Mechanism of Elimination from a Tightly Hydrogen-bonded Carbanion

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The base-promoted 1,2-elimination reaction of (**1**; R = OAc) with 1,4-diazabicyclo[2.2.2]octane in methanol is concluded to have a reverse stepwise preassociation mechanism.

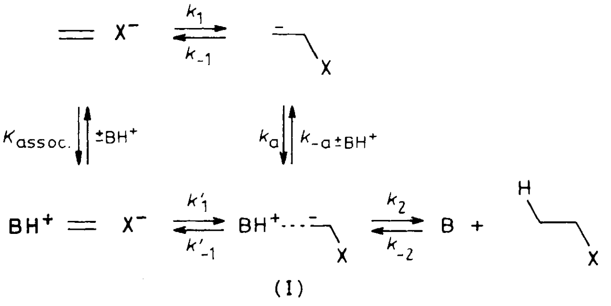
Stepwise base-promoted elimination reactions represent addition reactions in the reverse direction (Scheme 1).[1] A preassociation mechanism prevails when $k'_{-1} > k_{-a}$ and a liberated intermediate mechanism when $k_{-a} > k'_{-1}$.

Recently it was concluded that the (tightly) hydrogen-bonded intermediate (I) formed by a reversible or irreversible proton abstraction from the substrate in methanol[2] or in aqueous media[3] can be considerably stabilized by hydrogen bonding. The conjugate acid of negatively as well as uncharged bases can give rise to this stabilization, which is strongest for weak bases. Therefore the k_{-a} step in Scheme 1 does not represent only diffusional separation of the protonated base and the carbanion and usually has a significant energy barrier.

It has not previously been clear whether the expulsion of a poor leaving group such as acetoxy occurs by a one-step process (k'_{-1}) or if the hydrogen bond to the carbanion is broken first (k_{-a}) and a solvent-equilibrated carbanion is formed which in a subsequent step expels the leaving group X (k_{-1}). It is now reported that the expulsion of the departing acetoxy group occurs directly from the tightly hydrogen-bonded carbanion.

The system which has been studied is [1,3-$^2H_2$]-1-(2-R-isopropyl)indene (**1**), where R = OAc or OMe, in methanol with 1,4-diazabicyclo[2.2.2]octane (DABCO) in the presence of the conjugate acid (DABCOH$^+$, pK_a *ca.* 9.2[2]). The reaction of (**1**; R = OAc) (Scheme 2) gives competing 1,2-elimination and 1,3-proton transfer while (**1**; R = OMe) with this relatively weak base gives exclusively 1,3-proton transfer (k_{13} and $k_{23} = 0$). However, with methoxide or other bases of similar strength elimination accompanies the rearrangement of (**1**; R = OMe).[4]

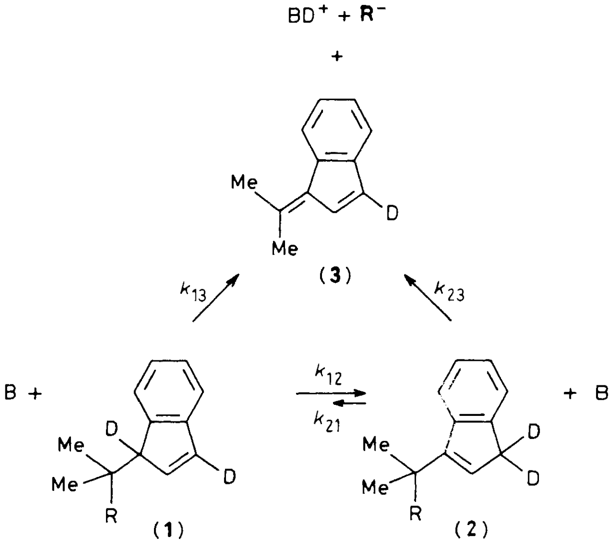
We have found that the 1,2-elimination and the 1,3-proton transfer are coupled *via* a common tightly hydrogen-bonded carbanion intermediate; in fact there are indications of two nonequilibrated tightly hydrogen-bonded intermediates in these reactions as shown in Scheme 3. Linear free energy relationships and the observation of greatly enlarged rearrangement isotope effects coupled with attenuated elimination isotope effects for the two competing reactions constitute strong evidence that the reactions are connected *via* tightly hydrogen-bonded carbanion intermediates.[2—5] It has also been concluded that there is a significant barrier towards rupture of the hydrogen bond for weak or moderately strong bases,[2,3] *i.e.*, the dissociation to a solvent-equilibrated carbanion is slower than the reprotonation of the carbanion to give the starting material or the rearrangement product. However, it has not previously been clear whether the hydrogen-bonded intermediate, formed by proton abstraction from (**1**; R = OAc) provides the elimination product directly *via* a one-step route (k'_{-1} in Scheme 1) or if a 'free' carbanion is involved (k_{-a}).



