598. *The Hydrolysis of Simple Amides catalysed by Carboxylic Acids.*

By K. G. Wyness.

The hydrolysis of amides in nearly neutral, buffered solutions of acetic acid at 220° shows kinetic dependence upon the concentration of carboxylic acid molecules. Consideration of structural, solvent, and deuterium-isotope effects suggests that the catalysis involves anhydride formation from the acetate ion and the amide conjugate acid, with subsequent rapid hydrolysis of the anhydride.

The possibility of catalysis in substitutions at a carbonyl-carbon atom by species other than the hydrogen and hydroxyl ion has frequently been discussed.[1–5] Recent work has focused attention on general base-catalysed hydrolysis of phenyl esters [3] and carboxylic anhydrides.[4] The only example of apparent general acid-catalysis in the hydrolysis of amides has recently been reported by Bender,[5] who found that the hydrolysis of phthalamic acid was subject to intramolecular catalysis by the un-ionised carboxyl group.

Although it has usually been assumed that with intermolecular catalysis amide hydrolysis is specifically hydrogen- and hydroxide-ion-catalysed, work reported here on the hydrolysis of simple *N*-substituted amides at 220° in buffered solutions of acetic acid shows that part of the hydrolysis is a reaction of the kinetic form $v = k[\text{HA}][\text{amide}]$, indicating an apparent catalysis by the un-ionised carboxyl group.

Table 1. *Hydrolysis of* N-n-*butylacetamide at* 220° *in buffered aqueous solutions.*

Concentrations are uncorrected for the expansion of the solvent.

Ionic strength	AcOH (M)	NaOAc (M)	NaCl (M)	Acid/ Buffer	pH *	10^5k (sec.$^{-1}$)	10^5k_{HA}
0·016	0·0128	0·0025	0·0135	5·15	5·0	1·11	
,,	0·0274	0·0053	0·0107	,,	,,	1·30	
,,	0·0408	0·0079	0·0081	,,	,,	1·46	
,,	0·0516	0·0100	0·0060	,,	,,	1·60	
,,	0·0633	0·0123	0·0037	,,	,,	1·74	
,,	0·0799	0·0155	0·0	,,	,,	1·94	12·3
0·062	0·0146	0·0042	0·0578	3·45	5·2	1·19	
,,	0·0350	0·0101	0·0519	,,	,,	1·50	
,,	0·0490	0·0142	0·0478	,,	,,	1·60	
,,	0·0639	0·0185	0·0435	,,	,,	1·80	
,,	0·0770	0·0223	0·0397	,,	,,	2·02	
,,	0·0808	0·0234	0·0386	,,	,,	2·07	
,,	0·0993	0·0288	0·0332	,,	,,	2·23	12·3
0·150	0·0271	0·0262	0·1238	1·04	5·7	1·25	
,,	0·0301	0·0290	0·1210	,,	,,	1·46	
,,	0·0558	0·0538	0·0962	,,	,,	1·65	
,,	0·0714	0·0690	0·0810	,,	,,	2·06	
,,	0·1095	0·1059	0·0441	,,	,,	2·47	
,,	0·1113	0·1075	0·0425	,,	,,	2·11	
,,	0·1357	0·1310	0·0190	,,	,,	2·53	
,,	0·1360	0·1315	0·0185	,,	,,	2·65	12·3

* Values calculated for a temperature of 218° by using K_a (acetic acid) $= 1{\cdot}72 \times 10^{-6}$, determined by Noyes and Cooper (*J. Amer. Chem. Soc.*, 1908, **30**, 193).

Table 1 shows first-order rate constants obtained for the hydrolysis of *N*-*n*-butylacetamide in acetic acid–sodium acetate buffer solutions of constant pH and ionic strength.

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[1] Dawson and Lowson, *J.*, 1927, 2444; 1929, 393; Dawson, Pycock, and Spivey, *J.*, 1933, 291.

[2] Rolfe and Hinshelwood, *Trans. Faraday Soc.*, 1934, **30**, 935; Hinshelwood and Legard, *J.*, 1935, 587.

