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# UNIT 6 NUCLEOPHILIC ADDITION TO CARBONYL COMPOUNDS

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## 6.1 INTRODUCTION

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In Unit 5 you have studied the addition reactions of carbon-carbon multiple bonded systems. In this unit we shall discuss the nucleophilic addition reactions of aldehydes and ketones. Both aldehyde and ketone contain the carbonyl group,  $>C=O$  and are often referred to collectively as carbonyl compounds. The remarkable reactivity of the carbonyl group makes the chemistry of aldehydes and ketones the backbone of synthetic organic chemistry. The double bond between the carbon and oxygen atoms in these compounds serves as a model for the reactions of many other functional groups containing  $\pi$  bonds between dissimilar atoms. Although the reactions of carbonyl compounds are quite simple their synthetic utility is enormous. In this unit we shall study the important nucleophilic reactions of aldehydes and ketones.

### Objectives

After studying this unit, you should be able to:

- describe the structure of carbonyl group, and explain its polarity,
- explain the relative reactivity of aldehydes and ketones,
- discuss the general mechanism of nucleophilic addition to carbonyl compounds,
- discuss the different reactions of aldehydes and ketones.

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## 6.2 NATURE OF THE CARBONYL GROUP

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A carbonyl group consists of a carbon doubly bonded to an oxygen atom (Fig. 6.1). The carbonyl double bond is similar in many respects to the carbon-carbon double bond of an alkene. Like carbon-carbon double bond of alkene, carbon-oxygen double bond of a carbonyl compound consists of one  $\sigma$  bond and one  $\pi$  bond. The

carbonyl carbon atom is  $sp^2$  hybridised and forms three  $\sigma$  bonds (two C-H bonds and one C-O bond) and an unhybridized  $p$  orbital is left on the carbon atom. The  $\sigma$  bond is formed by overlap of  $sp^2$  hybrid orbitals and a  $\pi$  bond is formed with oxygen by overlap of  $p$ -orbitals. Carbonyl compounds are planar and have bond angles of approximately  $120^\circ$ .

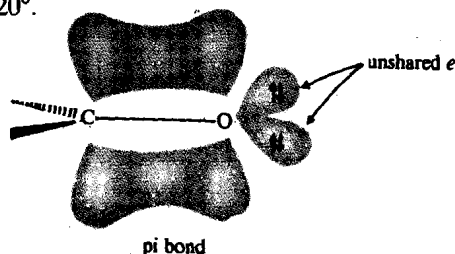
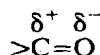


Fig. 6.1: Bonding in carbonyl compound.

Unlike carbon-carbon double bond, carbon-oxygen double bond is polar. This is because of the higher electronegativity of oxygen relative to carbon. The  $\pi$  electrons of the carbon-oxygen double bond get shifted towards the oxygen atom and the bond gets polarised. This electron imbalance in the  $\pi$  bond makes the carbon atom **electron-deficient** as a result the carbonyl group as a whole has an electron withdrawing effect. Thus, the carbonyl group has two active centres, viz.,



- The carbon carrying partial positive charge, called electrophilic or cationoid centre. This can be attacked by nucleophilic reagents.
- The oxygen carrying partial negative charge, called nucleophilic or anionoid centre. This can be attacked by electrophilic reagents.

### 6.3 KIND OF CARBONYL COMPOUNDS

Carbonyl compounds can be classified into two groups, based on the kind of reactions they undergo.

- Aldehydes and ketones
- Carboxylic acids and their derivatives, e.g., esters, acid chlorides, acid anhydrides and amides.

In aldehydes and ketones, the acyl units (RCO) are bonded to H and R, respectively. These substituents cannot serve as leaving groups. Therefore, the chemistry of these compounds is similar. The acyl units in carboxylic acids and their derivatives are bonded to substituents like oxygen, halogen or nitrogen that can serve as leaving groups. Hence, the chemistry of aldehydes and ketones is different from that of carboxylic acids and their derivatives.

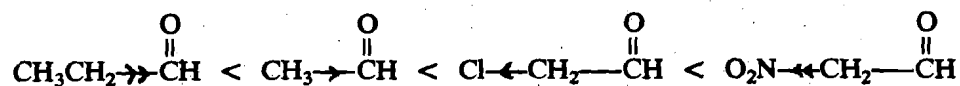
In this unit we shall discuss only the nucleophilic addition to aldehydes and ketones.

Before going into details of the reactions of carbonyl compounds, let us study the relative reactivity of aldehydes and ketones.

### 6.4 REACTIVITY OF CARBONYL COMPOUNDS

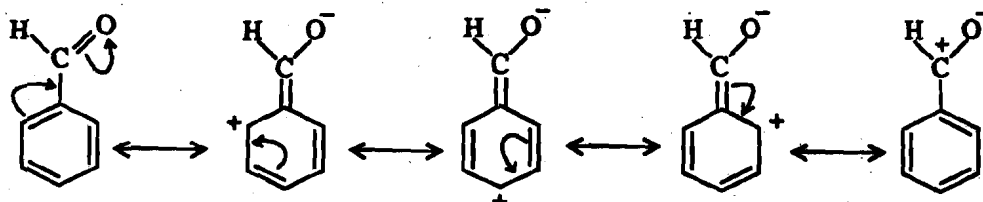
You have studied in Unit 1 that a nucleophilic addition reaction involves addition of a nucleophile to the partially positively charged carbon atom of the carbonyl group. The relative reactivities of aldehydes and ketones in nucleophilic addition reactions may be attributed partly to the extent of polarisation of the carbonyl carbon. The rate determining step involves the attack of nucleophile at the positively charged carbon atom. Therefore, the reactivity of the carbonyl group depends upon the magnitude of the positive charge on the carbonyl carbon. Thus, a greater positive charge means higher reactivity. If this partial positive charge is dispersed throughout the molecule then the carbonyl compound is less reactive. Electron withdrawing substituents at the carbonyl carbon, which increase its positive charge, increase its reactivity towards nucleophilic addition reactions. Similarly, electron donating substituents decrease its positive character and hence decrease the reactivity towards nucleophilic addition reaction.

You know that alkyl groups have electron releasing effect. Therefore, ketones, which contain two alkyl groups, are less reactive than aldehydes. Further chloroethanal, which contains the electron withdrawing chlorine atom, is more reactive than ethanal. Similarly, nitroethanal, where  $\text{NO}_2$  group has stronger electron withdrawing character than chlorine is more reactive than chloroethanal. Thus the order of reactivity is:



Aromatic aldehydes or ketones are less reactive than aliphatic aldehydes and ketones. This can be attributed to resonance interaction between the carbonyl group and the aromatic ring.

The result of this interaction is a weakening of the positive charge on the carbonyl carbon atom through dispersal of the charge within the ring.

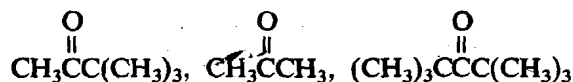


Steric factor also plays an important role in the relative reactivity of aldehydes and ketones. A bulky group in the vicinity of the carbonyl carbon presents greater steric hindrance than the smaller hydrogen atom to the approaching nucleophile.

With the above general ideas, it will be easier to study the reactions of aldehydes and ketones which we will take up in the next section.

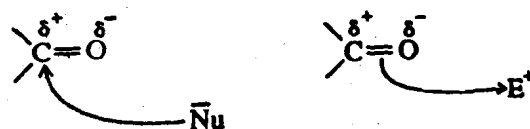
#### SAQ 1

Considering the steric factor, arrange the following compounds in the order of their reactivity.



