

Lecture 4: Nucleophilic Addition Reactions of Aldehydes and Ketones

Objectives:

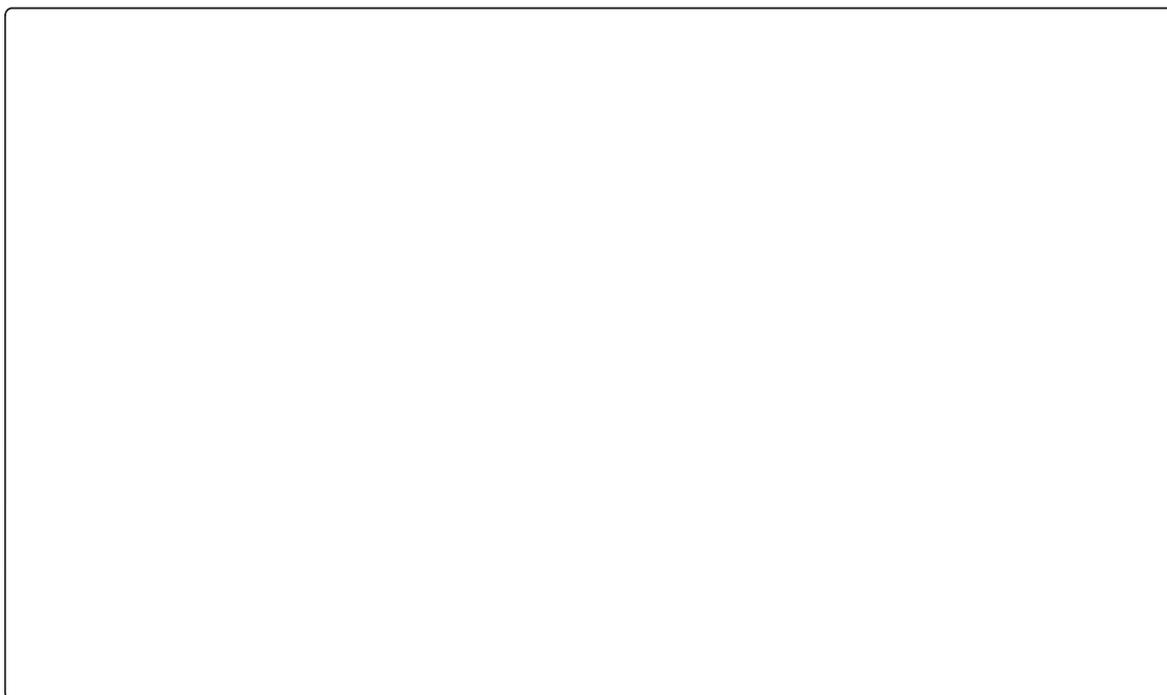
By the end of this lecture you will be able to:

- draw the mechanism of a nucleophilic addition reaction involving aldehydes and ketones;
- predict whether a nucleophilic addition reaction is likely to be reversible or irreversible using pK_a information;
- understand some of the selectivity issues involved in using metal hydride reagents for reducing carbonyl groups.

Introduction

Last lecture we saw how carbonyl groups behave as electrophiles and therefore react with nucleophiles. We spent some time discussing the mechanism of this reaction in detail. In this lecture we will show that the reaction of nucleophiles with carbonyl groups is very general. We will only concentrate on reactions of aldehydes and ketones; in the next lecture, we will see how the mechanism is modified slightly when we use carboxylic acid derivatives as the electrophiles.

From last time, the general reaction mechanism:

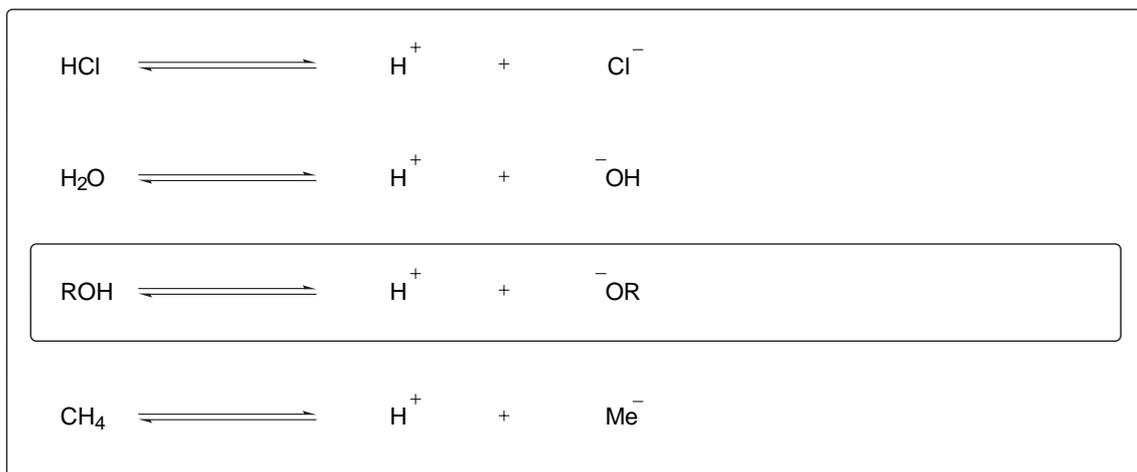


The first step in the reaction mechanism involves addition of the nucleophile to the trigonal planar aldehyde or ketone to form a tetrahedral intermediate. This first step can be a reversible or essentially an irreversible process; the pK_a of the conjugate acid of the nucleophile can provide some indication of the side on which this equilibrium will lie.

Recall that pK_a values provide an indication of the relative stability of an acid and its conjugate base. Acids with a low pK_a value dissociate readily; the conjugate base is very stable. An acid with a high pK_a value does not dissociate readily as the conjugate base is not very stable.

