Borderline between E1cB and E2 Mechanisms. Chlorine Isotope Effects in Base-Promoted Elimination Reactions

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The chlorine leaving group isotope effect has been measured for the base-promoted elimination reaction of 1-(2-chloro-2-propyl)indene (**1-Cl**) in methanol at 30 °C: $k^{35}/k^{37} = 1.0086 \pm 0.0007$ with methoxide as the base and $k^{35}/k^{37} = 1.0101 \pm 0.0001$ with triethylamine (TEA) as the base. These very large chlorine isotope effects combined with large kinetic deuterium isotope effects of 7.1 and 8.4, respectively, are consistent not with the irreversible E1cB mechanism proposed previously (*J. Am. Chem. Soc.* **1977**, *99*, 7926) but with the E2 mechanism with transition states having large amounts of hydron transfer and very extensive cleavage of the bond to chlorine.

Introduction

The mechanistic borderline between one-step and multistep reactions has always been of a large general interest to organic chemists. One of the most studied reactions is the base-promoted 1,2-elimination reaction. There has for a long time been a controversy about the position and the nature of the mechanistic borderline between stepwise elimination via a carbanionic intermediate (E1cB) and concerted one-step elimination (E2).[1,2] What is the dependence of mechanism on structure? Is a stepwise reaction possible for very efficient leaving groups? Do the mechanisms merge at the borderline, i.e., is there a mechanistic continuity, or are both pathways employed simultaneously? Figures 1a and 1b show schematic potential energy diagrams for reactions at the borderline for which the transition states are identical and different, respectively.

Chloride anion is normally an efficient leaving group in elimination reactions, and a putative carbanion intermediate with a β-chloro-substituent may not have a significant lifetime. The reaction then occurs through a one-step mechanism that is enforced by the nonexistence of a barrier for the departure of the leaving group (Figure 1a). However, it has been shown by employing a special type of reaction mechanism probe that the pyridine-promoted elimination of HCl from **1-Cl** in methanol (Scheme 1) occurs stepwise through a carbanion hydrogen bonded to the hydronated pyridine as shown schematically in Scheme 2.[3] This mechanism probe is based upon a combination of reaction branching and hydrogen isotope effects.[4] With stronger tertiary amines such as triethylamine (TEA) and with methoxide ion, there is no compet-

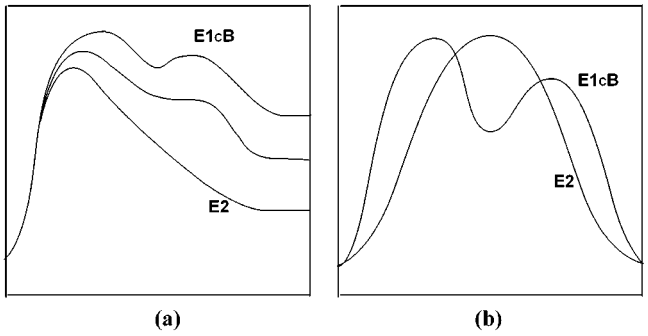
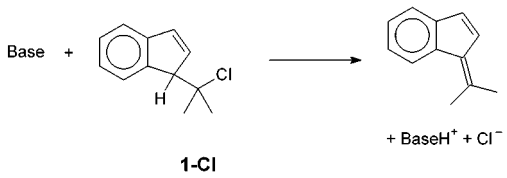


Figure 1. Schematic diagrams showing the potential energy−reaction coordinate diagrams for the E1cB−E2 mechanistic borderline: (a) merging at the mechanistic borderline, (b) nonequivalent transition states.

Scheme 1



1-Cl

Scheme 2

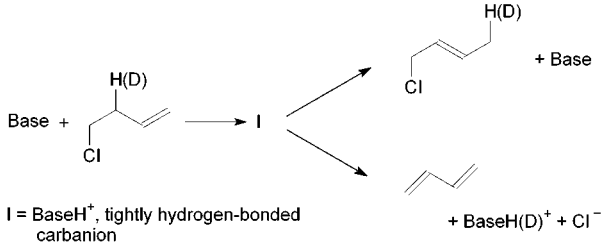


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Table 1. Kinetic Chlorine Isotope Effect for the Methoxide-Ion-Promoted Elimination Reaction of 1-Cl at 30.00 ± 0.03 °C[a] (See eq 1)