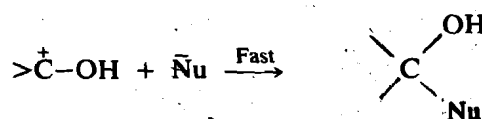
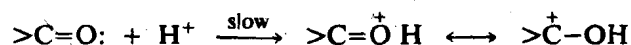
## 6.5 REACTIONS OF CARBONYL COMPOUNDS

Theoretically a carbonyl compound may be attacked either by a nucleophile or by an electrophile. Addition of the negative nucleophilic part of the reagent to the carbon atom or addition of the positive electrophilic part to the oxygen atom would give the same product ultimately.

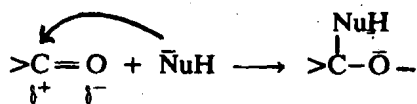


The addition reaction of carbonyl compounds, therefore, can theoretically proceed by the following two mechanism.

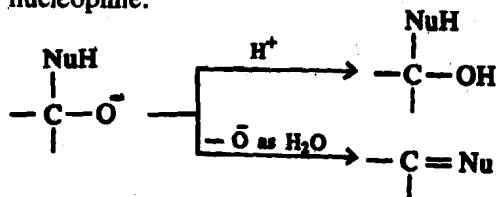
**Mechanism I:** In the first mechanism, the proton adds to the carbonyl oxygen in the first step (slow step). This further increases the electrophilic nature of the carbonyl carbon. In the next step (fast step) the nucleophile attacks the carbocation.



**Mechanism II:** In the second type of mechanism nucleophile attacks the polarised carbonyl carbon in the first step and forms an anionic intermediate.



This intermediate can undergo either protonation to form an alcohol, or it might expel oxygen as water to form a new double bond between carbon and the nucleophile.

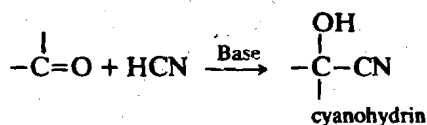


An acid catalysed reaction should follow mechanism I and the base catalysed mechanism II.

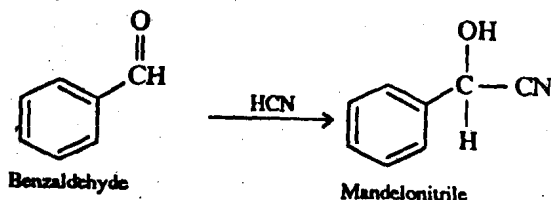
Now let us study some important reactions of aldehydes or ketones.

### 6.5.1 Reaction with Hydrogen Cyanide

Hydrogen cyanide (hydrocyanic acid) adds to the carbonyl compounds in aqueous solution or with anhydrous liquid HCN in the presence of catalytic amounts of an organic base to give cyanohydrins. Cyanohydrins are hydroxy nitriles.



For example, benzaldehyde gives the cyanohydrin (mandelonitrile) in 88% yield on treatment with HCN.



The reaction occurs very slowly when pure HCN is used, but becomes fast when a trace amount of base or cyanide ion is added. The function of the base is to increase the concentration of cyanide ion.

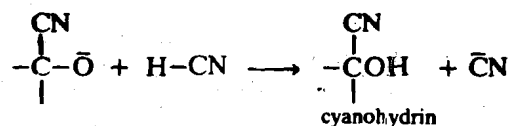
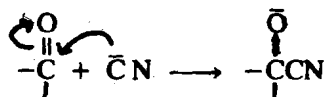


The reaction is reversible and the position of equilibrium depends on the usual steric and electronic factors that govern nucleophilic addition to carbonyl groups.

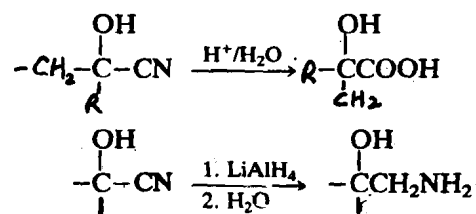
Aldehydes and unhindered ketones give good yields of cyanohydrin.

HCN is a very poisonous substance, it is not used directly in cyanohydrin formation. The reaction is carried out by mixing the carbonyl compound with aqueous sodium cyanide and then slowly acidifying the solution by a mineral acid.

**Mechanism:** In the first step, the cyanide ion attacks the carbonyl carbon to form an alkoxide ion intermediate. The alkoxide ion is basic and rapidly removes a proton from HCN present and generates a cyanide ion, in the second step.

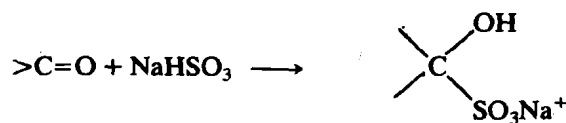


Cyanohydrins are also useful synthetic intermediates. An important consequence of the reaction is that one more carbon atom is added to the carbon chain. The cyano group may be converted to a carboxylic acid, by hydrolysis, or to a primary amine by reduction.

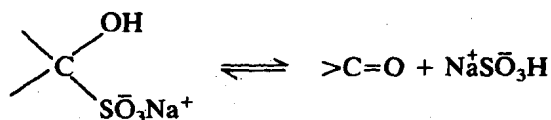


### 6.5.2 Reaction with Sodium Hydrogen Sulphite

Most of the aldehydes, some ketones (generally methyl ketone) and unhindered cyclic ketones react with sodium hydrogen sulphite (sodium bisulphite) to give a crystalline hydrogen sulphite adduct.



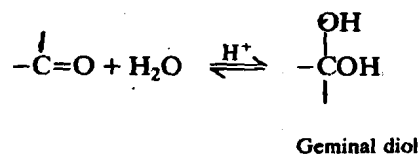
Ketones with bulky groups fail to add sodium hydrogen sulphite. On heating with dilute acid or aqueous sodium carbonate, bisulphite compound regenerates the carbonyl compound.



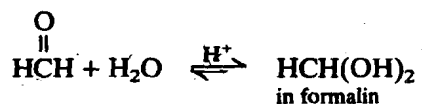
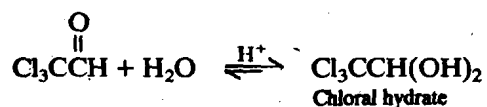
This reaction is often used for separation and purification of aldehydes and ketones from non-carbonyl compounds. When such a mixture is treated with sodium hydrogen sulphite, the aldehyde or ketone is converted into crystalline hydrogen sulphite adduct which can be separated. The crystalline adduct can be converted back into aldehyde or ketone.

### 6.5.3 Reaction with Water

Aldehydes and ketones react with water to form 1,1-diols, (geminal-diols) or hydrates. Hydrogen becomes bonded to the negatively polarised carbonyl oxygen and hydroxyl group to the positively polarised carbon. This reaction is reversible and the hydrate formed is generally too unstable to be isolated.

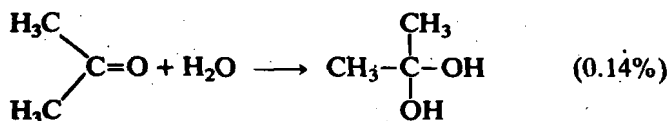
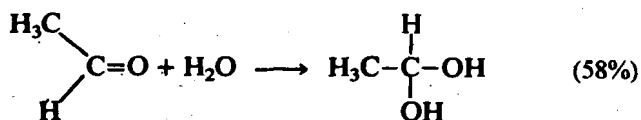
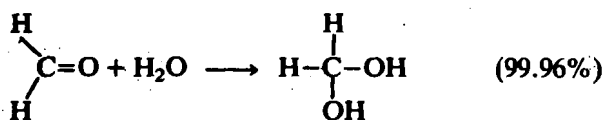


Stable hydrates are known in a few cases but they are rather exceptions, e.g., chloral hydrate or in formalin:



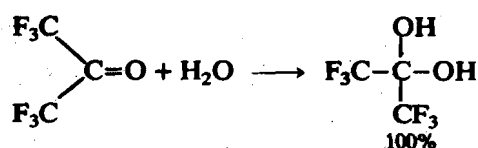
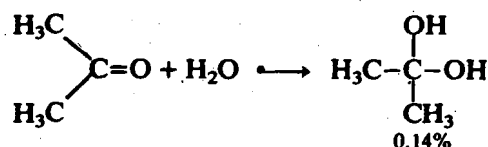
The rate of reaction depends on the nature of the carbonyl group and is influenced by the combination of electronic and steric effects.

