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LARGE CONCENTRATION EFFECTS ON THE MAGNITUDE OF SECONDARY ALPHA-DEUTERIUM KINETIC ISOTOPE EFFECTS

Kenneth Charles Westaway* and Zbigniew Waszczylo,
Chemistry Department, Laurentian University, Sudbury, Ont., P3E 2C6

and

Peter James Smith and Kanchugarakoppal S. Rangappa,
Chemistry Department, University of Saskatchewan, Saskatoon, Sask. S7N 0W0

Because the secondary alpha-deuterium kinetic isotope effects in some S_N2 and E2 reactions are strongly concentration dependent, isotope effects measured at a single concentration could lead to erroneous conclusions about the mechanisms and transition state structures.

Physical organic chemists have been using the magnitude of secondary hydrogen-deuterium kinetic isotope effects for several years to determine the mechanism of S_N reactions and to elucidate the structure of their transition states[1-4]. Measuring the kinetic isotope effect for a reaction involves determining the rate constants for the reaction of the two isotopically labelled compounds either separately[4,5] or in a competitive experiment[3,6] under the normal reaction conditions. Although it is accepted that small changes in the concentrations of the reactants might have small effects on the rate constants for the two isotopically substituted substrates, it is assumed that these changes would be equal or approximately equal for both substrates and that the isotope effect is a specific property of the reaction that is independent of the concentrations of the reactants or the method used to measure the isotope effect. We have found, however, that very large changes in the magnitude of these isotope effects can occur when very small changes are made in the concentration of the reactants.

Large changes in the magnitude of secondary alpha-deuterium kinetic isotope effects have been observed with very small changes in the concentrations of the reactants in the S_N2 reaction between n-butyl chloride and thiophenoxide ion in N,N-dimethylformamide at 20°C, equation 1,

$$CH_3CH_2CH_2CH_2\text{-}Cl + C_6H_5\text{-}S^- \longrightarrow CH_3CH_2CH_2CH_2\text{-}S\text{-}C_6H_5 + Cl^- \qquad [1]$$

and the E2 elimination reactions of 2-phenylethyl chloride and fluoride with potassium t-butoxide in t-butyl alcohol at 40°C, equation 2, Table 1.

$$C_6H_5\text{-}CH_2CH_2\text{-}Cl(F) + \underline{t}\text{-}BuO^- \longrightarrow C_6H_5\text{-}CH{=}CH_2 + \underline{t}\text{-}BuOH + Cl^-(F^-) \qquad [2]$$

Table 1. Secondary α-deuterium kinetic isotope effects for the S_N2 reaction between n-butyl chloride and thiophenoxide ion in DMF at 20°C and for the E2 reactions of 2-phenylethyl chloride and fluoride with potassium t-butoxide in t-butyl alcohol at 40°C.

Substrate	$n\text{-}C_3H_7\overset{*}{CH_2}\text{-}Cl$	$C_6H_5\text{-}CH_2\overset{*}{CH_2}\text{-}Cl$	$C_6H_5\text{-}CH_2\overset{*}{CH_2}\text{-}F$
[Substrate]	$4.45\text{-}4.77 \times 10^{-3}$ M	4.044×10^{-3} M	7.859×10^{-3} M
$[NaSC_6H_5]$	$8.57\text{-}8.63 \times 10^{-3}$ M		
[KOt-Bu]		0.0896 M	0.1618 M
$k_H.M^{-1}s^{-1}$	$(4.35 \pm 0.025^a) \times 10^{-2}$	$(5.54 \pm 0.009^a) \times 10^{-4}$	$(4.63 \pm 0.028^a) \times 10^{-5}$
$k_D.M^{-1}s^{-1}$	$(4.01 \pm 0.032^a) \times 10^{-2}$	$(6.86 \pm 0.029^a) \times 10^{-4}$	$(5.36 \pm 0.070^a) \times 10^{-5}$
$(k_H/K_D)\alpha$	1.085 ± 0.011^b	0.808 ± 0.004^b	0.862 ± 0.012^b
[Substrate]	$7.52\text{-}7.94 \times 10^{-3}$ M	4.044×10^{-3} M	7.891×10^{-3} M
$[NaSC_6H_5]$	$4.20\text{-}4.95 \times 10^{-3}$ M		
[KOt-Bu]		0.3060 M	0.3264 M
$k_H.M^{-}s^{-1}$	$(6.03 \pm 0.102^a) \times 10^{-2}$	$(7.16 \pm 0.020^a) \times 10^{-4}$	$(6.16 \pm 0.060^a) \times 10^{-5}$
$k_D.M^{-1}s^{-1}$	$(5.02 \pm 0.031^a) \times 10^{-2}$	$(6.23 \pm 0.019^a) \times 10^{-4}$	$(5.95 \pm 0.100^a) \times 10^{-5}$
$(k_H/k_D)\alpha$	1.190 ± 0.022^b	1.149 ± 0.010^b	1.036 ± 0.019^b

* indicates the point of isotopic substitution

a. Standard deviation. The average second order rate constants were obtained from three to five kinetic runs. The correlation coefficient for the least squares line in each kinetic run was > 0.999. The temperature was constant to within ± 0.02°C of the reported value throughout each kinetic run.

b. The error in the isotope effect is calculated using the formula:-

Error = $\pm\ (k_H/k_D).\{(\Delta k_H/k_H)^2 + (\Delta k_D/k_D)^2\}^{1/2}$ where Δk_H and Δk_D are the standard deviation for the rate constants for the undeuterated and deuterated reactants, respectively.

