CCCLXVII.—*The Hydrolysis of Acetamide.*

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When in extension of earlier work (Taylor, J., 1928, 1099, 1897; Taylor and Price, J., 1929, 2052) the reaction between nitrous acid and acetamide was investigated, it was found that, with the two reactants at 0·05N concentration, the rate of reaction at 25° did not become appreciable until the concentration of sulphuric acid in the solution was raised to 4N. No measurements have been recorded giving the rate of hydrolysis of acetamide at 25° by acids of this or greater concentration. Hence the velocity of this reaction in the presence of hydrochloric, hydrobromic and sulphuric acids has been measured together with the salt effect on the velocity with the first two acids. Further the salt effect on the rate of hydrolysis by 1·0N-sodium and potassium hydroxides

has been investigated. The somewhat unexpected results obtained appear to indicate that acetamide can form complexes with certain neutral salts and with hydrogen chloride and bromide, which are stable in solution and unable to undergo hydrolysis.

Materials.—Acetamide was recrystallised four times from dry acetone and kept over sulphuric acid. All solutions of acids and bases were referred to an approximately decinormal solution of sulphuric acid which had been standardised by three separate and concordant methods. Potassium chloride and iodide were recrystallised three times from water; and potassium bromide three times from pure aqueous alcohol. The sodium chloride and bromide were commercial A.R. samples. Sodium iodide was purified by recrystallising its compound with acetone three times from acetone. Solutions of the iodides were made up when required and used at once, since they tended to contain small traces of iodine after standing. Solutions of lithium chloride and bromide were obtained by dissolving known amounts of the carefully purified carbonate in the required amount of the accurately standardised acid and boiling gently to remove carbon dioxide. The thermostats were gas-heated; that at 25° was constant to within 0·05°, and those at the higher temperatures to within 0·2°.

Analytical Methods.—The velocity of hydrolysis was followed by estimating the ammonia formed. Two methods were used. The first was the oxidation of the ammonia by sodium hypobromite (compare Rüpp and Rössler, *Arch. Pharm.*, 1905, **243**, 104; Euler and Ölander, *Z. physikal. Chem.*, 1928, **131**, 107); the sample was pipetted from the reaction vessel into the quantity of acid or base necessary for its exact neutralisation, mixed with pure crushed ice; excess of a standard sodium hypobromite solution over that equivalent to the total amide and ammonia present was added and the flask was at once stoppered and left for 8 minutes; finally the solution was acidified, and the hypobromite estimated iodometrically. A correction must be applied, since the acetamide is hydrolysed to a small extent during the oxidation; this was effected by plotting the titres of hypobromite against time, extrapolating to zero time, and subtracting the value so found from all the titres. The correction is of the order of 0·1—0·2 c.c., and the procedure is sufficiently exact, since the reaction was studied only in its initial stages, so that the concentration of acetamide was approximately the same in all the estimations.

The second method was a modification of that used by Reid (*Amer. Chem. J.*, 1899, **21**, 285); the sample was neutralised as before, a large excess of pure magnesium sulphate added and then pure aqueous sodium hydroxide in amount less than the equivalent

of the magnesium. The free ammonia thus formed was distilled in steam, generated from dilute potassium hydrogen sulphate in a vessel with an efficient steam-trap, into a known amount of standard acid, which was finally back-titrated with baryta. Great care had to be taken to avoid the absence of volatile bases from all the reagents used.

The two methods gave identical results and were used indiscriminately, except with solutions containing an iodide, for which only the second is available.

Procedure.—In all experiments the concentration of acetamide was $0.05N$. Reaction mixtures were made up in the thermostat from solutions of known strength, and samples extracted at known times and analysed until the concentration of acetamide had fallen to 80—85% of its initial value. These concentrations were plotted against time and the best smooth curve was drawn; from the values read from this curve for intervals of 30 minutes, unimolecular velocity coefficients were calculated and their mean value taken. The use of unimolecular coefficients is justified, since the reaction is only followed in its initial stages. The average divergence of

TABLE I.

Velocity Coefficients.

Temperature 25°.

