

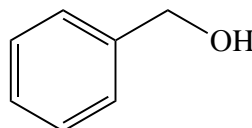
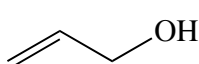
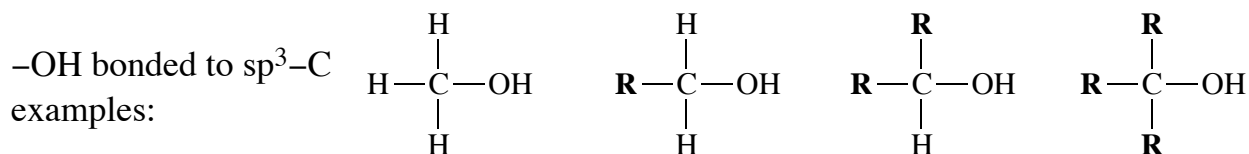
Lecture Notes
Chem 51B
S. King

Chapter 9 Alcohols, Ethers, and Epoxides

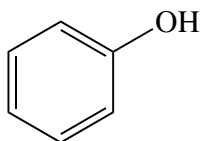
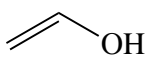
I. Introduction

Alcohols, ether, and epoxides are 3 functional groups that contain C–O σ -bonds.

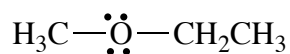
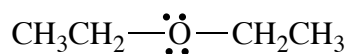
Alcohols: Contain a hydroxy group(–OH) bonded to an sp^2 or sp^3 hybridized carbon atom.



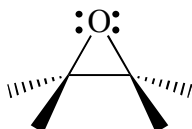
–OH bonded to sp^2 -C
examples:



Ethers: Have two alkyl groups bonded to an oxygen. The alkyl groups can be the same or different:



Epoxides: Ethers that are part of three-membered ring.



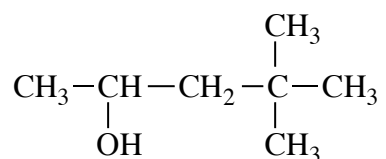
II. Nomenclature of Alcohols

Common name: Alkyl alcohol

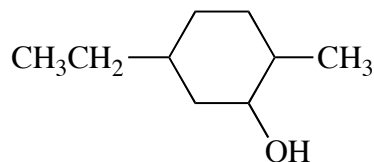
IUPAC: suffix: **-ol**.

The following rules are used to name a compound that has a functional group suffix:

1. Select the longest continuous carbon chain to which a hydroxyl (OH) is attached.
2. The parent chain is named by dropping the “e” of the alkane and adding “ol”.
3. Number the longest continuous carbon chain to give the carbon bearing the hydroxyl the lowest number. This number is included in the name.



4. A number is not needed to designate the position of a functional group suffix in a cyclic compound, because it is assumed to be in the 1-position.



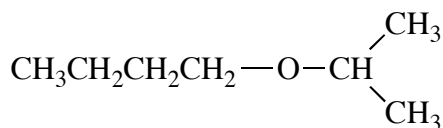
III. Nomenclature of Ethers

Common name: Name the two alkyl substituents (in alphabetical order), followed by the word “ether”

IUPAC: Name as alkane with an RO– substituent. An RO– substituent is named by replacing the –yl ending with –oxy

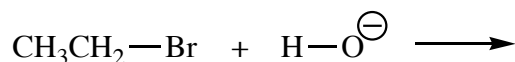
Examples:

$\text{CH}_3\text{O}-$	methoxy
$\text{CH}_3\text{CH}_2\text{O}-$	ethoxy
$\begin{array}{c} \text{CH}_3-\text{CH}-\text{O}- \\ \\ \text{CH}_3 \end{array}$	isopropoxy
$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_3-\text{C}-\text{O}- \\ \\ \text{CH}_3 \end{array}$	<i>tert</i> -butoxy

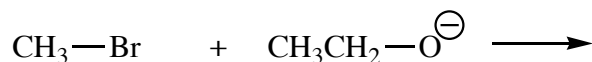


IV. Preparation of Alcohols, Ethers, Epoxides

Alcohols and ethers are common products of nucleophilic substitution.



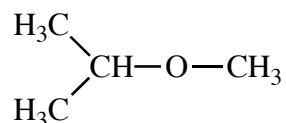
An ether is prepared by treating an alkoxide with an alkyl halide. This is known as a **Williamson ether synthesis**.



Care must be taken when synthesizing ethers!

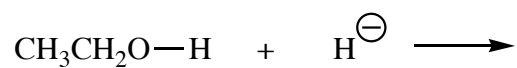
- Since alkoxides are strong bases, unhindered primary or methyl alkyl halides should be used since 2° halides will give predominant elimination and 3° alkyl halides will give elimination only.

Example: Synthesize the following ether, choosing reagents that would give the best yield:



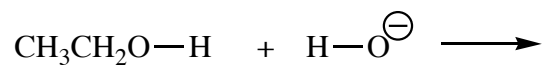
There are two possible combinations of alkoxide and alkyl halide:

A hydroxide is used to form alcohols, and an alkoxide is used to make an ether.
Alkoxide can be formed by treating an alcohol with NaH:

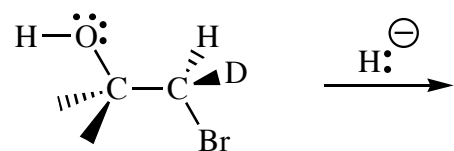


Q: Can HO⁻ be used to form an alkoxide from an alcohol?

