

Chapter 14: Ethers and Epoxides; Thiols and Sulfides

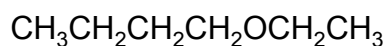
14.1 Introduction to Ethers – An ether group is an oxygen atom that is bonded to two carbons. The ether carbons can be part of alkyl, aryl, or vinyl groups.

14.2 Nomenclature of Ethers

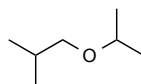
1. Name each –R group of the ether
2. Arrange them alphabetically
3. add “ether” to the name – three separate words

-or-

1. Make the larger of the –R groups the parent chain
2. Name the smaller of the –R groups as an alkoxy substituent



butyl ethyl ether
(1-ethoxybutane)

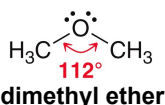
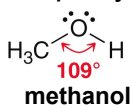
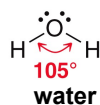


1-methylethyl 2-methylpropyl ether
(isobutyl isopropyl ether)
(1-isopropoxy-2-methylpropane)

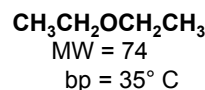
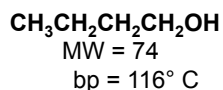
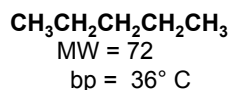
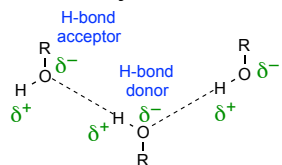
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14.3 Structure and Properties of Ethers

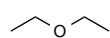
The O-atom of ethers is sp^3 hybridized



Ether can only act as a hydrogen bond acceptor



In general, the C-O bonds of ethers have low reactivity – this makes them good solvents for other reactions.



diethylether



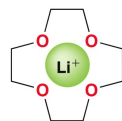
tetrahydrofuran



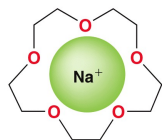
1,4-dioxane

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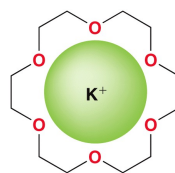
14.4 Crown Ethers (please read)



12-Crown-4
Solvates Li^+



15-Crown-5
Solvates Na^+

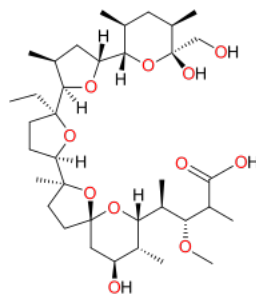
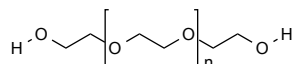


18-Crown-6
Solvates K^+



Polyethers

Polyethylene glycol (PEG)



Monensin – ionophore antibiotic

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16.5: Preparation of Ethers

a. Addition of alcohols to alkenes (recall hydration of alkenes in and oxymercuration from Chapter 9)

b. Condensation of alcohols (not very useful)

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c. *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°-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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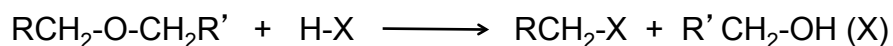
14.6 Reactions of Ethers – typical ethers are not very reactive

Acid Cleavage of Ethers

recall the reaction of an alcohol with HX to give a halide



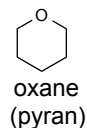
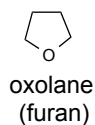
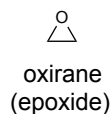
The mechanism for the acid cleavage of ethers is similar



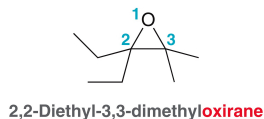
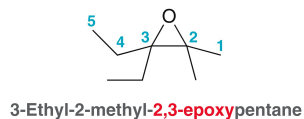
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Autoxidation (please read)

14.7 Nomenclature of Epoxides – a reactive cyclic ether



- The ether oxygen is treated as a substituent, and two numbers are given as designate its location; or
- Oxirane is used as the parent name



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14.8 Preparation of Epoxides

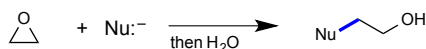
a. Reaction of alkenes with a peroxyacid (Chapter 9.9)

b. Base promoted ring closure of a vicinal halohydrin –this is an *intramolecular* Williamson ether synthesis.

