Model Calculations of Isotope Effects. Part 5.[1] Secondary Hydrogen Isotope Effects in the Solvolysis of Isopropyl Halides

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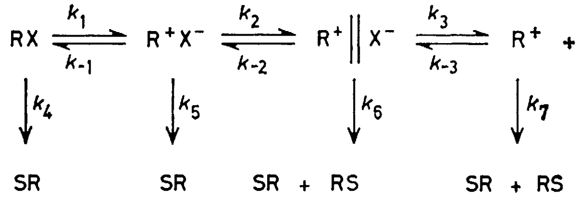
Model reaction systems in terms of reactant and transition state geometries and force fields have been developed to simulate S_N1 and S_N2 solvolyses of isopropyl halides. Equilibrium and kinetic isotope effects for α-deuterium (α-k_H/k_D) and β-deuterium (β-k_H/k_{D6}) substitution have been calculated, with transition state models being assigned structures using the *ab initio* geometry of the isopropyl cation as a basis. Values of α-k_H/k_D were found to be dependent on the identity of the leaving group and were, for ion-pair-like transition states, considerably larger than the values suggested by Shiner as ' maximum ' α-deuterium isotope effects in limiting solvolyses. The mechanistic consequences are examined. Solvent assistance to ionization appears to be a necessary component of simple secondary substrate solvolysis in that it is necessary to include a nucleophilically solvating water molecule in order to match the calculated and experiment values for the hydrolysis of isopropyl bromide.

THE question of the detailed mechanism of solvolysis of simple secondary alkyl halides and sulphonates (*i.e.* those reacting without anchimeric assistance or rearrangement) is still much in dispute. These substrates have long been recognised as being in a borderline mechanistic category between the extremes of S_N2 (primary substrates) and S_N1 (tertiary substrates). Even though the above symbols have acquired new meaning since their introduction,[2] no clear consensus of opinion has arisen regarding borderline cases. Indeed, the borderline area for non-solvolytic nucleophilic substitutions has also been the subject of recent and unresolved debate.[3,4]

Two clear and opposing lines of thought appear to be emerging on the mechanisms of secondary solvolysis. The first, due primarily to Shiner,[5,6] is based on the Winstein ion pair extension of the S_N1 mechanism (Scheme). He contends that while k_4 (S_N2 solvolysis) is the rate-determining step for solvolysis of primary substrates, in agreement with my view,[4] any one of the k_1, k_2, k_5, or k_6 steps may be rate-limiting in secondary solvolysis, depending on the nature of R, X, and the solvent. The evidence is based largely on secondary hydrogen kinetic isotope effects (k.i.e.).[7-11] The principal cause of the secondary α-hydrogen–deuterium isotope effect, α-k_H/k_D is recognised to be the loosening of the H–C$_\alpha$–X vibrational bending mode on proceeding from initial state (IS) to a carbocation-like transition state (TS), a process which involves $C_\alpha \cdots X$ bond weakening.



SCHEME SH = solvent

Thus α-k_H/k_D will be maximal, and will have a maximal dependence on the identity of X, when covalent binding between C$_\alpha$ and X in the TS is minimal. This should occur when the TS lies between the tight and loose ion pairs in the Scheme, *i.e.* when k_2 is rate limiting. In all other cases except for k_1 being rate-limiting, the loss of vibrational zero point energy upon partially breaking the C$_\alpha$–X bond is more or less compensated for by an increase in zero-point energy attendant on the partial making of an $HS \cdots C_\alpha$ bond, so that smaller, and in some cases inverse, k.i.e. will arise. When k_1 is rate limiting, the fact that only partial ionization of the $C_\alpha \cdots X$ bond has occurred, means that zero-point energy will have been only partially lost, and α-k_H/k_D will again be less than maximal.

Schleyer and his associates have consistently argued against Shiner's proposals.[12-16] In their view solvolysis reactions exhibit varying degrees of nucleophilic solvent assistance ranging from very strong (classical S_N2) to negligible (S_N1). In the borderline region between these extremes an S_N2 (intermediate) mechanism is held to operate, and nucleophilic solvent assistance is believed to produce a nucleophilically solvated ion pair.[16] Thus solvent nucleophilicity, alkyl structure, and the leaving group (in that the level of nucleophilic solvent assistance required may well depend on the extent of electrophilic assistance granted to aid leaving-group departure) determine the position of a given TS within the spectrum.

In particular the α-k_H/k_D for solvolysis of isopropyl *p*-bromobenzenesulphonate is inversely proportional to a parameter that measures the relative influence of solvent nucleophilicity.[16b] Thus the mechanism must shift from S_N1-like with k_1 rate-limiting, through an intermediate range of transition states, to S_N2-like as the solvent nucleophilicity increases on going from CF_3CO_2H to EtOH. Such variations can also be discerned in some systems studied by the Shiner group,[8-10,17] and of particular interest is the cyclopentyl arenesulphonate system.[10] The dependence of α-k_H/k_D on solvent properties fits the Schleyer proposal, as does the dependence of rates on solvent composition in aqueous ethanol and aqueous trifluoroethanol.[18] However, Shiner and his co-workers have fitted a large range of isotope effect and stereochemical data to the appropriate variant of the mechanism in the Scheme.[10c] They do concede that neither mechanistic competitor can deal successfully with all the questions raised.

