

Ethers, Epoxides, and Sulfides

Reading: Wade chapter 14, sections 14-1- 14-15

Study Problems: 14-33, 14-37, 14-38, 14-43, 14-44

Key Concepts and Skills:

- Draw and name ethers and heterocyclic ethers
- Explain how ethers can dissolve a wide range of substances including electrophilic reagents, and how ethers are compatible with organometallic reagents.
- Devise efficient laboratory syntheses of ethers and epoxides
- Predict the products of reactions of ethers and epoxides

Lecture Topics:

I. Ethers

General structure: R-O-R'

Examples: $\text{CH}_3\text{-O-CH}_3$ (dimethyl ether), $\text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3$ (diethyl ether)

Structure of tetrahydrofuran, THF:

•Ethers are good solvents for a variety of reasons:

-chemically inert

-unlike alcohols, ether molecules cannot hydrogen bond to each other, resulting in lower boiling points than alcohols.

- Because of their dipolar nature, ethers are good at dissolving a variety of polar and non-polar compounds:

•Ethers can H-bond with alcohols (resulting in solubility of alcohols in ethers) and they can solvate metal cations by coordination of the lone pairs on oxygen:

•Ethers are also essential solvents for the preparation and use of Grignard reagents. Highly basic species (NaNH_2 , RMgBr , RLi) react with protic solvents (H_2O , ROH) by deprotonation, but ethers are chemically inert and can stabilize metal ions by lone-pair coordination, a Lewis acid-Lewis base interaction:

•Ethers stabilize highly reactive electrophilic reagents (such as BH_3 , BF_3 , and even carbocations R_3C^+) by coordination of the oxygen lone pairs, a Lewis acid/Lewis base interaction:

Review the nomenclature of ethers presents in the text!

II. Cyclic Ethers are heterocyclic compounds.

Heterocycles are cyclic compounds containing at least one heteroatom (N, O, S)

Epoxides are three-membered rings containing oxygen. Epoxides are prepared from alkenes by the action of peracids such as MCPBA and CH_3COOOH (peracetic acid):

Oxetanes are four-membered cyclic ethers, **furans** are five-membered cyclic ethers, **pyrans** are six-membered cyclic ethers, and **dioxanes** are six-membered rings containing two oxygen atoms:

III. Spectroscopy:

IR- Other than in the fingerprint region of IR spectra (C-O stretch around $1000\text{-}1200\text{ cm}^{-1}$) there are no reliable absorptions indicating the presence of ethers.

NMR- Chemical shifts in both ^1H and ^{13}C spectra indicate the presence of ethers:

IV. Synthesis of ethers.

•The Williamson ether synthesis involves $\text{S}_{\text{N}}2$ attack of an alkoxide (generated by treating an alcohol with sodium hydride) on a primary alkyl halide:

•Alkoxymercuration allows us to prepare ethers from alkenes. The alcohol attacks the mercurinium ion at the more substituted carbon atom:

V. Reactions of Ethers

•Ethers are relatively unreactive to a variety of acidic and basic reagents, and this is why they are commonly used as solvents.

1. Ethers can be cleaved by the action of hydrohalic acids
2. In the presence of atmospheric oxygen, ethers undergo autoxidation to peroxides and dialkyl peroxides.

VI. Sulfides

Sulfides are the sulfur analogs of ethers: $\text{R-S-R}'$

Examples: CH_3SCH_3 (dimethyl sulfide), $\text{C}_6\text{H}_5\text{-S-CH}_3$ (methyl phenyl sulfide)

- Sulfides can also be easily prepared by the Williamson ether synthesis:

- Facile oxidation of sulfides occurs in the presence of mild oxidants: $\text{H}_2\text{O}_2/\text{CH}_3\text{COOH}$ or MCPBA. 1 equivalent of oxidant gives the **sulfoxide**; 2 equivalents gives the **sulfone**. Since sulfur is in the third row of the periodic table, it can hybridize empty 3d orbitals to create bonds to additional atoms:

- Because of the ease of their oxidation, sulfides are frequently used as mild reducing agents in ozonolysis.

