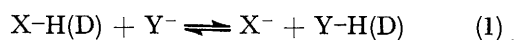


Solvent Dependence of Kinetic Hydrogen Isotope Effects for Simple Proton Transfer

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Kinetic hydrogen isotope effects for some simple proton transfer reactions, involving 2-nitropropane, nitroethane, and ethyl 2-methylacetoacetate as substrates, have been measured in a variety of solvent mixtures (dimethyl sulphoxide–water, acetonitrile–water, and 2,2,2-trifluoroethanol–water). Both rates and isotope effects vary considerably as the solvent composition is altered, but they show no correlation with the effect of the solvent on the overall free energy changes for the reactions. The results are discussed in relation to current theories of isotope effects.

THEORETICAL treatments predict that the magnitude of primary kinetic hydrogen isotope effects (k^H/k^D) for proton transfer reactions [equation (1)] should be related to the overall free energy change for the reaction.¹



Thus Westheimer,² on the basis of a model emphasising the importance of zero point energy associated with the 'symmetrical' stretch ($\bar{X} \cdots \text{H} \cdots \bar{Y}$) of the transition state, predicted that in a series of similar reactions, a maximum isotope effect should occur when the transition state is symmetrical. Assuming that ΔG gives a reasonable measure of transition state symmetry, this corresponds to a maximum value when ΔG is close to zero. Similarly, an alternative explanation¹ based on the quantum-mechanical tunnel effect predicts that the isotope effect should be largest for a symmetrical energy barrier, since calculations show that the tunnel correction will have a maximum value when ΔG (or ΔH) is zero.³

It has been known for some time that changes in ΔG [which for proton transfer (1) is proportional to ΔpK where $\Delta pK = pK_{XH} - pK_{YH}$] effected by the introduction of substituents into one or both reactants frequently result in large variations in k^H/k^D . In some cases there is evidence for a maximum in k^H/k^D in the neighbourhood of $\Delta pK = 0$,¹ in agreement with the predictions of the theoretical treatments.

The dependence of k^H/k^D on the nature of the solvent has received less attention. Earlier results for reactions involving proton transfer to hydroxide ions,⁴ or base-catalysed elimination reactions⁵ in mixtures of dimethyl sulphoxide with water (or alcohols) were consistent with a simple interpretation in terms of the effect of the solvent on ΔpK for the reactions. More recently however, results obtained by Caldin and Mateo^{6,7} for the reaction of 4-nitrophenylnitromethane with tetramethylguanidine in aprotic solvents show that the variation of k^H/k^D with solvent cannot be attributed solely to the effect of the solvent on ΔG . They found that k^H/k^D at 298 K varied between 11 and 50, and that this variation bore no

relation to the relatively small variations in ΔG (ca. 3 kcal mol⁻¹).

We now present the results of a study into the effects of solvent variation on k^H/k^D for some simple proton transfer reactions. The solvent systems Me₂SO–H₂O, MeCN–H₂O, and CF₃·CH₂·OH–H₂O were chosen to give a wide range in the rates of the reactions and also in the pK_a values of the substrates and bases used.

EXPERIMENTAL

Materials.—2-Nitropropane was purified by spinning-band distillation. G.l.c. and n.m.r. analysis showed it to be free from traces of 1-nitropropane and nitroethane.

2-Nitro[2-²H₁]propane was prepared by acetate-catalysed exchange of 2-nitropropane with D₂O in dimethyl sulphoxide. Deuterium oxide (25 g), 2-nitropropane (9 g), and sodium acetate (2.25 g) were heated in dimethyl sulphoxide (50 ml) to 70 °C for 3 h. The 2-nitropropane was extracted with ether, the extract dried (Na₂SO₄), and the ether removed by distillation. N.m.r. analysis showed that 94% deuteration had occurred (70% recovery). The procedure was repeated and the final product fractionally distilled. N.m.r. analysis showed the product to be a mixture of 2-nitro[2-²H₁]propane (97.6%) and 2-nitropropane (2.4%).

Nitroethane was dried (MgSO₄) and distilled.