The argument rages in a broader sense too. Bentley *et al.* argue against the involvement of appreciable ion-pair return in the solvolyses of tertiary substrates, claiming that nucleophilic solvent assistance prevents this even in these cases.[19] On the other hand it is claimed that the hydrolyses of almost all alkyl halides involve internal return and nucleophilic attack on preformed ion pairs.[20]

Returning to α-k_H/k_D as a criterion of mechanism, it is seen to be ambiguous in a quantitative sense from both sides of the argument unless the maximum value, corresponding to an unsolvated TS having minimal $C_\alpha \cdots X$ bonding, is known. Shiner's group has provided estimates for halide leaving groups by calculating k.i.e. for reactions (A) and (B) for the case where the TS force-field is independent of the identity of X.[21,22] These values are actually based on equilibrium isotope effects (e.i.e.) and have been transformed to k.i.e. by (a) making assumptions concerning the reduced partition functions for the TS and (b) basing the resultant relative k.i.e. upon a purported maximum value for X = Br of 1.125. These crucial k.i.e., which will be examined critically in the present work, are shown in Table 1. It has been implicitly assumed that they will be independent of alkyl group structure. The status of the X = Cl value as a maximum is already open to question; larger values than that shown have been experimentally realised, namely 1.20 ± 0.02 for solvolysis of p-MeOC$_6$H$_4$-CHCl$_2$ in 65% dioxan–water,[23] 1.24 for solvolysis of MeOCH$_2$Cl in propan-2-ol,[24] and 1.19 ± 0.02 for trifluoroethanolysis of phenethyl chloride.[25] It is not presently feasible to calculate α-k_H/k_D values for the more widely studied sulphonate leaving groups owing to the lack of a suitable force-field, but it is assumed that the maximum value lies in the range 1.22—1.26.[8-11,26-29] It must be emphasised that these are the largest values *so far observed*, and if in fact the arguments of Bentley[19] and Schleyer[15] are correct, the maximum corresponding to complete and unassisted ionization of the $C_\alpha \cdots O$ bond in the TS should be higher. There is some evidence that this may be so. The α-k_H/k_D value for expulsion of MeOH from the hydrazine adduct of methyl formate[30] (C_α–O cleavage to form an sp^2-hybridized carbonyl carbon rather than a cationic carbon) is 1.35, and values in the range 1.34—1.40 are found for reactions in which oxocarbonium ion formation is implicated.[31]

$$\mathrm{CH_3X} \longrightarrow {}^{+}\mathrm{CH_3} \cdots \mathrm{X}^{-} \qquad \text{(A)}$$

$$\mathrm{CH_2DX} \longrightarrow \overset{+}{\mathrm{C}}\mathrm{H_2D} \cdots \mathrm{X}^{-} \qquad \text{(B)}$$

TABLE 1

Maximum secondary α-deuterium isotope effects[a] for hypothetical methyl halide ionizations[b]

Substrate	CH$_3$F	CH$_3$Cl	CH$_3$Br	CH$_3$I
α-k_H/k_D	1.214	1.164	1.125	1.090

[a] For CH$_3$X *versus* CH$_2$DX at 25 °C. [b] Refs. 21 and 22.

In addition, large α-deuterium isotope effects of the order of 15% have recently been found for reactions which are undoubted S_N2 processes,[32] in contradiction to the view[5,6] that small if not inverse isotope effects should be exhibited. The usefulness of α-k_H/k_D as a criterion of mechanism is therefore weakened in view of this uncertain situation. The present work was therefore undertaken in order to assess one important aspect of the problem, namely the maximum value of α-k_H/k_D that can be expected for halide leaving groups.

CALCULATIONS

Geometric Model.—The model employed for both reactant and transition states for S_N1 calculations is shown in Figure 1. The bond order of the C_α–X (X = halogen) bond, n_{CX}, is unity for the reactant and less than unity for transition states. Bond angles were taken as tetrahedral in the IS and the angles θ in TS models were calculated from equation (1), which gives a planar carbocation for $n_{CX} = 0$. The bond lengths employed are shown in Table 2. The Pauling rule was used to estimate lengths of partial TS bonds.

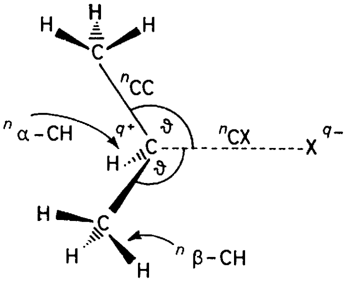


FIGURE 1 Geometric model for S_N1 solvolysis of isopropyl X

$$\theta = 90 + 19.47 n_{CX} \qquad (1)$$

Force Constants.—The general philosophy behind the estimation of TS force constants has been previously detailed.[33-36] For stretching of bonds between atoms i and j, the force constant F_{ij} is given by equation (2) where $F_{ij}{}^0$ is the stretching force constant for the intact bond ($n_{ij} = 1$). Angle bending force constants F_{ijk} for angles subtended by bonds i–j and j–k are given by equation (3) in which $F_{ijk}{}^0$ is the appropriate force constant for a tetrahedral angle when $n_{ij} = n_{jk} = 1.0$, and g_α is a geometry factor that deviates from unity as angles deviate from tetrahedral. If one of the bonds in question is the $C_\alpha \cdots X$ bond, these bonding force constants will approach zero as n_{CX} tends to zero in a carbocation-like TS, whereas it is more appropriate for them to transform into out-of-plane bending force constants for the planar cation.[36,37] This modification is accomplished by equation (4), where the out-of-plane bending force constant is taken as 0.2 aJ rad^{-2}. Torsional force constants were held at the IS value. Values of force constants (F^0) are also shown in Table 2.

$$F_{ij} = n_{ij} F_{ij}{}^0 \qquad (2)$$

$$F_{ijk} = g_\alpha (n_{ij} n_{jk})^{\frac{1}{2}} F_{ijk}{}^0 \qquad (3)$$

$$F_{\mathrm{CX},jk} = g_\alpha (n_{\mathrm{CX}} n_{jk})^{\frac{1}{2}} (F_{\mathrm{CX}}{}^0{}_{,jk} - 0.2) + 0.2 \qquad (4)$$

It must be emphasised that the adoption of equations (3) and (4) in preference to alternatives that have appeared[34,35] ensures that isotope effects are kept at relatively low values,

TABLE 2

Geometries and force constants [a, b]

