Chapter 18
Ethers and Epoxides; Thiols and Sulfides
Ethers and Their Relatives

- An **ether** has two organic groups (alkyl, aryl, or vinyl) bonded to the same oxygen atom, $R–O–R'$
- Diethyl ether is used industrially as a solvent
- Tetrahydrofuran (THF) is a solvent that is a cyclic ether
- **Thiols** ($R–S–H$) and **sulfides** ($R–S–R'$) are sulfur (for oxygen) analogues of alcohols and ethers

Diagram:
- **Diethyl ether**
- **Anisole** (methyl phenyl ether)
- **Tetrahydrofuran**
Why this Chapter?

- To finish covering functional groups with C-O and C-S single bonds

- Focus on ethers and look at thiols and sulfides before going on to C=O
18.1 Names and Properties of Ethers

- Simple ethers 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.
- R–O–R ~ tetrahedral bond angle (112° in dimethyl ether).
- Oxygen is *sp*³-hybridized.
- Oxygen atom gives ethers a slight dipole moment.

![Chemical structures](image)

- Isopropyl methyl ether
- Ethyl phenyl ether
- *p*-Dimethoxybenzene
- 4-tert-Butoxy-1-cyclohexene
18.2 Synthesis of Ethers

- Diethyl ether prepared industrially by sulfuric acid–catalyzed dehydration of ethanol – also with other primary alcohols
The Williamson Ether Synthesis

- Reaction of metal alkoxides and primary alkyl halides and tosylates
- Best method for the preparation of ethers
- Alkoxides prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH

Cyclopentanol $\xrightarrow{\text{NaH, THF}}$ Alkoxide ion $\xrightarrow{\text{CH}_3\text{I}}$ Cyclopentyl methyl ether (74%)
Silver Oxide-Catalyzed Ether Formation

- Reaction of alcohols with Ag$_2$O directly with alkyl halide forms ether in one step
- Glucose reacts with excess iodomethane in the presence of Ag$_2$O to generate a *pentaether* in 85% yield

\[
\begin{align*}
\text{\textit{\alpha-D-Glucose}} & \quad \text{CH}_3\text{I} & \quad \text{Ag}_2\text{O} \\
\text{\textit{\alpha-D-Glucose pentamethyl ether}} & \quad (85\%) & \quad + \quad \text{AgI}
\end{align*}
\]
Alkoxymercuration of Alkenes

- React alkene with an alcohol and mercuric acetate or trifluoroacetate
- Demercuration with NaBH₄ yields an ether
- Overall Markovnikov addition of alcohol to alkene

![Chemical structures showing alkoxymercuration of alkenes](image)
18.3 Reactions of Ethers: Acidic Cleavage

- Ethers are generally unreactive
- Strong acid will cleave an ether at elevated temperature
- HI, HBr produce an alkyl halide from less hindered component by S\text{N}2 (tertiary ethers undergo S\text{N}1)

\[
\text{Ethyl phenyl ether} \xrightarrow{\text{HBr, H}_2\text{O, Reflux}} \text{Phenol} + \text{CH}_3\text{CH}_2\text{Br} 
\]

\[
\text{Ethyl isopropyl ether} \xrightarrow{\text{H-I}} \left[ \begin{array}{c}
\text{H} \\
\text{CH}_3
\end{array} \right] \left[ \begin{array}{c}
\text{CH}_3 \\
\text{CH}_3
\end{array} \right] \text{CH}_3\text{CH}==\text{O} \xrightarrow{\text{S}\text{N}2} \text{Isopropyl alcohol} + \text{I-CH}_2\text{CH}_3 
\]
18.4 Reactions of Ethers: Claisen Rearrangement

- Specific to allyl aryl ethers, $\text{ArOCH}_2\text{CH=CH}_2$
- Heating to 200–250°C leads to an $o$-allylphenol
- Result is alkylation of the phenol in an $ortho$ position

**Reaction Scheme:**

- Phenol $+ \text{NaH}$ in THF solution $\rightarrow$ Sodium phenoxide $\rightarrow$ Allyl phenyl ether
- Claisen rearrangement at 250°C: Allyl phenyl ether $\rightarrow$ $o$-Allylphenol
Claisen Rearrangement Mechanism

- Concerted pericyclic 6-electron, 6-membered ring transition state
- Mechanism consistent with $^{14}$C labeling
18.5 Cyclic Ethers

- Cyclic ethers behave like acyclic ethers, except if ring is 3-membered
- Dioxane and tetrahydrofuran are used as solvents

1,4-Dioxane

Tetrahydrofuran
Epoxides (Oxiranes)

- Three membered ring ether is called an oxirane (root “ir” from “tri” for 3-membered; prefix “ox” for oxygen; “ane” for saturated)
- Also called epoxides
- Ethylene oxide (oxirane; 1,2-epoxyethane) is industrially important as an intermediate
- Prepared by reaction of ethylene with oxygen at 300 °C and silver oxide catalyst

\[
\text{H}_2\text{C} = \text{CH}_2 \xrightarrow{\text{O}_2, \text{Ag}_2\text{O}, 300 \, ^\circ\text{C}} \text{H}_2\text{C} = \text{CH}_2
\]
Preparation of Epoxides Using a Peroxyacid

- Treat an alkene with a peroxyacid

\[
\text{Cycloheptene} + \text{meta-Chloroperoxybenzoic acid} \rightarrow \text{CH}_2\text{Cl}_2 \text{ solvent} \rightarrow \text{1,2-Epoxycycloheptane} + \text{meta-Chlorobenzoic acid}
\]
Epoxides from Halohydrins

- Addition of HO-X to an alkene gives a halohydrin
- Treatment of a halohydrin with base gives an epoxide
- Intramolecular Williamson ether synthesis

