Chapter 11
Alcohols and Ethers

Nomenclature of Alcohols – Systematic names

1. Select the longest chain containing the hydroxyl and change the suffix ending of the parent alkane from -e to -ol
2. Number the parent to give the hydroxyl the lowest possible number
3. The other substituents take their locations accordingly

\[
\text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}_3\text{OH} \\
\text{CH}_3
\]

4-methyl-1-hexanol

Common alcohols with other groups

Phenols contain a hydroxyl group, but are not classified as an alcohol

Ether

Phenol

p-Methylphenol

a-Substituted phenol

General formula for a phenol

Nomenclature of Ethers

Common Names

- The groups attached to the oxygen are listed in alphabetical order

\[
\begin{align*}
\text{CH}_3\text{CH}(_3)\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3 & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3
\end{align*}
\]

- Ethers are named as having an alkoxyl substituent on the main chain

\[
\begin{align*}
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{CH}_3 & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{CH}_3 & \rightarrow \text{CH}_3
\end{align*}
\]

4-Methyl-2-pentane

1-Ethoxy-4-methylbenzene

1,2-Dimethoxymethane

Common Names of simple alcohols are still often used and are approved by IUPAC

Alcohols with two hydroxyls are called diols in nomenclature and glycols in common nomenclature

Examples

\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3 \\
\text{CH}_3\text{CH}(_3)\text{CH}(_3)\text{CH}(_3)\text{CH}_2\text{OH} & \rightarrow \text{CH}_3
\end{align*}
\]

Ethylene glycol

Propanediol

Trimethylene glycol

1,2-Propanediol
Cyclic ethers

Cyclic ethers can be named using the prefix oxa-

Three-membered ring ethers can be called oxiranes; commonly called epoxides and named as alkene oxides.

Four-membered ring ethers can be called oxetanes.

THF and dioxane are common solvents.

Name this compound

A. 4-hydroxyheptane
B. 4-heptanol
C. 4-propyl-1-pentanol
D. 2-propyl-1-pentanol

Physical Properties of Alcohols and Ethers

1. Ether boiling points are roughly comparable to hydrocarbons of the same molecular weight
   - Molecules of ethers cannot hydrogen bond to each other

2. Alcohols have considerably higher boiling points
   - Molecules of alcohols hydrogen bond to each other

3. Both alcohols and ethers can hydrogen bond to water and have similar solubilities in water (5°C or more insoluble)
   - Diethyl ether and 1-butanol have solubilities of about 8 g per 100 mL in water

How do we make alcohols?

1. Acid-Catalyzed Hydration of Alkenes
   - This is a reversible reaction with Markovnikov regioselectivity

2. Oxymercuration-demercuration
   - This is a Markovnikov addition which occurs without rearrangement

3. Hydroboration-Oxidation
   - This addition reaction occurs with anti-Markovnikov regiochemistry and syn stereochemistry
Alcohols from RX

- Alcohols are products of $S_N2$ and occasionally $S_N1$ reactions of RX.
- Limited usefulness as a synthesis route because RX is usually made from alcohol.

What reaction enables this conversion?

A. $H_2O$, dilute $H_2SO_4$
B. 1. $BH_3$  2. $H_2O_2$, $NaOH$
C. 1. $Hg(O_2CCF_3)_2$  2. $NaBH_4$, $NaOH$
D. $OsO_4$

Alcohols as Acids

- Alcohols have acidities similar to water.
- Sterically hindered alcohols such as tert-butyl alcohol are less acidic (have higher pKa values).
  - Why?: The conjugate base is not well solvated and so is not as stable.
- Alcohols are stronger acids than terminal alkynes and primary or secondary amines.
  
  Relative Acidity:
  $H_2O > ROH > RCOOH > H_2O > NH_2 > RH$

- An alkoxide can be prepared by the reaction of an alcohol with sodium or potassium metal.

Rough scale of acidities — MEMORIZE!

<table>
<thead>
<tr>
<th>Acid</th>
<th>Conjugate Base</th>
<th>pKa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong (HCl)</td>
<td>NaCl</td>
<td>-5</td>
</tr>
<tr>
<td>Organic (RCO$_2$H)</td>
<td>RCO$_2$Na</td>
<td>5</td>
</tr>
<tr>
<td>Alcohols, water</td>
<td>NaOCH$_3$, NaOH</td>
<td>15</td>
</tr>
<tr>
<td>Terminal alkene</td>
<td>Na C = CR</td>
<td>25</td>
</tr>
<tr>
<td>Amine NH, hydrogen</td>
<td>NaNH$_2$, NaH</td>
<td>35 (37)</td>
</tr>
<tr>
<td>Alkanes (sp$_3$C-H)</td>
<td>BuLi</td>
<td>45-50</td>
</tr>
</tbody>
</table>

Conversion of Alcohols into Leaving Groups

1. Monofunctionalized carbons are critical structures, both for their own purposes and as intermediates.
2. Hydroxyl groups are poor leaving groups.
3. Several methods are available to convert alcohols into better leaving groups.

