N- versus O-Protonation. Evidence from Nuclear Magnetic Resonance Spectra of [^{15}N]Acetamide in Fluorosulphuric Acid

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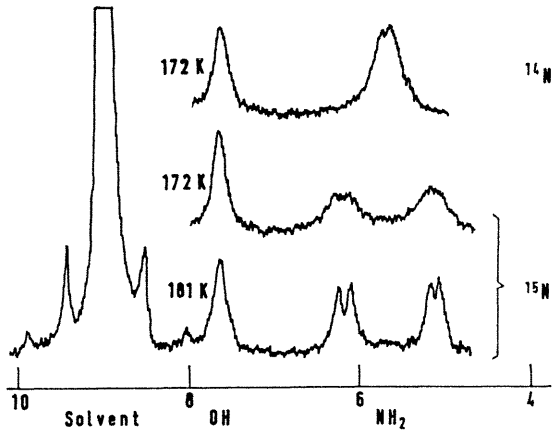
Summary As n.m.r. spectra of [^{15}N]acetamide in fluorosulphuric acid at low temperature confirm that the cation exists in the *O*-protonated form in that medium, it is concluded that *N*-protonated cations formed in dilute acids are converted into *O*-protonated cations in anhydrous acids owing to a medium effect associated with cation hydration.

N.M.R. spectra of amides in acid solutions have provided conflicting information on the site of their protonation. On the one hand, the spectra in dilute acid show NH exchange and the onset of free rotation in the cation,[1] both facts consistent with *N*-protonation, and on the other, the spectra in concentrated acids (sulphuric and perchloric) show nonequivalence of the groups attached to the nitrogen,[2,3] and the captured proton turns out to be nonequivalent with the other NH protons in primary and secondary amides in fluorosulphuric acid at low temperature,[4,5] both facts consistent with *O*-protonated structures of the cations. On the assumption that increasing acid concentration merely reduces the rate of proton exchange and stabilizes the cation formed in dilute acid, a generalization was made that the dominant form of the cation formed even in dilute acid must be the *O*-protonated form[1]. The *N*-protonated form was assumed to be present in only negligible amount to account for free rotation.[1] Studies of n.m.r. spectra in conjunction with chemical shifts caused by protonation[6] have shown that for a number of substituted acetamides and their *N*-methyl and *NN*-dimethyl derivatives the spectra throughout the protonation region up to virtually full protonation are entirely consistent with *N*-protonation and afford no evidence of any other type of protonation. It was therefore conceivable that the spectra in concentrated acids could be due to a fixation of structure of *N*-protonated cations by hydrogen-bonding with the solvent. The spectra reported in the literature[3-5] leave some room for ambiguity, *e.g.* the coupling of the NH protons in the formamide spectrum with the ^{14}N nucleus, which suggests tetrahedral symmetry around the nitrogen.[4] Also, in the low-temperature spectrum of acetamide in fluorosulphuric acid[4] the resonance of the captured proton has been reported as very broad (23·2 Hz) which could have been due to exchange, but could also have been due to the captured proton being on the nitrogen and in addition hydrogen-bonded to the solvent.

To resolve this ambiguity the spectra of [^{15}N]acetamide and ordinary acetamide were recorded in fluorosulphuric acid at low temperature under identical conditions on a Brüker n,m.r. spectrometer at 90 MHz. The results are shown in the Figure. The *C*-methyl resonance (not shown) was used as the lock signal. It can be seen that, while the two resonances of the NH_2 protons are split by the ^{15}N nucleus [J(^{15}N–H) 96·5 Hz and 92·5 Hz], the resonance of the captured proton, which is now well separated from the solvent peak and shows no evidence of exchange, remains quite unaffected by the substitution of ^{15}N for ^{14}N and cannot hence be due to a proton on the nitrogen. The spectrum is thus due to the *O*-protonated cation.



