Ethers and Epoxides; Thiols and Sulfides

B. Pharm. Semester-1
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Dr. BALAKUMAR CHANDRASEKARAN
Professor-Faculty of Pharmacy
Philadelphia University-Jordan

Learning Outcomes

At the end of this lesson, students will be able to describe

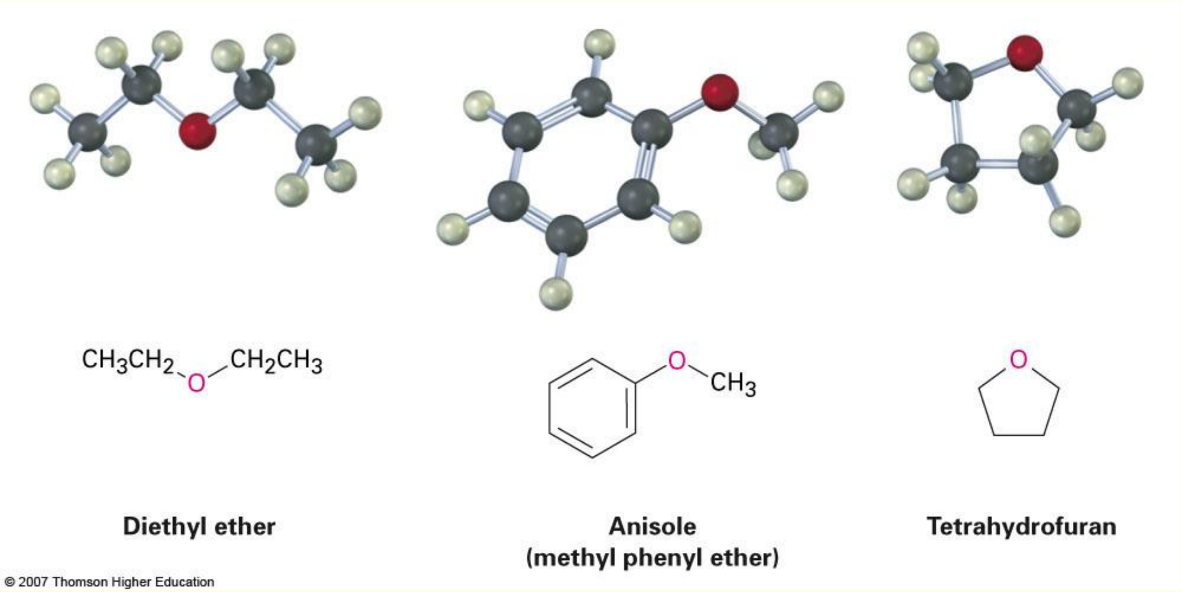
- **Ethers: Names and properties**
- **Ethers: Preparations and Reactions**
- **Cyclic Ethers: Epoxides**
- **Epoxides: Preparations and Reactions**
- **Crown Ethers**
- **Thiols and Sulfides**
- **Spectroscopy of Ethers**

Objective

The objective of this course is to give to the students of pharmacy the basic knowledge about the organic chemistry.

Ethers and Their Relative compounds

- An ether has two organic groups (alkyl, aryl, or vinyl) bonded to the same oxygen atom, R–O–R^1.
- Diethyl ether is used industrially as a solvent.
- Tetrahydrofuran (THF) is a solvent that is a cyclic ether.
- Thiols (R–S–H) and sulfides (R–S–R^1) are sulfur (for oxygen) analogs of alcohols and ethers.

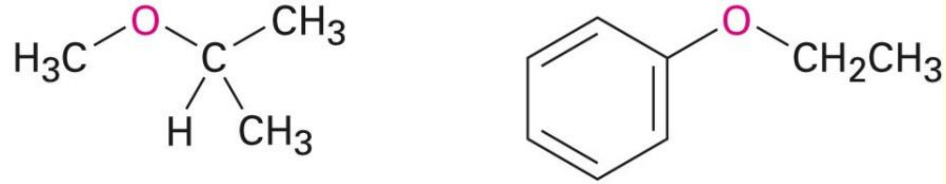


Why this Chapter?

- To finish covering functional groups with C-O and C-S single bonds.
- To focus on ethers and look at thiols and sulfides before going on to carbonyl group (C=O).

Names and Properties of Ethers

Ethers are named by identifying the two organic substituents and adding the word *ether*.



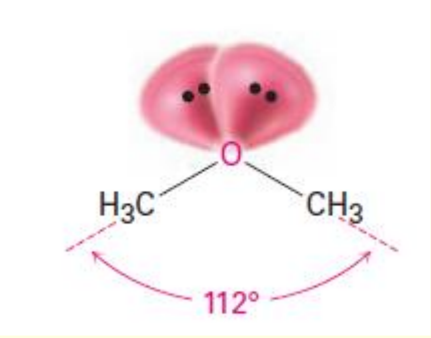
Isopropyl methyl ether **Ethyl phenyl ether**

Ethers If other functional groups are present, the ether part is considered an *alkoxy* substituent.

***p*-Dimethoxybenzene** **4-*tert*-Butoxy-1-cyclohexene**

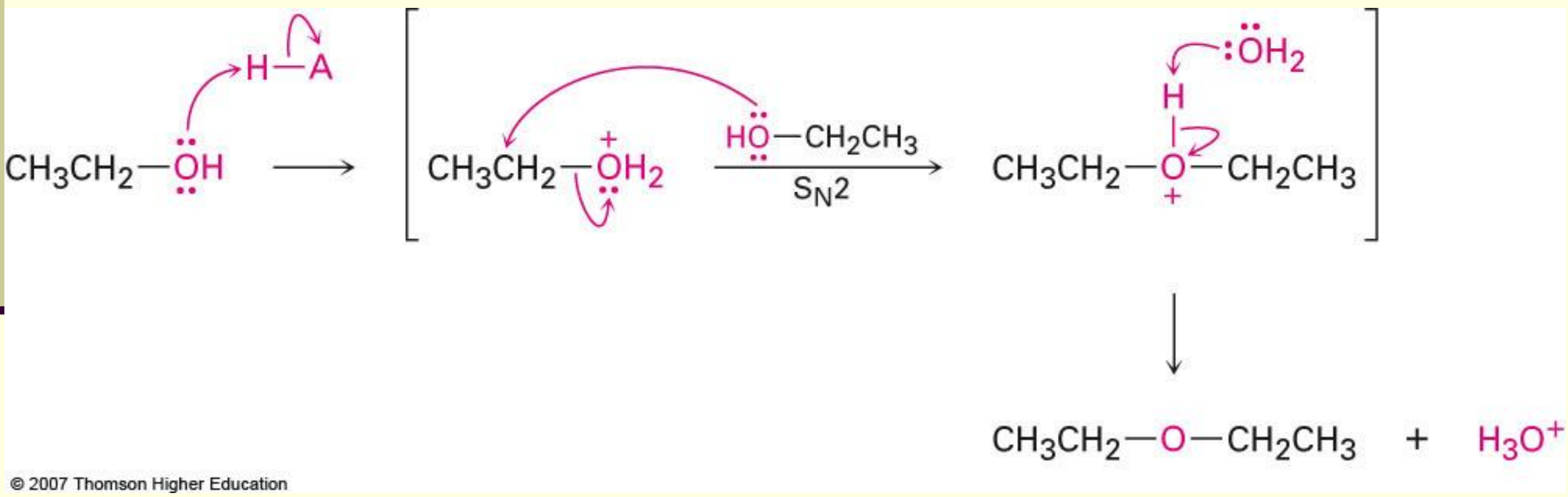
Names and Properties of Ethers

- Like alcohols, ethers have nearly the same geometry as water.
- The R-O-R bonds have an approximately tetrahedral bond angle (112° in dimethyl ether), and the oxygen atom is sp3-hybridized.
- The electronegative oxygen atom gives ethers a slight dipole moment, and the boiling points of ethers are often slightly higher than the boiling points of comparable alkanes.



