

# J3 NUCLEOPHILIC ADDITION

## Key Notes

### Definition

Nucleophilic addition involves the addition of a nucleophile to an aldehyde or a ketone. The nucleophile adds to the electrophilic carbonyl carbon.

### Overview

Charged nucleophiles undergo nucleophilic addition with an aldehyde or ketone to give a charged intermediate which has to be treated with acid to give the final product. Neutral nucleophiles require acid catalysis and further reactions can take place after nucleophilic addition.

### Related topics

Nucleophilic addition – charged nucleophiles (J4)  
Nucleophilic addition – nitrogen nucleophiles (J6)

Nucleophilic addition – oxygen and sulfur nucleophiles (J7)

## Definition

As the name of the reaction suggests, nucleophilic addition involves the addition of a nucleophile to a molecule. This is a distinctive reaction for ketones and

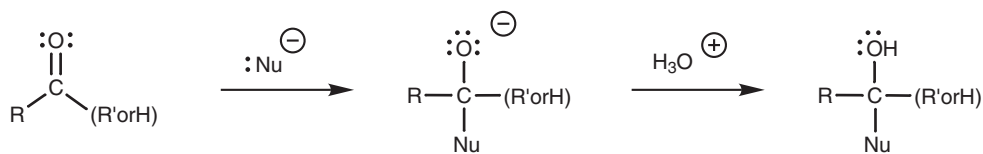


Fig. 1. Nucleophilic addition to a carbonyl group.

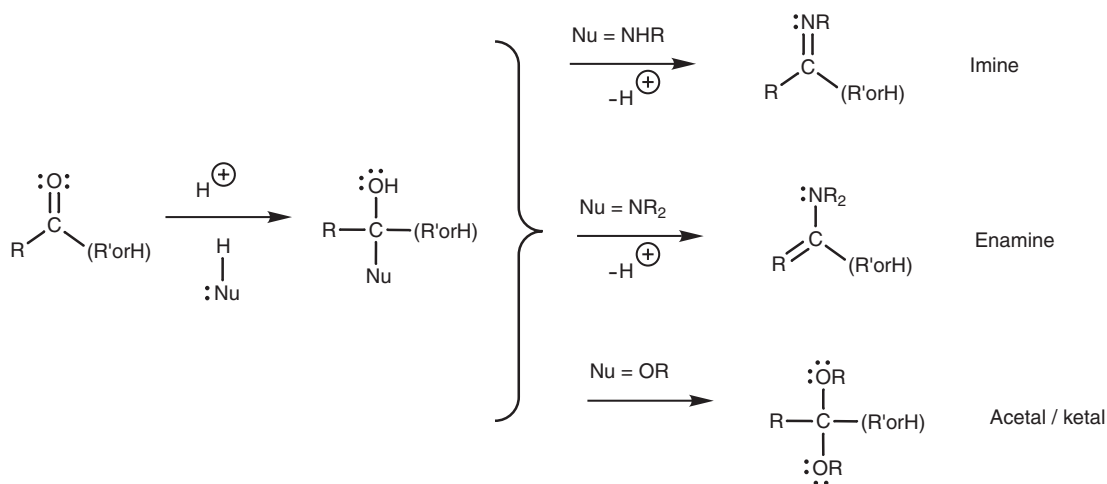


Fig. 2. Synthesis of imines, enamines, acetals, and ketals.

aldehydes and the nucleophile will add to the electrophilic carbon atom of the carbonyl group. The nucleophile can be a negatively charged ion such as cyanide or hydride, or it can be a neutral molecule such as water or alcohol.

**Overview**

In general, addition of charged nucleophiles results in the formation of a charged intermediate (*Fig. 1*). The reaction stops at this stage and acid has to be added to complete the reaction (Topic J4).

Neutral nucleophiles where nitrogen or oxygen is the nucleophilic center are relatively weak nucleophiles, and an acid catalyst is usually required. After nucleophilic addition has occurred, further reactions may take place leading to structures such as imines, enamines, acetals, and ketals (Topics J6 and J7; *Fig. 2*).

# J4 NUCLEOPHILIC ADDITION – CHARGED NUCLEOPHILES

## Key Notes

### Carbanion addition

Grignard reagents (RMgX) and organolithium reagents (RLi) are used as the source of carbanions. The reaction mechanism involves nucleophilic addition of the carbanion to the aldehyde or ketone to form a negatively charged intermediate. Addition of acid completes the reaction. Both reactions are important because they involve C–C bond formation allowing the synthesis of complex molecules from simple starting materials. Primary alcohols are obtained from formaldehyde, secondary alcohols from aldehydes and tertiary alcohols from ketones.

### Hydride addition

Lithium aluminum hydride (LiAlH<sub>4</sub>) and sodium borohydride (NaBH<sub>4</sub>) are reducing agents and the overall reaction corresponds to the nucleophilic addition of a hydride ion (H<sup>-</sup>). The reaction is a functional group transformation where primary alcohols are obtained from aldehydes and secondary alcohols are obtained from ketones.