sample	f[b]	$1/R_f$[c]	k^{35}/k^{37}[c,d]
		Methoxide Ion (Exp 1)	
A	0.0973	0.32104 ± 0.00023	1.0093
B	0.1883	0.32134 ± 0.00020	1.0088
C	0.2482	0.32160 ± 0.00024	1.0082
D1	1.0000	0.32385 ± 0.00014	
D2	1.0000	0.32393 ± 0.00019	
			average: 1.0088 ± 0.0008
		Methoxide Ion (Exp 2)	
I10	0.1140	0.31935 ± 0.00028	1.0092
H20	0.2304	0.31976 ± 0.00010	1.0084
G30	0.3403	0.32022 ± 0.00012	1.0074
F100	1.0000	0.32212 ± 0.00022	
			average: 1.0083 ± 0.0006

[a] Substrate concentration = 4.1−42 mM; base concentration = 0.0051 M. [b] Fraction of reaction determined by HPLC. [c] ± Standard deviation. [d] Chlorine isotope effect was calculated using eq 1.

ing 1,3-hydron transfer reaction; only elimination product is formed.[5] There are independent experimental results suggesting that the reaction of **1-Cl** with these stronger bases also occurs stepwise through an irreversible E1cB mechanism.[5] However, these results do not provide conclusive evidence for the E1cB mechanism.

A way to discriminate between the concerted E2 reaction mechanism with a substantial cleavage of the bond to the leaving group and the irreversible E1cB mechanism is by determining the chlorine leaving group isotope effect. We now report the results of such a study with methoxide ion and TEA as bases and discuss the mechanistic implications.

Results

The reaction of 1-(2-chloro-2-propyl)indene (**1-Cl**) with sodium methoxide or triethylamine (TEA) buffered with 3% of acetic acid, in methanol at 30 °C, provides exclusively the alkene 1-isopropylideneindene (**2**) (Scheme 1). The fraction (*f*) of alkene product **2** of the quenched reaction solutions was measured by HPLC. The reactions have been studied previously,[5] with the base in large excess, and showed extremely good pseudo-first-order kinetic behavior. In the present work, the reactions were run using much higher substrate concentrations, and the kinetic behavior with methoxide ion is not pseudo-first order but second-order. Analysis by HPLC showed very clean reactions, and the alkene **2** was found to be the sole product.

The results of the mass spectrometric analyses are presented in Tables 1 and 2 (see Experimental Section for more details). The chlorine isotope effects were calculated by means of eq 1.

$$k^{35}/k^{37} = \ln(1 - f)/[\ln(1 - (R_0/R_f)f)] \qquad (1)$$

Discussion

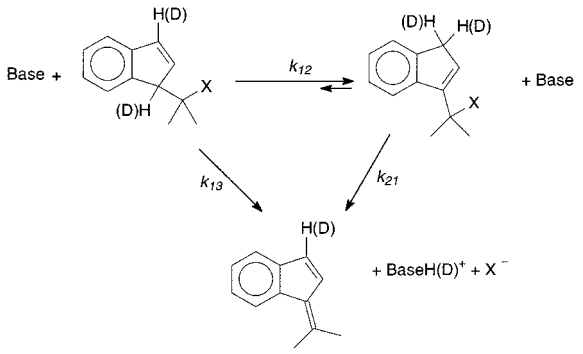
The interpretation of chlorine leaving group kinetic isotope effects is, in principle, more simple than the interpretation of hydrogen isotope effects since its magnitude increases monotonically with increasing cleavage of the C−Cl bond in the rate-limiting transition state.[6] Complete cleavage of the bond to carbon corresponds to an isotope effect of $k^{35}/k^{37} \sim 1.014$. The value should be dependent on the solvent. Thus, bond-breaking in a protic solvent is accompanied by hydrogen bonding of the incipient chloride ion, which results in less zero-point energy loss than in an aprotic solvent.[6]

Table 2. Kinetic Chlorine Isotope Effect for the TEA-Promoted Elimination Reaction of 1-Cl at 30.00 ± 0.03 °C[a] (See eq 1)

sample	f[b]	$1/R_f$[c]	k^{35}/k^{37}[c,d]
F10	0.1051	0.32015 ± 0.00022	1.0102
E20	0.2115	0.32036 ± 0.00025	1.0101
D30	0.3177	0.32059 ± 0.00011	1.0101
A100	1.0000	0.32333 ± 0.00034	
B100	1.0000	0.32309 ± 0.00016	
C100	1.0000	0.32328 ± 0.00011	
			average: 1.0101 ± 0.0001

[a] Substrate concentration = 4.4−43 mM; base concentration 1.00 M buffered with 0.03 M TEA·HOAc. [b] Fraction of reaction determined by HPLC. [c] ± Standard deviation. [d] Chlorine isotope effect was calculated using eq 1.

