^{1}H, ^{13}C, and ^{14}N Nuclear Magnetic Resonance Study of the Hydrogen Chloride–*NN*-Dimethylacetamide and Hydrogen Chloride–*N*-Methylacetamide Systems in Deuteriochloroform Solution

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Protonation shifts and ^{13}C T_1 values in the title systems are reported. Evidence is found for predominant *O*-protonation and for enhanced intermolecular association in the protonated forms of the amides.

DETERMINATION of the site of protonation in various acid–amide systems by n.m.r. methods has been an intriguing problem to chemists since the early days of applied n.m.r. spectroscopy.[1-3] Predominant *O*-protonation has now been established in almost all acid–amide systems studied so far.[4] The main evidence for *O*-protonation is increased proton–proton coupling constants across the amide bond, retained restricted rotation around the amide bonds upon protonation, and the observation of a separate ^{1}H peak at a very low field.[5] In special cases, the latter is unambiguously assignable to a $C{=}\overset{+}{O}{-}H$ proton.[5,6] By analogy, the presence of this peak also provides proof in other cases.

There is, however, clear evidence for partial *N*-co-ordination as well; the strongest evidence being the observation of increased rates to internal rotation around the amide bonds for certain ranges of acid : amide ratios. This rotation rate can readily be measured from ^{1}H or ^{13}C line shapes of the alkyl groups in symmetrically *N*-disubstituted amides.[4] An *N*-protonated amide will have a very rapid N–C rotation, since the partial double bond character of this bond will be destroyed upon *N*-protonation. Even if the amide is predominantly *O*-protonated the average N–C rotation rate will be strongly dominated by even a small fraction of such *N*-co-ordinated species, since there is rapid intermolecular H^+ exchange among the protonated molecules. A more complete discussion of these effects can be found in ref. 4.

Although inherently more powerful than ^{1}H n.m.r., ^{13}C n.m.r. has only very recently been used in studies of this kind. McClelland and Reynolds have reported a ^{13}C n.m.r. study of *NN*-dimethylformamide (DMF) in H_2O–H_2SO_4 solutions.[7] These authors concluded that DMF is predominantly *O*-protonated in these solutions, since non-equivalence of the ^{13}C methyl signals persists throughout the 0—100% H_2SO_4 solvent composition range. ^{13}C Protonation shifts are also given in this paper, although the reported values were expected to be uncertain, due to strong medium effects and the use of an external shift reference.

A calorimetric and ^{1}H n.m.r. study of HCl–*NN*-dimethylacetamide (DMA) in 1,2-dichloroethane solution was recently reported by Bernander and Olofsson.[8] These authors found clear evidence from both methods for initial *O*-protonation, followed by additional *N*-protonation past 1 : 1 HCl : DMA ratios. We found this system particularly suitable for an investigation of ^{13}C protonation shifts as a diagnostic tool regarding the predominant site of protonation in amides. It was, however, not possible to use exactly the same solution compositions as Bernander and Olofsson. For practical reasons $CDCl_3$ was used instead of 1,2-dichloroethane and it was also necessary to increase the DMA concentration as much as possible, since 5 mm tubes had to be used to enable parallel ^{1}H and ^{13}C n.m.r. runs to be made on the same samples. For comparison a brief

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[8] L. Bernander and G. Olofsson, *Tetrahedron*, 1972, **28**, 3251.

study was also made on the corresponding *N*-methylacetamide (NMA) system.

Exploratory ^{13}C T_1 and ^{13}C–{^1H} nuclear Overhauser effect (NOE) measurements were also made on unprotonated and fully protonated DMA and NMA. No such studies seem to have been reported previously. ^{14}N Line widths and protonation shifts of DMA were also recorded.

EXPERIMENTAL

Sample Preparations.—DMA and NMA were dried with 4 A molecular sieves. No impurities could be detected by n.m.r. Hydrogen chloride gas was obtained from Matheson Inc. and $CDCl_3$ from Ciba AG. The samples for the ^1H and ^{13}C titration study of DMA–HCl were prepared by standard techniques in a vacuum line in 5 mm medium wall tubes. These tubes were sealed off with a flame torch. The DMA concentration was kept constant *ca.* 1.3M in $CDCl_3$. Solubility problems were encountered at high HCl : DMA ratios at higher total concentrations.