### Cyanide addition

Reaction of aldehydes and ketones with HCN and KCN produce cyanohydrins. The cyanide ion is the nucleophile and adds to the electrophilic carbonyl carbon.

### Bisulfite addition

The bisulfite ion is a weakly nucleophilic anion which will only react with aldehydes and methyl ketones. The product is a water-soluble salt and so the reaction can be used to separate aldehydes and methyl ketones from larger ketones or from other water-insoluble compounds. The aldehyde and methyl ketone can be recovered by treating the salt with acid or base.

### Aldol reaction

The Aldol reaction involves the nucleophilic addition of enolate ions to aldehydes and ketones to form β-hydroxycarbonyl compounds.

## Related topics

Properties (J2)

Nucleophilic addition (J3)

Electronic and steric effects (J5)

Nucleophilic addition – nitrogen nucleophiles (J6)

Nucleophilic addition – oxygen and sulfur nucleophiles (J7)

Reactions of enolate ions (J8)

Organometallic reactions (L7)

## Carbanion addition

Carbanions are extremely reactive species and do not occur in isolation. However, there are two reagents which can supply the equivalent of a carbanion. These are Grignard reagents and organolithium reagents. We shall look first of all at the reaction of a Grignard reagent with aldehydes and ketones (*Fig. 1*).

The Grignard reagent in this reaction is called methyl magnesium iodide

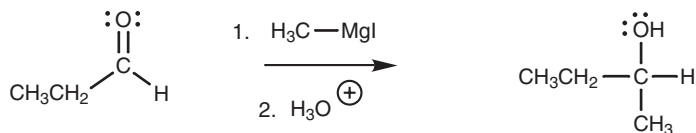


Fig. 1. Grignard reaction.

( $\text{CH}_3\text{MgI}$ ) and is the source of a methyl carbanion (Topic L7; Fig. 2). In reality, the methyl carbanion is never present as a separate ion, but the reaction proceeds as if it were. The methyl carbanion is the nucleophile in this reaction and the nucleophilic center is the negatively charged carbon atom. The aldehyde is the electrophile. Its electrophilic center is the carbonyl carbon atom since it is electron deficient (Topic J2).

The carbanion uses its lone pair of electrons to form a bond to the electrophilic carbonyl carbon (Fig. 3). At the same time, the relatively weak  $\pi$  bond of the carbonyl group breaks and both electrons move to the oxygen to give it a third lone pair of electrons and a negative charge (Step 1). The reaction stops at this stage, since the negatively charged oxygen is complexed with magnesium which acts as a counterion (not shown). Aqueous acid is now added to provide an electrophile in the shape of a proton. The intermediate is negatively charged and can act as a nucleophile/base. A lone pair of electrons on the negatively charged oxygen is used to form a bond to the proton and the final product is obtained (Step 2).



Fig. 2. Grignard reagent.

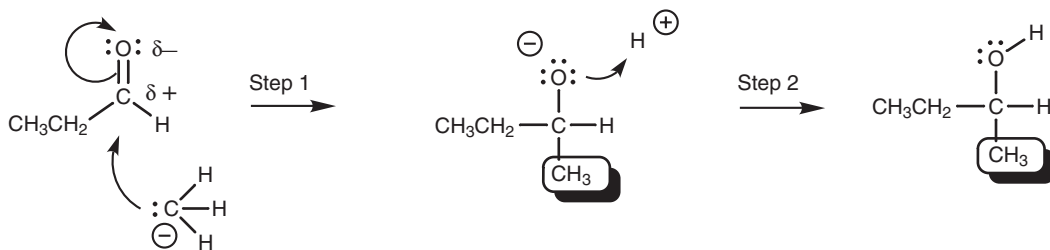


Fig. 3. Mechanism for the nucleophilic addition of a Grignard reagent.

The reaction of aldehydes and ketones with Grignard reagents is a useful method of synthesizing primary, secondary, and tertiary alcohols (Fig. 4). Primary alcohols can be obtained from formaldehyde, secondary alcohols can be obtained from aldehydes, and tertiary alcohols can be obtained from ketones. The reaction involves the formation of a carbon–carbon bond and so this is an important way of building up complex organic structures from simple starting materials.

The Grignard reagent itself is synthesized from an alkyl halide and a large variety of reagents are possible (Topic L7).

Organolithium reagents (Topic L7) such as  $\text{CH}_3\text{Li}$  can also be used to provide the nucleophilic carbanion and the reaction mechanism is exactly the same as that described for the Grignard reaction (Fig. 5).