Co-ordinate type		
(a) Bond stretches	r_i	F_{ij}
C_α–F	$1.4 - 0.3 \ln n_{\mathrm{CF}}$	$510 n_{\mathrm{CF}}$
C_α–Cl	$1.76 - 0.3 \ln n_{\mathrm{CCl}}$	$320 n_{\mathrm{CCl}}$
C_α–Br	$1.94 - 0.3 \ln n_{\mathrm{CBr}}$	$230 n_{\mathrm{CBr}}$
C_α–I	$2.14 - 0.3 \ln n_{\mathrm{CI}}$	$180 n_{\mathrm{CI}}$
C_α–H	$1.094 - 0.3 \ln n_{\alpha\text{-CH}}$	$480 n_{\alpha\text{-CH}}$ (Set A)
C_α–H	1.094	480 (Set B)
C_α–C_β	$1.534 - 0.3 \ln n_{\mathrm{CC}}$	$450 n_{\mathrm{CC}}$
C_β–H	$1.094 - 0.3 \ln n_{\beta\text{-CH}}$	$480 n_{\beta\text{-CH}}$
O–C_α	$1.43 - 0.3 \ln n_{\mathrm{OC}}$	$530 n_{\mathrm{OC}}$
H–O	0.957	770
(b) Angle bends	Angle	$F_{ijk}/(n_{ij}n_{jk})^{\frac{1}{2}}g_\alpha$
C_β–C_α–F	$\theta = 90 + 19.47 n_{\mathrm{CF}}$	1.0
C_β–C_α–Cl	$90 + 19.47 n_{\mathrm{CCl}}$	1.0
C_β–C_α–Br	$90 + 19.47 n_{\mathrm{CBr}}$	0.9
C_β–C_α–I	$90 + 19.47 n_{\mathrm{CI}}$	0.9
H–C_α–F	$90 + 19.47 n_{\mathrm{CF}}$	0.9
H–C_α–Cl	$90 + 19.47 n_{\mathrm{CCl}}$	0.8
H–C_α–Br	$90 + 19.47 n_{\mathrm{CBr}}$	0.7
H–C_α–I	$90 + 19.47 n_{\mathrm{CI}}$	0.6
C_β–C_α–C_β	$\phi = \cos^{-1}(1 - 1.5 \sin^2\theta)$	1.0
H–C_β–C_α	109.47	0.65
H–C_β–H	109.47	0.55
H–C_α–C_β	$\phi = \cos^{-1}(1 - 1.5 \sin^2\theta)$	0.65
H–O–H [c]	105	0.76
H–O–C_α [c]	109.47	0.66
O–C_α–C_β [c]	$90 + 19.47 n_{\mathrm{CX}}$	1.0
O–C_α–H [c]	$90 + 19.47 n_{\mathrm{CX}}$	0.68
(c) Torsions *etc.*		F_i
Ethane-type torsions		0.024
Out-of-plane bends		0.2

[a] Reactant values given for $n_{\mathrm{CX}} = 1.0$, $n_{\mathrm{OC}} = 0.0$. Stretching force constants in N m^{-1} (100 N m^{-1} = 1 mdyn Å^{-1}); other force constants in aJ rad^{-2} (1 aJ rad^{-2} = 1 mdyn Å rad^{-2}). [b] Force constants were average values obtained from standard sources cited in ref. 34 and from the following: ref. 49; C. G. Opaskar and S. Krimm, *Spectrochim. Acta*, 1967, **23A**, 2261; G. A. Crowder and H. K. Mao, *J. Mol. Struct.*, 1973, **18**, 33; G. A. Crowder, *J. Mol. Spectrosc.*, 1973 **48**, 467; G. A. Crowder and S. Ali, *J. Mol. Struct.*, 1975, **25**, 377; G. A. Crowder and C. Harper, *ibid.*, 1980, **68**, 89; A. B. Dempster and G. Zerbi, *J. Mol. Spectrosc.*, 1971, **39**, 1; R. G. Snyder and J. H. Schachtschneider, *ibid.*, 1969, **30**, 290; P. A. Gignère and M. Schneider, *Can. J. Chem.*, 1972, **50**, 152. [c] For solvent assistance models only.

in that a minimal amount of bending zero-point energy is lost on proceeding from IS to TS.

Hyperconjugation and β-k_H/k_{D6}.—As n_{CX} is decreased, the charge on C_α in a TS model, q^+, equal to $(1 - n_{\mathrm{CX}})$, increases and so does the capacity for C_β–H hyperconjugation. This has been recognised as the dominant factor in the determination of β-deuterium isotope effects.[38] It is therefore necessary to simulate the hyperconjugative shortening of the $C_\alpha$$\overset{...}{-}$$C_\beta$ bond and the lengthening of the C_β–H bonds in the TS in terms of q^+.

This was accomplished with reference to the calculated (*ab initio*, STO-3G) structures of propane [39] and the 1-methylethyl cation.[40] Bond lengths in the former were taken as those pertinent to $n_{\mathrm{CX}} = 1.0$ whilst those in the latter are appropriate for $n_{\mathrm{CX}} = 0$. The lengths in the cation relative to those in the neutral molecule were then substituted into the Pauling equation to give bond orders in the former, which were: $n_{\mathrm{CC}} = 1.146$, $n_{\beta\text{-CH}} = 0.924$ (and 1.003 for the hydrogens orthogonal to the plane of the vacant *p*-orbital). Thus in terms of q^+, assuming that all bond orders change in concert, values of n_{CC} and $n_{\beta\text{-CH}}$ are given by equations (5)—(7). Similarly, the change in bond angles

$$n_{\mathrm{CC}} = 1.0 + 0.146q^+ \quad (5)$$

$$n_{\beta\text{-CH}} = 1.0 - 0.076q^+ \quad (6)$$

$$n_{\beta\text{-CH}} = 1.0 + 0.003q^+ \quad (7)$$

on proceeding from IS to TS was expressed, in terms of n_{CX}, by the bond angle difference between propane and the 1-methylethyl cation.

Thus, in contrast to the situation described by Schowen *et al.*,[41] both bending and stretching force constants involving C_β–H bonds are varied as a function of the progress variable.

