Ethers and Epoxides;  
Thiols and Sulfides
Introduction

- **Ethers** are compounds with two organic groups (alkyl, aryl, or vinyl) bonded to the same oxygen atom, $\text{R–O–R}'$, in a ring or in an open chain.

- Diethyl ether
- Anisole (Methyl phenyl ether)
- Tetrahydrofuran (a cyclic ether)
Thiols (R–S–H)

• Thiols (R–S–H) and sulfides (R–S–R’) are sulfur analogs of alcohols and ethers, respectively

• Sulfur replaces oxygen

\[
\begin{align*}
\text{Ethanethiol} & \quad \text{Dimethyl sulfide} \\
\text{CH}_3\text{CH}_2\text{SH} & \quad \text{CH}_3\text{—S—CH}_3
\end{align*}
\]
Naming Ethers

- Ethers are named according to IUPAC rules:
  - Simple ethers with no other functional groups are named by identifying the two organic substituents and adding the word *ether*.
  - If other functional groups are present, the ether part is considered an *alkoxy* substituent.
  - Simple ethers with no other functional groups are named by identifying the two organic substituents and adding the word *ether*.
– If other functional groups are present, the ether part is considered an alkoxy substituent.
Practice Problem: Name the following ethers according to IUPAC rules

(a) CH₃CHOCHCH₃
(b) OCH₂CH₂CH₂CH₃
(c) OCH₃
(d) OCH₃
(e) CH₃CHCH₂OCH₂CH₃
(f) H₂C=CHCH₂OCH=CH₂

Diisopropyl ether
Cyclopentyl propyl ether
p-Bromoanisole or 4-Bromo-1-methoxybenzene

1-Methoxycyclohexene
Ethyl isobutyl ether
Allyl vinyl ether
Structure and Properties of Ethers

- The geometry around the O atom of an ether (ROR) is similar to that of water (HOH)
  - R-O-R has a tetrahedral bond angle (~112° in dimethyl ether)
  - The O atom is sp³-hybridized
- The oxygen atom gives ethers a slight dipole moment
Ethers have higher boiling points than alkanes with similar MW

<table>
<thead>
<tr>
<th>Ether</th>
<th>[Hydrocarbon]</th>
<th>Boiling point (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃OCH₃</td>
<td>CH₃CH₂CH₃</td>
<td>-25</td>
</tr>
<tr>
<td>CH₃CH₂OCH₂CH₃</td>
<td>CH₃CH₂CH₂CH₂CH₃</td>
<td>34.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49</td>
</tr>
<tr>
<td></td>
<td></td>
<td>158</td>
</tr>
<tr>
<td></td>
<td></td>
<td>136</td>
</tr>
</tbody>
</table>
Synthesis of Ethers

Ethers can be synthesized by:

i. Acid-catalyzed dehydration of alcohols

ii. Williamson ether synthesis

iii. Alkoxymercurcation of alkenes
Acid-catalyzed dehydration of alcohols

- **Symmetrical ethers** can be prepared by acid-catalyzed dehydration of primary alcohols ($S_{N2}$)

$$
\text{CH}_3\text{CH}_2-\text{O}:+\text{CH}_3\text{CH}_2-\text{O}^+ \xrightarrow{S_{N2}} \text{CH}_3\text{CH}_2-\text{O}^+\text{CH}_2\text{CH}_3 \rightarrow \text{CH}_3\text{CH}_2-\text{O}-\text{CH}_2\text{CH}_3
$$

- Acid-catalyzed dehydration of secondary and tertiary alcohols yield alkenes ($E1$)
The Williamson Ether Synthesis

- **Symmetrical** and **unsymmetrical ethers** can be prepared via the **Williamson ether synthesis**.
  - It is a process in which metal **alkoxides** react with primary alkyl halides and/or tosylates via $S_{N}2$.
  - It is the best method for the preparation of ethers.

![Chemical reaction diagram]

Cyclopentoxide ion

Cyclopentyl methyl ether (74%)
• Alkoxides are prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH

\[ \text{ROH} + \text{NaH} \rightarrow \text{RO}^-\text{Na}^+ + \text{H}_2 \]

Acid    Base    Sodium salt of the alcohol
Mechanism of the Williamson Ether Synthesis

• The Williamson ether synthesis involves an SN2 reaction of an alkoxide ion with a primary alkyl halide
  - An alkoxide nucleophile (RO-) displaces a halide ion (X-) via SN2
  - Primary halides and tosylates work best for SN2 because more hindered substrates undergo competitive E2 elimination of HX
Unsymmetrical ethers should be synthesized by reaction between the more hindered alkoxide ion and less hindered alkyl halide rather than vice versa.  

