Organic Chemistry II with Prof. Burke

Lecture Notes   http://camchem.rutgers.edu/~burke

Email   burke@camden.rutgers.edu

Room   Sci 114B

Office Hours   In the half-hour after each lecture or by appt.

Text   (a) "Organic Chemistry" Wade,
              5th, 6th, or 7th Edition

             (b) Solution Manual to Organic Chemistry

             (useful: organic model kit)

Do the chapter examples in the book

Learn as you go along

Aim for understanding, not memorization

Use Chemistry Department (Burke, Fazen, Roche) exams as a guide.
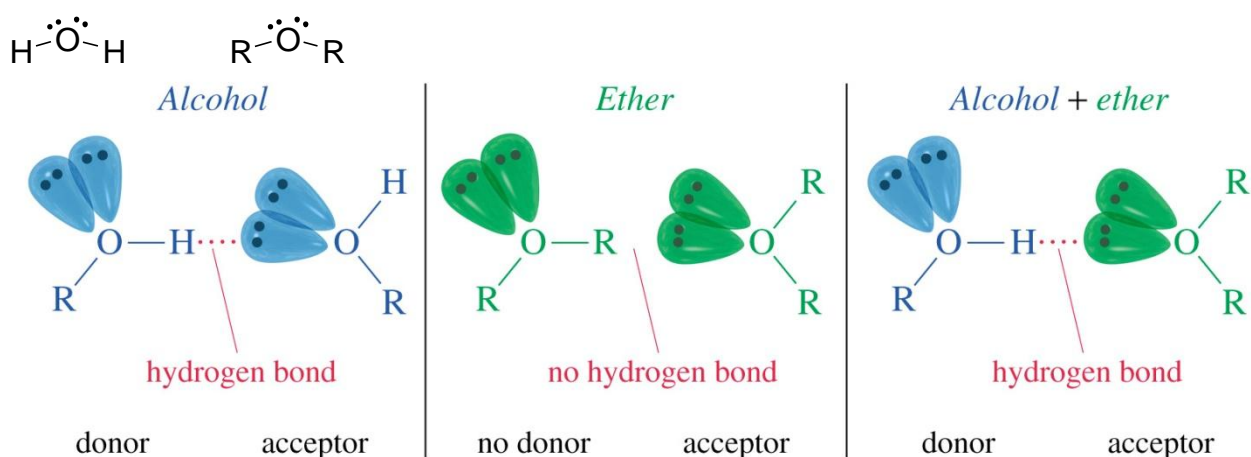
Ethers and Epoxides

A. Ethers
I. Introduction:
Ethers are a class of compound of the general formula   R-O-R'.

R and R' can be alkyl or aryl.

Structure
Ethers can be thought of as alkyl analogues of water.


Uses

Uses
Since ethers are relatively unreactive and are somewhat polar (due to the lone pairs on the oxygen), they are commonly used as solvents for organic reactions. (Diethyl ether and THF, the Grignard reaction).

Ethers will often form complexes with molecules that have vacant orbitals, enabling 'unstable' molecules to be used as reagents.
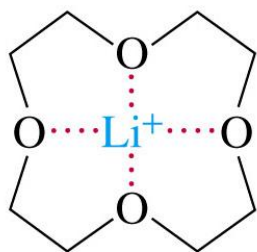
E.g. Hydroboration uses BH_3.THF
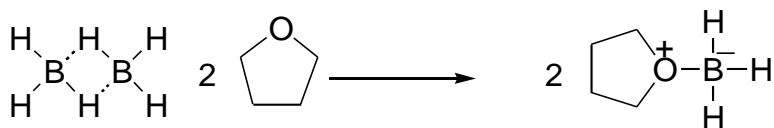
Crown ethers are macrocyclic ethers, which help to solvate metal cations, and thus allow inorganic salts to dissolve in organic solvents.
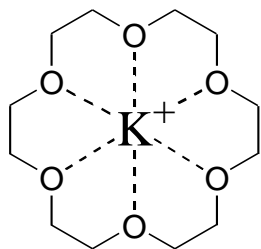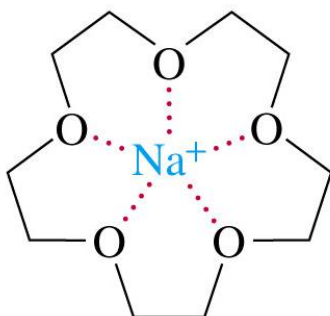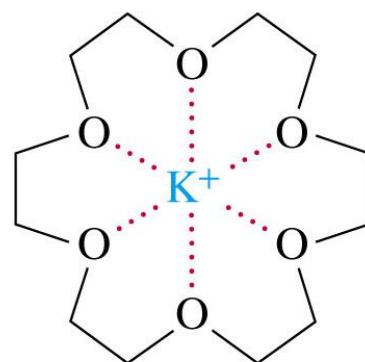
18-Crown-6

