Organic

ALDEHYDES AND KETONES

Both Aldehydes and ketones are characterized by the presence of the carbonyl group:

\[\text{O} \quad \text{C} \]

An aldehyde has one (or two) hydrogen(s) bonded to the carbon of the carbonyl group, a ketone has carbons bonded to the carbonyl carbon.

\[
\begin{align*}
\text{H} & | \quad \text{O} \\
(H)R-C=O & \quad R-C-R \\
\text{Aldehyde} & \quad \text{ketone}
\end{align*}
\]

The main difference between the C=C and C=O is that the double bond in the alkene lies between two atoms of the same element, carbon, whereas that of the carbonyl is positioned between two different elements, carbon and oxygen. Since oxygen is more electronegative than carbon, the carbon-oxygen double bond is polar.
Physical properties

Other than formaldehyde, which is gas, the simple Aldehydes and ketones are liquids less soluble in water and of lower boiling point than the corresponding alcohols.

Many Aldehydes have pleasant odors. In contrast, the low-molecular weight aliphatic Aldehydes have sharp unpleasant odors. in general even ketones of low molecular weight have rather pleasant odors.

Some important carbonyl compounds

- **Formaldehyde** is the main constituent of formalin, a solution of 37% formaldehyde in water. Formalin is used both to preserve tissue and an embalming fluid and has also been used as a surgical and general antiseptic.
- Formaldehyde in high concentrations is toxic to humans, but in lower concentrations it is an antiseptic. It is a powerfully disinfectant gas, sometimes used as a disinfectant for rooms, clothing..etc. the drug hexamethylene tetramine owes its activity as a urinary antiseptic to formaldehyde.

When formalin is evaporated at a reduced pressure, the solid polymer paraformaldehyde is produced. Gaseous formaldehyde is too reactive to be stored. Thus both liquid formalin and solid paraformaldehyde represent convenient, commercially available forms of formaldehyde.
Formaldehyde, interferes with our sense of smell by masking the odors of the other substances. Thus formaldehyde is often used as a commercial room deodorant in the form of heated paraformaldehyde.

The effect of formaldehyde on our sense of smell is temporary, but with time it may cause anosmia which can be terribly permanent.

- **Acetaldehyde**, like formaldehyde is not easily stored due to its very low boiling point (21) and high reactivity. So it is converted to the cyclic trimerparaldehyde by treatment with sulfuric acid. This stable liquid (b.p. 128°C) is used as hypnotic and sedative.
- **Acetone** is an excellent solvent for lacquer, resins and paint. In addition, acetone is a fine sterilizing agent in medicine. It is a germicide that is used in skin testing for allergies due to its high volatility combined with its germicidal effect.

In a healthy individual, acetone is found in very low concentrations in blood. However, uncontrolled diabetes or starvation creates an abnormal metabolism of fat, which leads to a buildup of acetone in the body. Since acetone is volatile, it travels to the lungs where it is expelled as “acetone breath”. By the time acetone can sick and needs immediate hospital treatment.

**Preparation of Aldehydes and Ketones**

1. The oxidation of primary or secondary alcohols is the classical method of preparation of Aldehydes and ketones. Chromic acid (acidified sodium dichromate) is frequently used in the laboratory, but industrially oxygen and catalysts are employed. When oxidizing primary alcohols.

\[
\text{CrO}_3\text{H}^+ \\
\text{R-CH}_2\text{-OH} \xrightarrow{65 \text{ C, H}_2\text{O}} \text{R-CHO} \quad \text{Aldehydes}
\]

\[
\text{CrO}_3\text{H}^+ \\
\text{R-CHOH-R} \xrightarrow{65 \text{ C, H}_2\text{O}} \text{R-CO-R} \quad \text{Ketones}
\]

Care must be taken that the aldehyde produced is not oxidized further to a carboxylic acid. This can be done by removing the aldehyde from the reaction mixture as soon as it is formed. This can be done quit easily by distillation, because Aldehydes have lower boiling point than that of the starting alcohol.
By carrying out the oxidation at a temperature slightly above the boiling point of the aldehyde, it can be removed by distillation as it forms and before it can be further oxidized. The preparation of propionaldehyde from the oxidation of 1-propanol by chromic oxide (CRO₃) in acid solution is an example of this method:

\[
\text{CrO}_3, \text{H}^+ \\
\text{CH}_3\text{CH}_2\text{CH}_2\text{OH} \rightarrow \text{CH}_3\text{CH}_2\text{CHO} \\
65 \degree \text{C, H}_2\text{O}
\]

