Organic Chemistry, *Fourth Edition*

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Chapter 9
Alcohols, Ethers, and Epoxides

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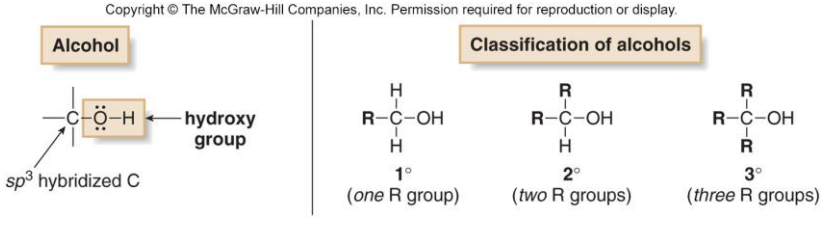
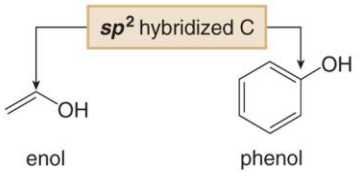
Alcohols—Structure and Bonding

- **Alcohols contain a hydroxy group (OH) bonded to an sp^3 hybridized carbon.**
- **They are classified according to the number of alkyl groups attached to carbon bearing the OH.**



Enols and Phenols

- **Compounds having a hydroxy group on a *sp*^{2} hybridized carbon—enols and phenols—undergo different reactions than alcohols.**



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Ethers

- **Ethers have two alkyl groups bonded to an oxygen atom.**

Ether

R–Ö–R

CH_3CH_2–Ö–CH_2CH_3	CH_3–Ö–CH_2CH_3
symmetrical ether	**unsymmetrical ether**
R groups are the **same.**	R groups are **different.**

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Epoxides

- **Epoxides are ethers having the oxygen atom in a three-membered ring.**
- **Epoxides are also called oxiranes.**

epoxide or oxirane

a strained, three-membered ring

- **The C-O-C bond angle for an epoxide must be 60°, a considerable deviation from the tetrahedral bond angle of 109.5°.**
- **Thus, epoxides have angle strain, making them more reactive than other ethers.**

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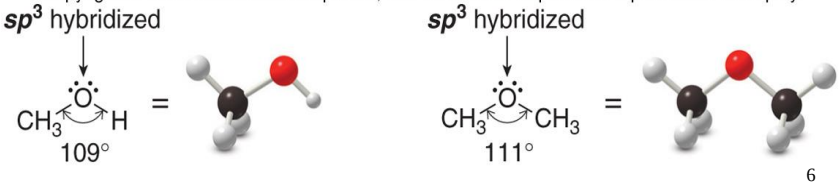
Oxygen Hybridization and Geometry

- **The oxygen atom in alcohols, ethers, and epoxides is sp^3 hybridized.**
- **Alcohols and ethers have a bent shape like that in H_2O.**
- **The bond angle around the O atom in an alcohol or ether is similar to the tetrahedral bond angle of 109.5°.**
- **Because the O atom is much more electronegative than carbon or hydrogen, the C-O and O-H bonds are both polar.**



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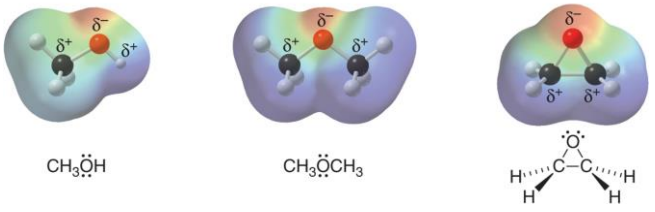
Electrostatic Potential Maps

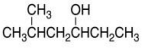
- **The oxygen atom in alcohols, ethers, and epoxides is *sp*^{3} hybridized.**
- **Alcohols and ethers have a bent shape like that in H_2O.**



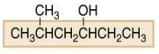
Naming Alcohols

HOW TO Name an Alcohol Using the IUPAC System

Example Give the IUPAC name of the following alcohol:



Step [1] Find the longest carbon chain containing the carbon bonded to the OH group.



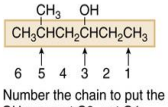
6 C's in the longest chain

6 C's → hexane → hexanol

- Change the ***-e*** ending of the parent alkane to the suffix ***-ol.***

Step [2] Number the carbon chain to give the OH group the lower number, and apply all other rules of nomenclature.

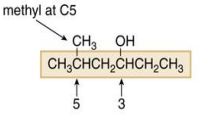
a. **Number** the chain.



- Number the chain to put the OH group at C3, not C4.

3-hexanol

b. **Name** and **number** the substituents.

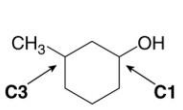


Answer: 5-methyl-3-hexanol

Naming Alcohols Attached to Rings

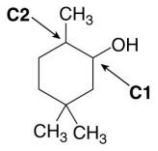
- **When an OH group is bonded to a ring, the ring is numbered beginning with the OH group.**
- **Because the functional group is at C1, the 1 is usually omitted from the name.**
- **The ring is then numbered in a clockwise or counterclockwise fashion to give the next substituent the lowest number.**

Figure 9.2



3-methylcyclohexanol

[The OH group is at C1; the second substituent (CH_3) gets the lower number.]



2,5,5-trimethylcyclohexanol

[The OH group is at C1; the second substituent (CH_3) gets the lower number.]

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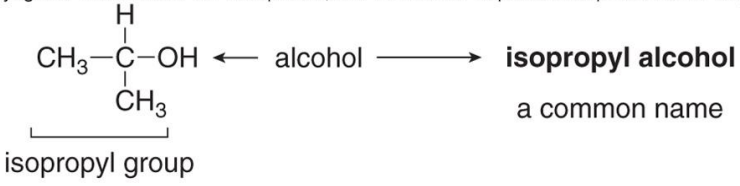
Common Names of Alcohols

- **Common names are often used for simple alcohols. To assign a common name:**
  - **Name all the carbon atoms of the molecule as a single alkyl group.**
  - **Add the word alcohol, separating the words with a space.**



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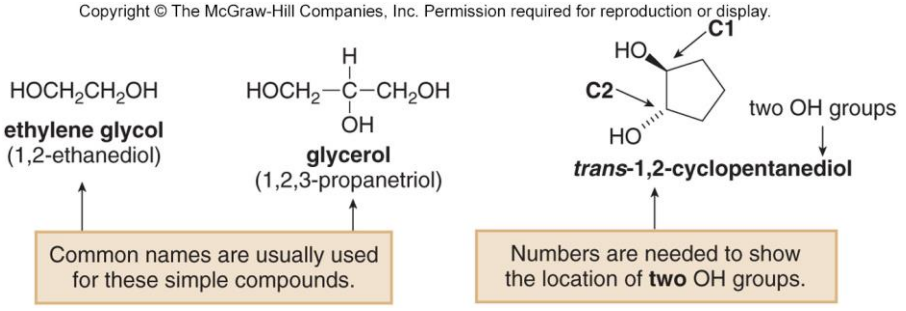
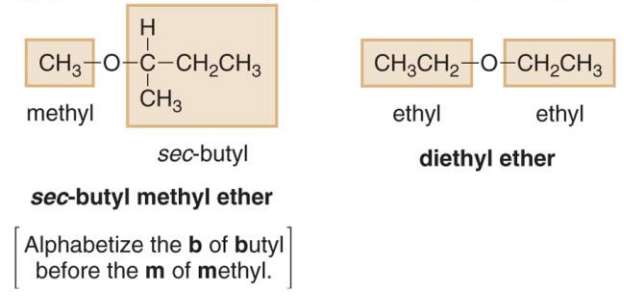
Diols and Triols

- **Compounds with two hydroxy groups are called diols or glycols.**
- **Compounds with three hydroxy groups are called triols.**



Naming Ethers

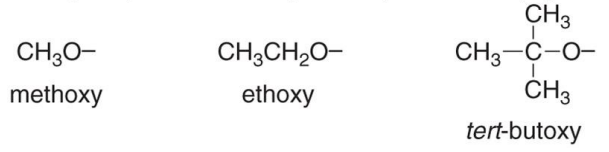
- **Simple ethers are usually assigned common names. To do so:**
  - **Name both alkyl groups bonded to the oxygen, arrange these names alphabetically, and add the word ether.**
  - **For symmetrical ethers, name the alkyl group and add the prefix "di-".**



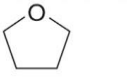
Naming Complex Ethers

- More complex ethers are named using the IUPAC system.
- One alkyl group is named as a hydrocarbon chain, and the other is named as part of a substituent bonded to that chain:
  - Name the simpler alkyl group as an alkoxy substituent by changing the -yl ending of the alkyl group to -oxy.
  - Name the remaining alkyl group as an alkane, with the alkoxy group as a substituent bonded to this chain.

Common alkoxy groups



- Cyclic ethers have an O atom in the ring. A common example is tetrahydrofuran (THF).



tetrahydrofuran
THF

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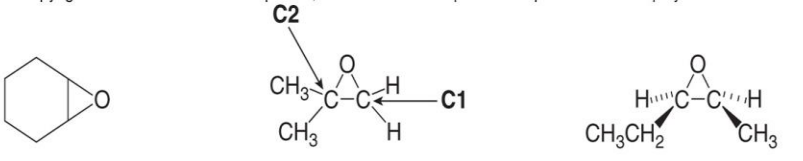
Naming Epoxides

- Epoxides can be named in three different ways—epoxyalkanes, oxiranes, or alkene oxides.

1. As an epoxyalkane
   a. Name the alkane chain or ring to which the O atom is attached
   b. Use the prefix "epoxy" to name the epoxide as a substituent.
   c. Use two numbers to designate the location of the atoms to which the O is bonded.



