Acidic and Basic Amide Hydrolysis

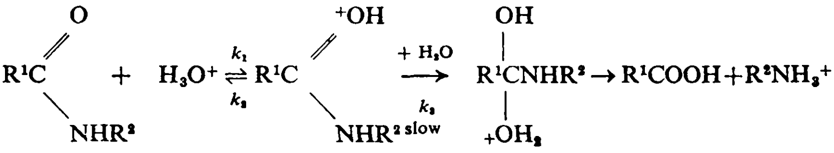
By Charmian O'Connor
CHEMISTRY DEPARTMENT, UNIVERSITY OF AUCKLAND, NEW ZEALAND

The rates of acid catalysed reactions depend on acid concentration. Most reactions are accelerated, and some rates reach a maximum, while others pass through a maximum and then decrease.[1,2] Recently it has been shown that this behaviour may be further complicated as some reactions which have a rate maximum at intermediate acid concentrations may decrease to a minimum and then increase in rate at high acid concentrations.[3,4] Amides exhibit all these patterns of behaviour and attempts have been made to explain them. These explanations have usually been based on small amounts of data.

The mechanism of basic amide hydrolysis is straightforward, and recent investigations have interpreted substituent, catalytic, and isotope effects.

1 Acid Hydrolysis

A. Substituent Effects.—The mechanism generally accepted (Scheme 1) for the hydrolysis of amides in dilute acid solution[5] involves attack by a water molecule on the conjugate acid of the amide (1) as the rate determining step.



(1)

Scheme 1

Reid[6] studied the acid catalysed hydrolysis of amides and showed that the rate was first order in both total amide and hydrogen ion concentrations, at least in reasonably dilute solutions. He also investigated the effect of substituents on the hydrolysis rates of substituted benzamides, and found there were no marked

[1] J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956; 4968; 4973; 4978.
[2] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', Cornell University Press, Ithaca, N.Y., 1953.
[3] D. Jaques, *J. Chem. Soc.*, 1965, 3874.
[4] K. Yates and R. A. McClelland, *J. Amer. Chem. Soc.*, 1967, **89**, 2686.
[5] M. L. Bender, *Chem. Rev.*, 1960, **60**, 53.
[6] E. E. Reid, *Amer. Chem. J.*, 1899, **21**, 284; *ibid.*, 1900, **24**, 397.

effects for *meta*- and *para*- substituents, but *ortho*- substituents retarded the rate. Leisten[7] found that when substituted benzamides were hydrolysed in concentrated perchloric acid solutions electronic effects occurred, and that electron-attracting groups accelerated, while electron-donating groups retarded, the rate. (Relative rates for hydrolysis of *p*-nitrobenzamide, benzamide, and *p*-toluamide in 7·19M $HClO_4$ at 95 °C were 1·40, 0·228, and 0·129 hr^{-1}.) Meloche and Laidler[8] found that the activation energy for hydrolysis of substituted benzamides in an ethanol–water mixture was raised by electron-attracting, and lowered by electron-donating, substituents. Bruylants and Kezdy[9] summarised results and suggested that increasing chain length in aliphatic R groups retarded the rate (n-butyramide twice as slow as propionamide), but halogen substituents enhanced the rate (trichloroacetamide twice as fast as chloroacetamide). Their conclusion was that polar effects are not as important as steric hindrance either by increased chain length or by *ortho*- substituents in substituted benzamides. Koshy[10] demonstrated the marked stabilising effect of the hydroxy-group in the *ortho*- position when he compared the stability of benzamide, salicylamide, and some *N*-substituted derivatives. Bolton and co-workers,[11] studying the hydrolysis of primary aliphatic amides in dilute acids, found that the hydrolysis was governed by a combination of steric and conjugative substituent effects.[11a] Their data for halogen-amides[11b] showed that amides might be slightly sensitive to polar effects.