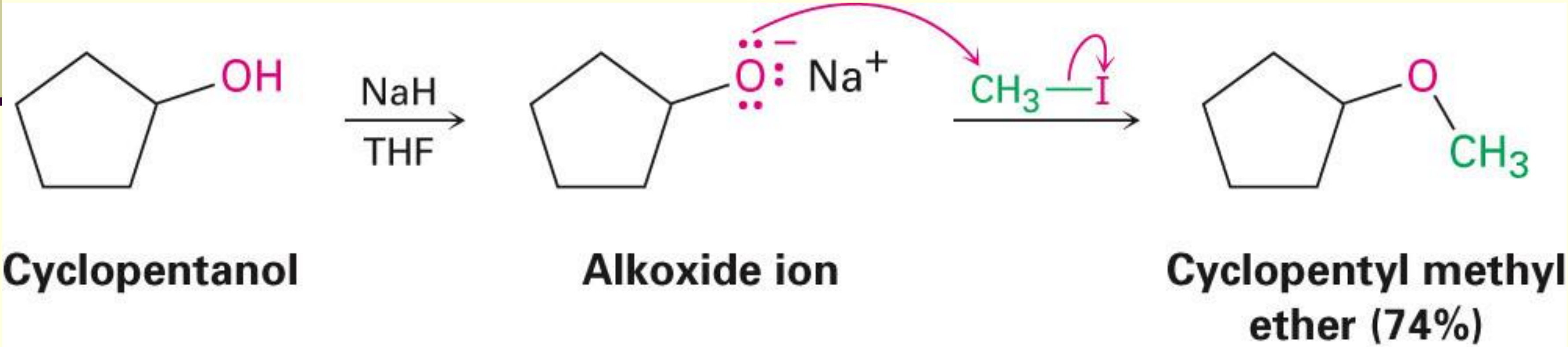
Synthesis of Ethers: Industry method

Diethyl ether is prepared industrially by sulfuric acid–catalyzed dehydration of ethanol – also with other primary alcohols.



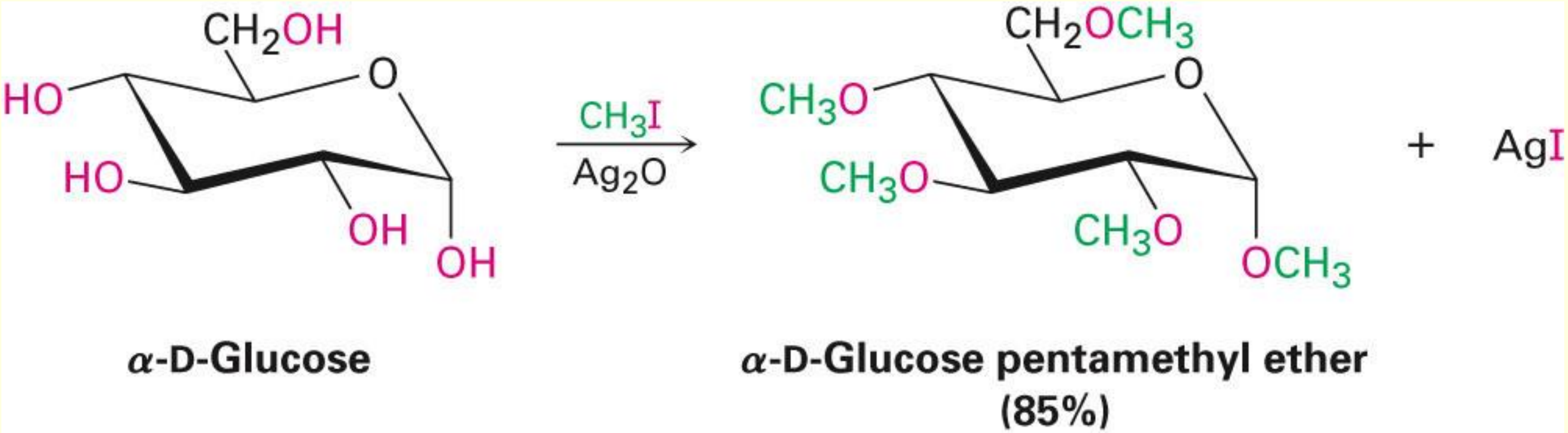
The Williamson Synthesis of Ethers

The most generally useful method of preparing ethers is by the *Williamson ether synthesis*, in which an alkoxide ion reacts with a primary alkyl halide or tosylate in an SN^2 reaction.
The alkoxide ion is normally prepared by reaction of an alcohol with a strong base such as sodium hydride, NaH.



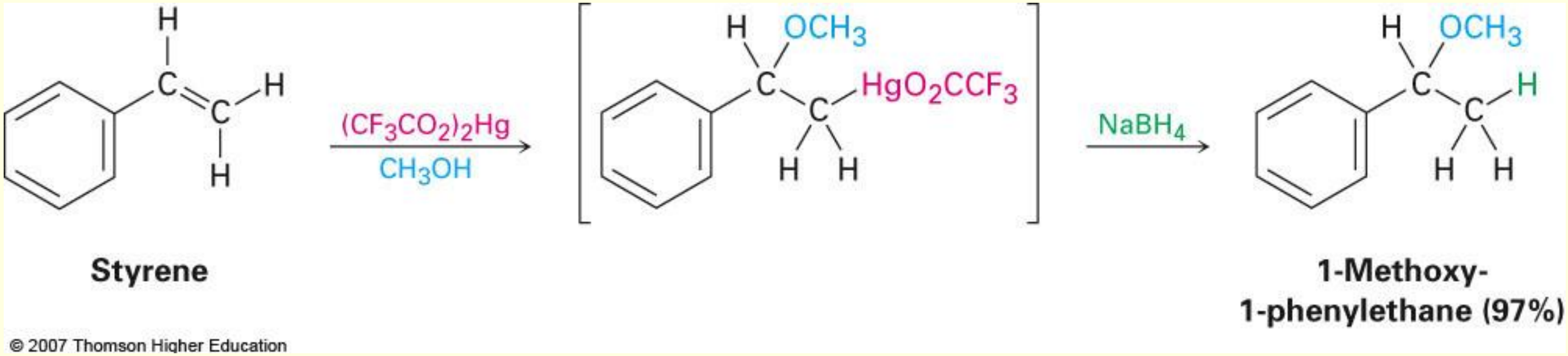
Silver Oxide-Catalyzed Ether Synthesis

Reaction of alcohols with Ag_2O directly with alkyl halide forms ether in one step
Glucose reacts with excess iodomethane in the presence of Ag_2O to generate a pentaether in 85% yield.



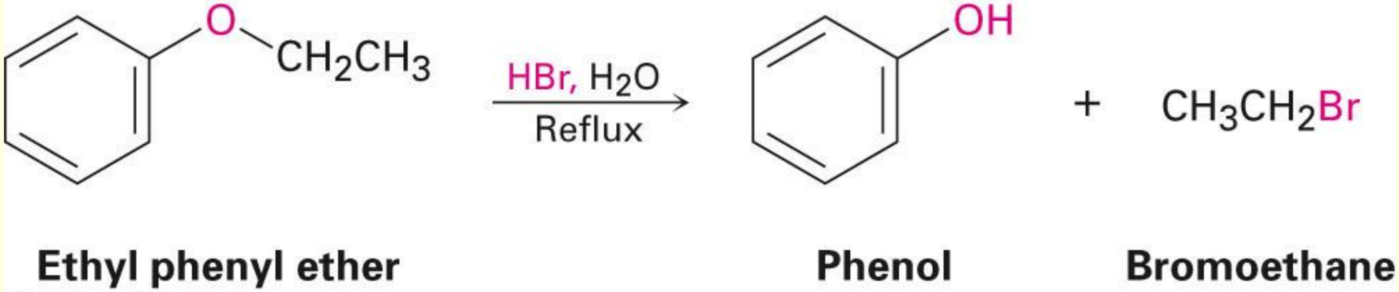
Alkoxymercuration of Alkenes

- Alkenes react with water in the presence of mercuric acetate to yield a hydroxymercuration product. Subsequent treatment with $NaBH_4$ breaks the C-Hg bond and yields the alcohol.
- Overall Markovnikov addition of alcohol to alkene takes place.