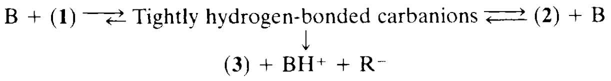
Scheme 1

The reactivity of (**1**; R = OAc) and (**1**; R = OMe) are very similar in methanol with stronger tertiary amines, *e.g.* triethylamine, $(k_{12}^{\mathrm{OAc}} + k_{13}^{\mathrm{OAc}})/k_{12}^{\mathrm{OMe}} = 2.5$,[4] and with methoxide ion, $k_{13}^{\mathrm{OAc}}/k_{12}^{\mathrm{OMe}} =$ *ca.* 1.3, since the proton is abstracted irreversibly in the rate-limiting step. The weaker base DABCO gives some internal return as shown by the deuterium isotope effect on the ionization of (**1**; R = OAc), $(k_{12}^{\mathrm{OAc}} + k_{13}^{\mathrm{OAc}})^{\mathrm{H}}/(k_{12}^{\mathrm{OAc}} + k_{13}^{\mathrm{OAc}})^{\mathrm{D}} = 5.1 \pm 0.2$,[3] and (**1**; R = OMe), $(k_{12}^{\mathrm{OMe}})^{\mathrm{H}}/(k_{12}^{\mathrm{OMe}})^{\mathrm{D}} = 5.6 \pm 0.4$ (the latter substrate yields the rearrangement product exclusively with tertiary amines). These effects are smaller than those measured with triethylamine (7.3 ± 0.6 and 7.7 ± 0.6, respectively, 30 °C).[4] The reactivity of (**1**; R = OAc) relative to (**1**; R = OMe) with DABCO is $(k_{12}^{\mathrm{OAc}} + k_{13}^{\mathrm{OAc}})/k_{12}^{\mathrm{OMe}} = 2.3$.†

Let us assume that the acetoxy leaving group is expelled from the 'free' carbanion (k_{-1} in Scheme 1). What will happen if we exchange the OAc group with OMe? Reasonably, a large



Scheme 2



$$\mathrm{B} + (\mathbf{1}) \rightleftharpoons \text{Tightly hydrogen-bonded carbanions} \rightleftharpoons (\mathbf{2}) + \mathrm{B}$$
$$\downarrow$$
$$(\mathbf{3}) + \mathrm{BH}^+ + \mathrm{R}^-$$

Scheme 3

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† The acetoxy group does not compete for proton removal as suggested by a referee. Thermal elimination occurs only at higher temperatures.[6]

Table 1. Analysis of protium incorporation accompanying the reaction of (**1**; R = OMe) in methanol.[a]

Base	[Base]/mM	[Base H$^+$]/mM	H content in (**2**; R = OMe)/atom %[b]
DABCO	100	5	0 ± 5
DABCO	100	500	3 ± 5

[a] Temp. 20.00 ± 0.03 °C; [(**1**; R = OMe)] 12 mM. [b] After about 50% reaction; determined by ^{1}H n.m.r. spectroscopy.

fraction of reaction will still proceed *via* the free carbanion. However, since the carbanion does not expel the methoxy group to yield the elimination product (**3**) under these conditions, it will be reprotonated by the solvent and other acids present to provide the rearrangement product (**2**) with protium incorporated. The amount of incorporation is expected to be *ca.* 43% since k_{13}/k_{12} for (**1**; R = OAc) is *ca.* 43/57. However, reaction of the deuteriated ether (**1**; R = OMe) with DABCO/DABCOH$^+$ results in an insignificant amount of incorporation of H in (**2**; R = OMe) (Table 1). Therefore, the results clearly indicate that the expulsion of the acetoxy group occurs from the tightly hydrogen-bonded intermediate and not from the solvent-equilibrated carbanion. Thus it is concluded that the base-promoted 1,2-elimination reaction of (**1**; R = OAc) with DABCO proceeds by a reverse stepwise preassociation mechanism.

The present results seem to be the first evidence of the departure of a leaving group directly from a tightly hydrogen-bonded intermediate. The expulsion of 'better' leaving groups from this type of intermediate should, of course, occur even more easily than that of OAc$^-$. Accordingly, several elimination reactions classified as *E*2 reactions may in fact be stepwise.

Received, 22nd August 1983; Com. 1144

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