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14.9 Enantioselective Epoxidation (please read) – the previous are stereospecific but not enantiospecific, and give racemic products. Epoxidations using a chiral catalysts can give epoxides in high enantiomeric excess.

14.10 Ring-opening of Epoxides – epoxides are more reactive than a typical ether do to the strain of the three-membered ring. Epoxides undergo ring-opening reaction with nucleophiles.



Nu:⁻ = HO⁻ (hydroxide)
RO⁻ (alkoxides)
RS⁻ (thiolates)
-CN (cyanide)
R-MgBr (Grignard reagents)
H⁻ (LAH)

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Regio- and stereochemistry of epoxide opening

Epoxides react with anionic nucleophiles (under basic conditions) through an S_N2 . The nucleophile adds to the less hindered (substituted) carbon of unsymmetrical epoxides and there is inversion of stereochemistry at the carbon undergoing substitution.

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The regiochemistry of epoxide opening under acidic conditions is dependent on the substitution of the epoxide.

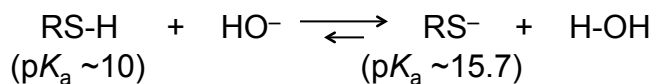
Nucleophiles will preferentially add to a tertiary carbon over primary or secondary under acidic conditions (S_N1 like regiochemistry). The ring opening proceeds with inversion of stereochemistry. Nucleophiles will preferentially add to a primary carbon over a secondary (S_N2 like regiochemistry).

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14.11 Thiols and Sulfides

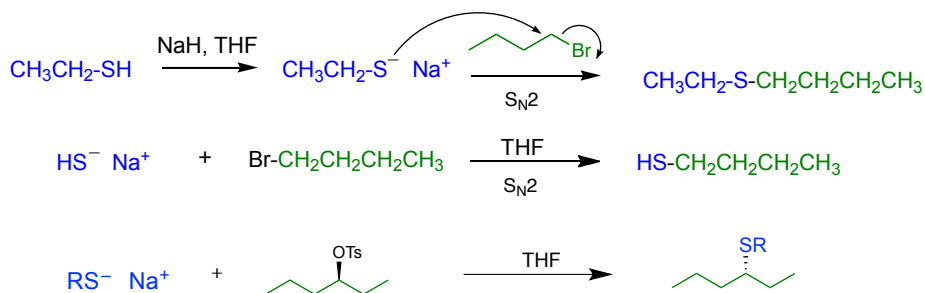
Thiols (mercaptans) are sulfur analogues of alcohols.

Thiols have a $pK_a \sim 10$ and are stronger acids than alcohols.



RS^- and HS^- are weakly basic and strong nucleophiles.

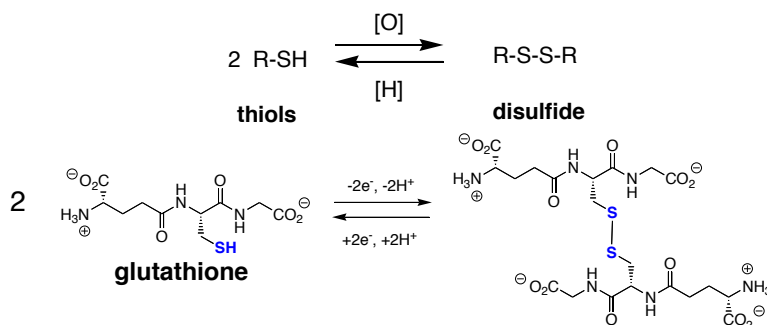
Thiolates react with 1° and 2° alkyl halides to yield sulfides ($\text{S}_\text{N}2$).



