

## Lecture 2

### Enols and Enolates

#### **Objectives:**

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

- 1) draw a mechanism for the incorporation of deuterium into sites  $\alpha$ -to a carbonyl group under acidic ( $\text{D}_2\text{O} / \text{D}^+$ ) or basic ( $\text{D}_2\text{O} / \text{OD}^-$ ) reaction conditions;
- 2) rationalise the position of keto-enol equilibria;
- 3) use  $\text{pK}_\text{a}$  values to select a base capable of abstracting a proton from a site  $\alpha$  to a carbonyl group;
- 4) choose appropriate bases for partial and complete enolisation of carbonyl groups.

#### **Keto-Enol Tautomerisation**

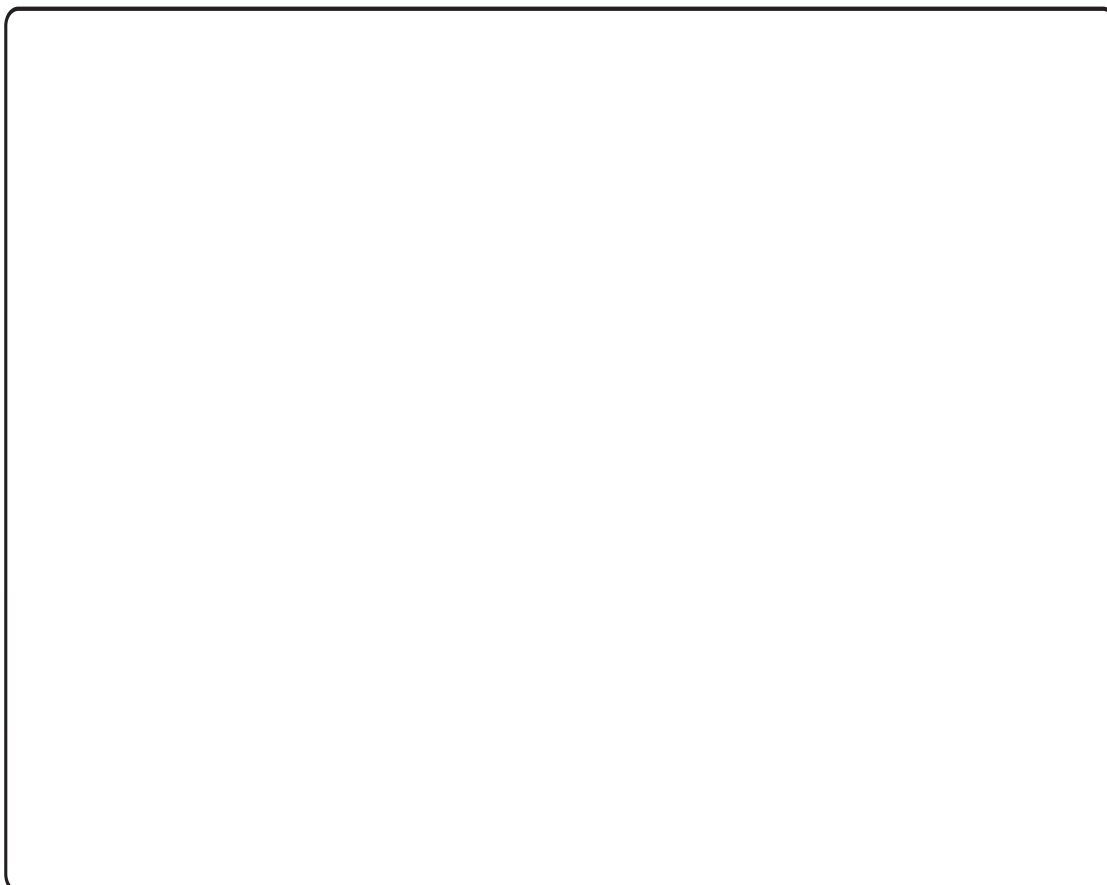
When acetone is exposed to  $\text{D}_2\text{O} / \text{D}_3\text{O}^+$  the  $\alpha$ -hydrogens are exchanged for deuterium atoms.



Taking a close look at the species in the reaction mixture reveals the presence of another molecule in addition to acetone. This additional species is the so-called **enol** tautomeric form of acetone. The presence of this second tautomeric form of acetone accounts for its ability to incorporate deuterium atoms into sites  $\alpha$  to the carbonyl group.



