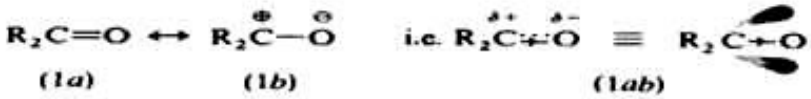
Nucleophilic Addition to Carbonyl Group (C=O)

A.

Carbonyl compounds exhibit dipole moments (μ) because the oxygen atom of the C=O group is more electronegative than the carbon:

$\mu = 2{\cdot}3$ D $\qquad\qquad$ $\mu = 2{\cdot}8$ D

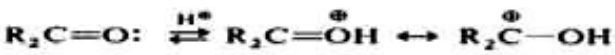
As well as the C→O inductive effect in the σ bond joining the two atoms, the more readily polarisable π electrons are also affected (*cf.* p. 22) so that the carbonyl group is best represented by a hybrid structure (1):



(1a) (1b) (1ab)

We would expect the C=O linkage, by analogy with C=C (p. 178), to undergo addition reactions; but whereas polar attack on the latter is normally initiated only by electrophiles, attack on the former—because of its bipolar nature—could be initiated either by electrophilic attack of $X^{\oplus}$ or X on oxygen or by nucleophilic attack of $Y^{\ominus}$ or Y: on carbon (radical-induced addition reactions of carbonyl compounds are rare). In practice, initial electrophilic attack on oxygen is of little significance except where the electrophile is an acid (or a Lewis acid), when rapid, reversible protonation may be a prelude to slow, rate-limiting attack by a nucleophile on carbon, to complete the addition, i.e. the addition is then acid-catalysed.

Protonation will clearly increase the positive character of the carbonyl carbon atom (2),



(2)

and thereby facilitate nucleophilic attack upon it. Similar activation, though to a lesser extent, can also arise through hydrogen-bonding of an acid (3), or even of a hydroxylic solvent (4), to the carbonyl oxygen atom:

(3) (4)

In the absence of such activation, weak nucleophiles, e.g. H_2O:, may react only very slowly, but strong ones, e.g. $^{\ominus}CN$, do not require such aid. Additions may also be base-catalysed, the base acting by converting the weak nucleophile HY into the stronger one, $Y^{\ominus}$, e.g. HCN + base $\longrightarrow$ $^{\ominus}CN$. Further, while acids may activate the carbonyl carbon atom to nucleophilic attack, they may simultaneously reduce the effective concentration of the nucleophile, e.g. $^{\ominus}CN + HA \longrightarrow HCN + A^{\ominus}$, $RNH_2 + HA \longrightarrow RNH_3^{\oplus} + A^{\ominus}$. Many simple addition reactions of carbonyl compounds are thus found to have an optimum pH; this can be of great importance for preparative purposes.

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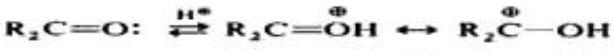

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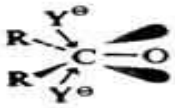
Remember

- For nucleophilic additions to carbonyl groups:
  - Acid catalysts work by making the carbonyl group more electrophilic
  - Base catalysts work by making the nucleophile more nucleophilic

So far as steric effects are concerned, the least energy-demanding direction of approach by the nucleophile to the carbonyl carbon atom will be from above, or below, the substantially planar carbonyl compound. It is also likely to be from slightly to the rear of the carbon atom (*cf.* 12), because of potential coulombic repulsion between the approaching nucleophile and the high electron density at the carbonyl oxygen atom:

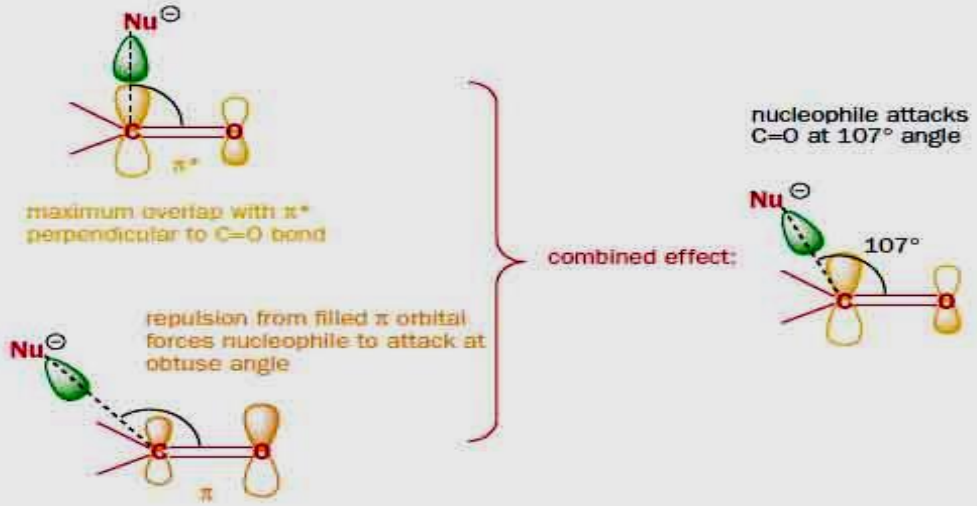


(12)

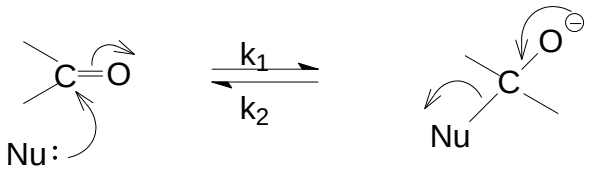
Increasing bulk in the R groups will slow the reaction as the sp^2 hybridised carbon atom in the original carbonyl compound (R—C—R bond angle ≈120°) is converted to an sp^3 hybridised carbon atom in the adduct—and in the preceding T.S.—(R—C—R bond angle ≈109°). The R groups thus move closer together as the reaction proceeds, i.e. the T.S. becomes more crowded, its energy level therefore increases and the reaction rate drops, as R increases in size. The observed drop in reaction rate, $H_2C{=}O > RHC{=}O > R_2C{=}O$, is thus determined by both electronic and steric effects. Increase in size of the nucleophile, with a given carbonyl compound, may also lead to a drop in reaction rate for the same reason.

