Chapter 17
Alcohols and Phenols
Alcohols and Phenols

• Organic derivatives of water
  – One of water’s hydrogens is replaced by an organic group

• Alcohols contain an –OH group connected to a saturated, $sp^3$-hybridized C atom
Alcohols and Phenols

• Methanol
  – Reactant in synthesizing formaldehyde (CH₂O) and acetic acid (CH₃CO₂H)

\[
\text{CO} + 2 \text{H}_2 \xrightarrow{400 \, ^\circ\text{C}} \text{Zinc oxide/chromia catalyst} \rightarrow \text{CH}_3\text{OH}
\]

• Ethanol
  – Used in industry as solvent or chemical intermediate
  – A solvent, fuel, and beverage

\[
\text{H}_2\text{C}═\text{CH}_2 \xrightarrow{\text{H}_2\text{O}} \text{H}_3\text{PO}_4 \xrightarrow{250 \, ^\circ\text{C}} \text{CH}_3\text{CH}_2\text{OH}
\]
Naming Alcohols and Phenols

• General classifications of alcohols are based on number of organic groups bonded to the hydroxyl-bearing carbon

A primary (1°) alcohol    A secondary (2°) alcohol    A tertiary (3°) alcohol

• IUPAC system names simple alcohols as derivatives of the parent alkane with a suffix -ol
Naming Alcohols and Phenols

• Rule 1
  – Select the longest carbon chain containing the hydroxyl group, and derive the parent name by replacing the -e ending of the corresponding alkane with -ol

• Rule 2
  – Number the chain from the end nearer the hydroxyl group
Naming Alcohols and Phenols

• Rule 3
  – Number substituents according to position on chain, listing the substituents in alphabetical order
Naming Alcohols and Phenols

• *phenol* is used as the parent name
  – Not *benzene*

• Name substituents on aromatic ring by their position from –OH

\[ \text{H}_3\text{C} - \text{OH} \quad \text{m-Methylphenol (m-Cresol)} \]
\[ \text{OH} - \text{NO}_2 \quad \text{2,4-Dinitrophenol} \]
Naming Priority

Highest ranking

1. Acids
2. Esters
3. Aldehydes
4. Ketones
5. Alcohols
6. Amines
7. Alkenes and Alkynes

Lowest ranking

8. Alkanes
9. Ethers
10. Halides
Worked Example

• Give IUPAC names for the following compounds
  a) 2-Methyl-4-phenyl-2-butanol
  b) 4-Bromo-3-methylphenol

• Solution:
  – The parent chain must contain the hydroxyl group
  – The hydroxyl group should receive the lowest possible number
    a) 2-Methyl-4-phenyl-2-butanol
    b) 4-Bromo-3-methylphenol
PROPERTIES OF ALCOHOLS AND PHENOLS
Properties of Alcohols and Phenols: Geometry

- Structure around O of alcohols or phenols are similar to that in water, $sp^3$-hybridized
  - Oxygen is $sp^3$ hybridized and tetrahedral
  - The H—O—H angle in water is 104.5°
  - The C—O—H angle in methyl alcohol is 108.9°
Properties of Alcohols and Phenols:

- Attraction of positively polarized –OH hydrogen atom from one molecule to the lone pair of electrons on a negatively polarized oxygen atom of another molecule:
  - Produces weak force that holds the molecules together
  - Raises the boiling temperature

![Image of molecular structures showing attraction forces between molecules]
Properties of Alcohols and Phenols: Basicity

• Weakly basic and weakly acidic
• As a weak base, protonated by strong acids to yield oxonium ions, $\text{ROH}_2^+$

\[
\begin{align*}
\text{An alcohol} & \quad + \quad \text{H--X} & \quad \rightleftharpoons & \quad \text{An oxonium ion} \\
\text{or } \text{ArOH} & \quad + \quad \text{HX} & \quad \rightleftharpoons & \quad \text{ArOH}_2^+ \quad \text{X}^- 
\end{align*}
\]
Properties of Alcohols and Phenols: Acidity

- As weak acids, dissociate slightly in dilute aqueous solution generating $\text{H}_3\text{O}^+$ and an alkoxide ion, $\text{RO}^-$ or phenoxide ion, $\text{ArO}^-$
Properties of Alcohols and Phenols: Acidity

• Strength of an acid in water can be expressed by an acidity constant, $K_a$

$$K_a = \frac{[A^-][H_3O^+]}{[HA]}$$

$$pK_a = -\log K_a$$

- Smaller $K_a$ and larger $pK_a$, less acidic
- Larger $K_a$ and smaller $pK_a$, more acidic
Properties of Alcohols and Phenols: Acidity Constants

<table>
<thead>
<tr>
<th>Compound</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;COH</td>
<td>18</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>16</td>
</tr>
<tr>
<td>H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>15.74</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;OH</td>
<td>15.54</td>
</tr>
<tr>
<td>CF&lt;sub&gt;3&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>12.43</td>
</tr>
<tr>
<td>p-Aminophenol</td>
<td>10.46</td>
</tr>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;SH</td>
<td>10.3</td>
</tr>
<tr>
<td>p-Methylphenol</td>
<td>10.17</td>
</tr>
<tr>
<td>Phenol</td>
<td>9.89</td>
</tr>
<tr>
<td>p-Chlorophenol</td>
<td>9.38</td>
</tr>
<tr>
<td>p-Nitrophenol</td>
<td>7.15</td>
</tr>
</tbody>
</table>
Properties of Alcohols and Phenols: Substitution Effects

- Effect of alkyl substitution on alcohol acidity is primarily due to solvation of alkoxide ion formed on acid dissociation.
- The more easily the alkoxide ion is solvated by water, the more its formation is energetically favored.

