9.1 Introduction—Structure and Bonding

- **Alcohols** contain a hydroxy group (OH) bonded to an \( \text{sp}^3 \) hybridized carbon.

\[
\begin{align*}
\text{alcohol} & : R-\overset{\cdot}{\text{O}}-\overset{\cdot}{\text{H}} \\
\text{ether} & : R-\overset{\cdot}{\text{O}}-\overset{\cdot}{\text{R}} \\
\text{epoxide} & : \overset{\cdot}{\text{O}}-\overset{\cdot}{\text{C}}=\overset{\cdot}{\text{C}}-\overset{\cdot}{\text{O}}
\end{align*}
\]
Compounds having a hydroxy group on a $sp^2$ hybridized carbon—enols and phenols—undergo different reactions than alcohols.

- **Ethers** have two alkyl groups bonded to an oxygen atom.

  - Ether
    - R–O–R
    - Symmetrical ether: $\text{CH}_3\text{CH}_2\text{O}–\text{CH}_2\text{CH}_3$
    - Unsymmetrical ether: $\text{CH}_3–\text{O}–\text{CH}_2\text{CH}_3$
    - R groups are the same.
    - R groups are different.

- Epoxides are ethers having the oxygen atom in a three-membered ring. Epoxides are also called oxiranes.

  - Epoxide or oxirane
  - An epoxide is a special type of ether.

- The C–O–C bond angle for an epoxide must be $60^\circ$, a considerable deviation from the tetrahedral bond angle of $109.5^\circ$. Thus, epoxides have angle strain, making them more reactive than other ethers.
9.2 Structure and Bonding

- The oxygen atom in alcohols, ethers and epoxides is sp³ hybridized. Alcohols and ethers have a bent shape like that in H₂O.
- The bond angle around the O atom in an alcohol or ether is similar to the tetrahedral bond angle of 109.5°.
- Because the O atom is much more electronegative than carbon or hydrogen, the C—O and O—H bonds are all polar.

\[ \text{sp}^3 \text{ hybridized} \]
\[ \text{CH}_3\overset{\text{O}}{\text{H}} \quad 109^\circ \]

\[ \text{sp}^3 \text{ hybridized} \]
\[ \text{CH}_3\overset{\text{O}}{\text{CH}_3} \quad 111^\circ \]

9.3 Nomenclature of Alcohols

**How To** Name an Alcohol Using the IUPAC System

**Example** Give the IUPAC name of the following alcohol:

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

**Step [1]** Find the longest carbon chain containing the carbon bonded to the OH group.

- Change the ending of the parent alkane to the suffix -ol.

**Step [2]** Number the carbon chain to give the OH group the lower number, and apply all other rules of nomenclature.

<table>
<thead>
<tr>
<th>a. Number the chain.</th>
<th>b. Name and number the substituents.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ \text{CH}_3\text{OH} ]</td>
<td>[ \text{CH}_3\text{OH} ]</td>
</tr>
<tr>
<td>[ \text{CH}_2\text{CH}_2\text{OH} ]</td>
<td>[ \text{CH}_3\text{OH} ]</td>
</tr>
<tr>
<td>[ \text{CH}_2\text{CH}_2\text{OH} ]</td>
<td>[ \text{CH}_3\text{OH} ]</td>
</tr>
<tr>
<td>Number the chain to put the OH group at C₅, not C₄.</td>
<td>3-Hexanol</td>
</tr>
<tr>
<td>Answer: 3-methyl-2-hexanol</td>
<td>5, 3</td>
</tr>
</tbody>
</table>

**6 Cs in the longest chain**

**6 Cs** → hexane → hexanol
• When an OH group is bonded to a ring, the ring is numbered beginning with the OH group.
• Because the functional group is at C1, the 1 is usually omitted from the name.
• The ring is then numbered in a clockwise or counterclockwise fashion to give the next substituent the lowest number.

Figure 9.2 Examples: Naming cyclic alcohols

- 3-methylcyclohexanol
  - The OH group is at C1; the second substituent (CH₃) gets the lower number.

- 2,5,5-trimethylcyclohexanol
  - The OH group is at C1; the second substituent (CH₃) gets the lower number.

• Common names are often used for simple alcohols. To assign a common name:
  - Name all the carbon atoms of the molecule as a single alkyl group.
  - Add the word alcohol, separating the words with a space.

isopropyl alcohol

a common name
• Compounds with two hydroxy groups are called diols or glycols. Compounds with three hydroxy groups are called triols and so forth.

\[
\text{HOCH}_2\text{CH}_2\text{OH} \quad \text{HOCH}_2\text{C}—\text{CH}_2\text{OH} \\
\text{ethylene glycol} (1,2-ethanediol) \quad \text{glycerol} (1,2,3-propanetriol)
\]

Common names are usually used for these simple compounds.

\[
\begin{align*}
\text{HO}_2\text{C}—\text{CH}_2\text{OH} \\
\text{two OH groups}
\end{align*}
\]

Numbers are now needed to show the location of two OH groups.