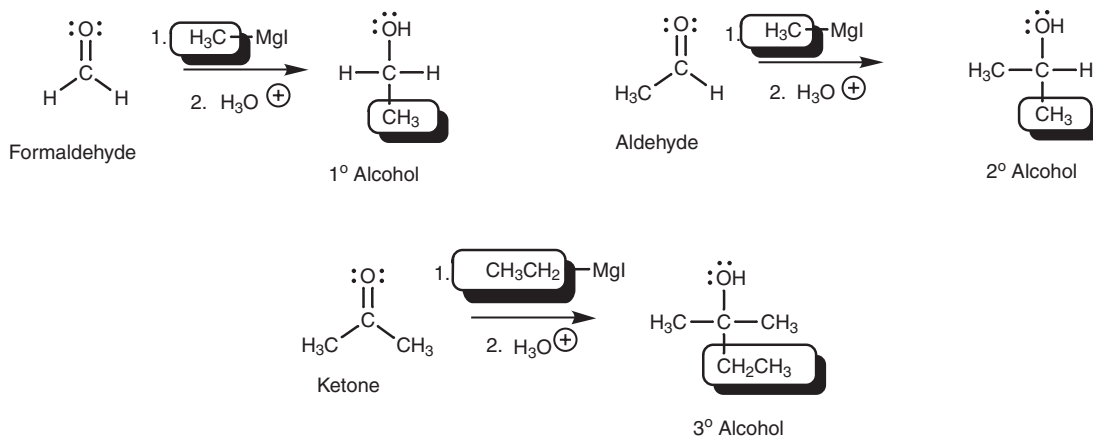


Fig. 4. Synthesis of primary, secondary, and tertiary alcohols by the Grignard reaction.

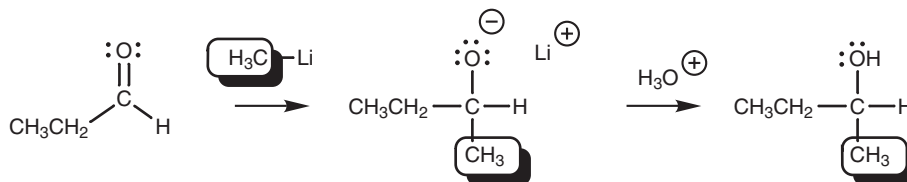


Fig. 5. Nucleophilic addition with an organolithium reagent.

### Hydride addition

Reducing agents such as sodium borohydride ( $\text{NaBH}_4$ ) and lithium aluminum hydride ( $\text{LiAlH}_4$ ) react with aldehydes and ketones as if they are providing a hydride ion ( $\text{H}^-$ ; Fig. 6). This species is not present as such and the reaction mechanism is more complex. However, we can explain the reaction by viewing these reagents as hydride equivalents ( $\text{H}^-$ ). The overall reaction is an example of a functional group transformation since the carbon skeleton is unaffected. Aldehydes are converted to primary alcohols and ketones are converted to secondary alcohols.

The mechanism of the reaction is the same as that described above for the Grignard reaction (Fig. 7). The hydride ion equivalent adds to the carbonyl group and a negatively charged intermediate is obtained which is complexed as a lithium salt (Step 1). Subsequent treatment with acid gives the final product (Step 2). It should be emphasized again that the mechanism is actually more complex than this because the hydride ion is too reactive to exist in isolation.

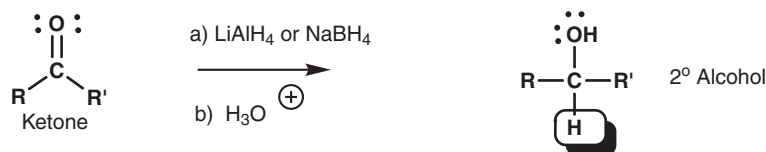


Fig. 6. Reduction of a ketone to a secondary alcohol.

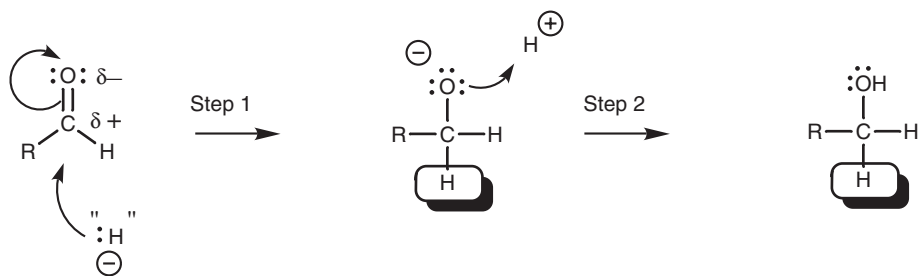


Fig. 7. Mechanism for the reaction of a ketone with  $\text{LiAlH}_4$  or  $\text{NaBH}_4$ .

