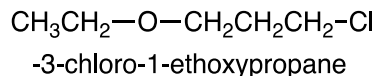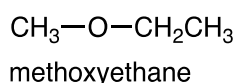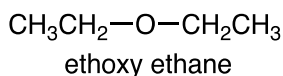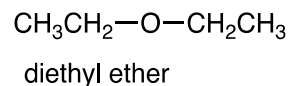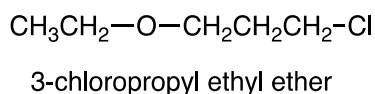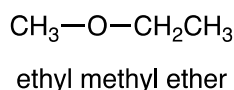# Chapter 17
# Ethers, Epoxides, Sulfides

Ethers are much less reactive than alcohols but epoxides – three-membered ring ethers – are very reactive as we saw in the last chapter.

**Nomenclature**

In substitutive IUPAC nomenclature ethers are named as alkoxy derivative derivatives of alkanes.

$CH_3CH_2$—O—$CH_2CH_3$         $CH_3$—O—$CH_2CH_3$       $CH_3CH_2$—O—$CH_2CH_2CH_2$–Cl
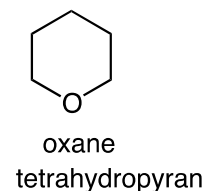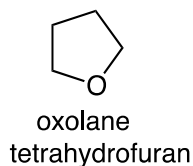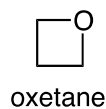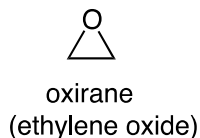    ethoxy ethane                      methoxyethane          -3-chloro-1-ethoxypropane

Functional class names: list the two alkyl groups in ROR' in alphabetical order as separate words followed by the word "ether".  If the two alkyl groups are the same, use "di-".

$CH_3$—O—$CH_2CH_3$          $CH_3CH_2$—O—$CH_2CH_2CH_2$-Cl        $CH_3CH_2$—O—$CH_2CH_3$

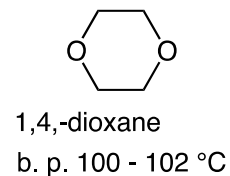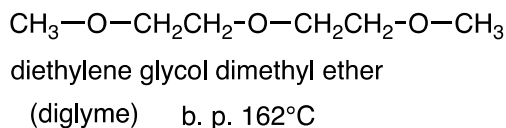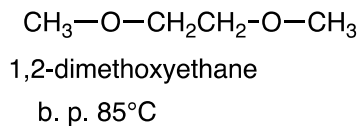ethyl methyl ether          3-chloropropyl ethyl ether          diethyl ether

Ethers can be symmetrical or unsymmetrical.  In unsymmetrical ethers, the two alkyl groups are different.

We can have cyclic ethers:



   oxirane
(ethylene oxide)            oxetane              oxolane                oxane
                                                tetrahydrofuran         tetrahydropyran
Number the ring starting at the oxygen.

Many compounds have more than one ether linkage.  For example, some diethers are useful solvents and there are useful solvents that contain multiple ethers.  These have higher boiling points and more ether linkages can be added to increase the boiling point even further.

$CH_3$—O—$CH_2CH_2$-O—$CH_3$          $CH_3$—O—$CH_2CH_2$-O—$CH_2CH_2$-O—$CH_3$

1,2-dimethoxyethane                diethylene glycol dimethyl ether
  b. p. 85°C                       (diglyme)    b. p. 162°C

1,4,-dioxane
b. p. 100 - 102 °C

Sulfur analogs of alkoxy groups are called alkylthio groups.  Name as sulfides or alkyl thio alkanes.

CH₃CH₂—S—CH₂CH₃

diethyl aulfide

or, ethyl thioethane

(cyclopentyl) -S-CH₃

cyclopentyl methyl sulfide

(methylthio)cyclopentane
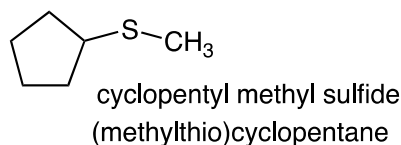
## Structure and Bonding

Ethers have large bond angles than water and alcohols due to van der Waals strain.

H-O-H 105°    H-O-CH₃ 108.5°    CH₃-O-CH₃ 112°    $(CH_3)_3C$-O-$C(CH_3)_3$ 132
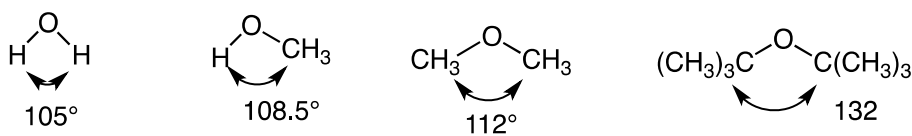
Typical C-O bond lengths are similar to C-O bonds in alcohols (~1.42 A°). These are shorter than typical C-C bonds (~1.52A°)

The most stable conformation of diethyl ether is the all-staggered anti-conformation. Tetrahydropyran is most stable in the chair conformation.

In a three-membered ring the bond angles are much small than normal tetrahedral angles and the C-C bond and C-O are slightly longer than normal due to the severe angle strain.
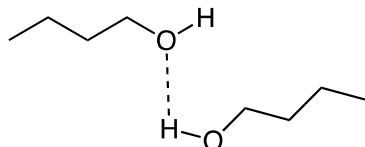
1.47 A°

CH₃-CH₂-O-CH₂-CH₃

diethyl ether

tetrahydropyran

C—O—C  angle = 61.5

C—C—O  angle = 59.2

1.44 A°
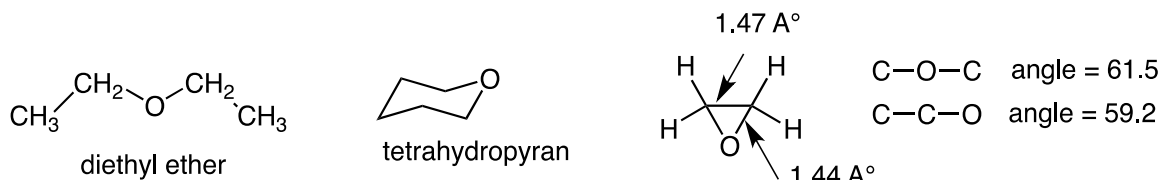
## Physical Properties

Look at diethyl ether as compared to pentane and 1-butanol.

| Compound | b. p. | $H_2O$ solubility (g/100 mL $H_2O$) | dipole |
|---|---|---|---|
| diethyl ether | 35 °C | 7.5 g/100 mL | 1.2 |
| pentane | 35 °C | ~0 g/100 mL | 0 |
| butanol | 117 °C | 9 g/ 100 mL | 1.7 |

So, we see that diethyl ether is more like pentane than an alcohol in terms of its boiling point. This means that there are little intermolecular interactions. Ethers are not capable of

hydrogen-bonding with themselves but they can accept hydrogen-bonds from water. So they are quite soluble in water; nearly as soluble as alcohols of comparable molecule size.
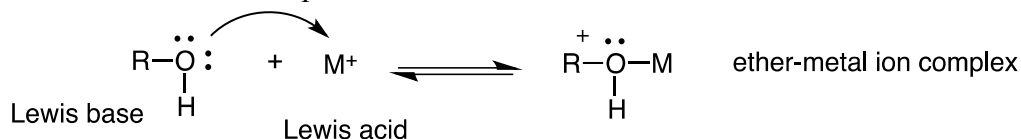
hydrogen bond between alcohols          Hydrogen bonding in ethers

No significant dipole moment for the C-H bond.
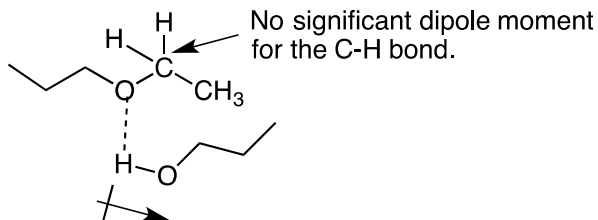
The ether has no polarized bond to a hydrogen but it does have the lone pair on the oxygen so it can accept an H-bond from the H that is attached to the alcohol oxygen.


