

**113.** *Amide Hydrolysis in Very Strong Acids. Part I.  
Cryoscopic Measurements in Anhydrous Sulphuric Acid.*

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The behaviour of 15 amides has been examined in 100% sulphuric acid, in search of a unimolecular mechanism of hydrolysis. First-order changes of freezing point were observed in 8 cases, as the amides were hydrolysed or sulphonated. The two processes were distinguished by observing the effect of added water on the freezing point of the solutions after the reactions had been followed to completion, and by qualitative examination of the reaction products. Six amides were shown to be hydrolysed.

THE effect of the acid concentration on the rate of hydrolysis in aqueous solutions of strong acids has been determined for several amides.<sup>1</sup> As the concentration is increased, the rate for a particular amide at first increases, then passes through a maximum, and finally decreases to very low values, a fact which has set the upper limit of acid concentration in previous kinetic investigations at about 10 molar. The reaction is thought to proceed

<sup>1</sup> (a) Ingold, "Structure and Mechanism in Organic Chemistry," G. Bell and Sons Ltd., London, 1953, p. 786; (b) Rabinowitch and Winkler, *Canad. J. Res.*, 1942, **20**, B, 73; (c) Edward and Meacock, *J.*, 1957, 2000; (d) Leisten, *J.*, 1959, 153.

throughout this region by the attack of water upon the conjugate acid of the amide, *i.e.*, by the A-2 mechanism.<sup>1</sup> Many carboxylic esters are hydrolysed by the A-2 mechanism in this region of acid concentration: but hydrolysis of esters in more concentrated acids proceeds by a different and probably unimolecular mechanism.<sup>2</sup> The corresponding mechanism for amides is:

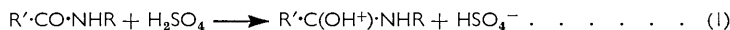


but no previous attempt has been made to determine whether, under appropriate conditions, amides might be hydrolysed in this way.

In seeking and demonstrating the occurrence of this type of hydrolysis it is necessary to use an acid which favours ionic dissociation, but which contains little or no free water so as to avoid hydrolysis by the A-2 route. Anhydrous sulphuric acid is an obvious choice, and the present paper is concerned with the behaviour of a number of differently substituted amides in this solvent. We have found only one previous observation of relevance: pentamethylbenzanilide is sulphonated and cleaved by sulphuric acid, the two processes occurring either synchronously or in rapid succession.<sup>3</sup>

Some of the results and conclusions in this and the following paper<sup>4</sup> have appeared in a preliminary report.<sup>5</sup>

Amides are strong bases in anhydrous sulphuric acid.<sup>6</sup> That this is true even of the very weakly basic amides listed in Table 1 is shown by the two-fold freezing-point depressions, in accordance with equation (1), which were obtained immediately on dissolution (see col. 2):

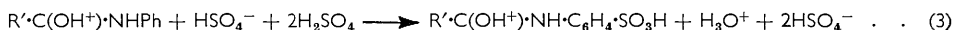


If an amide is to be hydrolysed in anhydrous sulphuric acid, the hydrolytic water must necessarily come from the sulphuric acid itself, affording sulphur trioxide which is known<sup>7</sup> to combine with hydrogen sulphate to form the hydrogen disulphate ion  $\text{HS}_2\text{O}_7^-$ . Carboxylic acids exist as acidium ions in this medium.<sup>8</sup> The equation for such a hydrolysis can therefore be written *a priori*:



The hydrogen disulphate ion produced should repress the self-dissociation which occurs in 100% sulphuric acid:<sup>9</sup>  $2\text{H}_2\text{SO}_4 \rightleftharpoons \text{H}_3\text{O}^+ + \text{HS}_2\text{O}_7^-$ . The hydrolysis might therefore be expected to produce rather less than four-fold depression of the freezing point, even though four particles appear on the right-hand side of expression (2).