---

9.3B Naming Ethers

• Simple ethers are usually assigned common names. To do so:
  - Name both alkyl groups bonded to the oxygen, arrange these names alphabetically, and add the word ether.
  - For symmetrical ethers, name the alkyl group and add the prefix “di-”.

\[
\begin{align*}
\text{CH}_3—\text{O—CH}_3 & \quad \text{CH}_3—\text{O—CH}_2\text{CH}_3 \\
methyl & \quad \text{sec-butyl methyl ether}
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3\text{CH}_2—\text{O—CH}_2\text{CH}_3 & \quad \text{CH}_3\text{CH}_2—\text{O—CH}_3 \\
\text{ethyl} & \quad \text{diethyl ether}
\end{align*}
\]

\[\text{Alphabetize the } b \text{ of butyl before the } m \text{ of methyl.}\]
• More complex ethers are named using the IUPAC system. One alkyl group is named as a hydrocarbon chain, and the other is named as part of a substituent bonded to that chain:
  - Name the simpler alkyl group as an alkoxy substituent by changing the –yl ending of the alkyl group to –oxy.
  - Name the remaining alkyl group as an alkane, with the alkoxy group as a substituent bonded to this chain.

![Common alkoxy groups](image)

- CH₃O⁻ methoxy
- CH₃CH₂O⁻ ethoxy
- CH₃⁻CH₂⁻CH₃ tert-butoxy

• Cyclic ethers have an O atom in the ring. A common example is tetrahydrofuran (THF).

9.3C Naming Epoxides

• Epoxides can be named in three different ways—As epoxyalkanes, oxiranes, or alkene oxides.

• To name an epoxide as an epoxyalkane, first name the alkane chain or ring to which the O atom is attached, and use the prefix “epoxy” to name the epoxide as a substituent. Use two numbers to designate the location of the atoms to which the O’s are bonded.

![1,2-epoxycyclohexane](image)

1,2-epoxycyclohexane  1,2-epoxy-2-methylpropane  cis-2,3-epoxypentane
• Epoxides bonded to a chain of carbon atoms can also be named as derivatives of oxirane, the simplest epoxide having two carbons and one oxygen atom in a ring.
• The oxirane ring is numbered to put the O atom at position one, and the first substituent at position two.
• No number is used for a substituent in a monosubstituted oxirane.

Epoxides are also named as alkene oxides, since they are often prepared by adding an O atom to an alkene. To name an epoxide in this way:

- Mentally replace the epoxide oxygen with a double bond.
- Name the alkene.
- Add the word oxide.
9.4 Physical Properties

- Alcohols, ethers and epoxides exhibit dipole-dipole interactions because they have a bent structure with two polar bonds.
- Alcohols are capable of intermolecular hydrogen bonding. Thus, alcohols are more polar than ethers and epoxides.

\[
\begin{align*}
\text{hydrogen bond} \\
\text{Increasing steric hindrance}
\end{align*}
\]

- Steric factors affect hydrogen bonding.

Table 9.1 Physical Properties of Alcohols, Ethers, and Epoxides

<table>
<thead>
<tr>
<th>Property</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boiling point (bp) and melting point (mp)</td>
<td>For compounds of comparable molecular weight, the stronger the intermolecular forces, the higher the bp or mp.</td>
</tr>
<tr>
<td>CH₃CH₂OH</td>
<td>CH₃COCH₂CH₃</td>
</tr>
<tr>
<td>bp 0 °C</td>
<td>bp 11 °C</td>
</tr>
<tr>
<td>Increasing boiling point</td>
<td></td>
</tr>
<tr>
<td>(CH₃)₂C-OH</td>
<td>CH₂CH₂CH₂CH₃</td>
</tr>
<tr>
<td>bp 83 °C</td>
<td>bp 98 °C</td>
</tr>
<tr>
<td>Increasing ability to hydrogen bond</td>
<td></td>
</tr>
</tbody>
</table>

| Solubility | Alcohol, ethers, and epoxides having ≤ 5 C's are H₂O soluble because they each have an oxygen atom capable of hydrogen bonding to H₂O (Section 3.4C). Alcohol, ethers, and epoxides having > 5 C's are H₂O insoluble because the nonpolar alkyl portion is too large to disperse in H₂O. Alcohol, ethers, and epoxides of any size are soluble in organic solvents. |

Key: VDW = van der Waals forces; DD = dipole-dipole; HB = hydrogen bonding
9.5 Interesting Alcohols, Ethers, and Epoxides

Figure 9.3 Ethanol—The alcohol in alcoholic beverages

- Ethanol is the alcohol in red wine, obtained by the fermentation of grapes.

