# Nuclear Magnetic Resonance Spectra of [$^{15}$N]Acetamide in Sulphuric and Fluorosulphuric Acid. The Question of the Cation Tautomeric Equilibrium

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N.m.r. spectra of [$^{15}$N]acetamide in 100% sulphuric acid and in fluorosulphuric acid are reported over a range of temperatures, as well as the effect of acid concentration in >75% sulphuric acid on the spectra of acetamide in these media. The low activation energies for exchange of the two NH sites are accounted for in terms of a tautomerization of the *O*-protonated cation into the *N*-protonated cation, which is present in negligible concentration in anhydrous acids. Its concentration increases upon dilution of sulphuric acid with water and exchange of NH protons with the solvent becomes rapid in 75% sulphuric acid. The *O*-protonated cation of acetamide is also not observable in 72% perchloric acid. The implications of the tautomeric equilibrium for the mechanism of acid hydrolysis of amides are discussed.

It has recently been suggested[1] that a tautomeric equilibrium, with a changeover from *N*-protonation in dilute aqueous acids to *O*-protonation in concentrated and anhydrous acids, accommodates all the facts afforded by the n.m.r. spectra of amides in these media and is also consistent with the known chemical behaviour of amides in aqueous strong acids. The spectra of [$^{15}$N]acetamide and ordinary acetamide in concentrated sulphuric acid and pure fluorosulphuric acid reported in this paper support this view, since the effect of the concentration of water in concentrated sulphuric acid on the spectra and the difference in the activation energies for rotation around the C–N bond between the solutions of the amide in 100% sulphuric acid and in pure fluorosulphuric acid can most easily be accounted for in terms of a tautomeric equilibrium. The tautomeric equilibrium also has considerable implications for the mechanism of acid hydrolysis of amides.

## EXPERIMENTAL

[$^{15}$N]Acetamide was a commercial sample, supplied by Prochem Ltd. It contained 95 atom % of the $^{15}$N isotope and was used without purification. Acetamide (B.D.H., laboratory reagent) was recrystallised from benzene.

Fluorosulphuric acid was a product of the Ozark–Mahoning Company and was used as obtained.

Sulphuric acid (B.D.H., AnalaR) was adjusted to 100% by mixing it with dilute oleum until a maximum freezing point (+10·4 °C) was obtained. Other concentrations of sulphuric acid were prepared by diluting the 100% acid with distilled water by weight.

The solutions of the amide in these solvents were 1M in the amide. The n.m.r. spectra were recorded mostly on a Brüker HFX n.m.r. spectrometer with a variable temperature probe, operating at 90 MHz, but some additional recordings were made on a Perkin-Elmer R10 spectrometer, operating at 60 MHz, at 33·5 °C. It was thought preferable not to introduce any internal references into the solutions, because sodium 2,2-dimethyl-2-silapentane-5-sulphonate (DSS) has proved unstable in the strongly acid media, especially in fluorosulphuric acid. The solvent peak was used as the reference and locking signal. The chemical shifts of both sulphuric acid and fluorosulphuric acid are very sensitive to the nature and the concentrations of the solutes present[2-4] and therefore the chemical shifts of the solvents and the solutions studied were determined relative to water as external reference. The solvent peak of both sulphuric acid and fluorosulphuric acid is shifted downfield by the dissolution of the amide (shifts of 0·22 and 0·60 p.p.m. found, respectively).

Double-resonance experiments were performed on the Brüker spectrometer in an attempt to establish the source of the broadening of the NH proton resonances.

