provide better control of the reaction and a higher yield is a common strategy in organic synthesis.

**PROBLEM 10.3**
On the basis of the bond cleavage shown for this reaction in Figure 10.1, predict the stereochemistry of the product. Explain.

PROBLEM 10.4
Show the products of these reactions:

a) \[ \text{Cl} \xrightarrow{\text{CH}_3\text{CO}_2^-\text{DMSO}} \text{NaOH} \xrightarrow{\text{H}_2\text{O}} \]

b) \[ \text{Br} \xrightarrow{\text{CH}_3\text{CO}_2^-\text{DMF}} \text{KOH} \xrightarrow{\text{H}_2\text{O}} \]

10.3 **Preparation of Ethers**

Ethers can be prepared by using an alcohol or its conjugate base, an alkoxide ion, as the nucleophile. A general equation for the reaction with alkoxide ion is

\[ \text{R}^-\text{O}^-\text{L} + \text{R}'\text{L} \xrightarrow{\text{S_N}_2} \text{R}^-\text{O}^-\text{R}' + :\text{L} \]

When an alkoxide ion is used as the nucleophile, the reaction is called a **Williamson ether synthesis**. Because the basicity of an alkoxide ion is comparable to that of hydroxide ion, much of the discussion about the use of hydroxide as a nucleophile also applies here. Thus, alkoxide ions react by the S_N_2 mechanism and are subject to the usual S_N_2 limitations. They give good yields with primary alkyl halides and sulfonate esters but are usually not used with secondary and tertiary substrates because elimination reactions predominate.

The alkoxide ion nucleophile is often prepared from the alcohol by reaction with sodium metal, as shown in the following equation for the formation of ethoxide ion from ethanol:

\[ 2 \text{CH}_3\text{CH}_2\text{O}^-\text{H} + 2 \text{Na}^- \xrightarrow{} 2 \text{CH}_3\text{CH}_2\text{O}^-\text{Na}^+ + \text{H}^-\text{H} \]

Because phenols are stronger acids than alcohols, nucleophilic phenoxide ions can be prepared by reacting the phenol with bases such as hydroxide ion or carbonate ion.
Several examples of the Williamson ether synthesis are given in the following equations:

\[
\text{ROH} + \text{K}_2\text{CO}_3 \rightarrow \text{RO}^- \text{K}^+ + \text{KHCO}_3
\]

In equations like this, the reagents over the arrow are added in a sequence of separate steps, not all at once. Thus, in step 1, sodium metal is added to excess hexanol, which is both a reactant and the solvent for the reaction. Only after the reaction of the sodium and the alcohol is complete and the conjugate base of the alcohol has formed is the reagent shown in step 2 added. In the second step, the alkoxide ion acts as a nucleophile, replacing the leaving group of iodoethane to form the ether.

Important Convention

In equations like this, the reagents over the arrow are added in a sequence of separate steps, not all at once. Thus, in step 1, sodium metal is added to excess hexanol, which is both a reactant and the solvent for the reaction. Only after the reaction of the sodium and the alcohol is complete and the conjugate base of the alcohol has formed is the reagent shown in step 2 added. In the second step, the alkoxide ion acts as a nucleophile, replacing the leaving group of iodoethane to form the ether.
CHAPTER 10  ■  SYNTHETIC USES OF SUBSTITUTION AND ELIMINATION REACTIONS

PROBLEM 10.5
Show the products of these reactions:

\[ \text{a) CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{CH}_3\text{CH}_2\text{O}^- \rightarrow \text{EtOH} \]

\[ \text{b) 1) Na} \rightarrow \text{2) CH}_3\text{I} \]

\[ \text{c) NaOH} \rightarrow \text{EtOH} \rightarrow \text{Cl} \]

PROBLEM 10.6
Diphenhydramine can also be synthesized by heating bromodiphenylmethane with the amino alcohol shown here. Offer a reason why the oxygen, rather than the nitrogen, of this compound acts as the nucleophile. What factor favors the N? What factor favors the O? Which factor is winning in this case?

\[ \text{H}_3\text{C} - \text{NCH}_2\text{CH}_2\text{OH} \]

\[ \text{H}_3\text{C} \]

An unsymmetrical ether can usually be prepared by two different Williamson ether syntheses. For example, the preparation of ethyl isopropyl ether could be accomplished by the reaction of ethoxide ion (nucleophile) with isopropyl bromide (electrophile) or by the reaction of isopropoxide ion (nucleophile) with ethyl bromide (electrophile), as shown in Figure 10.2. Which of these routes is better? Because alkoxide ions are strong

Figure 10.2
TWO POSSIBLE SYNTHESES OF ETHYL ISOPROPYL ETHER.

This reaction has the bromine attached to a secondary carbon. With a strong base like ethoxide ion, the major reaction is elimination (E2) rather than substitution (SN2), resulting in a poor yield of the desired ether.

In contrast, the bromine is attached to a primary carbon in this reaction. Much less elimination occurs, and the yield of the desired ether is higher here than in the other reaction. This is a better method for the synthesis of ethyl isopropyl ether.
bases, an unacceptable amount of elimination occurs if the leaving group is attached to a secondary carbon. Therefore, the route using the primary halide (ethyl bromide) will give a higher yield of the substitution product.

**PROBLEM 10.7**

Explain which route would provide a better synthesis of these ethers:

\[
\begin{align*}
\text{a)} & \quad \text{CH}_3\text{O}^- + \text{CH}_3\text{CCl} & \rightarrow & \text{CH}_3\text{COCH}_3 & \leftarrow & \text{CH}_3\text{I} + \text{CH}_3\text{CO}^- \\
\text{b)} & \quad \text{CH}_2\text{O}^- + \text{Br} & \rightarrow & \text{CH}_2\text{OCHCH}_2\text{CH}_3 & \leftarrow & \text{CH}_2\text{Br} + \text{CH}_3\text{CHCH}_2\text{CH}_3
\end{align*}
\]

**PRACTICE PROBLEM 10.1**

Show a method for synthesizing this ether from an alcohol and an alkyl halide:

\[
\text{OCH}_2\text{CH}_3
\]

**Solution**

To minimize competing elimination by the E2 mechanism, treat the conjugate base of the secondary alcohol with the primary alkyl halide:

\[
\begin{align*}
\text{OH} & \quad \rightarrow & \text{OCH}_2\text{CH}_3 \\
1) \text{Na} & \quad 2) \text{CH}_3\text{CH}_2\text{Br}
\end{align*}
\]

**PROBLEM 10.8**

Suggest a synthesis of these ethers starting with an alcohol and an alkyl halide:

\[
\begin{align*}
\text{a)} & \quad \text{CH}_3\text{OCH}_2\text{CH}_2\text{CH}_3 & \quad \text{b)} & \quad \text{c)}
\end{align*}
\]

Ethers can also be prepared by using alcohols as the nucleophiles:

\[
\text{R}–\text{O}–\text{H} + \text{R}’–\text{L} \rightarrow \text{R}–\text{O}–\text{R}’ + \text{HL}
\]

