The stereochemistry of solvent-promoted E1cB/E2 reactions of α-indenyl substituted ethyl halides

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The solvent-promoted elimination reactions of *threo*-1-(1-X-ethyl)indene 1-X (X = Cl, Br, I) and the corresponding *erythro* isomer 2-Br in 25 vol% acetonitrile in water at 55 °C, which are concluded to be of E1cB and E2 types, exhibit leaving-group dependent, non-stereospecific and stereospecific 1,2-elimination, respectively.

The classical view of base-promoted concerted E2 elimination reactions, *i.e.* reactions following the $A_{xh}D_HD_N$ mechanism,[1] is that a strong base is required and that the base and the leaving group are in *anti*-periplanar positioning to each other in the transition state.[2] Quite recently, the first example of a solvent-promoted E2 reaction was reported.[3] It was concluded that high acidity of the β-hydrogen is required for the water-promoted E2 reaction, otherwise competing stepwise solvolytic elimination and substitution reactions are predominant.

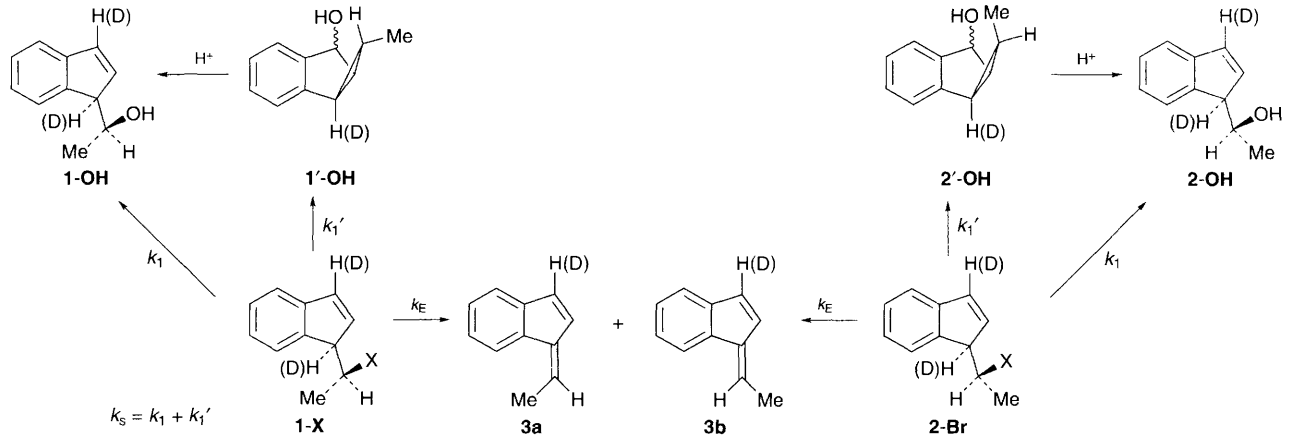
In this present study we used another α-substituted ethyl halide system with an even more acidic β-hydrogen (Scheme 1). Thus, solvent-promoted elimination of E2 and/or E1cB type (mechanisms $A_{xh}D_HD_N$ and $A_{xh}D_H{\ddagger}{*}D_N$, respectively) was expected to be even more favoured. This system has the advantage that the stereochemistry of the elimination could be studied.

The following experimental results show that the solvolytic elimination reactions of **1-X** and **2-Br** are of E2 and/or E1cB type. (i) The kinetic deuterium isotope effects on the elimination reactions are large and indicate rate-limiting hydron transfer (Table 1). They are too large to be attributable to elimination from reversibly formed ion-pair intermediates; isotope effects of about three are expected for such a mechanism involving dehydronation of a highly unstable carbocationic intermediate.[4] Moreover, only a low concentration of strong base is required to give elimination exclusively. It is unreasonable that a short-lived ion pair would show such a large selectivity.