## Crown Ethers

The unpaired electrons on oxygen can interact with metal ions in Lewis base/Lewis acid reactions to form a complex.

$$R-\overset{..}{\underset{H}{O}}: \quad + \quad M^+ \quad \rightleftharpoons \quad \overset{+}{R}-\overset{..}{\underset{H}{O}}-M \qquad \text{ether-metal ion complex}$$

Lewis base            Lewis acid

A single ether forms a relatively weak complex with a metal but a polyether can form a fairly strong complex, especially with macrocyclic polyethers. These are called crown ethers because they are roughly shaped like a crown.
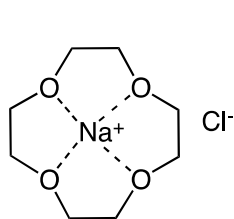
12-crown-4 (12-K-4)
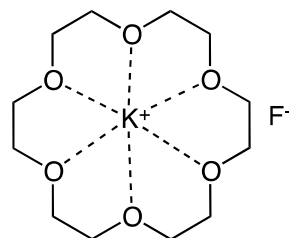
The '12' refers to the total number of atoms in the macrocyclic poolyether and the '4' refers to the number of oxygens.

18-crown-6 (18-K-6)

Depending on the number of atoms in the macrocycle and the number of oxygens, it is possible to discriminate between the smaller sodium cation and the larger potassium cation. Potassium fluoride, KF, is usually insoluble in organic solvents such as benzene but when 18-crown-6 is added, it dissolves. The $K^+$ forms a complex with the oxygens of the ether as shown.

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In protic solvents like water and alcohols, F⁻ is strongly solvated by ion-dipole forces and is not very basic or very nucleophilic but when complexed with 18-crown-6 in benzene, the F⁻ is essentially unsolvated and is an excellent nucleophile. Therefore the following reaction will occur using the crown ether but without it there is no reaction.



$$\text{(hexyl-Br)} \xrightarrow[\text{18-crown-6, 90 °C}]{\text{KF, benzene}} \text{(hexyl-F)}$$
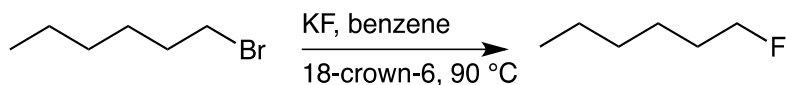
Polyether antibiotics such as monensin (pictured below) are similar to crown ethers. They form a complex with sodium and can carry the sodium through the hydrocarbon-like interior of a cell membrane to disrupt the normal balance of sodium ions in the cell and interfere with cellular respiration.
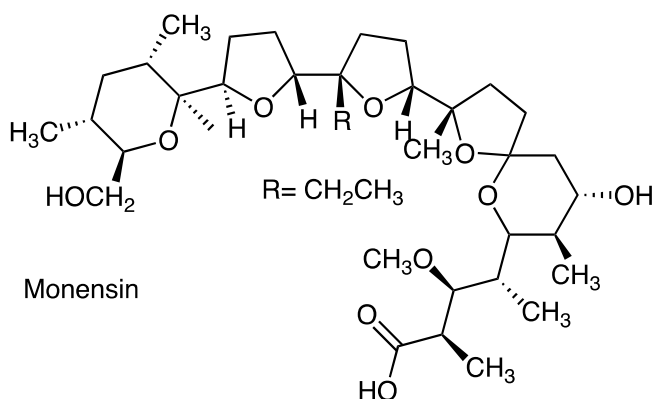


Four of the ether and two of the -OH groups wrap around the Na⁺.

Monensin

R= $CH_2CH_3$

Ionophores are ion carriers that transport ions in and out of the cell. They are also similar to the polyethers.

**Preparation of Ethers**

Symmetrical ethers can be synthesized by acid catalyzed dehydration of the corresponding alcohols as we saw in the last chapter.

$$2\ CH_3CH_2CH_2\text{—OH} \xrightarrow[\text{120 °C}]{H_2SO_4} CH_3CH_2CH_2\text{—O—}CH_2CH_2CH_3 + H_2O$$

Mechanism



4
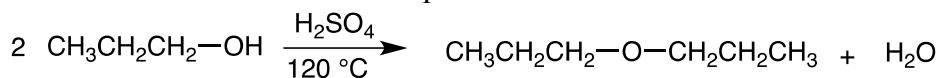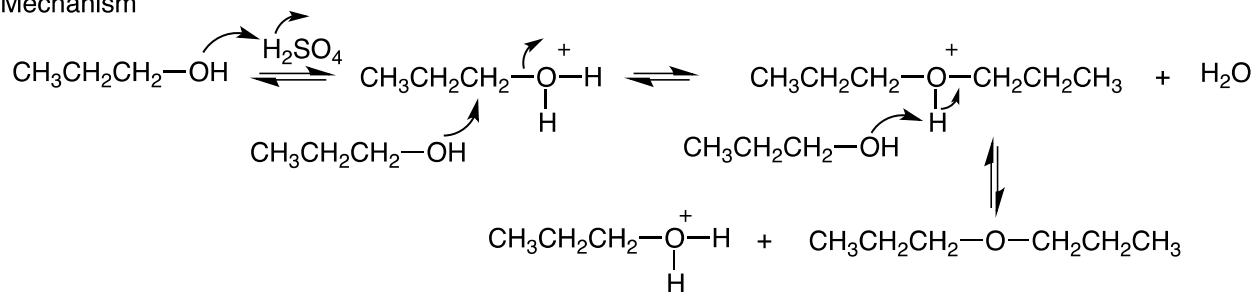
As we shall see, the reaction is reversible.  To drive the equilibrium in favor of ether formation, use an excess of alcohol in initially anhydrous conditions and remove the water as it is formed if possible.


**Williamson Ether Synthesis**

For unsymmetrical ethers, we need to use basic conditions.  This is a simple $S_N2$ reaction and is a very useful reaction.  We activate the alcohol by first removing the proton with a base to make the alkoxide. A relatively mild base such as sodium hydroxide will work because even though the alkoxide exists in roughly equal amount with the starting alcohol (Keq ~1), the second step of the reaction will drive the equilibrium to the right.  We can use a strong base such as sodium hydride, NaH.