If the leaving group is bonded to a secondary or tertiary carbon, the reaction usually follows the \( \text{S}_\text{N}1 \) mechanism and is the preferred method in order to avoid problems with
elimination. An alcohol must also be used as the nucleophile when the reaction is run under acidic conditions because alkoxide ions cannot exist in acid. Examples are provided by the following equations. In the first example, in which ethanol is the solvent, the reaction is an **ethanolysis**.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Ph} - \text{C} - \text{Cl} + \text{CH}_3\text{CH}_2\text{OH} \xrightarrow{\text{EtOH}} \text{Ph} - \text{C} - \text{OCH}_2\text{CH}_3 + \text{HCl} \quad (87\%) \\
2\text{OH} & \quad \text{OH} + \text{H}_2\text{SO}_4 \xrightarrow{\text{CH}_3(\text{CH}_2)_4\text{OH}} \text{Dipentyl ether} + \text{H}_2\text{O}
\end{align*}
\]

**PROBLEM 10.9**
Show the products of these reactions:

\[
\begin{align*}
a) \quad \text{Cl} & \xrightarrow{\text{CH}_3\text{OH}} \\
b) \quad \text{CH}_3 & \xrightarrow{\text{H}_2\text{SO}_4} \\
c) \quad \text{Ph}_2\text{CHOH} & + \text{HOCH}_2\text{CH}_2\text{Cl} \xrightarrow{\text{H}_2\text{SO}_4}
\end{align*}
\]

**PROBLEM 10.10**
Show all the steps in the mechanism for the reaction of 1-pentanol with sulfuric acid to form dipentyl ether.

Finally, it is worth noting that the formation of cyclic ethers by intramolecular nucleophilic substitutions is quite favorable if the resulting ring is three, five, or six membered, as shown in the following reactions:
PROBLEM 10.11
Show the steps in the mechanism for the reaction of trans-2-chlorocyclohexanol with sodium hydroxide shown in the previous equation. Explain why cis-2-chlorocyclohexanol does not give a similar reaction.

PROBLEM 10.12
Show the product, including stereochemistry, for this reaction:

PROBLEM 10.13
Because of the acidic conditions, this reaction proceeds by an S_N_1 mechanism. Which hydroxy group acts as the leaving group in the reaction? Show all the steps in the mechanism for this reaction:

10.4 Preparation of Esters

Esters can be prepared by employing carboxylate salts as nucleophiles, as shown in the following equation:

Because carboxylate salts are only weakly basic, elimination is not a problem when the leaving group is attached to a primary or secondary carbon. Several examples are provided in the following equations:

- O

- O

- O

- O
**PROBLEM 10.14**
Show the products of these reactions:

- **a)** 
  \[
  \begin{align*}
  &\text{Br} \\
  &\text{H}_3\text{C} \\
  &\text{CH}_3\text{CO}_2^- \quad \text{DMSO}
  \end{align*}
  \]

- **b)** 
  \[
  \begin{align*}
  &\text{Cl} \\
  &\text{CH}_2=\text{CH}_2 \quad \text{acetone}
  \end{align*}
  \]

- **c)** 
  \[
  \begin{align*}
  &\text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \\
  &\text{DMF}
  \end{align*}
  \]

## 10.5 PREPARATION OF ALKYL HALIDES

The preparation of alkyl halides by substitution reactions usually starts from alcohols because alcohols are widely available. Hydroxide ion is a poor leaving group, so the OH must first be converted into a better leaving group, either by protonation in acid or by conversion to a sulfonate or similar ester (see Section 8.9), as illustrated in the following equations:

- **S_{N}1** mechanism:
  \[
  \begin{align*}
  &\text{R}--\text{O}--\text{H} \quad \text{H}--\text{A} \quad \rightarrow \quad \text{R}--\text{O}--\text{H} \quad \rightarrow \quad \text{R}--\text{X} \quad + \quad \text{H}_2\text{O}
  \end{align*}
  \]

- **S_{N}2** mechanism:
  \[
  \begin{align*}
  &\text{R}--\text{O}--\text{H} \quad \text{R}'\text{SO}_2\text{Cl} \quad \rightarrow \quad \text{R}--\text{O}--\text{SO}_2\text{R}' \quad \rightarrow \quad \text{R}--\text{X} \quad + \quad \text{R}'\text{SO}_3^- \\
  \end{align*}
  \]

Protonation of the alcohol can be accomplished by using the halogen acids, HCl, HBr, and HI, which also provide the nucleophile for the reaction. These reaction conditions favor the \(S_{N}1\) mechanism, although primary alcohols still follow the \(S_{N}2\) path unless a resonance-stabilized carbocation can be formed. The acids HBr and HI work with most alcohols, but HCl, a weaker acid, requires the presence of ZnCl\(_2\) (a Lewis acid) as a catalyst when the alcohol is primary or secondary. Examples are shown in the following equations:

- **a)** 
  \[
  \begin{align*}
  &\text{CH}_3\text{CH}_2\text{CHCH}_3 \quad + \quad \text{HCl} \quad \text{ZnCl}_2 \quad \text{H}_2\text{O} \quad \text{CH}_3\text{CH}_2\text{CHCH}_3 \quad + \quad \text{H}_2\text{O} \quad (65\%)
  \end{align*}
  \]

- **b)** 
  \[
  \begin{align*}
  &\text{CH}_3\text{CHCH}_3 \quad + \quad \text{HCl} \quad \text{H}_2\text{O} \quad \text{CH}_3\text{CHCH}_3 \quad + \quad \text{H}_2\text{O} \quad (88\%)
  \end{align*}
  \]
PRACTICE PROBLEM 10.2

Show all the steps in the mechanism for the reaction of 1-butanol with HBr in water.

Solution

The reactant is a primary alcohol, so the mechanism must be S_N2. First the hydroxy group is protonated. Then bromide ion acts as a nucleophile.

PROBLEM 10.15

Show all the steps in the mechanism for the reaction of 2-methyl-2-butanol with HCl in water.

Conversion of the alcohol into a sulfonate ester followed by an S_N2 substitution using a halide nucleophile is another method that is commonly employed. Examples are provided in the following equations:

The sulfonate ester method requires two steps for the conversion of an alcohol into an alkyl chloride. A reagent that can accomplish this transformation in one step is thionyl chloride, SOCl₂. In a reaction very similar to the formation of sulfonate esters, this reagent replaces the hydrogen of the alcohol with a group that makes the oxygen a
weaker base and a better leaving group. However, this intermediate is not isolated. Instead, it reacts immediately with the nucleophilic chloride ion that is generated during its formation. (The mechanism may be $S_N1$ or $S_N2$, depending on the structure of the compound.) The leaving group then decomposes to sulfur dioxide and chloride ion. The overall process is outlined in Figure 10.3. As shown in the following equations, this procedure results in the formation of alkyl chlorides in good yields. The by-products are $SO_2$ and HCl, both gases, which makes isolation of the alkyl halide easier.

$$\text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{OH} + \text{SOCl}_2 \rightarrow \text{CH}_3(\text{CH}_2)_4\text{CH}_2\text{Cl} + \text{SO}_2(g) + \text{HCl}(g)$$

(61%)

$$\text{OH} + \text{SOCl}_2 \rightarrow \text{Cl} + \text{SO}_2(g) + \text{HCl}(g)$$

(75%)

The reagents PBr$_3$ and PI$_3$ can be used to convert alcohols to alkyl bromides and alkyl iodides in one step. The reactions are very similar to those described for thionyl chloride. First, the oxygen of the alcohol attacks the phosphorus, replacing a halogen.

