Solvent effects on the NMR shieldings of nitrogen atoms in azole and azine systems: their counterparts in the gas phase

J. Catalán

Departamento de Química Física Aplicada, Universidad Autónoma de Madrid, Cantoblanco, E-28049, Madrid, Spain

Received (in Cambridge, UK) 31st January 2001, Accepted 26th April 2001
First published as an Advance Article on the web 25th May 2001

The ^{14}N shieldings of 14 pyrrole and 39 pyridine nitrogens belonging to azoles, oxazoles, thiazoles, azines and indolizines measured in 13 different solvents in the same laboratory by Witanowski *et al*. are examined in the light of the solvent polarity/polarizability (SPP), solvent acidity (SA) and solvent basicity (SB) pure solvent scales. The results are explained in terms of the structural properties of the compounds. Based on the analysis of the solvent effect, the corresponding ^{14}N shieldings in the gas phase for the 53 nitrogens studied are obtained, the experimental determination of which is a major challenge.

Introduction

Biochemically significant compounds including amino acids (tryptophan, histidine), purine (adenines and guanines) and pyrimidine (thymines, cytosines) DNA bases, hemoproteins (porphyrins), sympathomimetic amines (histamines, serotonins) and plant hormones (gibberellins) possess molecular structures, an essential part of which is a heterocyclic fragment where one or more heteroatoms are nitrogens.

Nitrogen atoms in an aromatic ring occur in either of two different forms, *viz*. the pyridine-type or the pyrrole-type form. The pyridine-type form is present in both six- and five-membered aromatic ring systems, while the pyrrole-type form occurs only in five-membered ring moieties; occasionally, as in indolizine, it acts as the linkage between a six- and a five-membered ring. Although the nitrogen atom exhibits sp^2 hybridization in both forms, the electronic distribution in the two forms is rather different. Thus, while the pyrrole-type nitrogen donates an electron pair to the π aromatic system, the pyridine-type nitrogen retains them as a "lone pair" on the σ backbone of the compound. Both forms can endow compounds possessing them with acid properties (through a pyrrole-type nitrogen) or basic properties (through pyridine-type nitrogens).

The simultaneous presence of several heteroatoms in a heterocycle results in interesting electronic effects on acid properties (of the pyrrole site) or basic ones (of the pyridine sites), which allowed Taft *et al*.[1,2] to quantify so-called "proximity electrostatic effects". Because the incorporation of heteroatoms can substantially alter the polarity, acidity and basicity of a heterocycle, it can obviously dictate the interaction with its molecular environment. Such an interaction will depend not only on the nature of the heteroatoms but also on the way their properties are altered by the presence and number of additional heteroatoms in the compounds.

Typical examples of such compounds are azoles. An increase in the number of nitrogen atoms in their structure results in the following: (1) the gas-phase acidity increases by 24 kcal mol^{-1} from pyrrole[3] (ΔG°_{acid} = 350.9 kcal mol^{-1}) to tetrazole[4] (ΔG°_{acid} = 326.7 kcal mol^{-1}); (2) the gas-phase basicity decreases by 25 kcal mol^{-1} from imidazole[4] (ΔG°_{prot} = 215.6 kcal mol^{-1}) to tetrazole[2] (ΔG°_{prot} = 190.2 kcal mol^{-1}); and (3) the gas-phase dipole moment increases by 3.56 D from pyrrole (1.74 D[5]) to tetrazole (5.30 D[6]). It should be noted that the previous intrinsic acidities referred to the loss of the pyrrolic hydrogen in the gas-phase, whereas the intrinsic basicities are referred to the basicity of the most basic pyridine-type nitrogen in the compound.[7]

Witanowski *et al*. conducted a comprehensive NMR study in 13 different solvents (*viz*. cyclohexane, Et_2O, CCl_4, benzene, dioxane, acetone, DMSO, CH_2Cl_2, CH_3Cl, EtOH, MeOH, H_2O and CF_3CH_2OH) of five-membered (azole,[8] diazole,[9] triazole,[10] tetrazole,[11] oxazole,[12] oxadiazole,[12] thiazole[13] and thiadiazole[13]) and six-membered heterocycles (azines[14–16]), as well as ambivalent compounds (indolizine[17] and azaindolizines[17]) (see Fig. 1), for which they reported high-precision nitrogen shieldings corrected for bulk susceptibility. They considered every N–Me structure potentially present in azole compounds and reported comprehensive, interesting information about the shieldings for a wide variety of nitrogen sites. The electronic properties of some of the 53 nitrogens studied by these authors are strongly dependent on aza effects, as reflected in changes in their shieldings with the solvent. Despite the small number of solvents used, they were carefully chosen so that they spanned wide polarity, acidity and basicity ranges. However, they failed to span the low end of the acidity scale and the high end of the basicity scale. We shall comment further on this aspect later on.