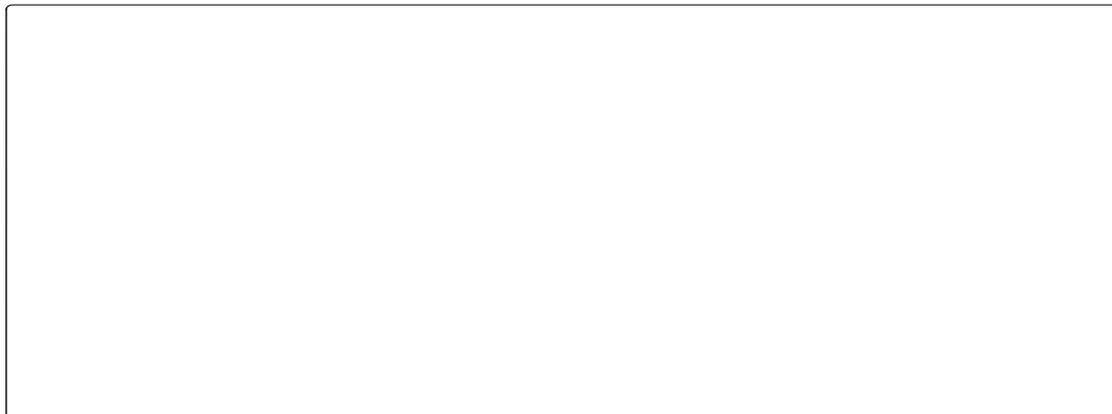
Note: we need to exercise some degree of caution here as pK_a values are often determined in water, which is only rarely the solvent in which nucleophilic addition reactions are carried out. Furthermore they refer to basicity, which is not the same as nucleophilicity. They also represent a thermodynamic property and many nucleophilic addition reactions involving aldehydes and ketones are kinetically controlled processes.

Consider the following nucleophiles: chloride, hydroxide and the methyl anion.

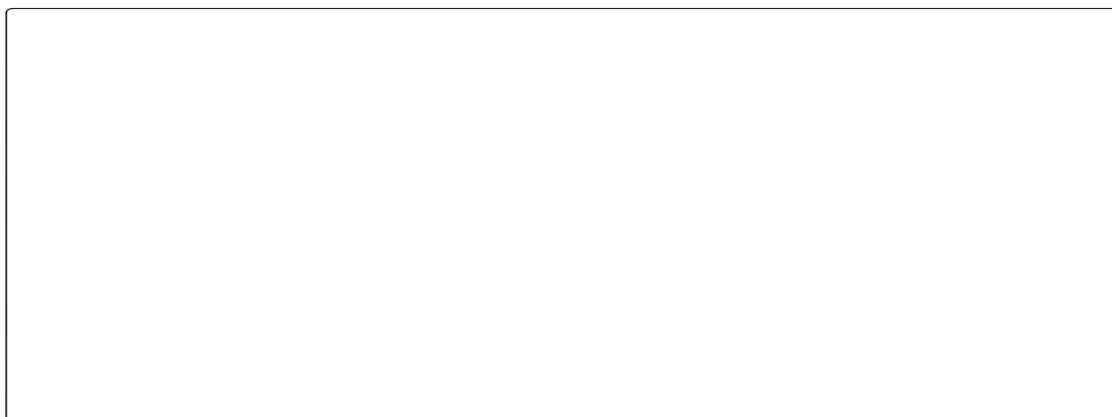


We need to compare the pK_a of the acid of the conjugate base, which is behaving as our nucleophile, with that of the alcohol.

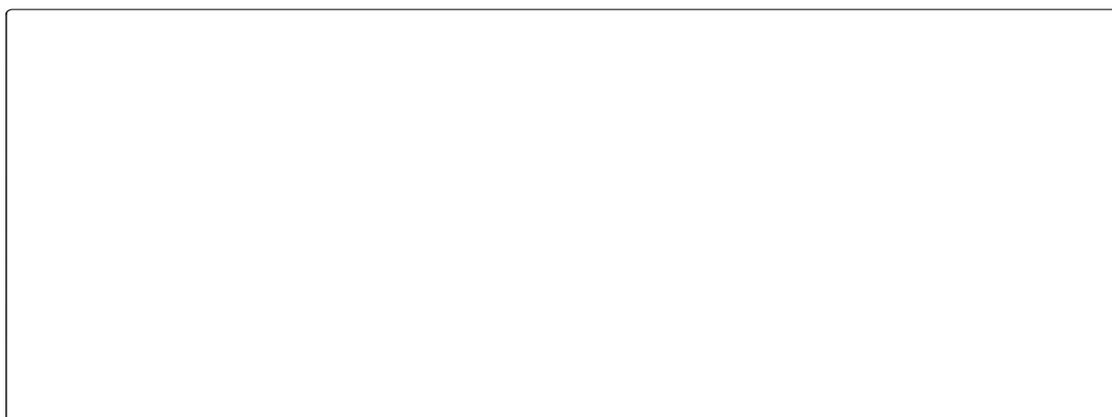
Chloride is a relatively good nucleophile; however it is much more stable than an alkoxide and so the equilibrium will lie on the side of the starting materials.



In contrast, the methyl anion is very unstable; reaction with a carbonyl group will be essentially irreversible and the equilibrium will lie on the side of the products.



Water and alcohols have very similar pK_a values and one would expect that the hydrate (the addition product) and the carbonyl group are both populated. We will see how other factors affect the degree of hydration later.



'Irreversible' Nucleophilic Addition Reactions

From our analysis of pK_a values, we can see that providing the $pK_a(\text{H-Nu}) \gg pK_a(\text{RO-H})$, then the addition of the conjugate base (Nu^-) will be essentially irreversible.