The samples for the ^{14}N and ^{13}C T_1 study were prepared by bubbling HCl gas to saturation into a *ca.* 30% solution of the amide in $CDCl_3$. This solution was then purged with dry nitrogen gas to remove excess of HCl. The HCl : DMA and HCl : NMA ratios were then measured from relative integrals in the ^1H spectra. It was found that the DMA solution absorbed 1 mole HCl per mole DMA when samples were prepared in this way, but the NMA solutions only *ca.* 0.6 mole HCl per mole NMA. These solutions were then transferred to 10 mm tubes for ^{13}C studies and to 14 mm tubes for the ^{14}N n.m.r. measurements.

Apparatus.—The ^{13}C and ^1H shift study was made at *ca.* 35 °C on a Bruker WP-60 Fourier transform spectrometer using 4 K points in the transformed spectra (accuracy 0.1 for ^{13}C and 0.01 p.p.m. for ^1H). The ^{13}C T_1 study was made at *ca.* 30 °C by standard inversion–recovery pulse method on a JEOL FX-60 Fourier transform spectrometer, using the JEOL auto-T_1 computer program. Each T_1 value is based on at least six points on the semilogarithmic magnetization–pulse delay plot. The random error limits of the quoted T_1 values are estimated to be typically 10%.

Nuclear Overhauser effects were determined by comparing normal spectra with spectra recorded with the gated decoupling technique (with the proton broad-band decoupler on only during acquisition). A delay of at least four times the longest T_1 was introduced between pulses to prevent NOE build-up.

The ^{14}N study was made at 25 °C on a Varian V-4200 spectrometer operating at 1.402 T field strength.

All ^1H and ^{13}C shift values are given with reference to internal tetramethylsilane.

RESULTS

For reasons given in the Discussion section it is assumed that DMA and NMA are predominantly *O*-protonated in these solutions.

^1H *and* ^{13}C *Titration Study of DMA.*—^1H *Results.* The results are shown in Figure 1. The titration curves are entirely consistent with the formation of a relatively strong 1 : 1 complex between HCl and DMA, with little or no indications of formation of a $(HCl)_2$,DMA complex. The '$C{=}\overset{+}{O}{-}H$' peak position agrees well with previously reported values in similar solvents.[8] At HCl : DMA ratios >1.0 its shift will be averaged with the shifts for free HCl and/or an $\overset{+}{N}{-}H$ proton, which explains the change of slope in the titration curve.* At low HCl : DMA ratios water contamination (water protons will exchange rapidly with the HCl protons) has a very strong influence on the shift of this signal, since in $CDCl_3$ water has a shift >10 p.p.m. upfield from $C{=}\overset{+}{O}{-}H$. Therefore even 1 mole percent H_2O contamination shifts this signal significantly upfield for the lowest HCl : DMA ratios. These values have been omitted in Figure 1.

