Deuterium Kinetic Isotope Effect in β-Elimination from (*p*-Acetylphenethyl)dimethylsulphonium Bromide. The Influence of Added Dimethyl Sulphoxide

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The effect of added dimethyl sulphoxide (Me_2SO) on the primary deuterium kinetic isotope effect for NaOH-catalysed β-elimination from (*p*-acetylphenethyl)dimethylsulphonium bromide has been measured over the range 6—70 mol %. Despite the large increase in reaction rate, no significant maximum in the isotope effect was observed. Substituent induced changes in k_2^H/k_2^D are shown to be larger than those caused by addition of Me_2SO, despite the large difference in relative rates.

IN recent publications [1-3] we have been concerned with the problem of relating *changes* in the magnitude of the primary deuterium kinetic isotope effect for base-catalysed *E*2 elimination reactions of phenethyl systems, to the differences in transition state structure *predicted* [4-6] as a result of changes in the various structural parameters. These structural parameters, such as the nature of the phenyl substituents, leaving groups, base, and solvent have been varied in the hope of inducing a ' Westheimer ' maximum,[7] since an unambiguous demonstration of such a maximum would constitute the best experimental support for the use of isotope effects as probes for the position of the proton in the transition state. The results so far reported have proved inconclusive and no evidence for a ' Westheimer ' maximum has in fact been obtained.

For base-catalysed *E*2 elimination from phenethyl compounds [reaction(1) where Z = a *meta*- or a *para*-

$$ZC_6H_4CL_2CH_2X + B \xrightarrow{k_2^L} ZC_6H_4CL=CH_2 + BL + X \quad (1)$$

substituent, L = H or D, X = $\overset{+}{S}Me_2$ or Br, and B = $KOBu^t-Bu^tOH$ or $NaOH-H_2O-Me_2SO$] k_2^H/k_2^D generally increases with the electron-withdrawing power of Z for both neutral (X = Br)[1,2] and charged (X = $\overset{+}{S}Me_2$)[2,3] substrates. For elimination from $ZC_6H_4CH_2CH_2Br$ in 50.2 mole % Me_2SO-H_2O[2] a maximum in the

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isotope effect was observed at $Z = p$-Ac; however comparison of the medium effect [2,3] of Me_2SO for $Z = p$-Ac and p-NO_2 revealed that this ' maximum ' was spurious. Apart from this, the isotope effects were insensitive to the Me_2SO concentration even though the reactivity varied by a factor of 10^5. Recently Baciocchi [8] has shown that k_2^H/k_2^D for phenethyl bromides in dimethylformamide is constant within experimental error, as the basicity of substituted phenoxide ions is varied over a range of 10^6. Thus in elimination from substituted phenethyl bromides, k_2^H/k_2^D is insensitive to changes in the nature of the base, solvent, and leaving group, significant changes being observed only with changes in ring substitution.[2,9]

The results for the charged substrates ($X = \overset{+}{S}Me_2$ and $\overset{+}{N}Me_3$) are similar with respect to the substituent effects [2,10-12] but it has been claimed that a ' Westheimer ' maximum has been observed for dimethylphenethylsulphonium bromide [13] and trimethylphenethylammonium bromide in OH^-–H_2O–Me_2SO solutions.[14,15] For $PhCH_2CH_2\overset{+}{S}Me_2$ a broad curve with a maximum value of *ca.* 7.0 is claimed at *ca.* 50 mole % (at 30°) and this value has been interpreted in terms of a ' half-transferred ' proton.[13] However the highest value obtained in 50.2 mole % Me_2SO (at 20°) for a series of $ZC_6H_4CH_2CH_2\overset{+}{S}Me_2$ compounds, occurs for $Z = p$-Ac.[2] Although no actual maximum value could be observed in this series, it is commonly assumed [10] that such a large value (9.6) indicates a ' nearly half-transferred ' proton in the transition state. Allowing for the temperature difference, we have the situation at 50.2 mole % Me_2SO in which a ' half-transferred ' proton is represented by two different values for the isotope effect. This is clearly inconsistent with the prediction of an invariant maximum value for the isotope effect.[7,16] This type of discrepancy and its implications has been anticipated by the calcuations of Katz and Saunders [17] which show that the isotope effect may not be a good indicator of proton position in elimination reactions if the extent of coupling of the C–H stretching with C–X stretching varies throughout a reaction series.