1,2-epoxycyclohexane | **1,2-epoxy-2-methylpropane** | ***cis*-2,3-epoxypentane**

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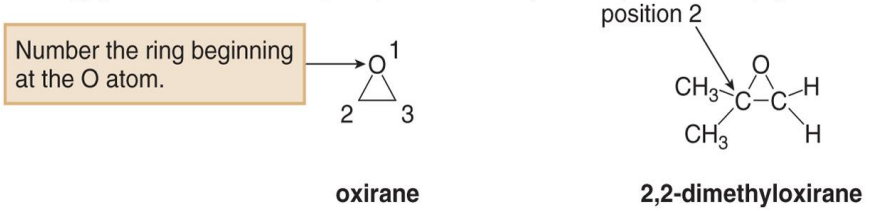
Naming Epoxides

2. <u>as Oxiranes</u>

- **the simplest epoxide having two carbons and one oxygen atom in a ring.**
- **The oxirane ring is numbered to put the O atom at position one, and the first substituent at position two.**
- **No number is used for a substituent in a monosubstituted oxirane.**



oxirane **2,2-dimethyloxirane**

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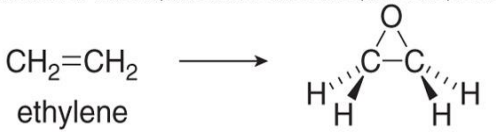
Naming Epoxides

3. <u>as alkene oxides</u>

- **since they are often prepared by adding an O atom to an alkene. To name an epoxide in this way:**
  1. **Replace the epoxide oxygen with a double bond.**
  2. **Name the alkene.**
  3. **Add the word oxide.**



ethylene oxide
oxirane

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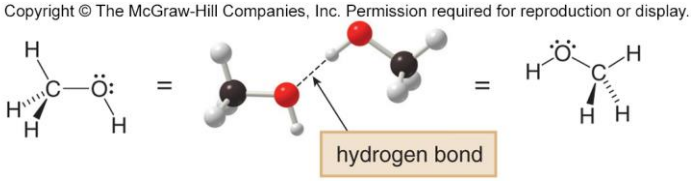
Hydrogen Bonding in Alcohols

- **Alcohols, ethers, and epoxides exhibit dipole-dipole interactions because they have a bent structure with two polar bonds.**
- **Alcohols are capable of intermolecular hydrogen bonding. Thus, alcohols are more polar than ethers and epoxides.**



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Sterics and Hydrogen Bonding

- **Steric factors affect hydrogen bonding.**

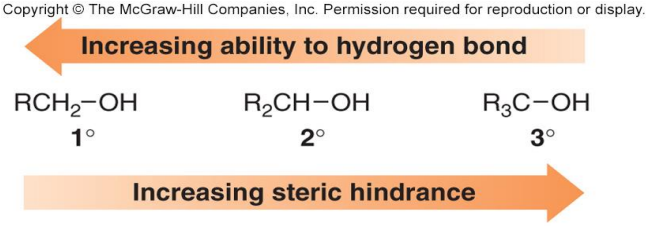

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Table 9.1 Physical Properties of Alcohols, Ethers, and Epoxides

Property	Observation
Boiling point and melting point	• For compounds of comparable molecular weight, the **stronger** the intermolecular forces, the **higher** the bp or mp. $CH_3CH_2CH_2CH_3$ (VDW, bp 0 °C) → $CH_3OCH_2CH_3$ (VDW, DD, bp 11 °C) → $CH_3CH_2CH_2OH$ (VDW, DD, HB, bp 97 °C) **Increasing boiling point**
	• Bp's **increase** as the extent of hydrogen bonding **increases.** $(CH_3)_3C-OH$ (3°, bp 83 °C) → $CH_3CH_2\underset{\displaystyle OH}{\underset{|}{C}}HCH_3$ (2°, bp 98 °C) → $CH_3CH_2CH_2CH_2-OH$ (1°, bp 118 °C) **Increasing ability to hydrogen bond** **Increasing boiling point**
Solubility	• Alcohols, ethers, and epoxides having ≤ 5 C's are H_2O soluble because they each have an oxygen atom capable of hydrogen bonding to H_2O (Section 3.4C). • Alcohols, ethers, and epoxides having > 5 C's are H_2O insoluble because the nonpolar alkyl portion is too large to dissolve in H_2O. • Alcohols, ethers, and epoxides of any size are soluble in organic solvents.

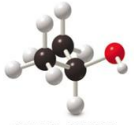
Key: VDW = van der Waals forces; DD = dipole–dipole; HB = hydrogen bonding

Some Simple Alcohols

Figure 9.3

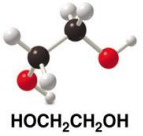
CH_3OH

- **Methanol (CH_3OH)** is also called wood alcohol, because it can be obtained by heating wood at high temperatures in the absence of air. Methanol is extremely toxic because of the oxidation products formed when it is metabolized in the liver (Section 12.14). Ingestion of as little as 15 mL causes blindness, and 100 mL causes death.



$(CH_3)_2CHOH$

- **2-Propanol [$(CH_3)_2CHOH$]** is the major component of rubbing alcohol. When rubbed on the skin it evaporates readily, producing a pleasant cooling sensation. Because it has weak antibacterial properties, 2-propanol is used to clean skin before minor surgery and to sterilize medical instruments.

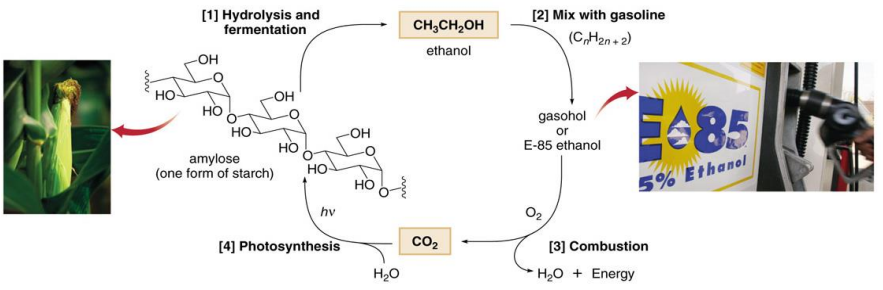


$HOCH_2CH_2OH$

- **Ethylene glycol ($HOCH_2CH_2OH$)** is the major component of antifreeze. It is readily prepared from ethylene oxide by reactions discussed in Section 9.15. It is sweet tasting but toxic.

Ethanol from Corn, a Renewable Fuel Source

Figure 9.4



(Corn); © Jupiterimages RF; (ethanol): Photo by Mark Wilson/Getty Images

- **Hydrolysis of starch and fermentation of the resulting simple sugars yield ethanol, which is mixed with hydrocarbons from petroleum refining to form usable fuels.**

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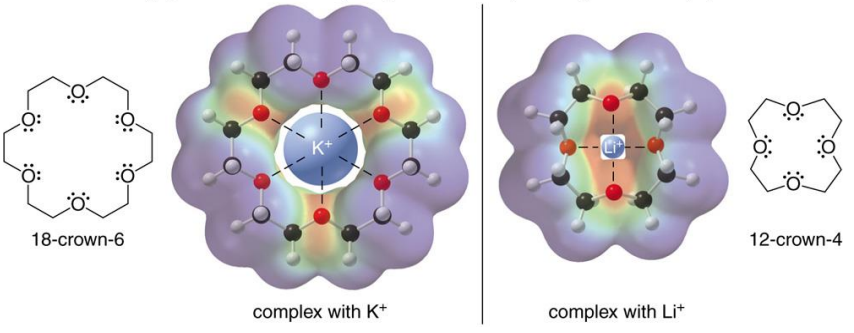
Crown Ethers



- A crown ether–cation complex is called a *host–guest* complex. The crown ether is the *host* and the cation is the *guest.*
- The ability of a host molecule to bind specific guests is called *molecular recognition.*

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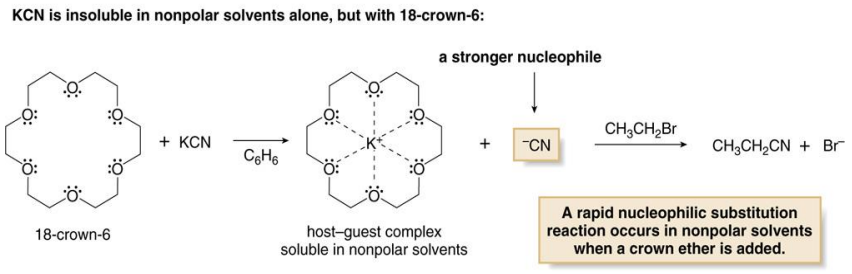
Use of Crown Ethers

- **The ability of crown ethers to complex cations can be exploited in nucleophilic substitution reactions.**
- **As the complexed cation goes into a solution it carries the anion with it to maintain neutrality.**
- **The relatively unsolvated anion is extremely nucleophilic.**

Figure 9.5



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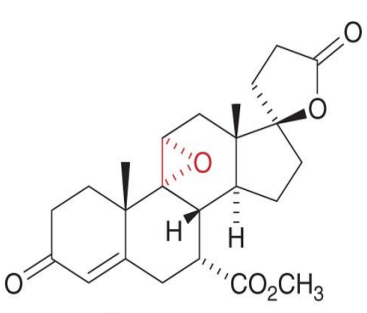
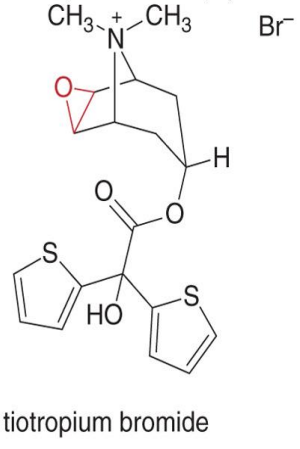
Interesting Molecules with Epoxides

- **Eplerenone (used by heart attack patients) and tiotropium bromide (a bronchodilator) contain epoxides.**





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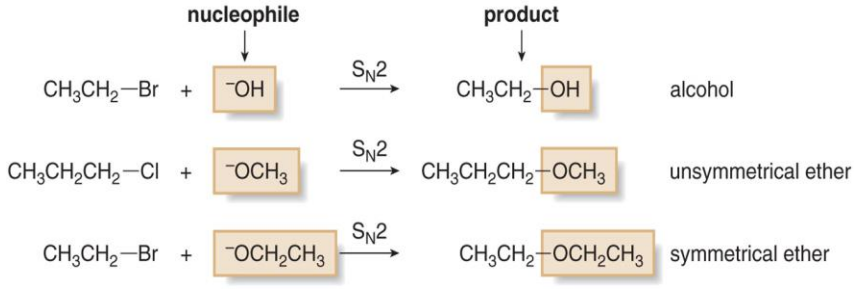
1. Preparation of Alchols and Ethers