The starting alcohol can be primary or secondary but when it is tertiary we start to see elimination reactions.  The alkyl halide or alkyl sulfonates portion should be primary; otherwise we start to see elimination reactions.
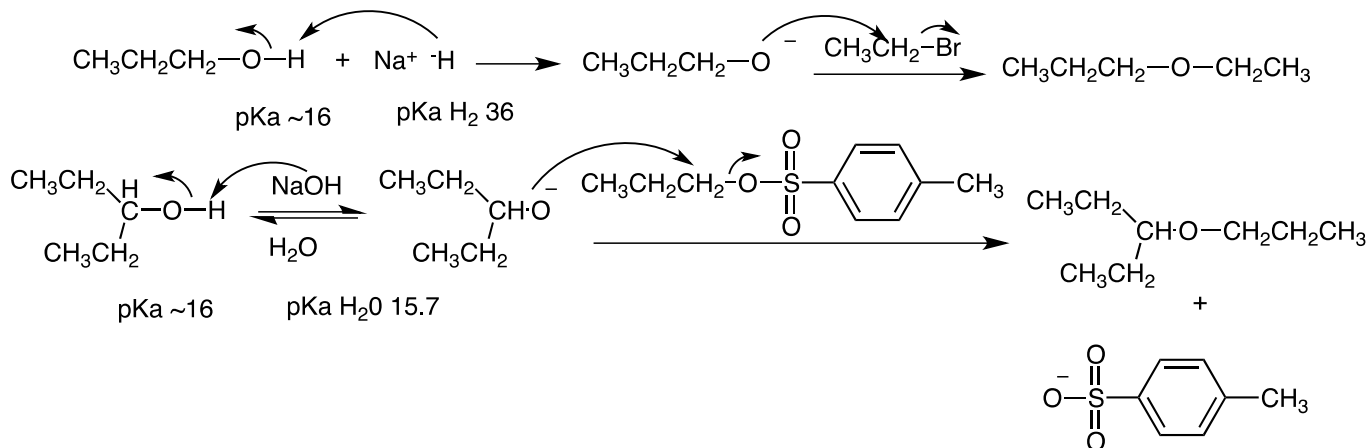
General Reaction:

R—O—H  +  base  ⟶  R—O⁻  →  R—X  ⟶  R—O—R'
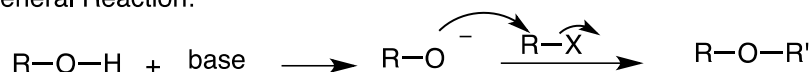
X= good leaving group such as halogen or sulfonate ester

R' should be non-hindered such as a primary alkyl halide; otherwise we start to see elimination.
R can be primary or secondary but with tertiary we start to see elimination.


For example:

CH$_3$CH$_2$CH$_2$—O—H  +  Na⁺ ⁻H  ⟶  CH$_3$CH$_2$CH$_2$—O⁻  CH$_3$CH$_2$—Br  ⟶  CH$_3$CH$_2$CH$_2$—O—CH$_2$CH$_3$

pKa ~16        pKa H$_2$ 36



pKa ~16        pKa H$_2$O 15.7

But if the alkyl halide component is secondary or tertiary or if the alcohol component is tertiary we start to see elimination.
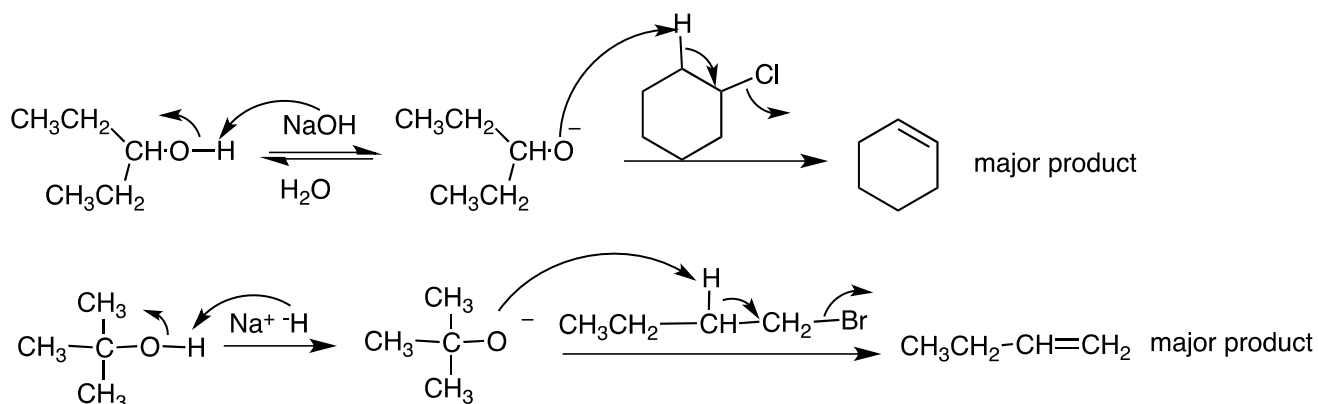
Tertiary alkoxides are very hindered and are realtively strong bases (pKa ~18) but poor nucleophiles. So we see elimination even with primary alkyl halide substrates.

So how do we make tertiary ethers (i.e. ethers with *t*-butyl groups)? We cannot use a tertiary alcohol or a tertiary alkyl halide. We need to use acid catalyzed addition of an alcohol to an alkene such a 2-methylpropene, a reaction we studied last semester.



Ex
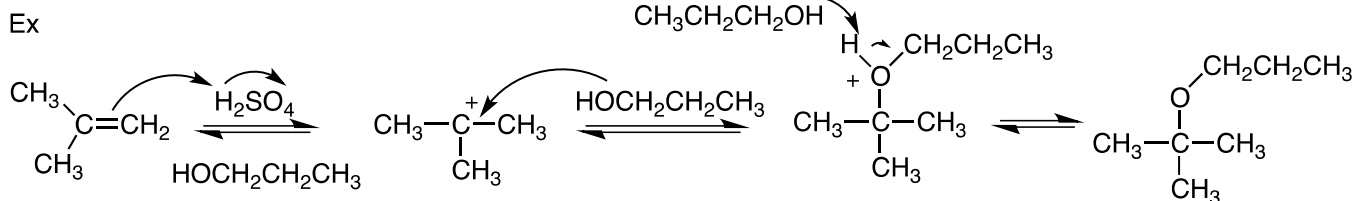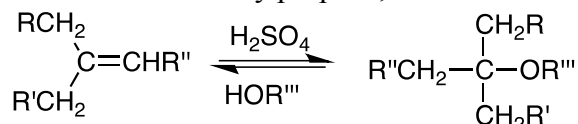


## Reactions of Ethers

Ethers are relatively unreactive. They are stable to (1) nucleophiles (2) strong bases (3) oxidizing agents (4) reducing agents.
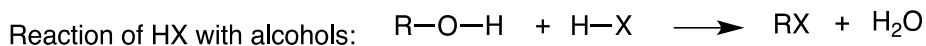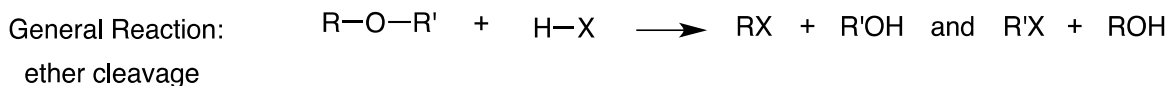


Not an acidic proton

$CH_3CH_2-O-CH-CH_3$     oxidizing reagents will not cleave a C-O bond.
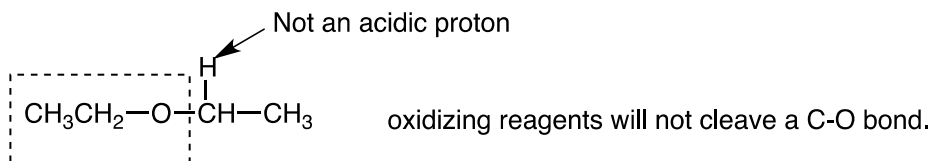
Not a good leaving group because $^-OCH_2CH_3$ is too strong a base.