[3] Bender and Turnquest, *J. Amer. Chem. Soc.*, 1957, **79**, 1652, 1656.

[4] Gold and Jefferson, *J.*, 1953, 1409.

[5] Bender, *J. Amer. Chem. Soc.*, 1957, **79**, 1258.

In an aqueous solution of an amide containing an acid HA, buffered by its anion A^-, the observed first-order rate constant of hydrolysis is given by the general expression: [6]

$$k = k_0 + k_{H^+}[H^+] + k_{OH^-}[OH^-] + k_{HA}[HA] + k_{A^-}[A^-]$$

At constant pH this equation reduces to:

$$\begin{aligned} k &= \text{Constant} + k_{HA}[HA] + k_{A^-}[A^-] \\ &= \text{Constant} + [HA]\{k_{HA} + k_{A^-}[A^-]/[HA]\} \end{aligned}$$

so that a plot of k against the acid concentration [HA] should be linear, of slope $k_{HA} + k_{A^-}[A^-]/[HA]$. The last column of Table 1 shows values of this slope for different values of the buffer ratio $[A^-]/[HA]$. The constancy of these figures indicates that k_{A^-} is sensibly zero and that the observed catalysis is due only to the un-ionised acid HA, or to its ions acting together.

At least three possible mechanisms fitting this kinetic form can be written for the catalysis. The first is represented by the classic mechanism of general acid-catalysis, involving rate-determining proton-transfer from the carboxylic acid to the amide without the intervention of solvent.[7] The resulting amide conjugate acid is then rapidly hydrolysed by a water molecule.

Mechanism I:

$$\begin{gathered} CH_3{\cdot}CO_2H + R'{\cdot}CO{\cdot}NHR \xrightarrow{k_1} R'{\cdot}CO{\cdot}NH_2R^+ + CH_3{\cdot}CO_2^- \text{ (slow)} \\ R'{\cdot}CO{\cdot}NH_2R^+ + H_2O \longrightarrow \text{Products (fast)} \\ \text{Rate} = k_1[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR] \end{gathered}$$

This process is most improbable on grounds of general chemical experience since it involves slow proton-transfer from an oxygen to a nitrogen atom, and fast fission of a strong C–N bond. The lack of marked solvent effect (Table 2) shows that the rate-determining step is not one in which ions are produced, while structural changes in R and R′ (Table 3) * show that increased basicity at the amide nitrogen atom does not accelerate the reaction, as the mechanism would require.

TABLE 2. *Effect of solvent polarity and ionic strength on the catalytic constant.*

Solvent	Ionic strength	$10^5 k_{HA}$
H_2O–dioxan (67% H_2O)	0·024	6·80
H_2O	0·016	12·3
H_2O	0·062	12·3
H_2O	0·150	12·3

TABLE 3. *The effect of structure. Relative catalytic constants in* 67% *aqueous dioxan.*

$CH_3{\cdot}CO{\cdot}NHR$	R =	Ph	H	Me	Et	Bu^n	Pr^i	Bu^t
	k_{HA} =	1·7	4·2	1·2	1	0·85	0·47	0·51
$R'{\cdot}CO{\cdot}NHBu^n$	R′ =		H	Me	Et	Pr^i	Bu^t	
	k_{HA} =		4·0	0·85	0·62	0·24	0·066	

The second mechanism is of the type suggested by Bender [5] for the hydrolysis of phthalamic acid. This is essentially a proton-catalysed nucleophilic carbonyl substitution, rather than a true general acid-catalysis, since the acetate ion acts as a nucleophilic reagent rather than as a base. The products of the rate-determining step would be the anhydride and the amine, with subsequent rapid hydrolysis of the anhydride.

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* The comparative rates quoted in Table 3 were measured in aqueous dioxan because some of the amides used were insoluble in water. The actual rate constants are tabulated in the Experimental section.

[6] Bell, " Acid-base Catalysis," Oxford, 1941, p. 60.

[7] Ref. 6, p. 124.