With increase of alkyl substitution on the carbonyl group, the reactivity of carbonyl compounds decreases, when treated with water under similar conditions. For example,



Methanal has no alkyl substituents to stabilise its carbonyl group and is converted almost completely to the corresponding diol (99.96%). The carbonyl group of ethanal is stabilised by one alkyl substituent and the carbonyl of propanone by two. Ethanal gives 58% while propanone gives only 0.14% of diols.

Reactivity of carbonyl compounds increases when electron-withdrawing groups are attached to the carbonyl carbon. For example, in contrast to the almost negligible hydration of propanone, the hexafluoropropanone is completely hydrated.



Now let us consider the steric effect on the rate of reactions. Let us examine the geminal diol products. The carbon atom that bears two hydroxyl group is  $sp^3$  hybridised. Its substituents are more crowded than they are in the starting aldehyde or ketone. Increased crowding can be better tolerated when the substituents are hydrogen than when they are alkyl groups. Diol of methanal is least crowded and hence formed in large amount. Diol of propanone on the other hand is more crowded, therefore, formed in a lesser amount. Finally, the amount of diol of ethanal is formed between the above two limits.

As the electronic and steric effects combine hydration of aldehydes becomes more favourable than that of ketones.

### SAQ 2

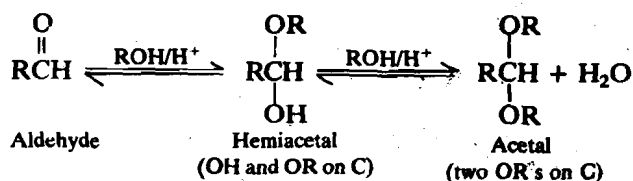
Which of the following compounds do you predict would form stable hydrates and why?



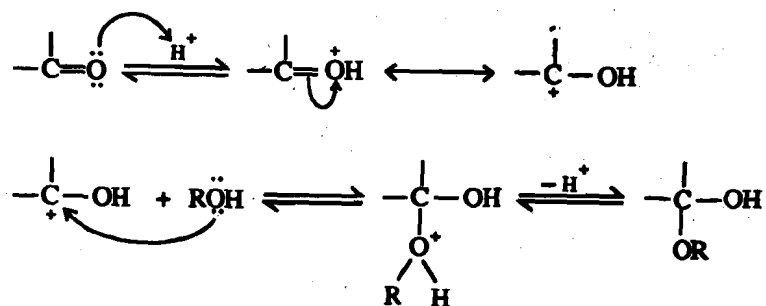
### 6.5.4 Reaction with Alcohol

Like water, an alcohol can undergo addition reaction with carbonyl group in the presence of an acid catalyst. It is also a reversible reaction. In most cases, the equilibrium lies to the aldehyde or ketone side. Addition of one molecule of an

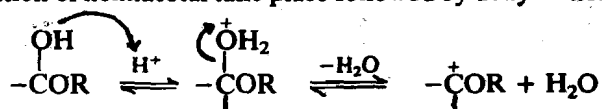
alcohol to an aldehyde or ketone gives **hemiacetal** or **hemiketal**, respectively. On the other hand, reaction of two molecules of alcohol to an aldehyde or a ketone, with the loss of water, give **acetal** or **ketal**, respectively. Unlike hydrates, acetals and ketals are quite stable and can be isolated.



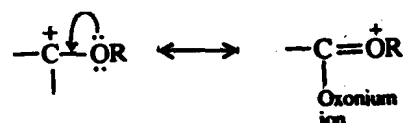
**Mechanism:** The mechanism of formation of hemiacetal is analogous to that of the acid catalysed hydration of an aldehyde.



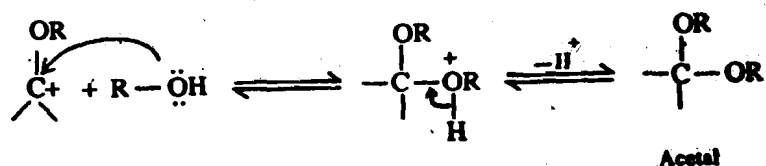
In the mechanism for acetal formation from the hemiacetal, again protonation and deprotonation, along with loss of water, are the major reaction steps. First protonation of hemiacetal take place followed by dehydration to give a carbocation.



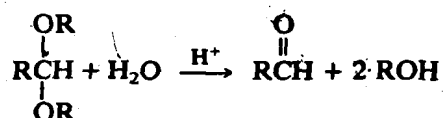
The carbocation is stabilised by electron release from its oxygen substituent to yield oxonium ion.



Attack by a second molecule of alcohol forms the protonated acetal which on deprotonation gives acetal.



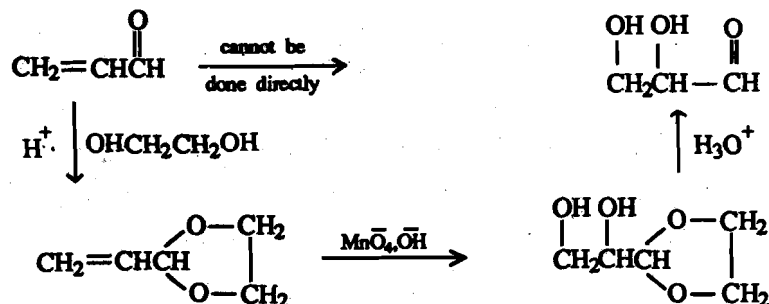
An acetal can be hydrolysed back into parent aldehyde and alcohol upon treatment with aqueous mineral acid even at room temperature.



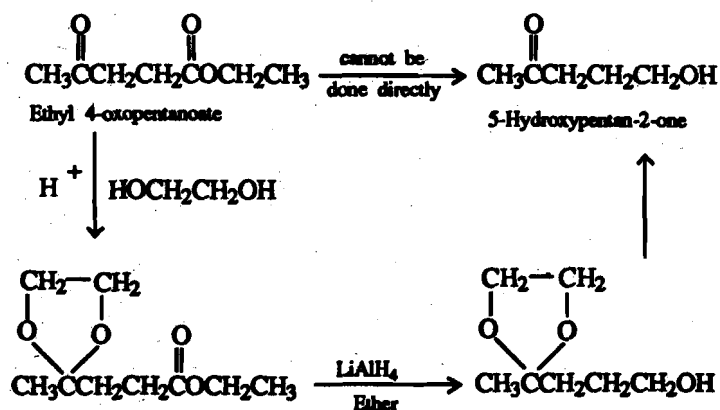
The mechanism is just the reverse of that for the formation of the acetal.

Now you will see how acetal formation and hydrolysis have been applied to synthetic organic chemistry as a means of carbonyl group protection. In some chemical reactions one functional group may interfere with intended reaction elsewhere in a complex molecule. We can often circumvent the problem in such cases by first

protecting the interfering functional group, carrying out the desired reaction, and then removing the protecting group. For example, if we wish to oxidise propenal to 2,3-dihydroxypropanal, there is an interference of the carbonyl group, since both the double bond (C=C and C=O) would be oxidised. But after converting the carbonyl group to an acetal, we can oxidise a carbon-carbon double bond in the molecule without oxidising the carbonyl group.



Since acetal formation is a reversible reaction it can be cleaved by hydrolysis to regenerate the carbonyl group. Thus, 2,3-dihydroxypropanal is obtained. Similarly take another example, conversion of ethyl 4-oxopentanoate to 5-hydroxypentan-2-one. We can not reduce the ester group directly by  $\text{LiAlH}_4$  as both the carbonyl groups would be reduced simultaneously. If we first protect the ketone by forming an acetal, subsequent ester reduction proceed normally and acetal can be cleaved to get back ketone.