In the light of the solvent acidity (SA), solvent basicity (SB) and solvent polarity/polarizability (SPP) pure solvent scales recently developed at the author's laboratory,[18–22] this paper reports the results of an analysis of the shieldings of various nitrogen atoms in the azoles and azines studied by Witanowski *et al*.[8–16] The results are explained on the basis of the structural properties of the compounds.

The pure solvent scales were developed from suitable probe/homomorph couples. Thus, the dipolarity/polarizability of a pure solvent can be characterized in terms of the solvatochromism of the probe 2-(*N*,*N*-dimethylamino)-7-nitrofluorene and its homomorph 2-fluoro-7-nitrofluorene; SPP values range from 0 in the absence of solvent (*i.e.* the gas phase) to 1 for DMSO.[18] The SB scale is based on the solvatochromism of the probe 5-nitroindoline and its homomorph *N*-methyl-5-nitroindoline; SB values range from 0 for the gas phase to 1 for tetramethylguanidine.[19] Finally, SA is evaluated from the solvatochromism of the probe *o*-*tert*-butylstilbazolium betaine dye and its homomorph *o*,*o*-di-*tert*-butylstilbazolium betaine dye, and encompasses values from 0 for the gas phase to 0.4 for ethanol.[20] The acidity of solvents more acidic than methanol

DOI: 10.1039/b101084k

(SA = 0.605) is evaluated by applying the solvatochromic comparison method[23] to solvatochromic measurements of the probe 3,6-diethyl-1,2,3,5-tetrazine.[21] Table 1 shows the SPP, SB and SA values for the 13 solvents used by Witanowski *et al*. to measure their ^{14}N shieldings. The use of eqn. (1) to apply these scales is discussed elsewhere.[22] In principle, any molecular property in a solvent series can be analysed by using a multiparameter equation of the type shown in eqn. (1), where SPP, SB and SA are typical of the solvent, while coefficients *s*, *a* and *b* pertain to the solute and describe its sensitivity to the polarity/polarizability, acidity and basicity of its environment, respectively. In our case, the shielding σ of a given environment will be obtained from (1) its value in the gas phase, σ_{gas}, as corrected with a term considering the sensitivity of the corresponding nitrogen site to the polarity/polarizability of the environment, *s*, times the polarity/polarizability value on the SPP scale; in addition to (2) a term considering the sensitivity of the nitrogen site to the acidity of the environment, *a*, times the acidity value on the SA scale; in addition to (3) a term considering the sensitivity of the nitrogen site to the basicity of the environment, *b*, times the basicity value on the SB scale.

$$\sigma = s\mathrm{SPP} + a\mathrm{SA} + b\mathrm{SB} + \sigma_{gas} \quad (1)$$

Table 1 The SPP (solvent polarity/polarizability), SB (solvent basicity), and SA (solvent acidity) values for the 13 solvents used by Witanowski *et al*. in measuring their ^{14}N shieldings

Solvent	SPP	SB	SA
Cyclohexane (**1**)	0.557	0.073	0.0
Diethyl ether (**2**)	0.694	0.562	0.0
Tetrachloromethane (**3**)	0.632	0.044	0.0
Benzene (**4**)	0.667	0.124	0.0
1,4-Dioxane (**5**)	0.701	0.444	0.0
Acetone (**6**)	0.881	0.475	0.0
Dimethyl sulfoxide (**7**)	1.0	0.647	0.072
Dichloromethane (**8**)	0.876	0.178	0.040
Chloroform (**9**)	0.786	0.071	0.047
Ethanol (**10**)	0.853	0.658	0.400
Methanol (**11**)	0.857	0.545	0.605
Water (**12**)	0.962	0.025	1.062
2,2,2-Trifluoroethanol (**13**)	0.908	0.107	0.893