![Methoxide ion, CH₃O⁻ (pKₐ = 15.54)](Methoxide.png)  ![tert-Butoxide ion, (CH₃)₃CO⁻ (pKₐ = 18.00)](tert-Butoxide.png)
Properties of Alcohols and Phenols: Inductive Effects

• Inductive effects are important in determining alcohol acidities
  – Electron-withdrawing groups make an alcohol a stronger acid by stabilizing the conjugate base

Electron-withdrawing groups stabilize the alkoxide ion and lower the $pK_a$.

$pK_a = 5.4$  
nonafluoro-tert-butyl alcohol

$pK_a = 18.0$  
tert-butyl alcohol
Properties of Alcohols and Phenols: Reactivity

• As weak acids, alcohols reactivity
  – Does not occur with weak bases
    • Amines
    • Bicarbonate ion
  – Limited with metal hydroxides
    • NaOH
  – Occurs with
    • Alkali metals
    • Strong bases
      – Sodium hydride
      – Sodium amide
      – Grignard reagents

• Alkoxides are bases used as reagents in organic chemistry
Properties of Alcohols and Phenols: Acidity

- Phenols are more acidic than alcohols due to resonance stabilization of the phenoxide ion.

\[
\text{Phenol} + \text{NaOH} \rightarrow \text{Sodium phenoxide (sodium phenolate)} + \text{H}_2\text{O}
\]

- Phenols with an electron-withdrawing substituent are more acidic and phenols with an electron-donating substituent are less acidic.
Worked Example

• Rank the following substances in order of increasing acidity
  a) \((\text{CH}_3\text{)}_2\text{CHOH}, \text{HC}≡\text{CH}, (\text{CF}_3\text{)}_2\text{CHOH}, \text{CH}_3\text{OH}\)
  b) Benzyl alcohol, phenol, \(p\)-hydroxybenzoic acid

• Solution:
  Least acidic                                              Most acidic
  a) \(\text{HC}≡\text{CH} \ < \ (\text{CH}_3\text{)}_2\text{CHOH} \ < \ \text{CH}_3\text{OH} \ < \ (\text{CF}_3\text{)}_2\text{CHOH}\)
  b) Benzyl alcohol \ < \ phenol \ < \ \(p\)-hydroxybenzoic acid
PREPARATION OF ALCOHOLS
Preparation of Alcohols: A Review

• Alcohols are derived from many types of compounds
• The alcohol hydroxyl can be converted to many other functional groups
Preparation of Alcohols: A Review

- Hydration of alkenes
  - Hydroboration-oxidation, yields the syn, non-Markovnikov hydration product
  - Oxymercuration-demercuration yields Markovnikov hydration product
Preparation of Alcohols: A Review

• Preparation of 1,2-diols
  – Cis-1,2-diols are prepared from direct hydroxylation of an alkene with OsO$_4$ followed by reduction with NaHSO$_3$
  – Trans-1,2-diols can be prepared from acid-catalyzed hydrolysis of epoxides
Worked Example

• Predict the products of the following reaction

\[
\text{1. } \text{Hg(OAc)}_2, \text{H}_2\text{O} \\
\text{2. } \text{NaBH}_4
\]

• Solution:

- Markovnikov product results from oxymercurylation/reduction
ALCOHOLS FROM CARBONYL COMPOUNDS
Alcohols from Carbonyl Compounds: Reduction

• Reduction of a carbonyl compound gives an alcohol
  – Addition of H to a C═O bond

\[
\begin{align*}
\text{A carbonyl compound} & \quad \xrightarrow{[\text{H}]} \quad \text{An alcohol} \\
\text{H} & \quad \text{C} \quad \text{O} \\
\text{C} & \quad \text{H}
\end{align*}
\]

where [H] is a reducing agent

• Any carbonyl compound can be reduced
  – Aldehydes
  – Ketones
  – Carboxylic acids
  – Esters
Alcohols from Carbonyl Compounds: Aldehydes and Ketones

• Reduction of aldehydes gives primary alcohols

\[
\begin{align*}
\text{An aldehyde} & \quad \text{A primary alcohol} \\
\end{align*}
\]

• Reduction of ketones gives secondary alcohols

\[
\begin{align*}
\text{A ketone} & \quad \text{A secondary alcohol} \\
\end{align*}
\]
Alcohols from Carbonyl Compounds: Reduction Reagent for Aldehydes and Ketones

- Sodium borohydride
  - $\text{NaBH}_4$ is not sensitive to moisture and can be used with either water or alcohol

\[\text{Aldehyde reduction}\]
\[
\begin{align*}
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH} \quad &\xrightarrow{1. \text{NaBH}_4, \text{ethanol}} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_3 \\
&\xrightarrow{2. \text{H}_3\text{O}^+} \\
\end{align*}
\]

- Butanal
  - 1-Butanol (85%) (a 1° alcohol)

\[\text{Ketone reduction}\]
\[
\begin{align*}
\text{C}_8\text{H}_{11}\text{C} \quad &\xrightarrow{1. \text{NaBH}_4, \text{ethanol}} \quad \text{C}_8\text{H}_{11}\text{C} \\
&\xrightarrow{2. \text{H}_3\text{O}^+} \\
\end{align*}
\]

- Dicyclohexyl ketone
  - Dicyclohexylmethanol (88%) (a 2° alcohol)
Alcohols from Carbonyl Compounds: Reduction Reagent for Aldehydes and Ketones

- Lithium aluminum hydride
  - More reactive than NaBH₄
  - Reacts violently with water
  - Decomposes explosively above 120 °C

![Chemical reaction]

2-Cyclohexenone → 2-Cyclohexenol (94%)
Alcohols from Carbonyl Compounds: Aldehydes and Ketones Mechanism of Reduction

- Addition of a nucleophilic hydride ion to the positively polarized, electrophilic carbon atom of the carbonyl group
- Alkoxide ion is protonated to yield the alcohol product