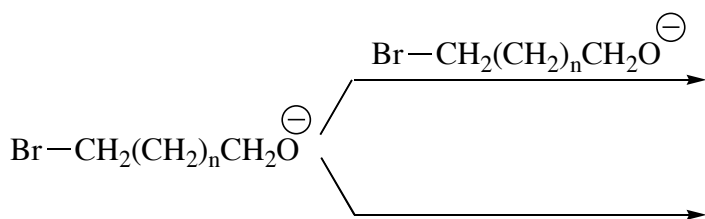
A:



An intramolecular version of the Williamson ether synthesis provides a route to epoxides:



A molecule that contains both a leaving group and a nucleophile can undergo either an *intramolecular* or an *intermolecular* substitution reaction.

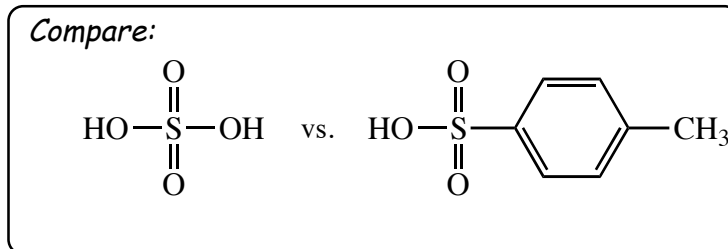
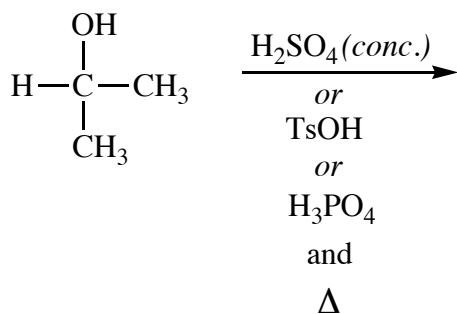


Q: Which route is favored?

A: It depends on the size of the ring!

V. Elimination Reactions of Alcohols: Dehydration

Alcohols, when heated in acid, are converted to alkenes in an elimination reaction. Sulfuric acid (H_2SO_4), *para*-toluene sulfonic acid (AKA: Tonic acid, abbreviated as TsOH) and phosphoric acid (H_3PO_4) are the most commonly used acids.



The mechanism depends on the structure of the alcohol. Under these strongly acidic conditions, both 2° & 3° alcohols undergo an E1 reaction, whereas 1° alcohols go undergo an E2 reaction. All three (1°, 2° and 3°) have the same first step, protonation of the hydroxyl group by the strong acid to make it a better LG:

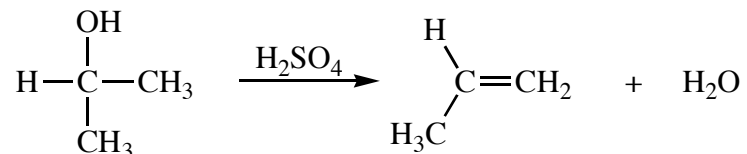
First step for all alcohols:

2° and 3° alcohols go through an E1 MECHANISM:

1° alcohols go through an E2 MECHANISM:

Because all of these steps are reversible, this is an equilibrium process. The two σ -bonds broken in this reaction are stronger than the π -bond formed in this reaction. Since equilibrium reactions favor the *more stable* products, the equilibrium is favored to the left. In order to obtain an alkene product, the reaction has to be driven to completion using **Le Chatelier's principle**:

☞ **Le Chatelier's principle:** A system at equilibrium will react to counteract any disturbance in the equilibrium.



To drive equilibrium:

Things to keep in mind about dehydration reactions:

❖ The rate of the reaction corresponds to the ease at which the carbocation is formed:

3° alcohol:

2° alcohol:

1° alcohol:

Q: Why does a 1° alcohol need forcing conditions?

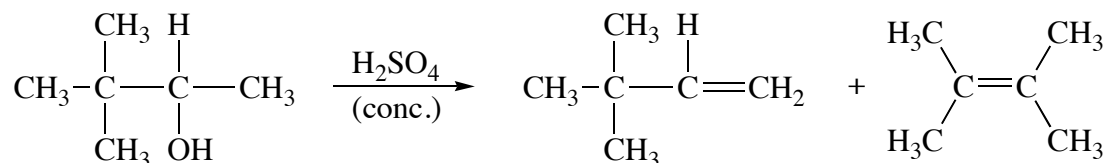
A:

- ❖ The stereochemical outcome of this E1 dehydration is the same as the stereochemical outcome of an E1 elimination of an alkyl halide:
- ❖ Carbocations commonly undergo rearrangements. This is a complication of any reaction involving a carbocation intermediate.

A. Carbocation Rearrangement

Some dehydration, E1, and S_N1 reactions give unexpected products in which the nucleophile appears to have added to the wrong carbon, or the carbon skeletons have been rearranged.