Mechanism II:

$$CH_3{\cdot}CO_2H \underset{K_{HOAc}}{\rightleftharpoons} CH_3{\cdot}CO_2^- + H^+$$

$$H^+ + R'{\cdot}CO{\cdot}NHR \rightleftharpoons R'{\cdot}CO{\cdot}NH_2R^+ \text{ (pre-equilibrium)}$$

$$CH_3{\cdot}CO_2^- + R'{\cdot}CO{\cdot}NH_2R^+ \xrightarrow[k_2]{} CH_3{\cdot}CO{\cdot}O{\cdot}OC{\cdot}R' + NH_2R \text{ (slow)}$$

$$H_2O \Big\downarrow \text{(fast)}$$

$$CH_3{\cdot}CO_2H + R'{\cdot}CO_2H$$

$$\text{Rate} = k_2 \,.\, (K_{HOAc}/K_{SH^+})[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR]$$

where K_{SH^+} is the dissociation constant of the amide conjugate acid.

The third possible mechanism involves hydrogen-bonded complex-formation between the amide and the carboxylic acid group, in equilibrium with the uncomplexed molecules. Such complexes may be more easily hydrolysed than the amide itself, by a mechanism similar to that suggested for esterification,[8] where, under certain conditions, catalysis by carboxyl groups is indicated.[2]

Mechanism III:

$$CH_3{\cdot}CO_2H + R'{\cdot}CO{\cdot}NHR \underset{K_{H\text{-bond}}}{\rightleftharpoons} CH_3{\cdot}CO_2H{-}R'{\cdot}CO{\cdot}NHR \text{ (pre-equilibrium)}$$

$$CH_3{\cdot}CO_2H{-}R'{\cdot}CO{\cdot}NHR + H_2O \xrightarrow[k_3]{} \text{Products (slow)}$$

$$\text{Rate} = k_3 \,.\, K_{H\text{-bond}}[CH_3{\cdot}CO_2H][R'{\cdot}CO{\cdot}NHR]$$

Both mechanisms II and III have ambiguous polar requirements, owing to their two-stage nature. Both are therefore consistent with the observed insensitivity of the reaction to changes in R (Table 3). The effect of successive α-methyl substitution in R′ is also that expected for bimolecular attack at the carbonyl-carbon atom, showing marked steric hindrance with increasing bulk in this substituent. A more discriminating test of mechanism, however, is provided by the effect of deuterium substitution.

In mechanism II the ratio of rates in H_2O and D_2O is given by

$$(k_H/k_D)_{HOAc} = (k_2)_H/(k_2)_D \,.\, K_{HOAc}/K_{DOAc} \,.\, K_{SD^+}/K_{SH^+}$$

The constant k_2, for nucleophilic attack by acetate ion on the amide conjugate acid, is expected to have a negligible isotope effect. K_{HOAc}/K_{DOAc} has the value 3·3 at 25°.[9] K_{SD^+}/K_{SH^+} for *N*-*n*-butylacetamide can be obtained by interpolation on the curve obtained by Rule and LaMer [9] relating this ratio to the dissociation constant of the proto-acid. For *N*-*n*-butylacetamide the latter has the value $pK_{SH^+} = 0{\cdot}15$,[10] and $K_{SD^+}/K_{SH^+} = 0{\cdot}55$. At 25° therefore, mechanism II affords a ratio $(k_H/k_D)_{HOAc} = 3{\cdot}3 \times 0{\cdot}55 = 1{\cdot}8$. If we can assume that an increase in temperature will not greatly affect the relative magnitudes of the dissociation constant ratios then the final ratio of approximately 1·8 will hold also at 220°.

The rate-constant ratio for mechanism III is given by

$$(k_H/k_D)_{HOAc} = (k_3)_H/(k_3)_D{\cdot}K_{H\text{-bond}}/K_{D\text{-bond}}$$

Information on the relative strengths of hydrogen and deuterium bonds is scanty, but it has been suggested [11] that the deuterium bond is slightly the more stable, so that $K_{H\text{-bond}}/K_{D\text{-bond}} < 1$. The change in k_3 on deuterium substitution is likely to be due almost entirely to the lower basicity of D_2O than of H_2O. In the hydrolysis of acetamide in concentrated acid, where it is assumed that most of the substrate is in the

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[8] Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 701.

