Extreme Deuterium Isotope Effects as Evidence of Ion-pair Intermediates in Base-promoted Elimination Reactions and Base-catalysed 1,3-Proton Transfer Reactions

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Reactions of 1-(1-acetoxy-1-methylethyl)indene (h-A) or its [1,3-$^2H_2$]-analogue (d-A) with tertiary amines in methanol result in competing base-promoted 1,2-elimination and base-catalysed 1,3-proton transfer to give 1-isopropylideneindene (h-C) {or its [3-^{2}H]-analogue (d-C)} and 3-(1-acetoxy-1-methylethyl)indene (h-B) {or its [1,1-$^2H_2$]-analogue (d-B)}. Furthermore, (h-B) and d-B) also undergo competing reactions among which a ' true ' base-promoted 1,4-elimination predominates over 1,3-proton transfer. Measured deuterium isotope effects on the reactions of (A) with the bases *N*-ethylpiperidine (EP), quinuclidine (Q), and diazabicyclo[2.2.2]octane (DABCO) were 7.0 ± 0.2, 7.1 ± 0.2, and 5.2 $^{+0.9}_{-0.7}$, respectively. These isotope effects were composed of the 1,3-proton transfer isotope effects 14.7 $^{+2.0}_{-2.3}$, 18.1 ± 1.1, and 7.9 $^{+1.0}_{-0.8}$, and the 1,2-elimination isotope effects 2.6 ± 0.8, 4.0 ± 0.3 and 1.9 $^{+0.6}_{-0.5}$, respectively. The results indicate that the 1,2-elimination and the 1,3-proton transfer reactions, which appear to be intramolecular, are coupled with at least one common ion-pair intermediate. These competitive isotope effects provide evidence of a new type, confirming previous indications that ion pairs may be intermediates in elimination and 1,3-proton transfer reactions.

The isotope effects on the reaction of (B), on the other hand were small: 1.33 ± 0.03, 1.63 ± 0.05, and 1.0 ± 0.1 with EP, Q, and DABCO, respectively. As the reactions were not accompanied by significant incorporation of protium into (d-B), these small isotope effects indicate the intermediacy of reversibly formed ion pairs. Thus the observations strongly suggest that all the above reactions involve at least one common ion pair.

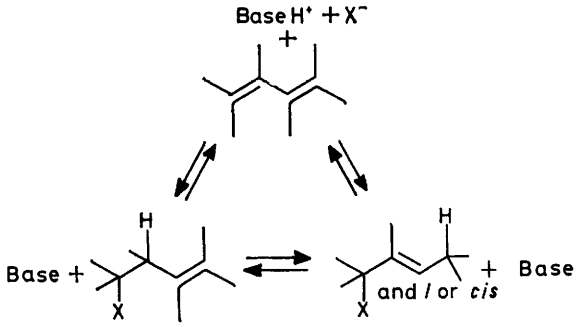
Complete internal consistency of the interpretations requires the introduction into the mechanism of another ion pair which is not in equilibrium with the first one.

It is well established that carbanion ion pairs and tightly solvated carbanions may be intermediates in 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]

This paper provides a full account of results[4a] which constitute strong evidence for $(E1cB)_{ip}$ mechanisms of reversible $[(E1cB)_{ip,R}]$ as well as irreversible $[(E1cB)_{ip,I}]$ type. A new type of ion-pair probe has been employed. Substrates have been chosen so that a base-catalysed 1,3-proton transfer reaction competes with base-promoted 1,2- or 1,4-elimination as generalized in Scheme 1.[4b]

Previous evidence that ion pairs are intermediates in proton transfer reactions has been based mainly upon observed parallel reactions which, for the sake of mechanistic simplicity, have been coupled with an intermediate(s).[1a,5] As a working hypothesis it was postulated that the present 1,3-proton transfer reaction proceeds *via* at least one ion pair.[4]

In contrast to earlier evidence, unusually large deuterium isotope effects[6] on the 1,3-proton transfer reaction were observed with some tertiary amines as catalysts in methanol as solvent since this reaction can compete with base-promoted 1,2-elimination. These results show not only that the 1,3-proton transfer reaction is stepwise but also that the competing 1,2-elimination involves irreversibly formed intermediates



SCHEME 1

and that the two reactions have at least one intermediate (ion pair) in common. On the other hand the 1,4-elimination reaction shows unusually small isotope effects with no competing D–H exchange of the substrate, indicating that reversibly formed ion pairs are intermediates.

A completely consistent interpretation of all results

[1] (*a*) D. J. Cram, ' Fundamentals of Carbanion Chemistry,' Academic Press, New York, 1965; (*b*) R. P. Bell, ' The Proton in Chemistry,' Chapman and Hall, London, 2nd edn., 1973; (*c*) J. R. Jones, ' The Ionisation of Carbon Acids,' Academic Press, London, 1973.

[2] F. G. Bordwell, *Accounts Chem. Res.*, 1970, **3**, 281; 1972, **5**, 374.

[3] (*a*) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, 1969, **91**, 368; (*b*) F. G. Bordwell, J. Weinstock, and T. F. Sullivan, *ibid.*, 1971, **93**, 4728; (*c*) V. Fiandanese, G. Marchese, and F. Naso, *J.C.S. Chem. Comm.*, 1972, 250; (*d*) M. Albeck, S. Hoz, and Z. Rappoport, *J.C.S. Perkin II*, 1972, 1248; (*e*) V. Fiandanese, G. Marchese, and F. Naso, *ibid.*, 1973, 1538.

[4] Preliminary reports, (*a*) P. Ahlberg and S. Bengtsson, *Chemica Scripta*, 1974, **6**, 45; (*b*) P. Ahlberg, *ibid.*, 1973, **4**, 33.

[5] (*a*) G. Bergson, I. Wallmark Rosser, and L. Meurling, *Chemica Scripta*, 1975, **8**, 150, and references therein; (*b*) J. Almy, D. C. Garwood, and D. J. Cram, *J. Amer. Chem. Soc.*, 1970, **92**, 4321, and references therein.

[6] L. Melander, ' Isotope Effects on Reaction Rates,' Ronald Press, New York, 1960; R. A. More O'Ferrall, in ' Proton-transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, p. 201.

involves introduction of another contact ion pair which is not in equilibrium with the first. Thus the 1,3-proton transfer reaction makes use of two ion-pair intermediates.

