Hydroxyl groups in natural compounds.

Alcohols

- Naturally occurring phenols: a hydroxyl group directly attached to an aromatic ring.

Phenols

- The –OH of an alcohol has a profound effect on physical properties.
- Compare the boiling points below.

Physical Properties of Alcohols

- The hydrogen (H-) in hydroxyl groups intermolecularly attracts water molecules.
- Alcohols with small carbon chains are miscible in water (they mix in any ratio).
- Alcohols with large carbon chains do not readily mix with water.

Physical Properties of Alcohols

- Molecules with large hydrophobic groups are generally insoluble in water.
- Alcohols with three or less carbons are generally water miscible.
- Alcohols with more than three carbons are not miscible, and their solubility decreases as the size of the hydrophobic group increases.
- Partition Coefficient: relative solubility of a compound (ratio) in octanol vs. water (Drug absorption & transport)
Stress? memory? cognition? …cheating?

Propranolol: orally administered anti-hypertensive β-blocker: blocks the action of epinephrine and norepinephrine on both β₁- and β₂-adrenergic receptors

"Basic sciences in the history of cardiovascular pharmacology"
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC325477/

Acidity of Alcohols and Phenols

<table>
<thead>
<tr>
<th>Increasing acidity</th>
<th>R = H</th>
<th>R = -NH₂</th>
<th>R = -OH</th>
<th>R = -X</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKa between 45 and 50</td>
<td>pKa between 35 and 40</td>
<td>pKa between 15 and 18</td>
<td>pKa between -10 and 3</td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>Cyclohexanol (pKa = 18)</td>
<td>Phenol (pKa = 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pKa = 15.7</td>
<td></td>
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</tbody>
</table>

Preparation of Alcohols

- What reagents did we use to accomplish this transformation?

R-X \rightarrow R-CH₂OH

- Substitution can occur by S_n1 or S_n2.

Primary:

ClCH₂CH₂OH + NaOH \rightarrow \text{S_n2} \rightarrow \text{ClCH₂CH₂OH + NaCl}

Tertiary:

ClCH₂CH₂CH₃ + H₂O \rightarrow \text{S_n1} \rightarrow \text{ClCH₂CH₂CH₃ + HCl}

Preparation of Alcohols

- Aniso-Catalyst hydrogenation (Section 3.6)
- Oxidation-reduction-demetalation (Section 3.3)
- Hydroboration-oxidation (Section 3.4)

Reactions:

- Catalytic Reduction
- Hydration of alkenes
- Hydroboration-oxidation of alkenes
- Hydrolysis of alkyl halides
- New Syntheses using Grignard reagents
- Organolithium reagents
Diols by hydroxylation of alkenes

New methods or reagents:
- Reduction of aldehydes and ketones
- Reduction of carboxylic acids
- Reduction of esters
- Reaction of Grignard reagents with epoxides

Question

Which compound is produced when cyclohexene reacts with OsO₄, (CH₃)₃COOH, tert-butyl alcohol, HO?

- A) CH₃CH=CHCH₂CH₂OH
- B) CH₃CH=CHCH₂CH₂CH₂O
- C) CH₃CH=CHCH₂CH₂CH₂CH₂
- D) CH₃CH=CHCH₂CH₂CH₂CH₂

Example: Catalytic Hydrogenation

\[
\text{CH}_3O-\text{CH} + \text{H}_2 \xrightarrow{\text{Pt, ethanol}} \text{CH}_3O-\text{CH}_2\text{OH}
\]

(92%)
Question

- Which isomer of \( \text{C}_4\text{H}_{10}\text{O} \) can be prepared by hydrogenation of a ketone?

  - A)
  - B)
  - C)
  - D)

Mechanism

Nucleophilic attack

Proton transfer

The resulting alcohol is then protonated to form an alcohol.

Metal Hydride Reducing Agents

Sodium borohydride (NaBH₄)
Lithium aluminum hydride (LiAlH₄)

Act as hydride donors (H⁻)
The analogous deuterated agents NaBD₄ and LiAlD₄ produce (D⁻) and work in the same way.

Example: Catalytic Hydrogenation

\[
\text{C}=\text{O} + \text{H}_2 \xrightarrow{\text{Pt}} \text{C}-\text{OH}\]

(93-95%)
Questions:

1. Reduction of acetaldehyde (CH$_3$CH=O) with NaBD$_4$ in H$_2$O produces:
   - A) ['Chemical Structure Image A']
   - B) ['Chemical Structure Image B']
   - C) ['Chemical Structure Image C']
   - D) ['Chemical Structure Image D']

2. Which one of the isomeric alcohols of formula C$_5$H$_{12}$O can be prepared by LiAlH$_4$ reduction of a ketone?
   - A) 1-pentanol
   - B) 2-methyl-2-butanol
   - C) 3-methyl-2-butanol
   - D) 2,2-dimethyl-1-propanol

Examples:

**Sodium Borohydride**

- Aldehyde
  - Reaction with NaBH$_4$ in methanol produces alcohols (82%)

- Ketone
  - Reaction with NaBH$_4$ in ethanol produces alcohols (84%)

**Lithium Aluminum Hydride**

- More reactive than sodium borohydride.
- Cannot use protic solvents: water, ethanol, methanol, etc.
- Diethyl ether is most commonly used solvent.