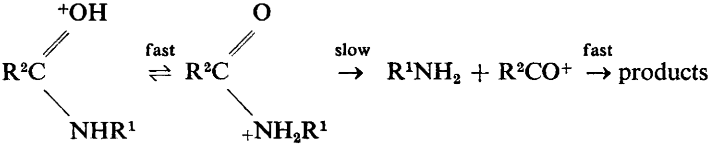
B. Occurrence of a Rate Maximum.—Since the acid hydrolysis of amides is reasonably slow, reactions may be carried out in quite high acid concentrations, and as the acid concentration is increased the hydrolysis rate increases to a maximum and then decreases. Benrath[12] was the first to discover this phenomenon and subsequent workers[13–16] indicate that it generally occurs. The position of the maximum appears to differ with respect to hydrogen ion concentration both with different amides and different mineral acids.[16]

C. Deuterium Isotope Effect.—Reitz[15] and Bunton, O'Connor, and Turney[17] have studied the deuterium isotope effect on the acid hydrolysis of acetamide and benzamide respectively in protium and deuterium oxide. Both investigations showed that the overall effect was to shift the entire rate of acidity profile so that the maximum occurred at lower hydrochloric acid concentration in D_2O than in

[7] J. A. Leisten, *J. Chem. Soc.*, 1959, 765.
[8] I. Meloche and K. J. Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.
[9] A. Bruylants and F. Kezdy, *Rec. Chem. Progr.*, 1960, **21**, 213.
[10] K. V. Koshy, *J. Pharm. Sci.*, 1969, **58**, 560.
[11] (*a*) P. D. Bolton and I. R. Wilson, *Austral. J. Chem.*, 1965, **18**, 795; (*b*) P. D. Bolton, *Austral. J. Chem.*, 1966, **19**, 1013; (*c*) P. D. Bolton and G. L. Jackson; *Austral. J. Chem.*, 1969, **22**, 527.
[12] A. Benrath, *Z. anorg. Chem.*, 1926, **151**, 53.
[13] H. V. Euler and A. Olander, *Z. phys. Chem. (Leipzig)*, 1927, **131**, 107.
[14] T. W. J. Taylor, *J. Chem. Soc.*, 1930, 2741.
[15] O. Reitz, *Z. phys. Chem. (Leipzig)*, 1939, **183**, 371.
[16] V. K. Krieble and K. A. Holst, *J. Amer. Chem. Soc.*, 1938, **60**, 2976.
[17] C. A. Bunton, C. J. O'Connor, and T. A. Turney, *Chem. and Ind.*, 1967, 1835.

H_2O. Bell[18] and Wiberg[19] account for this by stating that D_2O is a weaker base than H_2O because its ionic product is one fifth that of water. Hence for a reaction involving a substrate only partially protonated in a rapid pre-equilibrium, the rate determining step will occur faster in D_2O than in H_2O, *i.e.* $k_D/k_H > 1$. In higher acidities the substrate is essentially entirely protonated, and reaction of the protonated substrate becomes important in the kinetic rather than the equilibrium step. Since D_2O is less nucleophilic than H_2O a ratio $k_D/k_H < 1$ is observed. Both these observations and Arrhenius parameter work[20-22] are in accord with a bimolecular mechanism.

D. Unimolecular Mechanism.—During hydrolysis of the nitro-derivatives of acetanilide in sulphuric acid[22a,b,23] a more complex dependence of k_ψ (the pseudo first-order rate constant) on acid concentration was observed, *viz.*, a rate maximum at intermediate acidities followed by a minimum and subsequently increasing rate at high acid concentration. Duffy and Leisten[23] discuss their results in terms of a change in mechanism from $A_{Ac}2$ to $A_{Ac}1$. Similar rate profiles have more recently been observed for esters[3,4] and ethyl carbamate.[24] It is proposed[23] that Scheme 2 occurs above 70% w/w sulphuric acid,



Scheme 2

and in a unimolecular mechanism the position of protonation is important because dissocation of the oxygen-protonated form cannot seriously be considered to explain the reaction in highly acidic media.

Vinnik[22b] agrees that the mechanism changes from bimolecular to unimolecular at *ca.* 70% w/w sulphuric acid but differs in his explanation of the increasing rate of hydrolysis. He assumes that in concentrated solutions of sulphuric acid the protonated amide and molecules of undissociated sulphuric acid react. The activated complex incorporates the AH^+ ion and the sulphuric acid molecule, whereas in the bimolecular mechanism at low acidities it incorporates the amide, water molecules, and a proton.

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[18] R. P. Bell, 'Acid Base Catalysis', Oxford University Press, 1941.

[19] K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713.

[20] B. S. Rabinovitch and C. A. Winkler, *Canad. J. Res.*, 1942, **20**, *B*, 73.

[21] H. H. G. Jellinek and A. Garden, *J. Phys. and Colloid Chem.*, 1949, **53**, 996; H. H. G. Jellinek and J. R. Urwin, *J. Phys. Chem.*, 1953, **57**, 900.