Ethers such as diethyl ether and THF are moderately polar solvents and good at dissolving non-polar and moderately polar compounds. They are excellent solvents for Grignard and organolithium reactions as we saw.

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Ethers, however, are cleaved by acids.

## Acid-Catalyzed Ether Cleavage

The reaction is analogous to the reaction of alcohols with halogen acids, HX.

General Reaction:      $R-O-R'$   +   $H-X$   $\longrightarrow$   $RX$ + $R'OH$   and   $R'X$ + $ROH$

   ether cleavage

Reaction of HX with alcohols:   $R-O-H$ + $H-X$   $\longrightarrow$   $RX$ + $H_2O$

Usually the reaction is carried out with an excess of the HX and usually the alcohol that is formed initially is also converted to the alkyl halide. Using milder conditions, it is possible to isolate the alcohol intermediate.
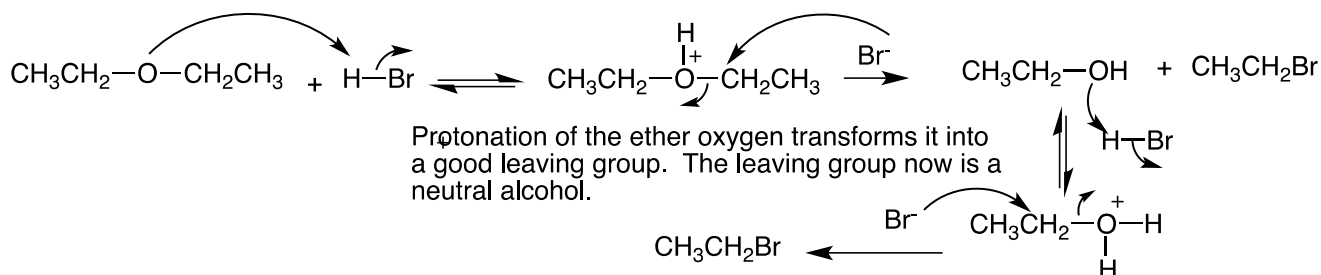


Note that unsymmetrical ethers can give two sets of products, since the bromine nucleophile can attack the carbon on either side of the protonate oxygen.
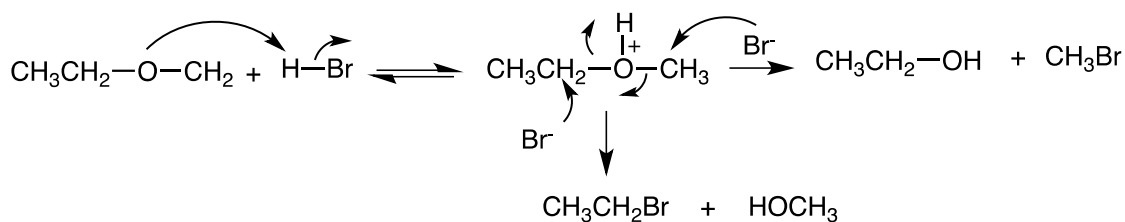


The reactivity order for the halogen acids is HI > HBr > >> HCl. This is consistent with increasing acidity and increasing nucleophilicity of the halogen anion. HF is not effective at cleaving ethers.

Cleavage of *t*-butyl ethers is particularly easy. The mechanism is most likely an S$_N$1 mechanism, since a relatively stable tertiary carbocation is formed. This is then attacked by the halogen anion.
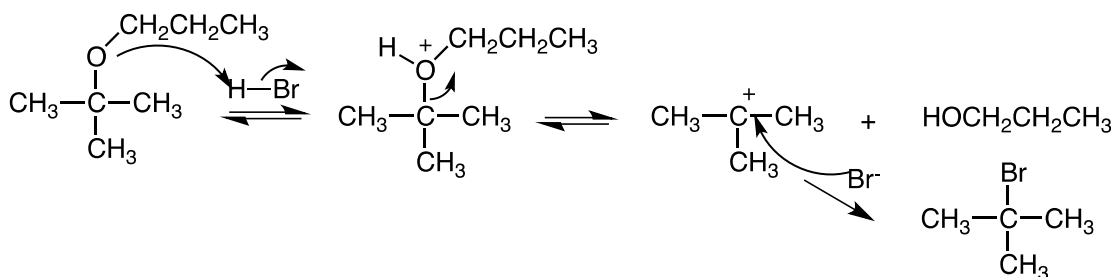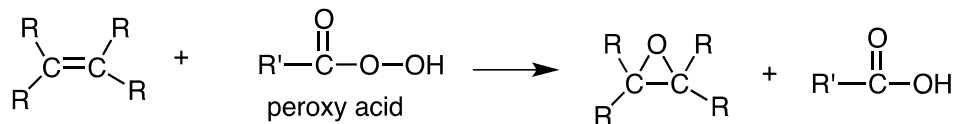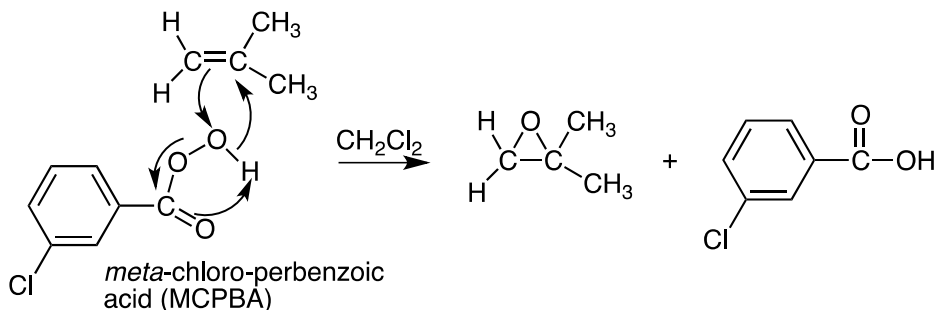
**Epoxides**
Preparation:

Epoxides can be prepared by two methods.

(1) From alkenes directly using a peroxy acid.

