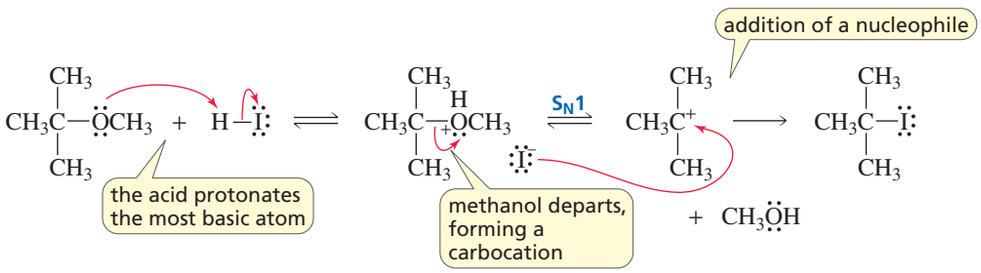



Like alcohols, ethers are activated by protonation. Ethers, therefore, undergo nucleophilic substitution reactions with HBr or HI. (HCl cannot be used because $Cl^-$ is too poor a nucleophile.) The reaction of ethers with hydrogen halides, like the reactions of alcohols with hydrogen halides, is slow. The reaction mixture must be heated to cause the reaction to occur at a reasonable rate.




What happens *after* the ether is protonated depends on the structure of the ether. If departure of ROH creates a relatively stable carbocation (such as a tertiary carbocation), an $S_N1$ reaction will occur—that is, the ROH group will leave.

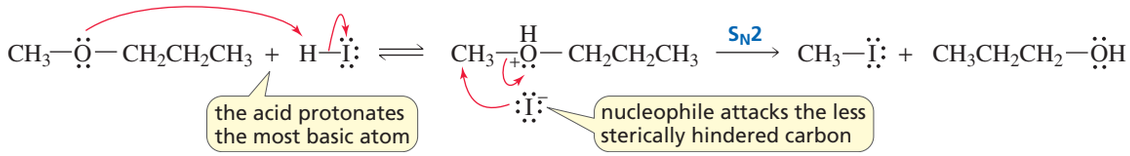
### MECHANISM FOR ETHER CLEAVAGE: AN $S_N1$ REACTION



- The acid protonates the oxygen, thereby converting the very basic $RO^-$ leaving group into the less basic ROH leaving group.
- The leaving group departs, forming a carbocation.
- The halide ion combines with the carbocation.

However, if departure of ROH would create an unstable carbocation (such as a methyl, vinyl, aryl, or primary carbocation), the leaving group cannot depart. Therefore, the reaction will be an $S_N2$ reaction—that is, the leaving group will be displaced by a nucleophile.

## MECHANISM FOR ETHER CLEAVAGE: AN $S_N2$ REACTION




- Protonation converts the very basic $RO^-$ leaving group into the less basic ROH leaving group.
- The halide ion preferentially attacks the less sterically hindered of the two alkyl groups.

**Ethers are cleaved by an $S_N1$ reaction unless the instability of the carbocation requires the cleavage to be an $S_N2$ reaction.**

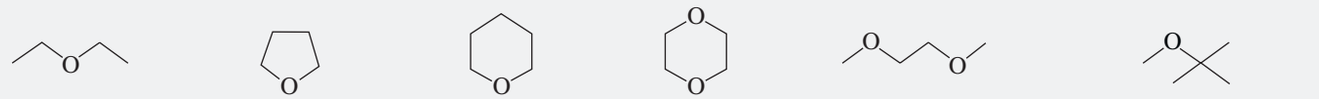
Ether cleavage forms only a substitution product because any alkene that would be formed in an elimination reaction would undergo electrophilic addition with HBr or HI to form the same alkyl halide that is obtained from the substitution reaction.

The reagents (such as $SOCl_2$, $PCl_3$, or TsCl) used to activate alcohols so that they can undergo nucleophilic substitution reactions cannot be used to activate ethers. When an alcohol reacts with one of these activating agents, a proton dissociates from the intermediate in the second step of the reaction and a stable product results.

However, when an ether reacts with one of these activating agents, the oxygen atom does not have a proton that can dissociate, so a stable product cannot be formed. Instead, the stable starting materials are reformed.

Because hydrogen halides are the only reagents that react with ethers, ethers are frequently used as solvents. Some common ether solvents are shown in Table 10.2.

**Table 10.2** Some Ethers Are Used as Solvents



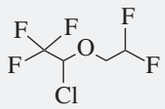

## Anesthetics

Because diethyl ether (commonly known as ether) is a short-lived muscle relaxant, it was at one time widely used as an *inhalation anesthetic*. However, it takes effect slowly and has a slow and unpleasant recovery period so, over time, other anesthetics, such as isoflurane, enflurane, and halothane, replaced it. Even so, diethyl ether is still used where trained anesthesiologists are scarce because it is the safest anesthetic for an untrained person to administer. Anesthetics interact with the nonpolar molecules of cell membranes, causing the membranes to swell, which interferes with their permeability.

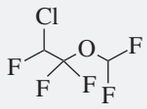
Sodium pentothal (also called thiopental sodium) is an *intravenous anesthetic*. The onset of anesthesia and the loss of consciousness occur within seconds of its administration. Care must be taken when administering sodium pentothal because the dose for effective anesthesia is 75% of the lethal dose. Because of this high level of toxicity, it cannot be used as the sole anesthetic but, instead, is generally used to induce anesthesia before an inhalation anesthetic is administered. Propofol, in contrast, has all the properties of the "perfect anesthetic": it can be administered as the sole anesthetic by intravenous drip, it has a rapid and pleasant induction period, and it has a wide margin of safety in trained hands. Recovery from the drug is also rapid and pleasant.

*(Continued)*

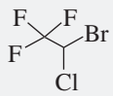
"ether"



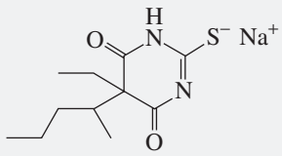
isoflurane



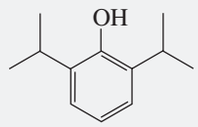
enflurane



halothane

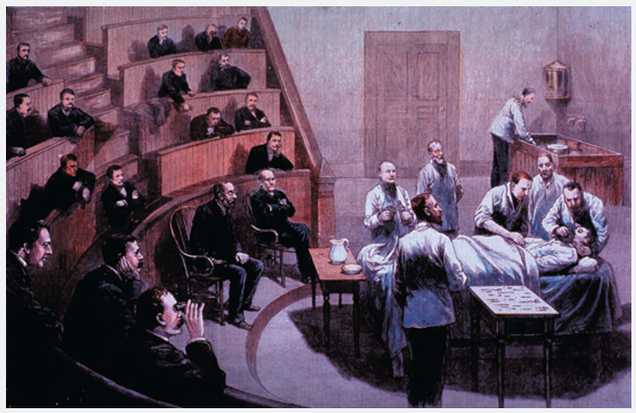


thiopental sodium
sodium pentothal



diprivan
propofol


amputation of a leg without anesthetic in 1528

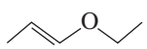


a painting showing the first use of anesthesia (ether) during surgery in 1846 at Massachusetts General Hospital by surgeon John Collins Warren

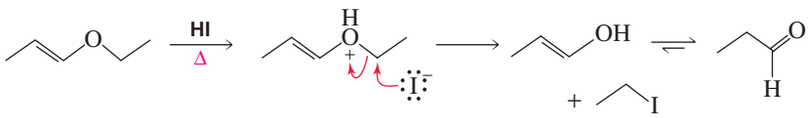
**PROBLEM 23 SOLVED**

**LEARN THE STRATEGY**

What are the major products obtained when the following ether is heated with one equivalent of HI:



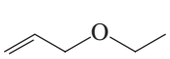
**SOLUTION** The reaction takes place by an $S_N2$ pathway because neither alkyl group will form a relatively stable carbocation (one would be vinylic and the other primary). Iodide ion attacks the carbon of the ethyl group because otherwise it would have to attack a vinylic carbon, and vinylic carbons are not attacked by nucleophiles (Section 9.13). Thus, the major products are ethyl iodide and an enol that immediately rearranges to an aldehyde (Section 7.7).

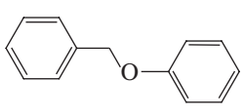


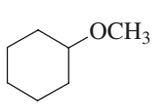

**PROBLEM 24**

**USE THE STRATEGY**

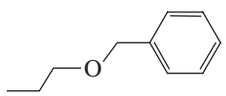
What are the major products obtained when each of the following ethers is heated with one equivalent of HI:

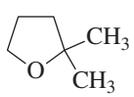
**a.** 

**c.** 

**e.** 

**b.** 

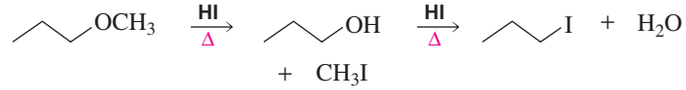
**d.** 

**f.** 

**PROBLEM 25 SOLVED**

Explain why methyl propyl ether forms both methyl iodide and propyl iodide when it is heated with excess HI.

**SOLUTION** On page 478, we saw that the $S_N2$ reaction of methyl propyl ether with an equivalent amount of HI forms methyl iodide and propyl alcohol because the methyl group is less sterically hindered than the propyl group to attack by the iodide ion. When there is excess HI, the alcohol product of this first reaction reacts with HI in another $S_N2$ reaction. Thus, the products are two alkyl iodides.

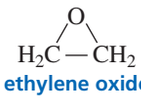



**PROBLEM 26 ♦**

Explain why HF and HCl cannot be used to cleave ethers in an $S_N2$ reaction.

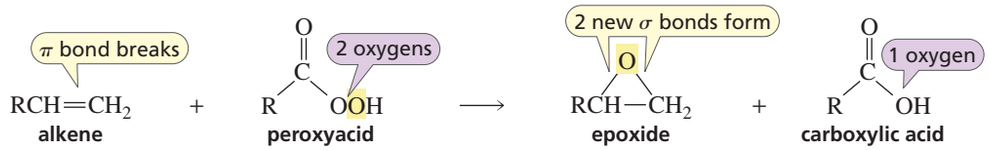
## 10.7 NUCLEOPHILIC SUBSTITUTION REACTIONS OF EPOXIDES

We saw that an alkene can be converted into an **epoxide,** a three-membered ring ether, by a peroxyacid (Section 6.10).

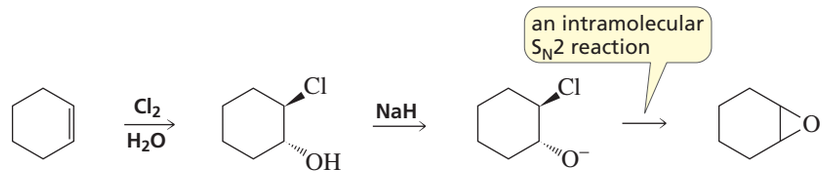


ethylene oxide

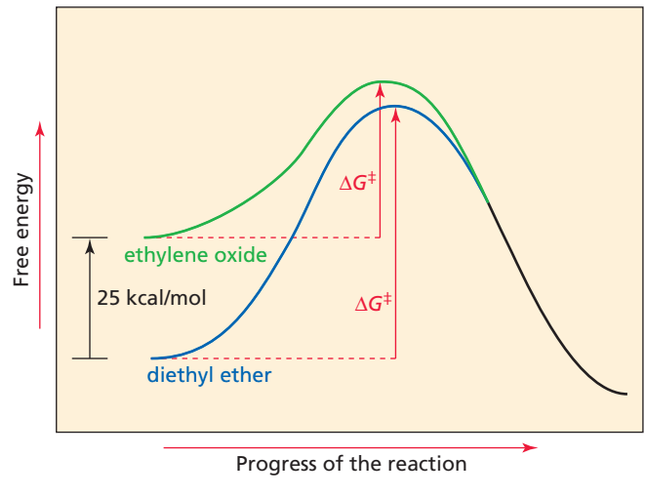
diethyl ether




An alkene can also be converted into an epoxide using $Cl_2$ and $H_2O$, followed by reaction with NaH (Sections 6.9 and 9.15).




Although an epoxide and an ether have the same leaving group, epoxides are much more reactive than ethers in nucleophilic substitution reactions because the strain in their three-membered ring is relieved when the ring opens (Figure 10.2). Epoxides, therefore, undergo nucleophilic substitution reactions with a wide variety of nucleophiles.

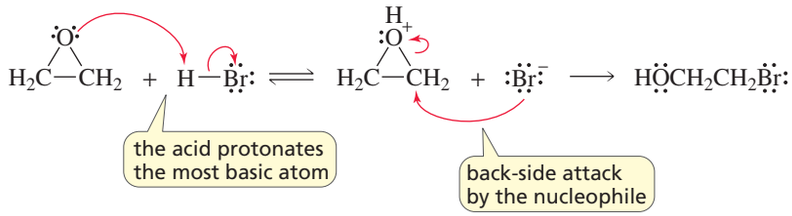



▶ **Figure 10.2**
**The reaction coordinate diagrams for nucleophilic attack of hydroxide ion on ethylene oxide and on diethyl ether. The greater reactivity of the epoxide is a result of the strain in the three-membered ring, which increases the epoxide's free energy.**

## Nucleophilic Substitution: Acidic Conditions

Epoxides, like other ethers, undergo substitution reactions with hydrogen halides. The mechanism of the reaction depends on whether it is carried out under acidic conditions or neutral/basic conditions. Under acidic conditions, the mechanism shown next is followed.

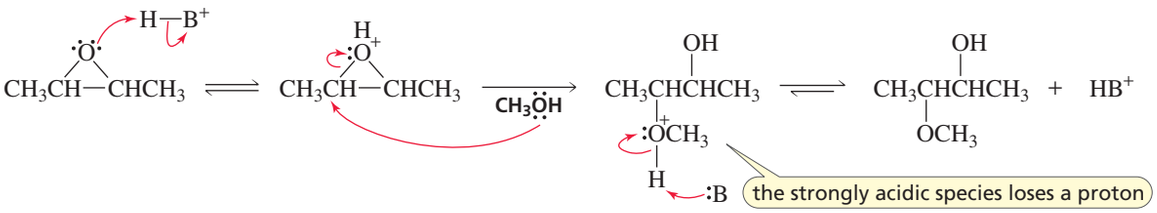
### MECHANISM FOR NUCLEOPHILIC SUBSTITUTION: ACIDIC CONDITIONS



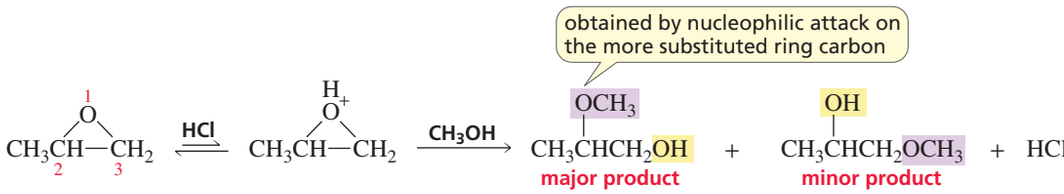

- The acid protonates the oxygen of the epoxide.
- The protonated epoxide undergoes back-side attack by the halide ion.

