Kinetic and Equilibrium Solvent Isotope Effects on the Deprotonation of a Salicylate Ion by Hydroxide Ion and General Bases

By **Frank Hibbert**, Department of Chemistry, King's College, Strand, London WC2R 2LS

Kinetic and equilibrium solvent isotope effects have been measured for proton transfer from 4-(3-nitrophenylazo)-salicylate ion (HA) to general bases (B) to examine whether a primary kinetic isotope effect is observed when proton transfer is occurring between bases of roughly equal strength for which $\Delta pK = pK_{HA} - pK_{BH^+} = 0$. The kinetic solvent isotope effects for catalysis by three tertiary amines (ΔpK −0.85, −0.27, and +0.58) are $k_B^{H_2O}/k_B^{D_2O}$ 2.0 ± 0.3, 2.2 ± 0.3, and 1.7 ± 0.2. Since for proton transfer to hydroxide ion (ΔpK −5.0) the observed isotope effect has a value $k_{OH^-}^{H_2O}/k_{OD^-}^{D_2O}$ of 1.5 ± 0.1, the primary isotope effect for these proton transfers must be small and independent of base strength over the range studied. An explanation in terms of the reaction mechanism is given.

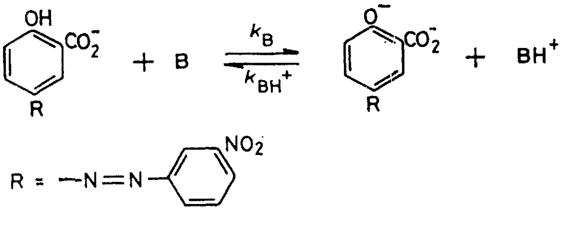
THERE have been very few detailed studies of kinetic isotope effects on proton transfers with oxygen or nitrogen acids and bases. One reason for this is that since these reactions are normally diffusion-controlled the primary kinetic isotope effects are expected to be small. Another reason is that the reactions occur too rapidly to be observable with commonly available kinetic techniques. A way round this latter problem is to study an overall slow reaction with a mechanism which involves proton transfer to or from the oxygen or nitrogen atom of a low concentration intermediate. Then even though the rate coefficient for the proton transfer in one direction is diffusion controlled, this step may be rate-limiting in the overall slow reaction. Kinetic solvent isotope effects on the proton transfer step can therefore be determined by measuring the isotope effect on the overall reaction. This procedure has been used by Kresge [1] and by Jencks [2] and it was found that the kinetic solvent isotope effect went through a sizeable maximum value (k^{H_2O}/k^{D_2O} 3—4) as the basicity of one of the species was changed and that the maximum occurred when the basicities of the two bases between which the proton was being transferred in the proton transfer step were equal. Thus for proton transfer represented by equation (1), as

$$HA + B \xrightleftharpoons{k_B} A^- + BH^+ \qquad (1)$$

the base B is varied a maximum in the isotope effect $k_B^{H_2O}/k_B^{D_2O}$ will be observed when $\Delta pK = pK_{HA} - pK_{BH^+} = 0$. At ΔpK 0 the transition state for the reaction involves a partially transferred proton and a primary isotope effect is observed. Away from ΔpK 0 the transition state is an encounter complex in which the proton is either fully or negligibly transferred and the isotope effect is much lower. An isotope effect maximum has been well established [3] for proton transfer from carbon acids in the region of ΔpK 0.

A slightly different procedure for examining kinetic isotope effects on proton transfer from oxygen acids is to study an acid in which the acidic proton is held in an intramolecular hydrogen bond. In this case the rate of proton removal is much reduced though it is usually still necessary [4] to use fast reaction equipment to follow the reaction. Kinetic solvent isotope effects $k_{OH^-}^{H_2O}/k_{OD^-}^{D_2O}$ have been obtained for proton transfer from intramolecularly hydrogen-bonded acids to hydroxide ion by measuring rate coefficients for proton removal by hydroxide ion in H_2O and deuterioxide ion in D_2O.[5-7] Of 16 reactions studied, the isotope effects were in the range 1.0—2.0 with an average value of 1.6 ± 0.2 except in one case for which $k_{OH^-}^{H_2O}/k_{OD^-}^{D_2O}$ 3.6 was observed.[7] In all these reactions proton transfer is occurring between bases which differ in pK by about seven units and it is therefore of interest to examine proton transfer for an intramolecularly hydrogen-bonded acid in the region of ΔpK 0. For this purpose it is necessary to find a reaction for which general base catalysis can be observed and where the hydroxide ion catalysed reaction does not dominate; suitable examples are quite rare. We have briefly reported [8] kinetic solvent isotope effects for proton transfer to general bases from a naphthylammonium ion with an $\overset{+}{N}H \cdots N$ hydrogen bond by making measurements in 70% Me_2SO-H_2O and 70% Me_2SO-D_2O. The isotope effects were close to unity for reaction between bases of roughly equal strength.

