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# Chemical reactivity of carbonyl compounds

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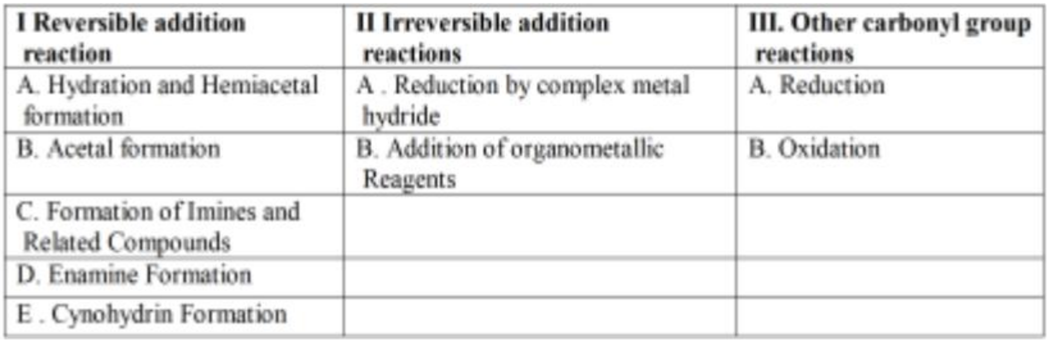
**Abstract**

Typical examples showing the chemical properties of carbonyl compounds are shown. Aldehydes and ketones undergoes reversible as well as irreversible addition reactions. Fig (1)

Various factor affecting these reactions are also explained with examples. The trend in the reactivity in the acid derivatives is also explained.

**Keywords:** hemiacetals, acetals, ketals, organometallics, imines, enamine, cyanohydrin, nucleophile



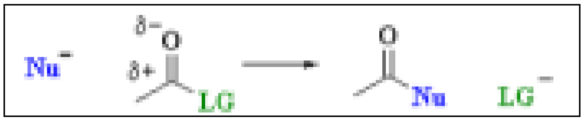
| I Reversible addition reaction | II Irreversible addition reactions | III. Other carbonyl group reactions |
|---|---|---|
| A. Hydration and Hemiacetal formation | A . Reduction by complex metal hydride | A. Reduction |
| B. Acetal formation | B. Addition of organometallic Reagents | B. Oxidation |
| C. Formation of Imines and Related Compounds | | |
| D. Enamine Formation | | |
| E . Cynohydrin Formation | | |

**Figure 1**

## 1. Introduction

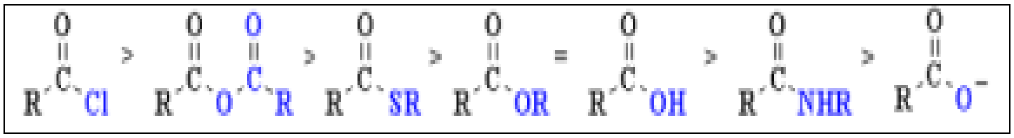
### Reactivity of carboxylic acid derivatives

Carboxylic acid derivatives react tend to react via nucleophilic acyl substitution where the group on the acyl unit, R-C=O undergoes substitution:



Note that *unlike* aldehydes and ketones, this reactivity of carboxylic acids *retains* the carbonyl group.

The observed reactivity order is shown below:

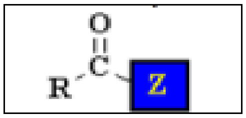


This reactivity order is important. We should be able to understand, rationalise and use it.

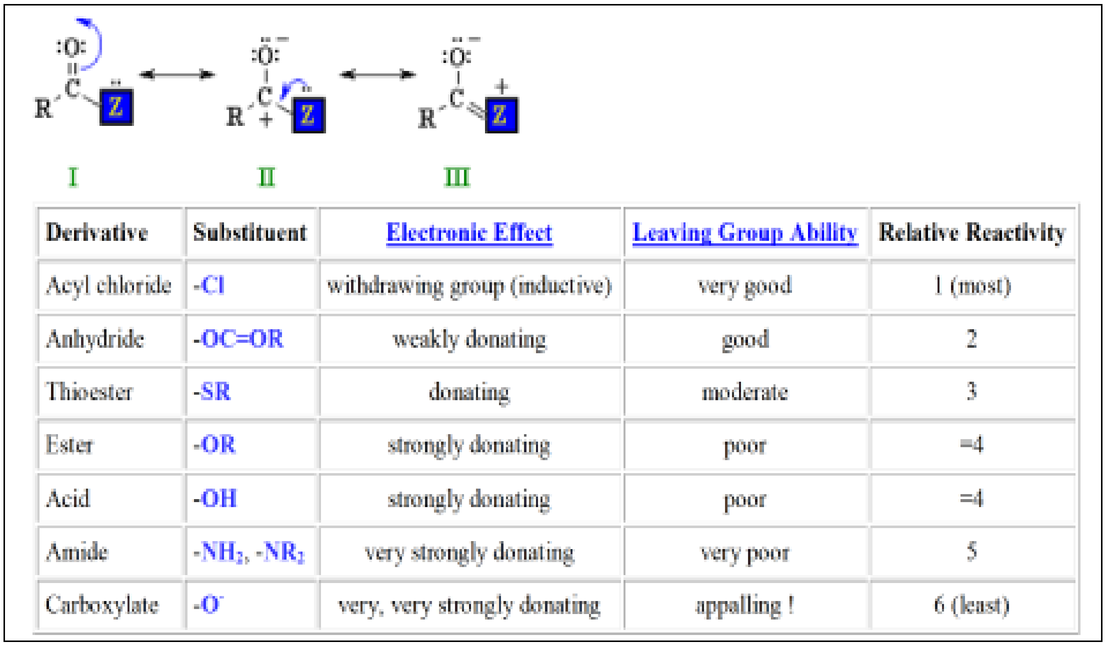
**There are 3 resonance structures to consider for carboxylic acid derivatives.**

