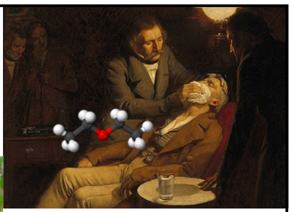
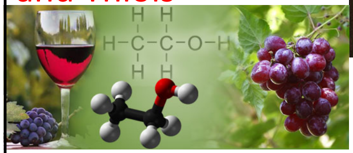
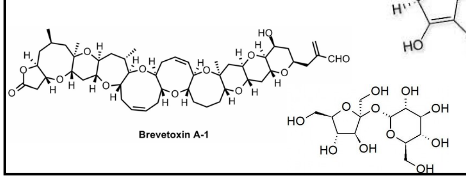
# Chapter 8

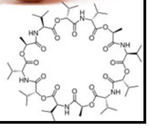
## Alcohols, Ethers, and Thiols







Brevetoxin A-1



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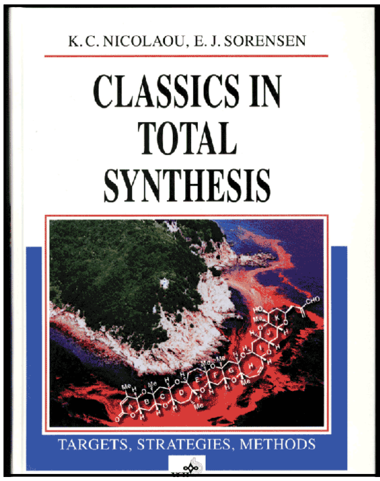

K.C. NICOLAOU, E. J. SORENSEN

CLASSICS IN TOTAL SYNTHESIS

TARGETS, STRATEGIES, METHODS

> *"…and the waters that were in the river were turned to blood. And the fish that were in the river died; and the river stank and the Egyptians could not drink of the water of the river…."*
> *Exodus 7:20-21*

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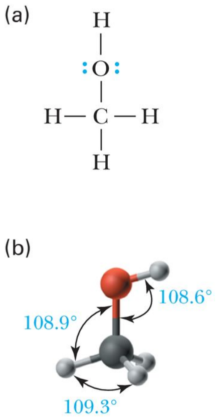
# Alcohols - Structure

- Figure 8.1 The functional group of an alcohol is an -OH (hydroxyl) group bonded to an $sp^3$ hybridized carbon.
  - Bond angles about the hydroxyl oxygen atom are approximately 109.5°.
- Oxygen is also $sp^3$ hybridized.
  - Two $sp^3$ hybrid orbitals form sigma bonds to carbon and hydrogen.
  - The remaining two $sp^3$ hybrid orbitals each contain an unshared pair of electrons.

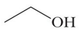


# Alcohols - Nomenclature

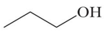
- IUPAC names
  - The parent chain is the longest chain that contains the -OH group.
  - Number the parent chain in the direction that gives the -OH group the lower number.
  - Change the suffix **-e** to **-ol**.
- Common names
  - Name the alkyl group bonded to oxygen followed by the word **alcohol**.

# Alcohols - Nomenclature

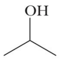
- Examples:



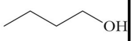
Ethanol
(Ethyl alcohol)



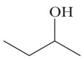
1-Propanol
(Propyl alcohol)



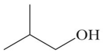
2-Propanol
(Isopropyl alcohol)



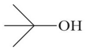
1-Butanol
(Butyl alcohol)



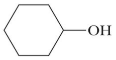
2-Butanol
(*sec*-Butyl alcohol)



2-Methyl-1-propanol
(Isobutyl alcohol)



2-Methyl-2-propanol
(*tert*-Butyl alcohol)



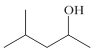
Cyclohexanol
(Cyclohexyl alcohol)

# Alcohols - Nomenclature

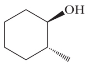
- **Problem**: Write the IUPAC name of each alcohol.

**(a)** $CH_3(CH_2)_6CH_2OH$

**(b)**



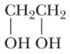
**(c)**



**(d)** $(CH_3CH_2CH_2)_2CHCH_2OH$

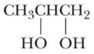
# Alcohols - Nomenclature

- Compounds containing
  - two -OH groups are named as diols,
  - three -OH groups are named as triols.
  - Compounds containing two -OH groups on are called glycols.