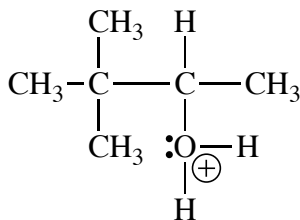
Example:



Q: *How does this happen?*

A:

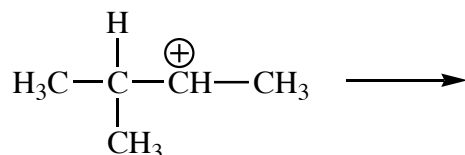
Look at the 2° carbocation formed in this example:



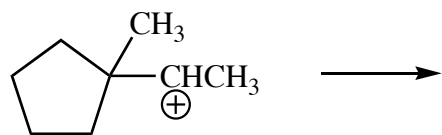
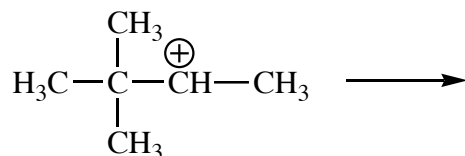
- The rearranged carbocation is a more stable 3° carbocation.

- The methyl migrates *with its pair of bonding electrons* from the carbon adjacent to the electron-deficient carbon. The carbon from which the group departs, as a result, becomes electron deficient and positively charged. This is called a **1,2-methyl shift**.
- ☛ Rearrangements of carbocations are a general phenomenon and occur when migration of a hydrogen, methyl group, or *other* alkyl group *leads to a more stable carbocation*:

1,2 H migration:

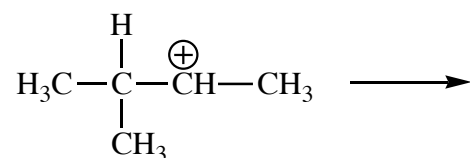


1,2 Alkyl migration:



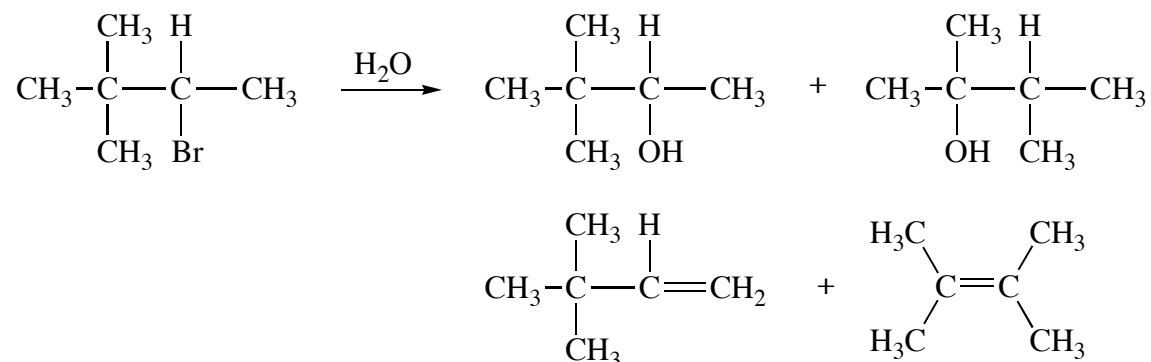
Q: In the first example above, a H migrates rather than a CH₃. Why?

A:

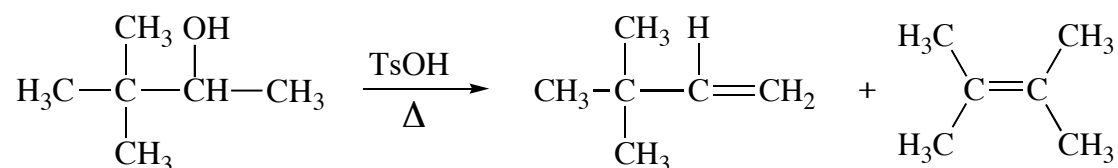


☛ **Whenever a reaction leads to the formation of a carbocation, you must check its structure for the possibility of rearrangement!**

$S_N1/E1$ example:



Dehydration example:



Summary of dehydration reaction reactions:

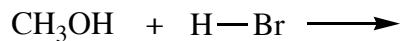
- Use H_2SO_4 (conc.) or TsOH + heat
- Works for 2° or 3° alcohols (*Don't use for 1° alcohols! Use alternative shown on page 27 of the notes.*)
- Watch for rearrangements, especially with 2° alcohols.
- Most highly substituted alkene is favored.

VI. Conversion of Alcohols to Alkyl Halides with H-X

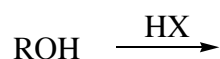
An alcohol *cannot* undergo a nucleophilic substitution reaction because it has a strongly basic leaving group that cannot be displaced by a nucleophile.



An alcohol *can* undergo substitution if its OH group is converted into a group that is a better leaving group. Treatment of an alcohol with H-X converts the bad leaving group, -OH, into a great leaving group, -X.



Primary, secondary, and tertiary alcohols all undergo nucleophilic substitution when treated with HI, HBr, and HCl to form alkyl halides.



