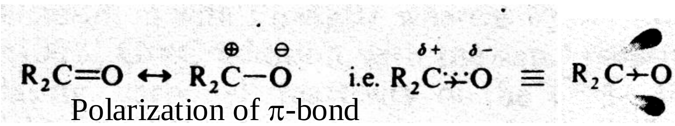
ADDITION TO C=O

C=O bond is polar because the oxygen atom is more electronegative than carbon. The polarization of both σ- and π-bond increase the electron density at the oxygen atom and consequently decrease the electron density at the carbonyl carbon atom. The carbon atom becomes positively polarized, and this positive character is known as **carbonyl activity.**

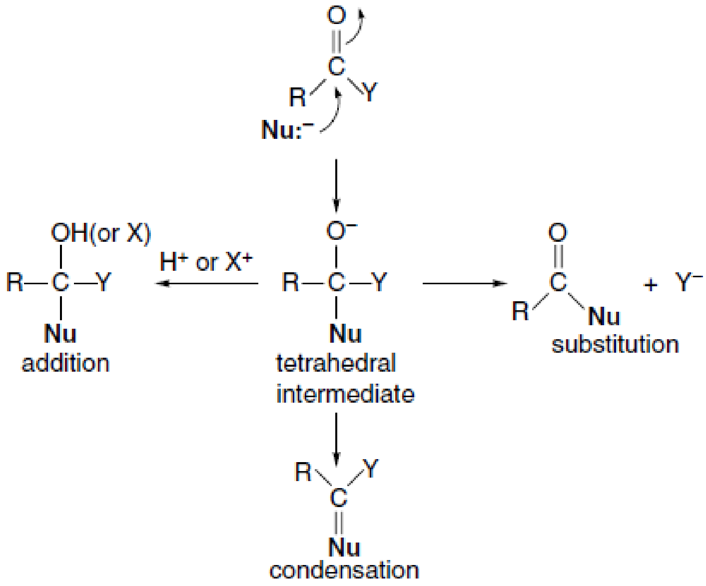
The carbonyl group is best represented by the following hybrid structure



Polarization of π-bond

Greater electron density at the oxygen end due to polarization of both σ-and π-bonds

In many reactions at carbonyl groups, a key step is the addition of a nucleophile, which generates a tetracoordinate carbon atom is called tetrahedral intermediate. The overall course of the reaction is then determined by the fate of this tetrahedral intermediate.

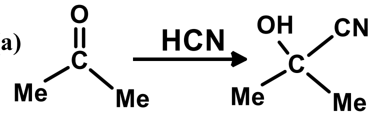


1. Addition occurs when the tetrahedral intermediate goes directly on to product.

2. Condensation occurs if the carbonyl oxygen is eliminated and a double bond is formed.

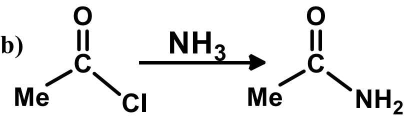
3. Substitution results when one of the groups is eliminated from the tetrahedral intermediate to re-form a carbonyl group.

(a)



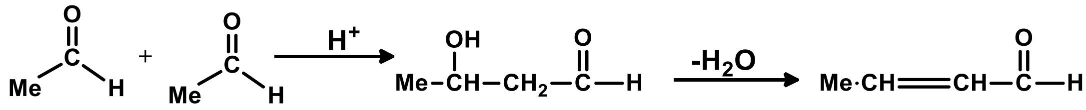
nucleophilic addition reaction

(b)



nucleophilic substitution reaction

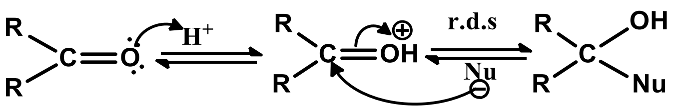
(c)



condensation reaction

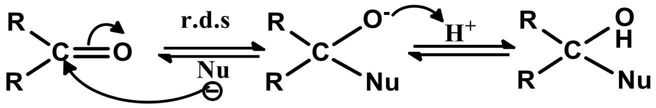
In broad terms, there are three possible mechanisms for addition of a nucleophile and a proton to give a tetrahedral intermediate in a carbonyl addition reaction.

(a) Protonation followed by nucleophilic attack on the protonated carbonyl group:

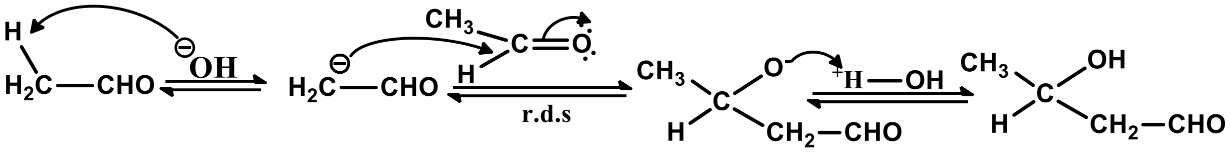


This is favoured for weak nucleophiles. The protonated carbonyl compound is more reactive toward such nucleophiles. The nucleophile may be neutral or a weakly basic anion. This mechanism is most likely to operate in relatively acidic medium.

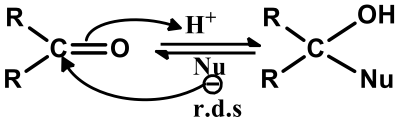
(b) Nucleophilic addition at the carbonyl group followed by protonation:



This is favoured for strongly basic nucleophiles. For example, carbanions cannot generally exist under acidic conditions, so carbanion additions occur under strongly basic conditions. These nucleophiles are more basic than carbonyl oxygens and are protonated in preference to the carbonyl group. In such systems, proton donors diminish the overall reaction rate by decreasing the amount of anionic nucleophile that is available for reaction.



(c) Concerted proton transfer and nucleophilic attack:



The concerted mechanism is observed for less basic nucleophiles. The simultaneous transfer of the proton at the carbonyl oxygen facilitates addition by species that are not sufficiently nucleophilic to react by mechanism (b). The general pattern is that the weaker and less basic the nucleophile, the more important the partial or complete protonation of the carbonyl group.

If we consider the reverse process, the same general relationships will hold.

Good leaving groups (which are poor nucleophiles) can be expected to follow path (a).

Poor leaving groups will follow path (b); and intermediate cases are likely to react by the concerted mechanism (c).

Factors affecting the reactivity of the carbonyl compounds:

Several factors influence the overall rate of a reaction under various conditions. Among the crucial factors are:

(1) Structural features of the carbonyl compound

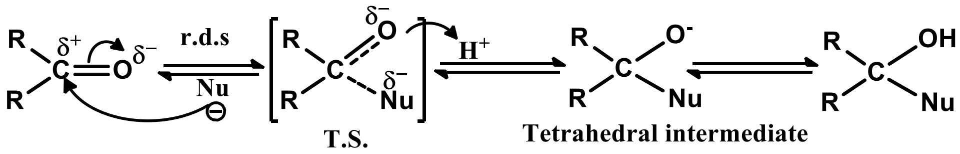
(2) The role of protons or other Lewis acids in activating the carbonyl group toward nucleophilic attack

(3) The reactivity of the nucleophilic species and its influence on subsequent steps

(4) The stability of the tetrahedral intermediate and the extent to which it proceeds to product rather than reverting to starting material.

(1) Structural features of the carbonyl compound: (a) Electronic factor:

In simple nucleophilic addition to the carbonyl group, where the attack by the nucleophile is the rate determining step, the positive character of the carbonyl carbon atom is reduced on going from stating material carbonyl to the T.S.

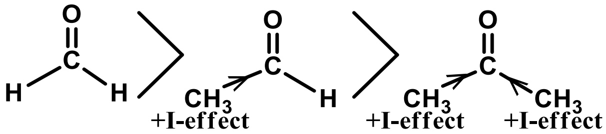


So with increasing the positive (electrophilic) character, i.e. the carbonyl activity, the initial attack by the nucleophile is more favourable and the T.S. corresponding to this reaction becomes more stable (due to greater delocalization of negative charge in the T.S.). Hence the reaction rate increases.

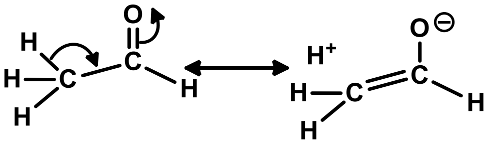
Thus any electron withdrawing (EWG) increases the electrophilic character (carbonyl activity) of the carbonyl as well as the rate of reaction.

On the other hand **electron donating (EDG) decreases the electrophilic character (carbonyl activity) of the carbonyl as well as the rate of reaction.**

The reactivity order of the following carbonyl is as follows—

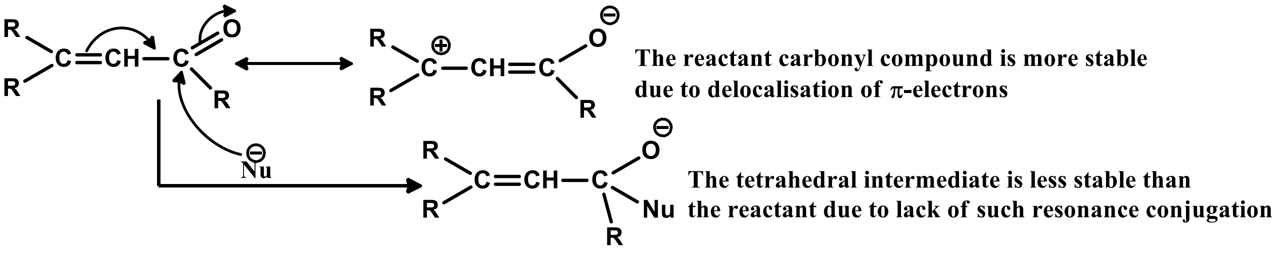


The +I effect and **hyper conjugative effect** of Me-group decreases the electrophilic character of the carbonyl carbon atom. Thus the reactivity decreases from left to right in the above series.