- **Alcohols and ethers are both common products of nucleophilic substitution.**



- **The preparation of ethers by the method shown in the last two equations is called the Williamson ether synthesis.**

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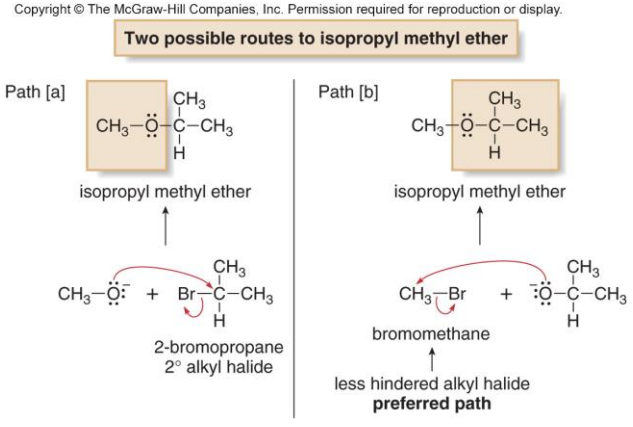
Williamson Ether Synthesis

- **In theory, unsymmetrical ethers can be synthesized in two different ways.**
- **In practice, one path is usually preferred.**
- **The path involving alkoxide attack on a less hindered alkyl halide is preferred.**



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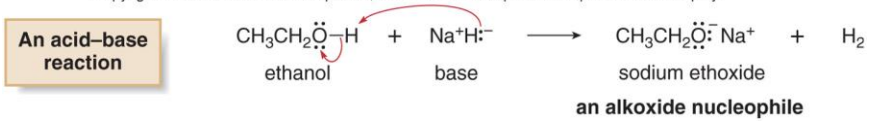
Preparation of Alkoxides

- **An alkoxide salt is needed to make an ether.**
- **Alkoxides can be prepared from alcohols by a Brønsted-Lowry acid-base reaction.**
- **For example, sodium ethoxide ($NaOCH_2CH_3$) is prepared by treating ethanol with NaH.**



- **NaH is an especially good base for forming alkoxide because the by-product of the reaction, H_2, is a gas that just bubbles out of the reaction mixture.**

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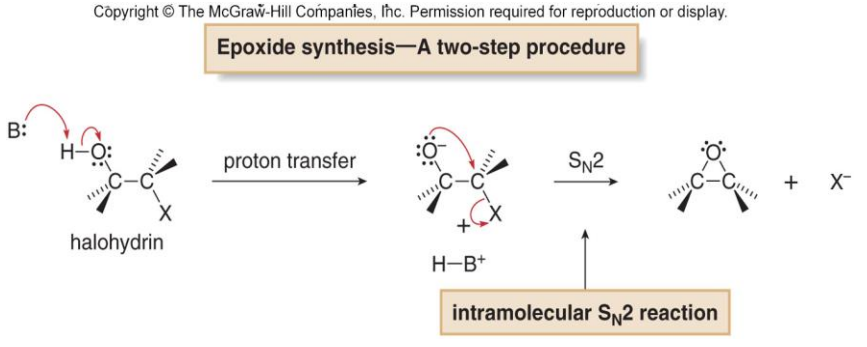
2. Epoxides from Halohydrins

- **Organic compounds that contain both a hydroxy group and a halogen atom on adjacent carbons are called halohydrins.**
- **In halohydrins, an intramolecular version of the Williamson ether synthesis can occur to form epoxides.**



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Reactions of alcohols

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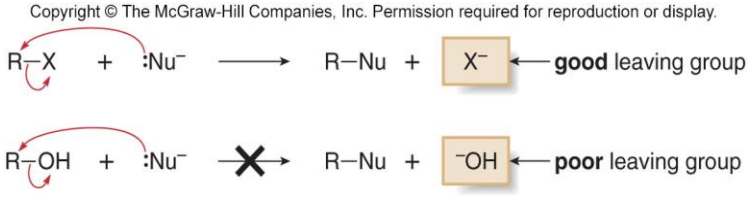
OH^- as a Leaving Group

- **Unlike alkyl halides in which the halogen atom serves as a good leaving group, the OH group in alcohols is a very poor leaving group.**



- **For an alcohol to undergo nucleophilic substitution, OH^- must be converted into a better leaving group.**

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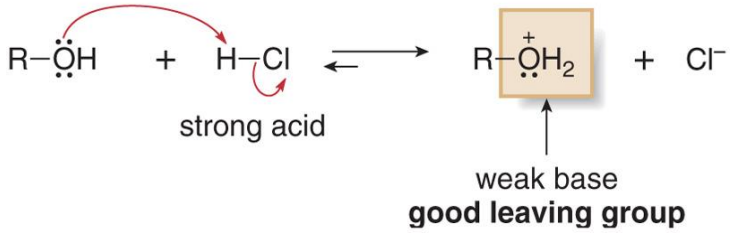
Substitution and Elimination Reactions of Alcohols

- **Treatment of alcohols with a strong acid protonates the O converting the bad leaving group $^{-}$OH into H_2O, a good leaving group.**
- **The pK_a of $(ROH_2)^+$ is ~ -2, so protonation of alcohols only occurs with very strong acids.**
- **This makes it possible to perform substitution and elimination reactions on alcohols.**



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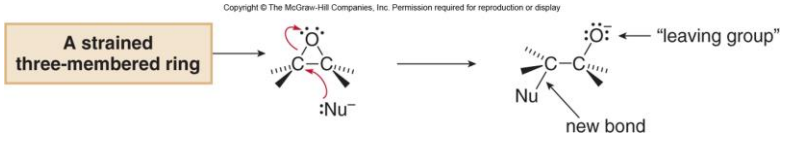
OR$^-$ as a Leaving Group

- **Like alcohols, ethers do not contain a good leaving group.**
- **Ethers undergo fewer useful reactions than alcohols.**

- **Epoxides have the same type of leaving group as ethers, OR$^-$.**
- **However, the leaving group is contained in a strained 3-membered ring.**
- **Nucleophilic attack opens the 3-membered ring and relieves angle strain.**



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Reactions of Alcohols

1. Dehydration

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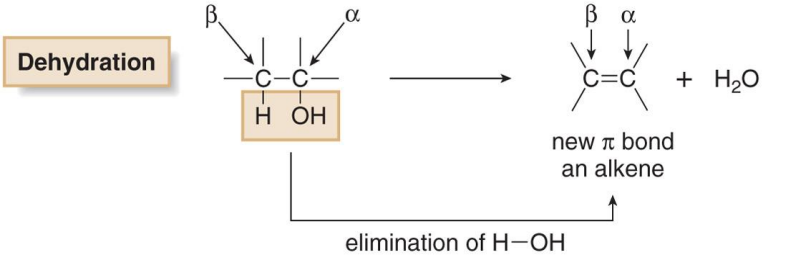
Reactions of Alcohols—Dehydration

1. Dehydration

like dehydrohalogenation, is a β elimination reaction in which the elements of OH and H are removed from the α and β carbon atoms respectively.



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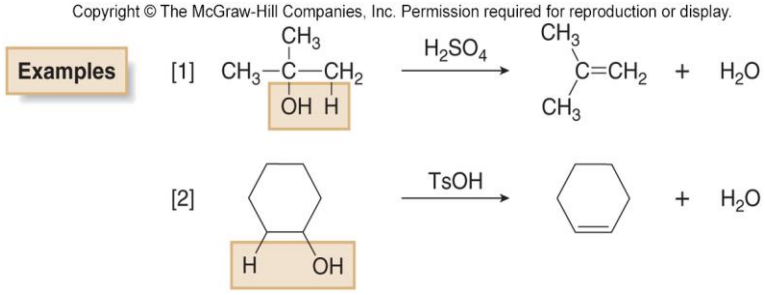
Dehydration Requires Strong Acids

- **Dehydration is typically carried out using strong acids: H_2SO_4 or phosphorus oxychloride ($POCl_3$) in the presence of an amine base.**
- **<u>Typical acids</u> used for alcohol dehydration are H_2SO_4 or *p*-toluenesulfonic acid (TsOH).**



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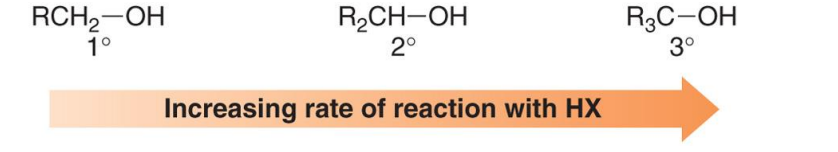
Dehydration and Alcohol Substitution

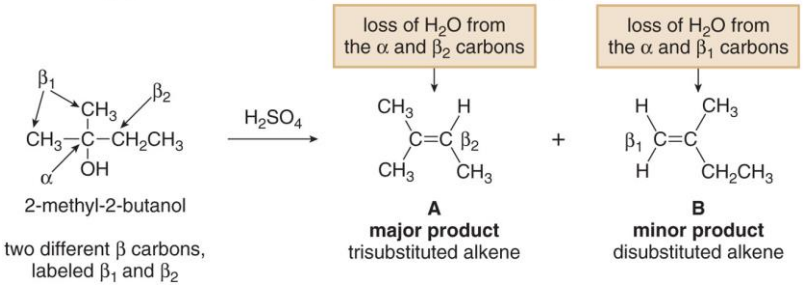
- **More substituted alcohols dehydrate more easily, giving rise to the following order of reactivity.**