[22] (*a*) M. I. Vinnik, I. M. Medvetskaya, L. R. Andreeva, and A. E. Tiger, *Russ. J. Phys. Chem.*, 1967, **41**, 128; (*b*) M. I. Vinnik and I. M. Medvetskaya, *Russ, J. Phys. Chem.*, 1967, **41**, 947; (*c*) M. I. Vinnik and I. M. Medvetskaya, *Russ. J. Phys. Chem.*, 1969, **43**, 345.

[23] J. A. Duffy and T. A. Leisten, *J. Chem. Soc.*, 1960, 853.

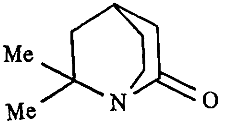
[24] V. C. Armstrong and R. B. Moodie, *J. Chem. Soc.* (*B*), 1969, 934.

E. Position of Protonation.—Several authors[8,9,25,26] have suggested that the acid-catalysed hydrolysis of amides may go *via* either of two mechanisms involving distinct intermediates and transition states, depending on whether the oxygen or nitrogen of the amide has been protonated. The following indicates some of the controversies regarding the position of protonation.

(i) *Theoretical considerations.* The usual justification for considering oxygen-protonation is that amides are mesomeric.[26] Proton addition could occur at the atom carrying the partial negative charge. Moreover, *O*-protonated amide ions are themselves mesomeric, unlike the *N*-protonated cations. Protagonists of nitrogen-protonation[27] have argued that the mesomeric stabilities would not be important enough to outweigh the inherently greater basicity of nitrogen over oxygen.

Theoretical calculations have been made[28] on the protonation in the gas phase of various carboxylic acid derivatives. The opposite site of protonation from that observed experimentally in solution was predicted for compounds containing two heteroatoms. Allowances made for stabilisation by solvation of the oxygen- but not the nitrogen-protonated forms of formamide were insufficient to reverse the order of energies of the two conjugate acids. The authors used as partial support for their prediction of nitrogen-protonation the lack of oxygen exchange[29,30] between benzamide and $H_2{}^{18}O$ in acid solution. However, Bender[29] explains that this result is not inconsistent with oxygen-protonation if in Scheme 1 $k_3 \gg k_2$.

(ii) *Chemical evidence.* Trialkylammonium salts are readily hydrolysed,[31] whereas amide hydrolysis is relatively difficult. Klages and Zange[31] considered this as evidence that the major component of the protonated amide was the *O*-protonated form, but that acid hydrolysis occurred through the *N*-protonated species. This interpretation was supported by Pracejus,[32] who made the amide (2) and found that it is rapidly hydrolysed. In (2) the lone pair of electrons on the nitrogen atom is in an orbital perpendicular to the π orbital of the $>C=O$ group,



(2)

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[25] J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2000; 2007; 2009.

[26] R. Huisgen and H. Brade, *Chem. Ber.*, 1957, **90**, 1432.

[27] J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Canad. J. Chem.*, 1960, **38**, 1518.

[28] A. C. Hopkinson, R. A. McClelland, K. Yates, and I. G. Csizimadia, *Theor. Chim. Acta*, 1969, **13**, 65.

[29] (*a*) N. L. Bender and R. D. Ginger, *J. Amer. Chem. Soc.*, 1955, **77**, 348; (*b*) M. L. Bender, Y. L. Chow, and F. Chloupek, *J. Amer. Chem. Soc.*, 1958, **80**, 5380.

[30] C. A. Bunton, T. A. Lewis, and D. R. Llewellyn, *Chem. and Ind.*, 1954, 1154.

[31] V. F. Klages and E. Zange, *Annalen*, 1957, **607**, 35.

[32] H. Pracejus, *Chem. Ber.*, 1959, **92**, 988.

thus preventing mesomerism, and it is likely that a *N*-protonated cation is formed.

(iii) *Basicities.* Huisgen and Brade[26] presented evidence pointing to the predominance of *O*-protonation. They found that *N*-substituents have less effect on the basicities of amides than on those of corresponding amines, suggesting that the basic centre of amides is further from the nitrogen atom than in amines.

However, application[27] of the Hammett equation[33] to basicities of *meta*- and *para*-substituted benzamides led to better correlation of $pK_{AH}{}^+$ with σ than with the σ^+ values required for protonation of the carbonyl oxygen of carboxyl groups,[34] suggesting, therefore, that amides protonate on nitrogen. However, the authors note that care is necessary in making this comparison, since the concept that all reactions comply with a set of unique σ or σ^+ values has been criticised.[35]

(iv) *Ultraviolet spectra.* Hantzsch[36] used the similarities in u.v. spectra of benzamide and ethylbenzamido-ether to suggest *O*-protonation. Edward *et al.*,[27] however, showed that the evidence was also compatible with *N*-protonation. The spectrum has also been interpreted in terms of two equilibria,[37] of which the first was assumed to involve *O*-protonation, and the second (occurring at low acidities) involved resonance of electronic structures. The hypsochromic shift observed for thioacetamide[38] was favoured as evidence of *N*-protonation.