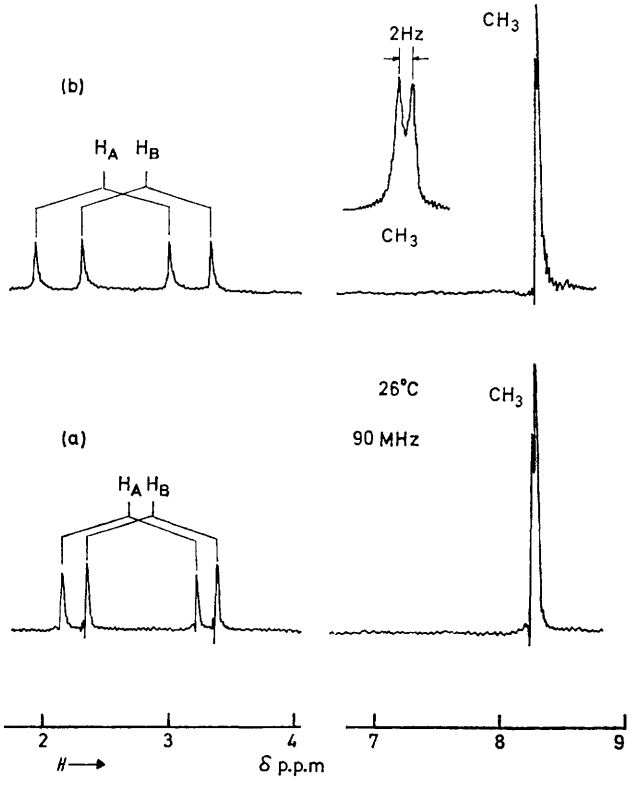



FIGURE 1 N.m.r. spectra of [$^{15}$N]acetamide at 26 °C and 90 MHz in (a) pure fluorosulphuric acid and (b) 100% sulphuric acid, both relative to the solvent peak as lock signal

## RESULTS

The spectra of the amide group of [$^{15}$N]acetamide in fluorosulphuric acid at low temperature have already been reported.[1] The spectra of [$^{15}$N]acetamide in pure fluorosulphuric acid and in 100% sulphuric acid at 26 °C are shown in Figure 1 relative to the solvent peaks as references.

[1] M. Liler, *Chem. Comm.*, 1971, 115.
[2] R. J. Gillespie and R. F. White, *Canad. J. Chem.*, 1960, **38**, 1371.
[3] R. J. Gillespie and T. Birchall, *Canad. J. Chem.*, 1963, **41**, 148.
[4] T. Birchall and R. J. Gillespie, *Canad. J. Chem.*, 1963, **41**, 2642.

The chemical shifts of the solvent peaks, relative to water as external reference, were found to be $-5{\cdot}95 \pm 0{\cdot}02$ p.p.m. for the fluorosulphuric acid solution and $-6{\cdot}17 \pm 0{\cdot}02$ p.p.m. for the sulphuric acid solution, which with a chemical shift of $-4{\cdot}73$ p.p.m. for water gives shifts on the $\delta$ scale of $-10{\cdot}68$ p.p.m. and $-10{\cdot}90$ p.p.m., respectively. These figures have been used in the recalculation of the chemical shifts to the $\delta$ scale in Table 1. Table 1 summarizes all the chemical shift and spin-coupling data for 26 °C.

The effect of diluting 100% sulphuric acid with water on the appearance of the spectrum of the $NH_2$ group of the acetamide cation is shown in Figure 2. The arrow indicates the approximate variable position of the solvent peak.

With increasing temperature all the lines in the spectrum shift downfield relative to the solvent peak (Table 2). There was no evidence of any change in the NH coupling constants with temperature. The resonance lines of the resonances with the solvent peak at *ca.* 110 °C. The resonance of the ammonium ion (doublet, $J$ 75 Hz) also appears at this temperature due to hydrolysis.