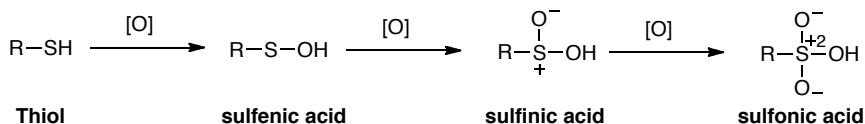
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Oxidation States of organosulfur compounds

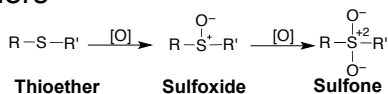
Thiols can be oxidized to disulfides



Oxidation of thiols to sulfonic acids

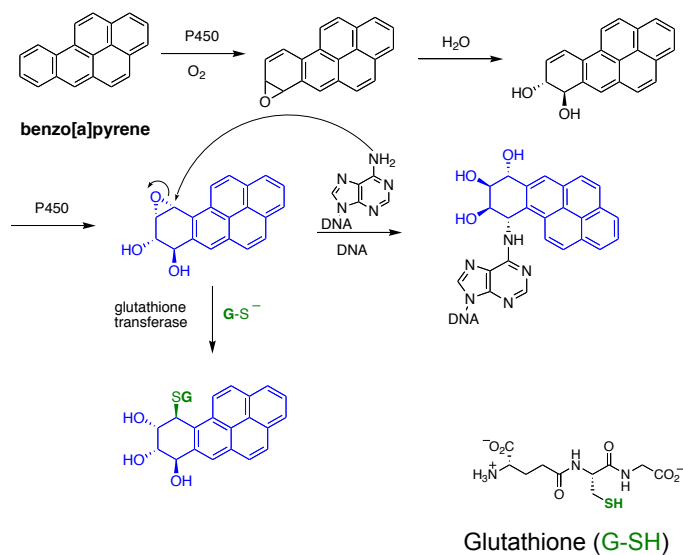


Oxidation of thioethers



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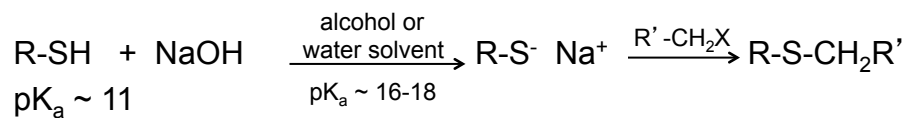
Bioactivation and detoxication of benzo[a]pyrene diol epoxide:



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Sulfides (thioethers) – sulfur analogs of ethers.

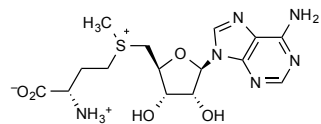
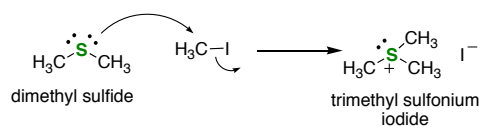
Reaction of a thiolate anions with 1° and 2° alkyl halides and tosylates (analogous to the Williamson ether synthesis)



Thiolates are more reactive nucleophiles and less basic than alkoxides

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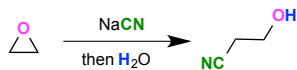
Alkylation of Sulfides to Sulfonium Salts – The sulfur atom of sulfides is much more nucleophilic than the oxygen atom of ethers, and will react with alkyl halides to give stable sulfonium salts.



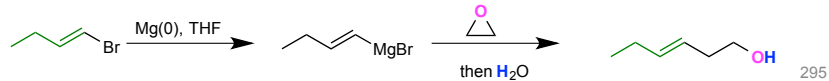
S-adenosylmethionine (SAM)

14.12 Synthesis Strategies Involving Epoxides

Epoxide ring opening by a nucleophile installs two functional groups on adjacent positions



or extend a carbon chain by 2 (or more)



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