Stepwise Base-Promoted Elimination of Hydrochloric Acid via Hydrogen-Bonded Carbanions Studied by Reaction Branching and Extreme Deuterium Isotope Effects. Parallel Carbocationic and Carbanionic Reactions

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Abstract: Reaction of 1-(2-chloro-2-propyl)indene (*h*-**1**-Cl) with pyridine (P) in methanol at 30 °C results in base-promoted 1,2 elimination competing with base-catalyzed 1,3-proton transfer to give 1-isopropylideneindene (*h*-**3**) and 3-(2-chloro-2-propyl)indene (*h*-**2**-Cl), respectively. The latter product solvolyzes rapidly, yielding the two isomeric methyl ethers 3-(2-methoxy-2-propyl)indene (*h*-**2**-OMe) and 1-isopropylidene-2-methoxyindan (*h*-**4**) and the elimination product 3-(2-propenyl)indene (*h*-**6**). Compound **1** also solvolyzes, slowly, yielding mainly 1-(2-methoxy-2-propyl)indene (*h*-**1**-OMe) and a small amount of 1-(2-propenyl)indene (*h*-**5**). Reaction of (1,3-$^2H_2$)-1-(2-chloro-2-propyl)indene (*d*-**1**-Cl) with P yields the same spectrum of products as the reaction of *h*-**1**-Cl. However, some of the products are formed in strikingly different amounts. These results provide important mechanistic information. The reactions have been studied quantitatively by using an HPLC procedure. The base-catalyzed 1,3-proton transfer, i.e., the formation of **2**-Cl, shows an unusually large kinetic deuterium isotope effect, 14.6 ± 1.0, while the corresponding kinetic deuterium isotope effect on the reaction of **1**-Cl with P is only 5.6 ± 0.3. The extreme deuterium isotope effect is proposed to originate from reaction branching, i.e., that the base-promoted elimination and the base-catalyzed rearrangement of **1**-Cl make use of at least one common hydrogen-bonded carbanion intermediate. Thus, it is concluded that the potent leaving group Cl^- may also eliminate by an E1cB mechanism.

There is controversy about the border line between E2 and E1cB reaction mechanisms.[1,2] What is the dependence of the mechanism on structure? Do base-promoted elimination reactions simultaneously make use of both types of mechanisms or do they merge on crossing the mechanistic border? Moreover, much remains to be discovered about the role of ion pairs and other hydrogen-bonded intermediates in proton-transfer reactions. A major reason for this lack of knowledge is the great difficulty in detecting short-lived intermediates in these reactions. In the present paper, we have applied a new reaction-mechanism probe to detect such elusive intermediates, and results are reported showing that the chloride anion may also be a leaving group in stepwise base-promoted elimination reactions.

The reaction-mechanism probe is based upon a combination of reaction branching and hydrogen isotope effects. A reaction system has been designed in which the substrate has the possibility to undergo both base-promoted elimination and base-catalyzed 1,3-proton transfer (Scheme I).

In both of these reactions, the 1-proton has to be abstracted. If the two reactions are not coupled with common intermediates as in Scheme I but are parallel reactions, we would expect a normal hydrogen isotope effect for each of the reactions. However, if the reactions are coupled, extreme hydrogen isotope effects may be observed, as will be indicated below.

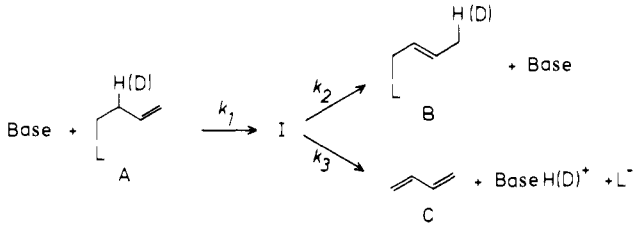
According to the steady-state approximation applied to the intermediate in Scheme I, the observed rate constant for the 1,3-proton-transfer reaction (k_{AB}) depends on the mechanistic rate constants, as in eq 1. For the observed deuterium isotope effect,

$$k_{AB} = k_1 \frac{k_2}{k_2 + k_3} \quad (1)$$

we obtain the expression in eq 2. Thus, the observed rearrangement isotope effect is a product of two primary isotope effects k_1^H/k_1^D and k_2^H/k_2^D and a third factor, the value of which depends on the relative importance of elimination from the hydrogen-bonded carbanion and the collapse of the intermediate to rearranged material. If $k_3 \gg k_2$, this factor is expected to be close to 1, since there is no proton transfer in the elimination of the hydrogen-bonded carbanion ion pair, and thus $k_3^H/k_3^D \sim 1$. Accordingly as a consequence of coupling of the reactions in Scheme I, we predict an extreme rearrangement isotope effect, since it is the product of two primary isotope effects. This novel probe of short-lived intermediates, the characteristics, possibilities, and limitations of which have been previously described, has been generalized.[2,3] Other extreme deuterium isotope effects reported

$$\frac{k_{AB}^H}{k_{AB}^D} = \frac{k_1^H}{k_1^D}\frac{k_2^H}{k_2^D}\frac{k_2^D + k_3^D}{k_2^H + k_3^H} \quad (2)$$

Scheme I



I = Base H$^+$, tightly hydrogen-bonded carbanion

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(1) (a) More O'Ferrall, R. A. *J. Chem. Soc. B*, **1970**, 274–277. (b) More O'Ferrall, R. A.; Warren, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 483–484. (c) More O'Ferrall, R. A.; Larkin, F.; Walsh, P. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1573–1579. (d) Carey, E.; More O'Ferrall, R. A.; Vernon, N. M. *Ibid.* **1982**, 1581–1586. (e) More O'Ferrall, R. A. Paper presented at the Proceedings from Symposium help at Uppsala, Sweden, 1977, Ahlberg, P., Sundelöf, L.-O., Eds.; Acta Universitatis Upsaliensis, Symposia Universitatis Upsaliensis, Annum Quingentesimum Celebrantis 12, Almqvist and Wiksell International: Storkholm, Sweden, pp 209–218. (f) Saunders, W. H., Jr. *Acc. Chem. Res.* **1976**, *9*, 19–25. (g) Baciocchi, E.; Ruzziconi, R.; Sebastiani, G. V. *J. Am. Chem. Soc.* **1983**; *105*, 6114–6120. (h) Gandler, J. R.; Jencks, W. P. *Ibid.* **1982**, *104*, 1937–1951. (i) Keefe, J. R.; Jencks, W. P. *Ibid.* **1983**, *105*, 265–279. (j) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161–169. (k) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375.