In a reaction very similar to the formation of a sulfonate ester (see Section 8.9), the oxygen of the alcohol displaces the chlorine. (The mechanism for this part of the reaction may involve more than one step, but the details are not important at this point.) The by-product is hydrogen chloride. This converts the oxygen to the chlorofulfite leaving group:

$$\text{O} + \text{S} \rightarrow \text{Cl}$$

This ion is a good leaving group because it is a weak base, as can be seen by its resemblance to bisulfite ion, the conjugate base of sulfurous acid, which is a moderately strong acid with a $pK_a$ of 1.9:

$$\text{O} \rightarrow \text{S} \rightarrow \text{OH}$$

Bisulfite ion

**Figure 10.3**
Mechanism of the reaction of an alcohol with thionyl chloride to produce an alkyl chloride.
and making the oxygen a better leaving group. Then the halide ion replaces this leaving group to produce the alkyl halide product. Several examples are provided in the following equations:

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} & \xrightarrow{\text{PBr}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} \ (93\%) \\
\text{CH}_3\text{CH}_2\text{CHCH}_3 & \xrightarrow{\text{PBr}_3} \text{CH}_3\text{CH}_2\text{CHCH}_3 \ (90\%) \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} & \xrightarrow{\text{PI}_3} \text{CH}_3\text{CH}_2\text{CH}_2\text{I} \ (90\%)
\end{align*}
\]

A final method sometimes employed to prepare alkyl halides uses an \( S_n2 \) reaction with one halogen as the leaving group and a different halide ion as the nucleophile, as shown in the following general equation:

\[
\begin{align*}
\text{R} & \text{–} \text{X} \xrightarrow{\text{R} \text{–} \text{X}'} \text{R} & \text{–} \text{X}'
\end{align*}
\]

However, this is an equilibrium reaction; the product can react with the displaced halide ion and reform the starting material. If the reaction is to be useful in synthesis, some method must be found to favor the product at equilibrium. If acetone is used as the solvent, the reaction of sodium iodide with alkyl chlorides or bromides can be used to prepare alkyl iodides. In this case the equilibrium favors the alkyl iodide because sodium chloride and sodium bromide (but not sodium iodide) are insoluble in acetone and precipitate, thus driving the equilibrium to the right according to Le Chatelier's principle.

\[
\begin{align*}
\text{CH}_3\text{CHCH}_2\text{C} & \equiv \text{N} + \text{NaI} \ & \xrightarrow{\text{acetone}} \text{CH}_3\text{CHCH}_2\text{C} & \equiv \text{N} + \text{NaBr} (s) \ (96\%)
\end{align*}
\]

**PROBLEM 10.16**

Show the products of these reactions:

a) ![Image](image1)

b) ![Image](image2)

c) ![Image](image3)

d) ![Image](image4)

e) ![Image](image5)

f) ![Image](image6)
PROBLEM 10.17
Suggest reagents that could be used to prepare these alkyl halides from alcohols:

10.6 Preparation of Amines

Ammonia and unhindered amines are good nucleophiles. Therefore, it would appear that amines should be readily prepared by reacting these nucleophiles with the appropriate alkyl halide or sulfonate ester in an S_N2 reaction, according to the following general equations:

\[
\begin{align*}
\text{NH}_3 + \text{R}^\prime \text{L} & \rightarrow \text{R}^+ \text{NH}_3 + \text{L} \\
\text{R}^{\prime}\text{NH}_2 + \text{R}^\prime \text{L} & \rightarrow \text{R}^+ \text{NH}_2\text{R}^\prime + \text{L} \\
\text{R}^{\prime}\text{NH}_2 + \text{R}^\prime \text{L} & \rightarrow \text{R}^+ \text{NH}_2\text{R}^\prime + \text{L} \\
\text{R}^{\prime}\text{NH}_2 + \text{R}^\prime \text{L} & \rightarrow \text{R}^+ \text{NH}_2\text{R}^\prime + \text{L}
\end{align*}
\]

As illustrated in the following reaction, this method provides acceptable yields of tertiary amines, using secondary amines as nucleophiles. Quaternary ammonium salts can also be prepared from tertiary amines as nucleophiles.
However, this reaction is much less useful when ammonia is the nucleophile because the initial product, a primary amine, is a stronger base and a stronger nucleophile than is ammonia. Therefore, the primary amine preferentially reacts as the nucleophile, producing a secondary amine as a by-product (see Figure 10.4). This problem is termed multiple alkylation because more than one alkyl group becomes attached to the nucleophile. Even when a large excess of ammonia is used to favor its reaction as the nucleophile, a significant amount of secondary amine is often formed. For similar reasons the use of a primary amine as the nucleophile results in the formation of a tertiary amine in addition to the desired secondary amine. (However, because of steric effects, a tertiary amine is not a stronger nucleophile than a secondary amine, so multiple alkylation is not a problem when a secondary amine is used as the nucleophile.)

**PROBLEM 10.18**

Show the products of these reactions:

a) \((\text{CH}_3\text{CH}_2)_2\text{NH} + \text{CH}_3\text{CH}_2\text{Br} \xrightarrow{\text{CH}_3\text{OH}}\)

b) \(\text{CH}_3\text{CH}_2\text{NCH}_3 + \text{CH}_3\text{I} \xrightarrow{\text{ether}}\)

---

Ammonia acts as the nucleophile in an S$_\text{N}$2 reaction, replacing the bromine.

In an equilibrium process, the resulting ammonium salt can lose a proton to a base such as ammonia to produce a primary amine. The primary amine is a stronger base and, therefore, a better nucleophile than ammonia.

Even when a large excess of ammonia is present, some of the primary amine reacts to produce a secondary amine.

\[\text{NH}_3 + \text{CH}_2\text{Br}^- \rightarrow \text{CH}_2\text{NH}_2^+ + \text{H}^+\]

In this particular case, in which an eightfold excess of ammonia is used, the product mixture consists of 53% of the primary amine and 39% of the secondary amine.

**Figure 10.4**

Machanism of multiple alkylation using ammonia as a nucleophile.
Because of the problem of multiple alkylation when ammonia reacts with alkyl halides, a multistep method, called the Gabriel synthesis, has been developed to prepare primary amines. This procedure resembles the acetate method for preparing alcohols (Section 10.2) in that carbonyl groups are attached to the nitrogen to decrease its reactivity. After the substitution has been accomplished, the carbonyl groups are removed to provide the desired primary amine. In the Gabriel synthesis the synthetic equivalent for ammonia is phthalimide. (An imide has two carbonyl groups bonded to the nitrogen.) The electrons on the nitrogen of phthalimide are not very basic or nucleophilic because of resonance involving both carbonyl groups:

Therefore, the proton on the nitrogen must be removed to use this nitrogen as a nucleophile. This hydrogen is relatively acidic (pKₐ = 9.9) because of resonance stabilization of the conjugate base, similar to that shown for phthalimide. Hydroxide ion is a strong enough base to remove this proton and generate the conjugate base of phthalimide. The reaction of this nucleophile with an alkyl halide or an alkyl sulfonate ester, by an S_N2 mechanism, produces a substituted phthalimide with an alkyl group bonded to the nitrogen. The electrons on the nitrogen of this alkylated phthalimide are not nucleophilic, so there is no danger of multiple alkylation. The carbonyl groups are then removed to give the desired primary amine in a reaction that is very similar to the ester hydrolysis described in Figure 10.1. The process is outlined in Figure 10.5 and an additional example is provided by the following equation:
The resulting phthalimide anion is a good nucleophile in the $S_{N}2$ reaction. Because of resonance, the electron pair on the nitrogen of phthalimide is not very basic or nucleophilic. The hydrogen on the nitrogen is much more acidic than a hydrogen of a normal amine because the conjugate base is stabilized by resonance. It is acidic enough to be removed completely by a base such as hydroxide ion.