36

Zaitsev's Rule

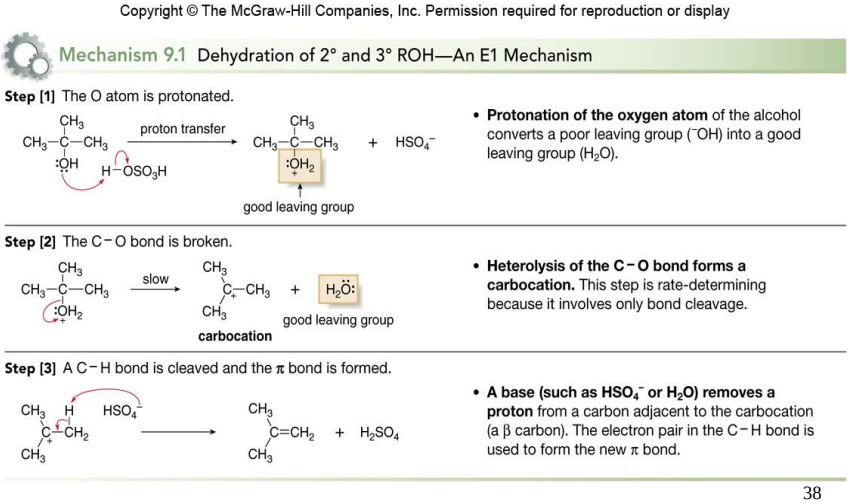
- **When an alcohol has two or three β carbons, dehydration is <u>regioselective</u> and follows the Zaitsev rule.**
- **The <u>more substituted alkene</u> is the major product when a mixture of constitutional isomers is possible.**



37

Dehydration by E1 Mechanism

- **2° and 3° alcohols react by an E1 mechanism**



38

Useful E1 Dehydration

- **The E1 dehydration of 2º and 3º alcohols with acid gives clean elimination products without any by-products formed from an S_N1 reaction.**
- **Clean elimination takes place because the reaction mixture contains no good nucleophile to react with the intermediate carbocation, so no competing S_N1 reaction occurs.**
- **This makes the E1 dehydration of alcohols much more synthetically useful than the E1 dehydrohalogenation of alkyl halides.**

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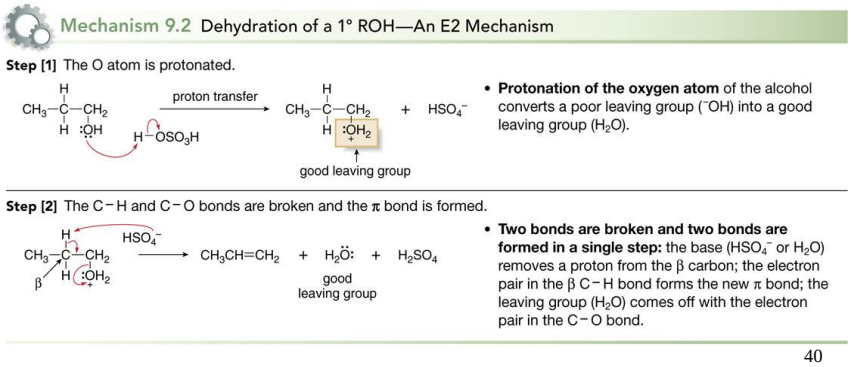
E2 Dehydration of 1º Alcohols

- **Since 1° carbocations are highly unstable, their dehydration cannot occur by an E1 mechanism involving a carbocation intermediate.**
- **However, 1° alcohols undergo dehydration by way of an E2 mechanism.**



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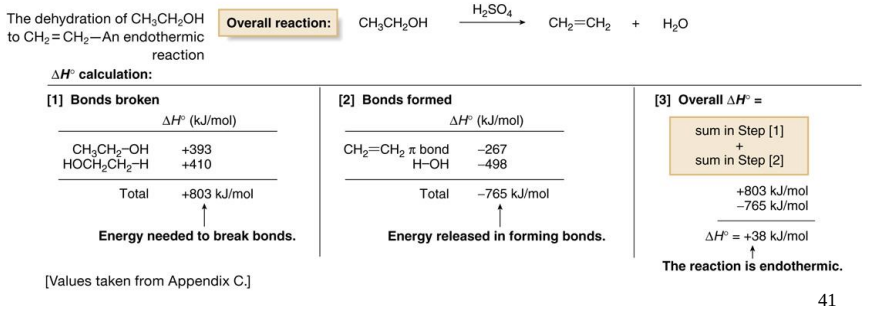
Enthalpy of Dehydration

- **Entropy favors product formation in dehydration,**
  - **since one molecule of reactant forms two molecules of the product.**
- **Enthalpy favors reactants,**
  - **since the two σ bonds broken in the reactant are stronger than the σ and π bonds formed in the products.**

Figure 9.6



[Values taken from Appendix C.]

41

Dehydration Reaction Equilibrium

- **According to Le Châtelier's principle, a system at equilibrium will react to counteract any disturbance to the equilibrium.**
- **One consequence of this is that removing a product from a reaction mixture as it is formed drives the equilibrium to the right, forming more product.**
- **Thus, the alkene, which usually has a lower boiling point than the starting alcohol, can be removed by distillation as it is formed,**
  - **thus driving the equilibrium to the right to favor production of more product.**

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Carbocation Rearrangements

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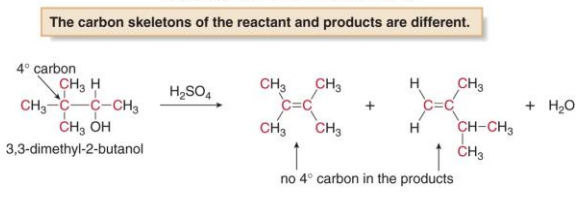
Carbocation Rearrangements

- **Often, when carbocations are intermediates, a <u>less stable carbocation will be converted</u> into a more stable carbocation by a shift of a hydrogen or an alkyl group.**
  - **This is called a rearrangement.**
- **How do we know that a rearrangement occurred?**
  - **There may be a product formed that has the double bond in and unexpected location.**



- **The carbon skeletons of the reactant and product are different.**

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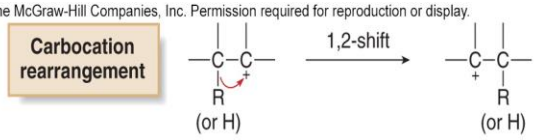
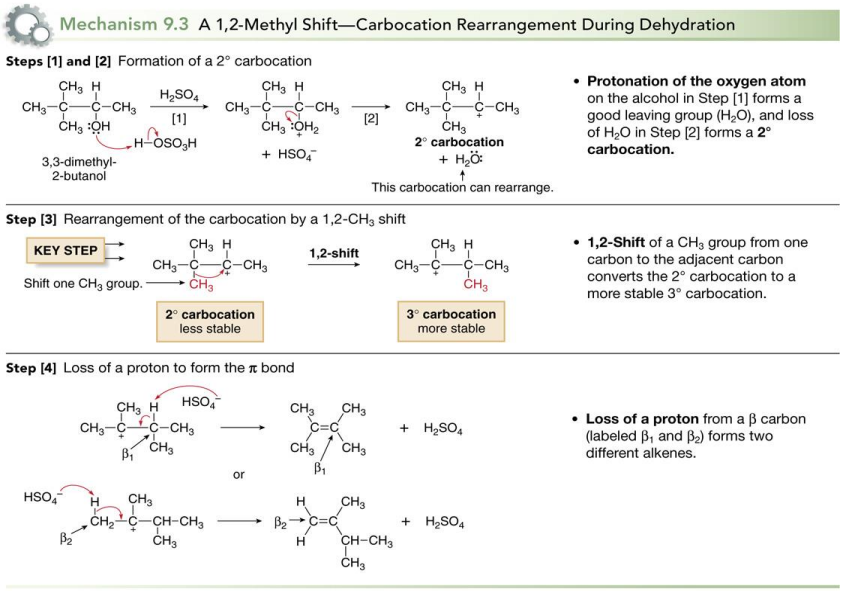
Carbocation Rearrangements

- **Because the migrating group in a 1,2-shift moves with two bonding electrons, the carbon it leaves behind now has only three bonds (six electrons), giving it a net positive (+) charge.**

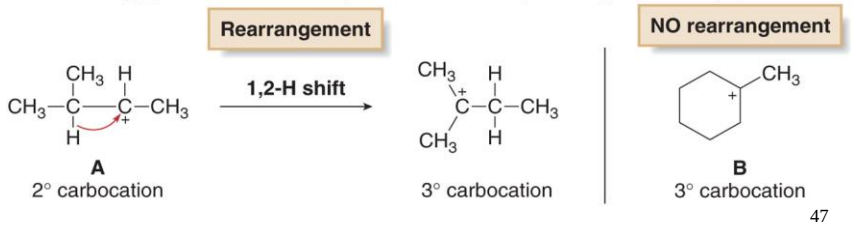


- Movement of a hydrogen atom is called a 1,2-hydride shift.
- Movement of an alkyl group is called a 1,2-alkyl shift.



1,2-Hydride Shifts

- **A 1,2-shift can convert a less stable carbocation into a more stable carbocation.**
- **Rearrangements are not unique to dehydration reactions.**
- **Rearrangements can occur whenever a carbocation is formed as a reactive intermediate.**
- **2° carbocation A rearranges to the more stable 3° carbocation by a 1,2-hydride shift, whereas carbocation B does not rearrange because it is 3° to begin with.**



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Dehydration of Alcohols Using $POCl_3$

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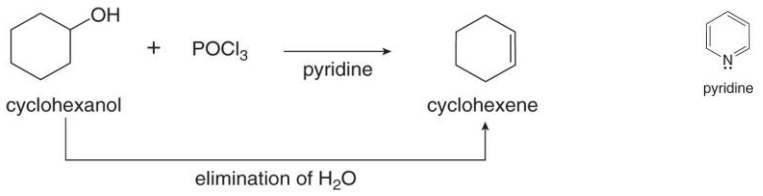
Dehydration of Alcohols Using $POCl_3$

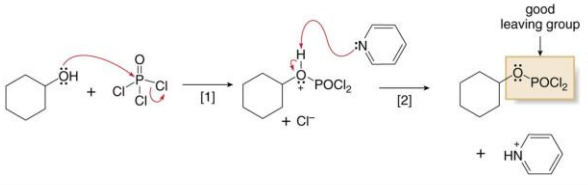
- **Some organic compounds decompose in the presence of strong acid, so other methods have been developed to convert alcohols to alkenes.**
- **A common method uses phosphorus oxychloride ($POCl_3$) and pyridine (an amine base) in place of H_2SO_4 or TsOH.**



- **$POCl_3$ serves much the same role as a strong acid does in acid-catalyzed dehydration.**
  - **It converts a poor leaving group (^-OH) into a good leaving group.**
  - **Dehydration then proceeds by an E2 mechanism.**

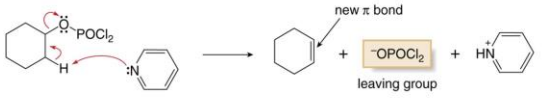
Mechanism 9.4 Dehydration Using $POCl_3$ + Pyridine—An E2 Mechanism

Steps [1] and [2] Conversion of OH to a good leaving group



- A two-step process converts an OH group into $OPOCl_2$, **a good leaving group:** reaction of the OH group with $POCl_3$ followed by removal of a proton.