Because epoxides are so much more reactive than ethers, the reaction takes place readily at room temperature, unlike the reaction of an ether with a hydrogen halide that requires heat.

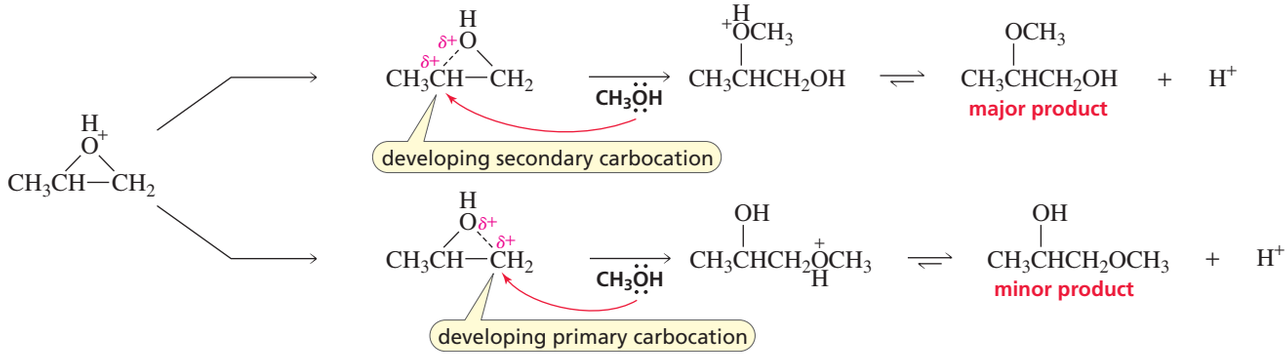
Protonated epoxides are so reactive that they can be opened by poor nucleophiles such as $H_2O$ and alcohols. ($HB^+$ is any acid in the solution, and :B is any base.)




If different substituents are attached to the two ring carbons of the protonated epoxide (and the nucleophile is something other than $H_2O$), the product obtained from nucleophilic attack on the 2-position of the oxirane ring will be different from that obtained from nucleophilic attack on the 3-position. The major product is the one resulting from nucleophilic attack on the *more substituted* carbon.




The more substituted carbon is more likely to be attacked because after the epoxide is protonated, it is so reactive that one of the C—O bonds begins to break even before the nucleophile has an opportunity to attack. As the bond starts to break, a partial positive charge develops on the carbon that is losing its share of oxygen's electrons. Therefore, the protonated epoxide breaks preferentially in the direction that puts the partial positive charge on the more substituted carbon, because a more substituted carbocation is more stable. (Recall that tertiary carbocations are more stable than secondary carbocations, which are more stable than primary carbocations.)



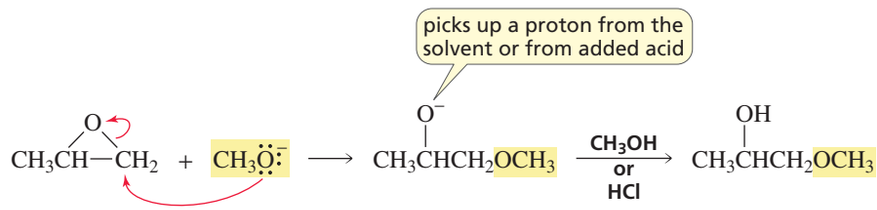

**Under acidic conditions, the nucleophile preferentially attacks the more substituted ring carbon.**

The best way to describe the reaction is to say that it occurs by a pathway that is partially $S_N1$ and partially $S_N2$. It is not a pure $S_N1$ reaction because a carbocation intermediate is not fully formed; it is not a pure $S_N2$ reaction, either, because the leaving group begins to depart before the compound is attacked by the nucleophile.

## Nucleophilic Substitution: Neutral or Basic Conditions

Although an ether must be protonated before it can undergo a nucleophilic substitution reaction (Section 10.6), the strain in the three-membered ring allows an epoxide to undergo nucleophilic substitution reactions without first being protonated (Figure 10.2). When a nucleophile attacks an unprotonated epoxide, the reaction is a pure $S_N2$ reaction.

### MECHANISM FOR NUCLEOPHILIC SUBSTITUTION: NEUTRAL OR BASIC CONDITIONS

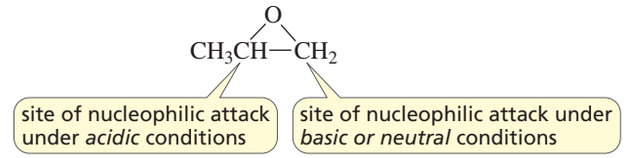



- The C—O bond does not begin to break until the carbon is attacked by the nucleophile. The nucleophile is more likely to attack the *less substituted* carbon because it is less sterically hindered.
- The alkoxide ion picks up a proton from the solvent or from an acid added after the reaction is over.

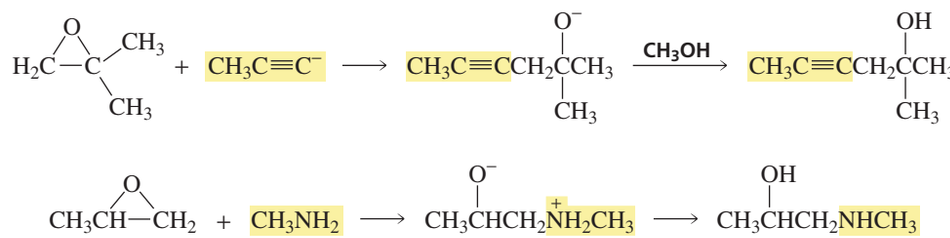
**Under neutral or basic conditions, the nucleophile preferentially attacks the less sterically hindered ring carbon.**

Thus, the site of nucleophilic attack on an unsymmetrical epoxide under neutral or basic conditions (when the epoxide *is not* protonated) is different from the site of nucleophilic attack under acidic conditions (when the epoxide *is* protonated).

**LEARN THE STRATEGY**

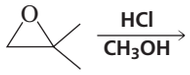


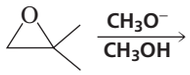

Epoxides are useful reagents because they can react with a wide variety of nucleophiles, leading to the formation of a wide variety of products.

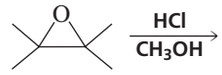


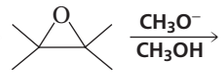
**PROBLEM 27 ♦** **USE THE STRATEGY**

Draw the major product of each of the following reactions:

**a.** 

**b.** 

**c.** 

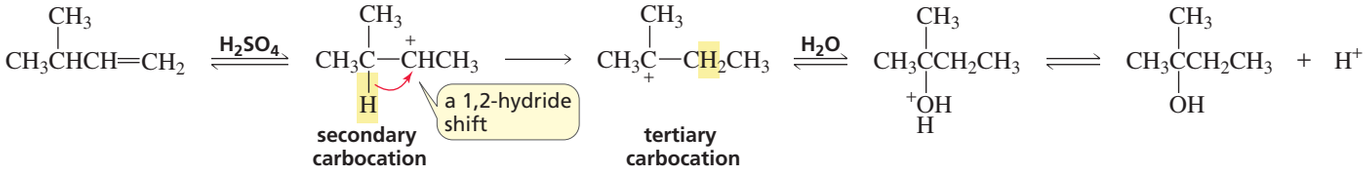
**d.** 

**PROBLEM 28 ♦**

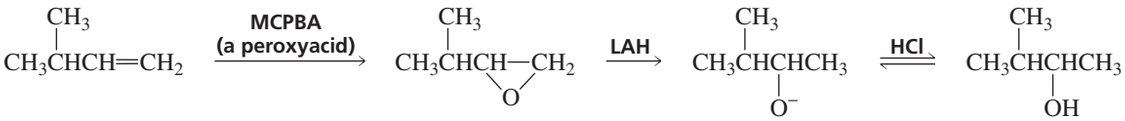
Would you expect the reactivity of a five-membered ring ether such as tetrahydrofuran (Table 10.2) to be more similar to the reactivity of an epoxide or to the reactivity of a noncyclic ether? Why?

## Converting an Alkene to an Alcohol Without a Carbocation Rearrangement

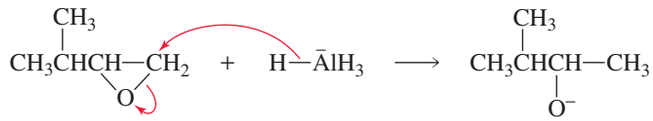
In Section 6.6, we saw that an *alcohol* can be prepared from the acid-catalyzed addition of water to an *alkene*. The reaction forms a carbocation intermediate, which will rearrange if the rearrangement leads to a more stable carbocation.




The alkene can be converted to the alcohol without a carbocation rearrangement, if the alkene is first converted to an epoxide (Section 6.10), which is then treated with a hydride ion donor such as lithium aluminum hydride (LAH). Addition of acid protonates the alkoxide ion.



The hydride ion is a nucleophile that attacks the less substituted carbon of the epoxide.



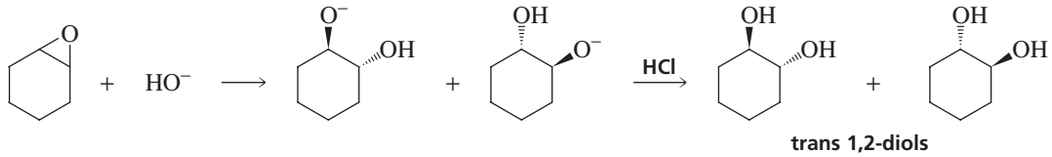
**PROBLEM 29**

How can the following compounds be prepared from 3,3-dimethyl-1-butene?

**a.** 2,3-dimethyl-2-butanol **b.** 3,3-dimethyl-2-butanol

## Trans and Cis Diols

The reaction of cyclohexene oxide with hydroxide ion leads to a **trans 1,2-diol,** because the $S_N2$ reaction involves back-side attack. A diol is also called a **glycol.** Because the OH groups are on adjacent carbons, 1,2-diols are also known as **vicinal diols** or **vicinal glycols.** (Recall that *vicinal* means that two substituents are on adjacent carbons; see Section 6.9.)



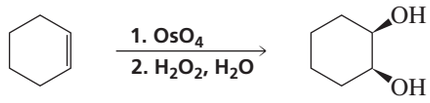

Notice that two stereoisomers are formed because the reaction forms two new asymmetric centers and only anti addition occurs (Section 6.13).

**PROBLEM 30**

What products are obtained from the reaction of cyclohexene oxide with

**a.** methoxide ion? **b.** methylamine?

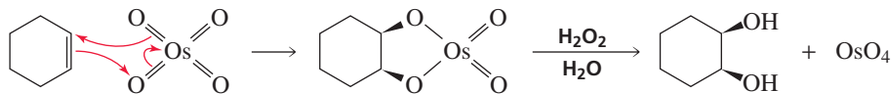
A **cis 1,2-diol** can be obtained by oxidizing an alkene with osmium tetroxide ($OsO_4$) followed by hydrolysis with aqueous hydrogen peroxide.




a cis 1,2-diol

The 1,2-diol is cis because addition of osmium tetroxide to the alkene is a syn addition—that is, both oxygens are delivered to the same side of the double bond.

## MECHANISM FOR CIS-GLYCOL FORMATION

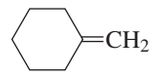



a cyclic osmate intermediate

- Osmium tetroxide forms a cyclic intermediate when it reacts with an alkene.
- The intermediate is hydrolyzed with aqueous hydrogen peroxide. Hydrogen peroxide re-oxidizes the osmium reagent back to osmium tetroxide. (Because osmium tetroxide is recycled, only a catalytic amount of this expensive and toxic oxidizing agent is needed.)

**PROBLEM 31**

What products are obtained from the reaction of each of the following alkenes with $OsO_4$ followed by aqueous $H_2O_2$?

**a.** $CH_3C(CH_3)=CHCH_2CH_3$ **b.** 

**PROBLEM 32**

What stereoisomers are obtained from the reaction of each of the following alkenes with $OsO_4$ followed by aqueous $H_2O_2$?

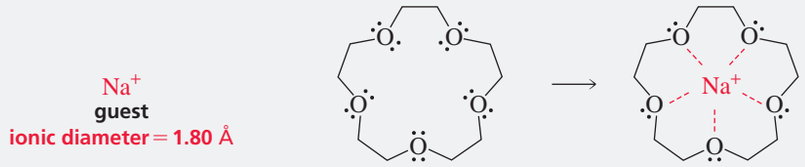
**a.** *trans*-2-butene **b.** *cis*-2-butene **c.** *cis*-2-pentene **d.** *trans*-2-pentene

**PROBLEM 33**

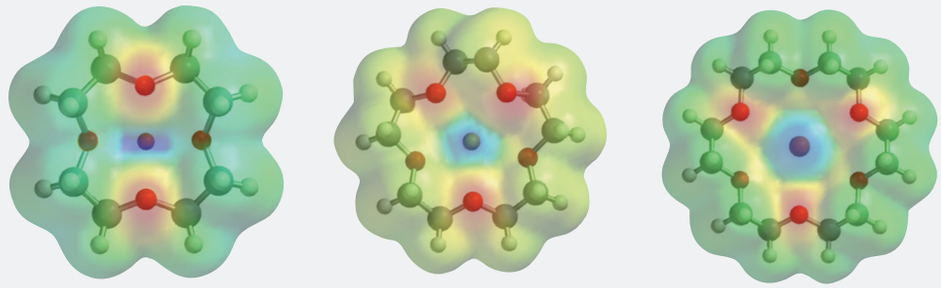
What stereoisomers are obtained from the reaction of the alkenes in Problem 32 with a peroxyacid followed by reaction with hydroxide ion?

## Crown Ethers—Another Example of Molecular Recognition

**Crown ethers** are cyclic compounds that contain several ether linkages around a central cavity. A crown ether specifically binds certain metal ions or organic molecules, depending on the cavity's size. The crown ether is called the host, and the species it binds is called the guest. Because the ether linkages are chemically inert, the crown ether can bind the guest without reacting with it. The *host–guest complex* is called an **inclusion compound.**



Crown ethers are named [X]-crown-Y, where X is the total number of atoms in the ring and Y is the number of oxygen atoms in the ring. Thus, [15]-crown-5 has 15 atoms in the ring, five of which are oxygens. [15]-Crown-5 selectively binds $Na^+$ because the ether's cavity diameter is 1.7 to 2.2 Å and $Na^+$ has an ionic diameter of 1.80 Å. Binding occurs through the interaction of the positively charged ion with the lone-pair electrons of the oxygen atoms that point into the cavity. The ability of a host to bind only certain guests is another example of molecular recognition (Section 5.14).