The above procedures are largely empirical, but practical justification is available. Model k.i.e. calculations on the solvolysis of t-butyl chloride have been based on the same or similar equations as those used here, and isotope effects for three isotopic atoms were successfully correlated with experimental values when q^+ was 0.8.[33] This value for charge development in the TS has been verified by other independent methods.

The C_α–H *Stretching Force Constant*.—The calculated C_α–H bond length in propane is 1.089 Å [39] and this lengthens to 1.113 Å upon ionization to the 1-methylethyl cation.[40] In terms of the Pauling equation, this means that $n_{\alpha\text{-CH}}$ decreases as q^+ increases, as described by equation (8). It was suspected, however, that this procedure might over estimate the loss of stretching and bending zero-point energy

$$n_{\alpha\text{-CH}} = 1.0 - 0.077q^+ \quad (8)$$

on proceeding from IS to TS, in that the bond length–force constant relationship may be dissimilar for charged and uncharged atoms.[42] For instance, *ab initio* calculations reveal that the C–O bond length increases on going from CH_3OH to CH_3O^-, but the calculated stretching force constants are the same in both species.[43] Thus in a second set of calculations, (Set B), $n_{\alpha\text{-CH}}$ was put equal to unity for all values of q^+. All other details of Sets A and B calculations were identical. One experimental fact of interest [44] that is reproduced by *ab initio* calculations is the increase in C–H bond lengths on going from ethane [45] to propane (methylene C–H).[39]

Nucleophilic solvent assistance was simulated by placing a water molecule in the TS model on the axis on the $C_\alpha \cdots X$ bond at varying distances from C_α. If the $O \cdots C_\alpha$ bond order is n_{OC} then the formal charge on the incipient cation is given by equation (9); the values thus obtained were

$$q^+ = 1 - n_{\mathrm{OC}} - n_{\mathrm{CX}} \quad (9)$$

substituted into equations (5)—(8) to calculate TS bond orders. Some solvent assistance calculations were performed using a trigonal bipyramidal model for the TS, but the results differed insignificantly from those based upon the solvated ion-pair model and are not reported.

Reaction Co-ordinate Models.—Reasonable values of the imaginary frequency, $\nu_L^\ddagger$ ($10i$—$100i$ cm^{-1}) in S_N1 calculations were obtained simply by giving the TS $C_\alpha \cdots X$ stretching force constant a negative value, usually -10 N m^{-1}. This procedure ensured that reaction co-ordinate motion involved movement of C_α and X in opposite directions, but it was found that the isopropyl moiety moved as a rigid structure. In order to simulate Walden inversion-type motion of the H_α and the CH_3 groups towards the departing X atom, an alternative involved the introduction of off-diagonal force constants in the TS force field, $F_{12}^\ddagger$, which coupled the $C_\alpha \cdots X$ stretch (positive force constant) with the H–$C_\alpha \cdots X$

and C_β–$C_\alpha \cdots$ X bending co-ordinates, according to equation (10), in which F_b is the appropriate TS bending constant. Reasonable values of $\nu_L^\ddagger$ again resulted.

$$F_{12}^\ddagger = 1.005(F_{CX}F_b)^{\frac{1}{2}} \qquad (10)$$

For the solvent assisted model, the $C_\alpha \cdots$ X and O $\cdots C_\alpha$ stretching co-ordinates were coupled as shown in equation (11). Neither α-k_H/k_D nor β-k_H/k_{D6} were seriously affected by the value of A employed (generally 1.02) but the central carbon isotope effect was sensitive. No changes in the hydrogen isotope effects were occasioned when A was varied as a function of n_{OC} and n_{CX}.[34,46] Again, the desired Walden inversion motion was not satisfactorily generated, and a modification involved use of additional off-diagonal

$$F_{12}^\ddagger = A(F_{CX}F_{OC})^{\frac{1}{2}}\ (A > 1) \qquad (11)$$

force constants which coupled the $C_\alpha \cdots$ X stretch to the C_β–$C_\alpha \cdots$ X and H–$C_\alpha \cdots$ X bends, and the O $\cdots C_\alpha$ stretch to the O $\cdots C_\alpha$–H and O $\cdots C_\alpha$–C_β bends according to equation (12).[46]

$$F_{12}^\ddagger = 0.3(F_{CX}F_b)^{\frac{1}{2}} \text{ or } 0.3(F_{OC}F_b)^{\frac{1}{2}} \qquad (12)$$

Equilibrium Isotope Effects.—These were calculated using models for the products of reaction (C) in which X^- was

$$R\text{–}X \rightleftharpoons R^+ + X^- \qquad (C)$$

absent, but which were otherwise identical to that in Figure 1 ($n_{CX} = 0$). No off-diagonal force constants were employed, and the geometry and force constants for the carbocations were based on equations (5)—(8), in which q^+ was set equal to unity.

Calculations of k.i.e. and e.i.e. were performed using a local variant of program BEBOVIB-IV.[47] A modification of the treatment of torsional modes[48] has not yet been incorporated into this program but, as will be seen later, torsions have no influence upon k.i.e. results.

RESULTS AND DISCUSSION

The S_N1 *Model.*—The models employed in all the calculations herein are largely empirical as far as TS force fields are concerned, although all TS force constants are systematic functions of q^+ (or n_{CX}). Examination of *all* adjustable parameters and assumptions would have involved a prohibitive amount of computer time, but the following did not significantly affect α-k_H/k_D and/or β-k_H/k_{D6}: (a) orientation of the methyl group with respect to the $C_\alpha \cdots$ X bond; (b) the value of the torsional force constant for the TS over the range of 0.002 to 0.2 aJ rad^{-2}; * (c) the C_α–H bond length as a function of halogen identity;[50] (d) use of Set A or B models (for β-k_H/k_{D6}); (e) simulating tetrahedral solvation of the leaving group in the TS by adding three H–O moieties.[33]

The employment of extra TS interaction force constants to generate Walden inversion motion raised α-k_H/k_D for Pr^{i}Br from 1.13 to 1.21 ($n_{CBr} = 0.5$) and from 1.36 to 1.41 ($n_{CBr} = 0.02$). To avoid over-estimation of α-k_H/k_D values in making comparisons with those of Shiner, the results in Table 3 were obtained simply by setting $F_{CX} = -10$ N m^{-1} in all cases. Values of n_{CX} in Table 3 range from 0.5 (half-broken $C_\alpha \cdots$ X bond) to 0.02 (ion-pair-like TS). Results for β-k_H/k_{D6} are not shown; these were but little dependent on halogen identity and ranged from around 1.25 ($n_{CX} = 0.5$) to 1.57 ($n_{CX} = 0.02$).