**Cyanide addition** Nucleophilic addition of a cyanide ion to an aldehyde or ketone gives a **cyanohydrin** (Fig. 8). In the reaction, there is a catalytic amount of potassium cyanide present and this supplies the attacking nucleophile in the form of the cyanide ion ( $\text{CN}^-$ ). The nucleophilic center of the nitrile group is the carbon atom since this is the atom with the negative charge. The carbon atom uses its lone pair of electrons to form a new bond to the electrophilic carbon of the carbonyl group (Fig. 9). As this new bond forms, the relatively weak  $\pi$  bond of the carbonyl group breaks and the two electrons making up that bond move onto the oxygen to give it a third lone pair of electrons and a negative charge (Step 1). The intermediate formed can now act as a nucleophile/base since it is negatively charged and it reacts with the acidic hydrogen of  $\text{HCN}$ . A lone pair of electrons from oxygen is used to form a bond to the acidic proton and the  $\text{H-CN}$   $\sigma$  bond is broken at the same time such that these electrons move onto the neighboring carbon to give it a lone pair of electrons and a negative charge (Step 2). The products are the cyanohydrin and the cyanide ion. Note that a cyanide ion started the reaction and a cyanide ion is regenerated. Therefore, only a catalytic amount

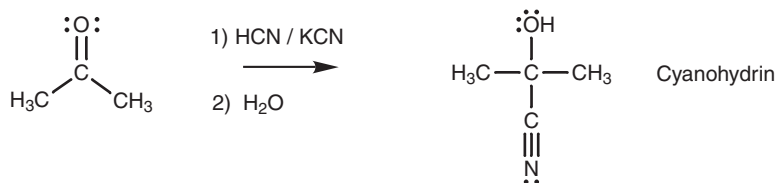


Fig. 8. Synthesis of a cyanohydrin.

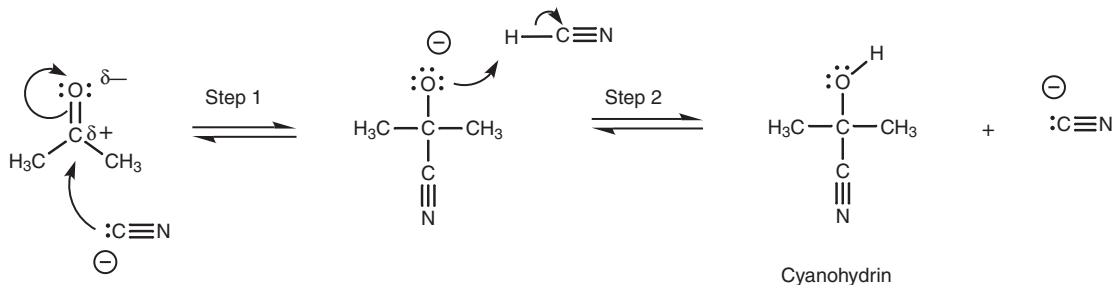


Fig. 9. Mechanism for the formation of a cyanohydrin.

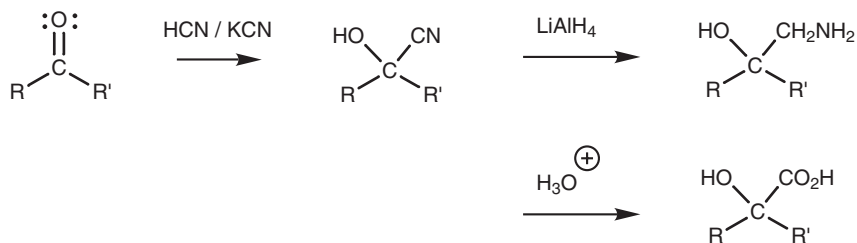


Fig. 10. Further reactions of cyanohydrins.

of cyanide ion is required to start the reaction and once the reaction has taken place, a cyanide ion is regenerated to continue the reaction with another molecule of ketone.

Cyanohydrins are useful in synthesis because the cyanide group can be converted to an amine or to a carboxylic acid (Topic O4; Fig. 10).

### Bisulfite addition

The reaction of an aldehyde or a methyl ketone with sodium bisulfite ( $\text{NaHSO}_3$ ) involves nucleophilic addition of a bisulfite ion ( $\text{:SO}_3\text{H}^-$ ) to the carbonyl group to give a water soluble salt (Fig. 11). The bisulfite ion is a relatively weak nucleophile compared to other charged nucleophiles and so only the most reactive carbonyl compounds will react. Larger ketones do not react since larger alkyl groups hinder attack (Topic J5). The reaction is also reversible and so it is a useful method of separating aldehydes and methyl ketones from other ketones or from other organic molecules. This is usually done during an experimental work up where the products of the reaction are dissolved in a water immiscible organic solvent. Aqueous sodium bisulfite is then added and the mixture is shaken thoroughly in a separating funnel. Once the layers have separated, any aldehydes and methyl ketones will have undergone nucleophilic addition with the bisulfite solution and will be dissolved in the aqueous layer as the water soluble salt. The layers can now

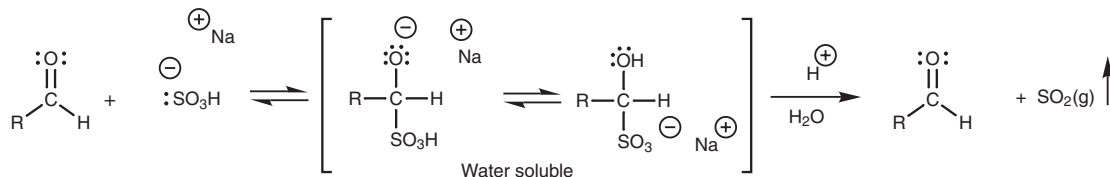


Fig. 11. Reaction of the bisulfite ion with an aldehyde.