1-propanol, b.p.97°C propanaldehyde, b.p. 49°C

2. Oxidation of diols with periodic acid or lead tetra-acetate gives aldehydes or ketones depending upon the structure of the diol.

\[
\begin{align*}
\text{CH}_2\text{-OCH}_3 \\
\text{CH}_3\text{-OH} \\
\text{CH}_2\text{OH} \\
\end{align*} \rightarrow \begin{align*}
\text{CH}_3\text{-OCH}_3 \\
\text{CH}_2=\text{O} \\
\text{CH}_2=\text{O} \\
\end{align*}
\]

General preparation of ketones

3. Hydration of alkynes always produces ketones except for the hydration of acetylene.

\[
\begin{align*}
\text{R-}\text{C} & \equiv \text{C-H} \rightarrow \text{R-C}=\text{CH}_2 \\
\text{R-}\text{C} & \equiv \text{C-H} + \text{H}_2\text{O} \rightarrow \text{R-C} & \equiv \text{CH}_2 \rightarrow \text{R-C}-\text{CH}_3 \\
\text{R-}\text{C} & \equiv \text{C-H} + \text{H}^+&/\text{Hg}^{++} & \rightarrow \text{R-C}=\text{CH}_2 & \rightarrow \text{R-C}-\text{CH}_3 \\
\text{R-}\text{C} & \equiv \text{C-H} + \text{H}^+&/\text{Hg}^{++} & \rightarrow \text{R-C}=\text{CH}_2 & \rightarrow \text{R-C}-\text{CH}_3
\end{align*}
\]
Reactions of Aldehydes and Ketones:

The reactions of Aldehydes and ketones can be grouped into two categories:

1. **Reactions of carbonyl group:**

   a. Basicity of the carbonyl oxygen: the carbonyl oxygen is weakly basic and thus reacts with Lewis and Bronsted acids. The reaction may be represented as follows:

   ![Chemical Reaction Diagram]

   Where $E^+$ is any electrophile

   - **Reduction of aldehydes and ketones**
     
     The reduction of Aldehydes and ketones form alcohols

     ![Reduction Diagram]

     Aldehyde $\rightarrow$ 1 alcohol

     - Oxidation

     Ketone $\rightarrow$ 2 alcohol

     Reduction

     Acetone $\rightarrow$ 2-Propanol

     $\text{CH}_3\text{CH}_2\text{CH}_2\text{OH}$
In living systems

b. Addition reactions: this is the most important reaction of carbonyl bond.

\[ \text{Malate} \quad \text{Oxaloacetate} \]

\[ \begin{align*}
\text{Oxidation of malate} & \quad \text{reduction of malate} \\
\text{Malate} & \quad \text{Oxaloacetate} \\
\end{align*} \]

\[ \text{Reduced enzyme bound nicotinamide} \]

Where E-Y is a general reagent

\[ \text{Addition of water: Most Aldehydes react with water to form an equilibrium mixture of the Aldehyde and an aldehyde hydrate:} \]

\[ \begin{align*}
\text{R-C-R} + \text{E-Y} & \rightarrow \text{R-C-R} \\
\end{align*} \]
These hydrates are 1,1-doils. They are usually too unstable to isolate and purify because they easily lose water to reform the aldehyde. Most ketones are less readily hydrated. In certain special cases, the 1,1-doil is sufficiently stable that it can be isolated. In these compounds the carbonyl carbon is bonded to one or more highly electronegative groups. Hexafluoroacetone is one of the few ketones that form stable hydrates. Chloral hydrate is another example of a stable hydrate. It is crystalline compound that is used in veterinary medicine as an anesthetic for animals.

\[
\begin{align*}
\text{CF}_3\text{CCF}_3 & \quad \text{CCL}_4\text{CH} \\
\text{OH} & \quad \text{OH}
\end{align*}
\]

Hexafluoroacetone hydrate  chlroral hydrate

**Addition of alcohols:**

Aldehydes react with alcohols in the presence of an acid catalyst to form **hemiacetal as product:**

\[
\begin{align*}
\text{Aldehyde} & \quad \text{Aldehyde hydrate}
\end{align*}
\]
Hemiacetal contains an alkoxy and an alcohol group, both bonded to the original carbon of the carbonyl group. In the presence of excess alcohol, a hemiacetal can react to form an acetal and water.

Hemiacetal can be formed within one molecule that contains a hydroxyl and an aldehyde group in the proper positions can form a five or six cyclic hemiacetal. For example:
Ketones react with alcohols in a similar manner to form hemiketals and ketals. For example:

\[
\begin{align*}
&\text{CH}_3\text{C}=O + \text{CH}_3\text{OH} \quad \text{H}^+ \\
\leftrightharpoons \\
&\text{CH}_3\text{C} + \text{OCH}_3 + \text{CH}_3\text{OH} \quad \text{H}^+
\end{align*}
\]

Acetone methanol Hemiketal ketal

Ketals like acetals, do not react with aqueous base but are readily cleaved by aqueous acid.

