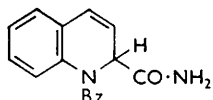**236.** *Catalysis by Ion-exchange Resins. Part I. The Hydrolysis of Amides in Aqueous Solutions.*

By P. D. Bolton and T. Henshall.

The hydrolysis of four unsubstituted and three N-substituted amides in aqueous solution, catalysed by a cation-exchange resin, has been studied, and energies and entropies of activation for the reactions have been calculated. A correction factor, based on the Helfferich two-phase approach, has been derived which brings the entropy factor into accord with Hammett's theory of resin catalysis. The same approach also accounts satisfactorily for the variation of the activation energy from that of an apparently equivalent homogeneous system.

IT has been observed by Collins[1] that the carbamoyl group in 1-benzoyl-1,2-dihydro-quinoline-2-carboxyamide (I) can be selectively hydrolysed by a cation-exchange resin; whilst the benzamido-group, which is simultaneously hydrolysed by standard methods, is retained intact.

(1)

Because of the general lack of specific effects noted in earlier studies of ester hydrolysis catalysed by ion-exchange resins,[2] quantitative investigations into some of the factors affecting the hydrolysis of amides under

[1] Collins, *Chem. and Ind.*, 1957, 736; Collins and Henshall, *J. Amer. Chem. Soc.*, 1958, **80**, 159.
[2] (a) Haskell and Hammett, *J. Amer. Chem. Soc.*, 1949, **71**, 1284; (b) Bernhard and Hammett, *ibid.*, 1953, **75**, 1798, 5834; (c) Bernhard, Garfield, and Hammett, *ibid.*, 1954, **76**, 991; (d) Riesz and Hammett, *ibid.*, 1954, **76**, 992; (e) Samelson and Hammett, *ibid.*, 1956, **78**, 524; (f) Chen and Hammett *ibid.*, 1958, **80**, 1329.

similar conditions were undertaken. A method of analysis has been developed and applied to the hydrolysis of simple amides, both primary and *N*-substituted, by a sulphonic acid cation-exchange resin. Energies and entropies of activation have been calculated and compared, where possible, with the results of homogeneous hydrolysis.

Previous studies of amide hydrolysis under homogeneous acid conditions are mainly based on the determination of the concentration of amine cation produced. In the resin-catalysed reaction, however, the acid catalyst, together with the amine, which is retained by the resin, can be removed from the reaction mixture by simple filtration; the organic acid is then titrated against standard alkali. An independent check is obtained by titrating the resin potentiometrically; the difference in exchange capacity before and after the hydrolysis is a measure of the extent of reaction.

EXPERIMENTAL

Preparation and Purification of Materials.—The resin. The commercial grade Amberlite IR-120 [3] resin was wet-sieved, and the 20—30 mesh material used for all experiments, except where otherwise stated.

To activate the resin, several volumes of 5% aqueous sodium chloride solution were passed through it, followed by a similar quantity of 10% hydrochloric acid. This was repeated thrice, after which the resin was thoroughly washed with several litres of de-ionised water. The regenerated resin was then drained and spread out in large shallow dishes to dry in air at 25°, near constancy in moisture content (around 25%) being reached in 2 weeks.

Amides. With the exception of 1-acetylpiperidine, which was obtained by standard methods,[4] all the amides used were commercial products and were purified by appropriate methods. For solid amides the attainment, after repeated recrystallisation, of a constant m. p. of the value given in the literature was accepted as a criterion of purity. For liquids the attainment of the literature values of both b. p. and refractive index was demanded. Solutions were prepared in water previously de-ionised by treatment with Amberlite MB-3.[3]

Alkali. Barium hydroxide solutions were standardised against "AnalaR" potassium hydrogen phthalate, phenolphthalein being used as indicator.

Experimental Procedure.—Agitation. Preliminary investigations showed that the rates of some of the hydrolyses were extremely slow, and the thermal stability of the resin catalyst imposed a limit of around 65° on the rate studies. It was therefore essential that the necessary continuous mixing of the resin and solution should cause the minimum of attrition of the resin particles. The following apparatus proved adequate: A stainless steel shaft was mounted in a roller bearing at an angle of about 15° to the vertical and was driven at the upper end through a speed-reducing pulley system. The lower end dipped into a thermostat tank and carried a series of clips to hold sealed glass tubes containing individual samples of reaction mixture. The shaft was turned at about 30 r.p.m. causing the tubes to be rotated in a plane inclined at 15° to the horizontal, and the gentle agitation of the liquid in the tubes kept the resin constantly and completely in motion without causing any detectable breakdown of the particles.