Bürgi–Dunitz trajectory: the angle of nucleophilic attack on aldehydes and ketones

Having introduced you to the sequence of events that makes up a nucleophilic attack at C=O (interaction of HOMO with LUMO, formation of new σ bond, breakage of π bond), we should now tell you a little more about the *direction* from which the nucleophile approaches the carbonyl group. Not only do nucleophiles always attack carbonyl groups at carbon, but they also always approach from a particular angle. You may at first be surprised by this angle, since nucleophiles attack not from a direction perpendicular to the plane of the carbonyl group but at about 107° to the C=O bond. This approach route is known as the **Bürgi–Dunitz trajectory** after the authors of the elegant crystallographic methods that revealed it. You can think of the angle of attack as the result of a compromise between maximum orbital overlap of the HOMO with π* and minimum repulsion of the HOMO by the electron density in the carbonyl π bond.



Any other portions of the molecule that get in the way of (or, in other words, that cause *steric hindrance* to) the Bürgi–Dunitz trajectory will greatly reduce the rate of addition and this is another reason why aldehydes are more reactive than ketones.



$K = \frac{k_1}{k_2}$; TS is product like

Apart from reaction with the strongest nucleophiles, e.g. $AlH_4^{\ominus}$ (p. 214), $\overset{\delta-}{R}Mg\overset{\delta+}{Br}$ (p. 221), many additions to C=O are reversible. In general, the factors that we have seen to affect the rate of reaction (k) influence the position of equilibrium (K) in much the same way; this is because the T.S. for simple addition reactions probably resembles the adduct a good deal more closely than it does the original carbonyl compound. Thus the Ks for cyanohydrin formation (*cf.* p. 212) are found to reflect this operation of both steric and electronic factors:

	K
CH_3CHO	very large
p-$NO_2C_6H_4CHO$	1420
C_6H_5CHO	210
p-$MeOC_6H_4CHO$	32
$CH_3COCH_2CH_3$	38
$C_6H_5COCH_3$	0·8
$C_6H_5COC_6H_5$	very small indeed

Highly hindered ketones, such as $Me_3CCOCMe_3$, may not react at all except possibly with very small, highly reactive nucleophiles.

For a given carbonyl compound, K will be influenced by the size of the nucleophile: thus the value of K for addition of the very bulky bisulphite anion ($S_2O_3^{2\ominus}$, p. 213) to $(MeCH_2)_2C{=}O$ is only 4×10^{-4}, compared with $K = 38$ for addition of HCN (above) to the very similar ketone, $MeCH_2COMe$. The value of K is also influenced by the nature of the atom in the nucleophile that attacks the carbonyl carbon atom, and of the bond that is thereby formed; as is observed in the following sequence for reaction with the same carbonyl compound:

$$^{\ominus}CN > RNH_2 > ROH$$

B. Simple addition reactions:

1.

1 Hydration

Many carbonyl compounds undergo reversible hydration in aqueous solution.

$$R_2C{=}O + H_2O \rightleftarrows R_2C(OH)_2$$

thus the K values at 20° for $H_2C{=}O$, $MeHC{=}O$ and $Me_2C{=}O$ are 2×10^3, 1·4, and 2×10^{-3}, respectively; this sequence reflects the progressive effect of increasing electron-donation. The ready reversibility of hydration is reflected in the fact that $H_2C{=}O$ can be distilled, as such, out of its aqueous solution. That a dynamic equilibrium actually is set up with $Me_2C{=}O$, though the ambient concentration of the hydrate is so low (its presence has been demonstrated in frozen Me_2CO/H_2O mixtures, however), may be demonstrated by working in $H_2{}^{18}O$:

$$Me_2C{=}O + H_2{}^{18}O \rightleftarrows Me_2C(OH)(\,{}^{18}OH) \rightleftarrows Me_2C{=}{}^{18}O + H_2O$$

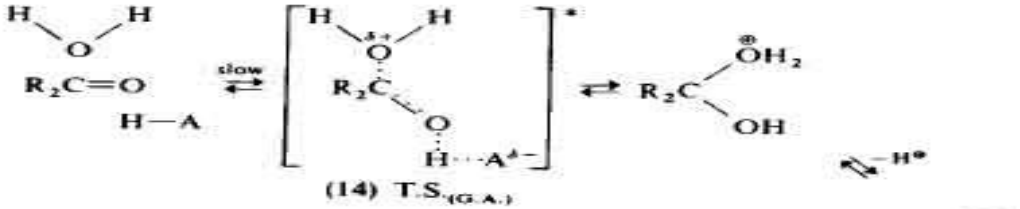
(13)

Incorporation of ^{18}O into the ketone occurs hardly at all under these conditions, i.e. at pH 7, but in the presence of a trace of acid or base it occurs [*via* the hydrate (13)] very rapidly indeed. The fact that a carbonyl compound is hydrated will not influence nucleophilic additions that are irreversible; it may, however, influence the position of equilibrium in reversible addition reactions, and also the reaction rate, as the effective concentration of free carbonyl compound, $[R_2C{=}O]$, is naturally reduced.

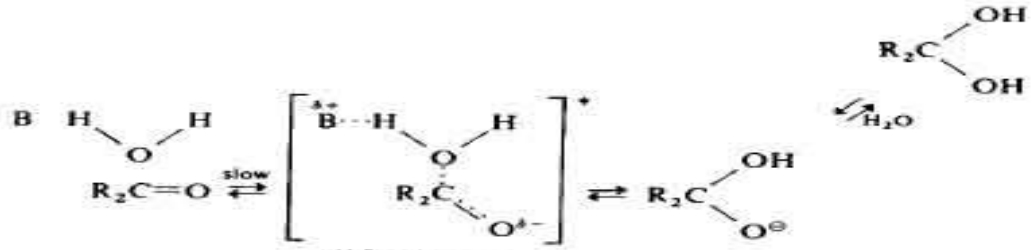
The chart shows the extent of hydration (in water) of a small selection of carbonyl compounds: hexafluoroacetone is probably the most hydrated carbonyl compound possible!

	equilibrium constant K		
acetone	0.001	chloral	2000
acetaldehyde	1.06		
formaldehyde	2280	hexafluoroacetone	1 200 000

Hydration is found to be susceptible to both general acid and general base (p. 74) catalysis, i.e. the rate-limiting step of the reaction involves *either* protonation of the carbonyl compound (general acid, 14), *or* conversion of H_2O into the more nucleophilic $^{\ominus}OH$ (general base, 15):



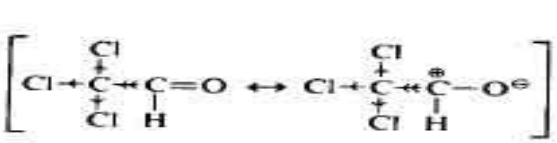
(14) $T.S._{(G.A.)}$



(15) $T.S._{(G.B.)}$

In contrast to Me_2CO, H_2CO hydrates quite readily at pH 7, reflecting the fact that its more positive carbonyl carbon atom undergoes attack by H_2O: without first requiring protonation of its carbonyl oxygen atom: it nevertheless hydrates very much faster at pH 4 or 11!

