Chapter 16: Ethers, Epoxides, and Sulfides

16.1: Nomenclature of Ethers, Epoxides, and Sulfides
(Please read)

16.2: Structure and Bonding in Ethers and Epoxides
The ether oxygen is \(sp^3\)-hybridized and tetrahedral. In general, the C-O bonds of ethers have low reactivity.

16.3: Physical Properties of Ethers
The O-H group of alcohols act as both an H-bond donor (Lewis acid) and H-bond acceptor (Lewis base). Ethers are only H-bond acceptors (Lewis base)

16.4: Crown Ethers (Please read)

16.5: Preparation of Ethers
Acid-Catalyzed . . .
   a) Condensation of Alcohols (not very useful) (Chapter 15.7)
   b) Addition of Alcohols to Alkenes (recall hydration of alkenes in Chapter 6.6 and oxymercuration on p. 258-261)
16.6: The Williamson Ether Synthesis (the workhorse of ether syntheses) - Reaction of an alkoxide with an alkyl halide or tosylate to give an ether. Alkoxides are prepared by the reaction of an alcohol with a strong base such as sodium hydride (NaH).

The Williamson ether synthesis is an $S_N2$ reaction.

The Williamson Ether Synthesis:
- Few restrictions regarding the nature of the alkoxide
- Works best for methyl- and $1^\circ$-halides or tosylates.
- E2 elimination is a competing reaction with $2^\circ$-halides or tosylates.
- $3^\circ$-halides undergo E2 elimination
- Vinyl and aryl halides do not react
16.7: Reaction of Ethers: A Review and Preview (please read)
The reactivity of the ether functional group is low
Over time ethers can react with O₂ to form hydroperoxides

16.8: Acid-Catalyzed Cleavage of Ethers
Recall the reaction of an alcohol with HX to give a halide (Ch. 4.11)
\[
R\text{CH}_2\text{-OH} + H\text{-X} \rightarrow R\text{CH}_2\text{-X} + H_2O
\]
The mechanism for the acid cleavage of ethers is similar
\[
R\text{CH}_2\text{-O-CH}_2\text{R'} + H\text{-X} \rightarrow R\text{CH}_2\text{-X} + R'\text{CH}_2\text{-OH}
\]
16.9: Preparation of Epoxides: A Review and Preview
1) Expoxidation of alkenes (Chapter 6.11)
2) Base promoted ring closure of a vicinal halohydrin (Ch. 6.11) 
   (this is an intramolecular Williamson ether synthesis)

16.10: Conversion of Vicinal Halohydrins to Epoxides

\[
\begin{align*}
R_{\text{C=CH}} & \quad + \quad X\cdot X & \quad + \quad \text{H}_2\text{O} & \quad \rightarrow \quad R_{\text{C=CH}}\text{H} \quad + \quad \text{HX} \\
\text{An Intramolecular Williamson synthesis} & \\
\text{HO} \quad R_{\text{C=CH}} & \quad + \quad \text{NaH} & \quad \rightarrow \quad R_{\text{C=CH}}\text{H} \quad + \quad \text{NaH}
\end{align*}
\]
### 16.11: Reactions of Epoxides with Anionic Nucleophiles

a) Nucleophilic epoxide ring-opening by Grignard reagents (Chapter 15.4)

b) Reductive opening of epoxide is achieved with LiAlH₄

\[
\begin{align*}
\text{Epoxide} & \xrightarrow{\text{LiAlH₄}} \text{Alcohol} \\
\end{align*}
\]

then H₂O⁺ 

(c) Epoxide ring-opening by other nucleophiles - The ring opening of an epoxide is an S₈N₂ reaction with nucleophiles such as amines and the anions of alcohols and thiols.
16.12: Acid-Catalyzed Ring Opening of Epoxides:
Epoxide opening with H-X gives a vicinal halohydrin

\[
\begin{align*}
R'\text{C}=\text{C}^\cdot \text{H}^\cdot + \text{H-X} & \rightarrow \text{H}^\cdot \text{R'\text{C}=\text{C}^\cdot \text{OH}} \\
\text{R'\text{C}=\text{C}^\cdot \text{H}^\cdot + \text{H-A} + \text{ROH} & \rightarrow \text{H}^\cdot \text{R'\text{C}=\text{C}^\cdot \text{OH} + \text{RO}}
\end{align*}
\]

