Kinetic Evidence for the Occurrence of 1,3-Proton Transfer through a Proton-switch Mechanism in the Aminolysis of Salicylate Esters

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The nucleophilic reactions of primary amines (pK_a range 5.97–10.85) with ionized methyl salicylate (MS^-) show significant solvent isotope (D_2O) effects. Ionized phenyl salicylate (PS^-) reveals high reactivity towards primary amines ($pK_a > 8.15$) and secondary amines (pK_a range 6.24–11.32) with essentially no solvent isotope effects. However, the nucleophilic reactions of primary amines of $pK_a \leqslant 8.15$ with PS^- do exhibit solvent isotope effects. These observations, coupled with the absence of nucleophilic reactivity of secondary amines towards MS^-, are attributed to the occurrence of 1,3-proton transfer in these reactions.

The essential feature of the cleavage of esters and amides catalysed by serine esterase has been attributed to the occurrence of intramolecular general acid–base catalysis.[1] The occurrence of intramolecular general base catalysis in the hydrolysis of salicylate esters has been shown elegantly first by Bender *et al.*[2] and later by Capon and Gosh.[3] Catalysis with no transferable proton at the reacting sites, such as tertiary amines, did not demonstrate the catalytic effects in the cleavages of *p*-nitrophenyl and phenyl salicylates.[2–4] Primary amines exhibited nucleophilic reactivity towards both methyl (MSH)[5] and phenyl (PSH)[6,7] salicylates, but secondary amines were found to be completely non-reactive and highly reactive towards MSH[5,6] and PSH,[6–8] respectively.

It is interesting to note that the nucleophilic second-order rate constants for the reactions of ionized phenyl salicylate (PS^-) with primary and secondary amines result in Brønsted plots of different slopes.[7] The nucleophilic reactivities of 2-methoxyethylamine, propylamine, morpholine, and pyrrolidine towards PS^- did not show any appreciable deuterium solvent isotope effect.[7] However, a significant deuterium solvent isotope effect was observed in the nucleophilic reaction of tris(hydroxymethyl)aminomethane ('Tris') with PS^-. The suggested reaction mechanism(s) for aminolysis of ionized phenyl[7] and methyl[5] salicylate (MS^-) could not explain the absence of nucleophilic reactivity of secondary amines towards MS^- and the presence of a significant deuterium solvent isotope effect in the reaction of Tris with PS^-. In an attempt to resolve these unexplained observations concerning the aminolysis of salicylate esters, deuterium solvent isotope effects on nucleophilic second-order rate constants were studied for the reactions of a few more primary and secondary amines with PS^- and four primary amines with MS^-. The effects of different concentrations of *N*-methylhydroxylamine on the cleavage of MS^- have been studied also. The results and probable mechanistic explanation(s) are described in this paper.

Experimental

Methyl salicylate (MSH) was synthesized as described elsewhere.[9] All other reagent grade chemicals used were obtained from BDH, Aldrich, or Fluka AG. Deuterium oxide with minimum isotopic purity 99.7% was obtained from BDH. The stock solutions of phenyl salicylate (PSH) were frequently prepared in acetonitrile and were kept below 0 °C if they were no in kinetic use.

The rates of aminolysis of salicylate esters were studied spectrophotometrically, in both H_2O and D_2O, by monitoring the disappearance of esters at 350 nm. The details of the kinetic procedure and data analysis are described elsewhere.[5,7]

Results

Deuterium Solvent Isotope Effect on Hydrolysis of MS^-.—The reaction rates for the cleavage of MS^- were studied at 30 °C and within $[OD^-]$ range 0.06–0.80 mol dm^{-3} in the solvents with minimum isotopic and acetonitrile contents of 98.7 and 1% v/v, respectively. The ionic strength at 1.0 mol dm^{-3} was maintained by KCl. The observed pseudo-first-order rate constants, $k_{obs}^{D_2O}$, obeyed equation (1) where $k_o^{D_2O}$ and k_{OD} represent pH-

$$k_{obs}^{D_2O} = k_o^{D_2O} + k_{OD}[OD^-] \quad (1)$$

independent first-order and OD^--catalysed second-order rate constants, respectively. The rate constants $k_o^{D_2O}$ and k_{OD} were calculated from equation (1) using a least-squares technique. These results are summarized in the Table. The fitting of the observed data to equation (1) is evident from the standard deviations associated with $k_o^{D_2O}$ and k_{OD} (Table).