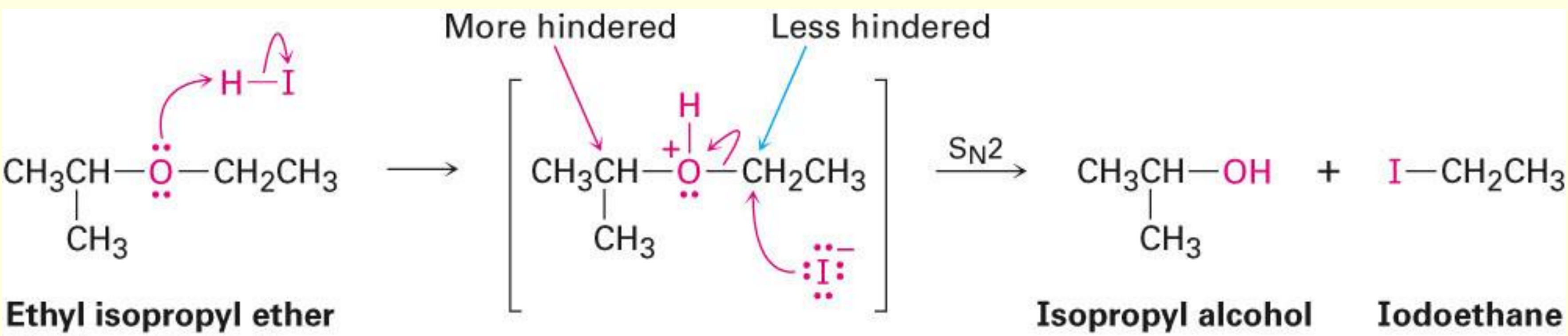
Reactions of Ethers: Acidic Cleavage

- Ethers are unreactive to many reagents used in organic chemistry, a property that accounts for their wide use as reaction solvents.
- Halogens, dilute acids, bases, and nucleophiles have no effect on most ethers.
- Ethers undergo only one truly general reaction—they are cleaved by strong acids.
- Aqueous HBr and HI both work well, but HCl does not cleave ethers.



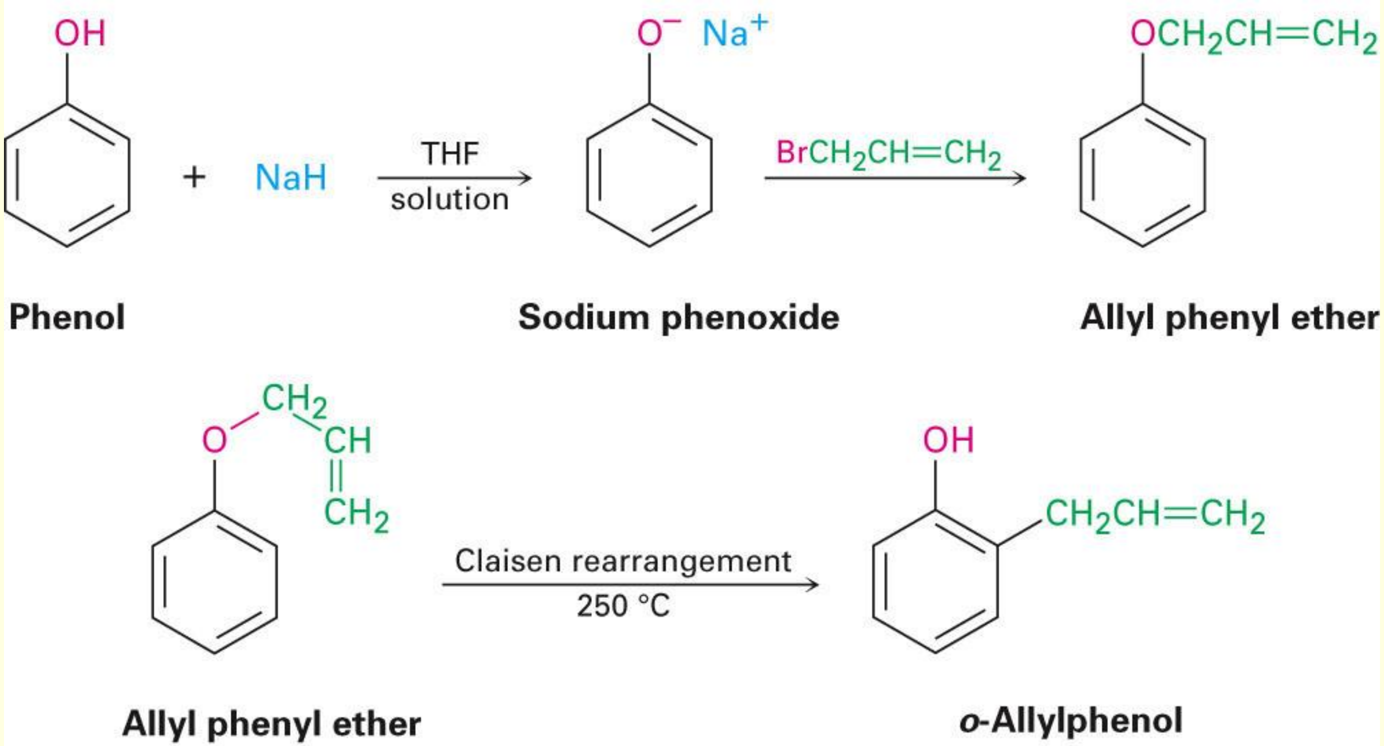
Reactions of Ethers: Acidic Cleavage

- Acidic ether cleavages are typical nucleophilic substitution reactions and take place by either SN^1 or SN^2 mechanisms depending on the structure of the substrate.
- Ethers with only primary and secondary alkyl groups react by an SN^2 mechanism, in which I_2 or Br_2 attacks the protonated ether at the less hindered site.



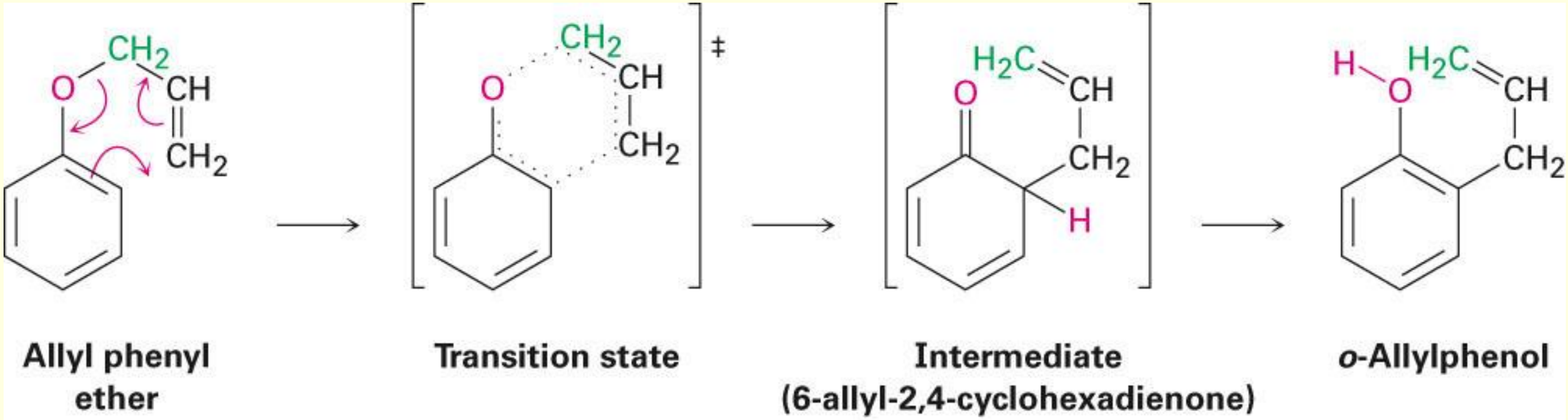
Reactions of Ethers: Claisen Rearrangement

- Specific to allyl aryl ethers, $ArOCH_2CH{=}CH_2$
- Heating to 200–250°C leads to an o-allylphenol
- Result is alkylation of the phenol in an ortho position.



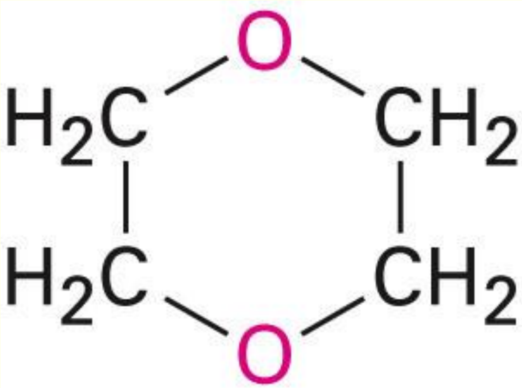
Reactions of Ethers: Claisen Rearrangement

Concerted pericyclic 6-electron, 6-membered ring transition state.