18-Crown-6 is the ideal size to incorporate a potassium ion, and allows organic solutions of ionic potassium salts to be prepared (purple benzene, KMnO$_4$).
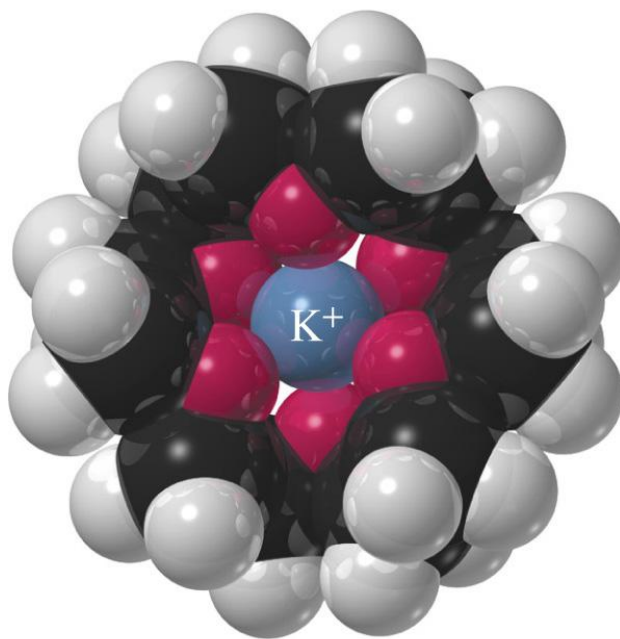
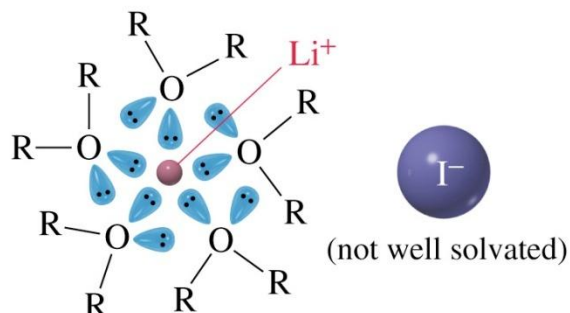12-crown-4
solvates Li$^+$

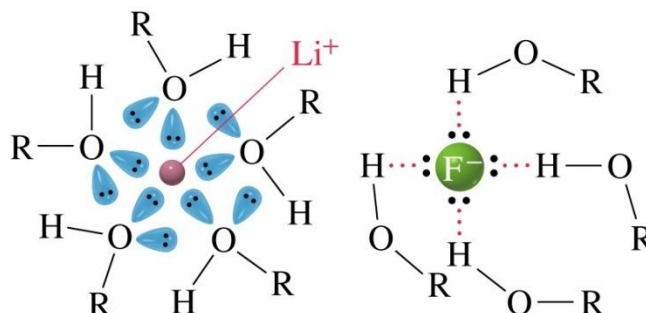15-crown-5
solvates Na$^+$

18-crown-6
solvates K$^+$

18-crown-6
with K$^+$ solvated

Ethers "differentially" solvate cations and anions. The cations are strongly bonded to the lone pairs of the ether, leaving the anions more available for attack (S_N2, $KMnO_4$, …)

ether solvates cations:
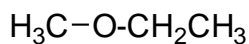
alcohol solvates cations and anions:
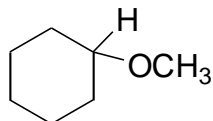
II. Nomenclature of ethers
Common names "trivial names" of ethers add the suffix ether after naming the groups on either side of the oxygen, e.g. methyl ethyl ether $H_3COCH_2CH_3$.

