666. *Catalysis by Ion-exchange Resins. Part II.*[1] *The Hydrolysis of Amides in Aqueous-organic Solvents.*

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Unequal distribution of the components of a binary aqueous-organic solvent between the two phases of a resin-catalysed reaction system makes relative solubility of the substrate in the two components of the solvent the main, but not the only, rate-influencing factor of such a system. In nearly anhydrous media, resin catalysts appear to show ideal behaviour to a surprisingly low degree of water composition, enabling the role of water as a reactant in the acid hydrolysis of acetamide to be demonstrated.

THE extension of studies of catalysis by ion-exchange resins to substrates containing aromatic groups necessitates the use of mixed aqueous-organic solvents. Previous work [2-5] has indicated that such solvents introduce factors complicating resin catalysis in addition to those found for the same solvents in homogeneous catalysis. Since these factors may be expected to influence any selectivity shown by ion-exchange resins in their catalytic function, the effect of solvent composition on the rate of hydrolysis of amides under such catalysis has been studied.

EXPERIMENTAL

Materials.—" AnalaR " acetone and " AnalaR " ethanol were dried over anhydrous calcium sulphate, and, after distillation through a 30″ glass column, were kept in an all-glass apparatus which allowed measured volumes to be taken without the solvents' coming into contact with the atmosphere.

The other materials used were as previously described.[1]

Standard Solutions.—For all aqueous-ethanol solvents, and for 0—90% (by volume) acetone in water, standard 0·2M-solutions were prepared by making a solution of the amide in an appropriate volume of anhydrous solvent up to 100 ml. with deionised water.

For the hydrolyses in 94—100% acetone, however, the amide was dissolved in ∼70 ml. of acetone, the appropriate volume of water was added by a pipette, and the solution then made up to 100 ml. with further anhydrous acetone. Hence the amount of water in the solution was known accurately over this range of solvent composition.

Differences in the two procedures arise from the non-ideality of aqueous-acetone mixtures. In converting the volume percentages into mole fractions account was taken of the amount of water present originally in the resin catalyst.

For the reactions of acetanilide in 15% and 30% v/v acetone, 0·1M-solutions were used, because of the low solubility of acetanilide in these solvents.

Analysis.—The kinetic procedure used was as previously described.[1]

For the reactions in aqueous ethanol the primary method of analysis was precluded since the organic acid product reacted with the ethanol under the influence of the resin. The secondary analytical method, *i.e.*, determination of loss in acidity of the resin, was therefore used and results were good.

Results.—The substrates were acetamide and acetanilide, these being chosen because one (acetamide) is readily soluble in water, while the other is only very slightly soluble.

The results obtained in aqueous acetone (both substrates) and in aqueous ethanol (acetamide only) are summarised in Tables 1 and 2, and in Fig. 1.

For acetamide a change in kinetic order from second to first occurred in aqueous acetone containing more than 70% by volume of acetone. This change in order is exemplified by the results of the typical experiments given in Table 3.

The second-order rate constants given in Table 1 for the hydrolysis of acetamide in aqueous

[1] Part I, Bolton and Henshall, *J.*, 1962, 1226.
[2] Haskell and Hammett, *J. Amer. Chem. Soc.*, 1949, **71**, 1284; Bernhard and Hammett, *ibid.*, 1953, **75**, 1798, 5834.
[3] Thomas and Davies, *J.*, 1952, 1607.
[4] Davies and Owen, *J.*, 1956, 1676.
[5] Mariani, *Ann. Chim. appl.*, 1949, **39**, 717.

TABLE 1.

Hydrolysis of acetamide and acetanilide in aqueous acetone.

Acetone in solvent		Acetamide (at 45·0°) $10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	Acetanilide (at 55·0°) $10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	Acetone in solvent			Acetamide (at 45·0°) $10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	Acetanilide (at 55·0°) $10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)
Vol. %	Mol. fraction			Vol. %	Mol. fraction	$10^5 k_1$ (sec.$^{-1}$)		
0	0	3·76		85	0·582	1·45	3·94	
10	0·027	3·39		90	0·690	1·45	3·94	0·564
15	0·041		4·73	94	0·732	1·28	3·48	
20	0·057	3·03		95	0·765	1·10	2·99	
30	0·095	3·02	2·40	96	0·794	0·945	2·57	
40	0·139		1·41	97	0·820	0·760	2·07	
50	0·195	2·95	1·02	98	0·853	0·562	1·52	
60	0·277	3·33	0·715	99	0·881	0·411	1·11	
70	0·363	3·89	0·534	100	0·933	0·294	0·80	

TABLE 2.