(2) (a) Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* **1979**, *101*, 7311–7317. (b) Thibblin, A. *Ibid.* **1983**, *105*, 853–858. (c) Thibblin, A. *Chem. Scr.* **1980**, *15*, 121–127. (d) Thibblin, A. *J. Chem. Soc., Chem. Commun.* **1984**, 92–93.

(3) (a) Ahlberg, P. *Chem. Scr.* **1973**, *3*, 183–189. (b) Ahlberg, P. *Ibid.* **1973**, *4*, 33–39. (c) Bengtsson, S.; Ahlberg, P. *Ibid.* **1974**, *6*, 45–46. (d) Thibblin, A.; Ahlberg, P. *Acta Chem. Scand., Ser. B* **1974**, *28*, 818–820. (e) Thibblin, A.; Ahlberg, P. *Ibid.* **1976**, *30*, 555–561. (f) Thibblin, A.; Bengtsson, S.; Ahlberg, P. *J. Chem. Soc., Perkin Trans. 2* **1977**, 1569–1577. (g) Thibblin, A.; Ahlberg, P. *J. Am. Chem. Soc.* **1977**, *99*, 7926–7930. (*i*) Thibblin, A.; Onyido, I.; Ahlberg, P. *Chem. Scr.* **1982**, *19*, 145–148. (j) Thibblin, A. *Ibid.* **1983**, *22*, 182–187.

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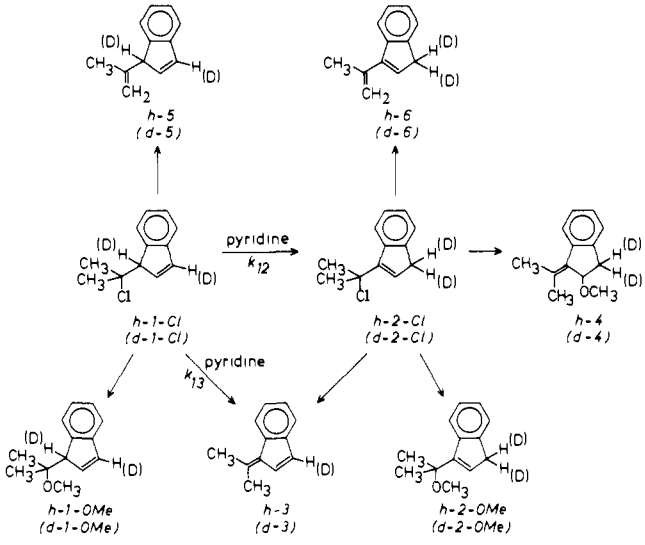
Table I. Product Compositions in the Reactions of **1**-Cl and **2**-Cl with 1.0 M Pyridine (P) in Methanol at 30.00 ± 0.03 °C in the Presence of 0.03 M PH^+

	area %[c]					
substrate[b]	**1**-OMe	**2**-OMe	**4**	**3**	**5** and **6**	**6**
h-**1**-Cl	0.5 ± 0.1	1.9 ± 0.1	1.2 ± 0.1	95.4 ± 0.2	1.0 ± 0.2	
d-**1**-Cl	2.6 ± 0.1	0.6 ± 0.1	0.4 ± 0.1	94.1 ± 0.6	2.1 ± 0.6	
h-**2**-Cl		59.5 ± 0.6	37.1 ± 0.5	1.7 ± 0.2		1.6 ± 0.3
d-**2**-Cl		60.0 ± 0.6	37.3 ± 0.5	1.0 ± 0.3		1.5 ± 0.2

[a] Not corrected for the relative response factors (extinction coefficients). [b] 0.7 or 2 mM (in the initial rate experiments). [c] Mean values from several experiments. The estimated errors are the standard deviations.

Scheme II



in the literature have also been proposed to originate from branched mechanisms rather than proton tunneling.[2a]

The Cl^--leaving group of **1**-Cl has been found to considerably stabilize the transition state passed on going from substrate to hydrogen-bonded carbanion intermediate by hyperconjugation. A unified interaction mechanism for E1cB and E2 transition states has been proposed.[2c,3g]

The results reported in the present investigation constitute further strong support for the conclusion that the pyridine-promoted elimination in methanol proceeds by an E1cB mechanism, or more exactly by a stepwise reverse preassociation mechansim. Comparison with earlier results and the need for internal consistency in interpretation of all results required the introduction of another hydrogen-bonded carbanion intermediate in the reaction mechanism.

Results

The reaction of 1-(2-chloro-2-propyl)indene (*h*-**1**-Cl) with pyridine (P) in the presence of 0.03 M PH^+ in methanol provides 1-isopropylideneindene (*h*-**3**) as the main product, accompanied by the ethers 1-(2-methoxy-2-propyl)indene (*h*-**1**-OMe), 3-(2-methoxy-2-propyl)indene (*h*-**2**-OMe), and 2-methoxy-1-isopropylideneindan (*h*-**4**) and the olefins 1-(2-propenyl)indene (*h*-**5**) and 3-(2-propenyl)indene (*h*-**6**) (Scheme II). It is concluded that the products *h*-**2**-OMe, *h*-**4**, and *h*-**6** originate from 3-(2-chloro-2-propyl)indene (*h*-**2**-Cl) which is initially obtained from *h*-**1**-Cl by a pyridine-catalyzed 1,3-proton-transfer reaction. This conclusion is based upon the observation that *h*-**2**-Cl reacts rapidly to form these products. Moreover, other indene derivatives with less efficient leaving groups easily undergo base-catalyzed 1,3-proton transfer.[3g]