Like phthalimide itself, the alkylated phthalimide is not nucleophilic, so there is no problem with multiple alkylation occurring. The next step of the process is to replace the carbonyl groups on the nitrogen with hydrogens. The desired amine is generated by reaction of the phthalimide with an aqueous base. The conditions are very similar to those of the ester cleavage shown in Figure 10.1. Again, the mechanism begins by attack of a hydroxide ion nucleophile at the electrophilic carbonyl carbon, ultimately breaking the bond between the carbonyl carbon and the nitrogen. (The mechanism for this reaction is covered in detail in Chapter 19.) A similar reaction occurs at the other carbonyl carbon. Overall, phthalimide is a synthetic equivalent for ammonia.

**Focus On Biological Chemistry**

**Biological Alkylations and Poisons**

Many of the reagents that are routinely used as substrates for $S_{N}2$ reactions in the laboratory are poisonous and must be used with caution. These compounds have a leaving group bonded to an unhindered carbon, so they are very reactive toward nucleophiles. They are called *alkylating agents* because they attach an alkyl group to the nucleophile.

Iodomethane is a prime example of a reactive alkylating agent. Because of its lack of steric hindrance and excellent leaving group, it is very reactive toward nucleophiles. Continued
It is a common reagent and often is the first choice when a chemist desires to attach a methyl group to a nucleophile. (Bromomethane and chloromethane might serve as well except that they are gases at room temperature and are therefore much more difficult to handle than liquid iodomethane.) Like the other reactive alkylating agents, iodomethane is poisonous because it reacts with nucleophiles, such as NH₂ and SH groups, in the organism, attaching a methyl group to them. Iodomethane can deactivate an enzyme and interfere with its biological function by alkylating a nucleophile at the active site and changing its nucleophilicity:

\[
\text{Enzyme} + \text{NH}_2 + \text{CH}_3\text{I} \rightarrow \text{Enzyme} + \text{NH}_2\text{CH}_3 + \text{I}^-
\]

In addition, iodomethane and similar reagents can act as carcinogens by alkylating the nitrogens in the bases of DNA. This can change how the base hydrogen bonds, resulting in a mutation.

Benzyl chloride is a powerful lacrimary (tear gas) that is intensely irritating to the skin, eyes, and mucous membranes. (Recall from Section 8.5 that the phenyl group increases the reactivity of this compound toward the S_N_2 mechanism by resonance stabilization of the transition state.) Chloroacetophenone is the active ingredient in mace and is used in tear gas. (Like the phenyl group of benzyl chloride, the carbonyl group of chloroacetophenone greatly increases its reactivity toward nucleophiles.)

One of the most infamous reactive alkylating agents is mustard gas, which was used as a chemical warfare agent during World War I. The sulfur of mustard gas acts as an intramolecular nucleophile to generate a cyclic sulfonium ion that is even more reactive as an alkylating agent. Note that it has two reactive electrophilic sites in each molecule. In heavy doses it can cause blindness and death, but its delayed effects, including cough; respiratory damage; and reddening, itching, and blistering of the skin, are more insidious.

\[
\text{CH}_2\text{Cl} \quad \text{O} \quad \text{C} \quad \text{CH}_2\text{Cl}
\]

Benzyl chloride  Chloroacetophenone
When we desire to attach a methyl group to a nucleophile in the laboratory, we often choose a simple reagent such as iodomethane. Living organisms cannot use this reagent because it is too reactive and too indiscriminate. Iodomethane will react with almost any nucleophile. Nature's iodomethane is a much more complex molecule called S-adenosylmethionine, or SAM. The leaving group in SAM is a disubstituted sulfur atom and confers just the right reactivity on the compound. SAM is used to methylate the nitrogen of norepinephrine in the biosynthesis of epinephrine (adrenaline) and also serves as the methylating agent in the biosynthesis of the important lipid phosphatidylcholine (lecithin) from phosphatidylethanolamine.

![Chemical structures of norepinephrine, epinephrine, and related compounds.](image)
PROBLEM 10.19
Show the products of these reactions:

\[
\text{a)} \quad \text{PhCH}_2\text{CH}_2\text{NH}_2 \quad \begin{array}{c}
\text{1) KOH} \\
\text{2) CH}_3\text{(CH}_2\text{)}_4\text{CH}_2\text{Br}
\end{array} \rightarrow \text{NaOH} \quad \text{H}_2\text{O}
\]

\[
\text{b)} \quad \text{PhCH}_2\text{CH}_2\text{NH}_2 \quad \rightarrow \text{NaOH} \quad \text{H}_2\text{O}
\]

PROBLEM 10.20
Suggest a method that could be used to prepare this amine from an alkyl halide:

\[
\text{PhCH}_2\text{CH}_2\text{NH}_2
\]

10.7 Preparation of Hydrocarbons

Hydrocarbons can be prepared by replacing a leaving group with a hydrogen, according to the following general equation. This requires a hydrogen with an unshared pair of electrons and a negative charge, that is, **hydride ion**, as the nucleophile.

\[
\text{H}^- + \text{R}^+ \rightarrow \text{R}^- + \text{H}^+
\]

**Hydride ion**

\[
\begin{array}{c}
\text{Li}^+ \\
\text{H}^- \\
\text{Al}^+ \\
\text{H}^+
\end{array} \quad \begin{array}{c}
\text{H}^- \\
\text{Na}^+ \\
\text{B}^- \\
\text{H}^+
\end{array}
\]

Lithium aluminum hydride  Sodium borohydride

Both lithium aluminum hydride, LiAlH₄, and sodium borohydride, NaBH₄, react as though they contain a nucleophilic hydride ion, although the hydrogens are covalently bonded to the metal atoms, either aluminum or boron. However, hydrogen is more electronegative than either of these metals, resulting in each hydrogen having a partial negative charge. Because of this polarization, the compounds react as sources of hydride ion. Lithium aluminum hydride is a very reactive compound and reacts vigorously (often explosively) with even weakly acidic compounds such as water and alcohols. It must be used in inert solvents such as ethers. Sodium borohydride is much less reactive and is often used in alcohols or alkaline water as solvent. With either reagent the reactions have the usual S_N2 limitations; that is, they work well only when the leaving group is
bonded to a primary or secondary carbon. The following equations provide examples of the use of these reagents to replace a leaving group with hydrogen:

\[
\begin{align*}
&\text{Br} \quad \text{CH}_3(CH_2)_4CHCH_3 + \text{LiAlH}_4 \quad \xrightarrow{\text{Et}_2\text{O}} \quad \text{H} \quad \text{CH}_3(CH_2)_4CHCH_3 \quad (92\%) \\
&\text{PhCH}_2\text{Br} + \text{NaBH}_4 \quad \xrightarrow{(\text{CH}_3\text{OCH}_2\text{CH}_2)_2\text{O}} \quad \text{PhCH}_2\text{H} \quad (86\%)
\end{align*}
\]

