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Solvent and protonation effects on nitrogen NMR shieldings of isoamides (α-aminoethers)

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Abstract

High-precision solvent-induced ^{14}N NMR shieldings are presented for some isoamides and their N-protonated forms. The results indicate that the major source of solute–solvent interactions, giving rise to nitrogen shielding variations, is solvent-to-solute hydrogen bonding where the lone pair electrons of the imino nitrogen act as the hydrogen-bond acceptor centre. This results in a remarkable shielding increase for the imino nitrogen atom. Another interaction which could be important, when NH moieties are present, is solute-to-solvent hydrogen bonding where the NH croup is engaged as a donor. In the present study this effect is found to be a modest one and produces nitrogen deshielding. The influence of non-specific interactions, arising from solvent polarity effects, is rather feeble compared with that for analogous imine systems. The direction and magnitude of this effect is correctly reproduced by molecular orbital calculations incorporating the Solvaton model for non-specific solute–solvent interactions. Protonation effects on the nitrogen shieldings of the isoamides are substantial, producing an increase in shielding of about 80 ppm. This is in accord with that observed for solvent-to-solute hydrogen bonding.

Keywords: Hydrogen bonding; Isoamide (α-imino ether); Nitrogen NMR shieldings; Protonation effects; Solvent effects

1. Introduction

The structures of isoamides, or α-iminoethers, Fig. 1, are isomeric with respect to the corresponding amides. The isoamides contain an imino-type moiety and differ from imines in that an OR croup is attached to the α carbon found in isoamides. Our previous studies on imines [1] and their aromatic analogues [2] show that nitrogen NMR shieldings are very sensitive to molecular interactions in solution. Both specific and non-specific solute–solvent interactions play significant roles in the variation of nitrogen shielding as a function of solvent.

In general the lone pair electrons on the imino nitrogen atom act as a strong acceptor site for solvent-to-solute hydrogen bonding. Such hydrogen bonding is usually responsible for a significant increase in nitrogen nuclear shielding. This offers a measure of the relative basicity of the various nitrogen atoms involved in hydrogen bonding. In addition, non-specific interactions such as those arising from solvent polarity also appear to produce a significant increase in imino nitrogen shielding as the solvent polarity increases. This shielding enhancement arises from the migration of electronic charge towards the imino nitrogen atom.

In the present work on isoamide systems we are concerned with the effects of the OR moiety at the

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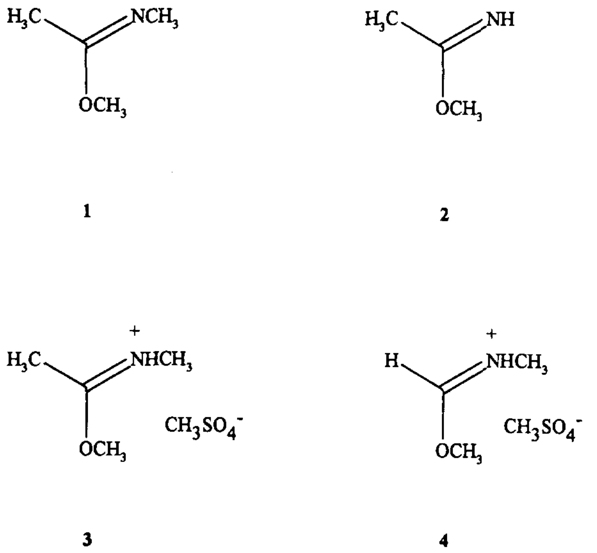

1 2 3 4

Fig. 1. Structures of the compounds studied.

α-carbon on the solute-to-solvent interactions as evidenced by nitrogen NMR shieldings. In addition to comparing the behaviour of the imino moiety in compound 1 (Fig. 1) with that of simple imines in a variety of solvents, we wish to study the effects of solute-to-solvent hydrogen-bond formation on nitrogen shieldings.

This is feasible for compound 2 owing to the presence of an NH moiety. A further aspect of this work is estimation of the influence of the effects of protonation of the imino moiety on its nitrogen shielding. The relevant compounds for this aspect of the investigation are numbers 3 and 4 (Fig. 1).

In this work we use the sign convention in which an increase in nuclear shielding has a plus sign [1–3]. Thus we employ the term 'nuclear shielding,' rather than 'chemical shift'. These two terms are equivalent in magnitude but are of opposite sign.

