The Substituent Dependence of the Primary Deuterium Kinetic Isotope Effect in Elimination from Phenethyl Bromides and Dimethyl(phenethyl)-sulphonium Bromides in 50·2 mole % Dimethyl Sulphoxide–Water

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Primary deuterium kinetic isotope effects (k_2^H/k_2^D) have been determined for 1,2-elimination from a series of substituted phenethyl bromides and dimethyl(phenethyl)sulphonium bromides in 50·2 mole % $Me_2SO–H_2O$. A maximum in the k_2^H/k_2^D ratio was observed for the phenethyl bromides but the existence of a maximum could not be determined for the dimethyl(phenethyl)sulphonium bromides. Some evidence for proton tunnelling is presented for the *p*-methoxy-compounds. Hammett ρ values were determined and the value was larger for the poorer leaving group.

THERE has recently been a divergence of opinion in the literature regarding the significance of the primary deuterium kinetic isotope effect. The established view [1-4] has been that the observation of large isotope effects reflects a situation in which the proton is half-transferred to a base at the transition state, while lower values are associated either with more, or less, extensive proton transfer. This view has been challenged on theoretical grounds.[5-7] In view of the complications imposed on the interpretation of kinetic isotope effects (by the uncertain influence of base structure, solvent variation, and especially by quantum mechanical tunnelling), it has been suggested [8] that comparison of isotope effects should be restricted to reactions of a series of similar substrates in a given reaction medium. Concerted 1,2-eliminations from phenethyl compounds fulfill this requirement and have been extensively studied under various conditions,[8] providing a considerable amount of isotope effect data.

The existence of a maximum in the isotope effect as the concentration of Me_2SO increases, has been demonstrated [9] for the hydroxide ion-catalysed elimination from dimethyl(phenethyl)sulphonium bromides in aqueous dimethyl sulphoxide solutions. A similar result has recently been reported for trimethyl(phenethyl)ammonium ions under the same base–solvent conditions.[8] However, we recently reported [10] the lack of significant variation in the isotope effects for a series of substituted phenethyl bromides in $KOBu^t–Bu^tOH$. The lack of variation in the latter system was attributed to either the difference in charge type of the leaving group, or to the base–solvent system used.

We have therefore decided to investigate the kinetic deuterium isotope effect for the hydroxide ion-catalysed 1,2-elimination from phenethyl compounds (I) in 50·2 mole % $Me_2SO–H_2O$ solutions. The concentration of Me_2SO chosen should lead to maximal isotope effects for both series of substrates,[9] thereby facilitating the possible observation of a maximum as Z is varied and also emphasising any difference between the charged ($\overset{+}{S}Me_2$) and neutral (Br) leaving groups.

$ZC_6H_4CL_2CH_2X$ Z = *meta*- or *para*-substituent
(I) L = H or D
X = Br or $\overset{+}{S}Me_2$

EXPERIMENTAL

Preparation of Phenethyl Bromides.—The preparation of these compounds has been described previously [10,11] and their physical constants agreed with those listed. The deuteriated compounds were prepared from the appropriate phenylacetic acid either by repeatedly refluxing the sodium salts in D_2O until mass spectra showed an acceptable level of deuteriation, or by an adaptation of the procedure described by Bélanger *et al.*[12] The deuteriated phenylacetic acids were then converted into the corresponding phenethyl bromides by the established procedures.[10,11]

Preparation of Dimethyl(phenethyl)sulphonium Bromides.[11]—These compounds were prepared from the corresponding phenethyl bromides by treatment with a solution of CH_3SH in ethanolic sodium hydroxide.[13] CH_3SH was produced *in situ* by heating the *S*-methylisothiouronium salt with sodium hydroxide solution.[14] The *S*-methylisothiouronium salt was prepared from thiourea, water, and dimethyl sulphate.[15] The intermediate sulphides were not isolated but were immediately converted into the corresponding dimethyl(phenethyl)sulphonium bromides by treatment with methyl bromide in nitromethane solution for *ca.* 48 h and the product purified by recrystallisation from ethanol–ether.[11]

This purification procedure was unsatisfactory for the Z = *p*- and *m*-NO_2 compounds. A satisfactory purification was achieved by dissolving the crude product in water, washing it with diethyl ether, and boiling the aqueous

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solution with decolourising charcoal. After filtration, the water was removed and the resultant crystals dried *in vacuo*. The product was then recrystallised as usual to give pale yellow crystals. Preparation of methyl [2,2-$^2H_2$]-*p*-nitrophenethyl sulphide from [2,2-$^2H_2$]-*p*-nitrophenethyl bromide (1·90 atoms D per molecule) resulted in extensive exchange of the deuterium atoms with the hydrogen atoms of the solvent (see Table 1.)