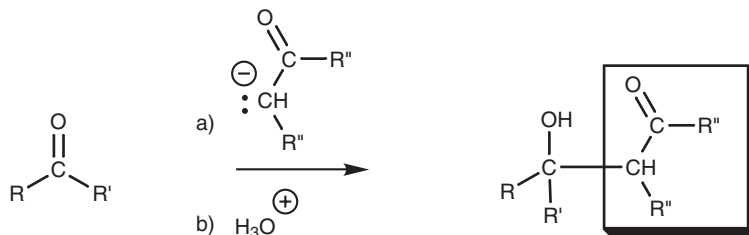


Fig. 12. The Aldol reaction.

be separated. If the aldehyde or methyl ketone is desired, it can be recovered by adding acid or base to the aqueous layer which reverses the reaction and regenerates the carbonyl compound.

**Aldol reaction**

Another nucleophilic addition involving a charged nucleophile is the Aldol reaction which is covered in Topic J8. This involves the nucleophilic addition of enolate ions to aldehydes and ketones to form  $\beta$ -hydroxycarbonyl compounds (*Fig. 12*).



# J5 ELECTRONIC AND STERIC EFFECTS

## Key Notes

### Reactivity

Aldehydes are more reactive to nucleophiles than ketones.

### Electronic factors

Alkyl groups have an inductive effect whereby they 'push' electrons towards a neighboring electrophilic center and make it less electrophilic and less reactive. Ketones have two alkyl groups and are less electrophilic than aldehydes which have only one alkyl group.

### Steric factors

The transition state for nucleophilic addition resembles the tetrahedral product. Therefore, any factor affecting the stability of the product will affect the stability of the transition state. Since the tetrahedral product is more crowded than the planar carbonyl compound, the presence of bulky alkyl groups will increase crowding and decrease stability. Since ketones have two alkyl groups to aldehyde's one, the transition state for ketones will be less stable than the transition state for aldehydes and the reaction will proceed more slowly. Bulky alkyl groups may also hinder the approach of the nucleophile to the reaction center – the carbonyl group.

### Related topics

Carbocation stabilization (H5)

Nucleophilic addition – charged nucleophiles (J4)

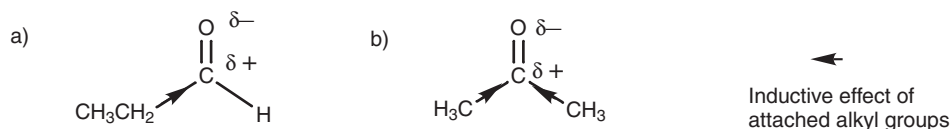
## Reactivity

Generally it is found that aldehydes are more reactive to nucleophiles than ketones. There are two factors (electronic and steric) which explain this difference in reactivity.

## Electronic factors

The carbonyl carbon in aldehydes is more electrophilic than it is in ketones due to the substituents attached to the carbonyl carbon. A ketone has two alkyl groups attached whereas the aldehyde has only one. The carbonyl carbon is electron deficient and electrophilic since the neighboring oxygen has a greater share of the electrons in the double bond. However, neighboring alkyl groups have an inductive effect whereby they push electron density towards the carbonyl carbon and make it less electrophilic and less reactive to nucleophiles (*Fig. 1*).

Propanal has one alkyl group feeding electrons into the carbonyl carbon, whereas propanone has two. Therefore, the carbonyl carbon in propanal is more electrophilic than the carbonyl carbon in propanone. The more electrophilic the



*Fig. 1. Inductive effect in (a) propanal; (b) propanone.*

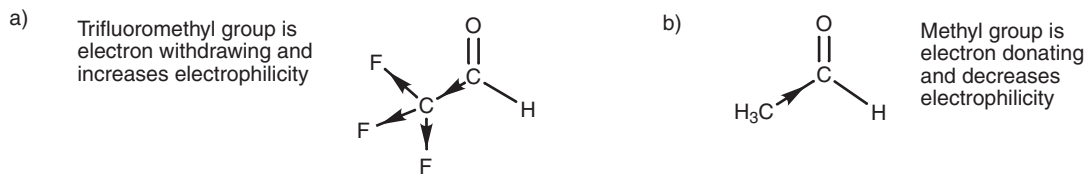


Fig. 2. Inductive effect of (a) trifluoroethanal; (b) ethanal.

carbon, the more reactive it is to nucleophiles. Therefore, propanal is more reactive than propanone.