$Li^+$ bound in [12]-crown-4 $Na^+$ bound in [15]-crown-5 $K^+$ bound in [18]-crown-6

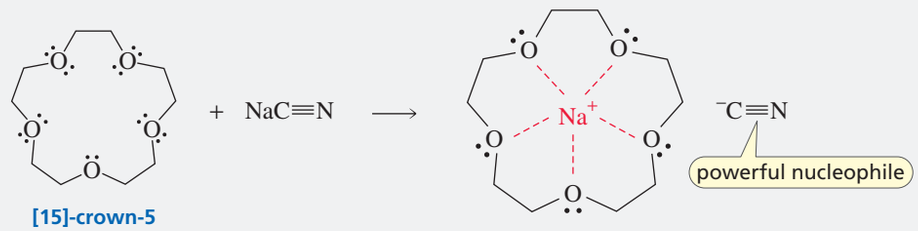
## Crown Ethers Can Be Used to Catalyze $S_N2$ Reactions

A problem that often arises in the laboratory is finding a solvent that will dissolve all the reactants needed for a given reaction. For example, if we want cyanide ion to react with 1-bromohexane, we must find a way of mixing sodium cyanide (an ionic compound soluble only in water) with the alkyl halide (an organic compound that is insoluble in water). If we mix an aqueous solution of sodium cyanide with a solution of the alkyl halide in a nonpolar solvent, there will be two distinct phases—an aqueous phase and a nonpolar phase—because the two solutions are immiscible. How, then, can a reaction between sodium cyanide and 1-bromohexane take place?


1-bromohexane

The two compounds can react with each other if [15]-crown-5 is added to the reaction mixture.

$Na^+$ binds in the cavity of [15]-crown-5 and the inclusion compound is soluble in the nonpolar solvent because the outside of the crown is composed primarily of nonpolar C—H bonds. The inclusion compound must carry a counterion to balance its positive charge. Thus, cyanide ion will also be in the nonpolar solvent, where it is a powerful nucleophile because it is not solvated. In this way, nucleophilic substitution reactions with alkyl halides that are soluble only in nonpolar solvents can readily take place.

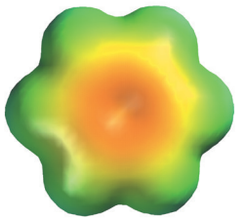



[15]-crown-5

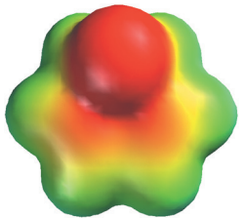
In the next reaction, the counter ion is $K^+$, which has a larger ionic diameter than $Na^+$, so a larger crown ether ([18]-crown-6) must be used.


# 10.8 ARENE OXIDES

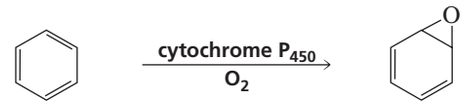
An **arene oxide** is a compound in which one of the "double bonds" of an aromatic hydrocarbon (also called an **arene**) has been converted into an epoxide. Formation of an arene oxide is the first step in changing an aromatic compound that enters the body as a foreign substance (for example, a drug, cigarette smoke, automobile exhaust) into a more water-soluble compound that can eventually be eliminated. The enzyme that converts arenes into arene oxides is called cytochrome $P_{450}$.



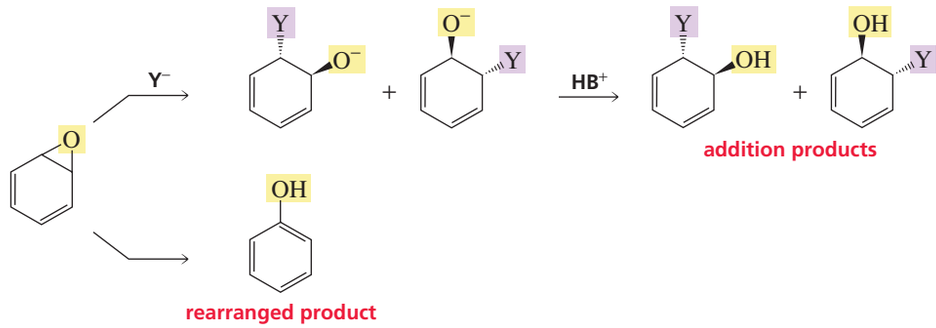
benzene



benzene oxide




An arene oxide can react in two ways. It can react as a typical epoxide, undergoing attack by a nucleophile ($Y^-$) to form addition products (Section 10.7). Notice that two addition products are formed because the reaction forms two new asymmetric centers and only anti addition occurs (Section 6.13). Alternatively, it can rearrange to form a phenol, which other epoxides cannot do.

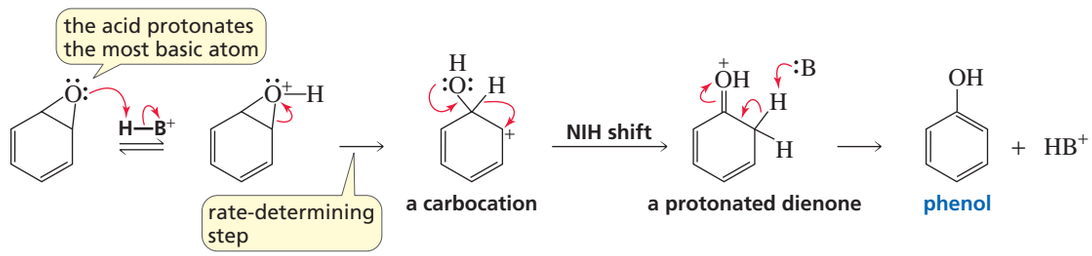



**PROBLEM 34**

Draw the mechanism for formation of the two addition products.

The mechanism for the rearrangement is shown next.

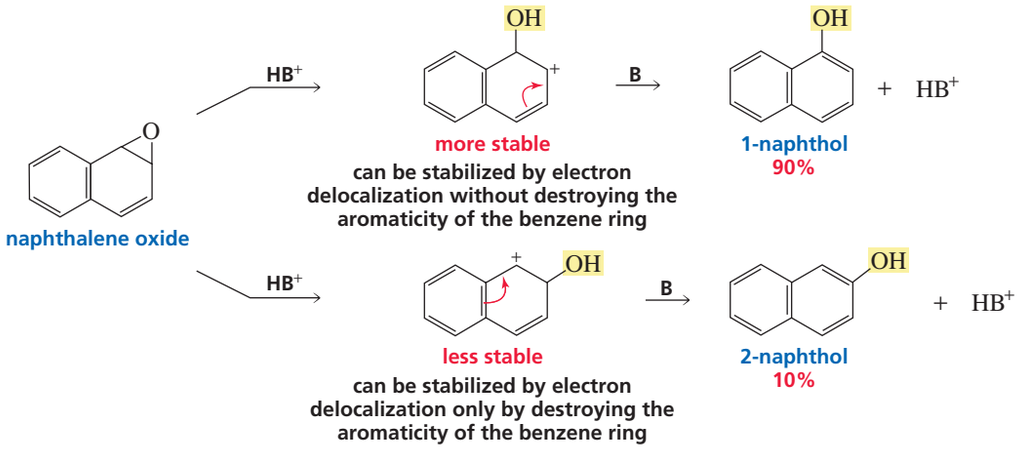
## MECHANISM FOR ARENE OXIDE REARRANGEMENT




- An acid protonates the arene oxide.
- The three-membered ring opens, forming a resonance-stabilized carbocation.
- The carbocation forms a protonated *dienone* as a result of a 1,2-hydride shift. This is called an *NIH shift* because it was first observed in a laboratory at the National Institutes of Health.
- Removal of a proton from the protonated dienone forms phenol.

Because formation of the carbocation is the rate-determining step, the rate of phenol formation depends on the stability of the carbocation. The more stable the carbocation, the more easily the ring opens to form the rearranged product.

Only one arene oxide can be formed from naphthalene because the "double bond" shared by the two rings cannot be epoxidized. Remember that benzene rings are particularly stable, so naphthalene is epoxidized only at a position that leaves one of the benzene rings intact.




Naphthalene oxide can rearrange to form either 1-naphthol or 2-naphthol. The carbocation leading to 1-naphthol is more stable because its positive charge can be stabilized by electron delocalization without destroying the aromaticity of the benzene ring on the left of the structure. In contrast, the positive charge on the carbocation leading to 2-naphthol can be stabilized by electron delocalization only if the aromaticity of the benzene ring is destroyed. (This can be seen by comparing the predicted stabilities of the resonance contributors of the two carbocations; see Problem 35.) Consequently, rearrangement leads predominantly to 1-naphthol.

**PROBLEM 35**

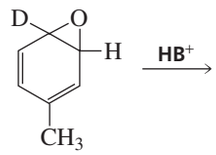
Draw all possible resonance contributors for the two carbocations in the preceding reaction. Use the resonance contributors to explain why 1-naphthol is the major product of the reaction.

**PROBLEM 36**

The existence of the NIH shift was established by determining the major product obtained from rearrangement of the following arene oxide, in which a hydrogen has been replaced by a deuterium.

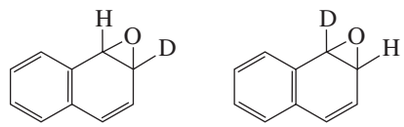
**a.** What would be the major product if the NIH shift occurs? (*Hint:* A C—H bond is easier to break than a C—D bond.)

**b.** What would be the major product if the carbocation forms phenol by losing $H^+$ or $D^+$, rather than by going through the NIH shift?




**PROBLEM 37**

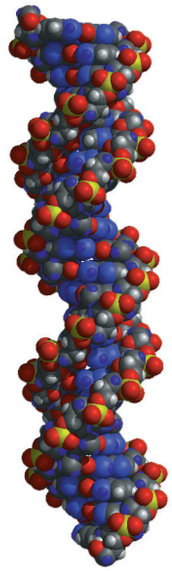
How do the major products obtained from rearrangement of the following arene oxides differ?




## Arene Oxides Can Be Carcinogens

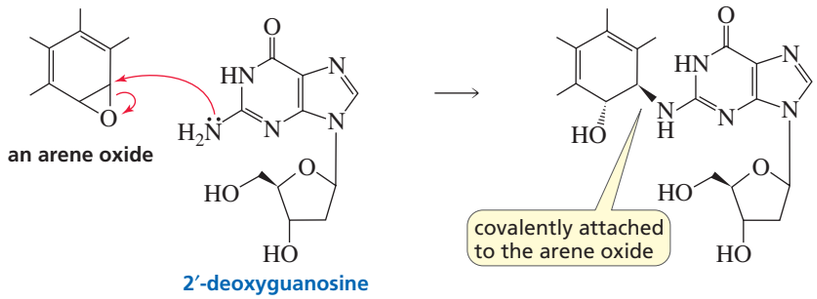
Some aromatic hydrocarbons are carcinogens—that is, compounds that cause cancer. Investigation has revealed, however, that the hydrocarbons themselves are not carcinogenic; the actual carcinogens are the arene oxides into which the hydrocarbons are converted in the body.

How do arene oxides cause cancer? We saw that nucleophiles react with epoxides to form addition products. 2′-Deoxyguanosine, a component of DNA (Section 26.1), has a nucleophilic $NH_2$ group that is known to react with certain arene oxides. Once a molecule of 2′-deoxyguanosine becomes covalently attached to an arene oxide, the 2′-deoxyguanosine can no longer fit into the DNA double helix. As a result, the genetic code will not be properly transcribed (Section 26.7), which can lead



segment of DNA

to mutations that cause cancer. Cancer results when cells lose their ability to control their growth and reproduction.




## Carcinogenicity is Determined by Carbocation Stability

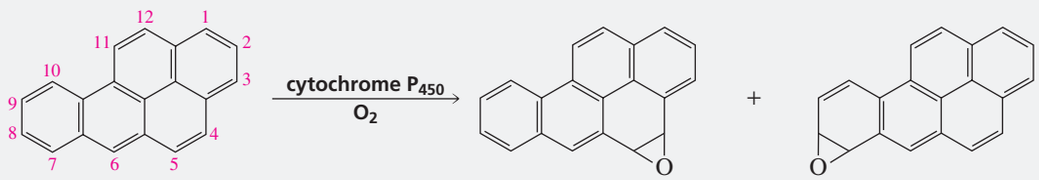
**The more stable the carbocation formed when the arene oxide opens, the less likely it is that the arene oxide is carcinogenic.**

Not all arene oxides are carcinogenic. Whether a particular arene oxide is carcinogenic depends on the relative rates of its two reaction pathways: rearrangement and reaction with a nucleophile. Arene oxide rearrangement leads to phenols that are not carcinogenic, whereas formation of addition products from nucleophilic attack by DNA can lead to cancer-causing products. Thus, if the rate of arene oxide rearrangement is faster than the rate of nucleophilic attack by DNA, then the arene oxide will be harmless. However, if the rate of nucleophilic attack is faster than the rate of rearrangement, the arene oxide will likely be a carcinogen.

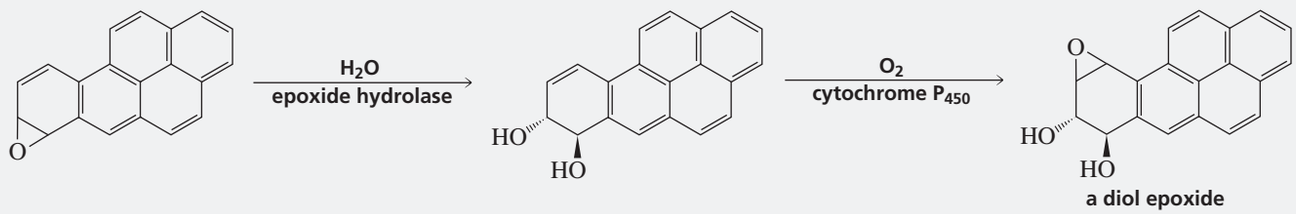
We saw that the rate-limiting step of arene oxide rearrangement is formation of the carbocation. Thus, the rate of the rearrangement reaction and, therefore, an arene oxide's cancer-causing potential depend on the stability of the carbocation. If the carbocation is relatively stable, then it will be formed relatively easily, so rearrangement will be fast and the arene oxide will most likely not be carcinogenic. On the other hand, if the carbocation is relatively unstable, then rearrangement will be slow and the arene oxide will more likely exist long enough to be attacked by nucleophiles and thus be carcinogenic. This means that *the more stable the carbocation formed when the epoxide ring of an arene oxide opens, the less likely it is that the arene oxide is carcinogenic.*

### Benzo[*a*]pyrene and Cancer

Benzo[*a*]pyrene is one of the most carcinogenic arenes. It is formed whenever an organic compound is not completely burned. For example, benzo[*a*]pyrene is found in cigarette smoke, automobile exhaust, and charcoal-broiled meat. Several arene oxides can be formed from benzo[*a*]pyrene. The two most harmful are the 4,5-oxide and the 7,8-oxide.



