

Hydrogen Bonding and Solvent Polarity Effects on the Nitrogen NMR Shielding of 1,2,4,5-Tetrazine

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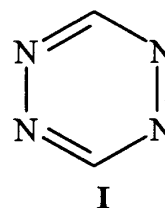
Results of the first extensive investigation of the nitrogen shielding of 1,2,4,5-tetrazine (**I**) are reported. Due attention is paid to solvent-induced nitrogen-shielding variations by a variety of solvents. A comparison is made with comparable, earlier, results for the other azine systems. The observed range of solvent-induced nitrogen-shielding variations of **I** is modest but significant, about 10 ppm. The major factor producing this variation is that due to solvent polarity effects, which is supported by the results of some shielding calculations based upon the Solvaton model. A smaller, but significant, contribution is produced by solvent-to-solute hydrogen bonding effects. This correlates well with the low nitrogen basicity of **I** as indicated by published *ab initio* molecular orbital calculations of gas-phase protonation energies. There is found a general correlation between nitrogen basicity with respect to hydrogen bonding and that with respect to protonation. GIAO/CHF nitrogen-shielding calculations are reported for all of the existing monocyclic heteroaromatic azine systems including **I** using a 6-31⁺⁺G** basis set. These appear to indicate that the inclusion of electron-correlation effects, reported for the SOLO method, does not result in a dramatic improvement in the calculated nitrogen shieldings. © 1997 Academic Press

INTRODUCTION

We have previously reported the results of NMR studies on the influence of solvents on the nitrogen shielding of, with one exception, all of the existing monocyclic parent azine heteroaromatics (1, 2). It transpires that the study of the solvent influence on the nitrogen shieldings in these systems provides an insight into the effects of solvent polarity and solvent-to-solute hydrogen bonding on these azines. The analysis of the overall nitrogen-shielding variation, as a function of solvent, in terms of these two effects provides a means of estimating the relative basicities of the nitrogen atoms involved with respect to hydrogen bonding.

The only parent monocyclic azine not included in our

published work on solvent-induced effects on nitrogen shieldings is 1,2,4,5-tetrazine:



The only available nitrogen-shielding data for this tetrazine (**I**) are from our early, low-precision, studies (3, 4). It is the purpose of the present report to expand this earlier work on **I** to include some high-precision ¹⁴N NMR measurements in a variety of solvents, the analysis of the results of these measurements in terms of both specific and nonspecific solute-solvent interactions, and a study of protonation effects.

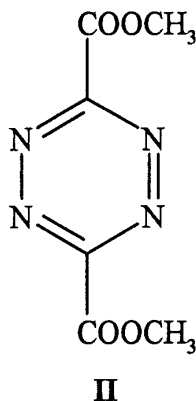
The protonation of compound **I** is of interest, since its basicity as estimated by *ab initio* Hartree-Fock molecular orbital calculations for gas-phase protonation energies using a 6-31G* basis set is predicted to be the lowest in the azine series with the exception of the N₄ of 1,2,4-triazine (5). We note that these gas-phase protonation energies correlate well with our estimates of hydrogen bonding effects on the nitrogen shieldings of the other azines studied (1, 2). Consequently, we may expect that compound **I** will experience a very weak influence on its nitrogen shielding due to solvent-to-solute hydrogen bonding effects. If this transpires to be the case our current NMR results for **I** will provide strong support for the general relationship between nitrogen atom basicities with respect to proton transfer and those with respect to hydrogen bonding.

In our work we employ the term “nitrogen shielding” rather than “nitrogen chemical shift” as discussed previously (1–4). Consequently, we use a sign convention for the nitrogen-shielding data which has a positive sign for an increase in nuclear shielding. This is opposite to that associated with the chemical-shift scale, while the two terms have the same magnitudes.

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RESULTS AND DISCUSSION

The high-precision ^{14}N NMR shieldings measured for **I** in a variety of solvents are reported in Table 1. The solvents chosen portray a wide range of properties with respect to hydrogen bonding and polarity effects. In addition we report the nitrogen shielding of the dicarbomethoxy derivative



in acetone solution, in order to estimate the relative magnitudes of substituent- and solvent-induced effects on the nitrogen shielding of **I**. The data reported in Table 1 show that the range of solvent-induced nitrogen-shielding variations for **I** is about 10 ppm. This is rather modest in comparison with the analogous ranges exhibited by the other azines (1, 2).

In order to unravel the various specific and nonspecific solute-solvent contributions to the solvent-induced nitrogen-shielding variations of **I** we employ the empirical scheme shown by the master equation (6, 7)

$$\sigma(i,j) = \sigma_o(i) + a(i)\alpha(j) + b(i)\beta(j) \quad [1]$$

$$+ s(i)[\pi^*(j) + d(i)\delta(j)],$$

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 ($\delta = 0.5$) 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_o . To separate the various specific and nonspecific contributions to the solvent-induced nitrogen-shielding variations, we have made use of the empirical scheme represented by the master equation [1] (6, 7).