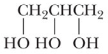
$$\underset{OH}{CH_2}\underset{OH}{CH_2}$$

1,2-Ethanediol
(Ethylene glycol)



$$CH_3\underset{HO}{CH}\underset{OH}{CH_2}$$

1,2-Propanediol
(Propylene glycol)

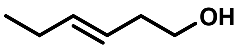


$$\underset{HO}{CH_2}\underset{HO}{CH}\underset{OH}{CH_2}$$

1,2,3-Propanetriol
(Glycerol, Glycerin)

## Alcohols - Nomenclature

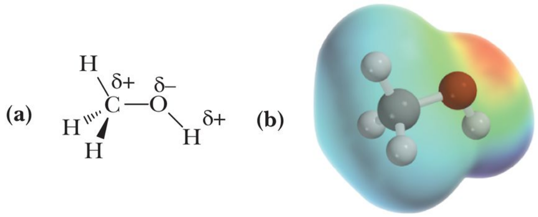
- **Unsaturated alcohols**
  - The double bond is shown by the infix -**en**-.
  - The hydroxyl group is shown by the suffix -**ol**.
  - Number the chain to give OH the lower number.



**trans-3-hexene-1-ol**
**(E)-3-hexene-ol**

## Physical Properties

- **Figure 8.2** Polarity of the C-O-H bond in methanol. (a) Partial positive charges on carbon and hydrogen and a partial negative charge on oxygen.
- (b) An electron density map showing the partial negative charge (red) and the partial positive charge (blue).

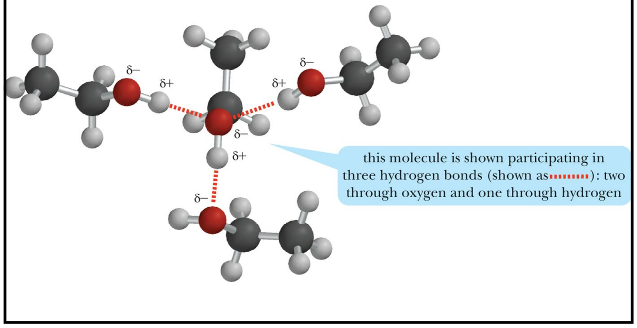


## Hydrogen Bonding

- Alcohols associate in the liquid state by hydrogen bonding.
- **Hydrogen bonding**: The attractive force between a partial positive charge on hydrogen and a partial negative charge on a nearby oxygen, nitrogen, or fluorine atom.
  - The strength of hydrogen bonding in alcohols is approximately 2 to 5 kcal/mol.
  - Hydrogen bonds are considerably weaker than covalent bonds (for example, 110 kcal/mol for an O–H bond).
  - Nonetheless, hydrogen bonding can have a significant effect on physical properties.

## Hydrogen Bonding

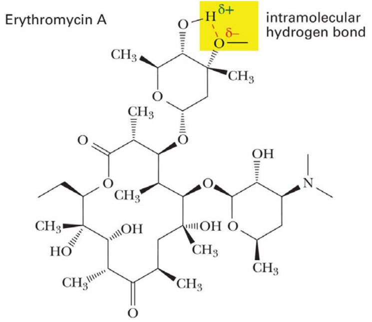
- **Figure 8.3** The association of ethanol molecules in the liquid state.



this molecule is shown participating in three hydrogen bonds (shown as ⋯⋯): two through oxygen and one through hydrogen

# Hydrogen Bonding Erythromycin

- **Problem**: Following is a structural formula for Erythromycin A, a widely used antibiotic. See next screen for questions.



# Hydrogen Bonding Erythromycin

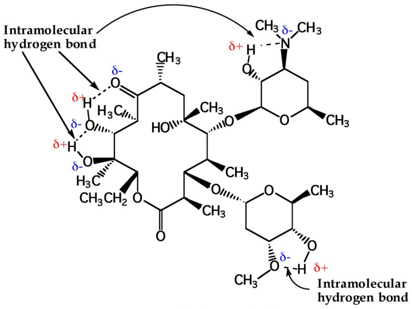
a) How many hydroxyl groups are present? Classify each as primary, secondary, or tertiary.

b) How many amine groups are present? Classify each as primary, secondary, or tertiary.

c) Four of the hydroxyl groups within Erythromycin A are involved in intramolecular (internal) hydrogen bonding. One of these is pointed out on the structural formula. Note that this hydrogen bond creates a five-membered ring. Locate the other three intramolecular hydrogen bonds and specify the size of the ring created by each.