Example: Synthesis of tert-butyl methyl ether

\[
\begin{align*}
\text{S_N}_2 \text{ reaction} &: \quad \text{CH}_3\text{C}^-\text{O}^- + \text{CH}_3\text{I} \quad \rightarrow \quad \text{CH}_3\text{C}^-\text{O}^-\text{CH}_3 + \text{I}^- \\
\text{E}_2 \text{ reaction} &: \quad \text{CH}_3\text{O}^- + \text{CH}_2\text{C}^-\text{Cl} \quad \rightarrow \quad \text{H}_2\text{C}\equiv\text{C} + \text{CH}_3\text{OH} + \text{Cl}^-
\end{align*}
\]
Alkoxymercuration of Alkenes

- **Ethers** can be prepared via **Alkoxymercuration of Alkenes** followed by **demercuration**
  
  - **Alkoxymercuration** occurs when an alkene reacts with an alcohol in mercuric acetate or trifluoroacetate.
  
  - **Demercuration** involves reduction of C-Hg by NaBH₄.
Mechanism of Alkoxymercuration/Demercuration

- The mechanism involves:

- Electrophilic addition of Hg\(^{2+}\) to an alkene, followed by reaction of intermediate cation with alcohol: Overall Markovnikov addition of alcohol to alkene

- Reduction of C-Hg by NaBH\(_4\)
Practice Problem: How would you prepare the ethyl phenyl ether? Use whichever method you think is more appropriate, the Williamson synthesis or the alkoxymercuration reaction.
Reactions of Ethers

Ethers undergo:

i. **Acidic Cleavage**

ii. **Claisen Rearrangement**
Acidic Cleavage

- **Ethers** are generally unreactive to most reagents but react with **strong acids** (**HI** and **HBr**) at high temperature.
  - HI, HBr produce an alkyl halide from less hindered component by **S_{N}2** (tertiary ethers undergo **S_{N}1**).
Mechanism of the Acidic Cleavage

- The acidic cleavage reaction takes place:
  - via $S_N2$ mechanism at the less highly substituted site if only primary and secondary alkyl are bonded to the ether O
  - via $S_N1$ or E1 mechanism if one of the alkyl groups bonded to the ether O is tertiary

Ethers with primary and secondary alkyl groups react with HI or HBr via $S_N2$ mechanism
  - $I^-$ or $Br^-$ attacks the protonated ether at the less hindered site

![Reaction mechanism diagram](image-url)
Ethers with a tertiary, benzylic, or allylic group react with HI or HBr via $S_N1$ or $E1$ mechanism.

- These can produce stable intermediate carbocations.

- **Example**: *tert*-Butyl cyclohexyl ether reacts via E1.

\[
\text{tert-Butyl cyclohexyl ether} \quad \xrightarrow{\text{CF}_3\text{CO}_2\text{H}, \quad 0^\circ \text{C}} \quad \text{Cyclohexanol (90\%)} + \quad \text{2-Methylpropene}
\]
Practice Problem: Predict the products of the following reaction

\[
\begin{align*}
\text{CH}_3 & \\
\text{CH}_3 \text{C} - \text{O} - \text{CH}_2\text{CH}_2\text{CH}_3 & \quad \xrightarrow{\text{HBr}} \\
\text{CH}_3 & \\
\end{align*}
\]

- Ethers with **primary** and **secondary alkyl** groups – via \( S_N2 \)
- Ethers with a **tertiary**, **benzylic**, or **allylic group** – via \( S_N1 \) or \( E1 \)

\[
\begin{align*}
\text{CH}_3 & \\
\text{CH}_3 \text{C} - \text{O} - \text{CH}_2\text{CH}_2\text{CH}_3 & \quad \xrightarrow{\text{HBr}} \\
\text{CH}_3 & \\
\text{CH}_3 & \quad \text{CH}_3 \text{C} - \text{Br} + \text{HOCH}_2\text{CH}_2\text{CH}_3 \\
\text{CH}_3 & \\
\text{CH}_3 & \\
\end{align*}
\]

** tert-Butyl propyl ether**
** 2-Bromo-2-methylpropane**
** 1-Propanol**
Claisen Rearrangement

- **Claisen rearrangement** is specific to **allyl aryl ethers**, \( \text{ArOCH}_2\text{CH} = \text{CH}_2 \)
  - Heating the allyl aryl ether to 200–250°C leads to an **\( o \)-allylphenol**
  - Result is alkylation of the phenol in an **ortho** position
Mechanism of the Claisen Rearrangement