It is useful to view the carboxylic acid derivatives as an acyl group, R-C=O, with a different substituent attached.

The important features of the carboxylic acid derivatives that influence their reactivity are governed by this substituent in the following ways: the effect the substituent has on the electrophilicity of the carbonyl Co if the substituent is electron donating, then the electrophilicity is reduced, \ less reactive o if the substituent is electron withdrawing, the the electrophilicity is increased,\more reactive the ability of the substitutent to function as a leaving group.



I and II are similar to those of aldehydes and ketones, but there is also a third possibility III where a lone pair on the heteroatom Z is able to donate electrons to the adjacent positive center. The stronger this electron donation from Z the less positive the carbonyl C and the less electrophilic the carbonyl group. The ability of Z to donate electrons is linked to its electronegativity...the more electronegative Z is, the less the stabilising effect.



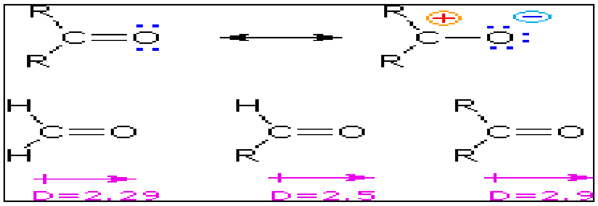
| Derivative | Substituent | Electronic Effect | Leaving Group Ability | Relative Reactivity |
|---|---|---|---|---|
| Acyl chloride | -Cl | withdrawing group (inductive) | very good | 1 (most) |
| Anhydride | -OC=OR | weakly donating | good | 2 |
| Thioester | -SR | donating | moderate | 3 |
| Ester | -OR | strongly donating | poor | =4 |
| Acid | -OH | strongly donating | poor | =4 |
| Amide | -NH$_2$, -NR$_2$ | very strongly donating | very poor | 5 |
| Carboxylate | -O$^-$ | very, very strongly donating | appalling ! | 6 (least) |

It is also useful to appreciate where aldehydes and ketones fit into the reactivity scale towards nucleophiles:

**Acyl halides > anhydrides > aldehydes > ketones > esters = carboxylic acids > amides**

**Properties of Aldehydes and Ketones**

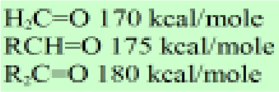
A comparison of the properties and reactivity of aldehydes and ketones with those of the alkenes is warranted, since both have a double bond functional group. Because of the greater electronegativity of oxygen, the carbonyl group is polar, and aldehydes and ketones have larger molecular dipole moments (D) than do alkenes. The resonance structures on the right illustrate this polarity, and the relative dipole moments of formaldehyde, other aldehydes and ketones confirm the stabilizing influence that alkyl substituents have on carbocations (the larger the dipole moment the greater the polar character of the carbonyl group). We expect, therefore, that aldehydes and ketones will have higher boiling points than similar sized alkenes. Furthermore, the presence of oxygen with its non-bonding electron pairs makes aldehydes and ketones hydrogen-bond acceptors, and should increase their water solubility relative to hydrocarbons. Specific examples of these relationships are provided in the following table.



| Compound | Mol. Wt. | Boiling Point | Water Solubility |
|---|---|---|---|
| $(CH_3)_2C=CH_2$ | 56 | -7.0 °C | 0.04 g/100 |
| $(CH_3)_2C=O$ | 58 | 56.5 °C | infinite |
| $CH_3CH_2CH_2CH=CH_2$ | 70 | 30.0 °C | 0.03 g/100 |
| $CH_3CH_2CH_2CH=O$ | 72 | 76.0 °C | 7 g/100 |
|  | 96 | 103.0 °C | insoluble |
|  | 98 | 155.6 °C | 5 g/100 |

The polarity of the carbonyl group also has a profound effect on its chemical reactivity, compared with the non-polar double bonds of alkenes. Thus, reversible addition of water to the carbonyl function is fast, whereas water addition to alkenes is immeasurably slow in the absence of a strong acid catalyst. Curiously, relative bond energies influence the thermodynamics of such addition reactions in the opposite sense.