![Diagram showing the mechanism of reduction and the formation of an alcohol from a carbonyl compound and an alkoxide ion intermediate.]
Alcohols from Carbonyl Compounds: Aldehydes and Ketones Reductions in Living Organisms

- Carried out by either of the coenzymes, NADH or NADPH
Alcohols from Carbonyl Compounds: Carboxylic Acids and Esters

• Carboxylic acids and esters are reduced to give primary alcohols

\[
\begin{align*}
&\text{R}^1\text{C}=\text{O} - \text{H} &\text{or} &\text{R}^1\text{C}=\text{O}\text{R}' \\
&\text{A carboxylic acid} &\text{An ester} &\text{A primary alcohol}
\end{align*}
\]

• Not as reactive as reductions of aldehydes and ketones
Alcohols from Carbonyl Compounds: Carboxylic Acids and Esters

- LiAlH$_4$ is used because NaBH$_4$ is not effective
  - Two hydrogens are bonded to the carbonyl carbon

**Carboxylic acid reduction**

\[
\text{CH}_3(\text{CH}_2)_7\text{CH}═\text{CH}(\text{CH}_2)_7\text{COH} \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3(\text{CH}_2)_7\text{CH}═\text{CH}(\text{CH}_2)_7\text{CH}_2\text{OH}
\]

9-Octadecenoic acid (oleic acid) → 9-Octadecen-1-ol (87%)

**Ester reduction**

\[
\text{CH}_3\text{CH}_2\text{CH}═\text{CHCOOCH}_3 \xrightarrow{1. \text{LiAlH}_4, \text{ether}} \xrightarrow{2. \text{H}_3\text{O}^+} \text{CH}_3\text{CH}_2\text{CH}═\text{CHCH}_2\text{OH} + \text{CH}_3\text{OH}
\]

Methyl 2-pentenoate → 2-Penten-1-ol (91%)
Worked Example

• What carbonyl compounds give the following alcohol on reduction with LiAlH$_4$?

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

• Solution:

[Chemical structures showing the reduction process]

– Benzyl alcohol may be the reduction product of an aldehyde, a carboxylic acid, or an ester
ALCOHOLS FROM CARBONYL COMPOUNDS: GRIGNARD REAGENTS
Alcohols from Carbonyl Compounds: Grignard Reagents

• Organohalides react with magnesium to produce Grignard reagents, RMgX

• Grignard reagents react with carbonyl compounds to yield alcohols

$$\text{R–X} + \text{Mg} \rightarrow \text{R–MgX}$$

A Grignard reagent

$$\left\{ \begin{array}{l} \text{R} = 1^\circ, 2^\circ, \text{or} \ 3^\circ \text{alkyl, aryl, or vinylic} \\
\text{X} = \text{Cl, Br, I} \end{array} \right\}$$

$$\text{O} \quad \stackrel{1. \text{RMgX, ether}}{\longrightarrow} \quad \text{OH}$$

$$\text{C} \quad \stackrel{2. \text{H}_3\text{O}^+}{\longrightarrow} \quad \text{C} \quad + \quad \text{HOMgX}$$
Grignard Reagents

\[
R-X + Mg \rightarrow \text{CH}_3\text{CH}_2\text{OCH}_2\text{CH}_3 \rightarrow \delta^{-}\delta^{+} R-Mg-X \rightarrow \text{organomagnesium halide (Grignard reagent)} \rightarrow R:^- + MgX
\]

- Formula \(R-Mg-X\) (reacts like \(R:^- + MgX\))
- Ethers are used as solvents to stabilize the complex
- Iodides are most reactive
- Fluorides generally do not react
- May be formed from primary, secondary, or tertiary alkyl halides

\(X = \text{Cl, Br, or I}\)
Addition to Carbonyl Compounds

- The carbonyl carbon is partial positive (electrophilic)
- Nucleophiles will attack the carbonyl, forming an alkoxide
Mechanism of Addition of the Organometallic to the Carbonyl

\[
\begin{align*}
R^{-} &\quad \overset{\delta^{+}}{\quad \overset{\delta^{-}}{\quad C=O}} &\quad \rightarrow &\quad R-C-\overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}^{-} \\
R-C-\overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}^{-} &\quad \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{H}}} &\quad \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}^{-} &\quad \\
\text{alkoxide} &\quad \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{H}}} &\quad \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}^{-} &\quad \text{(or } \text{H}_{3}\text{O}^{+}\text{)} &\quad \rightarrow &\quad R-C-\overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}H &\quad + &\quad \overset{\cdot}{\overset{\cdot}{\overset{\cdot}{O}}}^{-}H
\end{align*}
\]
Formation of Primary Alcohols Using Organometallics

- Reaction of a Grignard with formaldehyde will produce a primary alcohol after protonation.

\[
\begin{align*}
R\text{MgX} & \quad + \quad \begin{array}{c} H \\ \text{C} \quad \text{O} \\ H \\ H \end{array} & \quad \xrightarrow{\text{ether}} & \quad \begin{array}{c} R \\ \text{C} \quad \text{O}^- \quad \text{+MgX} \quad \xrightarrow{\text{H}_3\text{O}^+} & \quad \begin{array}{c} R \\ \text{C} \quad \text{H}_2 \quad \text{OH} \end{array}
\end{align*}
\]

Grignard reagent
formaldehyde
primary alcohol
Synthesis of 2º Alcohols

- Addition of a Grignard reagent to an aldehyde followed by protonation will produce a secondary alcohol.
Synthesis of $3^\circ$ Alcohols

- Tertiary alcohols can be easily obtained by addition of a Grignard to a ketone followed by protonation with dilute acid.
Solved Problem 2

Show how you would synthesize the following alcohol from compounds containing no more than five carbon atoms.