The kinetics of the reactions were studied by a sampling-quench high-performance liquid chromatography procedure. The reaction conditions and product compositions are shown in Table I. Relative to *h*-**1**-Cl, the corresponding (1,3-$^2H_2$) analogue *d*-**1**-Cl reacts much more slowly and gives much less of the rearrangement product **2**-Cl, as concluded from the low yield of the products **2**-OMe and **4**-OMe. The disappearance of **1**-Cl was measured

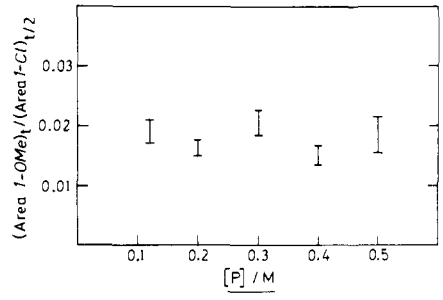


Figure 1. Rate of solvolysis (k_s) at different pyridine concentrations.

at appropriate intervals by comparing the peak area of **1**-Cl with that of 3-methylindene (R), which was added to the reaction solution as an internal standard. Strictly pseudo-first-order behavior was observed for the reaction in buffered pyridine–methanol solution. The observed rate constant consists of two pseudo-first-order rate constants, k_s and k_p', where k_s is the constant without added base and k_p' is the contribution from the base-promoted catalyzed reactions (eq 3).

$$-\frac{d[\mathbf{1}\text{-Cl}]}{dt} = (k_s + k_p')[\mathbf{1}\text{-Cl}] \quad (3)$$

In a separate experiment, the solvolysis of *h*-**1**-Cl in methanol was studied without added base. The main product was found to be **1**-OMe accompanied by a small amount of **3** and **5** (Table I). The rate constant k_s for formation of **1**-OMe was measured during the first 15% of reaction ($t_{1/2} \simeq 8$ weeks). The formation of **1**-OMe was also studied at different base concentrations but at constant buffer ratio. A possible decrease in k_s with increasing concentration of pyridine was not found (Figure 1). This indicates that the abstraction of a proton from the carbocation intermediate with pyridine is a much slower process than quenching with methanol.

When *h*-**2**-Cl or the (1,1-$^2H_2$) analogue *d*-**2**-Cl was reacted with pyridine in methanol under the same conditions as above, the main products were found to be **2**-OMe and **4** accompanied by small amounts of **3** and **6**. As shown in Table I, the product composition is the same, within experimental error, from reaction with labeled and unlabeled substrate. Since only a small amount of **3** is obtained, the solvolysis must be much faster than base-promoted elimination. The disappearance of *h*-**2**-Cl was found to have a rate constant of approximately 3×10^{-3} s^{-1}, i.e., with a half-life $t_{1/2} \approx 4$ min. The product composition did not change significantly during a period of 8 days which is the period during which the reaction of *d*-**1**-Cl was studied. Accordingly, it is possible in the kinetic studies with the substrate **1**-Cl to employ the formation of **4**, a compound which is clearly separated from the other components in the chromatogram, as a measure of the formation of **2**-Cl (k_{12} is proportional to k_{14}).

To obtain an accurate rate-constant ratio k_{14}^H/k_{14}^D ($=k_{12}^H/k_{12}^D$), it was necessary to utilize initial-rate measurements (see the Experimental Section). The measured rate constants and isotope effects are collected in Table II. We have previously measured k_p^H as 7.5 ± 0.4 M^{-1} s^{-1} (under slightly different experimental conditions) employing a quench-extraction ^1H NMR procedure.[3g]

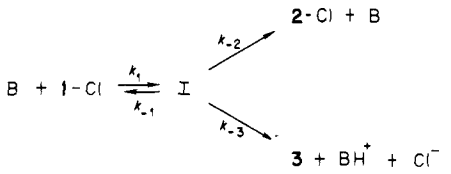
The incorporation of protium in *d*-**1**-Cl was measured to < 1 atom % H after 50% reaction with pyridine in methanol.

Table II. Rate Constants and Isotope Effects for Reactions of **1**-Cl in Methanol at 30.00 ± 0.03 °C

substrate	$10^6(k_p' + k_s)$,[a] s^{-1}	$10^6 k_s$,[b] s^{-1}	$10^6 k_p$, M^{-1} s^{-1}	k_p^H/k_p^D	$k_{12}^H/k_{12}^D = k_{14}^H/k_{14}^D$
h-**1**-Cl	8.12 ± 0.15	0.12 ± 0.02	8.0 ± 0.02	5.6 ± 0.4	14.6 ± 1.0
d-**1**-Cl	1.57 ± 0.07	0.14 ± 0.02	1.4 ± 0.01		

[a] Observed rate constant in the presence of 1.0 M pyridine. [b] Observed rate constant without added base.

Scheme III



I = BH^+, tightly hydrogen-bonded carbanion

Discussion

The increased isotope effect of the pyridine-catalyzed 1,3-proton transfer, $k_{12}^H/k_{12}^D = 14.6 \pm 1.0$, is a very strong indication that the reaction has a common intermediate with the 1,2 elimination (Scheme III). Much smaller values have been measured for 1,3-proton transfer that does not compete with elimination.[3f,g]

The competition between the elimination and the collapse of the tightly hydrogen-bonded carbanion which follows a rate-limiting transition state may account for the amplified rearrangement isotope effect, as shown below.