Just as electron-donating substituents inhibit hydrate formation, electron-withdrawing ones promote it. Thus K for the hydration of Cl_3CCHO (16) is $2{\cdot}7 \times 10^4$, and this aldehyde (tri-chloroethanal, chloral) does indeed form an isolable, crystalline hydrate (17). The powerfully electron-withdrawing chlorine atoms destabilise the original carbonyl compound, but not the hydrate whose formation is thus promoted:



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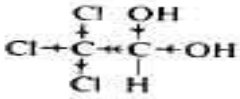
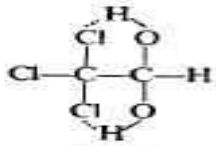
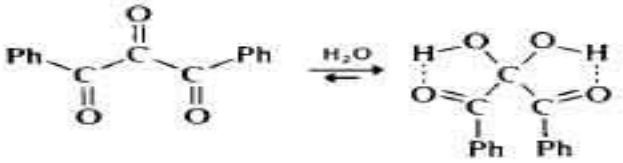


(17)



(17*a*)

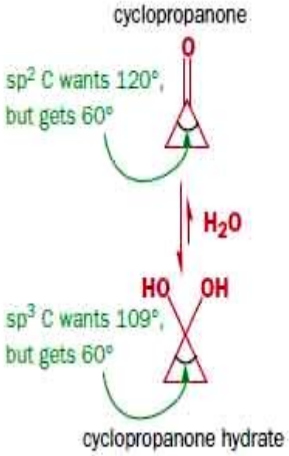
For the hydrate to revert to the original carbonyl compound it has to lose $^{\ominus}OH$ or H_2O:, which is rendered more difficult by the electron-withdrawing group. The hydrate from chloral is also stabilised through H-bonding (17*a*) between its OH groups (as shown by i.r. spectroscopy) and the highly electronegative chlorine substituents. Carbonyl groups can also be effective in stabilising hydrates, possibly through H-bonding as well as through electron-withdrawal, e.g. with diphenylpropantrione (18) which crystallises from water as the hydrate (19):



(18) (19)

Cyclopropanones—three-membered ring ketones—are also hydrated to a significant extent, but for a different reason. You saw earlier how *acyclic* ketones suffer increased steric hindrance when the bond angle changes from 120° to 109° on moving from sp^2 to sp^3 hybridization. Cyclopropanones

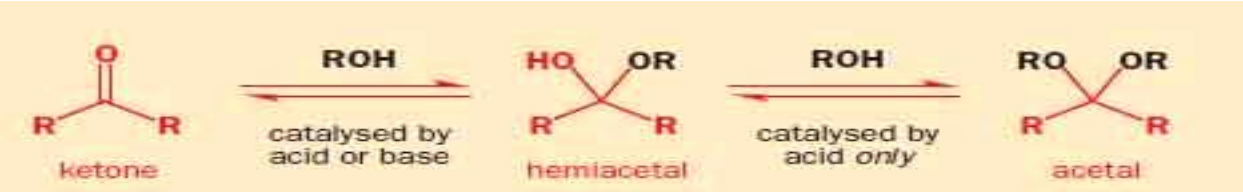
(and other small-ring ketones) conversely prefer the small bond angle because their substituents are already confined within a ring. Look at it this way: a three-membered ring is really very strained, with bond angles forced to be 60°. For the sp^2 hybridized ketone this means bending the bonds 60° away from their 'natural' 120°. But for the sp^3 hybridized hydrate the bonds have to be distorted by only 49° (= 109° – 60°). So addition to the C=O group allows some of the strain inherent in the small ring to be released—hydration is favoured, and indeed cyclopropanone and cyclobutanone are very reactive electrophiles.



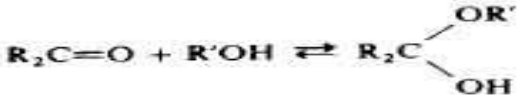
- The same structural features that favour or disfavour hydrate formation are important in determining the reactivity of carbonyl compounds with other nucleophiles, whether the reactions are reversible or not. Steric hindrance and more alkyl substituents make carbonyl compounds less reactive towards any nucleophile; electron-withdrawing groups and small rings make them more reactive.

Lesson-2

2. Reaction with alcohols: Formation of hemiacetals and acetals



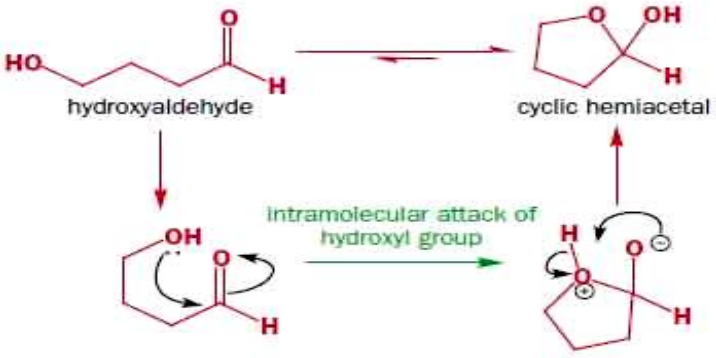
The reactions of carbonyl compounds with alcohols, R′OH, to yield hemi-acetals (22),



(22)

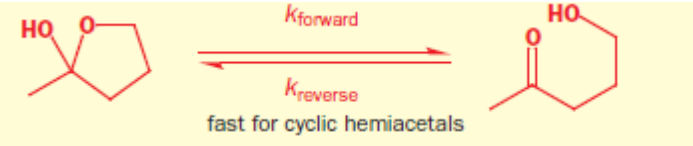
follows—hardly surprisingly—a very similar pattern to hydrate formation. It also is subject to general acid catalysis, but K for MeCHO/EtOH is only 0·50 compared with a value of 1·4 for H_2O; stable hemi-acetals may, however, be isolated from carbonyl compounds carrying electron-withdrawing groups, e.g. Br_3CCHO with EtOH.