We now report measurements of kinetic solvent isotope effects on proton transfer from 4-(3-nitrophenylazo)-salicylate ion to general bases (B) [equation (2)]. The



(2)

substrate is a weak acid (pK 11.16) with an $O-H \cdots O^-$ hydrogen bond. The kinetics of this reaction have been investigated previously.[9] Studies can be made in wholly aqueous solution thus permitting a more reliable analysis of the solvent isotope effects than was possible for the naphthylammonium ion in 70% Me_2SO-H_2O.

EXPERIMENTAL AND RESULTS

Equilibrium Measurements.—Equilibrium (2) between 4-(3-nitrophenylazo)salicylate ion and *N*,2,2,5,5-pentamethylpiperidine, triethylamine, or trimethylamine as the base was studied spectrophotometrically in aqueous solution at 6.5 °C and a total ionic strength of 0.50 mol dm^{-3}. The total concentration of 4-(3-nitrophenylazo)salicylate ion was 4.9×10^{-5} mol dm^{-3} and was introduced by injecting 0.01 cm^3 of a solution of the sodium salt in methanol into 2 cm^3 of the reaction solution which contained the amine and its protonated form as a buffer at concentrations between 0.01 and 0.10 mol dm^{-3}. The buffer ratios were chosen so that the equilibrium position between the salicylate ion and dianion could be measured accurately. Buffer solutions of *N*,2,2,5,5-pentamethylpiperidine and triethylamine were made up by weighing out the amine and partially neutralising with the appropriate volume of standard hydrochloric acid. Trimethylamine buffers were made up by weighing out the amine hydrochloride and adding the necessary volume of standard sodium hydroxide solution. The ionic strength of the solutions was adjusted to 0.50 mol dm^{-3} by addition of potassium chloride. In making up the buffers in D_2O it was not possible to avoid adding small quantities of H_2O. For triethylamine and *N*,2,2,5,5-pentamethylpiperidine buffers this amounted to 0.8 atom % H and for trimethylamine buffers 1.1 atom % H was added.

TABLE 1

Equilibrium solvent isotope effects [a]

$$HA + B \rightleftharpoons A^- + BH^+$$

$$K = [A^-][BH^+]/[HA][B]; \quad -\log K = \Delta pK = pK_{HA^-} - pK_{BH^+}$$

HA = 4-(3-nitrophenylazo)salicylate ion, pK_a 11.16

B	pK_{BH^+}	ΔpK	K^{H_2O}	K^{D_2O}	K^{H_2O}/K^{D_2O}
Hydroxide ion	16.2	−5.0	1.05×10^5 [b]		
2,2,5,5-Pentamethylpiperidine	12.01	−0.85	7.1 ± 0.3 (8.5 [b])	8.7 ± 0.3	0.82 ± 0.06
Triethylamine	11.43	−0.27	1.86 ± 0.1 (2.0 [b])	2.55 ± 0.1	0.73 ± 0.08
Trimethylamine	10.58	+0.58	0.265 ± 0.01 (0.21 [b])	0.329 ± 0.01	0.81 ± 0.05

[a] Ionic strength 0.50 mol dm^{-3}, 6.5 °C. [b] Previous results.[9]

The position of equilibrium (2) was determined from measurements of the absorbance due to 4-(3-nitrophenylazo)salicylate ion at 348 nm and due to the dianion at 442 nm. For each buffer at least two buffer ratios were studied. The results are given in Table 1. Although equilibrium constants for these reactions had been determined previously [9] in H_2O the measurements were repeated so that the studies in H_2O and D_2O were made under exactly the same conditions. The agreement with the previous results in H_2O is satisfactory as seen from the comparison in Table 1 but the present results are considered to be more accurate. Precise experiments to determine the solvent isotope effect on equilibrium (2) with B = OH^- and OD^- were not made because the concentrations of OH^- in H_2O and OD^- in D_2O required to bring about half-dissociation of 4-(3-nitrophenylazo)salicylate ion were *ca.* 5 and 3×10^{-4} mol dm^{-3}, respectively, and these were too low to permit accurate measurements.

