Solvent effects on nitrogen NMR shieldings in thiazole and thiadiazole systems

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High precision ^{14}N NMR measurements are reported for all six possible thiazole and thiadiazole molecules in a variety of solvents. Both solvent polarity and hydrogen bonding effects on the nitrogen nuclear shielding of the solutes are significant. Both types of effect produce an increase in the solute nitrogen shielding. Analysis of the experimental data, and molecular orbital studies, indicate that an increase in the polarity of the solvent favours the delocalization of the lone pair electrons from the sulfur atoms into the conjugated rings. This leads to an increase in electronic charge at the nitrogen atom(s) concerned. This effect is more pronounced than analogous effects observed for pyridine type nitrogen atoms in the corresponding diazole and triazole systems. The significant shielding effects which result from solvent to solute hydrogen bonding to ring nitrogen atoms are shown to be essentially local in origin. Thus the shielding concerned is that of the nitrogen atom directly involved in the hydrogen bonding.

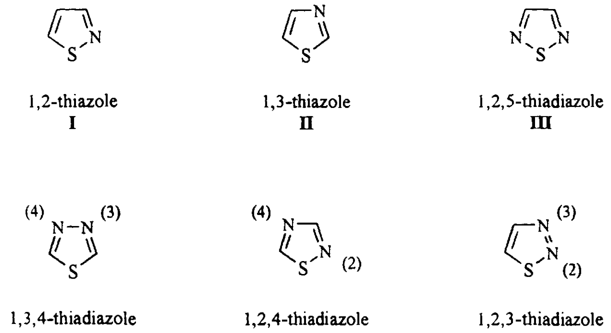
Introduction

We have previously shown that solvent effects on nitrogen NMR shieldings (chemical shifts) of nitrogenous heteroaromatics provide a valuable means of gaining an insight into solute-solvent interactions.[1-4] A study of solvent effects on nitrogen shieldings of solute molecules can lead to information both on solvent polarity and on hydrogen bonding effects between solvent and solute. An important aspect of this work is its ability to distinguish between non-equivalent nitrogen atoms in a heteroaromatic molecule. Our earlier work has involved not only five membered ring compounds[1-3] but six membered ring heteroaromatic compounds (azines)[4-6] and fused five and six membered ring systems (indolizines).[7] The solvent effects observed are both significant and variable in magnitude.

Two types of nitrogen environment are found in heteroaromatic compounds, namely the pyrrole- and pyridine-types. Five membered ring heteroaromatics of the azole family contain only one of the pyrrole-type nitrogen atoms and can contain one, or more, of the pyridine-type nitrogen atoms. With the exception of heavily fused ring systems six membered ring heteroaromatics contain only pyridine-type nitrogen atoms. There is a clear distinction in the effects of solvents on the nitrogen shieldings of these two types of atoms.[1-7] An increase in shielding by up to 10 ppm can be observed for pyridine-type nitrogen atoms due to solvent polarity effects. Hydrogen bond donor solvents can produce shielding increases by up to 25 ppm for this type of nitrogen atom. Such effects can be useful in determining the relative basicities of non equivalent nitrogen atoms in both five and six membered rings.

Solvent effects on the shielding of pyrrole-type nitrogen atoms are usually much smaller. Solvent polarity interactions usually make the most significant contribution to variations in the shielding of this type of nitrogen atom with change of solvent. The shielding change observed is opposite to that found for pyridine-type nitrogen atoms. For pyrrole-type nitrogen atoms hydrogen bonding influences are only important when the nitrogen is contained within an NH moiety such that the hydrogen atom can be involved in hydrogen bonding to basic centres in the solvent molecules.

Currently we are concerned with five membered ring heteroaromatics which are devoid of pyrrole-type nitrogens; namely thiazoles and thiadiazoles as shown in Fig. 1. These compounds are the sulfur analogues of the corresponding diazole and triazole systems in which the pyrrole-type nitrogen atoms have been replaced by sulfur atoms. All six of the structures shown in Fig. 1 are known and are studied in the present investigation. A major aim of which is to determine whether the pyridine-type nitrogens in compounds **I** to **VI** behave similarly to their analogues in the other heteroaromatic systems mentioned, as far as solute–solvent interactions on their shieldings are concerned. In addition we wish to study the competition in solvent hydrogen bond accepting properties between the sulfur and nitrogen atoms present in the solute molecules. This possibility for competition has not arisen in our previous studies on nitrogenous heteroaromatic systems.



