Chapter 14: Ethers, Epoxides, and Sulfides
Physical Properties

- Ethers can be symmetrical or not:
  - Dimethyl ether
  - Ethyl methyl ether
  - Methyl phenyl ether
- Linear or cyclic.
  - 1,4-Dioxane
  - Tetrahydrofuran (THF)
  - Epoxides
- Ethers are inert and make excellent solvents for organic reactions. **Epoxides are very reactive.**
- Boiling point of ethers is lower than alcohols since there is no hydrogen bonding.
Synthesis of Ethers (Review)

- **Williamson Ether Synthesis** *(14-5)*

\[
\begin{align*}
R\text{--O} & \rightleftharpoons R'\text{--X} \\
\rightarrow & \\
R\text{--O} & \cdot R' + \cdot X^- 
\end{align*}
\]

The alkoxide is commonly made by adding Na, K, or NaH to the alcohol (Section 11-14).

**Examples**

1. **cyclohexanol**
   
   \[
   \text{OH} \xrightarrow{(1) \text{ Na}} \xrightarrow{(2) \text{ CH}_3\text{CH}_2\text{OTs}} \text{OCH}_2\text{CH}_3
   \]
   
   ethoxycyclohexane (92%)

2. **3,3-dimethyl-2-pentanol**
   
   \[
   \text{OH} \xrightarrow{(1) \text{ NaH}} \xrightarrow{(2) \text{ CH}_3\text{I}} \text{OCH}_3
   \]
   
   2-methoxy-3,3-dimethylpentane (90%)
**Alkoxymercuration/Demercuration** (14-6)  
(CHEM201)

![Chemical reaction diagram](https://via.placeholder.com/150)

*Example*

\[ \text{CH}_3(\text{CH}_2)_3\text{CH}═\text{CH}_2 \quad \xrightarrow{(1) \text{Hg(OAc)}_2, \text{CH}_3\text{OH}} \quad \text{CH}_3(\text{CH}_2)_3\text{CH}═\text{CH}_3 \]

\[ \xrightarrow{(2) \text{NaBH}_4} \quad \text{CH}_3(\text{CH}_2)_3\text{CH}═\text{CH}_3 \]

1-hexene  
2-methoxyhexane, 80% (Markovnikov product)
Reactions of Ethers

- Ethers are unreactive (that is why they are good solvents)

- **Acid Cleavage** (14-8)
  
  To react, normal ethers require very drastic acidic conditions. Cleavage will occur. HI and HBr react, HCl does not react.
• The reaction follows two possible mechanisms. Ethers bearing at least one tertiary carbon will follow a $S_N1$ mechanism, those with only primary or secondary carbon on the oxygen follow a $S_N2$ process. (mechanism on next slide)

• Cleavage of ethers by $S_N2$ reaction, will always give the more substituted alcohol and least substituted alkyl halide.

• Cleavage by $S_N1$ will always give a tertiary halide and an alcohol.
$S_{N2}$ Mechanism of Ether Cleavage

$\text{R} \rightarrow \text{O} \quad \text{Br} \quad \text{H} \quad \leftrightarrow \quad \text{R} \quad \text{O} \quad \text{H} \quad \text{Br}^{-}$

$\text{Br}^{-} + \text{O} \quad \text{R} \quad \text{H} \quad \rightarrow \quad \text{Br} \quad \text{R} \quad \text{O} \quad \text{R}^{'}$

$\text{R}^{'} \quad \text{O} \quad \text{H} \quad \text{HBr} \quad \rightarrow \quad \text{R}^{'} \quad \text{Br} \quad + \quad \text{H}_{2}\text{O}$

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*Ethers bearing aromatic groups do not react further. In this case a phenol and alkyl halide is obtained.*

![Diagram](image-url)
Practice Question

- What are the major products of the following reactions? HI is used as the acid.

```
\[ \text{Ph-CH}_2\text{O-Ph} \rightarrow \text{PhCH}_2\text{OH} \]
\[ \text{C}_6\text{H}_{11}\text{O} \rightarrow \text{C}_6\text{H}_{11}\text{OH} \]
\[ \text{C}_6\text{H}_{13}\text{O} \rightarrow \text{C}_6\text{H}_{13}\text{OH} \]
```
• **Sulfides (thioethers)** (14-10)

• Sulfides can be prepared by $S_N2$ reaction of the deprotonated thiol and an alkyl halide.

\[
\text{CH}_3\text{CH}_2\text{S}^- \quad + \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{Br} \quad \rightarrow \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{S}^-\text{CH}_2\text{CH}_3 \quad + \quad \text{Br}^-
\]

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• Similar bases used in the deprotonation of alcohols are needed (Na, K, NaH, KH). Weaker bases will not deprotonate the thiol to the corresponding thiolate anion.