Figure 9.4 Some simple alcohols

- Methanol (CH₃OH) is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.

- 2-Propanol [(CH₃)₂CHOH] is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, 2-propanol is used to clean skin before minor surgery and to sterilize medical instruments.

- Ethylene glycol (HOCH₂CH₂OH) is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.15. It is sweet tasting but toxic.
9.5B Interesting Ethers

The ability of crown ethers to complex cations can be exploited in nucleophilic substitution reactions, as shown in Figure 9.5.

Figure 9.5 The use of crown ethers in nucleophilic substitution reactions

KCN is insoluble in nonpolar solvents alone, but with 18-crown-6:

A rapid nucleophilic substitution reaction occurs in nonpolar solvents when a crown ether is added.
Brevetoxin B is a naturally occurring polyether that interferes with Na⁺ ion transport across cell membranes.

9.5C Interesting Epoxides

- periplanone B
  - cockroach sex pheromone
- epothilone B
  - anticancer drug
9.6 Preparation of Alcohol, Ethers, and Epoxides

- Alcohols and ethers are both common products of nucleophilic substitution.

\[
\begin{align*}
\text{nucleophile} & \quad \overset{\text{S}_\text{N}2}{} \quad \text{product} \\
\text{CH}_3\text{CH}_2\text{Br} + \overset{\text{OH}}{} & \rightarrow \text{CH}_3\text{CH}_2\text{OH} \quad \text{alcohol} \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{Cl} + \overset{\text{OCH}_3}{} & \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{OCH}_3 \quad \text{unsymmetrical ether} \\
\text{CH}_3\text{CH}_2\text{Br} + \overset{\text{OCH}_3\text{CH}_3}{} & \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_3\text{CH}_3 \quad \text{symmetrical ether}
\end{align*}
\]

- The preparation of ethers by the method shown in the last two equations is called the **Williamson ether synthesis**.

In theory, unsymmetrical ethers can be synthesized in two different ways; in practice, one path is usually preferred.
• An alkoxide salt is needed to make an ether.
• Alkoxides can be prepared from alcohols by a Brønsted-Lowry acid—base reaction. For example, sodium ethoxide (NaOCH₂CH₃) is prepared by treating ethanol with NaH.

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

an alkoxide nucleophile

• NaH is an especially good base for forming alkoxide because the by-product of the reaction, H₂, is a gas that just bubbles out of the reaction mixture.

• Organic compounds that contain both a hydroxy group and a halogen atom on adjacent carbons are called halohydrins.
• In halohydrins, an intramolecular version of the Williamson ether synthesis can occur to form epoxides.
9.7 General Features—Reactions of Alcohols, Ethers, and Epoxides

- Recall that, unlike alkyl halides in which the halogen atom serves as a good leaving group, the OH group in alcohols is a very poor leaving group.

\[
\begin{align*}
R\text{-}X & \quad + \quad :\text{Nu}^- \\
\rightarrow & \quad R\text{-}\text{Nu} + \quad \text{X}^- & \text{good leaving group} \\
R\text{-}\text{OH} & \quad + \quad :\text{Nu}^- \\
\rightarrow & \quad R\text{-}\text{Nu} + \quad \text{OH}^{-} & \text{poor leaving group}
\end{align*}
\]

- For an alcohol to undergo nucleophilic substitution, OH must be converted into a better leaving group. By using acid, OH can be converted into H₂O, a good leaving group.

\[
\begin{align*}
R\text{-}\text{OH} & \quad + \quad \text{HCl} \quad \text{Strong acid} \\
\rightarrow & \quad R\text{-}\text{H₂} \quad + \quad \text{Cl}^- \quad \text{weak base} & \text{good leaving group}
\end{align*}
\]

9.8 Dehydration of Alcohols to Alkenes

- Dehydration, like dehydrohalogenation, is a β elimination reaction in which the elements of OH and H are removed from the α and β carbon atoms respectively.

\[
\begin{align*}
\text{Dehydration} & \quad \text{C}, \quad \text{OH} \\
\rightarrow & \quad \text{C} = \text{C} + \text{H}_2\text{O} \\
\text{new } \pi \text{ bond} & \quad \text{an alkene} \\
\text{elimination of } \text{H-OH} & \quad \text{formation of } \text{H}_2\text{O}
\end{align*}
\]

- Dehydration is typically carried out using H₂SO₄ and other strong acids, or phosphorus oxychloride (POCl₃) in the presence of an amine base.
9.8A General Features of Dehydration in Acid

• Typical acids used for alcohol dehydration are H₂SO₄ or p-toluenesulfonic acid (TsOH).