Analytical method. The procedure used was based on that described by Haskell and Hammett.[2a] Portions of air-dried resin (0·95—1·00 g.) were weighed into Pyrex-glass tubes, 15 mm. in diameter and approximately 15 cm. long. Samples of the same batch of resin were also weighed for a determination of moisture content by heating, in a controlled oven at 110°, to constant weight.[5]

Further samples were also taken for determination of exchange capacity. This was carried out by immersion of the resin overnight in a 10% solution of sodium chloride, followed by titration of the liberated acid.

Standard aqueous solutions of the amides were added to the reaction tubes, usually in the proportion of 10 ml. of solution to 1 g. of resin. The reaction tubes were then cooled in ice–water, sealed, and attached to the agitator.

[3] Manufactured by Rohm and Haas Co., Philadelphia, U.S.A.
[4] Wagner and Zook, "Synthetic Organic Chemistry," 5th Ed., Wiley, New York, 1953, p. 566.
[5] Vasilyev, *J. Appl. Chem. (U.S.S.R.)*, 1957, **30**, 1086.

Tubes were removed at fixed intervals, the resin separated from the reaction mixture by filtration and thoroughly washed with de-ionised water (150—200 ml.), and filtrate and washings titrated against standard barium hydroxide solution to determine the amount of organic acid produced.

Small corrections were applied for the time taken for the tubes to attain bath temperature, for the changes in concentration in both resin and amide due to the moisture content of the resin, and for the change in concentration due to the thermal expansion of the solvent.

Calculations.—Second-order rate constants were calculated from: (*a*) The integrated rate equation $k = [2 \cdot 303/t(a - b)] \cdot \log_{10} b(a - x)/a(b - x)$ 1. mole^{-1} sec.$^{-1}$ where a = initial concentration of resin expressed in equivalents of exchangeable hydrogen-ion per litre of solution;

$$b = \text{initial concentration of amide in moles l.}^{-1};\ \text{and}$$

$$x = \text{concentration of product in moles l.}^{-1} \text{ at time } t.$$

(*b*) The slopes of plots of $\log_{10} b(a - x)/a(b - x)$ against t.

Energies of activation (E_a) were obtained from the slopes of plots of $\log_{10} k$ against $1/T$. Entropies of activation (ΔS^*) were calculated from the equation:

$$\Delta S^* = 2 \cdot 303\ \boldsymbol{R}\ (\log_{10} A - \log_{10} kt/h) - \boldsymbol{R}$$

where A is the pre-exponential factor of the Arrhenius equation, and the other quantities have their usual significance.

RESULTS

The hydrolyses followed second-order kinetics in all cases up to at least 50%, and in most cases to 70% of the total reaction, these being calculated from the amount of acid produced.

Experiments were made with acetamide at 55°, in which the initial concentrations of both amide and resin were varied. The results are given in Table 1; a variation in rate constant of less than 3% is apparent over a reasonably wide range of reactant concentration, although a large increase in resin concentration (expt. viii) caused a 10% fall in rate constant.

TABLE 1.

Expt.	[Acetamide] (initial) (mole/l.)	[Resin] (initial) (equiv./l.)	$10^5 k$
(i)	0·0976	0·3744	10·22
(ii)	0·1465	0·3744	10·04
(iii)	0·1950	0·3744	10·06
(iv)	0·2450	0·3744	9·74
(v)	0·1978	0·1920	10·07
(vi)	0·1968	0·2673	10·22
(vii)	0·1956	0·3418	9·93
(viii)	0·1946	0·5680	9·15

The resin samples from experiment (iii), after filtration, were immersed in 10% aqueous sodium chloride solution and set aside overnight. The acid liberated was titrated potentiometrically; typical curves obtained for various stages of the hydrolysis are shown in the Fig. where the effect on the resin of increasing concentration of ammonium ions is reflected in the shape of the titration curves.

The loss in acidity of the resin with progress of reaction, as obtained from these curves, is compared in Table 2 with the concentration of acetic acid determined directly by titration of the reaction mixture. The reasonable agreement between these results confirms both the stoicheiometry of the reaction and the reproducibility and accuracy of the analytical method.