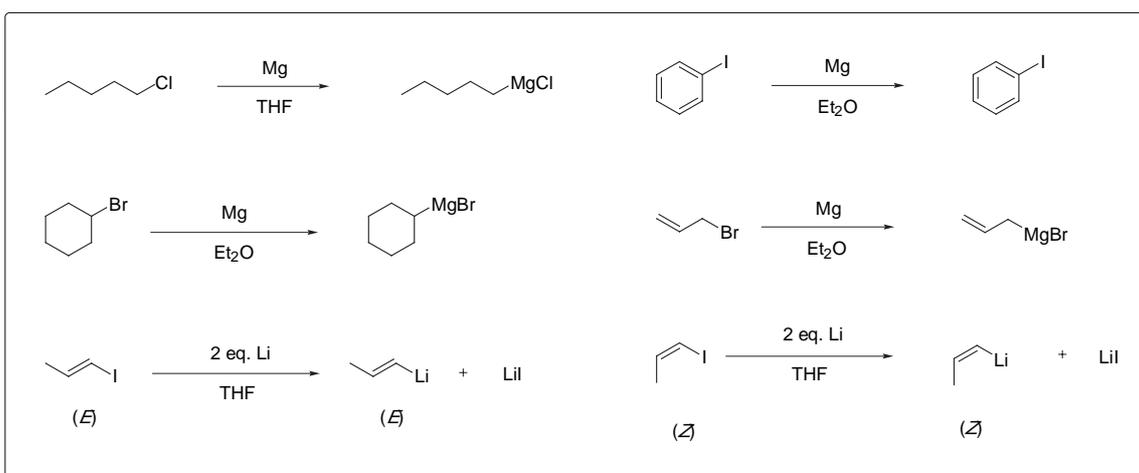
Many nucleophiles satisfy this requirement. We will consider a few of these.

Organolithium Reagents and Grignard Reagents

The addition of carbon nucleophiles into aldehydes and ketones provides one of the most effective ways of forming new C–C bonds, as well as alcohols. Many types of carbon nucleophiles have been developed for this purpose. Organolithium reagents and Grignard reagents are two of the most important and widely used.

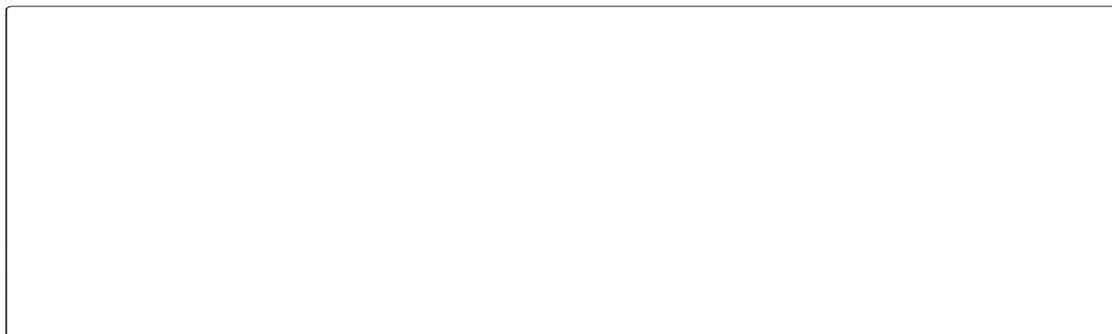
Preparation

There are many ways available for preparing organolithium and Grignard reagents. The most common method is to treat the corresponding alkyl halide (aryl, alkenyl and alkynyl halides also react) with the appropriate metal.

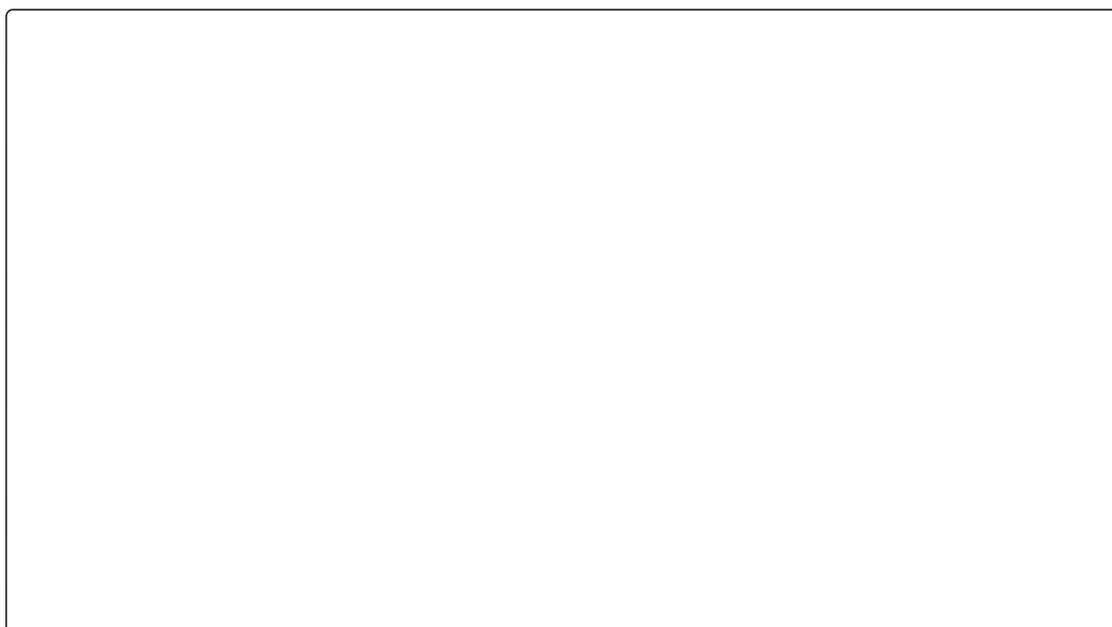


- Alkyl iodides and bromides are the most reactive; alkyl chlorides often require more forcing conditions.

