

Solvent Effects on the Amidic Bond

¹H Nuclear Magnetic Resonance Study of Acetamide and *N*-Methylacetamide

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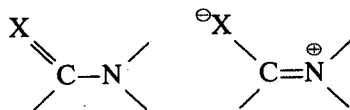
Received 17th March, 1981

The influence of various common basic solvents on the ¹H n.m.r. spectra of the N—H protons in *N*-methylacetamide and acetamide has been studied. The chemical shifts at infinite dilution show approximately linear relationships with the donor number of the solvent.

In strong donor solvents it is possible to observe the n.m.r. signals of two non-equivalent amidic protons in acetamide owing to the effect of the solvent on C—N rotation. The influence of the solvent on the chemical shifts and line splittings is discussed as well as the concentration effects by considering possible solute-solvent and solute-solute interactions.

The influence of the solvent on thioacetamide and some thioureas¹ has been found to occur *via* specific solute-solvent interactions. In these interactions both the amidic protons and the sulphur atom participate simultaneously, affecting the electron delocalization along the thioamidic bond. A similar effect has also been observed for *N*-methylacetamide by analysing the i.r. spectra in various media.^{2,3}

The electron delocalization described by the resonance ground-state structures



determines the height of the barrier for rotation about the C—N bond. The hindered rotation around the amidic bond and the existence of different rotamers have been extensively studied by n.m.r. spectroscopy.⁴

In order to obtain further information about the influence of the donor properties of solvents on the solute-solvent and solute-solute interactions occurring in amide solutions, we have studied the ¹H n.m.r. spectra of acetamide and *N*-methylacetamide in various common basic solvents.

EXPERIMENTAL

N-methylacetamide (Aldrich) and acetamide (Riedel De Haenag) were dried under vacuum on phosphorus pentoxide. The purity of the reagents was tested by their i.r. spectra. Solvents were purified by standard techniques⁵ and stored under nitrogen atmosphere over molecular sieves. Their purity was tested by running an n.m.r. spectrum at the highest amplitude of our equipment.

The ¹H n.m.r. spectra were run on a Varian T-60 spectrometer equipped with a T-6080 variable-temperature attachment using 5 mm o.d. tubes. The chemical shifts were determined using tetramethylsilane (TMS) as internal standard. Spectra were recorded for different concentrations of amide obtained by adding pure solvent to the probe. The chemical shift at infinite solution (δ_∞) was obtained by extrapolating to zero concentration the plot of δ against concentration (c).

RESULTS

The following ^1H n.m.r. spectra were investigated: *N*-methylacetamide (NMA) in 1,2-dichloroethane (DCE), nitromethane (NM), acetic anhydride (AA), acetonitrile (An), propan-1,2-diol carbonate (PDC), dioxan (Dx), ethylene sulphite (ES), methylacetate (Meac), ethylacetate, (Etac), diethyl ether (Et_2O), tetrahydrofuran (THF), trimethyl phosphate (TMP), tributyl phosphate (TBP), *N*-methylpyrrolidone (NMP), *NN*-dimethylacetamide (DMA), dimethylsulphoxide (DMSO) and hexamethylphosphoric triamide (HMPA); acetamide in acetonitrile, dioxan, methylacetate, acetone (Ac), tetrahydrofuran, trimethyl phosphate, tributyl phosphate, *N*-methylpyrrolidone, *NN*-dimethylacetamide, dimethylsulphoxide and hexamethylphosphoric triamide. At 35°C the spectra show practically negligible solvent effects for the methyl protons; however, the downfield signals corresponding to the NH and NH_2 protons show strong changes in chemical shift. In some cases there is even a splitting of the NH_2 signal.

Since the amidic protons also show strong concentration effects, the values reported here correspond to those calculated at infinite dilution (δ_∞).

The number of solvents and the concentration range studied were determined mainly by the solubility of the amide and the overlap of amide and solvent signals.

Fig. 1 and 2 show plots of the chemical shifts of the amidic protons at 35°C against the donor number of the solvent, N_D ,^{6,7} for NMA and acetamide, respectively. For NMA only one N—H signal was always observed, but for acetamide a splitting of the NH_2 proton resonances into two signals of equal area was observed at 35°C when the more basic solvents were used (fig. 2).

