Chapter 10: Structure and Synthesis of Alcohols
Physical Properties

Alcohols can be:

- **Primary alcohol**
  \[
  \text{CH}_3\text{—CH—CH}_2\text{OH}
  \]

- **Secondary alcohol**
  \[
  \text{CH}_3\text{—CH—CH}_2\text{CH}_3
  \]

- **Tertiary alcohol**
  \[
  \text{CH}_3\text{—C—OH}
  \]
• Most alcohols (C₁-C₁₂) are liquids at room temperature
• Bp much higher than alkanes of similar molecular weights (H-bonding)
**Acidity:** the H of the hydroxyl group is weakly acidic:

<table>
<thead>
<tr>
<th>Alcohol</th>
<th>Structure</th>
<th>$K_a$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>methanol</td>
<td>CH$_3$—OH</td>
<td>$3.2 \times 10^{-16}$</td>
<td>15.5</td>
</tr>
<tr>
<td>ethanol</td>
<td>CH$_3$CH$_2$—OH</td>
<td>$1.3 \times 10^{-16}$</td>
<td>15.9</td>
</tr>
<tr>
<td>2-chloroethanol</td>
<td>Cl—CH$_2$CH$_2$—OH</td>
<td>$5.0 \times 10^{-15}$</td>
<td>14.3</td>
</tr>
<tr>
<td>2,2,2-trichloroethanol</td>
<td>Cl$_3$C—CH$_2$—OH</td>
<td>$6.3 \times 10^{-13}$</td>
<td>12.2</td>
</tr>
<tr>
<td>isopropyl alcohol</td>
<td>(CH$_3$)$_2$CH—OH</td>
<td>$3.2 \times 10^{-17}$</td>
<td>16.5</td>
</tr>
<tr>
<td>tert-butyl alcohol</td>
<td>(CH$_3$)$_3$C—OH</td>
<td>$1.0 \times 10^{-18}$</td>
<td>18.0</td>
</tr>
<tr>
<td>cyclohexanol</td>
<td>C$<em>6$H$</em>{11}$—OH</td>
<td>$1.0 \times 10^{-18}$</td>
<td>18.0</td>
</tr>
<tr>
<td>phenol</td>
<td>C$_6$H$_5$—OH</td>
<td>$1.0 \times 10^{-10}$</td>
<td>10.0</td>
</tr>
</tbody>
</table>

**Comparison with Other Acids**

<table>
<thead>
<tr>
<th>Acid</th>
<th>Structure</th>
<th>$K_a$</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>water</td>
<td>H$_2$O</td>
<td>$1.8 \times 10^{-16}$</td>
<td>15.7</td>
</tr>
<tr>
<td>acetic acid</td>
<td>CH$_3$COOH</td>
<td>$1.6 \times 10^{-5}$</td>
<td>4.8</td>
</tr>
<tr>
<td>hydrochloric acid</td>
<td>HCl</td>
<td>$1 \times 10^{+7}$</td>
<td>−7</td>
</tr>
</tbody>
</table>
This hydroxyl proton can be removed with suitable bases. Bases such as KOH or NaOH are not strong enough. NaH, KH or Na\(\text{(s)}\), K\(\text{(s)}\) are usually used.

\[
\text{R–O–H} + \text{Na} \rightarrow \text{R–O}^- + \text{Na} + \frac{1}{2} \text{H}_2 \uparrow
\]

**Example**

<table>
<thead>
<tr>
<th>CH(_3)CH(_2)OH</th>
<th>Na</th>
</tr>
</thead>
<tbody>
<tr>
<td>ethanol</td>
<td>sodium metal</td>
</tr>
</tbody>
</table>

\[\text{CH}_3\text{CH}_2\text{O}^- + \text{Na} \rightarrow \text{CH}_3\text{CH}_2\text{O}^- + \text{Na} + \frac{1}{2} \text{H}_2 \uparrow\]

sodium ethoxide hydrogen gas

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In the case of phenols, the pKa of the hydroxyl group is around 10 and weaker bases can be used (NaOH, KOH, etc...)

\[
\text{phenol, } pK_a = 10.0 \quad + \quad \text{Na}^+ \text{OH}^{-} \quad \leftrightarrow \quad \text{sodium phenoxide} \quad pK_a = 15.7
\]
Synthesis of Alcohols (Review)