[9] Rule and LaMer, *J. Amer. Chem. Soc.*, 1938, **60**, 1981.

[10] Goldfarb, Mele, and Gutstein, *ibid.*, 1955, **77**, 6194.

[11] Hawthorne, *ibid.*, 1954, **76**, 6358; Herman and Hofstadter, *J. Chem. Phys.*, 1938, **6**, 534.

conjugate acid form,[12] the rate ratio should be a reliable measure of the nucleophilic power of D_2O relative to H_2O. The published[13] ratio, for 4N-acid at 25°, is 1·16. Since at higher temperatures the isotope effect becomes smaller, the final ratio $(k_H/k_D)_{HOAc}$ cannot be far from unity at 220°.

It is noted, for completeness, that the reaction by mechanism I is also expected to suffer a decrease in rate on substitution of solvent D_2O for H_2O. If we can assume that the difference in zero-point energy between the transition states for proton- and deuteron-transfer is unlikely to be large enough to affect appreciably the ratio of the rates in D_2O and H_2O, then we expect a value for $(k_H/k_D)_{HOAc}$ close to the theoretical maximum. This can be calculated from experimentally determined values for O–H(D) bond-stretching frequencies in acetic and deuteroacetic acid,[14] and a value $(k_H/k_D)_{HOAc} = 3{\cdot}1$ results for a temperature of 220°.

Table 4 shows results obtained from a series of runs in D_2O. The value of k_{DA} obtained yields a ratio $(k_H/k_D)_{HOAc} = 2{\cdot}0$.

TABLE 4. *Hydrolysis of* N-n-*butylacetamide at* 220° *in* D_2O, *catalysed by deuteroacetic acid.*

Ionic strength	AcOD (M)	AcONa (M)	NaCl (M)	Acid/ Buffer	10^5k (sec.$^{-1}$)	10^5k_{DA}	$(k_H/k_D)_{HA}$
0·0186	0·0218	0·0055	0·0131	4·0	0·69		
,,	,,	,,	,,	,,	0·72		
,,	0·0366	0·0092	0·0094	,,	0·86		
,,	0·0574	0·0144	0·0042	,,	1·01		
,,	0·0743	0·0186	0·0	,,	1·07		
0·019	0·0911	0·0194	,,	4·7	1·13		
0·030	0·1139	0·0296	,,	,,	1·27	6·12	2·0

The isotope effect therefore supports mechanism II. Structural and solvent effects are consistent with this reaction path, which is the same as that suggested by Bender[5] for the carboxylic acid-catalysed hydrolysis of phthalamic acid. Although this author has concluded that such an interaction between the carboxyl and the amide group occurs only intramolecularly, the present observations suggest that this is not necessarily the case.

EXPERIMENTAL

Materials.—The amides listed below were prepared by treating the corresponding amine with the carboxylic acid, anhydride, or chloride, and were purified by distillation at reduced pressure. *N*-Ethyl-, b. p. 140—141°/91 mm., *N*-*n*-propyl-, b. p. 112°/14 mm., *N*-*n*-butyl-, b. p. 121—122°/13 mm., and *N*-*iso*propyl-acetamide, b. p. 89—90°/9 mm.; *N*-*n*-butyl-propionamide, b. p. 122°/11 mm., -*iso*butyramide, b. p. 124—126°/12 mm., and -αα-dimethylpropionamide, b. p. 114°/12 mm.; *N*-*tert.*-butylacetamide was recrystallised from hexane and had m. p. 99°. The following amides were recrystallised from commercial products: acetamide, m. p. 81°; acetanilide, m. p. 115°; benzamide, m. p. 129°. " AnalaR " acetic acid and anhydrous sodium acetate were used without further purification. Dioxan was purified by distilling it from stannous chloride to remove peroxides, refluxing it over sodium for 12 hr, and redistilling it. The fraction boiling at 100°/760 mm. was collected.