Application of the steady-state approximation yields eq 4–7, which relate the phenomenological and microscopic rate constants and isotope effects. All the rate constants except k_{-3} involve

$$k_{12} = k_1 \frac{k_{-2}}{k_{-1} + k_{-2} + k_{-3}} \quad (4)$$

$$k_{13} = k_1 \frac{k_{-3}}{k_{-1} + k_{-2} + k_{-3}} \quad (5)$$

$$\frac{k_{12}^H}{k_{12}^D} = \frac{k_1^H}{k_1^D}\frac{k_{-2}^H}{k_{-2}^D}\frac{k_{-1}^D + k_{-2}^D + k_{-3}^D}{k_{-1}^H + k_{-2}^H + k_{-3}^H} \quad (6)$$

$$\frac{k_{13}^H}{k_{13}^D} = \frac{k_1^H}{k_1^D}\frac{k_{-3}^H}{k_{-3}^D}\frac{k_{-1}^D + k_{-2}^D + k_{-3}^D}{k_{-1}^H + k_{-2}^H + k_{-3}^H} \quad (7)$$

breaking or forming carbon–hydrogen bonds and are expected to exhibit substantial isotope effects since carbon–hydrogen bonds in substrates having pK_a values close to one another (the equilibrium constant for the corresponding acetates **1**-OAc and **2**-OAc is 20[3f]) are broken or formed in these processes.[2a,b] The isotope effect on k_{-3}, on the other hand, is expected to be close to 1, since k_{-3} only involves cleavage of a hydrogen bond to carbon.

As discussed several times previously, the implication of this reasoning is that the ionization isotope effect k_1^H/k_1^D is multiplied by a factor larger than unity which amplifies the rearrangement isotope effect (eq 6). On the other hand, the isotope effect of the 1,2-elimination reaction is attenuated by multiplication of the ionization isotope effect by a factor less than unity (eq 7), in accord with the experimental results.

According to eq 6, the degree of amplification is determined by the relative amount of elimination. A small fraction of elimination ($k_{-2} \gg k_{-3}$) implies a normal rearrangement isotope effect and a large attenuation of the elimination isotope effect. On the other hand, an enhanced fraction of elimination amplifies the rearrangement isotope effect and increases the elimination isotope effect. The maximum limits are obtained in the absence of internal return and equal the ionization isotope effect times the collapse isotope effect (i.e., $k_{12}^H/k_{12}^D \leq k_1^H/k_1^D \times k_{-2}^H/k_{-2}^D$) and the ionization isotope effect (i.e., $k_{13}^H/k_{13}^D \leq k_1^H/k_1^D$), respectively. A rearrangement isotope effect close to this upper limit ($k_{12}^H/k_{12}^D = 89 \pm 25$) has been measured for the quinuclidine-catalyzed 1,3-proton transfer of 1-(2-acetoxy-2-propyl)indene (**1**-OAc) in 35 wt % Me_2SO in water at 20 °C.[3j] This reaction competes very unsuccessfully with elimination; the isotope effect of the total reaction, $(k_{12}^H + k_{13}^H)/(k_{12}^D + k_{13}^D) = 9.1 \pm 0.2$, is consistent with a very small amount of internal return. In methanol with the same base and substrate, the isotope effects were found to be smaller, $(k_{12}^H + k_{13}^H)/(k_{12}^D + k_{13}^D) = 7.1 \pm 0.2$ and $k_{12}^H/k_{12}^D = 18.1 \pm 1.1$.[3f]

The measured isotope effect $(k_{12}^H + k_{13}^H)/(k_{12}^D + k_{13}^D)$ of 5.6 ± 0.4 for reaction of **1**-Cl is lower than those measured for reaction of **1**-Cl with stronger bases in methanol, where no 1,3-proton transfer was observed. The isotope effects 8.4 ± 0.4, 7.9 ± 0.5, and 7.1 ± 0.2 were obtained for the 1,2 elimination employing triethylamine, *N*-ethylpiperidine, and sodium methoxide, respectively, in methanol at 30 °C.[3g] It is also considerably lower than most of the isotope effects measured for the total reaction, i.e., 1,2 elimination plus 1,3-proton transfer, of 1-(2-acetoxy-2-propyl)indene (**1**-OAc) in methanol[3f] and in aqueous solvents.[3j] The largest value was measured with quinuclidine in Me_2SO–H_2O, $(k_{12}^H + k_{13}^H)/(k_{12}^D + k_{13}^D) = 9.1 \pm 0.2$.[3j] The magnitude has been found to increase with increasing solvent polarity and pK_a of the proton-abstracting tertiary amine. Thus, it is likely that the ionization of **1**-Cl with the weak base pyridine is subject to some internal return from a tightly hydrogen-bonded carbanion intermediate that is the cause of the moderate isotope effect measured in this work. An alternative explanation is a Melander–Westheimer effect; i.e., the transition state is unsymmetrical with respect to proton transfer.[4]

Another possible explanation for lower-than-maximum isotope effect may be that some of the elimination product is formed via a mechanism in which the proton abstraction takes place by a carbocation route. This mechanism would then require ionization to a carbocation or ion pair followed by proton abstraction by pyridine. It cannot be ruled out that a trace of **3** is formed by such a mechanism. However, according to the fact that the rate constant for the formation of **1**-OMe does not decrease with increasing concentration of base, only a negligible fraction of **3** is formed via a carbocation route. Exchange of protium for deuterium in the substrate is not significant and cannot explain the lower-than-maximum isotope effect.

Why is the rearrangement isotope effect k_{12}^H/k_{12}^D only 15 and not larger as expected in view of the large fraction of elimination? Internal return cannot be the sole reason. Calculations employing reasonable isotope effects on the microscopic rate constants yield a much larger value.

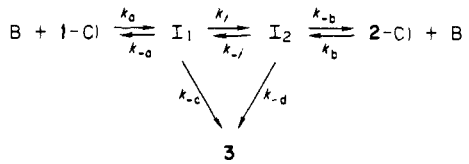
The possibility that the 1,3-proton transfer is not completely intramolecular may be ruled out by the following considerations. The closely related substrate *d*-**1**-OAc reacts with diazabicyclo[2.2.2]octane in methanol to give d-**2**-OAc with 100 ± 5% intramolecularity.[2d] Pyridine, which is a weaker base by 3–4 pK_a units, corresponds to a stronger acid and should hydrogen bond more strongly to the carbanion. Moreover, if a small part of the free carbanion is formed, it should rapidly expel Cl^- rather than undergo electrophilic attack by a solvent molecule or by PH^+.