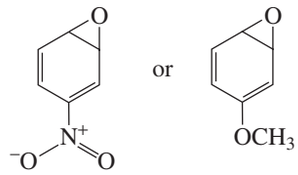

The 4,5-oxide is harmful because it forms a carbocation that cannot be stabilized by electron delocalization without destroying the aromaticity of an adjacent benzene ring. Thus, the carbocation is relatively unstable, so the epoxide tends not to open until it is attacked by a nucleophile (the carcinogenic pathway). The 7,8-oxide is harmful because it reacts with water (a nucleophile) to form a diol, which then forms a diol epoxide. The diol epoxide does not readily undergo rearrangement (the harmless pathway), because it opens to a carbocation that is destabilized by the electron-withdrawing OH groups. Because carbocation formation is slow, the diol epoxide can exist long enough to be attacked by nucleophiles (the carcinogenic pathway).



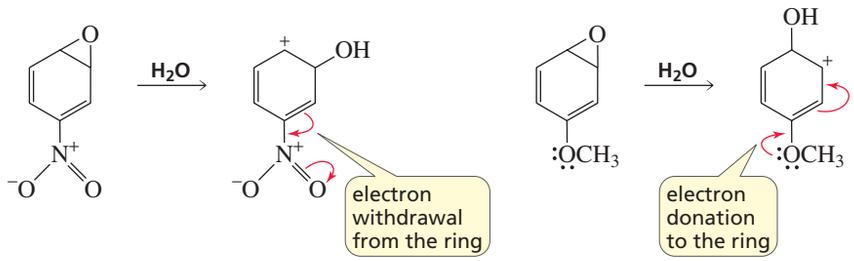
**PROBLEM 38 SOLVED**

**LEARN THE STRATEGY**

Which compound is more likely to be carcinogenic?




**SOLUTION** The nitro-substituted compound is more likely to be carcinogenic. The nitro group destabilizes the carbocation formed when the ring opens by withdrawing electrons from the ring by resonance (Section 8.10). In contrast, the methoxy group stabilizes the carbocation by donating electrons to the ring by resonance. Carbocation formation leads to the harmless product, so the nitro-substituted compound with a less stable (less easily formed) carbocation will be less likely to undergo rearrangement to a harmless product. In addition, the electron-withdrawing nitro group increases the arene oxide's susceptibility to nucleophilic attack, which is the cancer-causing pathway.



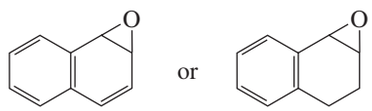

**PROBLEM 39**

Explain why the two arene oxides in Problem 38 open in opposite directions.

**PROBLEM 40**

**USE THE STRATEGY**

Which compound is more likely to be carcinogenic?




## Chimney Sweeps and Cancer

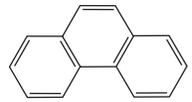
In 1775, British physician Percival Pott became the first to recognize that environmental factors can cause cancer when he observed that chimney sweeps had a higher incidence of scrotum cancer than the male population as a whole. He theorized that something in the chimney soot was causing cancer. We now know that it was benzo[*a*]pyrene.

**Percival Pott**

**A Victorian chimney sweep and his assistant—a boy small enough to fit inside narrow passages.**

**PROBLEM 41**

Three arene oxides can be obtained from phenanthrene.



phenanthrene

**a.** Draw the structures of the three phenanthrene oxides.

**b.** Draw the structures of the phenols that can be obtained from each phenanthrene oxide.

**c.** If a phenanthrene oxide can lead to the formation of more than one phenol, which phenol will be obtained in greater yield?

**d.** Which of the three phenanthrene oxides is most likely to be carcinogenic?

## 10.9 AMINES DO NOT UNDERGO SUBSTITUTION OR ELIMINATION REACTIONS

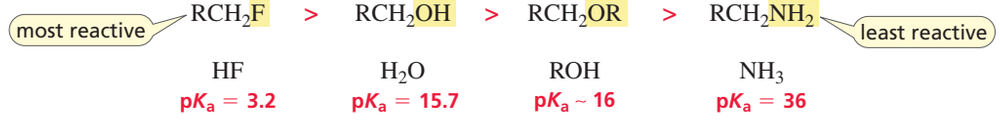
Although **amines,** like alkyl halides, alcohols, and ethers, have an electron-withdrawing group bonded to an $sp^3$ carbon, they are not included in Group II because they do not undergo substitution and elimination reactions.

An amine's lack of reactivity in substitution and elimination reactions can be understood by comparing the leaving propensity of its electron-withdrawing group with the leaving propensity of the electron-withdrawing groups of the compounds that do undergo substitution and/or elimination reactions.

The relative leaving propensities of the groups can be determined by comparing the p$K_a$ values of their conjugate acids, recalling that the weaker the acid, the stronger its conjugate base and the poorer the base is as a leaving group. The p$K_a$ values of the conjugate acids show that the leaving group of an amine ($^-NH_2$) is such a strong base that amines cannot undergo substitution or elimination reactions. (HF has been used for the comparison because F is in the same row of the periodic chart as O and N, but recall that an alkyl fluoride has the poorest leaving group of the alkyl halides.)

The stronger the base, the poorer it is as a leaving group.

**relative reactivities**



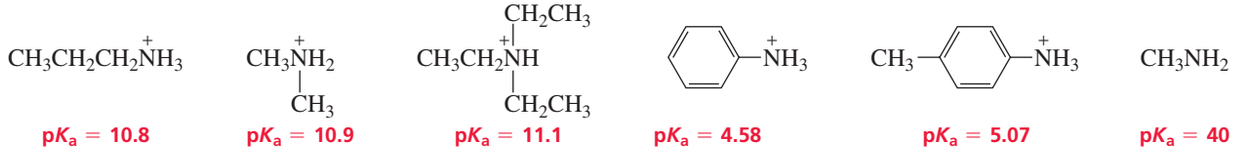

Protonating the amino group makes it a better leaving group, but not nearly as good as a protonated alcohol, which is almost 14 p$K_a$ units more acidic than a protonated amine.


Therefore, unlike protonated alcohols, protonated amines cannot undergo substitution and elimination reactions because even when protonated, the group is too basic to be displaced.

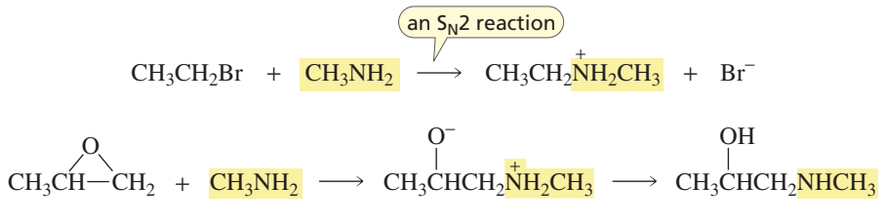
### Amines React as Bases and Nucleophiles

Although they cannot undergo substitution or elimination reactions, amines are extremely important organic compounds. The lone pair on its nitrogen allows an amine to react as both a base and a nucleophile.

Amines are the most common organic bases. We saw that protonated amines have p$K_a$ values of about 11 (Section 2.3) and that protonated anilines have p$K_a$ values of about 5 (Section 8.9). Neutral amines have very high p$K_a$ values. For example, the p$K_a$ of methylamine is 40.



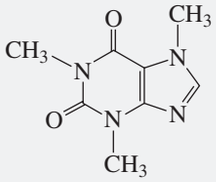
Amines react as nucleophiles in a wide variety of reactions. For example, we saw that they react as nucleophiles with alkyl halides and epoxides in $S_N2$ reactions.

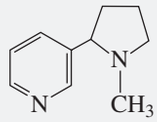


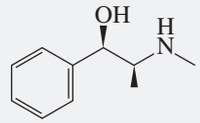

We will also see that they react as nucleophiles with a wide variety of carbonyl compounds (Sections 16.8, 16.9, 17.10, 17.18, and 17.19).

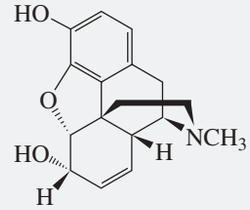
## Alkaloids

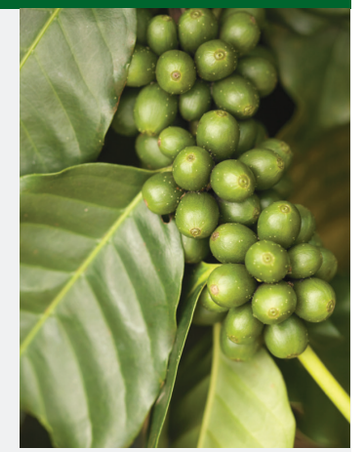
**Alkaloids** are amines found in the leaves, bark, roots, or seeds of many plants. Examples include caffeine (found in tea leaves, coffee beans, and cola nuts) and nicotine (found in tobacco leaves). Nicotine causes brain cells to release dopamine and endorphins, compounds that makes us feel good, thereby making nicotine addictive. Ephedrine, a bronchodilator, is an alkaloid obtained from *Ephedra sinica*, a plant found in China. Morphine, an analgesic, is an alkaloid obtained from opium, a milky fluid exuded by a species of poppy (p. 3).


caffeine


nicotine


ephedrine


morphine

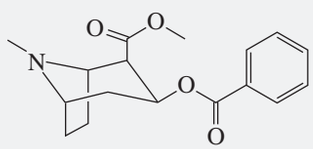

coffee beans

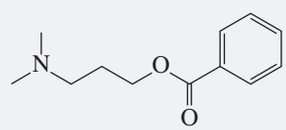
## Lead Compounds for the Development of Drugs

Medicinal agents used by humans since ancient times provided the starting point for the development of our current arsenal of drugs. The active ingredients were isolated from the herbs, berries, roots, and bark used by medicine men and women, shamans, and witch doctors. Scientists still search the world for plants, berries, flora, and fauna that might yield new medicinal compounds.

Once a naturally occurring drug is isolated and its structure determined, it can serve as a prototype in a search for other biologically active compounds. The prototype is called a **lead compound** (that is, it plays a leading role in the search). Analogues of the lead compound are synthesized and tested to see if they are more effective or have fewer side effects than the lead compound. An analogue may have a different substituent than the lead compound, a branched chain instead of a straight chain, a different functional group, or some other structural difference. Producing analogues by changing the structure of a lead compound is called **molecular modification.**

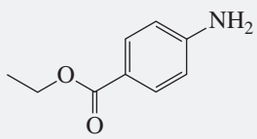
In a classic example of molecular modification, a number of synthetic local anesthetics were developed from cocaine, an alkaloid obtained from the leaves of *Erythroxylon coca,* a bush native to the highlands of the South American Andes (see p. 458). Cocaine is a highly effective local anesthetic, but it produces undesirable effects on the central nervous system (CNS), ranging from initial euphoria to severe depression. By dissecting the cocaine molecule step by step—removing the methoxycarbonyl group and cleaving the seven-membered-ring system—scientists identified the portion of the molecule that carries the local anesthetic activity but does not induce the damaging CNS effects. This knowledge provided an improved lead compound.


cocaine
**lead compound**

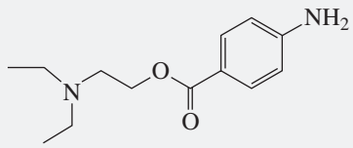

**improved lead compound**

*(Continued)*

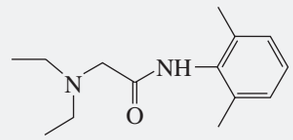
Hundreds of analogues were then synthesized. Successful anesthetics obtained by molecular modification were Benzocaine (a topical anesthetic), Novocain (used by dentists), and Xylocaine (one of the most widely used injectable anesthetics).



Benzocaine®



procaine
Novocain®



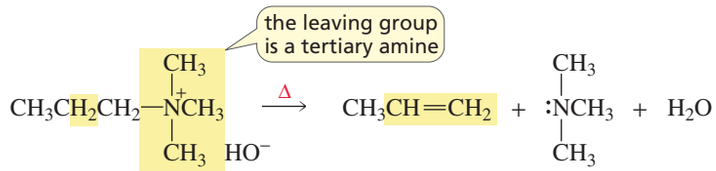
lidocaine
Xylocaine®

**PROBLEM 42**

Explain why the half-life (the time it takes for one-half of the compound to be metabolized) of Xylocaine is longer than that of Novocaine.

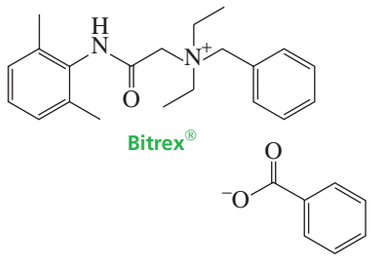
## 10.10 QUATERNARY AMMONIUM HYDROXIDES UNDERGO ELIMINATION REACTIONS

A **quaternary ammonium ion** can undergo an elimination reaction with a strong base such as hydroxide ion. The reaction is known as a **Hofmann elimination reaction.** The leaving group in a Hofmann elimination reaction is a tertiary amine. Because a tertiary amine is a relatively poor leaving group, the reaction requires heat.




quaternary ammonium ion

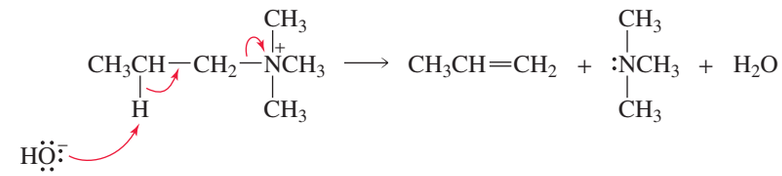
A Hofmann elimination reaction is an E2 reaction, which means the proton and the tertiary amine are removed in the same step (Section 9.7). Very little substitution product is formed.