The potentiometric curves also showed that Bromocresol Purple could be used as an indicator for the titration of resin samples, which in subsequent analyses gave results in excellent agreement with those from direct titration of carboxylic acid formed on hydrolysis.

The Effect of Variation of Resin Particle Size.—The effect of a large variation in resin-particle size on the rate of resin-catalysed hydrolysis was examined. In each case, 0·1M-acetamide solutions were used in the proportions of 1 g. of resin to 10 ml. of solution. The results are

given in Table 3. For an approximately 10-fold increase in surface area an increase of only 5% in the rate constant was observed.
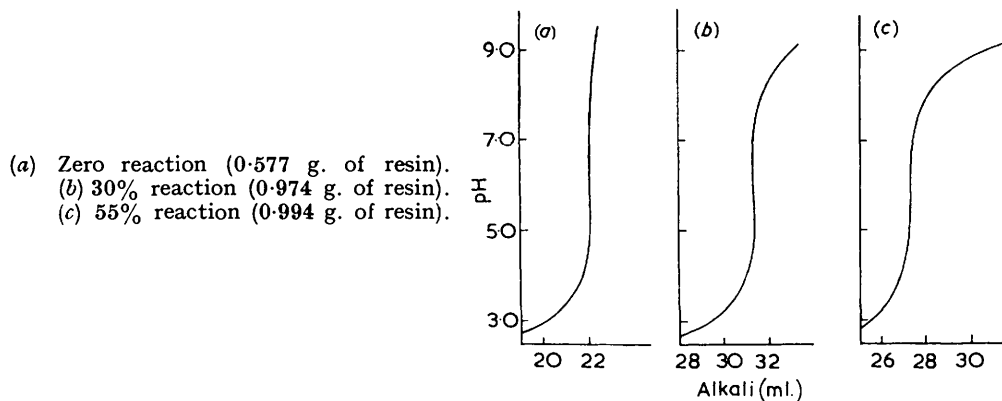
(a) Zero reaction (0·577 g. of resin).
(b) 30% reaction (0·974 g. of resin).
(c) 55% reaction (0·994 g. of resin).

TABLE 2.

	Direct titration			Titration of resin	
Time (10³ sec.)	[Acetic acid] (mole/l.)	$10^5 k$		Loss in acidity of resin (moles/l.)	$10^5 k$
1·26	0·009	10·0		0·010	11·2
2·64	0·018	9·93		0·019	10·5
4·44	0·028	9·69		0·028	9·69
7·14	0·042	9·74		0·046	10·8
10·8	0·059	9·70		0·061	10·2
18·0	0·085	9·76		0·088	10·3
25·2	0·105	9·88		0·106	10·0
32·4	0·121	9·93		0·120	9·80

TABLE 3.

Mesh size	Average diam. (mm.)	Relative surface area	$10^5 k$
16—20	1·0	1	9·72
20—30	0·7	1·4	9·94
30—50	0·4	2·5	10·0
100—200	0·1	10	10·4

TABLE 4.

Substrate	Temp.	$10^5 k$	E_a (kcal.)	$10^8 A$	ΔS (e.u.)
Acetamide	39·4°	2·11			
	45·0	3·79			
	55·0	10·0	19·9	17·7	−18·0
	63·05	20·5			
Propionamide	45·1	5·54			
	55·1	14·5	19·0	7·18	−20·2
	62·7	28·0			
Butyramide	39·4	1·64			
	44·6	2·75			
	54·9	7·90	20·0	16·7	−18·5
	63·2	15·7			
Isobutyramide	45·1	3·36			
	55·1	8·45	19·8	12·2	−19·1
	62·7	17·4			
N-Methylacetamide	45·1	0·138			
	54·9	0·404	22·6	46·6	−16·5
	63·1	0·939			
NN-Dimethylacetamide	45·1	0·167			
	54·9	0·465	21·4	8·78	−19·8
	63·1	1·03			
1-Acetylpiperidine	45·3	0·520			
	55·2	1·31	18·8	0·442	−25·6
	63·0	2·60			

a At 55°.

Activation Energies.—The temperature dependence of the specific rate constants, and the corresponding energies and entropies of activation for the amides studied are listed in Table 4. The amide solutions used were 0·2M, and in the proportion of 10 ml. of solution for 1 g. of air-dried resin. The two methods of analysis gave results in excellent agreement.