![Chemical structure of the alcohol](image)

Solution

This is a tertiary alcohol; any one of the three alkyl groups might be added in the form of a Grignard reagent. We can propose three combinations of Grignard reagents with ketones:

1. \[
\text{Cyclopentanone} + \text{CH}_3\text{CH}_2\text{MgBr} \quad \xrightarrow{(1) \text{ether solvent}} \quad \xrightarrow{(2) \text{H}_3\text{O}^+} \quad \text{Product}
\]
2. \[
\text{2-Methylcyclopentanone} + \text{CH}_3\text{MgBr} \quad \xrightarrow{(1) \text{ether solvent}} \quad \xrightarrow{(2) \text{H}_3\text{O}^+} \quad \text{Product}
\]
Any of these three syntheses would probably work, but only the third begins with fragments containing no more than five carbon atoms. The other two syntheses would require further steps to generate the ketones from compounds containing no more than five carbon atoms.
Alcohols from Carbonyl Compounds: Grignard Reagents

• Esters react with Grignard reagents to yield tertiary alcohols

\[
\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OCH}_2\text{CH}_3 + 2\text{CH}_3\text{MgBr} \rightarrow \text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} + \text{CH}_3\text{CH}_2\text{OH}
\]

Ethyl pentanoate

2-Methyl-2-hexanol (85%)
(a 3\text{°} alcohol)

• Grignard reagents do not give addition products with carboxylic acids
  – Acidic carboxyl hydrogen reacts with the basic Grignard reagent to yield a hydrocarbon and the magnesium salt of the acid
Mechanism with Esters

The organometallic attacks the carbonyl. The intermediate expels the alkoxide, forming a ketone.

Attack on an ester

The ketone reacts with a second equivalent of organometallic and forms a tertiary alkoxide. Protonation of the alkoxide forms the alcohol.
Limitations of Grignard Reagents

• If other reactive functional groups are present in the same molecule, Grignard reagent cannot be prepared from an organohalide

\[ \text{Br} \quad \text{Molecule} \quad \text{FG} \]

where \( \text{FG} = -\text{OH}, -\text{NH}, -\text{SH}, -\text{CO}_2\text{H} \)

\( \text{FG} = -\text{CH}, -\text{CR}, -\text{CNR}_2 \)

\( -\text{C} = \text{N}, -\text{NO}_2, -\text{SO}_2\text{R} \)

The Grignard reagent is protonated by these groups.

The Grignard reagent adds to these groups.
Worked Example

• Show the products obtained from addition of methylmagnesium bromide to the following compounds
  a) Cyclopentanone
  b) Benzophenone

• Solution:
  a) 
  \[
  \text{Cyclopentanone} \rightarrow \text{Product A}
  \]
  b) 
  \[
  \text{Benzophenone} \rightarrow \text{Product B}
  \]
REACTIONS OF ALCOHOLS
Reactions of Alcohols: Alkyl Halides

• Conversion of alcohols into alkyl halides
  – $3^\circ$ alcohols react with HCl or HBr by $S_N 1$ through carbocation intermediate
Limitations of HX Reactions

- Elimination competes with substitution
- Carbocation intermediate may undergo a rearrangement
- Limited ability to make alkyl halides
Reactions of Alcohols: Alkyl Halides

• Conversion of alcohols into alkyl halides
  – 3° alcohols react with HCl or HBr by $S_{N1}$ through carbocation intermediate
  – 1° and 2° alcohols are converted into halides by treatment with $\text{SOCl}_2$ or $\text{PBr}_3$ via $S_{N2}$ mechanism
Reactions with Phosphorus Halides

- Good yields with 1° and 2° alcohols
- PCl\(_3\) for alkyl chlorides (but SOCl\(_2\) better)
- PBr\(_3\) for alkyl bromides
- P and I\(_2\) for alkyl iodides (PI\(_3\) not stable)
Examples

\[
\begin{align*}
&\text{CH}_3\text{-C-CH}_2\text{OH} + \text{PBr}_3 & \rightarrow & \text{CH}_3\text{-C-CH}_2\text{Br} \\
&\text{neopentyl alcohol} & & \text{neopentyl bromide} (60\%)
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3(\text{CH}_2)_{14}\text{-CH}_2\text{OH} + \text{P/I}_2 & \rightarrow & \text{CH}_3(\text{CH}_2)_{14}\text{-CH}_2\text{I} \\
&(85\%) & & (85\%)
\end{align*}
\]

\[
\begin{align*}
&\text{OH} \quad \text{PBr}_3 & \rightarrow & \text{Br} \\
&\text{(90\%)} & & (90\%)
\end{align*}
\]
Mechanism with PBr₃

**Step 1:** Displacement of bromide ion, forming an excellent leaving group.

\[
\text{Oxygen attacks the phosphorus, displacing one of the halides.}
\]

**Step 2:** S\textsubscript{N}2 attack on the alkyl group.

- Oxygen attacks the phosphorus, displacing one of the halides
- Br\textsuperscript{-} attacks back-side (S\textsubscript{N}2)
Reaction of Alcohols with Thionyl Chloride

\[
\text{R—OH} \quad + \quad \text{Cl—S—Cl} \quad \xrightarrow{\text{heat}} \quad \text{R—Cl} \quad + \quad \text{SO}_2 \quad + \quad \text{HCl}
\]

- Thionyl chloride (SOCl\(_2\)) can be used to convert alcohols into the corresponding alkyl chloride in a simple reaction that produces gaseous HCl and SO\(_2\).
Mechanism of Thionyl Chloride Reaction

\[ \text{thionyl chloride} \rightarrow \text{chlorosulfite ester} + \text{HCl} \]

\[ \text{chlorosulfite ester} \rightarrow \text{ion pair} \rightarrow \text{chlorosulfite ester} \]
Thionyl chloride reacts with alcohols by various mechanisms that depend on the substrate, the solvent, and the temperature. Be cautious in predicting the structure and stereochemistry of a product unless you know the actual mechanism.
When 3-methyl-2-butanol is treated with concentrated HBr, the major product is 2-bromo-2-methylbutane. Propose a mechanism for the formation of this product.