Examples

[1] \( \text{CH}_3-\text{C}-(\text{CH}_2)\text{OH} \xrightarrow{\text{H}_2\text{SO}_4} \text{CH}_3-\text{C}=(\text{CH}_2)\text{H} + \text{H}_2\text{O} \)

[2] \( \text{HO-H} \xrightarrow{\text{TsOH}} \text{H} + \text{H}_2\text{O} \)

• More substituted alcohols dehydrate more easily, giving rise to the following order of reactivity.

\[ R\text{CH}_2\text{-OH} \quad 1^\circ \quad R_2\text{CH}\text{-OH} \quad 2^\circ \quad R_3\text{C}\text{-OH} \quad 3^\circ \]

Increasing rate of dehydration

• When an alcohol has two or three \( \beta \) carbons, dehydration is regioselective and follows the Zaitsev rule.
• The more substituted alkene is the major product when a mixture of constitutional isomers is possible.
9.8B The E1 Mechanism for the Dehydration of $2^\circ$ and $3^\circ$ Alcohols

- Secondary and $3^\circ$ alcohols react by an E1 mechanism, whereas $1^\circ$ alcohols react by an E2 mechanism.

**Mechanism 9.1 Dehydration of $2^\circ$ and $3^\circ$ ROH—An E1 Mechanism**

**Step [1]** The O atom is protonated.

- Protonation of the oxygen atom of the alcohol converts a poor leaving group ("OH") into a good leaving group ($\text{H}_2\text{O}$).

**Step [2]** The C–O bond is broken.

- E heterolysis of the C–O bond forms a carbocation. This step is rate-determining because it involves only bond cleavage.

**Step [3]** A C–H bond is cleaved and the new bond is formed.

- A base (such as $\text{HSO}_3^-$ or $\text{H}_2\text{O}$) removes a proton from a carbon adjacent to the carbocation (a $\beta$ carbon). The electron pair in the C–H bond is used to form the new $\alpha$ bond.

- The E1 dehydration of $2^\circ$ and $3^\circ$ alcohols with acid gives clean elimination products without any by-products formed from an $\text{S}_\text{N}1$ reaction.
- Clean elimination takes place because the reaction mixture contains no good nucleophile to react with the intermediate carbocation, so no competing $\text{S}_\text{N}1$ reaction occurs.
- This makes the E1 dehydration of alcohols much more synthetically useful than the E1 dehydrohalogenation of alkyl halides.
9.8C The E2 Mechanism for the Dehydration of 1° Alcohols

- Since 1° carbocations are highly unstable, their dehydration cannot occur by an E1 mechanism involving a carbocation intermediate. Therefore, 1° alcohols undergo dehydration following an E2 mechanism.

**Mechanism 9.2 Dehydration of a 1° ROH—An E2 Mechanism**

**Step [1]** The O atom is protonated.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{D}_{2} \text{SO}_{4} & \\
\rightarrow & \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{D}_{2} \text{O} & \\
\text{H} & \\
\text{SO}_{4}^{-} & \\
\downarrow & \\
\text{proton transfer} & \\
\rightarrow & \\
\text{CH}_{3} & \quad \text{OH} \\
\text{H} & \\
\text{H} & \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{D}_{2} \text{O} & \\
\downarrow & \\
\text{good leaving group} & \\
\end{align*}
\]

- Protonation of the oxygen atom of the alcohol converts a poor leaving group (OH) into a good leaving group (D₂O).

**Step [2]** The C–H and C–O bonds are broken and the σ bond is formed.

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{D}_{2} \text{SO}_{4} & \\
\rightarrow & \\
\text{H} & \quad \text{H} \\
\text{C} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{D}_{2} \text{O} & \\
\text{H} & \\
\text{H} & \\
\text{H} & \\
\text{H} & \\
\text{O} & \\
\text{H} & \\
\text{D}_{2} \text{O} & \\
\downarrow & \\
\text{good leaving group} & \\
\end{align*}
\]

- Two bonds are broken and two bonds are formed in a single step: the base (D₂SO₄ or H₂O) removes a proton from the β carbon, the electron pair in the β C–H bond forms the new σ bond, the leaving group (D₂O) comes off with the electron pair in the C–O bond.

9.8D Le Chatelier’s Principle

- Although entropy favors product formation in dehydration (i.e., one molecule of reactant forms two molecules of product), enthalpy does not, since the σ bonds broken in the reactant are stronger than the σ and π bonds formed in the products.