Catalyst.		k (min.$^{-1}$; log$_e$) $\times$ 10^4.
$4N\text{-}H_2SO_4$	(5·85, 6·05)	5·95
$5N$,,		6·58
$3N\text{-}HCl$		6·03
$4N$,,		5·14
$5N$,,	(3·57, 3·66)	3·61
$4N\text{-}HCl + 1N\text{-}LiCl$		5·11
,, $+ 1N\text{-}NaCl$		5·89
,, $+ 1N\text{-}KCl$	(5·87, 5·76)	5·81
$4N\text{-}HBr$		4·03
$5N$,,		3·27
$4N\text{-}HBr + 1N\text{-}LiBr$		3·59
,, $+ 1N\text{-}NaBr$		4·01
,, $+ 1N\text{-}KBr$		4·58
$1N\text{-}NaOH$	(23·6, 24·0)	23·8
,, $+ 2N\text{-}NaCl$		25·8
,, $+ 2\cdot5N\text{-}NaCl$		26·6
,, $+ 2N\text{-}NaBr$		23·0
,, $+ 3N\text{-}NaBr$		22·7
,, $+ 2N\text{-}NaI$		22·3
$1N\text{-}KOH$	(24·2, 23·8)	24·0
,, $+ 2N\text{-}KCl$	(25·5, 26·2)	25·8
,, $+ 2N\text{-}KBr$		26·3
,, $+ 2N\text{-}KI$		26·7

Temperature 40°.

$4N\text{-}HCl$	27·3

Temperature 41°.

$5N\text{-}HCl$	21·9

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the individual values from the mean was under 2% ; if it exceeded 5%, the results were rejected. Several of the reactions were measured more than once and the mean velocity coefficient agreed well, the maximum divergence being 3%.

The Hydrolysis by Acids.—The velocity coefficients at 25° are plotted against the normality of the acid catalyst in Fig. 1. Two results of Peskoff and Meyer (*Z. physikal. Chem.*, 1913, **82**, 129) for this temperature are included, recalculated on the basis used here.

The results for hydrochloric acid at 25° together with those at 40° or 41° give the temperature coefficient of the reaction velocity. For the 4N-acid it is 3·12 and for the 5N-acid 3·11, values which

FIG. 1.
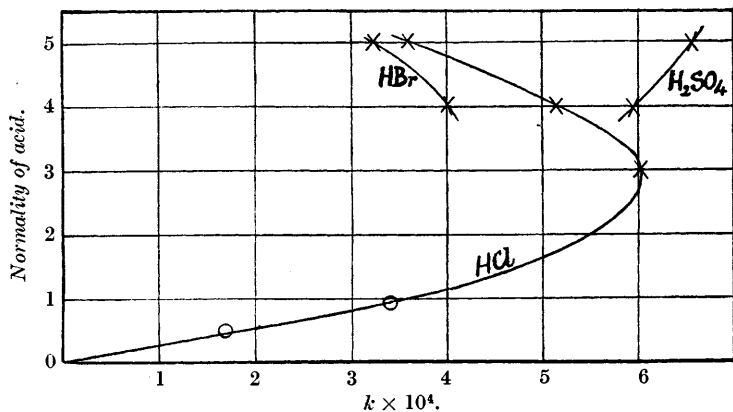
○ *Peskoff and Meyer*, loc. cit.   × *This paper.*

agree with that of Crocker (J., 1907, **91**, 593), 3·14 for the 1N-acid, and that of Sulo Kilpi (*Z. physikal. Chem.*, 1912, **80**, 165), 3·11 for the 1N- and the 0·5N-acid. For the hydrolysis of benzamide by hydrochloric acid Bolin (*Z. anorg. Chem.*, 1925, **143**, 210) found the value 3·1.

Velocity coefficients at 50° calculated by means of this temperature coefficient are plotted in Fig. 2, together with the results at that temperature of Euler and Ölander (*loc. cit.*). The agreement between their value for the 3N-acid and that found here is within the experimental error.