Solution

The alcohol is protonated by the strong acid. This protonated secondary alcohol loses water to form a secondary carbocation.
A hydride shift transforms the secondary carbocation into a more stable tertiary cation. Attack by bromide leads to the observed product.
Conversion of Alcohols into Tosylates

- Reaction of alcohols with $p$-toluenesulfonyl chloride in pyridine yields alkyl tosylates, ROTos
- C–O bond remains intact and configuration at a chirality center is maintained
- Resulting alkyl tosylates react like alkyl halides
Tosylate Esters

Alcohols can be converted to tosylate esters (ROTs) through a condensation with \( p \)-toluenesulfonic acid.

- The tosylate group is an excellent leaving group.

\[
R\text{-}O\overset{\mathcal{S}}{\mathcal{S}}H + HO\overset{\mathcal{S}}{\mathcal{S}}S\overset{\mathcal{S}}{\mathcal{S}}O\overset{\mathcal{S}}{\mathcal{S}}CH_3 \rightleftharpoons R\text{-}O\overset{\mathcal{S}}{\mathcal{S}}SO\overset{\mathcal{S}}{\mathcal{S}}O\overset{\mathcal{S}}{\mathcal{S}}CH_3 + H_2O
\]

\( p \)-toluenesulfonic acid

alkyl tosylate, ROTs

\( p \)-toluenesulfonate ester
Stereochemical Uses of Tosylates

- The $S_N2$ reaction of an alcohol via an alkyl halide proceeds with two inversions, giving a product with the same arrangement as the starting alcohol.
- The $S_N2$ reaction of an alcohol via a tosylate, produces inversion at the chirality center.
Reactions Using Tosylates: Substitution and Elimination

substitution

\[
\begin{align*}
\text{OH} & \quad \xrightarrow{\text{TsCl, pyridine}} \quad \text{OTs} \\
\text{C} & \quad \xrightarrow{\text{(substitution)}} \quad \text{Nuc} \\
\text{C} & \quad \text{Nuc} \\
\end{align*}
\]

or elimination:

\[
\begin{align*}
\text{OTs} & \quad \xrightarrow{\text{(elimination)}} \\
\text{C} & \quad \text{H} \\
\text{B} & \quad \text{C} \quad \text{C} \\
\text{C} & \quad \text{B} \quad \text{H} \\
\end{align*}
\]
**S_N2 Reactions with Tosylates**

- The reaction shows the S_N2 displacement of the tosylate ion (\(-\text{OTs}\)) from (S)-2-butyl tosylate with inversion of configuration.
- The tosylate ion is a particularly stable anion, with its negative charge delocalized over three oxygen atoms.

\[
\begin{align*}
\text{iodide} & \quad \text{(S)-2-butyl tosylate} \quad \text{S_N2} \quad \text{I} & \quad \text{(R)-2-butyl iodide} \quad \text{tosylate ion} \\
\end{align*}
\]

\[
\begin{align*}
-\text{OTs} & = \begin{bmatrix}
\vdots & \vdots & \vdots & \vdots \\
\vdots & \vdots & \vdots & \vdots \\
\vdots & \vdots & \vdots & \vdots \\
\vdots & \vdots & \vdots & \vdots \\
\end{bmatrix} \\
\text{tosylate ion} & \quad \text{resonance-stabilized anion}
\end{align*}
\]

- The reaction shows the S_N2 displacement of the tosylate ion (\(-\text{OTs}\)) from (S)-2-butyl tosylate with inversion of configuration.
- The tosylate ion is a particularly stable anion, with its negative charge delocalized over three oxygen atoms.
Tosylate esters are particularly useful: They are great leaving groups, often better than halides. Grignard reactions build alcohols, which are easily converted to tosylates for substitution or elimination.
Worked Example

• How can following transformation, a step used in the commercial synthesis of (S)-ibuprofen, be carried out?

• Solution:
  – In conditions run under $S_{N2}$, $-\text{OH}$ is a very poor leaving group
Worked Example

• Toluene sulfonate of the alcohol proceeds readily to give the desired product with inversion of configuration at the chirality center.
Dehydration of Alcohols to Yield Alkenes

• Tertiary alcohols are dehydrated using acid-catalyzed reactions
  – Follows Zaitsev’s rule thus yields a more stable alkene as the major product

• Reactivity is the result of the nature of the carbocation intermediate

\[
\begin{align*}
\text{CH}_3 & \quad \text{CH}_3 \\
\text{H}_3\text{C} - \text{C} - \text{CH}_2\text{CH}_3 & \quad \overset{\text{H}_3\text{O}^+, \text{THF}}{\text{\text{\text{\text{\text{25 °C}}}}}} \rightarrow \quad \text{CH}_3 \quad \text{C} = \text{CHCH}_3 & + & \text{CH}_2 \quad \text{C} - \text{CH}_2\text{CH}_3 \\
\text{2-Methyl-2-butanol} & \quad & \text{2-Methyl-2-butene} & & \text{2-Methyl-1-butene} \\
\text{Major product} & & \text{(trisubstituted)} & & \text{(disubstituted)} \\
\end{align*}
\]
Dehydration of Alcohols

- Alcohol dehydration generally takes place through the E1 mechanism
- Rearrangements are possible
- The rate of the reaction follows the same rate as the ease of formation of carbocations: $3^\circ > 2^\circ > 1^\circ$
- Primary alcohols rearrange, so this is not a good reaction for converting $1^\circ$ alcohols into alkenes
Mechanism of Dehydration: E1

Step 1: Protonation

\[
\begin{align*}
\text{H}_2\text{O} &\quad \text{H}^+ \\
\text{C} &\quad \text{C} \\
\end{align*}
\]

\[
\text{C} &\quad \text{C} \\
\text{C} &\quad \text{C} \\
\]