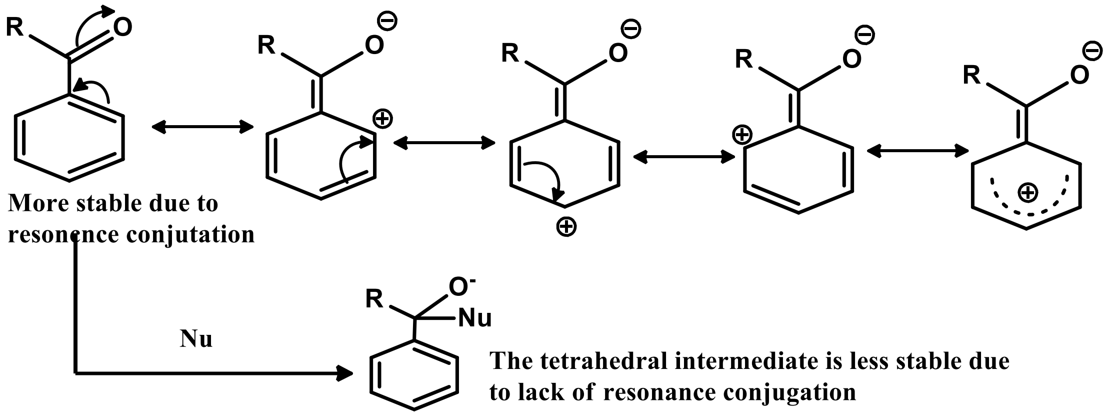
When C=O is conjugated with C=C or with benzene ring, the reactivity decreases.

This is due to **decrease of electrophilic character** of carbonyl carbon and **stabilization of the reactant carbonyl compound through resonance conjugation with C=C**, which is lost on proceeding to the T.S. or tetrahedral intermediate. Thus the **activation energy becomes very high**.



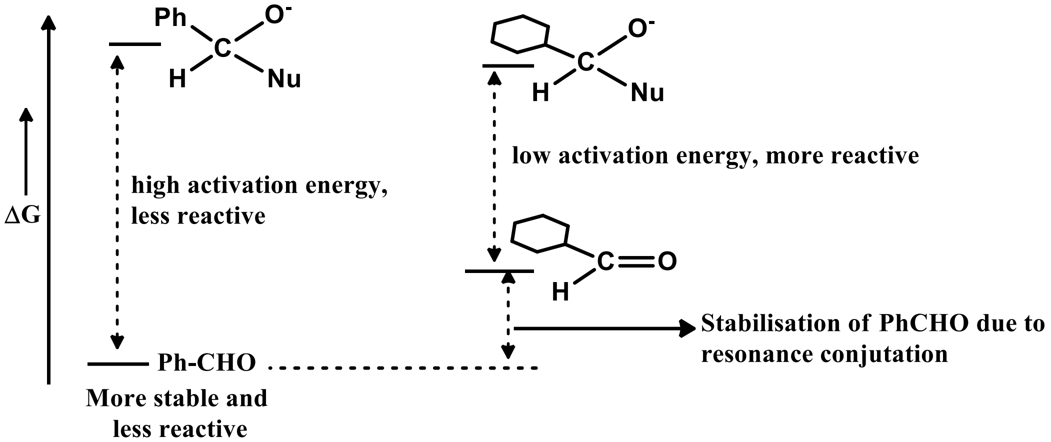
The reactant carbonyl compound is more stable due to delocalisation of π-electrons

The tetrahedral intermediate is less stable than the reactant due to lack of such resonance conjugation



More stable due to resonence conjutation

The tetrahedral intermediate is less stable due to lack of resonance conjugation



high activation energy, less reactive

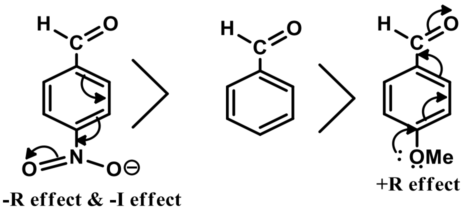
low activation energy, more reactive

Stabilisation of PhCHO due to resonance conjutation

More stable and less reactive

With **addition of electron withdrawing group at the *p*-position** of the benzene ring, **increases the electrophilic character** of the carbonyl carbon and hence initial attack by the nucleophile becomes more favourable. It also **increases the stability of the T.S** corresponding to the negatively charged tetrahedral intermediate.

Thus the rate of reaction of the following compounds decreases as follows—

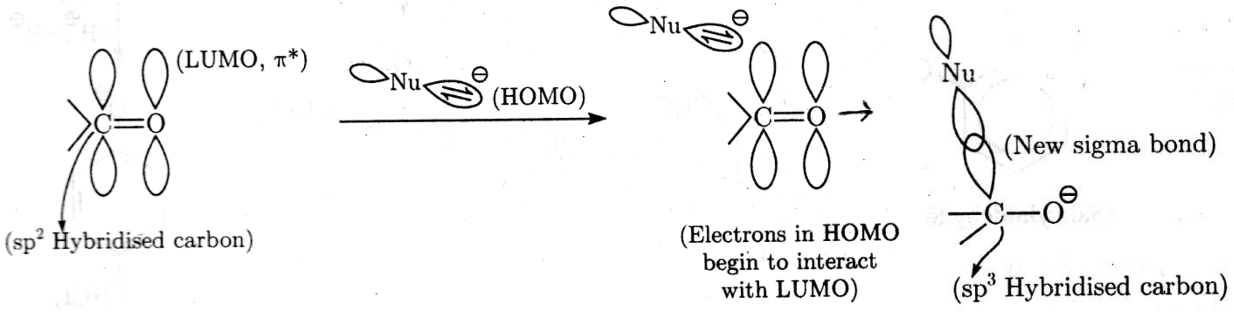


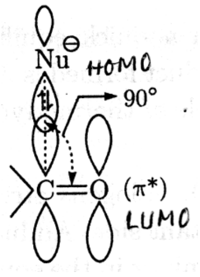
-R effect & -I effect

+R effect

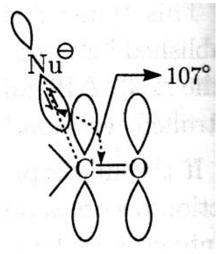
(b) Steric factor:

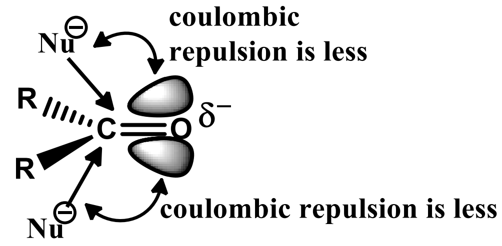
So far as steric effects are concerned, the more favourable and least energy demanding direction of approach of nucleophile to the carbonyl carbon atom will be from the above and below the planar carbonyl compound as there are interactions between the orbital of filled HOMO of nucleophile (Nu^-) to the vacant LUMO of C=O.





When Nu$^-$ approaches at right angle to the C=O the orbital **overlap becomes maximum** but there is some **columbic repulsion** between the filled π-MO of C=O and filled MO of Nu$^-$. To avoid this repulsion, Nu$^-$ attacks to the C=O at an angle of 107^0 this is known as **Burgi-Dunitz trajectory.**





Thus the nucleophile approaches **remote from carbonyl oxygen and closer to the alkyl group** to avoid the inter-electronic (columbic) repulsion between the approaching electron rich nucleophile and the electron rich carbonyl oxygen.

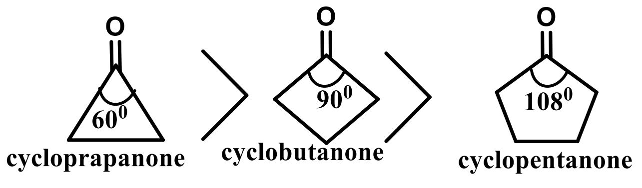
So **with increasing size of R─group, the rate of reaction decreases**. Because the initial attack by the nucleophile is less favourable due to increase of steric repulsion between R-groups and the approaching nucleophile.

Moreover, in this reaction, the tri-coordinated sp2 hybridised carbonyl carbon (surrounded by three groups) is converted to tetra coordinated sp3 hybridised atom (surrounded by four groups) in the tetrahedral intermediate. Thus the **T.S. is more crowded than that of starting carbonyl compound**.

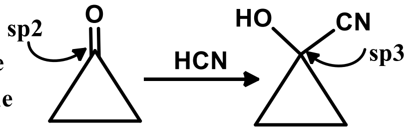
So the rate of reaction of formaldehyde > acetaldehyde > acetone; due to both electronic and steric reason.

The increasing **size of nucleophile** also increases steric crowding at T.S. thus the **rate of reaction decreases.**

In case of cyclic ketones the rate of reaction is as follows—



As the geometrical angle of cyclopropane ring is 60^0, whereas the sp2-hybrideised angle of carbonyl carbon is 120^0, so there is severe angle starin (Baeyer's strain) due to greater deviation of angle between the hybridised and geometrical angle

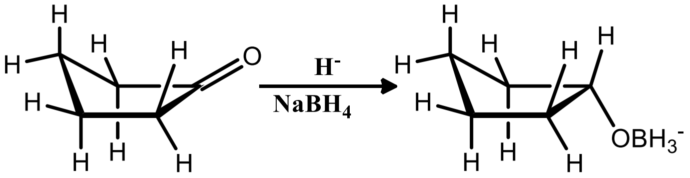


But in this product, the sp2 carbon is converted to sp3 ($109^028'$), so there is less deviation of angle and less angle strain, Thus during reaction there is some relief of angle strain which favours the reaction

From cyclopropane to cyclopentane the geometrical internal angle gradually increases thus the **angle strain decreases** so during the addition reaction the relief of angle strain decreases thus the **rate of reaction decreases.**

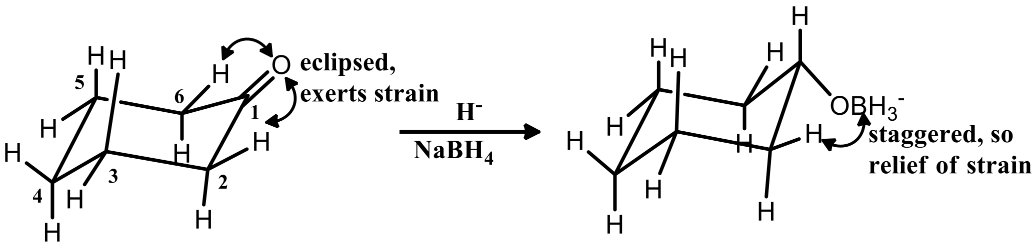
But **reactivity order of cyclopentanone is less than that of cyclohexanone**. Because the internal angle of cyclopentane ring is 108^0 whereas in cyclohexane (chair form) ring it is $109^028'$, almost same. So the angle strain (Baeyer's strain) between cyclopentanone and cyclohexanone is almost same. But during nucleophilic addition reaction of cyclopentanone the **torsional strain** increases due to change of hybridization of carbonyl carbon from sp2 to sp3. (The cyclopentanone has **eclipsing interaction** between 5 pair of H atoms only whereas the product has 6 pair eclipsing interaction and one pair H- OBH_3 interaction. Thus eclipsing or torsional interaction of the reactant is less than that of product.) Thus there is increase of strain during the addition reaction; which decreases the rate of reaction

eclipsing interaction between 5 pair H-atoms only. So it is more stable.