1-Nitro[1-²H₂]ethane was prepared from nitroethane by hydroxide-catalysed exchange with deuterium oxide as described by Bell and Goodall.⁸ Deuteration was essentially complete (n.m.r.) after two successive equilibrations with deuterium oxide (100-fold excess).

Ethyl 2-methylacetoacetate was purified by spinning-band distillation under reduced pressure. G.l.c. and n.m.r. analysis showed the product to be >99% pure; the remaining impurity was identified as ethyl acetoacetate.

Ethyl 2-methyl[2-²H₁]acetoacetate. A solution of ethyl 2-methylacetoacetate (0.1 mol dm⁻³) in deuterium oxide (>99.8%D) was kept for 4 days at 35 °C.⁹ N.m.r. analysis showed that 99% deuteration had been effected.

Dimethyl sulphoxide was distilled from calcium hydride under reduced pressure.

Acetonitrile was purified by successive distillations from calcium hydride, phosphorus pentoxide, and calcium

¹ R. P. Bell, *Chem. Soc. Rev.*, 1974, 513.

² F. H. Westheimer, *Chem. Rev.*, 1961, **61**, 265.

³ R. P. Bell, W. H. Sachs, and R. L. Tranter, *Trans. Faraday Soc.*, 1971, **67**, 1995.

⁴ R. P. Bell and B. G. Cox, *J. Chem. Soc. (B)*, 1970, 194; 1971, 783.

⁵ A. F. Cockerill, *J. Chem. Soc. (B)*, 1967, 967.

⁶ E. F. Caldin and S. Mateo, *J.C.S. Chem. Comm.*, 1973, 854.

⁷ E. F. Caldin and S. Mateo, *J.C.S. Faraday I*, 1975, **71**, 1876.

⁸ R. P. Bell and D. M. Goodall, *Proc. Roy. Soc. Ser. A*, 1966, **294**, 273.

⁹ R. P. Bell and J. R. Crooks, *Proc. Roy. Soc., Ser. A*, 1965, **286**, 285.

hydride. Trifluoroethanol was dried (Na_2SO_4) and distilled. Inorganic chemicals were of AnalaR grade.

pK_a Measurements.—pK_a Values of the various acids in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$, $\text{MeCN}-\text{H}_2\text{O}$, and $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$ were determined by potentiometric measurements with glass electrodes as described earlier.¹⁰ In some cases (2-nitropropane and nitroethane in Me_2SO -rich mixtures, and ethyl 2-methylacetoacetate in water) the anions were not sufficiently stable to enable potentiometric titrations to be carried out. In these cases several solutions of various buffer ratios were prepared by mixing the appropriate volumes of the substrate and sodium hydroxide, and the pH was measured as soon as equilibrium was reached.

The acidity constants K_a of the acids HA in solvent S are represented by equation (2), where the parameters γ

$$K_a = \frac{[\text{H}^+][\text{A}^-]}{[\text{HA}]} \cdot \frac{\gamma_{\text{H}^+}\gamma_{\text{A}^-}}{\gamma_{\text{HA}}} \quad (2)$$

are activity coefficients referred to infinite dilution in solvent S. The activity coefficients of ionic species were calculated from the Davies equation (3),¹¹ where A is the

$$-\log \gamma \pm = AI^{\frac{1}{2}}/(1 + I^{\frac{1}{2}}) - 0.3AI \quad (3)$$

Debye-Hückel function dependent upon the solvent dielectric constant and temperature. In mixtures for which the dielectric constants were not available ($\text{MeCN}-\text{H}_2\text{O}$ and $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$) it was assumed that there was a linear relationship between the dielectric constant and the mole fraction of the organic component of the solvent. The activity coefficients of neutral species were assumed to be unity. All measurements were carried out at 25 (± 0.1) °C. The results are listed in Table 1.

strate (SH). The rate of reaction of iodine with the solvents was found to be negligible. All measurements were made at 25 (± 0.2) °C.