RESULTS AND DISCUSSION

Reaction of 1-(1-acetoxy-1-methylethyl)indene (h-A) or its [1,3-$^2H_2$]-analogue (d-A) in methanol with the tertiary amines, *N*-ethylpiperidine (EP), quinuclidine (Q), and diazabicyclo[2.2.2]octane (DABCO), in the presence of the corresponding aminium acetate buffer, *i.e.* EPH^+AcO^- or QH^+AcO^-, gave the products 3-(1-acetoxy-1-methylethyl)indene (h-B) {or its [1,1-$^2H_2$]-analogue (d-B)} and 1-isopropylideneindene (h-C) {or its [3-^2H]-analogue (d-C)} (Scheme 2 and Table 1). After long reaction times the only product was (C). The

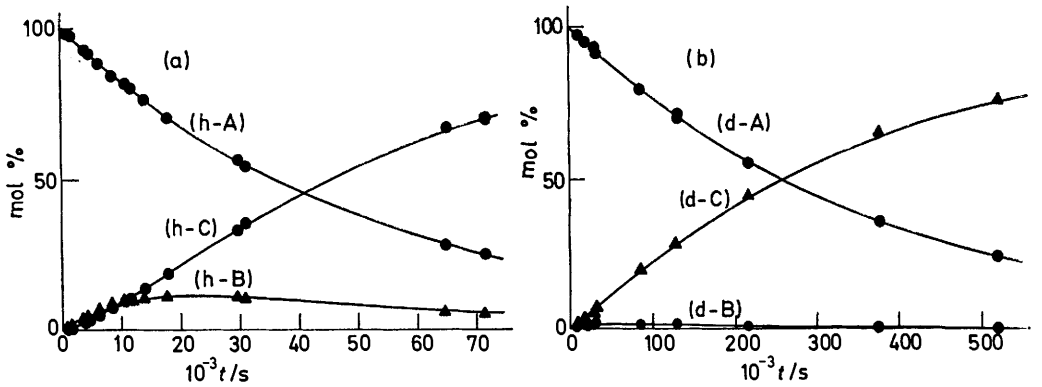


FIGURE 1 The time dependence of reactions of (a) (h-A), (h-B), and (h-C) and (b) (d-A), (d-B), and (d-C) in methanol with EP at 30.00 ± 0.03 °C. Initially the reaction solutions were 1.011M in EP, 0.030M in EPH^+AcO^-, and 0.010M in (A). The reaction system was analysed by the h.p.l.c. method; the curves shown are computer-simulated

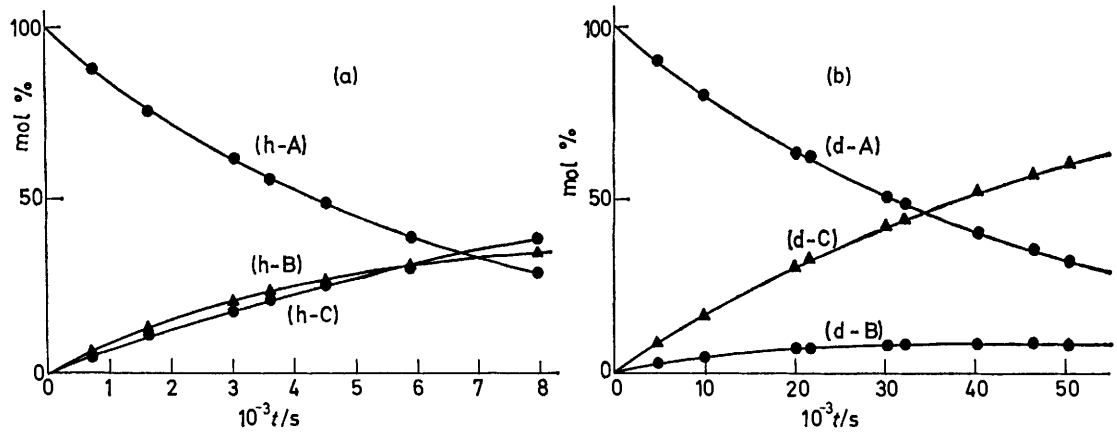


FIGURE 2 The time dependence of reactions of (a) (h-A), (h-B), and (h-C) and (b) (d-A), (d-B), and (d-C) in methanol with Q at 20.00 ± 0.03 °C. Initially the reaction solutions were 0.064 0M in Q, 0.0020M in QH^+AcO^-, and 6.2×10^{-4}M in (A) The reaction system was analysed by the h.p.l.c. method; the curves shown are computer-simulated

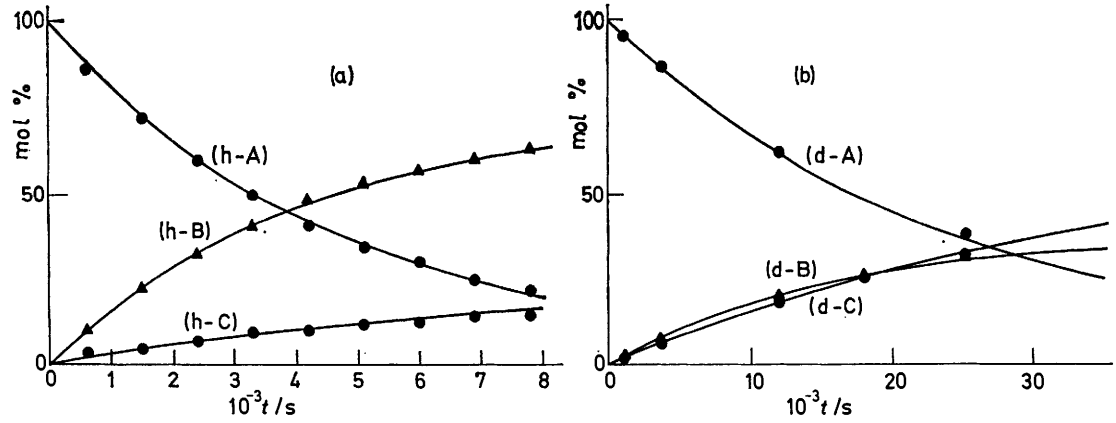
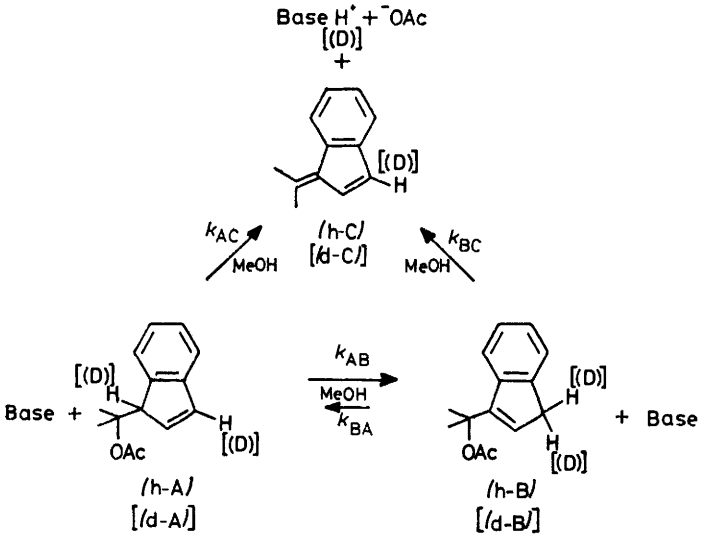


FIGURE 3 The time dependence of reactions of (a) (h-A), (h-B), and (h-C) and (b) (d-A), (d-B), and (d-C) in methanol with DABCO at 20.00 ± 0.03 °C. Initially the reaction solutions were 0.500M in DABCO and 0.030M in (A). The reaction system was analysed by the ^1H n.m.r. method; the curves shown are computer-simulated

reactions were studied by using a calibrated sampling–quench–high pressure liquid chromatography (h.p.l.c.) and/or a sampling–quench–extraction–^{1}H n.m.r. procedure. Some representative results are presented in Figures 1—3. When (B) [(h-B) or (d-B)] was treated in the same way, (C) was the main product, *i.e.* only small amounts of (A) were produced. The concentrations of the tertiary amines decreased only slightly during the reactions (at infinite time by only 1% by h.p.l.c. or 3 or 6% by ^{1}H n.m.r.) owing to consumption of base by the eliminated acetic acid. The base concentration can therefore be considered to be approximately constant during the kinetic runs and near first-order behaviour is expected.