**PROBLEM 10.21**
Show the products of these reactions:

a) \[ \text{I} \xrightarrow{\text{LiAlH}_4/\text{ether}} \]

b) \[ \text{CH}_2\text{Br} \quad \xrightarrow{\text{NaBH}_4/\text{CH}_3\text{OH}} \]

### 10.8 FORMATION OF CARBON–CARBON BONDS

Reactions that form carbon–carbon bonds are of great importance in organic synthesis because they enable smaller compounds to be converted to larger compounds. Forming these bonds by nucleophilic substitution reactions requires a carbon nucleophile—a carbanion (carbon anion), as shown in the following general equation:

\[
\text{R}^- + \text{R}^– \text{L} \quad \xrightarrow{\text{S}_\text{N}2} \quad \text{R}^– \text{R} + \text{:L}^–
\]

Two useful carbon nucleophiles are introduced in this section. Other important carbon nucleophiles are discussed in later chapters, especially Chapter 20.

The first of these carbon nucleophiles, cyanide ion, is a moderate base and a good nucleophile:

\[
\overset{\text{C} = \text{N}}{\text{Cyanide ion}}
\]

Cyanide ion reacts by the S_n2 mechanism and aprotic solvents are often employed to increase its reactivity. Yields of substitution products are excellent when the leaving group is attached to a primary carbon. Because of competing elimination reactions, yields are lower, but still acceptable, for secondary substrates. As expected for an S_n2 process, the reaction does not work with tertiary substrates. Substitution with cyanide ion adds one carbon to the compound while also providing a new functional group for additional synthetic manipulation. Some examples are given in the following equations:

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{Cl} + \overset{\text{Na}}{\text{C} = \text{N}} \quad \xrightarrow{\text{DMSO}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{C} = \text{N}^- + \text{NaCl} \quad (92\%)
\]
A second group of important carbon nucleophiles are the acetylide anions. These nucleophiles are generated by treating 1-alkynes with a very strong base, such as amide ion:

\[
R\overset{\text{C}}{\equiv}C\overset{\text{H}}{\rightarrow}\overset{\text{NH}_2}{\longrightarrow}\overset{\text{NH}_3}{\leftarrow}\overset{\text{C}}{\equiv}C:R
\]

As discussed in Chapter 4, a proton on a carbon–carbon triple bond is relatively acidic (\(pK_a = 25\)) because of the \(sp^3\) hybridization of the carbon to which it is bonded. The proton is acidic enough that it can be removed with some of the strong bases that are available to the organic chemist. Usually, sodium amide (NaNH\(_2\)), the conjugate base of ammonia (\(pK_a = 38\)), often in liquid ammonia as the solvent, is used to remove the proton. Amide ion is a strong enough base so that the equilibrium in the above equation lies entirely to the right. (Note that carbanions generated by removing protons from \(sp^3\) and \(sp^2\)-hybridized carbons are not generally available for use as nucleophiles in \(S_N2\) reactions because the protons attached to them are not acidic enough to be removed in this manner.)

Because acetylide anions are strong nucleophiles, they react by the \(S_N2\) mechanism. Good yields of substitution products are obtained only when the leaving group is attached to a primary carbon; secondary substrates give mainly elimination because the anion is also a strong base. Several examples are provided in the following equations. The last example shows how ethyne can be alkylated twice—both hydrogens can be replaced with alkyl groups in sequential steps!
**PROBLEM 10.22**
Show the products of these reactions:

a) ![Chemical structure](image1)

NaCN
DMSO

b) ![Chemical structure](image2)

1) NaNH₂, NH₃ (l)
2) CH₃CH₂CH₂Br

1) NaNH₂
2) CH₃I

c) ![Chemical structure](image3)

d) ![Chemical structure](image4)

1) NaNH₂, NH₃ (l)
2) CH₃CH₂Br

e) ![Chemical structure](image5)

1) NaNH₂
2) CH₃I

f) ![Chemical structure](image6)

**PROBLEM 10.23**
Suggest methods for preparing these compounds from alkyl halides:

a) ![Chemical structure](image7)

b) ![Chemical structure](image8)

c) ![Chemical structure](image9)

**10.9 PHOSPHORUS AND SULFUR NUCLEOPHILES**

Sulfur occurs directly beneath oxygen in the periodic table. Therefore, sulfur compounds are weaker bases but better nucleophiles than the corresponding oxygen compounds. Sulfur compounds are excellent nucleophiles in $S_N2$ reactions, and because they are relatively weak bases, elimination reactions are not usually a problem. Yields are good with primary and secondary substrates. For similar reasons, phosphorus compounds also give good yields when treated with primary and secondary substrates in $S_N2$ reactions. The following equations provide examples of the use of these nucleophiles:

$$\text{CH}_3\text{S}^- + \text{Cl}^-\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{ethanol}} \text{CH}_3\text{S}^-\text{CH}_2\text{CH}_2\text{OH} + \text{Cl}^- (80\%)$$
Triphenylphosphine is probably the most important phosphorus nucleophile for organic chemists because it produces phosphonium salts (see the preceding two equations). These phosphonium salts are starting materials for an important preparation of alkenes that will be discussed in Chapter 18.

**Problem 10.24**
Show the products of these reactions:

a) \[ \text{Cl} \quad \text{PhS}^- \quad \text{Na}^+ \quad \text{CH}_3\text{OH} \quad \xrightarrow{\text{benzene}} \quad \text{Ph}_3\text{P}^+ \quad \text{CH}_3\text{CH}_2\text{Br} \quad \xrightarrow{\text{ethanol}} \]

b) \[ \text{Ph}_3\text{P}^+ \quad \text{CH}_3\text{CH}_2\text{Br} \quad \xrightarrow{\text{benzene}} \quad \text{Ph}_3\text{P}^+\text{CH}_3\text{Br}^- \quad (99\%) \]

Triphenylphosphine is probably the most important phosphorus nucleophile for organic chemists because it produces phosphonium salts (see the preceding two equations). These phosphonium salts are starting materials for an important preparation of alkenes that will be discussed in Chapter 18.

**10.10 Ring Opening of Epoxides**

Section 8.9 discussed the generation of a leaving group, water, from an alcohol by protonation of the oxygen of the hydroxyl group. In a similar fashion, protonation of the oxygen of an ether also generates a leaving group—an alcohol in this case—as shown in the following equation:

\[ \text{R} - \overset{\text{O}}{\text{O}} - \text{R}' \quad \xrightarrow{\text{H}} \quad \text{R} - \overset{\text{H}}{\text{O}} - \text{R}' \quad \xrightarrow{\text{Nu}} \quad \text{R} - \overset{\text{O}}{\text{H}} + \text{R}' - \text{Nu} \]

This reaction requires more vigorous conditions than the reaction of alcohols, resulting in low yields in many cases. For this reason the reaction is not commonly used in synthesis. An epoxide (also known as an oxirane) is a three-membered cyclic ether:

Like cyclopropane, epoxides have a large amount of ring strain and are much more reactive than normal ethers. Because of this ring strain, one carbon–oxygen bond of an
Epoxide can be broken in a nucleophilic substitution reaction. The following equation shows an example:

Both of the carbons of the epoxide ring are electrophilic, so at first glance, either might be expected to react with the nucleophile, methoxide ion. However, reactions of epoxides under basic or neutral conditions, as in this case, usually follow an $S_N2$ mechanism. Therefore, the nucleophile reacts at the less hindered secondary carbon, with inversion of configuration.