Electron inductive effects can be used to explain differing reactivities between different aldehydes. For example the fluorinated aldehyde (Fig. 2) is more reactive than ethanal. The fluorine atoms are electronegative and have an electron-withdrawing effect on the neighboring carbon, making it electron deficient. This in turn has an inductive effect on the neighboring carbonyl carbon. Since electrons are being withdrawn, the electrophilicity of the carbonyl carbon is increased, making it more reactive to nucleophiles.

### Steric factors

Steric factors also have a role to play in the reactivity of aldehydes and ketones. There are two ways of looking at this. One way is to look at the relative ease with which the attacking nucleophile can approach the carbonyl carbon. The other is to consider how steric factors influence the stability of the transition state leading to the final product.

Let us first consider the relative ease with which a nucleophile can approach the carbonyl carbon of an aldehyde and a ketone. In order to do that, we must consider the bonding and the shape of these functional groups (Fig. 3). Both molecules have a planar carbonyl group. The atoms which are in the plane are circled in white. A nucleophile will approach the carbonyl group from above or below the plane. The diagram below shows a nucleophile attacking from above. Note that the hydrogen atoms on the neighboring methyl groups are not in the plane of the carbonyl group and so these atoms can hinder the approach of a nucleophile and thus hinder the reaction. This effect will be more significant for a ketone where there are alkyl groups on either side of the carbonyl group. An aldehyde has only one alkyl group attached and so the carbonyl group is more accessible to nucleophilic attack.

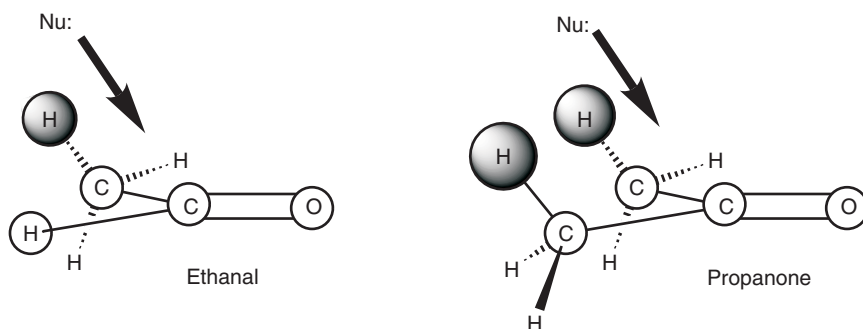


Fig. 3. Steric factors.

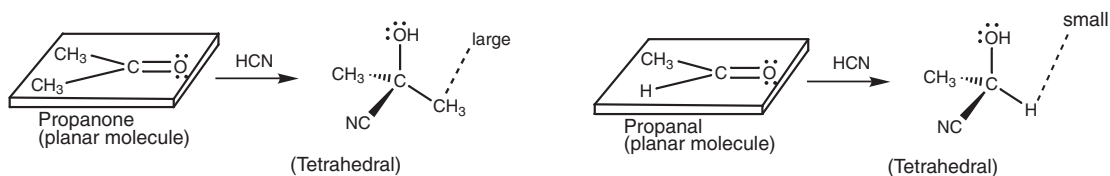


Fig. 4. Reactions of propanone and propanal with HCN.

We shall now look at how steric factors affect the stability of the transition state leading to the final product. For this we shall look at the reactions of propanone and propanal with HCN to give cyanohydrin products (Fig. 4).

Both propanone and propanal are planar molecules. The cyanohydrin products are tetrahedral. Thus, the reaction leads to a marked difference in shape between the starting carbonyl compound and the cyanohydrin product. There is also a marked difference in the space available to the substituents attached to the reaction site – the carbonyl carbon. The tetrahedral molecule is more crowded since there are four substituents crowded round a central carbon, whereas in the planar starting material, there are only three substituents attached to the carbonyl carbon. The crowding in the tetrahedral product arising from the ketone will be greater than that arising from the aldehyde since one of the substituents from the aldehyde is a small hydrogen atom.

The ease with which nucleophilic addition takes place depends on the ease with which the transition state is formed. In nucleophilic addition, the transition state is thought to resemble the tetrahedral product more than it does the planar starting material. Therefore, any factor which affects the stability of the product will also affect the stability of the transition state. Since crowding is a destabilizing effect, the reaction of propanone should be more difficult than the reaction of propanal. Therefore, ketones in general will be less reactive than aldehydes.

The bigger the alkyl groups, the bigger the steric effect. For example, 3-pentanone is less reactive than propanone and fails to react with the weak bisulfite nucleophile whereas propanone does (Fig. 5).

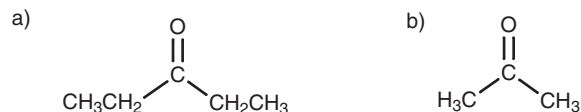


Fig. 5. (a) 3-Pentanone; (b) propanone.

