VI Functional Groups 1

In this chapter we will discuss oxygen containing functional groups commonly found in biological molecules:

Carboxylic Acid  Aldehyde  Ketone  Alcohol  Ether  Epoxide

6.1 Alcohols and Phenols

Alcohol: ROH, alkane in which a hydrogen is replaced with OH
Phenol: ArOH, aromatic ring with bonded OH

OH is also called Hydroxyl Group

Removal of the Hydrogen of the hydroxyl group in alcohols gives the Alkoxy Groups (alkoxides)

Examples:
Methoxy:

Ethoxy:

Pentoxy:
Removal of the Hydrogen of the hydroxyl group in phenols gives the Phenoxy Groups (phenoxides)

Phenoxy Group:

*How to make these alkoxides or phenoxides?*

Reaction of the alcohol or phenol with Na:

6.1.1 Nomenclature of Alcohols and Phenols

- Alcohols can be classified in analogy to alkylhalides as primary, secondary and tertiary alcohols:

| Primary | Secondary | Tertiary |
Saturated Alcohols:

- Longest alkyl chain followed by -ol

*Examples:*

Position of the alcohol is described by the number BEFORE the alkyl chain

*Examples:*

- Compounds containing two or more alcohols are called DIOLES, TRIOLES etc. with a positional number assigned to each OH group.

*Examples:*

If the alcohol is connected to a ring (not aromatic) the ring is numbered starting with the carbon connected to the hydroxyl group. The number in the direction that allows for the LOWEST numbers for other substituents

*Examples:*
Unsaturated Alcohols:

- To designate the double or triple bond of unsaturated alcohols, the -an of the parent hydrocarbon is changed to -en or -yn, respectively. The alcohol takes precedence in numbering the chain

Examples:

General IUPAC Method for naming alcohols:

1. Use the greek word for the number of carbons in the longest continuous chain (containing the alcohol)

2. Follow this by the suffix -an, -en, or -yn.

3. Add the suffix -ol to designate the alcohol functionality

4. Number the carbon chain, giving the lowest possible number to the alcohol group

5. Complete the name by naming all other groups by prefixes with their numerical position

Examples:
• Some alcohols have trivial names:

  Ethyl alcohol       Isopropyl alcohol

  Allyl alcohol

• Phenols are named accordingly to the rules for substituted benzene rings (see chapter 3)

  Examples:
6.1.2 Properties of Alcohols

• Very strong dipole moment ⇒ very polar group

• Boiling points increase with increased molecular weight

• The longer the alkyl group the less soluble the alcohol is in water

• Most important property ⇒ HYDROGEN BONDING
  - Like water, alcohol can undergo hydrogen bonding
  - This results in a stabilization of the three dimensional solvent structure
  ⇒ Higher boiling points than expected

6.1.3 Applications of Alcohols

• Basic alcohols are used in chemical processes
  - Methanol (wood alcohol) ⇒ Toxic

  - Ethanol (main ingredient of alcoholic drinks)

  - Isopropyl alcohol (rubbing alcohol)
Polyhydric alcohols

**Polyhydric alcohol:** alcohol with more than one hydroxy group

- Ethylene glycol (antifreeze)
  
  It has a very high boiling point (198°C)
  
  Also used as hydraulic fluid

- Glycerol
  
  Used as humectants (in tobacco)
  
  Manufacture of polymers
  
  Nitroglycerin:

Phenols

- Very important in medicine:

  Four potential properties:
  
  a) Antiseptic or disinfectant:
  
  b) Local anesthetic
  
  c) Skin irritancy
  
  d) Toxic when ingested

*Examples:*
- Antioxidant and Photographic Developer

*Examples:*

- Tetrahydrocannabinol (marijuana)
6.1.4 Preparation of Alcohols

1) Hydration of Alkenes

2) Nucleophilic Substitution

3) Reduction of Carbonyl Compounds

'Transfer of hydrogen atoms from surfaces to the carbonyl'

*General Reaction:*

3.1) Catalytic Hydrogenation (Ni, Zn, Rh, Ir)
3.2) Reduction by Lithium Aluminum Hydride or Sodium Borohydride