Step 2: Formation of the carbocation

\[
\begin{align*}
\text{H} &\quad \text{H}^+ \\
\text{C} &\quad \text{C} \\
\end{align*}
\]

\[
\text{C} &\quad \text{C} \\
\text{C} &\quad \text{C} \\
\text{O} &\quad \text{H} \\
\]

Step 3: Loss of a proton forms the alkene

\[
\begin{align*}
\text{H}_2\text{O} &\quad \text{H} \\
\text{C} &\quad \text{C} \\
\end{align*}
\]

\[
\text{C} &\quad \text{C} \\
\text{C} &\quad \text{C} \\
\text{H}_3\text{O}^+ &\quad \\
\]

\[
\text{C} &\quad \text{C} \\
\text{C} &\quad \text{C} \\
\text{H}_3\text{O}^+ &\quad \\
\]

Solved Problem 3

Predict the products of sulfuric acid-catalyzed dehydration of 1-methylcyclohexanol

1-Methylcyclohexanol reacts to form a tertiary carbocation. A proton may be abstracted from any one of three carbon atoms. The two secondary atoms are equivalent, and abstraction of a proton from one of these carbons leads to the trisubstituted double bond of the major product. Abstraction of a methyl proton leads to the disubstituted double bond of the minor product.
Dehydration of Alcohols to Yield Alkenes

- Phosphorus oxychloride ($\text{POCl}_3$) is also used in dehydration of alcohols
  - Dehydrates secondary alcohols and tertiary alcohols
  - Works under mild basic conditions
  - Undergoes reaction at low temperatures
  - Undergoes E2 mechanism

\[
\text{CH}_3\begin{array}{c} \text{POCl}_3 \text{Pyridine, 0 °C}\end{array}\text{CH}_3
\]

1-Methylcyclohexanol \quad 1-Methylcyclohexene (96%)
Dehydration with POCl₃

Direct E2 elimination of water does not occur because hydroxide ion is a poor leaving group.

1. The alcohol hydroxyl group reacts with POCl₃ to form a dichlorophosphate intermediate.

2. E2 elimination then occurs by the usual one-step mechanism as the amine base pyridine abstracts a proton from the neighboring carbon at the same time that the dichlorophosphate group is leaving.
Worked Example

• What product(s) are expected from dehydration of the following alcohols with POCl₃ in pyridine?
  – Indicate the major product in each case
  
  a) ![Chemical Structure]
  
  b) ![Chemical Structure]
Worked Example

• Solution:

\[ \text{H} \quad \text{CH}_3 \quad \text{H} \quad \text{OH} \quad \text{H} \quad \text{POCl}_3 \rightarrow \quad \text{CH}_3 \quad \text{C} \quad \text{H}_2 \]

3-Methylcyclohexene

\[ \text{C}_8 \text{H}_{10} \text{O} \rightarrow \text{C}_8 \text{H}_{10} \text{CH}_3 \]

a) In E2 elimination, dehydration proceeds most readily when the two groups to be eliminated have an anti periplanar relationship. In this compound, the only hydrogen with the proper stereochemical relationship to the –OH group is at C6. Thus, the non-Zaitsev product 3-methylcyclohexene is formed.
b) The major product has the more substituted double bond.
Conversion of Alcohols into Esters

- Reaction can be carried out in a single step with the use of a strong acid as catalyst.
Fischer Esterification

- Reaction of an alcohol and a carboxylic acid produces an ester
- Sulfuric acid is a catalyst
- The reaction is an equilibrium between starting materials and products, and for this reason the Fischer esterification is seldom used to prepare esters
Conversion of Alcohols into Esters

- Reaction can be carried out in a single step with the use of a strong acid as catalyst.
- by converting it into a carboxylic acid chloride, which then reacts with the alcohol.

- Increases the reactivity of carboxylic acid.
Reaction of Alcohols with Acyl Chlorides

The esterification reaction achieves better results by reacting the alcohol with an acyl chloride. The reaction is exothermic and produces the corresponding ester in high yields with only HCl as a by-product.
OXIDATION OF ALCOHOLS
Oxidation States

• Inorganic chemistry:
  – Oxidation is a loss of electrons
  – Reduction is a gain of electrons

• Organic chemistry
  – Oxidation: Gain of O, O₂, or X₂; loss of H₂
  – Reduction: Gain of H₂ (or H⁻); loss of O or O₂; and loss of X₂
  – Neither: The gain or loss of H⁺, H₂O, -OH, HX, etc is neither an oxidation nor a reduction
Oxidation of Alcohols

• Alcohols are oxidized to give carbonyl compounds

![Chemical structures showing the oxidation of primary, secondary, and tertiary alcohols to aldehydes, ketones, and no reaction, respectively.]

• Oxidation occurs with reagents, such as KMnO₄, CrO₃, and Na₂Cr₂O₇
Oxidation of Alcohols

• Primary alcohols are oxidized to either aldehydes or carboxylic acids
• To prepare aldehyde from a primary alcohol, I(V)-containing Dess–Martin periodinane in dichloromethane is used
Oxidation of $1^\circ$ Alcohols to Carboxylic Acids

- Chromic acid reagent oxidizes primary alcohols to carboxylic acids
- The oxidizing agent is too strong to stop at the aldehyde
Oxidation of Alcohols