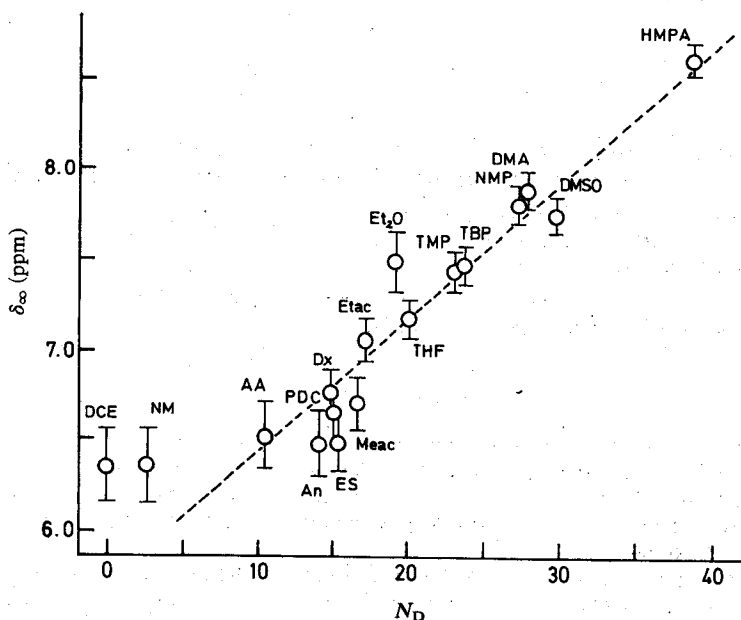


FIG. 1.—Relationship between the ^1H n.m.r. chemical shift at infinite dilution of the amidic proton in *N*-methylacetamide and the donor number of the solvents. δ (in ppm) is related to TMS as internal reference.

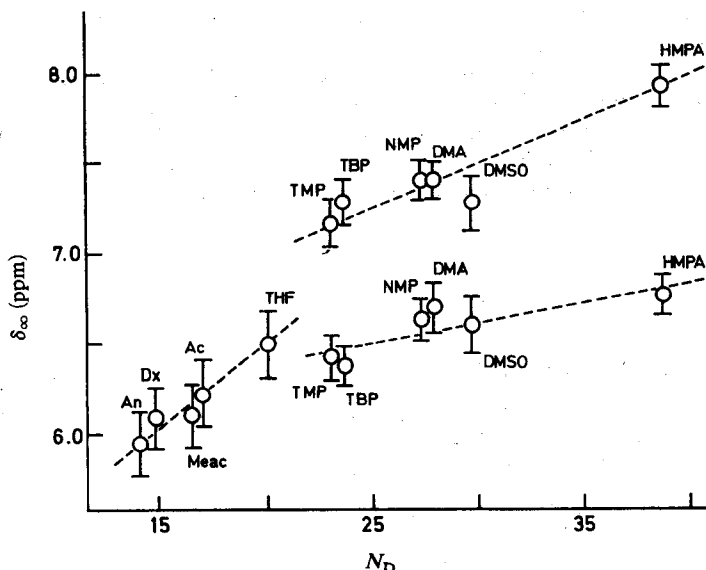


FIG. 2.—Relationship between the ^1H n.m.r. chemical shifts at infinite dilution of the amidic protons in acetamide and the donor number of the solvent. δ (in ppm) is related to TMS as internal reference.

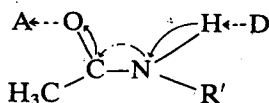
At temperatures higher than 35°C the two NH_2 signals for acetamide in the solvents with $N_D > 20$ approach each other, finally coalescing in the range $65\text{--}75^\circ\text{C}$. In those solvents with the lowest freezing points, TMP, TBP and HMPA, it could also be observed that at temperatures lower than 35°C the signals shifted downfield, diminishing their relative chemical shifts until, in some cases, they finally overlapped. The effect of temperature also increased with increasing amide concentration. At low temperatures the chemical shifts at infinite dilution cannot be calculated precisely, because of enhanced amide association (see below); however, an estimate of the relative chemical shifts between both signals at infinite dilution does not show a significant dependence of δ_∞ on temperature, so that the pattern shown in fig. 2 should be valid at any temperature.