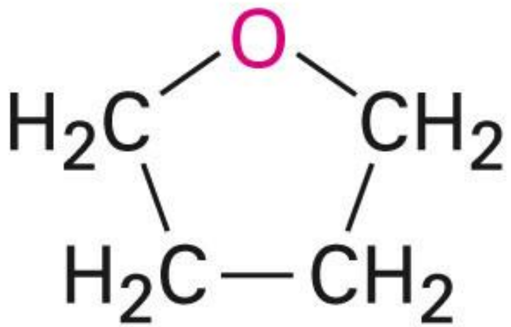


Cyclic Ethers: Epoxides

- Cyclic ethers behave like acyclic ethers, except if ring is 3-membered.
- Dioxane and tetrahydrofuran are used as solvents.



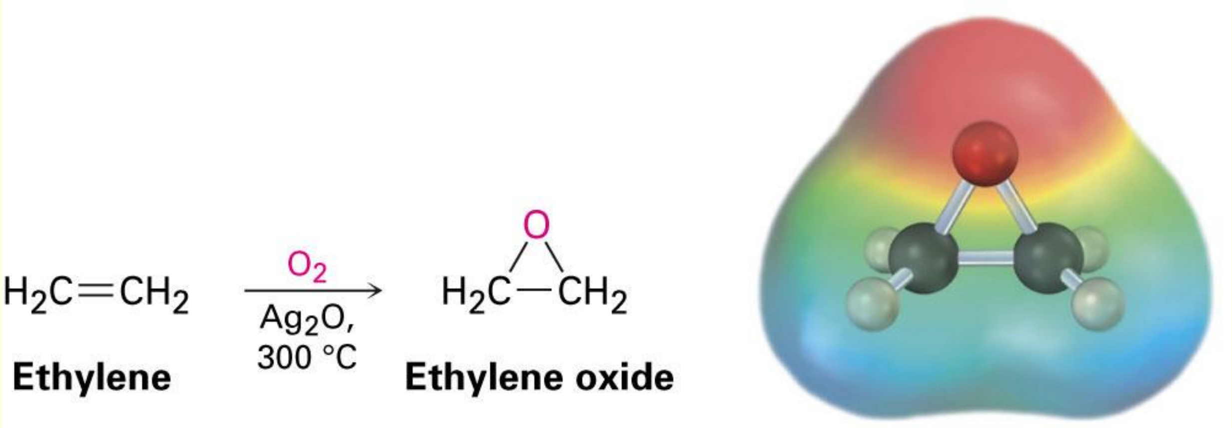
1,4-Dioxane



Tetrahydrofuran

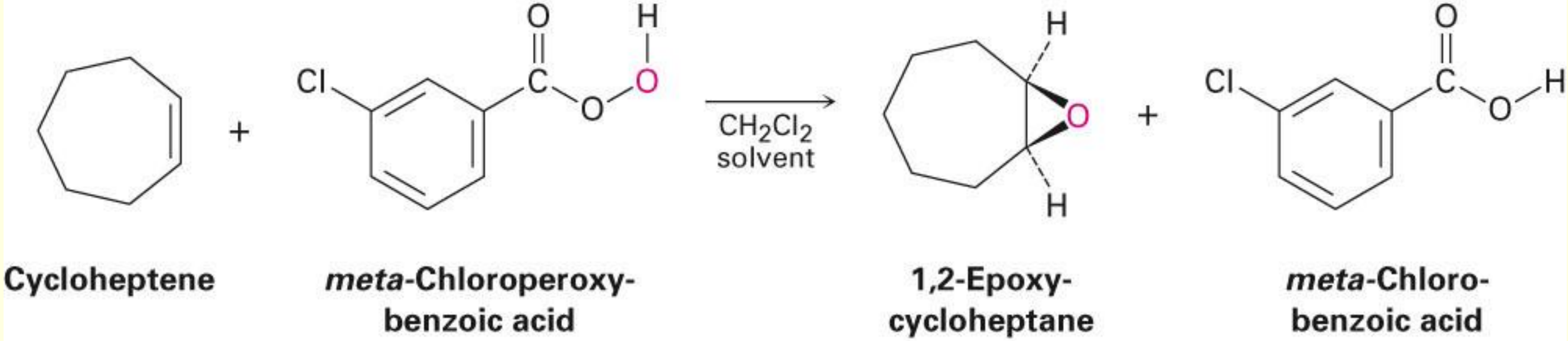
Epoxides (Oxiranes)

- Three membered ring ether is called an oxirane (root “ir” from “tri” for 3-membered; prefix “ox” for oxygen; “ane” for saturated), also called epoxides.
- Ethylene oxide (oxirane; 1,2-epoxyethane) is industrially important as an intermediate.
- **Prepared** by reaction of ethylene with oxygen at 300 °C and silver oxide catalyst.



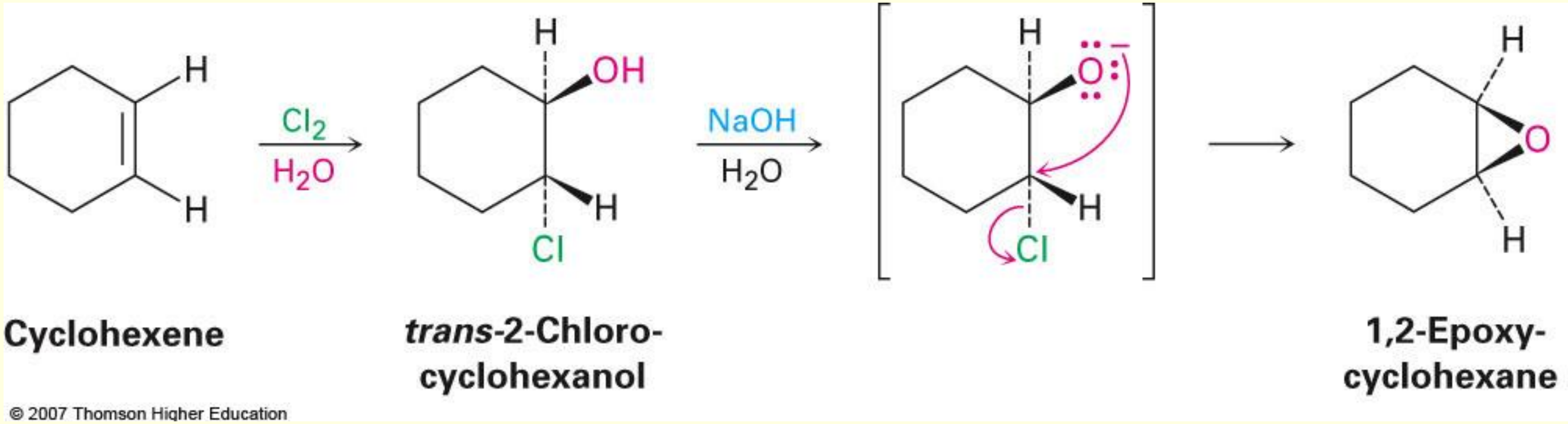
Preparation of Epoxides using a Peroxyacid

- Epoxides are usually prepared by the treatment of an alkene with a peroxyacid (RCO_3H), typically *m*-chloroperoxybenzoic acid.



