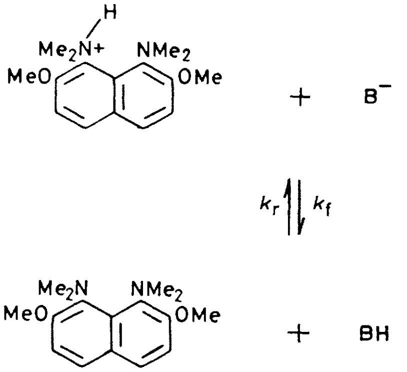
A Negligibly Small Primary Kinetic Isotope Effect for Slow Proton Transfer from a Protonated Amine

By Frank Hibbert*† and Heather J. Robbins
(*Department of Chemistry, Birkbeck College, Malet Street, London* WC1E 7HX)

Summary The primary kinetic isotope effect ($k^{\mathrm{H}}/k^{\mathrm{D}}$) for proton transfer from protonated 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene to bases has a value of unity even for reactions for which the proton donor and acceptor have similar pK values, a condition which would have been expected to lead to a maximum isotope effect.

Recently,[1] primary kinetic isotope effects have been measured for normal proton transfers involving oxygen and nitrogen acids, and a maximum in the isotope effect ($k^{\mathrm{H}}/k^{\mathrm{D}} = 3$—$4$) has been observed when the proton donor and acceptor have equal pK values. Previously this variation in isotope effect had been well established for proton transfer from carbon.[2] In contrast to these results, we have now found a negligibly small isotope effect for proton removal from a protonated amine by base catalysts of varying basicity including those for which the pK values of the protonated amine and the base catalyst are similar.



(1)

Kinetic studies of reaction (1) were made as described previously[3] using the temperature-jump technique with spectrophotometric detection. Measurements were made in 70% Me_2SO–H_2O (v/v) and 70% Me_2SO–D_2O at 25·0 °C and ionic strength 0·1 M with 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene (2×10^{-4} M) in the presence of excess of buffer ($B^- =$ phenolate, 2-methylphenolate, and trifluoroethoxide). The linear dependence of reciprocal relaxation time on buffer concentration for equilibrium (1) was investigated at different buffer ratios and the results were used to calculate values of k_f and k_r. The ratios of rate coefficients [$k_f^{(H_2O)}/k_f^{(D_2O)}$] determined in 70% Me_2SO–H_2O and 70% Me_2SO–D_2O for proton transfer from the protonated amine to three buffer bases are shown in the Table. The equilibrium constants for reaction (1) in 70% Me_2SO–H_2O [$K^{(H_2O)}$] and in 70% Me_2SO–D_2O [$K^{(D_2O)}$] were obtained from spectrophotometric measurements and the results were compatible with the ratios of rate coefficients k_f/k_r determined from the kinetic experiments in the two solvent mixtures. The reactions with $B^- = OH^-$ and OD^- were studied for solutions of 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene in 60% Me_2SO–H_2O and 60% Me_2SO–D_2O in the presence of excess of OH^- and OD^-. This reaction could not be studied in the 70% solvent mixtures because in the presence of reasonable concentrations of hydroxide ion in these solvents the equilibrium lies too far in favour of products.

Table[a]

B^-	$K^{(H_2O)}$	$K^{(D_2O)}$	$k_f^{(H_2O)}/k_f^{(D_2O)}$
PhO^-	0·15 ± 0·03	0·30 ± 0·03	0·93 ± 0·13
$2\text{-}MeC_6H_4O^-$	0·39 ± 0·02	0·83 ± 0·03	0·91 ± 0·11
$CF_3CH_2O^-$	22 ± 4	28 ± 9	1·21 ± 0·2
OH^- (or OD^-)	290 ± 40	713 ± 84	1·07 ± 0·1

[a] At 25·0 °C and ionic strength 0·1 M in 70% Me_2SO–L_2O (L = H or D) except for $B^- = OH^-$ which refers to 60% Me_2SO–L_2O.