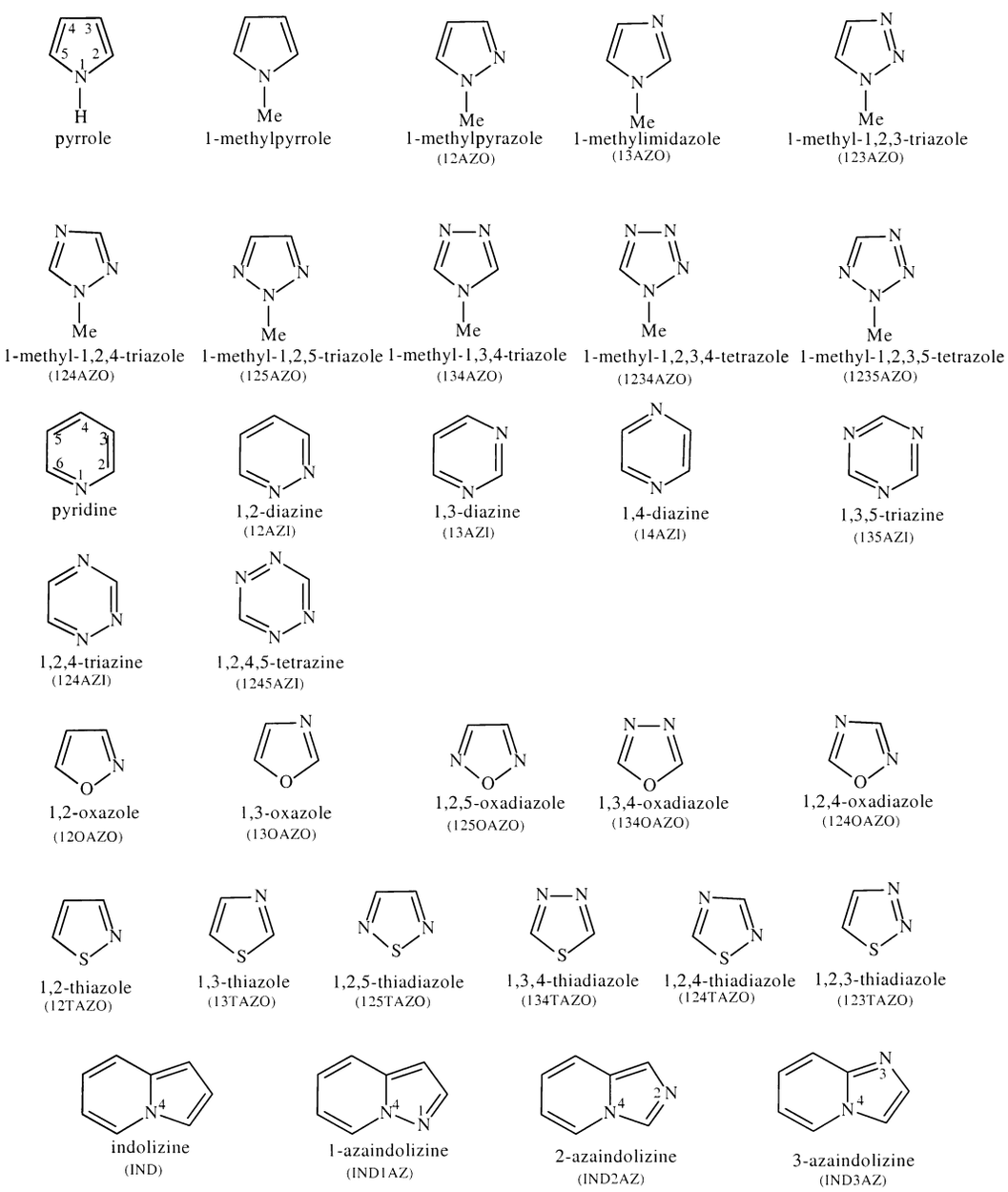

Fig. 1 Structure of the azoles, azines, oxazoles, thiazoles and indolizines studied, and numbering of the nitrogen atoms. Also, the abbreviations for the molecules used in the Tables are shown.

Obviously, the sensitivity quantities *s*, *a* and *b* must be related to the polarity, basicity and acidity of the nitrogen site in question in the heterocycle concerned.

The intrinsic values of the shieldings (σ_{gas}) for each nitrogen atom in the compounds considered are also reported. Gas-phase shieldings are rather difficult to obtain experimentally—to the author's knowledge, that for pyridine is the only one reported to date.[24]

Results and discussion

There have been two recent attempts to describe in theoretical terms the general solvent effect on the shieldings of some of the above-described nitrogen-containing heterocycles.[25,26] As shown below, however, the analysis should include not only the general contribution, but also the specific contribution of the solvent.

Table 2 shows the results obtained by fitting the shieldings of each nitrogen in the azoles and azines studied, which are grouped in the following categories: (1) pyrrole-type, (2) pyridine-type in azoles, (3) pyridine-type in azines, (4) pyridine-type in oxazoles, (5) pyridine-type in thiazoles and (6) pyridine-type in indolizines. As stated in the table, some fits excluded solvents with anomalous deviations (*e.g.* water in some cases, dioxane or trifluoroethanol in others, cyclohexane with nitrogen N^3 in 1,2,3,4-tetrazole).

Pyrrole-type nitrogens

The sensitivity of the shieldings of pyrrole-type nitrogens to the solvent is largely dependent upon the polarity/polarizability of the latter; by exception, pyrrole is highly sensitive to solvent basicity—in fact, a pyrrole N–H group can be a suitable probe for estimating solvent basicity.[22,27] An analysis of *s* (the coefficient that reflects the sensitivity to solvent polarity) reveals that the nitrogen shieldings for *N*-Me-azoles decrease markedly with increasing solvent polarity (*s* ranges from −16.6 for *N*-Me-1,2,4-triazole to −4.11 for *N*-Me-1,2,5-triazole). If *N*-Me-pyrrole is excluded, the sensitivity to solvent polarity increases with the dipole moment for the corresponding *N*-Me-azole (see Table 3). This can be ascribed to the low sensitivity of the nitrogens in *N*-Me-azoles to solvent basicity and acidity.