Deuterium Solvent Isotope Effect on Aminolysis of PS^- *and* MS^-.—The observed pseudo-first-order rate constants ($k_o^{H_2O}$) for hydrolysis of PS^- and MS^- were found to be independent of pH within its range of *ca.* 10.5–12.3. This characteristic of the reaction led us to study the kinetics of aminolysis of PS^- and MS^- by using unbuffered amine solutions (*i.e.*, amine solutions containing 100% free amine).

The rates of the reactions of PS^- and MS^- with hydroxylamine, hydrazine, propane-1,3-diamine, and methylamine and that of PS^- with *N*-methylhydroxylamine were studied by carrying out kinetic runs in a solvent containing 1% v/v MeCN and >98.7% D_2O. The observed pseudo-first-order rate constants ($k_{obs}^{D_2O}$) obtained within the pD range *ca.* 12–13 reasonably fit to equation (2) where $[AM]_T$ represents the total

$$k_{obs}^{D_2O} - k_o^{D_2O} - k_{OD}[OD^-] = k_n^{D_2O}[AM]_T \quad (2)$$

amine concentration and $k_n^{D_2O}$ is the nucleophilic second-order rate constant. The values of $k_o^{D_2O}$ and k_{OD} used are those listed in the Table for PS^- and MS^-, and $[OD^-] = 10^{pD}K_D/vOD$. The values of activity coefficients of OD^- (vOD) and OH^- (vOH) were assumed to be the same (0.70) at 1.0 mol dm^{-3} ionic strength,[7] and K_D, the ionic product of D_2O, is equal to

Table. Nucleophilic second-order rate constants, k_n, for aminolysis of ionized phenyl (PS^-) and methyl (MS^-) salicylates.[a]

Ester	Nucleophile	pK_a[b]	pH range	pD range[c]	$k_n^{H_2O}/10^{-3}$ dm^3 mol^{-1} s^{-1}	$k_n^{D_2O}/10^{-3}$ dm^3 mol^{-1} s^{-1}	$[A_M]_T$ range[d]/ mol dm^{-3}	No. of runs	$\frac{k_n^{H_2O}}{k_n^{D_2O}}$
PS^-	*N*-Methylhydroxylamine	6.24	11.04–11.66[e]	12.56–13.01	81.4 ± 0.6[e,f]	71.0 ± 0.7[f]	0.06–0.21	5	1.11
			10.92–11.44[e]		76.0 ± 0.6[e,f]				
	Morpholine	8.60			86.3 ± 0.5[e,g]	91.4 ± 1.0[e]			0.94
	Pyrrolidine	11.32	11.51–11.92[e]	12.42–12.67[e]	550 ± 18[e]	638 ± 23[e]			0.86
	Hydroxylamine	5.97	11.23–11.77[e]	12.58–13.00	101 ± 1[e]	83.4 ± 1.7	0.06–0.21	5	1.21
	Tris	8.14	11.07–11.74[e]		3.16 ± 0.06[e]	1.96 ± 0.01[e]			1.60
			11.32–11.84[e]		3.10 ± 0.04[e]				
	Hydrazine	8.15	11.68–12.46[e]	12.64–13.03	114 ± 1[e]	77.4 ± 0.3	0.06–0.21	5	1.43
			11.51–12.14[e]		107 ± 1[e]				
	2-Methoxyethylamine	9.45	11.34–12.24[e]	12.33–12.88[e]	16.8 ± 0.2[e]	16.2 ± 0.2[e]			1.04
	Propane-1,3-diamine	10.62 (pK_2)	11.96–12.32	12.40–12.77	66.0 ± 0.3	70.0 ± 0.4	0.06–0.21[h]	5,[i] 5	1.00
							0.06–0.21		
			11.50–11.99		65.0 ± 0.6		0.06–0.21[h]	5[i]	
			11.55–12.11[e]		79.6 ± 0.3[e]				
	Propylamine	10.79	11.54–12.11[e]	12.36–12.87[e]	50.0 ± 0.3[e]	59.4 ± 0.5[e]			0.84
	Methylamine	10.85	11.92–12.22	12.77–13.18	164 ± 2	158 ± 1	0.06–0.21[h]	5,[i] 5	1.16
					204 ± 10[e,g]		0.06–0.21		
	Hydroxide ion	15.74			1.24[e]	1.27[e]			0.98
	Water[j]	−1.74			0.360[e]	0.230[e]			1.56
MS^-	*N*-Methylhydroxylamine	6.24	10.94–11.67		0.020 ± 0.005[k]		0.08–0.72[h]	5[i]	
	Hydroxylamine	5.97	11.08–11.80	11.86–12.14	1.83 ± 0.02[l]	1.02 ± 0.02	0.10–0.90	5	1.79
	Hydrazine	8.15	11.13–12.10[l]	12.01–13.19	4.13 ± 0.05[l]	2.72 ± 0.06	0.10–0.70	5	1.77
					5.52 ± 0.73[l,g]				
	Propane-1,3-diamine	10.62 (pK_2)	11.93–12.30	12.56–12.90	0.193 ± 0.003	0.169 ± 0.002	0.20–0.70[h]	5,[i] 5	1.59
					0.345 ± 0.110[l,g]		0.20–0.70		
	Methylamine	10.85	11.70–12.21	12.03–12.92	0.787 ± 0.028	0.491 ± 0.023	0.09–0.81[h]	5,[i] 5	1.73
					0.912 ± 0.080[l,g]		0.10–0.90		
	Hydroxide ion	15.74			0.425[l]	0.408 ± 0.001	0.06–0.80[m]	4	1.04
	Water[j]	−1.74			0.107[l]	0.0621 ± 0.0005			1.72