Step [3] The C–H and C–O bonds are broken and the π bond is formed.

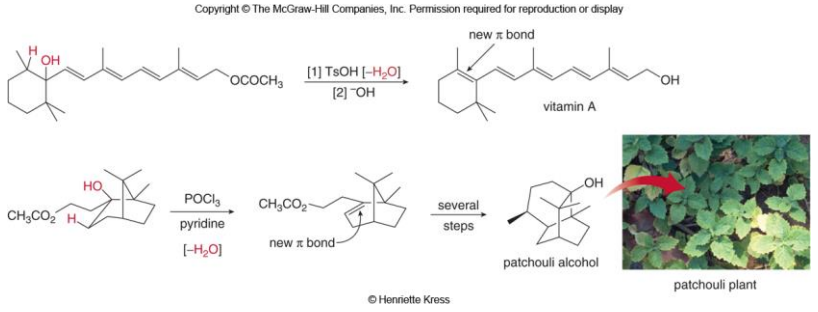


- **Two bonds are broken and two bonds are formed in a single step:** the base (pyridine) removes a proton from the β carbon; the electron pair in the β C–H bond forms the new π bond; the leaving group ($^-OPOCl_2$) comes off with the electron pair from the C–O bond.

Dehydration Reactions in Natural Products Synthesis

- **Patchouli alcohol has been used in perfumery because of its exotic fragrance.**

Figure 9.7



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2. Reactions of Alcohols

Formation of alkyl halides

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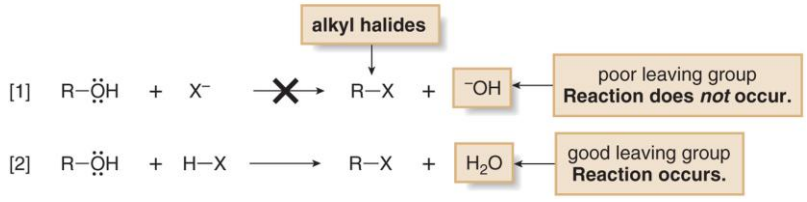
Reactions of Alcohols—to alkyl halides

2. Alcohols to Alkyl Halides

- **Substitution reactions do not occur with alcohols unless $^-$OH is converted into a good leaving group.**



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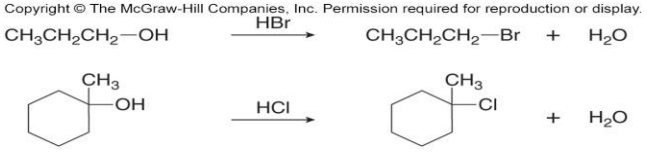
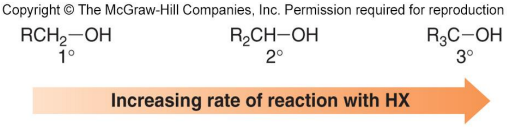
Conversion of Alcohols to Alkyl Halides with HX

- **The reaction of alcohols with HX (X = Cl, Br, I) is a general method to prepare 1°, 2°, and 3° alkyl halides.**



- **More substituted alcohols usually react more rapidly with HX:**



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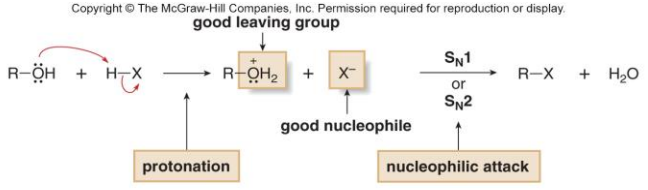
Mechanism of Reaction of Alcohols with HX

- **This order of reactivity can be rationalized by considering the reaction mechanisms involved.**

- **The mechanism depends on the structure of the R group.**



- Methyl and 1° ROH form RX by an S_N2 mechanism.
- Secondary (2°) and 3° ROH form RX by an S_N1 mechanism.

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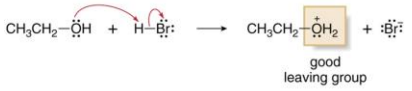
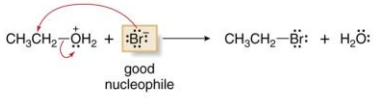
Mechanism 9.5 Reaction of a 1° ROH with HX—An S_N2 Mechanism

Step [1] The O atom is protonated.



- **Protonation of the OH group** forms a good leaving group (H_2O).

Step [2] The C – O bond is broken as the C – Br bond is formed.



- **Nucleophilic attack of Br^- and loss of the leaving group** occur in a single step.

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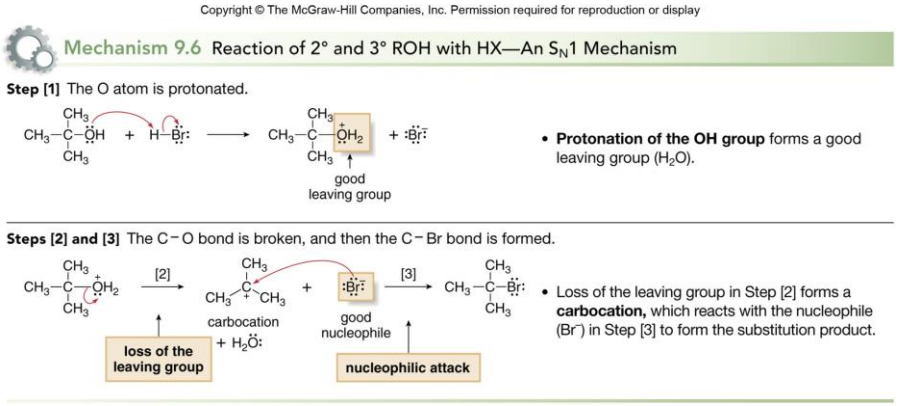
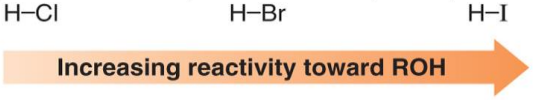


57

Reactivity of Hydrogen Halides

- **The <u>reactivity</u> of hydrogen halides increases with increasing acidity.**



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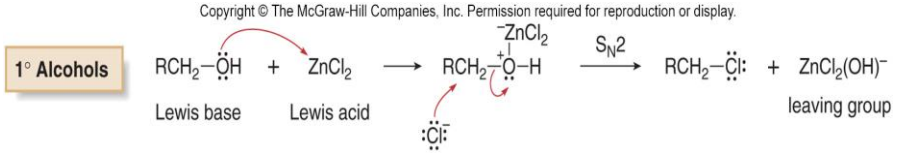
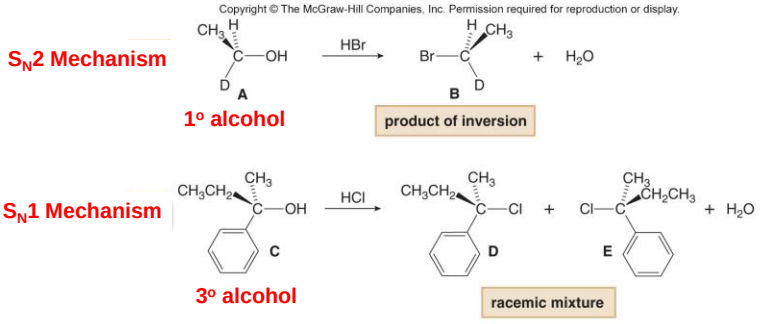
Reactivity of Hydrogen Halides

- **Cl^- is a poorer nucleophile than Br^- or I^-.**
  - **Reaction of 1º alcohols with HCl occurs only when an additional Lewis acid catalyst, usually $ZnCl_2$, is added.**
- **Complexation of $ZnCl_2$ with the O atom of the alcohol makes a very good leaving group that facilitates the S_N2 reaction.**



Stereochemistry of Reaction of Alcohols with HX

- **Knowing the mechanism allows us to predict the stereochemistry of the products when the reaction occurs at a stereogenic center.**



- The 1° alcohol **A** reacts with HBr via an S_N2 mechanism to yield the alkyl bromide **B** with **inversion** of stereochemistry at the stereogenic center.
- The 3° alcohol **C** reacts with HCl via an S_N1 mechanism to yield a **racemic mixture** of alkyl chlorides **D** and **E**, because a trigonal planar carbocation intermediate is formed.

