153. *Constitutional Effects on the Hydrolysis of Amides in Concentrated Acid Solutions.*

By J. A. Leisten.

The rates of hydrolysis of 13 amides in 5·9, 7·2, and 8·5M-perchloric acid have been measured at 95°. The *A*2 mechanism is confirmed both by the observed steric effects, and by the polar effects which are treated quantitatively. The variation in rate with acid concentration is similar for the amides studied, but is not even approximately predicted by the Hammett–Zucker hypothesis.

Several features of the hydrolysis of amides in aqueous acids suggest the *A*2 mechanism:[1]

$$R{\cdot}CO{\cdot}NH_2 + H_3O^+ \overset{\text{Fast}}{\rightleftharpoons} R{\cdot}CO{\cdot}NH_3^+ + H_2O \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (1)$$

$$R{\cdot}CO{\cdot}NH_3^+ + H_2O \xrightarrow{\text{Slow}} R{\cdot}CO_2H_2^+ + NH_3 \quad . \; . \; . \; . \; . \; . \; . \; . \; . \quad (2)$$

(The ammonia molecule then rapidly gains, and the carboxylic acidium ion rapidly loses, a proton. R may be an alkyl or an aryl group.) These features include constitutional effects in the amide molecule. Reid's experiments with substituted benzamides[2] show that the rate of hydrolysis in dilute acid, where equilibrium (1) lies to the left-hand side, is practically independent of polar influences in the molecule. It is clear from electronic principles that any change in the polar character of an amide would have opposite effects in steps (1) and (2) upon the overall rate of the reaction. Hence, in the absence of further knowledge Reid's results support, or at least accord with, the *A*2 mechanism. His results, however, require that the polar effects on steps (1) and (2) should be not only opposite, but nearly equal as well; and this leads to a more quantitative test of the mechanism with which the present work is concerned.

In principle, polar effects on step (2) can be separately examined by determining the rate of hydrolysis of differently substituted amides in a strongly acid solution, in which equilibrium (1) lies far to the right-hand side. Table 1 records the results of such measurements.

Table 1. *First-order rate constants for the hydrolysis of amides in aqueous perchloric acid solutions at* 95°.

Molarity of acid:	5·86	7·19	8·54
Acidity function, H_0:	−2·74	−3·75	−4·72
Amide *	*k* (hr.$^{-1}$)	*k* (hr.$^{-1}$)	*k* (hr.$^{-1}$)
p-Nitrobenzamide	—	1·40	0·53
m-Nitrobenzamide	1·92	1·10	0·44
m-Bromobenzamide	—	0·57	0·172
p-Bromobenzamide	—	0·39	—
Benzamide	0·64	0·228	0·073
m-Toluamide	—	0·188	0·057
p-Toluamide	0·37	0·129	—
p-tert.-Butylbenzamide	0·33	—	—
Anisamide	0·212	0·072	0·026
o-Bromobenzamide	—	0·099	—
o-Nitrobenzamide	—	0·040	—
o-Toluamide	—	0·027	—
Acetamide	2·27	0·88	0·332

* The amide concentration was 0·17M in each experiment.

The results show that in strongly acid conditions polar effects are large, and in the

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[1] (*a*) Ingold, " Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 785; (*b*) Bender, Ginger, and Kemp, *J. Amer. Chem. Soc.*, 1954, **76**, 3350; 1955, **77**, 348; (*c*) Edward and Meacock, *J.*, 1957, 2000.

[2] Reid, *Amer. Chem. J.*, 1899, **21**, 284; 1900, **24**, 397.

direction to be expected if they were exerted only on the second step of the $A2$ mechanism: electron-attracting substituents accelerate the hydrolysis and electron-donating substituents retard it. In order to derive more quantitative conclusions we must consider the hydrolysis of *meta*- and *para*-benzamides in the dilute acid region where equilibrium (1) lies to the left. Let k_{ov} be the overall, *i.e.*, the observed, second-order rate constant, K_1 the equilibrium constant of the first step, and k_2 the first-order rate constant of the second step: the water concentration is not included in the kinetic equations since it is effectively constant in each experiment. The observed rate of the reaction $= k_{ov}\,[\mathrm{R{\cdot}CO{\cdot}NH_2}][\mathrm{H_3O^+}]$. If we assume the $A2$ mechanism this rate also $= k_2\,[\mathrm{R{\cdot}CO{\cdot}NH_3^+}] = K_1k_2\,[\mathrm{R{\cdot}CO{\cdot}NH_2}][\mathrm{H_3O^+}]$.