TABLE 1

Physical properties for $ZC_6H_4CL_2CH_2\overset{+}{S}Me_2\overset{-}{Br}$ compounds

Z	L	M.p. (°C)	Atoms D per molecule
H	D	135—136	1·90
p-MeO	D	130—131	1·68
p-Cl	D	125·5—126	1·86
m-Br	H	142—144	
m-Br	D	141—142	1·88
p-Ac	D	119—120	1·90
p-NO_2	H	125—126	
p-NO_2	D	124—125	1·08

New compounds and their physical properties are listed in Table 1. All compounds were characterised by their n.m.r. and mass spectra.

Preparation of Solvents and Base Solution.—Dimethyl sulphoxide (Ajax Unilab.) was twice distilled under reduced pressure from calcium hydride and stored in a stoppered flask. Deionised water was distilled from alkaline potassium permanganate. Sodium hydroxide (1M) was prepared from standard concentrate (BDH CVS ampoule) by dilution with distilled water. Base concentrations were checked from time to time with standard hydrochloric acid using Bromocresol Green–Methyl Red as indicator.

Sodium hydroxide and substrate solutions were prepared in 50·2 mole % Me_2SO–H_2O to avoid heating effects on mixing.[9] Stock solutions were stable for at least two weeks, after which time fresh solutions were prepared.

Kinetics.—Both the phenethyl bromides and the dimethyl(phenethyl)sulphonium bromides are essentially completely converted into the corresponding olefins [9,10] and the rates were measured by following the appearance of the appropriate styrene spectrophotometrically. The measurements were taken at a wavelength of 260 nm for all substrates except for Z = *p*-Ac (280 nm) and *p*-NO_2 (310 nm).

Reactions with a half-life of $\geqslant 1$ min were followed on a Unicam SP 500 spectrophotometer in the thermostatted cell compartment, according to the procedure previously outlined.[10]

Rate constants were determined from pseudo-first-order plots since the base concentration was kept in excess (at least 10 : 1) over substrate concentration. The derived second-order rate constants (k_2) were independent of the base concentration; nevertheless isotope ratios were determined using a constant base concentration for each pair of substrates in order to minimise errors. The rate constants were calculated from a plot of $\log[\log(T_t/T_\infty)]$ against time. For the non-deuteriated substrates the rate constants (k_2^H) were calculated for the first two half-lives and were reproducible to within 2%. For the deuteriated substrates, since deuteriation was never 100%, the presence of some non-deuteriated material caused initial curvature of the kinetic plots. Thus only readings for times greater than 8 half-lives for the non-deuteriated substrate were used to determine k_2^D. In order to obtain reproducible values for $k_2^D(\pm 2\%)$ it was necessary to follow the reaction into the third half-life, particularly if the substrates contained $<1·9$ atoms D per molecule. If this was not done lower variable values were obtained for the ratio k_2^H/k_2^D.

Since the rate constants are sensitive to Me_2SO concentration,[9] the rate constant for *p*-chlorophenethyldimethylsulphonium bromide was measured each time a new batch of solvent was prepared. This k_2^H value never differed by more than ±2% for the different batches of solvent. Individual measurements of k_2^H and k_2^D therefore yielded reliable k_2^H/k_2^D ratios without resort to the mixed method used previously.[10]

For reactions with half-lives of <1 min it was necessary to use fast reaction techniques. Reactions were followed on a Durrum–Gibson D-110 stopped-flow spectrophotometer. Substrate solutions (10^{-4}M) and base solutions (usually *ca.* 10^{-2}M) were prepared in 50·2 mole % Me_2SO–H_2O at 20 ± 0·2° and allowed to reach thermal equilibrium in the drive syringes of the instrument. The instrument was then actuated and the optical density changes were recorded against time on a Hewlett–Packard 141B storage oscilloscope. The traces were photographed and then copied onto graph paper from which kinetic data were obtained and treated in the usual way.

All least squares calculations were performed on a Burroughs B6700 computer. The rate constants are given in Table 2.

RESULTS AND DISCUSSION

The Hammett Plot.—We plotted $\log k_2^H$ against σ for Z = *p*-MeO, H, *p*-Cl, and *m*-Br for both X = Br and $\overset{+}{S}Me_2$. The slope of the regression line (ρ) for X = Br was $2·03 \pm 0·12$ (r 0·998) and for X = $\overset{+}{S}Me_2$ the value was $3·13 \pm 0·04$ (r 0·996). The positive values obtained for both leaving groups confirm the greater extent of C–H bond breaking compared to C–X bond breaking at the transition state which is usually assumed for elimination from phenethyl systems.[16-19] The fact that the ρ value for X = $\overset{+}{S}Me_2$ is higher than that for X = Br is in agreement with the prediction [20] that compounds with ' Hofmann rule ' leaving groups should result in transition states of higher carbanion character than compounds having ' Saytzeff rule ' leaving groups.