**In living system:**

One of the simplest addition reactions of a carbonyl group in living systems is the enzyme-catalyzed hydration of a carbon dioxide to a bicarbonate ion according to the following equation:

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

The enzyme that catalyzes this reaction is widely distributed in mammals. It is especially active in tissues that are involved in respiration, such as blood cells.

- Addition of ammonia and its derivatives: Schiff base

Ammonia adds to the carbonyl group of Aldehydes and ketones. The initial product, in which the nitrogen is bonded to the carbon and one hydrogen is bonded to oxygen is unstable and spontaneously loses water to form an imine:
Compounds having the general structures $\text{RHC}=\text{NR'}$ and $\text{R}_2\text{C}=\text{NR'}$ are called aldimines and ketimines, respectively. These are also generally called Schiff bases. **The net result of the addition is to convert a** $\text{C}=\text{O}$ **double bond in to** $\text{C}=\text{N}$ **double bond.**

**In living system:**
Amino acids are synthesized in the living systems by the reverse transamination reaction:

$$\text{CH}_3\text{CO}_2\text{H} + \text{H}_2\text{N}\text{CH}_2\text{CO}_2\text{H} \xrightleftharpoons{E} \text{CHNH}_2 + \text{O}=\text{C} \text{CH}_2\text{CO}_2\text{H}$$

Alanine $\alpha$-Ketoglutaric acid pyruvic acid glutamic acid

Pyridoxal phosphate + Alanine $\xrightarrow{\text{Schiff base}}$ Schiff base + $\text{H}_2\text{O}$

Amino group carrier between the amino acid and the keto acid

\[\text{R} - \text{NH}_2 \xrightarrow{\text{H}^+} \text{NH} \]
Condensation reaction
In condensation reactions, two compounds are joined together (or condensed) to form a large compound:

- **Aldol condensation**: this is a reaction in which the carbonyl carbon of one molecule forms a bond with the α-carbon of another carbonyl containing molecule. For example:

![Diagram of aldol condensation]

Aldol = aldehyde + alcohol

Retro-aldol condensation: is the reverse of this reaction.

The aldol condensation is an equilibrium. The equilibrium constant for formation of products is favorable for most Aldehydes. However, for ketones, the reaction is much less favorable.

**In living system**
Example(1): carbohydrates are prepared in the living systems by an enzyme-catalyzed aldol condensation:
D-Glyceraldehyde 1,3-Dihydroxyacetone D-Fructose 1,6 diphosphate

3-phosphate phosphate

Where (P) = O

\[ \begin{align*}
\text{HO} & \quad \text{H} \quad \text{O} \\
(P)\text{OH}_2\text{C} & \quad \text{CHCCCH}_2\text{O}(P) \\
\text{H}_2\text{C} & \quad \text{CH}_2\text{O}(P)
\end{align*} \]

This is an example of stereospecificity of enzyme catalyzed reactions

Example(2): acetyl group of Acetyl-CoA reacts with many carbonyl groups in an aldol-like condensation.
- **Claisen condensation:**
  Esters undergo condensation reactions when treated with base.
  The overall result of a Claisen condensation is the transfer of an acyl group from one ester molecule to another.

**In living system**
The formation of Acetyl-CoA by an enzyme-catalyzed reaction of Acetyl-CoA.

C) Oxidation of Aldehydes. Aldehydes can be oxidized to carboxylic acids.

\[ \text{R-C-H} \xrightarrow{\text{Oxidation}} \text{R-C-OH} \]

2. Reactions involving the \( \alpha \)-carbon.

a) Acidity of the \( \alpha \)-hydrogen.
Aldehydes, ketons and esters react with strong bases (because they are very weak acids) to form carbanions (carbanions are anions in which the carbon bears a negative charge \( \text{CH}_3 \)).

The presence of the carbonyl group makes the C-H bond \( \alpha \) to it much more acidic than usual. The reason for this is that the carbanion can be stabilized by resonance. For example:

\[ \text{CH}_3\text{CCH}_3 + \text{OH}^- \xleftrightarrow{} \text{CH}_2\text{CCH}_3^- \xleftrightarrow{} \text{CH}_2 = \text{CCH}_3 \]

**Resonance-Stabalized enolate anion**
The formation of an enolate anion is the first step in the base-catalyzed condensation reactions of Aldehydes, ketones, esters, and diethyl malonate.