One pertinent comparison at this point is that between *N*-Me-pyrrole and indolizine, where *s* results in −15.98 and −4.33 by virtue of the latter compound being less polar ($\mu_{indolizine}$ = 1.13 D, $\mu_{N\text{-Me-pyrrole}}$ = 1.91 D) and possessing a greater molar volume than the former, which will result in larger cavities in the bulk solvent and hence in decreased interaction forces.

The shieldings of the pyrrole-type nitrogens in the three azaindolizines studied by Witanowski *et al.*[17] have *s* values that increase from 1-azaindolizine to 2-azaindolizine to 3-azaindolizine; their dipole moments exhibit the same trend (see Table 3).

Pyridine-type nitrogens in *N*-Me-azoles and indolizines

The presence of lone-pair electrons makes these nitrogens highly sensitive to solvent acidity but scarcely sensitive to solvent basicity, which results from interactions with C–H groups.

As can be seen from Table 2, the sensitivity of azoles to solvent acidity ranges from 27.56 for N^3 in *N*-Me-imidazole to the virtually negligible value (*a* = 1.88) for N^2 in *N*-Me-1,2,3,5-tetrazole; also, *a* appears to vary similarly to the basicity of the compounds, which is dictated by their pyridine-type nitrogens. As can be seen from Table 3, the *a* value, which measures the sensitivity of the nitrogen site to solvent acidity, decreases with decreasing basicity within each azole group, *viz*. in the imidazole > pyrazole sequence among the diazoles, the 1,3,4 > 1,2,4 ≈ 1,2,3 ⩾ 1,2,5 sequence among the triazoles and the 1,2,3,4 ≈ 1,2,3,5 sequence among the tetrazoles.

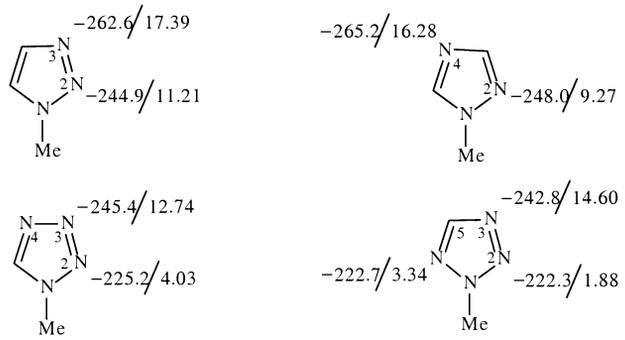

Fig. 2 Energy for protonation $-\Delta E_{prot}$/solvent acidity sensitivity of the pyridine-type nitrogens of azoles.

In azoles possessing different pyridine-type nitrogens, *a* also varies with the basicity of the corresponding molecular site (see Fig. 2). This is especially significant as basicity measurements, whether in the gas phase or in solution, only reflect the basicity of the most basic site in the neutral form of the compound concerned.

The shieldings of the pyridine-type nitrogens are virtually independent of the basicity of the solvent (see *b* values in Table 2); also, they must largely be the result of effects on other adjacent sites such as C–H bonds.

Table 4 shows the sensitivities of the shieldings of the different nitrogen sites in *N*-Me-azoles to solvent polarity in groups. Unlike pyrrole-type nitrogens, pyridine-type nitrogens exhibit shieldings that increase markedly with increasing solvent polarity; also, there are clear-cut exceptions to the rule established by Witanowski *et al.*[10] that all pyridine-type nitrogens in a compound depend identically on solvent polarity.

The sensitivity of pyridine-type nitrogens in azaindolizines to solvent acidity, *a*, increases in the same sequence as the basicity of these nitrogens (see the proton affinity (PA) and pK_a values in Table 3).

If increasing the solvent polarity causes the pyrrole-type nitrogen in an azole to be deshielded by further delocalizing the π system of its electron pair, then acceptor groups (pyridine-type nitrogens) should simultaneously gain charge and hence be markedly more shielded.

Pyridine-type nitrogens in azines

The nitrogens in these compounds are clearly more strongly shielded in the more polar solvents; in fact, *s* for these compounds ranges from 35 for 1,2-diazine to a negligible value for N^4 in 1,2,4-triazine (see Table 2). The only asymmetric azine studied, 1,2,4-triazine, is distinctive in that the shieldings of its nitrogens change by about 30 ppm among the solvents studied, whereas those of its N^4 atom differ by only 5.5 ppm at most. Only in diazines can one envisage a clear-cut relationship between *s* and polarity; in fact, their *s* values vary in the sequence 1,2-diazine > 1,3-diazine > 1,4-diazine, the respective dipole moments for which are 4.06, 2.22 and 0.24 D (see Table 3).

The sensitivity of these compounds to solvent acidity is clearly dictated by their basicity, as can be inferred from a comparison of their *a* values with the corresponding proton affinity (PA) and pK_a values (see Table 3). The shieldings of these compounds are clearly influenced by a weak effect due to solvent basicity (see the corresponding *b* values in Table 2).