In both cases the $\log k_2^H$ values for the strong *p*-($-M$) groups, Z = *p*-Ac and *p*-NO_2, lie off the regression line and require enhanced substituent constant values. The derived σ values are 0·97 (Z = *p*-Ac) and 1·39 (Z = *p*-NO_2) for X = Br, and 0·82 (Z = *p*-Ac) and 1·19 (Z = *p*-NO_2) for X = $\overset{+}{S}Me_2$, which are close to the σ^- value for each substituent, consistent with the development of a significant amount of negative charge at C-2 in the transition state.

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Kinetic Isotope Effects.—The primary kinetic isotope effects for X = Br and X = $\overset{+}{S}Me_2$ are listed in Table **3** and are arranged in order of increasing electron-withdrawing power of the phenyl substituents. All the isotope effects determined at 20° are higher than expected from theoretical considerations.[4] As noted previously,[10] secondary isotope effects in these systems are thought to be small and hence corrections for the effect of the second deuterium atom will not significantly reduce the observed values. There is some evidence [18,21] for non-classical behaviour in these eliminations which could account for the size of the isotope effects. The Arrhenius parameters have been calculated for *p*-methoxyphenethyl bromide and *p*-methoxyphenethyldimethylsulphonium bromide from the isotope effect data at 20, 30, and 40°. The values obtained for the difference in the activation energies ($E_a{}^D - E_a{}^H$), and the ratio of the pre-exponential factors, A_H/A_D, are given in Table 3. In both cases the difference in the activation energies is greater than the classical maximum value [22] of 5·1—5·5 kJ mol^{-1} and the A_H/A_D ratio is less than the lower limit of 0·5 expected in the absence of tunnelling.[22] Thus, it seems fairly certain that the isotope effects for Z = *p*-MeO are complicated by a tunnelling contribution. The values obtained here are very similar to those recently reported [10] for the potassium t-butoxide-catalysed elimination of *p*-methoxyphenethyl bromide in Bu^{t}OH, even though the steric effects should be quite different in the two systems. The question of whether a tunnelling contribution is important for the other substrates remains unanswered at present, although there is some evidence [9] that the difference in the activation energies for X = H is of a similar magnitude.

TABLE 2

Rate constants (l mol^{-1} s^{-1}) for $ZC_6H_4CL_2CH_2X$ in 50·2 mole % Me_2SO–H_2O

Z	L	t/°C	Z = $\overset{+}{S}Me_2$	Z = Br
			10^3k_2	10^3k_2
p-MeO	H	20	4·96 ± 0·05	2·92 ± 0·02
p-MeO	H	30	10·6 ± 0·1	6·59 ± 0·04
p-MeO	H	40	35·4 ± 0·1	14·3 ± 0·1
H	H	20	32·8 ± 0·3	8·17 ± 0·1
			$10k_2$	$10k_2$
p-Cl	H	20	2·10 ± 0·04	3·01 ± 0·03
m-Br	H	20	5·27 ± 0·01	5·84 ± 0·02
			k_2	k_2
p-Ac	H	20	11·9 ± 0·1	7·43 ± 0·02
p-NO_2	H	20	176·7 ± 1·0	53·5 ± 0·9
			10^4k_2	10^3k_2
p-MeO	D	20	7·26 ± 0·03	3·87 ± 0·02
p-MeO	D	30	18·7 ± 0·2	10·3 ± 0·1
p-MeO	D	40	66·1 ± 1·4	24·1 ± 0·1
H	D	20	44·4 ± 0·1	9·56 ± 0·01
			10^2k_2	10^2k_2
p-Cl	D	20	2·58 ± 0·02	3·42 ± 0·05
m-Br	D	20	6·29 ± 0·06	6·35 ± 0·05
p-Ac	D	20	124·2 ± 5·1	76·3 ± 0·1
p-NO_2	D	20		614·0 ± 12

TABLE 3

Isotope effects and Arrhenius parameters for reaction of $ZC_6H_4CH_2CH_2X$ with sodium hydroxide in 50·2 mole % Me_2SO–H_2O