The mechanism depends on the alcohol used:

1° alcohols & methanol: Reaction proceeds through an S_N2-type mechanism

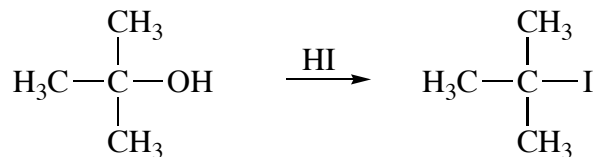


Step 1: Protonation of the alcohol

Step 2: Nucleophilic Displacement of H₂O

2° & 3° alcohols: Reaction proceeds through an S_N1-type mechanism

Example:



Step 1: Protonation of the alcohol

Step 2: Loss of H₂O to form carbocation

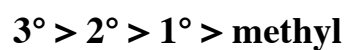
Step 3: Nucleophilic attack at the carbocation

Important points:

- order of reactivity of HX:



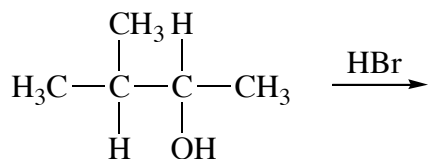
- order of reactivity of alcohols:



- **Reaction best for:**
- **Reaction doesn't work well for:**

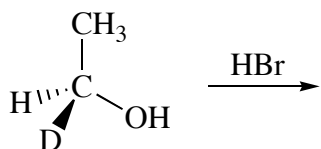
Q. Why doesn't this reaction work well for 2° substrates?

A. Secondary substrates can undergo both S_N1/E1 reactions, and S_N2/E2 reactions, depending on the conditions used. Under the conditions of this reaction (*strong aqueous acid*), S_N1/E1 pathways are favored over S_N2/E2 pathways for secondary substrates. So, the reaction proceeds by way of a carbocation intermediate, which can rearrange:

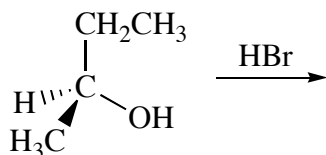


- Stereochemical outcome of the reaction: ***Depends on the substrate used!***

Primary alcohols:



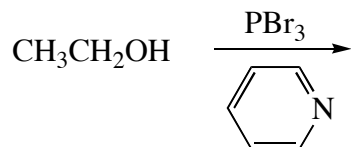
Secondary & Tertiary alcohols:



VII. Other Methods for Converting Alcohols into Alkyl Halides

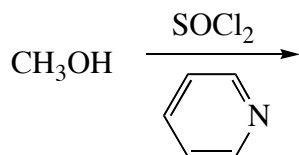
We have seen that alcohols can be converted to alkyl halides by treating them with HCl, HBr, or HI. Better yields can be obtained, and carbocation rearrangements can be avoided if a phosphorus trihalide (PCl_3 , PBr_3 , or PI_3), or thionyl chloride (SOCl_2) is used instead. These act the same way: *they convert an alcohol into an intermediate with a good leaving group that is readily displaced by a halide ion.*

A. PBr_3 /pyridine:



Mechanism:

B. SOCl_2 /pyridine:



Mechanism: *Different than Book! Don't use book mechanism on test!*

Important points about both reactions:

1. Don't do the mechanism this way:

Q: *Why not?*

A: The atom attached to the leaving group is NOT sp^3 -hybridized. S_N2 reactions only occur on sp^3 -hybridized atoms.

2. Don't deprotonate the alcohol first!

Q: *Why not?*

A:

3. Pyridine is used as a solvent in these reactions because it prevents the buildup of HBr or HCl and it is a poor nucleophile.

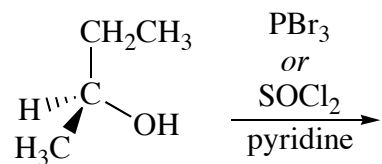
Q: Why don't we want buildup of HBr or HCl?

A:

4. These methods work for methyl, 1° & 2° alcohols

5. Yields are high for these reactions, and rearrangements are rare.

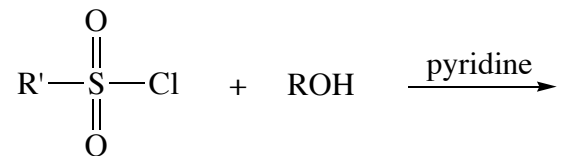
6. Both are stereospecific.



Advantages over HX reaction:

VIII. Converting Alcohols into Sulfonate Esters

Another way an alcohol can be converted into a great leaving group is to convert it into a sulfonate ester. This reaction converts an alcohol into a great leaving group.