Kinetic Measurements.—Forward and reverse rate coefficients for equilibrium (2) involving proton transfer from 4-(3-nitrophenylazo)salicylate ion to *N*,2,2,5,5-pentamethylpiperidine, triethylamine, trimethylamine, and to hydroxide ion were determined in H_2O and D_2O using the temperature-jump technique. In order to obtain the most accurate values for the kinetic isotope effect the experiments for each buffer in H_2O and D_2O were carried out under exactly the same conditions and at the same time so that instrument settings were identical.

Measurements were made with concentrations of 4-(3-nitrophenylazo)salicylate ion of 0.50 or 1.0×10^{-4} mol dm^{-3} in the presence of excess of the amines as buffers and also in unbuffered solution with excess of hydroxide ion. The results were obtained at 6.5 °C and at an ionic strength of 0.50 mol dm^{-3}. The amine buffers were made up using the same procedure as in the preparation of solutions for equilibrium measurements. The equilibrium position between the monoanion and dianion of 4-(3-nitrophenylazo)salicylate in a reaction solution thermostatted at 3.2 °C was disturbed by a temperature-jump of 3.3° brought about by a 35 kV discharge from a 0.01 μF capacitor. The reaction solution was thereby heated to 6.5 °C in *ca.* 6 μs and the shift in equilibrium position was observed by following the decrease in absorbance at 442 nm accompanying the decrease in concentration of the dianion. Relaxation times for the equilibrium were calculated from logarithmic plots of the change in absorbance against time. The relaxations were quite rapid with half-lives as short as 9 μs even at the reduced temperature of 6.5°. In order to ensure that heating of the reaction solution occurred as quickly as possible, solutions with high ionic strength (0.50 mol dm^{-3}) were used to reduce the resistance of the temperature-jump cell and a low capacitance (0.01 μF) was used for the discharge.

In solutions of sodium hydroxide and sodium deuterioxide relaxation times were measured at concentrations of OH^- and OD^- in the range 0.001—0.003 mol dm^{-3}. In these solutions the dependence of reciprocal relaxation time (τ) for the equilibration between 4-(3-nitrophenylazo)salicylate ion and dianion on base concentration is given by equation (3). Plots of τ^{-1} against $[OH^-]$ and $[OD^-]$ were

$$\tau^{-1} = k_{H_2O}[H_2O] + k_{OH^-}{}^{H_2O}[OH^-] \qquad (3)$$

linear and values of $k_{OH^-}{}^{H_2O}$ of $2.19 \pm 0.08 \times 10^7$ dm^3 mol^{-1} s^{-1} and $k_{OD^-}{}^{D_2O}$ of $1.48 \pm 0.1 \times 10^7$ dm^3 mol^{-1} s^{-1} were obtained from the slopes. The result, $k_{OH^-}{}^{H_2O}$ $2.4 \pm 0.2 \times 10^7$ dm^3 mol^{-1} s^{-1}, was obtained previously.[9]

Relaxation times were measured in buffer solutions at fixed buffer ratio with varying buffer concentrations in H_2O and D_2O. In triethylamine buffers, measurements were made at two buffer ratios ($[Et_3NH^+]/[Et_3N]$ 1.0 and 0.5). For *N*,2,2,5,5-pentamethylpiperidine a buffer ratio of 2.0 was used and for trimethylamine the buffer ratio was 0.33. In each buffer, relaxation times were measured at several buffer concentrations in the range 0.001—0.06 mol dm^{-3}. The dependence of reciprocal relaxation time on buffer concentration for equilibrium (2) is given by equation (4)

$$\tau^{-1} = k_{OH^-}[OH^-] + k_{H_2O}[H_2O] + (k_B + rk_{BH^+})\,[B] \quad (4)$$

in which r is the buffer ratio ($r = [BH^+]/[B]$). At fixed buffer ratio, plots of reciprocal relaxation time against buffer concentration were linear with intercept $k_{OH^-}[OH^-] + k_{H_2O}[H_2O]$ and gradient $k_B + rk_{BH^+}$. Values of k_B and k_{BH^+} for each buffer in H_2O and D_2O were calculated by combining the gradient of these plots with the value of the equilibrium constant determined for that buffer in H_2O and D_2O and the results for k_B are given in Table 2. The values of $k_B{}^{H_2O}$ which had been determined in the previous work [9] are given in Table 2 for comparison. The agreement is satisfactory although the present results are considered to be more accurate.