The Set B k.i.e. are, as expected, lower than those based on Set A for a given value of n_{CX}. Likewise, α-k_H/k_D is halogen-dependent since the H–C_α–X bending force constant decreases with increasing mass of X. The k.i.e. are not linear functions of n_{CX}, as is shown in Figure 2. This may be a consequence of the non-linear dependence of F_{HCX} upon n_{CX}. The most prominent feature of the results however is the fact that even the Set B k.i.e. are markedly larger than Shiner's 'maximum' values for complete ionization at the TS. This is true even for n_{CX} values in the 0.5—0.4 range. When the k.i.e. are expressed as percentages the discrepancy involves factors of between 1.5 and 2 for $n_{CX} = 0.02$.

TABLE 3

Computed α-deuterium isotope effects as a function of n_{CX} for the S_N1 model

Substrate	α-k_H/k_D [a]			
	n_{CX} = 0.5	0.25	0.05	0.02
Pr^{i}F (Set A)	1.144	1.248	1.390	1.432
Pr^{i}F (Set B)	1.089	1.160	1.270	1.306
Pr^{i}Cl (Set A)	1.137	1.234	1.361	1.397
Pr^{i}Cl (Set B)	1.083	1.147	1.244	1.275
Pr^{i}Br (Set A)	1.131	1.219	1.330	1.361
Pr^{i}Br (Set B)	1.077	1.134	1.216	1.241
Pr^{i}I (Set A)	1.123	1.201	1.296	1.320
Pr^{i}I (Set B)	1.069	1.118	1.185	1.205

[a] At 25 °C.

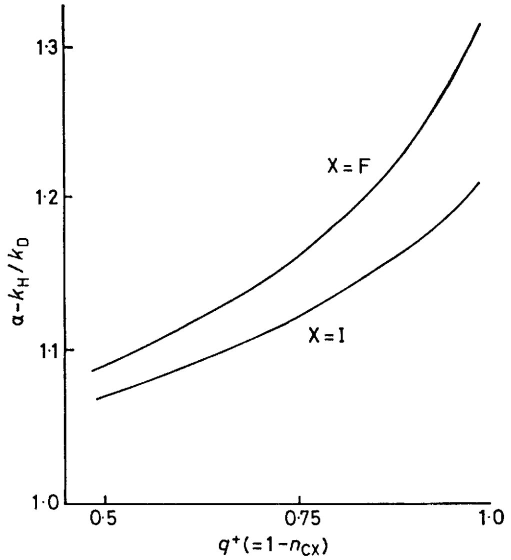


FIGURE 2 Plot of α-k_H/k_D *versus* n_{CX} for S_N1 models of isopropyl X (Set B, 25 °C)

This is an interesting finding as far as the use of α-k_H/k_D as a mechanistic tool is concerned. The uncertainty as to the relative merits of Set A *versus* Set B force-fields prevents presentation of a firm set of revised

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* This invalidates the suggestion[49] that an important contribution to β-k_H/k_{D6} in isopropyl bromide hydrolysis is differential freedom of rotation of methyl groups in IS and TS.

maxima. But, if these k.i.e. are judged as being more realistic than those presented by Shiner, it follows that the maximum α-k_H/k_D value for solvolysis of simple secondary alkyl halides may not yet have been experimentally realised. This in turn means that a mechanism in which the tight to loose ion pair conversion step is rate-limiting has yet to be unveiled.[*] Thus an experimental value for an unassisted solvolysis substantially lower than those reported here can be taken as an indication of rate-limiting ionization (k_1 step in the Scheme) with the $C_\alpha \cdots X$ bond only partially broken at the TS.

This assertion is only as good as the calculations upon which it is based. In the present work detailed and physically reasonable TS models have been employed, and no assumptions concerning relative values of TS reduced partition functions nor of temperature-independent factors have been made. Such assumptions have been made by Shiner, and he has converted soundly based e.i.e. to relative k.i.e. using them. The absolute k.i.e. are then based on an assumed α-$k_H/k_D = 1.125$ for CH_2Br,[22] a number which is not explicitly justified but which is identical with the experimental α-k_H/k_D for solvolysis of the *secondary* substrate PhCH(Br)CH_3 in 80% aqueous ethanol.[7] There is no compulsive evidence to the effect that this substrate is solvolysed with k_2 as rate-limting step,[6,25,51] and so it would appear that a circular argument has been employed, if my analysis of Shiner's procedure is correct. Thus my conclusion is not disqualified by these considerations.

A second alternative is that α-k_H/k_D is strongly substrate-dependent,[15] and is different for primary *versus* secondary substrates in particular. If so, the above criticism of Shiner's estimates is invalid, but it then follows that α-k_H/k_D is a most uncertain criterion of mechanism and/or transition state character. This statement properly applies only to relative α-k_H/k_D maxima in view of Shiner's TS approximations and the uncertainty in his relative to absolute conversion, and it is noteworthy that, relative to RBr, the k.i.e. range from 1.079 (X = F) to 0.969 (X = I) for CH_3X whilst from Table 3 the range is from 1.052 to 0.971, *i.e.* it is more compressed in the secondary case. But even if this alternative is true it would be necessary to use the present values as a mechanistic guide rather than the CH_3X values for the simple reason that no simple primary alkyl halide has yet been shown to solvolyse without solvent or anchimeric assistance.