The most striking feature of the two curves is that with hydrochloric acid there is an optimum concentration of acid (about 3N) where the velocity of hydrolysis is the greatest. With hydrobromic acid a similar maximum rate must exist, but in the case of sulphuric acid there is no sign of any bending back of the curve

with concentrations up to $5N$. There are three possible explanations for this phenomenon.

(i) As the acid concentration increases, the total ionic strength of the solution is increased, and the reaction is of the type which has a strong negative " primary " salt effect, in the sense in which Brönsted uses the term. This explanation can, however, be ruled out, since the reaction mechanism is either $CH_3 \cdot CO \cdot NH_2 + H_3O^+ \longrightarrow CH_3 \cdot CO \cdot OH + NH_4^+$, or, if Euler's hypothesis is accepted, $CH_3 \cdot CO \cdot NH_3^+ + H_2O \longrightarrow CH_3 \cdot CO \cdot OH + NH_4^+$, and these mechanisms, which are indistinguishable (Brönsted, *Trans. Faraday Soc.*, 1928, **24**, 631), will not have a primary salt effect of the required type. This is fully confirmed by the results obtained here for the salt effect which are discussed below. In all cases the salt effect

FIG. 2.

⊙ *Euler and Ölander*, loc. cit.   × *This paper.*
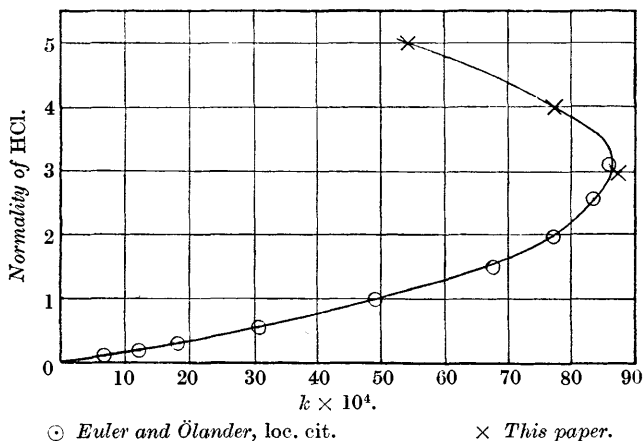
is quite small and in the normal cases (see below) it is an accelerating and not an inhibiting effect.

(ii) In solutions of high acid concentration the reaction may be quite different in mechanism from what it is in more dilute solutions, new kinds of molecular and ionic species being the actual reactants, so that it is unfair to compare the strong and the weak solutions. This explanation is very unlikely, because even with the solution strongest in acid the reaction shows the same abnormally large temperature coefficient as it does in the more dilute solutions.

(iii) If the three acids investigated are compared at $4N$- and $5N$-concentration, the widely different velocities indicate that some specific property of the acid itself is the cause. If the acid can unite with the amide to form in solution a complex which is unable to undergo hydrolysis, then it is possible that with high

concentrations of acid a large proportion of the amide is so combined and thus the apparent rate of hydrolysis is diminished.

The nature of the possible complex can be discovered by the following approximate treatment. In dilute solution the velocity coefficient is directly proportional to the normality of the acid; let it be assumed that this is true in all the solutions, and that, in addition, the velocity coefficient, k, is proportional to the fraction, f, of the amide which is free and not present as an unhydrolysable complex. Then we have $k = k_1 N f$, where N is the normality of the acid and k_1 is a constant which can be obtained from the results of Euler and Ölander in dilute solution, where f can be taken as unity. From this equation, values of f at 50° for a series of values of N can be obtained from the experimentally determined values of k which are shown in Fig. 1. They are given in Table II.

TABLE II.

Temperature 50°.

N.	f.	f_I.	f_{II}.	f_{III}.	p (mm. Hg $\times 10^2$).
1	0·917	0·822	0·951	0·931	0·3
2	0·698	—	—	—	2·5
3	0·514	0·606	0·470	0·496	8·3
4	0·350	0·536	0·194	0·336	24·0
5	0·196	0·480	0·072	0·207	74·5

If we assume the complex to be such that its concentration is governed by an equation of the type [amide][acid]/[complex] $= K$, from the experimental value of f at one concentration the value of K can be obtained, and from this the values of f at the other acid concentrations can be calculated; these are given in the Table as f_I, the value of f when N is 2 having been used to evaluate K. It will be seen that f_I does not fall off nearly fast enough with increasing values of N. This divergence cannot be due to the omission of activity coefficients in the equilibrium equation, since if the term [acid] refers to an ion, the activity factors will cancel out to a first approximation.