# Hydrogen Bonding Erythromycin

- **Solution**: Shown are the four intramolecular hydrogen bonds. They create one six-membered ring and three five-membered rings.



Erythromycin A

# Boiling Points

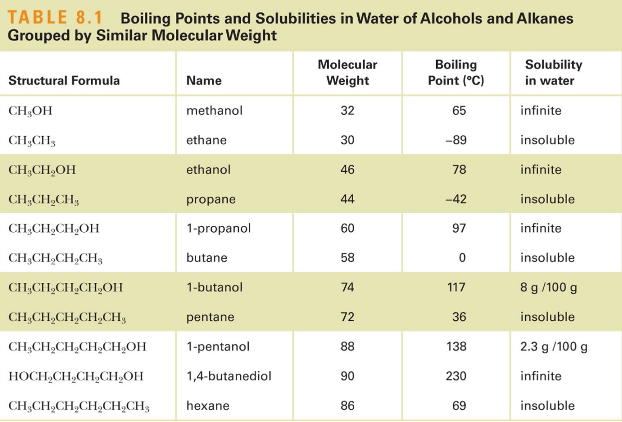
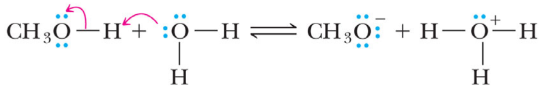


**TABLE 8.1 Boiling Points and Solubilities in Water of Alcohols and Alkanes Grouped by Similar Molecular Weight**

| Structural Formula | Name | Molecular Weight | Boiling Point (°C) | Solubility in water |
|---|---|---|---|---|
| $CH_3OH$ | methanol | 32 | 65 | infinite |
| $CH_3CH_3$ | ethane | 30 | –89 | insoluble |
| $CH_3CH_2OH$ | ethanol | 46 | 78 | infinite |
| $CH_3CH_2CH_3$ | propane | 44 | –42 | insoluble |
| $CH_3CH_2CH_2OH$ | 1-propanol | 60 | 97 | infinite |
| $CH_3CH_2CH_2CH_3$ | butane | 58 | 0 | insoluble |
| $CH_3CH_2CH_2CH_2OH$ | 1-butanol | 74 | 117 | 8 g /100 g |
| $CH_3CH_2CH_2CH_2CH_3$ | pentane | 72 | 36 | insoluble |
| $CH_3CH_2CH_2CH_2CH_2OH$ | 1-pentanol | 88 | 138 | 2.3 g /100 g |
| $HOCH_2CH_2CH_2CH_2OH$ | 1,4-butanediol | 90 | 230 | infinite |
| $CH_3CH_2CH_2CH_2CH_2CH_3$ | hexane | 86 | 69 | insoluble |

## Acidity of Alcohols

- Most alcohols are about the same or slightly weaker acids than water.



$(pK_a = 15.5)$ $(pK_a = 15.7)$

$$K_a = \frac{[CH_3O^-][H_3O^+]}{[CH_3OH]} = 3.2 \times 10^{-16}$$

$$pK_a = 15.5$$

  - Aqueous solutions of alcohols have the same pH as that of pure water.

## Acidity of Alcohols

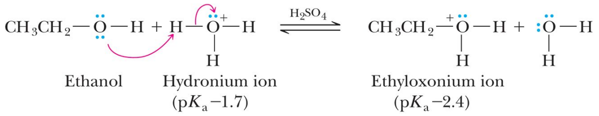
**TABLE 8.2** $pK_a$ **Values for Selected Alcohols in Dilute Aqueous Solution***

| Compound | Structural Formula | $pK_a$ | |
|---|---|---|---|
| hydrogen chloride | $HCl$ | −7 | Stronger acid |
| acetic acid | $CH_3COOH$ | 4.8 | ↑ |
| methanol | $CH_3OH$ | 15.5 | |
| water | $H_2O$ | 15.7 | |
| ethanol | $CH_3CH_2OH$ | 15.9 | |
| 2-propanol | $(CH_3)_2CHOH$ | 17 | |
| 2-methyl-2-propanol | $(CH_3)_3COH$ | 18 | Weaker acid |

*Also given for comparison are $pK_a$ values for water, acetic acid, and hydrogen chloride.

## Basicity of Alcohols

- In the presence of strong acids, the oxygen atom of an alcohol behaves as a weak base.
  - Proton transfer from the strong acid forms an oxonium ion.



