Alcohols

Alcohol – any organic compound containing a hydroxyl (R-OH) group

Uses: synthetic intermediate, cleanser, cosmetics, fuel, alcoholic beverages, etc.

Alcohols are an extremely important organic source
Nomenclature

For an alcohol the longest continuous chain containing the hydroxy group determines the root name and then an –ol is used as the suffix

\[
\text{CH}_3\text{CH}_2\text{OH} \quad \text{Ethanol}
\]

In numbering the chain, the hydroxy group takes priority to find the lowest number

\[
\text{CH}_3\text{CHOHCH}_2\text{CH}_3 \quad 2\text{-Butanol}
\]
Priority in Numbering

Of substituents learned so far, alcohol has the highest priority

![OH](image)

4-bromo-2-cyclohexen-1-ol

Alkenes have higher priority than halides or alkyl substituents

![Br](image)

3-bromocyclohexene

With only halides or alkyl substituents, the lowest number goes to the first substituent

![Br](image)

1-bromocyclohexane

(1 is not required)
All other nomenclature is identical to that previously learned

There are common names, however, with an aromatic ring

Benzene
(also called a phenyl group)

Phenol
(takes phenyl root with –ol suffix)
Physical Properties

There are two physical properties of alcohols that account for their behavior: molecular dipole and hydrogen bonding ability.

Dipole
The electronegative oxygen causes the molecule to have a dipole moment.

\[
\text{ethanol} \quad \quad \mu = 1.69 \text{D}
\]

This high dipole-dipole interaction causes alcohols to have a higher affinity for states where the dipoles can be aligned (therefore boiling point is higher).
Dipole-dipole interactions, however, are much weaker than hydrogen bonding interactions.

A hydrogen bond is an interaction between a weakly acidic hydrogen and a lone pair of electrons on a different atom.

Each hydrogen bond has an energy of ~4-5 Kcal/mol.

This is much smaller than a covalent bond (O-H ~ 104 Kcal/mol) but a compound can have multiple hydrogen bonds that need to be broken to “escape” the liquid phase (i.e. causes a higher boiling point).
Due to this hydrogen bonding ability of alcohols they are both hydrophilic and hydrophobic

Hydrophilic – “water loving”
Hydrophobic – “water hating”

Due to this property alcohols have a high water miscibility until the carbon chain becomes larger
Methanol versus Ethanol Biochemically

Ethanol (which is known to lower inhibitions and cause a lightheadedness) is oxidized biochemically to acetaldehyde

\[
\text{O} - \text{H} \quad \xrightarrow{\text{alcohol dehydrogenase}} \quad \text{O} - \text{H} \quad \xrightarrow{\text{aldehyde dehydrogenase}} \quad \text{O} - \text{H}
\]

The physiological side effects of consuming ethanol are due to the buildup of acetaldehyde (causes nausea, dizziness, seating, headaches, lower blood pressure)

The acetaldehyde is then oxidized biochemically to acetic acid

Some people have a nonfunctioning aldehyde dehydrogenase enzyme - these people experience the side effects of acetaldehyde with low ethanol consumption
Methanol also gets oxidized by the same enzyme

\[
\text{alcohol dehydrogenase} \quad \overset{\text{O}}{\text{C}}\overset{\text{H}}{\text{H}} \quad \overset{\text{O}}{\text{C}}\overset{\text{H}}{\text{H}}
\]

But due to one less carbon, this oxidation creates formaldehyde not acetaldehyde

Formaldehyde is toxic to the body because it disrupts other essential enzymes form working properly

Ethanol is consumed ~25 times faster than methanol by this enzyme
Acidity of Alcohols

The alcohol O-H bond is weakly acidic

We have already seen the use of alkoxides in substitution reactions

\[
\text{CH}_3\text{ONa} \quad \text{sodium methoxide}
\]

The alkoxides can be generated by reaction of an alcohol with sodium hydride

\[
\text{CH}_3\text{OH} \quad \text{NaH} \quad \rightarrow \quad \text{CH}_3\text{ONa} \quad \text{H}_2
\]
The acidity of an alcohol changes depending upon substitution