DISCUSSION

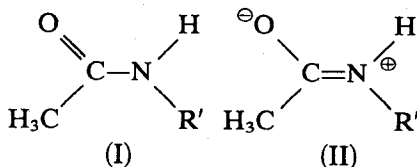
Hydrogen-bonding interactions induce downfield shifts in the n.m.r. signals of the interacting protons.⁸ The solvent effects on the chemical shifts of the amidic protons shown in fig. 1 and 2 can thus be interpreted as an increase in amide-solvent interactions through hydrogen bonding which increase with increasing donor strength of the solvents. The relatively linear relationships between δ_∞ and N_D (similar to those observed for some thioamidic compounds¹ and for the N—H bond stretching frequencies of NMA²) show that amidic protons in these compounds behave toward basic solvents like the Lewis acid SbCl_5 , and hence a donor-acceptor approach should be applicable to such interactions.

The splitting of the N—H₂ signals observed for acetamide in high donor media (fig. 2) parallels those reported for other primary amidic compounds at low temperatures,^{9,10} *i.e.* under suitable conditions for slow rotation around the C—N bond. A plausible interpretation of the two N—H peaks in acetamide spectra is therefore

the non-equivalence of the protons situated *cis* and *trans* about the carbonyl group. However, the reinforcement of the C—N linkage is in this case achieved by greater amide-solvent interactions. These results agree with our predictions about the solvent effect on the C—N amidic bond established by studying the influence of the donor and acceptor properties of solvents on NMA² and some thioamidic compounds.¹ Such effects have been explained by the bond-length variation rules, formulated within the framework of the donor-acceptor concept⁷



as well as by using the ground-state resonance structures



For NMA the configuration with the methyl group in the *trans* position is strongly predominant,¹¹ and hence no splitting of the N—H signal is observed.

The assignment of signals in acetamide spectra to *cis* and *trans* protons cannot be made from our experiments; however, for formamide, which also presents two non-equivalent protons on the nitrogen atom, the signal appearing to lower field has been assigned to the proton in the *trans* position. Nonetheless, the relative order of the *cis* and *trans* protons is not that expected from microwave studies of formamide,¹² which reveal that the *trans* N—H bond is 0.012 Å shorter than that of the *cis* N—H bond. Although there are undoubtedly other contributing factors to the screening constants besides the bond-length differences, it was suggested⁹ that this anomaly should be produced by hydrogen-bonding interactions that characterize the liquid state. This explanation seems to be reasonable since no discrepancy is observed when comparing the same gas-phase structural data¹² with spectroscopic data obtained for similar compounds in weaker coordinating media. Thus the spectra of formanilide in CHCl₃¹³ show the *cis* proton to be less screened than the *trans* one. Moreover, the stretching vibration of the N—H group in various *N*-monosubstituted amides dissolved in CCl₄ show higher frequencies for the *trans* than the *cis* N—H bond.¹⁴

The influence of media on the N—H bond properties discussed above are corroborated by our results. Assuming for acetamide the same assignment as that for formamide⁹ it can be clearly seen from fig. 2 that the *trans* proton (resonance at lower field) shows a greater dependence on N_D than the *cis* proton. For media of low donor number, an inversion of the relative positions of *cis* and *trans* proton signals could then be expected.

From the slopes of the curves in fig. 2 it is apparent that *trans* protons interact more strongly with the solvent than do *cis* protons. In this case, the non-equivalence of both *cis* and *trans* protons could be due at least partially to the different degrees of solvation of the two protons. This mechanism could be an alternative way of explaining the non-equivalence of amidic protons besides that based on the anisotropic magnetic contributions of the carbonyl group which is widely applied to the interpretation of n.m.r. spectra of substituted amides and related compounds.⁴