eclipsing interaction between 6 pair H-atoms and between H & OBH_3 group. So the product is less stable than the reactant

But in case of cyclohexanone, the **equatorial H-atoms (at C2 and C5) are eclipsed with the carbonyl** so the reactant molecule experiences higher strain than that of product where the cyclohexane ring has no such strain. Thus **there is some relief of strain during the addition reaction; which increases the rate of reaction.**



eclipsed, exerts strain

staggered, so relief of strain

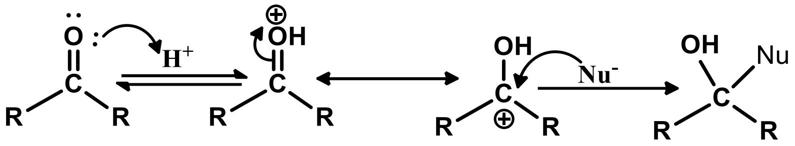
Rates of Reduction of Aldehydes and Ketones by Sodium Borohydride

Carbonyl compound	**$k \times 10^4 M^{-1} s^{-1}$**
Benzaldehyde	12,400
Benzophenone	1.9
Acetophenone	2.0
Acetone	15.1

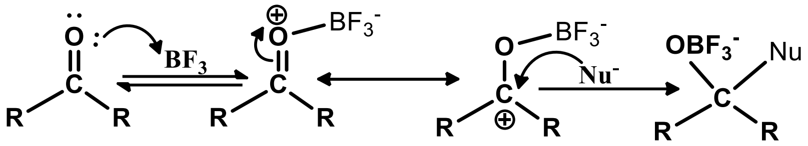
Cyclobutanone	264
Cyclopentanone	7
Cyclohexanone	161

2. The role of protons (acids) or other Lewis acids.

Many carbonyl addition and substitution reactions are carried out under acidic conditions or in the presence of Lewis acids. The **protonation or complexation with the carbonyl oxygen, increases the electrophilicity of the carbonyl carbon** as a result the initial attack by the nucleophile increases and the rate of reaction increases.

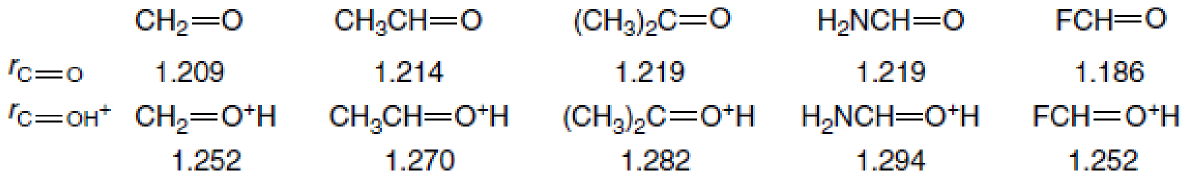


positive character or electrophilic characher of the carbonyl carbon increases so the attack by the nucleophile becomes favourable



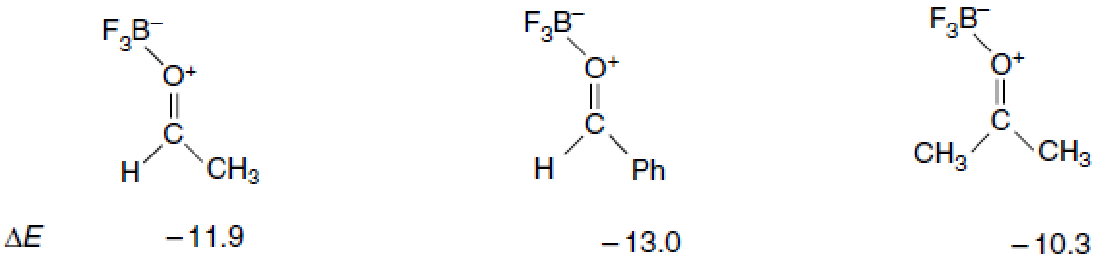
The protonation also results in a substantial **lengthening of the C=O** bond so the bond becomes weaker thus the reaction is faster.

The relative bond distance of C=O and protonated species of different compounds are as follows—

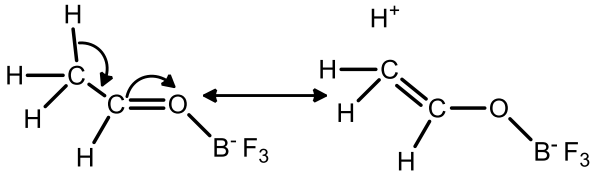


	$CH_2{=}O$	$CH_3CH{=}O$	$(CH_3)_2C{=}O$	$H_2NCH{=}O$	$FCH{=}O$
$r_{C=O}$	1.209	1.214	1.219	1.219	1.186
$r_{C=OH^+}$	$CH_2{=}O^+H$	$CH_3CH{=}O^+H$	$(CH_3)_2C{=}O^+H$	$H_2NCH{=}O^+H$	$FCH{=}O^+H$
	1.252	1.270	1.282	1.294	1.252

Lewis acids such as BF_3 normally adopt an *anti-* structure for aldehydes. Despite the unfavorable steric effect in acetone, the calculated energy of complexation with BF_3 is nearly as high as for acetaldehyde, presumably owing to the additional electron donation by the methyl groups (+I effect of Me) in acetone.

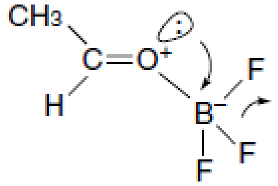


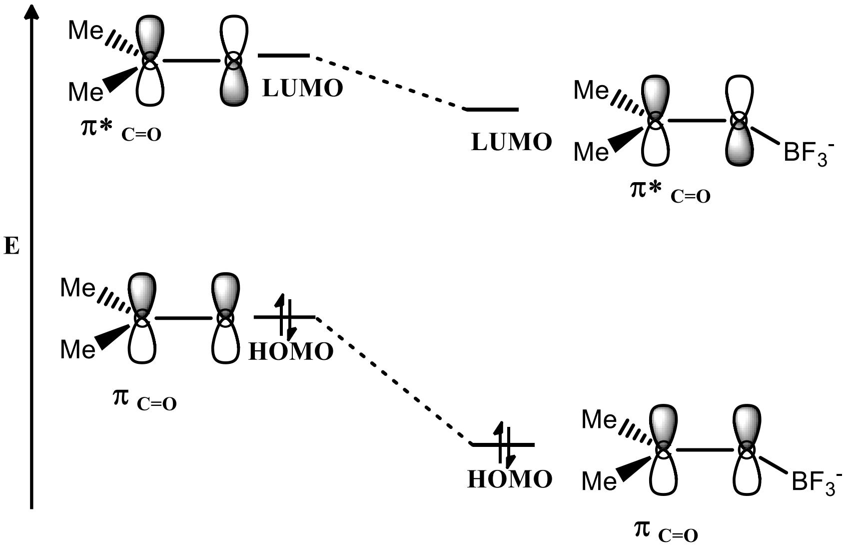
Furthermore, there are two significant hyperconjugative effects result from complexation with a Lewis acid. The donor effect of alkyl substituents is enhanced by the greater electrophilicity of the carbonyl oxygen.



hyperconjugation facilitates the reaction

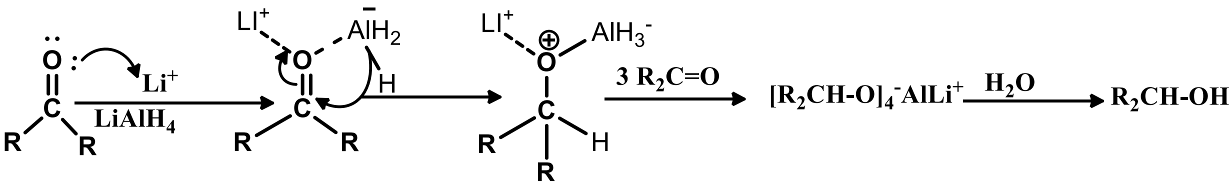
There is also an **interaction of the remaining unshared oxygen electrons with the σ^* orbital of the B – F bond.** The **interaction lowers the energy of both the π- and π^* orbitals and enhances the reactivity toward nucleophiles.**





Metal cations can also act as Lewis acids and they can make a complex with the carbonyl oxygen. As a result the carbonyl activity or electrophilic character increases consequently the rate of reaction increases.

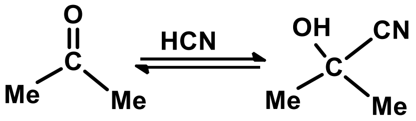
For example, in reduction of carbonyl by LiAlH4, the **Li^+ can make a strong complex with the carbonyl oxygen due to its smaller size and high charge density**. As a result the electrophilic character of the carbonyl carbon increases, which facilitates the nucleophilic attack of hydride ion (H^-) and the reduction process becomes faster.



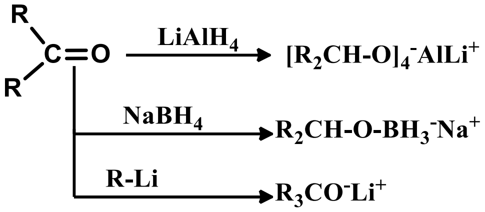
3. Reactivity of nucleophile:

As nucleophilic attack involves in the rate limiting step of the reaction, with increasing the nucleophilicity or the concentration of the nucleophile the rate of reaction increases.

For example, Many addition reactions are reversible but the presence of very strong nucleophiles e.g. AlH_4^-, BH_4^-, RMgBr, RLi, make the reaction almost unidirectional towards the forward direction.



The reaction is reversible as the nucleophile, CN^- is not so strong.



All the reactions are unidirectional as the nucleophiles are very strong.

4. Stability of the tetrahedral intermediate:

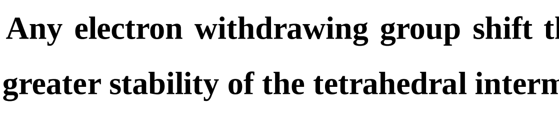
With increasing the stability of the tetrahedral intermediate as well as the corresponding T.S. by both electronic and steric factors, the rate of reaction increases.

As the T.S. or the tetrahedral intermediate is negatively charged species, so any electron with drawing group attached with the carbonyl carbon increases the stability of the intermediate due to greater delocalization of negative charge.