Extending the alkyl chain raises the $pK_a$

<table>
<thead>
<tr>
<th></th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{OH}$</td>
<td>15.5</td>
</tr>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{OH}$</td>
<td>15.9</td>
</tr>
</tbody>
</table>

Also increasing the branching increases the $pK_a$

<table>
<thead>
<tr>
<th></th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$(\text{CH}_3)_2\text{CHOH}$</td>
<td>17.1</td>
</tr>
<tr>
<td>$(\text{CH}_3)_3\text{COH}$</td>
<td>18.0</td>
</tr>
</tbody>
</table>

Both effects due to electron donating ability of methyl groups (inductive effect)
Placing an electron withdrawing group on alcohol will lower the $pK_a$

<table>
<thead>
<tr>
<th>Structure</th>
<th>$pK_a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{CH}_3\text{CH}_2\text{OH}$</td>
<td>15.9</td>
</tr>
<tr>
<td>$\text{ClCH}_2\text{CH}_2\text{OH}$</td>
<td>14.3</td>
</tr>
<tr>
<td>$\text{CF}_3\text{CH}_2\text{OH}$</td>
<td>12.4</td>
</tr>
<tr>
<td>$\text{CF}_3\text{CH}_2\text{CH}_2\text{OH}$</td>
<td>14.6</td>
</tr>
<tr>
<td>$\text{CF}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{OH}$</td>
<td>15.4</td>
</tr>
</tbody>
</table>

Also an inductive effect, the electronegative atom will inductively pull electron density away from alkoxide in the deprotonated form:

$$X\text{CH}_2\text{CH}_2\text{OH} \xrightarrow{\text{base}} X\text{CH}_2\text{CH}_2\text{O}^-$$
Phenol is more acidic relative to other alcohols

\[
\text{pK}_a \approx 10
\]

Greater acidity is due to the resonance forms of the phenolate that stabilize the negative charge
Synthesis of Alcohols

We have already learned numerous ways to synthesize an alcohol
Another route to alcohols is an addition to a carbonyl group

Carbonyl carbons can act as an electrophilic site
Addition to carbonyl creates an alkoxide

Work-up in acidic medium will therefore protonate alkoxide to create an alcohol
How do we create carbon-based nucleophiles?

We need to create a polarized bond between carbon and another atom.

There are two convenient ways to generate these carbon-based nucleophiles:

1) Grignard Reagents

\[ \text{R–Br} \xrightarrow{\text{Mg}} \text{R–MgBr} \]

Iodine is most reactive followed by bromine then chlorine.
(fluorine is relatively nonreactive towards Grignards)

Bond is polarized \( \text{acts like R-} +\text{MgBr} \)
If a Grignard reagent reacts with a carbonyl then an alcohol is produced

\[
\text{CH}_3\text{CH}_2\text{Br} \quad \xrightarrow{\text{Mg}} \quad \text{CH}_3\text{CH}_2\text{MgBr}
\]

\[
\text{CH}_3\text{CH}_2\text{MgBr} \quad \xrightarrow{\text{H}_+} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O}^- \quad \xrightarrow{\text{H}^+} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH}
\]
Second way to create a polarized bond is to use an organolithium compound

\[
\text{R–I} \quad \xrightarrow{2 \text{ Li}} \quad \text{R–Li} \quad \text{LiI}
\]

\[
\text{CH}_3\text{CH}_2\text{Br} \quad \xrightarrow{2 \text{ Li}} \quad \text{CH}_3\text{CH}_2\text{Li}
\]

\[
\text{CH}_3\text{CH}_2\text{Li} \quad \xrightarrow{\text{H}^+} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{O}^- \quad \xrightarrow{\text{H}^+} \quad \text{CH}_3\text{CH}_2\text{CH}_2\text{OH}
\]
Using Grignard Reagents (or Organolithiums) to Create Alcohols

Already saw how reaction with formaldehyde will create a 1° alcohol that has one additional carbon than starting material.

\[
\text{Br} \quad \text{Mg} \quad \text{H} \quad \text{OH}
\]
If reaction is between Grignard reagent and an aldehyde a $2^\circ$ alcohol is obtained.
A 2° alcohol can thus potentially be prepared in two ways using a Grignard reagent.