Weaker bases can be used with thiophenol since the proton is more acidic, pKa ~ 9.
Practice Question

• How would you make these sulfides using thiol and an alkyl halide?
Synthesis of Epoxides

- There are two common ways to make epoxides:
  - **Epoxidation of alkenes** (14.11) (CHEM201)

![Reaction Mechanism]

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- **Syn addition**
• **Base promoted cyclization of halohydrins**

• Treatment of the halohydrin with a base results in deprotonation of the hydroxyl. The anion can then attack the carbon bearing the halogen in a $S_N2$ fashion producing the epoxide.

\[
\begin{align*}
\text{C} - \text{C} & + \cdot \text{O} - \text{H} \\
\text{X} & \leftrightarrow \text{C} - \text{C} & \rightarrow \text{C} - \text{C} \\
\text{(X = Cl, Br, I)} & & \text{X}^{-}
\end{align*}
\]

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Treatment of the halohydrin with a base results in deprotonation of the hydroxyl. The anion can then attack the carbon bearing the halogen in a $S_N^2$ fashion producing the epoxide.

\begin{center}
\textit{Formation of the chlorohydrin}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (cyclopentene) at (0,0) {\includegraphics[width=0.2\textwidth]{cyclopentene.png}};
\node (chlorine) at (2.5,0) {\includegraphics[width=0.2\textwidth]{chlorine.png}};
\node (chloronium) at (5,0) {\includegraphics[width=0.2\textwidth]{chloronium.png}};
\node (trans-chlorohydrin) at (7.5,0) {\includegraphics[width=0.2\textwidth]{trans-chlorohydrin.png}};
\node (water) at (0,-1.5) {\includegraphics[width=0.2\textwidth]{water.png}};
\node (H2O) at (2.5,-1.5) {\includegraphics[width=0.2\textwidth]{H2O.png}};
\node (Cl-) at (5,-1.5) {\includegraphics[width=0.2\textwidth]{Cl-.png}};
\node (H+) at (7.5,-1.5) {\includegraphics[width=0.2\textwidth]{H+.png}};
\node (trans-chlorohydrin) at (7.5,-1.5) {\includegraphics[width=0.2\textwidth]{trans-chlorohydrin.png}};
\node (OH-) at (0,-2.5) {\includegraphics[width=0.2\textwidth]{OH-.png}};
\node (alkoxide) at (5,-2.5) {\includegraphics[width=0.2\textwidth]{alkoxide.png}};
\node (epoxide) at (7.5,-2.5) {\includegraphics[width=0.2\textwidth]{epoxide.png}};
\end{tikzpicture}
\end{center}

\begin{center}
\textit{Displacement of the chlorohydrin}
\end{center}

\begin{center}
\begin{tikzpicture}
\node (trans-chlorohydrin) at (0,0) {\includegraphics[width=0.2\textwidth]{trans-chlorohydrin.png}};
\node (alkoxide) at (2.5,0) {\includegraphics[width=0.2\textwidth]{alkoxide.png}};
\node (epoxide) at (5,0) {\includegraphics[width=0.2\textwidth]{epoxide.png}};
\end{tikzpicture}
\end{center}

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Because the base can act as a nucleophile and attack the carbon bearing the halogen directly in a $S_N2$ reaction, large bases (that are not nucleophilic) are usually used to avoid this side reaction.

- diisopropyl amine
- 2,6-lutidine
• Other cyclic ethers (those with 5, 6 or 7-members in the ring) can be prepared following this method, from haloalcohols.
Practice Question

• Complete the following reactions.