TABLE 1

N.m.r. spectra ($\delta$ in p.p.m.; $J$ in Hz) of the *O*-protonated cation of [$^{15}$N]acetamide in fluorosulphuric and in 100% sulphuric acid at 26 °C *

| | Fluorosulphuric acid | | 100% Sulphuric acid | | |
|---|---|---|---|---|---|
| | (a) † | (b) ‡ | (a) † | (b) ‡ | Water [5] |
| $\delta_{CH_3}$ | 8·24 | −2·44 | 8·24 | −2·66 | −2·03 |
| $\delta_A$ | 2·66 | −8·02 | 2·40 | −8·50 | −7·53 |
| $\delta_B$ | 2·84 | −7·84 | 2·76 | −8·14 | −6·78 |
| $\Delta\delta_{AB}$ | 0·177 | | 0·356 | | 0·756 |
| $\nu_0 \cdot \Delta\delta_{AB}$/Hz | 15·9 | | 32·0 | | 68·0 |
| $^2J(H_A - H_B)$ | | | | | 2·2 |
| $^1J(^{15}N - H_A)$ | 96·6 | | 96·0 | | 90·9 |
| $^1J(^{15}N - H_B)$ | 93·2 | | 92·8 | | 88·4 |
| $^3J(^{15}N - CH_3)$ | 1·8 | | 2·0 | | 1·3 |

* The resonance of the OH peak is observable only in fluorosulphuric acid at low temperature.[1,3] $\nu_0 = 90$ MHz.

† Shifts relative to the solvent peak as lock signal and internal reference. ‡ Shifts recalculated to the $\delta$ scale using water as external reference, for which $\delta = -4{\cdot}73$ p.p.m.

TABLE 2

Chemical shifts (p.p.m.) relative to the solvent peaks of the resonance lines of [$^{15}$N]acetamide in anhydrous acids at higher temperatures

| Temp. | Fluorosulphuric acid | | | 100% Sulphuric acid | | |
|---|---|---|---|---|---|---|
| (K) | $\Delta\delta_{CH_3}$ | $\Delta\delta_{H_A}$ | $\Delta\delta_{H_B}$ | $\Delta\delta_{CH_3}$ | $\Delta\delta_{H_A}$ | $\Delta\delta_{H_B}$ |
| 299 | 8·24 | 2·66 | 2·84 | 8·24 | 2·40 | 2·76 |
| 317 | 8·13 | 2·58 | 2·76 | 8·18 | 2·34 | 2·70 |
| 334 | 8·06 | 2·51 | 2·69 | 8·09 | 2·30 | 2·64 |
| 349 | 7·98 | 2·47 | 2·65 | 8·00 | 2·32 | 2·42 |
| 353 | | | | | Collapse | |
| 363 | 7·91 | 2·44 | 2·62 | | 2·30 | |
| 368 | | 2·42 | 2·60 | | 2·22 | |
| 373 | | 2·40 | 2·57 | | Collapse of the | |
| 378 | | 2·39 | 2·54 | | $^{15}$N–H coupling. | |
| 383 | | 2·39 | 2·52 | | Coalescence with | |
| 388 | | 2·39 | 2·50 | | the solvent peak | |
| 393 | | 2·40 | | | | |
| | | Collapse | | | | |

NH protons show exchange averaging at higher temperatures, with a striking difference in the coalescence temperatures between the solutions in sulphuric acid and in fluorosulphuric acid. While the two NH doublets of the cation in sulphuric acid collapse to one doublet at *ca.* 80 °C, the spectrum in fluorosulphuric acid is unchanged up to 90 °C and the collapse is observed only at 120 °C. At still higher temperatures in sulphuric acid solution the exchange of the NH protons clearly involves the solvent, since there is a collapse of the $^{15}$NH coupling and a final merging of the NH

