Secondary Deuterium Kinetic Isotope Effects associated with Multiple Deuteriation of Trimethylammonium Leaving Groups in Some *E*1 and *E*2 Reactions

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Summary Large normal ($k_H/k_D > 1$) secondary deuterium kinetic isotope effects have been observed in *E*1 and *E*2 reactions of some steroidal axial trimethylammonium salts when the leaving groups were partly or fully deuteriated; analogous but much smaller effects have been observed in *E*2 reactions of 2-phenylethyltrimethylammonium salts.

We report secondary deuterium isotope effects for elimination reactions of a selection of quaternary trimethylammonium salts in which some or all of the *N*-methyl groups are replaced by *N*-trideuteriomethyl groups.

Table. Secondary deuterium kinetic isotope effects in *E*1 and *E*2 reactions

Substrate[a]; degree of deuteriation in leaving group	Reagent–solvent	Reaction[b]	Method and analytical procedure[c]	k_H/k_D; standard deviations; temp./°C	k_H/k_D calc.[d] for 80 °C
$\text{Ch-6}\beta\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_3$	98·6% EtOH	*E*1	A,X	1·22 ± 0·03; 70	1·21
$\text{Ch-6}\beta\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_6$	98·6% EtOH	*E*1	A,X	1·47 ± 0·03; 70	1·45
$\text{Ch-6}\beta\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_9$	98·6% EtOH	*E*1	A,X	1·71 ± 0·04; 70	1·68
$\text{Ch-7}\alpha\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_9$	0·6-N KOH in 95% EtOH	*E*2	A,Y	1·59 ± 0·05; 70	1·57
$\text{Ch-3}\alpha\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_9$	0·6N-KOH in 95% EtOH	*E*2	A,Y	1·51 ± 0·05; 110	1·56
$\text{PhCH}_2\text{CH}_2\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_3$	0·1N-aqueous NaOH	*E*2	B,Z	1·05 ± 0·03; 80	1·05
$\text{PhCH}_2\text{CH}_2\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_6$	0·1N-aqueous NaOH	*E*2	B,Z	1·10 ± 0·03; 80	1·10
$\text{PhCH}_2\text{CH}_2\overset{+}{\text{N}}\text{Me}_3\overset{-}{\text{I}}$; $^2H_9$	0·1N-aqueous NaOH	*E*2	B,Z	1·12 ± 0·03; 80	1·12

[a] Ch = 5α-cholestanyl. [b] See refs. 1 and 2. The *E*2 reaction of the 6β-salt, and the *E*1 reaction of the 7α salt give similar large values for full deuteriation in the leaving groups, but sufficiently precise figures are not yet available. For an earlier less precise value for the *E*1 reaction of the 6β-salt see G. H. Cooper and J. McKenna, *Chem. Comm.*, 1966, 734. [c] Methods: A, ratio of separately determined rate constants; B, competitive procedure, low % decomposition. Analytical procedures: X, polarimetric; Y, products and unconsumed reactants separated and weighed; Z, u.v., ^{14}C radio counting. The non-deuteriated salt was randomly labelled with ^{14}C in the benzene ring. [d] $T \log k_H/k_D$ assumed constant.

The observed effects (see Table) are strikingly large for *E*1 and *E*2 reactions of axial steroidal ammonium salts; *E*2 transition states in such reactions are likely[1] to have marked *E*1 character. By contrast, the isotope effects for eliminations of 2-phenylethyl salts, with *E*2 transition states of expected near-*E*1*cB* character,[2] are comparatively low. The results suggest an interesting and experimentally fairly accessible criterion for helping to assign *E*2 reactions of substrates with 'onium leaving groups to different parts of the mechanistic spectrum, complementary to that based on the rather more difficult measurements of primary heavy-atom effects in these leaving groups. The heavy-atom effects and deuterium effects for a particular degree of deuterium substitution are expected to be roughly parallel in magnitude; ^{15}N effects for the steroidal substrates have not yet been measured but are predictably large (of their type) while the value for the *E*2 reaction of the 2-phenylethyl salt with aqueous hydroxide is reported[4] as 1·009 ± 0·001 at 97 °C, which is rather small. The simplest way of correlating the available information is based on the assumption of vibrationally structureless ammonium leaving groups, but improbably large secondary ^{14}C ($= {}^2H_2$) effects for leaving-group isotopy are thus predicted, and more sophisticated computations of transition-state structures for the elimination reactions are evidently required.

The secondary deuterium effects might be characterised as either 'steric' or 'inductive'; the former description seems preferable, and has been adopted for a reported[5] inverse effect in the reaction of $NN[^2H_6]$dimethylaniline with methyl toluene-*p*-sulphonate, where a similar query arose. It is of interest that the particularly strong steric interactions between the ammonium group, the 19-methyl group, and the 4-methylene group in the 6β-cholestanyl salt increase the isotope effect only a little relative to those observed for the two related axial salts, and the regular progressive effect of increasing deuteriation in the 6β-salt is also noteworthy in the same connection.

Increasingly large normal secondary deuterium kinetic isotope effects have also been observed in S_N2 reactions when the trialkylammonium leaving groups were progressively deuteriated at the α- (methyl) carbon atoms.

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[2] For a recent discussion see P. J. Smith and A. N. Bourns, *Canad. J. Chem.*, 1974, **52**, 749.

[3] See A. Fry in 'Isotope Effects in Chemical Reactions,' eds. C. J. Collins and N. S. Bowman, Van Nostrand Reinhold, New York, 1970, pp. 387—392; W. H. Saunders, Jr., and A. F. Cockerill, 'Mechanisms of Elimination Reactions,' Wiley, New York, 1973, pp. 87—92.

[4] A. N. Bourns and P. J. Smith, *Proc. Chem. Soc.*, 1964, 366.

[5] E. D. Kaplan and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 6644; K. T. Leffek and A. F. Matheson, *Canad. J. Chem.*, 1971, **49**, 439.