DISCUSSION

The acid-catalysed hydrolysis of unsubstituted amides under homogeneous conditions has been widely studied; the results are summarised by Bender.[6] Cation-exchange resins incorporating sulphonic acid groups can be regarded as insoluble strong acids, or as systems in which the hydroxonium ions are strongly localised. It therefore appears reasonable to expect that their catalytic activity will parallel that of a strong acid acting under homogeneous conditions, and further, that both should follow similar or even identical reaction mechanisms.

However, as is evident from Table 5 in which the results of both homogeneous and

TABLE 5.

	Resin catalysis				Homogeneous catalysis				
Substrate	Amide concn. (M)	Resin concn. (N)	E_a (kcal.)	ΔS (e.u.)	Amide concn. (M)	Acid concn. (N)	E_a (kcal.)	ΔS (e.u.)	Ref.
Acetamide	0·2	0·35	19·9	−18·0	0·05	0·05	18·1	−23·7	7a
					0·2	1·0	18·8	−20·9	8
					0·2	4·0	20·0	−19·1	8
					0·2	8·5	21·2	−20·0	8
Propionamide	0·2	0·35	19·0	−20·2	0·05	0·05	18·0	−23·8	7a
					0·2	1·0	18·6	−21·4	8
					0·2	4·0	19·4	−20·5	8
					0·2	6·5	19·7	−21·8	8
					0·2	8·5	20·2	−22·3	8
					0·2	10·1	21·4	−20·5	8
Butyramide	0·2	0·35	20·0	−18·5	0·05	0·05	18·0	−23·8	7a
Isobutyramide ...	0·2	0·35	19·8	−19·1	0·05	0·05	17·7	−25·7	7b

heterogeneous hydrolyses are compared, the resin catalysts do considerably affect the reaction rates and parameters.

Similar results have been observed by Haskell and Hammett [2a] in the resin-catalysed hydrolyses of esters, and they found also that the activation entropies for such reactions are considerably more negative than for their homogeneous counterparts. This they attributed to the imposition by the resin of greater restraints on the transition state.

The results, listed in Table 5, are apparently at variance with this concept in so far as amide hydrolysis is concerned, but, by a modification of the method suggested by Helfferich,[9] the results obtained in this study can be brought into consonance with those of Haskell and Hammett. The basis of Helfferich's method is the suggestion that in resin catalysis the liquids inside and outside the resin phase are to be treated as separate homogeneous systems, and the following is an extension of his thesis.

Let the resin-catalysed reaction be represented by:

$$\text{Amide (A)} + \text{Resin (R)} \longrightarrow \text{Products (x)}$$
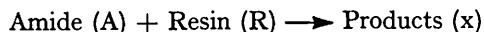
Let quantities relative to the resin and external liquid be denoted by barred and plain lower-case letters respectively, whilst capital letters refer to the whole reaction mixture *i.e.*, both phases.

[6] Bender, *Chem. Rev.*, 1960, **60**, 67.
[7] (a) Willems and Bruylants, *Bull. Soc. chim. belges*, 1951, **60**, 191; (b) de Roo and Bruylants, *ibid.*, 1954, **63**, 140.
[8] Rabinowitch and Winkler, *Canad. J. Res.*, 1942, **20**, B, 73.
[9] Helfferich, *J. Amer. Chem. Soc.*, 1954, **76**, 5567.

A distribution coefficient, λ, is defined by the equation

$$\lambda = \frac{\bar{c}_A}{c_A} = \frac{\bar{n}_A/\bar{v}}{n_A/v},\qquad\qquad (1)$$

wherein $\bar{n}_A$, $\bar{c}_A$, are the mole number and concentration, respectively, of amide in the resin phase, etc., and $\bar{v}$ is the corresponding resin phase volume.

Then, with $N_A = n_A + \bar{n}_A$ and $V = v + \bar{v}$, equation (1) can be rewritten as

$$\bar{n}_A = \left[\frac{\lambda \bar{v}}{V + (\lambda - 1)\bar{v}}\right]N_A. \qquad\qquad (2)$$

If reaction occurs entirely within the resin phase, and by a second-order process, the rate is given by eqn. (3); wherein $\bar{k}$ denotes the rate constant for this process, which need not necessarily equal that for the hydrolysis under homogeneous conditions with the same temperature and effective acidity.

$$\frac{dC_x}{dt} = \bar{k}\bar{c}_A\bar{c}_R = \left(\frac{\bar{k}}{\bar{v}^2}\right)\bar{n}_A\bar{n}_R \qquad\qquad (3)$$