Bitrex®

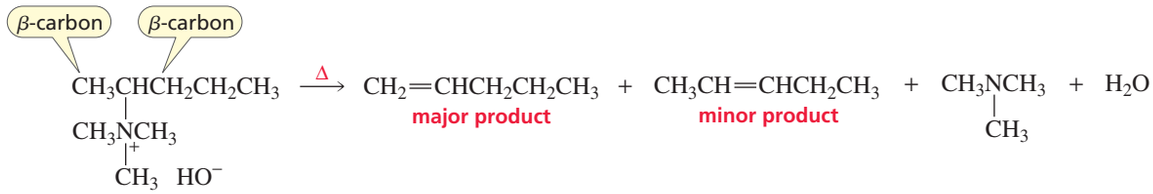
Bitrex, a quaternary ammonium salt, is nontoxic and one of the most bitter-tasting substances known. It is used to encourage deer to look elsewhere for food, it is put on the backs of animals to keep them from biting one another and on children's fingers to persuade them to stop sucking their thumbs or biting their fingernails, and it is added to toxic substances to keep them from being ingested accidentally.

### MECHANISM FOR THE HOFMANN ELIMINATION



- The tertiary amine is attached to the $\alpha$-carbon, and the proton is removed from the adjacent carbon (the $\beta$-carbon).

If the quaternary ammonium ion has more than one $\beta$-carbon, the major alkene product is the one obtained by removing a proton from the $\beta$-carbon bonded to the *most* hydrogens. For example, in the following reaction, the major alkene product is obtained by removing a proton from the $\beta$-carbon bonded to three hydrogens, and the minor alkene product results from removing a proton from the $\beta$-carbon bonded to two hydrogens.



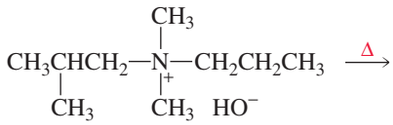
We saw that in an E2 reaction of an alkyl chloride, alkyl bromide, or alkyl iodide, the proton is removed from the β-carbon *bonded to the fewest hydrogens* (*Zaitsev's rule*; Section 9.7). Now, however, we see that in an E2 reaction of a quaternary ammonium ion, the proton is removed from the β-carbon *bonded to the most hydrogens* (anti-Zaitsev elimination).

**PROBLEM 43**

If a quaternary ammonium ion can undergo an elimination reaction with a strong base, why can't a protonated tertiary amine undergo the same reaction?

**PROBLEM 44 ♦**

What are the major products of the following reaction?



**PROBLEM 45 ♦**

What are the minor products of the preceding Hofmann elimination reaction?

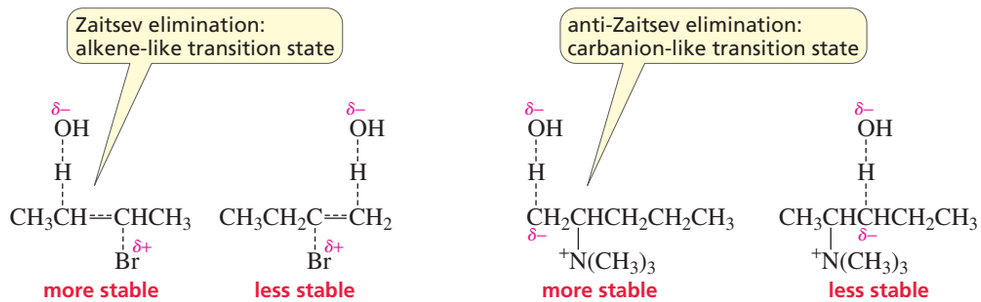
**PROBLEM 46 ♦**

What is the difference between the reaction that occurs when isopropyltrimethylammonium hydroxide is heated and the reaction that occurs when 2-bromopropane is treated with hydroxide ion?

**In a Hofmann elimination reaction, the proton is removed from the β-carbon bonded to the most hydrogens.**

## The Reason for anti-Zaitsev Elimination

Quaternary amines violate Zaitsev's rule for the same reason that alkyl fluorides violate it (Section 9.7). Alkyl halides, other than alkyl fluorides, have relatively good leaving groups that immediately start to depart when hydroxide ion starts to remove the proton, forming a transition state with an *alkene-like* structure. The proton is removed *from the β-carbon bonded to the fewest hydrogens* in order to achieve the most stable *alkene-like* transition state.

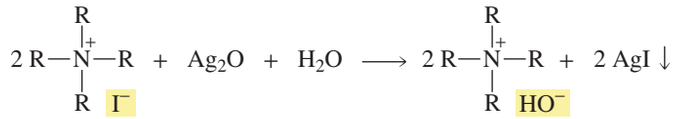



Quaternary ammonium ions and alkyl fluorides have poorer leaving groups that do not start to leave when hydroxide ion starts to remove a proton. Therefore, a partial negative charge builds up on the carbon from which the proton is being removed, giving the transition state a *carbanion-like* structure (Section 9.7). The proton is removed *from the β-carbon bonded to the most hydrogens* in order to achieve the more stable *carbanion-like* transition state. (Recall that primary carbanions are more stable than secondary carbanions, which are more stable than tertiary carbanions.) Steric factors also favor anti-Zaitsev elimination.

Because anti-Zaitsev elimination occurs in the Hofmann elimination reaction, *anti-Zaitsev elimination* is also known as *Hofmann elimination*.

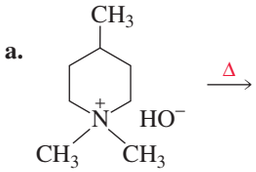
For a quaternary ammonium ion to undergo an elimination reaction, the counterion must be hydroxide ion, because a strong base is needed to remove the proton from the β-carbon. Halide ions are weak bases, so quaternary ammonium *halides* cannot undergo Hofmann elimination reactions. However, a quaternary ammonium *halide* can be converted into a quaternary ammonium

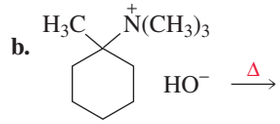
*hydroxide* by treatment with silver oxide and water. The silver halide precipitates, and the halide ion is replaced by hydroxide ion.

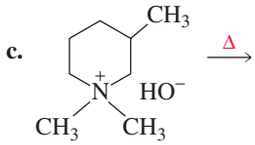


**PROBLEM 47 ♦**

What is the major product of each of the following reactions?

**a.** 

**b.** 

**c.** 

LEARN THE STRATEGY

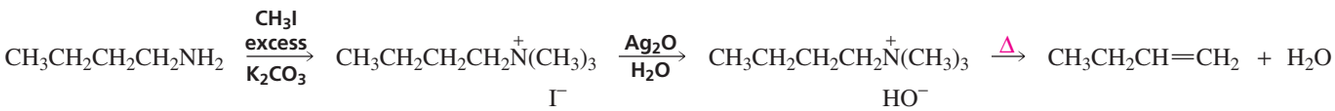
**PROBLEM 48 SOLVED**

Describe a synthesis for the following compound, using the given starting material and any necessary reagents:

$$CH_3CH_2CH_2CH_2NH_2 \longrightarrow CH_3CH_2CH{=}CH_2$$

**SOLUTION** Although an amine cannot undergo an elimination reaction, a quaternary ammonium hydroxide can. The amine, therefore, must first be converted into a quaternary ammonium iodide by reacting it with excess methyl iodide in a basic solution of potassium carbonate (see Problem 16 on pp. 404–405).

Treatment with aqueous silver oxide forms the quaternary ammonium hydroxide. Heat is required for the elimination reaction.



USE THE STRATEGY

**PROBLEM 49**

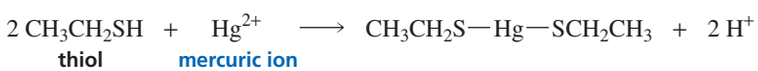
Describe a synthesis for each of the following compounds, using the given starting material and any necessary reagents:

**a.** $CH_3CH_2CH_2\underset{\displaystyle Br}{\underset{|}{C}}HCH_3 \longrightarrow CH_3CH_2CH_2CH{=}CH_2$ **b.**  $\longrightarrow CH_2{=}CH{-}CH{=}CH_2$

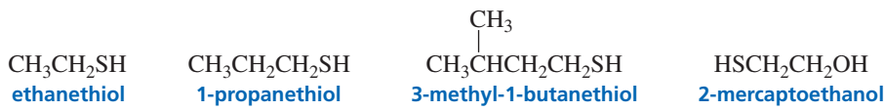
## 10.11 THIOLS, SULFIDES, AND SULFONIUM IONS

### Thiols

**Thiols** are sulfur analogues of alcohols. They used to be called mercaptans because they form strong complexes with heavy metal cations such as arsenic and mercury—that is, they capture mercury.

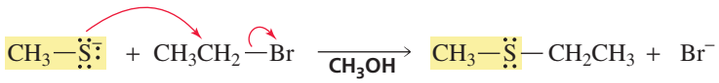


Thiols are named by adding the suffix *thiol* to the name of the parent hydrocarbon. If there is a second functional group in the molecule that is identified by a suffix, the SH group can be indicated by its substituent name, *mercapto*. Like other substituent names, it is placed before the name of the parent hydrocarbon.



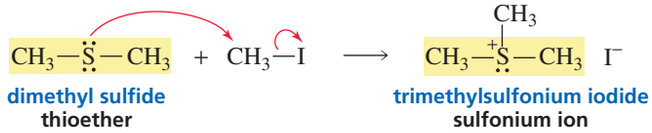
Because sulfur is not as electronegative as oxygen, thiols are not good at hydrogen bonding. Consequently, they have weaker intermolecular attractions and, therefore, considerably lower boiling points than alcohols (Section 3.9). For example, the boiling point of $CH_3CH_2SH$ is 37 °C, whereas the boiling point of $CH_3CH_2OH$ is 78 °C.

Sulfur atoms are larger than oxygen atoms, so the negative charge of the thiolate ion is spread over a larger volume of space than the negative charge of an alkoxide ion, causing the thiolate ion to be more stable (Section 2.6). Thiols, therefore, are stronger acids ($pK_a \sim 10$) than alcohols ($pK_a \sim 15$). The less basic thiolate ions are less well solvated than alkoxide ions, so in protic solvents, the larger thiolate ions are better nucleophiles than alkoxide ions (Section 9.2).



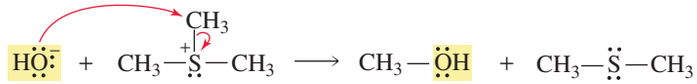

## Sulfides

The sulfur analogues of ethers are called **sulfides** or **thioethers.** Sulfur is an excellent nucleophile because its electron cloud is polarizable (Section 9.2). As a result, a thioether reacts readily with an alkyl halide to form a **sulfonium ion,** whereas an ether does not do the equivalent reaction because oxygen is not as nucleophilic as sulfur and cannot accommodate a positive charge as well as sulfur can.



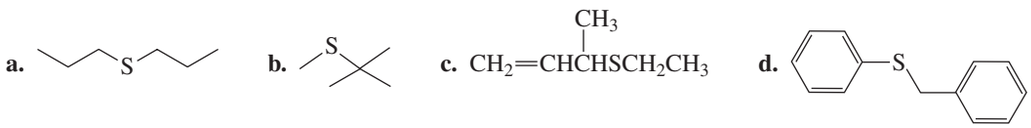

## Sulfonium Ions

The positively charged group of a sulfonium ion is an excellent leaving group, so a sulfonium ion readily undergoes nucleophilic substitution reactions. Like other $S_N2$ reactions, the reaction works best if the group undergoing nucleophilic attack is a methyl group or a primary alkyl group.




PROBLEM 50

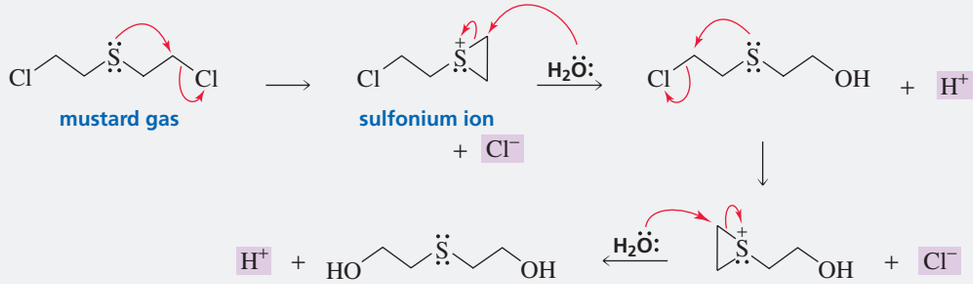
Using an alkyl halide and a thiol as starting materials, how would you prepare the following thioethers?




Low-molecular-weight thiols are noted for their strong and pungent odors, such as the odors associated with onions, garlic, and skunks. Natural gas is completely odorless and can cause deadly explosions if a leak goes undetected. As a result, a small amount of a thiol is added to natural gas to give it an odor so that gas leaks can be detected.

## Mustard Gas—A Chemical Warfare Agent

Chemical warfare occurred for the first time in 1915, when Germany released chlorine gas against French and British forces in the Battle of Ypres. For the remainder of World War I, both sides used a variety of chemical agents as weapons. One of the more common was mustard gas, a reagent that produces large blisters on exposed skin. Mustard gas is extremely reactive because its highly nucleophilic sulfur atom easily displaces a chloride ion by an intramolecular $S_N2$ reaction, forming a cyclic sulfonium ion that reacts rapidly with a nucleophile. The sulfonium ion is particularly reactive because of its strained three-membered ring and its excellent (positively charged) leaving group.




(Continued)

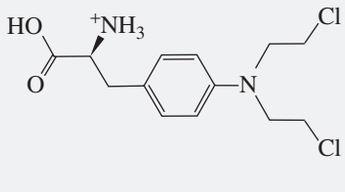
The blistering caused by mustard gas results from the high local concentrations of HCl produced when mustard comes into contact with water—or any other nucleophile—on skin or in lung tissue. Autopsies of soldiers killed by mustard gas in World War I revealed that they had extremely low white blood cell counts and defects in bone marrow development, indicating profound effects on rapidly dividing cells.

## Alkylating Agents as Cancer Drugs

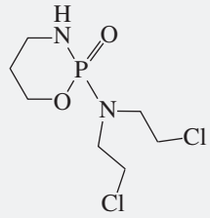
Because cancer is characterized by the uncontrolled growth and proliferation of cells, the discovery that mustard gas affected rapidly dividing cells suggested that it might be an effective antitumor agent. Therefore, chemists started looking for less reactive analogues of mustard gas that might be used in chemotherapy—that is, the use of chemicals in the treatment of cancer.

Because mustard gas forms a three-membered ring that can react rapidly with nucleophiles, its clinical reactivity is thought to be due to its ability to alkylate groups on the surface of DNA. Alkylating DNA can destroy it, which means that the rapidly growing cells of cancerous tumors are killed. Unfortunately, compounds used for chemotherapy can also kill normal cells. That is why many side effects, such as nausea and hair loss, are associated with cancer chemotherapy. The challenge for chemists now is to find drugs that target only cancer cells (Section 24.7).