Unfortunately sulphonation would also lead to a final *i*-factor of about 4:<sup>10</sup>



Whether such a freezing-point change is the result of hydrolysis or of sulphonation can be determined by "cryoscopic titration" with water. Hydrolysis produces a concentration of hydrogen disulphate ion, by equation (2), equal to the initial concentration of the amide. When water is now added the principle reaction to occur will be  $\text{HS}_2\text{O}_7^- + \text{H}_2\text{O} \longrightarrow \text{HSO}_4^- + \text{H}_2\text{SO}_4$ , which does not change the total number of solute particles. The freezing point of the solution will therefore remain nearly constant until the hydrogen

<sup>2</sup> (a) Ref. 1(a), p. 771; (b) Leisten, *J.*, 1956, 1572.

<sup>3</sup> Newman and Deno, *J. Amer. Chem. Soc.*, 1951, **73**, 3651.

<sup>4</sup> Duffy and Leisten, in the press.

<sup>5</sup> Duffy and Leisten, *Nature*, 1956, **178**, 1242. (The rate constants there recorded are in error by a constant factor.)

<sup>6</sup> Gillespie and Leisten, *Quart. Rev.*, 1954, **8**, 61.

<sup>7</sup> Brand, *J.*, 1946, 880; Gillespie, *J.*, 1950, 2516.

<sup>8</sup> Leisten, *J.*, 1955, 298.

<sup>9</sup> Gillespie, *J.*, 1950, 2515.

<sup>10</sup> Ref. 6, p. 60.

disulphate ion has been "neutralised;" then further additions will produce the nearly two-fold depression usual for water. On the other hand, added water will give the normal freezing-point depression from the first if sulphonation has occurred.

The amides in Table 1 were all found to give first-order changes of the freezing point when kept at the temperatures recorded in col. 5. The final *i*-factors (col. 3), determined

TABLE 1. *First-order rate constants from freezing-point measurements.*

Amide R	R·CO·NHR' *	Initial <i>i</i> -factor	Final <i>i</i> -factor	$i_{\infty}$	Reaction temp.	$10^3k$ (min. <sup>-1</sup> )
Ac	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	1.92	3.44	3.46	65.0°	15.7
Et·CO	"	1.95	3.52	3.55	60.0	22.2
Ac	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	2.01	3.84	3.84	55.8	14.1
Bz	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	†	3.58	3.70	8	13
<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	"	1.94	3.43	3.40	50.0	10.2
<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	"	†	3.05	3.11	8	14
		†	3.14	3.14	8	14
<i>p</i> -C <sub>6</sub> H <sub>4</sub> Me	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	2.13	3.27	3.37	50.2	39
<i>o</i> -C <sub>6</sub> H <sub>4</sub> Me	"	†	3.28	3.30	20.0	19

\* Concn. ~0.25M. † Greater than 2 and increasing rapidly.

when the freezing-points had become constant, vary from 3.1 to 3.8. By plotting the logarithm of ( $i_{\infty} - i$ ) against time, straight lines are obtained from the slopes of which values of the first-order rate constants can be found (col. 6). The values of  $i_{\infty}$ , chosen to give the best straight lines, correspond well with the experimentally determined final *i*-factors (cf. cols. 3 and 4). The results of the cryoscopic titrations are given in Table 2. From them it appears that the first six amides in Table 2 have been hydrolysed, and the next four sulphonated. Later it will be shown that these conclusions require modification; and that the last amide in Table 2, phthalamic acid, is a special case. Cryoscopic results

TABLE 2. *i*-Factors for water added to the reacted solutions.

Amide R	R·CO·NHR'	Molality of amide before reaction	Molality of water	<i>i</i> -Factor (for water)
Ac	3,5-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	0.146	0.062	0.10
			0.123	0.32
Et·CO	"	0.131	0.105	0.40
Ac	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	0.140	0.062	0.14
			0.092	0.18
			0.123	0.25
Bz	2,4-(NO <sub>2</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	0.139	0.062	0.14
<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	"	0.134	0.062	0.02
<i>o</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	"	0.129	0.123	0.34
Ac	Ph	0.166	0.062	1.73
Ac	<i>p</i> -C <sub>6</sub> H <sub>4</sub> Cl	0.163	0.062	2.04
<i>p</i> -C <sub>6</sub> H <sub>4</sub> Me	<i>p</i> -NO <sub>2</sub> ·C <sub>6</sub> H <sub>4</sub>	0.148	0.123	1.49
<i>o</i> -C <sub>6</sub> H <sub>4</sub> Me	"	0.151	0.062	1.36
Phthalamic acid	"	0.149	0.062	1.95