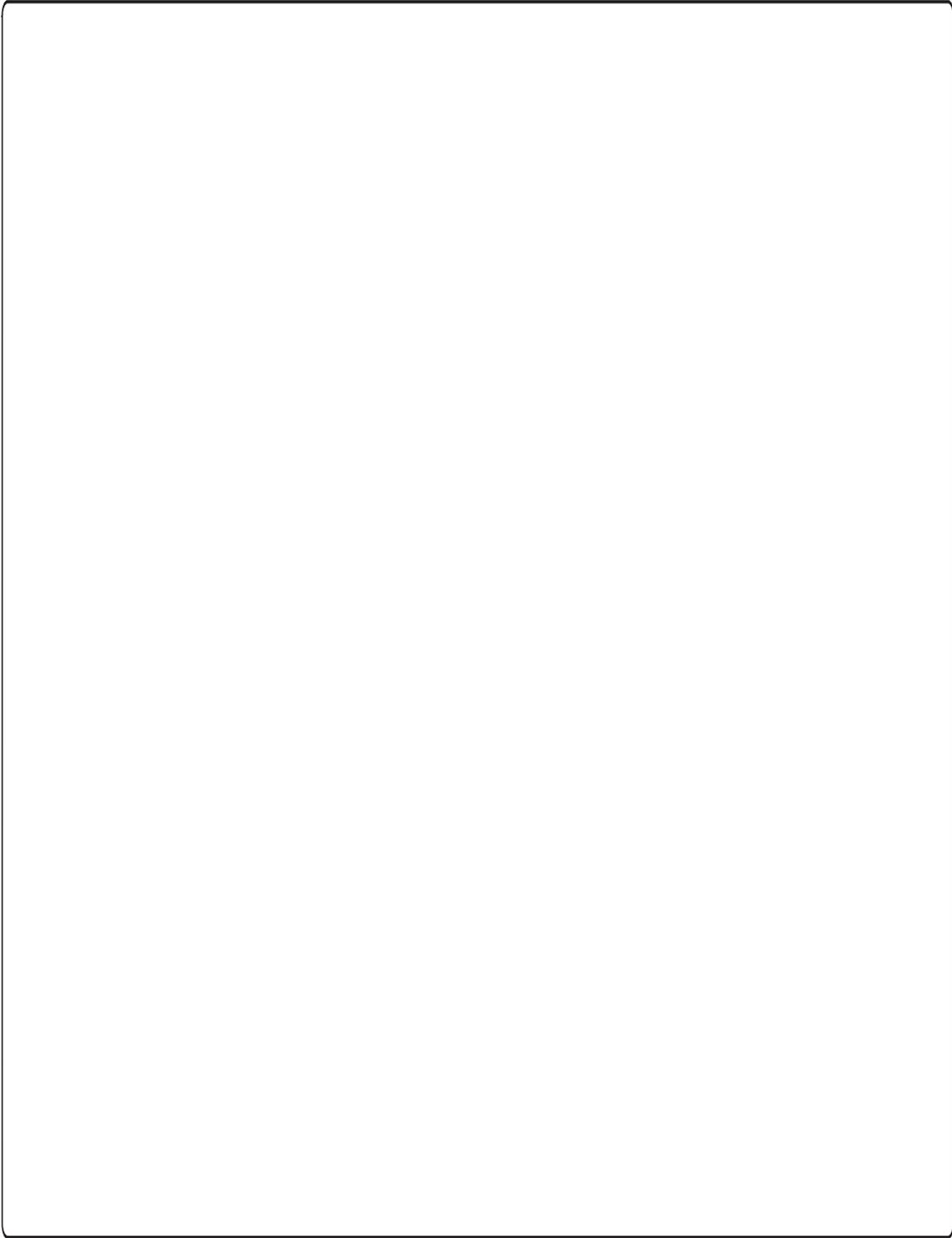
- Commonly used solvents for this reaction are polar aprotic ethers such as tetrahydrofuran (THF) and diethyl ether (Et₂O).



- Alkynyl Grignards and organolithiums are normally made by deprotonation methods. Unlike most C–H groups, which are non-acidic (high pK_a values), the pK_a of an acetylenic C–H is around 25, which brings it into the class of molecules that can be deprotonated with very strong bases:



Some Examples:



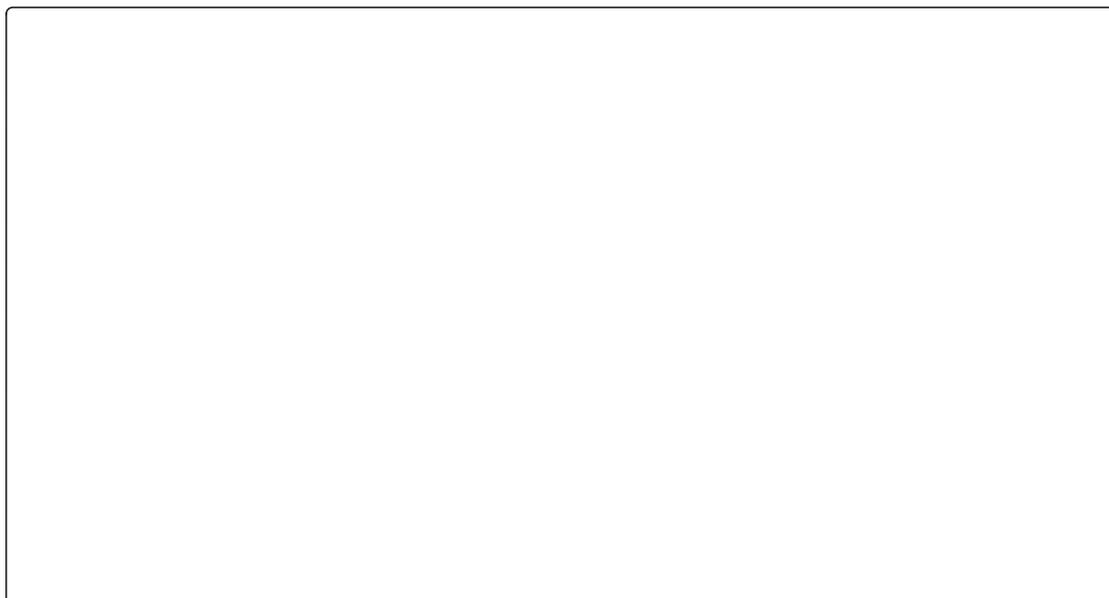
Hydride Reducing Agents

Just as the oxidation of alcohols provides one of the most common methods for forming aldehydes and ketones, the reverse reaction, reduction, is one of the best ways for preparing alcohols. A huge variety of reducing agents has been developed to satisfy a range of selectivity requirements. Hydride reducing agents based on boron and aluminium reagents are the most widely used. They are also 'irreversible' nucleophiles as hydride is a very poor leaving group.