Conversion of Alcohols into Alkyl Halides

Three general methods are available

1. Hydrogen halides
2. Phosphorus tribromide
3. Thionyl chloride

\[
R-OH \quad \rightarrow \quad R-X
\]

X = Br, Cl, $OSO_2R'$
**Reaction of Alcohols with Hydrogen Halides**

The order of reactivity is as follows:
- Hydrogen halide: HI > HBr > HCl > HF
- Type of alcohol: 3° > 2° > 1° < methyl

**Mechanism of the Reaction of Alcohols with HX**
- **S_N_1 mechanism** for 3°, 2°, allylic, and benzylic alcohols

\[
\begin{align*}
\text{Reaction of Alcohols with PBr}_3 \text{ and SOCl}_2 \\
\text{These reagents only react with 1° and 2° alcohols in S_N_2 reactions} \\
\text{Convert the hydroxyl to an excellent leaving group} \\
\text{No rearrangements}
\end{align*}
\]

**Thionyl chloride**

\[
\begin{align*}
\text{Often an amine is added to react with HCl formed in the reaction:} \\
R_2N^+ + HCl \rightarrow R_2NH^+ + Cl^-
\end{align*}
\]

**Sulfonate Esters: Tosylates, Mesylates, and Triflates**

The hydroxyl group of an alcohol can be converted to a good leaving group by conversion to a sulfonate ester

- Sulfonyl chlorides are used to convert alcohols to sulfonate esters
- Base is added to react with the HCl generated

\[
\begin{align*}
\text{A sulfonate ion (a weak base) is an excellent leaving group} \\
\text{If the alcohol OH is at a stereogenic center then the overall reaction} \\
\text{with the nucleophile proceeds with inversion of configuration} \\
\text{Formation of a sulfonate ester proceeds with retention of configuration}
\end{align*}
\]

Resume on 11/20
Triflate anion is such a good leaving group that even vinyl triflates can undergo $S_N1$ reaction.

Example of product in ethanol

**Synthesis of Ethers**

1. **Ethers by Intermolecular Dehydration of Alcohol**
   - Primary alcohols can dehydrate to ethers
     - This reaction occurs at lower temperature than the competing dehydration to an alkene
     - This method generally does not work with secondary or tertiary alcohols because elimination competes strongly

   \[
   \text{H}_3\text{C} \text{CH} = \text{CH}_2 \rightleftharpoons \text{H}_3\text{C} \text{CH}_2\text{OH} \rightleftharpoons \text{H}_3\text{C} \text{CH}_2\text{O}^- \text{H}^+ \rightleftharpoons \text{CH}_3\text{CH} = \text{CH}_2
   \]

   Predict the reaction mechanism!

2. **Williamson Ether Synthesis**
   - This is a good route for synthesis of unsymmetrical ethers

   \[
   \text{CH}_3\text{CH}_2\text{OH} + \text{R}-\text{Cl} \rightarrow \text{CH}_3\text{CH}_2\text{OR} + \text{HCl}
   \]

   Alkyl halide or sulfonate should be primary or methyl to avoid E2
   If $R = t$-butyl, $R'$ must be methyl
   Modest yields with secondary halides if both substrates unhindered
   Substitution is favored over elimination at lower temperatures

3. **Synthesis of Ethers by Alkoxymercuration-Demercuration**

   Same reaction as used for hydration of alkenes, except using an alcohol as the nucleophile (instead of the water)

   \[
   \text{R}+\text{HO}^- + \text{HO}^- \rightarrow \text{R}-\text{O}^- + \text{H}^+ \rightarrow \text{R}-\text{O}^- + \text{H}^+ \rightarrow \text{R}-\text{O}^- \text{H}^+ \rightarrow \text{R}-\text{O}^- \text{H}^+
   \]

4. **Ethers from carbocations plus alcohols**

   Generating a carbocation in an alcohol as solvent can lead to ethers

   \[
   \text{R}^+ \text{O}^- \text{H}^+ + \text{R}-\text{O}^- \text{H}^+ \rightarrow \text{R}-\text{O}^- \text{H}^+ \rightarrow \text{R}-\text{O}^- \text{H}^+
   \]