Therefore

$$k_{ov} = K_1k_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (3)$$

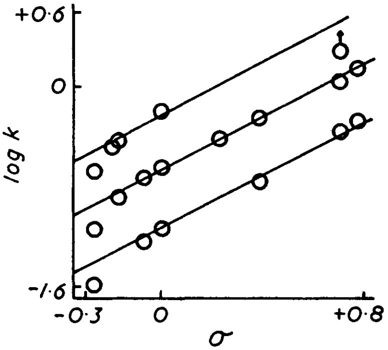
The constants for benzamide itself being denoted by the suffix 0, it follows from (3) that

$$\left(\frac{k}{k_0}\right)_{ov} = \left(\frac{K}{K_0}\right)_1\left(\frac{k}{k_0}\right)_2$$

and that

$$\log\left(\frac{k}{k_0}\right)_{ov} = \log\left(\frac{K}{K_0}\right)_1 + \log\left(\frac{k}{k_0}\right)_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

For side-chain reactions of *meta*- and *para*-benzene derivatives the Hammett equation, $\log k/k_0$ (or $\log K/K_0$) $= \sigma\rho$, applies generally.[3] σ is the substituent constant and ρ the reaction constant: ρ is a measure of the susceptibility of the reaction to polar substitution, a positive value meaning that the rate or the equilibrium constant is increased by electron-attracting substituents. Applying the Hammett equation to (4), we have



$$\rho_{ov} = \rho_1 + \rho_2 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (5)$$

Now ρ_{ov}, determined from Reid's results, is $+0{\cdot}118$;[3] and ρ_1, the reaction constant for the basic ionisation of amides, has been given the value $-0{\cdot}933$.[1c] From equation (5) we can thus predict the value $+1{\cdot}05$ for ρ_2. It being assumed for the present that equilibrium (1) lies far to the right in all the solutions studied, the rate constant in Table 1 may be identified with k_2, and the results used to determine ρ_2 directly. In the Figure, the logarithms of the rate constants are plotted against values of σ for each of the three perchloric acid solutions. The parallel straight lines are drawn with the calculated slope of $+1{\cdot}05$. The slopes of the least-square plots give values of ρ_2, and these are listed below, with the number of results from which ρ_2 is determined (n), the standard deviation (s), and the correlation coefficient (r), for the two more concentrated solutions.[4] The agreement between the

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[3] (*a*) Hammett, " Physical Organic Chemistry," McGraw-Hill, 1940, p. 184; (*b*) Jaffé, *Chem. Revs.*, 1953, **53**, 191.

[4] See ref. 3*b* for a discussion of *s* and *r*.

calculated and the determined values of ρ_2 is strong support, not merely for the *A*2 mechanism, but for the prevalence of this mechanism over the wide range of acidity from 0·5M-hydrochloric acid to 8·54M-perchloric acid.

$HClO_4$ (M)	ρ_2	*n*	*s*	*r*
7·19	1·12	8	0·071	0·989
8·54	1·19	6	0·055	0·995

It must now be considered that the reaction constants in equation (5) refer to the same temperature, whereas the value of ρ_1 was determined at 18°, that of ρ_2 at 95°, and that of ρ_{OV} at 100°. However, the reaction constant for the acid-catalysed hydrolysis of amides in aqueous alcohol, which corresponds to ρ_{OV}, has been shown to vary by only 0·26 over a 47° range of temperature,[5] and therefore the difference of 5° between the temperatures at which ρ_{OV} and ρ_2 have been obtained may be confidently disregarded. Moreover, pK_a values are in general insensitive to temperature:[6] still less sensitive will be a reaction constant calculated from pK_a values, for the temperature variations of the pK_a values will partially cancel in the calculation of the reaction constant. It is thus improbable that much error is introduced even by the large differences between the temperature at which ρ_1 and the other reaction constants were determined. It is noteworthy that the *A*2 mechanism already demands that equilibrium (1) should be insensitive to temperature. It can be shown that, in the dilute acid region where equation (5) holds, the observed activation energy is the sum of the standard enthalpy change in reaction (1) and the activation energy of step (2); whereas the latter alone is the observed activation energy in strongly acid solutions where k_2 is the observed rate constant. Thus, if the enthalpy change, which governs the temperature-dependence of equilibrium (1), is large, the observed activation energy should vary sharply in the region of acidity over which the position of the equilibrium moves from left to right. Such variations are not found.[7] Another assumption, already stated, is that the results in Table 1 all apply to systems in which equilibrium (1) lies far to the right-hand side. From the pK_a value for benzamide (—1·85 [1c]), the value for ρ_1 (—0·933), and the values of the acidity function for the three perchloric acid solutions,[8] it is possible to calculate the degree of conversion of the amides into their conjugate acids. The results are as follows. In the strongest (8·54M) solution, conversion into the conjugate acid is greater than 99% in all cases. In the 7·19M-solution the *least* basic amides, *m*- and *p*-nitrobenzamide, exist as conjugate acids to the extent of 95%. For these two solutions the assumption appears to be justified within experimental error. Even in the case of the weakest (5·86M) solution there is only one amide, *m*-nitrobenzamide, for which the proportion of conjugate acid, 65%, is so small as to produce an obvious error in the above calculations. This lone deviation can be observed in the Figure and is of the right magnitude for the explanation, a useful assurance that the present treatment is sound.