TABLE 2

Kinetic solvent isotope effects for reaction (2)

B	$10^{-6}k_B{}^{H_2O}$/dm^3 mol^{-1} s^{-1}	$10^{-6}k_B{}^{D_2O}$/ dm^3 mol^{-1} s^{-1}	$k_B{}^{H_2O}/k_B{}^{D_2O}$
Hydroxide ion	21.9 ± 1.0 (24 ± 2 [a])	14.8 ± 1.0	1.5 ± 0.1
N,2,2,5,5-Pentamethylpiperidine	1.95 ± 0.2 (1.4 ± 0.3 [a])	1.00 ± 0.1	2.0 ± 0.3
Triethylamine	1.46 ± 0.1 (1.7 ± 0.3 [a])	0.66 ± 0.08	2.2 ± 0.3
Trimethylamine	1.83 ± 0.15 (2.5 ± 1.0 [a])	1.05 ± 0.1	1.7 ± 0.2

[a] Previous results.[9]

DISCUSSION

The kinetic solvent isotope effects for proton transfer from 4-(3-nitrophenylazo)salicylate ion given in Table 2 are much lower than the calculated maximum primary isotope effect for proton transfer from an oxygen acid (k^H/k^D *ca.* 11) based on zero-point energy differences of O–H and O–D bonds.[10] The kinetic solvent isotope effect for proton removal by hydroxide ion, $k_{OH^-}{}^{H_2O}/k_{OD^-}{}^{D_2O}$ 1.5 ± 0.1, is similar to the values observed for other intramolecularly hydrogen-bonded acids.[5-7] Hydroxide ion is a much stronger base than the salicylate ion, $\Delta pK = pK_{HA} - pK_{H_2O} = -5.0$, and therefore proton transfer to hydroxide ion is a strongly thermodynamically favourable reaction.

The general base catalysts were chosen to cover the range around ΔpK 0 and for *N*,2,2,5,5-pentamethylpiperidine, triethylamine, and trimethylamine the ΔpK values are −0.85, −0.27, and +0.58, respectively. However the kinetic solvent isotope effects for proton removal by hydroxide ion and by general bases have very similar low values as shown in Table 2. This means that there is no maximum in the primary isotope effect for this reaction in the region of ΔpK 0 in contrast to the result obtained for other oxygen acids [1,2] and for carbon acids.[3] Our discussion will provide an explanation for this.

The equilibrium solvent isotope effects in Table 1 are within the range of values commonly observed for proton transfer equilibria. In terms of fractionation factor theory the ratio of equilibrium constants in H_2O and D_2O is given by equation (5) in which ϕ^R and ϕ^P are the