  - Thus, alcohols can function as both weak acids and weak bases.

## Reaction with Active Metals

- Alcohols react with Li, Na, K, and other active metals to liberate hydrogen gas and form metal alkoxides.
  - Na is oxidized to $Na^+$ and $H^+$ is reduced to $H_2$.

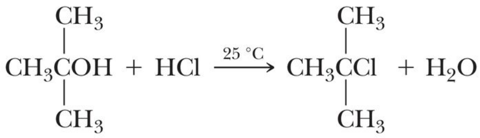
$$2\ CH_3OH + 2\ Na \longrightarrow 2\ CH_3O^-\ Na^+ + H_2$$

Sodium methoxide

  - Alkoxides are somewhat stronger bases than $OH^-$.
  - Alkoxides can be used as nucleophiles in nucleophilic substitution reactions.
  - They can also be used as bases in β-elimination reactions.

## Conversion of ROH to RX

- Water-soluble 3° alcohols react very rapidly with HCl, HBr, and HI.



$$\mathrm{CH_3\overset{CH_3}{\underset{CH_3}{C}}OH + HCl \xrightarrow{25\ ^{\circ}C} CH_3\overset{CH_3}{\underset{CH_3}{C}}Cl + H_2O}$$

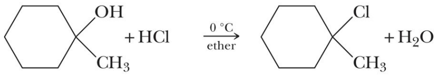
2-Methyl-2-propanol

2-Chloro-2-methylpropane

- Low-molecular-weight 1° and 2° alcohols are unreactive under these conditions.

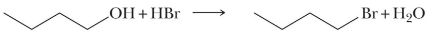
## Conversion of ROH to RX

- Water-insoluble 3° alcohols react by bubbling gaseous HCl through a solution of the alcohol dissolved in diethyl ether or THF.



1-Methylcyclohexanol

1-Chloro-1-methylcyclohexane



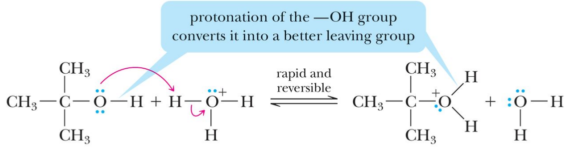
1-Butanol

1-Bromobutane (Butyl bromide)

- 1° and 2° alcohols require concentrated HBr and HI to form alkyl bromides and iodides.

## Reaction of a 3° ROH with HX

- 3° Alcohols react with HX by an $S_N1$ mechanism.
  - Step 1: Add a proton. Rapid and reversible proton transfer from the acid to the —OH group.



protonation of the —OH group converts it into a better leaving group

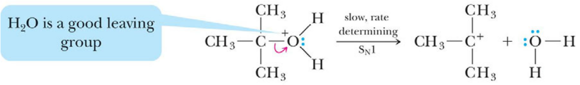
2-Methyl-2-propanol (*tert*-Butyl alcohol)

An oxonium ion

  - This proton-transfer converts the leaving group from OH⁻, a poor leaving group, to $H_2O$, a better leaving group.

## Reaction of a 3° ROH with HX

- Step 2: Break a bond to form a stable molecule or ion. Loss of $H_2O$ gives a 3° carbocation.

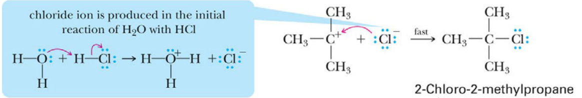


$H_2O$ is a good leaving group

An oxonium ion

A 3° carbocation intermediate

- Step 3: Reaction of an electrophile and a nucleophile to form a new covalent bond completes the reaction.

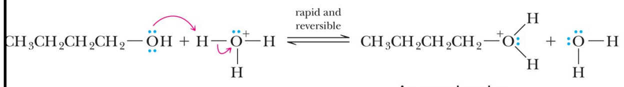


chloride ion is produced in the initial reaction of $H_2O$ with HCl

2-Chloro-2-methylpropane (*tert*-Butyl chloride)

## Reaction of a 1° ROH with HX

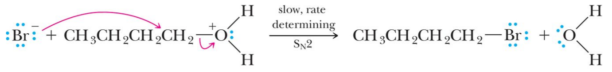
- 1° alcohols react with HX by an $S_N2$ mechanism.
  - Step 1: Add a proton. Proton transfer to OH converts $OH^-$, a poor leaving group, to $H_2O$ a better leaving group.