Hemiacetal formation is reversible, and hemiacetals are stabilized by the same special structural features as those of hydrates. However, hemiacetals can also gain stability by being cyclic—when the carbonyl group and the attacking hydroxyl group are part of the same molecule. The reaction is now an **intramolecular** (within the same molecule) addition, as opposed to the **intermolecular** (between two molecules) ones we have considered so far.



Why are cyclic hemiacetals stable?

Part of the reason for the stability of cyclic hemiacetals concerns entropy. Formation of an acyclic acetal involves a decrease in entropy (ΔS negative) because two molecules are consumed for every one produced. This is not the case for formation of a cyclic hemiacetal. Since $\Delta G = \Delta H - T\Delta S$, a reaction with a negative ΔS tends to have a more positiveΔG; in other words, it is less favourable. Another way to view the situation is to consider the rates of the forward and reverse processes. We can measure the stability of a cyclic hemiacetal by the equilibrium constant K for the ring-opening reaction: a large K means lots of ring-opened product, and therefore an unstable hemiacetal, and a small K means lots of ring-closed product: a stable hemiacetal. An equilibrium constant is simply the rate of the forward reaction divided by the rate of the reverse reaction. So, for a stable hemiacetal, we need a fast hemiacetals-forming reaction. And when the hemiacetal is cyclic that is just what we do have: the reaction is intramolecular and the nucleophilic OH group is always held close to the carbonyl group, ready to attack.

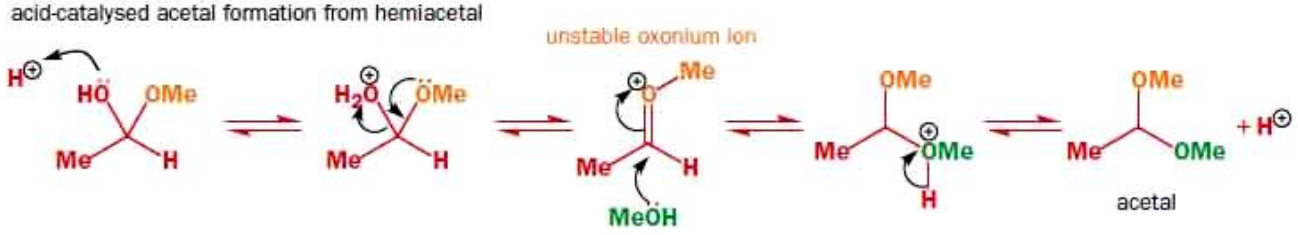


Now

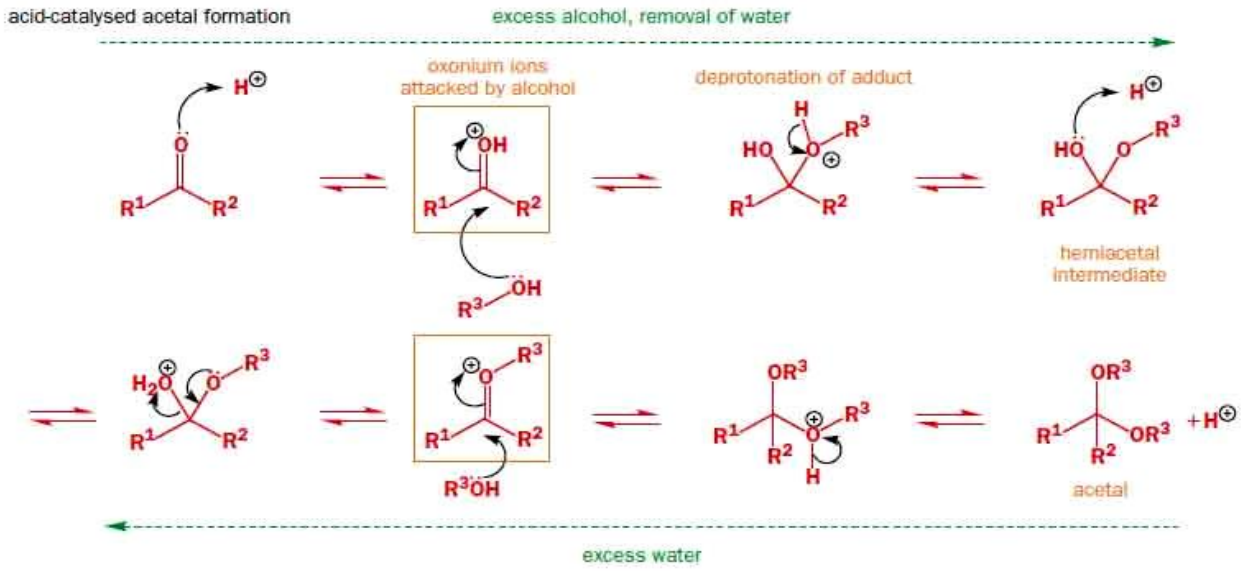
In the presence of acid (but not base!) hemiacetals can undergo an elimination reaction (different from the one that just gives back aldehyde plus alcohol), losing the oxygen atom that once belonged to the parent aldehyde's carbonyl group. The stages are:

1. Protonation of the hydroxyl group of the hemiacetal
2. Loss of water by elimination. This elimination leads to an unstable and highly reactive oxonium ion
3. Addition of methanol to the oxonium ion (breaking the π bond and not the σ bond, of course)
4. Loss of a proton to give the acetal

acid-catalysed acetal formation from hemiacetal



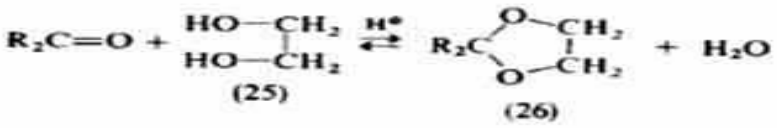
Just as protonated carbonyl groups are much more electrophilic than unprotonated ones, these oxonium ions are powerful electrophiles. They can react rapidly with a second molecule of alcohol to form new, stable compounds known as **acetals**. An oxonium ion was also an intermediate in the formation of hemiacetals in acid solution.