Hydrolysis of acetamide in aqueous ethanol at 55·0°

EtOH in solvent:							
Vol. %	0	10	20	30	50	70	80
Mol. fraction	0	0·033	0·071	0·116	0·234	0·416	0·542
$10^5 k_2$ (l. mole^{-1} sec.$^{-1}$) ...	9·94	9·20	8·65	8·15	8·35	8·70	8·90

TABLE 3.

Calculated rate constants for the hydrolysis of acetamide in 50% and 96% aqueous acetone.

	50% Acetone			96% Acetone	
Time (hr.)	$10^6 k_1$ (sec.$^{-1}$)	$10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	Time (hr.)	$10^6 k_1$ (sec.$^{-1}$)	$10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)
2·0	10·7	3·03	4·0	9·44	2·64
4·18	10·2	2·93	6·5	9·45	2·71
6·02	10·5	2·94	9·5	9·43	2·76
8·0	9·90	2·97	13·0	9·45	2·86
13·5	9·47	2·96	18·0	9·48	2·99
18·5	9·20	2·98	24·0	9·40	3·10

TABLE 4.

Energies and entropies of activation of acetamide and acetanilide in 70% acetone.

	Acetamide				Acetanilide		
Temp.	$10^5 k_2$ (l. mole^{-1} sec.$^{-1}$)	E_a (kcal. mole^{-1})	ΔS^* (e.u.)		$10^6 k_2$ (l. mole^{-1} sec.$^{-1}$)	E_a (kcal. mole^{-1})	ΔS^* (e.u.)
45·0°	4·00				2·11		
55·0	11·0	20·2	−17·1		5·11	19·7	−24·7
63·0	21·6						
63·3					11·5		

acetone of greater than 70% acetone content were calculated by dividing the experimentally obtained first-order constants by the initial concentration of resin (in milliequivalents of exchangeable hydrogen ion per l. of solution).

For the hydrolysis of acetanilide in 90% aqueous acetone a choice between first- and second-order rate equations was difficult to make, but, for comparison, the second-order equation was used to calculate the rate constant given.

No change in kinetic order was observable in aqueous ethanol of high ethanol content, but it is possible that the method of analysis used in this case is insufficiently sensitive to detect it.

Energies and entropies of activation of the two substrates were determined in 70% by volume acetone in water. This was the solvent used by earlier workers [2] in their studies of resin-catalysed ester hydrolyses. The results are given in Table 4, in which the rate constants have been corrected for thermal expansion of the solvent.

DISCUSSION

A resin-catalysed reaction system may be considered to be composed of two phases: the " active " phase within the resin catalyst, in which the reaction takes place, and the " inert " phase, being the solution extraneous to the resin catalyst.

It has been shown [3,4] that in mixed aqueous-organic solvents ion-exchange resins tend to concentrate water within the resin phase to the exclusion of the organic component. This effect creates a large difference in nature between the two phases of a resin-catalysed system, which may be expected to exert a considerable influence on the distribution of a substrate between the phases (*i.e.*, on λ^1), and hence on the rate of reaction; especially
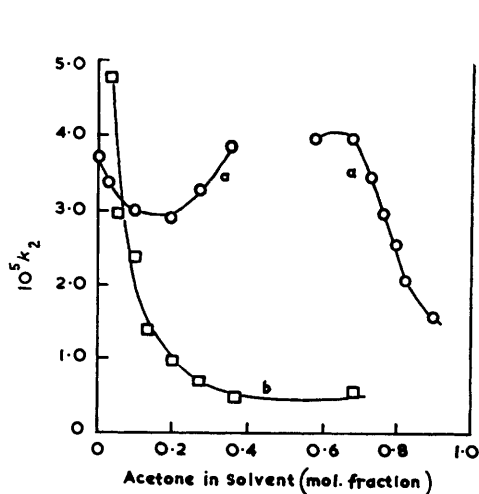

FIG. 1.   Rate of hydrolysis of (a) acetamide and (b) acetanilide in aqueous acetone.
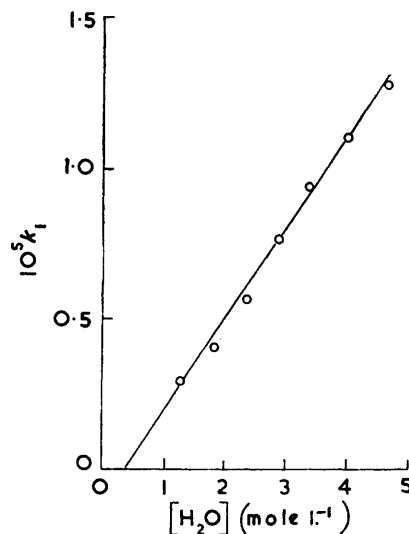

FIG. 2.   Plot of rate constants against water content of aqueous acetone for hydrolysis of acetamide.

will this be so where the substrate concerned shows much greater solubility in one of the two components of the solvent than in the other.

