Letter

Base-Promoted *Syn* and *Anti* 1,4-Elimination Reactions by Reverse Stepwise Preassociation Mechanisms

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Previously, base-promoted 1,2-elimination reactions in the mechanistic borderline region of E2 and E1cB have been found to involve intermediate ion pairs of hydrogen-bonded carbanions that expel the leaving group faster than they dissociate, i.e. they react by reverse stepwise preassociation mechanisms.[1-3] In this letter we present results showing that base-promoted 1,4-elimination reactions also make use of reverse stepwise preassociation mechanisms.

The 1,4-elimination from the two diastereoisomers of (1-$^2H_1$)-3-(1-chloroethyl)indene [**1** and **2**] promoted by 1,4-diazabicyclo[2.2.2]octane (DABCO) in methanol has a preferred *syn* stereochemistry.[4] In the present investigation, we have found that the stereospecificity is solvent- and base-dependent, and this provides the basis for our conclusions.

The reactions of **1** and **2** with DABCO, 1,8-diazabicyclo[5.4.0]-undec-7-ene (DBU) and methoxide were studied under the conditions given in Table 1. The formation of (3-^{2}H)-(*E*)-1-ethylideneindene [(^{2}H)-**3**] from **1** is an *anti* elimination of ^{1}HCl, while the same product is formed through a *syn* elimination of ^{1}HCl from **2**. Different rates of *syn* and *anti* pathways will therefore result in different product compositions from the two diastereoisomers. The rates of 1,4-elimination of **1** and **2** to give **3** and **4**, respectively, were determined by means of capillary GLC. The protium content in the 3-position of the products was determined by ^{1}H NMR spectrometry. From these results, all eight rate constants in Scheme 1 were calculated and the rate constant ratios k_{syn}/k_{anti} for the formation of (^{2}H)-**3** and (^{2}H)-**4**, respectively, were obtained. These ratios are collected in Table 1.

In contrast to the stereospecificity found in the reactions of **1** and **2** with DABCO in methanol, the methoxide-promoted reactions in methanol were, within experimental error, non-stereospecific. Furthermore, the reactions initiated by DBU in the same solvent were also non-stereospecific. However, in a non-polar solvent such as chloroform, the reactions with DBU show stereospecificity and proceeed with preference for *syn* elimination.

Table 1. Rate constant ratios k^H_{syn}/k^H_{anti} for base-promoted 1,4-elimination of ^{1}HCl from **1** and **2** calculated from observed rate constants and product compositions obtained at 30.00 ± 0.03 °C. The reaction solutions were 0.0001 M and 0.012 M in substrate in the GLC and NMR experiments, respectively.

Base	Solvent	[Base]/mol dm^{-3}		k^H_{syn}/k^H_{anti}	
		GLC	NMR	to (^{2}H)-**3**	to (^{2}H)-**4**
DABCO[a]	MeOH	0.030	0.10	3.7(3)	3.2(5)
DABCO[a]	DMSO	0.0014	0.20	2.1(3)	1.6(2)
DBU[a,b]	MeOH	0.010	0.065	1.2(2)	1.1(2)
DBU	$CDCl_3$	0.010	0.180	3.5(3)	2.4(3)
MeO^-K^+	MeOH	0.0027	0.068	1.1(2)	0.9(1)

[a]$BaseH^+$ (5 mole% of base) added for buffering. [b]The second-order rate constant and product composition is not affected by using half the concentration of $BaseH^+$.

We have proposed stepwise mechanisms for these 1,4-elimination reactions on the basis of primary deuterium isotope effects.[4] The isotope effects calculated from the rates of elimination of 3-(1-chloroethyl)indene (**5**) and (1,1-$^2H_2$)-3-(1-chloroethyl)indene (**6**) with different bases were found to vary considerably with the base strength. Furthermore, absence of ^{2}H/^{1}H exchange of the substrate together with the isotope effects indicate partially reversible formation of ion pairs from the substrate and base.

There is a possibility that the reactions take place by competing E1 and E1cB mechanisms. Slow formation of 3-(2-methoxyethyl)indene and 1-ethylidene-2-methoxyindan accompanies the elimination reactions in methanol.