Sodium Borohydride (NaBH_4)

Sodium borohydride is a relatively mild nucleophilic reducing agent; it therefore only reacts (at least readily) with the most electrophilic carbonyl functional groups *i.e.* aldehydes and ketones. Reduction of esters is very slow.

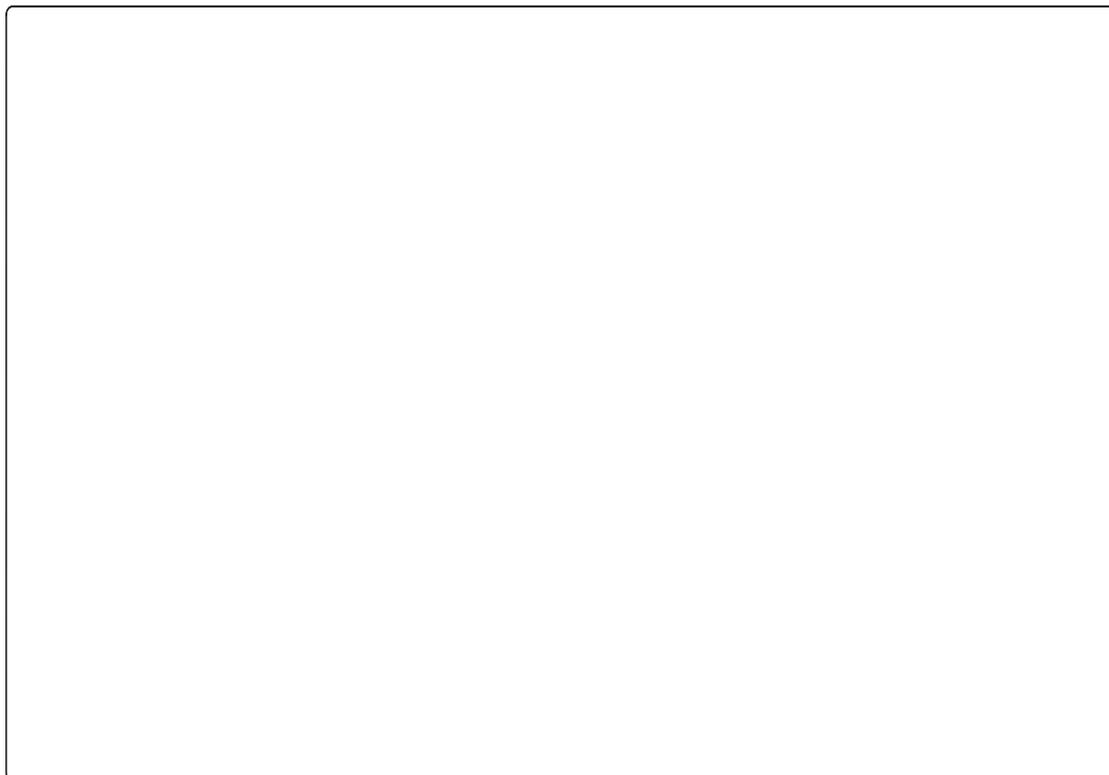
Thus NaBH_4 can therefore be used as a **chemoselective** reducing agent:



Although sodium borohydride is the most widely used reagent for reducing aldehydes and ketones, a detailed mechanistic understanding of the reaction is still lacking; some details however are known.

- All four hydrogen atoms can be transferred; hence 1 eq. NaBH_4 can reduce 4 eq. $\text{C}=\text{O}$ although usually an excess of borohydride is used.
- NaBH_4 is very soluble in H_2O , and MeOH ; it actually reacts with these solvents with the evolution of H_2 . Solvents of choice for this reaction are therefore EtOH or $i\text{PrOH}$, with which it reacts much more slowly.

For our purposes we can draw a mechanism for this reaction:

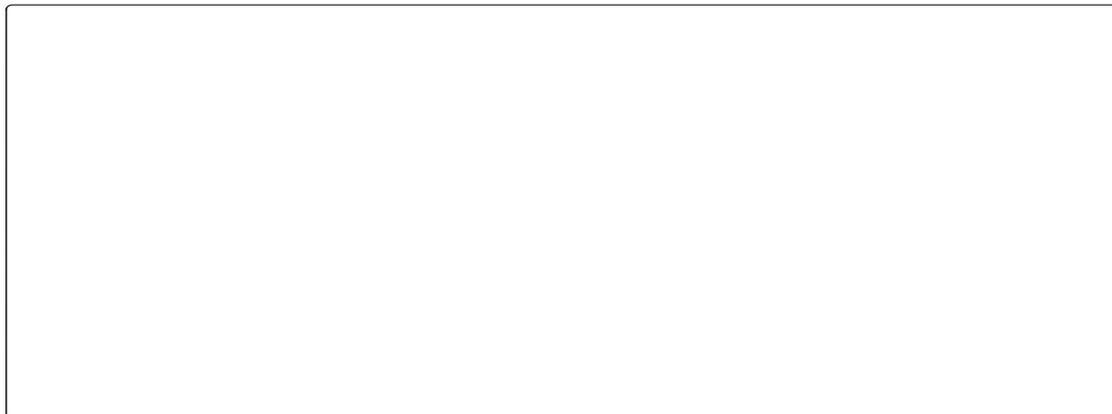


- Although the sodium counterion is not deemed particularly important, there is clearly an important effect on reactivity when other counterions are used. LiBH_4 , $\text{Mg}(\text{BH}_4)_2$ and $\text{Ca}(\text{BH}_4)_2$ are all more reactive than NaBH_4 (they reduce esters fairly readily). All these metals are fairly good Lewis acids; the cations have a higher charge density and will coordinate more strongly to the carbonyl oxygen thereby increasing its electrophilicity and therefore susceptibility to attack by nucleophiles.