In the preceding reaction the leaving group ($RO^-$) is a very strong base. As discussed in Chapter 8, $HO^-$ and $RO^-$ are much too basic to act as leaving groups in normal nucleophilic substitution reactions. In the special case of epoxides, however, even $RO^-$ can act as a leaving group because of the large amount of strain that is relieved when the carbon–oxygen bond is broken and the ring is opened.

Nucleophilic ring opening of epoxides can also be accomplished in acid solution. The oxygen is first protonated, making it a much better leaving group. Although these are typical $S_{N1}$ conditions, the actual mechanism is somewhere between $S_{N1}$ and $S_{N2}$—the reaction has characteristics of both mechanisms. The stereochemistry is that predicted for an $S_{N2}$ mechanism; the nucleophile approaches from the side opposite the leaving oxygen. The regiochemistry is that predicted for an $S_{N1}$ mechanism; the substitution occurs at the carbon that would be more stable as a carbocation. This often results in the carbon–oxygen bond that is broken under acidic conditions being different from the one that is broken under basic conditions, as can be seen by comparing the product in the following reaction with the one from the preceding reaction:

Another example, in which it can be seen that the reaction proceeds with inversion of configuration, is provided in the following reaction:

Because such reactions have features of both the $S_{N2}$ mechanism (stereochemistry) and the $S_{N1}$ mechanism (regiochemistry), they are said to follow a borderline $S_{N2}$ mechanism. The transition state geometry resembles that for an $S_{N2}$ reaction, but the bond to the leaving group is broken to a greater extent than the bond to the nucleophile is formed, resulting in considerable positive charge buildup on the carbon. Therefore, the transition state that has
this positive charge buildup on the carbon that would be the more stable carbocation is favored. The two possible transition states for the preceding reaction are as follows:

This transition state has a buildup of positive charge on the primary carbon, where it is less stable. As a result, no product is observed from this transition state.

This transition state has a buildup of positive charge on the carbon attached to the phenyl group. The phenyl group helps stabilize the positive charge, making this transition state more stable. The reaction pathway resulting in the observed product proceeds through this transition state.

Other examples of nucleophilic substitutions on epoxides are given in the following equations:

**PROBLEM 10.25**

Show the products of these reactions:

a) \( \text{CH}_3 \) + CH\(_2\)OH \( \xrightarrow{\text{H}_2\text{SO}_4, \text{CH}_3\text{OH}} \) CH\(_3\)O

b) \( \text{O}^- \rightarrow \text{H}_2\text{O} \rightarrow \text{CH}_3\text{OH} \)

c) 1) LiAlH\(_4\), ether  
  2) H\(_2\)O\(^+\), ether
Focus On

Uses of Epoxides in Industry

Epoxides are important intermediates in many industrial processes. For example, the reaction of the simplest epoxide, ethylene oxide, with water is employed to produce ethylene glycol, which is used in antifreeze and to prepare polymers such as Dacron. One method for the preparation of ethylene oxide employs an intramolecular nucleophilic substitution reaction of ethylene chlorohydrin:

\[
\text{Ethylene chlorohydrin} \xrightarrow{\text{Ca(OH)}_2} \text{Ethylene oxide} \xrightarrow{\text{H}_2\text{O}} \text{Ethylene glycol}
\]

Nucleophilic cyanide ion can also be used to open the epoxide ring. This reaction was employed in a now obsolete pathway for the preparation of acrylonitrile, which is used to make Orlon:

\[
\text{Acrylonitrile}
\]

Propranolol, a drug that is used to lower blood pressure, is prepared from the epoxide epichlorohydrin. First, the oxygen of 1-naphthol displaces the chlorine of epichlorohydrin in an S_N2 reaction. Then the epoxide ring is opened by the nucleophilic nitrogen of isopropylamine in another S_N2 reaction to form propranolol.
Elimination reactions are a useful method for the preparation of alkenes, provided that certain limitations are recognized. One problem is the competition between substitution and elimination. The majority of eliminations are done under conditions that favor the E2 mechanism. In these cases, steric hindrance can be used to slow the competing S_N2 pathway. Tertiary substrates and most secondary substrates give good yields of the elimination product when treated with strong bases. Sterically hindered bases can be employed with primary substrates to minimize substitution.

Another problem that occurs with eliminations is the regiochemistry of the reaction. As we saw in Chapter 9, most eliminations follow Zaitsev’s rule and produce the more highly substituted alkene as the major product. However, a significant amount of the less highly substituted product is also formed. In addition, mixtures of cis and trans isomers are produced when possible, further complicating the product mixture. Because separating a mixture of such isomers is usually a difficult task, elimination reactions are often not the best way to prepare alkenes. (Other methods will be described in subsequent chapters.) However, if only one product can be formed, or if one is expected to greatly predominate in the reaction mixture, then these elimination reactions can be quite useful.

Thus, reaction of an alkyl halide with a strong base can be employed for the preparation of an alkene, provided that a mixture of isomers is not produced. The strong bases that are commonly used for these eliminations are sodium hydroxide, potassium hydroxide, sodium methoxide (NaOCH_3), and sodium ethoxide (NaOCH_2CH_3). Potassium tert-butoxide (t-BuOK) is especially useful with less hindered substrates to avoid competing substitution. Sulfonate esters can also be used as leaving groups. Several examples are shown in the following reactions:

\[
\text{HC≡CCH}_2\text{CHCH}_3 + \text{KOH} \xrightarrow{\text{H}_2\text{O}} \text{HC≡CCH} = \text{CHCH}_3 (91\%)
\]

\[
\text{H}_3\text{C}-\text{C} = \text{CH}_3 + \text{NaOCH}_2\text{CH}_3 \xrightarrow{\text{EtOH}} \text{C}_2\text{H}_5 - \text{C} = \text{CH}_3 (97\%)
\]

\[
\text{CH}_3(\text{CH}_2)_2\text{CH}_2\text{C} = \text{Br} + \text{t-BuOK} \xrightarrow{\text{t-BuOH}} \text{CH}_3(\text{CH}_2)_2\text{CH} = \text{CH}_2 (85\%)
\]

**PROBLEM 10.26**
Show the products of these reactions:

a) \(\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2 + \text{t-BuOK} \xrightarrow{\text{t-BuOH}} \)

b) \( + \text{NaOCH}_2\text{CH}_3 \xrightarrow{\text{EtOH}} \)

c) \( + \text{CH}_3\text{ONa} \xrightarrow{\text{CH}_3\text{OH}} \)

d) \( + \text{KOH} \xrightarrow{\text{H}_2\text{O}} \)
PROBLEM 10.27
Explain whether these elimination reactions would be a good way to prepare these alkenes:

a) \[
\begin{array}{c}
\text{Cl} \\
\text{Cl}
\end{array}
\] + KOH $\xrightarrow{\text{H}_2\text{O}}$ \[
\begin{array}{c}
\text{O}
\end{array}
\]

b) \[
\begin{array}{c}
\text{PhCH}_2\text{CH}_3 \\
\text{Cl}
\end{array}
\] + NaOEt $\xrightarrow{\text{EtOH}}$ PhCH=CHCH$_3$