During the reaction, sp2 hybridised carbonyl carbon is converted to sp3 thus the intermediate is more crowded than the starting carbonyl compound. So with increasing the size of R and the nucleophile further increases the crowding of the intermediate and T.S. so it becomes less stable and the rate of reaction decreases.

Reversibility of the reaction:

Many carbonyl addition reactions are reversible, except the reaction with $LiAlH_4$, $NaBH_4$, R-Li, RMgBr etc, Thus overall results of reactions therefore depend on the position of the equilibrium. In general,, the factors that affect the rate of reaction (k) also influence the position of equilibrium (Keq) in much the same way. This is because the T.S. for simple addition reactions probably resembles the adduct (tetrahedral intermediate) a good deal more closely than it does the original reactant carbonyl compound. i.e. **the T.S acquire more (tetrahedral) intermediate character.**



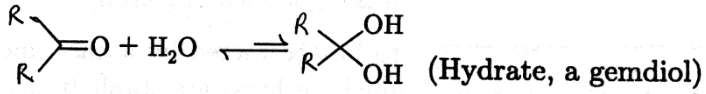
$$K_{eq} = \frac{k_1}{k_2}$$

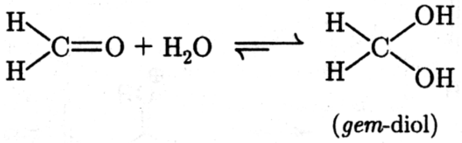
Any electron withdrawing group shift the equilibrium towards the forward direction due to greater stability of the tetrahedral intermediate.

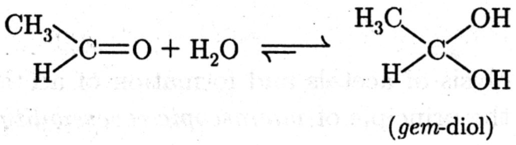
Any sterically crowded R-groups or nucleophile shift the equilibrium to the left due to destabilization of the T.S. corresponding to the intermediate.

Hydration Reaction:

Many carbonyl compounds undergo reversible hydration in aqueous solution.







The rate of reaction decreases from $H_2C=O$ to MeCHO to $Me_2C=O$, which is reflected in their K_{eq} values $2x10^3$, 1.4 and $2x10^{-3}$ respectively at 20^0C.

This is due to **decrease of electrophilic character of the carbonyl carbon** thus slow initial attack by the nucleophile H_2O and also **increase of steric crowding in T.S.** corresponding to the tetrahedral intermediate form folmaldehyde to acetone.

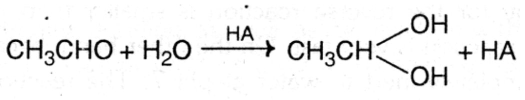
Addition of water (or formation of hydrates) to a carbonyl compound is a **reversible reaction** and the equilibrium lies over to **the left**.

Because **C=O bond dissociation energy is more than twice of C—O bond formation energy.** So the addition of water to a carbonyl function is usually an **endothermic reaction (ΔH^0 is +ve**) to the extent of 20 kJ/mol.

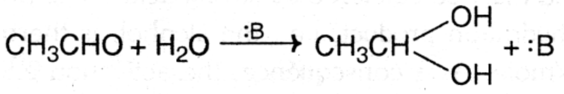
Moreover, **ΔS° for the forward reaction is negative** as two molecules of reactants (carbonyl compound and water give rise to only one molecule of product hydrate). Thus the forward reaction is both **energetically and entropically** unfavourable.

H_2CO hydrates quite readily at pH 7 compare to Me_2CO, reflecting the fact that its more positive carbonyl carbon atom undergoes attack by H_2O, without first requiring protonation of its carbonyl oxygen atom as the carbonyl carbon of formaldehyde is quite electrophilic. Nevertheless hydrates formation is very much faster at pH 4 (acidic medium) or 11(basic medium)

Thus the reaction is both acid and base catalysed.

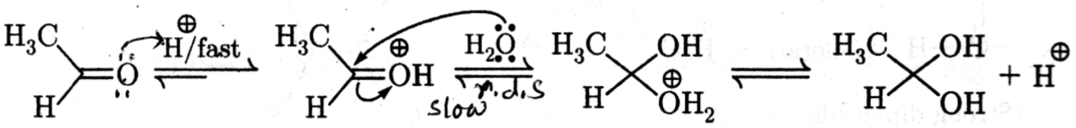


$$CH_3CHO + H_2O \xrightarrow{HA} CH_3CH(OH)_2 + HA$$

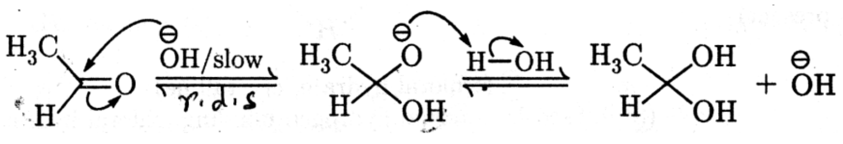


$$CH_3CHO + H_2O \xrightarrow{:B} CH_3CH(OH)_2 + :B$$

Mechanism of acid-catalyzed hydration:

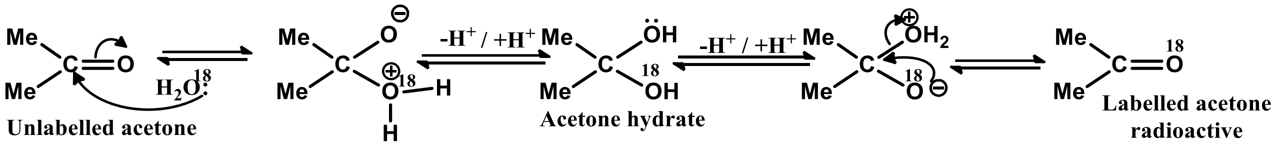


Mechanism of base-catalyzed hydration:

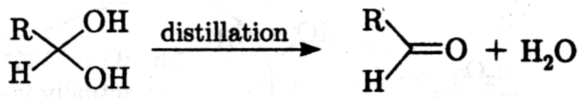


Evidence for the hydrate formation:

When acetone is dissolved in **water (radioactive H_2O^{18}) enriched with ^{18}O.** From the samples of the mixture collected periodically acetone is recovered and analyzed by mass spectroscopy. It is found that **acetone begins to acquire ^{18}O,** i.e**., the carbonyl ^{16}O exchanges with the water ^{18}O.** This isotopic exchange indicates that acetone hydrated to form symmetrical tetrahedral product, which loses H_2O^{18} and H_2O with equal ease.

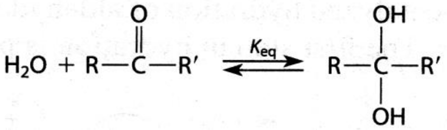


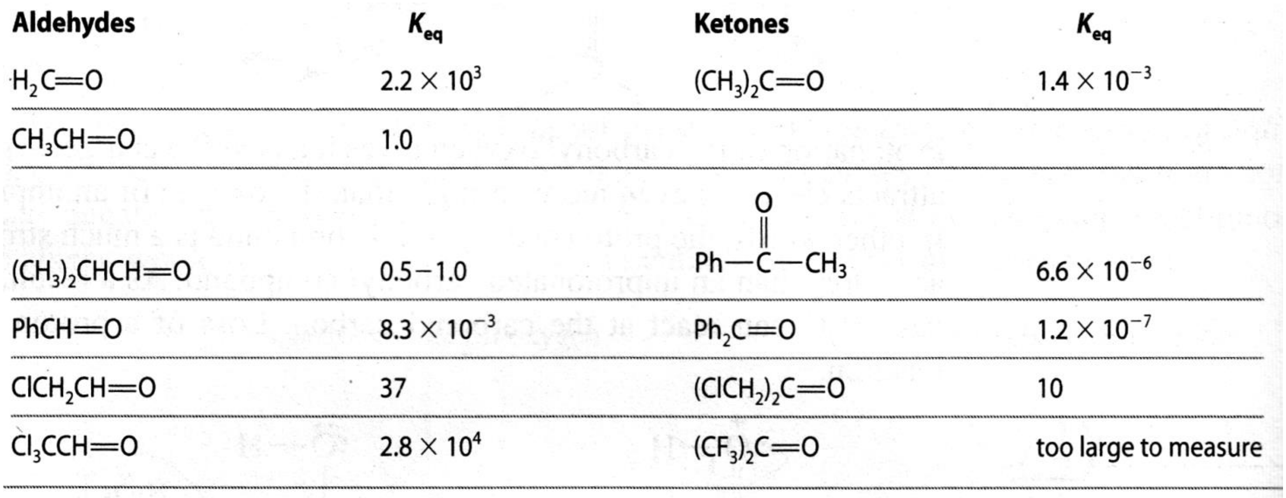
Generally gem-diols **cannot be isolated from aqueous solutions** in which they are formed. Because if we try to separate by distillation, evaporation of water displaces the overall equilibrium to the right as shown below and the gem-diol reverts to the carbonyl compound.



Just as electron-donating substituents inhibit hydrate formation, electron-withdrawing ones promote it. Because the electron-donating substituents decrease the electrophilic character of carbonyl compound thus the initial nucleophilic attack by H_2O becomes very slow. Whereas electron withdrawing substituents increase the positive character of the carbonyl so the nucleophilic attack by H_2O becomes more favourable thus the reaction is faster.

Equilibrium Constants for Hydration of some Aldehydes and Ketones:





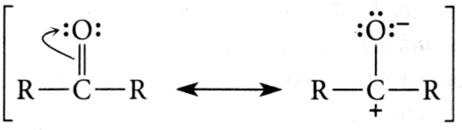
Aldehydes	K_{eq}	Ketones	K_{eq}
$H_2C{=}O$	2.2×10^3	$(CH_3)_2C{=}O$	1.4×10^{-3}
$CH_3CH{=}O$	1.0		
$(CH_3)_2CHCH{=}O$	0.5–1.0	$Ph{-}C({=}O){-}CH_3$	6.6×10^{-6}
$PhCH{=}O$	8.3×10^{-3}	$Ph_2C{=}O$	1.2×10^{-7}
$ClCH_2CH{=}O$	37	$(ClCH_2)_2C{=}O$	10
$Cl_3CCH{=}O$	2.8×10^4	$(CF_3)_2C{=}O$	too large to measure

What is the reason for the effect of structure on carbonyl addition?

The stability of the carbonyl compound relative to that of the addition product governs the ΔG° for addition. The primary effect on the hydration equilibrium is the difference in the stabilities of the carbonyl compounds. Greater stability in the carbonyl compound increases the energy change ΔG°, and hence decreases the equilibrium constant ($\Delta G° = -RT \ln K_{eq}$) for formation of an addition product.

