

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)

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16.5: Preparation of Ethers

Acid-Catalyzed . . .

- a) Condensation of Alcohols (not very useful)
- b) Addition of Alcohols to Alkenes (recall hydration of alkenes **6.10**)

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2) The Williamson Ether Synthesis (**Chapter 16.6**)

(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.

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The Williamson Ether Synthesis:

- Few restrictions regarding the nature of the the alkoxide
- Works best for methyl- and 1° -halides or tosylates.
- E2 elimination is a competing reaction with 2° -halides or tosylates
- 3° halides undergo E2 elimination
- Vinyl and aryl halides do not react

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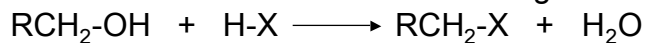
16.7: Reaction of Ethers: A Review and Preview (please read)

The reactivity of the ether functional group is low

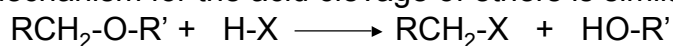
Over time ethers can react with O_2 to form hydroperoxides

16.8: Acid-Catalyzed Cleavage of Ethers

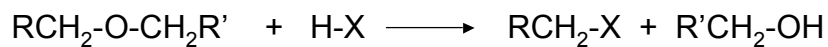
Recall the reaction of an alcohol with HX to give a halide (4.12)



The mechanism for the acid cleavage of ethers is similar



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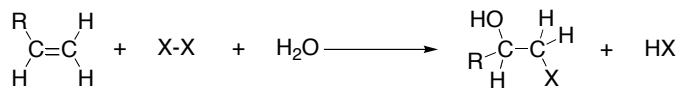
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16.9: Preparation of Epoxides: A Review and Preview

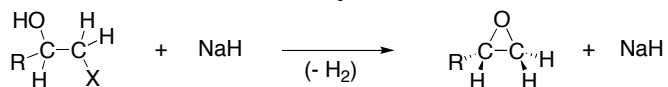
- 1) Epoxidation of alkenes (6.19)
- 2) Base promoted ring closure of a vicinal halohydrin (6.18)
(this is an *intramolecular* Williamson ether synthesis)
- 3) Sharpless Epoxidation (please read)

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16.10: Conversion of Vicinal Halohydrins to Epoxides



An *Intramolecular* Williamson synthesis



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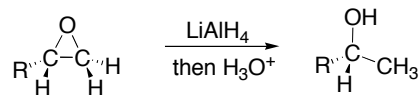
16.11: Reactions of Epoxides: A Review and Preview

- a) Nucleophilic epoxide ring-opening by Grignard reagents (15.4)
- b) Epoxide ring-opening by other nucleophiles
- c) Acid-catalyzed epoxide ring-opening

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16.12: Nucleophilic Ring Opening of Epoxides: The ring opening of an epoxide is an S_N2 reaction with nucleophiles such as amines and the anion of alcohols and thiols

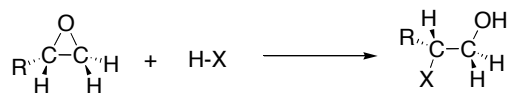
Reductive opening of epoxide is achieved with LiAlH_4



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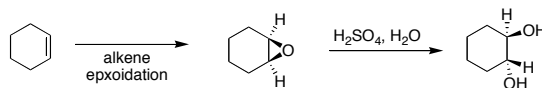
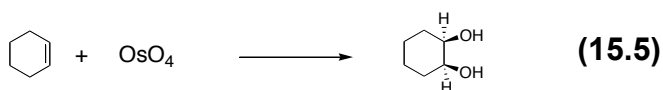
16.13: Acid-Catalyzed Ring Opening of Epoxides:

Epoxide opening with H-X gives a vicinal halohydrin
(reaction is not acid catalyzed)



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Preparation of syn- and anti- vicinal diols



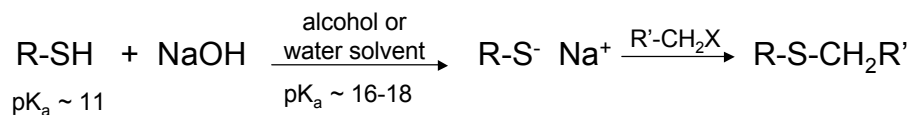
16.14 Epoxides in Biological Processes (please read)

In cells, epoxidation of C=C is carried out by enzymes called monooxygenases such as cytochrome P450's, flavoenzymes, etc., which activate O₂ and catalyze the oxygen transfer reaction

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16.15: Preparation of Sulfides