In dilute acid *ortho*-substituents in benzamide retard hydrolysis independently of their polar nature. The effect is clearly steric and according to present knowledge[9] it must operate on step (2), and not on step (1) which involves only a proton transfer. Similar effects should therefore be observable in the present work. The polar effects of substituents appear to be approximately similar in the *ortho*-position to those in the *para*-position.[10] Hence a rough estimate of steric retardation can be made by dividing the rate constant for an *ortho*-compound by that of the *para*-derivative. Some values of this ratio ($k_{\text{para}}/k_{\text{ortho}}$) are recorded below.

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[5] Meloche and Laidler, *J. Amer. Chem. Soc.*, 1951, **73**, 1712.
[6] See, *e.g.*, Stokes and Robinson, " Electrolyte Solutions," Butterworths, 1955, p. 500, 505.
[7] Rabinowitch and Winkler, *Canad. J. Res.*, 1952, **20**, *B*, 73.
[8] Paul and Long, *Chem. Revs.*, 1957, **57**, 1.
[9] See, *e.g.*, Brown, *J.*, 1956, 1248.
[10] Taft, *J. Amer. Chem. Soc.*, 1952, **74**, 3120.

Substituent:	CH_3	Br	NO_2
Hydrolysis conditions		k_{para}/k_{ortho}	
0·5M-HCl, 100°	8	—	43
7·19M-$HClO_4$, 95°	5	4	35

The steric effects are clearly present in concentrated acid and of the same general magnitude as those in dilute acid, providing further evidence that the same, bimolecular, mechanism operates under both sets of conditions.

The variation in the rate of hydrolysis of the amides in solutions of different acidity may be predicted by means of the Hammett–Zucker hypothesis.[11] The observed rate of an *A*2 reaction is that of the second step, which for amide hydrolysis is $k_2[R{\cdot}CONH_3{}^+]$. To the approximation of the acidity-function concept, and under the conditions where the pre-equilibrium lies to the left-hand side, $[R{\cdot}CONH_3{}^+] \propto h_0$, and therefore the observed rate $\propto k_2h_0$. For such a reaction the Hammett–Zucker hypothesis predicts that the rate will be proportional to the acid concentration. Hence k_2 should be proportional to the acid concentration divided by h_0. In Table 2 the variation of k_2 calculated in this way from the Hammett–Zucker hypothesis is compared with that found directly.

TABLE 2. *Calculated and observed variations of hydrolysis rate with acid concentration*

Hydrolysis conditions	$\frac{k_2 \text{ in } 5{\cdot}86\text{M-HClO}_4}{k_2 \text{ in } 7{\cdot}19\text{M-HClO}_4}$		$\frac{k_2 \text{ in } 7{\cdot}19\text{M-MClO}_4}{k_2 \text{ in } 8{\cdot}54\text{M-HClO}_4}$	
Amide	Obs.	Calc.	Obs.	Calc.
p-Nitrobenzamide	—	8·34	2·62	7·86
m-Nitrobenzamide	1·75	,,	2·51	,,
m-Bromobenzamide	—	,,	3·07	,,
Benzamide	2·82	,,	3·13	,,
m-Toluamide	—	,,	3·33	,,
p-Toluamide	2·87	,,	—	,,
Anisamide	2·93	,,	2·76	,,
Acetamide	2·57	,,	2·66	—
Average values	2·80 *	,,	2·87	7·86

* The low value for *m*-nitrobenzamide has been discounted as it arises from incomplete conversion into the conjugate acid.

The variations in rate are similar for the different amides; but the discrepancies between the observed and calculated values are large, and in the same direction as those found by Edward and Meacock for hydrolysis by sulphuric acid and hydrochloric acid.[1c] The calculated rates of hydrolysis in 8·54, 7·19, and 5·86M-acids are in the ratio 1 : 7·86 : 65·6. The experimental ratio, from the mean values at the bottom of Table 2, is 1 : 2·87 : 8·04. These results show a failure of the Hammett–Zucker hypothesis similar to that previously observed for aliphatic esters [13] and for ethylidene diacetate [14] in mineral acids of concentration greater than about 4M.

Experimental.—The amide specimens melted sharply in the ranges recorded in the literature. The solutions were prepared from " AnalaR " perchloric acid, and standardised against " AnalaR " benzoic acid. Benzamide and *m*-nitrobenzamide were hydrolysed in a flask from which samples were pipetted for analysis. Sealed tubes were used for the remaining amides which form sparingly soluble acids. Analysis was by the " formol " titration method.[12] Good first-order rate constants were obtained.

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[11] Zucker and Hammett, *J. Amer. Chem. Soc.*, 1939, **61**, 2779; Long and Paul, *Chem. Revs.*, 1957, **57**, 935.

[12] Northrop, *J. Gen. Physiol.*, 1926, **9**, 767.

[13] Bell, Dowding, and Noble, *J.*, 1955, 3106.

[14] Bell and Lukianenko, *J.*, 1957, 1686.