What factor stabilizes carbonyl compounds?

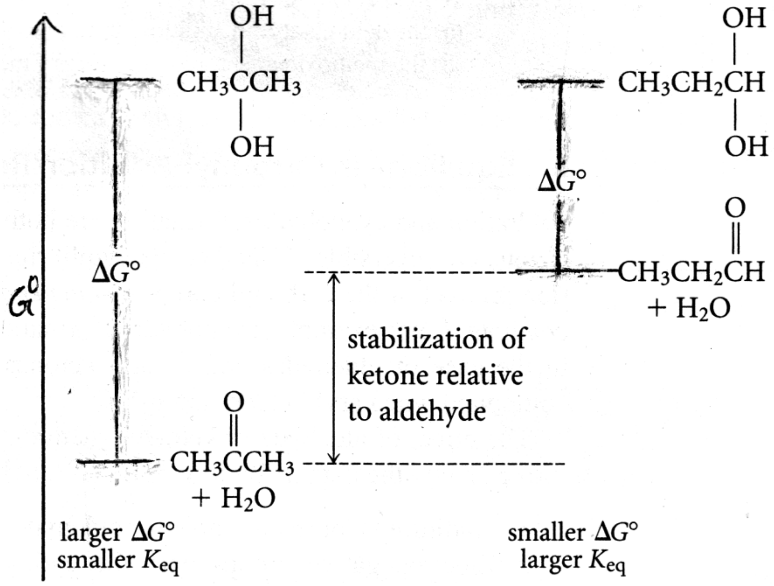
The major effects involved can be understood by considering the resonance structures of the carbonyl group:



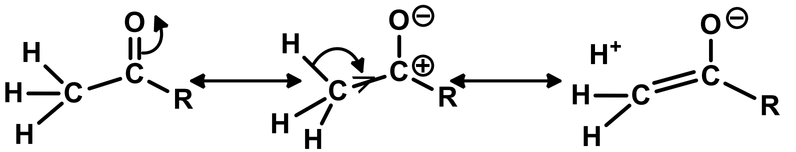
(A) (B)

The ionic structure (B), although not as important a contributor as the covalent structure (A), but it reflects the polarity of the carbonyl group and has the characteristics of a carbocation.

Therefore, anything that stabilizes carbocations also tends to stabilize carbonyl compounds. Because alkyl groups stabilize carbocations, ketones (R



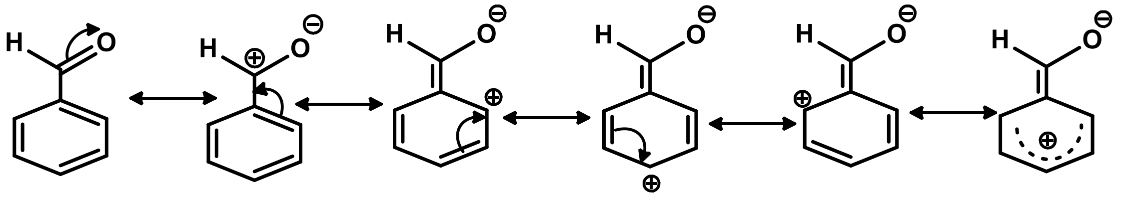
= alkyl) are more stable than aldehydes (R= H) due to +I effect and hyperconjugation effect of alkyl substituents,



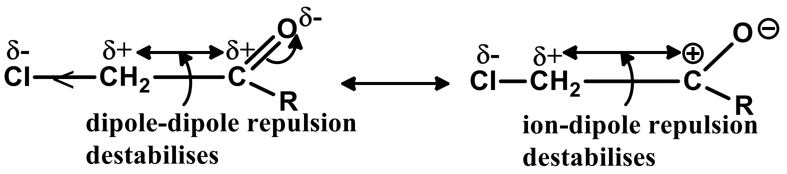
+I effect & hyperconjugative effect stabilise the ionic structure as well as the ketone.

A steric effect also operates in carbonyl addition. As the size of the groups bound to the carbonyl carbon increases, van der Waals repulsions in the corresponding addition compounds is greater as the central carbon is sp3 and tetracoordianted. The groups at the carbonyl carbon are closer together in the addition compound than in the carbonyl compound; hence, van der Waals repulsions are more pronounced in the addition compound. These van der Waals repulsions, in turn, raise the energy of the addition compound relative to the carbonyl compound and increase the ΔG° for addition.

Groups that are conjugated with the carbonyl group, such as the phenyl group of benzaldehyde, stabilize carbocations by resonance, and hence stabilize carbonyl compounds and the equilibrium becomes further unfavourable.



On the other hand **electronegative groups such as halogens destabilize carbocations** by their electron withdrawing (-I) effect and for the same reason destabilize carbonyl compounds due to **ion-dipole or dipole-dipole repulsion**. Thus, halogens make the equilibria for addition more favorable.



Q 1.1. Explain the following observations— Chloral usually forms a stable germinal diol whereas trimethyl acetaldehyde fails to do so. 2.5 **C.U. 1999**

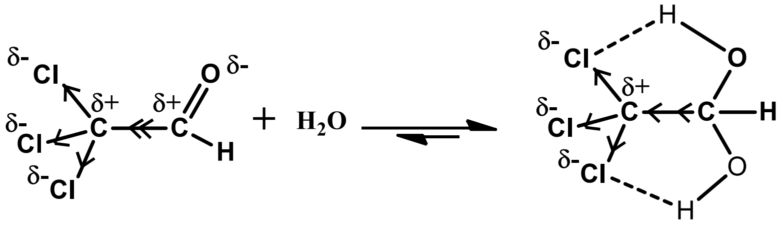
Q 1.2. Chloral usually forms a stable gemminal diol whereas trimethylacetaldehyde fails to do it. Explain the observation 2 **C.U. 2006**

Ans:

(i) In chloral, the three powerfully electron-withdrawing chlorine atoms impose positive charge on α-C-atom of $Cl_3C^{\delta+}$— group. So there is a strong electrostatic repulsion between

$Cl_3C^{\delta+}$— and the carbonyl carbon. But in the product gemminal diol, the O—H dipole is very less so this repulsion is also less. Thus the hydrate germinal diol is more stable than the chloral molecule.

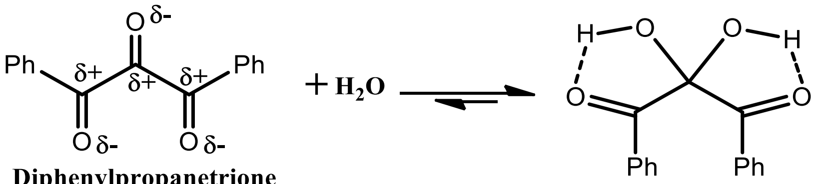
(ii) The electron withdrawing inductive effect of Cl atoms prevents departure of OH^- or H_2O to regenerate the carbonyl compound. Thus the equilibrium is favourable to the right.



(iii) Moreover the hydrate from chloral is also stabilized by strong intramolecular H-bonding between its OH groups and the highly electronegative chlorine substituents. So it is formed as a crystalline solid.

But in case of trimethyl acetaldehyde, the +I-effect of 3 Me-groups stabilize the carbonyl compound more effectively than the hydrate. Moreover the large size of Me_3C-group destabilize sterically, the tetra-coordinated (sp3) germinal diol than tri-coordinated carbonyl compound. Thus the equilibrium mostly lies on the left and germinal diol is not formed.

Similarly diphenylporpanetrione gives crystalline germinal diol product.



Diphenylpropanetrione

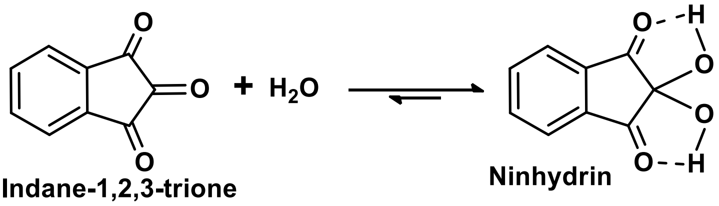
Crystalline solid

Because the positive ends of adjacent carbonyl dipoles repel each other electrostatically which destabilizes the reactant carbonyl compound.

Hydration at the middle carbonyl group reduces this destabilization considerably.

Moreover, the hydrate itself is stabilized by intramolecular hydrogen bonding as well as by electron-withdrawing inductive effect of the carbonyl groups that resists the loss of OH^- or H_2O to regenerate the original triketone. Thus the equilibrium almost lies on the product side.

Similarly, indane-1,2,3-trione easily hydrolyses to ninhydrin.

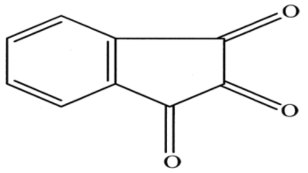


Indane-1,2,3-trione

Ninhydrin

Strong intramolecular H-bonding stabilises the ninhydrin molecule

Q 1.5. Compound (A) exists as a hydrate. Which carbonyl is hydrated and why? Explain.