Lithium Aluminium Hydride (LiAlH_4)

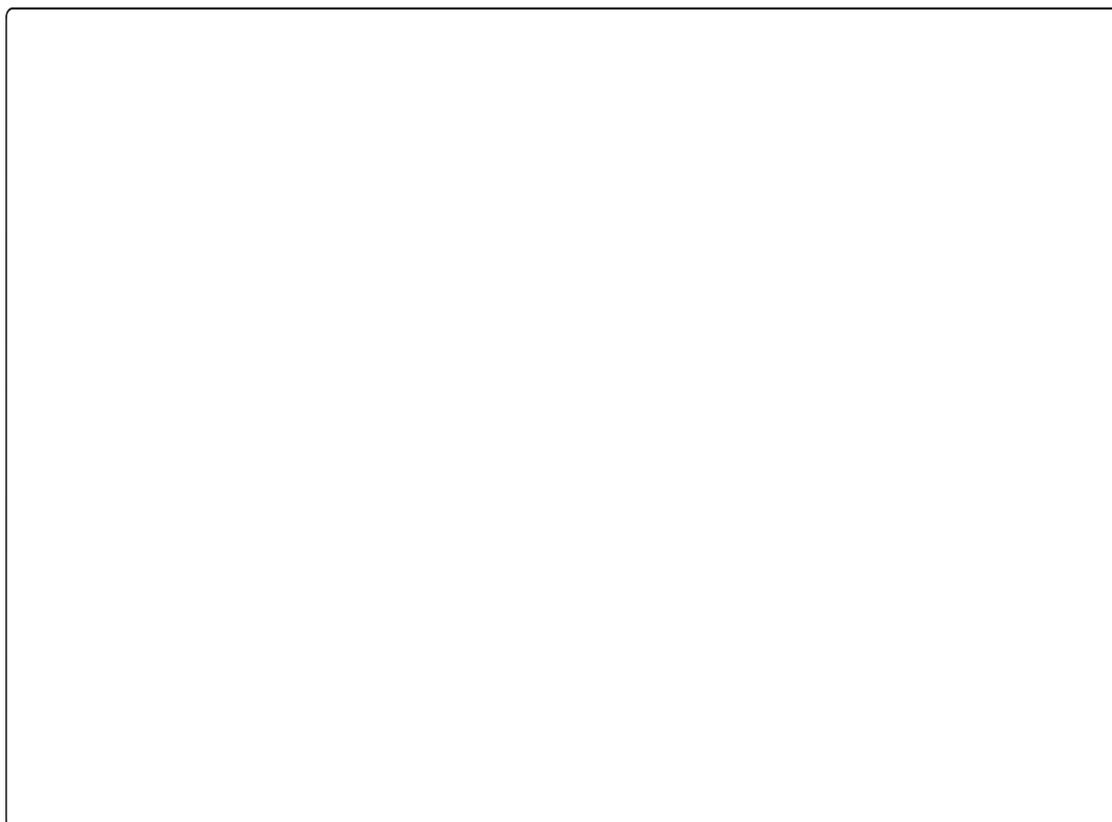
Lithium aluminium hydride is a very powerful nucleophilic reducing agent and is capable of reducing even weakly electrophilic carbonyl groups (*e.g.* esters, amides and even carboxylic acids). Compared with NaBH_4 , it is therefore NOT very chemoselective.

LiAlH_4 is a highly flammable reagent and therefore must be used with care. Reactions are normally carried out in ethereal solvents (*e.g.* THF, Et_2O); it reacts violently with protic solvents (*c.f.* NaBH_4)!



An issue of stereoselectivity

We have seen that chemoselectivity in reduction reactions can be controlled by careful choice of reducing agent. You should also be aware that reduction of ketones that have two different substituents generates a stereogenic centre. Thus we sometimes need to be able to carry out *stereoselective* reductions. You will hear more about this selectivity problem in future years.



'Reversible' Nucleophilic Addition Reactions

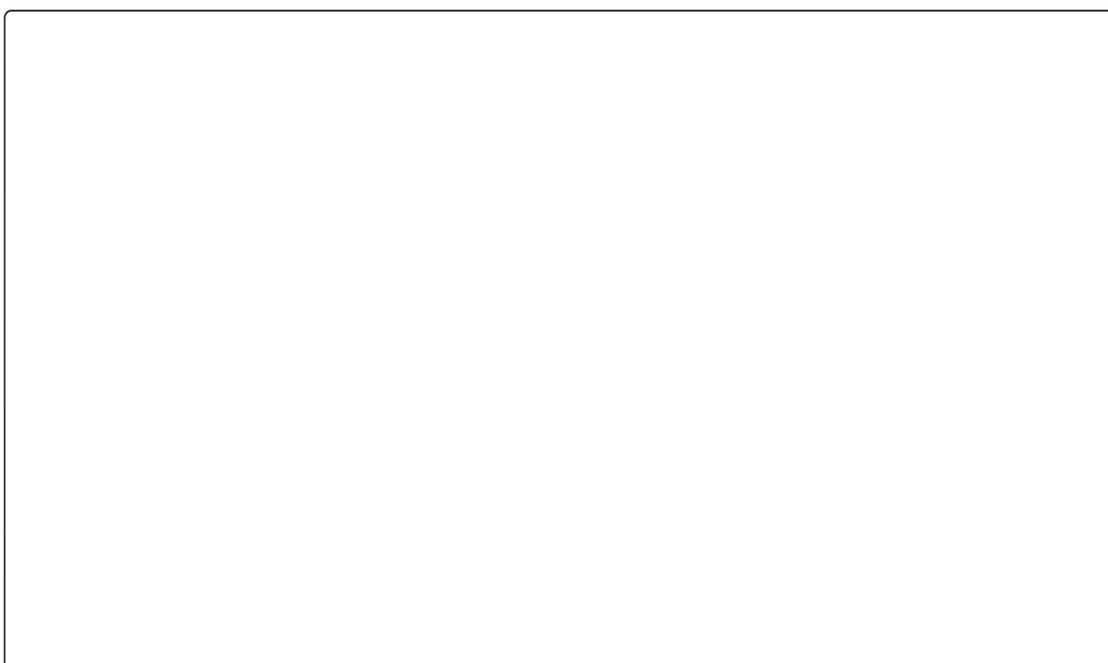
Hydration

As we have seen, some nucleophiles react reversibly with aldehydes and ketones such that both the starting carbonyl compound *and* the product can be present in significant amounts at equilibrium. The most important nucleophile falling into this category is water, which reacts with an aldehyde or ketone to form the corresponding hydrate.