Pyridine-type nitrogens in oxazoles and thiazoles

The shieldings of pyridine-type nitrogens in oxazoles and thiazoles increase with increasing solvent polarity/polarizability of their molecular environment; *s* ranges from 18 for 1,2-oxazole and 1,3,4-thiadiazole to 4 for N^4 in 1,2,4-oxadiazole and N^2 in 1,2,4-thiadiazole (see Table 2). As can be seen from the data in

Table 2 Results obtained by fitting the shieldings of each nitrogen in the aza heterocyclic compounds studied by Witanowski *et al*. *vs*. the corresponding SPP, SB and SA values of the solvents

Compound	Solvent [a]	r [b]	s	a	b	σ_{gas}
Pyrrole-type (N^1) in azoles						
Pyrrole	**12**	0.976	−15.31 ± 2.55		−10.50 ± 1.37	247.96 ± 1.85
N-Me-pyrrole	**5**	0.983	−15.98 ± 1.56	−1.04 ± 0.53	3.24 ± 0.71	243.62 ± 1.10
$N^1$12AZO	**12**	0.901	−9.04 ± 1.61	3.57 ± 0.71		186.11 ± 1.22
$N^1$13AZO		0.957	−12.16 ± 2.83	−3.63 ± 0.98	−1.60 ± 1.28	231.24 ± 1.99
$N^1$123AZO	**5**	0.975	−14.08 ± 2.83	−1.19 ± 0.53		156.73 ± 1.13
$N^1$124AZO		0.941	−8.28 ± 1.86	−0.72 ± 0.65	−2.30 ± 0.84	180.60 ± 1.30
$N^1$125AZO	**13**	0.975	−4.11 ± 1.47	1.54 ± 0.56	−0.770 ± 68	135.39 ± 1.03
$N^1$134AZO		0.977	−16.06 ± 2.60		−2.241 ± 18	234.30 ± 1.82
$N^1$1234AZO	**5**	0.983	−16.01 ± 1.81	−1.83 ± 0.61	−1.09 ± 0.82	167.81 ± 1.27
$N^1$1235AZO	**5**	0.961	−10.26 ± 1.17		−1.38 ± 0.62	112.78 ± 0.90
Pyridine-type in azoles adjacent to N^1: N^2 or N^5						
$N^2$12AZO	**12**	0.978	7.44 ± 4.85	25.56 ± 2.15		63.51 ± 3.69
$N^2$123AZO		0.978	−15.98 ± 4.17	11.21 ± 1.45	−3.98 ± 1.89	1.15 ± 2.92
$N^2$124AZO		0.978	7.09 ± 3.04	9.27 ± 1.06	−3.03 ± 1.38	76.40 ± 2.13
$N^{2,5}$125AZO	**13**	0.979	5.09 ± 2.12	7.37 ± 0.80	−2.69 ± 0.97	46.14 ± 1.49
$N^2$1234AZO	**11**	0.979	2.64 ± 1.04	4.03 ± 0.39		7.35 ± 0.79
$N^2$1235AZO	**12**	0.942	7.29 ± 1.33	1.88 ± 0.59		−6.60 ± 1.01
$N^5$1235AZO		0.936		3.34 ± 0.47	−2.11 ± 0.70	73.72 ± 0.30
Pyridine-type in azoles not adjacent to N^1: N^3 or N^4						
$N^3$13AZO	**12**	0.973	11.74 ± 6.23	27.56 ± 2.78		107.35 ± 4.76
$N^3$123AZO		0.955	9.70 ± 7.75	17.39 ± 2.69		17.62 ± 5.42
$N^4$124AZO		0.947	8.64 ± 4.41	16.28 ± 1.96		119.58 ± 3.35
$N^{3,4}$134AZO	**12**	0.977	24.77 ± 6.31	27.56 ± 2.80		35.50 ± 4.80
$N^3$1234AZO	**1**	0.985	13.41 ± 3.47	12.76 ± 1.08		−26.81 ± 2.72
$N^4$1234AZO	**12**	0.983	12.46 ± 2.83	14.52 ± 1.25		37.85 ± 2.15
$N^3$1235AZO	**12**	0.959	9.02 ± 4.24	14.60 ± 1.88		37.42 ± 3.22
Pyridine-type in azines						
12AZI	**12**	0.987	35.19 ± 7.50	36.01 ± 2.93	−9.75 ± 3.58	−50.57 ± 5.22
13AZI	**12**	0.983	10.74 ± 3.19	14.15 ± 1.24	−3.91 ± 1.52	75.93 ± 2.22
14AZI		0.985	9.35 ± 3.14	11.66 ± 1.09	−3.29 ± 1.42	38.56 ± 2.19
135AZI		0.971	7.03 ± 2.81	7.00 ± 0.98	−2.50 ± 1.27	92.38 ± 1.97
$N^1$124AZI		0.976	25.10 ± 7.31	19.08 ± 2.54	−3.58 ± 3.32	−62.86 ± 5.11
$N^2$124AZI		0.991	22.05 ± 3.58	18.07 ± 1.29		−17.38 ± 2.72
$N^4$124AZI		0.976		3.56 ± 0.84	−2.41 ± 1.27	80.90 ± 0.55
1245AZI	**5**	0.969	10.54 ± 2.41	4.18 ± 0.82	−1.99 ± 1.09	−20.75 ± 1.70
Pyridine-type in oxazoles						
12AZO	**13**	0.981	18.11 ± 3.87	11.91 ± 1.46	−2.51 ± 1.78	19.42 ± 2.70
13OAZO	**12**	0.981	8.34 ± 2.48	15.69 ± 1.39	−3.09 ± 1.70	116.34 ± 2.48
125OAZO		0.941	14.01 ± 3.63	5.75 ± 1.31		−49.08 ± 2.76
134OAZO	**13**	0.976	15.32 ± 3.40	13.64 ± 1.51		59.56 ± 2.58
$N^2$124OAZO		0.945	13.79 ± 4.07	5.41 ± 1.41	−2.65 ± 1.84	3.07 ± 2.84
$N^4$124OAZO	**13**	0.972	4.17 ± 1.50	5.34 ± 0.61		133.36 ± 1.14
Pyridine-type in thiazoles						
$N^2$12TAZO	**12**	0.977	14.67 ± 4.99	18.74 ± 1.95	−6.63 ± 2.38	71.87 ± 3.47
$N^3$13TAZO	**12**	0.982	11.33 ± 5.13	23.25 ± 2.00	−3.81 ± 2.45	47.89 ± 3.57
$N^{2,5}$125TAZO		0.947	10.39 ± 4.28	6.92 ± 1.49	−4.20 ± 1.94	26.22 ± 3.00
$N^{3,4}$134TAZO	**13**	0.979	17.99 ± 4.22	16.13 ± 1.73		−10.12 ± 3.21
$N^2$124TAZO	**13**	0.938	4.72 ± 2.77	5.03 ± 1.05	−3.01 ± 1.28	101.59 ± 1.94
$N^4$124TAZO	**13**	0.982	10.16 ± 2.85	10.08 ± 1.08	−2.01 ± 1.31	61.49 ± 1.99
$N^2$123TAZO	**13**	0.980	20.53 ± 3.79	10.11 ± 1.42	−4.08 ± 1.73	−48.83 ± 2.63
$N^3$123TAZO	**12**	0.987	14.00 ± 3.12	12.59 ± 1.18	−4.99 ± 1.44	−67.80 ± 2.19
Pyrrole- and pyridine-type in indolizines						
N^4IND		0.877	−4.33 ± 0.72			193.47 ± 0.58
N^4IND1AZ	**12**	0.974	−1.25 ± 0.71	3.83 ± 0.31		145.25 ± 0.54
N^1IND1AZ	**12**	0.978	6.24 ± 4.74	24.61 ± 2.11		87.51 ± 3.61
N^4IND2AZ	**13**	0.966	−4.68 ± 0.48		−0.33 ± 0.26	190.25 ± 0.36
N^2IND2AZ	**12**	0.979	9.66 ± 5.43	28.51 ± 2.41		98.58 ± 4.12
N^4IND3AZ	**12**	0.913	−3.26 ± 0.93	1.38 ± 0.36	−1.12 ± 0.45	182.24 ± 0.65
N^3IND3AZ	**13**	0.976	13.08 ± 6.17	29.32 ± 2.74		127.43 ± 4.70