Cyclohexene $\xrightarrow{\text{Cl}_2, \text{H}_2\text{O}}$ trans-2-Chloro-cyclohexanol $\xrightarrow{\text{NaOH}, \text{H}_2\text{O}}$ 1,2-Epoxy-cyclohexane
18.6 Reactions of Epoxides: Ring-Opening

- Water adds to epoxides with dilute acid at room temperature
- Product is a 1,2-diol (on adjacent C’s: *vicinal*)
- Mechanism: acid protonates oxygen and water adds to opposite side (*trans* addition)

![Chemical structures and reactions showing the ring-opening process of 1,2-epoxycyclohexane and cyclohexene to form trans-1,2-dibromo-cyclohexane.](image-url)
Halohydrins from Epoxides

- Anhydrous HF, HBr, HCl, or HI combines with an epoxide
- Gives *trans* product

A trans 2-halocyclohexanol

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

- Nucleophile preferably adds to less hindered site if primary and secondary C’s
- Also at tertiary because of carbocation character
Base-Catalyzed Epoxide Opening

- Strain of the three-membered ring is relieved on ring-opening
- Hydroxide cleaves epoxides at elevated temperatures to give trans 1,2-diols
Addition of Grignards to Ethylene Oxide

- 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

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{MgBr} + \text{H}_2\text{C} = \text{CH}_2 \xrightarrow{1. \text{Ether solvent}} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}
\]

Butylmagnesium bromide \hspace{2cm} Ethylene oxide \hspace{2cm} 1-Hexanol (62%)
18.7 Crown Ethers

- Large rings consisting of repeating (-OCH$_2$CH$_2$-) or similar units
- Named as $x$-crown-$y$
  - $x$ is the total number of atoms in the ring
  - $y$ is the number of oxygen atoms
  - 18-crown-6 ether: 18-membered ring containing 6 oxygen atoms
- Central cavity is electronegative and attracts cations
18.8 Thiols and Sulfides

- **Thiols** (RSH), are sulfur analogues of alcohols
  - Named with the suffix *-thiol*
  - SH group is called “mercapto group” (“capturer of mercury”)

CH$_3$CH$_2$SH  
**Ethanethiol**  

[Chemical structure of cyclohexanethiol]

[Chemical structure of m-Mercaptobenzoic acid]
Thiols: Formation and Reaction

- From alkyl halides by displacement with a sulfur nucleophile such as $-\text{SH}$
  - The alkylthiol product can undergo further reaction with the alkyl halide to give a symmetrical sulfide, giving a poorer yield of the thiol

\[ \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\_\text{Br} + \_\text{SH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\_\text{SH} + \text{Br}^- \]

1-Bromooctane  
1-Octanethiol (83%)
Sulfides

- **Sulfides** (RSR'), are sulfur analogues of ethers
  - Named by rules used for ethers, with *sulfide* in place of *ether* for simple compounds and *alkylthio* in place of *alkoxy*

\[
\begin{align*}
     & \text{H}_3\text{C} - \text{S} - \text{CH}_3 \\
     & \text{S} - \text{CH}_3 \\
     & 3\text{-}(\text{Methylthio})\text{cyclohexene}
\end{align*}
\]

- Dimethyl sulfide
- Methyl phenyl sulfide
Using Thiourea to Form Alkylthiols

- Thiols can undergo further reaction with the alkyl halide to give dialkyl sulfides
- For a pure alkylthiol use thiourea \((\text{NH}_2\text{(C=S)}\text{NH}_2)\) as the nucleophile
- This gives an intermediate alkylisothiourea salt, which is hydrolyzed cleanly to the alkyl thiourea
Reaction of an alkyl thiol (RSH) with bromine or iodine gives a disulfide (RSSR)

- The thiol is oxidized in the process and the halogen is reduced

\[
2 \text{R-SH} \xrightleftharpoons{\text{I}_2, \text{Zn}, \text{H}^+} \text{R-S-S-R} + 2 \text{HI}
\]

A thiol

A disulfide
Thiolates (RS⁻) are formed by the reaction of a thiol with a base.

Thiolates react with primary or secondary alkyl halide to give sulfides (RSR’).

Thiolates are excellent nucleophiles and react with many electrophiles.

Sodium benzenethiolate + CH₃I → Methyl phenyl sulfide (96%) + NaI
Sulfides as Nucleophiles

- Sulfur compounds are more nucleophilic than their oxygen-compound analogues
  - $3p$ valence electrons (on S) are less tightly held than $2p$ electrons (on O)
- Sulfides react with primary alkyl halides ($S_N2$) to give trialkylsulfonylum salts ($R_3S^+$)

\[
\text{Dimethyl sulfide} \quad \text{Iodomethane} \quad \text{Trimethylsulfonylum iodide}
\]
Sulfides are easily oxidized with H$_2$O$_2$ to the sulfoxide (R$_2$SO)

Oxidation of a sulfoxide with a peroxyacid yields a sulfone (R$_2$SO$_2$)

Dimethyl sulfoxide (DMSO) is often used as a polar aprotic solvent
18.9 Spectroscopy of Ethers

- **Infrared**: C–O single-bond stretching 1050 to 1150 cm\(^{-1}\) overlaps many other absorptions.

- **Proton NMR**: H on a C next to ether O is shifted downfield to \(\delta\) 3.4 to \(\delta\) 4.5
  - The \(^1\)H NMR spectrum of dipropyl ether shows this signal at \(\delta\) 3.4
  - In epoxides, these H’s absorb at \(\delta\) 2.5 to \(\delta\) 3.5 in their \(^1\)H NMR spectra

- **Carbon NMR**: C’s in ethers exhibit a downfield shift to \(\delta\) 50 to \(\delta\) 80