IUPAC names ethers by taking the more complex alkyl group the root name, and naming the remaining part as an alkoxy group.
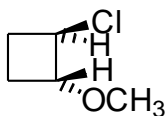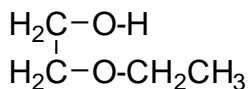
E.g.

$H_3C-O-CH_2CH_3$

methoxyethane

methoxycyclohexane

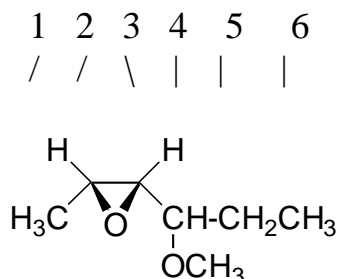trans-1-chloro-2-methoxycyclobutane

2-ethoxyethanol

Cyclic Ethers
Naming these **heterocyclic** compounds depends on the ring size and number of oxygens.
(It *can* be confusing at first…)

Epoxides
These 3 membered rings are named using the term "epoxy" as one substituent bridging two adjacent C atoms. (NOT like cyclopropane)

```
 1  2  3  4  5   6
 /  /  \  |  |   |
```

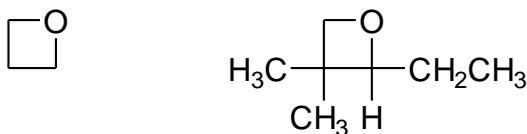H₃C, O, H, CH-CH₂CH₃, OCH₃ structure

cis-2,3-epoxy-4-methoxyhexane

(cis refers to the substituents, not the epoxide which <u>must</u> be cis/syn).

Epoxides have considerable ring strain.

Oxetanes
These are four membered rings with one oxygen.

oxetane   2-ethyl-3,3-dimethyloxetane

They are not considered a substituent but a ring such as cyclobutane. The O atom is understood as being in the first position.

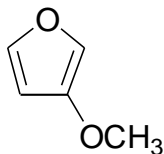Oxetanes have ring strain, but not as much as epoxides.

Furans
These are five membered rings with one oxygen and two double bonds.
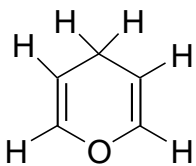(Furan is an "aromatic" molecule as is benzene.).
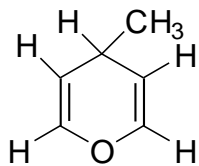
furan   tetrahydrofuran   3-methoxyfuran
             (THF)

Pyrans

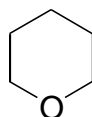These are six membered rings with one oxygen and two double bonds.

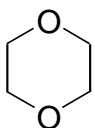pyran   4-methylpyran   tetrahydropyran
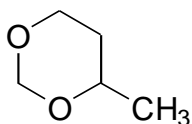   (THP)
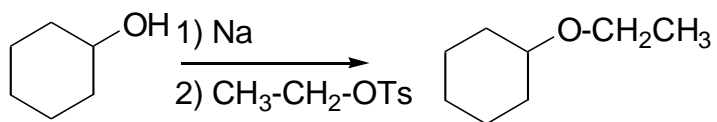
Dioxanes

These are six membered rings with two oxygens.
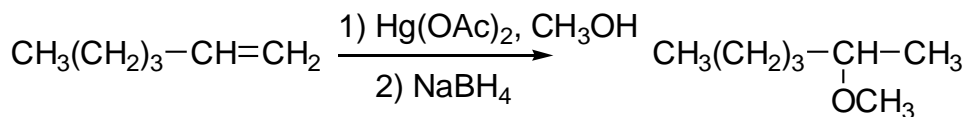

1,4-dioxane   4-methyl-1,3-dioxane

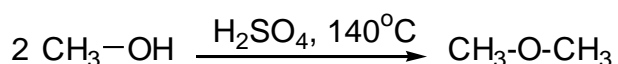## III. Ether Synthesis (Recap)