The methanolic solutions were buffered to exclude methoxide ion as an active base. The reaction rates increased somewhat rather than diminished on addition of the buffer salt (Table 2), proving that the tertiary



SCHEME 2

amine was the active compound. With triethylamine (TEA) as base,[4b] but under otherwise similar conditions it was previously shown that the rate equations (1)—(3)

$$d[(A)]/dt = \{-(k_{AB} + k_{AC})[(A)] + k_{BA}[(B)]\}[Base] \quad (1)$$

$$d[(B)]/dt = \{k_{AB}[(A)] - (k_{BA} + k_{BC})[(B)]\}[Base] \quad (2)$$

$$d[(C)]/dt = \{k_{AC}[(A)] + k_{BC}[(B)]\}[Base] \quad (3)$$

(*cf.* Scheme 2) are valid. The equilibrium constant $K_{eq}^{H} = [(h\text{-}B)]_{eq}/[(h\text{-}A)]_{eq}$ was determined to be 19.9 ± 2.0 at 30.00 ± 0.03 °C, and 20.8 ± 2.0 at 20.00 ± 0.03 °C in methanol with pyridine as catalyst. This weak base, although it yields a slow reaction, is much more effective as a catalyst of the 1,3-proton transfer than as a promoter of the elimination. Accordingly only a trace of (C) was found in these measurements.

Evaluation of the Rate Constants.—Figure 1 shows that the relations (4) and (5) between the observed and phenomenological rate constants are good approximations of the kinetics with *N*-ethylpiperidine (EP).[4b]

$$k_{obs.(A)} = k_{AB} + k_{AC} = k_{BC} - k_{AB}R \quad (4)$$

where $R = \lim_{t\to\infty} [(A)]/[(B)]$

$$k_{obs.(B)} = k_{BC} \quad (5)$$

These relations were used for evaluation of the phenomenological rate constants.

The reactions with quinuclidine (Q) and diazabicyclo[2.2.2]octane (DABCO) were faster than those with EP, and the reaction temperature was therefore lowered to 20 °C for practical reasons (Table 1). Figures 2 and 3 show that 1,4-elimination is less dominant with these bases. Therefore, the term $k_{BA}[(B)]$ in equations (1) and (2) is not negligible, and the evaluation of the phenomenological rate constants is therefore more complicated than when EP was used. However, accurate rate constants were obtained when the graphs in Figure 2 and 3 were computer-simulated by using the integrated expressions of equations (1)—(3) (see Experimental section).

Reaction conditions, rate constants, and isotope effects are collected in Tables 1—4.

TABLE 1

Initial reaction conditions and analytical methods for the reactions of (A), (B), and (E).[a] The same concentrations were used for both the h- and d-substrate

Analytical method	Base	[Base]/ M	[Buffer]/ M	[Substrate]/ M	Temp.[b] (*t*/°C)
^{1}H N.m.r.	EP	1.000	0.030	0.030	30.00
h.p.l.c.	EP	1.011	0.030	0.010	30.00
h.p.l.c.	Q	0.064 0	0.002 0	6.2×10^{-4}	20.00
^{1}H n.m.r.	DABCO	0.500		0.030	20.00

[a] The ether 1-(1-methoxy-1-methylethyl)indene (h-E) and its [1,3-$^2H_2$]-analogue (d-E) were only treated with EP; temp. 70 °C. [b] ± 0.03 °C.

TABLE 2

Observed rate constants and isotope effects obtained for the reactions with *N*-ethylpiperidine (EP); conditions as in Table 1

Run no.	Substrate	Analytical method	$10^7 k_{obs}$/ l mol^{-1} s^{-1}	k_{obs}^{H}/k_{obs}^{D}
1	(h-A)	^{1}H n.m.r.	200 ± 5	7.2 ± 0.4
2	(d-A)	^{1}H n.m.r.	27.8 ± 0.7	
3	81.1% (h-A), 18.9% (h-B)	^{1}H n.m.r.	200 ± 5	
4[a]	80.5% (h-A), 19.5% (h-B)	^{1}H n.m.r.	199 ± 5	
5	(h-B)	^{1}H n.m.r.	888 ± 22	1.36 ± 0.07
6	(d-B)	^{1}H n.m.r.	652 ± 16	
7[a]	(h-B)	^{1}H n.m.r.	829 ± 21	1.37 ± 0.08
8[a]	(d-B)	^{1}H n.m.r.	604 ± 16	
9	(h-A)	h.p.l.c.	193 ± 3[b]	7.0 ± 0.2
10	(d-A)	h.p.l.c.	27.5 ± 0.4[b]	
11	(h-B)	h.p.l.c.	852 ± 9[b]	1.33 ± 0.03
12	(d-B)	h.p.l.c.	640 ± 7[b]	

[a] Without buffer added initially. [b] Average value of two runs.

Search for Accompanying Exchange of Deuterium with Protium in the Reactions of (d-A) *and* (d-B).—The end-product (d-C) was analysed by ^{1}H n.m.r. for its protium content in the 3-position.[4b] Table 5 shows the results. Some of the runs were made with much higher substrate

concentration than normally used in the kinetic investigations. This means that the average buffer concentration is high during the reaction. In two such runs in Table 5 the protium incorporation was rather large (17 ± 6 and 12 ± 4%), but in all other runs there was no significant extra protium at the 3-position of the product (d-C). All three reactions are therefore concluded to proceed without significant exchange, and the 1,3-proton transfer reactions are highly intramolecular under the kinetic conditions used.

These results are completely consistent with the kinetic behaviour of (d-A) and (d-B). The curves obtained from plots of ln[mol % (d-A) and ln[mol % (d-B)] *versus* time are straight lines, which shows that the rate constant is constant throughout the reaction. Substantial protium incorporation in either (d-A) or (d-B) would result in considerable deviation from linearity.