The reason to the relatively small value of k_{12}^H/k_{12}^D is presumably that the intermediate formed from **1**-Cl has the conjugate acid of the base hydrogen-bonded to carbon 1 of the allylic anion which is converted to a second intermediate of the same type but with the aminium ion hydrogen-bonded to carbon 3. The intermediates cannot be in equilibrium with each other since that situation is kinetically indistinguishable from the one-intermediate mechanism of Scheme III.

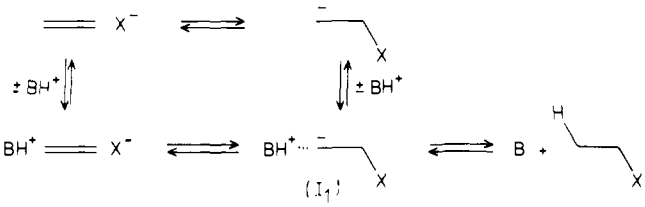
We have previously concluded that the reactions of **1**-OAc proceed in accord with this mechanistic model (Scheme IV), both

(4) (a) Melander, L. "Isotope Effects on Reaction Rates"; Ronald Press: New York, 1960; pp 24–32. (b) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265–273.

Scheme IV



Scheme V



with tertiary amines[3f] and with p-$NO_2C_6H_4O^-$.[2b] The assignment was based upon smaller amplifications of the rearrangement isotope effects than expected, as in this work, and, a ratio between the ionization isotope effects $(k_a^H/k_a^D)/(k_b^H/k_b^D)$ considerably larger than the expected value of ca. 0.9.[3f,3j] For example, a ratio of 2.5 was measured for the substrates **1**-OAc and **2**-OAc with quinuclidine in methanol.[3f] It was concluded that both I_1 and I_2 undergo elimination to the olefin **3**.

The following expression is obtained for the rearrangement rate constant k_{12} when the steady-state approximation is applied to Scheme IV:

$$k_{12} = k_a k_{-b} \frac{k_i}{(k_{-a} + k_{-c} + k_i)(k_{-b} + k_{-d} + k_{-i}) - k_i k_{-i}} \quad (8)$$

The rate constants k_i and k_{-i} for the interconversion of the hydrogen-bonded intermediates are expected to show low sensitivity to isotopic substitution. Thus, as discussed above for Scheme III, only k_a, k_{-a}, k_b, and k_{-b} should give normal isotope effects.

If we assume for the moment that internal return is negligible, i.e., $k_{-a} \ll k_{-c} + k_i$, it is easy to see the implications of different extremes of the two-intermediate mechansim. For example, if no elimination from I_1 occurs, our experimental data requires that $k_{-d} \gg k_{-b}$, which means that k_{12}^H/k_{12}^D has a maximum value equal to $(k_a^H/k_a^D)(k_{-b}^H/k_{-b}^D)$. This maximum is also attained when return of I_2 to I_1 is fast ($k_{-i} \gg k_{-b}$). A normal value of k_{12}^H/k_{12}^D is adopted if collapse if I_2 is much faster than return of I_2 to I_1 ($k_{-b} \gg k_{-i}$) and also much faster than reaction to olefin ($k_{-b} \gg k_{-d}$).

The moderate amplification of k_{12}^H/k_{12}^D obtained with **1**-Cl is probably the result of a large amount of elimination from I_1, a fast collapse of I_2 to **2**-Cl, and some return of I_1 to starting material. This conclusion is in accord with the magnitude of the rearrangement isotope effect which is obtained by simulation of eq 8, employing experimental data and expected rate constant ratios and isotope effects. However, it is not required that any elimination product arises from I_2 (as it was with **1**-OAc).

Indications have been obtained previously that the 1,2 elimination of HCl and the 1,3-proton transfer are coupled.[3g] Thus, the total reaction rate (=elimination plus 1,3-proton transfer) of **1**-X, where X is a potential leaving group, was found to increase with enhanced polarity of the substituent X and with increased ability of X to stabilize the transition state by hyperconjugation. However, enhanced leaving-group ability of X decreases the rearrangement rate drastically which strongly supports a coupled mechanism.

Intuitively, it appears reasonable that the expulsion of Cl^- occurs directly from the hydrogen-bonded intermediate(s) and not from the "free" solvent-equilibrated carbanion(s). Discussion of these mechanistic details may be based upon Scheme V.

The expulsion of X^- from I_1 corresponds to a reverse stepwise preassociation mechansim. It has recently been found that the elimination reaction of **1**-OAc with 1,4-diazabicyclo[2.2.2]octane (DABCO) in methanol has a mechanism of this type.[2d] This

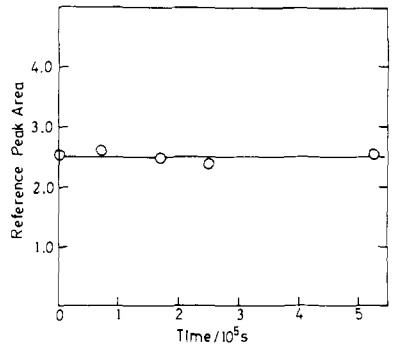


Figure 2. Check by HPLC of the stability of the reference, 3-methylindene, in buffered pyridine–methanol solution.

conclusion was based upon protium incorporation experiments with the corresponding methyl ether *d*-**1**-OMe. Of course, the expulsion of the more efficient leaving group Cl^- occurs more rapidly than that of ^-OAc. Moreover, the protonated acid (PH^+) of pyridine is a stronger acid than $DABCOH^+$, and this stabilizes the hydrogen-bonded intermediate relative to the solvent-equilibrated carbanion. The barrier for expulsion of the leaving group X^- is probably not influenced to the same extent by change in hydrogen-bonded acid. Accordingly, we conclude that the elimination of HCl from **1**-Cl also proceeds by the reverse stepwise preassociation mechanism.

Reaction of I_2 (Scheme IV) to **3** is a 1,4 elimination. It is not clear, if it occurs, whether Cl^- is expelled in just one step or whether it is a multistep process, i.e., proceeds via the free carbanion.

