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Ion-Pair Intermediates and Extreme Deuterium Isotope Effects in Partially Diastereospecific Base-Promoted Elimination Competing with Base-Catalyzed 1,3-Proton Transfer

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Abstract: Reaction of *threo-* or *erythro-*1-(1-acetoxyethyl)indene (**1**-*h* and **2**-*h*) with quinuclidine (Q) or sodium methoxide (NaOMe) in methanol results in base-promoted 1,2 elimination to give a mixture of (*E*)- and (*Z*)-1-ethylidenindene (**4a**-*h* and **4b**-*h*). In the reactions with Q, base-catalyzed 1,3-proton transfer producing 3-(1-acetoxyethyl)indene (**3**-*h*) competes with the eliminations. The latter compound undergoes base-promoted 1,4 elimination also yielding a mixture of **4a**-*h* and **4b**-*h*. The corresponding 1,3-dideuterated compounds **1**-*d* and **2**-*d* and the 1,1-dideuterated compound **3**-*d* yield, within experimental error, the same ratio of the elimination products (*E*)- and (*Z*)-[3-^{2}H]-1-ethylidenindene (**4a**-*d* and **4b**-*d*) as the protium analogues. With NaOMe, the kinetic isotope effects are $k^H{}_{14}/k^D{}_{14} = 6.6 + 1.8$ or -1.4, $k^H{}_{24}/k^D{}_{24} = 6.9 \pm 0.3$, and $k^H{}_{34}/k^D{}_{34} = 7.5 \pm 1.1$, respectively. The isotope effects measured with Q are $(k^H{}_{13} + k^H{}_{14})/(k^D{}_{13} + k^D{}_{14}) = 7.1 \pm 0.3$ and $(k^H{}_{23} + k^H{}_{24})/(k^D{}_{23} + k^D{}_{24}) = 7.3 + 1.6$ or -1.2, respectively. These deuterium isotope effects are composed of unusually large base-catalyzed 1,3-proton transfer isotope effects $k^H{}_{13}/k^D{}_{13} = 39 \pm 7$ and $k^H{}_{23}/k^D{}_{23} = 30 + 22$ or -11. They are large owing to competition between the 1,2 elimination and 1,3-proton transfer from a common intermediate. The 1,2-elimination isotope effects, on the other hand, have been attenuated by the competition: $k^H{}_{14}/k^D{}_{14} = 3.9 \pm 0.3$ and $k^H{}_{24}/k^D{}_{24} = 4.4 + 1.2$ or -1.0. Since significant incorporation of protium in **3**-*d* was not observed when starting from **1**-*d*, i.e., the 1,3-proton transfer is highly intramolecular, it is inferred that the 1,2 eliminations and the rearrangements are coupled and that they have at least one irreversibly formed ion pair in common, i.e., the 1,2 eliminations take place with $(E1cB)_{ip,I}$ mechanisms. The isotope effect on the 1,4-elimination reaction of **3** with Q is $k^H{}_{34}/k^D{}_{34} = 3.5 \pm 0.1$ and no incorporation of protium in **4a**-*d* and **4b**-*d* was observed. This indicates that the reaction proceeds via partially reversibly formed ion pairs. The ion pair and tightly solvated carbanion elimination reactions are partially diastereospecific. **1**-*h* gives 61 ± 2% syn 1,2 elimination with NaOMe and 94 ± 2% syn with Q while **2**-*h* yields 8 ± 2% syn with NaOMe and 14 ± 2% syn with Q. The 1,4 elimination gives a product ratio **4b**-*h*/**4a**-*h* of 23/77 with NaOMe and 14/86 with Q. The elimination mechanisms of the intermediates and the relationship between deuterium isotope effects and elimination reactions in general are discussed.

Carbanion ion pairs and tightly solvated carbanions are well-established intermediates in many reactions involving proton transfer from carbon.[1] However, the possible role of such intermediates in base-promoted elimination reactions has only recently received attention.[2,3] The intermediacy of reversibly formed ion pairs in some elimination reactions has been proposed. The main criterion for this mechanism $[(E1cB)_{ip,R}]$ has been small kinetic deuterium isotope effects.[3]

Recent work has demonstrated the usefulness of the base-catalyzed 1,3-proton transfer reaction as a probe of intermediates in elimination reactions (Scheme I).[4,5] The elimination of HCl from 1-(2-chloro-2-propyl)indene promoted by tertiary amines in methanol was shown to be stepwise and most likely to involve irreversibly formed ion pairs $[(E1cB)_{ip,I}]$.[4b] With sodium methoxide in methanol the elimination is of the $(E1cB)_I$ type.[4b] The chloro substituent (=leaving group) was found to assist the rate-determining proton transfer (ionization) considerably. The activation energy is lowered by 4 kcal mol^{-1} compared to that of the compound having methyl instead of chloro as substituent.[4b]

Scheme I

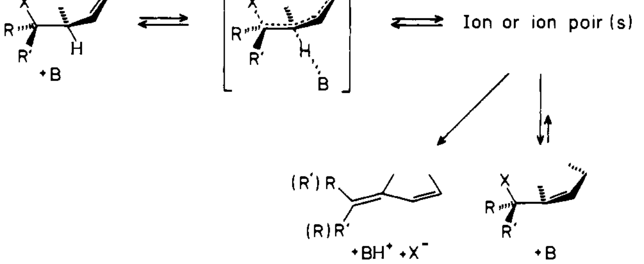

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Table I. Initial Reaction Conditions and Analytical Methods for the Reactions of **1**, **2**, and **3** in Methanol

anal. method	base	[base], mM	[buffer], mM	[substrate], mM	temp, °C
^{1}H NMR	NaOMe	26		26	20.00 ± 0.07
^{1}H NMR	NaOMe	60[a]		30[a]	29.96 ± 0.07[a]
UV	NaOMe	11		0.2	20.00 ± 0.07
^{1}H NMR	Q	5.3	0.15	5.3	30.00 ± 0.03
LC	Q	11	0.50	0.2	30.00 ± 0.03

[a] Experimental conditions for studies of product compositions.