The ketone and its enol tautomer are in equilibrium with one another. In the case of acetone, the equilibrium lies far over to the left-hand side. This can be readily rationalised by comparing the relative stabilities of a C=C and a C=O bond. Nevertheless the presence of even small amounts of this *nucleophilic* enol tautomer allows us to rationalise the observed incorporation of deuterium atoms into the  $\alpha$ -sites of a carbonyl compound under acidic conditions.



In the absence of acid, the rate of deuterium incorporation would be very low, although if left long enough, the same result would be observed, namely all  $\alpha$ -C-Hs would be exchanged for deuterium atoms. The presence of acid increases the rate of reaction by generating a small concentration of the protonated carbonyl compound (the carbonyl oxygen is behaving as a Brønsted base).



Last year we saw how protonation of a carbonyl group increases its electrophilicity. More importantly for our purposes, protonation of the carbonyl oxygen also increases the acidity of the  $\alpha$ -C-Hs. This means that a relatively weak base such as  $D_2O$  can be used to abstract the  $\alpha$ -C-H and form the enol tautomer.

The position of the keto-enol equilibrium closely follows the  $pK_a$  value of the  $\alpha$ -C-H (see last lecture). Thus in acetone only a very small proportion of the molecule will exist in the enol form. Compare this with acetylacetone in which the  $pK_a$  of the internal protons is 9. In this case the enol tautomer is much more heavily populated; the enol tautomer benefits from increased stabilisation owing to an internal H-bond and conjugation of the C=C bond with the remaining C=O group. A special case in which the enol is much more stable than its keto tautomer is phenol. In this example the enol form is greatly stabilised through the formation of an aromatic species.



### Base-Catalysed Hydrogen-Deuterium Exchange

When acetone is treated with  $\text{D}_2\text{O} / \text{OD}^-$ , it is also possible to exchange the  $\alpha\text{-C-Hs}$  for deuterium atoms. The mechanism is slightly different to that described for the acid case above. Since deuterioxide is a better Brønsted base than  $\text{D}_2\text{O}$ , an enol-type intermediate can be formed without having to activate the carbonyl group. Thus in the presence of  $\text{OD}^-$  a negatively charged species called an **ENOLATE** is formed. Note that an enolate is not a tautomer of the ketone as it has a different molecular formula.



## Forming Enolates

Enolates are reactive species and very important nucleophiles in synthesis; we need to be able to prepare them selectively.

We have seen that the  $pK_a$  of  $\alpha$ -C-Hs depends strongly on the type of carbonyl functional group. Since we know the  $pK_a$  of these protons we can now use our knowledge of  $pK_a$  values of various bases (B-H) to predict what types of base ( $B^-$ ) can be used to abstract protons from sites  $\alpha$ -to carbonyl groups.

Consider the following acid-base reaction:



Acid-base reactions, like any other reaction, are equilibrium processes. The position of the equilibrium in the above reaction will depend on the strength of the base and on the acidity of the  $\alpha$ -C-H group.

## Partial Enolisation

Condition:

If the  $pK_a$  of the  $\alpha$ -C-H in the carbonyl compound and the conjugate acid, B-H, of the base,  $B^-$ , are similar, then significant quantities of both reactants (*i.e.* the carbonyl compound and base  $B^-$ ) and products (*i.e.* the enolate and conjugate acid B-H) should be present at equilibrium. This assumes that the only process that is occurring is the acid-base reaction, which in reality is not the case. Enolates are good nucleophiles and ketones good electrophiles. Therefore, if an

enolate is formed in the presence of a ketone, you should expect the two to react. This is indeed the case: a self-condensation aldol reaction can occur to provide a  $\beta$ -hydroxy ketone product. We will discuss this so-called aldol reaction in much greater detail in later lectures.



If this type of condensation reaction is desired, we need to use a base that does not completely deprotonate the carbonyl compound *i.e.* we need to establish an equilibrium that contains significant amounts of both the enolate nucleophile and the ketone electrophile. This is best achieved when the  $pK_a$  of the carbonyl group and conjugate acid, B-H, of the base,  $B^-$ , are similar.

Consider the acid-base equilibrium between the alkoxide base, NaOEt, and acetone.