1) Williamson synthesis

ethoxycyclohexane

2) Alkoxymercuration-Demercuration

$$CH_3(CH_2)_3-CH=CH_2 \xrightarrow[\text{2) NaBH}_4]{\text{1) Hg(OAc)}_2,\ CH_3OH} CH_3(CH_2)_3-\underset{\underset{OCH_3}{|}}{CH}-CH_3$$

2-methoxyhexane
(Markovnikov product)

3) *Bimolecular* dehydration of Alcohols

$$2\ CH_3-OH \xrightarrow{H_2SO_4,\ 140^oC} CH_3\text{-O-}CH_3$$

IV. Reactions of Ethers
Typically ethers are stable and chemically inert, although they can undergo two types of reaction (1) *cleavage*, and (2) *oxidation*.

(1) Cleavage
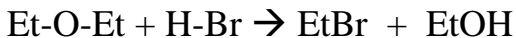Ethers are cleaved by H-Br and H-I, generating the corresponding alkyl halides.
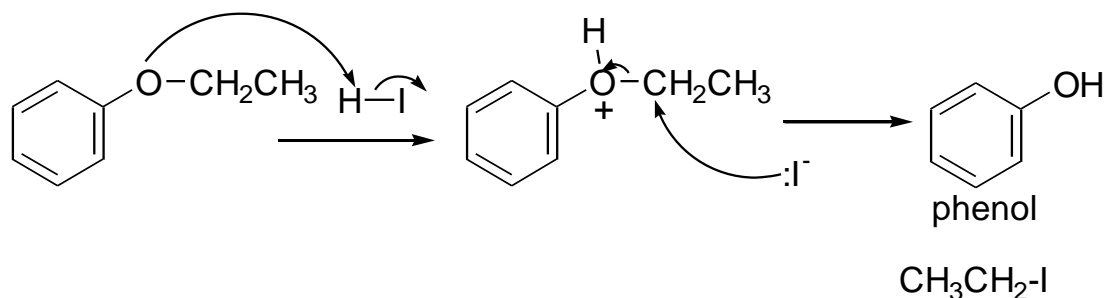
R-O-R' + excess H-X → R-X + R'-X

Ethers are stable to **bases**, but **acidic** conditions leads to the protonation of the ether oxygen, which then can undergo substitution reactions.

Et-O-Et + H-Br → EtBr + EtOH
Et-O-Et + 2H-Br → 2EtBr
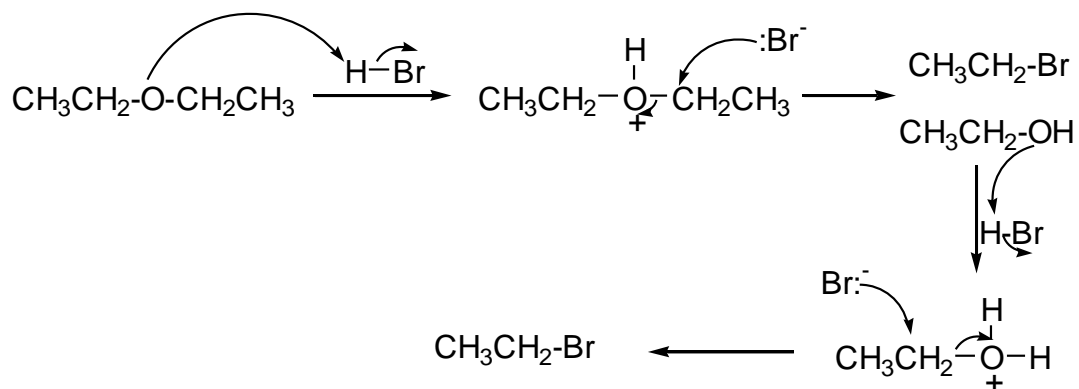
The alcohol produced reacts to generate a second molecule of alkyl halide.

Phenyl ethers are slightly different, and cleave to give alkyl halides and phenols.