This is a concerted *syn* addition. It is a very facile reaction and occurs rapidly at room temperature. It is thermodynamically favored since there is the breaking of a very weak O-O bond (~ 30 Kcal/mol) and a relatively weak π-bond and the formation of two stronger C-O bonds. The mechanism is shown below.
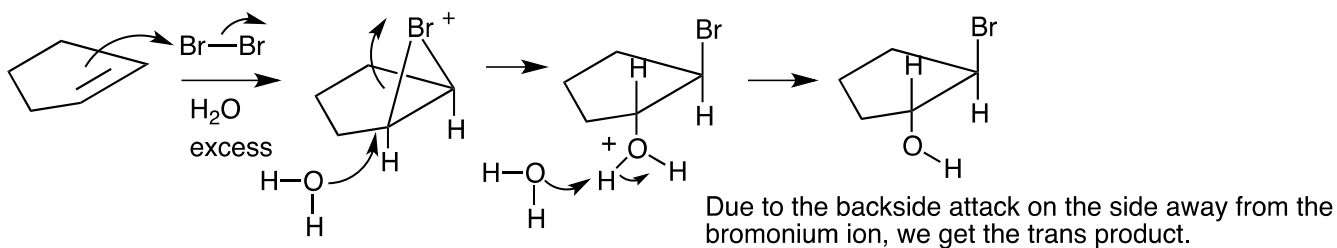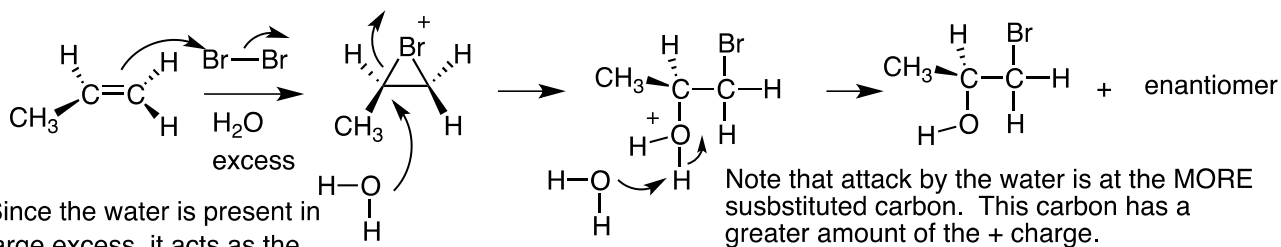
*meta*-chloro-perbenzoic acid (MCPBA)

We form the *cis*-product. It is not possible, of course to form a *trans* three-membered ring.
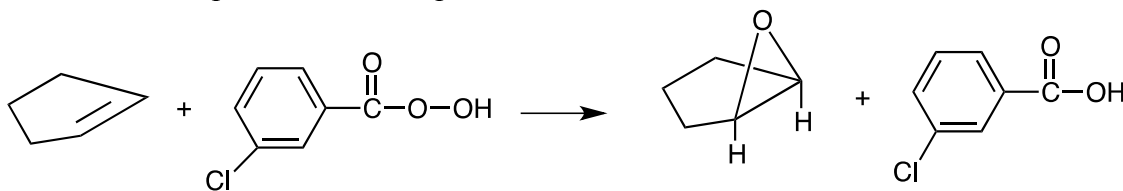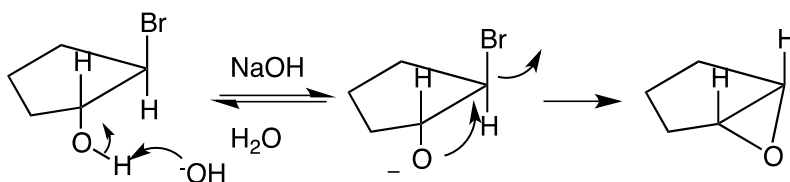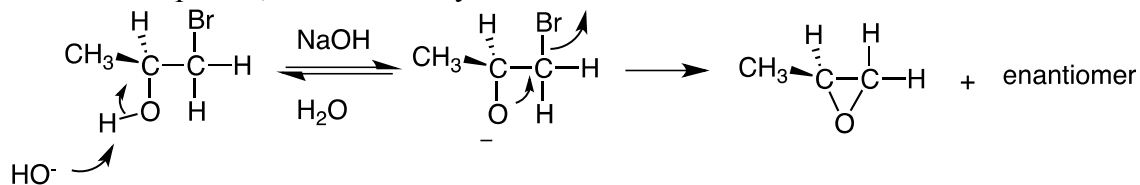
(2) We can also form epoxides from vicinal halohydrins in an intramolecular Williamson synthesis. Even though three-membered rings are very strained, this reaction works well because the nucleophilic alkoxide is so close to the electrophilic C-Br bond. Since this is an $S_N2$ reaction the alkoxide must come from the backside.

Recall that we form halohydrins from electrophilic addition to alkenes.



Since the water is present in large excess, it acts as the nucleophile rather than Br⁻.

Note that attack by the water is at the MORE susbstituted carbon. This carbon has a greater amount of the + charge.



Due to the backside attack on the side away from the bromonium ion, we get the trans product.

To form the epoxide, treat the halohydrin with a base such as NaOH.





The reaction is stereospecific. If you start with a *cis*-alkene, you will get a *cis*-epoxide and a *trans*-alkene give a *trans*-epoxide.

9

cis epoxide

trans epoxide
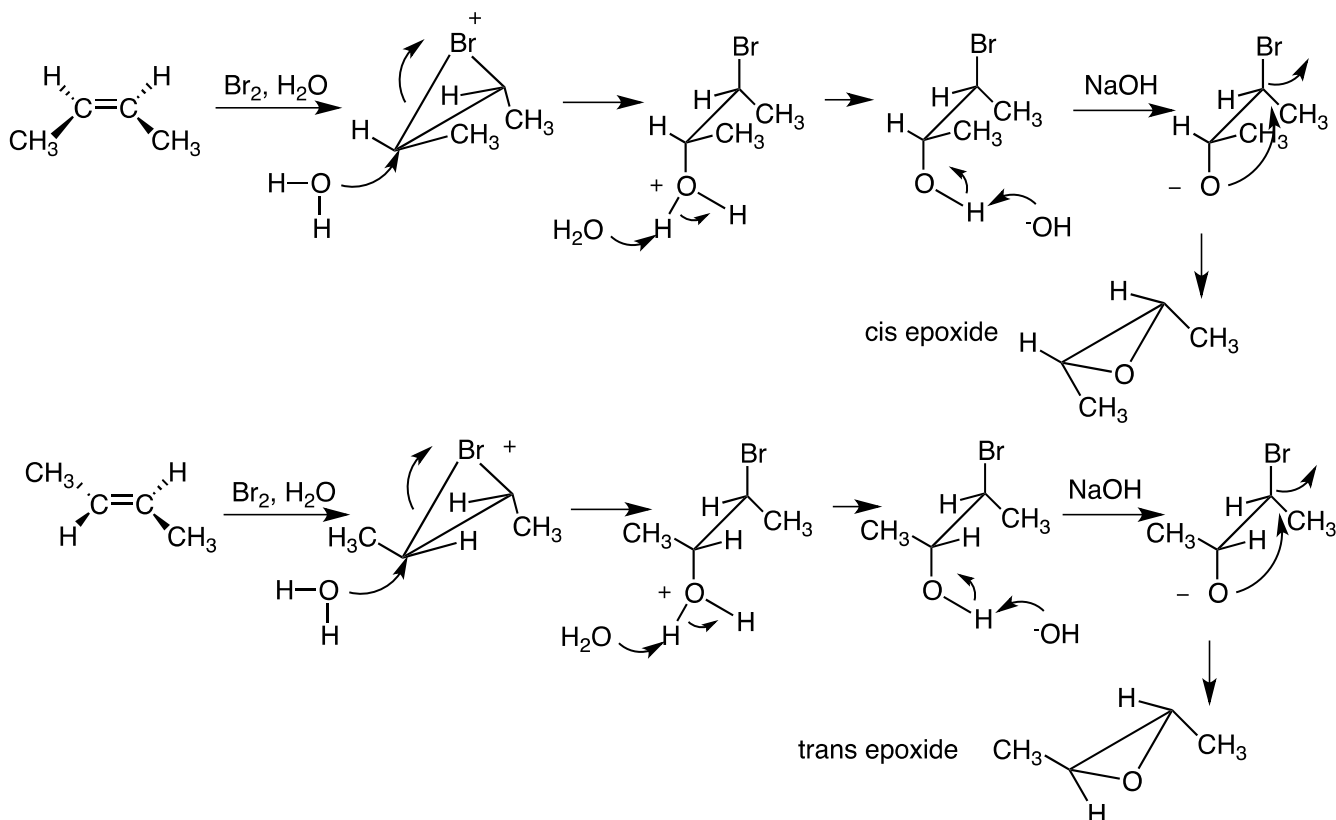
**Reactions of Epoxides Ring-Opening**