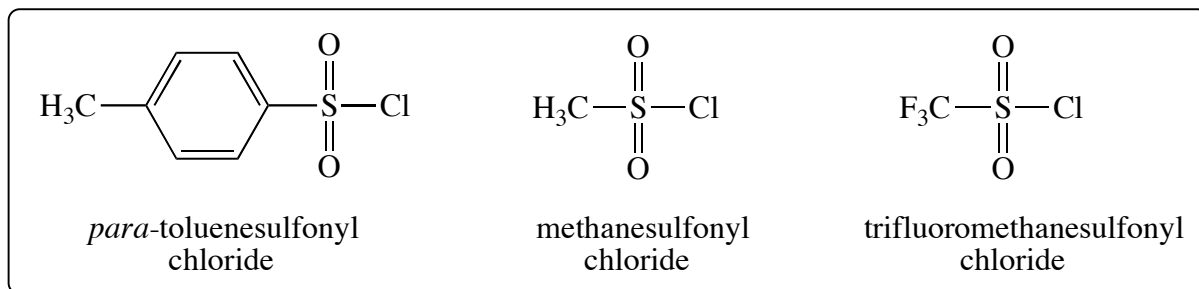
Mechanism for formation of sulfonate ester:

Don't do the mechanism this way:

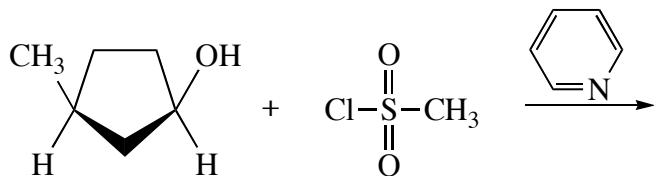
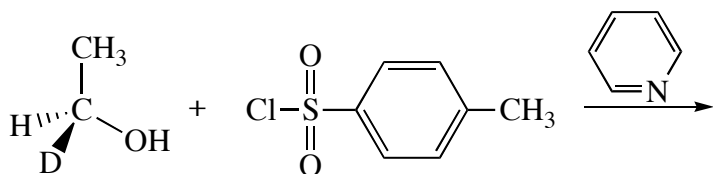
Q: *Why not?*

A:

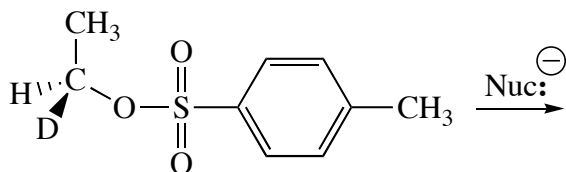
Several sulfonyl chlorides are available to activate alcohols, the most common being *para*-toluenesulfonyl chloride:



Examples (note the stereochemistry!)



The sulfonate esters formed can react with a variety of nucleophiles to undergo S_N2 reactions:



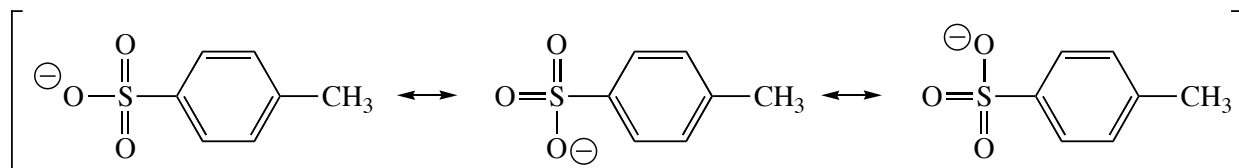
Notice the stereochemical result of this step!

Examples of common good nucleophiles:

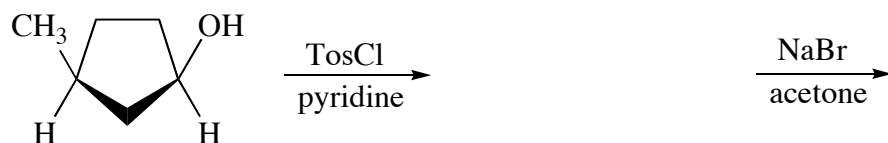
Q: Why is a sulfonate anion such a good leaving group?

A:

Why such a weak base?

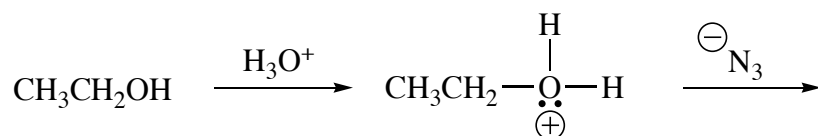


Use of NaX provides yet another route to alkyl halides:

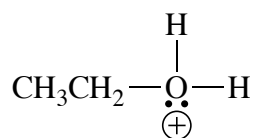


Summary: Alcohols can be converted to alkyl halides with HBr, HCl, HI or SOCl₂, pyridine or PBr₃, pyridine. In addition an alcohol can be converted into a tosylate, then treated with Br⁻, Cl⁻, or I⁻ to convert it into an alkyl halide. Once you have an alkyl halide or tosylate, you can do all of the substitution and elimination reactions seen in chapters 7 & 8.

What you *CANNOT* do:



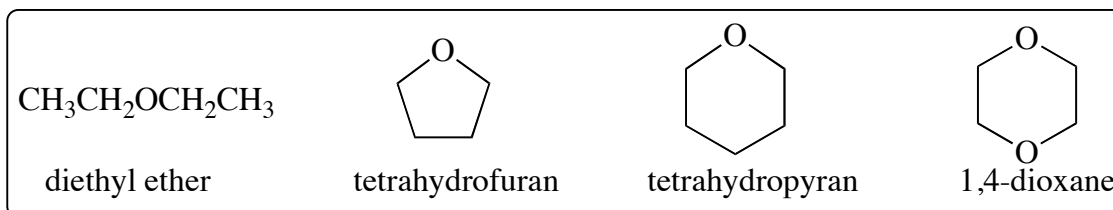
This will happen instead:



IX. Substitution Reactions of Ethers

Ethers, like hydrocarbons are *remarkably inert* to most chemical reactions. This is why they make such good solvents!