FIGURE

N.m.r. spectra thus strictly provide no evidence of *O*-protonation in dilute acid and throughout the protonation region for most amides and also provide firm evidence for the presence of *O*-protonated cations in anhydrous sulphuric acid and in pure fluorosulphuric acid. All aspects of the chemical behaviour of amides in dilute and moderately concentrated acids, including their acid–base behaviour in the protonation region (pK values,[6,12] substituent effects on basicity,[7,8] acidity function behaviour[9]), are also consistent with *N*-protonation. All the evidence is thus consistent with a changeover from *N*-protonation in the largely aqueous acid media to *O*-protonation in the anhydrous acid media.

This changeover can be understood in the same terms as the multiplicity of acidity functions in concentrated acids. A changeover is to be expected if the activity coefficient of the *N*-protonated form increases sufficiently relative to that of the *O*-protonated form with increasing acid concentration. The two types of conjugate acid of amides, the *N*-protonated and the *O*-protonated form, are likely to have different activity coefficients and to bind water by solvation through hydrogen bonding to different extents. Work done on relative activity coefficients of a variety of conjugate acids of very weak bases in aqueous acids over the past few years (reviewed by Boyd[10]) leads one to expect that cations with a localized charge, such as the *N*-protonated amide cations, would show more sharply rising activity coefficients with increasing acid concentration than cations with a delocalized charge, such as the *O*-protonated cations. It has in fact been found experimentally[11] that the activity coefficient of the benzoylammonium ion relative to the tetraethylammonium ion increases very sharply in sulphuric acid solutions up to 70%, even more than those of anilinium ions.

If we represent the equilibrium between the two tautomeric forms by the equation:

$$O{=}\underset{\displaystyle R}{\overset{\displaystyle +}{C}}{-}\overset{\displaystyle +}{N}H_3{\cdot}pH_2O \rightleftharpoons HO{\cdots}\underset{\displaystyle R}{\overset{\displaystyle +}{C}}{\cdots}NH_2{\cdot}qH_2O + rH_2O \quad (1)$$

with both cations hydrated, then it is reasonable to expect that r should be positive. Taking into account only the primary hydration by hydrogen bonding (*i.e.* $p = 4$, $q = 3$) a minimum estimate of $r = 1$ is obtained. The equilibrium constant for this reaction may be written as:

$$\frac{[\overset{\displaystyle +}{R}C(OH)NH_2\text{aq.}]f_{OH}a_{H_2O}^{r}}{[RCONH_3^{+}\text{aq.}]f_{NH}} = K \quad (2)$$

where f_{NH} and f_{OH} represent activity coefficients of the *N*- and the *O*-protonated forms, respectively, and a_{H_2O} is the activity of water. This equilibrium constant for benzamide may be estimated from the measured pK referring to *N*-protonation[8] and the estimated pK for carbonyl protonation[12] to be of the order of 10^{-4}. An analogous estimate for acetamide gives a value of about 10^{-6}. Both show the vast preponderance of the *N*-protonated form in the protonation region of these amides. If equation (2) is solved for the concentration ratio of the two forms

$$\frac{[\overset{\displaystyle +}{R}C(OH)NH_2\text{aq.}]}{[RCONH_3^{+}\text{aq.}]} = K\frac{f_{NH}}{f_{OH}a_{H_2O}^{r}} \quad (3)$$

it can be seen that as water activity decreases (by a factor of *ca.* 10^5 between 60 and 100% sulphuric acid) and the activity coefficient ratio rises with decreasing availability of water for cation hydration, a complete reversal in the position of the equilibrium in going to an anhydrous medium can easily be accounted for. The changeover from *N*-protonated cations in dilute and moderately concentrated acids to *O*-protonated cations in highly concentrated and anhydrous acids is thus a medium effect, due to decreasing availability of water for cation hydration.

The region of acid concentrations in which the changeover for various amides occurs is not exactly predictable, but n.m.r. spectra show line broadening of the NR_2 or the NHR resonances owing to the emergence of the *O*-protonated form only in the region of full protonation for *N*-methyl- and *NN*-dimethyl-acetamides[6] and *N*-alkylformamides,[13] and only at high degrees of protonation (*ca.* 90%) for *NN*-dialkylformamides.[13] The *O*-protonated form of *NN*-dialkylformamides appears thus to be relatively more stable.

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