Table 3 Comparison of the sensitivity of the heterocycle to solvent polarity (*s*), and solvent acidity (*a*) with the dipole moment of the compound, and the basicity of the corresponding nitrogen center, respectively

Azoles
Sensitivity (*s*) of the N^1 shielding to solvent polarity/polarizability

	s	μ_{exp}/D
1234AZO	−16.01	5.50[29]
135AZO	−16.06	
123AZO	−14.08	4.46[28]
13AZO	−12.16	3.77[28]
124AZO	−8.28	3.37[28]
1235AZO	−10.26	2.70[29]
12AZO	−9.04	2.25[28]
125AZO	−4.11	0.37[28]

Sensitivity (*a*) of the pyridine-type nitrogens to solvent acidity

	a	ΔE_{prot}[7]	pK_a[30]	q_{LPF}[7]
Diazoles				
$N^3$13AZO	27.56	−283.3	7.12	0.2507
$N^2$12AZO	25.56	−264.8	2.06	0.2185
Triazoles				
$N^{3,4}$134AZO	27.56	−270.2	3.40	0.2372
$N^3$123AZO	17.39	−262.6	1.23	0.2241
$N^4$124AZO	16.28	−265.2	3.20	0.2274
$N^{2,5}$125AZO	7.37	−243.5	<1	0.1956
Tetrazoles				
$N^4$1234AZO	14.52	−248.2	−3.00	0.2068
$N^3$1235AZO	14.60	−242.8	−3.25	0.1989