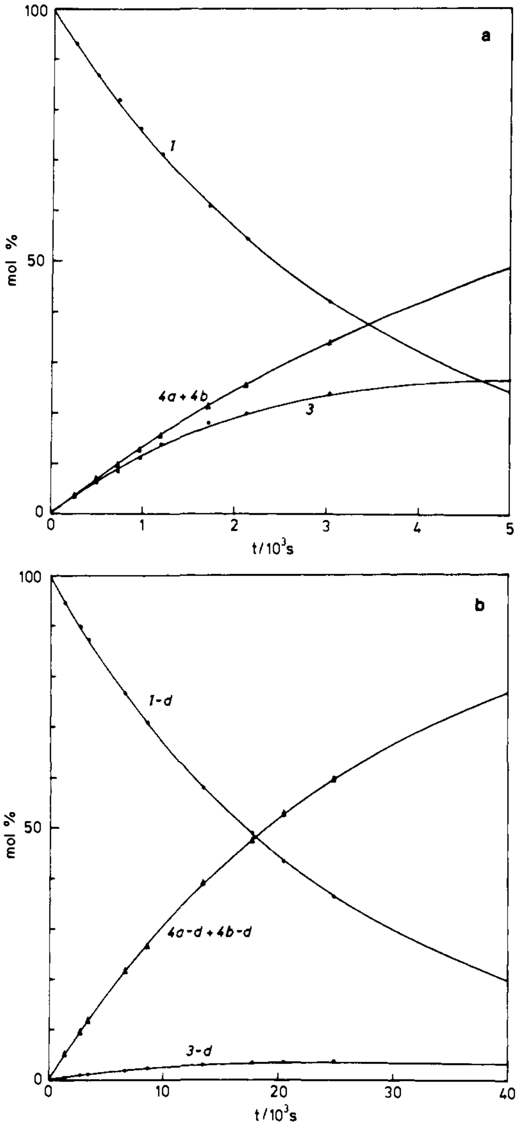
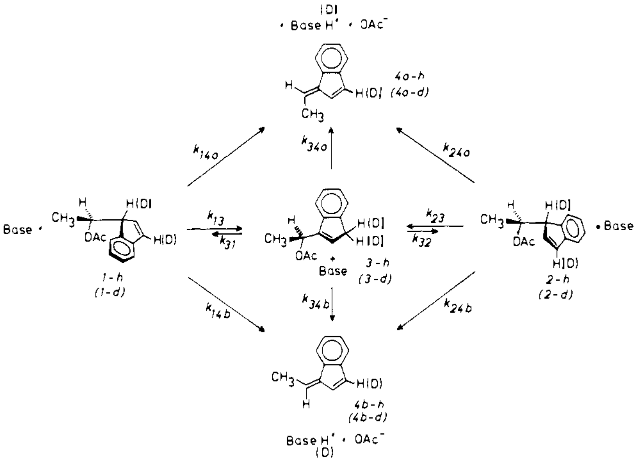


Figure 1. The time dependence of (a) **1**-*h*, **3**-*h*, and **4a**-*h* + **4b**-*h* and (b) **1**-*d*, **3**-*d*, and **4a**-*d* + **4b**-*d* in methanol with quinuclidine at 30.00 ± 0.03 °C. The curves shown are computer simulated and the points are the experimentally measured concentrations.

The above conclusions were based upon free-energy relationships[4b] and on observed unusually large as well as small isotope effects.[5] The quinuclidine-promoted elimination of acetic acid from 1-(2-acetoxy-2-propyl)indene was found to compete with base-catalyzed 1,3-proton transfer and an unusually large deuerium isotope effect (18.1 ± 1.1) was measured for the latter reaction.[5d] This shows that both reactions have at least one common ion-pair intermediate which is irreversibly formed from the substrate [$(\mathrm{E1cB})_{\mathrm{ip,I}}$]. Moreover, experimental support was obtained for the hypothesis of the existence of two ion-pair intermediates in 1,3-proton transfer reactions.

Scheme II



In this paper we report results on the stereochemistry of some base-promoted ion-pair elimination reactions which are partially diastereospecific. Possible mechanistic routes for departure of the leaving group are discussed. Further evidence for the participation of ion pairs in base-promoted elimination reactions is also presented. Isotope effects larger than that mentioned above and closer to the theoretical maximum for competition of this type have been measured. The relationships between deuterium isotope effects and the mechanisms of elimination reactions are discussed. Other unusually large isotope effects reported in the literature are interpreted as a result of competition.

Results

I. Reactions with Quinuclidine (Q). The reaction of *threo*-1-(1-acetoxyethyl)indene (**1**-*h*) or *erythro*-1-(1-acetoxyethyl)indene (**2**-*h*) with quinuclidine (Q) in methanol in the presence of the corresponding aminium acetate buffer,[6] i.e., $\mathrm{QH^+OAc^-}$, gives the products 3-(1-acetoxyethyl)indene (**3**-*h*) and (*E*)-and (*Z*)-1-ethylidenindene (**4a**-*h* and **4b**-*h*) (Scheme II). After long reaction times the only products are **4a**-*h* and **4b**-*h*. The kinetics of the reaction of **1** as well as of **3** were studied by a calibrated sampling-quench-high-performance liquid chromatography procedure (Table I, Figure 1). The kinetics of the reaction of **2** was investigated with a sampling-quench-^{1}H NMR method. The reactions of the corresponding [1,3-^{2}H$_2$]analogous **1**-*d* or **2**-*d* give much less rearrangement. Only small amounts of [1,1-^{2}H$_2$]-3-(1-acetoxyethyl)indene (**3**-*d*) are produced. The dominant products are (*E*)- and (*Z*)-[3-^{2}H]-1-ethylidenindene (**4a**-*d* and **4b**-*d*) (Scheme II and Figure 1b). Significant epimerization of either **1** or **2** does not take place during the reactions.

When starting with **3**-*h* or **3**-*d* the main products are **4a** and **4b**, i.e., only small amounts of **1** and **2** are produced. The concentration of Q decreases slightly during the reactions with **1** and **3**, and at infinite time less than 2% of base has been consumed by the eliminated acetic acid. The base concentration therefore can be considered to be approximately constant

Table II. Rate Constants for the Reactions of **1**, **2**, and **3** in Methanol with NaOMe at 20.00 ± 0.07 °C and Q at 30.00 ± 0.03 °C

base	substrate	$10^3(k_{i3} + k_{i4})$,[a] $M^{-1}\,s^{-1}$	$10^3 k_{i3}$,[a] $M^{-1}\,s^{-1}$	$10^3 k_{i4}$,[a] $M^{-1}\,s^{-1}$	$10^3 k_{34}$, $M^{-1}\,s^{-1}$
NaOMe	**1**-*h*[b]	37 ± 4		37 ± 4[c]	
	1-*d*[b]	5.6 ± 0.7		5.6 ± 0.7[c]	
	2-*h*[d]	230 ± 7		230 ± 7	
	2-*d*[d]	33.4 ± 1.0		33.4 ± 1.0	
	3-*h*[b]				60 ± 4
	3-*d*[b]				8.0 ± 0.6[c]
Q	**1**-*h*	26.6 ± 0.5	13.3 ± 0.6	13.3 ± 0.6	
	1-*d*	3.76 ± 0.11	0.34 + 0.05 or −0.04	3.42 + 0.13 or −0.10	
	2-*h*[b]	58 ± 6	27 ± 4	31 ± 4	
	2-*d*[b]	8.0 ± 0.8	0.9 ± 0.3	7.1 ± 0.8	
	3-*h*				10.6 ± 0.3
	3-*d*				3.04 ± 0.09

[a] i = 1 and 2, respectively. [b] The ^{1}H NMR procedure. [c] Ester cleavage accompanies the elimination of HOAc. [d] The UV procedure.

