Kinetic and Equilibrium Solvent Isotope Effects on Proton Transfer between Thiols and Amines in Aqueous Solution

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Proton transfer from the thiol groups in mercaptoacetate and 2-mercaptobenzoate to amines in aqueous solution occurs with rate coefficients which are two orders of magnitude below the diffusion limit. The S–H $\cdots$ O$^-$ hydrogen bond in 2-mercaptobenzoate is weak and has negligible effect on the rates of proton transfer. Solvent isotope effects on the equilibrium constants for reaction of mercaptoacetate with four amines are in the range $K(H_2O)/K(D_2O)$ = 0.52—0.59. Kinetic solvent isotope effects on the forward $[k_f(H_2O)/k_f(D_2O) = 2.4 \pm 0.4]$ and reverse $[k_r(H_2O)/k_r(D_2O) = 4.3 \pm 0.7]$ rate coefficients are large, but show no evidence for a maximum with changing base strength of the amines over a limited range. The behaviour of thiols is compared with that of oxygen and nitrogen acids.

The rate of proton transfer between simple oxygen and nitrogen acids and bases in aqueous solution is usually limited by the diffusion-controlled formation or dissociation of a hydrogen-bonded complex between the acid and the base.[1] Within the hydrogen-bonded complex, proton transfer occurs rapidly and does not affect the overall rate except, possibly, when the acid and base have similar pK values ($\Delta pK = 0$). At ΔpK 0, solvent isotope effects on the reaction are quite large and go through a maximum[2] as ΔpK is changed over a narrow range. This may imply that proton transfer within the hydrogen-bonded complex is partially rate-limiting at ΔpK 0, although the analysis is complicated because the overall kinetic solvent isotope effect involves primary, secondary, and medium effects. For most carbon acids, the proton-transfer step is slow and rate-limiting.[1,3] Primary kinetic isotope effects are large and a broad maximum is observed for reactions around ΔpK 0.[1b,4] Proton transfer involving sulphur acids has not been studied widely but the rates which have been obtained[5] for proton removal from methoxycarbonylmethanethiol and 2-hydroxyethanethiol are well below the diffusion limit. Values of kinetic isotope effects on proton transfer from sulphur are not available, but measurements of equilibrium isotope effects have been made. It is found that the fractionation factors (φ) for distribution of H as compared with D between the aqueous solvent and the thiol have values of 0.62 $\pm$ 0.02 and 0.55 $\pm$ 0.02 for ethanethiol and 2-hydroxyethanethiol, respectively.[6] These results differ considerably from the values of ca. 1.0 which have been measured for oxygen and nitrogen acids,[4] and as a consequence the ratios of acid dissociation constants of thiols in H$_2$O and D$_2$O [$K_a(H_2O)/K_a(D_2O)$ ca. 2.3] have values[7] lower than those found for oxygen acids of similar acidity [$K_a(H_2O)/K_a(D_2O)$ ca. 3.8].[8]

We now report kinetic and equilibrium studies of proton transfer from mercaptoacetate to amines in aqueous solution [equation (1)]. Solvent isotope effects have been measured for

$$HSCH_2CO_2^- + B \underset{k_r}{\overset{k_f}{\rightleftharpoons}} {}^-SCH_2CO_2^- + BH^+ \quad (1)$$
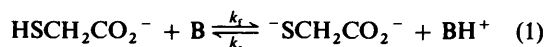
several of the amines over a limited range of base strength around $\Delta pK = pK_a(\text{thiol}) - pK_a(BH^+) = 0$ for the reaction. Rates have also been obtained for proton transfer from 2-mercaptobenzoate ion [equation (2)], to investigate the effect of an intramolecular S–H $\cdots$ O$^-$ hydrogen bond.
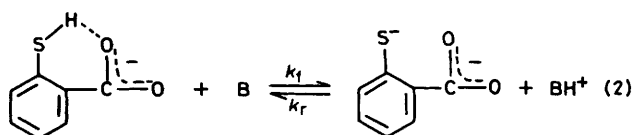
Experimental and Results

Materials.—Sodium mercaptoacetate, 2-mercaptobenzoic acid, tris(hydroxymethylamino)methane, and 2-amino-2-methylpropane-1,3-diol were commercial samples used without purification. Purification of 2-aminoethanol, t-butylamine, n-butylamine, and 2-amino-2-methylpropan-1-ol was carried out by refluxing the amine over solid potassium hydroxide followed by distillation under nitrogen. Buffer solutions were made up by partial neutralisation of the amines with standard hydrochloric acid and adjusted to ionic strength 0.1 mol dm^{-3} by addition of potassium chloride. To avoid decomposition of the thiols, buffer solutions were made up from distilled water through which nitrogen had been passed, and were handled under nitrogen.