PROBLEM 10.28
Explain which of these reactions would provide a better synthesis of 2-pentene:

\[
\begin{array}{cccc}
\text{Br} \\
\text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3 + \text{CH}_3\text{O}^- & \xrightarrow{\text{CH}_3\text{OH}} & \text{CH}_3\text{CH}==\text{CHCH}_2\text{CH}_3 \\
\text{Br}
\end{array}
\]

\[
\begin{array}{cccc}
\text{Br} \\
\text{CH}_3\text{CHCH}_2\text{CH}_2\text{CH}_3 + \text{CH}_3\text{O}^- & \xrightarrow{\text{CH}_3\text{OH}} & \text{CH}_3\text{CH}==\text{CHCH}_2\text{CH}_3 \\
\text{Br}
\end{array}
\]

10.12 PREPARATION OF ALKYNES

Alkynes can be prepared from dihaloalkanes by elimination of two molecules of HX. This reaction requires very strongly basic conditions so potassium hydroxide at elevated temperatures or the stronger base sodium amide (NaNH$_2$) is commonly employed. Examples are provided by the following equations:

\[
\begin{array}{cccccc}
\text{Br} & \text{Br} & \text{KOH} & \xrightarrow{\text{EtOH}} & \text{PhC}==\text{CPh} & + \\
\text{PhCH}==\text{CHPh} & + & 2 \text{KOH} & \xrightarrow{\Delta} & \text{PhC}==\text{CPh} & + \\
\text{KOH} & \left[\text{PhCH}==\text{CPh}\right] & \xrightarrow{\text{KOH}} & \text{PhCH}==\text{CH}_2 \\
\end{array}
\]

A vinyl halide

\[
\begin{array}{ccccccc}
\text{Br} & \text{Br} & 3 \text{NaNH}_2 & \xrightarrow{\text{NH}_3(l)} & \text{PhC}==\text{C}^+ \text{Na} & + \\
\text{PhCH}==\text{CH}_2 \\
\text{H}_2\text{O}
\end{array}
\]

In these reactions, elimination of the first molecule of HX results in the formation of a vinyl halide—an alkene with a halogen bonded to one of the carbons of the double bond. A second, more difficult elimination (this is why the strong base is necessary) pro-
duces the triple bond. Therefore, it is not surprising that vinyl halides can also be used to prepare alkynes, as shown in the following reactions:

\[
\text{PhCH}=\text{CH} + \text{KOH} \xrightarrow{\Delta} \text{PhC}≡\text{CH} + \text{H}_2\text{O} + \text{KBr} \quad (67\%)
\]

\[
\text{CH}_2\text{C}=\text{CH}_2 \quad 1) \text{NaNH}_2 \quad 2) \text{HCl} \quad (66\%)
\]

**PROBLEM 10.29**
Show the products of these reactions:

a) \[
\begin{array}{c}
\text{Br} \\
\text{C} \quad \text{CH}_2 \\
\text{CH}_3 \\
\end{array}
\xrightarrow{1) \text{NaNH}_2, \text{NH}_3(l) \quad 2) \text{HCl}} \quad \begin{array}{c}
\text{Br} \\
\text{C} \quad \text{CH}_2 \\
\text{CH}_3 \\
\end{array}
\]

b) \[
\begin{array}{c}
\text{Br} \\
\text{CH} \\
\text{CH}_2 \\
\text{Br} \\
\end{array}
\xrightarrow{2 \text{KOH} \quad \text{EtOH} \quad \Delta} \quad \begin{array}{c}
\text{CH}_3 \\
\text{CH} \\
\text{CH}_2 \\
\text{Br} \\
\end{array}
\]

### 10.13 Dehydration

Section 10.5 described the reaction of alcohols with the halogen acids, HX, to produce alkyl halides. If, instead of a halogen acid, a catalytic amount of sulfuric or phosphoric acid is used, the reaction takes a different pathway and an elimination product is formed. Because water is eliminated, the reaction is termed *dehydration*.

The mechanism for the dehydration of cyclohexanol to produce cyclohexene is shown in Figure 10.6. In general, these reactions follow the E1 mechanism, so tertiary alcohols are more reactive than secondary alcohols. (Note that this is one of the few cases in which the E1 mechanism is favored over the S_N1 mechanism.) At the carbocation stage, there is a competition between substitution and elimination. Under the conditions used for the dehydration reaction, elimination is favored, because there are no good nucleophiles present to cause substitution. The conjugate bases of sulfuric and phosphoric acids (HSO_4^- and H_3PO_4^-) are not very nucleophilic. Only a small amount of acid is needed because the reaction is acid catalyzed; that is, the acid is regenerated in the final step of the mechanism.

The dehydration reaction has some limitations. Because the mechanism is E1 and involves a carbocation, rearrangements are possible. Figure 10.7 shows an example of a dehydration involving a carbocation rearrangement. In addition, the reaction is not
practical when isomeric products can be formed unless there is some factor that causes one product to greatly predominate. As long as these limitations are recognized, the reaction can be useful, as illustrated in the following examples:

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
& \quad \text{CHCH}_3 \\
\text{Cl} & \quad \text{H}_2\text{SO}_4 \quad 120^\circ \text{C} \\
& \quad \text{Cl} \\
& \quad \text{Ph} \quad \text{OH} \\
& \quad \text{H}_3\text{PO}_4 \quad \Delta \\
& \quad \text{Ph} + \text{Ph} \\
\end{align*}
\]

(88%) (4%) (81%)

Figure 10.6
Mechanism of the E1 dehydration of cyclohexanol.

Water leaves, generating a carbocation. This is the E1 mechanism. Substitution by the competing \( S_N^1 \) mechanism is avoided because of the absence of good nucleophiles in the reaction mixture. In contrast, if an acid with a nucleophilic conjugate base, such as HCl, were used, substitution products would be formed.

A weak base in the reaction mixture, such as water, removes a proton to produce the alkene. This step regenerates the acid that was used in (1). Because the acid is not used up, the reaction is catalyzed by acid.

Click Mechanisms in Motion to view the Dehydration of Cyclohexanol.
PROBLEM 10.30
Show the products of these reactions:

\[ \text{a) } \begin{align*} \text{OH} & \xrightarrow{\text{H}_2\text{SO}_4, \Delta} \text{C} \text{H}_3 \\ \text{b) } & \xrightarrow{\text{H}_2\text{CCOH, CH}_3 \Delta} \text{CH}_3 \text{CH}_2 \text{CHCH}_3 \\ \text{c) } & \xrightarrow{\text{CH}_3 \text{OH, CH}_3 \text{CHCH}_3 \Delta} \text{H}_2\text{SO}_4 \end{align*} \]

10.14 Eliminations to Form Carbon–Oxygen Double Bonds; Oxidation Reactions

In beginning chemistry courses, oxidation is defined as a loss of electrons and reduction as a gain in electrons. To use these definitions with covalent compounds, oxidation states must be assigned to all the atoms. Although this can be done for organic compounds, we will use a simpler definition. In an organic chemist’s vocabulary an oxidation is a reaction that results in an increase in oxygen content of the compound and/or a decrease in hydrogen content. Similarly, a reduction is a reaction that results in a de-
crease in oxygen content of the compound and/or an increase in hydrogen content. According to these definitions, the conversion of an alcohol to a carbonyl group

\[
\begin{align*}
    \text{O} & \quad \text{H} \\
    \text{C} & \quad -2 \text{H} \\
    \text{H}
\end{align*}
\]

is an example of an oxidation reaction because two hydrogens are lost during the reaction. The reverse of this reaction, the addition of two hydrogens to the carbon–oxygen double bond, is a reduction.

