Alcohols, Ethers and Thiols

Structural Relationships

Ethanol:

Diethyl ether:

Ethanethiol:

Constitutional (Structural) Isomerism in Alcohols

Question: How many isomeric alcohols are there for ethanol, propanol, and butanol? Classify each as primary, secondary, or tertiary

Ethanol:

Propanol:

Butanol:
Alcohol Nomenclature

* Drop the -e in alkane and add -ol

* Include the alcohol in the longest chain and number so that the alcohol gets the lowest numbering (for cyclics, alcohol gets the 1 position)

* The common system naming of alcohols uses the alkyl portion as a substituent and then “alcohol”

* When the alcohol functionality is referred to as a substituent, it is identified by the term hydroxy

* Previous rules apply

Some examples:

\[
\text{Cl} \quad \text{OH}
\]

Recall the most rational method to name compounds containing both alkene and alcohol functionalities is to include both in the base name
Provide an alternative name for lactic acid, given the 3 C acid is propanoic acid

In the case of diols and triols, we retain the -e (don't ask me why - maybe it just sounds better):

1,2-propanediol:

1,2-ethanediol$	extsuperscript{1}$:

1,2,3-propanetriol:

The above saturated alcohols bearing 2 hydroxyl groups next to one another are commonly referred to as glycols

* Ethylene glycol (antifreeze) is made from ethylene via the epoxide which is where its name comes from

⊕ Epoxides are 3 membered cyclic ethers that are classified independently due to their reactivity

\textsuperscript{1} \text{What a difference a carbon makes! Propylene glycol is a non-toxic food and pharmaceutical additive, being principally metabolized to lactic and pyruvic acids, whereas ethylene glycol is automotive antifreeze and highly toxic. Partial hydrolysis of the 2 C epoxide leading to ethylene glycol gives diethylene glycol, which killed 105 people in 1937 and led to the creation of the US FDA}
Physical Properties of Alcohols

Question: Why is ethylene glycol used as antifreeze?

1.

2.

Consider alcohols as analogs of water; their ability to hydrogen bond confers water solubility and higher boiling points than the corresponding alkanes (Refer to table 14.3)

- Recall the balance between polar and non-polar portions of a molecule; e.g. butanol solubility = 8 g/100 mL H₂O

- Octanol is used as a membrane mimic/insoluble organic layer for determining the solubility characteristics of drug candidates. Interested individuals should search octanol-water partition coefficient

Question: Which of the following would have the greatest solubility in water?

[Chemical structures of the compounds]

Phenols - Nomenclature and Physical Properties

Name the following compounds

[Chemical structure of a phenol compound]
With regard to physical properties, there is an increased contribution to water solubility if the hydroxyl is attached to the aromatic ring (bear in mind the ring does contain 6 non-polar carbon atoms); however, the increase is not dramatic and so we will not distinguish them further in this class.

Ethers - Nomenclature and Physical Properties

Structure

O in a C sandwich or $R_3C-O-CR_3$, where R can be alkyl or H

Nomenclature

It is standard practice to name ethers employing the common nomenclature system with substituents attached to O. For example

Phenyl methyl ether  Diethyl ether  Methyl ethyl ether
Physical Properties

Notice that there is a disparity between the boiling point and water solubility of ethers:

- Ethanol: BP = 78 °C, infinite solubility in water
- Dimethyl ether: BP = -24 °C, infinite solubility in water

Why? Ethers cannot hydrogen bond with one another so the strongest forces of interaction are dipole interactions; however when considering water solubility, the water can act as a hydrogen bond donor to the ether (or any other oxygen) leading to the following very nice rule of thumb:

- Treat all oxygens the same when establishing relative water solubilities. We shall see this does change as we consider functional groups that have 2 heteroatoms in the group\(^2\), but for now this is a pretty good start.

Thiols - Nomenclature and Physical Properties

Stanky:

2-butene-1-thiol & 3-methyl-1-butanethiol

Question: One of the above compounds is incompletely named. Which is it and why?

Name by including the sulfhydryl in the longest carbon chain, then tack thiol to the end of the base name (without dropping the -e).

Question: Name the following compound

\[ \text{SH} \quad \text{Cl} \]

\[ \text{_______________________________________________} \]

\(^2\) For instance, ethanol and acetic acid have infinite water solubility, but the ester condensation product ethyl acetate has a solubility limit of 8.3 g/100 mL - not so very different than n-butanol!
Alternative nomenclature: mercaptans (mercury capturing)

Ethanethiol = Ethyl mercaptan = Mercaptoethane

Question: Give 2 alternative names for 1-butantelhio1

________________________________________________________________________

________________________________________________________________________

Physical properties:

Very small electronegativity difference between H and S (.4 electronegativity units) as such, the S-H bond is non-polar covalent

Ethanethiol bp = 35 °C  solubility 6.8 g/L @ 20 °C

Interestingly, because S is in the 3rd period it is “polarizable”, in a fashion similar to bromine (which helps explain why bromine is a good leaving group even though the electronegativity difference between C and Br is only 0.41) The 3rd period van der Waals radius of S also makes mercaptans slightly acidic.