$$CH_3CH_2CH_2CH_2{-}\ddot{O}H + H{-}\overset{+}{O}{-}H \xrightleftharpoons{\text{rapid and reversible}} CH_3CH_2CH_2CH_2{-}\overset{+}{O}H_2 + H_2O$$

An oxonium ion

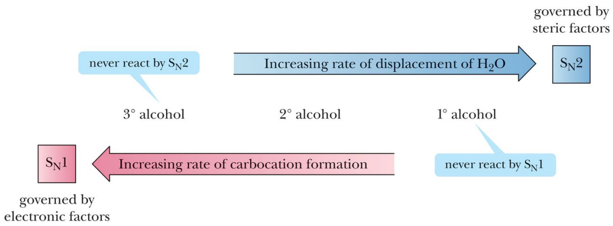
  - Step 2: Reaction of a nucleophile and an electrophile to form a new covalent bond and break a bond.



$$Br^- + CH_3CH_2CH_2CH_2{-}\overset{+}{O}H_2 \xrightarrow[S_N2]{\text{slow, rate determining}} CH_3CH_2CH_2CH_2{-}Br + H_2O$$

## Reaction of ROH with HX

- Reactions are governed by a combination of electronic and steric effects



governed by steric factors

never react by $S_N2$

Increasing rate of displacement of $H_2O$

$S_N2$

3° alcohol

2° alcohol

1° alcohol

$S_N1$

Increasing rate of carbocation formation

never react by $S_N1$

governed by electronic factors

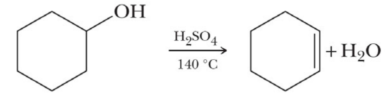
## Dehydration of Alcohols

- An alcohol can be converted to an alkene by elimination of —H and —OH from adjacent carbons (a ⍰-elimination).
  - 1° alcohols must be heated at high temperature in the presence of an acid catalyst, such as $H_2SO_4$ or $H_3PO_4$.
  - 2° alcohols undergo dehydration at somewhat lower temperatures.
  - 3° alcohols often require temperatures at or only slightly above room temperature.

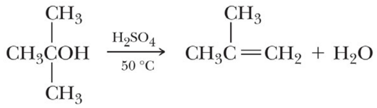
## Dehydration of Alcohols

- examples:

$$CH_3CH_2OH \xrightarrow[180\ °C]{H_2SO_4} CH_2{=}CH_2 + H_2O$$



Cyclohexanol Cyclohexene

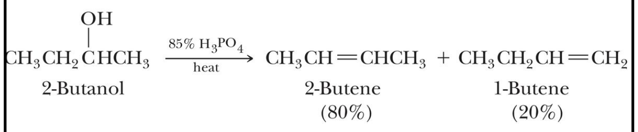


$$CH_3\overset{CH_3}{\underset{CH_3}{C}}OH \xrightarrow[50\ °C]{H_2SO_4} CH_3\overset{CH_3}{C}{=}CH_2 + H_2O$$

2-Methyl-2-propanol (*tert*-Butyl alcohol) 2-Methylpropene (Isobutylene)

# Dehydration of Alcohols

- When isomeric alkenes are obtained, the more stable alkene (the one with the greater number of substituents on the double bond) generally predominates (**Zaitsev's rule**).



$$CH_3CH_2\overset{OH}{\overset{|}{C}}HCH_3 \xrightarrow[\text{heat}]{85\%\ H_3PO_4} CH_3CH{=}CHCH_3 + CH_3CH_2CH{=}CH_2$$

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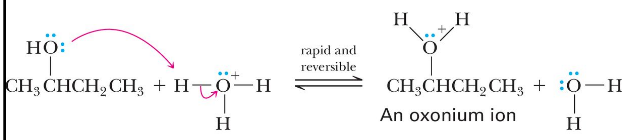
# Dehydration of a 2° Alcohol

- A three-step mechanism
  - **Step 1: Add a proton**. Proton transfer from $H_3O^+$ to the –OH group converts $OH^-$, a poor leaving group, into $H_2O$, a better leaving group.



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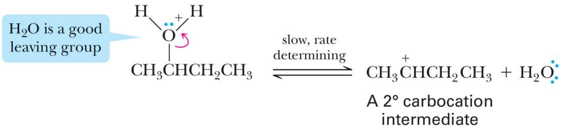
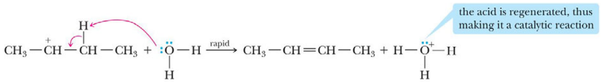
# Dehydration of a 2° Alcohol

- **Step 2: Break a bond to form a stable molecule or ion.** Loss of $H_2O$ gives a carbocation intermediate.