### SAQ 3

Consider the acid-catalysed reaction of ethanal with methanol. Write structural formulas for,

- The hemiacetal intermediate
- The carbocation intermediate
- The acetal product.

### 6.5.5 Reaction with Amines

Reactions of carbonyl compounds with amine can be classified into the following two categories.

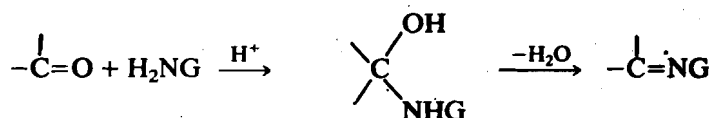
- Reaction with primary amines,
- Reaction with secondary amines.

#### Reaction with primary amines

In the presence of an acid catalyst a primary amine adds to carbonyl compounds to give an imine (compounds with C=N group). In this reaction the initial addition of  $\text{H}^+$  is followed by an attack of  $\text{H}_2\text{N-G}$ . Subsequent dehydration forms a

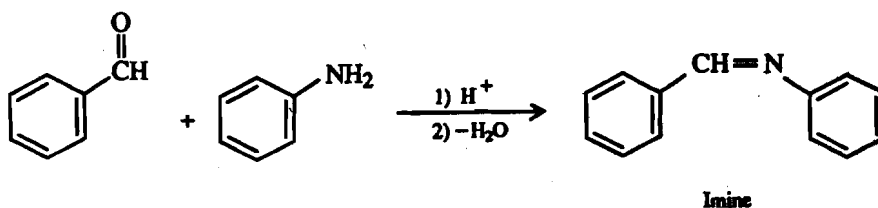
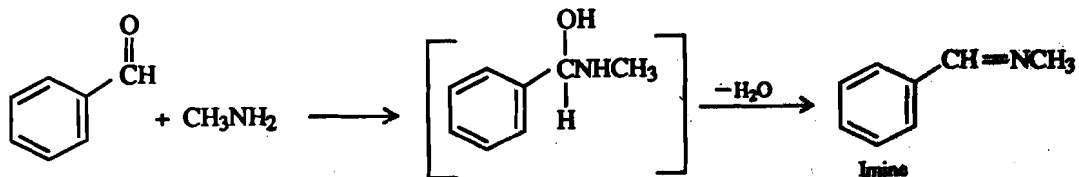


carbon-nitrogen double bond. The net result is substitution of oxygen by another group. Primary amines react with aldehydes or ketones to form corresponding N-alkyl or N-aryl substituted imines, which contain C=N group.

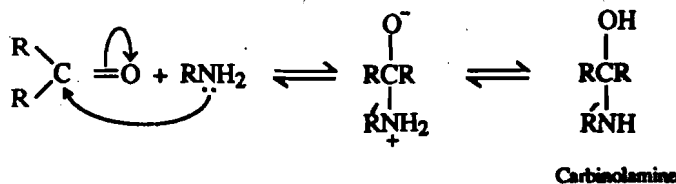


G = various groups      N-substituted

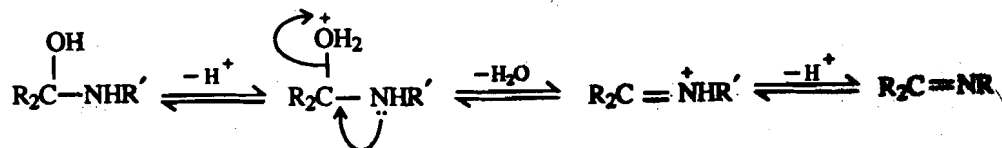
The unsubstituted imines, obtained by reaction with  $\text{NH}_3$ , are very unstable; while substituted imines, formed from  $\text{RNH}_2$ , are more stable. Substituted imines are also called Schiff bases.



**Mechanism:** Formation of a Schiff base is a two step reaction. In the first step, the nucleophile ( $\text{RNH}_2$ ) adds to the partially positive carbonyl carbon. This step is followed by proton shift from nitrogen to oxygen to give an intermediate called carbinolamine:

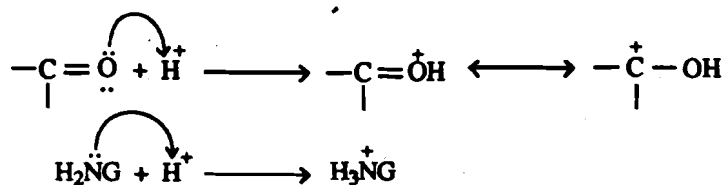


In the second step, the carbinolamine eliminates water and gives the imine.



Both the addition and the elimination steps of the reaction are sensitive to acid catalysis. Hence careful control of pH is essential. The rate of reaction is increased by an increase in acidity but beyond a certain limit, the rate decreases with further increase of acidity.

You can ask why is this so? This is because, these reactions are catalysed by acids, thus, protonation of the carbonyl compound as well as the reagent can take place.



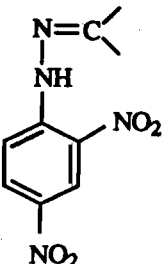
The first step of the reaction is the addition of the amine to the carbonyl group. In strongly acid medium, the concentration of the amine becomes very low because we get  $\text{GNH}_3$  in excess amounts. In other words, the rate of the first step decreases with increase in acidity as  $\text{GNH}_3$  is a poor nucleophile than  $\text{GNH}_2$ .

The second step involves the elimination of water. In acidic medium concentration of the protonated carbinolamine increases with the increasing acid concentration. (Remember  $-\text{OH}_2^+$  is a better leaving group than  $-\text{OH}$ ).

An increase in acidity causes step 2 to go faster, but step 1 to go slower, while decreasing acidity causes step 1 to go faster but step 2 to go slower. Between these two extremes is the optimum pH ( $\sim 3-4$ ), at which the rate of the over all reaction is the greatest. At this pH, some of the amine is protonated, but some are free to initiate the nucleophilic addition. At this pH, too, enough acid is present so that elimination of water in the second step can proceed at a reasonable rate.

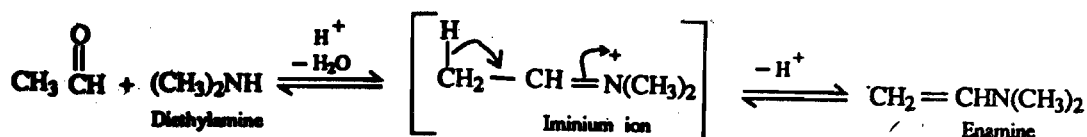
The names of reactants with different G, general condensation products and their class is given in Table 6.1. Many of these products are crystalline solids with sharp melting points. For this reason they are frequently employed for the preparation of aldehyde and ketone derivatives needed for identification.

Table 6.1 : Reaction of ammonia derivatives

G	Ammonia derivative	Product	Class of Product
$-\text{RAr}$ alkyl/aryl	$\text{RNH}_2/\text{ArNH}_2$ amine	$>\text{C}=\text{NR}/\text{C}=\text{NAr}$ N substituted imine	imine (Schiff base)
$-\text{OH}$	$\text{NH}_2\text{OH}$ hydroxylamine	$>\text{C}=\text{NOH}$ oxime	Oxime
$-\text{NH}_2$	$\text{H}_2\text{NNH}_2$ hydrazine	$>\text{C}=\text{NNH}_2$ hydrazone	hydrazone
			
		2,4-dinitrophenyl hydrazone	substituted hydrazone
$-\text{NHCONH}_2$	$\text{H}_2\text{NNHCONH}_2$ semicarbazide	$>\text{C}=\text{NNHCONH}_2$ semicarbazone	semicarbazone

### Reaction with Secondary Amines

Aldehydes and ketones with an  $\alpha$ -hydrogen react with secondary amines to yield iminium ions, which undergo further reaction to give enamines (vinylamines).



