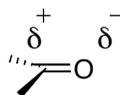**Aldehydes and Ketones**

Aldehydes and ketones contain a carbonyl group, in which the carbon atom is doubly bonded to an oxygen atom. The carbonyl group is highly polarized, with a very electrophilic carbon atom.

$$\overset{+}{\delta} \quad \overset{-}{\delta}$$
$$C=O$$

Many reaction of aldehydes and ketones start with nucleophilic attack at the carbon atom of the carbonyl group by a nucleophile (Nu:). The nucleophile always has a pair of electrons available but may or may not bear a negative charge. The electrons of the carbon-oxygen double bond then become localized on the oxygen atom to form an alkoxide ion. This alkoxide ion then reacts with an electrophile (E^+ which is usually a proton, H^+) to quench the negative charge. Alternatively (especially with weak nucleophiles), the oxygen is protonated first and then the nucleophile adds. The net result is an addition reaction.

$$\underset{/}{\overset{\backslash}{C}}=O \quad \xrightarrow{\text{Nu}^- \ E^+} \quad Nu-\overset{|}{\underset{|}{C}}-O-E$$
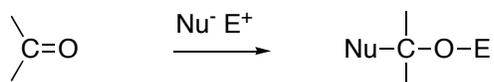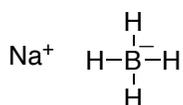
Many nucleophiles will react with the carbonyl group, and, depending on the reagents, reaction conditions, and nature of the intermediate formed, further reactions are possible before the final product is obtained. The most important step in all of these reactions is the bonding between a nucleophile and the carbon atom of the carbonyl group.
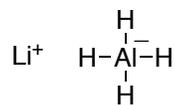
There are a variety of nucleophiles that react with aldehydes and ketones and can be classified as strong nucleophiles or weak nucleophiles. Strong nucleophilic attack onto ketones and aldehydes is an irreversible reaction whereas weak nucleophilic attack is reversible.

Strong Nucleophiles (H:⁻ and R:⁻)

Nucleophilic attack of the hydride ion (H:⁻) to the electrophilic carbon of the carbonyl group results in the reduction of aldehydes to primary alcohols and ketones to secondary alcohols. These reductions are done using sodium borohydride ($NaBH_4$) or lithium aluminum hydride ($LiAlH_4$) as shown below. Both of these reagents provide a source of the hydride ion, which is very basic and a powerful nucleophile.

<div align="center">

$$Na^+ \quad H-\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle H}{|}}{B}}{}^-\!-H \qquad\qquad Li^+ \quad H-\overset{\overset{\textstyle H}{|}}{\underset{\underset{\textstyle H}{|}}{Al}}{}^-\!-H$$
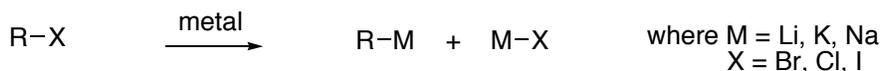
sodium borohydride   lithium aluminum hydride

</div>

Lithium aluminum hydride (also known as LAH) reacts violently with water and alcohols to generate hydrogen gas (H_2). Sodium borohydride reacts in a similar fashion, but is less reactive than LAH. Because sodium borohydride is less reactive than LAH, it is easier to handle and may be used with water or alcohol as the solvent. The reaction of sodium borohydride with carbonyl compounds is fast enough to compete successfully (i.e. reduce the carbonyl) with its decomposition reaction with water or alcohol.
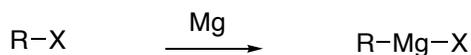
Nucleophilic attack of the alkyl anion (R:⁻) to the electrophilic carbon of the carbonyl group results in the transformation of aldehydes to secondary alcohols and ketones to tertiary alcohols. These reductions are done using organometallic reagents. Organometallic reagents are prepared by the reaction of alkyl halides with metals such as lithium, sodium, potassium or magnesium. Alkyl, aryl, and vinyl halides will react with metals. The organometallic reagents (RMgX) prepared from magnesium are named Grignard reagents, after Victor Grignard, a French chemist who discovered them at the beginning of the century.