- **Step 3: Take a proton away.** Proton transfer from an adjacent carbon to $H_2O$ gives the alkene and regenerates the acid catalyst.



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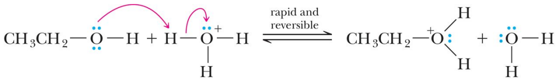
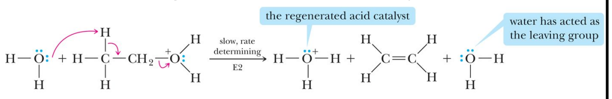
# Dehydration of a 1° Alcohol

- A two-step mechanism
  - **Step 1: Add a proton.** Proton transfer from the acid gives an oxonium ion.

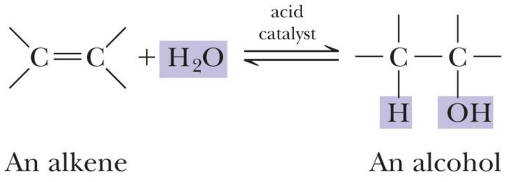


  - **Step 2: Take a proton away and loss of $H_2O$** gives the alkene and regenerates the acid catalyst.



# Hydration-Dehydration

- Acid-catalyzed hydration of an alkene and dehydration of an alcohol are competing processes.



  - Large amounts of water favor alcohol formation.
  - Scarcity of water or experimental conditions where water is removed favor alkene formation.

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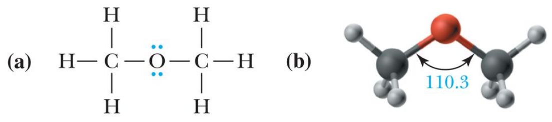
# Ethers - Structure

- **Figure 8.4** The functional group of an ether is an oxygen atom bonded to two carbon atoms.
  - Oxygen is *sp*$^3$ hybridized with bond angles of approximately 109.5°.
  - In dimethyl ether, the C–O–C bond angle is 110.3°.



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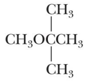
# Ethers - Nomenclature

- IUPAC
  - The parent alkane is longest carbon chain.
  - Name the -OR group as an alkoxy substituent.
- Common names:
  - Name the groups bonded to oxygen followed by the word ether.

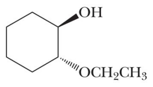
$CH_3CH_2OCH_2CH_3$

Ethoxyethane
(Diethyl ether)



$$CH_3O\overset{CH_3}{\underset{CH_3}{C}}CH_3$$

2-methyl-2-methoxypentanol
(*tert*-Butylmethyl ether)



(1*R*, 2*R*)-2-ethoxycyclohexanol

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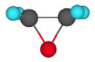
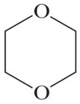
# Ethers - Nomenclature

- Although cyclic ethers have IUPAC names, their common names are more widely used.

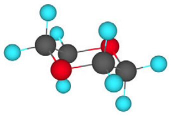
Ethylene oxide



Tetrahydrofuran (THF)

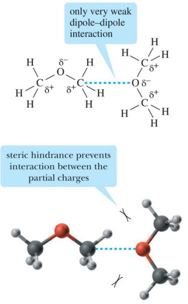


1,4-Dioxane



## Ethers - Physical Properties

- **Figure 8.5** **Ethers** are polar molecules.
  - – Each C-O bond is polar covalent.
  - – However, only weak attractive forces exist between ether molecules in the pure liquid.



## Ethers - Physical Properties

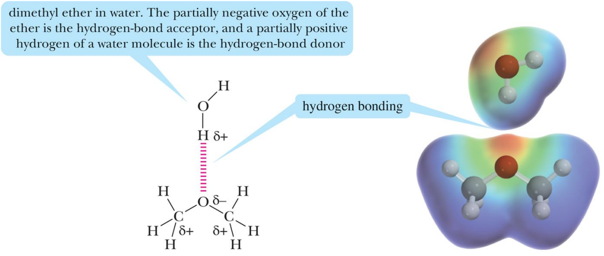
**Table 8.3** Boiling Points and Solubilities in Water of Some Alcohols and Ethers of Comparable Molecular Weight