Since there is no proton remaining on nitrogen of this intermediate iminium ion, the imine formation cannot occur. Instead an enamine is formed by loss of a proton from a carbon atom  $\beta$  to the nitrogen. This results in the formation of a double bond between  $\alpha$  and  $\beta$  carbon atoms.

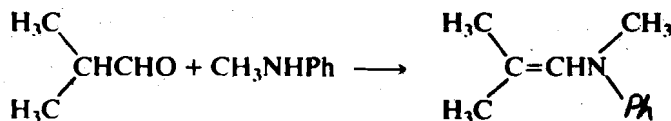
Like imine formation, enamine formation is reversible, and enamines can be converted back to the corresponding carbonyl compounds.

You must have noticed from the above that the mechanism of enamine formation is similar to the mechanism of imine formation. Reaction of aldehydes or ketones with primary and secondary amine may appear different but they are quite similar. Both

are typical examples of nucleophilic addition reaction in which the initially formed tetrahedral intermediate is not stable. Instead, the carbonyl oxygen is eliminated and a new carbon-nucleophile double bond is formed. You can practice this reaction by solving the following SAQ.

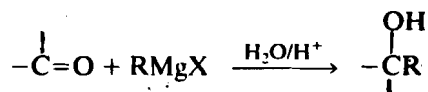
## SAQ 4

Write the mechanism of the following reaction,

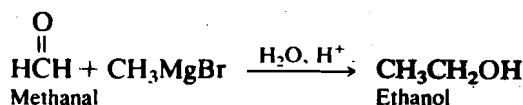


## 6.5.6 Reaction with Grignard Reagents

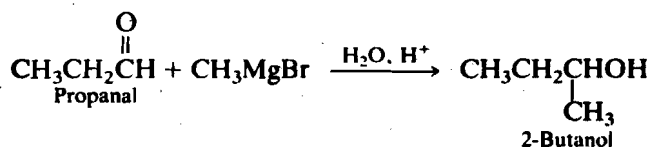
Developments in chemistry in the past 3-4 decades, has unravelled a large number of reactions of Grignard reagents with carbonyl group. The reaction of Grignard reagent with aldehydes or ketones gives alcohols. This is the most important method for preparing alcohols.



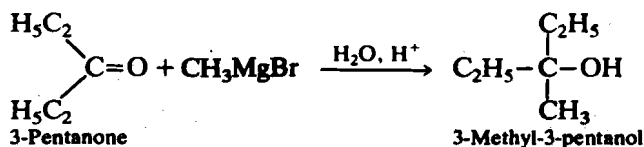
A large number of alcohols can be obtained from Grignard reactions depending upon the reagents used. For example, a Grignard reagent reacts with methanal to give a primary alcohol.



Reactions of Grignard reagent with other aldehyde except methanal yields a secondary alcohol. For example:



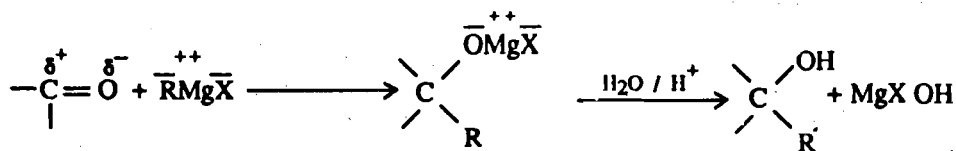
Similarly, reaction with ketones yields tertiary alcohols.



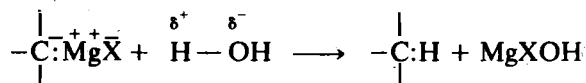
**Mechanism:** Analysing the charge distribution in the Grignard reagent, we find that since the magnesium bears the positive charge, the hydrocarbon portion of the reagent must have a negative charge and, therefore, should be a very powerful nucleophile.



When a Grignard reagent is mixed with an aldehyde or a ketone, the negative hydrocarbon group quickly attacks the positive carbonyl carbon and provides the two electrons needed for the new carbon-carbon bond. The  $\pi$  electrons are displaced by the oxygen, forming the alcohol salt which is hydrolysed to an alcohol with water in acidic medium.

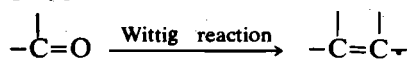


Note that the hydrocarbon portion of a Grignard reagent acts essentially as a carbanion. It is for this reason that Grignard reactions must be performed in dry ether. Even traces of moisture can neutralise the reagent.

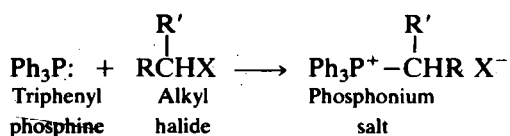


### 6.5.7 Wittig Reaction

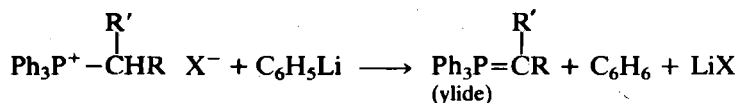
In 1954, George Wittig reported a method of synthesising alkenes from carbonyl compounds. This reaction is applicable to aldehydes and ketones and leads to replacement of carbonyl oxygen by the group =CRR' (where R and R' are hydrogen or alkyl group).



There are two main steps in Wittig reaction. In the first step, the nucleophilic reagent triphenylphosphine reacts with a primary or secondary alkyl halide to give a phosphonium salt.

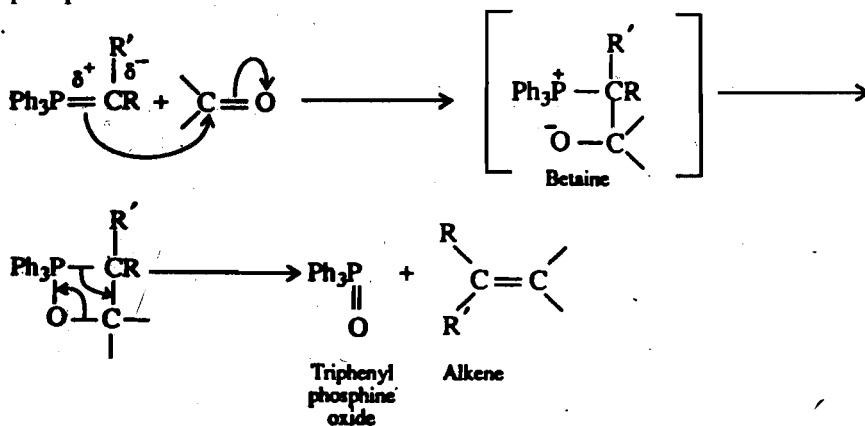


This phosphonium salt further reacts with a strong base, which abstracts a weakly acidic  $\alpha$ -hydrogen to give alkylidene triphenylphosphorane (a phosphorus ylide) commonly known as the Wittig reagent.

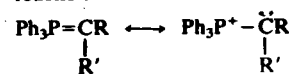


The resulting phosphorus ylide attacks the carbonyl carbon to form a dipolar intermediate called a **betaine**, which often undergoes elimination spontaneously to yield an alkene.

**Mechanism:** Mechanism of Wittig reaction has been the subject of much discussion, but evidence is now strongly in favour of the formation of an intermediate betaine. This betaine intermediate is unstable and rapidly fragments, probably by way of a second intermediate containing a four-membered ring, to an alkene and triphenylphosphine oxide.



The phosphorus ylides have a hybrid structure and it is the negative charge on carbon that is responsible for their characteristic reactions.

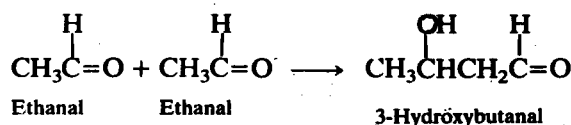


The great value of Wittig reaction is that pure alkenes of known structures can be prepared. The position at which the double bond is introduced is never in doubt. The double bond is formed between the carbonyl carbon of the aldehyde or ketone and the negatively charged carbon of the ylide.