- Secondary alcohols oxidize easily to give ketones.
- Effective with inexpensive reagents such as \( \text{Na}_2\text{Cr}_2\text{O}_7 \) in acetic acid.
- Cr(VI) reagent reacts with the alcohol to give a chromate intermediate followed by expulsion of a reduced Cr(IV) species.
Formation of the Acid Chromate Ion

\[ \text{Na}_2\text{Cr}_2\text{O}_7 + \text{H}_2\text{O} + 2\text{H}_2\text{SO}_4 \rightarrow 2\text{HO-Cr-OH} + 2\text{Na}^+ + 2\text{HSO}_4^- \]

sodium dichromate

\[ \text{CrO}_3 + \text{H}_2\text{O} \xrightarrow{\text{H}_2\text{SO}_4} \text{HO-Cr-OH} \rightleftharpoons \text{H}^+ + \text{O-Cr-OH} \]

chromium trioxide

chromic acid (H₂CrO₄)

chromic acid

acid chromate ion

- \text{CrO}_3 \text{ will also produce chromic acid in the presence of H}_2\text{SO}_4 \text{ and H}_2\text{O}
Oxidation Mechanism

*Formation of the chromate ester*

\[ R'\text{-C-O-H} + H\text{-O-Cr-OH} \rightarrow R'\text{-C-O-Cr-OH} + H_2O \]

*Formation Diagram:*

- Alcohol: \( R'\text{-C-O-H} \)
- Chromic acid: \( H\text{-O-Cr-OH} \)
- Chromate ester: \( R'\text{-C-O-Cr-OH} \)

*Elimination of the chromate ester and oxidation of the carbinol carbon*

\[ R'\text{-C-O-Cr-OH} \rightarrow R'\text{-C=O} + \text{H}_3\text{O}^+ + \text{Cr(OH)} \]

*Elimination Diagram:*

- Chromate ester: \( R'\text{-C-O-Cr-OH} \)
- Carbinol carbon: \( R'\text{-C=O} \)
- Chromic acid: \( \text{H}_3\text{O}^+ \)
- Chromium (VI): \( \text{Cr(OH)} \)

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Worked Example

• What products are expected from oxidation of the following compounds with CrO₃ in aqueous acid?
  – With the Dess–Martin periodinane?
    a) 1-Hexanol
    b) 2-Hexanol

• Solution:

<table>
<thead>
<tr>
<th>Starting material</th>
<th>CrO₃, H₃O⁺ Product</th>
<th>Periodinane Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) CH₃CH₂CH₂CH₂CH₂CH₂OH</td>
<td>CH₃CH₂CH₂CH₂CH₂CO₂H</td>
<td>CH₃CH₂CH₂CH₂CH₂CHO</td>
</tr>
<tr>
<td>(b) CH₃CH₂CH₂CH₂CH₂CHCH₃</td>
<td>CH₃CH₂CH₂CH₂CCH₃</td>
<td>CH₃CH₂CH₂CH₂CCH₃</td>
</tr>
</tbody>
</table>
PROTECTION OF ALCOHOLS
Protection of Alcohols

- Done to overcome incompatibility that might arise by protecting the interfering functional group

- Involves:
  -Introduction of a protecting group to block interfering function
  -Execution of the desired reaction
  -Removal of the protecting group

Acidic hydrogen

\[
\text{HO—CH}_2\text{CH}_2\text{CH}_2\text{—Br} \xrightarrow{\text{Mg, Ether}} \text{HO—CH}_2\text{CH}_2\text{CH}_2\text{—MgBr} \quad \text{Not formed}
\]
Protection of Alcohols

- Reaction of an alcohol with chlorotrimethylsilane in the presence of base yields an unreactive trialkylsilyl ether.

An alcohol + Chlorotrimethylsilane → A trimethylsilyl (TMS) ether + (CH₃CH₂)₃NH⁺Cl⁻

For example:

Cyclohexanol + (CH₃)₃SiCl → Cyclohexyltrimethylsilyl ether (94%)
TMS-Protected Alcohol During a Grignard Reaction

- Procedure for adding a protecting group and removing it from an alcohol

**Step 1**  Protect alcohol:

\[ \text{HOCH}_2\text{CH}_2\text{CH}_2\text{Br} + (\text{CH}_3)_3\text{SiCl} \xrightarrow{(\text{CH}_3\text{CH}_2)_3\text{N}} (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{Br} \]

**Step 2a**  Form Grignard reagent:

\[ (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{Br} \xrightarrow{\text{Mg, Ether}} (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{MgBr} \]

**Step 2b**  Do Grignard reaction:

\[ (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{MgBr} \xrightarrow{\text{1. CH}_3\text{CH, 2. H}_3\text{O}^+} (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3 \]

**Step 3**  Remove protecting group:

\[ (\text{CH}_3)_3\text{SiOCH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3 \xrightarrow{\text{H}_3\text{O}^+} \text{HOCH}_2\text{CH}_2\text{CH}_2\text{CHCH}_3 + (\text{CH}_3)_3\text{SiOH} \]
Worked Example

• Trimethylsilyl (TMS) ethers can be removed by treatment with fluoride ion as well as by acid catalyzed hydrolysis
  – Propose a mechanism for the reaction of cyclohexyl TMS ether with LiF
  – Fluorotrimethylsilane is a product

• Solution:

  – Reaction is \( S_{N2} \) reaction
    • Nucleophile displaces an alkoxide ion
PHENOLS AND THEIR USES
Phenols and Their Uses

- Phenols are synthesized using isopropylbenzene, commonly called cumene
  - Process yields two valuable chemicals at the same time
Synthesis of Phenol

1. Protonation of the hydroperoxy group on the terminal oxygen atom gives an oxonium ion...

2. ... which undergoes rearrangement by migration of the phenyl ring from carbon to oxygen, expelling water as the leaving group and giving a carbocation.

3. Nucleophilic addition of water to the carbocation yields another oxonium ion...
Synthesis of Phenol

4. . . which rearranges by a proton shift from one oxygen to another.