**TABLE 8.3** **Boiling Points and Solubilities in Water of Alcohols and Ethers Grouped by Similar Molecular Weight**

| Structural Formula | Name | Molecular Weight | Boiling Point (°C) | Solubility in Water |
|---|---|---|---|---|
| $CH_3CH_2OH$ | ethanol | 46 | 78 | infinite |
| $CH_3OCH_3$ | dimethyl ether | 46 | –24 | 7.8 g/100 g |
| $CH_3CH_2CH_2CH_2OH$ | 1-butanol | 74 | 117 | 7.4 g/100 g |
| $CH_3CH_2OCH_2CH_3$ | diethyl ether | 74 | 35 | 8 g/100 g |
| $CH_3CH_2CH_2CH_2CH_2OH$ | 1-pentanol | 88 | 138 | 2.3 g/100 g |
| $HOCH_2CH_2CH_2CH_2OH$ | 1,4-butanediol | 90 | 230 | infinite |
| $CH_3CH_2CH_2CH_2OCH_3$ | butyl methyl ether | 88 | 71 | slight |
| $CH_3CH_2CH_2CH_2OCH_3$ | ethylene glycol dimethyl ether | 90 | 84 | infinite |

## Ethers - Physical Properties

**Figure 8.6** Ethers are hydrogen bond acceptors only. They are not hydrogen bond donors.



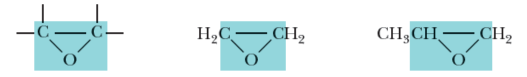
## Ethers - Physical Properties

- – The effect of hydrogen bonding is illustrated by comparing the boiling points of ethanol and dimethyl ether.

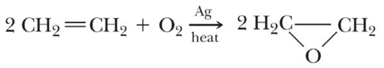
| $CH_3CH_2OH$ | $CH_3OCH_3$ |
|---|---|
| Ethanol | Dimethyl ether |
| bp 78 °C | bp –24 °C |

# Epoxides

- **Epoxide**: A cyclic ether in which oxygen is one atom of a three-membered ring.


Functional group of an epoxide
Ethylene oxide
Propylene oxide

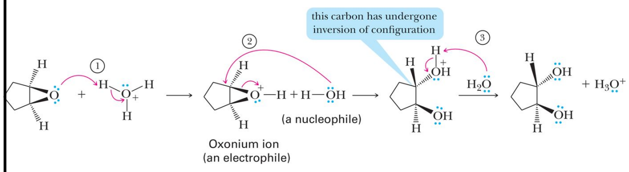
- Ethylene oxide is synthesized from ethylene and $O_2$.


$$2\,CH_2{=}CH_2 + O_2 \xrightarrow[\text{heat}]{Ag} 2\,H_2C\underset{O}{—}CH_2$$

Ethylene
Ethylene oxide

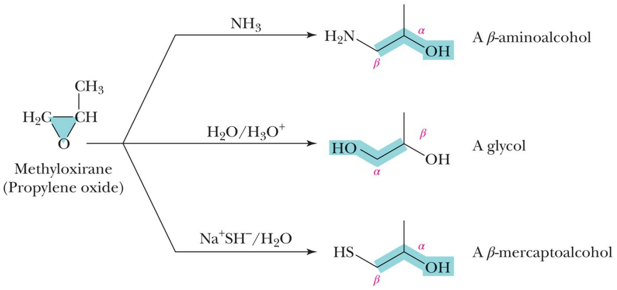
# Epoxide Ring Openings

- The mechanism of acid-catalyzed hydrolysis of an epoxide involves three steps.
- Step 1: **Add a proton**
- Step 2. **Reaction of an electrophile and a nucleophile to form a new covalent bond.**
- Step 3. **Take away a proton.**



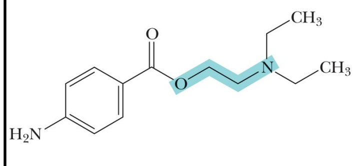
# Epoxide Ring Openings

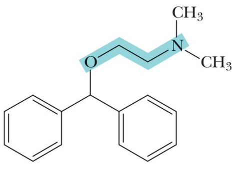
- The value of epoxides lies in the number of nucleophiles that will bring about ring opening, and the combinations of functional groups that can be synthesized from them.



