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HYDROLYSIS OF VERY REACTIVE METHYLATION AGENTS - A RAPID INJECTION N. M. R. INVESTIGATION.

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Abstract. By use of the recently described Rapid Injection N. M. R. technique it has been possible to measure the hydrolysis rates of 1, 2, and 3 at various temperatures; the activation parameters for these rapid reactions have been determined and discussed.

Methyl transfer reactions have attracted considerable attention recently as a testing ground for predictions of transition state structure from linear and non-linear free energy relations[1-4]. In this respect the reactions of extremely reactive methylation agents should be specially useful, however the available data are rather sparse. The hydrolyses of trimethyloxonium tetrafluoroborate 1, methyl trifluoromethanesulfonate 2, and methyl fluorosulfate 3, are too rapid at room temperature to be followed by conventional techniques. Kevill's titration technique allowed studies of the methanolysis of 1 only below -23°C, and of the hydrolyses of 2 and 3 at 0.4°C [5]. Direct comparison of the reactivities of 1, 2, and 3 has been made in acetonitrile towards the weakly nucleophilic arenesulfonate anions[4], and in sulfolane towards aromatic thiols, whose disappearance could be followed by UV spectroscopy[6].

We have lately described a novel Rapid Injection N. M. R. technique and demonstrated its utility for the measure of the solvolysis rate of 1 in water[7]. We have now expanded this study to encompass the hydrolyses of 1, 2, and 3 over the temperature range +5°C to +65°C in order to evaluate the activation parameters and assess the influence of substrate charge type for this important class of reactions.

The experimental technique has already been described[7]. However in the preliminary study 1 was injected into D_2O as a solution in nitromethane; this procedure was unsatisfactory for 2 and 3 as their lower solubility in water led to separation of the organic and aqueous phases. The problem was avoided by injecting all three substrates dissolved in trifluoroacetic acid - d_1

to give a final solvent composition $D_2O:CF_3CO_2D$ 95:5 (Solvent A). In a further series 1 was solvolysed in D_2O : DMSO-d_6 : CD_3NO_2 79:16:5 (Solvent B). The upper temperature limit of 65°C was enforced not by the rapidity of the reactions, (for 1 $t^{1/2}$ = 0.6 s.), but by the masking of the substrate resonance by the solvent residual proton resonance. The rate data and the associated activation parameters are collected in Tables I and II respectively.

Table I. Hydrolysis rates of $Me_3O^+BF_4^-$(1), $MeOSO_2CF_3$(2), $MeOSO_2F$(3) in D_2O

1 : Solvent B[a]		1 : Solvent A[b]		2 : Solvent A		3 : Solvent A	
T(°K)	k x $10^2(s^{-1})$	T(°K)	k x $10^2(s^{-1})$	T(°K)	k x $10^2(s^{-1})$	T(°K)	k x $10^2(s^{-1})$
				273.4	0.44[c]	273.4	0.14[d]
		276.8	0.65	277.0	0.79	276.8	0.24
283.3	1.43	282.1	1.22	282.6	1.20	282.5	0.43
				288.3	2.91		
296.6	4.47	295.3	4.47	295.6	5.22	297.3	2.04
309.2	12.9	308.4	19.0	312.6	24.2	310.3	9.02
322.3	31.8	322.0	56.3	322.0	42.2	322.4	27.5
334.3	77.6	330.8	99.2	330.4	75.6	336.0	73.0

a) D_2O : DMSO-d_6 : CD_3NO_2 79:16:5, b) D_2O : CF_3CO_2D 95:5, c) Data from reference 5 for 98% aq. acetonitrile, d) idem for 98% aq. dioxane.

Each rate constant was obtained from 3 injections each providing 6 points; the standard deviations were in all cases less than 2%.

Table II. Activation parameters for hydrolyses of $Me_3O^+BF_4^-$, $MeOSO_2CF_3$, $MeOSO_2F$.