Conversion of Alcohols to Alkyl Halides with $SOCl_2$ and PBr_3

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Conversion of Alcohols to Alkyl Halides with $SOCl_2$ and PBr_3

- **1° and 2° alcohols can be converted to alkyl halides using $SOCl_2$ and PBr_3.**
- **$SOCl_2$ (thionyl chloride) converts alcohols into alkyl chlorides.**
- **PBr_3 (phosphorus tribromide) converts alcohols into alkyl bromides.**
  - **Both reagents convert $^{-}$OH into a good leaving group in**
  - **Provide the nucleophile, either Cl^{-} or Br^{-}, to displace the leaving group.**

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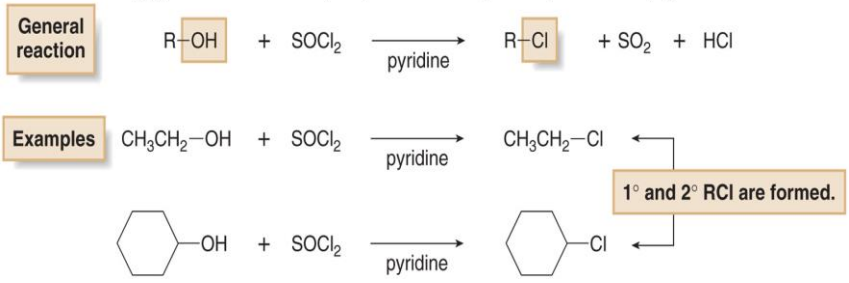
Conversion of Alcohols to Alkyl Chlorides with $SOCl_2$

- **When a 1° or 2° alcohol is treated with $SOCl_2$ and pyridine, an alkyl chloride is formed, with HCl and SO_2 as by-products.**



- **The mechanism of this reaction consists of two parts:**
  1. **Conversion of the OH group into a better leaving group.**
  2. **Nucleophilic substitution by Cl^- via an S_N2 reaction.**

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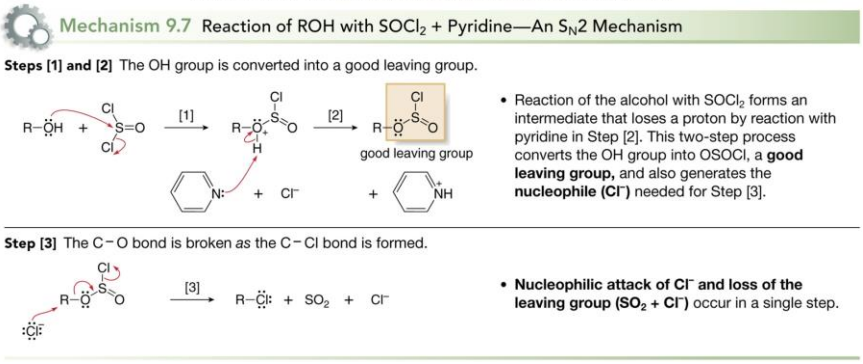

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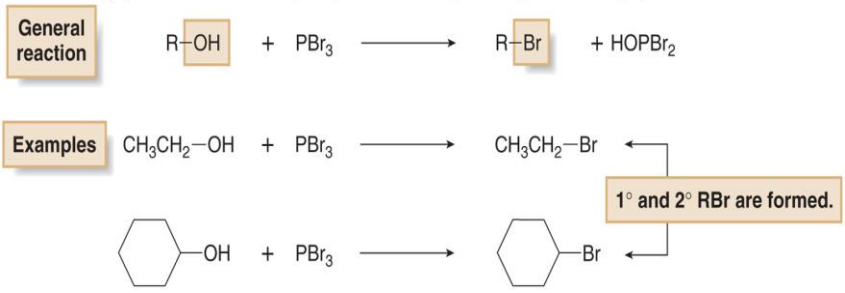
Conversion of Alcohols to Alkyl Bromides with PBr_3

- **Treatment of a 1° or 2° alcohol with PBr_3 forms an alkyl halide.**



- **The mechanism of this reaction also consists of two parts:**
  1. **Conversion of the OH group into a better leaving group.**
  2. **Nucleophilic substitution by Br^- via an S_N2 reaction.**

65

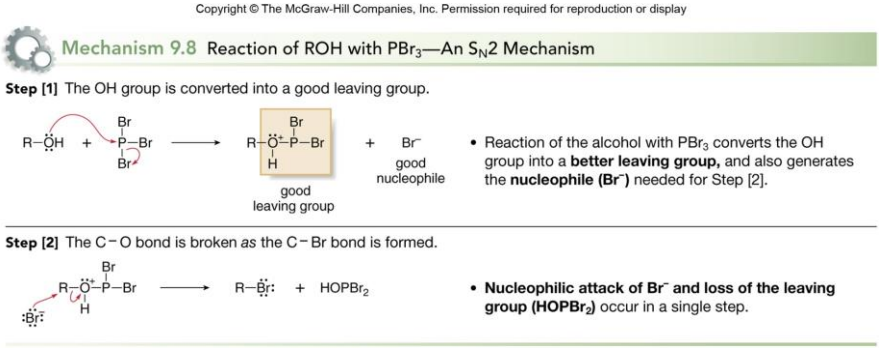


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Table 9.2 Summary of Methods for ROH → RX

Overall reaction	Reagent	Comment
ROH → RCl	HCl	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	$SOCl_2$	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RBr	HBr	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH
	PBr_3	• Best for CH_3OH, and 1° and 2° ROH • An S_N2 mechanism
ROH → RI	HI	• Useful for all ROH • An S_N1 mechanism for 2° and 3° ROH; an S_N2 mechanism for CH_3OH and 1° ROH

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Another form of leaving groups

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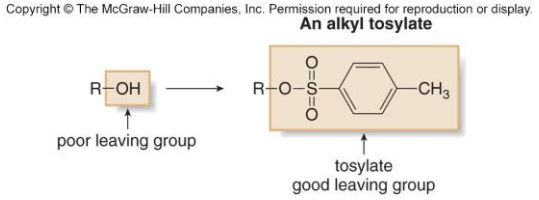
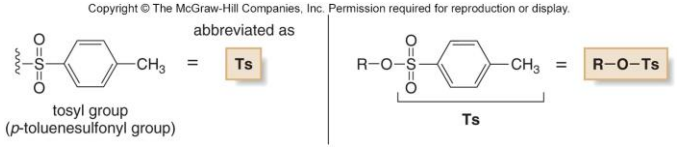
Tosylate as Leaving Group

- **Alcohols can be converted into alkyl tosylates.**
- **An alkyl tosylate is composed of two parts: the alkyl group R, derived from an alcohol; and the tosylate (short for *p*-toluenesulfonate), which is a good leaving group.**
- **A tosyl group, $CH_3C_6H_4SO_2^-$, is abbreviated Ts, so an alkyl tosylate becomes ROTs.**





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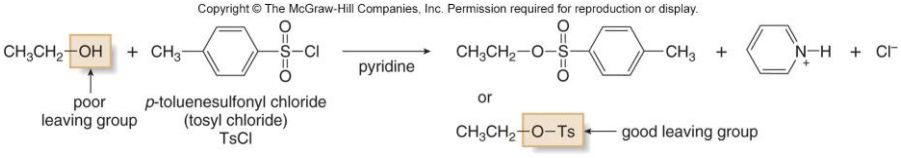
Formation and Use of Tosylates

- **Alcohols are converted to tosylates by treatment with *p*-toluenesulfonyl chloride (TsCl) in the presence of pyridine.**
- **This process converts a poor leaving group ($^-$OH) into a good one ($^-$OTs).**
- **Tosylate is a good leaving group because its conjugate acid, *p*-toluenesulfonic acid ($CH_3C_6H_4SO_3H$, TsOH) is a strong acid ($pK_a = -7$).**



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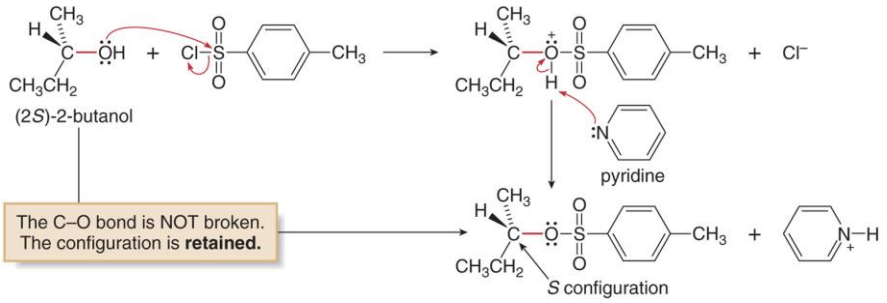
Stereochemistry of Tosylate Formation

- **(2*S*)-2-Butanol is converted to its tosylate with retention of configuration at the stereogenic center.**
- **The C-O bond of the alcohol is not broken when tosylate is formed.**



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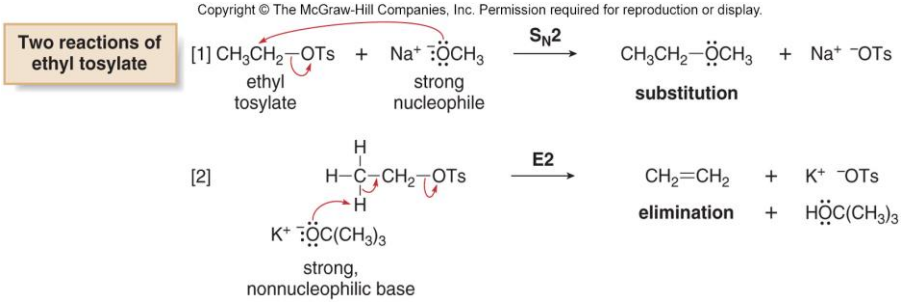
Substitution and Elimination of Tosylates

- **Because alkyl tosylates have good leaving groups, they undergo both nucleophilic substitution and β elimination, exactly as alkyl halides do.**
- **Generally, alkyl tosylates are treated with strong nucleophiles and bases, so the mechanism of substitution is S_N2, and the mechanism of elimination is E2.**



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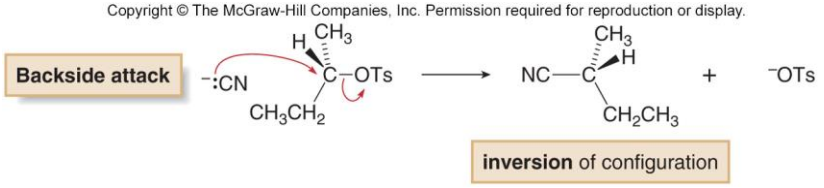
S_N2 Inversion When Replacing Tosylates

- **Because substitution occurs via an S_N2 mechanism, inversion of configuration results when the leaving group is bonded to a stereogenic center.**