(v) *Infrared and Raman spectra.* Evidence from these sources, *e.g.* shifts in frequency,[31] has generally been interpreted in terms of *N*-protonation, but Katritzky and Jones[39] state that some assumptions were not justified, and they do not consider that the evidence negates the possibility of *O*-protonation.

(vi) *Proton magnetic resonance.* The strongest support for *O*-protonation comes from ^1H n.m.r. Gillespie and Birchall[40] slowed down the rate of exchange of protons of acetamide, *NN*-dimethylacetamide, formamide, and dimethylformamide with the solvent by lowering the temperature and unambiguously assigned the spectra to the $C{=}OH^+$ group. The spectrum of pure liquid dimethylformamide[41] shows two peaks for the two methyl groups, which have different environments about the $OC{-}NMe_2$ bond as a result of its partial double bond character. These peaks remain unchanged in aqueous strong acids.[42] It is assumed then that the *O*-protonated form predominates in strong acid solution,

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[33] L. P. Hammett, 'Physical Organic Chemistry', McGraw-Hill, New York; 1940, p. 184.

[34] R. Stewart and K. Yates, *J. Amer. Chem. Soc.*, 1960, **82**, 4059.

[35] H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

[36] A. Hantzsch, *Ber.*, 1931, **64**, 667.

[37] A. R. Goldfarb, A. Mele, and N. Gutstein, *J. Amer. Chem. Soc.*, 1955, **77**, 6194.

[38] H. Hosoya, J. Tanaka, and S. Nagakura, *Bull. Chem. Soc. Japan*, 1960, **33**, 850.

[39] A. R. Katritzky and R. A. Jones, *Chem. and Ind.*, 1961, 722.

[40] R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41**, 148.

[41] W. D. Phillips, *J. Chem. Phys.*, 1955, **23**, 1363; H. S. Gutowsky and C. H. Holm, *ibid*, 1956, **25**, 1228.

[42] G. Fraenkel and C. Franconi, *J. Amer. Chem. Soc.*, 1960, **82**, 4478.

because the $NHMe_2$ group should be free to rotate. Similar results have been obtained with other amides.[43]*

(vii) *Conclusion.* It appears that the *O*-protonated form predominates but that *N*-protonation occurs to a small degree. Thus it is reasonable to postulate hydrolysis mechanisms involving a rapid protonation pre-equilibrium on either the oxygen or nitrogen atom. Acid dissociation constants in the literature are assumed to refer to the *O*-protonated conjugate acid. The *N*-protonated forms will be strong acids and will therefore exist only in small concentrations even in concentrated acid solutions.

F. Amide Acidity Function.—The original H_0 function has recently been recognised as having less applicability than was formerly supposed.[44] Yates[45] extended the idea of having a specific acidity function for a particular structural type of base to amides, by producing the H_A function, which is analogous to H_0, but applicable to the ionisation of amides by proton addition. H_A is based on a set of primary substituted benzamides, except in dilute acids where there is no substituted benzamide basic enough to be considerably protonated, so it is initially based on *p*-nitroaniline as the primary indicator. Bunnett and Olsen[46] noted this uncertainty and suggest that the whole function is too negative by *ca.* 0·3 units, and this will affect pK_{AH^+} values determined using H_A. The values have been measured in sulphuric[45a] and hydrochloric[45c] acids and the function tested[45b] for several amides other than those used originally, with generally good agreement.

Yates and Stevens[45b] stress that rate–acidity correlations of the Zucker–Hammett[47] or Bunnett *w*-function[1] types lose much significance if the correct acidity function for the particular base type being studied is not used.

G. Explanation of Rate Maximum.—Various attempts have been made to interpret the maximum and subsequent decrease in the acid hydrolysis rate profile. Benrath[48] suggested that the rate maximum occurred at the point of complete ionisation and the subsequent decrease might be due to complex salt formation. Taylor[14] thought this suggestion unlikely since the position of the maximum was independent of the amide concentration, and suggested that the mechanism might

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* Recently, however, this technique has provided the first direct proof of an equilibrium concentration of an *N*-protonated amide.