TABLE 3

Rate constants for the reactions of (A) and (B) with EP at 30.00 ± 0.03 °C and with Q or DABCO at 20.00 ± 0.03 °C

Base	Substrate	$10^6(k_{AB} + k_{AC})$ / l mol^{-1} s^{-1}	10^6k_{AB} / l mol^{-1} s^{-1}	10^6k_{AC} / l mol^{-1} s^{-1}	10^6k_{BC} / l mol^{-1} s^{-1}
EP [a]	(h-A)	19.3 ± 0.3	$14.8^{+0.8}_{-0.7}$	$4.49^{+1.04}_{-1.09}$	
	(d-A)	2.75 ± 0.04	1.00 ± 0.11 / -0.08	$1.75^{+0.12}_{-0.15}$	
	(h-B)				85.2 ± 0.9
	(d-B)				64.0 ± 0.7
Q [a,b,c]	(h-A)	2 516 ± 55	1 422 ± 55	1 094 ± 55	
	(d-A)	355 ± 4	78.8 ± 1.7	276 ± 3	
	(h-B)				572 ± 11
	(d-B)				351 ± 4
DABCO [b,d]	(h-A)	424 ± 22	355 ± 11	69 ± 11	
	(d-A)	80.8 ± 7.6	44.8 ± 3.6	36 ± 4	
	(h-B)				17.8 ± 0.8
	(d-B)				17.8 ± 1.0

[a] H.p.l.c. method; data are average values from two different runs. [b] Data obtained by computer simulation. [c] The same experiments were also performed with a much higher buffer concentration (0.022M), but the isotope effects did not change significantly. [d] ^{1}H n.m.r. method.

TABLE 4

Isotope effects on the reactions of (A) and (B) with EP at 30.00 ± 0.03 °C and with Q or DABCO at 20.00 ± 0.03 °C

Base	$\frac{k_{AB}^H + k_{AC}^H}{k_{AB}^D + k_{AC}^D}$	$\frac{k_{AB}^H}{k_{AB}^D}$	$\frac{k_{AC}^H}{k_{AC}^D}$	$\frac{k_{BC}^H}{k_{BC}^D}$
EP [a]	7.0 ± 0.2	$14.7^{+2.3}_{-2.0}$	2.6 ± 0.8	1.33 ± 0.03
Q [a,b]	7.1 ± 0.2	18.1 ± 1.1	$4.0^{+0.2}_{-0.3}$	1.63 ± 0.05
DABCO [b,c]	$5.2^{+0.9}_{-0.7}$	$7.9^{+1.0}_{-0.8}$	$1.9^{+0.6}_{-0.5}$	1.0 ± 0.1

[a] H.p.l.c. method; data presented are average values from two different runs. [b] Data obtained by computer simulation. [c] ^{1}H N.m.r.-method.

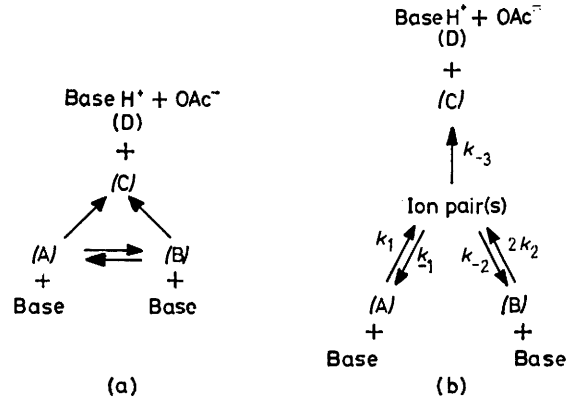
TABLE 5

Analysis of deuterium–protium exchange accompanying the reactions of (d-A) and (d-B) in methanol; runs with EP were performed at 30.00 ± 0.03 °C and those with Q and DABCO at 20.00 ± 0.03 °C

Substrate	[Substrate]/ M	Base	[Base]/ M	Initial [Buffer]/M	H incorp. in (d-C) [a] (atom %)
(d-A)	0.15	EP	1.00	0.030	1 ± 4
(d-B)	0.15	EP	1.00	0.030	0 ± 3
(d-A)	0.007 1	Q	0.060	0.002 0	1 ± 4
(d-B)	0.008 5	Q	0.064	0.002 1	0 ± 4
(d-B)	0.008 0	Q	0.88	0.15	17 ± 6
(d-A)	0.030	DABCO	0.49		0 ± 4
(d-B)	0.030	DABCO	0.48		0 ± 4
(d-B)	0.15	DABCO	0.50		12 ± 4

[a] Corrected for the protium content of the starting material (1.8 ± 1.0 atom %).

Mechanisms.—In light of the above results, let us consider two extreme mechanisms.[4b] In Scheme 3(a) the three reactions are not coupled through a common intermediate(s). On the other hand, in Scheme 3(b) all three reactions, the 1,2- and 1,4-elimination, and the 1,3-proton transfer are coupled through one common intermediate. We will refer to this mechanism as the one-ion-pair mechanism. If mechanism (a) properly describes the reactions with EP and Q, then the only reasonable cause of the unusually large rearrangement isotope effects observed would be considerable proton tunneling in the 1,3-proton transfer.[7] That this is not the case is concluded on the following grounds. The 1,3-proton transfer reaction of a model compound closely related to (A), 1-(1-methoxy-1-methylethyl)-indene (h-E) {or its [1,3-$^2H_2$]-analogue (d-E)} to 3-(1-



SCHEME 3

[7] E. S. Lewis, in ' Proton-transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, p. 317.

methoxy-1-methylethyl)indene (h-F) {or its [1,1-$^2H_2$]-analogue (d-F)} in methanol catalysed by EP (Table 1), was found to have a kinetic isotope effect, $k_{EF}^H/k_{EF}^D = 7.1 \pm 0.4$ (40 °C), close to the value observed for the reaction of (A) with EP (Table 2). The ether (E), which under these conditions only undergoes rearrangement, *i.e.* no elimination, was about half as reactive as the acetate (A). Thus the results are not compatible with Scheme 3(a), which demands normal isotope effects for both 1,2-elimination and rearrangement.*

The one-ion-pair mechanism. The Scheme 3(b) mechanism on the other hand could account for the results. A type (b) mechanism with only one eliminating intermediate of ion-pair type, or an equilibrium mixture of eliminating intermediates which is kinetically equivalent, is first considered. The steady-state approximation applied to this (b)-type mechanism yields the expressions (6)—(12), which relate the phenomenological and microscopic rate constants and isotope effects.