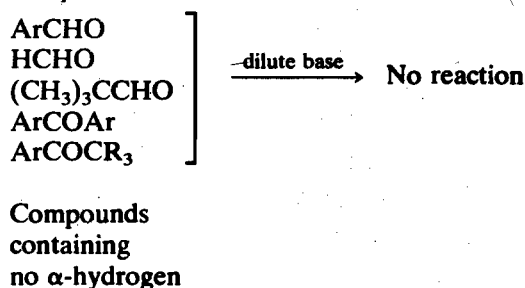
Wittig reaction is so important that it can be used commercially for the preparation of  $\beta$ -carotene, a yellow food-colouring agent. Wittig reaction is versatile, the alkyl halide used to prepare the ylide may be methyl, primary or secondary but not tertiary. The alkyl halide can also contain any other functionality such as a double bond or alkenyl groups.

### 6.5.8 Aldol Condensation

In the presence of a dilute base, such as aqueous NaOH, two or more molecules of an aldehyde or a ketone, containing an  $\alpha$ -hydrogen may combine to form a  $\beta$ -hydroxyaldehyde or  $\beta$ -hydroxyketone, a compound containing alcoholic and aldehydic or ketonic groups, respectively. This reaction is called aldol condensation. The product results from addition of one molecule of the carbonyl compounds to a second molecule in such a way that the  $\alpha$ -carbon of the first is attached to the carbonyl carbon of the second. For example, reaction between the two ethanal molecules.

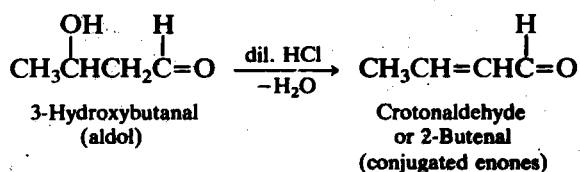


The starting aldehyde in an aldol condensation must contain an  $\alpha$ -hydrogen. If the aldehyde or ketone does not contain an  $\alpha$ -hydrogen, a simple aldol condensation cannot take place.

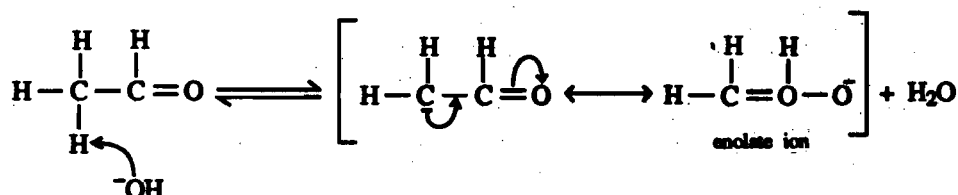


Since the  $\beta$ -hydroxyaldehyde has a carbonyl carbon with  $\alpha$ -hydrogen it can undergo further reaction to give trimers or tetramers. For simplicity we will show only the dimerisation product.

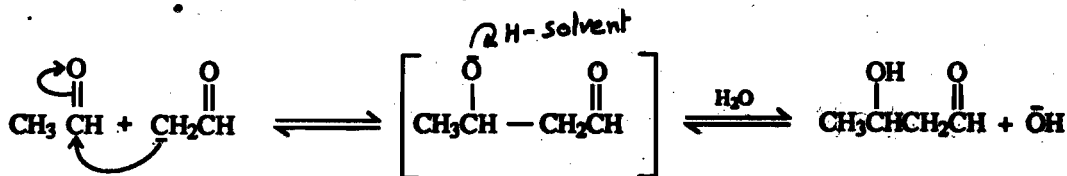
Aldol condensations are reversible reactions. The condensation product (a  $\beta$ -hydroxy carbonyl compound) loses a water molecule to form unsaturated aldehydes or ketones, (conjugated enones), e.g.,



**Mechanism:** Aldol condensation is a two step process. In the first step, the base abstracts a proton from the  $\alpha$ -carbon of the aldehyde to form enolate ion.



In the next step, the enolate ion attacks the carbonyl carbon of another aldehyde molecule to form an alkoxide ion, which abstracts a proton from water to yield the  $\beta$ -hydroxyaldehyde, regenerating  $\text{OH}^-$ .



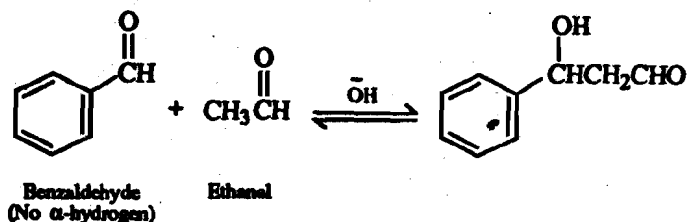
Alcohols generally do not undergo dehydration by dilute acid or base. However, aldol products undergo dehydration because in this case the double bond is in conjugation with the carbonyl group in the product.

#### Crossed aldol condensation

As mentioned above, an aldehyde without  $\alpha$ -hydrogen does not undergo aldol condensation. However, if such an aldehyde is mixed with an aldehyde that does have an  $\alpha$ -hydrogen, aldol condensation can occur. Aldol condensation between the two different carbonyl compounds is called crossed aldol condensation which is of two types:

In type one, both the carbonyl compounds have  $\alpha$ -hydrogen atoms. In these cases a mixture of four possible products may be formed. Because of the formation of such a mixture, this type of reaction is commercially of no use.

In type two, one of the carbonyl compound does not have an  $\alpha$ -hydrogen, e.g.,



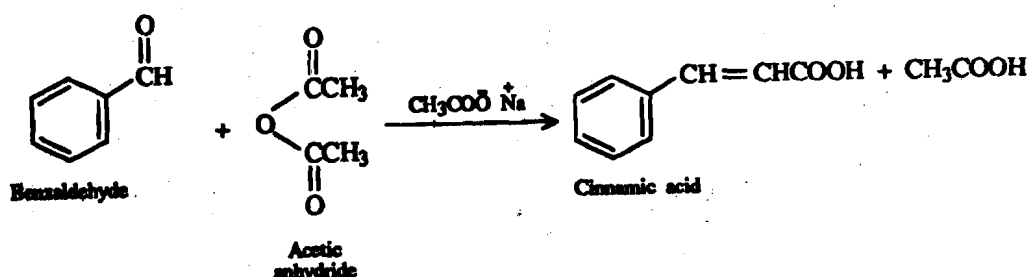
Methyl ketones can be used successfully in crossed aldol condensation with aldehydes that contain no  $\alpha$ -hydrogen.

### 6.5.9 Reactions Related to Aldol Condensation

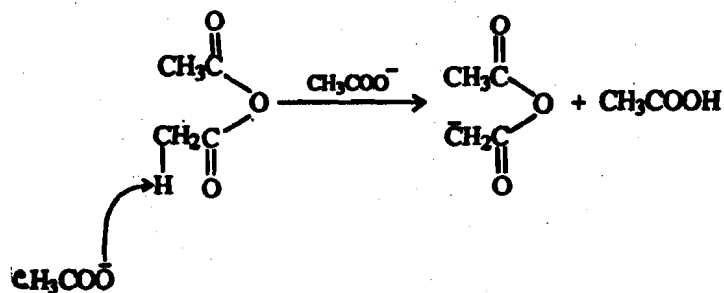
There are many reactions that are closely related to aldol condensation. At first glance each of these reactions may seem quite different from others. But a close examination of these reactions shows, that like aldol condensation each of these involves an attack by a carbanion formed from one molecule on the carbonyl group of another. Some such reaction are given below:

#### Perkin condensation

Perkin condensation is a reaction in which an aromatic aldehyde combines with anhydride of an aliphatic acid (having atleast two  $\alpha$ -hydrogen atoms) in the presence of salt of the same acid to yield an  $\alpha, \beta$ -unsaturated acid. In this reaction the catalyst used is generally the salt of the carboxylic acid related to the anhydride but it may be replaced by some other bases such as sodium carbonate, pyridine, etc. For example, benzaldehyde when heated with acetic anhydride in the presence of anhydrous sodium acetate gives cinnamic acid.