**Figure 9.6**

The dehydration of CH₃CH₂OH to CH₂=CH₂—An endothermic reaction

**ΔH° Calculation:**

<table>
<thead>
<tr>
<th>Bond Formation</th>
<th>ΔH° (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃CH₂OH</td>
<td>+96</td>
</tr>
<tr>
<td>HCO₂CH₂OH</td>
<td>+88</td>
</tr>
<tr>
<td>Total</td>
<td>+184</td>
</tr>
</tbody>
</table>

**Energy needed to break bonds.**

<table>
<thead>
<tr>
<th>Bond Formation</th>
<th>ΔH° (kcal/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₂=CH₂ = bond</td>
<td>-64</td>
</tr>
<tr>
<td>H=O</td>
<td>-119</td>
</tr>
<tr>
<td>Total</td>
<td>-183</td>
</tr>
</tbody>
</table>

**Energy released in forming bonds.**

\[\Delta H° = +9 \text{ kcal/mol}\]

The reaction is endothermic.
According to Le Châtelier’s principle, a system at equilibrium will react to counteract any disturbance to the equilibrium. One consequence of this is that removing a product from a reaction mixture as it is formed drives the equilibrium to the right, forming more product. Thus, the alkene, which usually has a lower boiling point than the starting alcohol, can be removed by distillation as it is formed, thus driving the equilibrium to the right to favor production of more product.

9.9 Carbocation Rearrangements

- Often, when carbocations are intermediates, a less stable carbocation will be converted into a more stable carbocation by a shift of a hydrogen or an alkyl group. This is called a rearrangement.
- Because the migrating group in a 1,2-shift moves with two bonding electrons, the carbon it leaves behind now has only three bonds (six electrons), giving it a net positive (+) charge.

- Movement of a hydrogen atom is called a 1,2-hydride shift.
- Movement of an alkyl group is called a 1,2-alkyl shift.
• A 1,2-shift can convert a less stable carbocation into a more stable carbocation.

• Rearrangements are not unique to dehydration reactions. Rearrangements can occur whenever a carbocation is formed as a reactive intermediate.

Consider the example below. 2° Carbocation A rearranges to the more stable 3° carbocation by a 1,2-hydride shift, whereas carbocation B does not rearrange because it is 3° to begin with.
9.10 Dehydration of Alcohols Using POCl₃ and Pyridine

- Some organic compounds decompose in the presence of strong acid, so other methods have been developed to convert alcohols to alkenes.
- A common method uses phosphorus oxychloride (POCl₃) and pyridine (an amine base) in place of H₂SO₄ or TsOH.

\[
\text{cyclohexanol} + \text{POCl}_3 + \text{pyridine} \rightarrow \text{cyclohexene} + \text{H}_2\text{O}
\]

- POCl₃ serves much the same role as a strong acid does in acid-catalyzed dehydration. It converts a poor leaving group (°OH) into a good leaving group.
- Dehydration then proceeds by an E2 mechanism.

Mechanism 9.4  Dehydration Using POCl₃ + Pyridine—An E2 Mechanism

Steps (1) and (2)  Conversion of OH to a good leaving group

\[
\text{C}_6\text{H}_{12} \text{OH} + \text{POCl}_3 \rightarrow \text{C}_6\text{H}_{12} \cdot \text{POCl}_3 + \text{HCl}
\]

Step (3)  The C–H and C–O bonds are broken and the new bond is formed.

- A two-step process converts an OH group into OPOCl₂, a good leaving group: reaction of the OH group with POCl₃ followed by removal of a proton.
- Two bonds are broken and two bonds are formed in a single step: the base (pyridine) removes a proton from the β carbon; the electron pair in the β C–H bond forms the new σ bond; the leaving group (OPOCl₂) comes off with the electron pair from the C–O bond.
Two examples of dehydration reactions used in the synthesis of natural products are given in Figure 9.7. Patchouli alcohol, a major component of the essential oil of the patchouli plant native to Malaysia, has been used in perfumery because of its exotic fragrance. In the 1800s, spices imported from India were often packed with patchouli leaves to ward off insects, thus permeating the clothing with the distinctive odor.

9.11 Conversion of Alcohols to Alkyl Halides with HX

- Substitution reactions do not occur with alcohols unless $\text{OH}$ is converted into a good leaving group.

\[ R-OH + X^- \rightarrow \text{alkyl halide} \]

- The reaction of alcohols with HX ($X = \text{Cl, Br, I}$) is a general method to prepare $1^\circ$, $2^\circ$, and $3^\circ$ alkyl halides.

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{OH} + \text{HBr} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} + \text{H}_2\text{O} \]

\[ \text{CH}_3\text{CH}_2\text{OH} + \text{HCl} \rightarrow \text{CH}_3\text{CHCl} + \text{H}_2\text{O} \]
• More substituted alcohols usually react more rapidly with HX:

\[
\begin{align*}
R\text{CH}_2\text{OH} & \quad 1^\circ \\
R_2\text{CH}\text{OH} & \quad 2^\circ \\
R_3\text{C}\text{OH} & \quad 3^\circ 
\end{align*}
\]

[Increasing rate of reaction with HX]

• This order of reactivity can be rationalized by considering the reaction mechanisms involved. The mechanism depends on the structure of the R group.

\[
\begin{align*}
R\text{H} + HX \quad \text{good leaving group} & \quad \text{protonation} \\
\text{RCH}_2\text{H} + X^- \quad \text{good nucleophile} & \quad \text{nucleophilic attack} \\
\rightarrow R-X + H_2O \\
\end{align*}
\]

• Methyl and 1° ROH form RX by an SN2 mechanism.
• Secondary (2°) and 3° ROH form RX by an SN1 mechanism.