$$k_{AB} = k_1 \frac{k_{-2}}{k_{-1} + k_{-2} + k_{-3}} \quad (6)$$

$$k_{BA} = 2k_2 \frac{k_{-1}}{k_{-1} + k_{-2} + k_{-3}} \quad (7)$$

$$k_{AC} = k_1 \frac{k_{-3}}{k_{-1} + k_{-2} + k_{-3}} \quad (8)$$

$$k_{BC} = 2k_2 \frac{k_{-3}}{k_{-1} + k_{-2} + k_{-3}} \quad (9)$$

$$\frac{k_{AB}^H}{k_{AB}^D} = \frac{k_1^H}{k_1^D}\left(\frac{k_{-1}^D}{k_{-2}^D} + \frac{k_{-3}^D}{k_{-2}^D} + 1\right)\Big/\left(\frac{k_{-1}^H}{k_{-2}^H} + \frac{k_{-3}^H}{k_{-2}^H} + 1\right) \quad (10)$$

$$\frac{k_{AC}^H}{k_{AC}^D} = \frac{k_1^H}{k_1^D}\left(\frac{k_{-1}^D}{k_{-3}^D} + \frac{k_{-2}^D}{k_{-3}^D} + 1\right)\Big/\left(\frac{k_{-1}^H}{k_{-3}^H} + \frac{k_{-2}^H}{k_{-3}^H} + 1\right) \quad (11)$$

$$\frac{k_{BC}^H}{k_{BC}^D} = \frac{k_2^H}{k_2^D}\left(\frac{k_{-1}^D}{k_{-3}^D} + \frac{k_{-2}^D}{k_{-3}^D} + 1\right)\Big/\left(\frac{k_{-1}^H}{k_{-3}^H} + \frac{k_{-2}^H}{k_{-3}^H} + 1\right) \quad (12)$$

Substantial effects of isotopic substitution are expected on the ionisation rate constants k_1 and k_2, and on the collapse rate constants k_{-1} and k_{-2} because carbon–hydrogen bonds are broken or formed in these processes. Collapse isotope effects have recently been reported for amine-catalysed 1,3-proton transfer reactions of 1,3-dialkylindenes.[5b] The isotope effect on k_{-3} on the other hand is predicted to be small since the major bond-breaking and bond-forming processes involving the proton are assumed to be over once the ion-pair stage is reached. It is also expected that the two collapse rate constants (k_{-1} and k_{-2}) have similar isotope effects.† This also applies to the ionisation rates k_1 and k_2.‡ Thus in equations (10)—(12) one expects $k_1^H/k_1^D \simeq k_2^H/k_2^D$, $k_{-1}^D/k_{-2}^D \simeq k_{-1}^H/k_{-2}^H$, $k_{-3}^D/k_{-2}^D > k_{-3}^H/k_{-2}^H$, and $k_{-1}^D/k_{-3}^D < k_{-1}^H/k_{-3}^H$. The implications of these assumptions are that in equation (10) the ionisation isotope effect k_1^H/k_1^D will be amplified, *i.e.* multiplied by a factor >1. A smaller k_{AB}^H/k_{AB}^D value than is observed is thus predicted for a rearrangement which is not competing with a 1,2-elimination. The cause of the amplified rearrangement isotope effect is thus the competition between two processes with different isotope effects, *i.e.* the elimination and collapse of the ion pair(s) which follow after a rate-determining ionisation step.

The isotope effect on the reaction of (E) is a good approximation to the ionisation isotope effect expected on the reactions of (A). With reference to equations (6) and (8), it is thus concluded that $(k_{AB}^H + k_{AC}^H)/(k_{AB}^D + k_{AC}^D) \leqslant k_1^H/k_1^D$. The similarity of these isotope effects on the reactions of (A) and of (E) suggests that $(k_{AB}^H + k_{AC}^H)/(k_{AB}^D + k_{AC}^D)$ is a good approximation to k_1^H/k_1^D, at least when EP and Q are employed.

For the 1,2- and 1,4-elimination reactions, on the other hand, the ionisation isotope effects [equations (11) and (12)] are attenuated, *i.e.* multiplied by a factor <1.

The design of the reaction system [4b] is thus crucial in determining the magnitude of the amplification and the attenuations. A normal rearrangement isotope effect will be observed if the substrate is mainly rearranging ($k_{-2} \ll k_{-3}$) and similarly a normal elimination isotope effect will result if $k_{-2} \ll k_{-3}$, *i.e.* the substrate is mainly undergoing elimination. Increasing amplification of the rearrangement isotope effect will be observed with an increasing fraction of elimination $[(k_{-3})/(k_{-2} + k_{-3})]$ and/or decreasing reversibility in the ionisation of (A). The attenuations, on the other hand, will increase with increasing fraction of rearrangement or increasing reversibility of the ionisation processes. What maximal rearrangement isotope effect could be expected for a 1,3-proton transfer reaction? Let us assume an ionisation isotope effect of 7, *i.e.* that the ionisation process is irreversible and that the collapse isotope effect is of the same magnitude as the ionisation isotope effect. If $k_{-3} \gg k_{-2}$, *i.e.* there is only a small fraction of rearrangement, a maximal rearrangement isotope effect of 49 would result. However, there are several factors that could attenuate an amplified rearrangement isotope effect: (1) the collapse isotope effect being smaller than assumed; (2) the fraction of elimination being too small; or (3) compound (A) being reversibly ionised.

When DABCO was used as catalyst a rearrangement isotope effect close to a normal value was obtained (Table 4), although it was larger than the isotope effect on the reaction of (A). The reason (2) is the most important when DABCO is used but (1) may also be of importance.

With EP or Q, the fraction of elimination is much larger than with DABCO, and accordingly larger rearrangement isotope effects are observed with these two bases. Possibly the latter is the reason (besides the temperature) why Q yields a higher rearrangement

* A referee comments: ' The authors eliminate the explanation of their apparently large isotope effects in terms of proton tunnelling on the grounds that a related compound shows a normal isotope effect. This argument must be speculative at best as many studies on proton transfer reactions showing indications of proton tunnelling suggest that the extent of tunnelling is very sensitive to the nature of both substrate and base.'

† Owing to a secondary isotope effect, k_{-2}^H/k_{-2}^D is probably somewhat smaller than k_{-1}^H/k_{-1}^D.

‡ Owing to a secondary isotope effect, k_2^H/k_2^D is probably somewhat larger than k_1^H/k_1^D.

isotope effect than EP. Also reason (1) may be of importance with EP and Q.

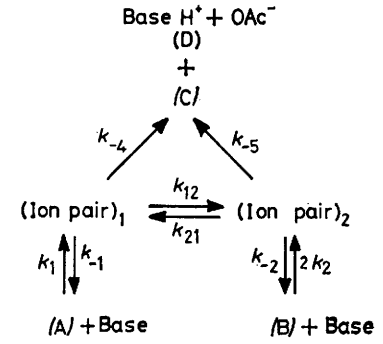
The influence of the base and the solvent on rate and deuterium isotope effect of the 1,4-elimination of (B) has been studied and a reaction mechanism involving reversibly formed ion pairs discussed.[8] As seen in Table 4 the isotope effects on the 1,4-elimination reaction with the various tertiary amines are small, and become even smaller when the secondary isotope effect caused by the second deuterium atom in (d-B) is taken into account. If a secondary isotope effect of 1.16 [8b,9] is used in correcting the observed isotope effect one obtains 1.15, 1.41, and 0.86 for EP, Q, and DABCO, respectively. As mentioned previously, the 1,4-elimination with the present bases is not accompanied by significant D–H exchange. This, in combination with unusually small isotope effects, indicates the reversible formation of ion pairs which return to (B) faster than they undergo elimination and which exchange with the media much more slowly than they undergo elimination. In contrast, sodium methoxide in methanol at 30 °C yields an isotope effect of 7.6 ± 0.4 for the 1,4-elimination which indicates that the reversibility has been substantially removed.[8b] The reactions of (A) with EP, Q, and DABCO make primary use of irreversibly formed intermediates as indicated by the normal isotope effects (*ca.* 7) obtained with EP and Q and the close to normal value with DABCO.