$$R-X \quad \xrightarrow{\text{metal}} \quad R-M \; + \; M-X \qquad \begin{array}{l}\text{where M = Li, K, Na} \\ \text{X = Br, Cl, I}\end{array}$$

A carbon-halogen bond is polarized with partial positive charge on the carbon and partial negative charge on the halogen. When a metal is introduced, the partial charge on the carbon is now negative since these metals do not accept a negative charge.

$$\overset{+}{\overset{\delta}{}}\;\overset{-}{\overset{\delta}{}} \atop R-X \quad \xrightarrow{\text{metal}} \quad \overset{-}{\overset{\delta}{}}\;\overset{+}{\overset{\delta}{}} \atop R-M$$

Metals such as lithium, sodium and potassium require two equivalents of metal to one equivalent of alkyl halide because these metals are monovalent. Magnesium on the other hand is divalent and only needs one equivalent.

$$R-X \quad \xrightarrow{Mg} \quad R-Mg-X$$

Hydride Addition

A general example of nucleophilic attack by hydride is shown below. The mechanism involves nucleophilic attack of the hydride to the electrophilic carbon atom of the carbonyl group. Rehybridization of the carbonyl carbon from sp^2 to sp^3 occurs, and a tetrahedral alkoxide ion intermediate is produced. The alkoxide ion that forms is then protonated in the work-up step, which usually involves the addition of water or an acid. The reaction is irreversible because the hydride species cannot stabilize the negative charge as well as the alkoxide.
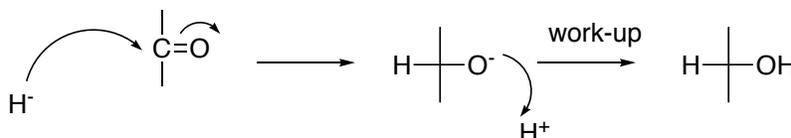
An example is the reduction of acetone to 2-propanol with sodium borohydride followed by a work-up step.

acetone   2-methyl-2-propanol
                              (tert-butyl alcohol)
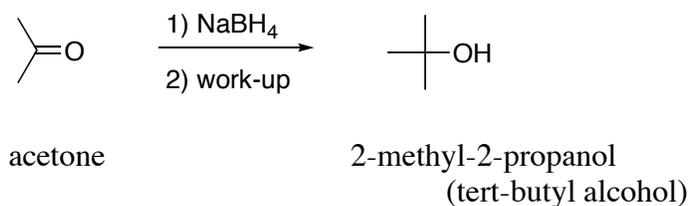
Another, more complicated example is the reduction of estrone to estradiol with lithium aluminum hydride followed by a work-up step. In this reaction 2 equivalents of the hydride anion are needed. The first step of the reaction involves the deprotonation of the phenol proton. The phenol proton is an acidic proton and will be deprotonated with a strong base such as the hydride anion to give hydrogen gas. The second step is nucleophilic attack of the hydride anion on the ketone to give the secondary alkoxide ion. A work-up step involving addition of an acid (HCl) then reprotonates the phenol and the alkoxide anion to give estradiol.

estrone   estradiol

1) LiAlH$_4$

2) HCl
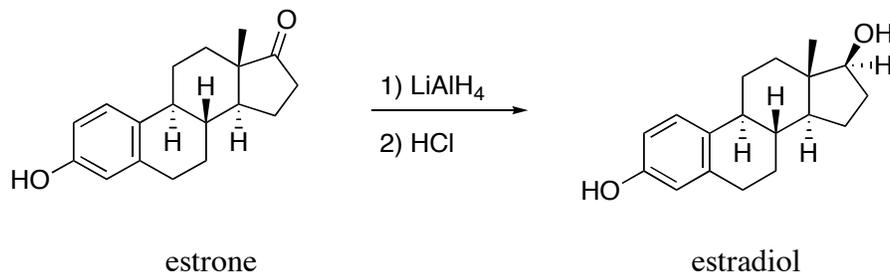
The hydride in the above example is shown to come from the bottom face of estrone due to the hindrance of the top face by the C13 methyl group. Shown below are the C and D rings of estrone.
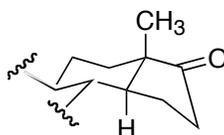
Another example is the reduction of cyclohexanone to cyclohexanol with sodium borohydride followed by an acidic aqueous work-up.