# J6 NUCLEOPHILIC ADDITION – NITROGEN NUCLEOPHILES

## Key Notes

### Imine formation

Primary amines react with aldehydes and ketones to give an imine or Schiff base. The reaction involves nucleophilic addition of the amine followed by elimination of water. Acid catalysis aids the reaction, but too much acid hinders the reaction by protonating the amine.

### Enamine formation

Secondary amines undergo the same type of mechanism as primary amines, but cannot give imines as the final product. Instead, a proton is lost from a neighboring carbon and functional groups called enamines are formed.

### Oximes, semicarbazones and 2,4-dinitrophenylhydrazones

Aldehydes and ketones can be converted to crystalline derivatives called oximes, semicarbazones, and 2,4-dinitrophenylhydrazones. Such derivatives were useful in the identification of liquid aldehydes and ketones.

### Related topics

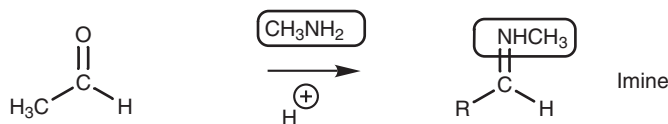
Nucleophilic addition (J3)  
Nucleophilic addition – charged nucleophiles (J4)

Nucleophilic addition – oxygen and sulfur nucleophiles (J7)

## Imine formation

The reaction of primary amines with aldehydes and ketones do not give the products expected from nucleophilic addition alone. This is because further reaction occurs once nucleophilic addition takes place. As an example, we shall consider the reaction of acetaldehyde (ethanal) with a primary amine – methylamine (*Fig. 1*). The product contains the methylamine skeleton, but unlike the previous reactions there is no alcohol group and there is a double bond between the carbon and the nitrogen. This product is called an **imine** or a **Schiff base**.

The first stage of the mechanism (*Fig. 2*) is a normal nucleophilic addition. The amine acts as the nucleophile and the nitrogen atom is the nucleophilic center. The nitrogen uses its lone pair of electrons to form a bond to the electrophilic carbonyl carbon. As this bond is being formed, the carbonyl  $\pi$  bond breaks with both electrons moving onto the oxygen to give it a third lone pair of electrons and a negative charge. The nitrogen also gains a positive charge, but both these charges can



*Fig. 1. Reaction of ethanal with methylamine.*

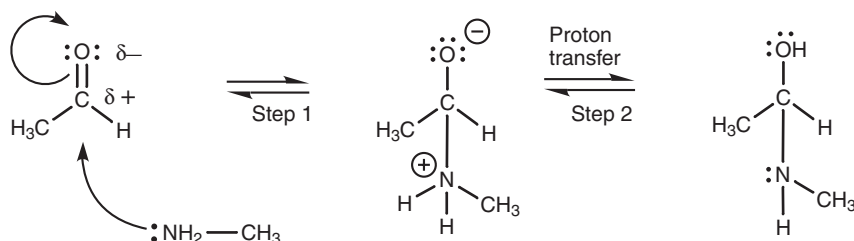


Fig. 2. Mechanism of nucleophilic addition.

be neutralized by the transfer of a proton from the nitrogen to the oxygen (Step 2). The oxygen uses up one of its lone pairs to form the new O–H bond and the electrons in the N–H bond end up on the nitrogen as a lone pair. An acid catalyst is present, but is not required for this part of the mechanism – nitrogen is a good nucleophile and although the amine is neutral, it is sufficiently nucleophilic to attack the carbonyl group without the need for acid catalysis. The intermediate obtained is the structure one would expect from nucleophilic addition alone, but the reaction does not stop there. The oxygen atom is now protonated by the acid catalyst and gains a positive charge (Fig. 3, Step 3). Since oxygen is electronegative, a positive charge is not favored and so there is a strong drive to neutralize the charge. This can be done if the bond to carbon breaks and the oxygen leaves as part of a water molecule. Therefore, protonation has turned the oxygen into a good leaving group. The nitrogen helps the departure of the water by using its lone pair of electrons to form a  $\pi$  bond to the neighboring carbon atom and a positive charged intermediate is formed (Step 4). The water now acts as a nucleophile and removes a proton from the nitrogen such that the nitrogen's lone pair is restored and the positive charge is neutralized (Step 5).

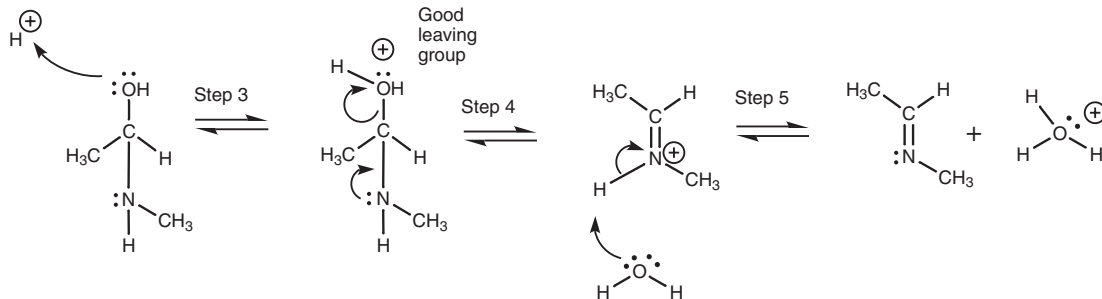


Fig. 3. Mechanism for the elimination of water.