The reaction mechanism is similar to other nucleophilic addition reactions. As water is a relatively poor nucleophile the rate of addition is slow. However, the rate of reaction can be increased by using acid or base. There are two ways of increasing the rate of reaction in a nucleophilic addition process; one is to increase the electrophilicity of the carbonyl group, the other is to increase the nucleophilicity of the nucleophile.

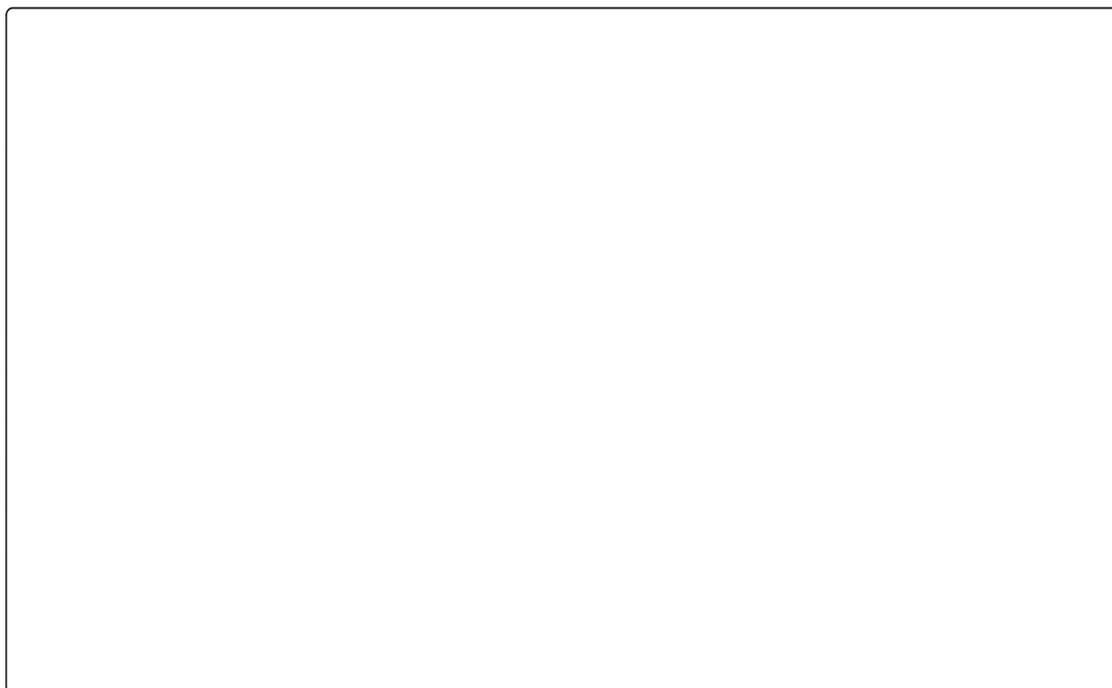
Acid-Catalysed Hydration



Under acidic conditions, the carbonyl group is partially protonated. The protonated species, being positively charged, is much more electrophilic than the neutral carbonyl compound, and therefore reacts more readily with nucleophiles.

N.B. Proton transfer between heteroatoms is rapid and reversible. It is also invariably an INTERmolecular process.

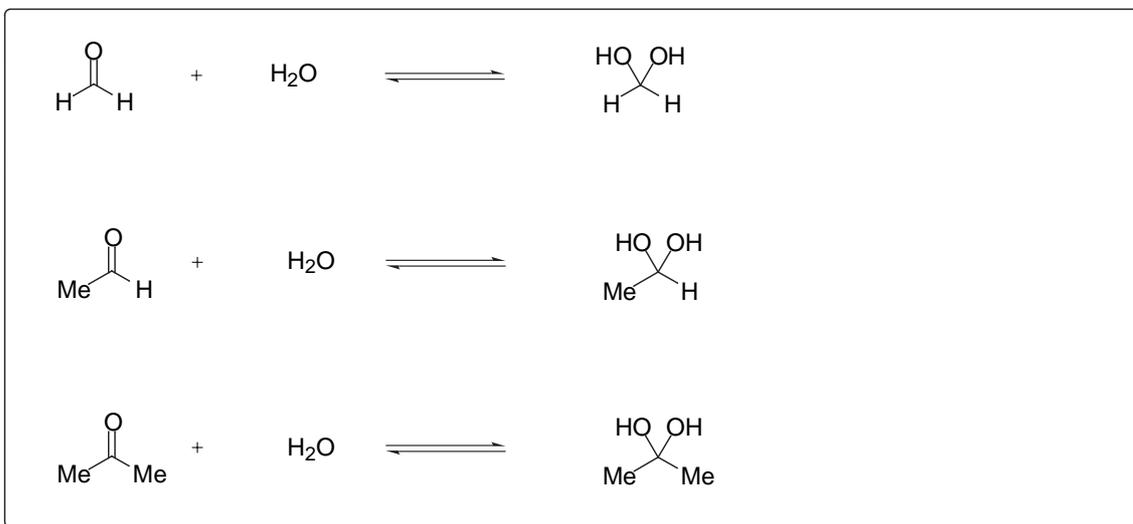
Base-Catalysed Hydration



Under basic conditions, hydroxide anion behaves as the active nucleophile. Since hydroxide is negatively charged it is more nucleophilic than neutral water (it is also much more basic).

All aldehydes and ketones are in equilibrium with their hydrates.