Table 1. Proton transfer from mercaptoacetate

B	K	$K(H_2O)/K(D_2O)$	$10^{-7}k_f$/dm^3 mol^{-1} s^{-1}	$10^{-7}k_r$/dm^3 mol^{-1} s^{-1}	$k_f(H_2O)/k_f(D_2O)$	$k_r(H_2O)/k_r(D_2O)$
CH$_3$C(CH$_2$OH)$_2$NH$_2$	0.062 $\pm$ 0.003	0.52 $\pm$ 0.1	0.25 $\pm$ 0.01	4.03 $\pm$ 0.1	2.29 $\pm$ 0.1	4.36 $\pm$ 0.1
HO[CH$_2$]$_2$NH$_2$	0.39 $\pm$ 0.03	0.59 $\pm$ 0.1	0.64 $\pm$ 0.1	1.66 $\pm$ 0.3	2.00 $\pm$ 0.4	3.53 $\pm$ 0.7
(CH$_3$)$_2$C(CH$_2$OH)NH$_2$	0.70 $\pm$ 0.1		0.48 $\pm$ 0.01	0.68 $\pm$ 0.02		
CH$_3$[CH$_2$]$_3$NH$_2$	6.35 $\pm$ 0.5	0.52 $\pm$ 0.1	0.67 $\pm$ 0.04	0.105 $\pm$ 0.01	2.99 $\pm$ 0.2	5.83 $\pm$ 0.9
(CH$_3$)$_3$CNH$_2$	8.49 $\pm$ 0.3	0.56 $\pm$ 0.2	0.50 $\pm$ 0.01	0.059 $\pm$ 0.001	2.06 $\pm$ 0.1	3.69 $\pm$ 0.3
OH$^-$	(5.4 $\pm$ 0.6) $\times$ 10^5	0.27 $\pm$ 0.03	9.0 $\pm$ 2.0	(1.7 $\pm$ 0.4) $\times$ 10^5	ca. 1.3	ca. 4.8

Table 2. Proton transfer from 2-mercaptobenzoate

B	K	$10^{-7} k_f/\text{dm}^3$ $\text{mol}^{-1} \text{ s}^{-1}$	$10^{-7} k_r/\text{dm}^3$ $\text{mol}^{-1} \text{ s}^{-1}$
$(CH_2OH)_3CNH_2$	1.29 ± 0.1	0.49 ± 0.1	0.38 ± 0.04
$CH_3C(CH_2OH)_2NH_2$	6.71 ± 0.5	0.43 ± 0.04	0.064 ± 0.01
OH^-	$(4.8 \pm 0.4) \times 10^7$	$ca.\ 5.5$	$ca.\ 1.0 \times 10^{-7}$

Equilibrium Measurements.—The equilibria between mercaptoacetate and five primary amines and between 2-mercaptobenzoate and two amines were studied spectrophotometrically at 5 °C in aqueous solution at ionic strength 0.1 mol dm^{-3}. Absorbance measurements were taken for solutions containing the thiol ($ca.\ 1.0 \times 10^{-4}$ mol dm^{-3}) in the presence of the amine as buffer, at various buffer ratios. Readings were taken at 245 nm for mercaptoacetate (ε_{RS^-} 3.9×10^3; ε_{RSH} 2.3×10^2 dm^3 mol^{-1} cm^{-1}) and at 270 nm for mercaptobenzoate (ε_{RS^-} 1.2×10^4; ε_{RSH} 3.3×10^3 dm^3 mol^{-1} cm^{-1}). Values of the equilibrium constants for reactions (1) and (2) are given in Tables 1 and 2. For mercaptoacetate, measurements were also made in D_2O and the values of the equilibrium solvent isotope effects are given in Table 1. The values of the equilibrium constants in Tables 1 and 2 were used to calculate values for the acid dissociation constants (K_a) of the thiol groups in mercaptoacetate and 2-mercaptobenzoate. The results pK_a 10.54 ± 0.04 and 8.59 ± 0.04, respectively, were obtained at 5 °C and ionic strength 0.1 mol dm^{-3}.