[a] $[PSH]_0 = 2 \times 10^{-4}$ mol dm^{-3}, $[MSH]_0 = 3 \times 10^{-4}$ mol dm^{-3}, 1% v/v MeCN in the aqueous reaction mixture, 1 mol dm^{-3} strength, 30 °C, and $\lambda = 350$ nm. [b] pK_a of conjugate acids of nucleophiles and the values of pK_a are obtained from Ref. 7. [c] pD = pH meter reading + 0.4 (P. J. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188) and the reaction mixtures contained >98.7% v/v D_2O. [d] Total amine concentration range. [e] From Ref. 7. [f] Error limits are standard deviations. [g] Values obtained using buffered amine solutions. [h] Total amine concentration range in 99% v/v H_2O solvent. [i] Total number of kinetic runs carried out in 99% v/v H_2O solvent. [j] Pseudo-first-order rate constant (with unit s^{-1}) for water catalysis. [k] Calculated from the relationship $k_{obs}^{H_2O} = k_o^{H_2O} + k_n^{H_2O}[AM]_T$, where $k_o^{H_2O} = (0.101 \pm 0.003) \times 10^{-3}$ s^{-1}. [l] Ref. 5. [m] Total NaOD concentration range.

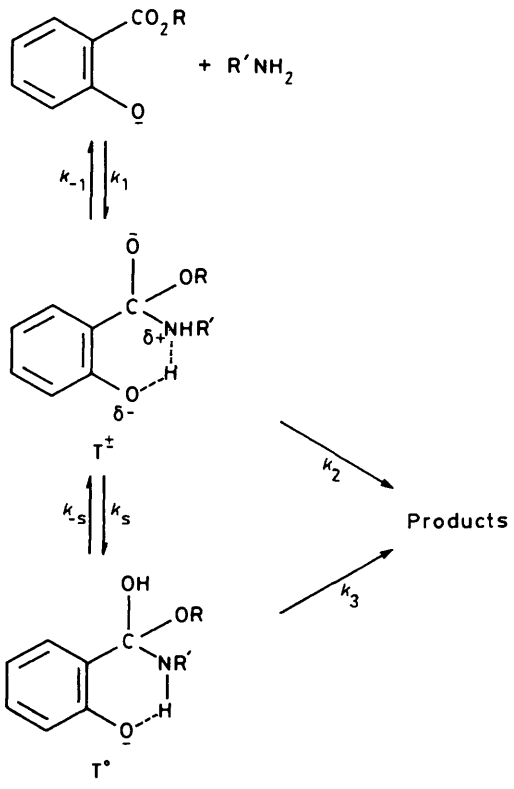
$K_w/6.53$,[2] where K_w = the ionic product of water = 1.449×10^{-14} mol^2 dm^{-6}.[4] The rate constants $k_n^{D_2O}$ were calculated from equation (2) by the use of a least-squares technique, and the results are summarized in the Table. The fitting of the observed data to equation (2) is evident from the standard deviations of $k_n^{D_2O}$ (Table).