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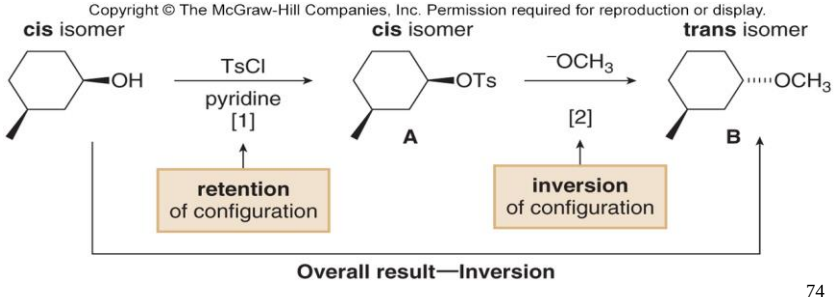
S_N2 withTosylates

- **Step [1], formation of the tosylate, proceeds with retention of configuration at a stereogenic center.**
- **Step [2] is an S_N2 reaction, so it proceeds with inversion of configuration because the nucleophile attacks from the backside.**
- **Overall there is a net inversion of configuration at a stereogenic center.**



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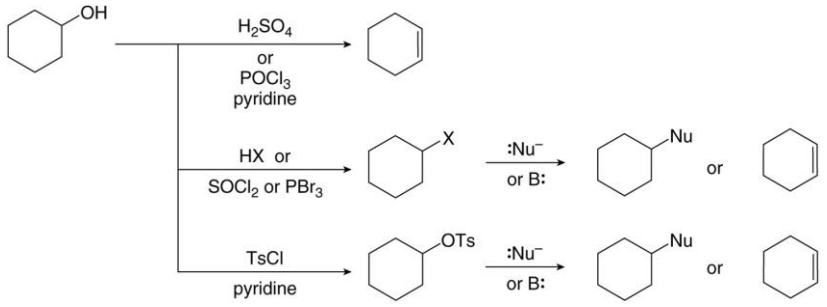
Summary of Substitution and Elimination
Reactions of Alcohols

Figure 9.8



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Reactions of ethers and epoxides

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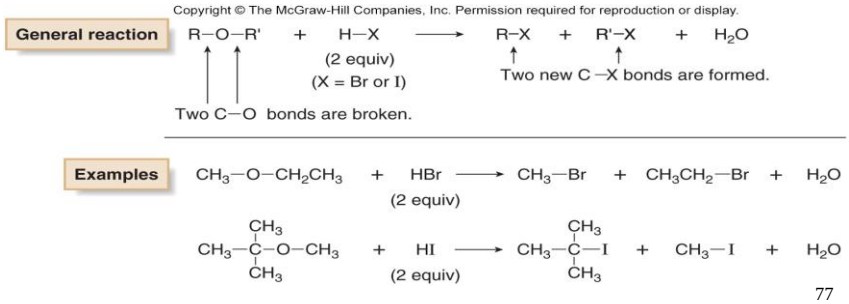
1. Reaction of Ethers with Strong Acid

- **In order for ethers to undergo substitution or elimination reactions,**
  1. **their poor leaving group must first be converted into a good leaving group by reaction with strong acids such as HBr and HI.**
  2. **HBr and HI are strong acids that are also sources of good nucleophiles (Br^- and I^-, respectively).**
- **When ethers react with HBr or HI, both C-O bonds are cleaved and two alkyl halides are formed as products.**



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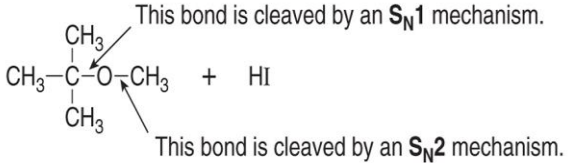
Mechanism of Ether Cleavage

- **The mechanism of ether cleavage is S_N1 or S_N2, depending on the identity of R.**
- **When 2° or 3° alkyl groups are bonded to the ether oxygen, the C-O bond is cleaved by an S_N1 mechanism involving a carbocation.**
- **With methyl or 1° R groups, the C-O bond is cleaved by an S_N2 mechanism.**



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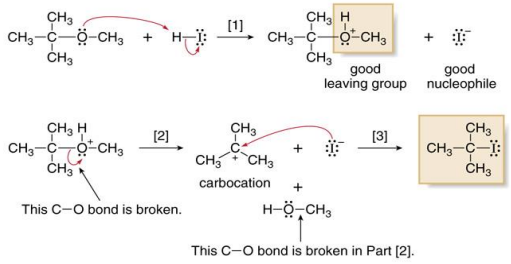
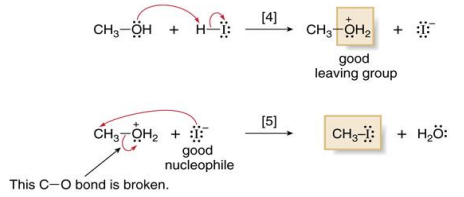
Mechanism 9.9 Mechanism of Ether Cleavage in Strong Acid—
$(CH_3)_3COCH_3 + HI \rightarrow (CH_3)_3CI + CH_3I + H_2O$

Part [1] Cleavage of the 3° C−O bond by an S_N1 mechanism



- **Protonation** of the O atom forms a good leaving group in Step [1]. Cleavage of the C−O bond then occurs in two steps: the bond to the leaving group is broken to form a **carbocation,** and then the bond to the nucleophile (I^-) is formed. This generates one of the alkyl iodides, **$(CH_3)_3CI$.**

Part [2] Cleavage of the CH_3-O bond by an S_N2 mechanism



- **Protonation of the OH group** forms a good leaving group (H_2O), and then nucleophilic attack by I^- forms the second alkyl iodide, **CH_3I,** and **H_2O.**

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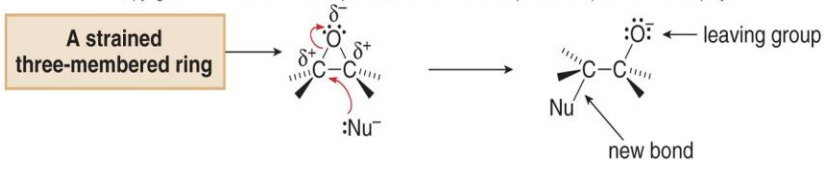
2. Reactions of Epoxides

- **Epoxides do not contain a good leaving group.**
- **Epoxides do contain a strained three-membered ring with two polar bonds.**
- **Nucleophilic attack opens the strained three-membered ring, making it a favorable process even with a poor leaving group.**



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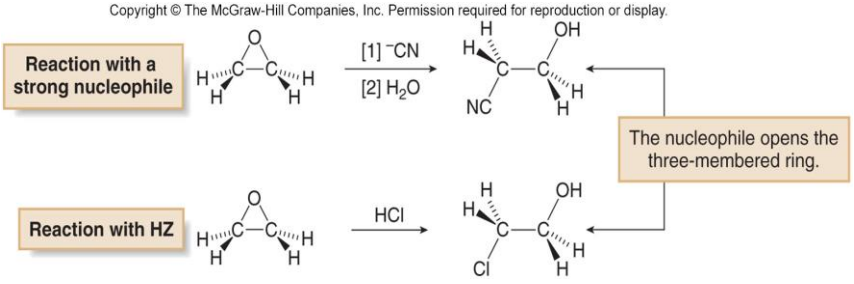
Addition of Nucleophiles to Epoxides

- **Nucleophilic addition to epoxides occurs readily with strong nucleophiles and with acids like HZ, where Z is a nucleophilic atom.**



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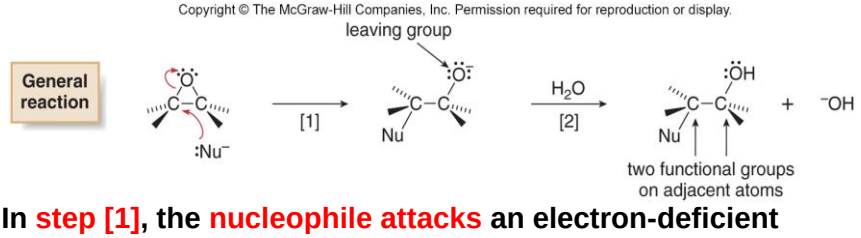
Mechanism of Epoxide Reactions

- **Virtually all strong nucleophiles open an epoxide ring by a two-step reaction sequence:**



- **In step [1], the nucleophile attacks an electron-deficient carbon, by an S_N2 mechanism, thus cleaving the C-O bond and relieving the strain of the three-membered ring.**
- **In step [2], the alkoxide is protonated with water to generate a neutral product with two functional groups on adjacent atoms.**
- **Common nucleophiles that open the epoxide ring include ^{-}OH, ^{-}OR, ^{-}CN, ^{-}SR, and NH_3.**

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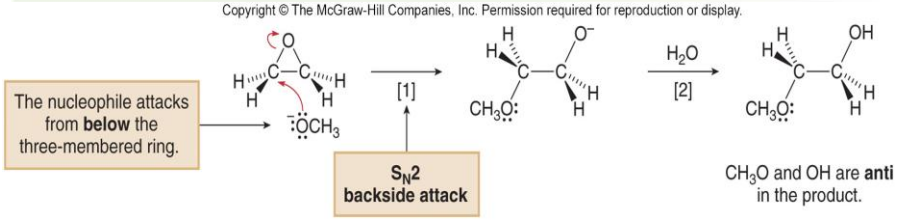
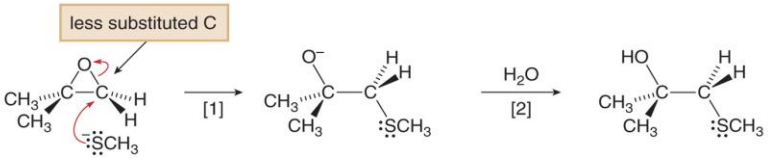
Stereochemistry of Epoxide Reactions

- The nucleophile opens the epoxide ring from the back side.



- In an unsymmetrical epoxide, the nucleophile attacks at the less substituted carbon atom.