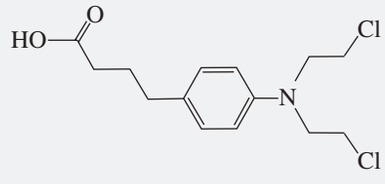
The cancer drugs shown here are all alkylating agents—they attach an alkyl group to a nucleophile on DNA under physiological conditions.



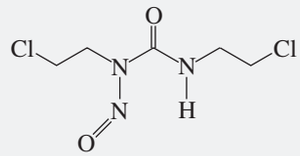

melphalan




cyclophosphamide



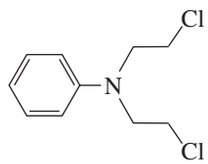

chloroambucil

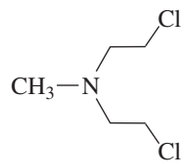


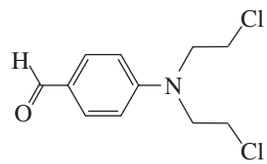

carmustine

**PROBLEM 51 ♦**

The following three nitrogen mustards were studied for possible clinical use. One is now used clinically, one was found to be too unreactive, and one was found to be too insoluble in water to be injected intravenously. Which is which? (*Hint:* Draw resonance contributors.)




**PROBLEM 52 ♦**

Why is melphalan a good cancer drug?

**PROBLEM 53**

Mechlorethamine, the drug in Problem 51 that is in clinical use, is so highly reactive that it can be administered only by physicians who are experienced in its use. Explain why the four cancer drugs in the box at the top of this page are less reactive alkylating agents.

# 10.12 METHYLATING AGENTS USED BY CHEMISTS VERSUS THOSE USED BY CELLS

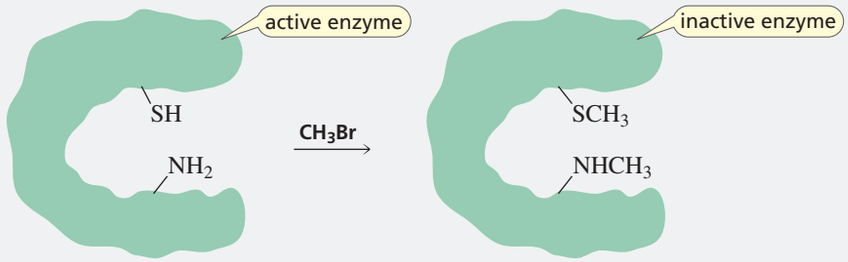
## Methyl Halides Are the Methylating Agents Used by Chemists

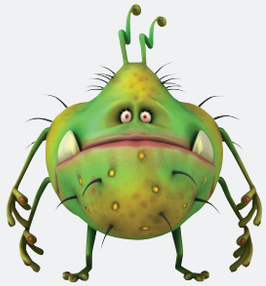
If an organic chemist wanted to put a methyl group on a nucleophile, methyl iodide would most likely be used as the methylating agent. Of the methyl halides, methyl iodide has the most easily displaced leaving group because $I^-$ is the weakest base of the halide ions. In addition, methyl iodide is a liquid at room temperature, so it is easier to handle than methyl bromide or methyl chloride, which are gases at room temperature. The reaction would be a simple $S_N2$ reaction.


Methyl halides, however, are not available to a cell. Because they are only slightly soluble in water, alkyl halides are not found in the predominantly aqueous environments of biological systems.

## Eradicating Termites

Alkyl halides can be very toxic to biological organisms. For example, methyl bromide has been used to kill termites and other pests. Methyl bromide works by methylating the $NH_2$ and SH groups of enzymes, thereby destroying the enzymes' ability to catalyze important biological reactions. Unfortunately, methyl bromide has been found to deplete the ozone layer (Section 12.12), so its use has been banned.

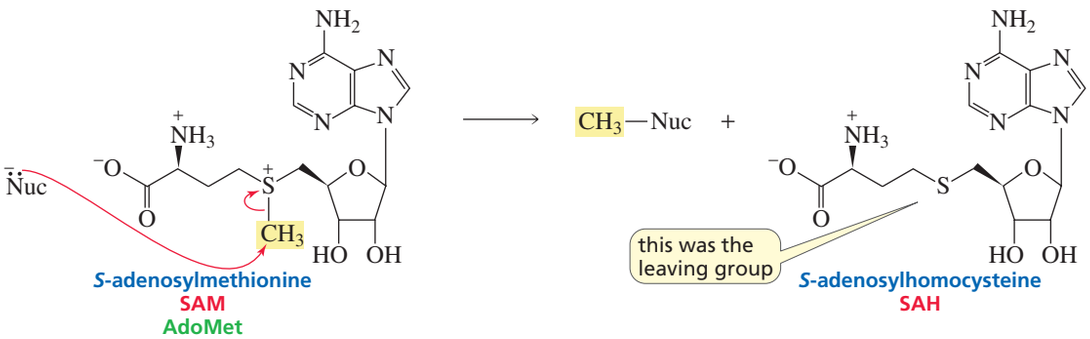


## *S*-Adenosylmethionine Is a Methylating Agent Used by Cells

Cells use *S*-adenosylmethionine (SAM; also called AdoMet), a water-soluble sulfonium ion, as a methylating agent. (A less common biological methylating agent is discussed in Section 23.7.)

Although SAM is a much larger and more complicated looking molecule than methyl iodide, it performs the same function—namely, it transfers a methyl group to a nucleophile. Remember that biological molecules are typically more complex than the molecules chemists use because of the need for molecular recognition (Section 5.14).




Notice that SAM is sulfonium ion (Section 10.11). The positively charged sulfur readily accepts the electrons left behind when the methyl group is transferred. In other words, the methyl group is attached to a very good leaving group, allowing biological methylation to readily take place.

## Examples of Biological Methylation Reactions

A specific example of a biological methylation reaction that uses SAM is the conversion of noradrenaline (norepinephrine) to adrenaline (epinephrine). The reaction uses SAM to provide the methyl group. Noradrenaline and adrenaline are hormones that stimulate the breakdown of glycogen—the body's primary fuel source (see p. 000). You may have felt this "adrenaline rush" when preparing for a challenging activity. Adrenaline is about six times more potent than noradrenaline. This methylation reaction, therefore, is very important physiologically.

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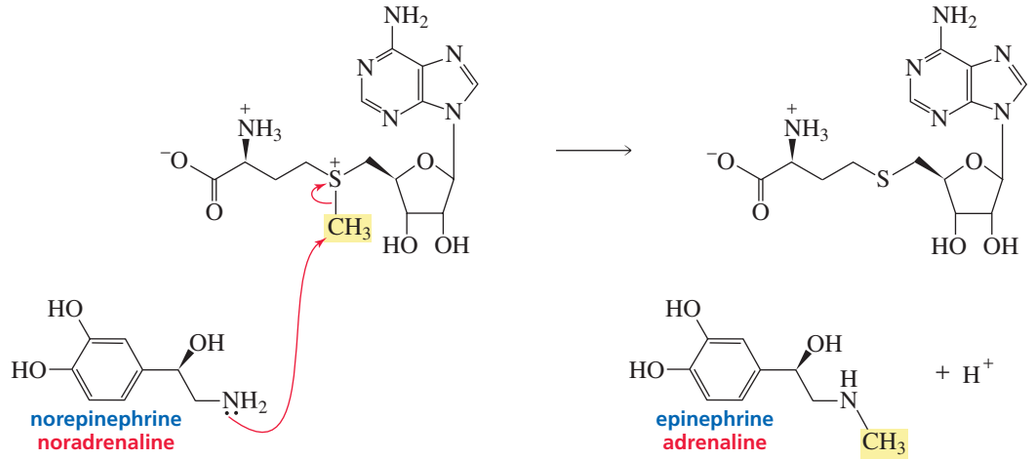
experiencing an adrenaline rush




The conversion of phosphatidylethanolamine, a component of cell membranes, into phosphatidylcholine, another cell membrane component, requires three methylations by three equivalents of SAM (p. 000).

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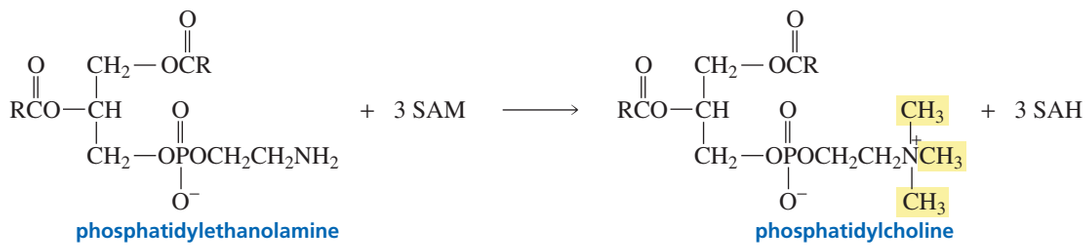


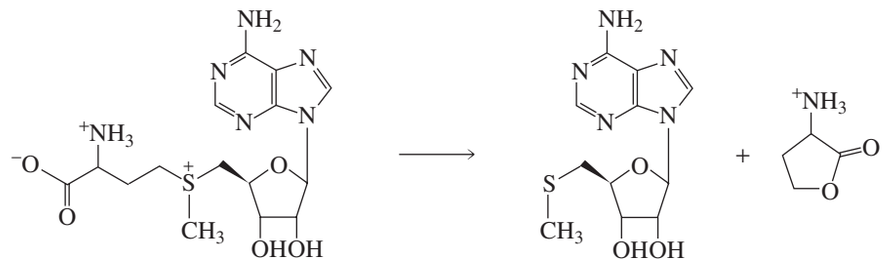

## *S*-Adenosylmethionine: A Natural Antidepressant

Marketed under the name SAMe (pronounced Sammy), *S*-adenosylmethionine is sold in many health food and drug stores as a treatment for depression and arthritis. Although SAMe has been used clinically in Europe for more than three decades, it has not been rigorously evaluated in the United States and, therefore, has not been approved by the FDA. It can be sold, however, because the FDA does not prohibit the sale of most naturally occurring substances as long as the marketer does not make therapeutic claims.

SAMe has also been found to be effective in the treatment of liver diseases, such as those caused by alcohol and the hepatitis C virus. The attenuation of injury to the liver is accompanied by an increase in the concentration of glutathione in the liver. Glutathione is an important biological antioxidant (Section 22.1). SAM is required for the biosynthesis of cysteine, one of the 20 most common naturally occurring amino acids (Section 22.9), which is required for the biosynthesis of glutathione.

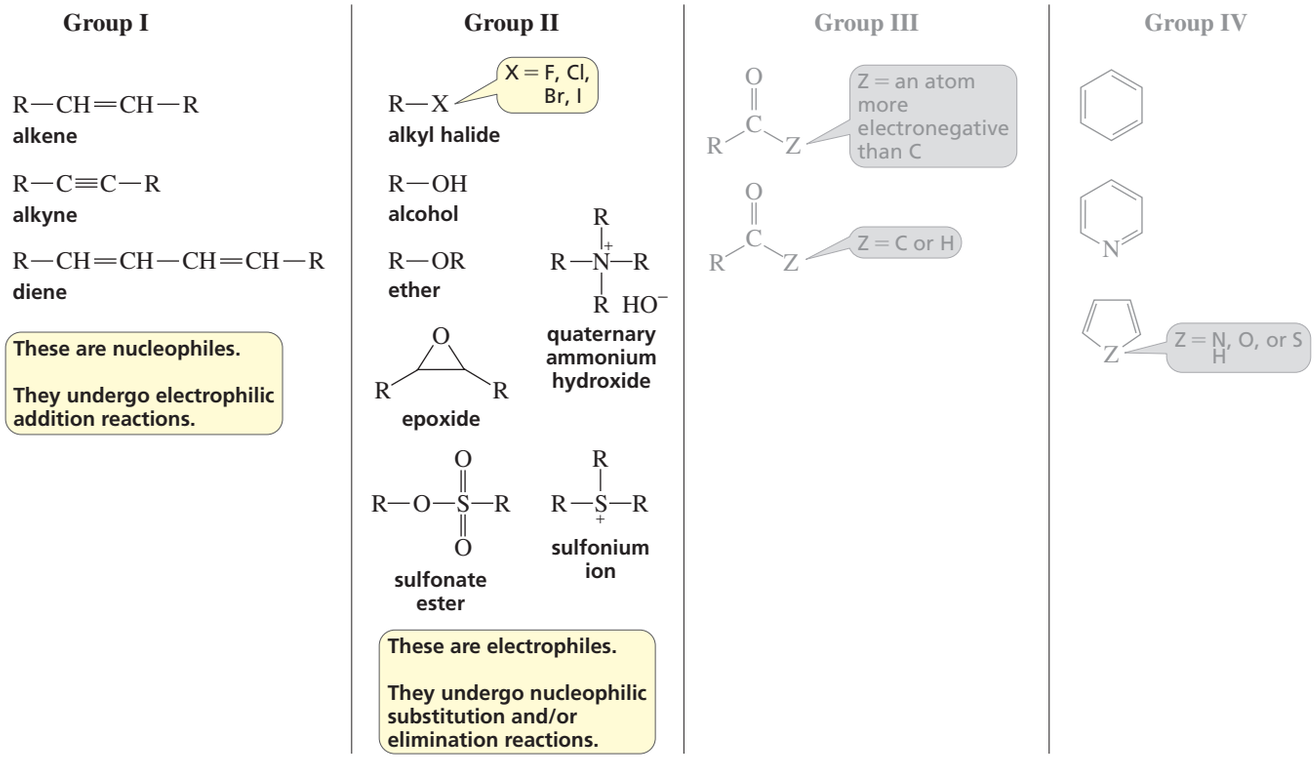
**PROBLEM 54**

Propose a mechanism for the following reaction:



# 10.13 ORGANIZING WHAT WE KNOW ABOUT THE REACTIONS OF ORGANIC COMPOUNDS

We saw that organic compounds can be put into families and all the members of a family react in the same way. We also saw that the families can be put into one of four groups all the members of a group react in similar ways. Now that we have finished studying the families in Group II, let's revisit it.




All the families in Group II are *electrophiles*, due to the partial positive charge on the carbon attached to the electron-withdrawing leaving group. As a result, the families in this group react with *nucleophiles*. The nucleophile can either attack the carbon to which the electron-withdrawing group is attached and substitute for it, or it can remove a hydrogen from an adjacent carbon and eliminate the electron-withdrawing group by forming an alkene. Thus, the families in Group II undergo nucleophilic substitution reactions and/or elimination reactions.