5. Elimination of phenol gives acetone as co-product and regenerates the acid catalyst.
Worked Example

• Show the mechanism for the reaction of $p$-methylphenol with 2-methylpropene and $\text{H}_3\text{PO}_4$ catalyst to yield the food additive BHT

• Solution:

  $\text{CH}_3\text{C}≡\text{CH}_2 \quad \text{H} \text{−} \text{OPO}_3\text{H}_2 \quad \leftrightarrow \quad (\text{CH}_3)_3\text{C}+ \quad + \quad \text{−OPO}_3\text{H}_2$

  – Phosphoric acid protonates 2-methylpropene, forming a tert-butyl carbocation
Worked Example

– Alkylation occurs ortho to the –OH group for both steric and electronic reasons

– Second tert-butyl carbocation alkylation forms BHT
REACTIONS OF PHENOLS
Reactions of Phenols

• Electrophilic aromatic substitution reactions
  – Hydroxyl group is a strongly activating substituent in electrophilic aromatic substitution reactions
  – Makes phenols substrates for:
    • Electrophilic halogenation
    • Nitration
    • Sulfonation
    • Friedel-Crafts reactions
Reactions of Phenols

• Oxidation of phenols
  – Oxidation of a phenol yields a 2,5-cyclohexadiene-1,4-dione, or quinone
  – Fremy's salt \([(KSO_3)_2NO]\) is used in more complex cases
Reactions of Phenols

- Quinones can be easily reduced to hydroquinones by reagents such as NaBH$_4$ and SnCl$_2$.
SPECTROSCOPY OF ALCOHOLS AND PHENOLS
Spectroscopy of Alcohols and Phenols

- Infrared spectroscopy
  - Alcohols have a strong C–O stretching absorption near 1050 cm⁻¹
  - Characteristic O–H stretching absorption occurs at 3300 to 3600 cm⁻¹
  - Exact position of the O–H stretch depends on the extent of hydrogen-bonding in the molecule

IR spectrum of Cyclohexanol
Worked Example

• Assume that you need to prepare 5-cholesten-3-one from cholesterol
  – How could IR spectroscopy be used to tell whether the reaction was successful?
  – What differences would you look for in the IR spectra of starting material and product?

![Chemical Structures](image-url)
Worked Example

- **Solution:**
  - Infrared spectra of cholesterol and 5-cholestene-3-one exhibit a unique absorption.
  - Cholesterol shows an $-\text{OH}$ stretch at $3300$–$3600\text{cm}^{-1}$.
  - 5-cholestene-3-one shows a $\text{C}=\text{O}$ stretch at $1715\text{ cm}^{-1}$.
  - In the oxidation of cholesterol to 5-cholestene-3-one, the $-\text{OH}$ band disappears and is replaced by a $\text{C}=\text{O}$ band.
  - No $-\text{OH}$ absorption should be visible on complete oxidation.
Spectroscopy of Alcohols and Phenols

• Nuclear magnetic resonance spectroscopy
  – Alcohol carbon absorptions fall in the range 50-80°
Spectroscopy of Alcohols and Phenols

• Nuclear magnetic resonance spectroscopy
  – Alcohol carbon absorptions fall in the range 50-80δ
  – Alcohols also show characteristic absorptions in the $^1\text{H}$ NMR spectrum
    • Electron-withdrawing effect of the nearby oxygen absorbs at the range of 3.4 to 4.5 δ
  – Spin-spin splitting is not often observed between O–H proton and neighboring protons on C
    • The O–H proton is rapidly exchanged for deuterium and the hydroxyl absorption disappears from the spectrum, on adding $\text{D}_2\text{O}$ to an NMR
Worked Example

• When the $^1$H NMR spectrum of an alcohol is run in dimethyl sulfoxide solvent rather than in chloroform, exchange of the O–H proton is slow and spin–spin splitting is seen between the O–H proton and C–H protons on the adjacent carbon. What spin multiplicities are expected for the hydroxyl protons in the following alcohols?
  a) 2-Methyl-2-propanol
  b) Cyclohexanol
Worked Example

• Solution:
  – Under conditions of slow exchange, the –OH signal of a tertiary alcohol (R₃COH) is unsplit
    • The signal of a secondary alcohol (R₂CHOH) is split into a doublet
    • The signal of a primary alcohol (RCH₂OH) is split into a triplet
  – a) 2-Methyl-2-propanol is a tertiary alcohol; its –OH signal is unsplit
  – b) Cyclohexanol is a secondary alcohol; its –OH absorption is a doublet
Spectroscopy of Alcohols and Phenols

• Mass spectrometry
  – Alcohols undergo alpha cleavage, a C–C bond nearest the hydroxyl group is broken, yielding a neutral radical plus a charged oxygen-containing fragment

\[
\begin{align*}
\text{RCH}_2\text{C}^{+}\text{OH}^+ & \xrightarrow{\text{Alpha cleavage}} \text{RCH}_2^+ + \text{C}^{+} \leftrightarrow \text{C}^{+} \\
\end{align*}
\]

  – Radical cation alcohols undergo dehydration to yield an alkene radical anion

\[
\begin{align*}
\text{H} \text{C}^{+} \text{OH}^+ & \xrightarrow{\text{Dehydration}} \text{H}_2\text{O} + \text{C}^{+} \\
\end{align*}
\]
Mass spectrum of 1-butanol ($M^1 = 74$)

**Alpha cleavage**

$[\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}]^+ + \text{CH}_2\text{OH}]^+$

$m/z = 31$

**Dehydration**

$[\text{CH}_3\text{CH}_2\text{CH}==\text{CH}_2]^+ + \text{H}_2\text{O}$

$m/z = 56$

Relative abundance (%) vs. $m/z$
Summary

• Alcohols are among the most versatile of all organic compounds, occur widely in nature, and are important industrially

• Functional groups are protected because Grignard reagents can’t be prepared from alkyl halides that contain reactive functional groups in the same molecule

• Phenols are aromatic counterparts of alcohols but are more acidic

• Phenols can be oxidized to quinones, and quinones can be reduced back to hydroquinones