**Examples:**

- Aldehyde
  - Reaction with LiAlH$_4$ in diethyl ether followed by water produces alcohols (86%)

- Ketone
  - Reaction with LiAlH$_4$ in diethyl ether followed by water produces alcohols (84%)

**Questions:**

- Which one of the isomeric alcohols of formula C$_5$H$_{12}$O can be prepared by LiAlH$_4$ reduction of a ketone?
  - A) 1-pentanol
  - B) 2-methyl-2-butanol
  - C) 3-methyl-2-butanol
  - D) 2,2-dimethyl-1-propanol

**Selectivity**

- Neither NaBH$_4$ or LiAlH$_4$ reduces carbon-carbon double bonds.
  - 1. LiAlH$_4$ in diethyl ether
  - 2. H$_2$O
  - (90%)
Preparation of Alcohols By Reduction of Carboxylic Acids and Esters

\[
\text{Reduction of Carboxylic Acids:}
\begin{align*}
\text{Gives Primary Alcohols} \\
\begin{array}{c}
\text{R} \\
\text{C}=\text{O} \\
\text{R} \\
\text{HO} \\
\text{H} \\
\text{H} \\
\text{CH}_{2}\text{OH}
\end{array}
\end{align*}
\]

lithium aluminum hydride is only effective reducing agent; not sodium borohydride

**Example: Reduction of a Carboxylic Acid**

\[
\begin{align*}
\text{COH} & \rightarrow \text{CH}_2\text{OH} \\
1. \text{LiAlH}_4 & \text{diethyl ether} \rightarrow \text{CH}_2\text{OH} \\
2. \text{H}_2\text{O} &
\end{align*}
\]

(78%)

**Mechanism**

- To reduce an ester, two hydride equivalents are needed.

**Example: Reduction of an Ester**

\[
\begin{align*}
\text{COCH}_2\text{CH}_3 & \rightarrow \text{CH}_3\text{OH} + \text{CH}_3\text{CH}_2\text{OH} \\
1. \text{LiAlH}_4 & \text{diethyl ether} \rightarrow \text{CH}_3\text{OH} + \text{CH}_3\text{CH}_2\text{OH} \\
2. \text{H}_2\text{O} &
\end{align*}
\]

(90%)

Reduction of Esters: Gives Primary Alcohols

Lithium aluminum hydride is overwhelmingly preferred for reductions of esters.
Sodium borohydride reduction is too slow.
Catalytic hydrogenation is used in industry, but requires a special catalyst, high temperature, and high pressure.
Question

• Which of the esters shown, after reduction with LiAlH₄ and aqueous workup, will yield two molecules of only a single alcohol?
  • A) CH₃CH₂CO₂CH₂CH₃
  • B) C₆H₅CO₂CH₂C₆H₅
  • C) C₆H₅CO₂C₆H₅
  • D) none of these

Answer: D.

Reduction with sodium borohydride reduces only the ketone, not the acid. For more examples of this type of problem, SEE: Skillbuilder 13.4.

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Question

• Select the best combination of reagents to prepare 2-phenylethanol from bromobenzene.
  • A) 1. Mg, diethyl ether; 2. ethylene oxide; 3. H₃O⁺
  • B) 1. Mg, diethyl ether; 2. acetaldehyde (CH₃CH=O); 3. H₃O⁺
  • C) 1. Mg, diethyl ether; 2. 2-chloroethanol; 3. H₃O⁺
  • D) 1. Mg, diethyl ether; 2. CH₃CH₂OCH₂CH₃; 3. H₃O⁺
Preparation of Diols:
Reduction of dicarbonyl compounds

Preparation of Diols

- If two carbonyl groups are present, and enough moles of reducing agent are added, both can be reduced.

\[ \text{H}_2 / \text{Pd} \]
1) LAH
2) H_2O
\[ \text{NaBH}_4 \]
\[ \text{MeOH} \]

Example: Reduction of a Diacetaldehyde

\[
\begin{align*}
\text{HCCH}_2\text{CHCH}_2\text{CH}_3 & \rightarrow \text{H}_2 (100 \text{ atm}) \text{ Ni, 125°C} \\
\text{HOCH}_2\text{CH}_2\text{CHCH}_2\text{CH}_2\text{OH} & \text{3-Methyl-1,5-pentanediol (81-83\%)}
\end{align*}
\]

Question

Which of the following reactions produce alcohols?

- A.
- B.
- C.
- D.
- E.

A. a, b
B. a, b, c
C. a, b, c, d
D. a, b, c, e
E. a, b, c, d, e