The reaction stops at the phenol stage since the **sp^2** carbon of the C-O bond does not allow the required S_N1 or S_N2 reactions to generate the second molecule of aryl halide. (When the oxygen atom is in conjugation it also is **sp^2** hybridized, e.g. $H_2C=CH−O−CH_3$)

(2) Oxidation of Ethers
Ethers may auto-oxidize if left in the presence of oxygen for extended periods of time (**Dangerous** in the laboratory).
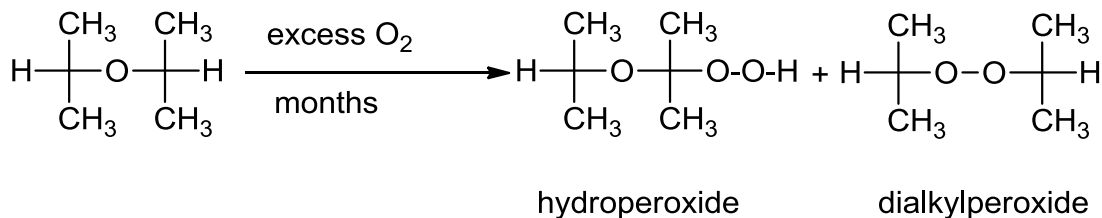
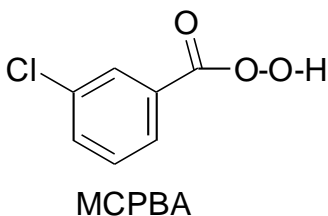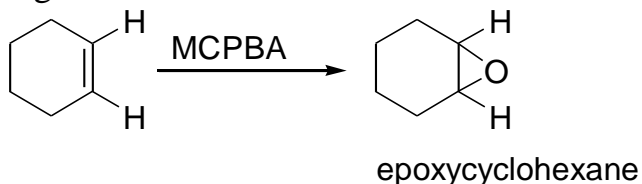The peroxides and hydroperoxides are unstable and explosive.

B. Epoxides
Unlike straight chain ethers, epoxides are very reactive (release of ring strain), and are useful intermediates because of their chemical versatility.
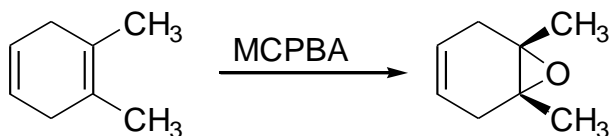
I. Synthesis
(1) Recall alkene and **peroxyacid** → epoxide and carboxylic acid
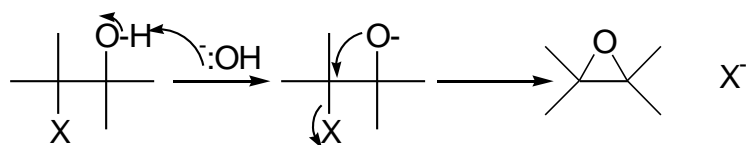
E.g.

epoxycyclohexane

MCPBA

MCPBA is one of the most common epoxidising reagents.
(*meta*-chloroperoxybenzoic acid)

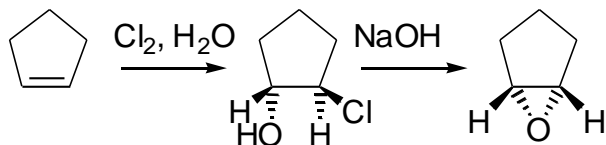Epoxidations work better for electron rich double bonds (alkyl donating groups).

(2) Synthesis from Halohydrins
When halohydrins are treated with base, an intramolecular cyclization occurs, and epoxides are formed.
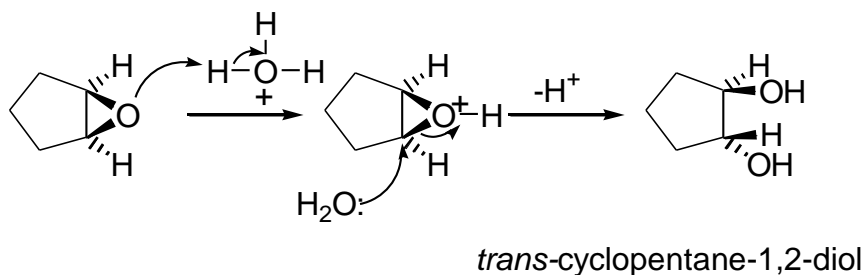