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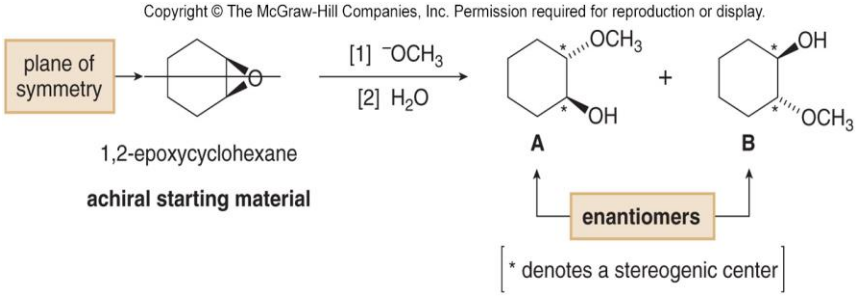
Stereochemistry of Reaction of a Meso Epoxide



- **Nucleophilic attack of $^{-}OCH3$ occurs from the backside at either C-O bond, because both ends are similarly substituted.**
- **Since attack at either side occurs with equal probability, an equal amount of the two enantiomers (i.e., a racemic mixture) is formed.**

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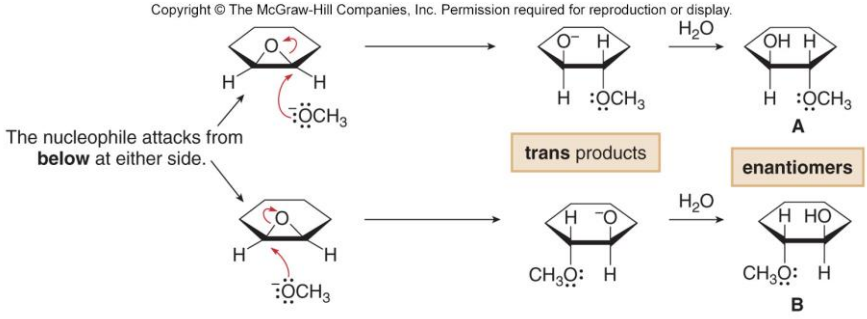
Achiral Reactants Yield Optically Inactive Products



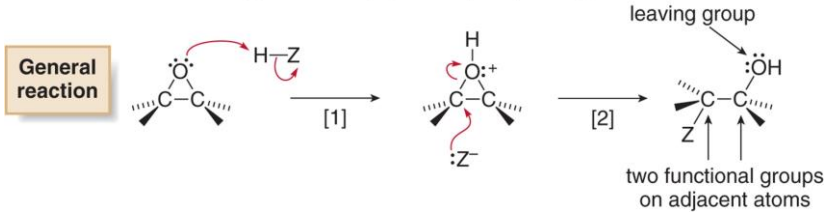
- Whenever an achiral reactant yields a product with stereogenic centers, the product must be achiral (meso) or racemic.

Optically inactive starting materials give optically inactive products!

85

Acidic Epoxide Ring Opening

- **Acids HZ that contain a nucleophile Z also open epoxide rings by a two-step sequence.**
  - **Step [1]: Protonation of the epoxide oxygen making the good leaving group (OH).**
  - **Step [2]: Nucleophile opens the epoxide ring via backside attack.**



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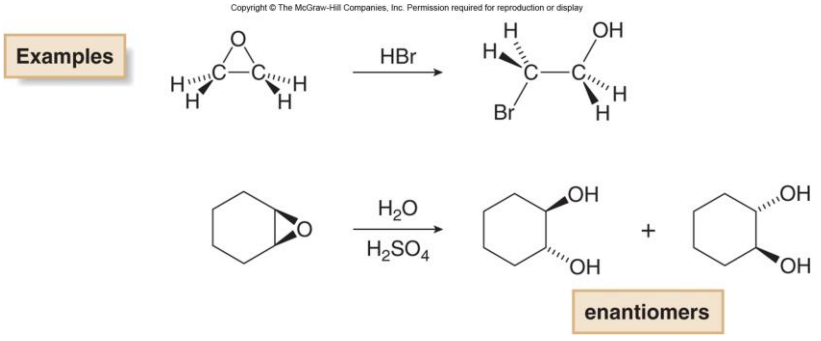
Acidic Epoxide Ring Opening

- **HCl, HBr, and HI, as well as H_2O and ROH in the presence of acid, all open an epoxide ring in this manner.**
- ***trans*-1,2-disubstituted cycloalkanes are formed from epoxides fused to rings.**



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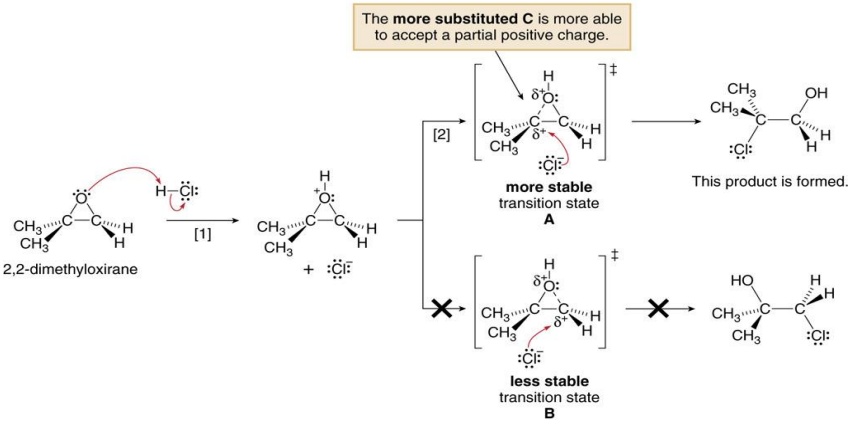
Opening an Epoxide Ring with HCl

Figure 9.9



- Transition state **A** is lower in energy because the partial positive charge (δ⁺) is located on the more substituted carbon. In this case, therefore, nucleophilic attack occurs from the back side (an S_N2 characteristic) at the more substituted carbon (an S_N1 characteristic).

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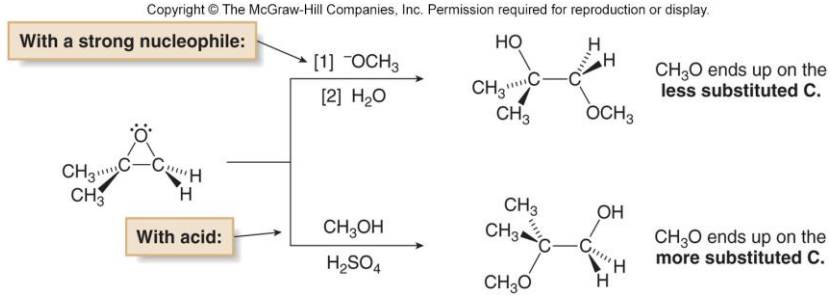
Regioselectivity of Epoxide Ring Opening

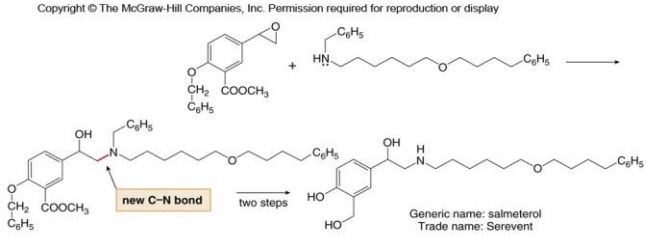
- **Ring opening of an epoxide with either a strong nucleophile or an acid HZ is regioselective because one constitutional isomer is the major or exclusive product.**
- **The site selectivity of these two reactions is exactly opposite.**

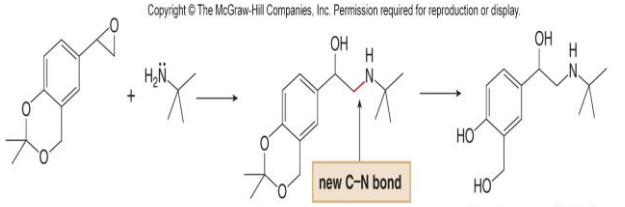


- With a strong nucleophile, :Nu⁻ attacks at the less substituted carbon.
- With an acid HZ, the nucleophile attacks at the more substituted carbon.

Synthesis of Bronchodilators from epoxides

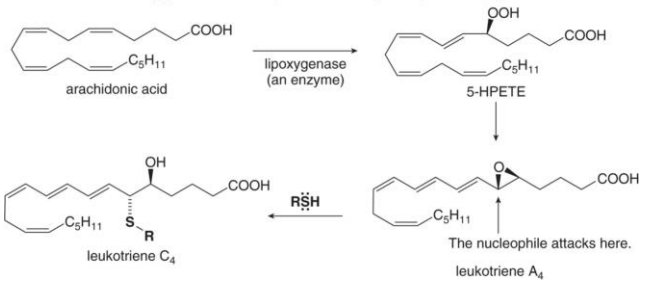
Figure 9.10

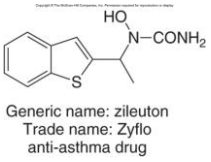




Leukotriene synthesis and Asthma drugs

- **Leukotrienes are synthesized in cells by oxidation of arachidonic acid to 5-HPETE.**
- **This is then converted to an epoxide, leukotriene A_4.**
- **Ring opening the epoxide yields leukotriene C_4.**
- **New asthma drugs act by blocking the synthesis of leukotriene C4, for example by inhibiting the enzyme lipoxygenase needed in the biosynthesis.**





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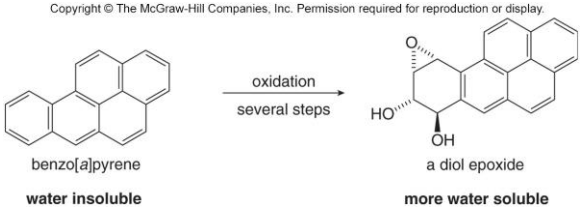
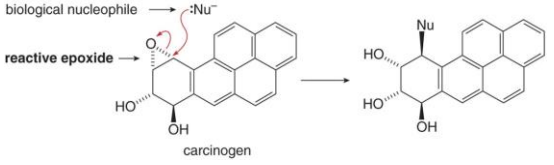
Health Effects of Epoxides

- **When polyaromatic hydrocarbons are inhaled or ingested, they are oxidized in the liver to species that often contain a highly reactive epoxide ring.**
- **The strained three-membered ring reacts readily with biological nucleophiles such as DNA or enzymes, leading to ring-opened products that often disrupt cell function, causing cancer or cell death.**





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