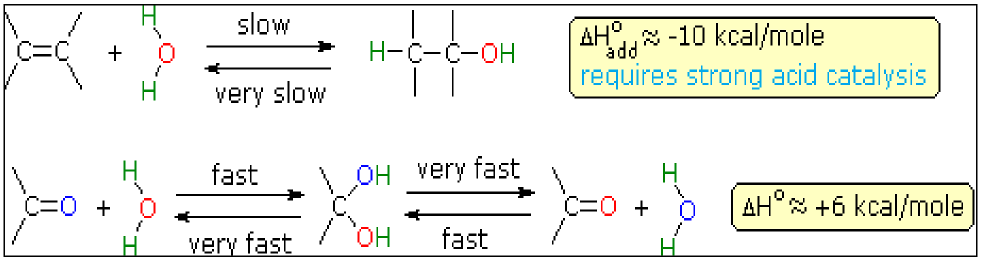
The C=C of alkenes has an average bond energy of 146 kcal/mole. Since a C–C ó-bond has a bond energy of 83 kcal/mole, the ð-bond energy may be estimated at 63 kcal/ mole (i.e. less than the energy of the sigma bond). The C=O bond energy of a carbonyl group, on the other hand, varies with its location, as follows:



$H_2C{=}O$ 170 kcal/mole
$RCH{=}O$ 175 kcal/mole
$R_2C{=}O$ 180 kcal/mole

The C–O ó-bond is found to have an average bond energy of 86 kcal/mole.

Consequently, with the exception of formaldehyde, the carbonyl function of aldehydes and ketones has a ð-bond energy greater than that of the sigma-bond, in contrast to the pi-sigma relationship in C=C. This suggests that addition reactions to carbonyl groups should be thermodynamically disfavored, as is the case for the addition of water. All of this is summarized in the following diagram (ÄH° values are for the addition reaction).



Although the addition of water to an alkene is exothermic and gives a stable product (an alcohol), the uncatalyzed reaction is extremely slow due to a high activation energy. The reverse reaction (dehydration of an alcohol) is even slower, and because of the kinetic barrier, both reactions are practical only in the presence of a strong acid.

## Reactions of Aldehydes and Ketones

### 1. Reversible Addition Reactions

### A. Hydration and Hemiacetal Formation

It has been demonstrated (above) that water adds rapidly to the carbonyl function of aldehydes and ketones. In most cases the resulting hydrate (a geminal-diol) is unstable relative to the reactants and cannot be isolated. Exceptions to this rule exist, one being formaldehyde (a gas in its pure monomeric state). Here the weaker pi-component of the carbonyl double bond, relative to other aldehydes or ketones, and the small size of the hydrogen substituents favor addition. Thus, a solution of formaldehyde in water (formalin) is almost exclusively the hydrate, or polymers of the hydrate. Similar reversible additions of alcohols to aldehydes and ketones take place. The equally unstable addition products are called hemiacetals.

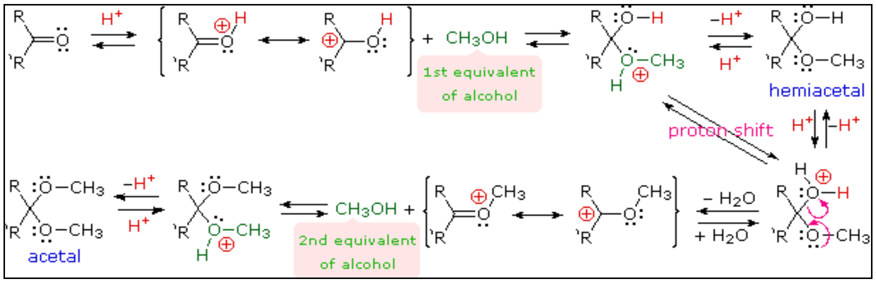
$R_2C{=}O + R'OH \rightleftharpoons R'O{-}(R_2)C{-}O{-}H$ (a hemiacetal)

### B. Acetal Formation

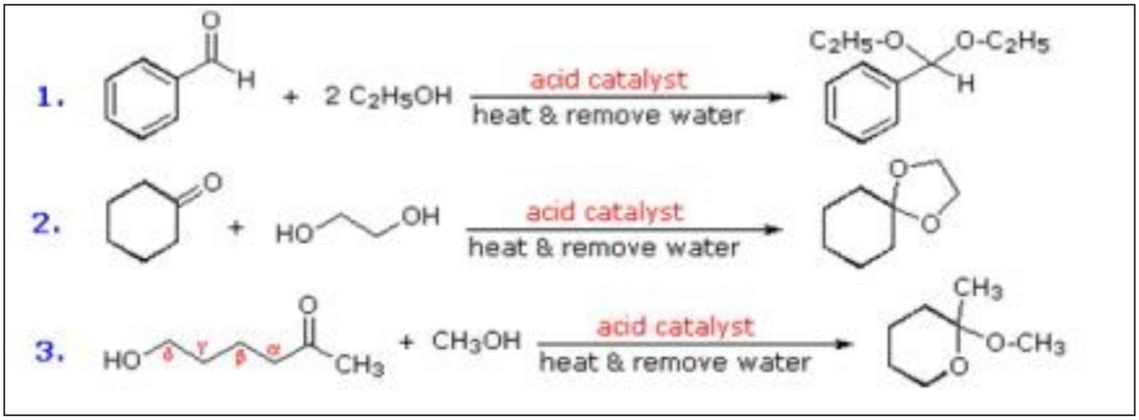
Acetals are geminal-diether derivatives of aldehydes or ketones, formed by reaction with two equivalents of an alcohol and elimination of water. Ketone derivatives of this kind were once called ketals, but modern usage has dropped that term. The following equation shows the overall stoichiometric change in acetal formation, but a dashed arrow is used because this conversion does not occur on simple mixing of the reactants.