- **Hydration**

(a) Direct (8.4)
Mechanism of Direct Hydration of Alkenes

*Step 1:* Protonation of the double bond forms a carbocation.

\[
\text{C} = \text{C} + \text{H}^+ \text{O}^- \text{H} \leftrightarrow \text{C} = \text{C}^+ + \text{H}_2\text{O}^-
\]

*Step 2:* Nucleophilic attack by water.

\[
\text{H} \quad \text{C} = \text{C}^+ + \text{H}_2\text{O}^- \leftrightarrow \text{H} : \text{O}^- \text{H}
\]

*Step 3:* Deprotonation to the alcohol.

\[
\text{H} : \text{O}^- \text{H} \quad \text{C} = \text{C} + \text{H}_2\text{O}^- \leftrightarrow \text{H} : \text{O}^- \text{H} \quad \text{C} = \text{C} + \text{H}_3\text{O}^+
\]
(b) Indirect (4.8)

(1) Oxymercuration/Demercuration (8.5)

Oxymercuration–Demercuration

\[ \text{C} = \text{C} + \text{Hg(OAc)}_2 + \text{H}_2\text{O} \rightarrow \text{C} = \text{C} + \text{HgOAc} + \text{NaBH}_4 \rightarrow \text{C} = \text{C} \]

(Markovnikov orientation)

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(2) Hydroboration/Oxidation (8.7)

Hydroboration–oxidation:

\[ \text{C} = \text{C} + \text{BH}_3 \cdot \text{THF} \rightarrow \text{C} = \text{C} + \text{H}_2\text{O}_2, \cdot \text{OH} \rightarrow \text{C} = \text{C} \]

anti-Markovnikov orientation (syn stereochemistry)

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- **Hydroxylation** (8.14)

 cis diols are produced since the reaction is syn
New Synthesis of Alcohols
(Nu attack on carbonyl compounds)

An excellent method to make alcohols. Depending on the type of carbonyl used, primary, secondary and tertiary alcohols are all available from this reaction.
2 types of reagents can deliver nucleophilic carbons to C=O:

- **Grignard reagent:** $R$-$\text{Mg}$-$X$
- **Alkyl Lithium:** $R$-$\text{Li}$

\[ \text{δ−} \quad \text{δ+} \quad \begin{array}{c} \text{R} \quad \text{MgX} \\ \text{δ−} \quad \text{δ+} \end{array} \quad \begin{array}{c} \text{R} \quad \text{Li} \\ \end{array} \]
**Synthesis of Grignard Reagents**

\[
R - X + Mg \quad \xrightarrow{\text{ether}} \quad \delta^- \quad \delta^-
\]

\[
R - Mg - X \quad \text{(organomagnesium halide)}
\]

Reacting like \( R^- \cdot MgX \)

---

\[
\text{Br} \quad \xrightarrow{\text{ether}} \quad \text{MgBr}
\]

\[
\text{Cl}\quad \text{CH}_3\text{CHCH}_2\text{CH}_3 + \text{Mg} \quad \xrightarrow{\text{ether}} \quad \text{MgCl} \quad \text{CH}_3\text{CHCH}_2\text{CH}_3
\]

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• **Alkyl Lithium** can be prepared in a similar way:

\[
\text{Br} \quad 2 \text{Li(s)} \quad \text{Li} \quad + \quad \text{Br} \\
\text{Cl} \quad 2 \text{Li(s)} \quad \text{Li} \quad + \quad \text{Cl}
\]

- reacts like \( \text{Ph}^- \)
- reacts like \( \text{CH}^+_2 \)
**Synthesis of 1° Alcohols (10.9)**

Grignards or alkyl lithium react with formaldehyde to produce primary alcohols. The carbon chain increases by one carbon from the original organometallic reagent.

\[
\text{Grignard reagent} + \text{formaldehyde} \rightarrow \text{primary alcohol}
\]

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**Synthesis of 2° Alcohols** (10.9)

Other aldehydes react to give secondary alcohols with either Grignard reagents or alkyl lithiums to produce secondary alcohols.
**Synthesis of 3° Alcohols (10.9)**

reaction of ketones with RLi or RMgX will produce tertiary alcohols
3° Alcohols by Acyl Substitution

(10.9)

Acid chlorides and esters react with either Grignard reagents or alkyl lithuims via the acyl substitution mechanism. Since the resulting product is a ketone, the reaction will continue and eventually produce the corresponding tertiary alcohol.
Mechanism of Acyl Substitution

In the presence of a Grignard or alkyl lithium the reaction will first produce a ketone which will continue to react to produce the corresponding 3° alcohol.