The rates of both the S_N2 and the E2 reactions were determined by following the change in the absorbance of diluted aliquots of the reaction mixture at 260 nm and 248 nm, respectively, for at least two half lives. A dilute sulfuric acid-95% ethanol solution was used to dilute the aliquots (quench the reaction and eliminate the strong absorptions due to thiophenoxide ion or t-butoxide ion in the aliquots from the S_N2 and E2 reactions, respectively). The deuterated substrates were at least 99% deuterated at the α-carbon and in accord with the conclusions of other investigators[12-14], no evidence of competing (side) reactions was found. The correlation coefficient for the least squares line was > 0.999 for each of the S_N2 and E2 kinetic runs.

The results in the first column of Table 1 show that the secondary α-deuterium kinetic isotope effect in the S_N2 reaction between n-butyl chloride and thiophenoxide ion changes markedly when the concentrations of the reactants are changed over a very narrow range. In fact, the variation in the magnitude of the isotope effect could lead to different mechanistic conclusions. For instance, the isotope effect of 1.085 (1.042/α-D) found when the substrate concentration was 4.50×10^{-3} M implies that the reaction proceeds by way of an S_N2 mechanism with a normal transition state[7,8]. The much larger isotope effect of 1.190 (1.091/α-D) found when the substrate concentration was 7.73×10^{-3} M on the other hand, is almost in the range expected for a carbonium ion mechanism and suggests that the reaction proceeds via an S_N2 mechanism with an extremely loose transition state or a carbonium ion (an S_N1) mechanism[9,10]. Thus, the conclusion one would have draw about the mechanism and transition state structure of this reaction depends on the concentrations of the reactants one happened to use in measuring the isotope effect.

The same marked change in the secondary alpha-deuterium kinetic isotope effect with concentration has been observed in the E2 elimination reaction of 2-phenylethyl chloride and 2-phenylethyl fluoride with potassium *t*-butoxide in *t*-butyl alcohol. Indeed, the changes in the magnitude of the isotope effect are large enough to indicate that the E2 transition states are very different or that the detailed mechanism changes when a different concentration of potassium *t*-butoxide is used. For example, the large, inverse isotope effects of 0.808 and 0.862 found for the E2 reactions of the 2-phenylethyl chloride and fluoride, respectively, at the lower concentrations of potassium *t*-butoxide, indicate that the steric crowding around the alpha carbon (the energy of the $C_\alpha H(D)$ out-of-plane bending vibrations) is increased markedly in going from the initial to the transition state in both reactions. If these isotope effects are determined at the higher concentrations of potassium *t*-butoxide, however, the conclusion concerning the nature of the transition state is quite different. The large, normal isotope effect of 1.149 found when a higher concentration of base is used in the 2-phenylethyl chloride reaction, indicates a loose transition state[3,11] with lower energy $C\text{-}_\alpha H(D)$ out-of-plane bending vibrations in the transition state. The larger isotope effect of 1.036 found at the higher base concentration in the 2-phenylethyl fluoride reaction also suggests that the transition state is looser when a high base concentration is used. Thus, very different transition state structures are suggested by the isotope effects measured at different base concentrations.

While we believe that the concentration effects on these isotope effects result from solvent effects on the ionic reactants in these reactions*, the important observation is that secondary α-deuterium kinetic isotope effects can be very concentration dependant. This means that chemists using these isotope effects to determine the mechanism of a reaction or the relative structures of the transition states in a series of closely related reactions will have to demonstrate that the isotope effect is independent of concentration before they can draw any conclusions about the mechanism or the structure of the transition state for a particular reaction with any certainty. Certainly, such a study is imperative for reactions carried out in organic solvents where ion pairing can occur.

Finally, it is worth noting that these concentration effects are not universal in S_N2 and E2 reactions. For example, the isotope effects found for the S_N2 reaction between n-butyl chloride and thiophenoxide ion in DMSO and in diglyme and for the closely related E2 reactions between potassium t-butoxide and 2-phenylethyl bromide, iodide and tosylate in t-butyl alcohol are all independent of concentration as expected*. This, and the fact that these concentration dependent isotope effects in DMF and in t-butyl alcohol have been confirmed in repeated experiments by different workers in our laboratories using the same procedures, substrates and base/solvent systems that were used to measure the concentration independent isotope effects in the S_N2 reaction in DMSO and in diglyme and the E2 reactions of the other 2-phenylethyl derivatives*, make us confident that this unexpected and significant result is correct.

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* Unpublished Results.

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