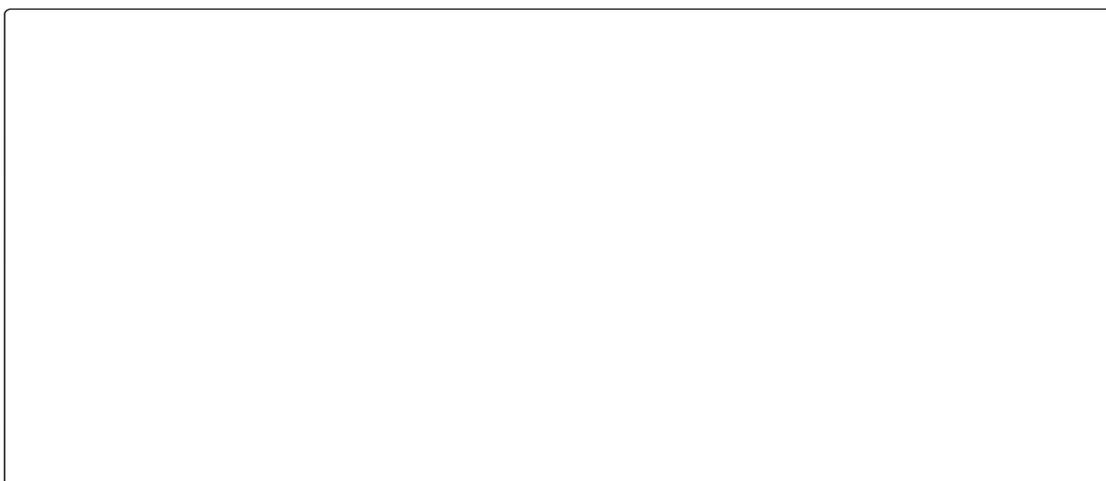
The position of this equilibrium depends on the relative stabilities of the carbonyl group and the hydrate.



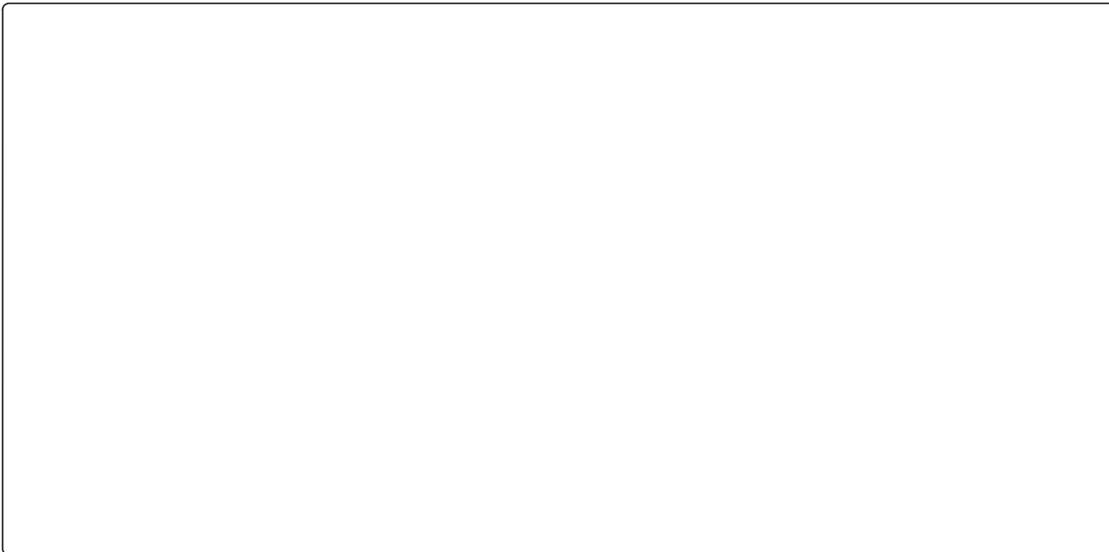
From the magnitudes of the equilibrium constants, it is clear that formaldehyde is strongly hydrated, whilst the equilibrium with acetone lies predominantly on the left. In water, acetaldehyde is approximately 50% hydrated.

We need to be able to rationalise these equilibria. Since this process is under thermodynamic control, if the equilibrium lies on the left then something must be stabilising the carbonyl group and/or destabilising the hydrate.

- Increased alkyl substitution about the carbonyl group leads to increased stabilisation of the group. Alkyl groups are electron-donating (they exert a +I inductive effect), and therefore effectively reduce the amount of δ^+ charge on the carbonyl carbon.



- On hydration, the carbonyl carbon goes from sp^2 -trigonal planar to sp^3 -tetrahedral. The two substituents are therefore pushed closer together leading to increased steric repulsions and an increased destabilisation.

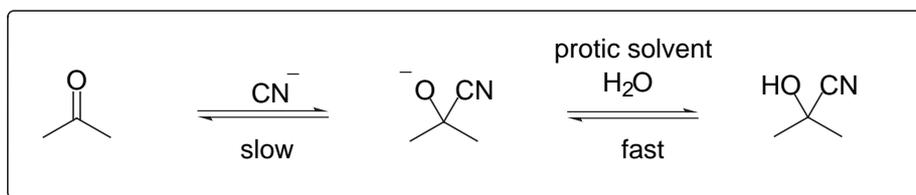


A consequence of these two factors is that ketones are far less hydrated than aldehydes.

Other factors such as the presence of electron-withdrawing groups or resonance-stabilising effects also affect the position of the equilibrium.

Cyanohydrin Formation

Cyanide also adds reversibly to aldehydes and ketones. This equilibrium reaction tends to lie in favour of starting materials. However, if the reaction is carried out in the presence of a proton donor, the equilibrium can be pulled over to the right:



Summary

Aldehydes and ketones are good electrophiles and react with a wide variety of nucleophiles. Some nucleophiles react effectively irreversibly; these include organolithium and Grignard reagents (C-nucleophiles) and various hydric reducing agents (NaBH_4 and LiAlH_4). The acids (H–Nu) of these nucleophiles (Nu^-) tend to have high $\text{p}K_a$ values. Other nucleophiles, such as water and cyanide react reversibly. The $\text{p}K_a$ values of the acids (H_2O , HCN etc) are comparable or lower than that of an alcohol. The position of these equilibria depends on a variety of factors that affect the relative stability of the starting materials and products.