Aminolysis of PS^- *and* MS^- *in Water.*—Unbuffered amine solutions were used to study the rates of reactions of PS^- with methylamine and propane-1,3-diamine and that of MS^- with *N*-methylhydroxylamine, methylamine, and propane-1,3-diamine in a solvent containing 99% v/v H_2O. The observed data were found to obey equation (2) with superscript D_2O substituted by H_2O and k_{OD} changed to k_{OH}. The values of $k_2^{H_2O}$ were calculated from equation (2) with $[OH^-] = 10^{pH}K_w/\nu_{OH}$ and $\nu OH = 0.70$. These results are shown in the Table. Although the rate constant $k_n^{H_2O}$ for the reaction of *N*-methylhydroxylamine with MS^- is associated with a standard deviation of nearly 25%, the contribution of the $k_n^{H_2O}$ term is negligible compared with the $k_o^{H_2O}$ and k_{OH} terms of equation (2). The maximum contribution of $k_n^{H_2O}$ turned out to be only 13%. These observations are consistent with previous results[5] which showed secondary amines to be unreactive towards MS^-.

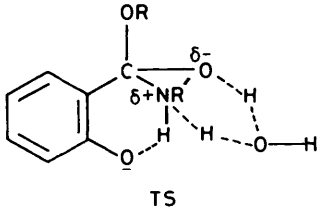
Discussion

It is clear that the presence and absence of nucleophilic reactivity of secondary amines towards PS^- and MS^-, respectively, derive from the direction of decomposition of the tetrahedral intermediate ($T^\pm$) shown in the Scheme. This intermediate is expected to form with all primary, secondary, and tertiary amines, but the absence of detectable reactivities of several tertiary amines towards PS^- indicates that the proton on the positive nitrogen (with primary and secondary amines) is hydrogen bonded to the phenoxide anion group.[4] This internal hydrogen bonding is expected to increase the energy barrier for the k_{-1} step and thus retard the collapse of $T^\pm$ back to the reactants.

The formation of the 'neutral' tetrahedral intermediate T° (ignoring the charge on the phenoxide anion of the salicylate) involves 1,3 proton transfer from the nitrogen to the carbonyl oxygen anion. Such 1,3 proton transfers generally occur through a proton-switch mechanism[10] which involves a solvent molecule in the transition state. It is clear that the formation of T° can be expected only with a primary amine (if the proposed internal hydrogen bonding in $T^\pm$ is correct) because with a secondary amine there is no proton available on the nitrogen for 1,3 proton transfer. It is evident from the suggested mechanism (Scheme) that a significant amount of solvent isotope effect



Scheme.



should result if the k_s step, or perhaps k_s coupled with k_3, is rate-determining; no such effect could be expected if the k_1 or k_2 step is rate-determining.

All the primary and secondary amines with respective pK_a ranges *ca.* 9.45–10.85 and 6.24–11.32 did not show the solvent isotope effects in their nucleophilic reactivities with PS^-: Tris and hydrazine ($pK_a \simeq 8.15$) did. These observations indicate that the k_s step does not occur in the reactions of secondary amines with PS^-. The observed solvent isotope effects with primary amines of $pK_a \leqslant 8.15$ reveal the occurrence of 1,3-proton transfer through TS before or in the rate-determining step. It appears that the energy barrier for the decomposition of $T^{\pm}$ involving the k_2 step with primary amines of $pK_a > 8.15$ is lower than that for the k_s step, which is conceivable in terms of the better leaving ability of the phenoxide ion of PS^-. However, with amines of relatively low basicity ($pK_a \leqslant 8.15$), the lowest energy barrier for decomposition of $T^{\pm}$ involves the k_{-1} step and the energy barrier for the k_s step becomes lower than that for the k_2 step. Thus product formation takes place through 1,3 proton transfer, *i.e.*, the k_s, k_3 route.

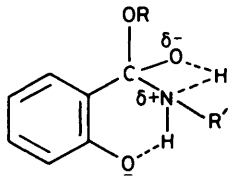
The absence of a deuterium solvent isotope effect in hydroxylaminolysis of PS^- is perhaps surprising if hydroxylamine ($pK_a = 5.97$) and hydrazine ($pK_a = 8.15$) were assumed to involve reaction mechanisms with the same rate-determining step in their nucleophilic reactivities towards PS^-. But as shown elsewhere,[7] the rate constants $k_n^{H_2O}$ for hydroxylamine and hydrazine do not fall on a Brønsted plot constructed using $k_n^{H_2O}$ for several primary amines, including Tris. The positive deviations from this Brønsted plot turned out to be 275-fold for hydroxylamine and 31-fold for hydrazine. These observations indicate that α-effect nucleophiles and other primary amines do not essentially involve the same rate-determining step in their reactions with PS^-. We believe, that in the ractions of NH_2OH, H_2NNH_2, and MeNHOH with PS^- the k_1 step (Scheme) is rate-determining. However, nearly 43% of the normal deuterium solvent isotope effect for H_2NNH_2 must have as its source something other than a simple mechanistic change.