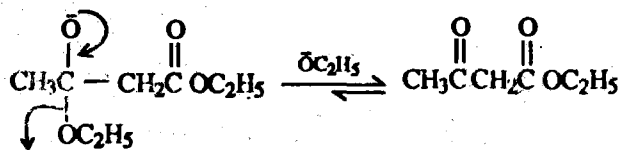


**Mechanism:** First the base abstracts the  $\alpha$ -hydrogen from the anhydride to form a carbanion.

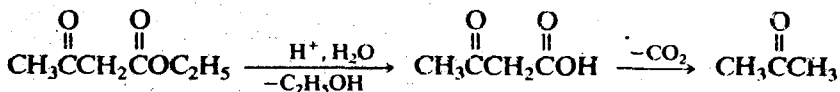




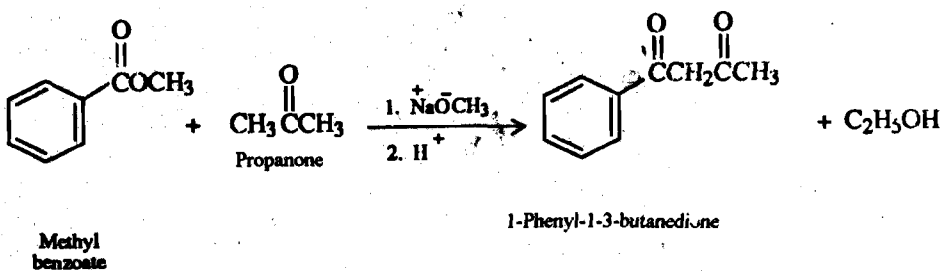
This intermediate anion is unstable. It expels ethoxide ion to yield ethylacetoacetate,



A  $\beta$ -keto ester can be hydrolysed by heating in acidic solution in which decarboxylation of the  $\beta$ -keto acid may occur.

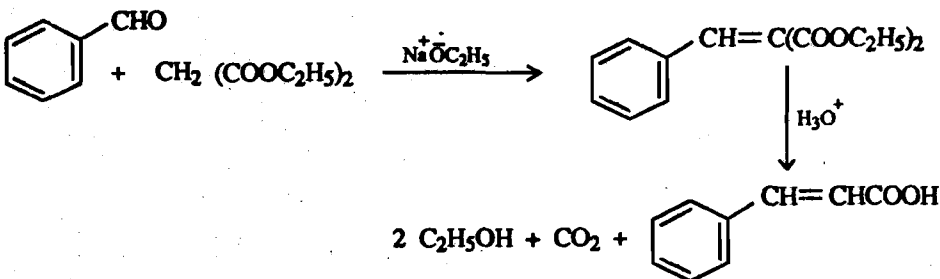


Two different esters can also be used in Claisen condensation. The Claisen condensation between two different esters, both having an  $\alpha$ -hydrogen is called **Crossed Claisen Condensation**. However, this type of reaction is not of synthetic importance, because in this case a mixture of products is obtained which is difficult to separate.



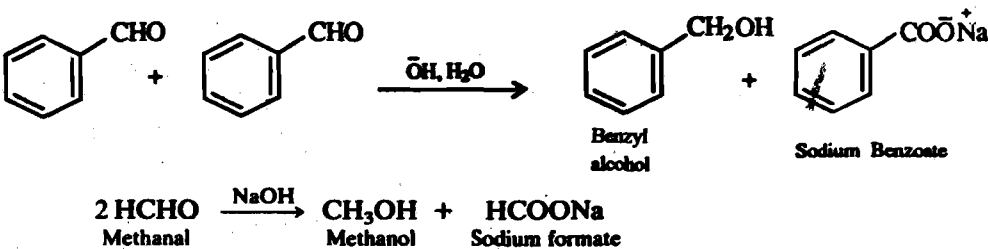
### Knoevenagel condensation

**Knoevenagel condensation** is a reaction of aldehydes and many ketones with a compound that has a hydrogen  $\alpha$  to two activating groups (such as  $\text{C}=\text{O}$  or  $\text{C}\equiv\text{N}$ ) in presence of base. For example, benzaldehyde can condense with diethyl malonate to yield  $\alpha, \beta$ -unsaturated diester,



### 6.5.10 Cannizzaro Reaction

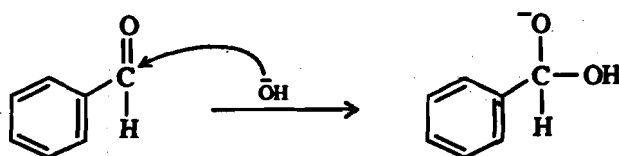
In contrast to aldol condensation this reaction takes place when aldehydes having no  $\alpha$ -hydrogen is treated with concentrated alkali or any other strong base. It undergoes self oxidation-reduction reaction and yields a mixture of an alcohol and a salt of the corresponding carboxylic acid. This reaction is known as **Cannizzaro reaction**. For example,



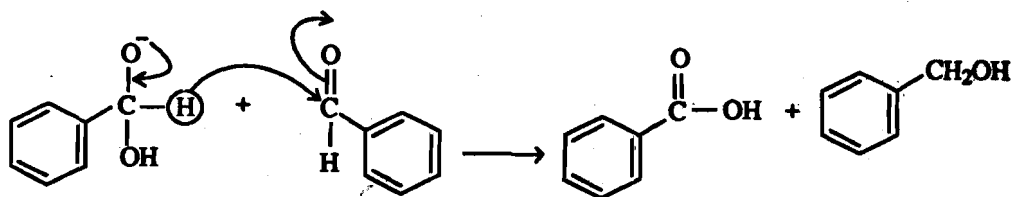
Cannizzaro reaction is shown by all aromatic aldehydes and aliphatic aldehydes which do not contain  $\alpha$ -hydrogen, e.g., methanal, trimethylethanal, etc. In general, a mixture of two different aldehydes undergoes a Cannizzaro reaction to give all possible products and is referred to as **crossed Cannizzaro reaction**.



**Mechanism:** The first step in the Cannizzaro reaction involves a nucleophilic attack of hydroxide ion on the carbonyl carbon of aldehyde to give an anion.

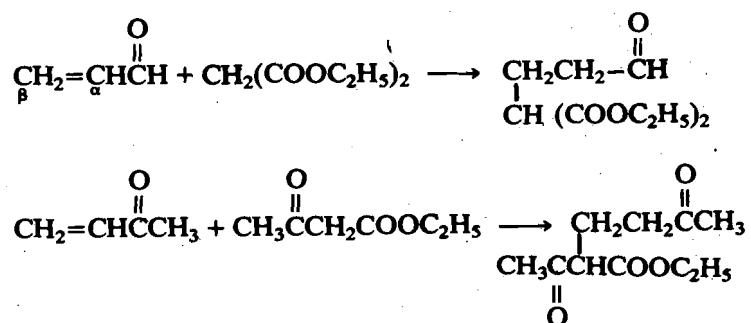


In the second step, transfer of a hydride ion from the tetrahedral intermediate to the second molecule of aldehyde takes place. The net result is that one molecule of aldehyde undergoes hydroxyl substitution for hydride and is thereby oxidised, whereas, a second molecule of aldehyde accepts the hydride and hence, is reduced to an alcohol.