- The reaction proceeds via a pericyclic mechanism:

- The mechanism is consistent with $^{14}$C labelling.
Cyclic Ethers: Epoxides

- Cyclic ether behaves like an acyclic ether, except if the ring is 3-membered
  - Dioxane and tetrahydrofuran are used as solvents
Epoxides (Oxiranes)

- An epoxide is a three-membered ring ether
  - It is also called an oxirane (root “ir” from “tri” for 3-membered; prefix “ox” for oxygen; “ane” for saturated)
  - It has a unique chemical reactivity (behaves differently from other open-chain ethers) due to the strain of the 3-membered ring
• **Ethylene oxide** (1,2-epoxyethane) is industrially important as an intermediate

  – It is the **simplest** epoxide (oxirane)

  – It is prepared by reaction of ethylene with oxygen at 300°C and silver oxide catalyst

\[
\begin{align*}
\text{H}_2\text{C} & \equiv \text{CH}_2 & \overset{\text{O}_2}{\overset{\text{Ag}_2\text{O}, 300^\circ\text{C}}{\longrightarrow}} & \text{H}_2\text{C} & \equiv \text{CH}_2 \\
\text{Ethylene} & & \text{Ethylene oxide} & \\
\end{align*}
\]
Preparation of Epoxides Using a Peroxyacid

- An epoxide is prepared by treatment of an alkene with a peroxyacid ($RCO_3H$)
  - $m$-chloroperoxybenzoic acid is a common per oxyacid used

\[
\begin{align*}
\text{Cycloheptene} & \quad \xrightarrow{\text{CH}_2\text{Cl}_2, 25^\circ\text{C}} \quad \text{1,2-Epoxycycloheptane} \\
& \quad \text{(78%)}
\end{align*}
\]
Preparation of Epoxides from Halohydrins

- An epoxide is prepared by treatment of a halohydrin with base
  - Addition of HO-X to an alkene gives a halohydrin
  - Treatment of a halohydrin with base eliminates HX and gives an epoxide
5. Ring-Opening Reactions of Epoxides

• There are two types of ring-opening reactions of epoxides:
  
i. Acid-Catalyzed Epoxide Opening
  
ii. Base-Catalyzed Epoxide Opening
Acid-Catalyzed Epoxide Opening

- Water adds to epoxides with dilute acid at room temperature
  - The product is a 1,2-diol, also called vicinal glycol (on adjacent C's: vicinal)
  - Epoxides react under milder conditions because of ring strain
Ethylene Glycol

• 1,2-ethanediol is synthesized from acid catalyzed hydration of ethylene oxide

  – Widely used as automobile antifreeze (lowers freezing point of water solutions)
Halohydrins from Epoxides

- Anhydrous HF, HBr, HCl, or HI also combines with an epoxide
  - This gives a trans product (halohydrin)

A trans 2-halocyclohexanol

where $X = F, Br, Cl, or I$
Regiochemistry of Acid-Catalyzed Opening of Epoxides

- When both epoxide carbon atoms are either primary or secondary, the nucleophile preferably attacks the less highly substituted site (less hindered site).

- When one of the epoxide carbon atoms is tertiary, the nucleophile attacks the more highly substituted site.

\[ \text{1,2-Epoxypropane} \quad \text{HCl} \quad \text{Ether} \quad \text{OH} \quad \text{Cl} \\
\text{1-Chloro-2-propanol (90%)} \quad \text{2-Chloro-1-propanol (10%)} \\
\]

\[ \text{2-Methyl-1,2-epoxypropane} \quad \text{HCl} \quad \text{Ether} \quad \text{Cl} \quad \text{OH} \\
\text{2-Chloro-2-methyl-1-propanol (60%)} \quad \text{1-Chloro-2-methyl-2-propanol (40%)} \]
Base-Catalyzed Epoxide Opening

- Unlike other ethers, epoxides can be cleaved by base as well as by acid
  - Strain of the three-membered ring is relieved on ring-opening
  - Hydroxide ion cleaves epoxides at elevated temperatures to give trans 1,2-diols

Methylenecyclohexane oxide

©2004 Thomson - Brooks/Cole

1-Hydroxymethylcyclohexanol (70%)
Addition of Grignards to Ethylene Oxide

- Grignard reagents cleave the ring of epoxides
  - Reaction of ethylene oxide with Grignard reagent adds $\text{CH}_2\text{CH}_2\text{OH}$ to the Grignard reagent’s hydrocarbon chain

- Acyclic and other larger ring ethers do not react