Some Typical Ether Solvents:

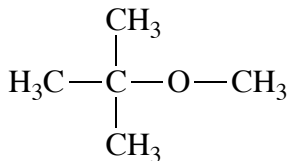


Ethers are, however, cleaved when *heated* with hot concentrated HI or HBr



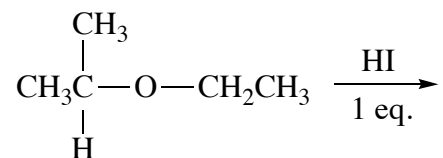
Mechanism:

Step 1: Protonation

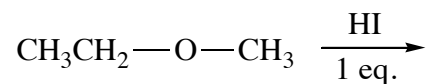


Step 2: $\text{S}_{\text{N}}1$ or $\text{S}_{\text{N}}2$ Depending on Substrate. *How to decide???*

1. *If* departure of L.G. gives a 2° or 3° carbocation, or a resonance stabilized carbocation, *then* a 2° or 3° carbocation, or a resonance-stabilized carbocation will form first.
2. *If* departure of a leaving group gives an unstable carbocation (e.g. methyl, vinyl, aryl, or unstabilized primary), then a carbocation will not form. The halide ion will attack the least hindered side.

Example 1:

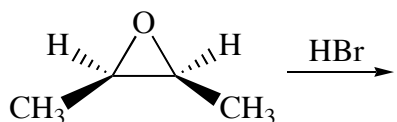
with a second equivalent of HI:

Example 2:**X. Reactions of Epoxides**

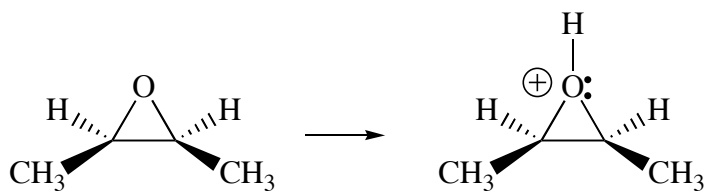
Ethers in which the oxygen atom is incorporated into a 3-membered ring are called epoxides (oxiranes.) Even though an epoxide and an ether have the same L.G., epoxides are much more reactive than ethers because the strain of the 3-membered ring is relieved when the ring opens.

A. Acid-Catalyzed Ring Opening

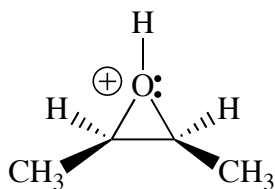
Epoxides are much more readily cleaved by acids than ethers. *The reaction is rapid even at 0°C.*



Mechanism:

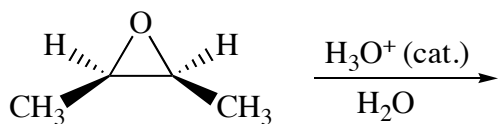


or

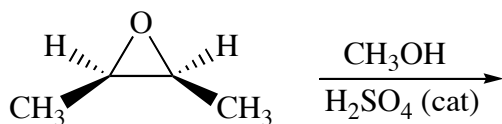


Protonated epoxides are so reactive that they can be opened by weak nucleophiles such as H₂O or alcohols.

Strong Acid catalyst + H₂O:

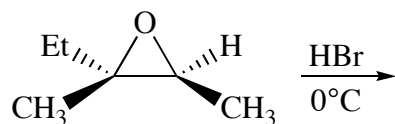


Strong acid catalyst + alcohol:

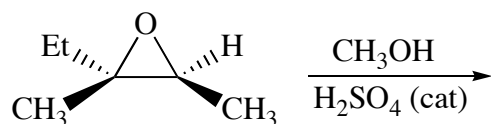


- ★ Acid catalysis assists the epoxide ring opening by providing a better leaving group (*an alcohol*) at the carbon undergoing nucleophilic attack. This is especially important when the nucleophile is a weak nucleophile (*such as an alcohol or water.*)

With unsymmetrical epoxides, the nucleophile only attacks on the most substituted side of the protonated epoxide, the side with the most partial positive charge, to give a single **regioisomer** (*one of two possible constitutional isomers.*)

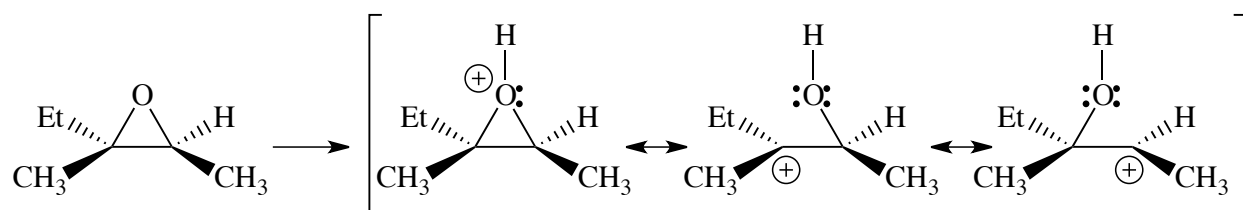


The *same* goes for other acid catalyzed epoxide ring reactions:



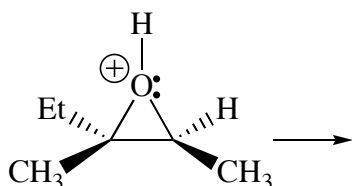
Q. Why is there only one **regioisomer**?