Scheme 3



The large chlorine isotope effects for the methoxide- and TEA-promoted reactions of 1.0086 (Table 1) and 1.0101 (Table 2), respectively, show that the reaction with these two bases involves extensive, but not complete, cleavage of the carbon−chlorine bond in the rate-limiting transition state. How should these results be interpreted mechanistically? There are, in principle, two elimination mechanisms consistent with these large chlorine isotope effects: (i) the concerted (synchronous) E2 mechanism and (ii) the reversible E1cB mechanism, in which the departure of the leaving group occurs in the second, rate-limiting step (see Appendix). However, previously reported results are not consistent with the reversible E1cB mechanism, as will be discussed in the following text, and we therefore conclude that the reactions with both methoxide ion and triethylamine are concerted E2 reactions. We are somewhat surprised by these results since there are previous reports suggesting that reactions with these bases are of the irreversible E1cB type. Let us look at these previous results in some detail.

The reaction system is shown in Scheme 3. The fraction of elimination in methanol is dependent on the leaving group and the nature of the base. Thus, with AcO^- as the leaving group and the tertiary amines triethylamine

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(TEA) or quinuclidine as the base, the 1,3-rearrangement product is formed approximately as fast as the elimination product.[7,8] With the weaker base pyridine, the alkene is the minor product. The elimination reaction of the deuterated acetate is not accompanied by any significant incorporation of protium in the alkene product.[8] The measured kinetic deuterium isotope effects $(k_{12}^{H} + k_{13}^{H})/(k_{12}^{D} + k_{13}^{D})$ on the disappearance of the substrate **1-OAc** are all large (7.3 (30 °C), 7.1 (20 °C), and 6.5 (30 °C) with TEA, quinuclidine, and methoxide ion, respectively). The isotope effects k_{12}^{H}/k_{12}^{D} and k_{13}^{H}/k_{13}^{D}, i.e., the isotope effects on the separate reactions, attain extreme values, e.g., $k_{12}^{H}/k_{12}^{D} = 18.1 \pm 1.1$ with quinuclidine at 20 °C,[8] which is not consistent with separate parallel reactions but requires that the reactions are coupled via a common intermediate (Scheme 2). With the more efficient leaving group Cl^-, rearrangement product is only observed with weak bases. The measured isotope effects with pyridine as the base at 30 °C of $k_{12}^{H}/k_{12}^{D} = 14.6 \pm 1.0$ and $k_{13}^{H}/k_{13}^{D} = 5.6 \pm 0.4$ also strongly indicate coupled reactions through a common hydrogen-bonded carbanion intermediate.[3] The measured isotope effects for the elimination with the stronger bases TEA and methoxide ion at the same temperature are large ($k_{13}^{H}/k_{13}^{D} = 8.4$ and 7.1, respectively), and no rearrangement product is formed.[5] These large kinetic deuterium isotope effects are consistent with the irreversible E1cB reaction mechanism as well as with the concerted E2 mechanism.

The irreversible E1cB mechanism for the TEA-promoted reaction is also suggested by other independent results showing that the total reaction rate increases substantially when passing from a "poor" putative leaving group to chloride ion, and the rearrangement rate decreases drastically when the putative leaving group is changed to a more efficient one.[5] There is roughly a linear dependence between $\log(k_{12} + k_{13})$ versus the Taft polar substituent constant σ^* for CH_2X (Figure 2). These plots give crude estimates of the rate constants for the tentative E1cB reactions of the chloride substrate.

The previously reported results with TEA and methoxide ion discussed above suggest the irreversible E1cB mechanism but are not conclusive evidence for such a mechanism. Let us examine the mechanistic borderline in more detail.

