Linear Solvation Energy Relationship. Part 11.† An Analysis of Nitrogen-15 Solvent Shifts in Amides

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The solvatochromic comparison method is used to unravel and rationalize solvent effects on the ^{15}N n.m.r. spectra of some *N*-unsubstituted, *N*-monoalkyl-, and *NN*-dialkyl-amides. It is shown that, in addition to solvent polarity–polarizability and type-A hydrogen bonding effects, type-B hydrogen bonding by the second protons of self-associated formamide leads to a significant dependence of the ^{15}N shifts on solvent β values. In the case of the *N*-monoalkylamides, however, self association is sufficiently strong that the dependence of the shifts on solvent β values is negligible.

MARTIN and his co-workers [1] have carried out a factor analysis study of solvent effects on nitrogen-15 n.m.r. shifts of some *N*-unsubstituted, *N*-alkyl-, and *NN*-dialkyl-amides, and have concluded that, ' two factors only are required to span the solvent effect space '. A main factor was stated to be ' related to some fundamental property of the amide bond, such as Lewis basicity of the carbonyl group '. A less important second factor appeared to be ' associated with the existence of proton donating properties of the NH group ', and was particularly important in the case of formamide. It was also suggested that, ' strong solvent effects on ^{15}N resonance in amides should be expected when using solvents where the reaction field [2] and the solvatochromic shift are important.'

We now confirm that these earlier workers' conclusions are essentially correct, and demonstrate that, when the multiple solvent effects are unravelled and quantified by means of the solvatochromic comparison method, it is possible to adduce a good deal of additional information regarding solvent–solute interactions from the same experimental results. When analysed by this method, medium effects are rationalized in terms of three scales of solvent properties: a π^* scale of polarity–polarizabilities describes the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect,[3] an α scale of hydrogen bond donor (HBD) acidities measures the solvent's ability to donate a proton in a type-A (solvent to solute) hydrogen bond,[3a,4] and a β scale of hydrogen bond acceptor (HBA) basicities provides an index of the solvent's ability to accept a proton in a type-B (solute to solvent) hydrogen bond.

When correlations are limited to aliphatic solvents, total medium effects are described in terms of linear combinations of dependences on these three solvent properties according to a generalized linear solvation energy relationship (l.s.e.r.) of the form (1). In earlier

$$XYZ = XYZ_o + s\pi^* + a\alpha + b\beta \qquad (1)$$

papers [3-5] we have described correlations (now numbering in the hundreds) where XYZ has been a position or intensity of maximal absorption in an i.r., n.m.r., e.s.r. or u.v.–visible absorption or fluorescence spectrum, a heat or free energy of solution or of transfer between solvents, or the logarithm of a rate or an equilibrium constant. In the present correlations, the XYZs are natural abundance $-\delta(^{15}N)$ values in p.p.m. of 0.20 mol fraction solutions of the amides relative to an external acidified solution of $^{15}NO_3Na$ in D_2O. The ^{15}N solvent shifts reported by the earlier workers for six amides in eight aliphatic solvents for which the solvatochromic parameters are known are assembled in the Table together with solvent π^*, α, and β values.

^{15}N Chemical shifts of 0.2 mole fraction solutions of amides in various solvents

Solvent	Solvatochromic parameters [c]			$-\delta(^{15}N)$ Values of amide solutes (p.p.m. from NO_3^-) [d]					
	π^*	α	β	DMF [a]	DMA [a]	FA [a]	MFA [a]	(*Z*)-BF [a]	(*E*)-BF [a]
Dioxan	0.55	Nil	0.37	274.7	280.8	267.8	267.8	232.5	230.5
Cyclohexanone	0.76	Nil	0.53	274.7	280.9	266.5	267.5	232.2	230.1
Hexamethylphosphoramide	0.87	Nil	1.05	274.4	280.5	262.3	266.7	232.1	230.5
Dimethyl sulphoxide	1.00	Nil	0.76	272.1	278.3	261.7	265.2	230.4	228.9
Nitromethane	0.80	0.29	(0.20) [b]	272.9	279.1	267.4	266.7	231.1	229.1
Methanol	0.60	0.98	0.62	269.2	274.7	263.7	263.7	228.8	226.6
Ethylene glycol	0.73	0.99	0.52	266.5	272.1	261.0	261.2	227.5	224.4
Water	1.09	1.10	0.18	264.1	269.7	259.3	259.3	226.0	223.3

[a] DMF = *NN*-Dimethylformamide; DMA = *NN*-dimethylacetamide; FA = formamide; MFA = *N*-methylformamide; (*Z*)-BF = (*Z*)-*N*-t-butylformamide; (*E*)-BF = (*E*)-*N*-t-butylformamide. [b] Estimated value. [c] Ref. 3*a*. [d] Ref. 1.