S. R. de Lockerente, O. B. Nagy, and A. Bruylants, *Org. Mag. Resonance*, 1970, **2,** 179, studied the protonation of five substituted anilides and in the case of 2,4 dinitroformanilide a new peak discovered at δ equals 8·25 was attributed to the formyl proton undergoing a diamagnetic displacement by reason of *N*-protonation, occurring because of enhanced basicity of the nitrogen atom.

[43] A. Berger, A. Loewenstein, and S. Meiboom, *J. Amer. Chem. Soc.*, 1959, **81,** 62.

[44] E. M. Arnett, *Progr. Phys. Org. Chem.*, 1963, **1,** 233.

[45] (*a*) K. Yates, J. B. Stevens, and A. R. Katritzky, *Canad. J. Chem.*, 1964, **42,** 1957; (*b*) K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43,** 529; (*c*) K. Yates and J. C. Riordan, *Canad. J. Chem.*, 1965, **43,** 2328.

[46] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem*, 1966, **44,** 899.

[47] L. Zucker and L. P. Hammett, *J. Amer. Chem. Soc.*, 1939, **61,** 2791.

[48] A. Benrath, *Z. anorg. Chem.*, 1926, **151,** 53.

change as the acid concentration increased. It was further suggested[16] that the decrease in rate was due to decreasing water activity. Ingold[2] explained that an increase in solute concentration reduces water activity, and when this effect was proportionally greater than its effect in enhancing acidity, the rate of hydrolysis fell. Edward and Meacock[25] accepted this explanation and extended it slightly to obtain an equation (1) which gave satisfactory theoretical rate–acidity profiles up to the maximum.

$$k_\psi = k\,K_{\mathrm{AH^+}}[\mathrm{H_3O^+}]/(K_{\mathrm{AH^+}} + h_0) \tag{1}$$

They regarded the hydrolysis of amides as a bimolecular process with the equation for the rate of the limiting stage including the ionised form of the reactant and water. They also suggested that the intermediate could be either the *O*- or *N*-protonated form, both forms leading to kinetically indistinguishable results. Vinnik *et al.*[22a] used equation (2) for that portion of the profile up to a minimum in the hydrolysis of *o*-nitroacetanilide,

$$k_{\mathrm{eff}} = kC_{\mathrm{H_3O^+}}/(1 + h_0/K_{\mathrm{B}}) \tag{2}$$

where k_{eff} is the effective rate constant, K_{B} is the acid dissociation constant, and k is the rate constant corrected for the degree of protonation of the substrate; this reduces to equation (1) in terms of the symbols used by Edward and Meacock. A convenient method for plotting the data to test this equation by rearranging to equation (3) was noted,[22a]

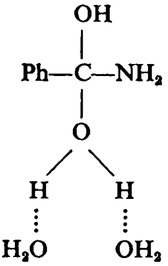
$$C_{\mathrm{H_3O^+}}/k_{\mathrm{eff}} = 1/k + h_0/kK_{\mathrm{B}} \tag{3}$$

and this gave a good linear plot up to the local minimum at *ca.* 75 % sulphuric acid More recently Vinnik and Medvetskaya[22c] used equation (2) in a slightly modified form (equation 4),

$$k_{\mathrm{eff}} = kC_{\mathrm{H_3O^+}}\,f_{\mathrm{A}}{}^{1-\beta} f_{\mathrm{H_3O^+}}{}^{1-\alpha}/(1 + h_0/K_{\mathrm{B}}) \tag{4}$$

where α and β are parameters independent of the solution. They state that for *o*-nitroacetanilide the rate constant is proportional to the hydronium ion concentration, therefore the product $f_{\mathrm{A}}{}^{1-\beta} f_{\mathrm{H_3O^+}}{}^{1-\alpha}$ is independent of water in solution, and the parameters α and β are unity. According to the mechanism proposed, equation (4) operated over the whole sulphuric acid concentration range and the activity of the activated complex was expressed in terms of the product of the ionised form of the anilide and sulphuric acid, $a^* = a_{\mathrm{AH^+}} \,.\, a_{\mathrm{H_2SO_4}}$. This relationship could not be tested because of the lack of physical data for 70—100 % w/w sulphuric acid.