1,2-thiazole
I

1,3-thiazole
II

1,2,5-thiadiazole
III

1,3,4-thiadiazole
IV

1,2,4-thiadiazole
V

1,2,3-thiadiazole
VI

Fig. 1 Structures of compounds studied

As in our earlier reports we use the expression 'nitrogen NMR shielding' rather than 'nitrogen chemical shift'. Consequently we employ a sign convention for the nitrogen shielding data which has a positive sign to denote an increase in the shielding, this is opposite to that associated with the chemical shift scale.

Results and discussion

The results of high precision ^{14}N NMR measurements of the nitrogen shieldings of compounds **I** to **VI** are given in Tables 1–6 respectively for solutions in a variety of solvents. The choice

Table 1 Solvent effects on the nitrogen NMR shielding of 1,2-thiazole[a]

Solvent	Measured	Calculated
Cyclohexane	+77.92	79.10
CCl_4	+79.62	79.64
Et_2O	+80.02	78.67
Benzene	+80.63	79.83
Dioxane	+80.97	80.53
DMSO	+82.01	81.36
Acetone	+82.11	81.80
CH_2Cl_2	+83.98	84.84
$CHCl_3$	+85.27	86.00
EtOH	+88.02	88.76
MeOH	+89.87	91.04
H_2O	+95.84	97.07
CF_3CH_2OH	+102.62	100.24

[a] Nitrogen NMR shielding (ppm) referred to neat nitromethane (Tables 1–6). All data are corrected for bulk susceptibility effects and related to 0.2 M solutions at +35.0 ± 0.2 °C.

Table 2 Solvent effects on the nitrogen NMR shielding of 1,3-thiazole[a]

Solvent	Measured	Calculated
Cyclohexane	+52.15	52.68
Et_2O	+53.95	53.42
CCl_4	+54.11	53.74
Benzene	+54.77	54.79
Dioxane	+54.96	54.51
Acetone	+55.47	56.11
DMSO	+56.24	55.96
CH_2Cl_2	+58.51	58.87
$CHCl_3$	+60.51	60.49
EtOH	+66.58	66.91
MeOH	+68.90	68.99
H_2O	+73.17	73.25
CF_3CH_2OH	+78.00	77.62

[a] All data are corrected for bulk susceptibility effects and related to 0.2 M solutions at +35.0 ± 0.2 °C.

Table 3 Solvent effects on the nitrogen NMR shielding of 1,2,5-thiadiazole[a]

Solvent	Measured	Calculated
Cyclohexane	+30.57	31.37
CCl_4	+31.46	31.74
Et_2O	+32.30	30.77
Benzene	+32.90	31.73
Dioxane	+33.05	32.74
DMSO	+33.56	33.47
Acetone	+33.82	33.52
EtOH	+34.57	35.15
CH_2Cl_2	+34.73	35.61
$CHCl_3$	+34.80	35.98
MeOH	+35.55	36.73
H_2O	+42.17	42.09
CF_3CH_2OH	+44.22	42.80

[a] All data are corrected for bulk susceptibility effects and related to 0.2 M solutions at +35.0 ± 0.2 °C.

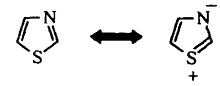
of solvents represents a large range of properties with respect to polarity and hydrogen bonding effects. The methods used to produce these results are given in the Experimental section. The results given are corrected for bulk susceptibility effects and have a precision such that the last digit quoted is uncertain.

The data reported in Tables 1–6 show that the effects of solvents on the nitrogen shieldings of the thiazoles and thiadiazoles are significant and range from about 11 ppm to about 30 ppm. In the case of compound **V** the range for N_4 is approximately twice that for N_2.

Table 4 Solvent effects on the nitrogen NMR shielding of 1,3,4-thiadiazole[a]

Solvent	Measured	Calculated
Cyclohexane 0.02 M	−2.71	−1.47
CCl_4	+1.38	0.27
Et_2O	+1.50	0.12
Benzene	+2.67	1.87
Dioxane	+3.86	3.08
Acetone	+4.80	5.40
DMSO	+7.03	6.60
CH_2Cl_2	+7.07	8.11
$CHCl_3$	+7.62	9.29
EtOH	+12.47	13.30
MeOH	+14.93	15.78
H_2O	+24.06	23.50
CF_3CH_2OH	+26.5	25.34

[a] All data are corrected for bulk susceptibility effects and related to 0.2 M solutions at +35.0 ± 0.2 °C.