Table III. Isotope Effects for the Reactions of **1**, **2**, and **3** in Methanol

base	$(k^H_{13} + k^H_{14})/(k^D_{13} + k^D_{14})$	k^H_{13}/k^D_{13}	k^H_{14}/k^D_{14}	$(k^H_{23} + k^H_{24})/(k^D_{23} + k^D_{24})$	k^H_{23}/k^D_{23}	k^H_{24}/k^D_{24}	k^H_{34}/k^D_{34}
NaOMe[a]	6.6 + 1.8 or −1.4		6.6 + 1.8 or −1.4	6.9 ± 0.3		6.9 ± 0.3	7.5 ± 1.1
Q[b]	7.1 ± 0.3	39 ± 7	3.9 ± 0.3	7.3 + 1.6 or −1.2	30 + 22 or −11	4.4 + 1.2 or −1.0	3.5 ± 0.1

[a] At 20.00 ± 0.07 °C. [b] At 30.00 ± 0.03 °C.

during the kinetic runs and near first-order behavior is expected. The methanolic solutions were buffered to exclude methoxide as an active base.[5]

The reactions follow the rate laws

$$d[\mathbf{1}]/dt = -\{(k_{13} + k_{14})[\mathbf{1}] - k_{31}[\mathbf{3}]\}[\text{base}] \quad (1)$$

$$d[\mathbf{2}]/dt = -\{(k_{23} + k_{24})[\mathbf{2}] - k_{32}[\mathbf{3}]\}[\text{base}] \quad (2)$$

$$d[\mathbf{3}]/dt = \{k_{13}[\mathbf{1}] + k_{23}[\mathbf{2}] - (k_{31} + k_{32} + k_{34})[\mathbf{3}]\}[\text{base}] \quad (3)$$

$$d[\mathbf{4}]/dt = \{k_{14}[\mathbf{1}] + k_{24}[\mathbf{2}] + k_{34}[\mathbf{3}]\}[\text{base}] \quad (4)$$

where $k_{14} = k_{14a} + k_{14b}$, $k_{24} = k_{24a} + k_{24b}$, and $k_{34} = k_{34a} + k_{34b}$. Tautomeric equilibrium constants were determined in methanol using pyridine as catalyst at 29.96 ± 0.07 °C: $[\mathbf{3}\text{-}h]_{eq}/[\mathbf{1}\text{-}h]_{eq} = 20 \pm 4$, $[\mathbf{3}\text{-}h]_{eq}/[\mathbf{2}\text{-}h]_{eq} = 25 \pm 4$, and $[\mathbf{1}\text{-}h]_{eq}/[\mathbf{2}\text{-}h]_{eq} = 1.3 \pm 0.2$. Pyridine was used since it is a much better catalyst for the 1,3-proton transfer than a promoter of the elimination. Accordingly, only traces of elimination products were obtained in the present experiments.

The rate constants for the reactions of the deuterated compounds were evaluated using eq 5–7, which were found to be good approximations of eq 1–3 for the experiments starting with **1**-*d*, **2**-*d*, and **3**-*d*, respectively.

$$d[\mathbf{1}\text{-}d]/dt = -(k^D_{13} + k^D_{14})[\mathbf{1}\text{-}d][\text{base}] \quad (5)$$

$$d[\mathbf{2}\text{-}d]/dt = -(k^D_{23} + k^D_{24})[\mathbf{2}\text{-}d][\text{base}] \quad (6)$$

$$d[\mathbf{3}\text{-}d]/dt = -k^D_{34}[\mathbf{3}\text{-}d][\text{base}] \quad (7)$$

However, with the protium compounds the evaluation is more complex since none of the terms of eq 1 and 2 can be neglected (cf. Figure 1). The concentrations of reactants and products of the reactions were therefore computer simulated using the integrated expressions of eq 1–4.[5d] The rate constants are collected in Table II. No significant incorporation of protium in the products was found. Thus **3** formed from **1**-*d* contains 10 + 6 or − 10 atom % H, and **4** formed from **1**-*d* and **3**-*d* has 0 ± 10 atom % H and 1 ± 10 atom % H incorporated, respectively. The deuterium isotope effects for the reactions of **1**, **2**, and **3** are collected in Table III.

Table IV. Product Compositions Obtained with **1**, **2**, and **3** in Methanol at 30 °C

substrate	base	100(**4b**)/(**4a** + **4b**)	1,2 elimination % syn[a]
1-*h*	NaOMe[b]	37.1 ± 2.0	61 ± 2
2-*h*		8.1 ± 2.0	8 ± 2
3-*h*		22.6 ± 2.0	
1-*h*	Q[c]	9.4 ± 2.0	94 ± 2
1-*d*		7.3 ± 2.0	93 ± 2
2-*h*		13.8 ± 2.0	14 ± 2
2-*d*		15.0 ± 2.0	15 ± 2
3-*h*		13.5 ± 2.0	
3-*d*		13.8 ± 2.0	

[a] Corrected for the elimination product obtained via rearranged material. [b] The same stereochemical results were obtained with KOMe.[7] [c] [QHOAc] = 0.15 mM.

II. Reactions with sodium methoxide were studied using ^{1}H NMR and UV procedures (Table I). Mixtures of the olefins **4a** and **4b** are produced but no epimerization of either **1** or **2** or any rearrangement products were detected. A small amount of methoxide-promoted ester cleavage accompanies the slowest reacting substrates, **1**-*h*, **1**-*d*, and **3**-*d*. The rate constants reported in Table II have been corrected for this side reaction.

III. The stereochemistry of the 1,2- and 1,4-elimination reactions was studied using ^{1}H NMR spectrometry (Table I). As shown in Table IV the 1,2 eliminations of **1** and **2** with Q or NaOMe are all partially diastereospecific and have significantly different product compositions. The amounts of syn elimination obtained with **1**-*d*, **2**-*d*, and **3**-*d* were the same within experimental error as with the protium analogues.

Discussion

I. Reactions with Quinuclidine (Q). As shown in Table III, the deuterium isotope effects on the total reaction rates of **1**

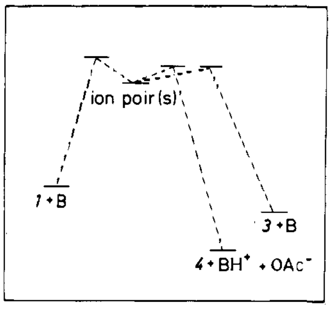
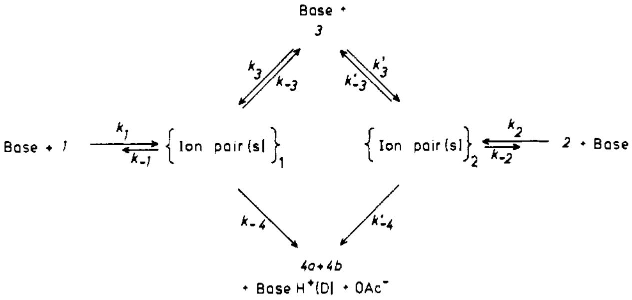


Figure 2. Free-energy diagram for the reaction of **1** with quinuclidine showing the competition between 1,3-proton transfer and elimination via a common ion-pair intermediate(s). A similar diagram can be drawn for **2**.