Overall, a molecule of water has been lost in this second part of the mechanism. Acid catalysis is important in creating a good leaving group. If protonation did not occur, the leaving group would have to be the hydroxide ion which is a more reactive molecule and a poorer leaving group.

Although acid catalysis is important to the reaction mechanism, too much acid can actually hinder the reaction. This is because a high acid concentration leads to protonation of the amine, and prevents it from acting as a nucleophile.

## Enamine formation

The reaction of carbonyl compounds with secondary amines cannot give imines since there is no NH proton to be lost in the final step of the mechanism. However, there is another way in which the positive charge on the nitrogen can be

neutralized. This involves loss of a proton from a neighboring carbon atom (Fig. 4). Water acts as a base to remove the proton and the electrons which make up the C–H  $\sigma$  bond are used to form a new  $\pi$  bond to the neighboring carbon. This in turn forces the existing  $\pi$  bond between carbon and nitrogen to break such that both the  $\pi$  electrons end up on the nitrogen atom as a lone pair, thus neutralizing the charge. The final structure is known as an enamine and can prove useful in organic synthesis.

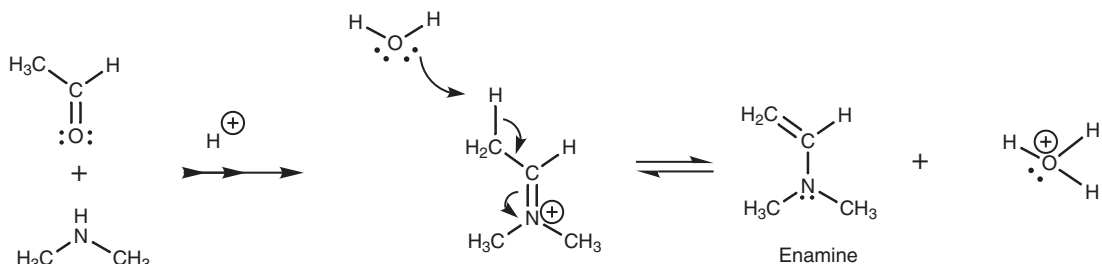


Fig. 4. Mechanism for the formation of an enamine.

### Oximes, semicarbazones and 2,4-dinitrophenylhydrazones

The reaction of aldehydes and ketones with hydroxylamine ( $\text{NH}_2\text{OH}$ ), semicarbazide ( $\text{NH}_2\text{NHCONH}_2$ ) and 2,4-dinitrophenylhydrazine takes place by the same mechanism described for primary amines to give oximes, semicarbazones, and 2,4-dinitrophenylhydrazones, respectively (Fig. 5). These compounds were frequently synthesized in order to identify a liquid aldehyde or ketone. The products are solid and crystalline, and by measuring their melting points, the original aldehyde or ketone could be identified by looking up melting point tables of these derivatives. Nowadays, it is easier to identify liquid aldehydes and ketones spectroscopically.

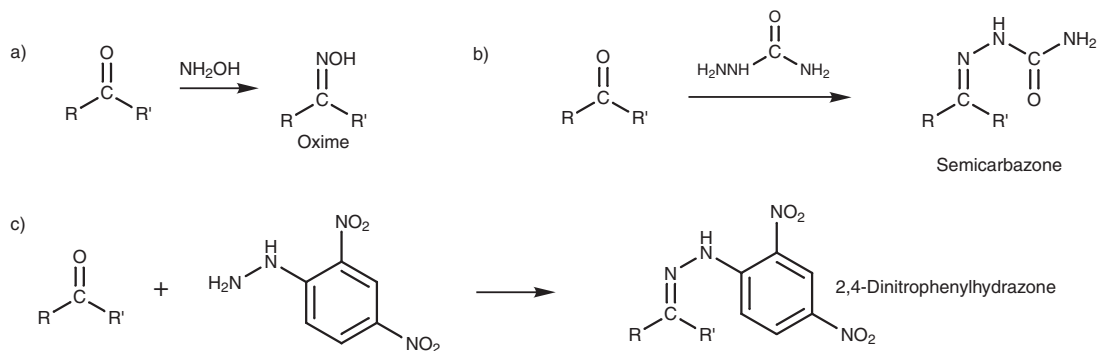


Fig. 5. Synthesis of oximes, semicarbazones, and 2,4-dinitrophenylhydrazones.