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

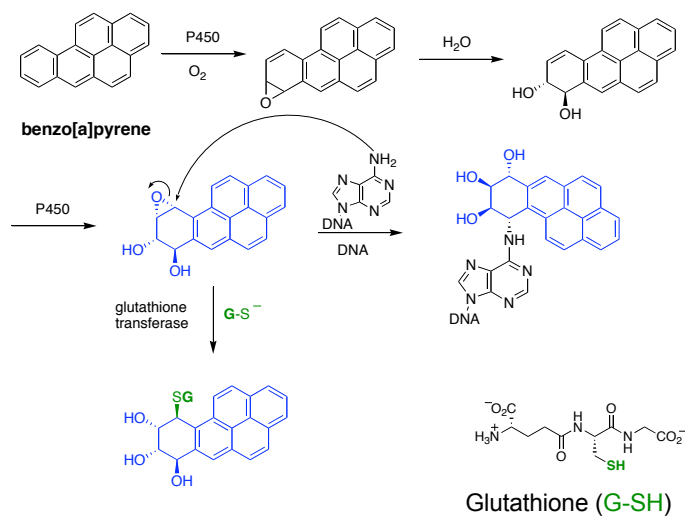


Thiolates are more reactive nucleophiles and less basic than alkoxides

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16.14 Epoxides in Biological Processes (please read)

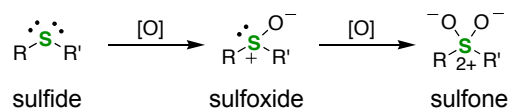
Bioactivation and detoxication of benzo[a]pyrene diol epoxide:



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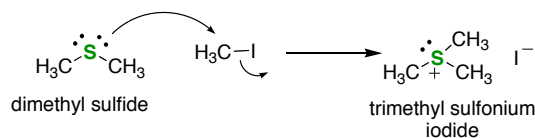
16.16: Oxidation of Sulfides: Sulfoxides and Sulfones (Please read)

Unlike ethers, sulfides can be oxidized to sulfoxides and further oxidized to sulfones



16.17: 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.

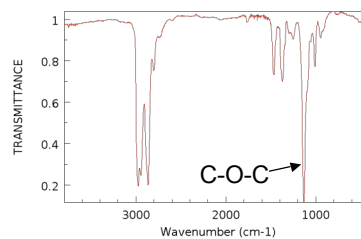


See S-adenosylmethionine (p. 685)

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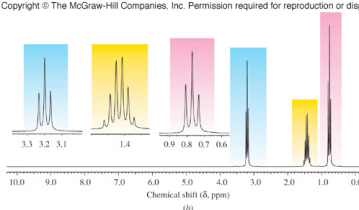
16.18: Spectroscopic Analysis of Ethers and Epoxides

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

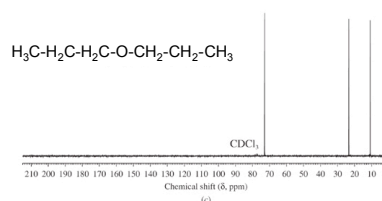


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^1H NMR: protons on the carbons that are part of the ether linkage are deshielded relative to alkanes. The chemical shift of these protons is from $\delta = 3.5 - 4.5$ ppm



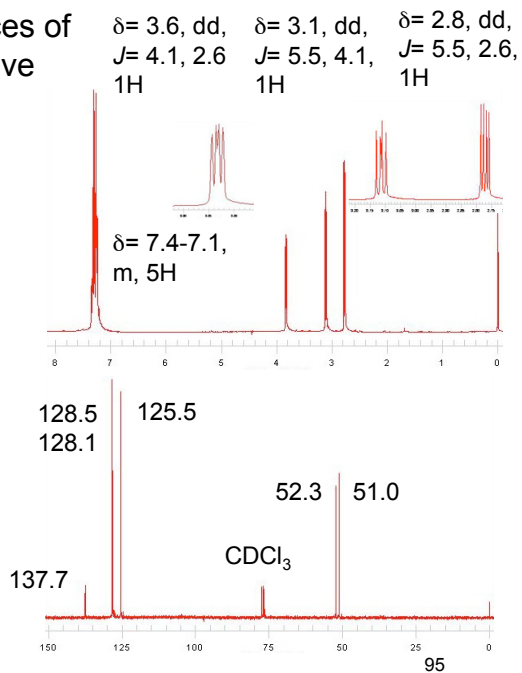
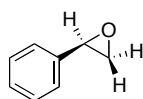
^{13}C NMR: the chemical shift of carbons that are part of the ether linkage are in the range of $\delta = 50 - 80$ ppm



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Protons and carbon resonances of an epoxide are shielded relative to those of a typical ethers

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



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