The zwitterionic tetrahedral intermediate $T^{\pm}$ is likely to form in the reactions of MS^- with both primary and secondary amines. However, with the poor leaving group methoxide anion, this first-formed intermediate with a secondary amine is more likely to lose the positive charged nitrogen atom and reverse the original addition, *i.e.*, the energy barrier for the k_2 step is so high compared with that for the k_{-1} step that none of the $T^{\pm}$ molecules get through this barrier to form product. With a primary amine a second hydrogen is available, and 1,3 proton transfer can therefore occur to produce the 'neutral' intermediate T°. Once this proton transfer has occurred the nitrogen atom is no longer a good leaving group, since it has lost its positive charge; forward decomposition of the tetrahedral intermediate can now occur, even though this involves loss of the poor methoxide-ion leaving group. Schmir and Cunningham[11] have similarly reported the decomposition route of a tetrahedral intermediate in which the neutral species lost an oxygen leaving group whereas the zwitterion lost the nitrogen. The observed solvent isotope effects (Table) in the reactions of MS^- with primary amines of pK_a range 5.97–10.85 indicate the occurrence of 1,3 proton transfers before or during the rate-determining step of these reactions.

It should be noted that the very similar deuterium isotope effect values for the reactions of NH_2OH, H_2NNH_2, $MeNH_2$, and $H_2NCH_2CH_2CH_2NH_2$ with MS^- do not mean that all these reactions involve the same transition state, *i.e.*, the same Brønsted plot. The α-effect nucleophiles have been found to deviate positively by many orders of magnitude from a Brønsted plot obtained for normal primary amine nucleophiles.[5]

It is interesting to note that the deuterium solvent isotope effects for hydrolysis of PS^- ($k_o^{H_2O}/k_o^{D_2O} = 1.56$) and MS^- ($k_o^{H_2O}/k_o^{D_2O} = 1.72$) are similar to those for the reactions of Tris with PS^- and four primary amines with MS^-, respectively.

One might argue that the deuterium solvent isotope effect ($k_n^{H_2O}/k_n^{D_2O}$) for 1,3 proton transfer through TS is likely to be larger than 1.7. Hence a small deuterium solvent isotope effect as measured here can arise from a general solvation, *i.e.*, a secondary kinetic isotope effect.[12] Although such a perception cannot be denied completely, we are reluctant to consider it as the sole reason for the observed low values of $k_n^{H_2O}/k_n^{D_2O}$ for the following reasons. Jencks and Carriuolow[13] observed deuterium solvent isotope effects of 1.24 and 1.09, respectively, for the nucleophilic and general-base-catalysed glycinolysis of phenyl acetate, and 1.00 and 1.20 for the nucleophilic cleavage of *p*-nitrophenyl acetate with ammonia and piperidine, respectively. The deuterium solvent isotope effect for general-base-catalysed ammonolysis of *p*-nitrophenyl acetate was found to be 1.46.[13] However, the uncatalysed aminolysis of phenyl and *p*-nitrophenyl acetates have been conclusively shown to involve a proton-switch mechanism.[14] The most probable cause for the low deuterium solvent isotope effects observed in the present study could be ascribed to the occurrence 1,3 proton transfer through both TS and TS_1. Shain and Kirsch[15] have provided evidence for the occurrence of intramolecular hydrogen bonding (similar to TS_1) in the tetrahedral addition adduct formed in the hydrolysis of methyl and ethyl benzoates catalysed by hydroxide ion.



TS_1

The possibility of $T^{\pm}$ being converted into the product through a transition state involving proton transfer from nitrogen to the leaving group (methoxide or phenoxide) cannot be ruled out in favour of the route involving T°.* Although the transition state involving 1,3 proton transfer from nitrogen to the leaving group through an intermediate similar to $T^{\pm}$ in the aminolysis of aryl and alkyl acetates has not been suggested,[14] the occurrence of such a transition state is not inconceivable in the aminolysis of salicylate esters. The reason for this may be attributed to the fact that the nucleophilic reactivities of primary, secondary, and tertiary amines towards acetate esters appear to constitute a single Brønsted plot,[14] while the reactions of PS^- with primary and secondary amines reveal Brønsted plots of different slopes and tertiary amines do not show detectable reactivities towards salicylate esters.[4]

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