The Zucker–Hammett hypothesis[47] breaks down in even moderately concentrated acids when applied to amides. In 1961 Bunnett[1] presented the Hydration Parameter Treatment, which attempted to overcome the problem of disentangling the roles of proton and water molecule. He plotted ($\log k_\psi - \log \alpha$) *vs.* $\log a_{\mathrm{H_2O}}$, where α (the fraction of protonated substrate) equals $h_0/(h_0 + K_{\mathrm{AH^+}})$, and obtained slopes ($w$) which he classified according to mechanism. Yates and Stevens[45b] criticised Bunnett's relationship, saying that w parameters for reactions of substrates which do not follow H_0 as bases cannot be simply related to hydration changes in the rate determining step, and devised a modification using H_A to calculate α. Without relying on an acidity function, α can be obtained spectrophotometrically and a value of *ca.* 3 was obtained (over a fairly small acidity range) for the number of water molecules in the transition state (3) during hydrolysis of benzamide.[45b,49]



(3)

The non-linearity of *w* treatment plots is thought to be due to a decrease in the number of water molecules in the transition state with increasing acid concentration.[17] Bunnett[1] noted that if a *w* plot showed persistent curvature then a plot of $\log k_\psi - \log [\mathrm{HX}]/(h_0 + K_{\mathrm{AH}^+})$ *vs.* $\log a_{\mathrm{H_2O}}$ (for a moderately basic substrate) might be linear with a slope of w^*, but this modification did not give linear plots for benzamide, *N*-methylbenzamide, or *NN*-dimethylbenzamide.[17]

The linear free energy relationship (l.f.e.r.) proposed by Bunnett and Olsen[50] is the most general treatment for reaction rates (equation 5)

$$\log k_\psi + H_0 = \phi\,(H_0 + \log\,[\mathrm{H}^+]) + \log k_2^0 \qquad (5)$$

k_2^0 is the second-order rate constant at infinite dilution. The slope parameter ϕ characterises the response of the reaction rate to changing acid conditions and its values are approximately the same for a series of compounds, and may be related to changes in hydration parameters. Bunton *et al.*[17] applied the l.f.e.r. to their data without obtaining linear plots. Bunnett and Olsen[50] discussed several reasons for non-linearity, including a suggestion that the reaction may be occurring *via* two pathways simultaneously.

Because all these theories, involving only a one-term mechanistic pathway, seemed to be inadequate for amides, Bunton *et al.*[17] formulated a new reaction scheme involving two transition states (4) and (5), arising from two distinct mechanistic paths involving protonation on both oxygen and nitrogen.

Two assumptions were made, *viz.* the activity coefficients of the free amides.[51] and activity coefficient ratios of ions of like charge[1] are essentially independent of the medium. The Brønsted–Bjerrum rate equation then gives equation (6),

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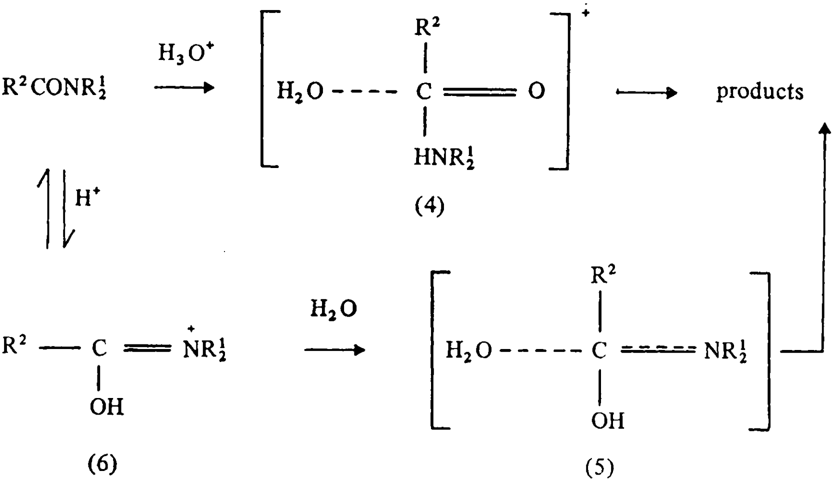
[49] R. B. Moodie, P. D. Wale, and T. J. Whaite, *J. Chem. Soc.*, 1963, 4273.

[50] J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1899; 1917.

[51] F. A. Long and W. F. McDevit, *Chem. Rev.*, 1952, **51**, 119; N. C. Deno and C. Perizzolo, *J. Amer. Chem. Soc.*, 1957, **79**, 1345.