9.11A Two Mechanism for the Reaction of ROH with HX

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**Mechanism 9.5** Reaction of a 1° ROH with HX—An SN2 Mechanism

**Step (1)** The O atom is protonated.

\[
\text{CH}_3\text{CH}_2\text{OH} + H_2\text{Br} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{Br} + \text{HBr} \quad \text{(good leaving group)}
\]

• Protonation of the OH group forms a good leaving group (HBr).

**Step (2)** The C-O bond is broken as the C-Br bond is formed.

\[
\text{CH}_3\text{CH}_2\text{Br} + \text{Br}^- \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{Br}^- + \text{H}_2\text{O} \quad \text{(good nucleophile)}
\]

• Nucleophilic attack of Br⁻ and loss of the leaving group occur in a single step.
The reactivity of hydrogen halides increases with increasing acidity.

Because Cl\(^-\) is a poorer nucleophile than Br\(^-\) or I\(^-\), the reaction of 1\(^{\circ}\) alcohols with HCl occurs only when an additional Lewis acid catalyst, usually ZnCl\(_2\), is added. Complexation of ZnCl\(_2\) with the O atom of the alcohol makes a very good leaving group that facilitates the S\(_{\nu2}\) reaction.
Knowing the mechanism allows us to predict the stereochemistry of the products when the reaction occurs at a stereogenic center.

- The 1° alcohol (A) reacts with HBr via an S_N2 mechanism to yield the alkyl bromide (B) with inversion of stereochemistry at the stereogenic center.
- The 3° alcohol (C) reacts with HCl via an S_N1 mechanism to yield a racemic mixture (D and E), because a trigonal planar carbocation intermediate is formed.

---

**9.12 Conversion of Alcohols to Alkyl Halides with SOCl₂ and PBr₃**

- Primary and 2° alcohols can be converted to alkyl halides using SOCl₂ and PBr₃.
- **SOCl₂** (thionyl chloride) converts alcohols into alkyl chlorides.
- **PBr₃** (phosphorus tribromide) converts alcohols into alkyl bromides.
- Both reagents convert OH into a good leaving group in situ—that is, directly in the reaction mixture—as well as provide the nucleophile, either Cl⁻ or Br⁻, to displace the leaving group.
9.12A Reaction of ROH with SOCl₂

• When a 1° or 2° alcohol is treated with SOCl₂ and pyridine, an alkyl chloride is formed, with HCl and SO₂ as byproducts.

\[
\text{General reaction: } \quad R\text{-OH} + \text{SOCl}_2 \xrightarrow{\text{pyridine}} R\text{-Cl} + \text{SO}_2 + \text{HCl}
\]

**Examples**

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{-OH} + \text{SOCl}_2 & \xrightarrow{\text{pyridine}} \text{CH}_3\text{CH}_2\text{-Cl} \\
\text{PhOH} + \text{SOCl}_2 & \xrightarrow{\text{pyridine}} \text{PhCl}
\end{align*}
\]

1° and 2° RCl are formed.

• The mechanism of this reaction consists of two parts: conversion of the OH group into a better leaving group, and nucleophilic cleavage by Cl⁻ via an \( S_N2 \) reaction.

---

**Mechanism 9.7 Reaction of ROH with SOCl₂ + Pyridine—An \( S_N2 \) Mechanism**

Steps [1] and [2]: The OH group is converted into a good leaving group.

\[
\begin{align*}
\text{R-OH} + \text{Cl}^- & \xrightarrow{[1]} \text{R-O}^+ \cdot \text{Cl}^- \\
\text{R-O}^+ \cdot \text{Cl}^- & \xrightarrow{[2]} \text{R-Cl} + \text{OH}^-
\end{align*}
\]

• Reaction of the alcohol with SOCl₂ forms an intermediate that loses a proton by reaction with pyridine in Step [2]. This two-step process converts the OH group into OSOCl, a good leaving group, and also generates the nucleophile (Cl⁻) needed for Step [3].

Step [3]: The \( \text{C-O} \) bond is broken as the \( \text{C-Cl} \) bond is formed.

\[
\text{R-Cl} + \text{SO}_2 + \text{Cl}^- \xrightarrow{[3]} \text{R-C} = \text{O}
\]

• Nucleophilic attack of Cl⁻ and loss of the leaving group (SO₂ + Cl⁻) occur in a single step.
9.12B Reaction of ROH with PBr₃

- Treatment of a 1° or 2° alcohol with PBr₃ forms an alkyl halide.

\[
\text{General reaction} \quad \text{R-OH} + \text{PBr}_3 \rightarrow \text{R-Br} + \text{HOPBr}_2
\]

- The mechanism of this reaction also consists of two parts: conversion of the OH group into a better leaving group, and nucleophilic cleavage by Br⁻ via an S₈2 reaction.