2. Experimental

The compounds studied were prepared by previously published procedures [4,5]. Particular care was taken in the NMR measurements to use only very pure and dry solvents as previously reported [3]. All solutions were prepared and handled in glove bags. The ^{14}N shielding measurements were taken on a Bruker AM500 Spectrometer at 35 ± 0.2°C, as maintained by a VT unit, at a frequency of 36.14 MHz. Random and systematic errors were reduced to below 0.1 ppm for the solute-nitrogen shieldings in different solvents. External neat liquid nitromethane was used as a reference by means of 10 mm/4 mm o.d. coaxial tubes. The inner tube contained 0.3 M nitromethane in acetone-d_6; the nitrogen shielding of this solution is + 0.77 ppm from that of neat liquid nitromethane [3]. This value is obtained from measurements using concentric spherical

Table 1
Solvent effects on the nitrogen NMR shieldings of some isoamide systems

Solvent	Nitrogen NMR shielding (ppm) referred to neat liquid nitromethane[a]			
	Compound 1	Compound 2	Compound 3	Compound 4
Cyclohexane	+ 154.54	+ 159.10	–	–
Et_2O	+ 155.29	+ 159.21	–	–
CCl_4	+ 155.61	+ 159.27	–	–
Benzene	+ 155.35	+ 159.61	–	–
Dioxane	+ 155.63	+ 159.70	–	–
Acetone	+ 155.83	+ 159.51	+ 239.35	+ 238.17[b]
DMSO	+ 155.53	+ 156.38	–	–
CH_2Cl_2	+ 157.60	+ 163.60	–	–
CHO_3	+ 160.16	+ 165.85	–	–
EtOH	+ 164.92	+ 170.17	–	–
MeOH	+ 167.49	+ 174.77	–	–
H_2O	+ 168.7	+ 176.83	–	–
CF_3CH_2OH	+ 178.8	+ 184.43	–	–

[a] All data are corrected for bulk susceptibility effects and related to 0.05 M solutions at + 35 ± 0.2°C. [b] The ^{14}N signal is a doublet due to $^{1}J(^{14}N-^{1}H) = 64 \pm 2$ Hz which corresponds to $^{1}J(^{15}N-^{1}H) = 90 \pm 2$ Hz.

sample/reference containers in order to eliminate bulk susceptibility effects. The value of + 0.77 ppm is used as a conversion constant. Thus the contents of the inner tube act both as a reference, with respect to neat nitromethane as standard, and as a deuterium lock for the NMR Spectrometer. The exact resonance frequency of the ^{14}N signal of neat nitromethane is 36.141524 MHz, from which a value of 36.136826 MHz is obtained for the bare nitrogen nucleus [3]. This latter value is used in conjunction with the relevant resonance frequency differences to calculate the nitrogen shieldings relative to that of neat nitromethane.

Lorentzian line-shape fitting of the ^{14}N signals was used to produce values for the precise resonance frequencies of both the samples used and of the external standard. Dilute solutions were used in the present study hence their susceptibilities are assumed to be equal to those of the corresponding solvent at 35°C.

3. Results and discussion

The results of high precision ^{14}N NMR measurements for compounds 1 to 4 are given in Table 1 for solutions in a variety of solvents.

The solvents chosen represent a large range of hydrogen-bonding properties and polarity. As a function of solvent we observe that the nitrogen shielding range, for both compounds 1 and 2, is large, about 25 ppm. Although this is large it is smaller than that observed for acetone *N*-methylimine in the same set of solvents [1]. To obtain a more detailed analysis of the solvent-induced nitrogen shielding changes we employ an empirical scale of solvent properties as given in Table 2. These data can be used together with the master equation (eqn (1)) [6,7]. To separate the various specific and non-specific contributions to the solvent-induced nitrogen shielding variations, we have made use of the empirical scheme represented by the master equation (Refs. [6,7] and references cited therein).

$$\sigma(i,j)=\sigma_o(i)+a(i)\alpha(j)+b(i)\beta(j)+s(i)[\pi*(j)+d(i)\delta(j)] \qquad (1)$$

where i and j denote the solute and solvent respectively; σ is the nitrogen shielding, α represents the hydrogen-bond donor-strength of the solvent, β gives its hydrogen-bond acceptor-strength, π^* is its polarity/polarizability and δ is a correction for polychlorinated solvents (δ = 0.5) and aromatic solvents (δ = 1). The corresponding response of the

Table 2

Solvent parameters used and least-squares fitted solute parameters for a set of master equations (eqn (1))

Solvent	α	β	π^*	δ	Dielectric constant
Cyclohexane	0	0	0	0	1.87
Et_2O	0	0.47	0.27	0	3.89
CCl_4	0	0	0.29	0.5	2.21
Benzene	0	0.10	0.59	1	2.25
Dioxane	0	0.37	0.55	0	2.19
Acetone	0.07	0.48	0.72	0	19.75
DMSO	0	0.76	1.00	0	45.80
CH_2Cl_2	0.22	0	0.80	0.5	8.54
$CHCl_3$	0.34	0	0.76	0.5	4.55
EtOH	0.86	0.77	0.54	0	24.20
MeOH	0.98	0.62	0.60	0	30.71
H_2O	1.13	0.18	1.09	0	76.70
CF_3CH_2OH	1.51	0	0.73	0	–

Compound	σ_0 (ppm)	*a* (ppm/unit scale)	*b* (ppm/unit scale)	*s* (ppm/unit scale)	*d* (dimensionless)	Correlation coefficient, *r*
1	+ 155.0 ± 0.4	+ 11.9 ± 0.4	+ 0.1 ± 1.4	+ 0.5 ± 0.4	− 0.7 ± 1.7	0.997
2	+ 160.1 ± 0.8	+ 17.3 ± 0.6	− 5.3 ± 1.3	+ 0.9 ± 1.3	− 1.1 ± 1.6	0.996

[a] The constants were recalculated for a temperature of 35°C from the data available in Ref. [10].

solute nitrogen-shielding to a given solvent property is given by the solute terms *a*, *b*, *s* and *d*. The nitrogen shielding in the reference state, cyclohexane solution, is given by σ_0.