Table 2 lists the solvent parameters used in the present study, as reported elsewhere (6, 7), together with the least-squares-fitted estimates of the solute nitrogen-shielding responses and the linear correlation coefficients for the experi-

TABLE 1
Solvent Effects on the Nitrogen NMR Shieldings
of 1,2,4,5-Tetrazine Systems

Solvent	Nitrogen NMR shielding (ppm) referred to neat liquid nitromethane ^a	
	I	II
Cyclohexane	-15.74	
CCl ₄	-14.61	
Et ₂ O	-13.47	
Benzene	-13.01	
Dioxane	-11.70	
Acetone	-11.62	-13.70
DMSO	-11.60	
CH ₂ Cl ₂	-12.07	
CHCl ₃	-12.74	
EtOH	-12.15	
MeOH	-10.62	
CF ₃ CH ₂ OH	-7.95	
H ₂ O	-5.46	

^a All data are corrected for bulk susceptibility effects and related to 0.01 M solutions at $+35 \pm 0.2^\circ\text{C}$.

mental shieldings with respect to those produced by Eq. [1]. The value of a reported for **I** in Table 2 is significant, but small, and comparable with that found for the N_4 in 1,2,4-triazine (2) for which $a = +1.1$ ppm/unit scale. The term a relates to the effects of solvent-to-solute hydrogen bonding, on the solute nitrogen shielding, and the rather small value of a found here for **I** is in good agreement with the estimation of gas-phase protonation energies (5). The calculated gas-phase data show that N_4 of 1,2,4-triazine and compound **I** have the lowest protonation energies of the azines studied, and depart significantly in value from those of the other azines considered. These include pyridine, pyridazine, pyrimidine, pyrazine, 1,3,5-triazine, and 1,2,4-triazine (1, 2, 9). Consequently, our value of a provides support for a parallel relationship for the basicities of nitrogen atoms with respect to full proton transfer and those with respect to hydrogen bonding in the azine systems concerned.

The effects of solvent polarity on the nitrogen shielding, shown by the value of the s term, are unexpectedly quite significant for the nonpolar compound **I** and comparable to those found for most of the other azines (1, 2). The positive value found for s (Table 2) indicates that the nitrogen shielding of **I** increases as the polarity of the solvent increases. This finding is supported by the results of some INDO/S parameterized molecular orbital calculations of the nitrogen shielding of **I** within the framework of the Solvaton model (10, 11). In this model the nonspecific solute-solvent interactions are characterized by the dielectric (ϵ) of the solvent medium. As shown in Table 3, the results of the Solvaton calculations show that the nitrogen shielding of **I**

TABLE 2
Solvent Parameters Used and Least-Squares Fitted Solute Parameters for a Set of Master Equations [1]

Solvent	α	β	π^*	δ	Dielectric constant ^a
Cyclohexane	0	0	0	0	1.87
Et ₂ O	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 ₂ Cl 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 ₂ O	1.13	0.18	1.09	0	76.70
CF ₃ CH ₂ OH	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
I	-15.1 ± 0.9	$+2.4 \pm 0.9$	-1.6 ± 1.5	$+5.5 \pm 1.3$	-0.4 ± 0.3	0.94

^a The constants were recalculated for a temperature of 35°C from the data available in Ref. (8).

increases with an increase in ϵ , thus supporting the value found for s . The values of the terms b and d reported for compound **I** in Table 2 are insignificant and are not considered further.

Compound **II** represents a 1,2,4,5-tetrazine system substituted with two strong electron-withdrawing carbomethoxy groups. Compound **II** is essentially insoluble in all of the solvents used in this work with the exception of acetone. If we compare its nitrogen shielding with that of **I** in acetone, the substituent effect of the two carbomethoxy groups is found to be rather meager, about -2 ppm. The range of solvent-induced effects on the nitrogen shielding of **I** is much larger, about 10 ppm. Consequently, caution should be exer-

cised in any attempt to investigate substituent effects on the nitrogen shielding of **I** without taking due account of solvent effects.

Recently, some *ab initio* molecular orbital nuclear-shielding calculations were reported for all of the monocyclic azine systems (12). The procedure used was the second-order-correlated localized-orbital local-origin method (SOLO) which includes electron-correlation effects. It is claimed that the inclusion of these effects in the calculations of nitrogen shieldings represents a significant improvement in the results over those obtained by coupled Hartree-Fock (CHF) methods (12). With a view to verifying this claim, we have performed some gauge-included atomic-orbital (GIAO) calculations at the CHF level of the nitrogen shieldings of the azine heteroaromatic ring systems. The results of these calculations, which do not include electron-correlation effects, are given in Table 4. For comparison purposes we include in Table 4 experimental high-precision ¹⁴N-shielding data, with respect to nitromethane. The experimental results were obtained on dilute solutions in an inert solvent, cyclohexane, and corrected for bulk susceptibility effects of the solvent.