TABLE 3. *Further cryoscopic results.*

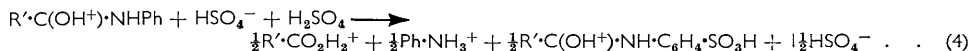
Amide *	Initial <i>i</i> -factor	Change of <i>i</i> -factor
Acetamide .....	1.90	2.11 after 21 hr. at 90°
Propionamide .....	1.99	2.23 after 15½ hr. at 90°
<i>N</i> -Chloroacetyl-3,5-dinitroaniline .....	1.92	2.26 after 15½ hr. at 90°
Phthalamic acid .....	3.74	3.70 after 13 min. at 70°
Acetanilide .....	†	3.88 after 2½ hr. at 25°
<i>p</i> -Chloroacetanilide .....	1.99	3.32 after 15½ hr. at 90°
Isobutyramide .....	1.92	4.59 after 17 hr. at 90°
<i>p</i> -Chloroaniline .....	1.98	2.11 after 20 hr. at 90°
3,5-Dinitroaniline .....	1.87	1.87 after 15 min. at 60°
2,4-Dinitroaniline .....	1.94	No change at room temp.
<i>o</i> -Nitrobenzoic acid .....	1.72	No change at room temp.

\* Concn. ~0.25M. † Greater than 2 and increasing rapidly.

from which rate constants cannot be calculated, whether through the slowness or the complexity of the reaction or through an insufficiency of experimental observations, are

contained in Table 3. The last four results suggest that, as might be expected, in sulphuric acid the hydrolysis products are more stable than the amides themselves.

Hydrolysis without sulphonation, and sulphonation without hydrolysis, have so far been considered, but various combinations of the two may occur as consecutive or simultaneous reactions. The ways in which these would affect the freezing-point changes both during the reactions and on subsequent additions of water are easily predicted, and only one of them will be considered here, since this alone can seriously affect the validity of the conclusions so far reached. If sulphonation and hydrolysis were to occur side by side, the measured rate constant would be the sum of those for sulphonation and hydrolysis, and the final *i*-factor would be lower than if either reaction occurred alone, reaching a theoretical minimum of 3, according to equation (4), when both reactions have the same rate:



It is thought that of the six amides which have been shown to be hydrolysed, one, 2,4-dinitro-*N*-*o*-nitrobenzoylaniline, is probably sulphonated in a side reaction to a small extent; and that of the amides shown to sulphonate, two, *p*-nitro-*N*-*o*- and *p*-toluoylaniline, are also hydrolysed to an appreciable extent. This is suggested by the final *i*-factors for these three amides which have the lowest values in Table 1, and by other evidence in Part II.<sup>4</sup>

To confirm the interpretations of the cryoscopic results, the products of the reactions were examined qualitatively. Hydrolysis products were identified in those cases where the cryoscopic results indicated hydrolysis, but not for acetanilide and *p*-chloroacetanilide where sulphonation was indicated. The products from the toluanilides were not examined. Phthalimide was shown to be produced by the reaction of phthalamic acid in sulphuric acid. This, and the *i*-factor of nearly 4, is well explained by the equation:



The results in Table 1 reveal constitutional effects on the rate of hydrolysis. These are discussed in Part II, together with results obtained in other acid solvents.<sup>4</sup>