The overall solvent isotope effects [$k_f^{(H_2O)}/k_f^{(D_2O)} =$ *ca.* 1] shown in the Table for the reactions involving buffers consist of a primary isotope effect (H–N^+ *vs.* D–N^+ bond breakage) and a medium effect. Since medium effects are generally small the results in the Table show that the primary isotope effect on proton transfer involving 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene is close to unity. In the case of proton transfer to $B^- = OH^-$ a secondary isotope effect is involved (OH^- *vs.* OD^-) but since this effect will be quite small, the primary isotope effect on this reaction must also be close to unity. Hence

---

† Correspondence to: Department of Chemistry, King's College, Strand, London WC2R 2LS.

proton removal from protonated 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene to various bases is characterised by a primary isotope effect of unity which is independent of the strength of the base catalyst. This behaviour is in contrast to the results which have been obtained for proton transfer from other nitrogen and oxygen acids[1] and carbon acids.[2]

The relaxation times measured for equilibrium (1) are in the range 10^{-1}—10^{-3} s as opposed to the 10^{-7}—10^{-9} s range expected for proton transfer with an amine. The reactions are slow because the acidic proton in protonated 1,8-bis-(dimethylamino)-2,7-dimethoxynaphthalene is strongly intramolecularly hydrogen-bonded.[3] The first step in proton removal involves a rapid equilibrium to give a low concentration of a non-hydrogen-bonded species from which the proton is removed by buffer base in a diffusion-controlled step.[3] The isotope effect is given[4] by $k_f^{(H_2O)}/k_f^{(D_2O)} = \phi_R/\phi_\psi\phi_\Delta$ where ϕ_R is the fractionation factor of the hydrogen-bonded proton in the protonated amine, ϕ_ψ is the fractionation factor of the same proton in the transition state, and ϕ_Δ is the differential medium effect between the reactants and the transition state. For the two-step mechanism the rate-determining step is a strongly thermodynamically favourable proton transfer‡ from a non-hydrogen-bonded protonated amine, and since this step is diffusion-controlled the assumption will be made that $\phi_\psi = 1{\cdot}0$ and that ϕ_Δ results entirely from the different viscosities of the two solvents. We have measured $\phi_R = 0{\cdot}87 \pm 0{\cdot}05$ for protonated 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene[5] and $\phi_\Delta = 0{\cdot}917$ was calculated from the measured ratio of viscosities of 70% Me_2SO–H_2O and 70% Me_2SO–D_2O. Hence the calculated isotope effect is $k_f^{(H_2O)}/k_f^{(D_2O)} = 0{\cdot}95 \pm 0{\cdot}05$ which is close to the measured values.

It seems likely that similar low isotope effects ($k^H/k^D < 2{\cdot}0$) will be observed for other intramolecularly hydrogen-bonded acids providing the same mechanism of proton transfer applies. This could be important in explaining the values of kinetic solvent isotope effects for enzyme catalysed reactions[6] where proton transfers take place between acid and base groups having similar pK values and which are involved in hydrogen bonding.

(*Received, 24th October* 1979; *Com.* 1133.)

---

‡ With $B^- = PhO^-$ $\Delta pK = ca.$ 7 for the proton transfer step in this mechanism. A sizable isotope effect for this step would be expected for proton transfer to a base which is 7 pK units weaker than phenolate ion. However in this case the equilibrium for the overall reaction would be too far in favour of reactants to permit study by a relaxation technique.

[1] N.-Å. Bergman, Y. Chiang, and A. J. Kresge, *J. Amer. Chem. Soc.*, 1978, **100**, 5954; M. M. Cox and W. P. Jencks, *ibid.*, p. 5957.

[2] R. A. More O'Ferrall in 'Proton Transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, ch. 8, p. 201.

[3] F. Hibbert and H. J. Robbins, *J. Amer. Chem. Soc.*, 1978, **100**, 8239.

[4] W. J. Albery in ref. 2, ch. 9, p. 263.

[5] A value of $\phi_R = 0{\cdot}90 \pm 0{\cdot}01$ has been determined for protonated 1,8-bis(dimethylamino)naphthalene in aqueous solution by using n.m.r. spectroscopy to measure the distribution of deuterium between the solvent (50% H_2O–D_2O) and the protonated amine (A. J. Kresge, personal communication).

[6] J. P. Elrod, R. D. Gandour, J. L. Hogg, M. Kise, G. M. Maggiora, R. L. Schowen, and K. S. Venkatasubban, *Chem. Soc. Faraday Symp.*, 1975, **10**, 145.