Scheme 3

$$k_\psi C_A = (k_1 C_A C_{H^+} + k_2 C_6)\, a_w \tag{6}$$

where C_A is the stoicheiometric concentration of amide. Substituting for α (the amount of protonated amide), equation (6) gives equation (7).

$$k_\psi / \alpha a_w = k_1 C_{H^+}(1-\alpha)/\alpha + k_2 \tag{7}$$

This treatment correlated their data well.[17] Criticism of this two-term treatment came from Armstrong, Farlow, and Moodie,[52] who did not dispute the possibility of both *O*- and *N*-protonation but believed that the assumption about the activity coefficient (*i.e.* cancellation of f_{H^+} with $f^{\ddagger}$) was unrealistic. Instead they treated their results for butyramide hydrolysis in sulphuric and perchloric acids by plotting log k_P *vs.* log a_w. (k_P is the specific first order rate constant for hydrolysis of the protonated substrate.) The plots showed curvature which they said was typical of a bimolecular mechanism. The hydrolysis data of carbamates has recently been treated similarly.[24]

2 Basic Hydrolysis

The kinetics of basic amide hydrolysis are relatively uncomplicated. In 1899 Reid[6] showed that the reaction was second order, and most recent investigations have included substitutent, catalytic, and isotope effects.

A. Mechanism.—The mechanism generally accepted[5] for basic amide hydrolysis involves a reaction scheme (Scheme 4) in which an intermediate (7) partitions to give products or regenerate reactants, and, provided the oxygen atoms in (7) become equivalent by rapid proton transfers, this reverse step leads to oxygen exchange.

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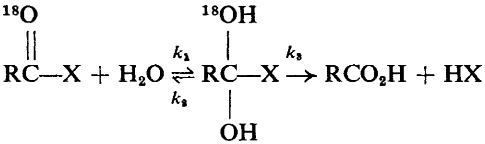
[52] V. C. Armstrong, D. W. Farlow, and R. B. Moodie, *J. Chem. Soc.* (*B*), 1968, 1099.



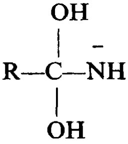
$$\mathrm{R}\overset{\overset{18}{}\mathrm{O}\,\|}{\mathrm{C}}\mathrm{—X} + \mathrm{H_2O} \underset{k_2}{\overset{k_1}{\rightleftharpoons}} \mathrm{R}\underset{\mathrm{OH}}{\overset{^{18}\mathrm{OH}}{\mathrm{C}}}\mathrm{—X} \xrightarrow{k_3} \mathrm{RCO_2H} + \mathrm{HX}$$

(7)

Scheme 4

The rate constants for exchange and hydrolysis are then related by $k_e/k_h = k_2/2k_3$. In the basic hydrolysis of primary and secondary amides, where $k_e/k_h > 1$, the rate of hydrolysis should therefore be considerably less than that of formation of the intermediate (7).[29a,30,53]

There is evidence that the equilibration of the oxygen atoms in (7) is not always faster than its breakdown,[54] and it was suggested that the relatively fast oxygen exchange during the alkaline hydrolysis of amides arose because the negative charge could be located on the nitrogen atom of the intermediate, as in (8).[30,53]



$$\mathrm{R—}\underset{\mathrm{OH}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{—\overset{-}{N}H}$$

(8)

There is direct evidence for the formation of tetrahedral intermediates in the alkaline hydrolysis of anilides.[55-57] The amide residue should be a poorer leaving group than either hydroxy- or alkoxy-groups, and the ready return of (7) to reactants is expected. The alkaline hydrolysis of *NN*-dimethylbenzamide, where structures like (8) cannot be formed, was not accompanied by oxygen exchange.[58]

Bender and Ginger[29a] found that k_e/k_h for benzamide increased with increasing temperature, and they calculated the activation parameters for the step involving the intermediate and for the difference of two subsequent steps in which the intermediate is partitioned. The ratio decreased with increasing hydroxyl ion concentration and the values were greater in deuterium than in protium oxide. The deuterium solvent isotope effect[58] upon k_e/k_h suggests either that interoxygen proton transfers are fast or that k_2 and k_3 both depend upon rate-limiting proton transfers between oxygen or nitrogen atoms.

Absence of oxygen exchange during hydrolysis of carboxyl derivatives does

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[53] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4183; 4189.

[54] (*a*) C. A. Bunton and D. N. Spatcher, *J. Chem. Soc.*, 1956, 1079; (*b*) M. L. Bender, R. D. Ginger, and J. P. Unik, *J. Amer. Chem. Soc.*, 1958, **80**, 1044.