VII. Epoxides

1. Synthesis:

- Peracid oxidation of alkenes is the most common method for synthesis of epoxides (see above)
- Base-promoted cyclization of halohydrins is another common synthetic method for preparing epoxides.

Interestingly, 1,4-halohydrins yield tetrahydrofurans upon cyclization; a mild, non-nucleophilic base such as 2,6-lutidine is necessary for this operation.

2. Reactions of epoxides.

a. Acid-catalyzed ring opening. In this reaction, a Bronsted or Lewis acid serves to activate the epoxide oxygen as a good leaving group, and a nucleophile opens the epoxonium ion via SN2 backside attack:

Regiochemistry .Under acidic conditions, nucleophiles attack activated epoxides at the most substituted carbon, since this carbon is more electrophilic by virtue of the greater stability of the more substituted carbocation resonance form of the activated epoxide:

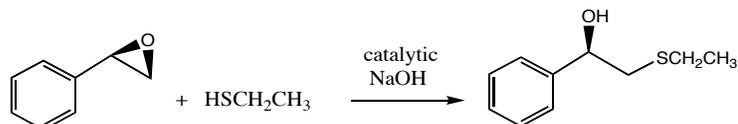
b. Base-catalyzed ring opening. Strong nucleophiles are able to open epoxides; the ring strain (~25 kcal/mol) of epoxides makes the oxygen atom a good leaving group. Grignard and organolithium reagents, which are very strongly nucleophilic/basic, also can ring-open epoxides.

Regiochemistry. Under basic conditions, nucleophiles attack the sterically less hindered carbon atom of the epoxide:

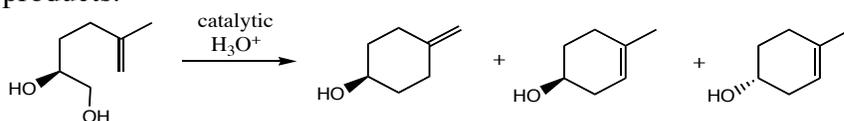
•Grignard Reagents (RMgBr), organolithiums (RLi), and LiAlH₄, provide the strong nucleophiles R⁻ and H⁻ which also attack epoxides at the less substituted carbon atom of the epoxide:

Additional Problems for practice:

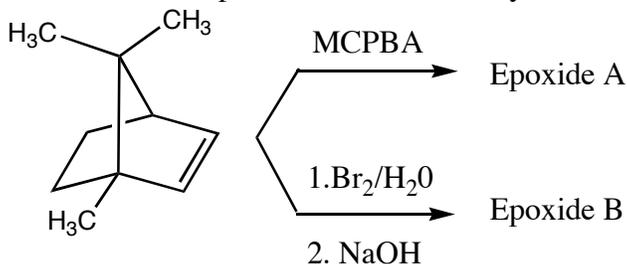
1. Draw a mechanism for the following reaction, and rationalize the stereochemical outcome:



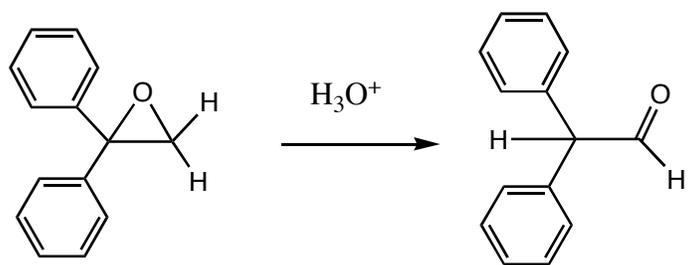
2. Draw a likely mechanism for the following reaction, rationalizing the formation of all products:



3. Two different epoxides, A and B are generated under the following conditions. Predict the structure of each epoxide and rationalize your result.



4. Treatment of 1,1 diphenyl-1,2-epoxyethane with aqueous acid yields diphenylacetaldehyde as the major product. Propose a mechanism to account for the reaction.



diphenylacetaldehyde