- Alkyl halides have excellent leaving groups, so they undergo substitution and/or elimination reactions with ease.
- Alcohols have much poorer leaving groups, so they need to be activated before they can undergo nucleophilic substitution and/or elimination reactions.
- Ethers, like alcohols, have poor leaving groups, but unlike alcohols, they can be activated only by protonation and they undergo only substitution reactions.
- Epoxides are more reactive than acyclic ethers because of the angle strain in the three-membered ring. Thus, they readily undergo substitution reactions whether or not they are activated by protonation.
- Quaternary ammonium hydroxide ions undergo elimination reactions. Because the leaving group is poor, the reaction requires heat and forms the less substituted elimination product.
- Sulfonate esters and sulfonium salts have good leaving groups, so they readily undergo substitution reactions.

## ESSENTIAL CONCEPTS

### Section 10.1

- The leaving groups of alcohols and ethers are stronger bases than halide ions, so alcohols and ethers must be "activated" before they can undergo a substitution or elimination reaction.
- An alcohol can be activated by protonation. Therefore, it undergoes nucleophilic substitution reactions with HI, HBr, and HCl to form alkyl halides. These are $S_N1$ reactions in the case of secondary and tertiary alcohols and $S_N2$ reactions in the case of primary alcohols.
- $S_N1$ reactions form carbocation intermediates, so carbocation rearrangements can occur.

### Section 10.2

- An alcohol can also be converted into an alkyl halide by $PBr_3$, $PCl_3$, or $SOCl_2$. These reagents convert the alcohol into an intermediate that has a leaving group that is easily displaced by a halide ion.

### Section 10.3

- Converting an alcohol into a sulfonate ester is another way to activate an alcohol for subsequent reaction with a nucleophile that is a better nucleophile substitution than a halide ion.
- Tertiary alcohols can form sulfonate esters but they are too sterically hindered to undergo a subsequent reaction with a nucleophile.
- Converting an alcohol to an alkyl halide with a hydrogen halide followed by reaction with a nucleophile forms a substitution product with the same configuration as the alcohol, whereas converting an alcohol to a sulfonate ester followed by reaction with a nucleophile forms a substitution product with a configuration opposite that of the alcohol.

### Section 10.4

- An alcohol undergoes dehydration (elimination of a water molecule) when it is heated with an acid.
- Dehydration is an E1 reaction in the case of secondary and tertiary alcohols and an E2 reaction in the case of primary alcohols.
- Tertiary alcohols are the easiest to dehydrate, and primary alcohols are the hardest.
- The major product of alcohol dehydration is the more stable alkene.
- If the alkene has stereoisomers, the stereoisomer in which the largest groups are on opposite sides of the double bond will be the major product.
- E1 reactions form carbocation intermediates, so carbocation rearrangements can occur.
- Dehydration of secondary and tertiary alcohols can take place by an E2 reaction if a good leaving group is put on the alcohol before the elimination reaction.

### Section 10.5

- Chromic acid oxidizes primary alcohols to carboxylic acids and secondary alcohols to ketones.
- PCC, hypochlorous acid, and the Swern oxidation oxidizes primary alcohols to aldehydes and secondary alcohols to ketones.

### Section 10.6

- Ethers undergo nucleophilic substitution reactions with HBr or HI and heat; if departure of the leaving group creates a relatively stable carbocation, an $S_N1$ reaction occurs; otherwise, an $S_N2$ reaction occurs with the nucleophile attacking the less sterically hindered of the two alkyl groups.

### Section 10.7

- Ring strain causes an epoxide to be more reactive than an ether.
- Epoxides undergo nucleophilic substitution reactions. Under acidic conditions, the nucleophile adds to the more substituted ring carbon; under neutral or basic conditions, it adds to the less sterically hindered ring carbon.
- To convert an alkene to an alcohol without a carbocation rearrangement, first convert the alkene to an epoxide and then react the epoxide with NaH.
- Epoxidation of cyclohexene followed by reaction with hydroxide ion forms a trans 1,2-diol.
- Reaction of cyclohexene with osmium tetroxide followed by hydrolysis with hydrogen peroxide forms a cis 1,2-diol.

### Section 10.8

- Aromatic hydrocarbons (arenes) are oxidized to arene oxides that undergo nucleophilic addition or rearrange to form phenols.
- The more stable the carbocation formed during rearrangement, the less likely the arene oxide is carcinogenic.

### Section 10.9

- Amines cannot undergo substitution or elimination reactions because their leaving groups are very strong bases.

### Section 10.10

- A quaternary ammonium hydroxide undergoes an E2 reaction (a Hofmann elimination) if it is heated. Hydroxide ion removes a proton from the $\beta$-carbon bonded to the most hydrogens.

### Section 10.11

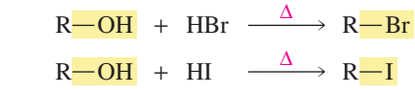
- Thiols are stronger acids and have lower boiling points than alcohols.
- Thiolate ions are weaker bases and better nucleophiles than alkoxide ions are in protic solvents.
- Thioethers react with alkyl halides to form sulfonium ions, which have excellent leaving groups, so they undergo substitution reactions with ease.

### Section 10.12

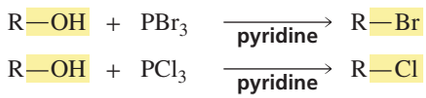
- *S*-Adenosylmethionine, the most common biological methylating agent, is a sulfonium ion.

## SUMMARY OF REACTIONS

**1.** Converting an *alcohol* to an *alkyl halide* (Sections 10.1 and 10.2). The mechanisms are shown on pages 460, 461, 464, and 465.

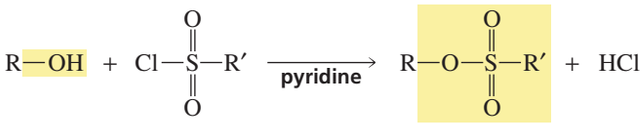



**relative rate: tertiary > secondary > primary**

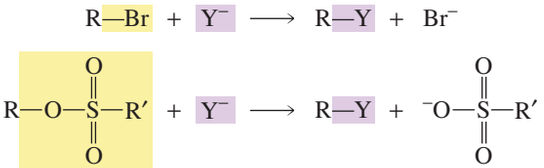



**only for primary and secondary alcohols**

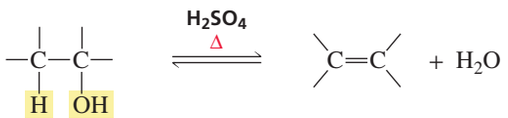
**2.** Converting an alcohol to a *sulfonate ester* (Section 10.3). The mechanism is shown on page 466.



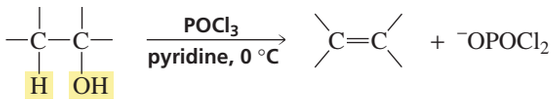

**3.** Using an $S_N2$ reaction to convert an *activated alcohol* (an alkyl halide or a sulfonate ester) to a *compound with a new group bonded to the $sp^3$ carbon* (Section 10.3). The mechanism is shown on p. 466.



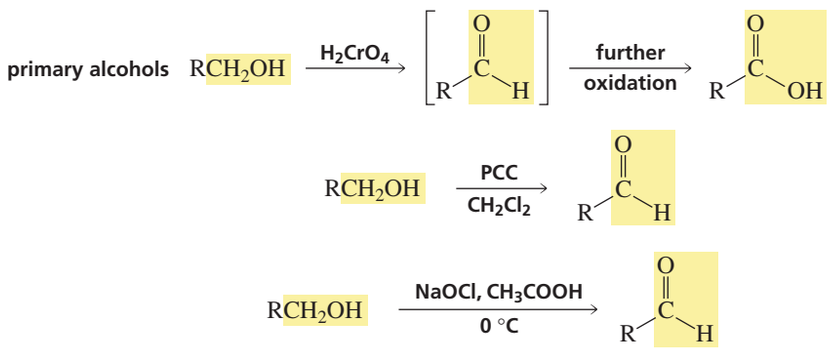

**4.** Elimination reactions of alcohols: dehydration (Section 10.4). The mechanisms are shown on pages 468 and 470.

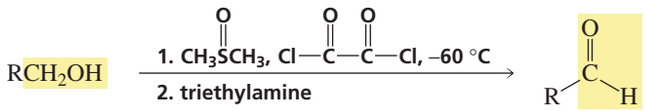



**relative rate: tertiary > secondary > primary**

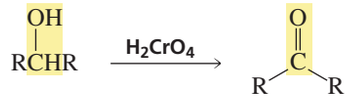


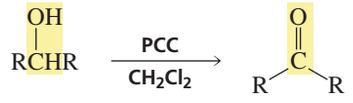

**5.** Oxidation of alcohols (Section 10.5). The mechanism is shown on page 475.

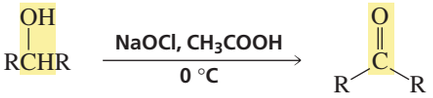


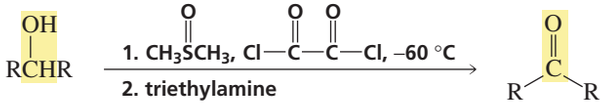



secondary alcohols



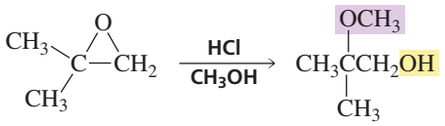



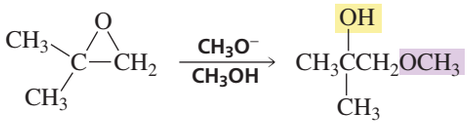

**6.** Nucleophilic substitution reactions of ethers (Section 10.6). The mechanisms are shown on pages 477 and 478.


**HX = HBr or HI**

**7.** Nucleophilic substitution reactions of *epoxides* (Section 10.7). The mechanisms are shown on pages 481 and 482.

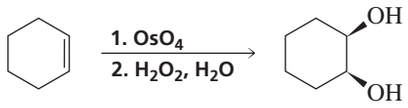


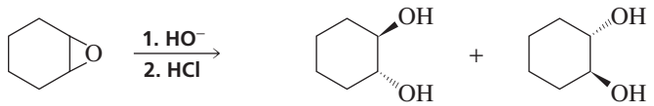

**under acidic conditions, the nucleophile attacks the more substituted ring carbon**



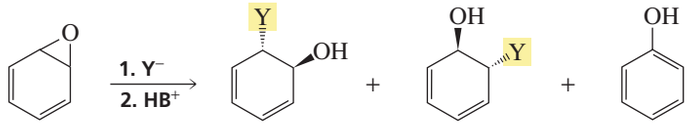

**under neutral or basic conditions, the nucleophile attacks the less sterically hindered ring carbon**

**8.** Formation of cis and trans 1,2-diols (Section 10.7). The mechanism is shown on page 484.

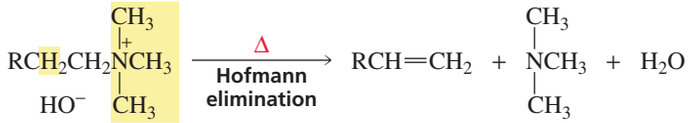


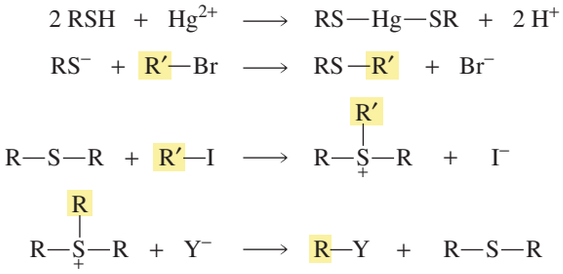

**9.** Reactions of *arene oxides:* ring opening and rearrangement (Section 10.8). The mechanism is shown on page 486.




**10.** Elimination reactions of *quaternary ammonium hydroxides;* the proton is removed from the $\beta$-carbon bonded to the most hydrogens (Section 10.10). The mechanism is shown on page 492.



**11.** Reactions of thiols, sulfides, and sulfonium ions (Section 10.11). The mechanisms are shown on page 495.



## PROBLEMS

**55.** What is the product of each of the following reactions?

**a.** $CH_3CH_2CH_2OH$ —(1. methanesulfonyl chloride; 2. $CH_3CO^-$)→

**b.** $CH_3CH_2CH_2CH_2OH + PBr_3$ —(pyridine)→

**c.** $CH_3CHCH_2CH_2OH$ ($CH_3$) —(1. *p*-toluenesulfonyl chloride; 2. $^-O$-C$_6$H$_4$)→

**d.** $CH_3CH_2CH_2CH_2OH$ —($H_2SO_4$, Δ)→

**e.** $CH_3CH_2CH$—C(O)(CH$_3$)(CH$_3$) —($CH_3O^-$, $CH_3OH$)→

**f.** $CH_3CH_2CH$—C(O)(CH$_3$)(CH$_3$) —(HCl, $CH_3OH$)→

**g.** $CH_3CHCH_2CH_2OH$ ($CH_3$) —($SOCl_2$, pyridine)→

**56.** Indicate which alcohol in each pair undergoes an elimination reaction more rapidly when heated with $H_2SO_4$.

**a.** $CH_2OH$ or $CH_2CH_2OH$

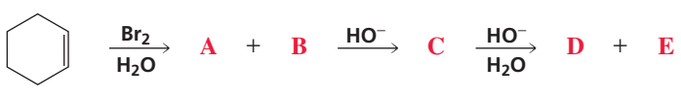
**b.** OH or OH

**c.** $CH_3$, OH or $CH_3$, OH

**d.** OH or OH

**e.** OH or OH

**57.** Identify **A**–**E.**



**58.** Starting with (*R*)-1-deuterio-1-propanol, how could you prepare

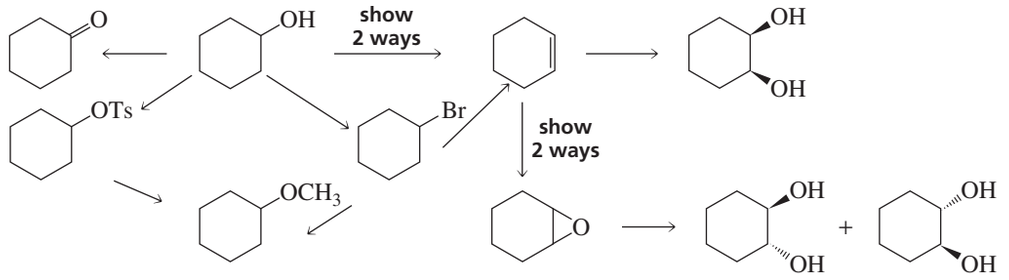
**a.** (*S*)-1-deuterio-1-propanol? **b.** (*S*)-1-deuterio-1-methoxypropane? **c.** (*R*)-1-deuterio-1-methoxypropane?

**59.** When heated with $H_2SO_4$, both 3,3-dimethyl-2-butanol and 2,3-dimethyl-2-butanol are dehydrated to form 2,3-dimethyl-2-butene. Which alcohol dehydrates more rapidly?