Azines
Sensitivity (*s*) of the nitrogen shieldings to solvent polarity/polarizability

	s	μ_{exp}[32]
12AZI	35.19	3.94
13AZI	10.74	2.33
14AZI	9.35	0.22
135AZI	7.03	0

Sensitivity (*a*) of the pyridine-type nitrogens to solvent acidity

	a	PA (gas)[2]	pK_a[31]
12AZI	36.01	215.6	2.24
13AZI	14.15	210.5	1.23
14AZI	11.66	209.0	1.1
135AZI	7.00	201.1	
1245AZI	4.18	<0	

Oxazoles and thiazoles
Sensitivity (*s*) of the nitrogen shieldings to solvent polarity/polarizability

	s	μ_{exp}[32] (gas)
12OAZO	18.11	2.90
13OAZO	8.34	1.50
$N^4$124OAZO	4.17	1.2
125OAZO	14.01	3.38
12TAZO	14.67	2.44
13TAZO	11.33	1.61
125TAZO	10.39	1.56
134TAZO	17.99	3.28

Sensitivity (*a*) of the pyridine-type nitrogen shieldings to solvent acidity

	a	PA (gas)[33]	pK_a[31]
13TAZO	23.25	213.2	2.51
130AZO	15.69	208.4	0.8
120AZO	11.91	202.3	−2.03

Table 3 (*Contd.*)
Indolizines
Sensitivity (*a*) of the pyridine-type nitrogen shieldings to solvent acidity

Indolizines	*s*	μ_{exp}[32] (benzene)
IND1AZ	−1.25	2.18
IND2AZ	−4.68	3.25
IND3AZ	−3.26	3.47
N-Me-pyrrole	−15.98	1.91
IND3AZ	−4.33	1.13

Sensitivity (*a*) of the pyridine-type nitrogen shieldings to solvent acidity

	a	PA (gas)[33]	pK_a[31]
N^1IND1AZ	23.97	218.5	1.43
N^2IND2AZ	27.99	226.3	5.54
N^3IND3AZ	29.32	229.9	6.79

Table 4 Sensitivity of the solvent polarity (*s*) of the nitrogen shieldings of *N*-Me-azoles

Azole	N^1	N^2	N^3	N^4	N^5
12AZO	−9.04	7.44			
13AZO	−12.16		11.74		
123AZO	−14.08	15.98	9.70		
124AZO	−8.28	7.09		8.64	
125AZO	−4.11	5.09			5.09
134AZO	−16.06		24.77	24.77	
1234AZO	−16.01	2.64	13.41	13.41	
1235AZO	−10.26	7.24	9.02		[a]

[a] Negligible sensitivity.

Table 3, this trend in *s* is related to the polarity of the compounds, as reflected in their dipole moments.

It can also be seen from Table 3 that the sensitivity of the shieldings of these compounds to solvent acidity, measured by *a*, is a reflection of the basicity of their pyridine-type nitrogens (taking into account the corresponding proton affinities or pK_a values).

Intrinsic shieldings, σ_{gas}

The independent term in the multiparameter equation used for applying the pure solvent scales [eqn. (1)] must be related to the value of the quantity to be fitted, *viz*. the shielding in the absence of solvent (*i.e.* in the gas phase). That the gas phase is accurately described by the pure solvent scales has previously been confirmed for such cases as (1) the O–O component in the ^{1}La electronic transition of anthracene;[18] (2) the peaks for the γ_0, A and C electronic transitions of C_{60};[35] (3) the fluorescence emission maxima for substances that follow an ESIPT mechanism;[36] (4) the S=O stretching frequencies of dimethyl sulfoxide;[21] and (5) the gas-phase rate constant of solvolysis of *tert*-butyl chloride.[37]

To the author's knowledge, there have been two attempts at theoretically approximating the corresponding intrinsic values of the shieldings of azoles and azines, both made by Witanowski *et al.*[11,16,25] In one,[25] they recently evaluated the shieldings of the nitrogens in all *N*-Me-azoles using a high computational level. They optimized the molecular geometries of these compounds at the MP2 level, using the 6-311G** basis set and employed the optimized geometries to calculate the corresponding shieldings, using a multiconfiguration SCF (MCSCF) wavefunction constructed with Huzinaga basis sets consisting of a [9s5p1d/5s4p1d] set for C and N atoms, and a [5s1p/3s1p] set for H atoms. The absolute values of the shieldings, σ_{calc}, for the different pyridine- and pyrrole-type nitrogens

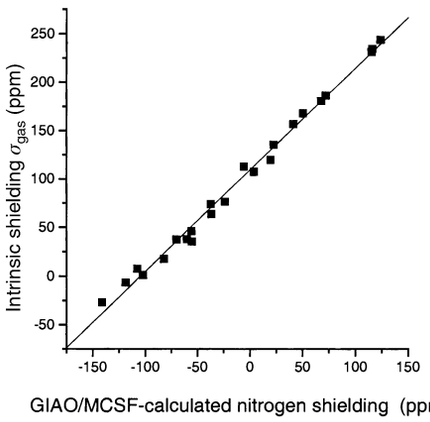

Fig. 3 A plot of intrinsic nitrogen shieldings, σ_{gas} (see Table 2), with respect to neat liquid nitromethane, *vs*. GIAO/MCSF-calculated absolute nitrogen shieldings for the azole systems by Witanowski *et al.*, see eqn. (2).