Again, the same strong electrophilic oxonium ion can combine with water molecule to shift the reaction in the reverse direction.

Acetal formation is reversible (K for MeCHO/EtOH is 0·0125) but the position of equilibrium will be influenced by the relative proportions of R′OH and H_2O present. Preparative acetal formation is thus normally carried out in excess R′OH with an anhydrous acid catalyst. The equilibrium may be shifted over to the right either by azeotropic distillation to remove H_2O as it is formed, or by using excess acid catalyst (e.g. passing HCl gas continuously) to convert H_2O: into the non-nucleophilic $H_3O^{\oplus}$. Hydrolysis of an acetal back to the parent carbonyl compound may be effected readily with dilute acid. Acetals are, however, resistant to hydrolysis induced by bases—there is no proton that can be removed from an oxygen atom, *cf.* the base-induced hydrolysis of hydrates: this results in acetals being very useful *protecting groups* for the C=O function, which is itself very susceptible to the attack of bases (*cf.* p. 224).

Acetal formation does not normally take place with ketones under these conditions (i.e. with simple alcohols), but they can often be made to react with 1,2-diols, e.g. (25), to form cyclic acetals (26):



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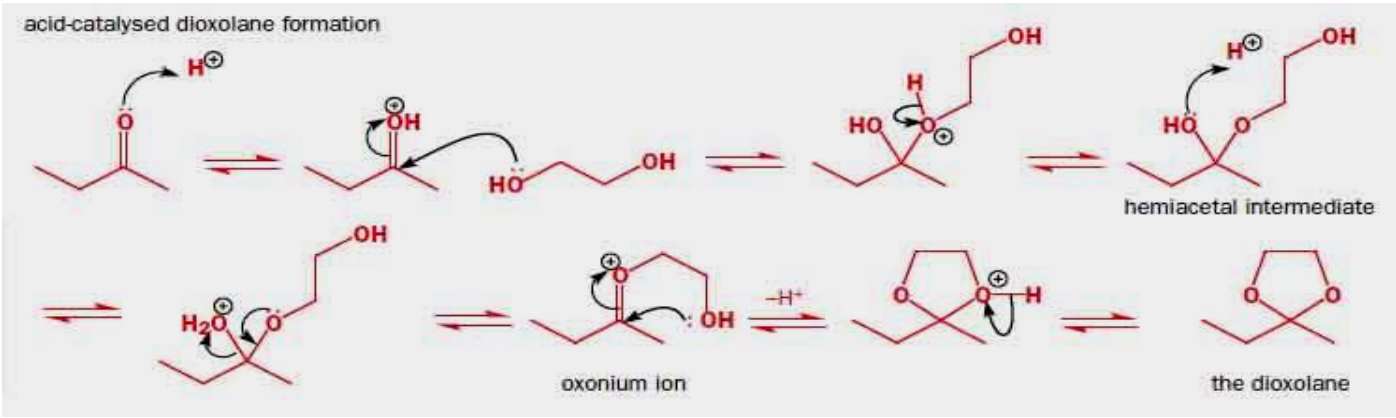


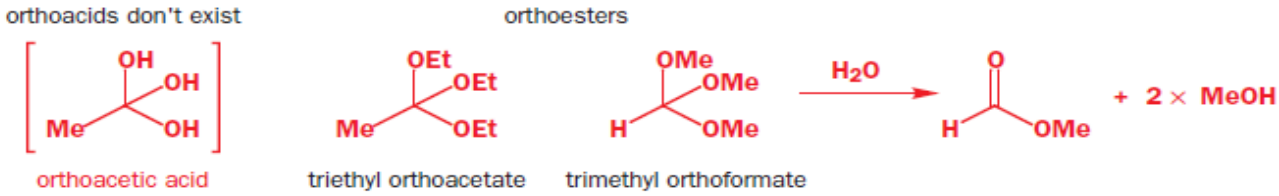
Cyclic acetals like this are more resistant to hydrolysis than acyclic ones and easier to make—they form quite readily even from ketones. Again, we have entropic factors to thank for their stability. For the formation of a cyclic acetal, two molecules go in (ketone plus diol) and two molecules come out (acetal plus water), so the usually unfavourable entropy factor is no longer against us. And, as for hemiacetals (see the explanation above), equilibrium tends to lie to the acetal side because the intramolecular ring-closing reaction is fast. Water is still generated, and needs to be got rid of: in the example above you can see that water was distilled out of the reaction mixture. This is possible with these diols because they have a boiling point above that of water (the boiling point of ethylene glycol is 197 °C). You can't distil water from a reaction mixture containing methanol or ethanol, because the alcohols distil too! One very useful piece of equipment for removing water from reaction mixtures containing only reagents that boil at higher temperatures than water is called a **Dean Stark head**

Dean Stark head

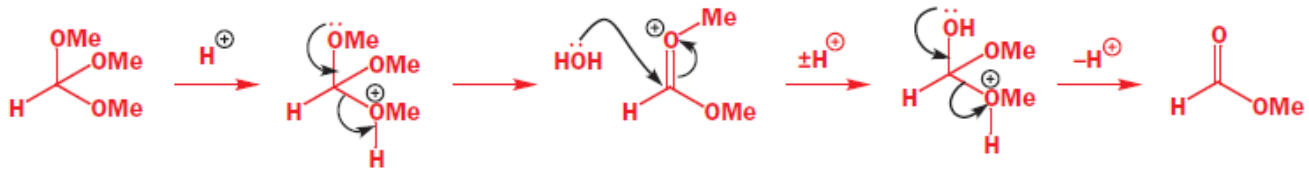
When a mixture of toluene and water boils, the vapour produced is a constant ratio mixture of toluene vapour and water vapour known as an azeotrope. If this mixture is condensed, the liquid toluene and water, being immiscible, separate out into two layers with the water below. By using a Dean Stark apparatus, or Dean Stark head, the toluene layer can be returned to the reaction mixture while the water is removed. Reactions requiring removal of water by distillation are therefore often carried out in refluxing toluene or benzene under a Dean Stark head.