R2C=O + 2 R’OH -----→ R2C (OR’)2 + H2O (an acetal)

In order to achieve effective acetal formation two additional features must be implemented. First, an acid catalyst must be used; and second, the water produced with the acetal must be removed from the reaction. The latter is important, since acetal formation is reversible. Indeed, once pure acetals are obtained they may be hydrolyzed back to their starting components by treatment with aqueous acid. The mechanism shown here applies to both acetal formation and acetal hydrolysis by the principle of microscopic reversibility.



Some examples of acetal formation are presented in the following diagram. As noted, p-toluenesulfonic acid (pKa = -2) is often the catalyst for such reactions. Two equivalents of the alcohol reactant are needed, but these may be provided by one equivalent of a diol (example #2).



The importance of acetals as carbonyl derivatives lies chiefly in their stability and lack of reactivity in neutral to strongly basic environments. As long as they are not treated by acids, especially aqueous acid, acetals exhibit all the lack of reactivity associated with ethers in general.

Among the most useful and characteristic reactions of aldehydes and ketones is their reactivity toward strongly nucleophilic (and basic) metallo-hydride, alkyl and aryl reagents (to be discussed shortly). If the carbonyl functional group is converted to an acetal these powerful reagents have no effect; thus, acetals are excellent protective groups, when these irreversible addition reactions must be prevented.

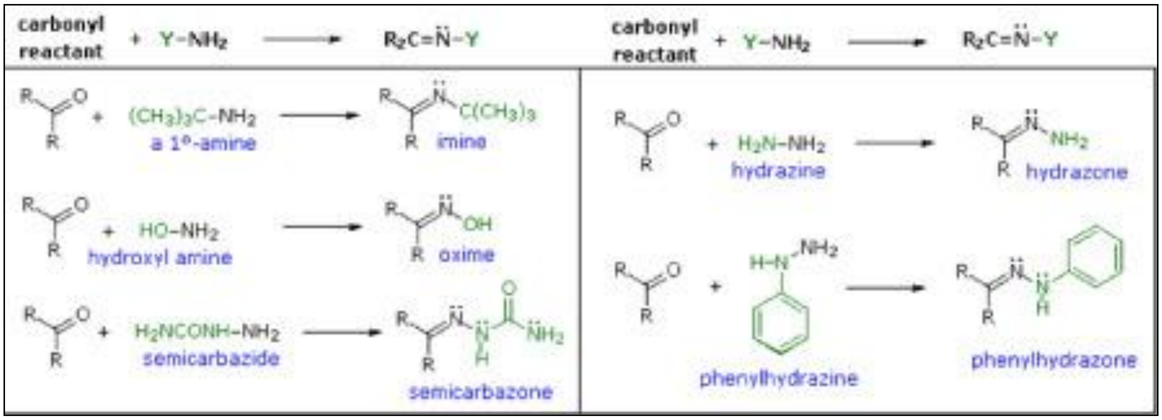
**B. Formation of Imines and Related Compounds**

The reaction of aldehydes and ketones with ammonia or 1º-amines forms imine derivatives, also known as Schiff bases, (compounds having a C=N function). This reaction plays an important role in the synthesis of 2º-amines, as discussed earlier. Water is eliminated in the reaction, which is acid-catalyzed and reversible in the same sense as acetal formation.

R2C=O + R’NH2 ------→ R’NH–(R2)C–O–H R2C=NR’ + H2O

An addition-elimination mechanism for this reaction was proposed, and an animation showing this mechanism is activated by the button.

Imines are sometimes difficult to isolate and purify due to their sensitivity to hydrolysis. Consequently, other reagents of the type Y–NH2 have been studied, and found to give stable products (R2C=N–Y) useful in characterizing the aldehydes and ketones from which they are prepared. Some of these reagents are listed in the following table:

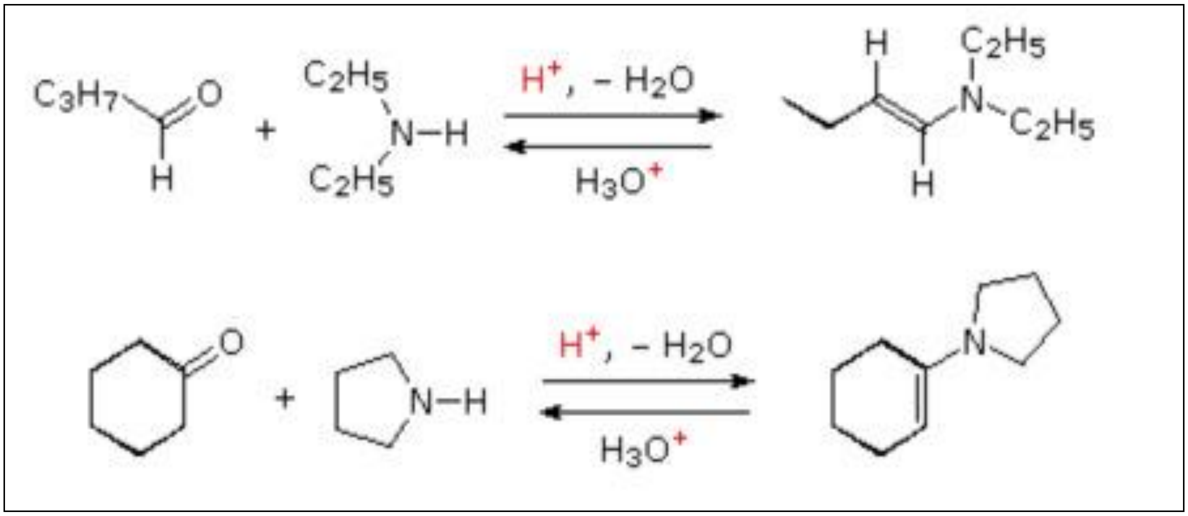


With the exception of unsubstituted hydrazones, these derivatives are easily prepared and are often crystalline solids - even when the parent aldehyde or ketone is a liquid. Since melting points can be determined more quickly and precisely than boiling points, derivatives such as these are useful for comparison and identification of carbonyl compounds. If the aromatic ring of phenylhydrazine is substituted with nitro groups at the 2- & 4-positions, the resulting reagent and the hydrazone derivatives it gives are strongly colored, making them easy to identify.

It should be noted that although semicarbazide has two amino groups (–NH2) only one of them is a reactive amine. The other is amide-like and is deactivated by the adjacent carbonyl group.

**D. Enamine Formation**

The previous reactions have all involved reagents of the type: Y–NH2, i.e. reactions with a 1º-amino group. Most aldehydes and ketones also react with 2º-amines to give products known as enamines. Two examples of these reactions are presented in the following diagram. It should be noted that, like acetal formation, these are acid-catalyzed reversible reactions in which water is lost. Consequently, enamines are easily converted back to their carbonyl precursors by acid-catalyzed hydrolysis. A mechanism for enamine formation may be seen by pressing the “Show Mechanism” button.

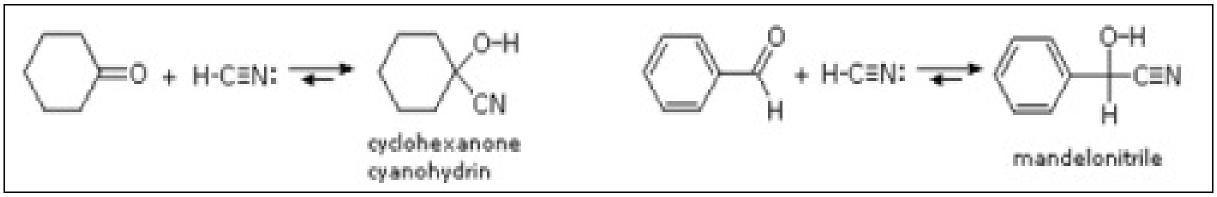


### E. Cyanohydrin Formation

The last example of reversible addition is that of hydrogen cyanide (HCa”N), which adds to aldehydes and many ketone to give products called cyanohydrins.

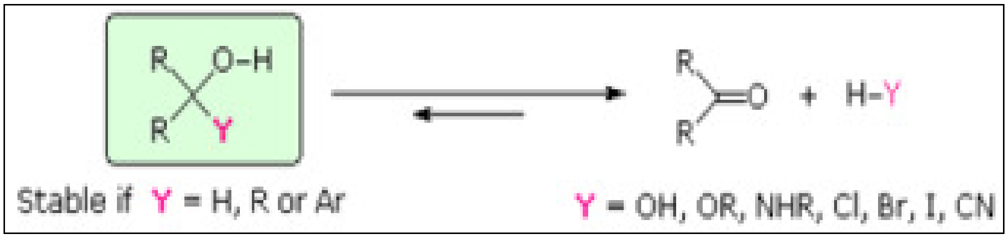
$$RCH{=}O + H{-}C{\equiv}N \rightleftharpoons RCH(OH)CN \text{ (a cyanohydrin)}$$

Since hydrogen cyanide itself is an acid (pKa = 9.25), the addition is not acid-catalyzed. In fact, for best results cyanide anion, Ca”N(-) must be present, which means that catalytic base must be added. Cyanohydrin formation is weakly exothermic, and is favored for aldehydes, and unhindered cyclic and methyl ketones. Two examples of such reactions are shown below. The cyanohydrin from benzaldehyde is named mandelonitrile.



### 2. Irreversible Addition Reactions

The distinction between reversible and irreversible carbonyl addition reactions may be clarified by considering the stability of alcohols having the structure shown below in the shaded box.



If substituent Y is not a hydrogen, an alkyl group or an aryl group, there is a good chance the compound will be unstable (not isolable), and will decompose in the manner shown. Most hydrates and hemiacetals (Y = OH & OR), for example, are known to decompose spontaneously to the corresponding carbonyl compounds. Aminols (Y = NHR) are intermediates in imine formation, and also revert to their carbonyl precursors if dehydration conditions are not employed. Likewise, á-haloalcohols (Y = Cl, Br & I) cannot be isolated, since they immediately decompose with the loss of HY. In all these cases addition of H–Y to carbonyl groups is clearly reversible.