We have now measured the effect of added Me_2SO on the k_2^H/k_2^D value for p-$AcC_6H_4CH_2CH_2\overset{+}{S}Me_2$ at 30° since if the value in 50.2 mole % Me_2SO does represent a ' half-transferred proton ', a Westheimer maximum should be induced by changing the Me_2SO concentration.[13] Such an observation would provide confirmation of Katz and Saunders' calculations and indirectly support the application of Westheimer theory to concerted elimination reactions. It will be of interest to compare these results with those previously published for the neutral substrates.[3]

EXPERIMENTAL

The preparation of (p-acetylphenethyl)dimethylsulphonium bromide and its dideuteriated analogue have been described elsewhere.[2] The level of deuteriation was determined by mass spectrometry (1.90 atoms D molecule^{-1}). Solvents were purified as previously [2] and Me_2SO mixtures were prepared at the temperature of the measurements (30 ± 0.1°). As usual a constant base concentration was used, for each Me_2SO concentration.

Kinetics.—The rates were followed essentially as outlined previously [2,3] either on a Unicam SP 500 spectrophotometer or a Durrum–Gibson D110 stopped-flow spectrophotometer, depending on the half-life of the reaction.[2] No difficulties were experienced in the measurement of k_2^H, irrespective of the half-life, the error consistently being *ca.* 2.0%. As discussed in previous papers [2,3] the determination of true k_2^H/k_2^D values depends mainly on the measurement of k_2^D. Thus no data points for kinetic runs on the deuteriated compound, using the SP 500 instrument, were collected until 50% of the reaction was completed, by which time the protium impurity was insignificant.[18] The runs were then followed for a further 1.5—2 half-lives. The minimum requirement at each Me_2SO concentration was at least ***three*** runs agreeing to 3% or better. Providing stable infinities could be obtained no difficulty was experienced in meeting this requirement.

For the faster reactions, which were followed on the stopped flow spectrophotometer, it was possible to offset the first 50—70% of the reaction, by adjusting the voltage controls, and monitor the remainder. The best results were obtained by producing traces which covered 1.2—2 half-lives of the reaction on a single oscilloscope sweep. Sweeps obtained using faster time bases produced multiple curves which did not always match due to a significant retriggering delay. At each setting at least three traces were recorded resulting in *ca.* 20 kinetic runs per determination. Confirmation that this procedure yielded consistent and reliable values for k_2^D was provided by collecting several sets of data commencing at different time intervals after mixing. The results in 70.0 mole % are shown in Table 1. The results clearly show that the elimination reaction follows first-order kinetics to 95% reaction and hence that the k_2^D value obtained is satisfactorily independent of the extent of reaction used in its estimation, between 50—95%.

No measurements were made beyond 70 mole % Me_2SO since autoxidation becomes a problem which cannot confidently be overcome using the stopped-flow method and it is not clear what effect autoxidation would have on the results.

Ion-pairing effects were shown to be negligible in this system since the rate constants were independent of the base concentration.

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TABLE 1

Values of k_2^D for NaOH-catalysed elimination from *p*-Ac-$C_6H_4CD_2CH_2\overset{+}{S}Me_2\overset{-}{Br}$ in 70.0 mole % Me_2SO-H_2O measured by stopped-flow spectrophotometry

Average k_2^D/ $dm^3\ mol^{-1}\ s^{-1}$	Percentage of reaction completed after mixing	Number of half-lives covered
42.0	68.0	2.6
42.6	73.0	1.2
40.8	90.0	1.2
43.0	93.2	2.4

(Mean value 42.2 ± 0.98 $dm^3\ mol^{-1}\ s^{-1}$).

RESULTS AND DISCUSSION

Rate Constants.—The measured rate constants along with the derived isotope effect ratios are given in Table 2. The errors in the isotope effects are derived from the standard deviations of the individual rate constants. There is a large rate acceleration (*ca.* 90 000) with increasing concentrations of Me_2SO between 6 and 70 mole %. This increase is very similar to that reported elsewhere for phenethyl bromides [3] and dimethylphenethylsulphonium bromides [13] over the same range of Me_2SO concentrations. The fact that the magnitude of the rate enhancement is virtually independent of the nature of the leaving group [3] or the *para*-substituent [3] confirms that the increase is due to those factors which lead to an enhanced solvent basicity. The increase in thermodynamic basicity of the solvent can be expressed by the function H_- [19,20] and plots of log k_2^L against $H_- + \log C_{H_2O}$ [21] are satisfactorily linear. The slopes of the plots are near unity for both substrates (0.985, *r* 0.998 for log k_2^H and 0.980, *r* 0.998 for log k_2^D) as expected for a reaction for which a proton transfer constitutes the rate-determining step. Since the rate constants for 6.0 mole % Me_2SO lay off the best straight line through all the points they were excluded from the calculations of the slopes. It appears doubtful whether a direct comparison should be made between parameters determined in the highly aqueous region of solvent compositions and those determined in the more non-aqueous environments. For example rate and activation parameters for hydroxide-ion catalysed hydrolysis of 3,3-dimethylpentane-2,4-dione [22] in Me_2SO-H_2O mixtures show a discontinuity below *ca.* 20 mole %.