Kinetic Measurements.—Kinetic studies of proton transfer from mercaptoacetate and 2-mercaptobenzoate to amines [equations (1) and (2)] were made using the temperature-jump method. The reaction conditions were the same as those used in the equilibrium measurements, with the same amines as buffers. The chemical relaxation resulting from a temperature perturbation of 4.6 °C was observed by following the decrease in absorbance due to a decrease in the concentration of the thiolate anions, at 248 nm for mercaptoacetate and at 270 nm for mercaptobenzoate. Relaxation times were measured at various buffer concentrations for each buffer at a fixed buffer ratio ($r = $ [B]/[BH$^+$]). The linear dependence of reciprocal relaxation time (τ^{-1}) on buffer concentration was compatible with equation (3) in which k_f and k_r are the forward and reverse rate coefficients for proton transfer from the thiols to buffer (B) in equations (1) and (2), and k_{OH^-} and k_{H_2O} are the forward and

$$\tau^{-1} = k_{OH^-}[\text{OH}^-] + k_{H_2O}[\text{H}_2\text{O}] + (k_f r + k_r)[\text{BH}^+] \quad (3)$$

reverse rate coefficients for proton transfer to hydroxide ion. For each buffer, measurements were made in at least two buffer ratios and the gradients of the plots of τ^{-1} against buffer concentration were combined with the value of the equilibrium constant of the reaction to give values of k_f and k_r. The intercepts of the plots of τ^{-1} against buffer concentration were used to calculate values for k_{OH^-} and k_{H_2O}. The rate coefficients are collected in Tables 1 and 2. For mercaptoacetate, the kinetics of proton transfer in buffers of 2-amino-2-methylpropane-1,3-diol, 2-aminoethanol, n-butylamine, and t-butylamine were also studied in D_2O and values of the kinetic solvent isotope effects are given in Table 1.

Discussion

An Eigen plot [1] for the variation of the forward (k_f) and reverse (k_r') rate coefficients for proton transfer from mercaptoacetate to amines of various base strengths (ΔpK') is given in the Figure. A statistical correction has been applied to the measured values
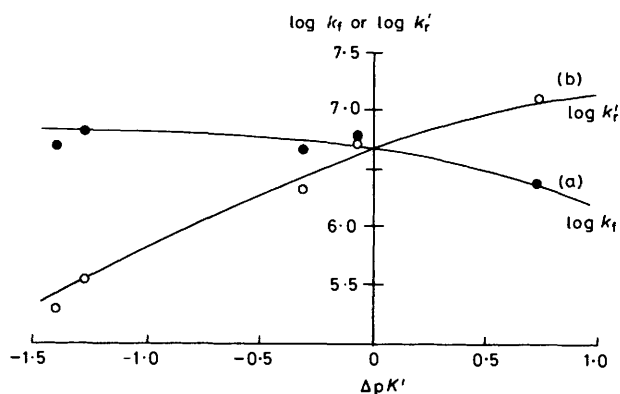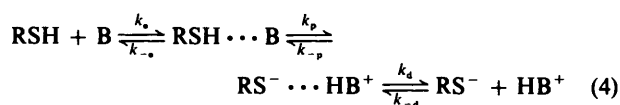

Figure. Variation of the rate coefficients in (a) the forward (log k_f) and (b) the reverse (log k_r') direction with the equilibrium constant (ΔpK') for the deprotonation of mercaptoacetate by primary amines. The values of log k_r' and ΔpK' are statistically corrected (see text)

of the rate coefficient (k_r) and equilibrium constant (K) for the reaction because in the reverse direction the protonated amine can donate one of three protons to the thiolate anion whereas in the forward direction the thiol possesses a single ionisable proton. The corrected values are related to the measured values by the equations log $k_r' = \log(k_r/3)$ and Δp$K' = -\log(3K)$. The limiting value of k_r', reached at Δp$K > 0$, for which reaction in the reverse direction is thermodynamically favourable, exceeds the limit in k_f reached at Δp$K < 0$ because of the different charge type of the reactions in the forward and reverse directions. In both directions the limits are about two orders of magnitude below the diffusion limits observed for proton transfer with oxygen and nitrogen acids.[1] In equation (4) the mechanism generally accepted [1] for reaction of oxygen and nitrogen acids in aqueous solution is written for proton transfer from a thiol. Equation (5) is obtained by applying the steady-state approximation to the hydrogen-bonded complexes. If the