For all the reactions the rate law shown in equations (4) and (5) was obeyed over at least 90% of reaction. In

$$-d[\text{I}_2^*]/dt = -d[\text{SH}]/dt = k_e[\text{SH}] \quad (4)$$

$$\text{where} \quad k_e = k_0 + k_B[\text{B}] \quad (5)$$

equations (4) and (5), $[\text{I}_2^*] = [\text{I}_2] + [\text{I}_3^-]$ and B refers to the added base. Values of k_B^{H} were determined from plots of k_e against $[\text{B}]$. Values of k_0 were generally small, and often negligible, as compared with $k_B[\text{B}]$. To minimize errors in the measured isotope effects, rates of deprotonation and dedeuteriation were determined simultaneously using identical buffer-solvent systems. It was usual (except where k_0 was large) to use only one base concentration in determining $k_B^{\text{H}}/k_B^{\text{D}}$, chosen so that the observed first-order rate constant k_e was given by $k_e = k_B[\text{B}]$ (*i.e.* k_0 was negligible). Where appropriate, experimental values of k_B^{D} were corrected to take into account the presence of any small amounts of protio-impurities in the deuterio-compounds. Individual rate constants in a given solvent mixture were reproducible to within $\pm 5\%$. Kinetic isotope effects, obtained by direct comparison of the protio- and deuterio-substrates in the same buffer-solvent system as described above, were also reproducible to within $\pm 5\%$.

2-Nitropropane.—Rates of proton transfer and isotope effects were measured in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$ with acetate, chloroacetate, and fluoride as bases. Base concentrations were in the range 0.02–0.1 mol dm⁻³ (up to 0.4 mol dm⁻³ in aqueous chloroacetate buffers), with [2-nitropropane] *ca.* 5×10^{-2} – 5×10^{-2} mol dm⁻³, $[\text{I}^-]$ 0.01 mol dm⁻³, and initial iodine

TABLE 1
pK_a Values of acids in solvent mixtures at 25 °C

(1) $\text{Me}_2\text{SO}-\text{H}_2\text{O}$		pK _a of acid ^a					Ethyl 2-methylacetoacetate
Vol % Me_2SO	$\text{CH}_3\cdot\text{CO}_2\text{H}$	$\text{ClCH}_2\cdot\text{CO}_2\text{H}$	HF	2-Nitropropane	Nitroethane		
0	4.75 ^b	2.89	3.16 ^c	7.74 ^d	9.03	12.4	
50	5.82 ^e	4.20 ^e	4.86		(8.60) ^e	(12.4) ^f	
70	7.12	5.06	6.74	11.0	10.2	12.3	
80	(7.08) ^e	(4.81) ^e			11.7	12.7	
	7.95	5.56	8.23	12.1			
	(8.00) ^h	(5.69) ^h					
100	12.6 ⁱ			16.2 ^j	16.4 ^j		
(2) $\text{MeCN}-\text{H}_2\text{O}$		pK _a of acid ^a			(3) $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$		
Vol % MeCN	$\text{CH}_3\cdot\text{CO}_2\text{H}$	Nitroethane	$\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}$	$\text{CH}_3\cdot\text{CO}_2\text{H}$	Nitroethane		
50	6.19	10.63	50	5.7 ₈	10.2 ₈		
			80	7.1 ₁	11.5 ₀		

^a ± 0.1 . ^b A. Albert and E. P. Serjeant, 'Determination of Ionization Constants,' Chapman and Hall, London, 1971. ^c A. J. Kresge and Y. Chiang, *J. Phys. Chem.*, 1973, **87**, 822. ^d M. H. Davies, *J.C.S. Perkin II*, 1974, 1018. ^e D. Turnbull and B. H. Maron, *J. Amer. Chem. Soc.*, 1943, **65**, 212; G. W. Wheland and J. Farr, *ibid.*, p. 1433. ^f P. Rumpf and R. Raynaud, *Compt. rend.*, 1960, **250**, 1501. ^g 20 °C; J. C. Halle, R. Gaboriaud, and R. Schaal, *Bull. Soc. chim. France*, 1970, 2047. ^h E. H. Baughman and M. M. Kreevoy, *J. Phys. Chem.*, 1974, **78**, 421. ⁱ I. M. Kolthoff, M. K. Chantooni, and S. Bhowmick, *J. Amer. Chem. Soc.*, 1968, **90**, 23.