Scheme III



and **2** are substantial (≈7), as was expected. However, the rearrangement isotope effects are unusually large: $k^{H}_{13}/k^{D}_{13} = 39 \pm 7$ and $k^{H}_{23}/k^{D}_{23} = 30 + 22$ or -11. Two interpretations of these observations are plausible. One is that the rearrangement and elimination are separate reactions and that considerable proton tunneling contributes to the rate of the 1,3-proton transfer reaction. The other alternative is a mechanism involving a common intermediate(s) of the ion-pair type for the rearrangement and elimination (Scheme III, Figure 2). Evidence for the ion-pair mechanism, i.e., leaving-group effects and extreme kinetic deuterium isotope effects, has been reported recently for a closely related system.[4,5] Considerable tunneling was excluded on the ground that a closely related model compound [1-(2-methoxy-2-propyl)indene], which only rearranges under the reaction conditions, was found to have a normal kinetic rearrangement isotope effect (7.1 ± 0.4, 40 °C).[5d]

The consistency of the results with the ion-pair mechanism (Scheme III) is shown in the following. The steady-state approximation applied to the mechanism in Scheme **III**, assuming no interconversion of the diastereomeric ion pairs 1 and 2, yields eq 8-17, which relate the phenomenological and microscopic rate constants and isotope effects.

$$k_{13} = k_1 \frac{k_{-3}}{k_{-1} + k_{-3} + k_{-4}} \tag{8}$$

$$k_{14} = k_1 \frac{k_{-4}}{k_{-1} + k_{-3} + k_{-4}} \tag{9}$$

$$k_{23} = k_2 \frac{k'_{-3}}{k_{-2} + k'_{-3} + k'_{-4}} \tag{10}$$

$$k_{24} = k_2 \frac{k'_{-4}}{k_{-2} + k'_{-3} + k'_{-4}} \tag{11}$$

$$k_{31} = k_3 \frac{k_{-1}}{k_{-1} + k_{-3} + k_{-4}} \tag{12}$$

$$k_{32} = k'_3 \frac{k_{-2}}{k_{-2} + k'_{-3} + k'_{-4}} \tag{13}$$

$$k_{34} = k_3 \frac{k_{-4}}{k_{-1} + k_{-3} + k_{-4}} + k'_3 \frac{k'_{-4}}{k_{-2} + k'_{-3} + k'_{-4}} \tag{14}$$

$$\frac{k^{H}_{13}}{k^{D}_{13}} = \frac{k^{H}_{1}}{k^{D}_{1}} \frac{k^{H}_{-3}}{k^{D}_{-3}} \frac{k^{D}_{-1} + k^{D}_{-3} + k^{D}_{-4}}{k^{H}_{-1} + k^{H}_{-3} + k^{H}_{-4}} \tag{15}$$

$$\frac{k^{H}_{14}}{k^{D}_{14}} = \frac{k^{H}_{1}}{k^{D}_{1}} \frac{k^{H}_{-4}}{k^{D}_{-4}} \frac{k^{D}_{-1} + k^{D}_{-3} + k^{D}_{-4}}{k^{H}_{-1} + k^{H}_{-3} + k^{H}_{-4}} \tag{16}$$

$$\frac{k^{H}_{34}}{k^{D}_{34}} = \frac{k^{H}_{3} \dfrac{k^{H}_{-4}}{k^{H}_{-1} + k^{H}_{-3} + k^{H}_{-4}} + k'^{H}_{3} \dfrac{k'^{H}_{-4}}{k^{H}_{-2} + k'^{H}_{-3} + k'^{H}_{-4}}}{k^{D}_{3} \dfrac{k^{D}_{-4}}{k^{D}_{-1} + k^{D}_{-3} + k^{D}_{-4}} + k'^{D}_{3} \dfrac{k'^{D}_{-4}}{k^{D}_{-2} + k'^{D}_{-3} + k'^{D}_{-4}}}$$

The results in Table II imply that

$$\frac{k^{H}_{34}}{k^{D}_{34}} \approx \frac{k^{H}_{3}}{k^{D}_{3}} \frac{k^{H}_{-4}}{k^{D}_{-4}} \frac{k^{D}_{-1} + k^{D}_{-3} + k^{D}_{-4}}{k^{H}_{-1} + k^{H}_{-3} + k^{H}_{-4}} \tag{17}$$

As discussed before,[5d] large and similar isotope effects are expected on the ionization rate constants k_1, k_2, and k_3, as well as on the collapse rate constants k_{-1}, k_{-2}, k_{-3}, and k'_{-3}, since carbon–hydrogen bonds in substrates having pK_a values close to one another are broken or formed in these processes.[8] Moreover, it is expected that the isotope effects on k_{-4} and k'_{-4} are small because the major bond-breaking and bond-forming processes involving the hydrogen are assumed to be over once the ion pair is formed. The implication of this reasoning is that the ionization isotope effects k^{H}_{1}/k^{D}_{1} and k^{H}_{2}/k^{D}_{2} are amplified, i.e., multiplied by factors larger than unity. The competition between the elimination and the collapse of the ion pairs, which follows the rate-determining ionizations, is thus the cause of the amplified rearrangement isotope effects k^{H}_{13}/k^{D}_{13} and k^{H}_{23}/k^{D}_{23}. On the other hand, the isotope effects on the 1,2- and 1,4-elimination reactions are attenuated by multiplication of the ionization isotope effects by factors less than unity.

The magnitude of the amplifications and attenuations is determined by the relative amount of rearrangement and elimination. A small fraction of elimination ($k_{-3} \gg k_{-4}$) results in a normal rearrangement isotope effect but a large attenuation of the elimination isotope effect. The amplification, on the other hand, is increased by an enhanced fraction of elimination $[k_{-4}/(k_{-1} + k_{-3} + k_{-4})]$. The elimination isotope effect simultaneously increases up to its maximum value which equals the ionization isotope effect.

Reversibility of the ionization process has an attenuating effect on both the rearrangement and elimination isotope effect. From eq 8 and 9 the following relationship between the ionization isotope effect and the observed rate constants is obtained: $k^{H}_{1}/k^{D}_{1} \geq (k^{H}_{13} + k^{H}_{14})/(k^{D}_{13} + k^{D}_{14})$. The equality holds for irreversible ionization. The experimental value 7.1 ± 0.3 for $(k^{H}_{13} + k^{H}_{14})/(k^{D}_{13} + k^{D}_{14})$ is close to that obtained with methoxide ion (Table III) and the ionization isotope effects reported previously.[4b,5]

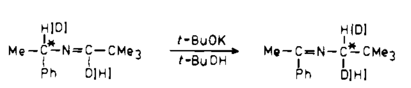
The fraction of elimination increases with increasing strength of the base. Thus methoxide gives exclusively elimination while pyridine gives very little and quinuclidine similar amount of elimination and rearrangement. This is, of course, due to the fact that a weaker base corresponds to a stronger acid, i.e., a better protonating agent.[5d]

The observed rearrangement isotope effect of 39 ± 7 (Table III) is thus about five times larger than the ionization isotope effect. A maximum isotope effect of 49 could result if $k_{-4} \gg k_{-3}$, if the ion pairs are irreversibly formed and by assuming $k^{H}_{1}/k^{D}_{1} = k^{H}_{-3}/k^{D}_{-3} = 7$. However, as discussed above, there are several factors that may cause the 1,3-proton transfer isotope effect to be smaller.