$KO^tBu$  is a stronger base than NaOEt ( $pK_a(^tBuOH) \sim 18$ ,  $pK_a(EtOH) \sim 16$ ). The  $pK_a$  difference between the acidic protons is now only 1  $pK_a$  unit; thus when  $KO^tBu$  is used as the base, the ratio

of ketone to enolate will be of the order 10:1 *i.e.* there would be about 10% enolate in solution at equilibrium (assuming neither the enolate nor ketone react further).

When it is desirable to generate the enolate of a standard ketone in small quantities, an *alkoxide* base is ideal. However with  $\beta$ -keto-esters or 1,3-diketones, alkoxide bases will cause essentially complete deprotonation. This is because the  $pK_a$  of the internal proton in these types of carbonyl compounds is around 9-12 (see lecture 1 for a list of  $pK_a$  values). To achieve partial enolisation of these types of carbonyl group, a much milder base such as sodium bicarbonate ( $\text{NaHCO}_3$ ;  $pK_a(\text{H}_2\text{CO}_3) \sim 6.3$ ) or sodium carbonate ( $\text{Na}_2\text{CO}_3$ ;  $pK_a(\text{HCO}_3^-) \sim 10.3$ ) can be used.



**NOTE:** all bases are potential nucleophiles. Alkoxide addition to the carbonyl group is reversible in the case of ketones and is therefore usually not a problem. Other reactions, *e.g.* self-condensation aldol processes and subsequent dehydration however, can occur, and steps sometimes need to be taken to prevent such processes. The use of so-called 'non-nucleophilic' bases avoids many potential chemoselectivity problems. Most non-nucleophilic bases have the nucleophilic centre surrounded by sterically very demanding substituents. Tertiary amines (*e.g.* Hünig's base  $i\text{-Pr}_2\text{NEt}$ ) and secondary lithium amides (*e.g.* LDA) are important examples of non-nucleophilic bases.



## Complete Enolisation

Condition:

Important 'strong' bases for complete enolisation of ketones:

lithium diisopropylamide	lithium tetramethylpiperidide	lithium hexamethyldisilazide
LDA	LTMP	LHMDS
$pK_a(\text{Pr}_2\text{NH}) \sim 36$ (DMSO)	$pK_a(\text{TMP}) \sim 37$ (DMSO)	$pK_a(\text{TMS}_2\text{NH}) \sim 30$ (DMSO)
		potassium and sodium analogues also used

For LDA the  $pK_a$  difference between acetone (26.5 when measured in DMSO) and diisopropylamine (36 in DMSO) is  $\sim 10$  (*i.e.* very large). Consequently treatment of a ketone with 1 equivalent of LDA causes essentially complete deprotonation to form the corresponding lithium enolate.

Deprotonation with lithium amides proceeds rapidly at low temperature in polar, aprotic solvents. The typical conditions for preparing the lithium enolate of a ketone are 1 eq LDA, THF,  $-78^\circ\text{C}$ . Significantly, since all of the ketone is effectively converted into the corresponding enolate, self-condensation aldol reactions can be avoided.

## Summary

Ketones (and related molecules) exist in two so-called tautomeric forms, a keto form, with which you are already very familiar, and an enol form. The position of the equilibrium between these two tautomers depends on the molecule, but there is often a close correlation with the  $pK_a$  of the  $\alpha$ -C-H group: the lower the  $pK_a$ , the further is the equilibrium shifted over to the enol form.

The presence of the enol tautomer allows for the incorporation of deuterium into the  $\alpha$ -sites of carbonyl groups. Deuterium exchange is catalysed by acid or base. Under basic catalysis, the deprotonated form of the enol, namely the enolate, behaves as the nucleophilic intermediate.

Enolates are very important carbon nucleophiles; we therefore need very efficient methods for preparing them. Appropriate choice of base is particularly important, as this will determine the extent of deprotonation and therefore the position of the acid-base equilibrium.

If partial enolisation is desired it is best to select a base,  $B^-$ , in which the conjugate acid ( $B-H$ ) has a  $pK_a$  that is similar to the  $pK_a$  of the  $\alpha$ -C-H. In this way only a small quantity of the nucleophilic enolate will be produced at any one time. For standard ketones, metal alkoxides are suitable bases for this purpose.

More often, complete enolisation is required to avoid self-condensation processes. In this case very strong bases such as lithium amides (*e.g.* LDA) are ideal. The large difference in the  $pK_a$  value of  $R_2N-H$  and the  $\alpha$ -C-H in a carbonyl compound ensures that deprotonation is essentially complete and effectively irreversible.