The two-ion-pair mechanism. A closer inspection of the data reveals some inconsistencies that could have far-reaching mechanistic implications. Thus when $(k_1^H/k_1^D)/(k_2^H/k_2^D)$ is calculated from the data in Table 4 and equation (13), which is derived from equations (11) and (12), the following ratios are obtained: 2.0 ± 0.6

$$\frac{k_1^H}{k_1^D}\Big/\frac{k_2^H}{k_2^D} = \frac{k_{AC}^H}{k_{AC}^D}\Big/\frac{k_{BC}^H}{k_{BC}^D} \qquad (13)$$

(EP), $2.5 \begin{smallmatrix}+0.2\\-0.3\end{smallmatrix}$ (Q), and $1.9 \begin{smallmatrix}+0.9\\-0.6\end{smallmatrix}$ (DABCO). Even larger values than these are obtained after correction for secondary isotope effects.

These large values are surprising in view of the following. The elimination reactions of (A) and (B) with sodium methoxide in methanol show deuterium isotope effects of 6.5 ± 0.4 and 7.6 ± 0.4,[8b,10] respectively, consistent with the modest pK_a difference between (A) and (B) as expressed by the equilibrium constant. Since these elimination reactions presumably are irreversible *E*1cB reactions, these values should be measures of the isotope effects on k_1 and k_2, respectively; we therefore conclude that these isotope effects are similar. It seems reasonable that these isotope effects should remain similar when tertiary amines are used instead of methoxide in the reactions. However the large values above indicate that either k_2^H/k_2^D diminishes considerably in going from methoxide to the tertiary amines or that the one-ion-pair mechanism cannot consistently account for all the results. Such insufficiency is removed by extending the one-ion-pair mechanism to the two-ion-pair mechanism shown in Scheme 4.



SCHEME 4

The kinetic consequences of the one-ion-pair mechanism [Scheme 3(b)] also cover those of any ion-pair mechanism with more than one eliminating ion pair as long as the ion pairs which are eliminating are in equilibrium with each other. In the two-ion-pair mechanism (Scheme 4) the interconversion of the ion pairs competes with the elimination process instead of being in equilibrium and indistinguishable as in the one-ion-pair mechanism. The Scheme 4 mechanism accounts for the results as follows. If one ion-pair (IP_2) returns to (h-B) faster than it either eliminates or isomerises to IP_1, this would account for the small 1,4-elimination isotope effects observed. In the reactions of (A), on the other hand, part of the elimination product must originate from IP_1. This is so since IP_2, once formed, mainly collapses to (B) and much larger k_{AC}/k_{AB} values are observed than are expected on the basis of the small 1,4-elimination isotope effects. It seems reasonable that the two ion pairs are of the contact type with the substituted ammonium ion in the ion pair hydrogen bonded by C-1 or -3. Such intermediates have been proposed in studies of amine-catalysed 1,3-proton transfers of 1,3-dialkylidenes.[5b] However, these results did not necessitate the introduction of the second ion pair.

The mechanism of elimination by the ion pairs. Obviously the ion pairs are intermediates in both 1,2- and 1,4-elimination reactions. It is not clear, however, which mechanism the ion pairs employ in the elimination(s). Two possible mechanisms may be visualized for the elimination reactions of the ion pairs, *i.e.* a concerted [11] one-step process or a multi-step process. The first step in the multi-step process could be irreversible concerted (this process involves partial breakage of the bond to the leaving group) or non-concerted dissociation of the ion pairs with a subsequent elimination of the carbanion formed. The substantial incorporation of protium in (d-C) formed from (d-B) at high buffer

[8] (*a*) P. Ahlberg, *Chemica Scripta*, 1975, **8**, 49; (*b*) A. Thibblin and P. Ahlberg, *Acta Chem. Scand.* (*B*), 1976, **30**, 555.
[9] Ref. 1*c*, p. 150.
[10] A. Thibblin and P. Ahlberg, to be published.
[11] W. H. Saunders, jun., *Accounts Chem. Res.*, 1976, **9**, 19, and references therein.

concentrations (Table 5) could indicate the intermediacy of free carbanions which return to ion pair(s) at a rate comparable with the rate of elimination. It could also indicate a reaction in which the buffer participates in electrophilic substitution on the ion pair.

Experimental results show that ion-pair formation from (A) is assisted by the leaving group. In other words, the reaction presumably takes place in a concerted way, in the same manner as base-catalysed 1,3-proton transfer reactions are assisted by some potential leaving groups as β-substituents.[10,12]

It is interesting to note the mechanistic difference between the reactions discussed above, which have been established as stepwise and as having common intermediates, and the competing processes such as thermal epimerisation, rearrangement, and acetic acid elimination previously studied. The thermal acetic acid elimination and the other two competing reactions were shown *not* to have a common intermediate.[13]

Reactivity comparisons with various bases. The relative reactivities of rearrangement and elimination of (h-A) (k_{AB}/k_{AC}) decrease with increasing basicity (Table 6).

TABLE 6

Relative reaction rates calculated from data obtained with (h-A) and (h-B) in methanol as solvent at 30 °C [a] (Table 4)

Base	$k_{AB} + k_{AC}$	k_{AB}/k_{AC}
Pyridine [b]	0.031	Large
DABCO [a,c]	23	5.1
TEA [d]	1	2.3
EP	1.0	3.3
Q [a]	270	1.3
NaOMe	857	<0.002

[a] A factor of 2 has been used to convert the rate constants from 20 to 30 °C. [b] Ref. 10. [c] The rate constants have been divided by the statistical factor 2. [d] Ref. 4*b*.

In the one-ion-pair mechanism, this function equals k_{-2}/k_{-3}, *i.e.* the rate of collapse relative to elimination of the ion pair. It is expected that the collapse rate will increase with increasing acidity of the substituted ammonium ion in the ion pair.[14] The elimination rate of the ion pair, on the other hand, is presumably less affected by a variation in the structure of the substituted ammonium ion than the collapse rate. In line with this reasoning it was found that pyridine (pK_a 5.2) * only gave a trace of the elimination product and that DABCO (pK_a 8.7) * gave more rearrangement than Q (pK_a 10.6),* EP, and TEA.