There is yet another way of examining the source of the discrepancy between the two set of estimates. While criticism can be levelled at Shiner's treatment of transition states, none is applicable to his IS calculations, in that complete force fields which accurately reproduce measured vibrational frequencies have been used by him. Consequently his relative e.i.e. for processes (13) and (14) must be sound. The IS force fields used in the present

$$\mathrm{CH_3X \rightleftharpoons CH_3^+ + X^-} \tag{13}$$

$$\mathrm{CH_2DX \rightleftharpoons CH_2D^+ + X^-} \tag{14}$$

work lack the necessary off-diagonal elements for accurate reproduction of frequencies, and it is worth considering whether or not this is the basic cause of the problem.

Accordingly, values of α-K_H/K_D, the e.i.e. for the processes in equations (15) and (16), have been calculated using the present diagonal force-fields. Values in the

$$\mathrm{(CH_3)_2CHX \rightleftharpoons (CH_3)_2CH^+ + X^-} \tag{15}$$

$$\mathrm{(CH_3)_2CDX \rightleftharpoons (CH_3)_2CD^+ + X^-} \tag{16}$$

first column of Table 4 are of course dependent upon whether Set A or B formulae have been employed. Of more relevance are the e.i.e. relative to X = Br, which are displayed in the second column. These are in fact the equilibrium constants for the reaction in equation (17) and are not dependent on empirical models for the

$$\mathrm{(CH_3)_2CDBr + (CH_3)_2CHX \rightleftharpoons (CH_3)_2CHBr + (CH_3)_2CDX} \tag{17}$$

cation. Comparison of the relative e.i.e. with the fundamentally precise Shiner values for the methyl analogue of equation (17) in column 4 reveals excellent agreement. Indeed, calculations performed here for the methyl analogue using diagonal force constants only (column 3) are also in accord with Shiner's values. Therefore no penalty is enacted by the neglect of off-diagonal force constants in the initial states as far as relative e.i.e. are concerned.

TABLE 4

Equilibrium isotope effects for RX ionization [a]

X	α-K_H/K_D ($\mathrm{Pr^iX}$)	Rel. α-K_H/K_D ($\mathrm{Pr^iX}$)	Rel. α-K_H/K_D (MeX)	Rel. α-K_H/K_D (MeX, ref. 22)
H (Set A)	1.240	0.914		
H (Set B)	1.131	0.914	0.916	0.918
F(Set A)	1.455	1.071		
F (Set B)	1.327	1.071	1.073	1.079
Cl (Set A)	1.408	1.037		
Cl (Set B)	1.284	1.037	1.038	1.035
Br (Set A)	1.358	1.000	1.000	
Br (Set B)	1.238	1.000	1.000	1.000
I (Set A)	1.308	0.963		
I (Set B)	1.191	0.963	0.961	0.969

[a] At 25 °C.

Also calculated but not shown were values of β-K_H/K_{D6}. These were almost independent of the identity of X in $\mathrm{Pr^iX}$ and lay in the vicinity of 1.53.

It is apparent that the e.i.e. are close to the k.i.e. for $n_{CX} = 0.02$. This means that such e.i.e. may be of

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[*] This must be qualified, since most experimental α-k_H/k_D values pertain to compounds such as ArCH(X)CH_3,[8] where charge on C_α can be delocalized by resonance. Thus q^+ and $1 - n_{CX}$ will not normally be equivalent as has been assumed here, and this factor, along with a greater increase in n_{CC} as n_{CX} decreases, will lead to a lowering of α-k_H/k_D, especially for Set A cases. The present results thus pertain to simple alkyl systems only. However, preliminary calculations for phenethyl X models yield α-k_H/k_D values which are still significantly higher than the Shiner 'maxima,' even when the consequences of partial delocalization of charge are taken into account.

value in estimating maximum values of α-k_H/k_D for various leaving groups. The lack of a reliable estimate for arenesulphonate solvolysis has already been mentioned, and it is now perhaps relevant to point out that e.i.e. for the acid-catalysed dehydration of diphenylmethanols (H_2O as leaving group) range up to values of 1.35.[52] If C_α–O cleavage in the departure of H_2O is a satisfactory model for an arenesulphonate leaving group, it follows that the maximum α-k_H/k_D for the latter may in fact be *ca.* 1.35, rather than the 1.22—1.26 range presently considered to be appropriate. If anything the arenesulphonate k.i.e. value could be higher than 1.35, since relief of non-bonded interactions on going from IS to TS, demonstrated to be of importance for OSO_2Ar,[53] should be greater than for H_2O and should therefore lead to a larger value of α-k_H/k_D.[32b, 54]

Therefore it is tentatively suggested that the maximum value of α-k_H/k_D for arenesulphonate solvolysis has yet to be experimentally realised.

It is almost a tenet of model k.i.e. calculations that the provision of accurate force fields for IS and TS models is not as important as how valence force constants are changed on going from one to the other. This has already been illustrated by the relative e.i.e. results. Nevertheless this aspect was more closely investigated.

TABLE 5

Effect of inclusion of off-diagonal force constants on α-k_H/k_D and β-k_H/k_{D6} for isopropyl bromide, S_N1 model, Set B [a]

Description of force-field	K.i.e.	n_{CBr} = 0.5	0.25	0.05	0.02
Diagonal force constants from Table 2	α-k_H/k_D	1.077	1.134	1.216	1.241
	β-k_H/k_{D6}	1.275	1.417	1.543	1.561
Diagonal force constants from Table 2; off-diagonal force constants from ref 55	α-k_H/k_D	1.031	1.076	1.151	1.166
	β-k_H/k_{D6}	1.240	1.427	1.552	1.576
Diagonal and off-diagonal force constants from ref. 55	α-k_H/k_D	1.068	1.121	1.197	1.210
	β-k_H/k_{D6}	1.281	1.422	1.546	1.569

[a] At 25 °C, $F^{\ddagger}_{CBr} = -10$ N m^{-1}.