(ii) Another independent, strong indication for a one-step mechanism (E2) or an irreversible carbanion mechanism ($E1cB_I$) is provided by the Brønsted parameters measured for **1-I**, **1-Br** and **2-Br** of β = 0.38, 0.37 and 0.47, respectively, measured with substituted acetate anions. The catalytic constants for water as base fall below the Brønsted lines by factors of 11, 15 and 4, respectively. Very small β values are expected for a mechanism in which a reversibly formed, unstable carbocationic intermediate is dehydronated in the rate-limiting step.[4] Accordingly, these substantial β values exclude reactions through ion pairs, either coupled with the substitution reactions or as separate reactions.

(iii) The high stereospecificity of the reaction of **2-Br** (Table 2) supports an E2 mechanism with an *anti*-periplanar positioning of the hydron-abstracting water molecule and the leaving group.

(iv) The faster elimination with the iodide **1-I** than with the bromide **1-Br** is not consistent with an ion-pair mechanism in which the leaving group acts as the hydron-abstracting base.[4b]



Scheme 1

Table 1 Rate constants and kinetic deuterium isotope effects for the reactions of **1-X** and **2-Br** in 25 vol% acetonitrile in water[a]

Substrate	Base	10^6k_{obs}[b]	10^6k_E	10^6k_S	k_{obs}^H/k_{obs}^D	k_E^H/k_E^D	k_S^H/k_S^D
1-I	solvent[c]	250[e]	50.4	200	1.2	5.1	1.02
1-I	HFIP[-d]	624 × 10^3[f]	624 × 10^3[f]	—	6.8	6.8	—
1-Br	solvent[c]	195[e]	14.2	181	1.07	5.0	1.01
1-Br	HFIP[-d]	230 × 10^3[f]	230 × 10^3[f]	—	6.5	6.5	—
2-Br	solvent[c]	75.8[e]	50.5	25.3	2.0	4.6	0.94
2-Br	HFIP[-d]	1210 × 10^3[f]	1210 × 10^3[f]	—	6.3	6.3	—

[a] Substrate concentration 0.1 mmol dm^{-3}. [b] $k_{obs} = k_E + k_S$. [c] 55 °C; pH 2.8. [d] 25 °C; $(CF_3)_2CHO^-$. [e] In s^{-1}. [f] In $dm^3\ mol^{-1}\ s^{-1}$.

Solvolytic substitution competes with the elimination (Scheme 1). The relatively large rate constants of the solvolytic substitution reactions are attributable to homoallylic participation. Solvolysis is more dominant with the *threo* isomer. Thus, substitution is seven times faster with **1-Br** than with **2-Br**. This is reasonable since faster carbocation formation is expected from the *threo* isomer owing to generation of a more stable homoallylic carbocation. The substitution product **1′-OH** is isomerized under slightly acidic conditions to give the thermodynamically more stable alcohol **1-OH**. Owing to the homoallylic participation, the overall substitution reaction shows a very high configuration retention.

Does any elimination product come from the carbocation intermediate? Possibly, it yields a trace of alkene but, as discussed above, the large elimination isotope effects reported are not consistent with a major fraction of alkene formed by a carbocation route. Accordingly, solvolysis of the 3,5-dinitrobenzoate ester of **1′-OH** in carbonate-buffered aqueous acetone at 80 °C yields only **1′-OH**.[5]

The stereochemical studies (Table 2) with **2-Br** show high stereospecificity with solvent and other bases. The stereochemical results of the base-promoted reactions with the other diastereoisomer **1-X** are dependent on several factors. *Anti* elimination is favoured by: (i) high efficiency of the leaving group; (ii) strong base; (iii) a negatively charged base; acetate anion yields more *anti* elimination than hexamethylenetetramine (HMTA) despite similar pK_a values (4.8 and 5.1, respectively); (iv) high polarity of the solvent (with HMTA as base). The base-promoted reactions of the acetates **1-OAc** and **2-OAc** have been found to be partially diastereospecific.[6]

How to distinguish between $E1cB_I$ and E2 reaction mechanisms? This is difficult since theoretical calculations show that a partial bond breaking to the putative leaving group L occurs in the transition state of hydron-transfer reactions.[7] A periplanar positioning between the base and L is preferred. This assistance to hydron removal by hyperconjugative interaction from the electron-withdrawing group L implies some resemblance between E2 and E1cB transition-state structures.[6–8]