---

**Mechanism 9.8 Reaction of ROH with PBr₃—An S₈2 Mechanism**

**Step (1)** The OH group is converted into a good leaving group.

\[
\text{R-OH} + \text{Br} \rightarrow \text{R-O}^- + \text{Br}^-
\]

- Reaction of the alcohol with PBr₃ converts the OH group into a better leaving group, and also generates the nucleophile (Br⁻) needed for Step (2).

**Step (2)** The C-O bond is broken as the C-Br bond is formed.

\[
\text{R-O}^- + \text{Br} \rightarrow \text{R-Br} + \text{HOPBr}_2
\]

- Nucleophilic attack of Br⁻ and loss of the leaving group (HOPBr₂) occur in a single step.
### Table 9.2 Summary of Methods for ROH → RX

<table>
<thead>
<tr>
<th>Overall reaction</th>
<th>Reagent</th>
<th>Comment</th>
</tr>
</thead>
</table>
| ROH → RCI        | HCl     | • Useful for all ROH  
|                  |         | • An $S_{N}1$ mechanism for 2° and 3° ROH; an $S_{N}2$ mechanism for CH₂OH and 1° ROH |
|                  | SOCl₂   | • Best for CH₂OH, and 1° and 2° ROH  
|                  |         | • An $S_{N}2$ mechanism |
| ROH → RBr        | HBr     | • Useful for all ROH  
|                  |         | • An $S_{N}1$ mechanism for 2° and 3° ROH; an $S_{N}2$ mechanism for CH₂OH and 1° ROH |
|                  | PBr₃    | • Best for CH₂OH, and 1° and 2° ROH  
|                  |         | • An $S_{N}2$ mechanism |
| ROH → RI         | HI      | • Useful for all ROH  
|                  |         | • An $S_{N}1$ mechanism for 2° and 3° ROH; an $S_{N}2$ mechanism for CH₂OH and 1° ROH |

---

### 9.13 Tosylate—Another Good Leaving Group

- Alcohols can be converted into alkyl tosylates.
- An **alkyl tosylate** is composed of two parts: the alkyl group R, derived from an alcohol; and the tosylate (short for $p$-toluenesulfonate), which is a good leaving group.
- A **tosyl group**, CH₃C₆H₄SO₂⁻, is abbreviated Ts, so an alkyl tosylate becomes ROTs.

![An alkyl tosylate](image)

![Tosyl group](image)

---

[Image]
Alcohols are converted to tosylates by treatment with \( p \)-toluenesulfonyl chloride (TsCl) in the presence of pyridine.

This process converts a poor leaving group (\( \text{\textit{\textbf{\textdegree}} \text{OH} \)) into a good one (\( \text{\textit{\textbf{\textdegree}} \text{OTs} \)).

Tosylate is a good leaving group because its conjugate acid, \( p \)-toluenesulfonic acid (\( \text{CH}_3\text{C}_6\text{H}_4\text{SO}_3\text{H}, \text{TsOH} \)) is a strong acid (\( \text{pK}_a = -7 \)).

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} & \quad + \quad \text{TsCl} \quad \text{pyridine} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{O}^+\text{Ts}^- \quad + \quad \text{TsOH} \\
\text{poor} & \quad \text{leaving group} & \quad \circ & \quad \text{good leaving group}
\end{align*}
\]

(S)-2-Butanol is converted to its tosylate with retention of configuration at the stereogenic center. Thus, the \( \text{C—O} \) bond of the alcohol is not broken when tosylate is formed.

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} & \quad + \quad \text{TsCl} \quad \text{pyridine} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O}^+\text{Ts}^- \quad + \quad \text{TsOH} \\
\text{(S)-2-butanol} & \quad \circ & \quad \text{S configuration}
\end{align*}
\]
Because alkyl tosylates have good leaving groups, they undergo both nucleophilic substitution and β elimination, exactly as alkyl halides do.

Generally, alkyl tosylates are treated with strong nucleophiles and bases, so the mechanism of substitution is $S_{N2}$, and the mechanism of elimination is $E2$.

Because substitution occurs via an $S_{N2}$ mechanism, inversion of configuration results when the leaving group is bonded to a stereogenic center.

We now have another two-step method to convert an alcohol to a substitution product: reaction of an alcohol with TsCl and pyridine to form a tosylate (step 1), followed by nucleophilic attack on the tosylate (step 2).
• Step 1, formation of the tosylate, proceeds with retention of configuration at a stereogenic center.
• Step 2 is an $S_N2$ reaction, so it proceeds with inversion of configuration because the nucleophile attacks from the backside.
• Overall there is a net inversion of configuration at a stereogenic center.