EXPERIMENTAL

^{1}H N.m.r. analyses were made with either a Varian A 60D or a JEOL FX 100 spectrometer. The latter instrument was employed in the analysis of the D–H exchange experiments. G.l.c. analyses of the bases were made with a 2.5 m × 3 mm steel column packed with 20% Ucon LB-550-X, 20% KOH on Chromosorb P (80—100 mesh) (180 kPa N_2 at 80 °C). For the high-pressure-liquid-chromatography (h.p.l.c.) analyses, a Waters 6000A solvent delivery system and 440 absorbance detector were employed. The analytical column was a Waters μBondapak C18 (4 mm × 0.3 m) system and as mobile phase a solution of 40 wt. % ethanol (spectroscopic quality) in water was used.

Solvent and Bases.—Methanol (Fluka for u.v. spectroscopy) stored over 0.3 nm molecular sieves (Merck or Fluka) was used as solvent for the kinetic studies without further purification. *N*-Ethylpiperidine (EP), synthesized from piperidine and ethyl bromide,[16] was distilled through a spinning-band column (Nester-Faust) or a split-tube column (Fisher HMS 300). After distillation, ^{1}H n.m.r. and g.l.c. analysis showed that the piperidine content was <0.01%. This high purity was needed to avoid significant reaction caused by piperidine, which is much more reactive than EP. Quinuclidine (Q) was liberated from its hydrochloride (Fluka purum), dried (CaO), and sublimed twice at reduced pressure. G.l.c. and ^{1}H n.m.r. analysis established its high purity. Diazabicyclo[2.2.2]octane (DABCO) (Kebo) was recrystallized twice from light petroleum. No impurities were detected by ^{1}H n.m.r. spectroscopy. All bases were stored in the deep-freeze under dry nitrogen.

Substrates.—The syntheses of the acetates (h-A), (d-A), (h-B), and (d-B) and the isopropylideneindenes (h-C) and (d-C) as well as their purification has been reported, together with ^{1}H n.m.r. analysis of the deuterium content of (d-A) and (d-B).[4b] H.p.l.c. analysis of compounds (A) and (B) showed high purity, with no significant impurity.

The methyl ethers (h-E) and (d-E) were made by aluminium trichloride-promoted methylation of 1-(1-hydroxy-1-methylethyl)indene and its [1,3-$^2H_2$]-analogue, respectively, with diazomethane in ether.[12] The ethers (h-F) and (d-F), which were products of EP-catalysed rearrangements of (h-E) and (d-E), respectively, were not isolated but analysed in solution.

Kinetics.—All glassware was cleaned with chromic acid and rinsed with water, dilute ammonium hydroxide, and distilled water before drying at 150 °C at least overnight. All kinetic runs were performed at constant temperature in a HETO 01 PT 623 thermostat. The temperature was measured with a calibrated mercury thermometer (accuracy ±0.02 °C). During the runs the temperature did not deviate more than 0.01 °C from the average value (t), and thus the absolute temperature was $t \pm 0.03$ °C.

Quench–Extraction—^{1}H n.m.r. procedure. The base was weighed directly into the reaction flask and the buffer solution, prepared from equimolar amounts of base and acetic acid, and most of the methanol were added, leaving space only for the substrate solution. The latter was made by weighing the substrate into a small tube and dissolving it in methanol. The solutions were thermostatted before adding the substrate solution and the final volume was adjusted with a few drops of methanol. Calibrated 50 or 100 ml measuring flasks stoppered with TFE-coated corks were used as reaction flasks. In kinetic runs which lasted for more than 24 h ampoules were used as reaction flasks.

* These pK_a values refer to water as solvent.[15]

[12] P. Ahlberg, *Chemica Scripta*, 1973, **3**, 183.
[13] A. Thibblin and P. Ahlberg, *Chemica Scripta*, 1976, **10**, 27; *Acta Chem. Scand.* (*B*), 1976, **30**, 973.
[14] Ref. 1*b*, p. 206.
[15] (*a*) D. D. Perrin, 'Dissociation Constants of Organic Bases,' Plenum Press, New York, 1965; (*b*) T. A. Spencer, M. C. R. Kendall, and I. D. Reingold, *J. Amer. Chem. Soc.*, 1972, **94**, 1250, and references therein.
[16] R. C. Elderfield, A. E. Hydorn, E. Schencker, and K. K. Wyckoff, *J. Org. Chem.*, 1959, **24**, 1299.

From the measuring flask or ampoule 10 ml of the reaction solution was withdrawn with a 10 ml pipette and rapidly transferred to a 60 ml stop-cocked tube containing carbon tetrachloride (1 ml), 1M-hydrochloric acid (30 ml), and ice (10 g). The mixture was shaken for 1 min and centrifuged. The carbon tetrachloride layer was transferred to an n.m.r. tube. The methyl region of the ^1H n.m.r. spectrum (Figure 4) was integrated and the mol % of each of the three components was evaluated. The same amount of carbon tetrachloride (1 ml), measured with a syringe, was used for each extraction, which allowed overall calibration of the analytical procedure; the sums of the integrals of the methyl groups were constant within $\pm 2\%$. No trend in this integral sum in either direction was observed within a kinetic run. This analytical procedure was also calibrated as follows. Different mixtures of (A), (B), and (C) were prepared by weighing and then rapidly dissolved in the basic solution, which was immediately

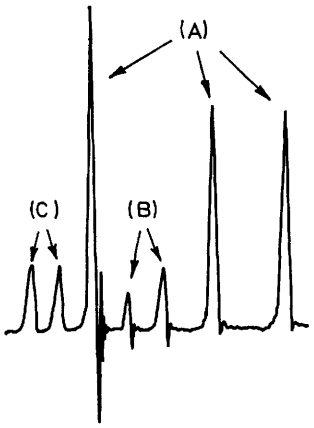


FIGURE 4 Methyl region of ^1H n.m.r. spectrum of reaction products

quenched, extracted, and analysed. The estimated mol % of each component did not deviate by more than 1 mol % from the value calculated from the original weights.

Small amounts of (d-B) formed in the kinetic runs starting with (d-A) and with EP as base were measured by using triangulation instead of electronic integration. This method was also calibrated, and the deviations of estimated and calculated (from weight data) values were <0.2 mol %. Consideration was always given to the influence of ^{13}C satellites and rotational side bands in ^1H n.m.r. spectra.