To obtain eq 8–17 it has been assumed that the diastereomeric ion pairs do not interconvert. If they interconvert at all, the rate must be smaller than or comparable to the collapse rates since otherwise consistence with the stereochemical results is not obtained (see section V). Interconversion complicates the equations considerably but the qualitative conclusions of the above discussion are not altered.

Recently indications were presented that the 1,3-proton transfer reaction proceeds via two ion pairs.[5d] The large difference found between the apparent ionization isotope effects (the ratio between the isotope effects of 1,2 elimination and 1,4 elimination was measured as 2.5 + 0.2 or −0.3 instead of ~1 as was expected) for the two isomers 1- and 3-(2-acetoxy-2-propyl)indene with Q in methanol was interpreted using two ion pairs in nonequilibrium. These intermediates are likely to be of the contact ion-pair type with the aminium ion hydrogen bonded to either C-1 or C-3 of the anion. However, the results presented in the present paper do not necessitate the assumption of more than one ion pair for each 1,3-proton transfer since the ratios $(k^{H}{}_{14}/k^{D}{}_{14})/(k^{H}{}_{34}/k^{D}{}_{34})$ and $(k^{H}{}_{24}/k^{D}{}_{24})/(k^{H}{}_{34}/k^{D}{}_{34})$ both are close to unity.[5d]

II. Generalization and Other Examples of Competition Isotope Effects. The requirements for a reaction system to show extreme isotope effects due to competition may be generalized. From Scheme IV and eq 18–20 we conclude that *competition between two processes having different isotope effects and which follow a common rate-determining step sensitive to isotopic substitution results in an amplified observed isotope effect for the overall reaction which proceeds via the competing process with the largest isotope effect. The other overall reaction will show an attenuated isotope effect. If the isotope effect on the rate-determining step is substantial, the amplification may yield an unusually large overall isotope effect. Reversibility, on the other hand, decreases the amplification and the attenuation.*



5-H(D) 6-H(D)

$$\frac{k^{H}{}_{AB}}{k^{D}{}_{AB}} = \frac{k^{H}{}_{A}}{k^{D}{}_{A}} \frac{k^{H}{}_{-B}}{k^{D}{}_{-B}} \frac{k^{D}{}_{-A} + k^{D}{}_{-B} + k^{D}{}_{-C}}{k^{H}{}_{-A} + k^{H}{}_{-B} + k^{H}{}_{-C}} \tag{18}$$

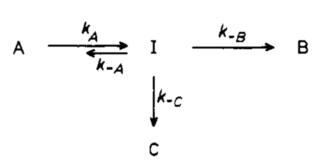
$$\frac{k^{H}{}_{AC}}{k^{D}{}_{AC}} = \frac{k^{H}{}_{A}}{k^{D}{}_{A}} \frac{k^{H}{}_{-C}}{k^{D}{}_{-C}} \frac{k^{D}{}_{-A} + k^{D}{}_{-B} + k^{D}{}_{-C}}{k^{H}{}_{-A} + k^{H}{}_{-B} + k^{H}{}_{-C}} \tag{19}$$

$$\frac{k^{H}{}_{-B}}{k^{D}{}_{-B}} > \frac{k^{H}{}_{-C}}{k^{D}{}_{-C}} \Rightarrow \frac{k^{H}{}_{AB}}{k^{D}{}_{AB}} \geq \frac{k^{H}{}_{A}}{k^{D}{}_{A}} \geq \frac{k^{H}{}_{AC}}{k^{D}{}_{AC}} \tag{20}$$

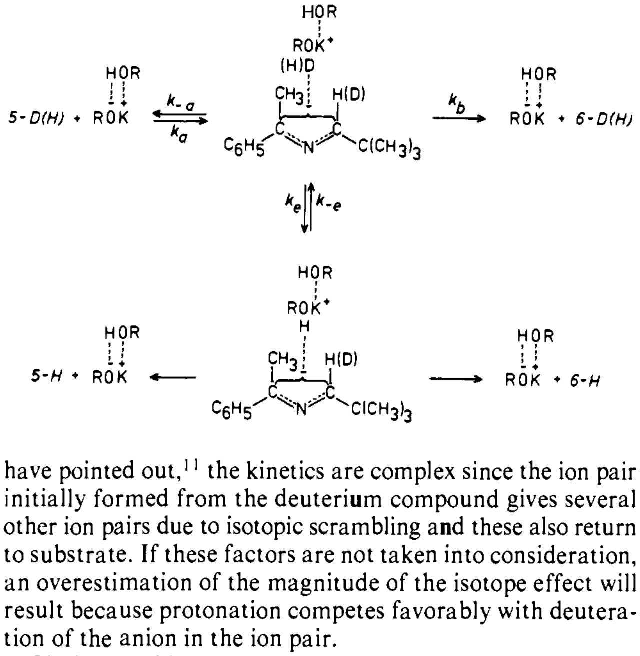
From this generalization it is concluded that processes such as intramolecular rearrangement and intramolecular return to starting material which compete with exchange may show amplified kinetic isotope effects. Cram et al. concluded that **5** ionizes with a kinetic isotope effect of ca. 3 at 75 °C[9] to an ion pair involving the potassium ion. Approximate isotope effects of intramolecular return to starting material and rearrangement were calculated as 34 ± 19 and 27, respectively. The results were discussed using a mechanistic model with azaallylic carbanion ion pairs as intermediates (Scheme V). It was concluded that these isotope effects are composite and represent combinations of large numbers of individual rate constants.[9] However, by the competition model presented above, the results are conveniently understood. The ion-pair collapses (k_{-a} and k_b) having substantial isotope effects compete with exchange (k_e) with a small isotope effect.

Large isotope effects, e.g., $k^H/k^D = 45$, attributed to tunneling, have been found by Caldin and co-workers in proton-transfer reactions of 4-nitrophenylnitromethane with bases containing the imine group.[10] However, as Blanch and Rogne have pointed out,[11] the kinetics are complex since the ion pair initially formed from the deuterium compound gives several other ion pairs due to isotopic scrambling and these also return to substrate. If these factors are not taken into consideration, an overestimation of the magnitude of the isotope effect will result because protonation competes favorably with deuteration of the anion in the ion pair.