Preparation of Epoxides using Halohydrins

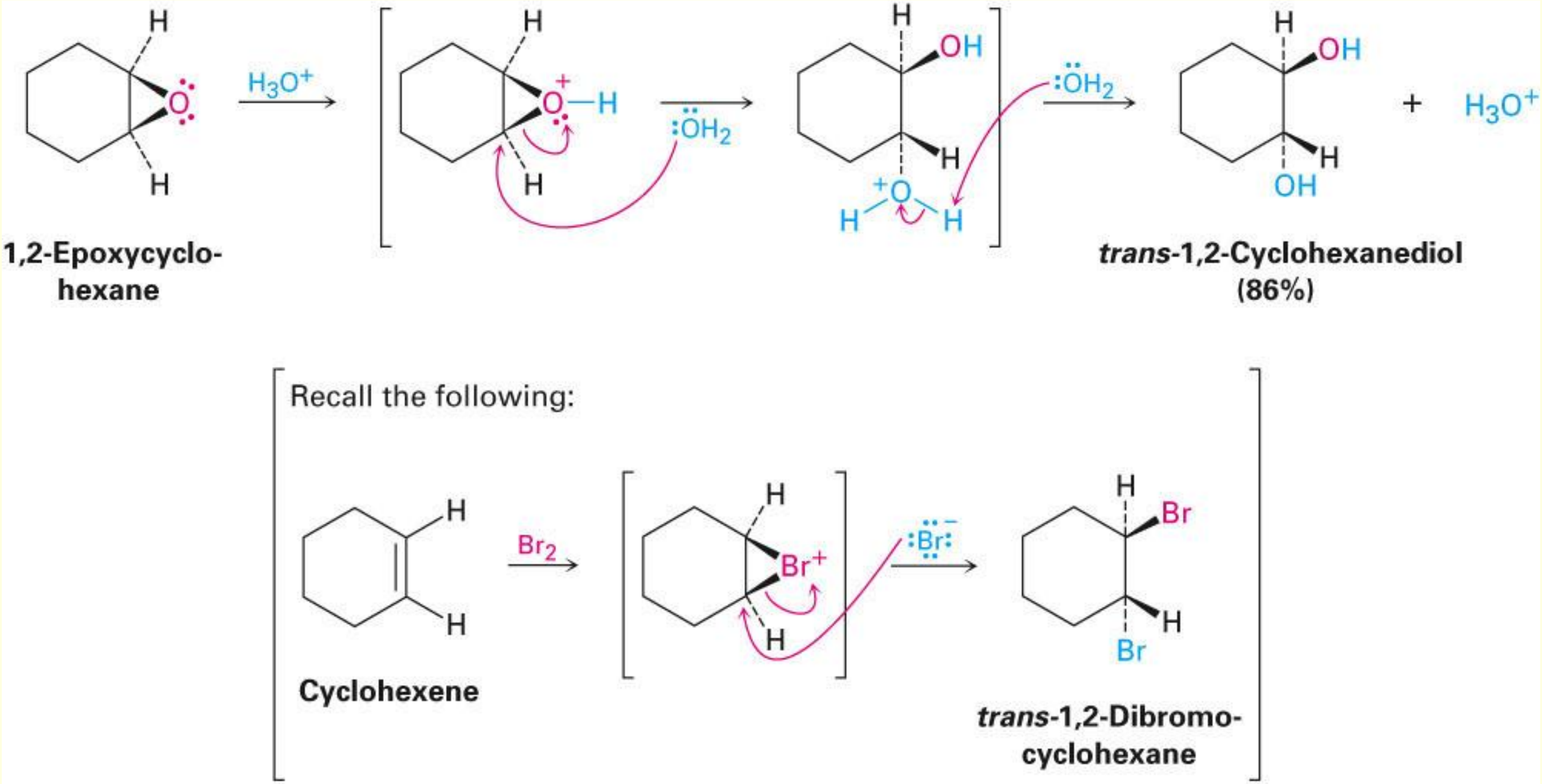
- When a halohydrin is treated with base, HX is eliminated and an epoxide is produced by an intramolecular Williamson ether synthesis.
- That is, the nucleophilic alkoxide ion and the electrophilic alkyl halide are in the same molecule.



Reactions of Epoxides: Ring-Opening

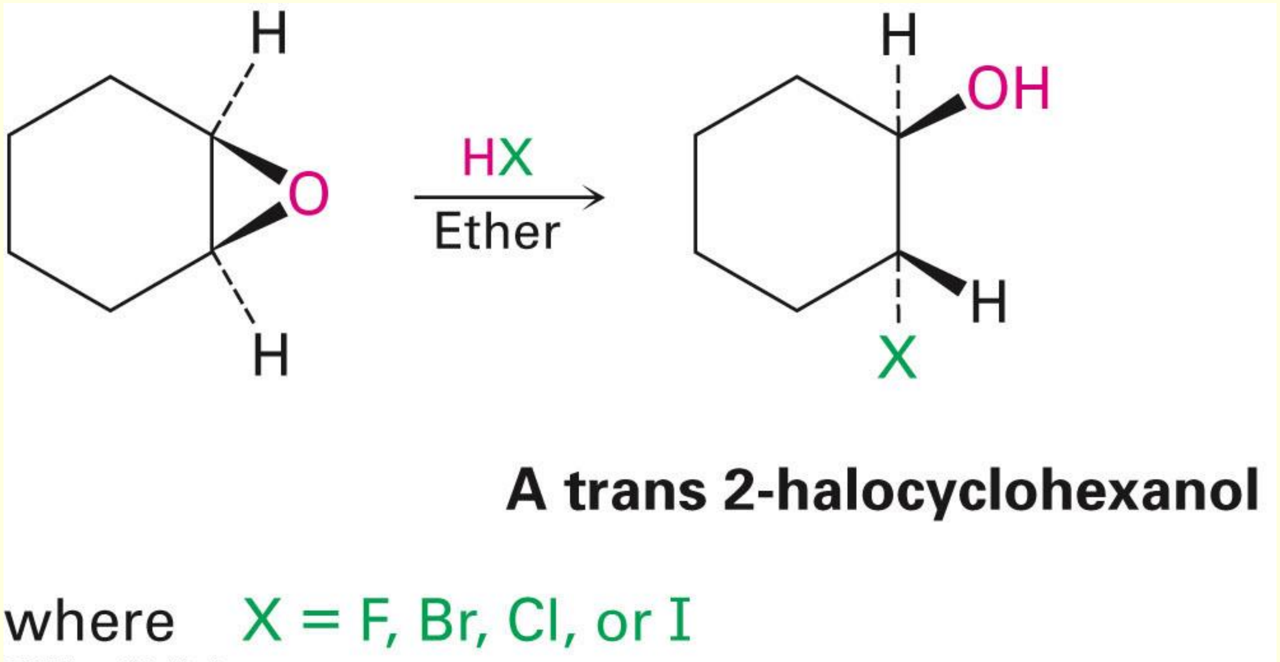
- **Acid-Catalyzed Epoxide Opening**: Epoxides are cleaved by treatment with acid just as other ethers are, but under much milder conditions because of ring strain.
- Water adds to epoxides with dilute acid at room temperature.
- Product is a 1,2-diol (on adjacent C's: vicinal).
- Mechanism: acid protonates oxygen and water adds to opposite side (trans addition).

Reactions of Epoxides: Acid-catalyzed Ring-Opening



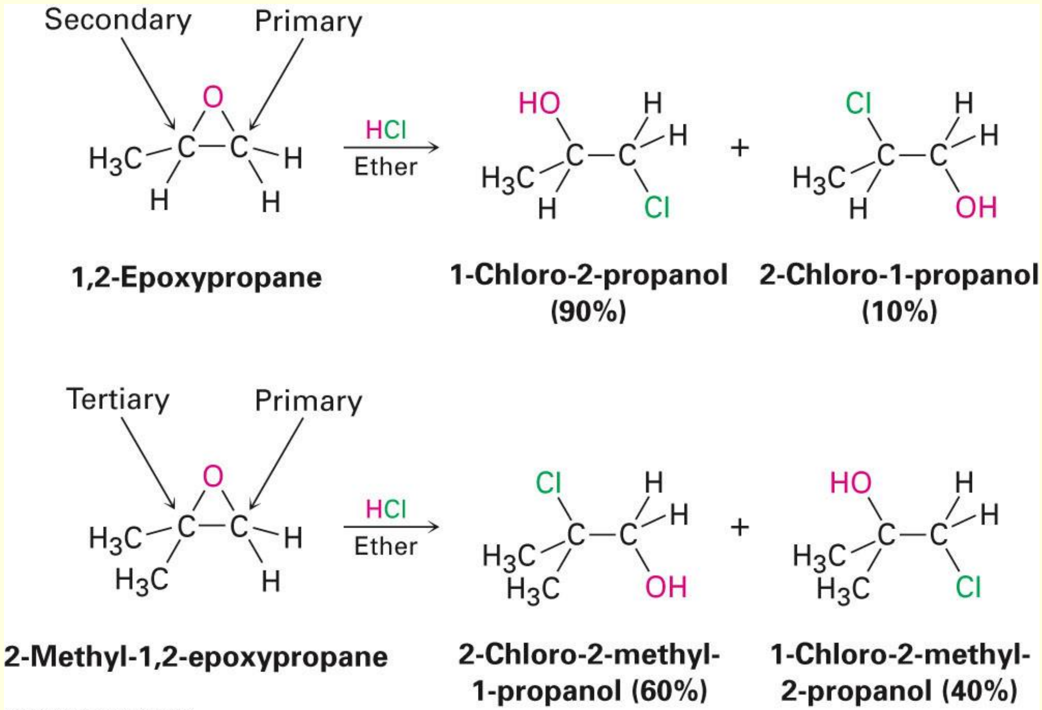
Reactions of Epoxides: Acid-catalyzed Ring-Opening using halohydrins

- Epoxides can also be opened by reaction with acids other than H_3O^+.
- If anhydrous HX is used, for instance, an epoxide is converted into a trans halohydrin.