We consider it very likely that many other base-promoted elimination reactions follow a reverse stepwise preassociation mechanism. This hypothesis is supported by the fact that many elimination reactions from relatively acidic substrates show low kinetic deuterium isotope effects. These low effects may be caused by internal return from a tightly hydrogen-bonded carbanion which expels the leaving group more easily than the conjugate acid of the proton-abstracting base diffuses away. The stabilization of the intermediate is obtained both from the hydrogen bonding and from hyperconjugation of the potential leaving group. A classical example is the triethylamine-promoted elimination of HBr from *cis*-1,2-dibromoethene in dimethyl formamide investigated by Miller and co-workers.[5] The isotope effect of this reaction was measured as $k^H/k^D = 1.0$. Elimination reactions that exhibit large isotope effects are usually more difficult to classify.

Parallel E2, E1, and E1cB Reactions? Another alternative to the relatively low elimination isotope effect and the smaller value of the rearrangement isotope effect than expected may be that a part of the elimination of HCl occurs via a parallel E2 reaction having a relatively low isotope effect. The existence of a carbocation intermediate is indicated by the production of solvolysis products. An E1 route should therefore be possible with pyridine provided that the base-carbocation complex has a lifetime long enough ($>10^{-13}$ s) to be considered as an intermediate. However, as discussed above, this route is of very little importance in this system since the carbocation intermediate is attacked much more rapidly by the methanol to give ether than it undergoes proton abstraction by pyridine or methanol. The transition state of the E1 mechanism has a substantial bond rupture to the leaving group. The E1cB mechanism has the proton approximatively half transferred in the transition state. The E2 transition state, on the other hand, should involve a less transferred proton than that of the E1cB route as well as less bond rupture to the leaving group than the E1 route. The three possible routes are visualized in Figure 3.

Experimental Section

General. The high-performance liquid chromatography (HPLC) analyses were made with a Hewlett-Packard 1084 B liquid chromatograph equipped with a variable wavelength detector. The column was a reversed-phase C8 (4.6 × 230 mm), and the mobile phase was 45 vol % ethanol in water. The samples were analyzed at 254 nm (reference

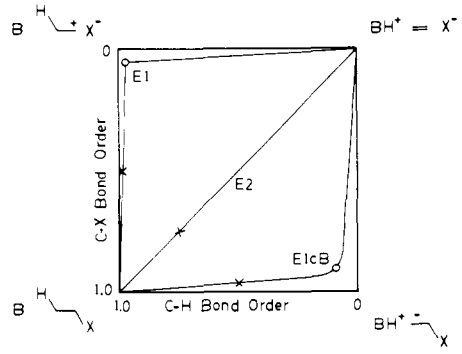


Figure 3. Reaction coordinate energy diagram for elimination of HCl from **1**-Cl promoted by pyridine in methanol. The energy contours are omitted. The rate-limiting transition states are indicated by crosses and the intermediates by dots.

beam 430 nm). The ^{1}H NMR analyses were carried out with a JEOL FX 100 spectrometer equipped with a 5-mm dual probe or a JEOL FX 60 spectrometer with a 5-mm or 10-mm probe. The kinetics were performed in a HETO 01 PT 623 thermostat at a constant temperature of 30.00 ± 0.03 °C measured with a calibrated mercury thermometer. Methanol (Merck, for UV spectroscopy) was stored over 0.3-nm molecular sieves. Pyridine (Mallinckrodt, p.a.) was stored over 0.5-nm molecular sieves and potassium hydroxide for 4–8 days and then decanted and distilled from potassium hydroxide and 0.5-nm molecular sieves in a dry nitrogen atmosphere. Gas–liquid chromatography was used to determine the purity of pyridine.[3f] 1,1,1-Trichloroethane (Analytical Reagent, BDH Chemicals Ltd.) was used without any purification. Anhydrous sulfuric acid was made by addition of fuming sulfuric acid (p.a.) to 98% sulfuric acid (p.a.).[6] A stock solution of pyridine was prepared by dissolving freshly distilled pyridine in dry methanol followed by addition of anhydrous sulfuric acid.

Substrates. The syntheses of the starting materials 1-(2-chloro-2-propyl)indene (*h*-**1**-Cl) and (1,3-$^2H_2$)-1-(2-chloro-2-propyl)indene (*d*-**1**-Cl), together with the syntheses of the rearranged isomers 3-(2-chloro-2-propyl)indene (*h*-**2**-Cl) and (1,1-$^2H_2$)-3-(2-chloro-2-propyl)indene (*d*-**2**-Cl), from the corresponding alcohols have been published previously.[3g] HPLC analyses of small samples of **2**-Cl solvolyzed in methanol showed a residue of less than 0.4% of starting material. ^{1}H NMR analyses showed less than 3% of olefin **3**. The syntheses of 3-(2-methoxy-2-propyl)indene (**2**-OMe), 1-isopropylidene-2-methoxyindan (**4**), and 3-(2-propenyl)indene (**6**) have been reported recently.[7] The deuterium content in the 1 and 3 positions of *d*-**1**-Cl was 98.2 ± 1.0 atom % (^{1}H NMR),[3g] and the deuterium content of *d*-**2**-OH, from which *d*-**2**-Cl was made, was 98.3 ± 1.0 atom % in the 1 position (^{1}H NMR).

Determination of Observed Rate Constant ($k_p + k_s$) of Reaction of 1-Cl with Pyridine. Base solution (3 mL) was thermostated in a 5-mL reaction vessel equipped with a TFE stopcock (high-vacuum type). Internal standard (0.6 μL), 3-methylindene (R), was added. The reaction was initiated by injecting 4 μL of the substrate under nitrogen. Samples (300 μL) were withdrawn and quenched by shaking vigorously with a mixture of 500 μL of 1,1,1-trichloroethane, 30 mL of sulfuric acid (20 mM), and 20 g of ice. After centrifugation, the trichloroethane phase was shaken once more with 30 mL of water and 20 g of ice followed by a second centrifugation. A part of the trichloroethane phase (180 μL) was finally diluted with 500 μL of ethanol and analyzed 3 times with HPLC (Figure 4). The rate constant was obtained from a semilogarithmic plot of the area ratio of **1**-Cl and R vs. time. A check was made in a separate experiment that a second wash in the extraction procedure did not alter the product composition.