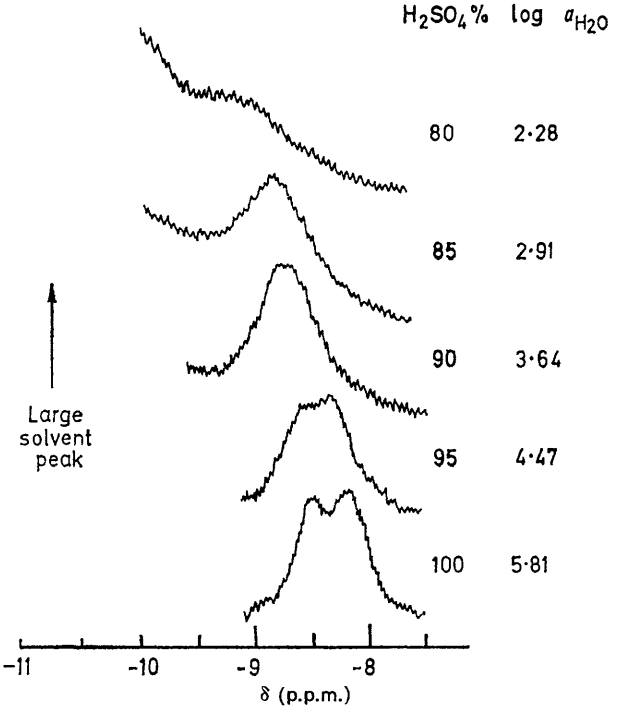
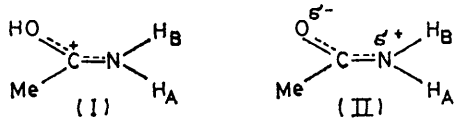



FIGURE 2 The n.m.r. spectrum of the $NH_2$ group of acetamide in concentrated sulphuric acid of variable concentration at 33·5 °C and 60 MHz

Double irradiation of the centre of the methyl resonance led to a sharpening of the peaks of the NH protons. Under double irradiation the line-widths of the peaks of both NH protons become identical.

## DISCUSSION

*N.m.r. Spectra of the* O*-Protonated Cation of Acetamide.*—The spectra of [$^{15}$N]acetamide in sulphuric acid and in fluorosulphuric acid, shown in Figure 1, are compared with those in water in Table 1. The fact that the low-field NH peak of the *O*-protonated cation (I) shows a larger splitting by the $^{15}$N nucleus than the high-field peak, as is also found in the spectra of the unprotonated amide (II) in water and other solvents,[5] may be used to




assign the low-field peak to the NH proton *cis* to the methyl group ($H_A$). However, unlike the spectrum in water, the spectra of the cation show the $H_A$ resonance broadened more than the $H_B$ resonance (half-widths 1·8 and 1·4 Hz, respectively, in fluorosulphuric acid, and 2·4 and 1·8 Hz in sulphuric acid). By double irradiation of the methyl protons both peaks become of identical width, which means that the broadening is due to

[5] M. Liler, *J. Magnetic Resonance*, 1971, **5**, 333.

coupling to the methyl group. There is no broadening due to the OH proton, probably owing to its rapid exchange with the solvent. The lines in sulphuric acid are in addition viscosity broadened. Since the low-field resonance is broadened more than the high-field resonance, the above assignment seems to be confirmed, because in allylic systems the *cis*-couplings are usually larger than the *trans*-couplings,[6] and cation (I) contains an allylic-type system of bonds.

The $^{15}N$–H coupling constants in the cation are considerably larger than those in the unprotonated amide in water, corresponding to a change from a flat pyramidal geometry at the nitrogen in the amide to a planar $sp^2$ configuration in the cation (*cf.* ref. 7) The difference in the coupling constants of the $H_A$ and the $H_B$ protons to the $^{15}N$ nucleus in the cation of 3·2—3·4 Hz is also greater than the corresponding differences in the spectra of the unprotonated amide in water (Table 1) and other solvents,[5] and is also presumably due to a difference in bond lengths.

One further difference between the amide and its cation is in the magnitude of the geminal coupling, which is 2·2 Hz in the unprotonated amide in water and is unresolvable in the cation. The $^{15}N$–$CH_3$ coupling is, on the contrary, enhanced by protonation, and the values of 1·8 and 2·0 Hz are both within 0·1 Hz equal to the coupling reported in *N*-methyl-2-hydroxy-3-acetonaphthone imine, for an element of structure $CH_3$–$\overset{|}{C}$=$^{15}N$– in which a double C–N bond is present.[8] This may mean that the C–N bond is virtually double in the *O*-protonated cation of the amide, which would be the case if the positive charge were carried predominantly on the nitrogen, but the charge delocalization shown in structure (I) could equally be responsible for it, since the partial positive charge on the carbon would further be spread by hyperconjugation into the methyl group, thus imparting some partial double-bond character to the C–C bond.