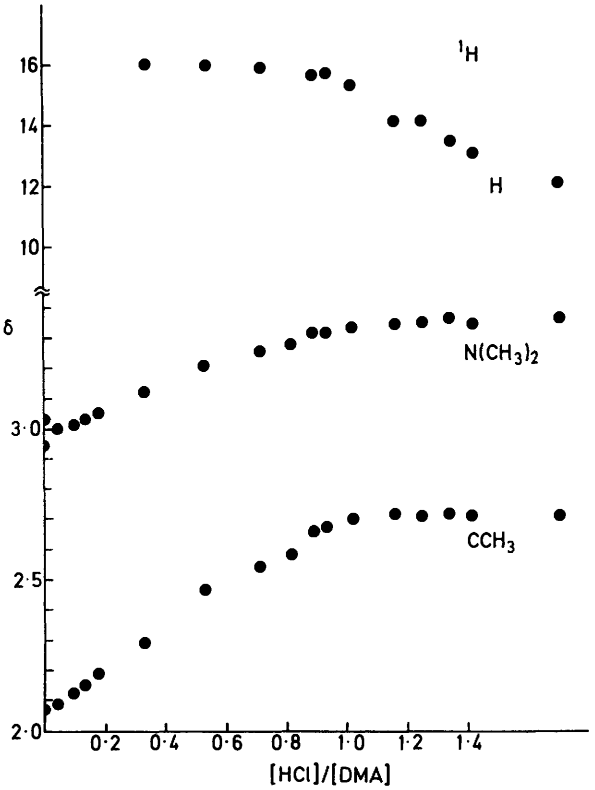

FIGURE 1 Observed ^1H n.m.r. shifts in the HCl–DMA system

^{13}C *Results.* Also the ^{13}C titration study (Figure 2) suggests the formation of a 1 : 1 HCl–DMA complex, perhaps with some indication of further 2 : 1 $(HCl)_2$,DMA formation from the $(CH_3)_2N$ shift curve. The C=O titration curve has the opposite slope to the one reported by McClelland and Reynolds for DMF in H_2SO_4.[7] However, their curve has a strange shape and is probably strongly influenced by medium effects.

It is interesting to note that even with the large ^{13}C shift difference between the *N*-methyl signals (*ca.* 60 Hz) in DMA, these signals coalesce already around HCl : DMA ratios of 0.05 at 35 °C.†

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* From extrapolation of this curve to HCl : DMA 2.0 one can estimate that the position of the exchanging second peak is δ *ca.* 4; a shift value which suggests 'free' HCl rather than a *N*-co-ordinated proton. [For example the shift of the 'acid proton' in $(C_2H_5)_3N$,HBr in $CDCl_3$ is δ *ca.* 10.5.]

† Effects of this type may well have influenced many determinations of amide barriers to internal rotation, as pointed out by Spaargaren *et al.*[9] Halogenated hydrocarbons have often been used as high temperature solvents. If the n.m.r. tubes are sealed off under inadequate conditions, HCl will be formed by pyrolysis.

[9] K. Spaargaren, P. K. Korver, P. J. van der Haak, and Th. J. de Boer, *Org. Magnetic Resonance*, 1971, **3**, 615.

^{13}C T$_1$ *Measurements.* As seen in the Table, ^{13}C longitudinal relaxation times decrease strongly upon protonation. The effect is real and not due to introduction of paramagnetic impurities, since the protonated compounds do show a maximum theoretical NOE (η *ca.* 2.0). Therefore the ^{13}C relaxation must be dominated by proton–carbon dipolar interaction.[10] The only reasonable interpretation for the large decrease in T_1 appears to be formation of larger molecular aggregates or chains, held together by hydrogen bonds and/or electrostatic attraction forces. Effects of a similar nature have been reported in a ^{13}C T_1 study of Bu^{n}NH$_2$ in CF$_3$CO$_2$H solution.[11]