The product ratios at 100% reaction were extrapolated from the data at 15–70% reaction of **1**-Cl.

The ratio (area of **1**-Cl)/(area of R) varied with $2\sigma = 1\%$ for six analyses of the same sample. Estimation of errors was based on the maximum error in the determination of ($k_p^H + k_s^H$) and ($k_p^D + k_s^D$) in four and five kinetic runs, respectively, and the error in base concentration.

Determination of the Rate of Solvolyses (k_s) of 1-Cl in Methanol. Methanol (3 mL) was thermostated in a gas-tight reaction vessel in a dry nitrogen atmosphere. After 4 μL of the substrate and 0.6 μL of 3-methylindene (R) were injected, 100 μL of the solution was transferred to 1.5-mL sealed vials, containing 900 μL of prethermostated methanol. The samples were analyzed by HPLC during 15% reaction.

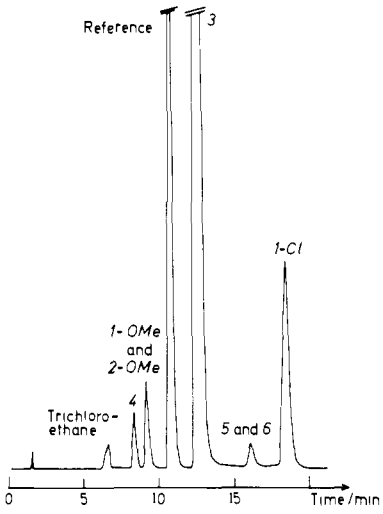


Figure 4. HPLC chromatogram from the reaction of *h*-**1**-Cl with pyridine in buffered methanol solution.

A rate constant, k_s, for the disappearance of **1**-Cl was obtained from a plot of mol % **1**-OMe vs. time, assuming **1**-OMe to be the only product since only traces of **3** and **5** were formed. The error in k_s was estimated from the maximum error in the determination of mol % **1**-OMe. The used extinction-coefficient ratio for **1**-OMe and **1**-Cl was ϵ(**1**-OMe)/ϵ(**1**-Cl) = 1.27.

Studies of Product Composition at Different Base Concentrations. A series of five concentrations of pyridine (P) in methanol was prepared from the buffered stock solution of P. Reaction conditions were otherwise as described for the determination of the observed rate constants above but without addition of reference. Samples (1500 μL) were withdrawn after 25 h, the reaction time being the same for all base concentrations, and quenched by shaking with mixtures of 500 μL of 1,1,1-trichloroethane and 30 mL of sulfuric acid (15, 13, 10, 7, and 3 mM for 0.1, 0.2, 0.3, 0.4, and 0.5 M P, respectively). The mixtures were centrifugated, and the trichloroethane phase was washed once more with 20 g of ice in 30 mL of water, followed by centrifugation. The trichloroethane phase was then diluted with 500 μL of ethanol and analyzed with HPLC. All peaks were enlarged and integrated with a desk computer equipped with a digitizer.

Plots of area ratio between **3** and **1**-OMe vs. base concentration yielded an intercept close to zero. The rate of formation of **1**-OMe, k_s, for a given concentration of base is

$$\frac{d[\textbf{1}\text{-OMe}]}{dt} = k_s[\textbf{1}\text{-Cl}]$$

During the initial time, t, of reaction, this can be approximated by

$$\frac{\Delta[\textbf{1}\text{-OMe}]}{\Delta t} = k_s \frac{[\textbf{1}\text{-Cl}]_0 + [\textbf{1}\text{-Cl}]_t}{2}$$

The rate constant k_s, as a function of base concentration, can be represented by plotting the ratio between the area of **1**-OMe at the time of quenching, t, and the mean peak area of **1**-Cl during the time interval Δt vs. base concentration (Figure 1). The error in each data point is the maximum error in determining the ratio for two samples from the same reaction medium quenched at the same time.

The stability of the reference in the reaction medium was checked in the following way. A buffered base solution of 3-methylindene (3 mM, i.e., the same concentration as in the kinetic runs) was thermostated at 30.00 ± 0.03 °C during a time interval corresponding to $t_{1/2}$ of *d*-**1**-Cl in the medium. Double samples (300 μL) were withdrawn from the solution by using a 500-μL syringe and quenched by the extraction procedure described for the kinetic experiments. The trichloroethane solution (200 μL) was diluted with 500 μL of ethanol. The samples (50 μL) were analyzed by HPLC and the mean values of that area of R for the double samples were ploted vs. time (Figure 2). No other products were detected.

Reaction of 2-Cl with Pyridine. Base solution (3 mL) was thermostated under nitrogen, and 3 μL of each of **2**-Cl and R was injected. Samples were withdrawn and quenched by the same procedure used in the kinetic experiments with **1**-Cl. The product composition was studied during the time corresponding to 75% reaction of **1**-Cl in the same me-

(5) Kwok, W. K.; Lee, W. G.; Miller, S. I. *J. Am. Chem. Soc.* **1969**, *91*, 468–476.

(6) Gordon, A. J.; Ford, R. A. "The Chemist's Companion"; Wiley: New York, 1972; pp 436.

(7) Thibblin, A. *J. Chem. Soc., Perkin Trans. 2*, in press.

dium. Each sample was analyzed twice with HPLC with a maximum error of <1% in the determination of (area of **2**-OMe)/(area of R) and (area of **4**)/(area of R) and a maximum error of <10% in the determination of (area of **3**)/(area of R) and (area of **6**)/(area of R).

The rate of disappearance of *h*-**2**-Cl was measured by withdrawing samples of the reaction solution and allowing the unreacted *h*-**2**-Cl to react with 25 vol % acetonitrile/water to form the corresponding allylic alcohols before carrying out the extraction procedure.[7] Analyses were made by HPLC. Plots of ln [(area of alcohols)/(area of R)] vs. time yielded the rate constant.