Analysing first the results for dimethylformamide (DMF) and dimethylacetamide (DMA), these indicators are non-hydrogen bond donors (b 0), so that the $b\beta$ term in equation (1) should drop out and the appropriate correlations should be with π^* and α. Accordingly, the

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least squares multiple linear regression equations with these two parameters are (2a) and (3a). Equations (2a) and (3a) show a slightly greater dependence on solvent

$$-\delta(\text{DMF}) = 279.3 - 6.52\pi^* - 7.22\alpha \quad (2a)$$
$$r \text{ (correlation coefficient) } 0.980$$

$$-\delta(\text{DMA}) = 285.3 - 6.28\pi^* - 7.80\alpha \quad (3a)$$
$$r\ 0.980$$

polarity and a slightly lesser dependence on solvent HBD acidity for DMF relative to DMA, the latter effect being in accord with the fact that DMF (β 0.69) is a slightly weaker HBA base than DMA (β 0.76).

It is also instructive to carry out the multiple parameter correlations with π*, α, and β [equations (2b) and (3b)]. As might be expected for these non-protic

$$-\delta(\text{DMF}) = 279.0 - 6.55\pi^* - 7.11\alpha + 0.50\beta \quad (2b)$$
$$r\ 0.980$$

$$-\delta(\text{DMA}) = 285.3 - 6.30\pi^* - 7.74\alpha + 0.26\beta \quad (3b)$$
$$r\ 0.981$$

indicators, equations (2b) and (3b) show statistically insignificant dependences on β, with only minor differences in the coefficients of π* and α and no improvements in the goodness of the statistical fits relative to equations (2a) and (3a). It is fair to conclude, therefore, that the important solvent influences on $-\delta(^{15}\text{N})$ of DMF and DMA are solvent polarity–polarizability and type-A hydrogen bonding by protic solvents to the carbonyl oxygens.

The solvation picture is completely different with formamide (FA). Here the multiple linear regression equation with π* and α [equation (4a)] shows statistically unsatisfactory correlation ($r > 0.90$ is usually considered statistically satisfactory correlation in linear free energy relationships;[6] we have arbitrarily established $r > 0.95$ as a requirement for satisfactory correlation in multiple parameter equations). Allowing also a dependence of $-\delta(^{15}\text{N})$ on solvent β values in equation (4b), however, leads to a significant improvement in the goodness of the statistical fit, with important dependencies being shown on all three solvatochromic parameters. The relevant correlation equations are (4a) and (4b). From equation (4b) it is fair to conclude that

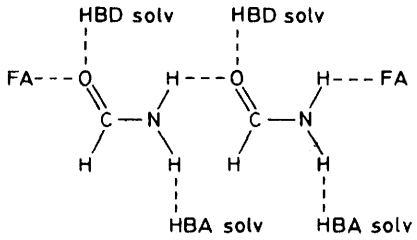
$$-\delta(\text{FA}) = 273.6 - 10.70\pi^* - 3.23\alpha \quad (4a)$$
$$r\ 0.839$$

$$-\delta(\text{FA}) = 276.8 - 10.34\pi^* - 4.45\alpha - 5.49\beta \quad (4b)$$
$$r\ 0.961$$

dominant solvent effects on ^{15}N n.m.r. shifts of formamide include solvent polarity–polarizability, type-A hydrogen bonding by HBD solvents to the carbonyl oxygen, and type-B hydrogen bonding by the amide hydrogens to HBA solvents.

We also see important structural effects on the ^{15}N n.m.r. spectra on comparing the coefficients of π* and α (the *s* and *a* terms) in equations (2)—(4). Thus, in earlier papers,[3b,d] it was shown that bulky alkyl substituents insulating u.v.–visible or i.r. chromophores from solvent molecules lead to decreases in the dependencies of the absorption maxima on solvent polarity–polarizability. In the present instances, two *N*-methyl substituents, separating the amide nitrogen atoms from solvent molecules, lead to decreases in the *s* values from 10.3 for FA to 6.3—6.5 for DMF and DMA.

Also, formamide is strongly self-associated, with cyclic dimers and linear polymers resulting from intermolecular bonds by amide protons to amide carbonyl groups [7] (see also below). Type-A hydrogen bonds by protic solvents to FA must therefore involve a *second* hydrogen bond to the other free electron pair of the carbonyl oxygen, *i.e.* structure (A). On this basis, the



(A)

lower *a* value of 4.5 for FA, compared with 7.2 and 7.8 for DMF and DMA, is explained by the fact that the HBD solvents are forming first hydrogen bonds to the carbonyl oxygen atoms of DMF and DMA, but second hydrogen bonds to the carbonyl oxygen of FA. Huyskens [8] has convincingly demonstrated that, when an HBA base accepts two hydrogen bonds (donates two electron pairs) on the same atom, the strength (and hence the solvatochromic effect) of the second bond is significantly weaker than the first.