[55] S. S. Biechler and R. W. Taft, *J. Amer. Chem. Soc.*, 1957, **79**, 4927.

[56] P. M. Mader, *J. Amer. Chem. Soc.*, 1965, **87**, 3191.

[57] R. L. Schowen and G. W. Zuorick, *J. Amer. Chem. Soc.*, 1966, **88**, 1223; R. L. Schowen, H. Jayaraman, L. Kershner, and G. W. Zuorick, *ibid.*, 4008.

[58] C. A. Bunton, B. Nyak, and C. J. O'Connor, *J. Org. Chem.*, 1968, **33**, 572.

not distinguish between unfavourable partitioning of (7) or slow isotopic scrambling of its oxygen atoms. There are many anilide hydrolyses for which proton transfers to and from the leaving group are kinetically important and there is strong evidence that slow proton transfers are involved in the decomposition of tetrahedral intermediates.[53,57] Bender and Thomas[53] explained thus the structural effects upon k_e/k_h for anilide hydrolyses, but Shain and Kirsch[59] have suggested that this earlier experimental work[53] was in error.

The solvent isotope effect, $k_{OH^-}/k_{OD^-} > 1$, for the basic hydrolysis of benzamide[58] is similar to that found for acetamide,[15] but for *NN*-dimethylbenzamide[58] the ratio $k_{OH^-}/k_{OD^-} < 1$. This difference was considered to arise because of the solvent isotope effect upon partitioning of (7).

B. Substituent Effects.—Reid[6] investigated the effect of nuclear substituents on the rates of basic hydrolysis of benzamide and observed that *meta*- and *para*-substituents such as —NH_2, —OMe, and —Me retarded the rate, whilst —I, —Br, and —NO_2 accelerated it. All *ortho*- substituents retarded it.

Electron-attracting groups lowered the activation energy of substituted-benzamide hydrolyses, while electron-repelling groups raised it.[8]

The structures and reactivities of an extensive range of primary amides, in which substituent changes were confined to alkyl groups, were correlated well by a Taft-type steric energy equation. Bolton[11b] re-examined these hydrolyses and found the data to be better correlated by an equation including polar, steric, and conjugative influences of the substituents.

Anilides are generally stable towards basic hydrolysis, but compounds containing strongly electron-attracting groups in the acyclic part of the molecule are hydrolysed fairly rapidly. Moreover, the rate may not be proportional to the hydroxide ion concentration. Orders either greater or less than unity have been observed,[5,29a,53,54a,55–57] when either the amide itself was sufficiently acidic to be partially ionised, *e.g.* trifluoroacetanilide,[55,56] or when (7) could be further ionised.

C. Catalysis.—Eriksson and Holst[60] showed that in the hydrolysis of trifluoro- and trichloro-acetanilide, breakdown of (7) to products was catalysed not only by a second hydroxyl ion but also by species able to donate or accept a proton simultaneously, *e.g.* by HCO_3^-, $H_2PO_4^-$, and HPO_4^{2-} ions. Cationic acids of the amine type, *e.g.* monoethanolamine, which cannot both donate and accept a proton in a concerted mechanism and are therefore supposed to act only as general acids, can be very effective catalysts.[61] The reactions were characterised as nucleophilic or general basic attack of the amine and were first-order both in unionised substrate and amine base. Whereas bulky groups completely inhibited the activity of the cation as a general acid, the same groups seemed to assist its

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[59] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, 1968, **90**, 5848.
[60] S. O. Eriksson and C. Holst, *Acta Chem. Scand.*, 1966, **20**, 1892.
[61] S. O. Eriksson and L. Bratt, *Acta Chem. Scand.*, 1967, **21**, 1812.

action as a basic catalyst. Thus, *e.g.* triethanolamine was an unexpectedly effective catalyst.

The hydrazinium and hydroxylammonium ions were very effective in catalysing the breakdown of the tetrahedral intermediate formed between trifluoroacetanilide and hydroxyl ions,[62] and the constants for these catalyses gave, together with the constants for acids of the ammonium cation type,[61] a Brønsted plot with slope 0·9. The reaction rates with these two catalysts were calculated with an equation containing terms first and second order in base.

3 Conclusion

The kinetics of acidic amide hydrolysis are subject to uncertainty. It may be argued that there is no reason why there should be any simple relation between the various parameters. The kinetics of basic amide hydrolysis are, however, clearly understood.

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[62] S. O. Eriksson, *Acta Chem. Scand.*, 1968, **22**, 892.