The E1cB–E2 Borderline. There are two principally different types of borderlines between stepwise and one-step reactions as discussed in the following text for the base-promoted reactions. Either there is a gradual decrease in the barrier for departure of the leaving group in the two-step reaction when going to a more efficient leaving group as shown in Figure 1a or, alternatively, the two reactions occur in parallel and the change to a more efficient leaving group gives rise to a lower barrier for the concerted reaction owing to an increased stabilization of the concerted one-step transition state (Figure 1b). The first alternative corresponds to a merging of the transition states at the borderline, and the concerted E2 reaction is enforced by the nonexistence of a lifetime for the putative intermediate. Accordingly, the transition state of such an E2 reaction resembles that of the E1cB reaction. Only a minor amount of breaking of the bond to the leaving group is expected. The change in mechanism with change in leaving group, from irreversible E1cB for **1-OAc** to synchronous, concerted E2 for **1-Cl**, does not correspond to a merging of mechanisms; the transition states close to the borderline are not similar in structure. The results do not give clear-cut information about the mechanism of methoxide-promoted elimination of **1-OAc**; the reaction can be of either the E1cB or the E2 type.

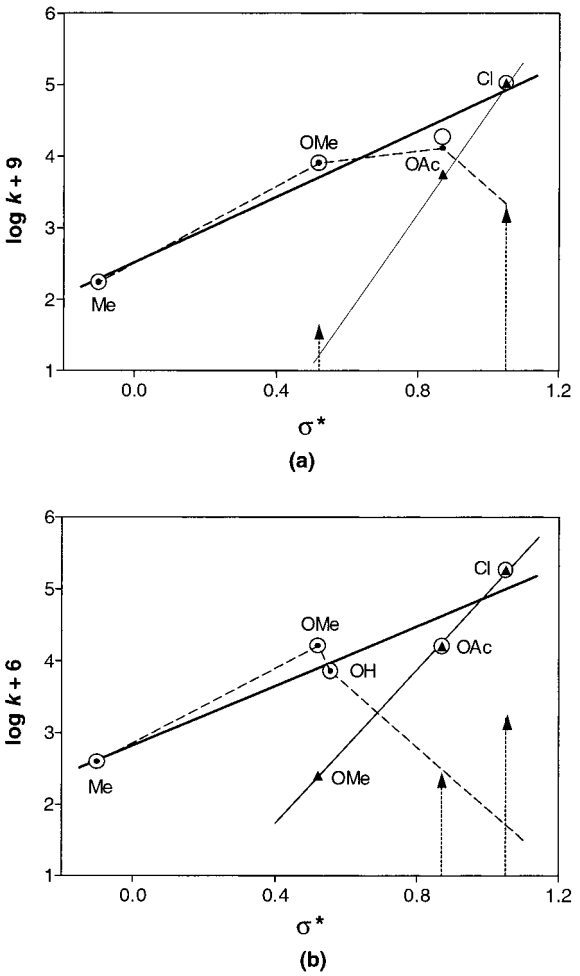

Figure 2. Reaction of **1-X** in methanol with (a) TEA or (b) MeONa. Plot of log *k* versus the Taft polar substituent constant σ^* for CH_2X: $k = k_{12} + k_{13}$ (○, solid thick line), $k = k_{12}$ (●, dashed line), and $k = k_{13}$ (▲, solid thin line) (Scheme 3). The arrowheads represent the *estimated* maximum rate of rearrangement (k_{12}) and elimination (k_{13}) (from ref 5).

There is also a change in mechanism for the reaction of **1-Cl** with change in base, from irreversible E1cB for pyridine to synchronous, concerted E2 with TEA. This mechanistic change is also of the nonmerging type. The experimental results with pyridine require coupled reactions through a common carbanion intermediate (Scheme 3), but this does not exclude that a significant part of the alkene is formed by a parallel E2 pathway.[3]

The leaving group chlorine isotope effect for the E2 reaction with TEA is somewhat larger than that of the reaction with MeO^-. This is in accordance with the variable transition state theory (cf. More O'Ferrall–Jencks diagram) for a concerted E2 reaction with a "diagonal" transition state.[9–13] The measured kinetic isotope effects and the conclusions about mechanisms are summarized in Table 3.