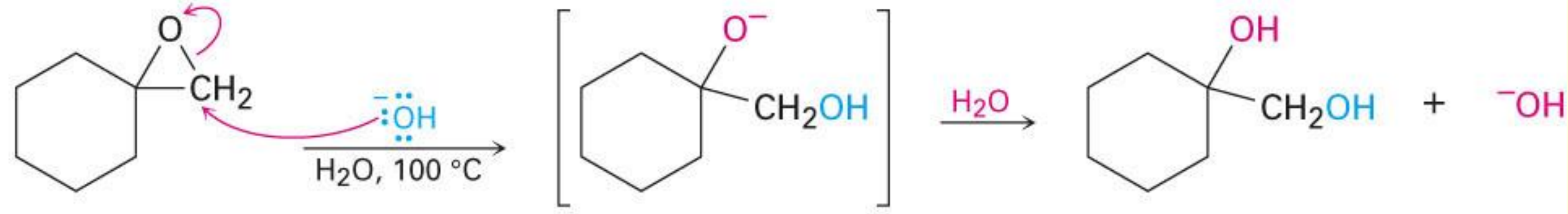
Regiochemistry of Acid-Catalyzed Opening of Epoxides

- The regiochemistry of acid-catalyzed ring-opening depends on the epoxide’s structure, and a mixture of products is often formed.
- When both epoxide carbon atoms are either primary or secondary, attack of the nucleophile occurs primarily at the less highly substituted site—an SN2-like result.



Reactions of Epoxides: Base-catalyzed Ring-Opening

- Unlike other ethers, epoxide rings can be cleaved by bases and nucleophiles as well as by acid.
- Although an ether oxygen is normally a poor leaving group in an SN^2 reaction, the strain of the three-membered ring causes epoxides to react with hydroxide ion at elevated temperatures.

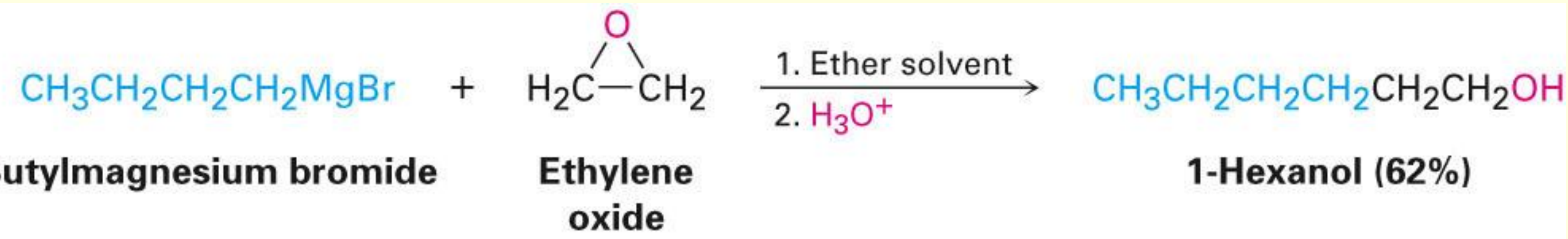


Methylenecyclohexane oxide

1-Hydroxymethyl-cyclohexanol (70%)

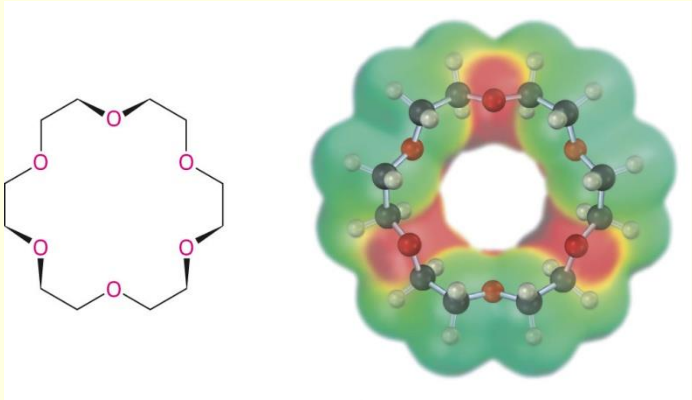
Addition of Grignard reagent to Ethylene Oxide

- Nucleophilic ring-opening occurs when epoxides are treated with Grignard reagents.
- Ethylene oxide is frequently used, thereby allowing the conversion of a Grignard reagent into a primary alcohol having two more carbons than the starting alkyl halide.



Crown Ethers

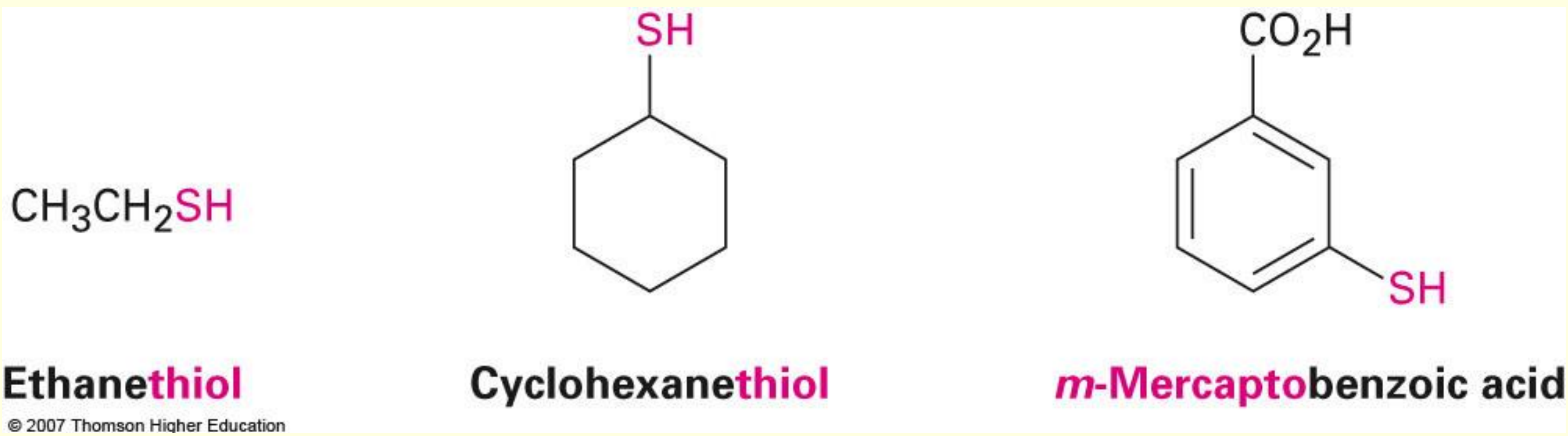
- Large rings consisting repeating (-OCH_2CH_2-) or similar units Named as x-crown-y
- x is the total number of atoms in the ring
- y is the number of oxygen atoms
- 18-crown-6 ether: 18-membered ring containing 6 oxygen atoms
- Central cavity is electronegative and attracts cations.



18-Crown-6 ether

Thiols and Sulfides

- Thiols (RSH), are sulfur analogs of alcohols
- Named with the suffix -thiol
- SH group is called “mercapto group” (“capturer of mercury”), Thiols, sometimes called mercaptans.