$$\text{RSH} + \text{B} \underset{k_{-a}}{\overset{k_a}{\rightleftharpoons}} \text{RSH} \cdots \text{B} \underset{k_{-p}}{\overset{k_p}{\rightleftharpoons}}$$

$$\text{RS}^- \cdots \text{HB}^+ \underset{k_{-d}}{\overset{k_d}{\rightleftharpoons}} \text{RS}^- + \text{HB}^+ \quad (4)$$

$$k_f = k_a k_p k_d/(k_p k_d + k_{-a} k_d + k_{-p} k_{-a});$$
$$k_r = k_{-a} k_{-p} k_{-d}/(k_p k_d + k_{-a} k_d + k_{-p} k_{-a}) \quad (5)$$

$$k_f = k_a/(1 + k_a/K k_{-d}); \quad k_r = k_{-d}/(1 + K k_{-d}/k_a) \quad (6)$$

proton-transfer step in equation (4) is fast compared with formation and dissociation of the complexes, equation (5) is reduced to (6). The data for 2-mercaptoacetate can be fitted by equation (6) and the curves in the Figure are constructed using the values k_a 7×10^6 dm^3 mol^{-1} s^{-1} and k_{-d} 5.6×10^7 dm^3 mol^{-1} s^{-1}. It is interesting that the results for mercaptoacetate can be fitted by making the assumption that proton transfer occurs rapidly as compared with formation and dissociation of the hydrogen-bonded complexes, whereas most of the evidence suggests that for oxygen and nitrogen acids the proton-transfer step is partially rate-limiting at ΔpK $ca.$ 0.[1,9] This may indicate a difference in the mechanisms of proton transfer for thiols as compared with oxygen and nitrogen acids, although a better test of equation (6) would have been provided by data over a wider range of ΔpK. The present range was limited by our experimental technique. The magnitude of the displacement of the equilibrium between the thiol and its anion becomes small and difficult to follow if solutions are studied in which the thiol is only slightly or almost fully dissociated. Thus buffers which differ markedly in their pK values from the thiol can only be

studied with large buffer ratios. In order to ensure reliable buffering, buffer ratios larger than 20:1 or smaller than 1:20 were not used.

The rate coefficients measured for proton transfer involving 2-mercaptobenzoate have values similar to those observed for mercaptoacetate. For example, the result k_f 0.43 ± 0.04 × 10^7 dm^3 mol^{-1} s^{-1} was found for proton transfer between 2-mercaptobenzoate and 2-amino-2-methylpropane-1,3-diol, to be compared with k_f 0.67 ± 0.04 × 10^7 dm^3 mol^{-1} s^{-1} for deprotonation of mercaptoacetate by n-butylamine. The equilibrium constants (K) for the reactions are 6.7 and 6.4, respectively. For proton transfer from phenol to n-propylamine[10] the equilibrium constant has a similar value (4.1), but proton transfer occurs about 100-fold more rapidly with a rate coefficient k_f 6.6 × 10^8 dm^3 mol^{-1} s^{-1}. It might have been expected that the results for 2-mercaptobenzoate would be modified by the presence of an intramolecular S–H $\cdots$ O$^-$ hydrogen bond. In the case of proton transfer from 2-hydroxybenzoate to hydroxide ion, reaction occurs 1 000-fold more slowly than for phenol,[10] as a result of the intramolecular hydrogen bond. Proton transfer is slow because reaction takes place through a low concentration of an open form intermolecularly hydrogen-bonded to solvent.[10] Since the rates of proton transfer for mercaptoacetate and 2-mercaptobenzoate are similar, it follows that for 2-mercaptobenzoate the equilibrium to give the open form hydrogen-bonded to solvent cannot be too unfavourable. Hence the intramolecular hydrogen bond is weak and has a negligible effect on the rates of proton transfer.