Kinetic Measurements.—The proton transfer reactions were followed by measuring the rates of iodination of the substrates using a Gilford 2400 spectrophotometer. The iodination reactions were followed under conditions where the rate determining step was the deprotonation of the sub-

strates $\leq 10^{-4}$ mol dm⁻³. The results are listed in Table 2.

The isotope effect in aqueous solution for transfer to acetate is larger than that reported by Bell and Goodall ($k^{\text{H}}/k^{\text{D}} = 7.6$).⁸ Our value for $K_{\text{OAc}}^{\text{H}}$ in aqueous solution of

¹⁰ B. G. Cox and A. Gibson, *Chem. Soc. Faraday Symposium*, 1975, **10**, 107.

¹¹ C. W. Davies, 'Ion Association,' Butterworth, London, 1962, equation (3.1).

$2.71 \times 10^{-6} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ is in close agreement with Davies' value¹² of $2.64 \times 10^{-6} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$, but differs from that of $3.02 \times 10^{-6} \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ reported by Bell and Goodall.⁸ The discrepancy may result from an inadequate allowance for the effects of a small quantity of nitroethane in the sample used by the latter workers.⁸

TABLE 2

Kinetic hydrogen isotope effects for proton transfer from 2-nitropropane to bases in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$ at 25 °C.

(1) Base = acetate

Vol % Me_2SO	$10^6 k_{\text{OAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^6 k_{\text{OAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{OAc}}^{\text{H}}/$ $k_{\text{OAc}}^{\text{D}}$	ΔpK^a
0	2.71	0.282	9.6	3.0
30	6.15	0.642	9.6	
50	25.6	2.72	9.4	3.7
70	180	23.4	7.7	3.9
80	547	76.0	7.2	4.1
90	6 330	945	6.7	
95	14 700	2 450	6.0	3.8 ^b

(2) Base = chloroacetate

Vol % Me_2SO	$10^7 k_{\text{ClOAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^7 k_{\text{ClOAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{ClOAc}}^{\text{H}}/$ $k_{\text{ClOAc}}^{\text{D}}$	ΔpK^a
0	2.7	0.32	8.4	4.9
30	6.1	0.75	8.2	
50	15.0	2.07	7.3	5.3
70	78.0	9.7	8.0	5.9
90	910	14.6	6.3	c

(3) Base = fluoride

Vol % Me_2SO	$10^7 k_{\text{F}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^7 k_{\text{F}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{F}}^{\text{H}}/k_{\text{F}}^{\text{D}}$	ΔpK^a
0	2.55	0.546	4.8	4.6
50	90	19.6	4.6	4.6
70	1 460	310	4.7	4.3
80	7 810	1 609	4.8	3.9

^a $\Delta pK = pK_a(2\text{-nitropropane}) - pK_a(\text{base})$; results from Table 1. ^b Value for 100% Me_2SO . ^c Value in 80% = 6.5

Nitroethane.—Rates of proton (and deuteron) transfer from nitroethane to acetate in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$, $\text{MeCN}-\text{H}_2\text{O}$, and $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$ have been measured. The experimental conditions and methods were the same as for 2-nitropropane, except that nitroethane concentrations were *ca.* 0.15 mol dm^{-3} . The results are listed in Table 3.

Ethyl 2-Methylacetoacetate.—Rate constants and isotope effects for proton transfer from ethyl 2-methylacetoacetate to acetate and fluoride were measured in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$. Substrate concentrations were *ca.* $10^{-3} \text{ mol dm}^{-3}$, base concentrations $0.01-0.1 \text{ mol dm}^{-3}$, $[\text{I}^-]$ 0.01 mol dm^{-3} , and initial iodine concentrations *ca.* $10^{-4} \text{ mol dm}^{-3}$. When calculating k_{B} , allowance was always made for the amount of substrate consumed during the reactions (<10%). A small loss of iodine at the beginning of the reaction was attributed to the small amount of ethyl acetoacetate impurity present in the sample (see earlier).