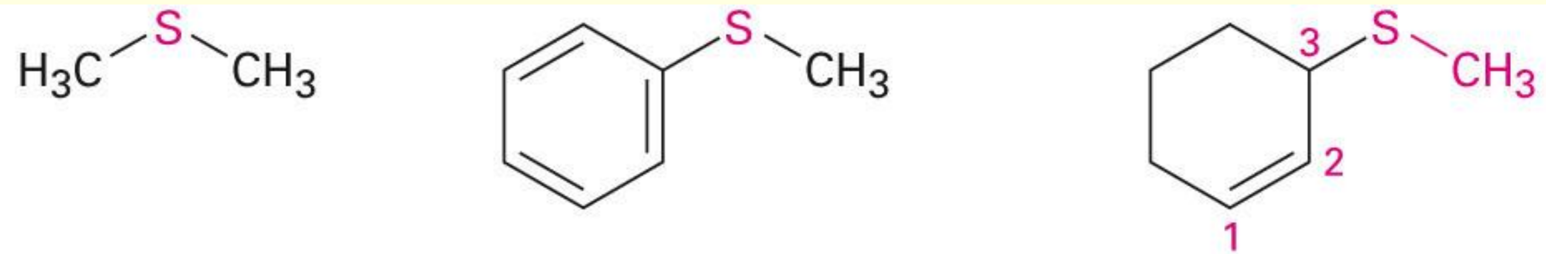


Thiols: Preparation and reaction

- From alkyl halides by displacement with a sulfur nucleophile such as –SH
- The alkylthiol product can undergo further reaction with the alkyl halide to give a symmetrical sulfide, giving a poorer yield of the thiol.
- Thiols are usually prepared from alkyl halides by SN^2 displacement with a sulfur nucleophile such as hydrosulfide anion, ^-SH.

Sulfides

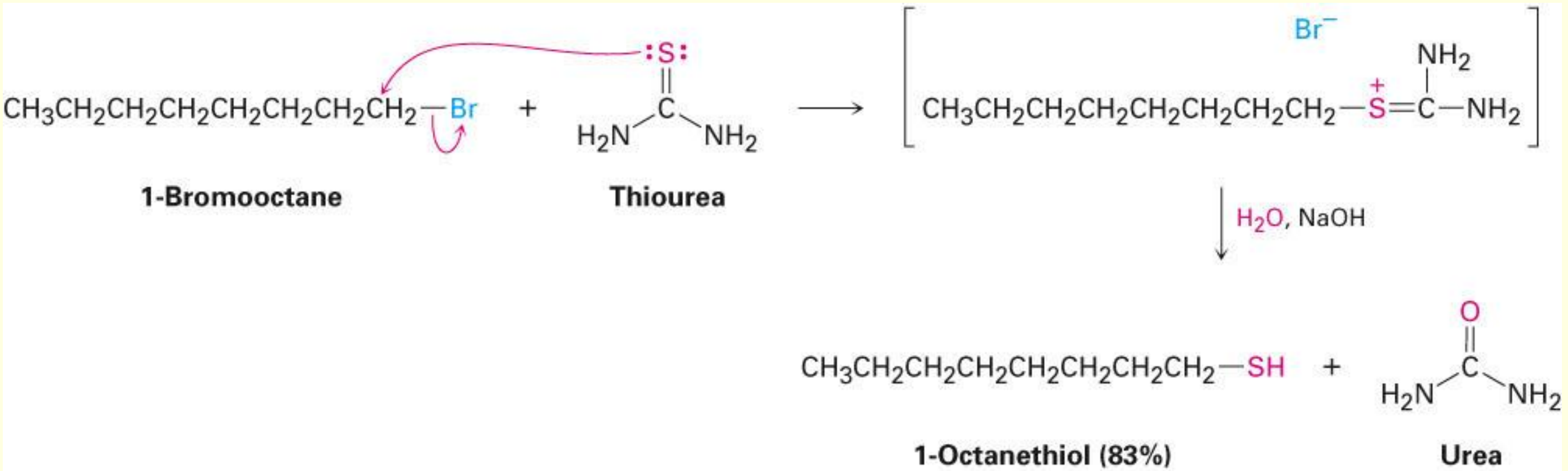
- Sulfides (RSR^1), are sulfur analogs of ethers.
- Named by rules used for ethers, with sulfide in place of ether for simple compounds and alkylthio in place of alkoxy



Dimethyl sulfide | Methyl phenyl sulfide | 3-(Methylthio)cyclohexene

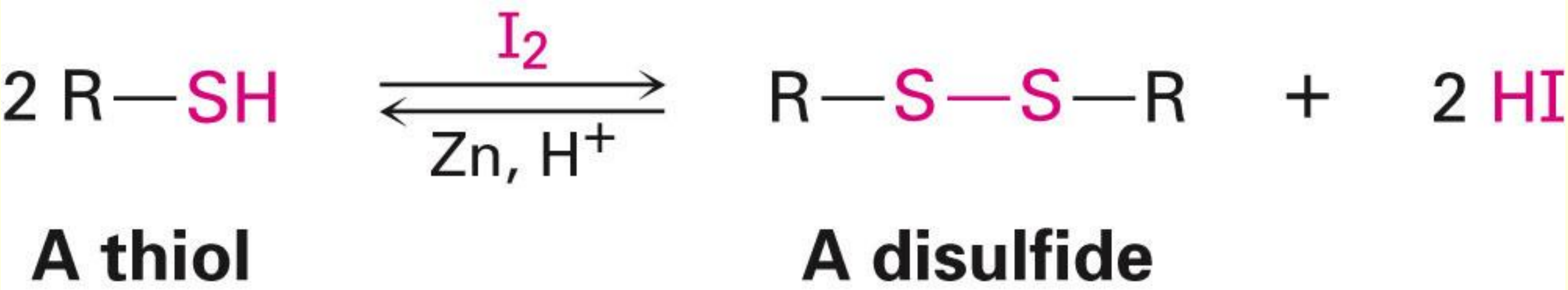
Using Thiourea to Form Alkylthiols

- Thiols can undergo further reaction with the alkyl halide to give dialkyl sulfides.
- For a pure alkylthiol use thiourea ($NH_2(C{=}S)NH_2$) as the nucleophile.
- This gives an intermediate alkylisothiourea salt, which is hydrolyzed to alkyl thiourea.



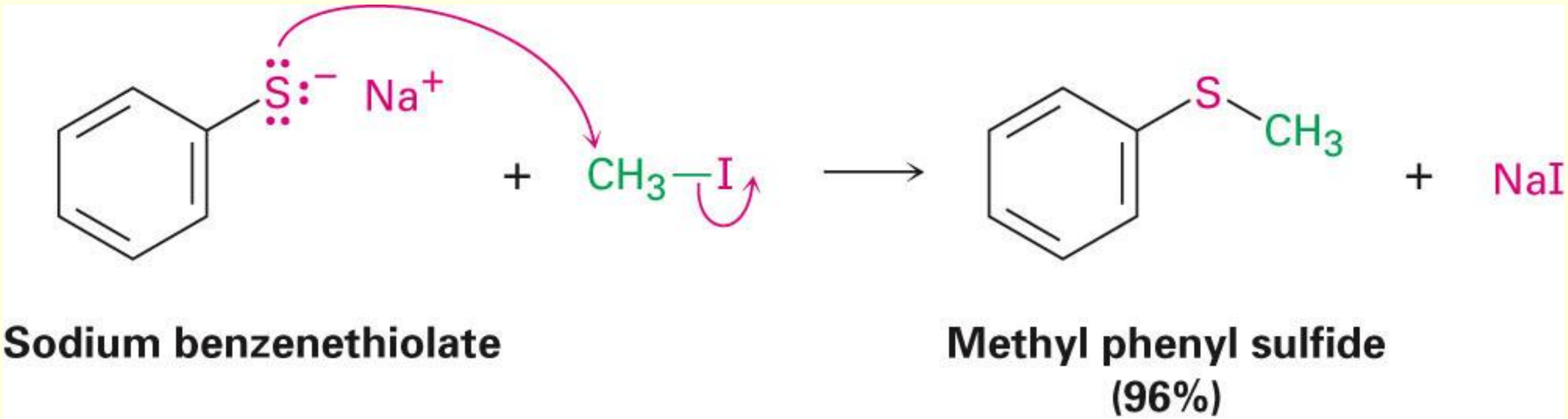
Oxidation of Thiols to Disulfides

- Reaction of an alkyl thiol (RSH) with bromine or iodine gives a disulfide (RSSR).
- The thiol is oxidized in the process and the halogen is reduced.



