You have, in fact, already met some reactions in which the carbonyl oxygen atom can be lost, but you probably didn’t notice at the time. The equilibrium between an aldehyde or ketone and its hydrate (p. 000) is one such reaction.

When the hydrate reverts to starting materials, either of its two oxygen atoms must leave: one came from the water and one from the carbonyl group, so 50% of the time the oxygen atom that belonged to the carbonyl group will be lost. Usually, this is of no consequence, but it can be useful. For example, in 1968 some chemists studying the reactions that take place inside mass spectrometers needed to label the carbonyl oxygen atom of this ketone with the isotope $^{18}\text{O}$.

By stirring the ‘normal’ $^{16}\text{O}$ compound with a large excess of isotopically labelled water, $\text{H}_2^{18}\text{O}$, for a few hours in the presence of a drop of acid they were able to make the required labelled compound. Without the acid catalyst, the exchange is very slow. Acid catalysis speeds the reaction up by making the carbonyl group more electrophilic so that equilibrium is reached more quickly. The equilibrium is controlled by mass action—$^{18}\text{O}$ is in large excess.

We need now to discuss hemiacetals though you may well wonder why – they retain the carbonyl oxygen and they are unstable. We need to discuss them as a preliminary to the much more important acetics. Hemiacetals are halfway to acetics.

**Aldehydes can react with alcohols to form hemiacetals**

When acetaldehyde is dissolved in methanol, a reaction takes place: we know this because the IR spectrum of the mixture shows that a new compound has been formed. However, isolating the product is impossible: it decomposes back to acetaldehyde and methanol.

The product is in fact a hemiacetal. Like hydrates, most hemiacetals are unstable with respect to their parent aldehydes and alcohols: for example, the equilibrium constant for reaction of acetaldehyde with simple alcohols is about 0.5 as we saw in Chapter 13.
This equilibrium constant $K$ is defined as:

$$K = \frac{[\text{hemiacetal}]}{[\text{aldehyde}][\text{MeOH}]}$$

So by making [MeOH] very large (using it as the solvent, for example) we can turn most of the aldehyde into the hemiacetal. However, if we try and purify the hemiacetal by removing the methanol, more hemiacetal keeps decomposing to maintain the equilibrium constant. That is why we can never isolate such hemiacetals in a pure form.

**Only a few hemiacetals are stable**

Like their hydrates, the hemiacetals of most ketones (sometimes called hemiketals) are even less stable than those of aldehydes. On the other hand, some hemiacetals of aldehydes bearing electron-withdrawing groups, and those of cyclopropanones, are stable, just like the hydrates of the same molecules.

Hemiacetals that can be formed by intramolecular cyclization of an alcohol on to an aldehyde are also often stable, especially if a five- or six-membered ring is formed. You met this in Chapter 6—many sugars (for example, glucose) are cyclic hemiacetals, and exist in solution as a mixture of open-chain and cyclic forms.

**Acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol parents**

Acyclic hemiacetals form relatively slowly from an aldehyde or ketone plus an alcohol, but their rate of formation is greatly increased either by acid or by base. As you would expect, after Chapters 12 and 13, acid catalysts work by increasing the electrophilicity of the carbonyl group.
Base catalysts, on the other hand, work by increasing the nucleophilicity of the alcohol by removing the OH proton before it attacks the C=O group. In both cases the energy of the starting materials is raised: in the acid-catalysed reaction the aldehyde is destabilized by protonation and in the base-catalysed reaction the alcohol is destabilized by deprotonation.

You can see why hemiacetals are unstable: they are essentially tetrahedral intermediates containing a leaving group and, just as acid or base catalyses the formation of hemiacetals, acid or base also catalyses their decomposition back to starting aldehyde or ketone and alcohol. That’s why the title of this section indicated that acid or base catalysts increase the rate of equilibration of hemiacetals with their aldehyde and alcohol components—the catalysts do not change the position of that equilibrium!

To summarize

Hemiacetal formation and decomposition are catalysed by acid or base.

Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid

We said that a solution of acetaldehyde in methanol contains a new compound: a hemiacetal. We’ve also said that the rate of formation of hemiacetals is increased by adding an acid (or a base) catalyst to an alcohol plus aldehyde mixture. But, if we add catalytic acid to our acetaldehyde–methanol
Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid

mixture, we find not only that the rate of reaction of the acetaldehyde with the methanol increases, but also that a different product is formed. This product is an acetal.

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

Oxonium ions have three bonds to a positively charged oxygen atom. All three bonds can be σ bonds as in H$_3$O$^+$ or Meerwein’s salt, trimethyloxonium fluoroborate, a stable (though reactive) compound described in Chapter 21, or one bond can be a π bond as in the acetal intermediate. The term ‘oxonium ion’ describes either of these structures. They are like alkylated ethers or O-alkylated carbonyl compounds.

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. Before reading any further, it would be worthwhile to write out the whole mechanism of acetal formation from aldehyde or ketone plus alcohol through the hemiacetal to the acetal, preferably without looking at the fragments of mechanism above, or the answer below.

Formation of acetals and hemiacetals

Hemiacetal formation is catalysed by acid or base, but acetal formation is possible only with an acid catalyst because an OH group must be made into a good leaving group.