The solvent isotope effect [$K(H_2O)/K(D_2O)$] on the equilibrium between mercaptoacetate and four primary amines has an average value of 0.55 ± 0.03. In terms of fractionation factor theory,[11] the isotope effect is given by equation (7), in which φ_S^R and φ_S^P are the fractionation factors of solvating water molecules in the reactants and products respectively and φ^R and φ^P are the fractionation factors of the acidic protons in the thiol and the ammonium ion. The secondary isotope effect

$$K(H_2O)/K(D_2O) = \varphi^R \varphi_S^R/\varphi^P \varphi_S^P \qquad (7)$$

of the two protons in the amine and two of the three protons in the protonated amine is expected to be small and has been ignored. For 2-hydroxyethanethiol, φ = 0.55 has been measured and for ammonium ions the value φ = 1.0 is normally expected.[4,12] Substitution of these values into equation (7) gives good agreement with the experimental result for $K(H_2O)/K(D_2O)$ providing the medium effect is small (φ_S^R/φ_S^P = 1.0).

The kinetic solvent isotope effect for reaction of mercaptoacetate with four different amines is fairly constant, with a value of 2.4 ± 0.4 in the forward direction [$k_f(H_2O)/k_f(D_2O)$] and 4.3 ± 0.7 in the reverse [$k_r(H_2O)/k_r(D_2O)$]. These isotope effects include contributions from primary, secondary, and medium effects. The value of $k_f(H_2O)/k_f(D_2O)$ is lower than the maximum value of the primary isotope effect of about 6, calculated[1b,4] on the basis of the difference in zero point energy of S–H and S–D bonds. There is no evidence for a maximum in the value of the kinetic solvent isotope effect in the region of ΔpK 0 as has been reported for proton transfers from oxygen and nitrogen acids,[2] although our data do not rule out the possibility of a shallow broad maximum. The absence of a sharp maximum may suggest that there is little contribution to the overall rate from the proton-transfer step. The difference in isotope effects on the forward and reverse reactions reflects the magnitude of the equilibrium isotope effect and this arises from the unusual value of φ (0.55) observed[6] for the fractionation factor of thiol protons as compared with the protons in an ammonium ion.

The kinetic solvent isotope effect can be expressed by equation (8), where φ^R and $\varphi^{\ddagger}$ are the fractionation factors of the transferring proton in the reactant and the transition state, respectively, and φ_S^R and $\varphi_S^{\ddagger}$ are the fractionation factors of solvating water molecules. The secondary isotope effect of the two protons in the amine and the same two protons in the transition state is assumed to be negligibly small. If the medium effect on the reaction is low ($\varphi_S^R/\varphi_S^{\ddagger}$ = 1.0) and is combined with the known value φ^R = 0.55 and the measured value of

$$k_f(H_2O)/k_f(D_2O) = \varphi^R \varphi_S^R/\varphi^{\ddagger} \varphi_S^{\ddagger} \qquad (8)$$

$k_f(H_2O)/k_f(D_2O)$, the result $\varphi^{\ddagger}$ = 0.24 is predicted for the transferring proton in the transition state. This low value could be accounted for by a transition state resembling a hydrogen-bonded complex since quite low values of φ have been directly measured for such species.[13] However if it is considered that a value of $\varphi^{\ddagger}$ between φ^R = 0.55 and φ^P = 1.0 (the latter as in the product) is more likely, say $\varphi^{\ddagger}$ = 0.78, a large medium effect $\varphi_S^R/\varphi_S^{\ddagger}$ = 3.4 would be required to account for the observed value of $k_f(H_2O)/k_f(D_2O)$. The most reasonable explanation of the observed isotope effect is the operation of a modest medium effect ($\varphi_S^R/\varphi_S^{\ddagger}$ ca. 2) on a transition state with $\varphi^{\ddagger}$ ca. 0.5. The large value of $k_r(H_2O)/k_r(D_2O)$ then follows from the magnitude of the equilibrium solvent isotope effect which arises from the unusual value φ^R = 0.55.

The present results illustrate the differences in proton-transfer behaviour of thiols as compared with oxygen and nitrogen acids. Intramolecular S–H $\cdots$ O$^-$ hydrogen bonds appear to be much weaker than O–H $\cdots$ O$^-$ bonds and have a less important rate-retarding effect on proton transfer. The rates of proton transfer from thiols are about 100-fold below the rates for oxygen and nitrogen acids. Kinetic solvent isotope effects on proton transfer to and from sulphur are large, but no sharp maximum is observed like that found for oxygen and nitrogen acids. The reasons for these differences are obscure, at present, but may relate to differences in the solvation and hydrogen-bonding ability of thiols.

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