$$K^{H_2O}/K^{D_2O} = \phi^R\phi_S{}^R/\phi^P\phi_S{}^P \qquad (5)$$

reactant and product fractionation factors, respectively, for the transferred proton and $\phi_S{}^R$ and $\phi_S{}^P$ are the fractionation factors of solvating water molecules in the reactants and products. To a good approximation [11] we can assume $\phi_S{}^R = \phi_S{}^P$ and ϕ^P 1.0. However, the factor ϕ^R refers to the intramolecularly hydrogen-bonded proton in 4-(3-nitrophenylazo)salicylate ion and there is evidence to indicate that this fractionation factor will have a value below unity. Attempts to measure ϕ^R directly for salicylate ion and for 4-(3-nitrophenylazo)-salicylate ion by n.m.r. were unsuccessful because of limited solubility and because in the presence of sufficient acid to prevent rapid exchange of the phenolic proton, the carboxy-group was protonated. The result, ϕ 0.90 ± 0.01, has been measured [12] in 50% H_2O–D_2O by n.m.r. for the hydrogen-bonded proton in protonated 1,8-bis(dimethylamino)naphthalene and ϕ 0.87 ± 0.05 has been obtained for protonated 1,8-bis(dimethylamino)-2,7-dimethoxynaphthalene in 70% Me_2SO–15% H_2O–15% D_2O. The value of the fractionation factor of an intramolecularly hydrogen-bonded proton in an acid can be derived from measurements of the dissociation constant of the acid in H_2O–D_2O mixtures and ϕ 0.84 has been obtained for the monoanion of maleic acid in this way.[13] Actually if the fractionation factor for the proton in an intramolecularly hydrogen-bonded acid has a lower value than the fractionation factor for a non-hydrogen-bonded acid (ϕ 1.0) the ratio of acid dissociation constants (K^{H_2O}/K^{D_2O}) should be lower for hydrogen-bonded acids. An examination of tabulated data [14] is not conclusive on this point. If we assume ϕ^R 0.80 in the present case and substitute this value into equation (5) good agreement is obtained with the observed equilibrium isotope effects in Table 1.

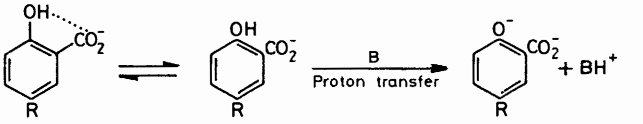
The ratio of rate coefficients for proton removal from 4-(3-nitrophenylazo)salicylate ion by general bases in H_2O and D_2O is given by equation (6) in which $\phi^‡$ and $\phi_S{}^‡$ are transition state fractionation factors for the proton which is undergoing transfer and for the water of solvation respectively. The value of $\phi^R/\phi^‡$ refers to the

$$k_B{}^{H_2O}/k_B{}^{D_2O} = \phi^R\phi_S{}^R/\phi^‡\phi_S{}^‡ \qquad (6)$$

$$k_{OH^-}{}^{H_2O}/k_{OD^-}{}^{D_2O} = \phi^R\phi_S{}^R\phi_{OH}{}^R/\phi^‡\phi_S{}^‡\phi_{OH}{}^‡ \qquad (7)$$

primary isotope effect on the reaction. In the case of proton transfer to hydroxide ion two additional fractionation factors are needed to account for the secondary isotope effect on hydroxide ion as shown in expression (7) where $\phi_{OH}{}^R$ and $\phi_{OH}{}^‡$ refer to the hydroxide ion proton in reactant and transition state, respectively. Values for the transition state fractionation factors can be estimated from the known reaction mechanism.

We have provided evidence[9] that proton transfer from 4-(3-nitrophenylazo)salicylate ion occurs in at least two steps as shown in reaction (8). The first step is a rapid opening of the intramolecularly hydrogen-bonded acid and is followed by attack by base on the non-hydrogen-bonded species which is present in low concentration. The second step is a normal proton transfer since reaction is between a non-hydrogen-bonded oxygen acid (HA′) and a nitrogen base. There is a close similarity between this mechanism and those of the reactions studied by Kresge[1] and Jencks.[2] A normal proton transfer from a low concentration intermediate is involved in each case. The mechanism in reaction (8) can be used to explain the kinetic solvent isotope effects which have been observed.



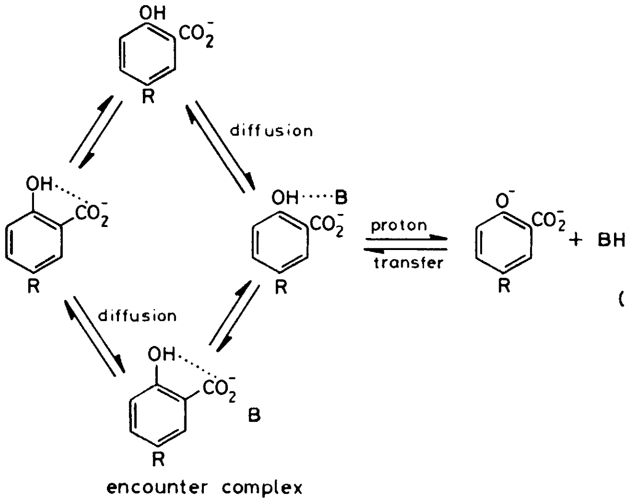
(8)

$$\mathrm{HA} \rightleftharpoons \mathrm{HA'} \xrightarrow{\mathrm{B}} \mathrm{A^-} + \mathrm{BH^+}$$