Example:

![Chemical diagram](image1)

**Figure 9.8** Summary: Nucleophilic substitution and β elimination reactions of alcohols

![Chemical diagram](image2)
9.14 Reaction of Ethers with Strong Acid

- In order for ethers to undergo substitution or elimination reactions, their poor leaving group must first be converted into a good leaving group by reaction with strong acids such as HBr and HI. HBr and HI are strong acids that are also sources of good nucleophiles (Br⁻ and I⁻ respectively).
- When ethers react with HBr or HI, both C—O bonds are cleaved and two alkyl halides are formed as products.

\[
\text{General reaction: } \quad \text{R—O—R'} + \text{H—X} \quad (X = \text{Br or I}) \rightarrow \text{R—X} + \text{R’—X} + \text{H}_2\text{O}
\]

- Two C—O bonds are broken.
- Two new C—X bonds are formed.

**Examples**

\[
\text{CH}_3\text{O—CH}_2\text{CH}_3 + \text{HBr} \rightarrow \text{CH}_3\text{—Br} + \text{CH}_3\text{CH}_2\text{—Br} + \text{H}_2\text{O}
\]

\[
\text{CH}_3\text{O—CH}_3 + \text{HI} \rightarrow \text{CH}_3\text{—I} + \text{CH}_3\text{—I} + \text{H}_2\text{O}
\]

- The mechanism of ether cleavage is $S_{N1}$ or $S_{N2}$, depending on the identity of R.
- When $2^\circ$ or $3^\circ$ alkyl groups are bonded to the ether oxygen, the C—O bond is cleaved by an $S_{N1}$ mechanism involving a carbocation. With methyl or $1^\circ$ R groups, the C—O bond is cleaved by an $S_{N2}$ mechanism.

Example: In the reaction of (CH$_3$)$_3$COCH$_3$ with HI, the $3^\circ$ alkyl group undergoes nucleophilic substitution by an $S_{N1}$ mechanism, resulting in the cleavage of one C—O bond. The methyl group undergoes nucleophilic substitution by an $S_{N2}$ mechanism, resulting in the cleavage of the second C—O bond.
9.15 Reactions of Epoxides

- Recall that epoxides do not contain a good leaving group.
- Epoxides do contain a strained three-membered ring with two polar bonds.
- Nucleophilic attack opens the strained three-membered ring, making it a favorable process even with a poor leaving group.
• The reaction occurs readily with strong nucleophiles and with acids like HZ, where Z is a nucleophilic atom.

![Reaction with a strong nucleophile](image1)

![Reaction with HZ](image2)

• Virtually all strong nucleophiles open an epoxide ring by a two-step reaction sequence:

![General reaction](image3)

• In step 1, the nucleophile attacks an electron-deficient carbon, thus cleaving the C—O bond and relieving the strain of the three-membered ring.
• In step 2 the alkoxide is protonated with water to generate a neutral product with two functional groups on adjacent atoms.
• Common nucleophiles that open the epoxide ring include −OH, −OR, −CN, −SR and NH₃. With these strong nucleophiles, the reaction occurs by an S_N2 mechanism.
Consider the following real examples:

- The nucleophile opens the epoxide ring from the back side.

Let's now consider the stereochemical consequences of the reaction of 1,2-epoxycyclohexane with $\text{OCH}_3^-$.

Nucleophilic attack of $\text{OCH}_3^-$ occurs from the backside at either C-O bond, because both ends are similarly substituted. Since attack at either side occurs with equal probability, an equal amount of the two enantiomers (i.e., a racemic mixture) is formed.
Optically inactive starting materials give optically inactive products!

- Acids HZ that contain a nucleophile Z also open epoxide rings by a two-step sequence.
- HCl, HBr and HI, as well as H₂O and ROH in the presence of acid, all open an epoxide ring in this manner.
Ring opening of an epoxide with either a strong nucleophile or an acid HZ is regioselective because one constitutional isomer is the major or exclusive product.

Note that the site selectivity of these two reactions is exactly opposite.

- With a strong nucleophile: $\text{Nu}^-$ attacks at the less substituted carbon.
- With an acid HZ, the nucleophile attacks at the more substituted carbon.
Figure 9.10 The synthesis of two bronchodilators uses the opening of an epoxide ring.

9.17 Important Epoxide Ring Opening Reactions

• When polyaromatic hydrocarbons are inhaled or ingested, they are oxidized in the liver to species that often contain a highly reactive epoxide ring.
• The strained three-membered ring reacts readily with biological nucleophiles such as DNA or enzymes, leading to ring-opened products that often disrupt cell function, causing cancer or cell death.