   Works well only for $R = \text{C}^+$
Use of t-butyl ethers as protecting groups

Protecting group: a group added to insulate one sensitive functional group to allow a reaction at another part of the molecule

• Protecting group is later removed

Step 1: Formation of t-butyl ether to protect a hydroxy group

\[ \text{R-CH}_2\text{OH} + \text{H}_2\text{SO}_4 \rightarrow \text{R-CH}_2\text{O}^+ + \text{Bu}^- \]

Step 2: Reaction elsewhere

Step 3: Removal of t-butyl group with dilute aqueous acid

Example: t-butyl ethers as protecting group

Challenge: the alkylation of an alkyne by an alkyl halide that also contains a hydroxy group

Reactions of Ethers

Acyclic ethers are generally unreactive, except for cleavage by very strong acids to form the corresponding alkyl halides

• Dialkyl ethers undergo S_N_2 reaction to form 2 equivalents of the alkyl bromide

Epoxides: a reactive cyclic ether

• Epoxides are three-membered ring cyclic ethers

Because of ring strain in the three-membered ring, these ethers are reactive and useful intermediates

Epoxides are formed by reaction of alkenes with peroxy acids

This process is called epoxidation and involves syn addition of oxygen

One step transfer of an oxygen atom via a cyclic transition state

Silyl Ether Protecting Groups

Silyl ethers are widely used protecting groups for alcohols

• The tert-butyldimethylsilyl (TBDMS) ether is common
• The protecting group is introduced by reaction of the alcohol with the chlorosilane in the presence of an aromatic amine base
• The silyl ether protecting group is removed by treatment with fluoride ion (e.g., from tetrabutyl ammonium fluoride)
Magnesium monoperxyphthalate (MMPP) is a common and safe peroxoacid for epoxidation.

Epoxidation is stereospecific
- Epoxidation of cis-2-butene gives the meso cis oxirane
- Epoxidation of trans-2-butene gives the racemic trans oxirane

Epoxides are much more reactive than regular ethers
- Strain energy is released in opening the three-membered ring
- Acid-catalyzed opening of an epoxide occurs by initial protonation of the oxygen, making the epoxide even more reactive
- Acid-catalyzed hydrolysis of an epoxide leads to a 1,2-diol

Reaction of Epoxides

Epoxides are much more reactive than regular ethers
- Strain energy is released in opening the three-membered ring
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Epoxides + HZ
- Acids that contain a nucleophile Z also open epoxide rings by a two-step sequence.
- HCl, HBr and HI, as well as H₂O and ROH in the presence of acid, all open an epoxide ring in this manner.

Epoxides + HZ examples

What does second example tell us about mechanism?

Summary of information
- Not pure S₅₁ (no free carbocation):
  - no loss of stereochemistry
  - no rearrangements
- Not regular S₅₂
  - Nucleophile would go to 1°
  - 3°<2°<1°
Merged mechanism

Bridged ion maintains stereochemistry (backside), but directs incoming nucleophile to more stable carbocation.

Base-catalyzed reaction with strong nucleophiles (e.g., an alkoxide or hydroxide) occurs by an $S_{N}2$ mechanism

- The nucleophile attacks at the less sterically hindered carbon of the epoxide

Summary of epoxide openings

- Ring opening of an epoxide with either a strong nucleophile or an acid $H_{Z}$ is regioselective.
- Site selectivity of these two reactions is exactly the opposite!

Anti 1,2-Dihydroxylation of Alkenes via Epoxides

Opening of the following epoxide with water under acid catalyzed conditions gives the trans diol

Epoxidering-opening is a stereospecific process
Options for synthesis of diols

1. MMPP
2. HOO
3. -OH (acid)

Predict the product via epoxide

Example in the synthesis of a bronchodilator

Predict the product

Phase Transfer Catalysis

- General problem: anionic nucleophiles tend to be soluble in water, but not organic solvents

Purple benzene??

Crown ethers

CH₃(CH₂)₇CH=CH₂ (in benzene)
80°C X₂
aqueous KOH, 50°C
CH₃(CH₂)₇C=O + H₂O + CO₂
(99%)
Examples of crown ethers in synthesis

K\(^+\)CN\(^-\) + RCH\(_2\)X \rightarrow \text{15-crown-5} \cdot \text{K}^+ \rightarrow \text{RCH}_{12}CN + \text{K}^+X^-

\[\text{C}_8\text{H}_{18}\text{Cl}_3 = \text{K}^+ \rightarrow \text{C}_14\text{H}_{26}\text{Cl}_6F + \text{K}^+\text{Cl}^-\]

Polyketides come from epoxide polymerization

Drevetoxin D: R =

Drevetoxin C: R =

brevetoxin B, C (5-6)