While differences in the coupling constants in the amide cations in fluorosulphuric acid and in 100% sulphuric acid are not large, there is a remarkable difference in the relative chemical shifts of the two non-equivalent NH protons. The relative shift is twice as large in sulphuric acid as in fluorosulphuric acid (Figure 1). Both are considerably smaller than the relative shifts in water (Table 1) and other solvents.[5] This relative chemical shift is thus highly medium sensitive.

*The Effect of Acid Concentration on the Spectrum of the* O-*Protonated Cation.*—The spectrum of the *O*-protonated cation in 100% sulphuric acid, discussed in the preceding section, undergoes changes as the acid is diluted with water. These changes have been studied using ordinary acetamide and therefore the resonances of the two NH protons are considerably broadened by interaction with the $^{14}N$ quadrupole (Figure 2). The non-equivalence of the two NH protons is clear in the 100% acid, but as water is added exchange averaging becomes apparent and at higher water concentrations rapid exchange with the solvent sets in. These spectral changes are readily explainable in terms of the cation tautomeric equilibrium:

$$CH_3-\overset{OH}{\overset{|}{C}}=NH_2,l\,H_2O + m\,H_2O \underset{k_r}{\overset{k_f}{\rightleftharpoons}} Me-\overset{O}{\overset{\|}{C}}-\overset{+}{N}H_3,n\,H_2O$$

in which higher water activities progressively favour the *N*-protonated form, because this is more stabilized by hydration (*i.e.* $n > l$) owing to its localized positive charge.[1]

Hydrogen-bonding stabilization of ammonium ions is a well known phenomenon.[9] It has gained further support recently from studies of acidity functions for the protonation of primary and tertiary nitroanilines [10] and diarylolefins.[11] Differences in cation hydration affect the activity coefficients of the conjugate acids, which are not measurable quantities, but a direct demonstration of differences in *relative* activity coefficients of a number of cations in sulphuric acid solutions has been possible.[12] In terms of these results a cation with a smaller hydration requirement, such as the *O*-protonated cation of amides, is favoured in highly acidic media of low water activity. In aqueous acid the *N*-protonated cation is favoured, for acetamide in an approximate ratio of $10^6$ : 1, obtainable from the measured $pK_{BH^+}$ of acetamide of −0·93 [13] and the estimated $pK_{BH^+}$ for carbonyl protonation in the same medium of *ca.* −6·7.[14a] This corresponds to a standard free energy change for tautomerization of about −33 kJ $mol^{-1}$, which is of the order of magnitude of hydrogen bonding energies. The p*K* values of protonated acetamide and its *NN*-dimethyl derivative are entirely consistent with those of other substituted ammonium ions.[14b]

Figure 2 shows, apart from acid concentrations, also the activities of water in the mixtures (data from ref. 15). These are seen to increase more than a 1000-fold between 100% and 80% acid. A 100-fold increase in the activity of water (*ca.* 90% acid) is seen to lead to the coalescence of the two peaks. In this medium the life-time of the two NH states at 33·5 °C may be estimated [16] from the formula:

[6] J. W. Emsley, J. Feeney, and L. H. Sutcliffe, ' High Resolution N.M.R. Spectroscopy,' Pergamon Press, 1966, vol. 2, p. 737.
[7] G. Binsch, J. B. Lambert, B. W. Roberts, and J. D. Roberts, *J. Amer. Chem. Soc.*, 1964, **86**, 5564.
[8] G. O. Dudek and E. P. Dudek, *J. Amer. Chem. Soc.*, 1964, **86**, 4283.
[9] A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1949, 1293.
[10] E. M. Arnett and G. W. Mach, *J. Amer. Chem. Soc.*, 1964, **86**, 2671.
[11] N. C. Deno, P. Groves, and G. Saines, *J. Amer. Chem. Soc.*, 1959, **81**, 5790.
[12] R. H. Boyd, *J. Amer. Chem. Soc.*, 1963, **85**, 1555.
[13] M. Liler, *J. Chem. Soc.*, 1969, 385.
[14] M. Liler, ' Reaction Mechanisms in Sulphuric Acid and Other Strong Acid Solutions,' Academic Press, London, 1971, (*a*) p. 134; (*b*) p. 107—108; (*c*) p. 199.
[15] W. F. Giauque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *J. Amer. Chem. Soc.*, 1960, **82**, 62.
[16] J. A. Pople, W. G. Schneider, and H. J. Bernstein, ' High-Resolution Nuclear Magnetic Resonance,' McGraw-Hill Book Co., Inc., 1959, p. 100 ff.

$$\tau = \frac{\sqrt{2}}{2\pi(\nu_A - \nu_B)}$$

to be *ca.* 0·01 s. The molarity of water in this solution is *ca.* 10M, but most of it is protonated according to the Raman spectra of the solutions.[17,18] In concentrated sulphuric acid the mechanism for averaging the resonances of the two NH protons in the *O*-protonated cation is by tautomerization *via* a deprotonation–*N*-protonation path involving the solvent. The OH proton is in rapid exchange with the solvent at room temperature, and its resonance separates from the solvent peak only at low temperature.[1,3] The rate of formation of the *N*-protonated form is given by

$$\text{Rate} = k_f[\text{Me}-\overset{\overset{\text{OH}}{|}}{\underset{|}{\text{C}}}=\overset{+}{\text{N}}\text{H}_2][\text{H}_2\text{O}]^m$$

and is determined by the concentration of water. Thus the first order tautomerization constant involves the concentration of water and is therefore medium dependent.

When rapid exchange of NH protons with the solvent occurs, n.m.r. spectra no longer afford any evidence of the presence of the *O*-protonated form. This is the case in *ca.* 75% sulphuric acid. In 72% perchloric acid, in which water activity is of the same order of magnitude as in 75% sulphuric acid (as may be estimated by an extrapolation from the accurate measurements up to 61·2% acid by Haase *et al.*[19]), the spectra of the *O*-protonated cations of primary amides are not observable, *i.e.* no NH resonance separates out of the solvent peak. Chemical shift measurements[13] show that acetamide is protonated to the extent of 99·9% in 72% sulphuric acid and at any lower acidity there is rapid exchange of the NH protons with the solvent. Light absorption measurements are the only possible means of estimating the position of the tautomeric equilibrium under such conditions. Substantial changes in the ultraviolet spectrum of benzamide between 60 and 97% sulphuric acid have in fact been reported and ascribed to a medium effect.[20a] These changes are consistent with the view that there is a tautomeric change of the cation from the *N*-protonated form to the *O*-protonated form over this acid concentration range. This is further supported by a demonstration that the benzamide spectrum in 59·3% sulphuric acid is almost identical with that of unprotonated acetophenone in 50% sulphuric acid,[20b] whereas that in 100% sulphuric acid is virtually identical with that of ethyl benzimidate in the same solvent.[21]

Finally, it is instructive to enquire under what conditions the spectrum of the *N*-protonated cation would be observed. An analogy with the protonation of methylamine[22] suggests that the n.m.r. spectrum of the *N*-protonated cation of acetamide would be observed in solutions of acidity some $10^{10}$ times greater than that at the point of half-protonation, *provided that the medium remains aqueous.* This clearly cannot be achieved with any aqueous acid system, because acetamide is half-protonated in 19% sulphuric acid ($a_{H_2O} = 0{\cdot}89$) and it is impossible to increase acidity without substantially reducing the activity of water. It is not impossible, however, that *N*-protonated cations will be sufficiently stable in some other solvents. Olah and Szylagyi[23] in fact report the spectra of both the *O*-protonated cation of *N*-acylaziridine in ' magic acid ' (fluorosulphuric acid–antimony pentafluoride, diluted with sulphur dioxide) and the *N*-protonated cation as hexafluoroantimonate in liquid sulphur dioxide. Presumably the latter solvent has a sufficient capacity for stabilization of the *N*-protonated cation by hydrogen bonding. Bruylants and his collaborators[24] also provide some n.m.r. evidence for the presence of the *N*-protonated form of dinitro-2,4-formanilide in acetone–45% chlorosulphuric acid and suggest a variable tautomeric ratio depending on the medium.