Measurement of Rearrangement Isotope Effect (k_{12}^H/k_{12}^D). To 100 mL of the buffered base solution was added 0.6 μL of 3-methylindene (R). The same stock solution of base was used in the reactions of both *h*-**1**-Cl and *d*-**1**-Cl. About 0.06 g of the substrate was weighed into a 25-mL flask sealed with a tight TFE septum, and the reaction was initiated by filling the flask with prethermostated base solution. Four samples were withdrawn after 10% reaction and quenched by the extraction procedure described above. Trichloroethane solution (230 μL) was transferred after the second centrifugation and diluted with 500 μL of ethanol. The samples were analyzed 3–8 times with HPLC and the peaks of R and **4** were then greatly enlarged, so that the areas could be integrated with a desk computer equipped with a digitizer.

The isotope effect of the formation of the ether, **4**, is also the isotope effect on the rearrangement since the product compositions obtained from *h*-**2**-Cl and *d*-**2**-Cl were found to be constant and equal, within experimental error. In an initial-rate experiment, the concentration of **1**-Cl was approximated with the average concentration at time zero and the sampling time. Accordingly, the formation of **4** will be linear (eq 9). The

$$\frac{\Delta[\mathbf{4}]}{\Delta t} \approx k_{14}([\mathbf{1}\text{-Cl}]_0 + [\mathbf{1}\text{-Cl}]_t)/2 \tag{9}$$

$$\frac{k_{12}^H}{k_{12}^D} = \frac{k_{14}^H}{k_{14}^D} = \frac{\left(\dfrac{\text{area of } (h\text{-}\mathbf{4})}{\text{area of R}}\right)}{\left(\dfrac{\text{area of } d\text{-}\mathbf{4}}{\text{area of R}}\right)} \frac{\Delta t^D}{\Delta t^H} \frac{[d\text{-}\mathbf{1}\text{-Cl}]_0 + [d\text{-}\mathbf{1}\text{-Cl}]_t^D}{[h\text{-}\mathbf{1}\text{-Cl}]_0 + [h\text{-}\mathbf{1}\text{-Cl}]_t^H} \tag{10}$$

isotope effect was calculated by employing eq 10. The error in determining the area ratio of *h*-**4** and R was estimated to $2\sigma = 3\%$ and the error in area ratio of *d*-**4** and R to $2\sigma = 10\%$. Evaluation of the error in the rearrangement isotope effect was based on the average of maximum errors from five experiments.

Isotopic-Exchange Experiments. The extent of incorporation of protium into *d*-**1**-Cl was determined by ^{1}H NMR analysis (100 MHz, CCl_4) of a sample from the reaction of *d*-**1**-Cl using the same concentration of substrate, base, and buffer as in the determination of the rearrangement isotope effect. The reaction solution (25 mL) was quenched after 52% reaction by shaking it vigorously with a mixture of 25 mL of 0.5 M aqueous sulfuric acid solution and 5 mL of carbon tetrachloride. The organic phase was washed with water until neutral and once with brine and then evaporated to 1 mL.

Registry No. *h*-**1**-Cl, 64909-94-0; *h*-**2**-Cl, 98800-46-5; deuterium, 7782-39-0.

The Octant Rule. 17. Front Octant Effects: Synthesis and Circular Dichroism of *syn*-(1′*R*)-Spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] and *syn*-(1′*S*)-Spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)][1]

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Abstract: Optically active (1*R*,3*S*)-4(*R*)(a)-methyladamantan-2-one (**3**) has been synthesized and converted to the isomeric *syn*- (**1**) and *anti*-(1′*R*)-spiro[cyclobutan-2-one-1,2′-(4′(a)-methyladamantane)] (**2**) by spiroannelation methods. Similarly, (1*S*,4*R*)-*exo*-2(*R*)-methylbicyclo[2.2.1]heptan-7-one (**15**) was converted to *syn*-(1′*S*)-spiro[cyclobutan-2-one-1,7′-(2′-*exo*-methylnorbornane)] (**14**). The ring skeletons of **1** and **14** are essentially symmetric, and all normal back octant (rule) perturbers cancel. The lone dissymmetric methyl group, however, lies in front of the carbonyl oxygen and is observed to control the sign and magnitude of the circular dichroism Cotton effect with a strong front octant contribution.

The octant rule[2,3] for the n → π* transition of saturated alkyl ketones was formulated over 25 years[4] ago and has since become one of the most important chirality rules for extracting stereochemical and conformational information from optically active ketones. The octant rule is derived from the local symmetry (C_{2v}) of the carbonyl group and a consideration of the relevant orbitals of the n → π* transition. The two well-defined carbonyl symmetry planes (*XZ* and *YZ*, Figure 1) divide all space about the C=O (C at origin) group into quadrants (hence a quadrant rule) and a third, ill-defined, non-symmetry-derived nodal surface further divides all space into octants (hence the octant rule). The shape of this third nodal surface was crudely *approximated* as a plane (A, Figure 1) bisecting the C=O bond, and recently it has become more accurately pictured on the basis of theory[3a] and experiment[3b] as a convex surface (B, Figure 1) cutting *behind* the carbonyl carbon and bending outward in the +*Z* direction. The octant occupied by a particular perturber determines the sign of its contribution to the rotatory strength of the n → π* transition. Reflection of the perturber across either of the *XZ* or *YZ* symmetry planes leads to a mirror image molecular fragment and hence one with an oppositely signed rotatory strength contribution. Since the third nodal surface does not follow from symmetry,

(1) For Part 16, see: Lightner, D. A.; Pak, C. S.; Crist, B. V.; Rodgers, S. L.; Givens, J. W., III *Tetrahedron*, in press.

(2) (a) Moffitt, W.; Woodward, R. B.; Moscowitz, A.; Klyne, W.; Djerassi, C. *J. Am. Chem. Soc.* **1961**, *83*, 4013–4018. (b) The octant rule was given earlier in: Djerassi, C. "Optical Rotatory Dispersion"; McGraw-Hill: New York, 1961; Chapter 13. (c) For leading references, see: Deutsche, C. W.; Lightner, D. A.; Woody, R. W.; Moscowitz, A. *Annu. Rev. Phys. Chem.* **1966**, *20*, 407–448.

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