cyclohexanone   cyclohexanol

1) NaBH$_4$

2) work-up

Alkyl Anion Additions

Just like hydride addition, alkyl addition is an irreversible reaction due to the fact that the alkoxide anion can stabilize the negative charge much better than the alkyl anion, as mentioned above.

An example is the addition methyl lithium to acetone followed by a work-up to yield 2-methyl-2-propanol. Adding methyl lithium is equivalent to adding CH_3^-.

| acetone | tetrahedral intermediate | 2-methyl-2-propanol |

Another example is the addition of methyl lithium to estrone to yield the tertiary alcohol. The methyl group adds on the bottom face due to the same arguments given above for the hydride attack of estrone to yield estradiol. Two equivalents of methyl lithium are needed for this reaction. One equivalent is needed to attack the carbonyl group and the other is to deprotonate the acidic phenol proton. Acidic aqueous work-up then reprotonates both the phenoxide anion at C-3 and the alkoxide at C-17 to give the phenol and the alcohol, respectively.

estrone

Another example is the addition of a lithium acetylide to estrone to yield ethinylestrone. Ethinylestrone is a major component in many birth control pills. This compound is very active in keeping the female body think it is pregnant.

estrone   ethinyl estrone

Weak Nucleophiles

Attack by weak nucleophiles on ketones and aldehydes under basic conditions is shown below with the general mechanism. The first step involves the reversible attack of the nucleophile to form the alkoxide anion, which is then protonated. The reaction is usually acid catalyzed and always reversible. In fact, most such reactions are done under acidic conditions, in which case the mechanism involves initial protonation of the oxygen as discussed in the previous class. Under basic conditions, many such reactions have an equilibrium that lies to the side of starting materials (i.e. ketone or aldehyde).
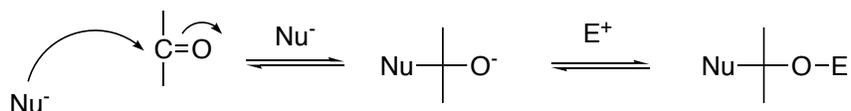
The weak nucleophiles include: hydroxide ion ($^-$OH) or water (H_2O), alkoxide anion ($^-$O-R) or alcohols (H-O-R), cyanide ion ($^-$CN) or hydrogen cyanide (HCN) and amines (H-NRR' where R and R' can be H or alkyl).

Hydrate Formation

Aldehydes and ketones undergo reaction with water in a reversible fashion to yield 1,1-diols, or geminal diols. The nucleophilic addition of water to ketones and aldehydes is slow in pure water but is catalyzed by acid. An example of hydrate formation is the reversible reaction of chloral (2,2,2-trichloroethanal) with water to form the hydrated species. Due to the inductive electron-withdrawing effect of chlorine, the equilibrium in water lies to the right (hydrated form).

chloral   hydrate form
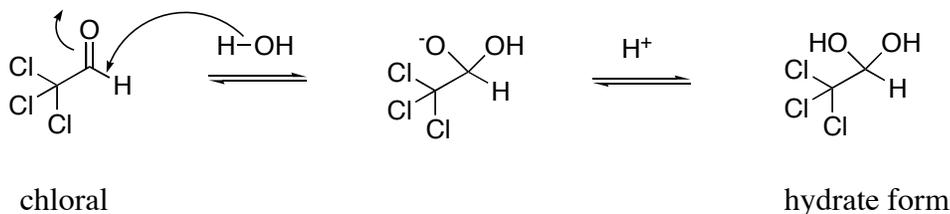
Hemi-Acetal Formation