3.3) Grignard Synthesis

3.4) Hydroboration

3.5) Oxymercuration
6.1.5 Reaction Sites in Alcohols and Phenols

• In both cases two polar bonds:

• Two lone pairs on the oxygen

Unshared lone pairs on the oxygen make these compounds Lewis Bases
⇒ A H⁺ can be attacked by these lone pairs creating an oxonium ion

**Oxonium Ion**: Ion formed by the bonding of a hydrogen ion to the oxygen of an alcohol or ether

*Example:*
6.1.6 Reaction of Alcohols

A) Acid-Base Reactions
Remember:
Brønsted acids are proton donors
Brønsted bases are proton acceptors

Alcohols can act as both: acids and bases
⇒ amphoteric substances

Alcohols have a $pK_a$ of approximately 15 - 19
Phenols have a $pK_a$ of approximately 10 ⇒ more acidic than alcohols (more stable anion)

Why important? ⇒ Reactivity
Phenols can be neutralized by $\text{OH}^-$ ($pK_a = 15$), alcohols not

*Example:*

⇒ Alcohols can exist as alkoxides in basic solution, alcohols in neutral solutions and oxonium ions in acidic solution

Remember the influence of substituents on the acidity constants
B) Formation of Esters
Alcohols can form esters with inorganic and organic acids

*Examples:*

C) Nucleophilic Substitutions
- Alcohols react with hydrogen halides to give alkyl halides

*Example:*

This can happen via $S_N^1$ or $S_N^2$:

Mechanism of $S_N^1$: 
Mechanism of $S_{N2}$:

In analogy to alkyl halides, primary alcohols proceed via $S_{N2}$ while secondary and tertiary alcohols prefer $S_{N1}$

- Other ways to synthesize alkyl halides include the reaction of alcohols with $\text{SOCl}_2$ or $\text{PX}_3$

*Examples:*
D) Dehydration of alcohols

- Alcohols can be dehydrated (removal of water) with an acid to form alkenes

General Mechanism:

'Remember the stereochemistry of Eliminations, the Zaitsev rule'

Primary alcohols go E2, secondary and tertiary E1

*Mechanism of E1:*

*Mechanism of E2:*
E) Oxidation of Alcohols

**Oxidation:** Removal of hydrogen from carbon-oxygen single bond or insertion of oxygen in a molecule

**Examples:**
- **Primary Alcohols**

- **Secondary Alcohols**

What about tertiary alcohols?

You need oxidizing reagent:
- Jones reagent: CrO\(_3\), H\(_2\)SO\(_4\)
- Na\(_2\)Cr\(_2\)O\(_7\), H\(^+\)

What if you want to stop at the aldehyde stage and do not want to oxidize the starting material to the acid?
- PCC: C\(_5\)H\(_6\)NCrO\(_3\)Cl)

*Example:*
6.1.7 Reaction of Phenols

- C-O bond very hard to break
  ⇒ no nucleophilic substitutions

- As discussed above, phenols are more acidic
- The acid strength can be increased by having electron-withdrawing groups on the ring

A) Oxidation of Phenols
- Phenols are easily oxidized

Example:
6.1.8 Sulfur Analogues

- Sulfur analogues of alcohols and phenols exist and are called thiols or mercaptans

**Thiol**: RSH, alkane in which a hydrogen has been replaced by SH

- They have terrible odor

  *Example Skunks:

- Thiols are stronger acids than alcohols with $pK_a$ values around 8
- They undergo the same reaction as alcohols but are more reactive
6.2 Ethers and Epoxides

**Ether:** ROR, oxygen with two organic groups

**Epoxide:** Three-membered ring cyclic ether (also called oxiranes)

*Examples:*

6.2.1 Nomenclature

- **Trivial names:**
  - Ethers are often named as 'alkyl alkyl ether'
  - find the names of the two organic groups bonded to the oxygen and name them in alphabetical order followed by ether

  *Examples:*

- **IUPAC Names:**
  - Find the longest continuous carbon chain
  - Name the other organic part (chain) by its alkoxy group name
  - put both together starting with the alkoxy part
Examples:

- Cyclic Ethers

Most of the small ring cyclic ethers have common names:
6.2.2 Physical Properties

- Ethers have two polar C-O bonds
- No OH group $\Rightarrow$ no proton donor ability
- However, two lone pairs $\Rightarrow$ possible proton acceptor
- No hydrogen bonding ability (no OH) $\Rightarrow$ lower boiling points than alcohols

6.2.3 Synthesis of Ethers

Most common method is the Willimanson Ether Synthesis, which is a basic nucleophilic substitution

*Example:*

General Mechanism $S_N2$: 
• primary halides work best, WHY?