As a check on the method, the value of k_{OAc} in aqueous solution was also measured by using an excess of bromine as a scavenger. For these reactions, ethyl 2-methylacetoacetate concentrations were *ca.* $10^{-3} \text{ mol dm}^{-3}$, initial $[\text{Br}_2]$ *ca.* $3 \times 10^{-3} \text{ mol dm}^{-3}$, and $[\text{Br}^-]$ 0.01 mol dm^{-3} . The value of k_{OAc} of $4.31 \times 10^3 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ so obtained was in excellent agreement with the value of $4.26 \times 10^3 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$ obtained by reaction with iodine. Both

values, however, are higher than the reported value of $3.23 \times 10^3 \text{ mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$.⁹

The results are listed in Table 4.

TABLE 3

Kinetic hydrogen isotope effects for proton transfer from nitroethane to acetate in solvent mixtures at 25 °C

(i) $\text{Me}_2\text{SO}-\text{H}_2\text{O}$

Vol % Me_2SO	$10^5 k_{\text{OAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^5 k_{\text{OAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{OAc}}^{\text{H}}/$ $k_{\text{OAc}}^{\text{D}}$	ΔpK^a
0	3.26	0.553	5.9	4.1
30	9.94	1.58	6.3	
50	42.1	5.64	7.5	4.2
70	295	45.5	6.5	4.5

(ii) $\text{MeCN}-\text{H}_2\text{O}$

Vol % MeCN	$10^5 k_{\text{OAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^5 k_{\text{OAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{OAc}}^{\text{H}}/$ $k_{\text{OAc}}^{\text{D}}$	ΔpK^a
0	3.26	0.553	5.9	4.1
30	5.61	0.751	7.5	
50	7.30	0.833	8.8	4.4
65	7.89	0.950	8.3	
80	9.92	1.29	7.7	

(iii) $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$

Vol % $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}$	$10^5 k_{\text{OAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^5 k_{\text{OAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{OAc}}^{\text{H}}/$ $k_{\text{OAc}}^{\text{D}}$	ΔpK^a
0	3.26	0.553	5.9	4.1
25	2.89	0.308	9.3	
50	1.68	0.177	9.5	4.4
65	1.49	0.184	7.9	
80	0.86	0.133	6.4	4.4

^a $\Delta pK = pK_a(\text{nitroethane}) - pK_a(\text{acetate})$; results from Table 1.

TABLE 4

Kinetic hydrogen isotope effects for proton transfer from ethyl 2-methylacetoacetate to bases in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$ at 25 °C

(1) Base = acetate

Vol % Me_2SO	$10^3 k_{\text{OAc}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^3 k_{\text{OAc}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{OAc}}^{\text{H}}/$ $k_{\text{OAc}}^{\text{D}}$	ΔpK^a
0	4.26	0.71	6.0	7.7
30	13.1	2.25	5.8	
50	41.8	6.65	6.3	6.5
60	79.8	14.0	5.7	
70	223	40.6	5.5	5.6

(2) Base = fluoride

Vol % Me_2SO	$10^4 k_{\text{F}}^{\text{H}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$10^4 k_{\text{F}}^{\text{D}}/$ $\text{mol}^{-1} \text{ dm}^3 \text{ s}^{-1}$	$k_{\text{F}}^{\text{H}}/k_{\text{F}}^{\text{D}}$	ΔpK^a
0	3.52	1.17	3.0	9.4
70	92.6	34.2	2.7	7.4
50	1 390	559	2.5	6.0

^a $\Delta pK = pK_a(\text{ethyl 2-methylacetoacetate}) - pK_a(\text{base})$; values from Table 1.