Scheme IV



Scheme V



Similar problems have been encountered in the study of bifunctionally catalyzed 1,3-proton transfer by a secondary amidine.[12]

III. Reactions with Sodium Methoxide. The large isotope effects (Table III) and the fact that the substrates do not epimerize, undergo hydrogen exchange, or rearrange indicate irreversible formation of carbanions, i.e., an $(E1cB)_I$ mechanism for the elimination or a one-step mechanism (E2). Strong support for the $(E1cB)_I$ mechanism for the methoxide-promoted reactions is that the closely related substrates 1-(2-acetoxy-2-propyl)indene and 3-(2-acetoxy-2-propyl)indene react stepwise and irreversibly under the same conditions.[4b,5c] The 1,2- and 1,4-elimination rates of these substrates were found to be 17% of the rate for **1** and 27% of that for **3**, respectively.[5c,13] Some of the difference may be accounted for by steric hindrance in the proton abstraction. No evidence for a one-step 1,4-elimination reaction has been reported in the literature. The fact that **3** reacts somewhat faster than **1**, i.e., there is no extra substantial driving force for 1,2 elimination, also suggests that all substrates react stepwise. The reaction of **3** probably proceeds via two intermediates since delocalized carbanions in hydroxylic solvents seem to have only one hydrogen bond per anion.[5d,14]

The nonstereospecificity found in the elimination with methoxide or tertiary amines (Table IV and section V) also supports the above mechanistic conclusions.

IV. The relation between kinetic isotope effect and mechanism for elimination reactions should exhibit a pattern that depends on the lifetime of the "intermediate" (Figure 3).[15] The acidifying effect of the leaving group on ionization[4] is taken into account as shown by the small slope of the E1cB line, i.e., the leaving group acts acidifying by partial bond breaking. The transition state X could be considered as a hydrogen-bonded carbanion and is at the border between E1cB and E2 mechanisms.[15c]

An elimination reaction proceeding via a carbanion of in-

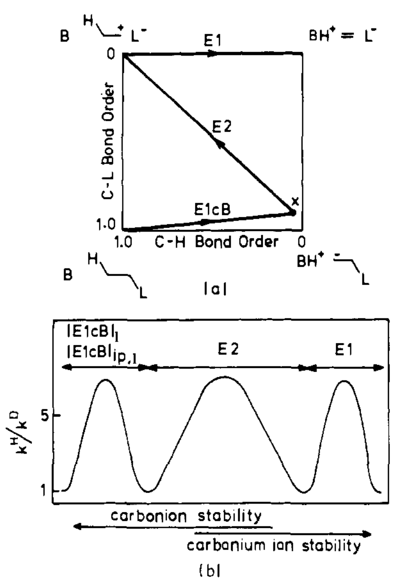


Figure 3. Schematic diagram illustrating (a) the effect of hypothetical thermodynamic stability of the intermediate (in the direction of the arrow) on *the position of the transition state* for a particular leaving group L (the departure of the leaving group is assumed not to be rate determining in the stepwise mechanisms); (b) the dependence of the kinetic deuterium isotope effect on mechanisms and stabilities of intermediates.

termediate stability thus shows a substantial isotope effect. A less stable carbanion results in a low isotope effect since the amount of proton transfer in the transition state is large. A carbanion that is so unstable that it cannot exist forces the reaction to be one-step concerted (transition state X in Figure 3a is reached).[15] The isotope effect of the latter reaction could be small or large depending on the degree of proton transfer in the transition state and the degree of coupling to other processes.[16] The above predicted large isotope effect for a stepwise reaction assumes a "good" leaving group, i.e., the reprotonation of the carbanion is slow compared with the departure of the leaving group $[(\mathrm{E1cB})_\mathrm{I},(\mathrm{E1cB})_{\mathrm{ip,I}}]$. When the reprotonation competes successfully with departure of the leaving group $[(\mathrm{E1cB})_\mathrm{R}$, $(\mathrm{E1cB})_{\mathrm{ip,R}}]$, the observed isotope effect is small but, of course, the ionization isotope effect is still large for carbanions of intermediate stability. Thus we have found that closely related substrates may show elimination isotope effects which could be anywhere from being substantial to about unity depending on the degree of reversibility with which the intermediates are formed.[5]

This view is consistent with the recently discussed relationship between the discrimination isotope effect and carbanion stability in reactions related to the reverse of elimination reactions.[15b] Accordingly, a free carbanion route and a one-step route show a large discrimination isotope effect while the intermediate situation, i.e., a H-bonding mechanism, shows a small one.

V. Stereochemistry and Mechanisms of the Departure of the Leaving Group. Several reaction mechanisms could be envisaged to account for the stereochemical results of Table IV. Previously we have pointed out that an electron-withdrawing group (potential leaving group) should assist proton removal by hyperconjugative interaction (cf. above).[4] This implies a unifying view of one-step (E2) and multistep elimination reactions (Schemes I and III). Accordingly, a periplanar positioning between the base and the leaving group is expected in the proton-abstracting transition state. If the intermediate maintains the periplanar conformation during the subsequent step(s), an even closer similarity between E2 and E1cB reactions results. Naso and co-workers have studied methoxide-promoted eliminations of *erythro*-1-chloro- and *erythro*-1-bromo-1,2-diphenyl-2-*p*-tolylsulfonylethane, which could be $(\mathrm{E1cB})_\mathrm{I}$ reactions of this category.[17]

According to the model, the partially stereospecific elimination producing **4a** and **4b** (Table IV) should proceed via an ionization step in which the base and the leaving group are anti and/or syn to each other. As a result of these reactions one may have a mixture of syn and anti ion pairs or tightly solvated carbanions with hydrogen bonds to C1. These intermediates could isomerize so that C3 becomes hydrogen bonded instead of C1.

The mechanism of the elimination by the ion pairs could be concerted or a first dissociation of the contact ion pairs to solvent-separated or "free" ions, with subsequent departure of the leaving group. The high intramolecularity of the 1,3-proton transfer reaction indicates that, if the ion pairs dissociate to these species, the dominant reaction is not reprotonation but departure of the leaving group.

When using *N,N*-diisopropylethylamine for the elimination reactions the same stereochemical results within experimental error were obtained as with NaOMe.[18] This sterically hindered base is most likely in the anti position during the ionization step. The similarity of the stereochemical outcome suggests that these eliminations make use of a common intermediate which could be a tightly or loosely solvated carbanion which undergoes conformational changes in competition with departure of the leaving group.

The significantly different stereochemical results obtained with Q suggest a through-space interaction between the acetoxy group and the positively charged aminum ion favoring ion pairs of syn conformation.

Experimental Section

General. The ^{1}H NMR analyses were either made with a Varian A-60D or a JEOL FX 100 spectrometer equipped with a 5-mm dual probe (^{1}H, ^{13}C). A Varian Cary 118 spectrophotometer was used in the UV kinetics. The high-performance liquid chromatography (LC) analyses were carried out with a Waters 6000A solvent delivery system and absorbance detector (Model 440) using a Waters μBondapak C18 analytical column (4 × 300 mm). The mobile phase was a solution of 35 wt % ethanol (spectroscopic quality) in water.

All glassware were cleaned with chromic acid and rinsed with water, dilute ammonium hydroxide, and distilled water before drying at 120 °C at least overnight. The kinetic runs were performed at constant temperature in a HETO 01 PT 623 thermostat or in a jacketed UV cell (10 mm, Hellma 160B) thermostated with water via a short insulated tube. The UV-cell holder was thermostated with water from a second thermostat. The temperature was measured with calibrated mercury thermometers with absolute accuracies of ±0.02 and ±0.05 °C. During the runs the temperatures of the baths did not deviate more than 0.01 and 0.02 °C, respectively, from the average value and thus the absolute temperatures (t) were $t \pm 0.03$ and $t \pm 0.07$ °C, respectively.