With examples of the contrasting patterns of solvatochromic behaviour being provided by FA on the one hand, and DMA and DMF on the other, we shall next compare the two parameter and three parameter correlations for the three monosubstituted amides, *N*-methylformamide (MFA), (*Z*)-*N*-t-butylformamide [(*Z*)-BF], and (*E*)-*N*-t-butylformamide [(*E*)-BF]. The possibilities considered are: (a) that self-association is so strong that the *N*-monoalkylamides should show no solvatochromic effects of type-B hydrogen bonding by the amide protons to HBA solvents, as evidenced by statistically insignificant dependencies of $-\delta(^{15}\text{N})$ on solvent β values; (b) that self-association patterns are completely disrupted to form type-B hydrogen bonds to HBA solvents, in which case the ^{15}N shifts should show strong dependencies on solvent β values; and (c) that self-association patterns are partially disrupted, leading to nominal dependencies of $-\delta(^{15}\text{N})$ on β values of the more basic HBA solvents only. Our *a priori* expectation had been that the solvatochromic comparisons would show (b) or (c) to be the case. As will be demonstrated, however, all three monoalkylamides followed the pattern of solvatochromic behaviour corresponding to case (a).

The pertinent correlation equations are, for *N*-methylformamide, (5a) and (6a), for (*Z*)-*N*-t-butylformamide, (6a) and (6b), and for (*E*)-*N*-t-butylformamide, (7a) and (7b).

$$-\delta(\mathrm{MFA}) = 272.0 - 6.23\pi^* - 5.30\alpha \quad (5a)$$
$$r\ 0.971$$

$$-\delta(\mathrm{MFA}) = 272.3 - 6.20\pi^* - 5.42\alpha - 0.51\beta \quad (5b)$$
$$r\ 0.971$$

$$-\delta[(Z)\text{-BF}] = 235.2 - 4.21\pi^* - 4.25\alpha \quad (6a)$$
$$r\ 0.983$$

$$-\delta[(Z)\text{-BF}] = 235.2 - 4.22\pi^* - 4.22\alpha + 0.12\beta \quad (6b)$$
$$r\ 0.983$$

$$-\delta[(E)\text{-BF}] = 233.1 - 3.77\pi^* - 5.09\alpha \quad (7a)$$
$$r\ 0.977$$

$$-\delta[(E)\text{-BF}] = 232.8 - 3.86\pi^* - 4.99\alpha + 0.55\beta \quad (7b)$$
$$r\ 0.978$$

It is seen that the monoalkylamides follow the dialkylamide pattern of behaviour and differ from formamide in four important regards: (1) the *r* values for the correlations with π^* and α are statistically quite satisfactory; (2) allowing also a dependence on β leads to no significant improvement in correlation; (3) the coefficients of π^* and α undergo only minimal changes on going from the two parameter to the three parameter equations; and (4) the coefficients of β are of relatively minor magnitudes (and, indeed, are of the wrong sign in two of three cases). From the above, we can conclude that the ^{15}N n.m.r. solvent shifts of the monoalkylamides are influenced by solvent polarity–polarizability and by type-A hydrogen bonding by HBD solvents to the carbonyl oxygens, but that there is no significant solvatochromic effect of type-B hydrogen bonding by the carboxamide protons to HBA solvents.

That the monoalkylamides self-associate rather than hydrogen-bond to solvents, even when the solvent is as strong a HBA base as hexamethylphosphoramide (HMPA, β 1.05), is quite surprising to us. We would have expected the monoalkylamides to be about as basis as the dialkylamides (DMF, β 0.69; DMA, β 0.76), and therefore significantly weaker hydrogen bond acceptors than HMPA. Further, the n.m.r. spectra were determined in solutions where the HMPA solvent was present in four times the molar concentration of the monoalkylamide solute. The essentially undisturbed self-association complexes under these conditions serve as strong confirmation for Huyskens observation [8] that, when an amphiprotic indicator acts simultaneously as HBD acid and HBA base, both the donor and acceptor bond strengths are significantly greater than when the indicator acts only as donor or only as acceptor.

Again important structural information is elucidated on comparing the coefficients of π^* and α for the various amides. Thus, the significantly lower *s* values of 3.8—4.2 for the *N*-t-butylamides, compared with 6.3—6.5 for the *NN*-dimethylamides, show that a single t-butyl group is more effective than two *N*-methyl groups in insulating the nitrogen atom from the solvent. Also, the lower *a* value of 4.25 for the (*Z*)-*N*-t-butylamide, compared with 5.09 for the (*E*)-*N*-t-butylamide, is consonant with the fact that in the former instance the t-butyl group also insulates the hydrogen bond acceptor site from hydrogen bond donor solvents.

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