The widely different results with hydrochloric and hydrobromic acids suggest that the complex formation may be concerned with undissociated molecules of the acids, the concentration of which can be measured by the partial pressure of the acid above the solution. For hydrochloric acid, values of the partial pressure at 50° are given by Zeisburg (*Chem. Metallurg. Eng.*, 1925, **32**, 326) and by Tannakis (*Compt. rend.*, 1923, **177**, 174); the partial pressures obtained graphically from their results are given in Table II in the column p.

If the concentration of the complex is given by an equation of the form [amide]p/[complex] $= K$ (in which activity coefficients

can be neglected, since no ionic species are involved), from the observed value of f at one concentration the values at other concentrations can be calculated; they are given in Table II as f_{II}. The agreement is much better, but they fall off much too fast at high concentrations of acid.

If we take the concentration of the complex to be given by an equation of the type [amide]^2p/[complex] $= K$, calculated values of f can be obtained in a similar way; these are given as f_{III}. The agreement with the observed values is extremely good for all concentrations.

Now acetamide forms two solid compounds with hydrogen chloride, $2CH_3 \cdot CO \cdot NH_2, HCl$ and $CH_3 \cdot CO \cdot NH_2, HCl$ (Strecker, *Annalen*, 1857, **103**, 322; Pinner and Klein, *Ber.*, 1877, **10**, 1896), of which the first is the more easily obtained and is the more stable. The second loses hydrogen chloride on standing over caustic soda, giving the first, and this gives up no more hydrogen chloride to the soda. The above approximate treatment indicates that this stable complex exists also in solution, since its concentration would be governed by an equilibrium equation of the third of the types discussed above.

From the measurements of Zeisburg (*loc. cit.*) and of Bates and Kirschman (*J. Amer. Chem. Soc.*, 1919, **41**, 1997) the partial pressures of hydrogen chloride over its solutions at 25° can be obtained, and the calculations repeated with the velocity coefficients measured at that temperature. The results are in Table III.

TABLE III.

N.	f.	f_{III} calc.	p (mm. Hg $\times 10^3$).
3	0·543	—	7·8
4	0·349	0·325	27·7
5	0·195	0·203	96·5

The assumption that the complex $2CH_3 \cdot CO \cdot NH_2, HCl$ exists in solution again leads to satisfactory results; for low values of acid concentration the values of velocity coefficient and partial pressure are too uncertain to be relied on, though, if the most probable values are taken, the concordance is as good as with the higher concentrations.

Werner (*Ber.*, 1903, **36**, 154) obtained a compound of similar composition from hydrogen bromide and acetamide, so the results obtained with this acid can be explained in the same way; no compound of acetamide and sulphuric acid has been described and my attempts to prepare one failed; this may be the reason for the absence of any bending back of the curve when this acid is the catalyst in the hydrolysis.

The Salt Effect on the Hydrolysis by Acids.—On Brönsted's theory the effect to be expected is a small and accelerating one. With $4N$-hydrochloric acid as catalyst, this is found to be the case with both sodium and potassium chlorides, the velocity increasing by the factor 1·14 when the salt concentration is $1N$. Lithium chloride, however, fails to accelerate the reaction at all. With hydrobromic acid, potassium bromide gives the expected effect with a factor of increase of 1·13 for $1N$ salt; but sodium bromide has no apparent effect and lithium bromide represses the reaction. The same effects have been found qualitatively by Acree and Nodling (*Amer. Chem. J.*, 1907, **38**, 495), who describe sodium and potassium chlorides as positive catalysts and lithium chloride as a weak negative catalyst. The results with changing acid concentration suggest that this surprising difference between the salts may be due to a specific interaction between certain of the salts and the amide. If this is true, the behaviour of the various salts should be independent of the mechanism of the hydrolysis.