# Epoxides as Building Blocks

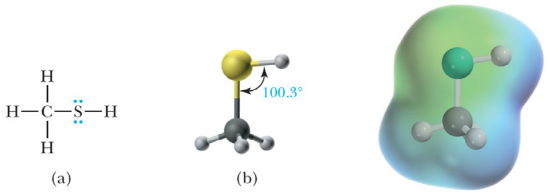
- Following are structural formulas for two common drugs, each synthesized in part with ethylene oxide as a building block.


Procaine
(Novocaine)


Diphenhydramine
(Benadryl)

# Thiols - Structure

- **Figure 8.7** The functional group of a thiol is an -SH (sulfhydryl) group bonded to an *sp*$^3$ hybridized carbon.



# Thiols - Nomenclature

IUPAC names

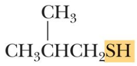
- The parent chain is the longest chain that contains the -SH group.
  - Add -**thiol** to the name of the parent chain.

Common names

  - Name the alkyl group bonded to sulfur followed by the word **mercaptan**.
  - Alternatively, indicate the -SH by the prefix **mercapto**.

$CH_3CH_2SH$

Ethanethiol
(Ethyl mercaptan)


$CH_3CH(CH_3)CH_2SH$

2-Methyl-1-propanethiol
(Isobutyl mercaptan)

$HSCH_2CH_2OH$

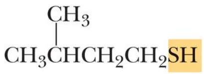
2-Mercaptoethanol

# Thiols - Physical Properties

- Low-molecular-weight thiols have a STENCH

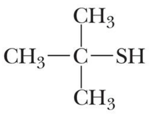
$CH_3CH{=}CHCH_2SH$

2-Butene-1-thiol

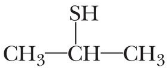

$CH_3CH(CH_3)CH_2CH_2SH$

3-Methyl-1-butanethiol

Natural gas odorants:


$(CH_3)_3C{-}SH$

2-Methyl-2-propanethiol
(*tert*-Butyl mercaptan)


$CH_3{-}CH(SH){-}CH_3$

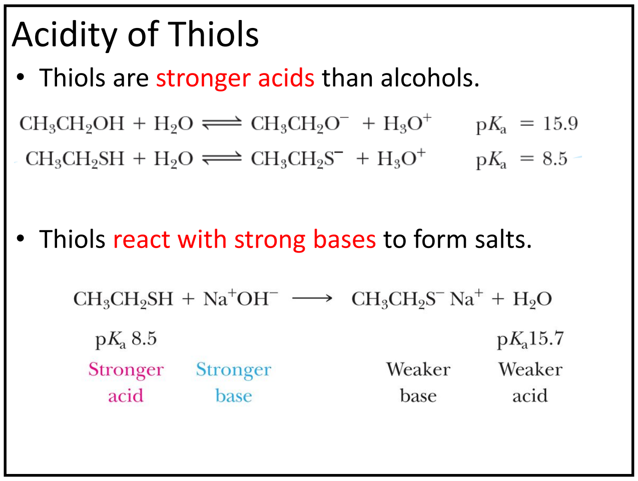
2-Propanethiol
(Isopropyl mercaptan)

# Thiols - Physical Properties

- The difference in electronegativity between S and H is 2.5 – 2.1 = 0.4
- Because of their low polarity, thiols
  - show little association by hydrogen bonding.
  - have lower boiling points and are less soluble in water than alcohols of comparable MW.

**TABLE 8.4** **Boiling Points of Three Thiols and Three Alcohols with the Same Number of Carbon Atoms**

| Thiol | Boiling Point (°C) | Alcohol | Boiling Point (°C) |
|---|---|---|---|
| methanethiol | 6 | methanol | 65 |
| ethanethiol | 35 | ethanol | 78 |
| 1-butanethiol | 98 | 1-butanol | 117 |



# Acidity of Thiols

- Thiols are stronger acids than alcohols.

$$CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^- + H_3O^+ \qquad pK_a = 15.9$$

$$CH_3CH_2SH + H_2O \rightleftharpoons CH_3CH_2S^- + H_3O^+ \qquad pK_a = 8.5$$

- Thiols react with strong bases to form salts.

$$CH_3CH_2SH + Na^+OH^- \longrightarrow CH_3CH_2S^- Na^+ + H_2O$$

| $CH_3CH_2SH$ | $Na^+OH^-$ | $CH_3CH_2S^- Na^+$ | $H_2O$ |
|---|---|---|---|
| $pK_a$ 8.5 | | | $pK_a$15.7 |
| Stronger acid | Stronger base | Weaker base | Weaker acid |