IIa **IIb**

Fig. 2 Conventional representation of two of the possible electronic structures of 1,3-thiadiazole. Results of the present work show that an increase is solvent polarity should favour structure **IIb**

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 (1) (refs. 8, 9 and refs. cited therein),[8,9] where i

$$\sigma(\mathrm{i},\mathrm{j}) = \sigma_0(\mathrm{i}) + a(\mathrm{i})\alpha(\mathrm{j}) + b(\mathrm{i})\beta(\mathrm{j}) + s(\mathrm{i})[\pi^*(\mathrm{j}) + d(\mathrm{i})\delta(\mathrm{j})] \quad (1)$$

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 ($\delta = 0.5$) and aromatic solvents ($\delta = 1$). The corresponding response of the 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.

The solvent parameter sets employed in the present work are given in Table 7 together with the least-squares fitted estimates of the solute nitrogen shielding responses and the linear correlation coefficients for the comparison of the experimental and calculated nitrogen shieldings.

As reported in Table 7 the values obtained for the parameter d are insignificant. The most important terms are a and s which correspond to the responses of solute nitrogen shielding to hydrogen bond donation from the solvents and to changes in solvent polarity/polarizability respectively. The values of the s terms given in Table 7 are all positive in sign showing that an increase in solvent polarity produces an increase in the solute nitrogen shielding. These values are similar to those found for the pyridine-type nitrogen atoms in diazole and triazole systems.[2,3] However, the present values are, in general, larger in magnitude. This is intuitively correct since such effects on nitrogen shieldings can be attributed to an increase in the delocalization of lone pair electrons from pyrrole-type nitrogen atoms in the case of azoles[2,3] and sulfur in the present case, as shown in Fig. 2. By considering various aromaticity scales[10,11] among potentially aromatic five membered ring heterocycles, the most aromatic are those containing sulfur atoms. This includes the thiazoles and thiadiazoles concerned. Consequently the relatively large values for the s terms of the compounds studied here, in comparison with those for azole systems, is consistent with this viewpoint.

INDO/S-SOS solvaton molecular orbital calculations of nitrogen shielding as a function of solvent dielectric, ε,[12] support this interpretation as shown by the results given in Table 8. These calculations correctly predict both the sign and order of magnitude of the change in solute nitrogen shielding as the dielectric of the solvent increases.

As shown in Table 7 the most significant term is *a* which represents the influence of solvent to solute hydrogen bonding on the nitrogen shielding of the solute. The values of the *a* term are invariably positive in sign such that hydrogen bonding from solvent to solute produces an increase in the solute nitrogen shielding.

There is the question of whether the effect on nitrogen shielding due to hydrogen bonding is a local one, *i.e.* it arises from a direct hydrogen bond to the nitrogen atom in question. The alternative could be that the nitrogen shielding change could arise from significant hydrogen bonding effects at other acceptor sites, nitrogen or sulfur. To gain some insight into this situation we have performed some semi-empirical molecular orbital calculations of the TNDO/2 and PM3 types. The TNDO/2 method is essentially an INDO based scheme where the parameterization is not unique for a given element but includes various types of bonding of the atom concerned. We have used this method for the nuclear shielding calculations. The PM3 method was used for the geometry optimizations, this is known to give reliable geometric representations of polar molecules. Both of these techniques are available in software packages produced by Hypercube Inc.

Water molecules were used as hydrogen bond donors in the computer simulations together with the solute molecules as hydrogen bond acceptors. Initially a single water molecule was allowed to approach either a nitrogen or sulfur atom of a given solute molecule. The geometry of the whole system was then optimized, the resulting geometry is found to be essentially planar. When hydrogen bonding to nitrogen occurs the corresponding hydrogen bond length is about 185 pm. When hydrogen bonding occurs to sulfur the resulting structure is non-planar with about 40° between the plane of the ring atoms and the hydrogen bond. The length of the hydrogen bond is estimated to be 260 pm. Table 9 contains the results of TNDO/2