Oxidation of a primary alcohol produces an aldehyde. Further oxidation of an aldehyde to produce a carboxylic acid occurs readily. Therefore, if it is desired to stop the reaction at the aldehyde stage, special reagents must be employed. Secondary alcohols are oxidized to ketones. Tertiary alcohols are inert to most oxidizing reagents.

To accomplish the preceding reactions, it is necessary to replace the hydrogen on the oxygen with some group that can act as a leaving group—that is, a group that can leave with the bonding pair of electrons. The following equation shows the similarity of this process to the other eliminations presented in this chapter. The difference here is that the “leaving group” is on an oxygen rather than a carbon.
The species that are used as leaving groups in this reaction are most commonly metals in high oxidation states. When the metals leave, taking the electron pair of the metal–oxygen bond with them, they are “reduced.” A large number of oxidation reagents have been developed for use in various situations. Ones based on chromium in the +6 oxidation state are very useful. Three chromium oxidation reagents are listed in Table 10.1 along with two reagents (Ag₂O and KMnO₄) that are effective for the oxidation of aldehydes to carboxylic acids. A simplified mechanism for the oxidation of 2-propanol to 2-propanone with chromic acid, H₂CrO₄, is illustrated in Figure 10.8. Examples of oxidations using these reagents are shown in the following equations:

\[
\begin{align*}
\text{OH} & \quad \text{Na}_2\text{Cr}_2\text{O}_7 \quad \text{H}_2\text{SO}_4 \quad \text{H}_2\text{O} \\
\text{CH}_2\text{CH}_3 & \quad \text{O} \\
\text{CH}_2\text{CH}_3 & \quad \text{Na}_2\text{Cr}_2\text{O}_7 \quad \text{H}_2\text{SO}_4 \quad \text{H}_2\text{O} \\
\text{CH}_2\text{Cl}_2 & \quad \text{CrO}_3 \quad \text{2} \\
\text{CH}_3\text{(CH}_2\text{)Cl}_2 & \quad \text{O} \\
\text{CH}_3\text{(CH}_2\text{)Cl}_2 & \quad \text{CrO}_3 \quad \text{2} \\
\text{H} & \quad \text{(82%)} \\
\text{OH} & \quad \text{(90%)} \\
\text{H} & \quad \text{(93%)} \\
\text{H} & \quad \text{(82%)} \\
\text{H} & \quad \text{(97%)} \\
\text{H} & \quad \text{(84%)} \\
\end{align*}
\]
Show the products of these reactions.

b) $\text{CH}_2\text{Cl}_2$

The products are acetone and chloroform.

a) $\text{OH} \rightarrow \text{CrO}_3$  
\[ \text{H}_2\text{SO}_4, \text{H}_2\text{O} \rightarrow \text{acetone} \]

The products are acetone and chromate.

PROBLEM 10.31
Show the products of these reactions.

a) $\text{OH} \rightarrow \text{CrO}_3$  
\[ \text{H}_2\text{SO}_4, \text{H}_2\text{O} \rightarrow \text{acetone} \]

The products are acetone and chromate.

b) $\text{OH} \rightarrow \text{PCC}$  
\[ \text{CH}_2\text{Cl}_2 \rightarrow \text{acetone} \]

The products are acetone and chloroform.
Focus On

Environmentally Friendly Chemistry
(Green Chemistry)

Chromium in the +6 oxidation state, Cr(VI), is a very important and effective oxidant in the organic laboratory. The major drawback to the use of reagents based on this species is that the product, Cr(III), is toxic. Chromium is just one example of a toxic heavy metal that requires quite expensive disposal procedures.

Is there a more environmentally friendly reagent available to accomplish the oxidation of alcohols? Recently, it has been shown that sodium hypochlorite (NaOCl) in acidic solution is an excellent reagent for the oxidation of secondary alcohols to ketones. Examples are shown in the following equations:

\[
\text{OH} \quad \text{CrO}_2 \cdot 2\text{pyridine} \quad \text{CH}_2\text{Cl}_2 \quad \text{PCC} \quad \text{CH}_2\text{Cl}_2
\]

\[
\text{Ag}_2\text{O} \quad \text{H}_2\text{O} \quad \text{THF}
\]

\[
\text{c)} \quad \text{OH} \quad \text{CH}_2
\]

\[
\text{d)} \quad \text{OH} \quad \text{CH}_2\text{Cl}_2
\]

\[
\text{e)} \quad \text{CH}
\]

Sodium hypochlorite is an inexpensive, environmentally benign reagent that is available in the form of “swimming pool chlorine,” the material that is used to disinfect...
swimming pools. An even more convenient source is laundry bleach, a 5.25% solution of sodium hypochlorite that is available in most grocery stores.

The mechanism for this reaction is thought to involve initial chlorination of the hydroxy group to form an alkyl hypochlorite intermediate. An E2 elimination of HCl from this intermediate produces the ketone:

![Chemical Reaction Diagram](image-url)

The development of environmentally safe reagents that can be used to replace more toxic materials in organic reactions is an area that deserves and is receiving considerable research attention, especially in industrial laboratories. All chemists need to be conscious of the effect on the environment of each reaction that they run.

10.15 The Strategy of Organic Synthesis

A common problem that an organic chemist faces in the laboratory is the lack of availability of a compound. Perhaps the compound is needed to test as a new pharmaceutical or to test a postulated reaction mechanism. If the compound is not available from a chemical supply house, the chemist is faced with the task of synthesizing it. The first step is to check the chemical literature to determine whether anyone else has ever prepared that compound. If the compound has never been prepared or if the reported preparation is difficult or of low yield, the chemist must design a new synthesis of the compound. How does an organic chemist approach such a problem?

The chemist does not begin by considering how to convert some compound that is available into the desired compound, the target. Instead, the question that is asked is “What reaction could I use to make the target compound from a simpler compound?” The simpler compound then becomes the new target compound, and the process is repeated until a commercially available compound is reached. Overall, many steps may be involved in the proposed synthesis. This process of working backward from the target compound is called retrosynthetic analysis. Often, several routes to the target compound can be envisioned. The best route depends on a number of factors, such as the number of steps, the yield of each step, and the overall cost. In fact, which route is “best” often depends on why the compound is needed. When a small amount of the compound is needed in a research laboratory, time is often the most important consideration. In contrast, cost is of utmost importance for a compound that is to be prepared on a large scale for commercial purposes.

Some examples will help clarify this process. Suppose the target is benzylic cyclopentyl ether:

![Chemical Structure](image-url)