Epoxides react with nucleophiles in ring-opening reactions in both (1) basic and (2) acid conditions.
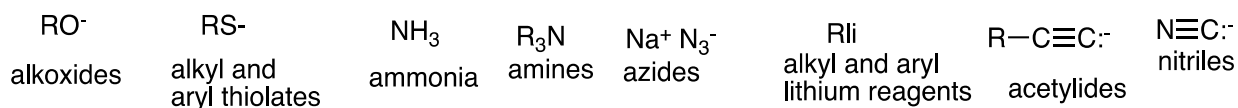
(1) In basic conditions the nucleophile attacks the epoxide directly at the less-substituted product.  This is an $S_N2$ like process in which the new C-Nucleophile bond and the OH group are trans.
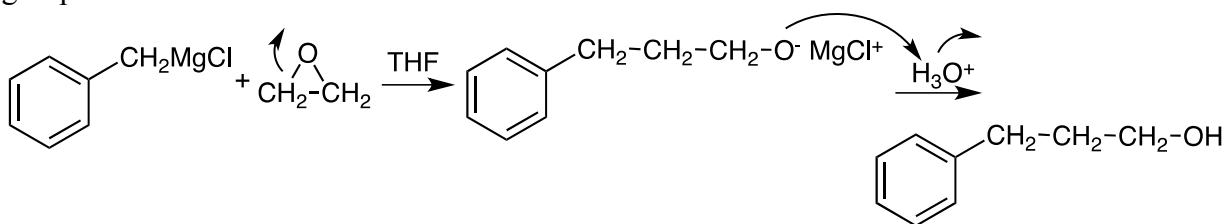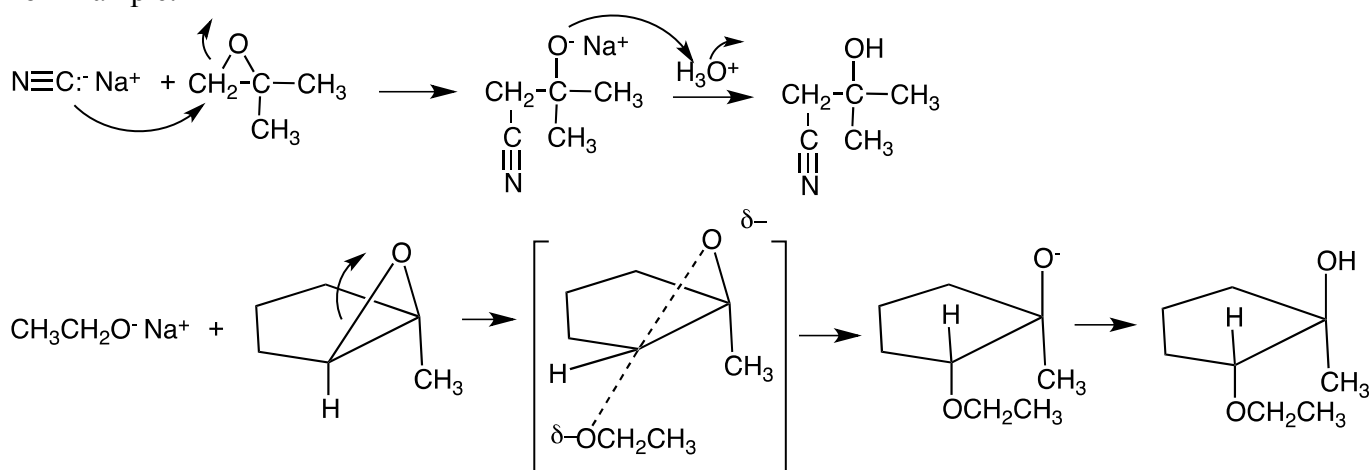


Again, attack is at the LESS substituted carbon because is less hindered.
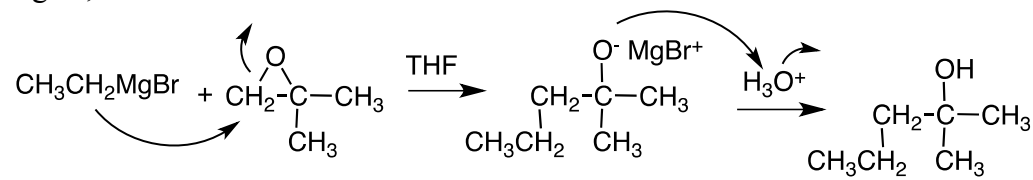
Other nucleophiles besides Grignards will attack epoxides and all attack at the less substituted carbon to give the *trans* product.

| RO⁻ | RS⁻ | NH₃ | R₃N | Na⁺ N₃⁻ | Rli | R—C≡C:⁻ | N≡C:⁻ |
|---|---|---|---|---|---|---|---|

$RO^-$ alkoxides    $RS^-$ alkyl and aryl thiolates    $NH_3$ ammonia    $R_3N$ amines    $Na^+ N_3^-$ azides    $Rli$ alkyl and aryl lithium reagents    $R-C\equiv C:^-$ acetylides    $N\equiv C:^-$ nitriles

For Example:



Note here how the substituent that is at the carbon that is attacked moves during the reaction, just like in an S_N2 reaction and we get inversion of configuration at that carbon.

We can make the *trans* 1,2-diol by nucleophile attack on the epoxide using sodium hydroxide.
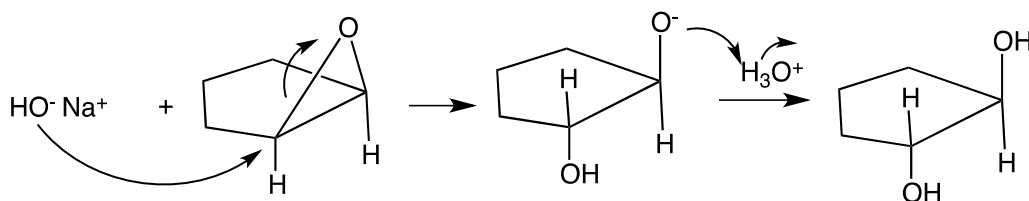


Lithium aluminum hydride, LiAlH₄, will reduce the epoxide to the alcohol by attack of hydride (H:⁻) at the less substituted carbon.
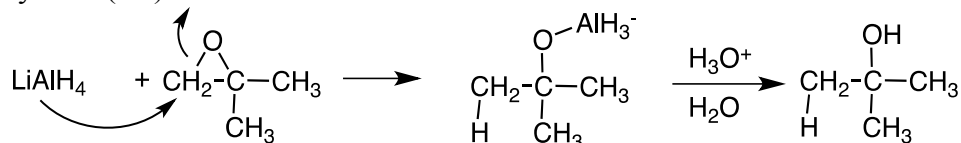
## Acid Catalyzed Ring Opening of Epoxides

Epoxides will also react with nucleophiles under acidic conditions to give the ring opening reaction. In acidic conditions we cannot have strongly basic nucleophiles present. Those most commonly used at the halides ($I^-$, $Br^-$, $Cl^-$), water, $H_2O$, and alcohols, $ROH$. In acidic conditions the nucleophile attacks at the more substituted carbon. Because there is lots of carbocation character and, as we know, the more substituted carbon is the one that is best able to stabilize the positive charge.