For comparison, what would the water solubility be if S were replaced by C in ethanethiol?

Answer: Nil

What would the water solubility be if ethanethiol were first treated with NaOH?

Answer: \(\infty\)

What would the water solubility be if sulfur were substituted with oxygen in ethanethiol?

Answer: \(\infty\)
Reactivity of Alcohols

Acidity & Basicity of Alcohols

Not very - again, consider alcohols as analogs of water; as such, they do not lower the pH of water when mixed, which is the practical definition of an acid.

Acid-catalysed dehydration to alkenes

Why acid catalysis? What is the good leaving group in this case?

- Notice that the most substituted alkene is formed; as an example:

  ![Catalysis Example](attachment:image.png)

  - We used the same catalyst to generate alcohols from alkenes. This is a nice example of microscopic reversibility. Also recall that heat favors elimination ($\Delta G = \Delta H - T\Delta S$) and the addition or removal of water can influence the direction of reaction by LeChâtelier's principle.

Oxidation of Alcohols

Combustion? Oui!

$C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O$

With KMnO$_4$ or K$_2$Cr$_2$O$_7$

1$^\circ$ alcohols: $RCH_2$OH $\rightarrow$ $RCHO$ $\rightarrow$ $RCO_2H$

2$^\circ$ alcohols: $RR'CH$-OH $\rightarrow$ $RR'C$=O

3$^\circ$ alcohols: $RR'R''C$-OH $\rightarrow$ No Reaction

Notice that for oxidation to occur the C bearing the hydroxyl must have H attached.
When dichromate is used ($\text{Cr}_2\text{O}_7^{2-}$), chromium changes from the +6 to the +3 oxidation state. $\text{Cr}^{+6}$ is orange, $\text{Cr}^{+3}$ is green; as such, oxidation by $\text{Cr}^{+6}$ is a convenient test for the presence of primary and secondary alcohols - so much so that this reaction was used in old school breathalyzers.

**Alcohols as Nucleophiles (this is a big deal):**

*Carboxylic acid + alcohol $\rightarrow$ ester!*

Example: Isopentyl alcohol + acetic acid $\rightarrow$ Banana oil! (isopentyl acetate)

*Acid anhydride + alcohol $\rightarrow$ ester!*

Example: salicylic acid + acetic anhydride $\rightarrow$ aspirin

*Ester + alcohol $\rightarrow$ different ester (trans-esterification)*

The binding of amino acids to tRNA
Phenol Reactivity

Due to delocalization of the electron pair, phenol is significantly more acidic than a typical alcohol, and will lower the pH of an aqueous solution *slightly*. Phenol has a \( pK_a = 10 \) which is high compared to acetic acid \( (pK_a = 4.75) \) but much lower than a typical alcohol \( (pK_a = 16) \), and comparable to the conjugate acid of ammonia (ammonium ion, \( pK_a = 9.3 \)). The classic name for phenol is carbolic *acid*.

- Resonance helps us understand why - phenol vs. cyclohexanol:

This same electron delocalization into the benzene ring activates phenols towards substitution on the benzene ring in at the ortho and para positions:

\[
\text{OH} \hspace{1cm} + \hspace{1cm} \text{Br}_2 \rightleftharpoons \text{FeBr}_3
\]

Ether Reactivity

- Ethers are considered unreactive, though if you ever come across an old can of ether bear in mind ethers tend to form explosive peroxides over time

- Being relatively unreactive and still possessing an oxygen makes ethers very useful solvents for dissolving molecules of intermediate polarity
Thiol Reactivity

We generally consider the thiol as the direct analog of the hydroxyl, undergoing the same reactions:

The central intermediate in the metabolism of foods is acetyl CoA, which is a thioester

While the reactions of thiols are analogous with alcohols, there are 2 important exceptions:

- Acidity: Even though the electronegativity between S & H is slight, the hydrogen can be removed as a proton. The acidity of a sulfhydryl is about that of phenol, since you are spreading the negative charge over a larger S atom
  - As such we can expect a reaction between thiols and strong bases like NaOH

- Thiols are able to redox cycle to form disulfides, as demonstrated by the important cellular component glutathione (GSH)
The diagram illustrates the process of oxidative stress leading to cell death. The cycle begins with the conversion of GSSG to GSH, which is then involved in the production of reactive oxygen species (ROS) such as 
\[ \text{H}_2\text{O}_2 \xrightarrow{Fe^{2+}} \text{Fe}^{3+} + \text{O}_2 \]

These ROS can lead to lipid peroxidation, protein modification, and DNA damage. 
- Lipid peroxidation leads to inner mitochondrial membrane damage.
- Proteins can be modified due to oxidative damage.
- DNA can be directly damaged by ROS.

Ultimately, these processes culminate in cell death.
- Glutathione can also act as a nucleophile (in much the same way a hydroxyl does). This helps protect us from acetaminophen (Tylenol®) overdose...until we run out, then the party’s over.