Preparation of syn- and anti- vicinal diols

\[
\begin{align*}
\text{C} & + \text{OsO}_4 \rightarrow \text{R'\text{C}=\text{C}^\cdot \text{OH}} \quad (15.5) \\
\text{alkene epoxidation} & \rightarrow \text{H}\text{SO}_4, \text{H}_2\text{O} \rightarrow \text{R'\text{C}=\text{C}^\cdot \text{OH}}
\end{align*}
\]

16.13 Epoxides in Biological Processes (please read)
In cells, epoxidation of C=C is carried out by enzymes called monooxygenases such as cytochrome P450’s, flavoenzymes, etc., which activate O\(_2\) and catalyze the oxygen transfer reaction
Bioactivation and detoxication of benzo[a]pyrene diol epoxide:

\[
\begin{align*}
\text{benzo[a]pyrene} & \xrightarrow{\text{P450}} \text{benzo[a]pyrene diol epoxide} \xrightarrow{\text{P450}} \text{benzo[a]pyrene diol} \xrightarrow{\text{H}_2\text{O}} \text{benzo[a]pyrene} \\
& \xrightarrow{\text{glutathione transferase}} \text{DNA} \\
& \xrightarrow{\text{G-S}^-} \text{DNA} \\
& \text{Glutathione (G-SH)}
\end{align*}
\]

16.14: Preparation of Sulfides
Reaction of a thiolate anions with 1° and 2° alkyl halides and tosylates (analogous to the Williamson ether synthesis)

\[
\begin{align*}
\text{R-SH} + \text{NaOH} \xrightarrow{\text{alcohol or water solvent}} \text{R-S}^- \xrightarrow{\text{pK}_a \sim 11} \text{R-CH}_2\text{X} \xrightarrow{\text{pK}_a \sim 16-18} \text{R-SCH}_2\text{R'}
\end{align*}
\]

Thiolates are more reactive nucleophiles and less basic than alkoxides.
16.15: Oxidation of Sulfides: Sulfoxides and Sulfones
(please read) – Unlike ethers, sulfides can be oxidized to sulfoxides and further oxidized to sulfones

\[
\begin{align*}
R\cdot S\cdot R' & \xrightarrow{[O]} R\cdot S\cdot O\cdot R' \\
& \xrightarrow{[O]} R\cdot S\cdot O\cdot S\cdot O\cdot R'
\end{align*}
\]
sulfide \quad \text{sulfoxide} \quad \text{sulfone}

16.16: Alkylation of Sulfides: Sulfonium Salts (Please read)
The sulfur atom of sulfides is much more nucleophilic than the oxygen atom of ethers, and will react with alkyl halides to give stable sulfonium salts.

See S-adenosylmethionine (p. 669)

16.17: Spectroscopic Analysis of Ethers, Epoxides and Sulfides

**IR spectroscopy:** not particularly diagnostic for the ether functional group. Strong C-O single bond stretch between 1050-1150 cm\(^{-1}\)

**\(^1\)H NMR:** protons on the carbons that are part of the ether linkage are deshielded relative to alkanes. The chemical shift of these protons is from \(\delta = 3.0 - 4.0 \text{ ppm}\)

**\(^{13}\)C NMR:** the chemical shift of carbons that are part of the ether linkage are in the range of \(\delta = 50 - 80 \text{ ppm}\)
Protons and carbon resonances of an epoxide are shielded relative to those of a typical ethers.

$^1$H NMR: $\delta = 2.2 - 3.2$ ppm
$^{13}$C NMR: $\delta = 40 - 60$ ppm

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{H}
\end{align*}
\]

C$_9$H$_{10}$O$_2$

\[
\begin{align*}
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{H} & \quad \text{H}
\end{align*}
\]