6.2.4 Reactions of Ethers

• Very inert, do not react easily

Only good reaction is the treatment of ethers with HI or HBr to yield alkyl halides

*Examples:*

If you have two different alkyl groups on an ether, which one reacts?
6.2.5 Epoxides

- Very important class of reactive intermediates
- Very reactive because of ring strain

Preparation:
Reaction of an oxygen source with a double bond

*Example:*

Good oxygen sources:

- Ag, O₂, heat, pressure
- Peroxy acids (RCO₃H
- m-chloroperoxybenzoic acid (MCPBA)

- Stereochemistry is the same in an epoxide formation using MCPBA (cis stays cis, trans stays trans)

*Example:*
• Reactions:

A) Acid Catalyzed Ring Opening

*Example and Mechanism (S_N2):*

B) Ring Opening by Nucleophiles

Nuc⁻: OH, SH, NH₃, OR, SR, RNH₂

*Example:*

• Direction of Ring Opening

Different under acidic or basic conditions:
Basic conditions:
Nuc attacks at the less hindered primary carbon

*Example:*

Acidic conditions:
H\(^+\) attacks the oxygen creating a positive charge with resonance structures:

stability of the positive charge determines the stereochemistry

*Example:*
6.3 Aldehydes and Ketones

**Carbonyl:** The carbon oxygen double bond  
**Aldehyde:** Functional group in which at least one H is bonded to a carbonyl  
**Ketone:** Functional group in which two organic substituents are bonded to a carbonyl

*Examples of Aldehydes and Ketones:*

Resonance Structures of the Carbonyl Group:

Important functional groups containing the carbonyl group:
6.3.1 Nomenclature

a) IUPAC Names:

Aldehydes: Suffix -al at the end of the carbon chain name

Example:

Ketones: Suffix -one id added at the end of the longest carbon chain

Example:

Priority of use of suffix:

<table>
<thead>
<tr>
<th>Functional group</th>
<th>Suffix</th>
<th>Prefix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Highest priority:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldehyde</td>
<td>al</td>
<td>oxo</td>
</tr>
<tr>
<td>Ketone</td>
<td>one</td>
<td>oxo</td>
</tr>
<tr>
<td>Alcohol</td>
<td>ol</td>
<td>hydroxy</td>
</tr>
<tr>
<td>Lowest priority:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amine</td>
<td>amine</td>
<td>amino</td>
</tr>
</tbody>
</table>
Examples:

Rule of naming aldehydes and ketones:

1) Determine and name the longest continuous chain of carbon compounds CONTAINING the functional group of highest priority

2) Follow the root name with the suffix -an if all carbon bonds are single bonds, -en if the chain contains a carbon-carbon double bond, and -yn if it contains a carbon-carbon triple bond

3) Name the most important functional group with the appropriate suffix

4) Number the carbon chain, giving the lowest number to the functional group named by the suffix (next are carbon-carbon multiple bonds with double bonds taking precedence over triple bonds when otherwise the direction of the numbering does not make a difference). Complete the suffix by assigning numbers of the most important functional group and carbon-carbon multiple bonds

5) Name all other groups with prefixes (in alphabetical order) and assign them the appropriate numbers
Examples:

b) Common Names:
A large number of smaller carbonyl compounds have common names:

<table>
<thead>
<tr>
<th>Formaldehyde</th>
<th>Acetaldehyde</th>
<th>Acetone</th>
<th>Propionaldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Butyraldehyde</td>
<td>Methyl-ethyl-ketone</td>
<td>Diethylketone</td>
<td></td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>Acetophenone</td>
<td>Benzophenone</td>
<td></td>
</tr>
</tbody>
</table>
The suffix carbaldehyde is sometimes used to designate an aldehyde group attached to a non-aromatic ring