**Attack on an acid chloride**

\[
\begin{align*}
\text{R-MgX} & \quad \text{R'} & \quad \text{C=O}^+ \\
\text{Cl} & \quad & \quad \text{intermediate} \\
\text{acid chloride} & \quad & \quad \text{ketone} \\
\end{align*}
\]

**Attack on an ester**

\[
\begin{align*}
\text{R-MgX} & \quad \text{R'} & \quad \text{C=O}^+ \\
\text{R''-O}^+ & \quad & \quad \text{intermediate} \\
\text{ester} & \quad & \quad \text{ketone} \\
\end{align*}
\]

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Here is an example of this reaction using two equivalent of grignard reagent with an ester.
I^o Alcohols With 2 Extra Carbons on the Alkyl Chain. (10.9)

These compounds are generated by the reaction of RLi or RMgX with epoxides.
- Epoxides are electrophilic due to the ring strain.
- 2 extra carbons will be added to the alkyl chain.

Example
Limitations of Grignard Reagents

- **Grignards are good nucleophiles but in the presence of acidic protons it will acts as a strong base.**
  - **No** water or other acidic protons like O—H, N—H, S—H, or terminal alkynes.
- **No other electrophilic multiple bonds, like C≡N, C≡N, S=O, or N=O.**
Practice Question

What is the major organic product of the following reactions. Disregard stereoisomers.

1) CH₃MgBr
2) H₃O⁺

1) CH₃MgBr
2) H₃O⁺
3-Methyl-3-hexanol can be prepared from the reaction of 2-pentanone and ethylmagnesium bromide as shown below. What other combination or grignards and ketones can be used to prepare this compound?
Reduction of Carbonyl Compounds (10.11)

- Reduction of the carbonyl group also produces alcohol by nucleophilic attack to the carbon of the carbonyl. In this case the nucleophile is the hydride ion. Protonation of the resulting alkoxide ion gives the alcohol.

![Chemical structures showing the reduction of a carbonyl group to an alcohol](image)
2 common reagents to carry out this transformation are:

**LiAlH$_4$**: lithium aluminum hydride

**NaBH$_4$**: sodium borohydride

\[ \text{Na}^+ \overset{\text{H}}{\begin{array}{c} \text{H} \\ \text{B} \\ \text{H} \end{array}} \text{Li}^+ \overset{\text{H}}{\begin{array}{c} \text{H} \\ \text{Al} \\ \text{H} \end{array}} \]

sodium borohydride  

lithium aluminum hydride

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NaBH₄ is selective only for ketones, aldehydes and acid chlorides. LiAlH₄ will reduce all carbonyl compounds.
This selectivity can be used in synthesis to control which functional group reacts.
Mechanism of Hydride Reduction of Carbonyls
(Ketones and Aldehydes)
Mechanism of Acid Chloride/Ester Reduction

- In the case of esters and acid chlorides, two equivalents of the hydride are transferred since the first product is a ketone. 1° alcohols are produced.
Catalytic Hydrogenation (10.11)

- Similar to the hydrogenation of alkene seen in CHEM201, addition of $\text{H}_2$ to the carbonyl of ketones and aldehydes is possible resulting in the formation of alcohols.

\[
\begin{align*}
\text{O} & \quad \text{C} \quad + \quad \text{H}_2 \quad \xrightarrow{\text{Raney Ni}} \quad \text{OH} \\
\text{CH} & 
\end{align*}
\]
This reaction is also complementary to the reduction using metal hydrides as it allow for other reduction to take place.
Practice Questions

- Complete the following reactions.

\[
\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{O} \quad 1) \text{LiAlH}_4 \\
\quad \quad \quad 2) \text{H}_3\text{O}^+ 
\]

\[
\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOCH}_3 \quad \text{NaBH}_4 \quad \text{MeOH} 
\]

\[
\text{CH}_2=\text{CH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH} \quad 1) \text{LiAlH}_4 \\
\quad \quad \quad 2) \text{H}_3\text{O}^+ 
\]