Recall that *trans* halohydrins are produced from alkenes by reaction with halogens in the presence of water. (Chlorine water or related reagents).
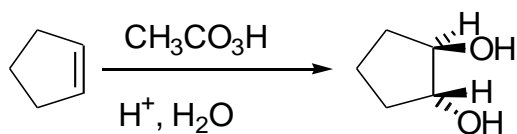
(3) Acid Catalyzed ring Opening
Epoxides react to **release** their considerable (25kcal/mol) strain energy.

(a) Recall that the acidic hydrolysis of epoxides gives **anti** diols.

trans-cyclopentane-1,2-diol

This overall transformation (alkene → anti 1,2-diol) can be achieved in one step by reaction with aqueous peroxyacids.
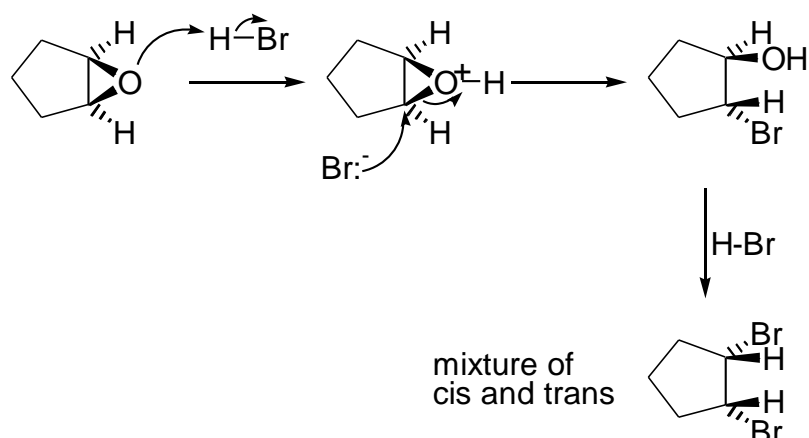

(b) Epoxides can be ring opened by <u>alcohols</u> with acidic catalysis to generate alkoxy alcohols with **anti** stereochemistry.
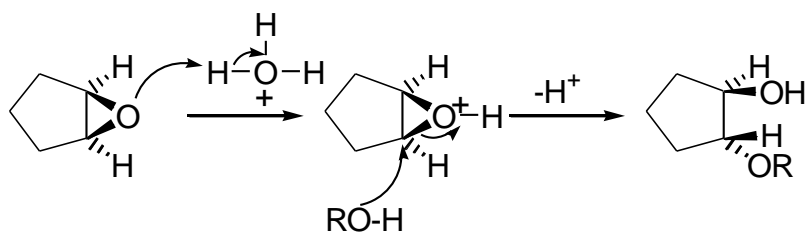
(4) Hydrohalic Acids
Epoxides react with H-X to produce halohydrins, which react further with H-X to generate 1,2-dihalides.

H—Br

Br:⁻

H-Br

mixture of
cis and trans

(However it is synthetically easier just to add X_2 to an alkene).

(5) Base Catalyzed Ring Opening
Normal ethers and alcohols do not undergo nucleophilic substitution or eliminations because the alkoxide and hydroxide anions are not good leaving groups. (That is why acid catalysis is required for both).