Equations (2) and (3) in combination lead to eqn. (4),

$$\frac{dC_x}{dt} = \frac{\bar{k}\lambda}{\bar{v}[V + (\lambda - 1)\bar{v}]} N_A\bar{n}_R \qquad\qquad (4)$$

and thence by eqns. (5) and (6) to the customary kinetic form (7) in terms of initial concentrations:

$$N_A = N°_A - N_x \qquad\qquad (5)$$

$$\bar{n}_R = N_R = N°_R - N_x \qquad\qquad (6)$$

$$\frac{dC_x}{dt} = \frac{\bar{k}\,\lambda\,V^2}{\bar{v}[V + (\lambda - 1)\bar{v}]} (C°_A - C_x)(C°_R - C_x) \qquad (7)$$

The experimental rate constants are calculated on the basis of eqn. (8); and hence the relation of $\bar{k}$ to the experimental rate constant k_e is expressed in eqn. (9),

$$\frac{dC_x}{dt} = k_e(C°_A - C_x)(C°_R - C_x) \qquad\qquad (8)$$

$$k_e = \frac{\lambda V^2}{\bar{v}[V + (\lambda - 1)\bar{v}]} \bar{k} \qquad\qquad (9)$$

or, in terms of $\theta = \bar{v}/V$, by

$$k_e = \frac{\lambda \bar{k}}{\theta[1 + (\lambda - 1)\theta]} \qquad\qquad (10)$$

(The parameter θ may be regarded as a measure of the effective acidity of the resin under the particular conditions obtaining.)

The determination of θ was relatively simple, but λ caused greater difficulty. However, by using a colorimetric method to determine amide concentration in the external phase of resin–aqueous amide systems at diffusion equilibrium, an estimate has been made from which it appears that for acetamide λ is close to, but slightly greater than, unity.

Application of eqn. (10) with $\lambda = 1$ to the results for the hydrolysis of acetamide, leads to an activation entropy of -22 e.u., a value in closer accord with the concepts of Haskell and Hammett than is -18 e.u. as obtained from the uncorrected rate constants (Table 5).

The assumption of a constant equilibrium value for λ implies, as Helfferich has indicated, that the catalysis involves a reaction-controlled, and not a diffusion-controlled, mechanism.

This assumption has been adequately justified in the present case by the results of those experiments (Table 3) in which the effect on the rate of hydrolysis of variation in resin particle size was studied. That the rate of reaction remains almost unaffected by such a large increase in physical surface area of the catalyst would appear to eliminate the possibility of a diffusion-controlled mechanism. These results show good agreement with those of a similar study of ester hydrolyses carried out by Haskell and Hammett.[2a]

It is also apparent from Table 5 that the activation energies of the amide hydrolysis under homogeneous conditions increase with increasing acid concentration. For acetamide and propionamide the values obtained for the resin-catalysed hydrolysis are considerably higher than would be expected on the basis of an acid concentration of 0·35N, but lie closer to the values for homogeneous hydrolysis at 4·0N.

However, the concept of complete restriction of the catalyst to a small portion of the reaction volume, implies that its *effective concentration*, H_E, as defined in eqn. (11), is much higher than its apparent concentration.

$$H_E = \text{Exchange capacity of the resin/Pore volume of the resin} \qquad . \quad (11)$$

For Amberlite IR-120, the exchange capacity is of the order of 5·15 mequiv./g. of dry resin, and the pore volume was found to have a value of approximately 1·3 ml.; hence for this resin, $H_E \approx 4·0N$, in support of Helfferich's thesis.

Table 1 provides additional support, for between an apparent resin concentration of 0·1N (expt. i) and 0·6N (expt. viii), the second-order rate constant falls in value by only 10%, whilst von Euler and Olander[10] observed, over the same acid range in homogeneous hydrolysis, a decrease of the order of 25%. By eqn. (10), however, the effective concentration of catalyst is the same throughout the series of experiments; only θ is increased, because of the increase in $\bar{v}$ for the same overall volume, and this causes a small decrease in rate constant.

An analysis of the significance of the results obtained for the substituted amides is, for the moment, precluded, since experimental data on their homogeneous hydrolysis do not appear to be available for comparison. Without this it is impossible to say whether the effects of substitution in the amide molecule are due to the introduced substituent or to peculiarities of the resin catalyst.

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[10] von Euler and Olander, *Z. phys. Chem.,* 1927, **131,** 107.