TABLE 2

Rate constants and isotope effects for *p*-$AcC_6H_4CL_2CH_2\overset{+}{S}Me_2\overset{-}{Br}$ at 30°

Mole % Me_2SO	[NaOH]/M	ΔpK [a]	k_2^H [b]/$dm^3\ mol^{-1}\ s^{-1}$	$10k_2^D$ [b]/$dm^3\ mol^{-1}\ s^{-1}$	k_2^H/k_2^D
6.0	0.3	19.6	0.003 99 ± 0.000 07	0.005 07 ± 0.000 07	7.9 ± 0.2
22.2	0.04	18.2	0.114 ± 0.002 4	0.133 ± 0.004	8.6 ± 0.4
32.6	0.005	17.3	0.997 ± 0.05	1.08 ± 0.015	9.2 ± 0.6
50.7	0.05	15.9	16.31 ± 0.23	17.36 ± 0.69	9.4 ± 0.5
59.5	0.025	15.2	71.08 ± 1.95	75.01 ± 1.8	9.5 ± 0.5
63.9	0.025	14.8	163.0 ± 1.5	178.8 ± 9.8	9.2 ± 0.6
69.6	0.01	14.4	375.4 ± 3.4	421.8 ± 9.8	8.9 ± 0.3

[a] Calculated according to McLennan and Wong,[26] assuming a pK_a value for Z = *p*-Ac of 32.8 and assuming that the substrate is similar to the indicators used to measure H_-. [b] Substrate concentration was *ca.* 9.6 × 10^{-5}M.

Isotope Effects.—Once again,[1-3] the values are all larger (*ca.* 2×) than predicted from theoretical treatments of concerted *E*2 reactions [17,23] and are sufficiently different to give some cause for concern. It is customary to dismiss such ' large ' values as due to ' proton tunnelling ' but although the thermodynamic parameters for *p*-$CH_3OC_6H_4CH_2CH_2Br$ are abnormal for both the OH^-–H_2O–Me_2SO and $KOBu^t$–Bu^tOH base systems and for *p*-$CH_3OC_6H_4CH_2CH_2\overset{+}{S}Me_2$ in OH^-–H_2O–Me_2SO, the k_2^H/k_2^D values for the *p*-methoxy-substituent are always the *lowest* of the series.[1,2] The question of tunnelling contributions for the other substituted phenethyl compounds is unresolved, but for *m*-$NO_2C_6H_4CH_2CH_2Br$ in $KOBu^t$–Bu^tOH the difference in the activation energies is normal yet k_2^H/k_2^D (8.7) is significantly higher than the value for *p*-methoxy. We do not however place too much reliance in these pre-exponential factors and activation energy differences, since the uncertainty in the isotope effects turns out to be as large as the difference caused by a 10° rise in temperature. Also it is difficult to understand why the abnormal parameters in $KOBu^t$–Bu^tOH and NaOH–H_2O–Me_2SO should be the same, when the steric requirements of the base–solvent systems are so different. Thus a contribution from tunnelling in these systems is still somewhat problematical but appears unlikely.

Our isotope effects are slightly larger than comparable literature values, (mainly because our measurements allow an estimate of the limiting k_2^D value) but since similar large values are obtained for the most electron withdrawing substituents in the three systems that we have studied,[1,2] two of which have been further corroborated by the Me_2SO measurements of this work and elsewhere,[3] we believe that the values are significant. As discussed elsewhere [1,2,24] secondary isotope effects are believed to be too small to account for the magnitude, thus either the theoretical treatments of concerted *E*2 processes are incomplete or eliminations from substituent-activated phenethyl bromides and dimethylphenethylsulphonium bromides are not very concerted.[17]

p-Nitrotoluene is known [25] to undergo a ready ionis-

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ation in $KOBu^t$–Bu^tOH, at a rate [26] of *ca.* 0.06 $dm^3\ mol^{-1}\ s^{-1}$, which may be compared with the value for olefin formation from p-$NO_2C_6H_4CH_2CH_2Br$, in the same solvent,[1] of 10.5 $dm^3\ mol^{-1}\ s^{-1}$. Assuming a ρ value of 5.0 for ionisation from substituted *p*-nitrotoluenes, based on the ρ values for carbanion formation in other systems [27] and a $\Delta\sigma^*$ value of 0.52 for the difference between the CH_2Br and H groups,[28] we may calculate that the expected rate of ionisation for p-$NO_2C_6H_4CH_2CH_2Br$ will be 20.0 $dm^3\ mol^{-1}\ s^{-1}$. Thus the calculated rate for ionisation and the observed elimination rate are identical within experimental error, which is a necessary condition for operation of an ' irreversible ' carbanion mechanism. Such evidence is admittedly circumstantial, but Bordwell [29,30] has shown quite convincingly that if carbanions can be formed they provide a far greater driving force for ejection of the leaving group than does double bond formation.