Epoxides are different though. The release of strain when an epoxide is opened more than compensates for the poor leaving group ability, and so epoxides will open under nucleophilic conditions.
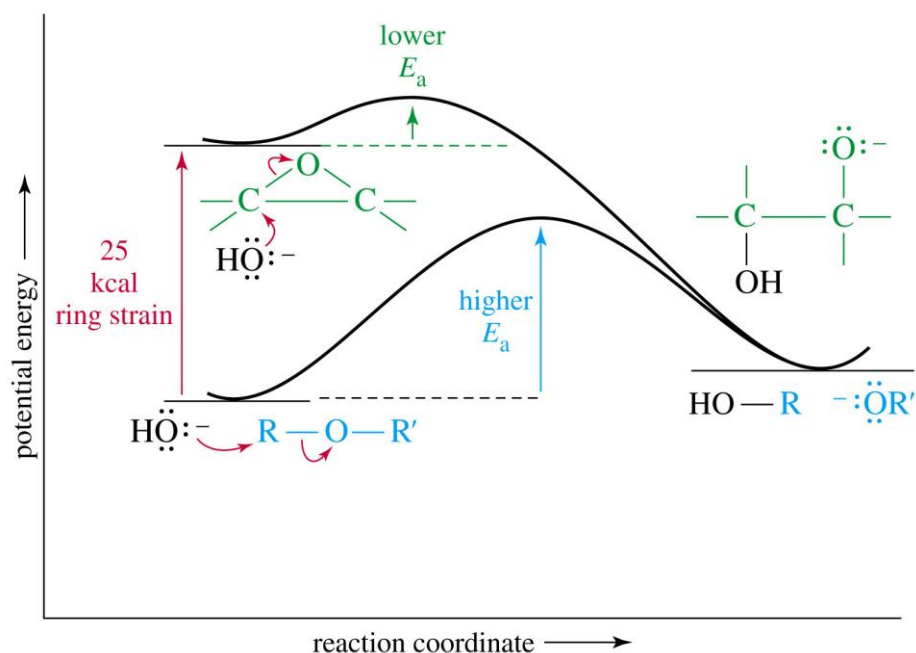
lower
E_a

25
kcal
ring strain

HÖ:⁻

higher
E_a

HÖ:⁻   R—O—R′

:Ö:⁻

OH

HO—R   ⁻:ÖR′

potential energy →

reaction coordinate →

Figure 14-8

The strained epoxide has a lower E_a than the corresponding straight chain ether. (Hammond's Postulate)

The reaction of hydroxide (or alkoxide) with a *symmetric* epoxide generates anti diols (or alkoxy alcohols) identical to those produced under acidic conditions.
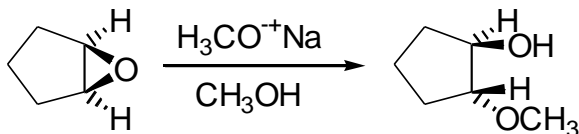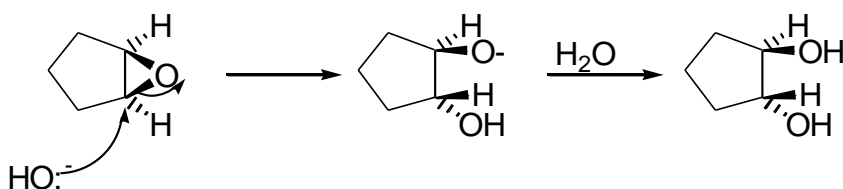
(Remember that sodium alkoxides can be formed by adding sodium metal to the corresponding alcohol.)

CHALLENGE: Make the following ether starting with only cyclopentanol and a series of any reagents:
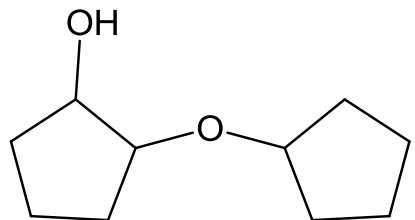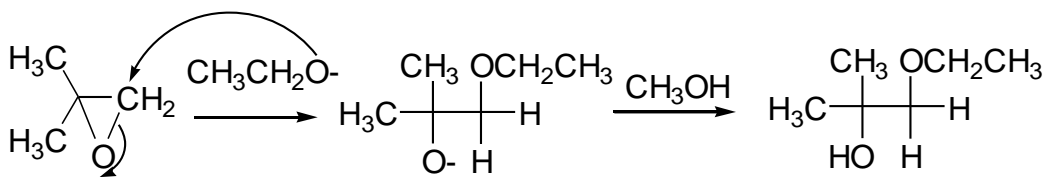