As the acetone content of an aqueous-acetone mixture is increased, an increasing proportion of the total water of the solvent is held by the resin phase; and a substrate such as acetanilide, which is much less soluble in water than in acetone, will be excluded from the active phase to a continuously increasing extent.   To this may be attributed the fall in reaction rate found experimentally for acetanilide (Fig. 1b).   Acetamide is rather more soluble in water than in acetone; hence, for this substrate a rise in reaction rate with increasing acetone content may be predicted.

Simultaneously, however, for both substrates the decreasing dielectric constant of the medium will tend to cause a lowering of the reaction rate.[6]   This secondary rate-influencing factor will reinforce the main distribution effect in the case of acetanilide, but will oppose it in the case of acetamide, leading to the resultant experimental curves found (Figs. 1a and b).

In aqueous ethanol the same considerations may be expected to apply; and a similar curve was found for acetamide in this mixed solvent.

In view of the difference in nature of the active and the inert phase of the system,

[6] Laidler and Landskroener, *Trans. Faraday Soc.*, 1956, **52**, 200.

obedience to the Laidler–Eyring [7] or Laidler–Landskroener [6] equation, requiring a correlation between reaction rate and the apparent dielectric constant of the medium, was not expected and was not found. It is difficult to reconcile these results with those of Mariani,[5] who found an apparent obedience to the Laidler–Eyring equation for resin-catalysed ester hydrolyses in aqueous acetone.

Ion-exchange resins are being used to an increasing extent as catalysts in organic syntheses, where they have many advantages over the homogeneous acids and bases which they replace; [8] and the present results emphasise that care must be taken in the choice of a suitable solvent for a resin-catalytic operation. For a reaction involving a substrate only sparingly soluble in water, the solvent most likely to give the fastest reaction and greatest yield appears to be that containing the minimum amount of organic component necessary to dissolve the substrate.

Sulphonic acid resins, like their homogeneous counterparts, may be expected to become weak (partially ionised) acids in media of very low dielectric constant. This appears to explain the change in kinetic order found in aqueous acetone of high acetone content. For under these conditions, the reaction in effect takes place in a buffered system; and the reaction shows an apparent independence of variation in hydroxonium ion concentration.

The expectation that under nearly anhydrous conditions practically all the water present in a resin-catalysed reaction system would be concentrated in the active resin phase, hence minimising secondary effects such as variation of dielectric constant, made it likely that such a system would show extended ideality of behaviour and enable the role of water as a reactant in a hydrolytic reaction such as amide hydrolysis to be demonstrated. The experiments in solvents of low water content (95—100% volume of acetone) were carried out to ascertain this.

An analysis of the reaction mechanism of amide hydrolysis [9,10] has indicated that, provided the acidity of the medium remains constant, a condition approximately validated by the obedience to the first-order law in solvents of low water content, then the hydrolysis rate should obey a law of the form: Rate $= k[\text{Amide}][\text{H}_2\text{O}]$. Experimental rate constants (now designated k_e) given in Table 1 were obtained on the basis of: Rate $= k_e[\text{Amide}]$. This is because the concentration of water is still sufficiently in excess of that of the amide for it to be considered as unchanged during any one reaction. Hence, $k_e = k[\text{H}_2\text{O}]$.

A plot of k_e against the concentration of water gave the straight line predicted by the above analysis (Fig. 2), but it did not pass through the origin. The point at which the line cut the horizontal axis was found from a large-scale plot to correspond to a water concentration of ~0·35M, a value very close to the titratable concentration of catalyst used in each of the experiments (0·369N). This appears to indicate that one molecule of water is bound to each proton in the system, and that any water so bound is not available for hydrolysis.

However, many of the rate-influencing factors in the system are intrinsically dependent on the amount of water present; and it is possible that alternative, more complex interpretations of the results could be proposed. Nevertheless, a surprising degree of ideality in such systems has been shown to exist, and further work is in progress which is attempting to extend the usefulness of this approach.

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[7] Laidler and Eyring, *Ann. New York Acad. Sci.*, 1949, **39**, 303; Glasstone, Laidler, and Eyring, " The Theory of Rate Processes," McGraw-Hill, New York, 1941, p. 419.
[8] Glenat, *Chimie et Industrie*, 1956, **75**, 292.
[9] Edward and Meacock, *J.*, 1957, 2000.
[10] Bolton, Ph.D. Thesis, London, 1961.