

## 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) (Chapter 15.7)
- b) Addition of Alcohols to Alkenes (recall hydration of alkenes in Chapter 6.6 and oxymercuration on p. 258-261)

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**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.

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The Williamson Ether Synthesis:

- Few restrictions regarding the nature of the 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

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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<sub>2</sub> to form hydroperoxides

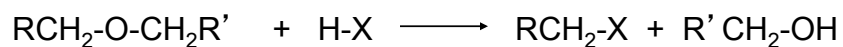
**16.8: Acid-Catalyzed Cleavage of Ethers**

Recall the reaction of an alcohol with HX to give a halide (Ch. 4.11)



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The mechanism for the acid cleavage of ethers is similar



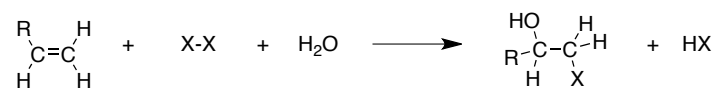
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### 16.9: Preparation of Epoxides: A Review and Preview

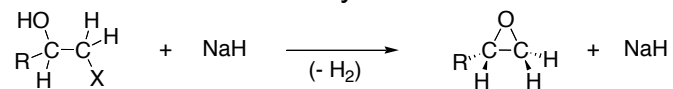
- 1) Epoxidation of alkenes (Chapter 6.11)
- 2) Base promoted ring closure of a vicinal halohydrin (Ch. 6.11)  
(this is an *intramolecular* Williamson ether synthesis)

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### 16.10: Conversion of Vicinal Halohydrins to Epoxides



An *Intramolecular* Williamson synthesis

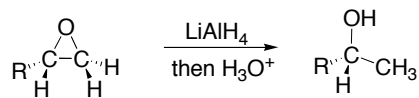


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### 16.11: Reactions of Epoxides with Anionic Nucleophiles

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

b) Reductive opening of epoxide is achieved with  $\text{LiAlH}_4$

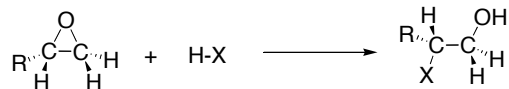


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c) Epoxide ring-opening by other nucleophiles - The ring opening of an epoxide is an  $\text{S}_{\text{N}}2$  reaction with nucleophiles such as amines and the anions of alcohols and thiols.

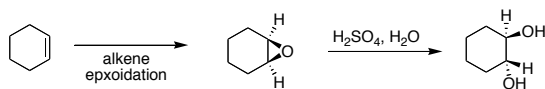
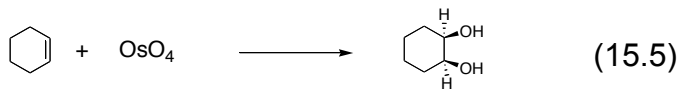
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**16.12: Acid-Catalyzed Ring Opening of Epoxides:**  
Epoxide opening with H-X gives a vicinal halohydrin



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Preparation of syn- and anti- vicinal diols

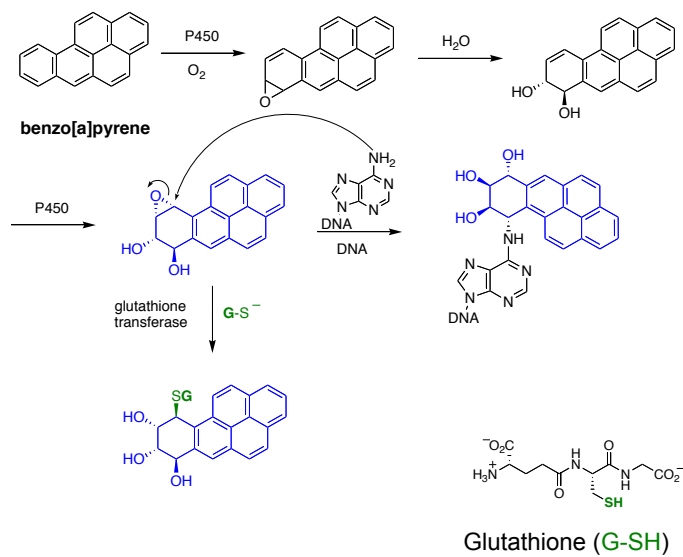


**16.13 Epoxides in Biological Processes** (please read)

In cells, epoxidation of C=C is carried out by enzymes called monooxygenases such as cytochrome P450's, flavoenzymes, etc., which activate O<sub>2</sub> and catalyze the oxygen transfer reaction

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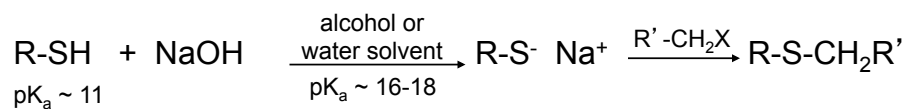
### Bioactivation and detoxication of benzo[a]pyrene diol epoxide:



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### 16.14: Preparation of Sulfides

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

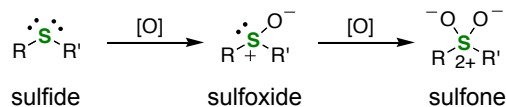


Thiolates are more reactive nucleophiles and less basic than alkoxides

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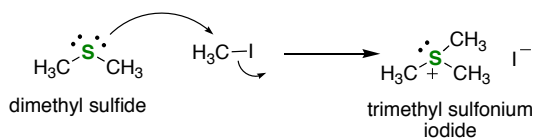
### 16.15: Oxidation of Sulfides: Sulfoxides and Sulfones

(please read) – Unlike ethers, sulfides can be oxidized to sulfoxides and further oxidized to sulfones



### 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)

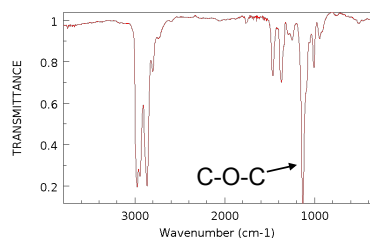
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### 16.17: Spectroscopic Analysis of Ethers, Epoxides and Sulfides

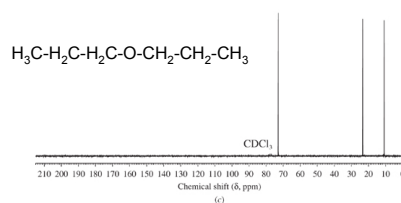
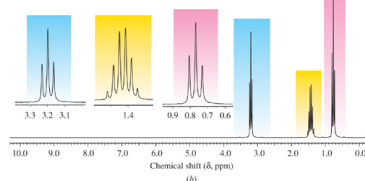
**IR spectroscopy:** not particularly diagnostic for the ether functional group. Strong C-O single bond stretch between 1050-1150  $\text{cm}^{-1}$

**$^1\text{H}$  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  $\delta = 3.0 - 4.0$  ppm

**$^{13}\text{C}$  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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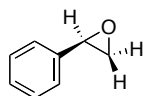
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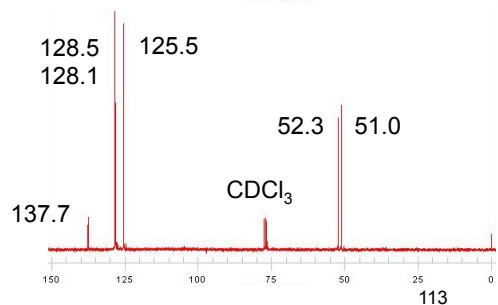
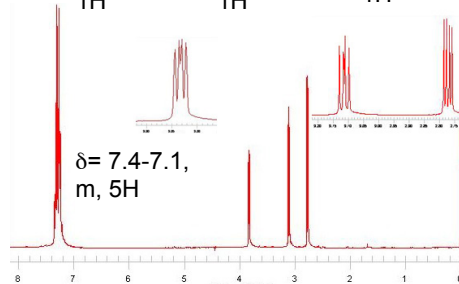
Protons and carbon resonances of an epoxide are shielded relative to those of a typical ethers

$^1\text{H}$  NMR:  $\delta = 2.2 - 3.2$  ppm

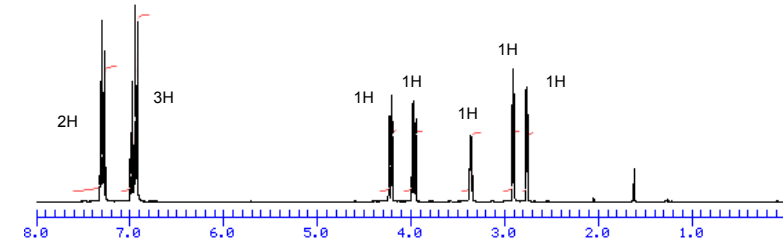
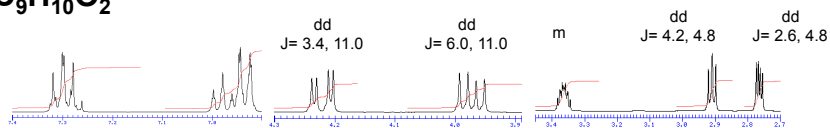
$^{13}\text{C}$  NMR:  $\delta = 40 - 60$  ppm



$\delta = 3.6$ , dd,  $J = 4.1, 2.6$ , 1H  
 $\delta = 3.1$ , dd,  $J = 5.5, 4.1$ , 1H  
 $\delta = 2.8$ , dd,  $J = 5.5, 2.6$ , 1H



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



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