It has been possible to assign the E1cB mechanism to the base-promoted 1,2-elimination reaction of the closely related tertiary substrate 1-(2-chloro-2-propyl)indene by demonstrating that it has an intermediate in common with the base-catalysed 1,3-hydron transfer reaction using tertiary amines in methanol as catalysts (Scheme 2).[8e] In the same way, a common intermediate has been demonstrated for the secondary chloride **1-Cl**.[9] The intermediate was postulated to be the carbanion hydrogen-bonded to the hydronated base, as indicated by the dashed line in Scheme 2.

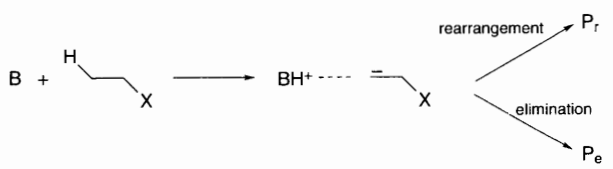
One piece of evidence for a common carbanion intermediate is the fact that the total reaction rate increases substantially when passing from a 'poor' putative leaving group to chloride, but the rearrangement rate decreases drastically when the leaving group is changed, *e.g.* from OMe to Cl.[8b] However, the reaction of the chloride with strong base does not show any rearrangement product. The existence of a barrier for expulsion of Cl^- from the hydrogen-bonded hydronated amine–carbanion intermediate does not necessarily imply that there is a barrier for expulsion of Cl^- from the corresponding complex with methanol (which is the acid formed by the hydron-abstraction by methoxide ion). Accordingly, it is possible that the reaction has an E2 mechanism that is *enforced* by the disappearance of a barrier for expulsion of the chloride leaving group.

It is difficult to make a clear-cut assignment of mechanism to the elimination reactions. The mechanisms may either be of $E1cB_I$ or E2 type. However, we propose that all the observed *anti* elimination is of one-step E2 type owing to the absence of a barrier to departure of the leaving group in the putative intermediate. The E2 transition state is significantly stabilized by partial bond breaking to the leaving group in the transition state. The *syn* elimination is proposed to occur in a stepwise fashion *via* a hydrogen-bonded intermediate. The *syn* mode with **1-X** is favoured by the absence of steric interaction of the methyl group with the adjacent phenyl hydrogen. It may also be favoured by a through-space interaction between the leaving group and the hydronated base.[6]

Table 2 Stereochemistry of the elimination reactions of **1-X** and **2-Br** in 25 vol% acetonitrile in water

Substrate[a]	Base	T/°C	Base conc./ mol dm^{-3}	*Anti*-elimination (%)
1-I	water	55	—	80
1-I	HMTA[b,c]	25	0.55	94
1-I	HMTA[b,d]	25	0.29	85
1-I	NaOAc[e]	25	0.75	95
1-I	NaOH	25	0.075	96
1-Br	water	55	—	85
1-Br	HMTA[b,c]	25	0.55	83
1-Br	HMTA[b,d]	25	0.29	37
1-Br	NaOAc[e]	55	0.75	95
1-Br	NaOH	25	0.075	94
2-Br	water	55	—	99
2-Br	HMTA[b,c]	25	0.55	99
2-Br	HMTA[b,d]	25	0.29	97
2-Br	NaOH	25	0.075	99
1-Cl	HMTA[b,c]	25	0.55	29
1-Cl	HMTA[b,d,f]	25	0.29	9

[a] Substrate concentration 0.1 mmol dm^{-3}. [b] Hexamethylenetetramine. [c] Buffer ratio [base]/[Hbase$^+$] = 5.5. [d] In methanol, buffer ratio [base]/Hbase$^+$] = 7.6. [e] Buffer ratio [AcO^-]/[HOAc] = 100. [f] The same result has been reported previously at 30 °C.[9]



Scheme 2

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