A plot of the data given in Table 4 is presented in Fig. 1 which shows a good linear correlation between the calculated and experimental nitrogen shieldings. The relevant linear-regression equation is

$$\sigma_{\text{exp}} = 0.7609 \sigma_{\text{calc}} + 100.06. \quad [2]$$

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 (in ppm) with respect to that for $\epsilon = 2$
	Compound I
4	+2.21
8	+3.48
10	+3.81
20	+4.14
40	+4.16
80	+4.17

TABLE 4
Experimental and *ad Initio* Calculated Magnetic Shielding of Nitrogen in Azine Heteroaromatic Ring Systems

Compound and nitrogen atom	Experimental NMR shielding of nitrogen for dilute solutions in cyclohexane, reference to neat nitromethane (ppm)	GIAO/CHF-calculated absolute shielding, 6-31 ⁺⁺ G** basis set, optimized geometries (present work)
1,2,5-Triazine	+95.36 ^a	+2.9
Pyrimidine (1,3-diazine)	+80.30 ^a	-22.3
Pyridine	+57.70 ^b	-59.8
Pyrazine (1,4-diazine)	+42.17 ^a	-89.7
1,2,4-Triazine, N-1	-51.16 ^c	-203.6
1,2,4-Triazine, N-2	-6.84 ^c	-123.5
1,2,4-Triazine, N-4	+79.95 ^c	-37.5
1,2,4,5-Tetrazine	-15.74 ^d	-155.4
Pyridazine (1,2-diazine)	-35.31 ^a	-170.8

^a Data from Ref. (1).

^b Data from Ref. (9), recalculated in Ref. (1).

^c Data from Ref. (2).

^d Data from the present work.

The corresponding standard deviation is 8.1 ppm with a correlation coefficient of 0.991. A similar analysis of the SOLO-calculated and experimental data for the azines, given in Ref. (12), yields a slope for the regression line of 0.7407, which is slightly less than our value of 0.7609. The standard deviation for the SOLO results is 5.1 ppm and the correlation coefficient is 0.996, which is a slight improvement over our results. Thus, it is possible that the small differences between the two sets of fitted data show a slight improvement for the results of the SOLO calculations over those obtained by the GIAO/CHF method. However, the differences are small, and the inclusion of electron-correlation effects in the calculation of azine nitrogen shieldings does not appear to be very significant.

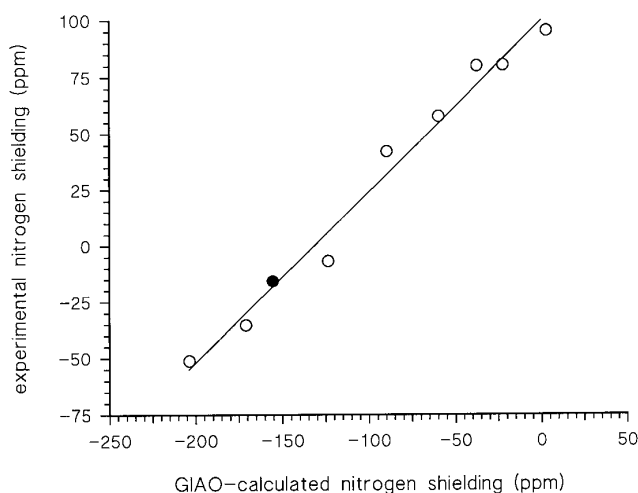


FIG. 1. A plot of experimental nitrogen shieldings, with respect to external nitromethane, against GIAO/CHF-calculated absolute nitrogen shieldings for the azine systems considered in Table 4. The solid circle, ●, represents compound I.

EXPERIMENTAL

The compounds studied were prepared in a multistep synthesis by previously published procedures (13, 14). Very pure and dry solvents were used in the NMR measurements as reported previously (1, 2). The solutions were prepared and handled under a dry argon atmosphere in glove bags. The ¹⁴N-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 (1, 2). 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 ¹⁴N signal of neat nitromethane is 36.141524 MHz, from which a value of 36.136826 MHz is obtained for the bare nitrogen nucleus (1, 2). 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 ¹⁴N signals was used to produce values for the precise resonance frequencies of both the samples and 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 GIAO/CHF *ab initio* nitrogen-shielding calculations

were performed using the Gaussian 94 suite of programs, rev. D.3 (15), on an ESCOM Pentium/120 MHz-based system at the Institute of Organic Chemistry in Warsaw. The calculations were performed using the 6-31⁺⁺G** basis set for both geometry optimization and nitrogen-shielding calculations. This basis set puts both polar and diffuse functions on hydrogen and the heavy atoms and appears to be a satisfactory choice for polar molecules containing lone-pair electrons. The INDO/S Solvaton calculations of nitrogen shieldings as a function of solvent dielectric (10, 11) were performed on the University of Surrey HP Central system using INDO-optimized geometries.

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