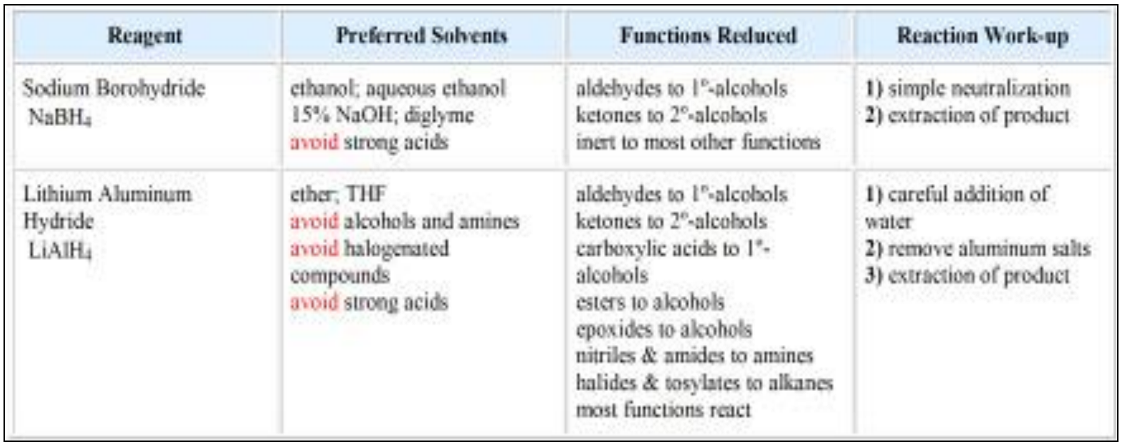
If substituent Y is a hydrogen, an alkyl group or an aryl group, the resulting alcohol is a stable compound and does not decompose with loss of hydrogen or hydrocarbons, even on heating. It follows then, that if nucleophilic reagents corresponding to H:(–), R:(–) or Ar:(–) add to aldehydes and ketones, the alcohol products of such additions will form irreversibly. Free anions of this kind would be extremely strong bases and nucleophiles, but their extraordinary reactivity would make them difficult to prepare and use. Fortunately, metal derivatives of these alkyl, aryl and hydride moieties are available, and permit their addition to carbonyl compounds.

### A. Reduction by Complex Metal Hydrides

Addition of a hydride anion to an aldehyde or ketone would produce an alkoxide anion, which on protonation should yield the corresponding alcohol. Aldehydes would give 1º-alcohols (as shown) and ketones would give 2º-alcohols.

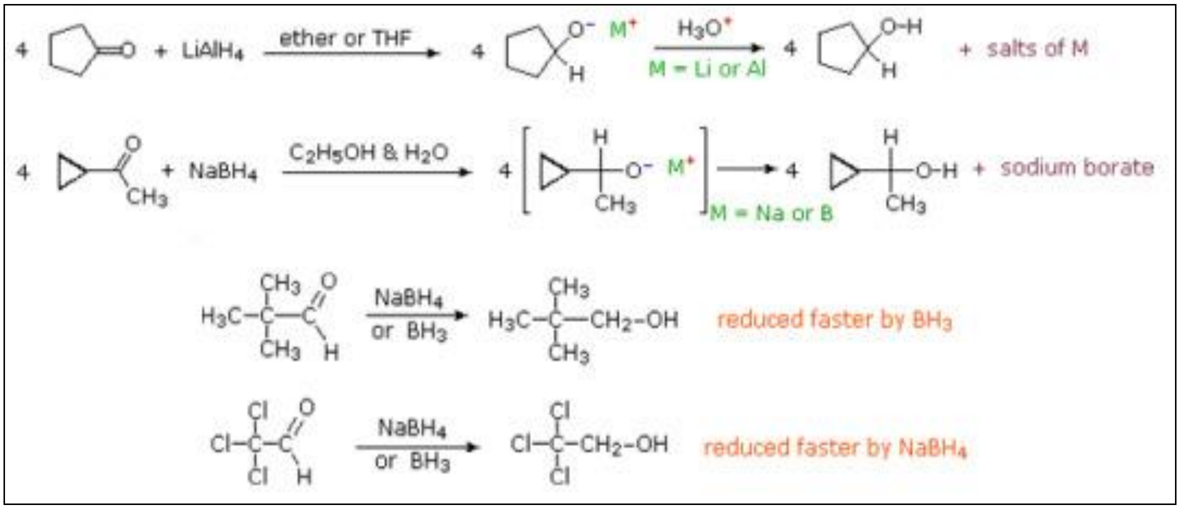
$$RCH{=}O + H:^{(-)} \longrightarrow RCH_2O^{(-)} + H_3O^{(+)} \longrightarrow RCH_2OH$$

Two practical sources of hydride-like reactivity are the complex metal hydrides lithium aluminum hydride ($LiAlH4$) and sodium borohydride ($NaBH4$). These are both white (or near white) solids, which are prepared from lithium or sodium hydrides by reaction with aluminum or boron halides and esters. Lithium aluminum hydride is by far the most reactive of the two compounds, reacting violently with water, alcohols and other acidic groups with the evolution of hydrogen gas. The following table summarizes some important characteristics of these useful reagents.



