

STUDY GUIDE FOR CHAPTER 16

1. Definition.
 - A. Ethers – compounds with oxygen atom bound to two alkyl (or aryl) groups;
 - B. Epoxides – the smallest cyclic ethers, with three-membered rings;
 - C. Sulfides – analogs of ethers, with sulfur instead of oxygen;
2. Nomenclature:
 - A. Ethers – can be named either as alkoxyalkanes or as alkyl ethers. In the second case the alkyl groups are written in alphabetical order;
 - B. Sulfides – can be named either as alkylthioalkanes or alkyl sulfides.
 - C. Cyclic ethers and sulfides – IUPAC has a designated suffix for each ring size:
 - a. Three-membered – “**-irane**”: oxirane, thiirane, azirane;
 - b. Four-membered – “**-etane**”: oxetane, thietane, azetane;
 - c. Five-membered – “**-olane**”: oxolane, thiolane, azolane;
 - d. Six-membered – “**-ane**”: oxane, thiane, azane;
 - e. Seven-membered – “**-epine**”: oxepine, thiepine, azepine;

If more than one heteroatom is present in the ring, then prefixes are used: 1,4-dioxane, dioxirane, etc.
3. Electronic Structure of Ethers and Epoxides – they contain sp^3 -hybridized, tetrahedral oxygen in analogy with alcohols and water. The bond angles at oxygen are similar. Because of electronegativity difference, the molecules possess dipole moments, comparable with those of alcohols.
4. Physical properties:
 - A. Boiling points – considerably lower than those of isomeric alcohols, more comparable to alkanes. Reason: Ether molecules cannot form hydrogen bonds between themselves.
 - B. Solubility – solubility in water is similar to that of alcohols. Reason: Ethers can form hydrogen bonds with molecules possessing mobile hydrogen atoms, such as water or alcohols. Ethers participate as hydrogen bond acceptors with the lone pairs of oxygen. Conclusion: Ethers cannot serve as H-bond donors, but can be H-bond acceptors.
5. Ethers as Lewis Bases. Crown Ethers – due to the unshared pairs at oxygen, ethers can serve as relatively strong *Lewis* bases and form various complexes with *Lewis* acids: $\text{BH}_3\cdot\text{THF}$, $(\text{C}_2\text{H}_5)_2\text{O}\cdot\text{BF}_3$. Ethers can also coordinate to various metal cations, particularly alkali (or alkaline earth) metals. One group of cyclic ethers, the so-called crown ethers are particularly good at binding metal cations. They have different cavity sizes and are thus capable of binding different cations (different in size!). 18-Crown-6 is best for K^+ , 15-crown-5 is most suitable for Na^+ , while 12-crown-4 is best for Li^+ . Because of their strong binding ability, crown ethers are often added to reactions with ionic reagents, in which the reacting part is the anion (e.g. alkali fluorides, cyanides, azides, permanganates, etc.). The cation is bound by the crown ether, which ensures solubility, while the anion, in the organic solvent, is practically free of solvation and thus very reactive.
6. Preparation of ethers:
 - A. Condensation of two alcohol molecules, catalyzed by acid – industrial method for the preparation of symmetrical ethers: diethyl ether, diisopropyl ether;
 - B. Addition of alcohol to alkene, catalyzed by acid – industrial method for the preparation of mixed ethers – MTBE;
 - C. *Williamson* ether synthesis – $\text{S}_{\text{N}}2$ reaction of alkoxide and alkyl halide. Works best with methyl or primary halides. Retrosynthetic analysis: One must never choose a tertiary (or aryl) halide as a starting material in the *Williamson* ether synthesis!!
7. Preparation of epoxides:
 - A. Epoxidation of alkenes with peracids (Chapter 6);

- B. Base-promoted ring closure of vicinal halohydrines – an intramolecular analog to the *Williamson* ether synthesis. Halohydrines are prepared by addition of halogen in the presence of water (Chapter 6).

8. Reactions of Ethers:

- A. Acid-catalyzed cleavage – conducted with hydrohalic acids (mostly HI and HBr, HCl less efficient!). In the case of dialkyl ethers, it involves TWO S_N2 reactions, yielding TWO molecules of alkyl halides (same or different). In the case of aryl ethers, the aryl part is converted only to phenol.
- B. Formation of peroxides – ethers react slowly with atmospheric oxygen (or other oxidizers) to form explosive peroxides.

9. Reactions of Epoxides:

- A. Ring-opening in basic conditions (Nucleophilic ring-opening) – reactions take place in conditions in which strong nucleophiles can exist. The reaction is initiated by a direct attack of the nucleophile on the epoxide ring, leading to ring-opening. The nucleophile attacks the less substituted (i.e. less sterically congested carbon);
- B. Ring opening in acidic conditions – the reaction requires a preliminary step of protonation (and activation) of the epoxide, followed by a nucleophilic attack. The nucleophile attacks the more substituted (more positively charged) carbon of the epoxide ring. Thus, the two sets of conditions provide for opposite regiochemistry. The attack of the nucleophile, in acidic or basic conditions, is always from the backside and results in an *anti*-stereochemistry. Thus, epoxidation followed by hydrolysis achieves *anti*-hydroxylation, while oxidation of alkenes with OsO_4 results in *syn*-hydroxylation.

10. Sulfides.

- A. Preparation – it is based on a reaction analogous to the *Williamson* ether synthesis, utilizing alkylthiolate anions instead;
- B. Oxidation – sulfides can be oxidized to sulfoxides or sulfones. Sulfoxide is an intermediate stage and can be achieved either by special reagents (such as sodium metaperiodate) or 1 equivalent of oxidizer such as peracid. Often employed practically is the mixture of hydrogen peroxide and acetic acid, which is believed to generate peracetic acid in the reaction conditions.
- C. Alkylation of sulfides – even though neutral, sulfides are still quite strong nucleophiles and can be alkylated to produce sulfonium salts;

11. Spectroscopy of Ethers, Epoxides and Sulfides.

- A. 1H NMR – for ethers most characteristic are the shifts of H-atoms on a carbon attached to oxygen. In sulfides their signals are about 1 ppm upfield shifted. Three-membered rings tend to exhibit considerably upfield shifted H-signals. This counter-balances the effect of oxygen, resulting in a compromise average shift of about 2.5 ppm.
- B. ^{13}C NMR – carbon atoms attached to oxygen are at 60 – 85 ppm. In sulfides their signals are significantly more upfield.
- C. MS – ethers tend to undergo α -cleavage, resulting in a stabilized carbocation;