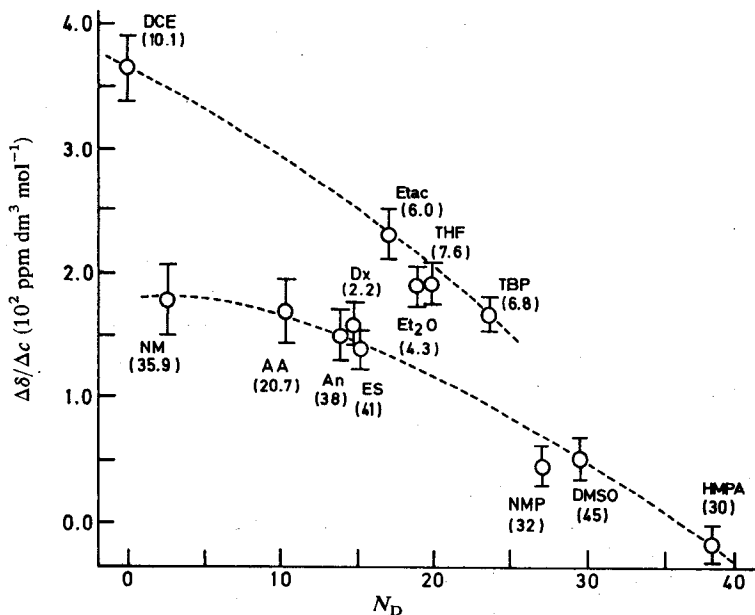
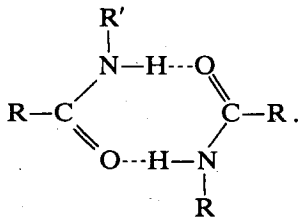


FIG. 3.—Relationship between the slopes of the shift (δ) with respect to the amide concentration (c), $\Delta\delta/\Delta c$, and the donor number of the solvent. The dielectric constant of each solvent is given in brackets.

In the preceding discussion we have considered only the chemical shifts at infinite dilution. However, relatively strong concentration shifts, generally towards lower field, were almost always observed. From this effect, quantitatively expressed by the slopes $\Delta\delta/\Delta c$, information about solute-solute interactions can be obtained. As expected, the relevance of hydrogen-bond interactions in amide association can be deduced from the curves shown in fig. 3 for *N*-methylacetamide, when the relation between $\Delta\delta/\Delta c$ and the solvent-donor strength can be appreciated. Moreover, the influence of the dielectric constant of the medium on these interactions can also be seen in fig. 3. This fact reveals that the participation of polar structure, partially represented by resonance structure (II), can cause solute-solute dipolar associations. The $\Delta\delta/\Delta c$ values for acetamide reproduced in table 1 show essentially the same pattern as those for NMA. However, the effect of concentration on the *cis* proton is stronger than that on the *trans* proton; *i.e.* a pattern in some ways opposite to that observed for the solvent effect. These trends agree well with the assignment proposed above, and they indicate further the contribution of dimeric structures such as



Finally, the influence of temperature on the acetamide spectra can also be explained according to previous assignment and interactions considered above. Although

TABLE 1.—DEPENDENCE OF CHEMICAL SHIFT ON CONCENTRATION IN ACETAMIDE SOLUTIONS

solvent	$\Delta\delta/\Delta c^a$ (10^2 ppm dm ³ mol ⁻¹)	
	<i>cis</i>	<i>trans</i>
acetonitrile (An)		9
dioxan (Dx)		27
methylacetate (Meac)		41
acetone (Ac)		17
tetrahydrofuran (THF)		20
trimethylphosphate (TMP)	8	
tributylphosphate (TBP)	34	40
<i>N</i> -methylpyrrolidone (MMP)	9	50
dimethylsulphoxide (DMSO)	14	14
hexamethylphosphoric triamide (HMPA)	3	3

^a $\Delta\delta/\Delta c$ is the slope of the shift δ (ppm) with respect to the amide concentration c (mol dm⁻³) at infinite dilution.

both *cis* and *trans* proton signals shift towards lower field on lowering the temperature, the effect on the resonance of a proton in the *cis* position is larger because of enhanced amide association, so that finally the two signals overlap. By raising the temperature a qualitatively normal pattern is observed, since the signals coalesce as expected for fast rotation around the C—N bond.

This work was supported by the "Servicio de Desarrollo Científico" of the University (Grant Q 546 813 4). We thank Mr. S. Alegria for running the n.m.r. spectra.

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