18a: Ethers and Epoxides; Thiols and Sulfides

Based on McMurry’s *Organic Chemistry, 7th edition*
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) analogs of alcohols and ethers

![Diethyl ether, Anisole (methyl phenyl ether), Tetrahydrofuran](image)
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
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- $R-O-R \sim$ tetrahedral bond angle (112° in dimethyl ether).
- Oxygen is $sp^3$-hybridized.
- Oxygen atom gives ethers a slight dipole moment.
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

\[
\text{Cyclopentanol} \xrightarrow{\text{NaH, THF}} \text{Alkoxide ion} \xrightarrow{\text{CH}_3^-} \text{Cyclopentyl methyl ether (74%)}
\]
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

\[ \text{Ag}_2\text{O} + 5\text{CH}_3\text{I} \rightarrow \text{CH}_3\text{O} - \text{O} - \text{CH}_3 \]
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 Reaction Diagram]

Styrene

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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 $S_{N2}$ (tertiary ethers undergo $S_{N1}$)

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

\[\text{Ethyl isopropyl ether} \xrightarrow{\text{HI}} \begin{cases} \text{Less hindered} & \rightarrow \text{Isopropyl alcohol} + \text{I}_2\text{CH}_2\text{CH}_3 \\ \text{More hindered} & \rightarrow \text{Iodoethane} \end{cases}\]
18.4 Reactions of Ethers: Claisen Rearrangement

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

![Chemical reactions and structures]
Claisen Rearrangement Mechanism

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

\[ \text{Allyl phenyl ether} \rightarrow \text{Transition state} \rightarrow \text{Intermediate (6-allyl-2,4-cyclohexadienone)} \rightarrow \text{o-Allylphenol} \]
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
Preparation of Epoxides Using a Peroxyacid

- Treat an alkene with a peroxyacid

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

- Addition of HO-X to an alkene gives a halohydrin
- Treatment of a halohydrin with base gives an epoxide

Cyclohexene → trans-2-Chloro-cyclohexanol $\xrightarrow{\text{NaOH, H}_2\text{O}}$ 1,2-Epoxycyclohexane

Intramolecular Williamson ether synthesis
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)
Halohydrins from Epoxides

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

\[
\begin{align*}
\text{H} & \quad \text{O} \\
\text{H} & \quad \text{H}
\end{align*}
\quad \xrightarrow{\text{HX, Ether}} \quad
\begin{align*}
\text{H} & \quad \text{OH} \\
\text{H} & \quad \text{H} \\
\text{X} & \quad \text{H}
\end{align*}
\]

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.
**FIGURE 18-2** Ring-opening of 1,2-epoxy-1-methylcyclohexane with HBr. There is a high degree of $S_N1$-like carbocation character in the transition state, which leads to backside attack of the nucleophile at the tertiary center and to formation of a product isomer that has $\text{--Br}$ and $\text{--OH}$ groups trans.
Base-Catalyzed Epoxide Opening

- Strain of the three-membered ring is relieved on ring-opening

\[
\begin{align*}
\text{Methylenecyclohexane oxide} & \quad \text{H}_2\text{O, 100 °C} \\
\text{1-Hydroxymethylcyclohexanol (70%)}
\end{align*}
\]

- Hydroxide cleaves epoxides at elevated temperatures to give trans 1,2-diols
Addition of Grignards to Ethylene Oxide

- Adds –CH₂CH₂OH to the Grignard reagent’s hydrocarbon chain

\[
\text{Butylmagnesium bromide} + \text{Ethylene oxide} \rightarrow \text{1-Hexanol (62%)}
\]

- Acyclic and other larger ring ethers do not react
18.7 Crown Ethers

- Large rings consisting repeating (-OCH₂CH₂-) 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
Uses of Crown Ethers

- Complexes between crown ethers and ionic salts are soluble in nonpolar organic solvents
- Creates reagents that are free of water that have useful properties
- Inorganic salts dissolve in organic solvents leaving the anion unassociated, enhancing reactivity

**KMnO₄** solvated by 18-crown-6 (this solvate is soluble in benzene)
The image shows the ionic radii of various cations and the corresponding molecular structures. The ionic radii are as follows:

- **Li^+**: 0.78 Å
- **Na^+**: 0.97 Å
- **K^+**: 1.33 Å
- **Rb^+**: 1.48 Å
- **Cs^+**: 1.67 Å

The molecular structures correspond to:

- [12]: 1.20 - 1.50 Å
- [15]: 1.70 - 2.20 Å
- [18]: 2.60 - 3.20 Å
- [21]: 3.40 - 4.30 Å
Novel Process Employs Crown Ethers for Removing Technetium from Alkaline Waste Solutions

SRTALK process for removing technetium from nuclear waste

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

\[ \text{CH}_3\text{CH}_2\text{SH} \]
18.8 Thiols and Sulfides

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

![Chemical structures of ethanethiol, cyclohexanethiol, and m-mercapto benzoic 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

$$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{Br} + \text{SH} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{SH} + \text{Br}^-$$

1-Bromooctane (83%)
Sulfides

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

- **Sulfides** *(RSR’)*, are sulfur analogs of ethers

- Named by rules used for ethers, with
  - *sulfide* in place of *ether* for simple compounds and
  - *alkylthio* in place of *alkoxy*
Thiols can undergo further reaction with the alkyl halide to give dialkyl sulfides.

For a pure alkylthiol use thiourea (NH$_2$(C=S)NH$_2$) as the nucleophile. This gives an intermediate alkylisothiourea salt, which is hydrolyzed cleanly to the alkyl thiol.
Oxidation of Thiols to Disulfides

- 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

\[
2 \text{RSH} \xrightleftharpoons{I_2, \text{Zn, H}^+} \text{RSSR} + 2 \text{HI}
\]

A thiol \hspace{1cm} A disulfide
Sulfides

- **Thiolates** \( (RS^-) \) are formed by the reaction of a thiol with a base
- Thiolates react with primary or secondary alkyl halide to give sulfides \( (RS'R') \)
- Thiolates are excellent nucleophiles and react with many electrophiles

\[
\text{Sodium benzenethiolate} \quad \text{Methyl phenyl sulfide (96%)}
\]

\[
\text{Sodium benzenethiolate} + \text{CH}_3\text{-I} \rightarrow \text{Methyl phenyl sulfide} + \text{NaI}
\]
Sulfides as Nucleophiles

- Sulfur compounds are more nucleophilic than their oxygen-compound analogs
  - 3p electrons valence electrons (on S) are less tightly held than 2p electrons (on O)
- Sulfides react with primary alkyl halides ($S_{N2}$) to give trialkylsulfonium salts ($R_3S^+$)

\[
\text{CH}_3\text{CH}_3\text{S} + \text{CH}_3\text{I} \xrightarrow{\text{THF}} \text{CH}_3\text{S}^+\text{CH}_3\text{I}^- \\
\text{Dimethyl sulfide} \quad \text{Iodomethane} \quad \text{Trimethylsulfonium iodide}
\]
Oxidation of Sulfides

- Sulfides are easily oxidized with \( \text{H}_2\text{O}_2 \) to the sulfoxide \((\text{R}_2\text{SO})\)
- Oxidation of a sulfoxide with a per oxyacid yields a sulfone \((\text{R}_2\text{SO}_2)\)
- Dimethyl sulfoxide (DMSO) is often used as a polar aprotic solvent

![Chemical Structures]

- Methyl phenyl sulfide
- Methyl phenyl sulfoxide
- Methyl phenyl sulfone

**Dimethyl sulfoxide**
(a polar aprotic solvent)
THE CHEMISTRY OF GARLIC

WHAT CAUSES GARLIC BREATH?

There are four major volatile organic compounds responsible for 'garlic breath': diallyl disulfide, allyl methyl sulfide, allyl mercaptan, and allyl methyl disulfide. None of these compounds are present in garlic until it is crushed or chopped.

When garlic is mechanically damaged, enzymes convert the compound allin to allicin (which gives chopped garlic its aroma). This is then broken down further into the afore-mentioned volatile compounds.

Allyl methyl sulfide is broken down in the body more slowly than the other three compounds, so it is the primary volatile responsible for garlic breath. It can pass into the bloodstream & organs, and is excreted via sweating, breathing, and through the urine. Its effects can last up to a day!

A few foods have been shown to have some effect on reducing garlic breath, including parsley & milk.

WHAT GIVES GARLIC ANTIBACTERIAL PROPERTIES?

Sulfur-containing organic compounds give garlic some antibacterial properties. Antimicrobial effects have been shown to increase as the number of sulfur atoms in the compounds increases.

The organosulfur compounds can penetrate the cell membranes of bacteria cells, and combine with certain enzymes or proteins to alter their structure, injuring the cells.

Allicin, formed initially when garlic is crushed, also has antibacterial properties.