2-(cyclopentyloxy)cyclopentanol

Note well: Orientation of Ring Opening
Unsymmetrical epoxides give products with different regiochemistry with
(1) **basic** opening compared to (2) **acidic** opening.
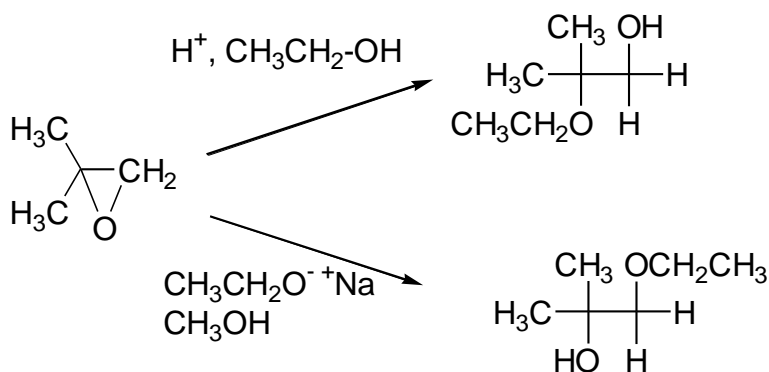
(1) Under *basic* conditions, the alkoxide simply attacks the least sterically
hindered epoxide carbon in an S_N2 displacement.

(2) Under *acidic* conditions, the alcohol *seems* to attack the more hindered
carbon, but it is more complicated.

The protonated epoxide has several resonance structures (The very strained,
cyclic "*onium*" *ion,* $C-OH^+$ single bonds are some of the few examples of
resonance not involving double bonds.).

$$\left[\begin{array}{ccc} \text{(I)} & \text{(II)} & \text{(III)} \end{array}\right]$$
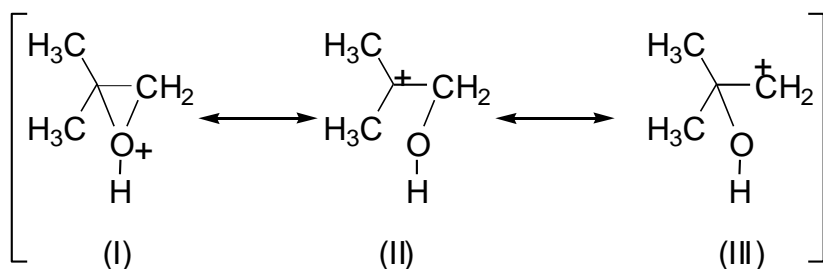
Structure II is a **major** contributor since the cation is more highly substituted and therefore more stable.
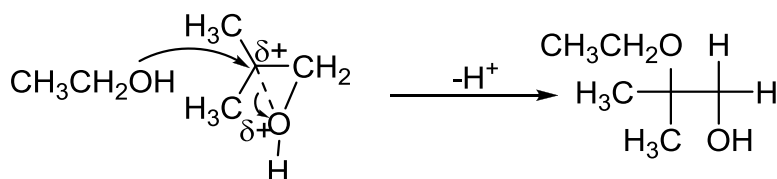
The nucleophile attacks the carbon with greatest positive partial charge. This gives an S_N1 –*like* mechanism. Remember the differences in the S_N1 to S_N2 spectrum. Substrate: $3°$ to $1°$; Nucleophile: (weak or strong) to strong; Leaving Group: 'good' to (good or bad). *Let's figure this out in class.*

(6) Organometallic Reagents
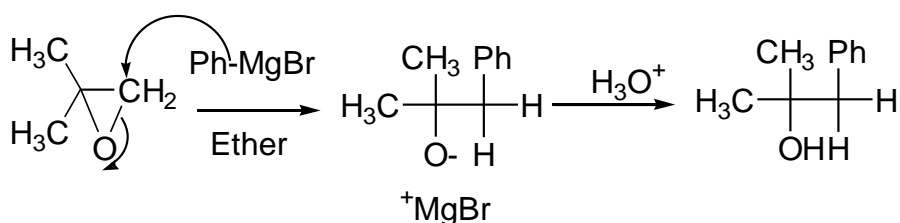
Grignard and organolithium reagents also attack epoxides at the least hindered carbon to generate alcohols (after acidic workup).

The sulfur equivalents to alcohols, ethers, and protonated epoxides are covered in the following part of Chapter 14b: Thiols, thioethers, and sulfonium ions.