Solvent Effect on k_2^H/k_2^D.—The isotope effects are shown in Table 2 together with the appropriate Me_2SO concentration and the estimated ΔpK values. There is clearly little variation in the mean k_2^H/k_2^D value which cannot be accounted for by experimental error, despite the fact that there is a rate acceleration of *ca.* 90 000 over the estimated ΔpK range of 5 units. If the value for 6.0 mole % Me_2SO is excluded, for the reasons mentioned earlier, then neither a maximum in k_2^H/k_2^D, nor any linear dependence with ΔpK is observed as the Me_2SO concentration is increased. In fact, allowing for a temperature difference between the data of Tables 2 and 3 of 0.5—10°, the entire spread of k_2^H/k_2^D values obtained in this work does not extend as far as the value for Z = *m*-Br in Table 3. Even if the point for 6.0 mole % is included Tables 2 and 3 clearly show that the substituent effect is a much more important factor in determining the isotope effect than is the Me_2SO concentration, a result which is in agreement with other reports for neutral and charged substrates.[12,31,32]

TABLE 3

Isotope effects [2] for reaction of $ZC_6H_4CH_2CH_2\overset{+}{S}Me_2$ with NaOH in 50.2 mole % Me_2SO–H_2O at 20°

Z	*p*-MeO	H [b]	*p*-Cl	*m*-Br	*p*-Ac
10^3k_2H [a]	4.96	32.8	210	527	11 900
k_2^H/k_2^D	6.8	7.4	8.1	8.4	9.6
	±0.1	±0.1	±0.2	±0.1	±0.5

[a] $dm^3\ mol^{-1}\ s^{-1}$. [b] k_{MeO}/k_{Ac} = 2 300.

It is claimed [13] that the results for $PhCH_2CH_2\overset{+}{S}Me_2$ constitute a Westheimer maximum, but if this is so the maximum is so broad as to be virtually imperceptible in practice. This ' maximum ' rests on two values; one in H_2O which is manifestly a different solvent from the Me_2SO–H_2O systems used; and one for which the half-life ($t_{\frac{1}{2}}^H$ 5 s) is at the limits of conventional kinetic techniques, in solutions which are subject to autoxidation.[13] Also the k_2^D values determined in this work may be subject to an additional error since data points were collected before all the non-deuteriated material had reacted.[13] The data up to 70 mole % are encompassed equally well by a straight line and if the appropriate temperature correction (1.0) is applied to these values, the entire range of results lie between the values for Z = *p*-MeO and Z = H listed in Table 3. Thus we are driven to the conclusion that for sulphonium salts no compelling evidence for the existence of a Westheimer maximum is to be found in the data for addition of Me_2SO, despite the very large increase in absolute rate. Hence the different isotope effects, for Z = H[13] and *p*-Ac,[2] need not indicate different maximum values (for 50% transfer) and thus no strong support for the calculations of Katz and Saunders is provided by the present results. While we acknowledge that it is possible in retrospect to rationalise all the available literature data, including the present work, in terms of one or other of the theoretical treatments available,[4-6,16,17] no completely consistent picture emerges. Since an unambiguous Westheimer maximum remains to be demonstrated for an *E*2 elimination reaction,* the relationship between the observed kinetic isotope effects and the changes in transition state structure *predicted* on the basis of the current theoretical models for such reactions, must remain a matter for speculation.

The more fundamental question of why substituent effects (rate acceleration 2 300) alter the isotope effect for neutral and charged substrates while an increase in solvent basicity (rate acceleration 90 000) does not, remains unanswered. It is clear however, that the customary habit of assuming that a high isotope effect *necessarily* indicates a symmetrical transition state [10] must be treated with some degree of caution, even for systematic changes within a series of similar substrates in a given reaction medium.

We thank the University Grants Committee for the funds to purchase the stopped-flow spectrophotometer.

[5/1117 *Received, 9th June,* 1975]

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* Some unpublished results, kindly provided by Professor W. H. Saunders, jun., suggest that for Z = $\overset{+}{N}Me_3$ a maximum which is larger than the experimental errors is observed as the Me_2SO concentration is varied.

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