Materials. Methanol (Fluka for UV spectroscopy) stored over 0.3-nm molecular sieves was used as solvent without further purification. A stock solution of NaOMe was prepared by adding methanol-washed pure-cut pieces of sodium to dry methanol. The concentration was determined by titration of aliquots of this stock solution with 0.1 M HCl. Quinuclidine (Q) was liberated from its hydrochloride (Fluka purum), dried (CaO), and sublimed twice at reduced pressure. GLC and ^{1}H NMR analysis established its high purity. The NaOMe solution and Q were stored in a freezer under dry nitrogen.

The syntheses, purification, and deuterium content of the 1-(1-acetoxyethyl)indenes (**1**-*h* and **2**-*h*), 3-(1-acetoxyethyl)indene (**3**-*h*), and the mixture of (*E*)- and (*Z*)-ethylidenindene (**4a**-*h* and **4b**-*h*) as well as the deuterated compounds **1**-*d*, **2**-*d*, **3**-*d*, and **4a**-*d* plus **4b**-*d* have been reported previously.[6]

Kinetics. LC Procedure. A reaction flask equipped with a tight TFE septum was filled with 5 mL of base solution containing buffer. After thermostating, 10 μL of a substrate solution (0.10 M in methanol) was injected with a syringe. During the run, aliquots (400 μL) were withdrawn with a syringe and rapidly transferred to a small tube containing 18 μL of a quench solution consisting of 15.6 mL of 2 M sulfuric acid diluted to 250 mL with 35 wt % ethanol in water. After the solution was shaken, indicator paper showed the pH to be ca. 6. About 30 μL of this homogeneous, quenched reaction solution was injected onto the analytical LC column. The areas under the three separated peaks of **1**, **3**, and **4a** plus **4b** were measured with a digital integrator (Venture Mk II). The relative extinction coefficients for the compounds together with the measured areas gave the mole percent of each compound in the mixture. The relative extinction coefficients were determined using several standard mixtures of **1**, **3**, **4a**, and **4b** prepared by weighing. A difference in extinction coefficients between **4a** and **4b** was measured. Thus the olefin mixture (one peak) with the ratio **4a**/**4b** = 9.4/90.6 had 2.5% larger relative area than the mixture with the ratio **4a**/**4b** = 13.5/86.5. However, since the ratio **4a**/**4b** during a kinetic run with Q is nearly constant (can be concluded from Table IV), the error caused by using a constant relative extinction coefficient for the mixture of the olefins is very small, and can be neglected when calculating the isotope effects.

Each area determination did not deviate from the mean of the results of three injections by more than 0.3 mol % and usually by less than 0.1 mol %. A datum point in Figure 1 is the average of data from three different injections from the same quench solution. To check the material balance during the kinetic runs, biphenyl was used as an internal standard in a run with **1**-*d*. The observed rate constant, from a plot of ln [(area **1**-*d*)/(area biphenyl)] vs. time, was the same within experimental error as obtained without the standard.

Kinetics. NMR Procedure. The second-order kinetics with NaOMe were carried out in a reaction flask consisting of two compartments. Substrate solution (30 mL) was placed in one of the compartments and base solution (10 mL) in the other one. After thermostating, the reaction was started by inverting the flask. Aliquots (10 mL) were withdrawn with a pipet and rapidly transferred to a 60-mL stopcocked tube containing CCl_4 (0.6 mL), 1 M HCl (30 mL), and ice (10 g).[5d] The mixture was shaken for 1 min and centrifuged. The CCl_4 layer was transferred to an NMR tube. The methyl region of the ^1H NMR spectrum was integrated and the mole percent of each of the components evaluated. The two-point kinetics with Q using the ^1H NMR procedure were carried out as described in the section "Product Analysis . . .".

Kinetics. UV Procedure. The absorbance at an absorption maximum (307 nm) of the products **4a** and **4b** was measured as a function of time using a digital printout. The reactions were started by adding 4 μL of the substrate solution (0.01 M in methanol) to the cell filled with thermostated base solution (1.5 mL). Pseudo-first-order rate constants were evaluated from plots of ln ($A_\infty - A$) vs. time.

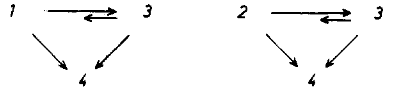
Determination of the Equilibrium Constants. For this purpose a rearrangement catalyst (pyridine) that gave a minor amount of elimination (<3% after 68 days) was used. Mixtures of **1**-*h*, **2**-*h*, and **3**-*h* were prepared with compositions close to the equilibrium composition. The equilibrium in methanol was thus approached from both sides with 1 M pyridine as catalyst. The analyses were carried out by the ^1H NMR procedure.[5d]

Search for D-H Exchange. **3**-*d* (8.7 mM) was reacted with quinuclidine ([Q] = 110 mM, [QH^+OAc^-] = 5.7 mM) for 10 half-lives. In the analyses, which were carried out by the quench-extraction-^1H NMR procedure, the area of the olefinic protons was compared with the areas of the methyl group and the aromatic protons. The ratio of these areas was compared with the same ratio for a reference solution of **4a**-*h* and **4b**-*h* made from **3**-*h*. Assuming deuterium exchange only possible at the 3 position resulted in 1 ± 10 atom % H incorporated in **4a** + **4b** (after correction for the H content of the starting material **3**-*d*[6]). A similar experiment starting from **1**-*d* resulted in 0 ± 10 atom % H incorporated in **4a** + **4b**. Moreover, reaction of **1**-*d* (the same reaction conditions) produced **3** after 2 half-lives which contained 10 + 6 or −10 atom % H in the 1 position.

Product Analysis of Olefins. The reactions with NaOMe and KOMe were carried out in a V-formed flask; 5 mL of substrate solution (0.06 M) was placed in one of the shanks and 5 mL of base solution (0.12 M) in the other. The flask was placed in a thermostat. After 10 min, the reaction was started by inverting the flask; 90 min later the reaction mixture was quenched according to a method previously described[5d] and analyzed by ^1H NMR.

The reactions with quinuclidine (Q) were carried out as above but with lower concentration of reactants (Table I). The slower reactions of the deuterated substrates were run in glass ampules. The quenching was carried out as above (time > $10t_{1/2}$) but with 0.5 mL of CCl_4; 0.1 mL of C_6D_6 (99 atom % D) was added to the NMR tube. The analyses were made on the JEOL FX 100 spectrometer.

Scheme VI



Evaluation of Rate Constants and Estimation of Errors. The rate constants of the reactions with Q were evaluated using a combination of manual treatment, which gave approximate values of $k_{13} + k_{14}$, $k_{23} + k_{24}$, and k_{34} from plots of ln (mol % starting material) vs. time, and computer simulation. When using the latter method, which has been described in detail previously,[5d] the reaction system was approximated according to Scheme VI. This is a satisfactory approximation since no epimerization of the starting materials **1** or **2** could be detected after 60% reaction,[19] i.e., <1.0% epimerization.