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2 **C.U. 2018**

Q 1.3. Cyclopropanone has been obtained only as the water addition product, 1,1-cyclopropanediol. Explain. 2 **C.U. 2001**

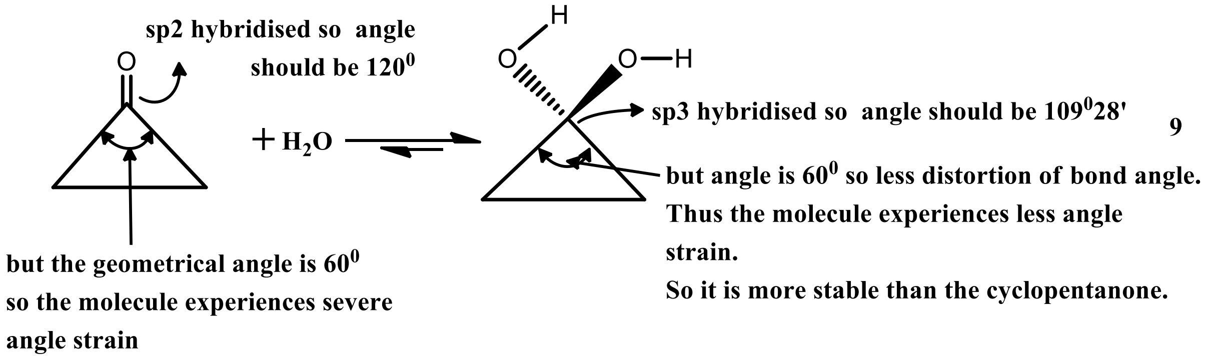
Q 1.3. Cyclopropanone has been obtained only as the water addition product, 1,1-cyclopropanediol. Explain. **C.U. 2001**

Q 1.4. Chloral reacts rapidly with ethanol to give hemiacetal, but gives acetal very slowly in the presence of anhydrous acid. Explain. **2 C.U. 2016**

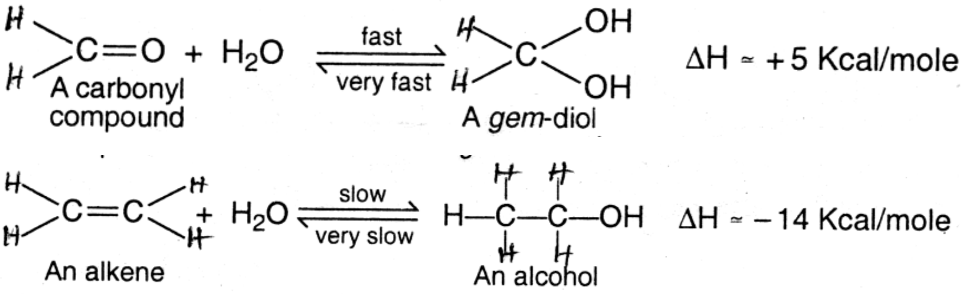
The bond angles around the carbonyl group of cyclopropanone should be 120^0 due to sp2 hybridization of carbonyl carbon, whereas the geometrical angle of <C—CO—C is 60° (internal angle of a equilateral triangle). The **angle of distortion is greater**, so the compound experiences severe angle strain or Baeyer's strain which is about 120° — 60° = 60°.

Addition of water to the carbonyl bond creates a tetrahedral (sp3) centre in which the preferred <C—C—C is 109 °28'. Thus the **hydrate experiences less angle strain**, about 109°28' — 60° = 49°28' (the angle of distortion is less).

As the angle strain (I strain) for the hydrate is less than that for cyclopropanone, so the hydrate is more stable than cyclopropanone. Thus the equilibrium of this reaction is favoured to the product 1,1-cyclopropanediol (germinal diol).

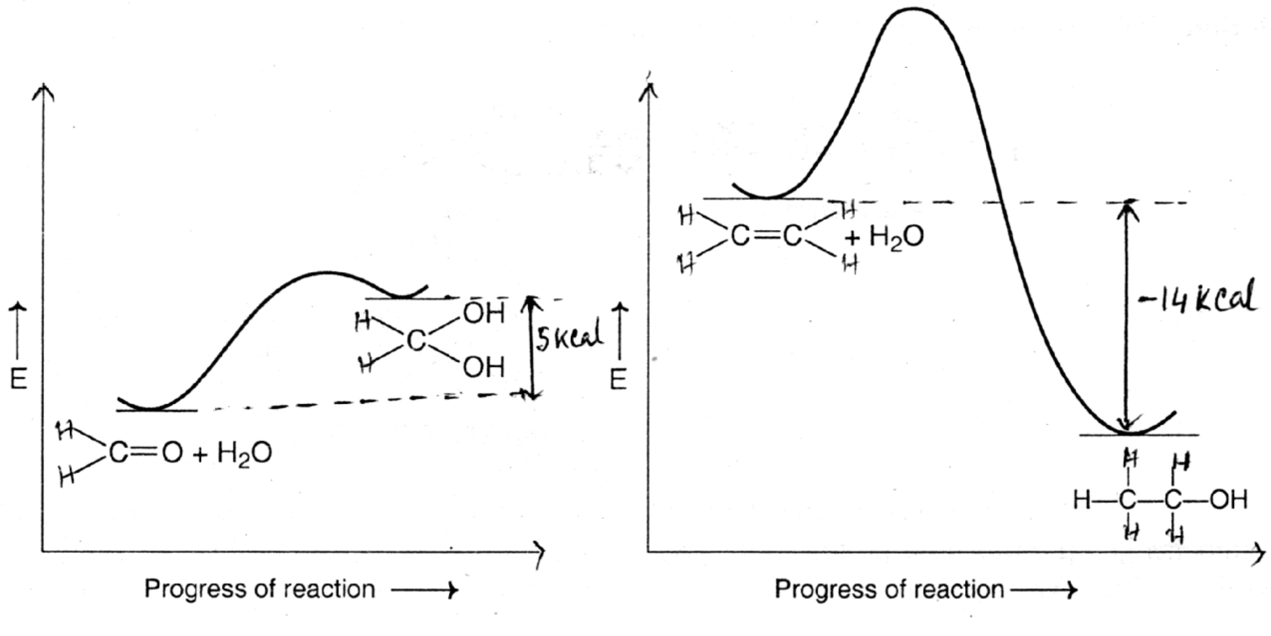


Comparison of hydration of alkenes and carbonyl compounds:



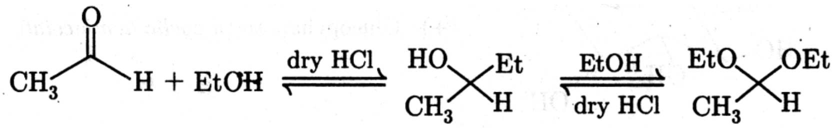
The carbonyl double bond adds polar reagents rapidly due to its dipolar character. The hydration of the carbonyl compound is a fast reaction. The reaction is endothermic. Bond energy calculations indicate that the hydration product is thermodynamically less stable than the carbonyl compound by about 5 Kcal/mole As a consequence, the **activation energy for the reverse reaction is smaller** than that of the forward reaction and because of this, the reverse reaction is very fast.

On the other hand, because of its nonpolar character, the alkene double bond is completely inert to water at pH 7. The reaction is normally **quite slow because of large activation energy** and must be catalyzed by strong acids. The process is exothermic. Bond energy calculations show that the hydration product, i.e., the alcohol, is thermodynamically more stable than the alkene by about 14 Kcal/mole. As a consequence, the activation energy for the reverse reaction is very large and so the reaction is very slow.

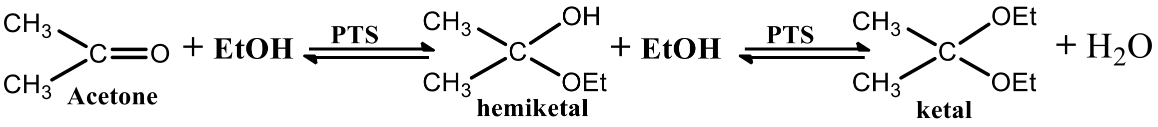


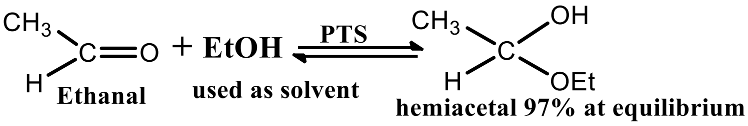
Addition of alcohol to carbonyl compounds:

In presence of acid catalyst, addition of alcohols to aldehydes gives **hemiacetals** (‘hemi’ means half; hemiacetal i.e. half acetal) and finally **acetals**. On the other hand addition of alcohol to ketones gives **hemiketals and ketals.**



Aldehyde hemiacetal acetal

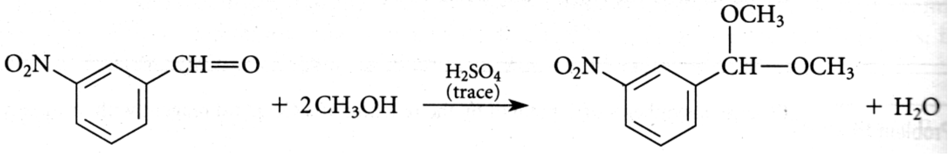




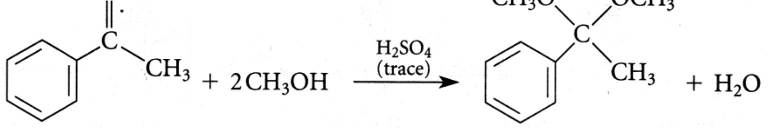
Formation of acetal / ketal

When an aldehyde or ketone reacts with a large excess of an alcohol in the presence of trace of strong acid, an acetal is formed.

An acetal is a compound in which two ether oxygens are bound to the same carbon. In other words, acetals are the ethers of gem-diols.

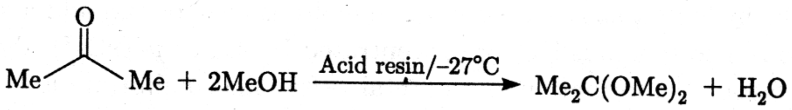


m-nitrobenzaldehyde *m*-nitrobenzaldehyde dimethylacetal 76-85% yield



Acetophenone acetophenonedimethylacetal 82% yield

Ketones undergo similar reactions when they are dissolved in an alcohol. The unstable products are sometimes called **hemiketals**, which is no longer recommended by IUPAC. The preferred usage is to call them **hemiacetals** as well i.e. **hemiacetals or hemiketals are now equivocal.** Acetals derived from ketones were once called ketals, but this name is no longer used.