Overcoming entropy: orthoesters

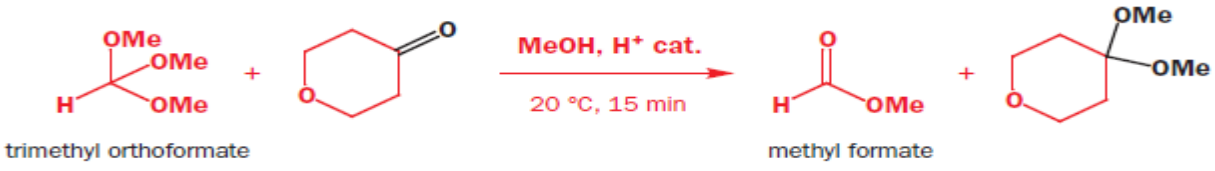
We have already mentioned that one of the factors that makes acyclic *hemi*acetals unstable is the unfavourable decrease in entropy when two molecules of starting material (aldehyde or ketone plus alcohol) become one of product. The same is true for acetal formation, when three molecules of starting material (aldehyde or ketone plus 2 × alcohol) become two of product (acetal plus H2O). We can improve matters if we tie the two alcohol molecules together in a diol and make a cyclic acetal: we discuss cyclic acetals in the next section. Alternatively, we can use an **orthoester** as a source of alcohol. Orthoesters can be viewed as the 'acetals of esters' or as the triesters of the unknown 'orthoacids'—the hydrates of carboxylic acids. They are hydrolysed by water, catalysed by acid, to ester + 2 × alcohol.



Here is the mechanism for the hydrolysis—you should be feeling quite familiar with this sort of thing by now.

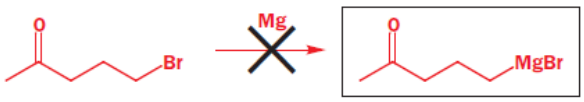


Ketones or aldehydes can undergo **acetal exchange** with orthoesters. The mechanism starts off as if the orthoester is going to hydrolyse but the alcohol released adds to the ketone and acetal formation begins. The water produced is taken out of the equilibrium by hydrolysis of the orthoester.

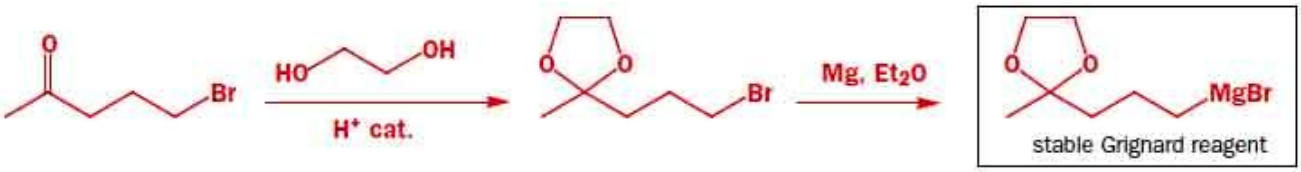


Why are acetals important?

One important use is as *protecting groups*. For example, one important synthesis of a steroid class of compound requires a Grignard reagent with this structure.



Yet this compound cannot exist: it would react with itself. Instead, this Grignard reagent is used, made from the same bromoketone, but with an acetal-forming step.



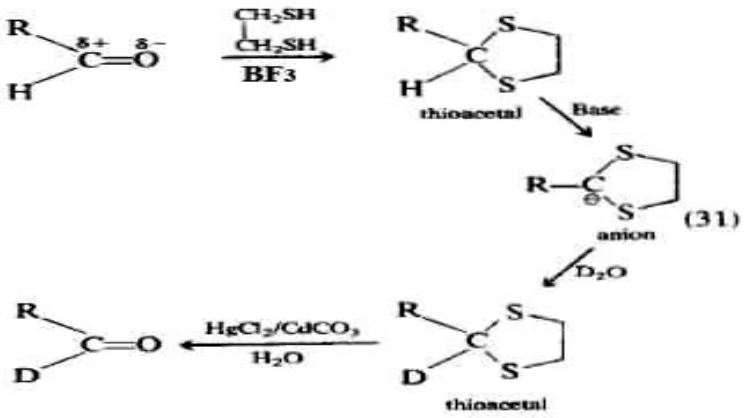
Acetals, as we stressed, are stable to base, and to basic nucleophiles such as Grignard reagents, so we no longer have a reactivity problem. Once the Grignard reagent has reacted with an electrophile, the ketone can be recovered by hydrolysing the acetal in dilute acid. The acetal is functioning here as

a **protecting group** because it protects the ketone from attack by the Grignard reagent. Protecting groups are extremely important in organic synthesis.

Lesson-3

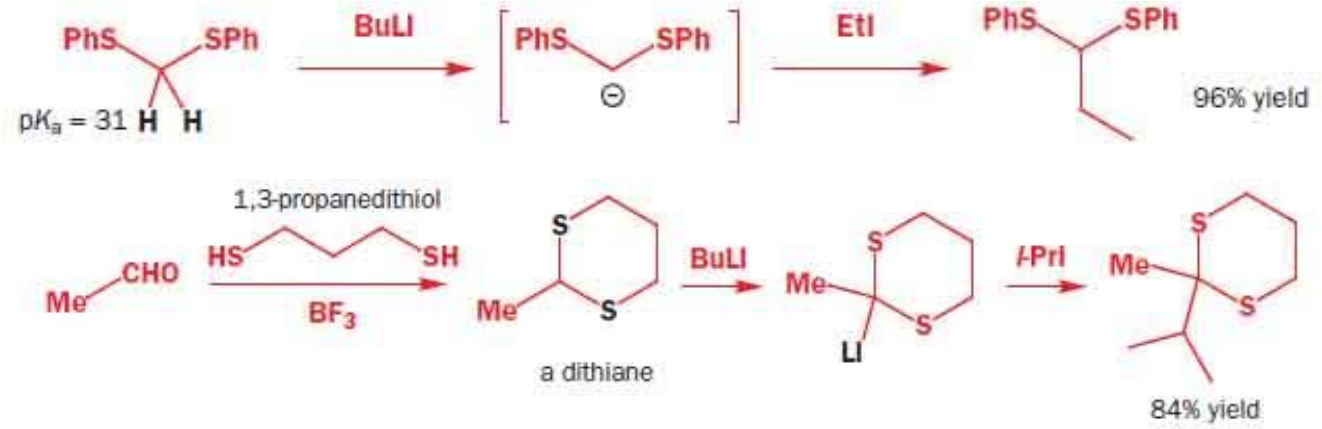
3. Reaction with thiols: Formation of thioacetals