When starting from pure **1** the concentrations of **1**, **3**, and **4** (equal to **4a** + **4b**) vary as follows:

$$\text{mol \% } \mathbf{1} = a_1 e^{-m_1 t} + (100 - a_1)e^{-m_2 t}$$

$$\text{mol \% } \mathbf{3} = b_1 e^{-m_1 t} - b_1 e^{-m_2 t}$$

$$\text{mol \% } \mathbf{4} = 100 + c_1 e^{-m_1 t} - (100 + c_1)e^{-m_2 t}$$

In these equations the parameters are related to the rate constants by the equations[20,21]

$$a_1 = 100(k_{13} + k_{14} - m_2)/(m_1 - m_2)$$

$$b_1 = 100k_{13}/(m_2 - m_1)$$

$$m_1 = [(k_{13} + k_{14} + k_{31} + k_{34})^2/4 - k_{13}k_{34} - (k_{31} + k_{34})k_{14}]^{1/2} + \frac{1}{2}(k_{13} + k_{14} + k_{31} + k_{34})$$

$$m_2 = -[(k_{13} + k_{14} + k_{31} + k_{34})^2/4 - k_{13}k_{34} - (k_{31} + k_{34})k_{14}]^{1/2} + \frac{1}{2}(k_{13} + k_{14} + k_{31} + k_{34})$$

Analogous equations are obtained in experiments starting from pure **2**.

The rate constants for the kinetics with NaOMe using the ^1H NMR method were obtained from slopes of $(2/M - 2/M_0)$ vs. time. M is the sum of the concentration of substrate and base at the time of sampling ($[\text{substrate}]_0 \approx [\text{base}]_0$). In the reactions in which ester cleavage accompanied methoxide-promoted elimination, the total rate constant was obtained as the intercept of plots of ln (100/mol % substrate)/($t[\text{base}]_{\text{av}}$) vs. time. The product ratio of olefins/alcohol extrapolated to time zero provided the additional information required to evaluate the elimination rate constant.

All estimated errors are considered as maximum errors derived from maximum systematic errors and random errors. The maximum errors of the directly measured quantities were thus allowed to propagate as systematic errors into derived quantities, e.g., isotope effects.

Acknowledgment. We thank the Swedish Natural Science Research Council for financial support.

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(8) Owing to a secondary isotope effect, $k^{H}{}_{-3}/k^{D}{}_{-3}$ is probably somewhat smaller than $k^{H}{}_{-1}/k^{D}{}_{-1}$ or $k^{H}{}_{-2}/k^{D}{}_{-2}$. Accordingly, $k^{H}{}_{3}/k^{D}{}_{3}$ is expected to be somewhat larger than $k^{H}{}_{1}/k^{D}{}_{1}$ or $k^{H}{}_{2}/k^{D}{}_{2}$. Cf. Alder, R. W.; Baker, R.; Brown, J. M. "Mechanism in Organic Chemistry"; Wiley-Interscience: New York, 1971; pp 18–20.

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(19) Methanol in water (45 wt %) was used for these experiments since it is a better solvent for separating **2** and **3**.

(20) In ref 5d the expression for a_1 and b_1 have lost the factor 100 in transformation of mole fraction into mole percent.

(21) We thank Professor L. Melander for pointing out the simplification of b_1 in ref 5d.

Cation–Anion Combination Reactions. 17.[1] Reactivities of Alkylthiolate Ions in Aqueous Solution

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Abstract: Rate constants and, where possible, equilibrium constants for the reactions of several alkylthiolate ions with a series of triarylmethyl cations, *p*-dimethylaminophenyltropylium ion, and 2,4-dinitroiodobenzene have been determined in aqueous solution at 25 °C. Brønsted β values for these reactions are very small, 0.0–0.3, although the Brønsted α value for variation of the triarylmethyl cation is ca. 0.5. Quite generally, alkyl thiolate ions are 10^4–10^5 more reactive than hydroxide ion toward all of the electrophiles studied here. The present data together with literature data for reactions of alkylthiolates with other electrophiles clearly show that the carbonyl group is unique as an electrophilic center in exhibiting very low thiolate/hydroxide rate constant ratios. Neither Hard–Soft Acid–Base concepts nor extended Marcus theory is capable of rationalizing the extensive data. We suggest that the development of a highly localized negative charge on oxygen in the carbonyl–nucleophile adducts is the controlling factor, perhaps through a solvent effect, for the unique behavior of the carbonyl group in these reactions.

Introduction

We have previously reported rate constants for the reactions of thioglycollate ion in water,[2] and of thiophenoxide ion in methanol,[3] with triarylmethyl cations, aryltropylium ions, and 2,4-dinitrohalobenzenes. Jencks and his co-workers have reported rate constants for reactions of a number of alkyl- and arylthiolates with esters and thiol esters,[4] and of alkylthiolates with acetaldehyde.[5] Unfortunately, no common thiolate was studied in reactions with the electrophiles both in Jencks' and our own laboratories, although the available data clearly indicated that the thiolates, relative to hydroxide ion, react much less rapidly with carbonyl compounds than with the electrophiles studied by us.[1]

There are, of course, several rationalizations which might be offered to account for the above observation. Hard–Soft Acid–Base concepts[6] would simply class the carbonyl compounds as much "harder" electrophiles than the others. We have previously[1] commented on some of the apparent inconsistencies of this rationalization applied to the available data. Extended Marcus theory[7] offers a possibly more attractive rationalization of the data. According to this theory, the low thiolate/hydroxide rate ratio might arise from a low equilibrium constant ratio for carbonyls as compared with other electrophiles. The necessary equilibrium data to test this theory were not available, however.

In the present work, we report rate and equilibrium constants for reactions of several electrophiles with some of the same alkylthiolates studied by Jencks.[4] The new data allow conclusions to be drawn regarding both of the rationalizations mentioned above.

Experimental Section

Materials. The sources of all of the electrophilic reagents used in this study have been described in previous papers of the series.[1] Inorganic salts and buffer components were commercial reagent grade materials used without further purification. Commercial samples of thiols were distilled under vacuum or nitrogen and stored under nitrogen.

Solutions were prepared from water which had been distilled from basic permanganate under nitrogen and further degassed with nitrogen immediately prior to use. Solutions were stored under nitrogen and all transfers were made by using either inverted funnel or glove-bag techniques. All stock solutions of thiols were used within a few hours of preparation.

Spot checks of the thiol solutions for possible oxidation were made either spectrophotometrically or by repetition of kinetic runs, and always indicated less than 5% loss of thiol from the first to last run in any set of experiments.

Reaction Products. Spectra of the products of the reactions of thiolates with carbonium ions were identical with the spectra of the carbinols above 320 nm. The spectra below 320 nm were obscured by the excess thiolate used to force the reactions to completion. For the

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