*The Effect of Temperature on the Spectra of* O-*Protonated Cations.*—The activation energy for the exchange of NH protons between the sites A and B for the *O*-protonated cation of [$^{15}$N]acetamide can be calculated from the temperature dependence of the lifetimes of these states. These are obtainable from the relative chemical shift[16] using the formula:

$$\frac{\text{Separation of peaks}}{\text{Separation of peaks at large } \tau} = \left[1 - \frac{1}{2\pi^2\tau^2(\nu_A - \nu_B)^2}\right]^{\frac{1}{2}}$$

since the peaks of the NH protons are sharp and well separated at large $\tau$. The logarithms of $\tau$ values plotted against $1/T$ have yielded activation energies of $60 \pm 6$ kJ mol$^{-1}$ for the cation in fluorosulphuric acid and $43 \pm 6$ kJ mol$^{-1}$ for the cation in 100% sulphuric acid. Consistent with this, the coalescence temperature of the two peaks is much higher in fluorosulphuric acid (120 °C) than in 100% sulphuric acid (80 °C).

There are two possible pathways by which exchange of the two NH sites may take place: (1) by rotation around the C–N bond, which should have a greater double bond character in the *O*-protonated cation than in the unprotonated amide, and (2) by conversion of the *O*-protonated cation into the *N*-protonated cation in which rotation around the C–N bond is free.

The activation energies for exchange found in fluorosulphuric acid and in 100% sulphuric acid are both lower than the activation energies of 63—71 kJ mol$^{-1}$ found for rotation in the unprotonated amide.[5] In fact, all activation energies for rotation in *O*-protonated amide

[17] T. F. Young, L. F. Maranville, and H. M. Smith, in ' The Structure of Electrolyte Solutions,' ed. W. J. Hamer, Wiley, New York, 1959.

[18] M. I. Vinnik and N. G. Zarakhani, *Zhur. fiz. Khim.*, 1960, **34**, 2671.

[19] R. Haase, H. K. Dücker, and H. A. Küppers, *Ber. Bunsengesellschaft Phys. Chem.*, 1965, **69**, 97.

[20] (*a*) J. T. Edward and S. C. R. Meacock, *J. Chem. Soc.*, 1957, 2000; (*b*) J. T. Edward, H. S. Chang, K. Yates, and R. Stewart, *Canad. J. Chem.*, 1960, **38**, 1518.

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

[22] E. Grunwald, A. Loewenstein, and S. Meiboom, *J. Chem. Phys.*, 1957, **27**, 630.

[23] G. A. Olah and P. J. Szylagyi, *J. Amer. Chem. Soc.*, 1969, **91**, 2949.

[24] S. R. de Lockerente, O. B. Nagy, and A. Bruylants, *Org. Mag. Resonance*, 1970, **2**, 179.

cations so far reported in the literature are approximately equal to or a little larger than the values for the unprotonated amides.[25,26] This is inconsistent with the view that rotation occurs around a C–N bond, which has a greater double-bond character than the C–N bond in the unprotonated amide. The difference between the bond energies of a single and a double C–N bond is 309 kJ [27] and activation energies of this order of magnitude would be expected for rotation around a virtual double-bond present in the *O*-protonated amide. The small activation energies found experimentally seem to rule out this mechanism of exchange.