When you look at our version of this complete mechanism you should notice a remarkable degree of similarity in the two halves. The reaction starts with a protonation on carbonyl oxygen and, when
you get to the temporary haven of the hemiacetal, you start again with protonation of that same oxygen. Each half goes through an oxonium ion and each oxonium ion adds the alcohol. The last step in the formation of both the acetal and the hemiacetal is the loss of a proton from the recently added alcohol.

This is about as complex a mechanism as you have seen and it will help you to recall it if you see it in two halves, each very similar to the other. First, form the hemiacetal by adding an alcohol to the C=O π bond; then lose the OH group by breaking what was the C=O σ bond to form an oxonium ion and add a second alcohol to form the acetal. From your complete mechanism you should also be able to verify that acetal formation is indeed catalytic in acid.

Making acetals

Just as with the ester formation and hydrolysis reactions we discussed in Chapters 12 and 13, every step in the formation of an acetal is reversible. To make acetals, therefore, we must use an excess of alcohol or remove the water from the reaction mixture as it forms, by distillation, for example.

In fact, acetal formation is even more difficult than ester formation: while the equilibrium constant for acid-catalysed formation of ester from carboxylic acid plus alcohol is usually about 1, for
Acetals are formed from aldehydes or ketones plus alcohols in the presence of acid.

Acetal formation from aldehyde and ethanol (shown above), the equilibrium constant is $K = 0.0125$. For ketones, the value is even lower: in fact, it is often very difficult to get the acetals of ketones (these used to be called ketals) to form unless they are cyclic (we consider cyclic acetals later in the chapter). However, there are several techniques that can be used to prevent the water produced in the reaction from hydrolysing the product.

Overcoming entropy: orthoesters

We have already mentioned that one of the factors that makes acyclic hemiacetals 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 $2 \times$ alcohol) become two of product (acetal plus $H_2O$). 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 $+ 2 \times$ 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.
Acetals hydrolyse only in the presence of acid

Just as acetal formation requires acid catalysis, acetals can be hydrolysed only by using an acid catalyst. With aqueous acid, the hydrolysis of acyclic acetals is very easy. Our examples are the two acetals we made earlier.

\[
\begin{align*}
\text{Me} & \quad \text{O} & \quad \text{O} & \quad \text{Me} \\
\text{O} & \quad \text{O} & \quad \text{Me} & \quad 3\% \text{ HCl, H}_2\text{O} & \quad 30 \text{ min} & \quad \text{MeCHO} + 2 \text{ BuOH} \\
\text{R} & \quad \text{O} & \quad \text{Me} & \quad 2 \text{ M H}_2\text{SO}_4 & \quad \text{CHO} + 2 \text{ MeOH}
\end{align*}
\]

\textbf{Acetal hydrolysis}

Acetals can be hydrolysed in acid but are stable to base.

We won’t go through the mechanism again—you’ve already seen it as the reverse of acetal formation (and you have a hint of it in the orthoester hydrolysis just discussed), but the fact that acetals are stable to base is really a very important point, which we will use on p. 000 and capitalize on further in Chapter 24.

Cyclic acetals are more stable towards hydrolysis than acyclic ones

Of course you want us to prove it: well—

\[
\begin{align*}
\text{MeO} & \quad \text{O} & \quad \text{O} & \quad \text{MeO} & \quad \text{CF}_2\text{CO}_2\text{H} & \quad \text{H}_2\text{O} & \quad \text{CHCl}_3 \text{ (solvent)} & \quad 0 \degree \text{C, } 1 \text{ h} & \quad 96\% \text{ yield} \\
\text{ethylene glycol} & & & & & & & & &
\end{align*}
\]

The acetals you have met so far were formed by reaction of two molecules of alcohol with one of carbonyl compound. Cyclic acetals, formed by reaction of a single molecule of a diol, a compound containing two hydroxyl groups, are also important. When the diol is ethylene glycol (as in this example) the five-membered cyclic acetal is known as a dioxolane.

\[
\begin{align*}
\text{me} & \quad \text{O} & \quad \text{OH} & \quad \text{HO} & \quad \text{HO} & \quad \text{HO} & \quad \text{OH} & \quad \text{OH} \\
\text{cat. TsOH, heat, remove water by distillation} & & & & & & & & &
\end{align*}
\]

Before looking at the answer below, try to write a mechanism for this reaction. If you need it, use the mechanism we gave for the formation of acyclic acetals.

We hope you didn’t make the mistake of missing out the oxonium ion step!
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 \(\Delta S^\circ\) 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: there is a picture of this in Chapter 13.

Modifying reactivity using acetals

Why are acetals so important? Well, they’re important to both nature and chemists because many carbohydrates are acetals or hemiacetals (see the box below). One important use that chemists have put them to is as protecting groups.

One important synthesis of the steroid class of compounds (about which more later) requires a Grignard reagent with this structure.

![Unstable structure](image)

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.

![Stable Grignard reagent](image)

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

### Acetals in nature

We showed you glucose as an example of a stable, cyclic hemiacetal. Glucose can, in fact, react with itself to form an acetal known as maltose.

![Maltose](image)

Maltose is a disaccharide (made of two sugar units) produced by the enzymatic hydrolysis of starch or cellulose, which are themselves polyacetals made up of a string of glucose units.