Carbonyl compounds react with thiols, RSH, to form hemi-thioacetals and thioacetals, rather more readily than with ROH; this reflects the greater nucleophilicity of sulphur compared with similarly situated oxygen. Thioacetals offer, with acetals, differential protection for the C=O group as they are relatively stable to dilute acid; they may, however, be decomposed readily by $H_2O/HgCl_2/CdCO_3$. It is possible, using a thioacetal, to reverse the polarity of the carbonyl carbon atom in an aldehyde; thereby converting this initially electrophilic centre into a nucleophilic one in the anion (31):



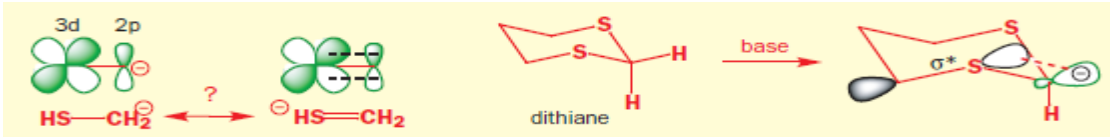
This reversal of polarity at an atom, which is referred to as an *ümpolung*, cannot be effected directly on RCHO itself. The anion

(31) on treatment with D_2O, followed by hydrolysis, results in conversion of the original aldehyde, RCHO, into its deuterio-labelled analogue, RCDO, selectively and in high yield. Alterna-tively, the anion (31) may be alkylated (e.g. with R'I), and the original aldehyde, RCHO, then converted into a ketone RR'CO.



In general, thioacetals can be made in a similar way to 'normal' (oxygen-based) acetals–by treatment of an aldehyde or a ketone with a thiol and an acid catalyst—though a Lewis acid such as BF3 is usually needed rather than a protic acid. The most easily made, most stable toward hydrolysis, and most reactive towards alkylation are cyclic thioacetals derived from 1,3-propanedithiol, known as **dithianes**.

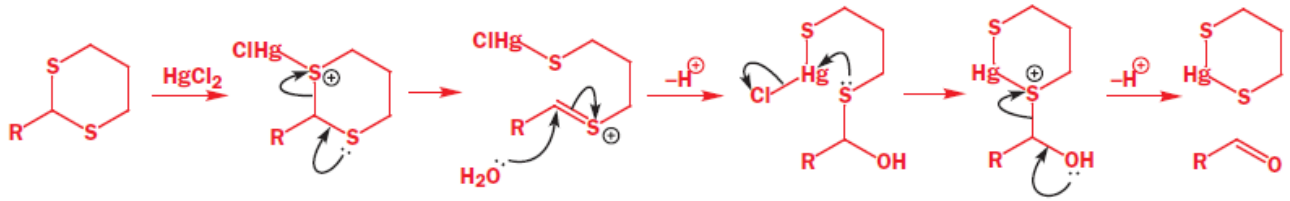
It was long thought that delocalization into sulfur's empty 3d orbitals provided the anion stabilization required, but theoretical work in the last 20 years or so suggests this may not be the case. For example, ab initio calculations suggest that the C–S bond in –CH2SH is longer than in CH3SH. The converse would be true if delocalization into the sulfur's d orbitals were important. Delocalization would shorten the bond because it would have partial double bond character. More likely as an additional factor is delocalization into the s* orbital of the C–S bond on the other side of the sulfur atom—the equatorial proton of dithiane is more acidic than the axial one, and the equatorial anion is more stable because it is delocalized into the C–S bond's σ* orbital.



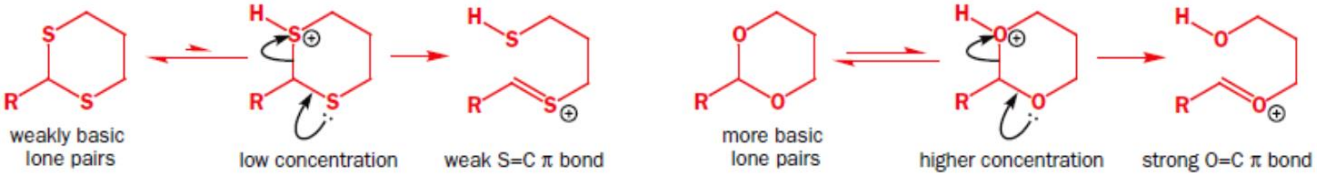
Deprotection of thioacetals

Dithianes are rather more stable than acetals, and a mercury reagent has to be used to assist their hydrolysis. Mercury(II) and sulfides form strong coordination complexes, and the mercury catalyses the reaction by acting as a sulfur-selective Lewis acid.

■ Thiols are also known as **mercaptans** because of their propensity for 'mercury capture'.



There are two reasons why the normal acid-catalysed hydrolysis of acetals usually fails with thioacetals. Sulfur is less basic than oxygen, so the protonated species is lower in concentration at a given pH, and the sulfur 3p lone pairs are less able to form a stable p bond to carbon than are the oxygen 2p lone pairs.



The most obvious solution to this problem is to provide a better electrophile than the proton for sulfur. Mercury, Hg(II), is one solution.

Lesson-4

4. Reaction with HCN: Formation of cyanohydrin

Although addition of HCN could be looked upon as a carbanion reaction, it is commonly regarded as involving a simple anion. It is of unusual interest in that it was almost certainly the first organic reaction to have its mechanistic pathway established (Lapworth 1903). HCN is not itself a powerful enough nucleophile to attack C=O, and the reaction requires base-catalysis in order to convert HCN into the more nucleophilic $^{\ominus}CN$; the reaction then obeys the rate law:

$$\text{Rate} = k[R_2C{=}O][^{\ominus}CN]$$

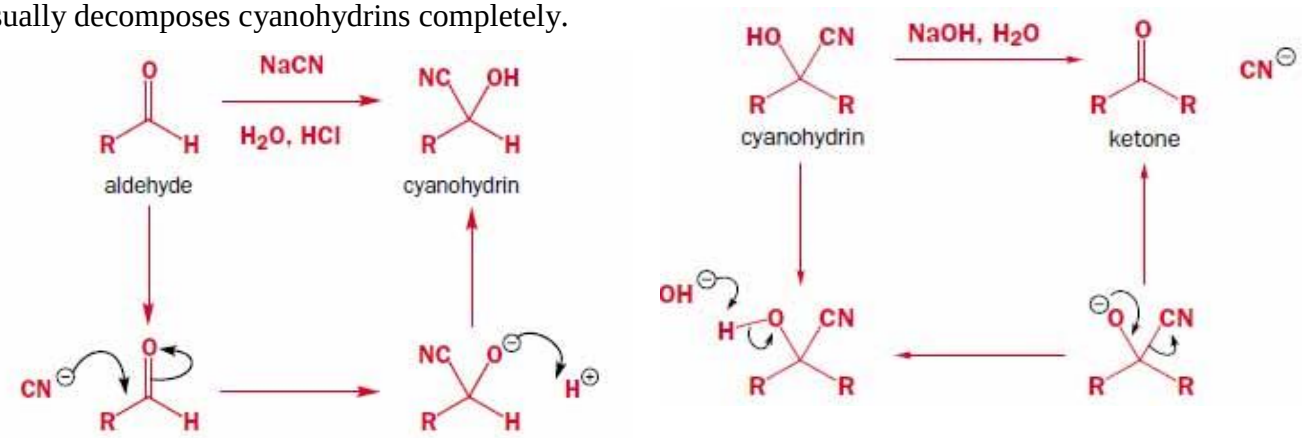
The addition of $^{\ominus}CN$ is reversible, and tends to lie over in favour of starting materials unless a proton donor is present; this pulls the reaction over to the right, as the equilibrium involving the cyanohydrin is more favourable than that involving the intermediate anion (32):

$$R_2C{=}O \overset{^{\ominus}CN}{\underset{\text{slow}}{\rightleftharpoons}} R_2C(O^{\ominus})(CN) \overset{HY}{\underset{\text{fast}}{\rightleftharpoons}} R_2C(OH)(CN) + Y^{\ominus}$$

(32)

Attack by $^{\ominus}CN$ is slow (rate-limiting), while proton transfer from HCN or a protic solvent, e.g. H_2O, is rapid. The effect of the structure of the carbonyl compound on the position of equilibrium in cyanohydrin formation has already been discussed earlier.

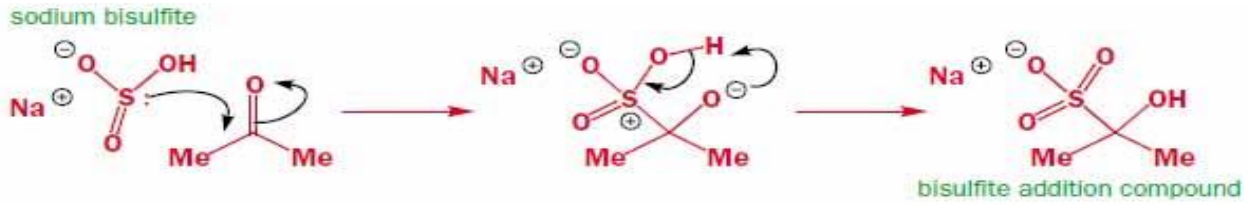
Cyanohydrins are prepared by using NaCN in presence of an acid. Cyanohydrin formation is reversible: just dissolving a cyanohydrin in water can give back the aldehyde or ketone you started with, and aqueous base usually decomposes cyanohydrins completely.



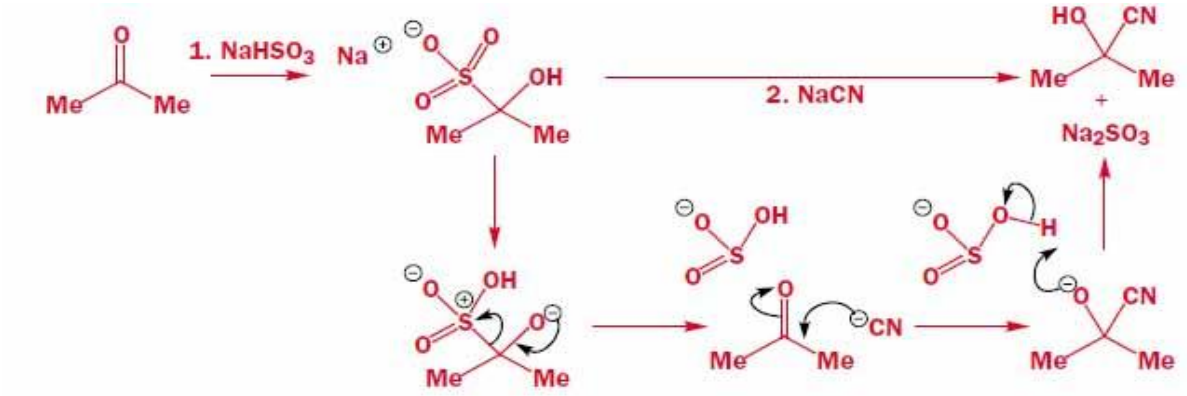
5. Addition of $NaHSO_3$: Formation of bisulfite addition compounds.

Sodium bisulfite, $NaHSO_3$, adds to aldehydes and some ketones to give what is usually known as a **bisulfite addition compound**. The reaction occurs by nucleophilic attack of a lone pair on the carbonyl group, just like the attack of cyanide. This leaves a positively charged sulfur atom but a simple proton transfer leads to the product. Generally aldehydes, methyl ketones and some cyclic ketones give bisulfite compounds in preparative scales.

The products are useful for two reasons. They are usually crystalline and so can be used to purify liquid aldehydes by recrystallization. This is of value only because these reactions, like several you have met in this chapter, is reversible. The bisulfite compounds are made by mixing the aldehyde or ketone with saturated aqueous sodium bisulfite in an ice bath, shaking, and crystallizing. After purification the bisulfite addition compound can be hydrolyzed back to the aldehyde in dilute aqueous acid or base.



The reversibility of the reaction makes bisulfite compounds useful intermediates in the synthesis of other adducts from aldehydes and ketones. For example, one practical method for making cyanohydrins involving bisulfite compounds is reacting acetone first with sodium bisulfite and then with sodium cyanide to give a good yield (70%) of the cyanohydrin.



What is happening here? The bisulfite compound forms first, but only as an intermediate on the route to the cyanohydrin. When the cyanide is added, reversing the formation of the bisulfite compound provides the single proton necessary to give back the hydroxyl group at the end of the reaction. No dangerous HCN is released (always a hazard when cyanide ions and acid are present together).