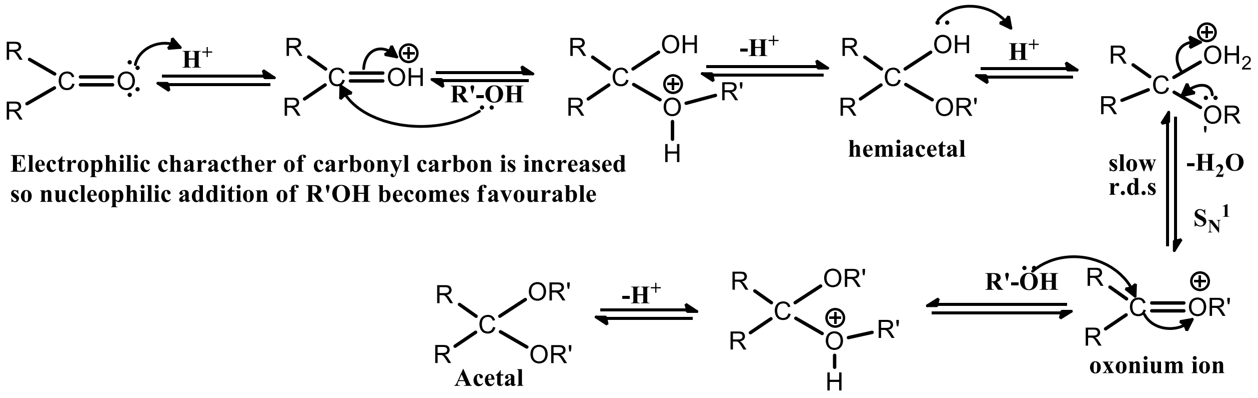


$$MeCOMe + 2MeOH \xrightarrow{\text{Acid resin/–27°C}} Me_2C(OMe)_2 + H_2O$$

Salient feature of the reaction:

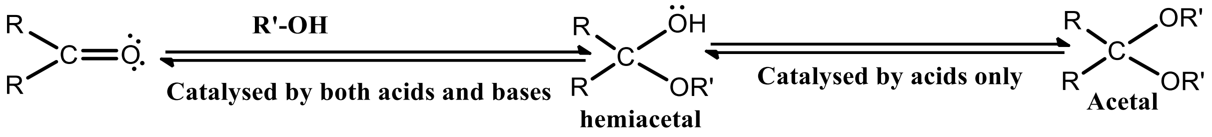
- The formation of hemiacetal is similar to hydrate formation.
- The reaction is catalysed by both acid and base.
- It is an equilibrium reaction and the equilibrium is mostly lies on the left for simple aldehydes or ketones.
- The equilibrium constant for addition of EtOH with MeCHO is only 0.50 compared with a value of 1.4 for H_2O (hydration reaction).
- The first step in the mechanism of acetal formation is acid-catalyzed addition of the alcohol to the carbonyl group to give a hemiacetal—a compound with an —OR and —OH group on the same carbon (hemi=half; hemiacetal= half acetal).
- Formation of acetals from hemi-acetals requires **specific acid catalysis**, ***p*-toluenesulphonic acid (PTS) H_2SO_4 or HCl gas** is used.
- However, **loss of H_2O** (S_N1 mode) from protonated hemiacetal **is slow and rate limiting step** of the reaction.
- The formation of acetals is reversible. The reaction is driven to the right either by the **use of excess alcohol as the solvent or by removal of the water by-product, or both.**
- In this reaction **water can be removed as an azeotrope with benzene** and **Dean Stark Apparatus (DSA)** is used (a special type of apparatus by which water is removed). (The benzene-water azeotrope is a mixture of benzene and water that has a lower boiling point than either benzene or water alone.)

- **Mechanism of hemiacetal and acetal formation: (a) Acid catalysed:**



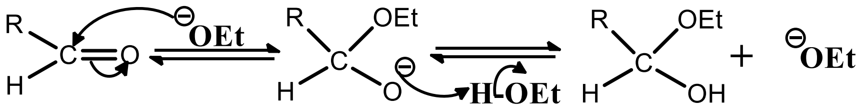
Electrophilic characther of carbonyl carbon is increased so nucleophilic addition of R'OH becomes favourable

- The hemiacetal reacts further when the —OH group is protonated and water is lost to give a relatively **stable carbocation**, an **α-alkoxy carbocation or oxonium ion.**
- The formation of hemiacetals is **catalyzed by both acids and alkali.**
- However, the conversion of hemiacetals into acetals is catalyzed **only by acids** as in this medium **H_2O being a good leaving group and can easily be removed to form stable oxonium ion**.
- Whereas in basic medium **–OH^- is not so good leaving group.** This is why acetal formation, which is a combination of the two reactions, is catalyzed by acids but not by bases.



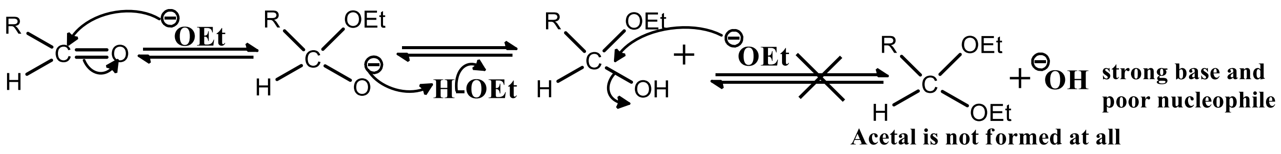
- **Base catalysed formation of hemiacetal only:**

better nucleophile than EtOH



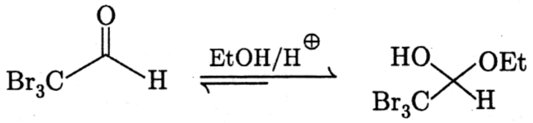
In base catalysed reaction of carbonyl with the alcohol only hemiacetal is formed not acetals:

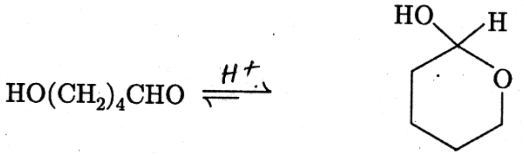
Because in the second step loss of OH^- form the hemiacetal is required to form acetal. But this does not occur as the **OH^- is a strong base and poor leaving group** so the formation of acetal is not occurred.



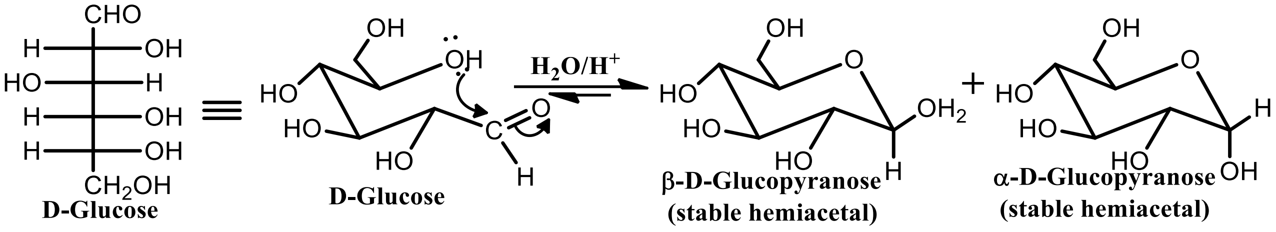
- Most open chain hemiacetals are too unstable to be isolated.
- However **cyclic hemiacetals with 5- or 6- membered rings are comparatively more stable**.
- Stable hemi-acetals may, however, be isolated from carbonyl cornpounds carrying **electron-withdrawing groups,** e.g. Br_3CCHO with EtOH.

Examples of some stable hemiacetals:

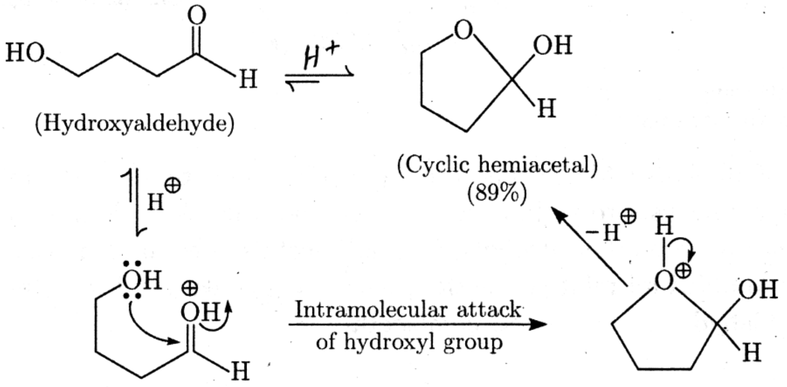


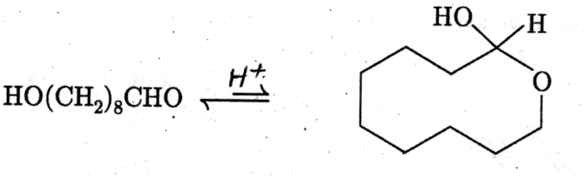


5-Hydroxypentanal 94% at equilibrium

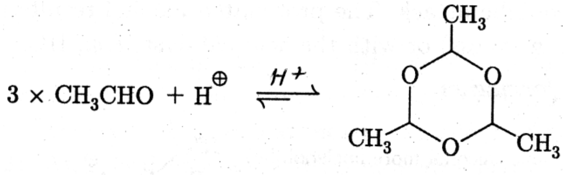


D-Glucose D-Glucose β-D-Glucopyranose (stable hemiacetal) α-D-Glucopyranose (stable hemiacetal)





(10–membered ring, 9%)

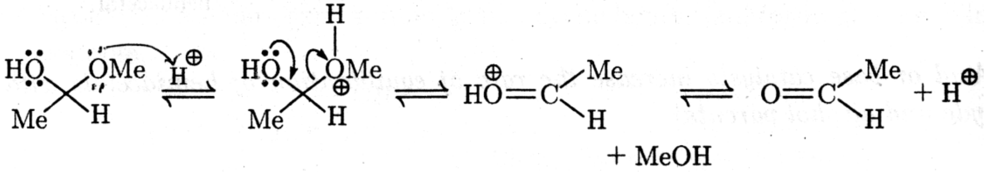


(Paraldehyde)

- The stability of cyclic hemiacetals is partly **due to entropy factor**.
- Formation of an acyclic hemiacetal involves a **greater decrease in entropy** ($\Delta S°$ more negative) because two molecules are consumed for formation of each acyclic hemiacetal molecule. Whereas for the formation of a cyclic hemiacetal— one molecule of hydroxyaldehyde is involved. So in this case only very small rotational randomness (rotational entropy) is decreased with no change in large translational randomness (translational entropy).
- As the reaction is reversible so hemiacetals and hemiketals are hydrolysed readily in presence of dilute acids or bases

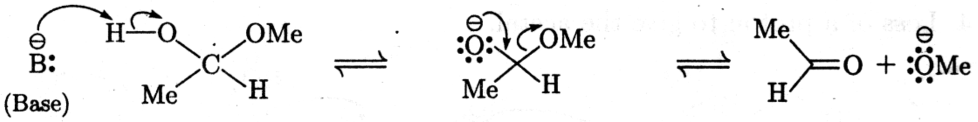
- Acetals in the presence of acid and excess water are transformed rapidly back into the corresponding carbonyl compounds and acohols; this process is called **acetal hydrolysis.**
- The mechanism of acetal hydrolysis is the reverse of the mechanism of acetal formation (as expected from the principle of microscopic reversibility).
- Hence, hydrolysis of acetal is acid-catalyzed. (like formation of hemiacetal)

Hydrolysis of hemiacetals / hemiketals: Acid catalysed:



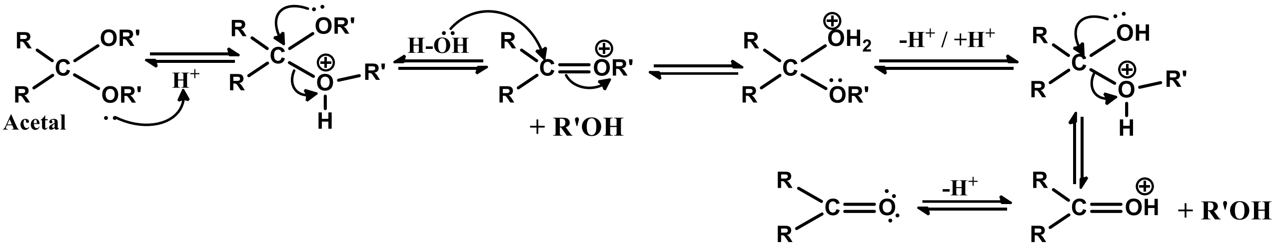
Protonation in the 1st step makes protonated methanol which behaves as a good leaving group thus this hydrolysis is favourable.