The differences in basicities between reactants and products for the overall acid–base reaction of 4-(3-nitrophenylazo)salicylate ion with bases are given in Table 1. For reaction with the tertiary amines the overall proton transfer is occurring between bases of roughly equal strength ($\Delta pK = pK_{HA} - pK_{BH^+} = 0$) and this is the condition for which a large primary isotope effect has been observed on proton transfer from oxygen acids.[1,2] However, since the actual proton transfer occurs from the open form of the acid (HA′) the basicities of the acid–base partners in this step are not well matched. The equilibrium constant between the closed and open forms of the acid has an estimated value of 1×10^{-3} so that for the proton transfer step in reaction (8) the difference in pK between the reaction partners is given by $\Delta pK = pK_{HA'} - pK_{BH^+}$ and has values of ΔpK of −8.0, −3.85, −3.27, and −2.42 for reaction with hydroxide ion, *N*,2,2,5,5-pentamethylpiperidine, triethylamine, and trimethylamine, respectively. The isotope effect maximum in proton transfer from an oxygen acid occurs at ΔpK 0 and falls quite sharply away from ΔpK 0 so that the primary isotope effect on the proton transfer step in reaction (8) will be small for all the bases studied. A sizeable isotope effect for the proton transfer step and for the overall reaction would be expected for reaction with general bases which are two to three pK units weaker than the tertiary amines studied here. Experiments with the weaker bases tris-(hydroxymethyl)aminomethane and 2-amino-2-methylpropane-1,3-diol were carried out using these amines as buffers, but at the lowest buffer concentrations which could be used the chemical relaxations were too rapid ($t_{\frac{1}{2}}$ 2 μs) for accurate measurements. We have previously found that the forward rate coefficient in equation (2) is largely independent of the strength of the base B but the value of the reverse rate coefficient increases as B is made a weaker base.[9]

A low primary isotope effect for the proton transfer step in reaction (8) implies that $\phi^\ddagger$ in expression (6) has a value close to unity. In the case of proton transfer to hydroxide ion since the proton transfer step in reaction (8) is strongly thermodynamically favourable in the forward direction the transition state will involve negligible proton transfer to hydroxide ion and therefore the fractionation factor ratio $\phi_{OH}{}^{R}/\phi_{OH}{}^{\ddagger}$ in expression (7) will be close to unity. If the proton in the transition state was fully transferred to hydroxide ion, $\phi_{OH}{}^{R}/\phi_{OH}{}^{\ddagger}$ 0.57 would be expected[15] but the value in the present case will be much closer to unity. Hence reaction (8) and expressions (6) and (7) nicely explain why the kinetic solvent isotope effects for proton transfer to hydroxide ion and to tertiary amines have similar low values. This will be found generally for intramolecularly hydrogen-bonded acids at ΔpK 0 and a large isotope effect will only be observed some way from ΔpK 0.