The Salt Effect on the Hydrolysis by Alkalis.—With alkalis, the mechanism of the reaction is probably different from that in the presence of acids, the temperature coefficient of the reaction velocity being 2·2 (Crocker and Lowe, *J.*, 1907, **91**, 952). The results in Table I show, however, that the difference between the effects of the various salts still persists. Here the iodides can be investigated; potassium iodide gives a normal effect and sodium iodide has a markedly repressing action.

Now it is impossible to attribute the repressing effect to the individual ions, for it is not found with the sodium ion in sodium chloride, nor with the bromide ion in potassium bromide; but it occurs when the sodium and bromide ions co-exist in sodium bromide. It is a property of associated ions or undissociated molecules. Acetamide is known to form solid complexes with sodium bromide and sodium iodide and is known not to form them with sodium chloride and with the halides of potassium (Titherley, *J.*, 1901, **79**, 413; Menschutkin, *J. Russ. Phys. Chem. Soc.*, 1909, **40**, 1415). The lithium salts have not been investigated, but the formation of complexes with acetamide and the formation of solid hydrates are so closely parallel (Menschutkin, *loc. cit.*) that there is little doubt that complexes exist here too. If these complexes exist in solution and, when so combined, the acetamide is unable to undergo hydrolysis, the results obtained receive some explanation.

The possibility remains, however, that the phenomenon under discussion has nothing to do with an interaction of the abnormal salts with the acetamide, but with the water. If the vapour pressure of salt solutions is taken as a measure of the active mass

of the water, there is little support for this view, for the ratios of
the vapour pressure of aqueous solutions of sodium chloride and
sodium bromide to that of pure water only differ at $3N$-concen-
tration by 0·76%, and at $4N$-concentration by 1·49% (data from
Gmelin's " Handbuch," 8th Edn., " Natrium," 1928).

There is evidence from another source that amide–salt com-
plexes exist in solution. Braun (*J. Amer. Chem. Soc.*, 1918, 40,
1186) measured the velocity of crystallisation of supercooled form-
amide in the presence of the alkali halides. With the salt at $0·1N$-
concentration, the velocity is decreased by a factor which lies
between 2·12 and 2·05 for all the potassium halides, and which is
2·33 for sodium bromide, 2·35 for sodium iodide, and 2·45 for
lithium chloride and bromide. Here the various salts differ in
their effect and, as with the hydrolysis discussed here, the lithium
salts are the most abnormal.

In conclusion it may be pointed out that the condition for com-
plex formation between an alkali halide and acetamide seems to
be the possibility of considerable ionic " deformation," in Fajans'
sense of the phrase, the deformation being greater the smaller the
kation and the larger the anion. According to Fajans the sulphate
ion cannot easily be deformed, so that the absence of any indication
of complex formation with sulphuric acid is in agreement with
this view.

Summary.

1. Measurements have been made of the velocity of hydrolysis
of acetamide at 25° by 3, 4, and $5N$-hydrochloric acid, and by 4
and $5N$-hydrobromic and sulphuric acids, at 40° by $4N$-hydro-
chloric acid and at 41° by $5N$-hydrochloric acid.

2. The effect on the velocity of hydrolysis by $4N$-hydrochloric
and hydrobromic acids of the alkali salts of these acids has been
investigated.

3. The salt effect on the velocity of hydrolysis by $1N$-sodium
and potassium hydroxides of the presence of the alkali halides has
been measured.

4. With hydrochloric and hydrobromic acids, but not with
sulphuric acid, at one concentration of acid (about $3N$) the velocity
of hydrolysis is a maximum ; causes for this phenomenon are dis-
cussed ; quantitative evidence is given for the view that the first
two acids form complexes with the amide which are unable to
undergo hydrolysis.

5. The effect of any salt is the same whether the hydrolysis is
by acid or by alkali. The differences between the behaviour of
the individual salts suggest that acetamide can form with certain

salts complexes which are stable in solution and unable to undergo hydrolysis.

6. The abnormal salt effect must be due to associated ions and is favoured by the possibility of great ionic deformation.