Exchange of hydrogen nuclei between the two NH sites in the *O*-protonated cation through conversion into the *N*-protonated cation will be determined by the rate of that process. This is analogous to the case of rotation around the C–N bond in the amides in dilute acid, where rotation is induced by *N*-protonation and the lifetimes of the protons in the two non-equivalent positions are inversely proportional to the hydrogen ion concentration.[28] The activation energies found by experiment are therefore activation energies for the tautomerization reaction. Since this occurs *via* a deprotonation–reprotonation path involving the solvent, the rate in sulphuric acid, which is less acidic and has a higher water activity than fluorosulphuric acid, may be expected to be higher. Water has a catalytic effect on the interconversion of the two forms and hence provides a path of lower activation energy in sulphuric acid (in which $a_{H_2O} = 1{\cdot}56 \times 10^{-6}$), as compared with fluorosulphuric acid in which it is entirely absent. Since the interconversion of the two forms occurs *via* proton transfers involving the solvent, at high rates of this process, averaging of the two NH resonances and also of the NH resonances and the solvent resonance would be expected, as is indeed found (Table 2). The tautomerization mechanism of exchange of the two sites thus accounts for all the experimental observations.

*Implications.*—The tautomeric changeover of amide cations from *N*-protonation in aqueous acids to *O*-protonation in anhydrous acids has considerable implications for the mechanism of hydrolysis of amides. On the assumption that the dominant form of the cation in aqueous acids is the *O*-protonated form, it has proved impossible to formulate a satisfactory mechanism of acid-catalysed hydrolysis of amides.[24,29,30] In particular the virtual absence of oxygen exchange in the acid-catalysed hydrolysis of amides, demonstrated in dilute acid [31] and recently confirmed in both dilute and 8·4M-hydrochloric acid,[32] cannot be reconciled with an *O*-protonated reactant, because in the nucleophilic attack by water molecules upon such a species the same intermediate as in alkaline hydrolysis of amides would be formed, containing $NH_2$ as the leaving group. This is a poor leaving group and consequently acid hydrolysis of amides should then be accompanied by fast oxygen exchange, as is alkaline hydrolysis.[31] Also, if $NH_2$ were the leaving group, it would be impossible to account for an excellent relationship of the logarithms of $k_{hydr}/k_{exch}$ with $\sigma_m$ constants of the leaving groups, which has been found to hold for the rates of hydrolysis and oxygen exchange of *all* carboxylic acid derivatives, $-NH_3^+$ being the leaving group for amides in acid solution.[14c]

Another feature of the acid hydrolysis of amides upon which the tautomeric equilibrium has a considerable bearing is the rate maximum observed in moderately concentrated acid. This has usually been understood to arise from a progressive protonation of amides with increasing acidity of the solutions coupled with decreasing water activity.[20,33–35] Since water takes part in the hydrolysis step of the reaction, plots of log $k_{obs}$ — log $h_A/(K_{BH^+} + h_A)$ *vs.* log $a_{H_2O}$ have been assumed to yield information on the number of water molecules in the transition state ($n = 3 \pm 0{\cdot}4$ was found to fit the data).[34] An alternative suggestion has been made by de Lockerente *et al.*[24] that the maximum in the rate of hydrolysis of amides corresponds to a maximum in the concentration of the *N*-protonated form in a medium-dependent tautomeric equilibrium of the two forms, and some evidence has been provided to support it. This however involves n.m.r. spectra in methanolic sulphuric acid. The fact that oxygen exchange in the hydrolysis of benzamide and its *N*-methyl and *NN*-dimethyl derivatives is absent even in 8·4M-hydrochloric acid,[32] *i.e.* beyond the rate maximum at 3—4M-acid, seems to conflict with this suggestion. It is unlikely that the concentrations of *O*-protonated cations are significant at these acid concentrations, at least for primary amides. Amides containing highly electron-withdrawing *N*-substituents have been shown to undergo unimolecular hydrolysis in concentrated sulphuric acid by fission of the *N*-protonated form,[36] which is therefore still present in that medium in kinetically significant amounts. The production of the ammonium ion from [$^{15}$N]acetamide in sulphuric acid at 110 °C, observed in this work, presumably also occurs by this mechanism.

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