Although the absence of an isotope effect maximum is explained by reaction (8), if the values $\phi^\ddagger$ 1.0, ϕ^{R} 0.80, and $\phi_{OH}{}^{R}/\phi_{OH}{}^{\ddagger}$ 1.0 are substituted into equations (6) and (7) the predicted isotope effects for reaction with general bases and hydroxide ion are around unity, which is lower than the observed values. The discrepancy seems too large to be accounted for by a small medium effect ($\phi_{S}{}^{R}/\phi_{S}{}^{\ddagger} >$ 1.0) on the reaction. It is possible that the primary isotope effect for the reaction involving general bases may have a value slightly above unity ($\phi^\ddagger < 1.0$) because the proton transfer step in mechanism (8) is within two to four units of ΔpK 0. The data of Kresge[1] and Jencks[2] show that although the isotope effect maximum is quite sharp at ΔpK 0, within a few units of ΔpK 0 a small primary isotope effect is observed. For reaction with hydroxide ion the proton transfer step is well removed from the condition ΔpK 0. Consequently a small primary isotope effect on the reaction with general bases may account for the slight difference in isotope effects for reaction with hydroxide ion and general bases and when taken together with a small medium effect on both reactions could account for the observed isotope effects having values above unity. An alternative explanation for the discrepancy between the observed isotope effects and the value of unity predicted by equations (6) and (7) is to consider the more detailed mechanism for the reaction shown in (9). In the upper part of reaction (9) the mechanism consists of a rapid opening of the internal hydrogen bond, diffusion, and proton transfer. The diffusion step is rate-limiting and the transition state for the reaction resembles a hydrogen-bonded pair between the open form of the acid and the base catalyst. However, if the open form of the salicylate ion can undergo conformational change to the closed form more rapidly than the base catalyst can diffuse away, the reaction will occur by a pre-association mechanism[16] shown in the lower part of reaction (9). In this case the three steps for reaction are diffusion, reorganization within the encounter complex, and proton transfer. The second step is rate-limiting in the forward direction. For both mechanisms the transition states resemble a hydrogen-bonded pair between the open form of the acid and the base catalyst. It is conceivable that a sizeable isotope effect is associated with formation of the hydrogen-bonded pair. Fractionation factors for protons in hydrogen-bonded pairs have recently been measured [13] in acetonitrile as solvent and values considerably below unity have been obtained; for example ϕ 0.31 has been measured for hydrogen bis-(4-nitrophenolate) $NO_2C_6H_4O^- \cdots H{-}OC_6H_4NO_2$. If this effect gives rise to an isotope effect in the present case ($\phi^\ddagger < 1.0$) similar results should be observed in other oxygen and nitrogen proton transfers. It is not clear from the data which were used to define an isotope effect maximum [1,2] whether the isotope effects for the reactions away from ΔpK 0 are unity on both sides of the maximum. However an isotope effect, $k_B^{H_2O}/k_B^{D_2O}$ *ca.* 2, has been observed in proton transfer from nitramide [17] in the region away from ΔpK 0 and this value is similar to the results obtained here.



(9)

Equipment grants from the Royal Society are gratefully acknowledged.

[1/354 *Received, 2nd March*, 1981]

REFERENCES

[1] N-Å. Bergman, Y. Chiang, and A. J. Kresge, *J. Am. Chem. Soc.*, 1978, **100**, 5954.

[2] M. M. Cox and W. P. Jencks, *J. Am. Chem. Soc.*, 1978, **100**, 5956.

[3] 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.

[4] For an example where the half-life is in the seconds range see R. W. Alder, N. C. Goode, N. Miller, F. Hibbert, K. P. P. Hunte, and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 1978, 89.

[5] J. L. Haslam, E. M. Eyring, W. W. Epstein, R. P. Jensen, and C. W. Jaget, *J. Am. Chem. Soc.*, 1965, **87**, 4247; E. M. Eyring and J. L. Haslam, *J. Phys. Chem.*, 1966, **70**, 293.

[6] M. Miles, E. M. Eyring, W. W. Epstein, and M. Anderson, *J. Phys. Chem.*, 1966, **70**, 3490.

[7] J. L. Haslam and E. M. Eyring, *J. Phys. Chem.*, 1967, **71**, 4471.

[8] F. Hibbert and H. J. Robbins, *J. Chem. Soc., Chem. Commun.*, 1980, 141.

[9] F. Hibbert and A. Awwal, *J. Chem. Soc., Perkin Trans. 2*, 1978, 939.

[10] R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., p. 227.

[11] W. J. Albery in 'Proton Transfer Reactions,' eds. E. F. Caldin and V. Gold, Chapman and Hall, London, 1975, ch. 9, p. 263.

[12] A. J. Kresge, personal communication.

[13] M. M. Kreevoy and T. M. Liang, *J. Am. Chem. Soc.*, 1980, **102**, 3315. In this work data for the equilibrium between maleic acid and the monoanion in $H_2O{-}D_2O$ were analysed to give a value for the fractionation factor of the proton in the monoanion assuming a fractionation factor of unity for the undissociated acid.

[14] P. M. Laughton and R. E. Robertson in 'Solute–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Dekker, New York, 1969, ch. 7, p. 399.

[15] F. A. Long and E. A. Walters, *J. Phys. Chem.*, 1972, **76**, 362.

[16] W. P. Jencks, *Acc. Chem. Res.*, 1976, **9**, 425.

[17] A. J. Kresge, Y. C. Tang, A. Awwal, and D. P. Onwood, *J. Chem. Soc., Chem. Commun.*, 1980, 310.