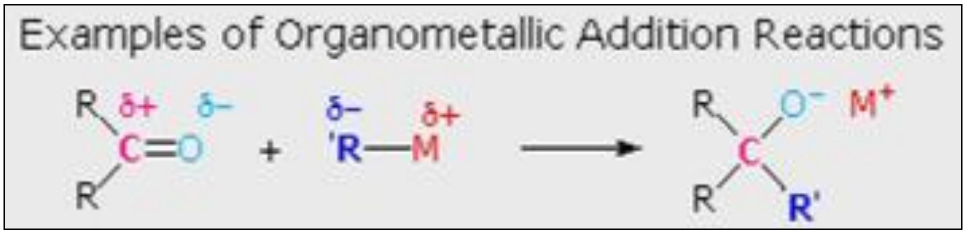
| Reagent | Preferred Solvents | Functions Reduced | Reaction Work-up |
|---|---|---|---|
| Sodium Borohydride<br>$NaBH_4$ | ethanol; aqueous ethanol<br>15% NaOH; diglyme<br>avoid strong acids | aldehydes to 1º-alcohols<br>ketones to 2º-alcohols<br>inert to most other functions | 1) simple neutralization<br>2) extraction of product |
| Lithium Aluminum Hydride<br>$LiAlH_4$ | ether; THF<br>avoid alcohols and amines<br>avoid halogenated compounds<br>avoid strong acids | aldehydes to 1º-alcohols<br>ketones to 2º-alcohols<br>carboxylic acids to 1º-alcohols<br>esters to alcohols<br>epoxides to alcohols<br>nitriles & amides to amines<br>halides & tosylates to alkanes<br>most functions react | 1) careful addition of water<br>2) remove aluminum salts<br>3) extraction of product |

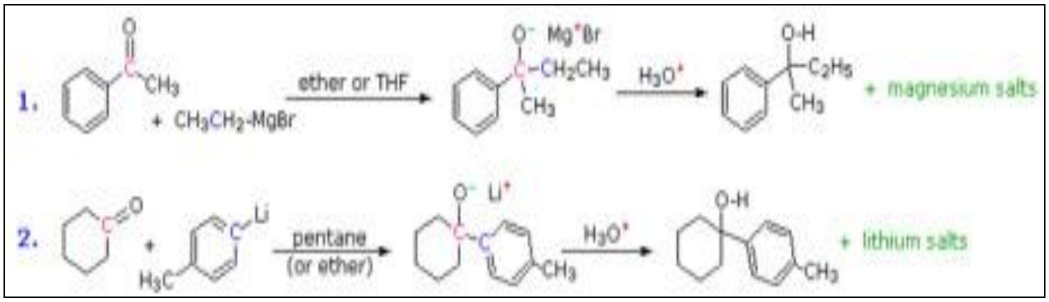
Some examples of aldehyde and ketone reductions, using the reagents described above, are presented in the following diagram.



### B. Addition of Organometallic Reagents

The two most commonly used compounds of this kind are alkyl lithium reagents and Grignard reagents. They are prepared from alkyl and aryl halides, as discussed earlier. These reagents are powerful nucleophiles and very strong bases (pKa's of saturated hydrocarbons range from 42 to 50), so they bond readily to carbonyl carbon atoms, giving alkoxide salts of lithium or magnesium. Because of their ring strain, epoxides undergo many carbonyl-like reactions, as noted previously. Reactions of this kind are among the most important synthetic methods available to chemists, because they permit simple starting compounds to be joined to form more complex structures. Examples are shown in the following diagram.





### 3. Other Carbonyl Group Reactions

### A. Reduction

The metal hydride reductions and organometallic additions to aldehydes and ketones, described above, both decrease the carbonyl carbon's oxidation state, and may be classified as reductions. As noted, they proceed by attack of a strong nucleophilic species at the electrophilic carbon. Other useful reductions of carbonyl compounds, either to alcohols or to hydrocarbons, may take place by different mechanisms. For example, hydrogenation (Pt, Pd, Ni or Ru catalysts), reaction with diborane, and reduction by lithium, sodium or potassium in hydroxylic or amine solvents have all been reported to convert carbonyl compounds into alcohols.

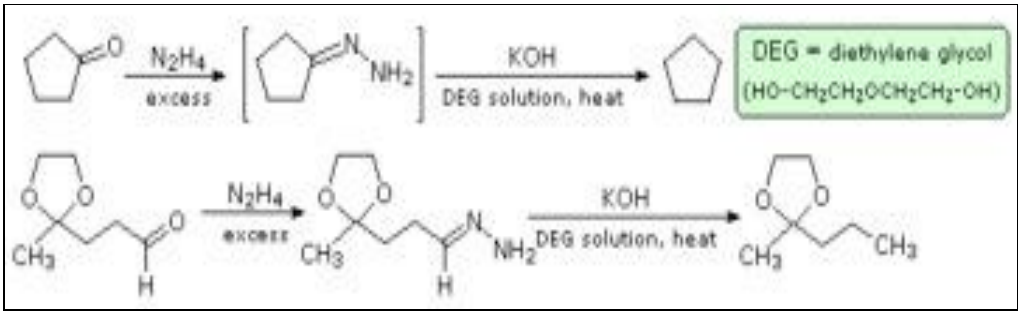
However, the complex metal hydrides are generally preferred for such transformations because they give cleaner products in high yield.