## EXPERIMENTAL

**Materials.**—Commercial samples of acetamide, propionamide, isobutyramide, and acetanilide were recrystallised from water, and *p*-chloroacetanilide from ethanol. *p*-Nitroacetanilide was purified by precipitation from 80% sulphuric acid with ice, washing with water, and recrystallisation from ethanol. The following compounds were prepared and purified by the methods given in the references: *N*-acetyl-3,5-dinitroaniline; <sup>11</sup> *N*-benzoyl-2,4-dinitroaniline; <sup>12</sup> *N*-*p*-nitrobenzoyl-2,4-dinitroaniline; <sup>13</sup> phthalamic acid; <sup>13</sup> *N*-*p*-nitrobenzoyl-2,4-dinitroaniline. <sup>14</sup> *p*-Nitro-*N*-*p*-toluoylaniline was prepared by treating *o*-toluoyl chloride <sup>15</sup> with *p*-nitroaniline at 230°, and recrystallising the product from ethanol; the *p*-toluoyl analogue was prepared similarly. All these compounds melted sharply close to the recorded m. p.s. 3,5-Dinitro-*N*-propionylaniline was prepared by heating 3,5-dinitrobenzazide <sup>11</sup> (3 g.) with propionic anhydride (9 ml.) and concentrated sulphuric acid (2 drops) at 100°. When no more gas appeared to be evolved the mixture was cooled and poured into water. The solid obtained was recrystallised from ethanol: it had m. p. 157° (Found: C, 44·9; H, 3·7; N, 17·4. C<sub>9</sub>H<sub>9</sub>O<sub>5</sub>N<sub>3</sub> requires C, 45·2; H, 3·8; N, 17·6%). *N*-Chloroacetyl-3,5-dinitroaniline was prepared in a similar way, by using chloroacetic anhydride (12 g.) in place of propionic anhydride; it had m. p. 138° (Found: C, 37·0; H, 2·7; N, 15·6. C<sub>8</sub>H<sub>6</sub>O<sub>5</sub>N<sub>3</sub>Cl requires C, 37·0; H, 2·3; N, 16·2%).

**Cryoscopic Measurements.**—The measurements of *i*-factors and of rate constants were carried out as in previous work.<sup>2b</sup> The rate constants were determined graphically; a typical

<sup>11</sup> Blanksma and Verberg, *Rec. Trav. chim.*, 1934, **53**, 988.

<sup>12</sup> Kym, *Ber.*, 1899, **32**, 2178.

<sup>13</sup> Aschan, *Ber.*, 1886, **19**, 1402.

<sup>14</sup> Van Horsen, *Rec. Trav. chim.*, 1936, **55**, 249.

<sup>15</sup> Davies and Perkin, *J.*, 1922, 2207.

set of results is given below, the rate constant being calculated for each point from 17% to 90% hydrolysis by the formula:  $k = \frac{2.303}{t} \log \frac{i_{\infty} - i_0}{i_{\infty} - i_t}$ . The results are for the hydrolysis of *N*-acetyl-3,5-dinitroaniline at 65.0°. The value of  $i_{\infty}$  was taken as 3.46, and, determined graphically,  $k = 15.7 \times 10^{-3} \text{ min.}^{-1}$ .

Time (min.) .....	0	10	25	40	57.5	145.5	816
$i$ -Factor .....	1.92	2.18	2.43	2.63	2.86	3.30	3.44
$10^3 k$ (min. <sup>-1</sup> ) .....	—	18.7	16.1	15.5	16.4	15.6	—

Oleum was adjusted to 100% sulphuric acid, with its freezing point as the criterion, by adding water from an "Agla" micro-syringe fitted with a long L-shaped glass needle. The advantages of this technique are that small amounts of water can be added accurately, and beneath the surface of the acid so that no water is vaporised. The cryoscopic titrations were conveniently performed in this way.

*Product Analyses.*—After the final freezing-point measurements the solutions were poured on ice, and the mixture was examined for the products of hydrolysis. As an example, *N-p*-nitrobenzoyl-2,4-dinitroaniline, on reaction in sulphuric acid and dilution, gave a yellow precipitate which was separated, washed, and treated with dilute aqueous alkali. The solid residue was shown by mixed m. p. to be 2,4-dinitroaniline. The alkaline solution on acidification gave a precipitate which was similarly shown to be *p*-nitrobenzoic acid.

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