A. Bonding in the protonated epoxide is unsymmetrical with the more highly substituted carbon bearing considerable δ^+ - charge! The nucleophile attacks this carbon even though it is more highly substituted.

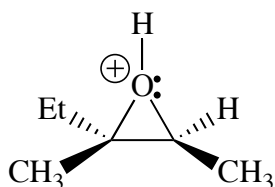


Hybrid of the two best resonance structures:

Q. Why couldn't the intermediate in this reaction be an ordinary carbocation?

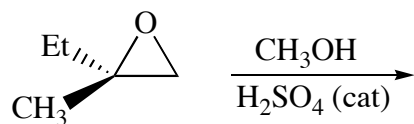


A. If the intermediate was a carbocation, the nucleophile could attack from the top and the bottom face of the carbocation, giving a mixture of stereoisomers. The stereochemistry of the product clearly shows attack of the nucleophile **only on the bottom face of the epoxide**. The intermediate must therefore be more like a protonated epoxide than like a planar carbocation.



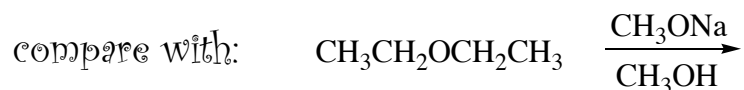
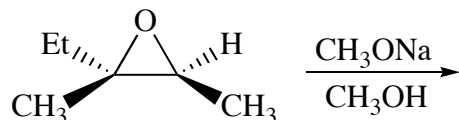
Do I expect you to draw all of the resonance structures and the hybrid on an exam? NO. Here is a sample test question:

Sample Question: Predict the product for the following reaction and provide a mechanism for its formation. Show all lone pairs, charges and curly arrows. Do not combine two steps into one

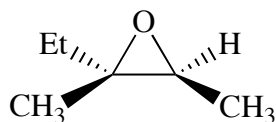


B. Nucleophilic Ring Opening

Strong nucleophiles, such as alkoxides, will open the strained ring of an epoxide *without acid catalysis* (acyclic ethers do not undergo this reaction).



Mechanism: Under basic conditions or with strong nucleophile, DO NOT PROTONATE THE EPOXIDE FIRST!



Notice the regioselectivity in this reaction!

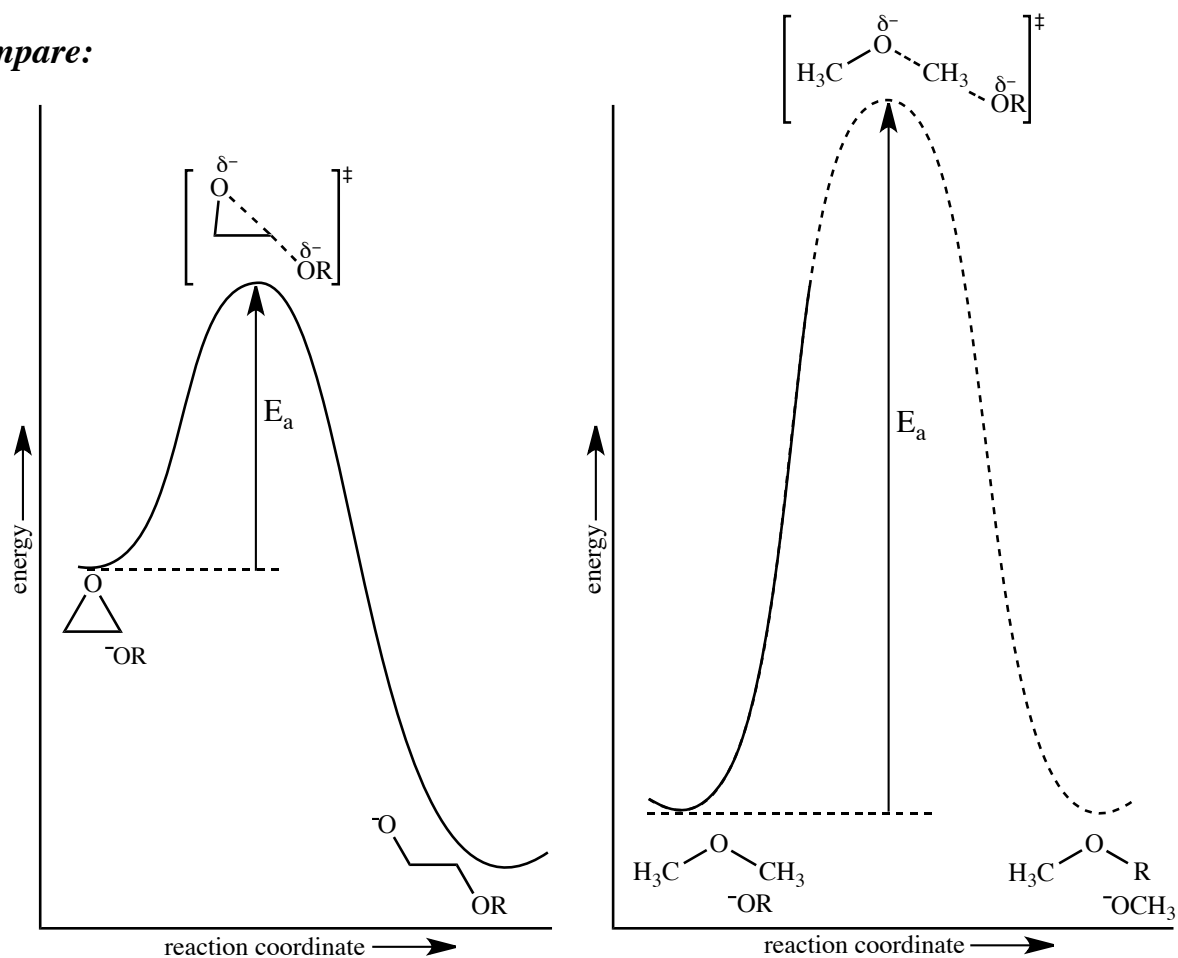
- With strong nucleophiles, attack occurs at the less highly substituted carbon