DISCUSSION

The results presented in Tables 2-4 show that no correlations are observed between the effects of varying solvent composition on $k^{\text{H}}/k^{\text{D}}$ and ΔpK ; in some cases large variations in isotope effects with little change in ΔpK are observed, whereas in others the isotope effects remain constant with varying ΔpK . This is most strikingly illustrated by the results in Table 3 for the reaction between nitroethane and acetate in the various solvent mixtures. In each of the solvent systems, the isotope effects go through a distinct maximum as the

¹² M. H. Davies, *J.C.S. Perkin II*, 1974, 1018.

concentration of the organic component of the mixture is increased; however, ΔpK in all cases is almost constant at 4.3 pK units. Also, k^H/k^D shows no correlation with the reaction rate. Thus in $\text{Me}_2\text{SO}-\text{H}_2\text{O}$ there is a 100-fold rate increase, in $\text{MeCN}-\text{H}_2\text{O}$ a 3-fold increase and in $\text{CF}_3\cdot\text{CH}_2\cdot\text{OH}-\text{H}_2\text{O}$ a 5-fold decrease in rate as the fraction of the organic component increases.

At first sight, it would seem difficult to rationalise these results in terms of either of the above mentioned theoretical treatments,^{1,2} both of which emphasise the importance of the symmetry of the transition state, or the energy barrier, in determining the magnitude of the isotope effect. It has recently been pointed out,^{1,7} however, that the tunnel correction could be quite sensitive to the nature and extent of involvement of the solvent in the proton transfer. This is because if the proton transfer involves simultaneous rotation or translation of solvent molecules, the effective mass for passage across the energy barrier will be greater than unity, and hence the tunnel correction will be reduced. The results of Caldin and Mateo^{6,7} for the reaction of 4-nitrophenyl-nitromethane with tetramethylguanidine can be sensibly explained in terms of such an effect. A more detailed discussion of the present results along these lines is, however, difficult because in mixed solvents we do not know the nature of the solvent species involved with the transition state.

It is more difficult to interpret the results according to the model developed by Westmeier² and later workers.¹³⁻¹⁵ Any interaction between the solvent and the transition state could of course affect the real vibrations of the transition state, and hence the observed isotope effect. However, unless involvement of the solvent could lead to very substantial changes in the bond strengths, such an effect is likely to be small.

In addition to the influence of the solvent on the frequencies and zero point energies of the transition state vibrations, and on the tunnel correction for proton transfer, there is one other factor that may be relevant to the solvent dependence of hydrogen isotope effects. This concerns the extent to which the necessary solvent reorganization occurring during a reaction can keep pace with the transfer of the proton.¹⁶ It is clear from the

results presented here, and earlier,^{4,10} showing the sensitivity of the rates to solvent variation, that substantial changes in the solvation energy occur on going from the reactants to the transition state. Such changes would be expected to be accompanied by a significant degree of reorientation of the solvent molecules. The involvement of the solvent need not be restricted to the actual site of the proton transfer; for example, thermodynamic studies on the ionization of nitroalkanes^{10,17,18} ($\text{R}^1\text{R}^2\text{-CHNO}_2$) indicate a substantial stabilization by the solvent of the product anion $[\text{R}^1\text{R}^2\text{C}=\text{N}^+(\text{O}^-)]_2$ in protic solvents. This presumably comes from H-bonding to the oxygen atoms of the nitro-group. Similar interactions should occur between the solvent and the negative charge developing on the carbonyl oxygen during ionization of ketones. Since the deuteron moves more slowly than the proton, this effect could influence the magnitude of the isotope effect. It may also be quite sensitive to the extent of involvement of the solvent in the reaction. It may be relevant here¹⁹ that in many of the studies in mixed aqueous solvents, the observed isotope effects pass through maxima in the region 0–50 vol % of the organic component of the solvent mixture.^{4,5,20,21} It is in this region that extrema in many of the solvent properties, such as viscosities, excess heats of mixing, *etc.*, occur, and also extrema in the enthalpies and entropies of solution of solutes are observed.^{19,22,23}

Finally, although the present results refer to the effect of solvent variations on a given substrate-base pair, it is now clear, from comparative studies of acidities in solution and in the gas phase,^{18,24-26} that for a related series of (anion) bases in a single solvent there is a systematic variation of the solvation energy with the basic strength. This means that even for a series of related reactions in a single solvent, in which either the substrates or bases are varied, there will be a variation in the extent of solvent involvement in the reaction, so that the present results should be relevant to the general question of the variation of kinetic isotope effects within a single solvent.

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