Table 2 also contains the least-squares-fitted values of the solute nitrogen-shielding responses and the linear correlation coefficients for the experimental shielding values of compounds 1 and 2, with respect to those obtained from eqn (1). Unfortunately we have been unable to perform a similar analysis for compounds 3 and 4 since they are either essentially insoluble in crucially important solvents or they solvalise to the corresponding amide derivatives.

Turning to a consideration of the parameters *a*, *b*, *s* and *d* given in Table 2, for compound 1 the only one of these parameters with a significant value is *a* which is positive in sign and about one half of the magnitude of that found for acetone *N*-methylimine [1]. Thus the imino nitrogen atom in compound 1 has a basicity towards hydrogen bonding which is significantly less than that in aliphatic imine systems. This situation is likely to be a consequence of competitive effects from the OCH_3 in the isoamide system. The OCH_3 group can act both as a competitive hydrogen-bond-acceptor centre and as an electron withdrawer. It is of particular note that the *s* term is essentially insignificant for compound 1 which indicates that changes in solvent polarity have little effect on the solvent-dependence of the nitrogen shielding. This contrasts strongly with the results found for acetone *N*-methylimine [1], where the *s* term has a value of about + 7 ppm/unit scale. This finding for compound 1 is intuitively correct since the central carbon atom is flanked by two essentially electron-withdrawing groups, NCH_3 and OCH_3.

The results given in Table 2 for compound 2 are, with one important exception, very similar to those found for compound 1. The exception resides in the value of the *b* term which represents solute-to-solvent hydrogen-bonding. For compound 1 *b* is approximately zero, for compound 2 it is significant in magnitude and negative in sign, about − 5 ppm/unit scale. This value reflects the hydrogen-bond donor ability of the NH group in compound 2. A comparable situation is found for the nitrogen shielding of the NH group in pyrrole where *b* has a value of − 8 ppm/unit scale [8]. In general it appears that if NH groups act as hydrogen-bond donors to solvent molecules then significant nitrogen deshielding occurs.

As shown in Table 1 the total nitrogen shielding variations for compounds 1 and 2, as a function of solvent, are approximately the same. However the factors which are responsible are not the same in both cases. For compound 2 the *a* term is significantly larger than it is for compound 1 but this increase is totally compensated for by the negative *b* term found for compound 2.

The effects of solvent polarity/polarizability interactions on the nitrogen shielding variations of both compounds 1 and 2, as a function of solvent, are essentially insignificant as shown by the values of the *s* terms in Table 2. Any influence these interactions may have are slightly biased towards an increase in nitrogen shielding as the solvent polarity increases. This conclusion is strongly supported by the results of some nitrogen-shielding calculations performed within the framework of the Solvaton model as shown in Table 3. The use of the Solvaton model in molecular orbital calculations of nitrogen shieldings is described elsewhere [9]. Suffice it to say that these calculations of nitrogen nuclear shieldings are performed using INDO/S parameters and describe the nitrogen shielding of the solute as a function of the dielectric constant (ε) of the surrounding solvent medium.

Compounds 3 and 4 (Fig. 1) provide the possibility of estimating protonation effects on nitrogen NMR shieldings. Comparing the observed shieldings of compounds 1 and 3 (Table 1) we find a shielding increase for compound 3 in excess of 80 ppm. This is typical of the increase observed upon the protonation of imino nitrogen atoms [3]. The cations 3 and 4

Table 3
Nitrogen shielding increments induced by varying the dielectric constant (ε) of the medium as calculated by the Solvaton model

ε	Nitrogen shielding increment (ppm) with respect to that for ε = 2	
	1	2
4	+0.5	+0.7
8	+0.7	+1.1
10	+0.8	+1.2
20	+0.9	+1.3
40	+0.9	+1.3
80	+0.9	+1.3

can be considered as analogues of the corresponding O-protonated amides. From this point of view the effect of O protonation of an amide results in a nitrogen deshielding of about 35 ppm, as obtained from a comparison with nitrogen shielding data for the corresponding amides [3]. The N protonation effect on the nitrogen shielding of the isoamide structures concerned is much larger than that due to solvent-to-solute hydrogen bonding, but it is of the same sign. This observation is consistent with the view that full protonation can be considered as the limiting stage of hydrogen bonding.

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