Table 5 Solvent effects on the nitrogen NMR shielding of 1,2,4-thiadiazole[a]

	Measured		Calculated	
Solvent	N_4	N_2	N_4	N_2
Cyclohexane	+65.66	+103.14	66.65	104.11
CCl_4	+67.15	+103.69	67.03	103.88
Et_2O	+67.59	+104.46	66.24	102.77
Benzene	+68.32	+103.78	67.06	103.22
Dioxane	+68.65	+104.35	68.17	104.08
Acetone	+69.51	+104.49	69.29	104.39
DMSO	+69.67	+103.35	69.06	103.65
CH_2Cl_2	+70.60	+106.14	71.81	106.39
$CHCl_3$	+71.25	+106.10	72.68	106.79
EtOH	+73.36	+105.43	74.32	105.97
MeOH	+75.21	+106.74	76.34	107.36
H_2O	+81.75	+111.67	82.14	111.53
CF_3CH_2OH 0.2 M	+86.41	+113.72	84.35	112.93

[a] All data are corrected for bulk susceptibility effects and related to 0.06 M solutions at +35.0 ± 0.2 °C.

Table 6 Solvent effects on the nitrogen NMR shielding of 1,2,3-thiadiazole[a]

	Measured		Calculated	
Solvent	N_3	N_2	N_3	N_2
Cyclohexane	−61.69	−39.19	−61.00	−38.47
Et_2O	−60.56	−35.97	−62.02	−37.80
CCl_4	−59.76	−37.23	−60.39	−37.34
Benzene	−58.95	−35.20	−60.35	−36.56
Dioxane	−59.14	−34.26	−59.26	−34.42
Acetone	−58.50	−32.80	−57.93	−32.42
DMSO	−57.21	−31.26	−58.41	−31.52
CH_2Cl_2	−55.72	−31.45	−54.12	−30.23
$CHCl_3$	−54.94	−31.29	−53.10	−29.67
EtOH	−53.06	−29.89	−52.47	−29.36
MeOH	−51.55	−28.56	−49.73	−27.08
H_2O	−41.10	−17.76	−41.52	−18.74
CF_3CH_2OH	−37.0	−17.5	−38.88	−18.58

[a] All data are corrected for bulk susceptibility effects and related to 0.2 M solutions at +35.0 ± 0.2 °C.

Table 7 Solvent parameters used and least-squares-fitted solute parameters for a set of master eqns. (1)

Solvent	α	β	π^*	δ	ε[a]
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 (atom)	σ_0 (ppm)	*a* (ppm/unit scale)	*b* (ppm/unit scale)	*s* (ppm/unit scale)	*d* (dimensionless)	Correlation coefficient *r*
I	+79.1 ± 1.0	+11.5 ± 0.9	−3.9 ± 1.6	+5.3 ± 1.5	−0.4 ± 0.3	0.988
II	+52.7 ± 0.4	+14.7 ± 0.3	−0.6 ± 0.6	+3.7 ± 0.5	0.0 ± 0.2	0.999
III	+31.4 ± 0.9	+4.9 ± 0.8	−4.4 ± 1.4	+5.5 ± 1.3	−0.4 ± 0.2	0.971
IV	+14.7 ± 0.9	+13.0 ± 0.8	−2.2 ± 1.6	+9.8 ± 1.4	−0.2 ± 0.2	0.993
V (N2)	+104.1 ± 0.7	+4.4 ± 0.6	−4.6 ± 1.1	+3.1 ± 1.0	−0.7 ± 0.4	0.975
V (N4)	+66.6 ± 1.0	+9.1 ± 0.9	−4.0 ± 1.7	+5.5 ± 1.5	−0.4 ± 0.3	0.982
VI (N2)	−38.5 ± 1.0	+8.1 ± 0.9	−4.6 ± 1.6	+10.4 ± 1.5	−0.4 ± 0.2	0.986
VI (N3)	−61.0 ± 1.2	+11.0 ± 1.1	−6.5 ± 1.9	+7.5 ± 1.7	−0.4 ± 0.2	0.985

[a] The constants were recalculated for a temperature of 35 °C from the data available in ref. 21.

nitrogen shielding calculations for such optimized structures. These results show that the nitrogen shielding is essentially only influenced by hydrogen bonding between the nitrogen atom in question and the incoming water molecule. Hydrogen bonding to sulfur does not have any appreciable effect on the nitrogen shielding as shown in Table 9.