*Examples:*

6.3.2 Properties of Aldehydes and Ketones

Strong Dipole:

- boiling points are higher than the ones of alkanes of the same molecular weight (reason are dipole-dipole interactions)

- boiling points are lower than comparable alcohols (no hydrogen bonds, carbonyl compounds only have hydrogen bonding acceptors but NO hydrogen bonding donors)

6.3.3 Synthesis of Aldehydes and Ketones

a) Hydration of Alkynes
b) Ozonolysis of Alkenes

c) Friedel-Crafts Reaction

d) Oxidation of Alcohols

6.3.4 Addition Reactions of Aldehydes and Ketones

A) General Considerations:

Structure:
General Reactions:

General Mechanism:
Base-catalyzed:

Acid-catalyzed:

B) Oxidations:
Aldehydes can be oxidized to carboxylic acids:
Q1 Can you oxidize Ketones? If no this is an easy test to distinguish aldehydes from ketones

C) Grignard Addition:

Grignard Reagent: The reagent RMgX developed by Nobel laureate Victor Grignard

Preparation of the Grignard Reaction:

Reaction:

Mechanism:
D) Addition of Hydrogen Cyanide:

**Nitrile**: Compound with a carbon-nitrogen triple bond

**Cyanohydrin**: Carbon with both an OH and a CN bonded

General Reaction:

Reaction Mechanism:

Careful: HCN is very toxic

E) Addition of Water:

- Addition of water to a carbonyl compound creates a HYDRATE

General Reaction:
This is an equilibrium reaction and the equilibrium lies very strongly on the side of the starting materials

F) Addition of Alcohols:

**Hemiacetal:** Carbon bonded to both an OH and OR group

**Acetal:** Carbon bonded to two OR groups

**Hemiketal** and **Ketals** are the ketone analog.

General Reaction:

Reaction Mechanism:
• The addition of Alcohols is very important in Carbohydrate (sugar) chemistry

G) Addition of Amines:

• Amines are Lewis Bases and add the same way alcohols do

General Reaction:

**Imine:** Compound with a carbon-nitrogen double bond

*Examples:*
6.3.5 Other Reactions of Aldehydes and Ketones

A) Already Discussed Reactions:

• Reduction to alcohols using sodium borohydride and lithium aluminum hydride:

• Reduction to alcohols using catalytic hydrogenation:
• Reduction to a methylene group

B) Reaction on the alpha carbon (and the acidic Hydrogen)

\( \alpha \text{-Hydrogen:} \) hydrogen on a carbon connected to a carbonyl group

General Reactivity of the alpha carbon:
• Resonance stabilization of the alpha carbon (in the ion and non-ion form) ⇒ Keto-Enol Tautomerism

**Enolate:** Resonance stabilized carbanion resulting from abstraction of an α-Hydrogen  
**Enol:** Compound with OH bonded to a carbon-carbon double bond  
**Tautomers:** Two easily interconvertible structural isomers  
**Tautomerism:** An equilibrium between two structural isomers

*Examples:*
• The ALDOL Condensation

**Aldol Condensation:** Base-catalyzed reaction between two aldehyde or ketone molecules to form a product with both alcohol and carbonyl groups

General Reaction:

- Possible problem Dehydration:
General Mechanism:

- Crossed or mixed Aldol reactions:

  **Crossed Aldol Condensation:** Aldol condensation between two different aldehydes and ketones

  *Examples:*
- Aldol Additions in Nature:

Examples:
Summary of Chapter 6:

⇒ Functional Groups
⇒ Alcohols and Phenols
  → Nomenclature
  → Properties
  → Applications
⇒ Preparation of Alcohols and Phenols
⇒ Reactions of Alcohols and Phenols
⇒ Sulfur Analogues
⇒ Ethers and Epoxides
  → Nomenclature
  → Properties
⇒ Preparation of Ethers
⇒ Reactions of Ethers
⇒ Preparations and Reactions of Ethers
⇒ Aldehydes and Ketones
  → Nomenclature
  → Properties
⇒ Preparation of Aldehydes and Ketones
⇒ Addition Reactions
⇒ Aldol Reaction