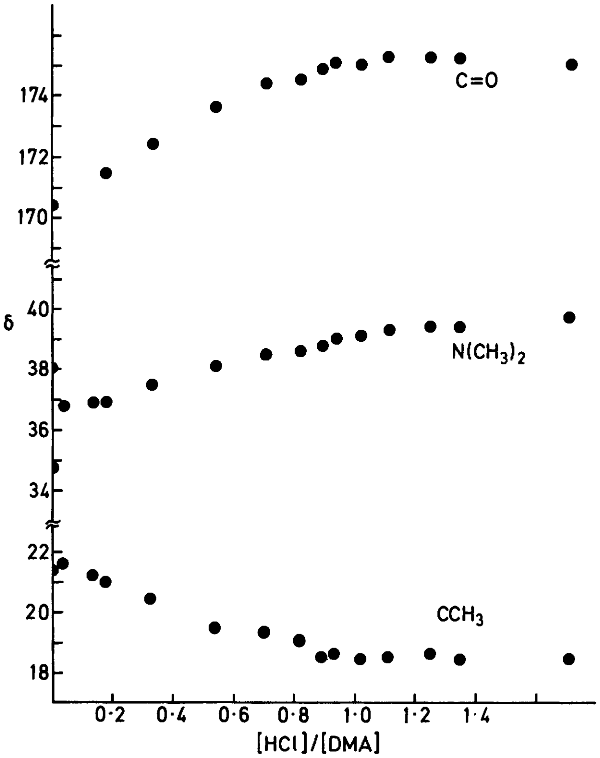

FIGURE 2 Observed ^{13}C n.m.r. shifts in the HCl–DMA system

		Protonation shifts (p.p.m.) ^{a}		^{13}C T_1 Values (s) ^{e}	
		^{1}H	^{13}C	Free amide	Protonated amide
DMA	(CH$_3$)$_2$N	+0.37	+2.9	13 (both)	3.1 ^{d}
	*C*H$_3$C	+0.64	−3.1	11	3.3 ^{d}
	C=O		+4.9	~40	7.7 ^{d}
NMA	CH$_3$N	+0.37 ^{b}	+2.4 ^{b}	6.8	1.8 ^{c}
	HN	+4.9 ^{b}			
	*C*H$_3$C	+0.48 ^{b}	−4.5 ^{b}	6.7	1.3 ^{c}
	C=O		+6.0 ^{b}	16	1.8 ^{c}

[a] δ(fully protonated amide) − δ(free amide). Downfield protonation shifts are thus given as positive. [b] Recalculated to 100% protonation (see Experimental section). [c] For *ca.* 60% protonated NMA (see Experimental section). [d] For fully protonated DMA. [e] Random error limits of T_1 values are typically ±10%.

The change in T_1 in our case would correspond to an increase in the rotational correlation time of *ca.* 4.[10]

^{14}N *Results.* Upon protonation the ^{14}N resonance of DMA shifts downfield 70 ± 10 p.p.m. and increases in width from *ca.* 270 to *ca.* 1 600 Hz (peak-to-peak line widths on the derivative of the absorption curve). Neglecting possible changes in the electric field gradient at the ^{14}N nucleus, the six-fold line width increase is consistent with the ^{13}C T_1 changes. (The ^{14}N spectra were recorded at a *ca.* 5 °C lower than the ^{13}C spectra.)

DISCUSSION

From n.m.r. data on HCl–DMA alone there is strictly no way to determine whether *O*- or *N*-protonation predominates. The *N*-methyl signals coalesce already at a very low HCl : DMA ratio which, according to the above discussion, only suggests that *some* *N*-protonation occurs. However, HCl–NMA shows four signals in its ^{1}H spectrum already at room temperature. Following the arguments of Gillespie and Birchall,[3] one of these cannot be an N–H signal and therefore must be a $C{=}\overset{+}{O}{-}H$ signal. A similar signal, at much the same shift, is seen in the HCl–DMA spectra and, furthermore, all corresponding ^{1}H and ^{13}C protonation shifts have the same sign and similar values for HCl–DMA and HCl–NMA, as seen in the Table. This provides conclusive proof that DMA also is predominantly *O*-protonated by HCl in CDCl$_3$.

The proton shift changes to low field appear reasonable in terms of the electron-withdrawing effect on the amide upon complexation. ^{13}C and ^{14}N shifts, on the other hand, are largely dominated by the paramagnetic term, and therefore are best interpretable through quantum mechanical calculations. These, in turn, require knowledge of the molecular geometry of the compound under study.

Very recent experimental studies of protonation shifts in amines have shown that *N*-protonation usually causes upfield ^{13}C shifts of N–C carbons.[12,13] This supports our conclusion that NMA and DMA are predominantly *O*-protonated, since we observed downfield shifts of these carbons.

In contrast to our results Bernander and Olofsson obtained clear evidence for the uptake of a second mole of HCl to form (HCl)$_2$,DMA.[8] These measurements were, however, made at a much lower DMA concentration in a different solvent. Our ^{13}C T_1 measurements indicate that there is strong intermolecular association of HCl–DMA and HCl–NMA. In more dilute solutions, as in the work by Bernander and Olofsson, such association will be less important. Therefore a possible interpretation of the difference in protonation behaviour might be that intermolecular association of HCl–DMA and HCl–HCl,DMA are competitive processes.

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