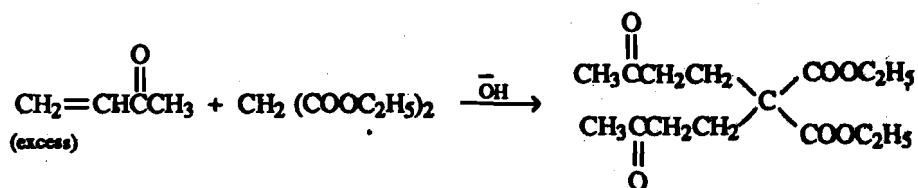


### 6.5.11 Michael Addition

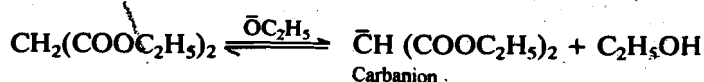
Nucleophiles and carbanions generally do not add to isolated carbon-carbon double bonds. However, when an electron withdrawing group like C=O is present in conjugation with a carbon-carbon double bond, carbanions add to the conjugated system at the site of electron deficiency, i.e., the  $\beta$ -carbon atom. Such addition reactions are known as **Michael addition**. In other words, addition of active methylene compounds to carbon-carbon double bond of  $\alpha, \beta$ -unsaturated carbonyl compounds in the presence of basic catalyst is known as Michael addition. The following examples are illustrative:



If an excess of the  $\alpha, \beta$ -unsaturated carbonyl compound is used, it is possible to achieve dialkylation.



**Mechanism:** We take here the condensation of ethyl malonate with propenal as an example. In the first step of Michael reaction the base removes an  $\alpha$ -hydrogen atom from ethyl malonate to generate the corresponding carbanion (enolate anion).

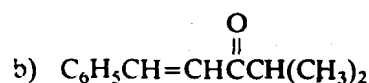
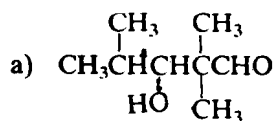




- Carbonyl compounds can be classified into two groups:
  - (a) aldehyde and ketone and (b) carboxylic acid and their derivatives.
- Electron withdrawing substituents at the carbonyl carbon increase its reactivity while electron donating substituents decrease its reactivity in nucleophilic addition reactions.
- Bulky groups, substituted at carbonyl carbon, present greater steric hindrance to the approaching nucleophile.
- HCN adds to the carbonyl compounds in the presence of a basic catalyst to give cyanohydrins.
- Most of the aldehydes and some ketones react with sodium hydrogen sulphite to give hydrogen sulphite adducts.
- The addition of one molecule of an alcohol to an aldehyde or ketone gives a hemiacetal or a hemiketal, respectively. On the other hand, the reaction of two molecules of alcohol to an aldehyde or a ketone, with the loss of water, gives acetal or ketal, respectively.
- Since acetal formation is a reversible reaction it can serve as a protecting group for carbonyl compounds.
- Primary amines react with aldehydes or ketones to form the corresponding N-alkyl or N-aryl substituted imines. This reaction is sensitive to acid catalysis. Therefore, a careful control of pH is essential. Secondary amines react with aldehydes or ketone to give enamines.
- Reactions of Grignard reagents with aldehydes or ketones gives alcohols.
- Two or more molecules of aldehydes or ketones, containing  $\alpha$ -hydrogens may combine to form  $\beta$ -hydroxyaldehyde or  $\beta$ -hydroxyketone respectively. This reaction is known as Aldol condensation. There are a large number of reactions related to aldol condensation, e.g., Perkin, Claisen, Knoevenagel, etc.
- When an aldehyde having no  $\alpha$ -hydrogen is treated with concentrated alkali, self oxidation-reduction occurs to yield a mixture of an alcohol and the salt of the corresponding carboxylic acid. This reaction is known as Cannizzaro reaction.
- With compounds having a carbon-carbon double bond in conjugation with an electron withdrawing group addition of carbanions may occur at the  $\beta$ -position. This reaction is known as Michael addition reaction.

## 6.7 TERMINAL QUESTIONS

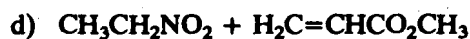
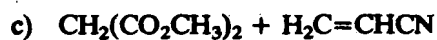
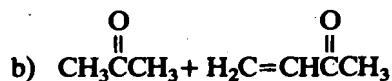
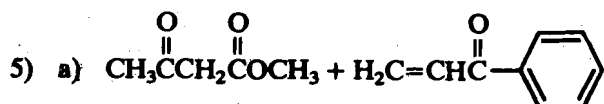
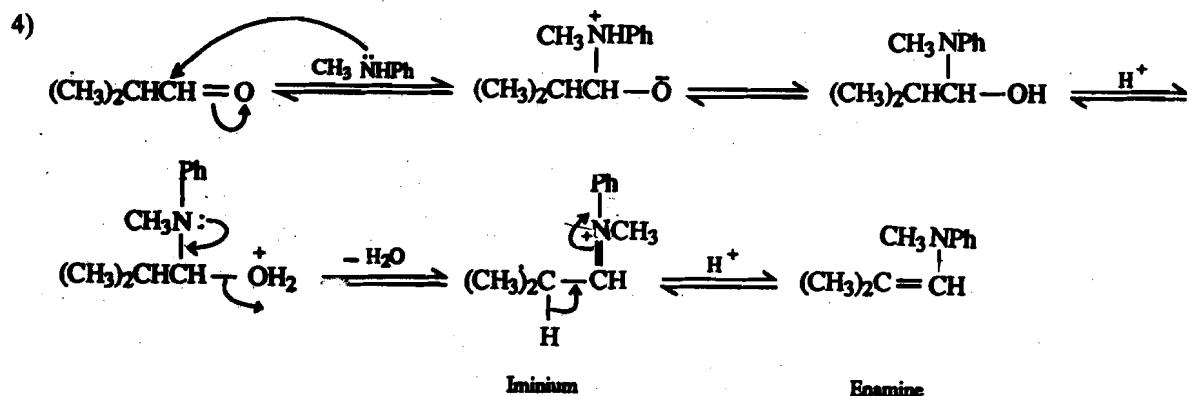
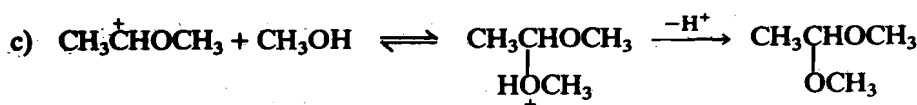
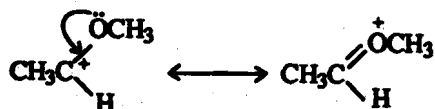
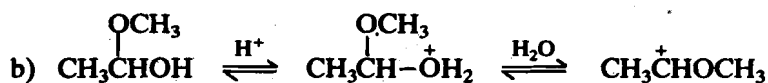
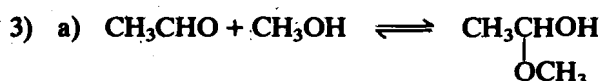
- 1) List the following aldehydes in terms of increasing reactivity.  
 $\text{CH}_3\text{CHO}$ ,  $\text{Cl}_3\text{CCHO}$ ,  $\text{ClCH}_2\text{CHO}$ ,  $\text{Cl}_2\text{CHCHO}$
- 2) Write the structure of the carbinolamine intermediate and the imine/enamine product formed in the reaction of each of the following:
  - a) Ethanal and benzylamine
  - b) Propanal and dimethylamine
- 3) Show how would you prepare the following compounds by an aldol/cross aldol condensation:?



- 4) Show in detail the mechanism of Knoevenagel reaction of diethyl malonate and benzaldehyde.
- 5) Suggest two synthetic routes to 2-butanol from an aldehyde and a Grignard reagent.

## Self-assessment Questions

- 1)  $\text{CH}_3\overset{\text{O}}{\parallel}\text{CCH}_3 > \text{CH}_3\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)_2 > (\text{CH}_3)_3\overset{\text{O}}{\parallel}\text{C}(\text{CH}_3)_3$   
 2) Compound (a) will form the most stable hydrate, because of electron-withdrawal by the Cl atoms.



## Terminal Questions