The aldehyde can be used on either “halve” of the retrosynthetic analysis.
Additionally, if Grignard reagent is reacted with a ketone a 3° alcohol is obtained.
Acid Chloride and Esters

If a carboxylic acid group is modified a Grignard reagent can react (carboxylic acids will not react due to acid-base considerations)

\[
\begin{array}{ccc}
\text{O} & \text{O} & \text{O} \\
\text{R} & \text{R} & \text{R} \\
\text{OH} & \text{OCH}_3 & \text{Cl} \\
carboxylic acid & methyl ester & acid chloride
\end{array}
\]

All three carbonyl derivatives can be interconverted (will be covered in later chapter)
Addition of one equivalent of Grignard reagent to an acid chloride (or ester) creates a tetrahedral alkoxide with a good leaving group.

\[
\begin{align*}
\text{R} & \quad \text{Cl} \\
\text{R} & \quad \text{MgBr} \\
\text{R} & \quad \text{O}^- \\
\end{align*}
\]

The chloride will leave in a subsequent step to regenerate the carbonyl group.

\[
\begin{align*}
\text{R} & \quad \text{O}^- \\
\text{R} & \quad \text{Cl} \\
\end{align*}
\]

The ketone will react again with the Grignard reagent to create a 3° alcohol.

\[
\begin{align*}
\text{R} & \quad \text{R} \\
\text{R} & \quad \text{O} \\
1) \text{R-MgBr} \\
\text{R} & \quad \text{R} \\
2) \text{H}^+ \\
\end{align*}
\]
Grignard reagents will also react with epoxides

The Grignard reacts in a $S_N^2$ manner therefore will react at least hindered carbon with inversion of configuration

Generates an alcohol which is two carbons removed from Grignard addition
Besides being good nucleophiles, Grignard reagents and organolithiums are STRONG bases.

Carbon based anions (without resonance stabilization) have pKₐ values > 50.

Remember that carboxylic acids have pKₐ of ~ 4 and alcohols ~ 16.

Follow directly from electronegativity trend.

<table>
<thead>
<tr>
<th></th>
<th>H₃C—CH₃</th>
<th>H₃C—NH₂</th>
<th>H₃C—OH</th>
<th>F—H</th>
</tr>
</thead>
<tbody>
<tr>
<td>pKₐ</td>
<td>~50</td>
<td>~36</td>
<td>~16</td>
<td>~3</td>
</tr>
</tbody>
</table>
Due to this high basicity, Grignard reagents CANNOT be used with even weakly acidic compounds.

Equilibrium is driven by acid-base reaction

\[
\text{H}_3\text{C} \text{MgBr} \quad \text{H}_2\text{O} \quad \rightarrow \quad \text{CH}_4 \quad \text{HO}^- 
\]

Therefore NO alcohols or amines (or any labile hydrogens) can be present anywhere in the molecule for a Grignard reaction.
Another Problem: Grignard reagents are NOT selective

Grignard reagents are strong nucleophiles so they will react with any electrophilic double bond (reactivity versus selectivity)

This is good to react with carbonyl groups, but if any other reactive groups are present they will also react

Will react with various multiple bond structures

\[
\begin{align*}
\text{C} &= \text{N} & \text{C} &= \text{N} & \text{N} &= \text{O} & \text{S} &= \text{O} & \text{O} &= \text{C} &= \text{O}
\end{align*}
\]

Cannot react at one site preferentially if more than one reactive site is present
One effect of these side reactions: Grignard reagents can be used to reduce alkyl halides to alkanes.

If an acidic hydrogen source is present an alkane is generated.

Therefore this represents a reduction of the alkyl halide.
Another way to reduce alkyl halides is to use Lithium Aluminum Hydride.

Can consider LAH as a source of hydride (H⁻) anions.

If LAH is reacted with an alkyl halide an alkane is formed.
LAH can also be used to create alcohols

The hydride anion can react as a nucleophile with an electrophilic carbonyl group

Therefore a ketone upon reaction with LAH creates a 2° alcohol
Likewise an aldehyde is reduced to a 1° alcohol with LAH

In essence these reductions are adding hydrogen to both ends of the carbonyl bond, both the carbon and oxygen of the original double bond are bonded to a new hydrogen.
Sodium Borohydride will also reduce a ketone and aldehyde to a 2° and 1° alcohol, respectively.