Snyder has provided a force field which includes 43 off-diagonal elements for isopropyl bromide.[55] Frequencies can be reproduced to within ± 6.8 cm^{-1}. 35 of these interaction force constants, which pertain to higher frequency modes, were selected, and for the IS model were combined both with Snyder's converged diagonal force constants and with the averaged diagonal force constants in Table 2. In the former case the standard deviation between observed and calculated frequencies was 9.2 cm^{-1} and in the latter 14.0 cm^{-1}. These can be compared with the ± 37.7 cm^{-1} obtained using the simple valence force field. The formulation of TS off-diagonal force constants must necessarily be empirical. If co-ordinates m and n, having diagonal force constants $F_{mm}{}^0$ and $F_{nn}{}^0$ are coupled using an off-diagonal element $F_{mn}{}^0$ in the IS, it was assumed that the TS off-diagonal element was given by equation (18), in which $F_{mm}{}^{\ddagger}$ and $F_{nn}{}^{\ddagger}$ are the diagonal TS force constants evaluated in the usual

$$F_{mn}{}^{\ddagger} = F_{mn}{}^0(F_{mm}{}^{\ddagger}/F_{mm}{}^0)(F_{nn}{}^{\ddagger}/F_{nn}{}^0) \qquad (18)$$

way. Results of Set B k.i.e. calculations thus performed are shown in Table 5. The first pair of rows contain data using the averaged diagonal force constants (Table 3) alone. The second two rows were calculated from these averaged diagonal force constants plus the Snyder off-diagonals, whilst the third pair of rows contain results based on the almost complete Snyder force field

It is clear that β-k_H/k_{D6} is scarcely affected by force-field variation. However, values of α-k_H/k_D are significantly reduced, although for both the hybrid and the Snyder force fields they are still greater than the Shiner maxima for $n_{CBr} = 0.02$. Use of the more elaborate reaction co-ordinate formulation designed to simulate Walden inversion motion raised all values of α-k_H/k_D. In fact the α-k_H/k_D value recorded for the hybrid force-field is the lowest obtained in a large number of futile attempts to force agreement between isopropyl halide and methyl halide results.* It is still, for $n_{CBr} = 0.02$, too high.

This reinforces the earlier conclusion that the Shiner k.i.e. maxima, even if valid for methyl halides, have no practical value for the solvolysis of secondary halides, and that no simple secondary alkyl halide has yet been shown to solvolyse in an unassisted fashion *via* rate-limiting ion-pair conversion.

Solvent Assistance Model. Comparison of Experimental and Theoretical Results.—Leffek and his co-workers have measured both α-k_H/k_D and β-k_H/k_{D6} for isopropyl bromide hydrolysis in water.[49, 56] Their results, neglecting an unexplained discrepancy in the latter value as it appears in two different papers,[49, 57] are shown in the top row of Table 6. The number of isotopic atoms for which k.i.e. have been measured is too few, and the number of adjustable parameters used in formulating a force-field is too great to permit a confident assignment of TS structure based on a successful match of the experimental and theoretical k.i.e. Nonetheless the results of such a search were instructive.

TABLE 6

Experimental and theoretical k.i.e. for isopropyl bromide hydrolysis at 60 °C [a]

n_{CBr}	n_{OC}	α-k_H/k_D	β-k_H/k_{D6}	k_{12}/k_{13} [b]
(Experimental)		1.069	1.318	
0.25	0.05	1.069	1.300	1.022
0.05	0.25	1.071	1.332	1.015
0.25 [c]	0.05 [c]	1.065	1.274	1.041
0.05 [c]	0.25 [c]	1.068	1.313	1.030

[a] All Set B results. [b] The C_α carbon-13 k.i.e. [c] Calculated using extra interaction force constants to generate Walden inversion motions [equation (12)].

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* The extent of model testing can be judged from the fact that the computer output finally making its way into this paper represents only *ca.* 5% of the total computer time consumed by this project.

No S_N1 model of any kind gave a correlation of both α-k_H/k_D and β-k_H/k_{D6} at 60 °C (latter results not shown) for a given value of n_{CBr}. An unassisted S_N1 process can be confidently rejected, even when Table 5 results are taken into account.

Attention is now turned to S_N2-like models in which C_α is nucleophilically solvated by a single water molecule. Two progress variables n_{CBr} and n_{OC}, are now required to describe the TS, and calculations were restricted to cases where $n_{OC} + n_{CBr} \leqslant 1.0$. A systematic survey was undertaken, using a range of n_{OC} and n_{CBr} values and a variety of models for the reaction co-ordinate motion, all in both the Set A and B formats. Details are not shown, but it suffices to state that for values of q^+ [equation (9)] less than *ca.* 0.3, α-k_H/k_D was inverse and so the survey was concentrated on looser models for the TS. It is accepted that inverse α-k_H/k_D values for S_N2 reactions proceeding through tighter transition states are the norm.[5,6,58]

It is seen from Table 6 that only two TS models, both with $q^+ = 0.7$ and in the Set B category, yield any degree of agreement with experiment. One is very ion-pair-like: $n_{OC} = 0.25$, $n_{CBr} = 0.05$ [an S_N2 (intermediate) process [16]], and the other involves a 75% broken $C_\alpha \cdots Br$ bond which is but poorly compensated by $O \cdots C_\alpha$ bond making. Values of the central carbon k.i.e., k_{12}/k_{13} have been included to show the effect on this isotope effect of varying the reaction co-ordinate formulation, and it is obvious that no firm claim as to ' solving ' the TS structure can be made until at least this isotope effect has been measured. Furthermore, there are two provisos concerning the attempted matching of experimental and theoretical β-k_H/k_{D6} values.