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Table 3. Measured Isotope Effects at 30.00 ± 0.03 °C and Mechanistic Assignments for the Base-Promoted Reactions of 1-OAc and 1-Cl

	substrate				
	1-OAc		1-Cl		
	k^H/k^D	Mechanism	k^H/k^D	k^{35}/k^{37}	Mechanism
pyridine		E1cB	5.6		E1cB
TEA	7.3[a]	E1cB	8.4	1.0101[c]	E2
MeO^-	6.5[b]	?	7.1	1.0087[c]	E2

[a] From ref 7. [b] From ref 24. [c] From Tables 1 and 2.

Irreversible E1cB Reaction with a Large Amount of Hyperconjugation? It has been suggested that the effect of the leaving group on the rate of irreversible E1cB reactions is only a polar one, i.e., an inductive effect on the rate-limiting hydron-abstracting step.[1] Accordingly, any positive element effect in addition to this polar effect has been suggested to be evidence for an E2 mechanism. However, theoretical calculations have shown that a partial bond breaking to the putative leaving group (L) occurs in the transition state of hydron-abstracting reactions and that periplanar positioning between the base and L is preferred.[14] This assistance to hydron removal by hyperconjugative interaction from the electron-withdrawing group L implies some resemblance between E2 and E1cB transition-state structures.[2,3,5,15−19]

Accordingly, a hypothetical E1cB reaction of a substrate with a chloride leaving group is expected to involve some bond-breaking to the chloride leaving group in the rate-limiting ionization transition state. However, it is very difficult to accommodate in a stepwise mechanism such very large chlorine leaving group isotope effects as 0.86 and 1.01%, as measured for the reaction of **1-Cl** with strong bases (see Appendix). We find it most likely that these large isotope effects, combined with the large hydrogen isotope effects, are strongly indicative of a synchronous E2 mechanism. Consistently, there are large element effects: $k_{Br}/k_{Cl} = 10$ with methoxide ion and $k_{Br}/k_{Cl} = 5$ with TEA.[17] The situation resembles the concerted S_N2 reaction in which there is a synergism between an efficient entering nucleophile and an efficient departing leaving group.[20,21]

Previous reports on chlorine isotope effects include the dehydrochlorination reaction of $PhCH(Me)CH_2Cl$ with ethoxide ion in ethanol,[22] $k^{35}/k^{37} = 1.00590 \pm 0.00013$ (75 °C), and the reaction of $(4\text{-}NO_2C_6H_4)_2CHCHCl_2$ with methoxide ion in methanol,[23] $k^{35}/k^{37} = 0.99995 \pm 0.00026$ (30 °C). The E2 and the irreversible E1cB mechanism, respectively, were assigned to these reactions.

Experimental Section

General Procedures. NMR spectra were recorded at 25 °C with a Varian Unity 300 or 400 MHz spectrometer. Chemical shifts are indirectly referenced to TMS via the solvent signal (chloroform-d_1 7.26 and 77.0 ppm). The high-performance liquid chromatography analyses were carried out with a Hewlett-Packard 1090 liquid chromatograph equipped with a diode-array detector on an Inertsil 5 ODS-3 (3 × 100 mm) reversed-phase column. The mobile phase was a solution of acetonitrile in water. The reactions were run at a constant temperature controlled by a HETO 01 PT 623 thermostat bath. The ratio of chlorine isotopes was measured using a modified, hybrid model MI 1201E FAB isotope ratio mass spectrometer (PO Electron, Ukraine).

Materials. Diethyl ether and tetrahydrofuran were distilled under nitrogen from sodium and benzophenone. Methanol and acetonitrile were of HPLC quality and HPLC UV gradient quality, respectively. Isooctane was of HPLC grade. Sodium methoxide solution was prepared by dissolving clear-cut pieces of sodium in methanol under dry nitrogen. Triethylamine (Merck, p.a.) was purified by drying over KOH overnight followed by distillation from 3,5-dichlorobenzoyl chloride.[24] All other chemicals used for the kinetic experiments were of p.a. quality and used without further purification.