1) Cl₂, H₂O

2) 2,6-lutidine

1) Br₂, H₂O

2) diisopropylamine
Reactions of Epoxides

- Many products can be formed from epoxides. In all cases, the product will have **vicinal difunctional groups** due to the opening of the epoxide ring.

- This ring opening of the epoxide can take place directly with a charged nucleophile or with a weak nucleophile under acidic conditions.

$$\text{NuOH} \xleftrightarrow{\text{Nu}^-} \text{O} \xrightarrow{\text{Nu}^- \text{H}^+} \text{NuOH}$$
Depending on the conditions used, the nucleophile will attack the most or the least substituted carbon of the epoxide.
• **Acidic Ring Opening** (14-12)

If the acid bears a nucleophile (conjugate base) within its structure (HCl, HBr, HI), no other nucleophile is necessary. (This is the reverse of the base-promoted cyclization of halohydrins).
• But if the conjugate base of the acid ($\text{H}_2\text{SO}_4$) is not nucleophilic, other weak nucleophiles (water, alcohols) can be used.

![Chemical Structures]

1,2-epoxycyclopentane

trans-2-methoxy cyclopentanol (82%) (mixture of enantiomers)
• For unsymmetrically substituted epoxides, the nucleophile will attack the most substituted carbon and the hydroxyl group will be located on the least substituted carbon of the original epoxides (similar to Markovnikov rule for alkenes).

• This is due to the transition state leading to the product. If compared to a carbocation, the more substituted the better in terms of stability.
2,2-dimethyloxirane

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

\[ \text{CH}_3 \]

\[ \text{H}^+, \text{CH}_3\text{CH}_2\text{OH} \]

2-ethoxy-2-methyl-1-propanol
acid-catalyzed product

\[ \text{CH}_3\text{CH}_2\text{O}^- , \text{EtOH} \]

1-ethoxy-2-methyl-2-propanol
base-catalyzed product

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• **Ring Opening with Strong Nucleophile (14-13)**

When charged nucleophiles are used, it is not necessary to protonate the epoxide. The reaction will proceed by a $S_N^2$ mechanism, hence the nucleophilic attack will be at the least substituted carbon of the epoxide for steric reasons.

![Chemical structures](image-url)

1,2-epoxycyclopentane

$\rightarrow$

$\rightarrow$

$\rightarrow$

$\rightarrow$

$\rightarrow$

trans-cyclopentane-1,2-diol (mixture of enantiomers)
\[
\text{H}_2\text{C} = \text{CH}_2 + :\text{NH}_3 \xrightarrow{\text{H}_2\text{O}} \text{CH}_2 = \text{CH}_2 + ^+\text{NH}_3 \rightarrow \text{HOCH}_2\text{CH}_2^+\text{NH}_2
\]

ethylene oxide  ammonia  ethanolamine

\[
\text{HOCH}_2\text{CH}_2^+\text{NH}_2 \xrightarrow{\text{O}} (\text{HOCH}_2\text{CH}_2)_2^+\text{NH} \xrightarrow{\text{O}} (\text{HOCH}_2\text{CH}_2)_3^+\text{N:}
\]

ethanolamine  diethanolamine  triethanolamine

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Under basic conditions, the ring opening is opposite to that observed under acidic conditions and the nucleophile attacks the least substituted carbon.
• **Epoxides with Grignards** (14-15)

• We have seen in the synthesis of alcohols that Grignard reagents and alkyl lithium react with epoxides to give primary alcohols with 2 extra carbons in the chain.
propylene oxide (methylloxirane) + cyclohexyllithium  → ether → H₃O⁺ → 1-cyclohexyl-2-propanol

2-cyclohexyl-2-ethylloxirane + phenylmagnesium bromide  → ether → H₃O⁺ → 2-cyclohexyl-1-phenyl-2-butanol
Practice Questions

- What are the major products of the following reactions?

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{CH}_3\text{OH} \\
\text{O} & \quad \xrightarrow{\text{CH}_3\text{O}^-} \quad \text{CH}_3\text{OH}
\end{align*}
\]
• Which alcohol is produced when ethylene oxide is treated with these reagents followed by aqueous acid?

\[
\text{O} \\
\text{ethylene oxide}
\]

\[
\text{MgBr}
\]

\[
\text{CH}_2\text{Li}
\]

\[
\text{MgCl}
\]