Substrate	Solvent	$\Delta H^‡$(kcal mol^{-1})	$\Delta S^‡$(cal deg^{-1} mol^{-1})	No of points
$Me_3O^+BF_4^-$	B	14.1 ± 0.2[a]	- 17.3 ± 0.5	5
$Me_3O^+BF_4^-$	A	16.6 ± 0.4	- 8.5 ± 1.2	6
$MeOSO_2CF_3$	A	15.5 ± 0.5	- 12.2 ± 1.6[b]	8
$MeOSO_2F$	A	17.7 ± 0.3	- 6.5 ± 0.9[b]	7

a) Errors given are the standard deviations, b) includes Kevill's data (one point).

Kevill's data for the hydrolyses of 2 in 98% aqueous acetonitrile and of 3 in 98% aqueous dioxane at +0.3°C fit remarkably well the Arrhenius plot for our data obtained with 95% deuterated aqueous trifluoroacetic acid. This result indicates that the water nucleophilicity is only slightly affected by the presence of 1.2 mol % acid, and secondly it provides a further example fo the negligable solvent isotope effect on S_N2 solvolyses involving sulfonate leaving groups[1].

Allowing for the statistical factor of 3 favouring the reaction of 1, one finds that the triflate anion is a better leaving group in water than the neutral dimethyl ether. The oxonium ion had previously been found to be 12 times more reactive than 2 towards methanol at -23.4°C, and 4.7 times more reactive towards acetonitrile at 0°C. In the latter case the enthalpy of activation for the reaction of 1 was determined to be 3 kcal greater than that for the reaction of 2. Our results for aqueous solution show that the reactivity order is controlled by the enthalpy term, as the entropies of activation are effectively indistinguishable based on 95% confidence limits rather than the standard deviations quoted in Table II. Furthermore the hydrolyses of the much less reactive methyl methanesulfonate and methylarenesulfonates have activation entropies also in the range of -8 to -12 cal deg^{-1} mol^{-1} [8]. So no distinction can be made between the activation parameters for attack of water on a neutral or on a charged substrate. Such a situation has been found by Lewis for reactions of neutral phenyl thioethers with 1 and 2 in sulfolane[6]. Water can reasonably be expected to solvate an anionic leaving group better than a neutral one, therefore our results establish that for the reactions with both substrate types there is little change in charge localization between the ground and transition states. Abraham has shown that the transition state for Menschutkin reactions in water behaves as a polarizable nonelectrolyte, closer in nature to the reactants than to the product ion pair[9,10]. Such an image should be even more appropriate to displacement reactions of diffusely charged sulfonate groups.

In parenthesis we note that the unusual activation parameters, notably the positive entropy of activation, found at 12°C for the hydrolysis of methyl perchlorate[11,12], do not result from the excellence of the leaving group, as 1 and 2, which react more rapidly by a factor of 35 at 24°C, do so by a straightforward S_N2 mechanism.

Finally the difference in activation parameters found for the hydrolysis of 1 in solvents A and B deserves comment. In aqueous solution containing 5.9 mol % of the basic cosolvent DMSO, the enthalpy of activation is lower by 2.5 kcal mol^{-1} than that found for solvent A containing 1.2 % acid; correspondingly the entropy of activation is more negative in the former solvent. The effects of cosolvents on the experimental enthalpy of activation for proton abstraction by water have recently been considered by Symons[13]. In his analysis basic cosolvents provide more water molecules with free lone pairs (LP_f) i.e. the reactive species, and hence reduce the temperature dependence of their liberation from structured water. Our results illustrate the corresponding effect on the nucleophilicity of water, amplified by the fact that in Solvent A the acidic cosolvent would reduce the number of LP_f (by less than 50% even assuming a coordination number of 3 for H_3O^+). Symons considered that cosolvent effects on S_N2 reactions should be minor, as an increase in the number of LP_f should decrease the number of free OH bonds (OH_f) necessary for incipient anion solvation. However as we have shown above, negative charge development or positive charge disperal is not apparently important in the transition states of these hydrolyses, and so the effect on LP_f should be predominent.

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