Since both boron and aluminum are in the same column of the periodic table they share similar chemical properties.
The reactivity increases down the periodic table. Therefore, aluminum is more reactive than boron. (LAH is more reactive than NaBH₄.)

Due to this increased reactivity, LAH will not work in alcoholic or aqueous solvents—it reacts with the solvent before reducing the carbonyl group. Therefore, need to work-up LAH reactions in a SECOND step.

This is not true with NaBH₄; these reactions CAN occur in alcoholic solvents.
Due to the increased reactivity, LAH can reduce other carbonyl functional groups that NaBH₄ cannot.
Sodium Borohydride (NaBH₄) is thus more selective than LAH
Thiols

Similar to the chemistry of alcohols
(sulfur is in the same column as oxygen)

Nomenclature
Follow the same rules as learned for alcohols but use –thiol suffix instead of -ol

\[
\begin{array}{ll}
\text{CH}_3\text{OH} & \text{methanol} \\
\text{CH}_3\text{SH} & \text{methanethiol}
\end{array}
\]
Differences between alcohols and thiols

Thiols are stronger acids due to charge being placed on more polarizable sulfur and a weaker S-H bond.

\[
\begin{align*}
\text{OH} & \rightarrow \text{O}^- & \text{pKa} \sim 16 \\
\text{SH} & \rightarrow \text{S}^- & \text{pKa} \sim 10
\end{align*}
\]

Thiols have less hydrogen bonding than alcohols due to sulfur being less electronegative than oxygen.
Thiolate anions are more nucleophilic than alkoxide anions

Due to the more polarizable sulfur, and bigger atom which results in less solvation in protic solvents, the thiolate is more nucleophilic than an oxygen anion

\[
\text{CH}_3\text{SH} + \text{NaOH} \rightarrow \text{CH}_3\text{S}^- \\
\text{CH}_3\text{S}^- + \text{Br} \rightarrow \text{CH}_3\text{SBr}
\]

This increased nucleophilicity allows the formation of sulfonium salts

\[
\text{CH}_3\text{SCH}_3 + \text{CH}_3\text{I} \rightarrow \text{CH}_3\text{SCH}_3^+\text{I}^-
\]

Same reaction does not occur readily with ethers
Sulfonium salts are used as alkylating agents

trimethylsulfonium iodide

Similar to $S_N2$ reactions observed with methyl halides
These sulfonium salts are used as methylating agents biologically.

Methyl iodide cannot be used in living cells—low water solubility and too reactive (will react nonselectively with amines).

Common methylating agent in living cells is S-Adenosyl methionine (SAM).

![SAM and SAH structures](attachment:chem.png)
One example:
Conversion of norepinephrine to epinephrine
Thiols can be oxidized to form a disulfide bond

\[ \text{H}_3\text{C} \text{SH} \xrightarrow{\text{mild oxidation}} \text{H}_3\text{CS} \text{SCH}_3 \]

thiol \hspace{2cm} \text{disulfide}

This process is used in proteins to link together cysteine amino acids

\[ \text{HS} \text{NH}_3 \xrightarrow{\text{oxidation}} \xleftarrow{\text{reduction}} \text{O} \text{NH}_3 \text{S} \text{S} \text{NH}_3 \text{O} \]

cysteine \hspace{2cm} \text{cystine}

The disulfide bond thus can lock the protein in a particular shape
The formation of the disulfide bridge can change the properties of the protein.
A cosmetic application of disulfide bridges

Human hair consists of a protein (keratin) that contains a large percentage of cysteine (~4 times the amount found in other proteins)
The cysteine forms disulfide bonds to keep the hair in a particular shape

To change the shape:
A reducing agent is applied which breaks the disulfide bonds
The hair is then rearranged into a desired shape (curlers or combing)
An oxidizer is added to maintain the new shape of the hair

To change straight hair to curly this is called a “permanent”
To change curly hair to straight this is called a “hair straightening”
Stronger oxidation of thiols generates sulfonic acids

With mild oxidation the thiol can be converted to a disulfide, stronger oxidation however oxidizes the sulfur to a sulfonic acid

Typically use potassium permanganate or nitric acid for this oxidation (use strong conditions, usually heat)