Base catalysed:



Hydrolysis of acetals can be carried only acidic medium:

Mechanism:

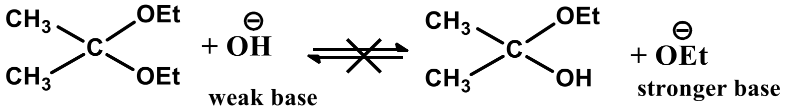


Base catalysed hydrolysis of acetal is not possible

Q 2. 1. Acetals are stable to alkali but readily hydrolysed by dilute acids.—Explain 3. C.U. 1991

Acetals are quite stable in Alkali as hydrolysis does not occur in this medium. Because–

(i) RO^- (alkoxide) is a stronger base and very poor leaving group so very dilute weaker base OH^- can not replace RO^- effectively.



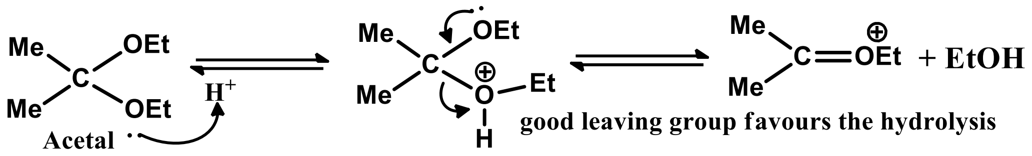
(ii) The poor electron withdrawing character of RO-group (containing sp3 hybridised O-atom) can not develope sufficient electrophilic character (+ve character) of the central carbon atom so initial nucleophilic attack by OH^- is not favourable.

(iii) The central carbon of acetal is crowded and tetra-coordinated so back side attack by OH^- is unfavourable moreover, the pentavalent T.S. of S_N2 hydrolysis involves high energy.

Thus hydrolysis of acetals is not favourable in basic medium so it is quite stable in this medium.

But in dilute acid medium, protonation results the formation of EtOH which is a good leaving group that favours the hydrolysis.

Moreover in presence of an excess of water in dilute acid, the equilibrium favours the formation of the aldehyde / ketone.



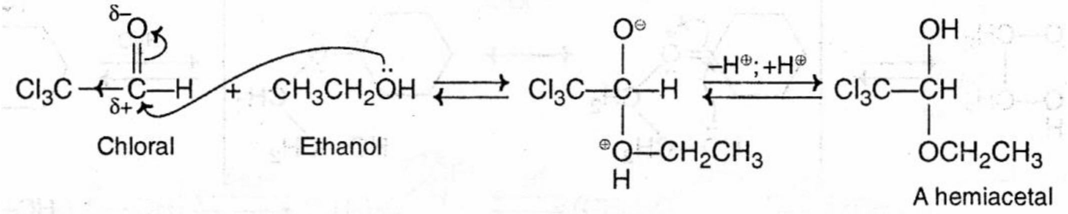
Q 2.3. Account for the following observations: Acetals and Ketals are labile in aqueous acid but their formation also requires acidic catalyst. **3 C.U. 1998**

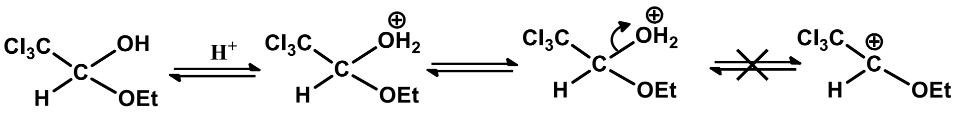
Ans: Acetals and ketals are labile in aqueous acid as they readily hydrolyse to aldehyde or ketones. Because in presence of dilute acid they get protonated to make a good leaving group alcohol, ready removal of ROH leads to hydrolysis.

Presence of large excess water molecule and formation of stable C=O (compare to two C–O bonds) shift the equilibrium to the right.

But the formation of acetals and ketals require acid catalyst to increase the electrophilic character of carbonyl Carbon so that the initial nucleophilic attack by ROH becomes favourable. Moreover the protonation of hemiacetal / hemiketal make H_2O, being a good leaving group favours the reaction.

- **Chioral reacts rapidly with ethanol to give hemiacetal, but gives acetal very slowly in the presence of anhydrous acid.**





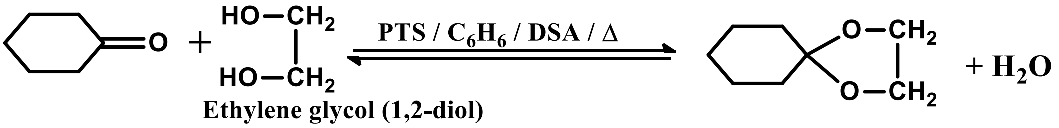
Very unstable due to strong -I effect of CCl_3 group, so acetal formation does not occur

The hemiacetal of chloral is formed easily because of the strong —I effect of the —CCl_3 group that promotes nucleophilic addition of alcohol to the carbonyl carbon.

The hemiacetal is converted to acetal very slowly in the presence of acid because, the electron-withdrawing —CCl_3 group inhibits the loss of water from the protonated hemiacetal (the rate-determining step) to generate the carbocation.

➢ Formation of Cyclic acetals:

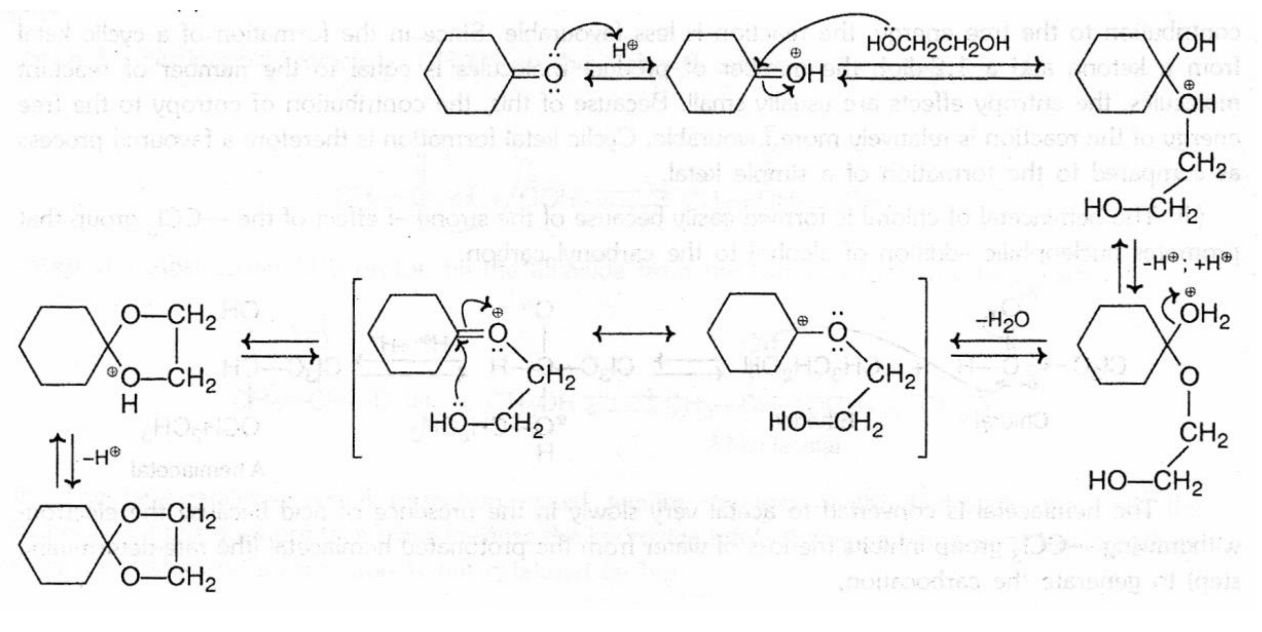
In acetal formation reactions, two equivalents of alcohols are involved. However, **1,2- and 1,3-diols** contain two —OH groups within the same molecule. Hence, **one equivalent of a 1,2- or 1 ,3-diol can react** to form a five or six membered cyclic acetal.



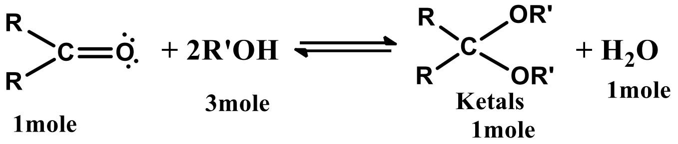
Ethylene glycol (1,2-diol)

Propane-1,3-diol

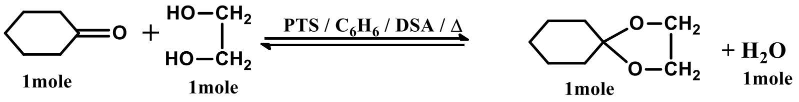
➢ Mechanism:



- **The acid-catalyzed formation of a cyclic acetal from a ketone is a favoured process compare to acyclic acetal.**



ΔS^0 is negative as number of molecules decreases
3moles reactants are converted to 2 moles products



ΔS^0 is less negative as number of molecules same
2moles reactants are converted to 2 moles products
so there is small decrease of vibrational and rotational entropy

- The formation of a simple acyclic acetal from a ketone and a simple alcohol involves a **decrease in the number of molecules**, there is a **considerable decrease in translational entropy (ΔS° is more negative)**. Because of this unfavourable entropy contribution to the free energy, the reaction is less favourable.
- But in the formation of a cyclic acetal from a ketone and a 1,2-diol, the number of product and reactant molecules remain same, so there is **small decrease of vibrational and rotational entropy(ΔS° is less negative).** Thus formation of cyclic acetal is entropically more favourable.