General Reaction:
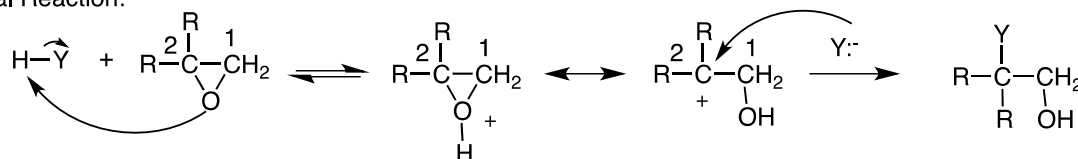


More of the (+) charge is on the more substituted carbon since it has electron donating alkyl groups that help to stabilize the charge.

We still see backside attack because there is still a partial bond to C2. A good way to represent the two resonance structures, which contribute to the overall structure, is to show one of the bonds as longer than the other.



Composite structure.
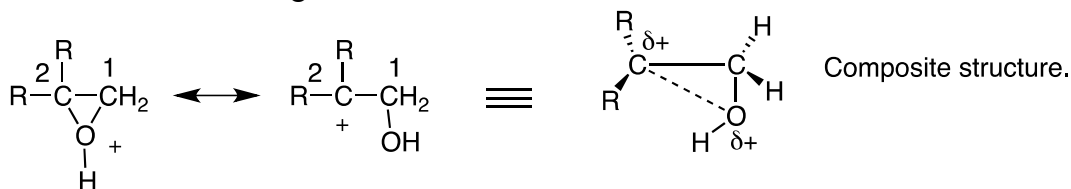
Also, in the transition state bond breaking is more advanced than bond formation considerable (+) charge develops at the more substituted carbon, the one that is best able to support this charge.



Examples:



12
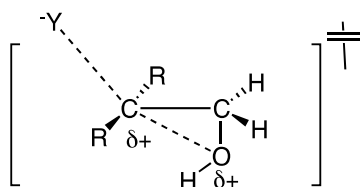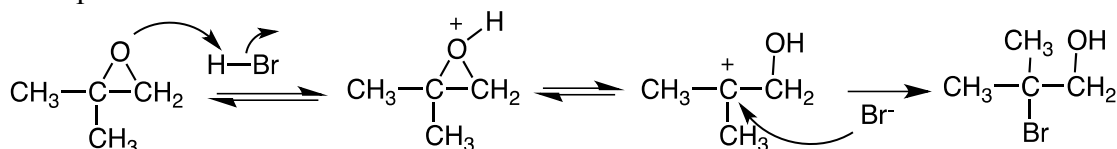
In this case we see that both **C1** and **C2** are secondary but **C1** is second and benzylic so carbocation **A** is much more stable than carbocation **A** and so the major product will result from backside attack on **C1**.

$H_2SO_4$

$HOCH_2CH_3$

**A**

**B**

$CH_3CH_2OH$

$CH_3CH_2OH$
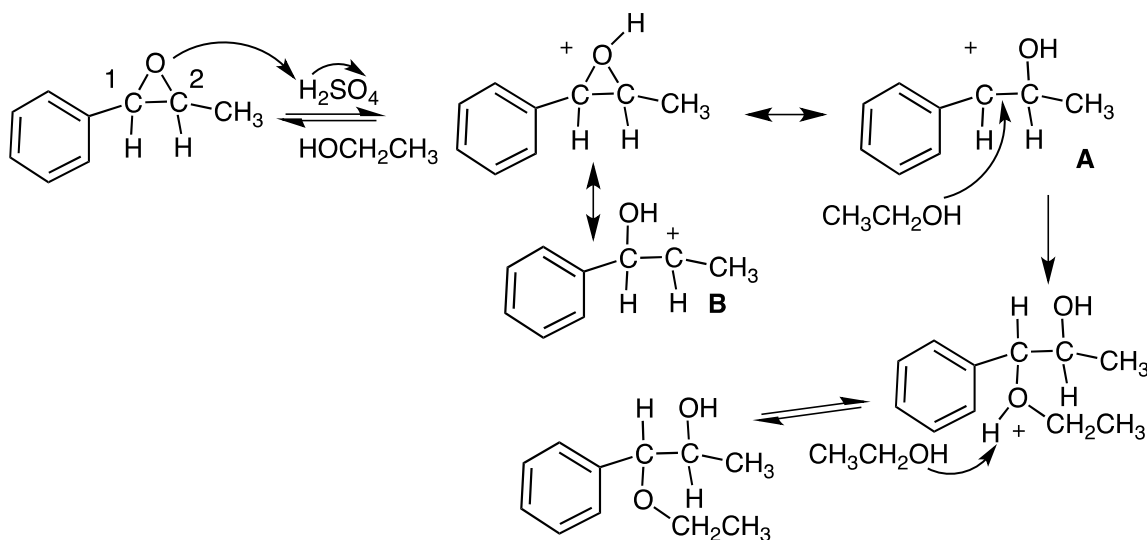
We still see inversion of configuration.

$H_2SO_4$

$HOCH_3$

$HOCH_3$

$CH_3OH$

$CH_3OH$
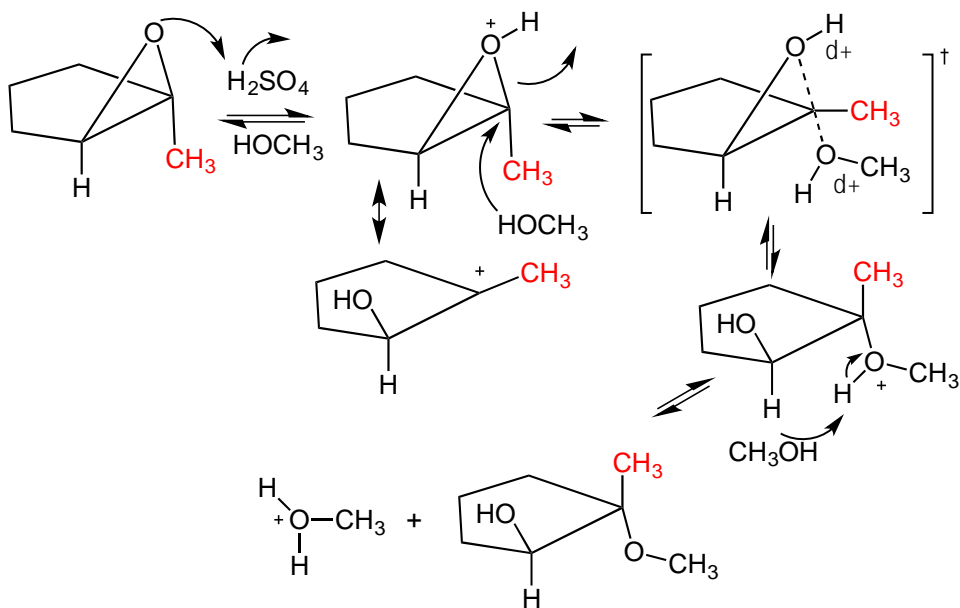
**Preparation of Sulfides**
The sulfur analogs of ether are prepared just like ethers:

R—S⁻ Na⁺  +  R'—X  ⟶  R—S—R'

alkane thiolate anion          R' can be primary or secondary
                               alky halide or tosylate.
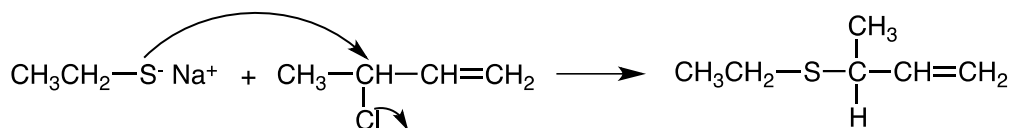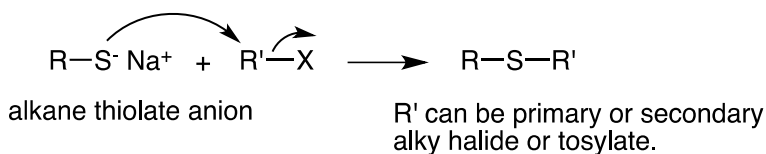
CH₃CH₂—S⁻ Na⁺  +  CH₃—CH—CH=CH₂  ⟶  CH₃CH₂—S—C—CH=CH₂
                         |                          |
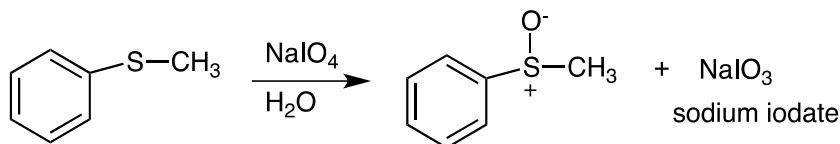                         Cl                         CH₃ / H

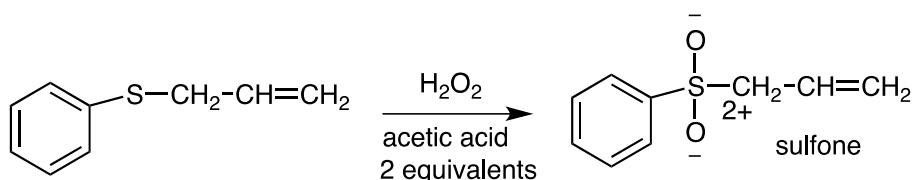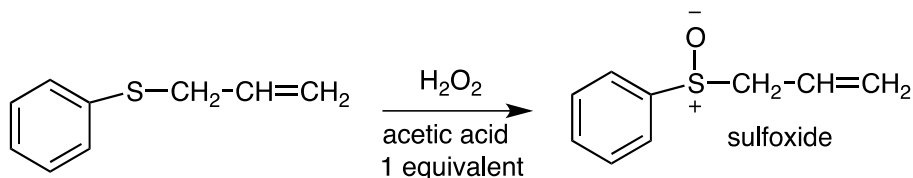## Oxidation of Sulfides: sulfoxides and sulfones

One major difference between ethers and sulfides (thio-ethers) is in their behavior toward oxidation.  Ethers are stable toward oxidation but the sulfur of sulfides can be oxidized, first to the sulfoxide (one oxygen added to the sulfur) or the sulfone (two oxygen atoms added to the sulfur).

R—S—R'  —oxidize→  R—S⁺—R' (with O⁻)  ⟷  R—S—R' (with O double bond)  —oxidize→  R—S²⁺—R' (with O⁻ and O)  ⟷  R—S—R' (with two O double bonds)

sulfoxide                                    sulfone
(recall dimethyl sulfoxide or DMSO)
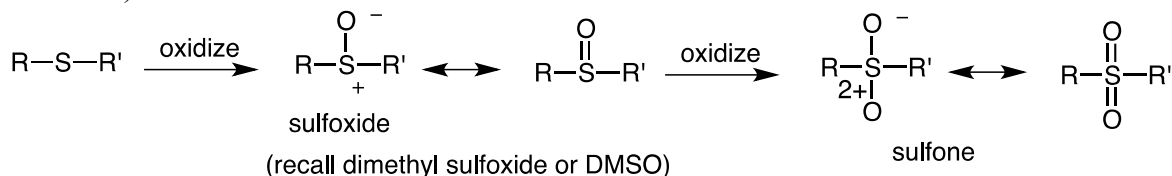
To form the sulfoxide, use sodium metaperiodate (NaIO₄).  It will stop the oxidation at the sulfoxide stage.

[benzene ring]—S—CH₃  —NaIO₄ / H₂O→  [benzene ring]—S⁺—CH₃ (with O⁻)  +  NaIO₃

                                                           sodium iodate

Peroxy acids in methylene chloride can also be used.  Peroxides can also be used.  Using one equivalent will oxidize the sulfide to the sulfoxide and two equivalents will oxidize the sulfide to the sulfone.

[benzene ring]—S—CH₂-CH=CH₂  —H₂O₂ / acetic acid / 1 equivalent→  [benzene ring]—S⁺—CH₂-CH=CH₂ (with O⁻)

                                                                        sulfoxide

[benzene ring]—S—CH₂-CH=CH₂  —H₂O₂ / acetic acid / 2 equivalents→  [benzene ring]—S²⁺—CH₂-CH=CH₂ (with O⁻ and O⁻)

                                                                        sulfone

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## Alkylation of Sulfides: Sulfonium salts

Sulfur is a much better nucleophile than oxygen and it reacts readily with alkylating agents to form sulfonium salts. These are more stable than their oxygen analogs and undergo several useful reactions.
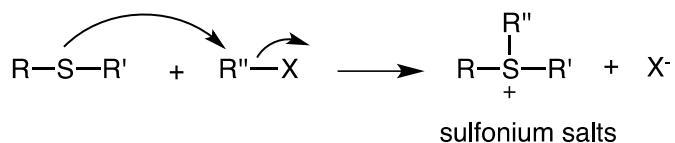


sulfonium salts

These sulfonium salts are important in biological chemistry. For example, SAM, s-adenosylmethionine is a naturally occurring sulfonium salt and acts as a methyl transfer agent.
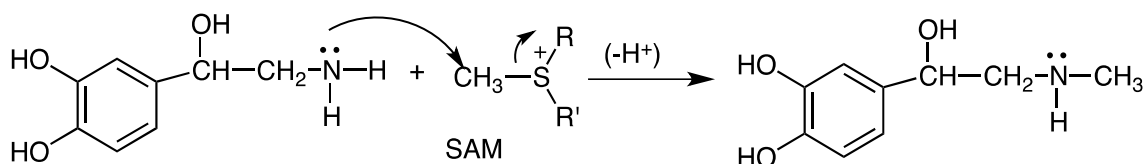


S-adenosylmethionine, SAM, is formed from the amino acid methionine and adenosine triphosphate, ATP.