Aldehydes and ketones may also be reduced by hydride transfer from alkoxide salts. The reductive conversion of a carbonyl group to a methylene group requires complete removal of the oxygen, and is called deoxygenation. In the shorthand equation shown here the [H] symbol refers to unspecified reduction conditions which effect the desired change. Three very different methods of accomplishing this transformation will be described here.

$$R_2C{=}O + [H] \longrightarrow R_2CH_2 + H_2O$$

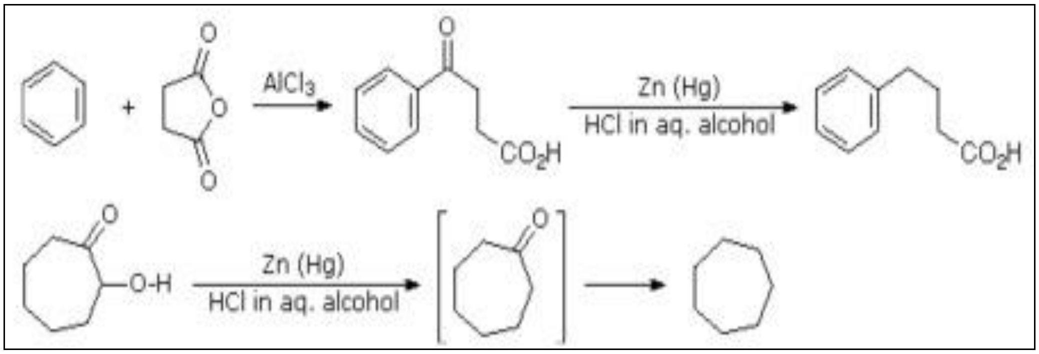
### 1. Wolff-Kishner Reduction

Reaction of an aldehyde or ketone with excess hydrazine generates a hydrazone derivative, which on heating with base gives the corresponding hydrocarbon. A high-boiling hydroxylic solvent, such as diethylene glycol, is commonly used to achieve the temperatures needed. The following diagram shows how this reduction may be used to convert cyclopentanone to cyclopentane. A second example, in which an aldehyde is similarly reduced to a methyl group, also illustrates again the use of an acetal protective group.



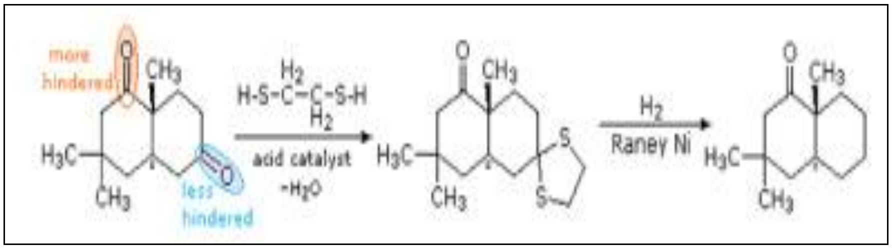
### 2. Clemmensen Reduction

This alternative reduction involves heating a carbonyl compound with finely divided, amalgamated zinc. in a hydroxylic solvent (often an aqueous mixture) containing a mineral acid such as HCl. The mercury alloyed with the zinc does not participate in the reaction, it serves only to provide a clean active metal surface.



### 3. Hydrogenolysis of Thioacetals

In contrast to the previous two procedures, this method of carbonyl deoxygenation requires two separate steps. It does, however, avoid treatment with strong base or acid. The first step is to convert the aldehyde or ketone into a thioacetal, as described earlier. These derivatives may be isolated and purified before continuing the reduction. The second step involves refluxing an acetone solution of the thioacetal over a reactive nickel catalyst, called Raney Nickel.



### B. Oxidation

The carbon atom of a carbonyl group has a relatively high oxidation state. The most common and characteristic oxidation reaction is the conversion of aldehydes to carboxylic acids.

$$RCH=O + [O]\ RC(OH)=O$$

In discussing the oxidations of 1º and 2º-alcohols, we noted that Jones' reagent (aqueous chromic acid) converts aldehydes to carboxylic acids, presumably via the hydrate. Other reagents, among them aqueous potassium permanganate and dilute bromine, effect the same transformation. Even the oxygen in air will slowly oxidize aldehydes to acids or peracids, most likely by a radical mechanism. Useful tests for aldehydes, Tollens' test, Benedict's test & Fehling's test, take advantage of this ease of oxidation by using Ag(+) and Cu(2+) as oxidizing agents (oxidants).

$$RCH=O + 2\,[Ag(+)\,OH(-)] \longrightarrow RC(OH)=O + 2\,Ag\ (\text{metallic mirror}) + H_2O$$

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