**60.** What is the major product obtained from the reaction of 2-ethyloxirane with each of the following reagents?

**a.** 0.1 M HCl **b.** $CH_3OH/HCl$ **c.** 0.1 M NaOH **d.** $CH_3OH/CH_3O^-$

**61.** Write the appropriate reagent over each arrow.

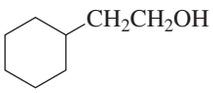


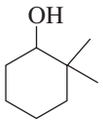

**62.** What alkenes would you expect to be obtained from the acid-catalyzed dehydration of 1-hexanol?

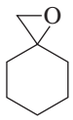
**63.** What is the major product(s) of each of the following reactions?

**a.** $CH_3COCH_2CH_3$ (with $CH_3$ and $CH_3$ substituents) + HBr, $\Delta$

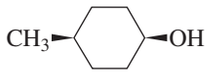
**b.** $CH_3CHCH_2OCH_3$ (with $CH_3$ substituent) + HI, $\Delta$

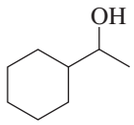
**c.**  $H_2CrO_4$

**d.**  $H_2SO_4$, $\Delta$

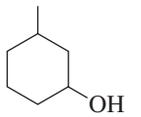
**e.**  HCl, $CH_3OH$

**f.**  $CH_3O^-$, $CH_3OH$

**g.**  1. TsCl/pyridine 2. NaC≡N

**h.**  NaOCl, $CH_3COOH$, 0 °C

**i.** $CH_3CHCH_2\overset{+}{N}CH_2CH_3$ (with $CH_3$, $CH_3$, $HO^-$), $\Delta$

**j.**  + HBr, $\Delta$

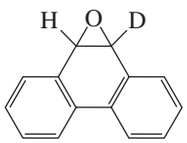
**64.** In Section 10.12, we saw that *S*-adenosylmethionine (SAM) methylates the nitrogen atom of noradrenaline to form adrenaline, a more potent hormone. If SAM methylates an OH group attached to the benzene ring instead, it completely destroys noradrenaline's activity.

**a.** Show the mechanism for the methylation of the OH group by SAM.

**b.** Which reaction is more apt to occur, methylation on nitrogen or methylation on oxygen?


noradrenaline — a biologically inactive compound

**65.** When deuterated phenanthrene oxide undergoes a rearrangement in water to form a phenol, 81% of the deuterium is retained in the product.




**a.** What percentage of the deuterium will be retained if an NIH shift occurs?

**b.** What percentage of the deuterium will be retained if an NIH shift does not occur?

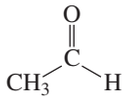
**66.** An unknown alcohol with a molecular formula of $C_7H_{14}O$ was oxidized to an aldehyde with HOCl. When an acidic solution of the alcohol was distilled, two alkenes were obtained. The alkene formed in greater yield was determined to be 1-methylcyclohexene. The other alkene formed the original unknown alcohol when treated with $BH_3$/THF followed by $H_2O_2$, $HO^-$, and $H_2O$. Identify the unknown alcohol.

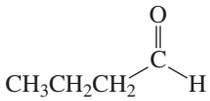
**67.** Explain why the acid-catalyzed dehydration of an alcohol is a reversible reaction, whereas the base-promoted dehydrohalogenation of an alkyl halide is an irreversible reaction.

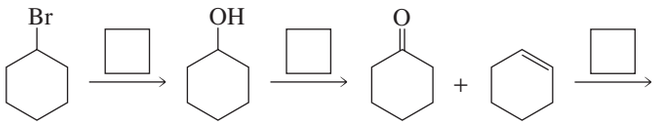
**68.** Explain why (*S*)-2-butanol forms a racemic mixture when it is heated in sulfuric acid.

<Au/Ed: Problems reordered to better fill page.>

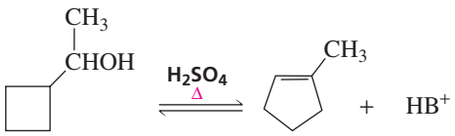
**69.** Fill in each box with the appropriate reagent:

**a.** $CH_3CH_2CH{=}CH_2 \xrightarrow[2.\ \square]{1.\ \square} CH_3CH_2CH_2CH_2OH \xrightarrow{\square} CH_3CH{=}CHCH_3 \xrightarrow{\square}$ 

**b.** $CH_3CH_2CH{=}CH_2 \xrightarrow[2.\ \square]{1.\ \square} CH_3CH_2CH_2CH_2OH \xrightarrow{\square}$ 

**c.** 

**70.** Propose a mechanism for the following reaction:

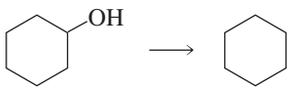


**71.** What product would be formed if the four-membered ring alcohol in Problem 70 were heated with an equivalent amount of HBr rather than with a catalytic amount of $H_2SO_4$?

<Au/Ed: Problem number revised due to reordering of problems.>

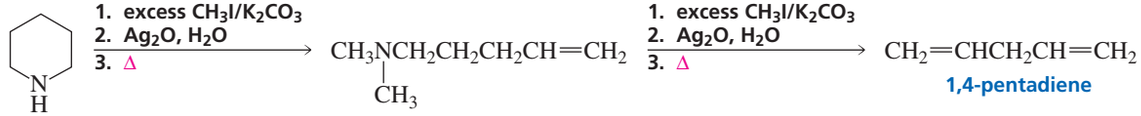
**72.** Which of the following ethers would be obtained in greatest yield directly from alcohols?

**73.** Using the given starting material, any necessary inorganic reagents, and any carbon-containing compounds with no more than two carbons, indicate how the following syntheses could be carried out:

**a.** 

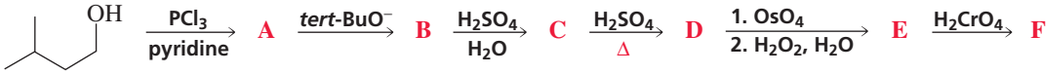
**b.** $CH_3CH_2CH_2CH_2Br \longrightarrow CH_3CH_2CH_2\overset{O}{\overset{\|}{C}}OH$

**74.** When piperidine undergoes the series of reactions shown here, 1,4-pentadiene is obtained as the product. When the four different methyl-substituted piperidines undergo the same series of reactions, each forms a different diene: 1,5-hexadiene; 1,4-pentadiene; 2-methyl-1,4-pentadiene; and 3-methyl-1,4-pentadiene. Which methyl-substituted piperidine forms which diene?

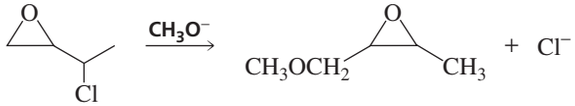


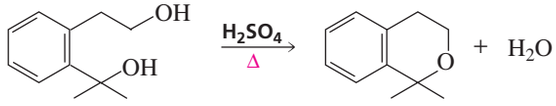

**75.** When 3-methyl-2-butanol is heated with concentrated HBr, a rearranged product is obtained. When 2-methyl-1-propanol reacts under the same conditions, a rearranged product is not obtained. Explain.

**76.** Draw structures for compounds **A–F.**




**77.** Propose a mechanism for each of the following reactions:

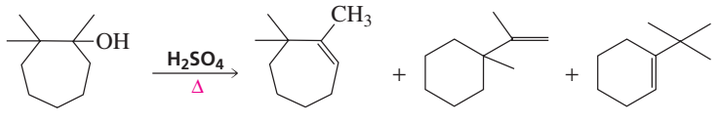
**a.** 

**b.** 

**78.** How could you synthesize isopropyl propyl ether, using isopropyl alcohol as the only carbon-containing reagent?

**79.** When ethyl ether is heated with excess HI for several hours, the only organic product obtained is ethyl iodide. Explain why ethyl alcohol is not obtained as a product.

**80.** When the following seven-membered ring alcohol is dehydrated, three alkenes are formed. Propose a mechanism for their formation.

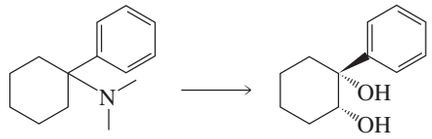



**81.** Ethylene oxide reacts readily with $HO^-$ because of the strain in the three-membered ring. Explain why cyclopropane, a compound with approximately the same amount of strain, does not react with $HO^-$.

**82.** Describe how each of the following compounds could be synthesized from the given starting material.

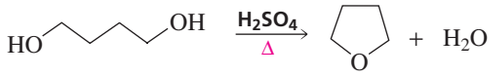
**a.**


**b.**

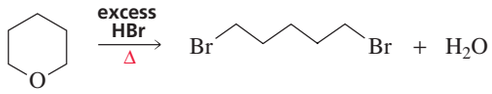



**83.** Propose a mechanism for each of the following reactions:

**a.**



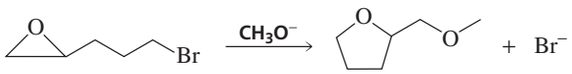

**b.**




**84.** Triethylene glycol is one of the products obtained from the reaction of excess ethylene oxide and hydroxide ion. Propose a mechanism for its formation.


triethylene glycol

**85. a.** Propose a mechanism for the following reaction:




**b.** A small amount of a product containing a six-membered ring is also formed. Draw the structure of that product.

**c.** Why is so little six-membered ring product formed?

**86.** Propose a mechanism for the following reaction:

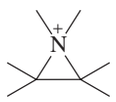

**87.** Early organic chemists used the Hofmann elimination reaction as the last step of a process known as a **Hofmann degradation**—a method used to identify amines. In a *Hofmann degradation,* an amine is methylated with excess methyl iodide in a basic solution, treated with silver oxide to convert the quaternary ammonium iodide to a quaternary ammonium hydroxide, and then heated to allow it to undergo a Hofmann elimination. Once the alkene product is identified, working backward gives the structure of the amine. Identify the amine in each of the following cases:

**a.** 4-Methyl-2-pentene is obtained from the Hofmann degradation of a primary amine.

**b.** 3-Methyl-1-butene is obtained from the Hofmann degradation of a primary amine.

**c.** 2-Methyl-1-3-butadiene is obtained from two successive Hofmann degradations of a secondary amine.

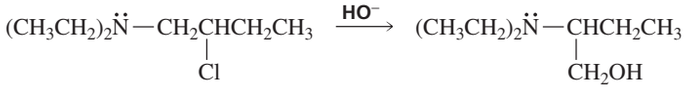
**88.** An ion with a positively charged nitrogen atom in a three-membered ring is called an aziridinium ion. The following aziridinium ion reacts with sodium methoxide to form compounds **A** and **B**:




aziridinium ion

If a small amount of aqueous $Br_2$ is added to **A,** the reddish color of $Br_2$ persists, but the color disappears when $Br_2$ is added to **B.** When the aziridinium ion reacts with methanol, only **A** is formed. Identify **A** and **B.**

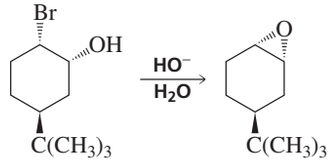
**89.** The following reaction takes place several times faster than the reaction of 2-chlorobutane with $HO^-$:

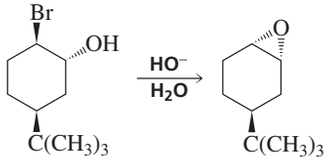


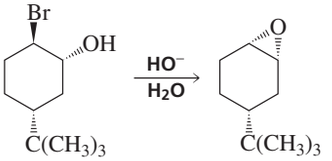

**a.** Explain the enhanced reaction rate.

**b.** Explain why the OH group in the product is not bonded to the carbon that was bonded to the Cl group in the reactant.

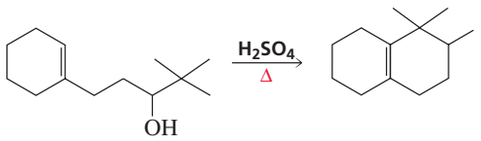
**90.** Which of the following reactions occurs most rapidly?

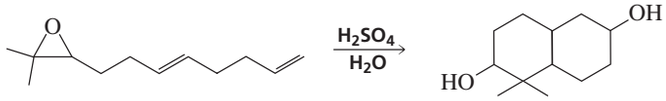
A 

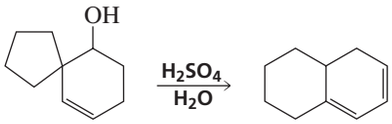

B 


C 

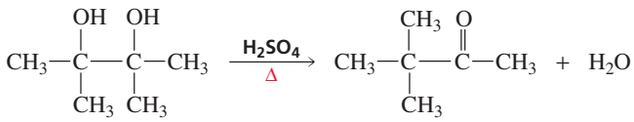

**91.** Propose a mechanism for each of the following reactions:

**a.** 


**b.** 


**c.** 

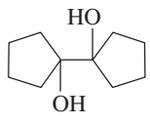

**92.** A vicinal diol has OH groups on adjacent carbons. The dehydration of a vicinal diol is accompanied by a rearrangement called the **pinacol rearrangement.** Propose a mechanism for this reaction.



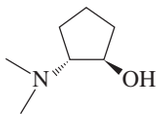

**93.** Although 2-methyl-1,2-propanediol is an unsymmetrical vicinal diol, only one product is obtained when it is dehydrated in an acidic solution.

**a.** What is this product? **b.** Why is only one product obtained?

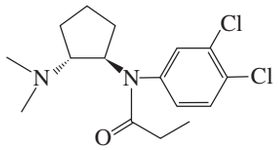
**94.** What product is obtained when the following vicinal diol is heated in an acidic solution?




**95.** Two stereoisomers are obtained from the reaction of cyclopentene oxide and dimethylamine. The *R,R*-isomer is used in the manufacture of eclanamine, an antidepressant. What other isomer is obtained?

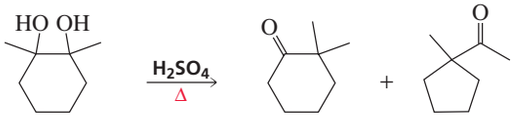


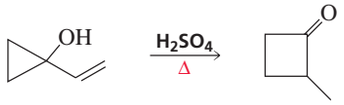

***R,R*-isomer**




**eclanamine**

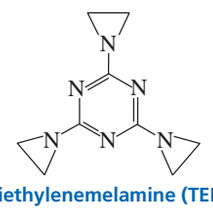
**96.** Propose a mechanism for each of the following reactions:

**a.** 


**b.** 


**97.** Triethylenemelamine (TEM) is an antitumor agent. Its activity is due to its ability to cross-link DNA.

**a.** Explain why it can be used only under slightly acidic conditions.
**b.** Explain why it can cross-link DNA.




**triethylenemelamine (TEM)**