1-(2-Chloro-2-propyl)indene (1-Cl). Compound **1-Cl** and 1-isopropylideneindene (**2**) were prepared by previously published methods.[5]

Determining the Chlorine Kinetic Isotope Effects. The leaving group isotope effects were determined for the base-promoted elimination reaction of 1-(2-chloro-2-propyl)indene (**1-Cl**) at 30.00 ± 0.03 °C by the following procedure. The reaction was initiated by addition of prethermostated base solution (2 mL of 0.11 mM sodium methoxide or 10 mL of 4.00 M TEA buffered with 0.12 M TEA·HOAc) to a prethermostated solution of the substrate (38 or 30 mL, respectively) in a 50 mL reaction vessel placed in a water thermostat bath. The reaction was quenched by quickly pouring the reaction solution into a separatory funnel containing 100 mL of water, 2 mL of HNO_3 (concentrated), and 40 mL of isooctane. After separation, the aqueous phase was extracted three times with 10 mL portions of isooctane. The combined isooctane phases were placed in the freezer for later analysis.

Potassium nitrate (8 g) was added to the aqueous phase, and the volume was reduced to about 50 mL using an evaporator. Silver nitrate solution (5 mL, 1.0 M) was then added to the warm solution (50 °C), which was placed in a dark place overnight prior to filtration through a preweighed sintered glass filter. Finally, the filter with the AgCl precipitate was weighed and the amount of AgCl calculated.

The fraction of reaction was determined by analyzing the combined isooctane phases, obtained in the separation step described above, employing HPLC. The analysis showed only two components, **1-Cl** and **2**, which were baseline separated. The alkene **2** was the sole product after a long reaction time. The relative response factors were determined by analyzing mixtures of the two pure components prepared by weighing.

The mass spectrometric analysis of the chlorine isotopes was carried out by a previously published method.[25] The silver plate that is mounted on the tip of the probe of the isotope ratio mass spectrometer was washed with nitric acid, water, and acetone. Then, approximately 5 mg of silver chloride was deposited on the clean silver plate and the plate was heated gently to melt the sample. Precautions were taken not to exceed 480 °C and to keep the dimensions of the samples constant (about 0.2 mm thick and 4 mm in diameter). The silver plate with the adhered solid sample was mounted on the tip of the direct insertion probe. Xenon atoms (6 keV) hitting the surface of the probe at an incidence angle of 45° were used for ionization. The negative ions formed in this way were accelerated through a 5 kV potential and detected in a

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Faraday cup collector system. The total ion current under the above conditions is stable for about 1 h. The spectra contained almost exclusively chlorine peaks at 35 and 37 *m*/*z*. The mean value of the isotopic ratio for each measurement was obtained from about 50 separate determinations, each of which was an average of 10 individual measurements.

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Appendix. Kinetic Isotope Effects for an E1cB Reaction with Internal Return

$$B + HRX \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} BH^+ \cdots\cdots \bar{R}X \xrightarrow{k_2} BH^+ + R + X^- \quad (2)$$

The steady-state approximation yields the following relation between the observed rate constant (k) and the microscopic rate constants of eq 2:

$$k = k_1 k_2/(k_{-1} + k_2) \quad (3)$$

Accordingly, the following expressions for the kinetic isotope effects are obtained (heavy isotopes are denoted by primes):

$$k/k' = (k_1/k_1')(k_2/k_2')(k_{-1}' + k_2')/(k_{-1} + k_2) \quad (4)$$

Let us assume that internal return is three times slower than cleavage of the bond to the leaving group ($k_2/k_{-1} = 3$) and that the isotope effect on the dehydronation of the substrate is very large ($k_1^H/k_1^D = 9$) and that k_{-1}^H/k_{-1}^D has a similar value. Moreover, let us assume a complete cleavage of the carbon−chlorine bond in the transition state of the second step, i.e., $k^{35}/k^{37} = 1.014$. The observed isotope effects derived from eq 4 are then

$$k^H/k^D = 7.0$$

$$k^{35}/k^{37} = 1.0035$$

A somewhat smaller kinetic deuterium isotope effect on k_{-1} yields a slightly larger isotope effect, e.g., $k_{-1}^H/k_{-1}^D = 4$ yields $k^H/k^D = 7.3$.

The derived chlorine isotope effect of 1.0035 is much smaller than the effect of 1.0101 measured with TEA. Such a large chlorine isotope effect requires that internal return is substantially faster than departure of the leaving group. However, this is not consistent with such a large deuterium isotope effect as $k^H/k^D = 8.4$.

Thus, we conclude that the very large measured kinetic deuterium and chlorine isotope effects *cannot* be accommodated in a stepwise carbanion mechanism.

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