Hemiacetal formation is similar to hydration but alcohols are used instead of water as the nucleophile. This reaction is reversible and is especially favored if you can form 5 or 6 membered rings as in sugars. An example of hemiacetal formation is the addition of methanol to formaldehyde to yield the hemiacetal.

acetone   hemi acetal
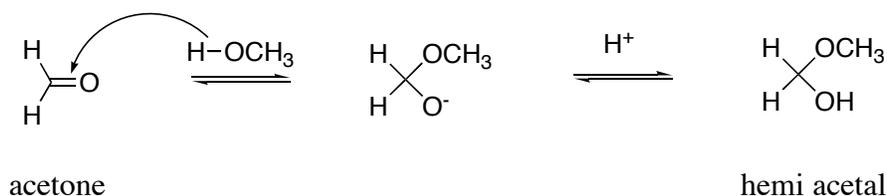
Cyanohydrin Formation

Aldehydes and ketones react with hydrogen cyanide (HCN) to yield cyanohydrins. Cyanohydrin formation works best with aldehydes but also works with certain ketones. An example of cyanohydrin formation is the addition of HCN to benzaldehyde to yield the cyanohydrin. Cyanide is strongly nucleophilic, and addition occurs by a typical nucleophilic addition pathway. Protonation of the anionic intermediate yields the cyanohydrin.

benzaldehyde   cyanohydrin
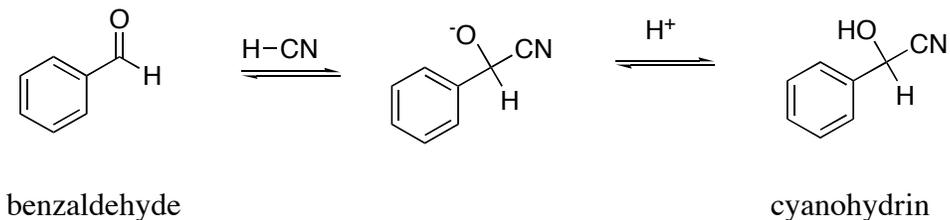
Cyanohydrin formation is particularly interesting because of the further chemistry that can be done. For example, nitriles (RCN) can be reduced with LAH to yield primary amines (RCH_2NH_2) and can be hydrolyzed by aqueous acid to yield carboxylic acids.

In order to avoid the dangers inherent in handling such a toxic gas as hydrogen cyanide (HCN), it is usually generated during the reaction by adding an acid (H_2SO_4) to a mixture of carbonyl compound and excess sodium cyanide (NaCN).

Aminal Formation

Aminal formation is similar to that of hydration except the nucleophile is an amine functionality. An example is the addition of methylamine to acetone to yield the aminal product in a reversible fashion.

acetone   methylamine   aminal

Further reaction of the aminal can take place in which the elements of water (H_2O) are eliminated to yield an imine functionality as shown below. This elimination occurs with aminals, hemiacetals and the Wittig reagent (will talk about later).

aminal   imine

An example of imine formation is the addition of methyl amine to cyclohexanone to yield an imine through the aminal intermediate as shown below.

cyclohexanone   aminal   imine

Specialized Imines

Reaction of ketones and aldehydes with hydroxylamine are particularly useful because the products in these reactions (called oximes) are usually crystalline and easy to handle. Such crystalline derivatives are sometimes prepared as means of identifying liquid ketones and aldehydes. An example involves the addition of hydroxylamine with acetone to yield the oxime product.

acetone   hydroxylamine   aminal   oxime

An important variant of the imine forming reaction is treatment of the ketone or aldehyde with hydrazine (H_2NNH_2). This is an extremely valuable synthetic method for converting ketones and aldehydes into alkanes using the Wolff-Kishner reaction, which will be discussed later. An example involves the addition of hydrazine to acetone to yield the hydrazone.

acetone   hydrazine   hydrazone