We also note that water hydrogen bonded to a second ring nitrogen atom does not influence the shielding of the nitrogen of interest. Thus, at this level of approximation, where only one water molecule approaches the solute molecule and is hydrogen bonded to only one of the potential acceptor sites, then the effect on the nitrogen shielding is essentially a local one. Namely, only for that nitrogen atom involved in the hydrogen bonding is a significant increase in shielding observed.

In order to compare these calculated results with some experimental ones we employ the experimental differences in nitrogen shielding found between aqueous and DMSO solutions of compounds **I** to **VI**. This choice is made on the basis of approximately equal polarities on the π^* scale (Table 7) for these two solvents and the fact that DMSO is not a hydrogen bond donor (Table 7). Consequently the observed nitrogen shielding differences for a given solute molecule, dissolved in these two solvents, should be due to hydrogen bonding between water and the solute molecule only. The calculated results given in Table 9 are obtained from a model which includes as many water molecules as there are potential solute acceptor sites for hydrogen bonds.

A fairly good agreement between the calculated and observed nitrogen shielding changes, due to hydrogen bonding, is reported in Table 9. The calculated data show the correct sign and a reasonable magnitude for the hydrogen bonding effects.

The b term results given in Table 7 account for the effects of solute to solvent hydrogen bonding on the nitrogen shielding of the solute. These data appear to be significant. Five membered ring heteroaromatics containing N, O and S atoms are known as carbon acids.[13] Available information indicates that 1,2-thiazole should be more acidic than the 1,3-isomer. The values of b found in the present investigation are in accord with this view.

Table 8 Nitrogen shielding increments induced by varying the dielectric constant (ε) of the medium as calculated by the solvation model

Compound	Nitrogen shielding increment (in ppm) with respect to $\varepsilon = 2$			
	$\varepsilon = 4$	$\varepsilon = 8$	$\varepsilon = 10$	$\varepsilon = 40$
I	+1.9	+2.8	+3.0	+3.2
II	+1.2	+1.8	+2.0	+2.2
III	+1.7	+2.5	+2.7	+2.9
IV	+1.1	+1.7	+1.9	+2.1
V (N2)	+1.8	+2.7	+2.9	+3.1
V (N4)	+1.2	+1.8	+2.0	+2.1
VI (N2)	+1.7	+2.5	+2.7	+2.9
VI (N3)	+1.2	+1.8	+2.0	+2.1

Experimental

The compounds studied were either prepared by published procedures, **I**,[14] **III**,[15] **IV**,[16] **V**[17] and **VI**[18] or are available commercially, compound **II**. Particular care was taken in the NMR measurements to use very pure and dry solvents as reported previously.[1–6] All solutions were prepared and handled under a dry argon atmosphere 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.[19] This value is obtained from measurements using concentric spherical 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 36.141 524 MHz, from which a value of 36.136 826 MHz is obtained for the bare nitrogen nucleus.[19] 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 lineshape 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.

The INDO/S solvaton calculations of the nitrogen shieldings as a function of solvent dielectric[12] were performed on the University of Surrey HP Central system using INDO optimised geometries based upon standard structures.[20] The TNDO/2 shielding calculations and PM3 geometry optimization calculations were carried out at the Institute of Organic Chemistry of the Polish Academy of Sciences using a Hector 486DX 50MHz system and Hyperchem release 4.0 and HyperNMR software packages from Hypercube Inc.

Table 9 Nitrogen shielding increments induced by hydrogen bonding between water molecules and hydrogen bond acceptor sites in thiazole and thiadiazole systems studied

Compound	Acceptor sites involved	TNDO/2-calculated increment (ppm) in the nitrogen shielding with respect to an isolated molecule concerned	Experimental difference (ppm) in the nitrogen shielding between aqueous and DMSO solutions
I	S	0	
I	N and S	+14	+13.8
II	S	+1	
II	N and S	+15	+17.0
III	N2, N5 and S	+10	+8.6
IV	N3, N4 and S	+15	+17.0
V (N2)	N2, N4 and S	+15	+16.7
V (N4)	N2, N4 and S	+9	+8.3
VI (N2)	N2, N3 and S	+14	+16.1
VI (N3)	N2, N3 and S	+15	+16.0

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