Method.—Buffered solutions were prepared by adding a known quantity of standard sodium hydroxide solution to a solution of acetic acid. Successive dilution with a sodium chloride solution of concentration equal to that of the acetate provided a series of solutions of constant pH and ionic strength, differing only in concentration of acid and buffer. For runs in aqueous dioxan and in deuterium oxide, solid anhydrous sodium acetate was used to buffer the acid. Stock solutions prepared in this way were used to make up final mixtures by addition to the amide (usually about 0·3M), which was weighed accurately into volumetric flasks. Solutions

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[12] Ref. 6, p. 148.

[13] Reitz, *Z. phys. Chem.*, 1939, *A*, **183**, 371.

[14] Wilmshurst, *J. Chem. Phys.*, 1956, **25**, 1171.

in deuterium oxide were prepared in a dry-box. The concentrations of the buffer constituents in the final solutions were determined by titration.

1 ml. quantities of the amide solution were pipetted into small ampoules constructed from resistance glass tubing of 4 mm. bore. These were sealed under nitrogen and ten or twelve were immersed together in an electrically heated silicone-oil bath controlled by a mercury-in-glass regulator and electronic relay within ±0·1°. Tubes were taken out at intervals and quenched in cold water. The extent of hydrolysis was measured by titrating the amine produced, in 68 : 32 w/w phenol–methanol, with methanolic 0·05N-hydrochloric acid, to thymol-blue. The total titre was the sum of that due to amine and that corresponding to the sodium acetate used as buffer. The latter was determined separately from the initial reaction mixture. First-order rate constants were determined graphically, the final extent of reaction (about 10%) being small enough for the reverse amidation to remain negligible.

The following are details of a typical run. 0·345N-*N*-*n*-Butylacetamide was hydrolysed at 220° in aqueous solution 0·0408N in acetic acid and 0·0079N in sodium acetate, the total ionic strength being made up to 0·016 with sodium chloride. 5 ml. samples were titrated, after reaction, in phenol–methanol with 0·0474N-hydrochloric acid. The control titre corresponding to the constant sodium acetate concentration was 0·80 ml. The rate constants are in this case integrated values (see Table).

Time (min.)	0	10	20	30	40	50	60	70	80	90	100	110	120
Titre, less control (extent of reaction expressed as ml. of 0·0474N-acid)	0	0·30	0·62	0·98	1·30	1·60	1·86	2·16	2·53	2·78	3·04	3·32	3·64
$10^5 k$ (sec.$^{-1}$)	—	1·38	1·43	1·52	1·48	1·50	1·45	1·45	1·48	1·47	1·43	1·45	1·47

For comparison of k_{HA} in different amides, 67 : 33 v/v water–dioxan was used as solvent owing to the insolubility of some of the amides in pure water. The catalytic constants shown below were calculated in each case from the slope of the graph of total rate constant k against acetic acid concentration, which varied from 0·03N to 0·16N. The ratio of acid to buffer was 6·8, and the ionic strength 0·024, throughout. Not less than 4, and usually 5 or 6, points were used to define the straight line.

Amide	$BzNH_2$	$AcNH_2$	AcNHMe	AcNHEt	$AcNHPr^n$
$10^5 k_{HA}$	3·51	34·1	9·36	8·07	6·93
Amide	$AcNHPr^i$	$AcNHBu^t$	AcNHPh	$AcNEt_2$	$H{\cdot}CO{\cdot}NHBu^n$
$10^5 k_{HA}$	3·81	4·08	13·6	6·15	32·0
Amide	$AcNHBu^n$	$Et{\cdot}CO{\cdot}NHBu^n$	$Pr^i{\cdot}CO{\cdot}NHBu^n$	$Bu^t{\cdot}CO{\cdot}NHBu^n$	
$10^5 k_{HA}$	6·80	4·97	1·90	0·536	

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RESEARCH DEPT., BRITISH NYLON SPINNERS LTD.,
PONTYPOOL, MON.

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