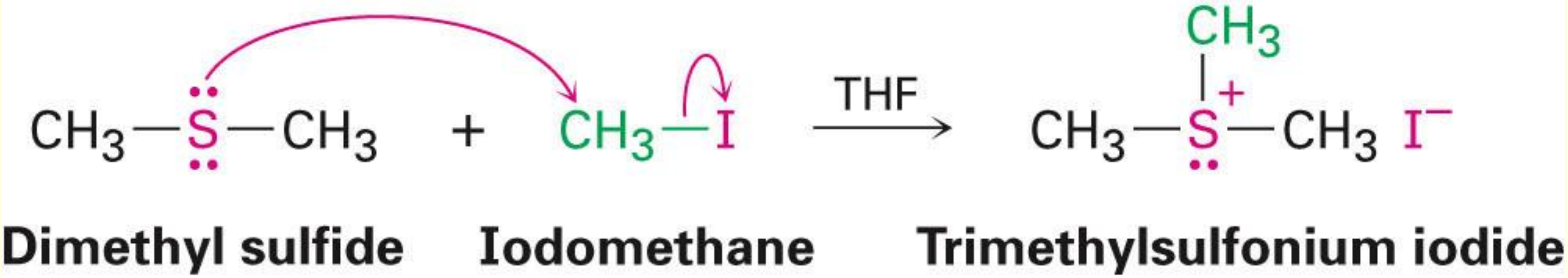
Thiolates

- Thiolates (RS^-) are formed by the reaction of a thiol with a base
- Thiolates react with primary or secondary alkyl halide to give sulfides (RSR')
- Thiolates are excellent nucleophiles and react with many electrophiles.



Sulfides as Nucleophiles

- Sulfur compounds are more nucleophilic than their oxygen-compound analogs.
- 3p electrons valence electrons (on S) are less tightly held than 2p electrons (on O).
- Sulfides react with primary alkyl halides (SN^2) to give trialkylsulfonium salts (R_3S^+)

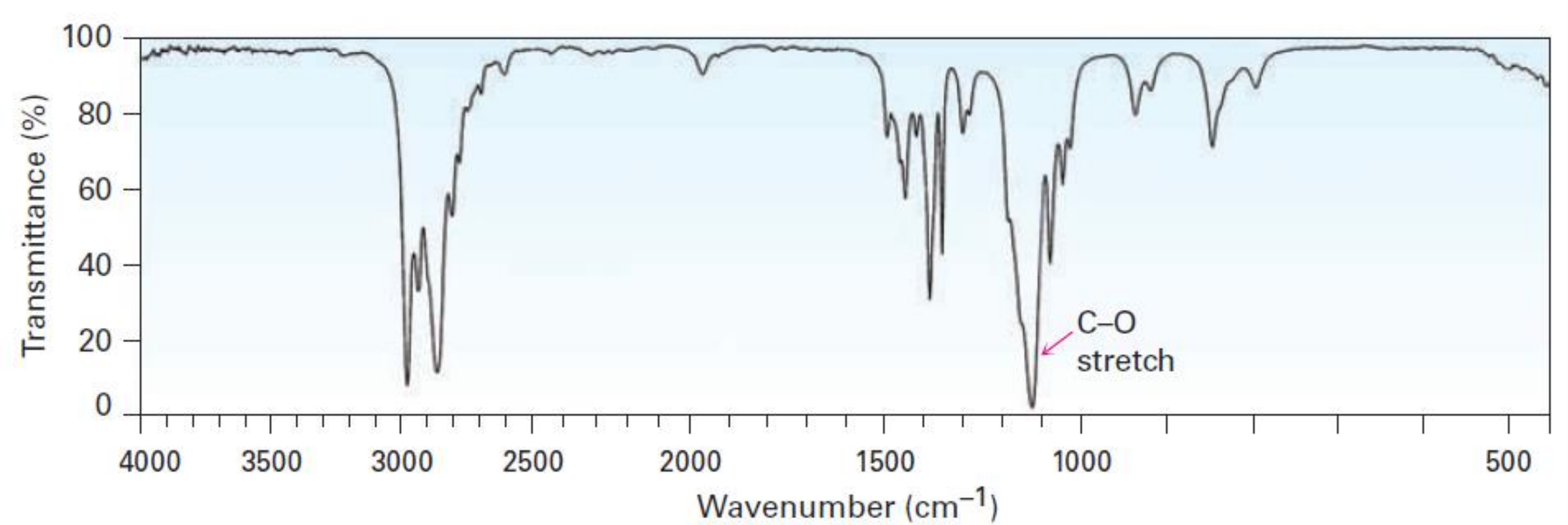


Oxidation of Sulfides

- Sulfur Sulfides are easily oxidized with H_2O_2 to the sulfoxide (R_2SO).
- Oxidation of a sulfoxide with a peroxyacid yields a sulfone (R_2SO_2).
- Dimethyl sulfoxide (DMSO) is often used as a polar aprotic solvent.

IR Spectroscopy of Ethers

Characteristic C–O stretching absorption in the range 1050 to 1150 cm^{-1}

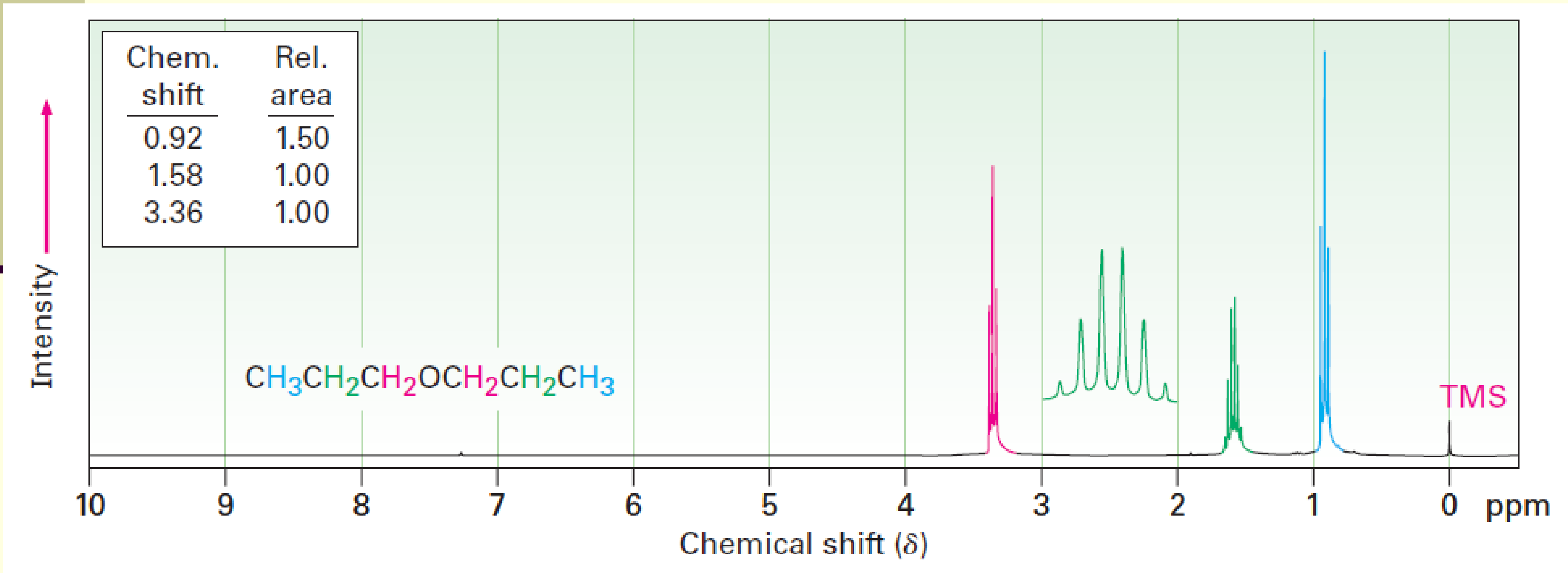


The infrared spectrum of diethyl ether, $CH_3CH_2OCH_2CH_3$.

NMR Spectroscopy of Ethers

[1]H NMR: Proton NMR: H on a C next to ether O is shifted downfield to δ 3.4 to δ 4.5 ppm. Dipropyl ether shows this signal at δ 3.4 ppm.

[13]C NMR: Carbons show downfield shift δ 50 to δ 80 ppm.



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