Z	t/°C	X = $\overset{+}{S}Me_2$	X = Br
		$k_2{}^H/k_2{}^D$	$k_2{}^H/k_2{}^D$
p-MeO	20	6·8 ± 0·1	7·6 ± 0·1
	30	5·6 ± 0·1	6·4 ± 0·1
	40	5·3 ± 0·1	5·9 ± 0·1
H	20	7·4 ± 0·1	8·5 ± 0·2
p-Cl	20	8·1 ± 0·2	8·8 ± 0·2
m-Br	20	8·4 ± 0·1	9·2 ± 0·1
p-Ac	20	9·6 ± 0·5	9·7 ± 0·3
p-NO_2	20		8·7 ± 0·3
		($E^D - E^H$)/ kJ mol^{-1}	($E^D - E^H$)/ kJ mol^{-1}
p-MeO		9·7 ± 0·6	9·5 ± 0·4
		A_H/A_D	A_H/A_D
p-MeO		0·13	0·15

Substituent Effect on the $k_2{}^H/k_2{}^D$ Ratio.—For both leaving groups a systematic increase in the magnitude of the isotope effect is observed as Z is varied up to *p*-Ac. However the absolute values for X = $\overset{+}{S}Me_2$ are lower than for the corresponding values for X = Br. A maximum in the $k_2{}^H/k_2{}^D$ ratio is apparent for the phenethyl bromides, since there is a small but significant decrease from Z = *p*-Ac to Z = *p*-NO_2. There is no general agreement about the shape of the maximum when tunnelling contributions are important [3,7] and for a concerted reaction such as ours, it is not possible to relate the substituent effect on $k_2{}^H/k_2{}^D$ to Bell's Δp*K* parameter,[23] hence the maximum cannot be classified as broad, or sharp. Therefore we cannot comment on the sensitivity of the $k_2{}^H/k_2{}^D$ ratio to any changes in transition state structure brought about by changes in Z. The existence of a maximum could not be established for the dimethyl(phenethyl)sulphonium bromides, since the $k_2{}^H/k_2{}^D$ ratio could not be measured for Z = *p*-NO_2.

The *E*2 reaction of dimethyl(phenethyl)sulphonium ion with hydroxide ion in water has been shown to be near the *E*1cB end of the *E*2 spectrum of transition states,[9] with the proton more than 50% transferred to the base. Thus the increase in $k_2{}^H/k_2{}^D$ as the substituent is changed from Z = *p*-MeO to *p*-Ac in 50·2 mole % Me_2SO–H_2O must indicate a decreasing extent of proton transfer. This result is wholly consistent with the prediction [24] that electron-withdrawing substituents at C-2 will result in transition states which are more reactant-like.

The transition-states for elimination from the phenethyl bromides are less ' carbanion-like,' as shown by the lower ρ value, than those for the dimethyl(phenethyl)sulphonium bromides; however, it seem likely that the proton is still >50% transferred to the base.[25] There-

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fore, the increase in k_2^H/k_2^D for the phenethyl bromides as Z is changed from *p*-MeO to *p*-Ac must again indicate a decreasing extent of proton transfer. It is tempting to interpret the subsequent decrease in k_2^H/k_2^D on changing Z from *p*-Ac to *p*-NO_2, in terms of an extent of proton transfer now <50%. However, Brønsted correlations for $PhCH_2CH_2Br$ (β 0·54) and *p*-$NO_2C_6H_4$-CH_2CH_2Br (β 0·67) with substituted phenoxide bases,[26] indicate a more product-like transition state for the latter compound. This suggests that the extent of proton transfer to the base is greater for Z = *p*-NO_2 than for Z = *p*-Ac. Thus a maximum in the isotope effect has been observed even though the actual extent of proton transfer to the base may never be <50%.

It is of interest to compare these changes in the isotope effect for 1,2-elimination from phenethyl bromides as Z is varied, with the lack of such variation [10,27] observed in the $KOBu^t$–Bu^tOH base-solvent system. The lack of variation in these latter systems is most likely related to the $KOBu^t$–Bu^tOH base system rather than to the presence of a good leaving group (X = Br) since variations in the isotope effect have now been demonstrated for the leaving groups X = Br, $\overset{+}{S}Me_2$ (ref. 9), and $\overset{+}{N}Me_3$ in the Me_2SO–H_2O system, either by varying the phenyl substituent, or by varying the Me_2SO concentration.[8]

The assumptions implicit in this interpretation of the results have recently been challenged by several authors.[5-7,28] However neither the existing literature data, nor the present results, provide a clear test of these criticisms, as applied to *E*2 elimination reactions. The fact that for elimination from phenethyl systems there is a reasonable degree of internal consistency among the experimental observations at present available, their interpretation, and the theoretical predictions [24,29] leads us to accept, at present, the view that the primary kinetic isotope effect is related in some way to the proton position in the transition state.

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