Quench–h.p.l.c. procedure. Kinetics with EP. A reaction flask (5 ml) equipped with a tight TFE-septum was filled with 5 ml of thermostatted base solution containing buffer. After 10 min in the thermostat, 10 μl (*ca.* 10 mg) of (A) was injected with a syringe and the solution was homogenized by shaking. The crystalline substrate (B) was weighed into the flask, which was then filled with the thermostatted base–buffer solution. When the kinetic run lasted for more than 24 h, the reaction mixture was distributed into small ampoules. From the flask or ampoule, 0.20 ml of the reaction solution was withdrawn with a syringe and rapidly transferred to a small tube containing 0.85 ml of a quench solution consisting of 2M-sulphuric acid in 40 wt % ethanol–water (15.6 ml 2M-H_2SO_4 diluted to 250 ml). Indicator paper showed the pH to be *ca.* 6. About 10 μl of this homogeneous quenched reaction solution was injected onto the analytical h.p.l.c. column. The areas under the separated peaks of (A), (B), and (C) were measured with a disc integrator. The relative extinction coefficients for the compounds were measured and these, together with the above areas, gave the mol % of each compound in the mixture. The relative extinction coefficients were determined using several standard mixtures of (A), (B), and (C) in ethanol–water prepared by weighing. 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 0.15 mol %. A data point in Figures 1 and 2 is the average of data from three different injections from the same quench solution.

Kinetics with Q. The preparation of the reaction solutions and the analytical procedure for the reaction mixtures were as with EP except as follows. The reactions were initiated by injection of 5 μl of a substrate solution (0.62M in methanol) into the thermostatted base–buffer solution. Samples (0.20 ml) were quenched with 60 μl of the quench solution. To check the material balance during the reactions, the following experiment was performed. Compound (B) was weighed into a flask, dissolved in dry methanol, and thermostatted at 20 °C. With a pipette, 3.00 ml of the solution was transferrred to a narrow-necked measuring flask and base and buffer were added. The concentrations of the reagents were as in the kinetic runs (Table 1). After 12 half-lives the reaction mixture was quenched with sulphuric acid solution and the volume adjusted. Of this quenched solution 15 μl was injected onto the h.p.l.c. column. The chromatogram showed only one peak, and the mean of results from 4 injections was calculated. As a reference, 3.00 ml of the original solution of (B) was diluted to the mark in the same narrow-necked measuring flask as above. Also 4 injections (15 μl) were made with this solution. As the relative extinction coefficients of (B) and (C) had already been determined, the possible loss of material during the reactions could be estimated to be $<1\%$.

Determination of the Equilibrium Constant ($K_{eq}^{H} = [(h\text{-}B)]/[(h\text{-}A)]$.—For this purpose a rearrangement catalyst (pyridine) was used that gave little elimination. Mixtures of (h-A) and (h-B) were prepared with compositions close to the equilibrium composition. The equilibrium was thus approached from both sides with 1M-pyridine in methanol in the presence of 0.030M-pyridine–acetic acid buffer. The analyses were made by the h.p.l.c. procedure described above. Values of K_{eq}^{H} were determined to be 19.9 ± 2.0 at 30.00 ± 0.03 °C and 20.8 ± 2.0 at 20.00 ± 0.03 °C.

Determination of Protium Content in the Product (d-C).—It was established that neither the elimination reactions nor the rearrangement of (d-A) and (d-B) with the various bases was accompanied by any significant deuterium–hydrogen exchange during the kinetic runs on the basis of the measured insignificant protium content at the 3-position of (d-C) (Table 5). This protium content was estimated as follows. The 2-position of (d-C) was assumed to contain no deuterium. The areas of the ^1H n.m.r. signals from the 2- and 3-protons (which are close together) were compared with the areas of the signals due to the aromatic protons in (d-C). The quotient of these areas was compared with the same quotient of a reference solution of (h-C) made from (h-B). The results are summarized in Table 5.

Evaluation of Rate Constants and Estimation of Errors.—The rate constants of the kinetics with EP, Q, and DABCO were evaluated by the manual method described above using plots of ln [mol % (A)] and ln [mol % (B)] *versus* time.

However, in the kinetics with Q and DABCO, the approximations used in the manual treatment were not as good as with EP or triethylamine (TEA), and to obtain more accurate phenomenological rate constants the concentration *vs.* time curves of Figures 2 and 3 were computer-simulated.

The rate equations of an analogous generalized reaction system have been worked out by Alberty and Miller.[17] The integrated expressions of equations (1)—(3) have the following forms.

Starting from pure (A) the concentrations of (A), (B), and (C) vary as follows:

$$\text{mol \% (A)} = a_1e^{-m_1t} + (100 - a_1)e^{-m_2t}$$
$$\text{mol \% (B)} = b_1e^{-m_1t} - b_1e^{-m_2t}$$
$$\text{mol \% (C)} = 100 + c_1e^{-m_1t} - (100 + c_1)e^{-m_2t}$$

Starting from pure (B), on the other hand, the following variations are obtained:

$$\text{mol \% (A)} = a_1e^{-m_1t} - a_1e^{-m_2t}$$
$$\text{mol \% (B)} = b_1e^{-m_1t} + (100 - b_1)e^{-m_2t}$$
$$\text{mol \% (C)} = 100 + c_1e^{-m_1t} - (100 + c_1)e^{-m_2t}$$

In these equations the parameters are related to the rate constants by the following equations:

$$a_1 = (k_{AB} + k_{AC} - m_2)/(m_1 - m_2)$$
$$b_1 = (k_{AB} + k_{AC} - m_1)(k_{AB} + k_{AC} - m_2)/k_{BA}(m_1 - m_2)$$
$$m_1 = [(k_{AB} + k_{AC} + k_{BA} + k_{BC})^2/4 - k_{AB}k_{BC} - (k_{BA} + k_{BC})k_{AC}]^{1/2} + \tfrac{1}{2}(k_{AB} + k_{AC} + k_{BA} + k_{BC})$$
$$m_2 = -[(k_{AB} + k_{AC} + k_{BA} + k_{BC})^2/4 - k_{AB}k_{BC} - (k_{BA} + k_{BC})k_{AC}]^{1/2} + \tfrac{1}{2}(k_{AB} + k_{AC} + k_{BA} + k_{BC})$$

A desk computer (Hewlett-Packard 9815A) connected to a plotter (Hewlett-Packard 9862A) was programmed with the integrated expressions above. The input in the calculations was the phenomenological rate constants, which were either guessed or taken from the manual treatment. The output was the concentration *vs.* time curves for (A), (B), and (C), and these data were compared with the experimental data. The input parameters were adjusted until the best fit to the observations was obtained. The various rate constants were varied independently through intervals which at their ends gave maximal deviation from the best fit. However, the curves were kept within experimental concentration error limits, *i.e.* ± 0.4 mol % in the h.p.l.c.-measured kinetics and ± 2 mol % in the ^{1}H n.m.r.-measured kinetics with DABCO. The best fits obtained are shown in Figures 1—3. All estimated errors are considered as maximum errors derived from maximum systematic errors and random errors estimated from calibration data. The maximum errors of the directly measured quantities were thus allowed to propagate as systematic errors into derived quantities, *e.g.* isotope effects. However, since only one stock solution for each base–buffer was used in all h.p.l.c. kinetic measurements, the error of the base concentration was not included in the error calculation. This error was $\leqslant 0.1\%$ in the concentration of EP and $\leqslant 0.4\%$ in Q.

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[17] R. A. Alberty and W. G. Miller, *J. Chem. Phys.*, 1957, **26**, 1231.