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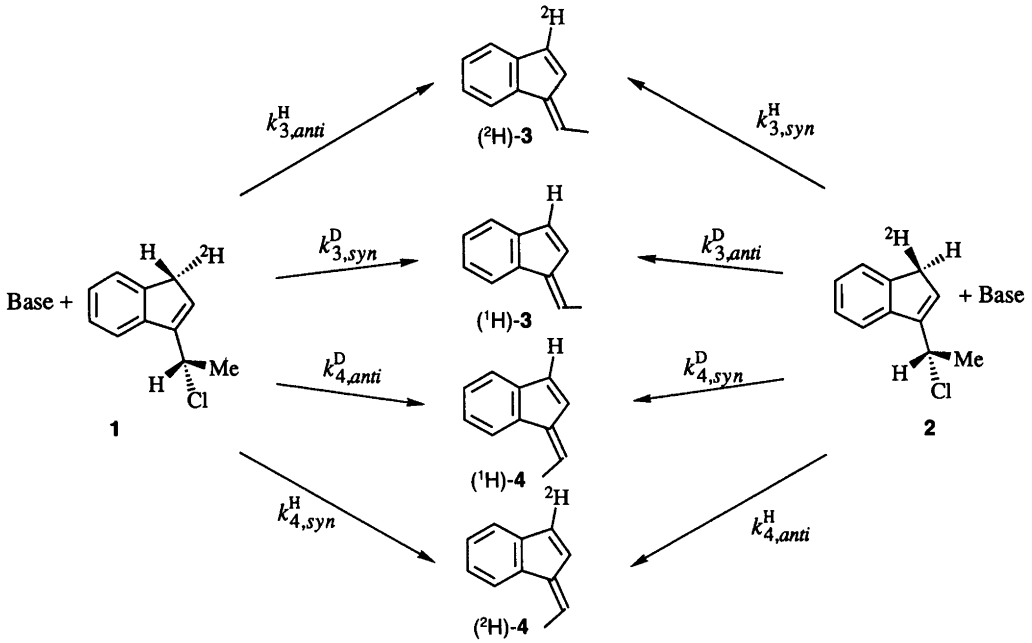

Scheme 1.

Solvolysis is most likely to take place via a carbocation ion pair.[5] In the presence of base, deprotonation of the carbocation to yield **3** or **4** may compete with the reaction with methanol to yield the methyl ethers. The rate of solvolysis is independent of DABCO concentration, as no decrease in the rate of formation of methyl ethers with increasing DABCO concentration was observed. This demonstrates that all DABCO-promoted elimination takes place via an E1cB mechanism. It also rules out the possibility that the 1,4-eliminations are the result of an initial 1,2-elimination to yield a vinylindene through an E1 route followed by a rearrangement to **3** or **4**.

Competing E2 and E1cB mechanisms is another possibility. However, the fact that the primary deuterium isotope effects change significantly with a moderate change in pK_a of the base although there is little change in stereoselectivity from **5** when different bases are used does not support this. Furthermore, using a given base while varying the solvent does not cause any significant change in the product composition from **5**, whereas large changes in stereospecificity in the reactions of **1** and **2** are observed.

The non-stereospecificity observed with methoxide and DBU in methanol indicates that a solvent-equilibrated carbanion is formed in these reactions and that rotation of the chloroethyl group is fast compared to elimination of Cl^-. Rehydronation of the free carbanion must be slow compared to elimination, as only negligible amounts of protium are incorporated into the products from **6** with all bases. When the 1,4-elimination reactions are promoted by DBU or methoxide in methanol, the mechanism is therefore E1cB.

In contrast, the stereospecificity found in the DABCO-promoted 1,4-elimination reactions is an indication that the elimination of Cl^- occurs directly from the carbanion–$DABCOH^+$ ion pair, i.e. that a reverse stepwise preassociation mechanism is operating. This also seems to be the case when a more polar solvent such as DMSO is used instead of methanol, although the preference for *syn* elimination is less pronounced.

It has been shown previously in stepwise base-promoted 1,2-elimination reactions that the stabilization of the carbanion by hydrogen bonding to the protonated base is larger for weaker bases.[6–8] When DABCO is used in the 1,4-elimination of **5**, the energy barrier for dissociation of the intermediate ion pair is therefore expected to be larger than for elimination by methoxide or DBU. Attractive electrostatic forces are also expected to contribute more to the stabilization of the intermediate ion pair between protonated DABCO and the carbanion than when the conjugate acid of the base is a neutral species such as methanol or an amidinium ion with a π-delocalized charge.

Little is known about the stereochemistry and mechanisms of 1,4-elimination reactions.[9–14] The presumably stepwise 1,4-eliminations from *cis*- and *trans*-9,10-di-X-dihydroanthracene derivatives (X = halogen, OH, OAc, OCOPh) by sodium hydroxide in ethanol–dioxane mixtures were found by Cristol *et al.* to be *syn* stereospecific.[10] Another base-promoted 1,4-elimination yielding predominantly *syn* stereochemistry is the potassium *t*-butoxide promoted 1,4-elimination from a 2,6-dichlorobenzoate derivative of cyclohexene in the presence of a crown ether in xylene studied by Hill and Bock.[12] None of these systems allow rotation

around the C(1)-C(2) bond however. A stereoselective 1,4-elimination was reported by Breitholle and Stammer.[14] They found that one of the steps in the conversion of *N*-cinnamoylamino acids to unsaturated azalactones through treatment with a pyridine perbromide/acetic anhydride/pyridine mixture was a 1,4-dehydrobromination. The elimination was shown not to be stereospecific by examination of the products obtained from the two diastereoisomers of an *N*-mandeloylphenylglycine derivative.

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4. Ölwegård, M. and Ahlberg, P. *J. Chem. Soc., Chem. Commun.* (1989) 1279. *Corrigendum*: In this communication, *syn* and *anti* should be exchanged for *anti* and *syn*, respectively, throughout the text, including the title and Table 1, except when reference is made to previous work (last three paragraphs). Furthermore, (**1a**) and (**1b**) in Scheme 1 should be exchanged for (**1b**) and (**1a**), respectively.
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