The first is that the origin of this k.i.e. in the present model is purely hyperconjugative [5,6] and its magnitude therefore depends only on q^+. In reality other factors, some of unclear origin as far as vibrational effects are concerned,[59] may be involved. For instance, it has been suggested that an inverse inductive CH_3/CD_3 isotope effect of *ca.* 0.955 per methyl group may be operative.[38a,60] Multiplication of β-k_H/k_{D6} values in Table 5 by $(0.955)^2$ weakens the agreement between theory and experiment somewhat, but more importantly, consideration of this factor forces theoretical and experimental results for the unassisted S_N1 model even further apart.

The second proviso concerns the possibility that the experimental β-k_H/k_{D6} is contaminated by a primary k.i.e. for rate-limiting, solvent-promoted dehydrobromination. Although the reported olefin yield is only 0.7%,[57] there are likely to be experimental difficulties in measuring the yield of a volatile olefin in a reaction conducted in water, and no check experiments, such as the establishment of a material balance of products, were mentioned, although precautions were taken to minimize volatility losses.[57] If this is in fact a real possibility then α-k_H/k_D as measured will also be composite.[61] Thus I am in no way even tentatively capable of assigning a structure to the TS for the hydrolysis of isopropyl bromide, but I can state with reasonable confidence that solvent assistance is required. It is noteworthy that calculated values of both α-k_H/k_D and β-k_H/k_{D6} at given n_{CBr} decrease as n_{OC} is increased, in line with the Schleyer explanation that variable isotope effects are a consequence of varying degrees of solvent assistance.[16]

The final matter that requires consideration is the temperature dependance of β-k_H/k_{D6} for hydrolysis of isopropyl bromide. The k.i.e. has been found to be almost temperature independent, increasing if anything with increasing temperature.[49] On the other hand the present models predict a normal temperature dependence, with β-k_H/k_{D6} decreasing with increasing temperature, and values of $\Delta H_D^\ddagger - \Delta H_H^\ddagger$ range between 0.13 and 0.27 kcal mol^{-1}. It has already been shown that the explanation advanced by the original authors is untenable.

Such anomalies in secondary deuterium isotope effects have also been noted in the base-catalysed hydrolysis of methyl acetate (CH_3COOCH_3 *versus* CD_3COOCH_3) and other esters.[62] It would probably be possible to model the temperature anomalies, but it is likely that bizarre force-fields would be required.[63] A physically reasonable explanation for anomalies has however been presented by Schowen and his co-workers,[62] and I believe that it provides an attractive rationale of the facts in question. It must be recognised that for any nucleophilic substitution reaction in solution, solvent reorganization must precede or accompany heavy atom reorganization on proceeding from IS to TS. If water is the nucleophile, any number of parallel competing pathways involving specific nucleophilic solvation and non-specific solvation of other polar sites may be envisaged, depending upon the degree of co-ordination of the water molecules involved. For instance the present S_N2 model contains a single unco-ordinated water molecule, and no account has been taken of the possibility that parallel pathways involving nucleophilic attack by water dimers, trimers, *etc.*, each bearing a free lone pair of electrons, can occur. Furthermore, solvation of other polar TS sites such as the partially positively charged β-bond hydrogens has been neglected (and this could influence isotope effects). It is therefore reasonable to suggest that parallel and serial pathways, having different isotope effects and temperature dependences, should exist, whatever the overall mechanism of solvolysis. The recipe for the Schowen model is therefore complete, and thus the anomalous temperature dependence could be simulated, were sufficient pathways considered.[62] This analysis has not been performed because the initial parameters required would be guesses at best, and the temperature dependence of the release of free water molecules and small hydrogen-bonded clusters from larger clusters in the bulk solvent [64] would also have to be guessed. There can be no doubt however that the Schowen model is capable, *in principle*, of reproducing erratic β-k_H/k_{D6} temperature dependences and, most importantly, of doing so on the basis of a physically valid picture of solvolysis.

An alternative model for the anomalous temperature dependence of β-k_H/k_{D6} could possibly be fashioned on the basis of mathematical models involving $\Delta C_p^\ddagger$ for the temperature dependence of the individual rate constants themselves.[20] I reject this on two grounds. First, the current curve-fitting procedure used to correlate rate–temperature data involves the presence of temperature on both sides of the regression equation:[20] a statistical device that almost invariably improves the quality of fit of data to mathematical models that may be spurious.[65] Secondly, the model in question now apparently requires internal return to be an important component in *all* solvolyses, even of primary halides.[20] This postulation is not supported by any independent evidence, and has in fact been amply demonstrated by Abraham[66] to be wrong. Abraham's analysis has been neither questioned nor refuted, and in addition the flaw in the original reasoning that led to the internal return proposal[67] has been exposed by him and myself.[68] A more recent argument in favour of the internal return mechanism for methyl halide hydrolysis and based on entropy correlations[69] also suffers from the statistical flaw mentioned above. Thus there is no physical or experimental basis for this alternative.

Conclusions.—I conclude first that the maximum α-k_H/k_D values estimated by Shiner are inappropriate for the solvolysis of simple secondary alkyl halides, and that no demonstration of a k_2 rate-limiting mechanism has yet been given for such reactions. I tentatively question whether the α-k_H/k_D maximum for arenesulphonate solvolysis has yet been attained.

Secondly, and with a reservation concerning a solvent assistance model that because of its simplicity does not reproduce the temperature dependence of β-k_H/k_{D6}, I conclude that a nucleophilic solvent molecule is necessarily present in the TS for isopropyl bromide hydrolysis. The timing of its getting there is a question that model k.i.e. calculations of the present type are not capable of answering.[33] There are two possibilities for concerted reactions; the first involves classical S_N2 attack leading directly to covalent product whilst in the second the immediate product is a solvated ion pair formed in an S_N2 (intermediate) process. Rate-limiting nucleophilic attack on a tight ion pair formed without solvent assistance is not disqualified by this conclusion either. Yet such an intermediate would have to exist in a nucleophilic environment for a finite time, which runs counter to the finding that potentially more stable intermediates than this do not exist in aqueous solution and are bypassed by enforced concerted pathways.[32d,70]

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