Q. *An alkoxide is a leaving group in this reaction!!!!* How can this be???

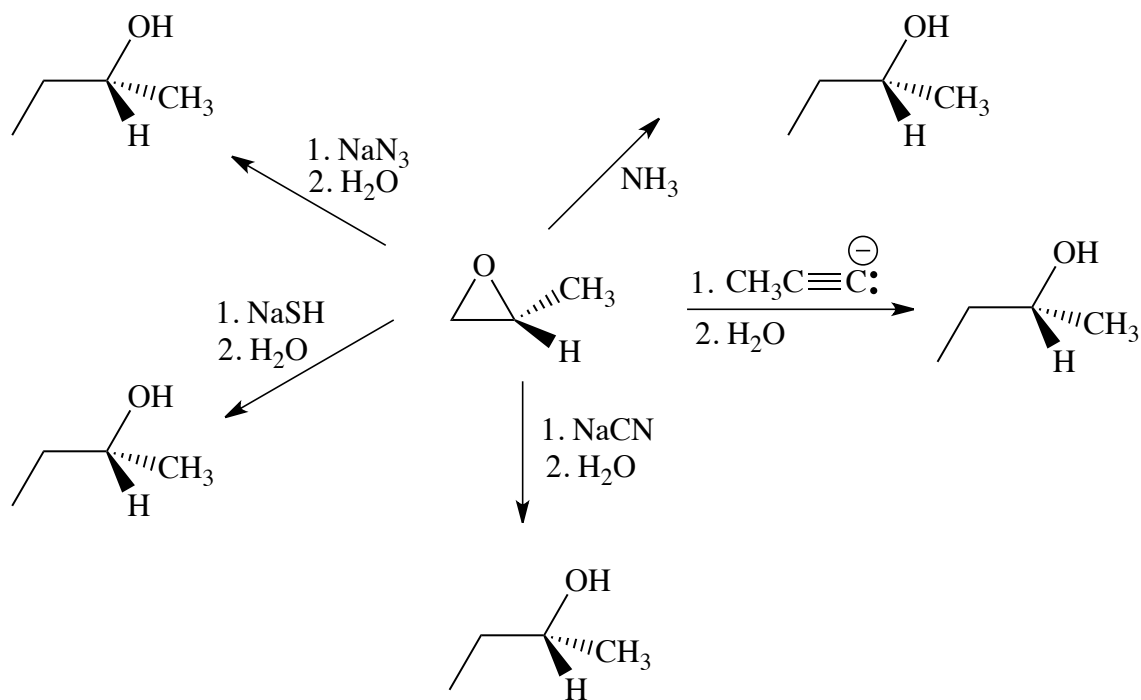
A. Two reasons:

- The three-membered ring is very strained.
- Strain is relieved by lengthening of the C-O bond in the transition state.

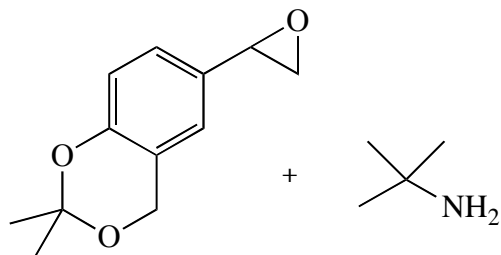
Compare:



A number of good nucleophiles will also react with epoxides:



An interesting application of nucleophilic epoxide ring opening to synthesize a bronchodilator:



** For intramolecular deprotonation,
must be able to make 5 or 6-membered
ring transition state

Alternative to dehydration of 1° alcohols: Make hydroxyl into a good leaving group and then do E2 elimination using a strong hindered base!