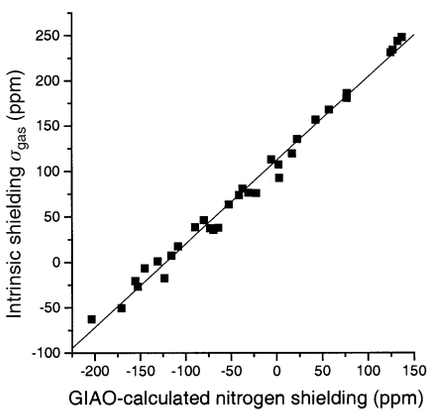

Fig. 4 A plot of intrinsic nitrogen shieldings, σ_{gas} (see Table 2), with respect to neat liquid nitromethane, *vs*. GIAO/CHF-calculated absolute nitrogen shieldings for the azole and azine systems by Witanowski *et al.*, see eqn. (3).

of these compounds exhibited a high similarity with the independent terms in the corresponding fitting equation, σ_{gas} [eqn. (2)] (see Fig. 3), with $n = 23$, $r = 0.996$ and standard deviation (sd) = 7.39 ppm.

$$\sigma_{gas} = (1.048 \pm 0.020)\sigma_{calc} + (109.39 \pm 1.56) \qquad (2)$$

It should be noted that this fit not only has a near-unity slope but also has an intercept quite consistent with the value assigned by Witanowski *et al.*[11,16,38] to nitromethane (−112.156 ppm).

In a previous attempt, Witanowski *et al.*[11,16] evaluated shieldings by using the GIAO/CHF *ab initio* nitrogen-shielding calculations on geometries optimized with a 6-31++G** basis set. They compared the σ_{GIAO} values thus obtained for azoles[11] and azines[16] with their experimental counterparts in cyclohexane and found good linear correlations, albeit with slopes that differed markedly from unity (*viz*. 0.8804 for azoles and 0.7609 for azines). Fig. 4 shows a plot of the σ_{GIAO} values of Witanowski *et al.* against the corresponding σ_{gas} values obtained by analysing the solvent effect on azoles and azines in this work. Consistency between the two quantities, which are related by eqn. (3), is excellent ($n = 32$, $r = 0.994$, sd = 9.50 ppm).

$$\sigma_{gas} = (0.921 \pm 0.018)\sigma_{GIAO} + (112.26 \pm 1.78) \qquad (3)$$

Again, the slope is close to unity and the independent term of the fit accurately reproduces the shielding of nitromethane.[11,16,38]

The sole experimental nitrogen shielding available for these compounds in the gas phase is that reported by Duthaler and Roberts[24] for pyridine. The corresponding ^{15}N shieldings for pyridine measured with respect to $H^{15}NO_3$ in cyclohexane, CCl_4, benzene, pyridine, DMSO, CH_2Cl_2, $CHCl_3$, MeOH, trifluoroethanol and in the gas phase are consistent with the values on the pure solvent scales to which they are related by eqn. (4), with $n = 10$, $r = 0.990$ and sd = 2.12 ppm.

$$\delta^{15}N = (11.89 \pm 3.29)SPP - (9.06 \pm 3.61)SB + (35.16 \pm 2.41)SA + (50.06 \pm 1.97) \qquad (4)$$

It should be noted that the independent term in eqn. (4) is quite consistent with the experimental value in the gas phase: 51.4 ± 1.8 ppm.[24]

The high uncertainties in some *a*, *b*, *s* and σ_{gas} values can have various origins. Thus, the shieldings of pyridine-type nitrogens in the azoles studied may encompass not only the measured effect but also a side effect due to the conformation adopted by the methyl group. Note that the shieldings for N^2 and N^5 in *N*-Me-1,2,5-triazole calculated by Witanowski *et al.* (−54.6 and −58.36 ppm) are not identical, nor are those of N^3 and N^4 in *N*-Me-1,3,4-triazole (−58.26 and −52.98 ppm, respectively). The presence of solvents interacting specifically with positions adjacent to N^1 (the methylated nitrogen) may alter shieldings not only through specific interaction but also through a change in the conformation of the methyl group. One other difficulty inherent in these data arises from the potential influence of the solvent effect from a neighbouring, solvatable site in the compound. Such is the case with the shieldings of N^4 in indolizines: while those for 2-aza- and 3-azaindolizine hardly change and appear to be exclusively influenced by the solvent polarity/polarizability, that for 1-azaindolizine increases markedly with increasing solvent acidity. One other example is provided by the *N*-Me-pyrrole/*N*-Me-pyrazole couple: the shielding of N^1 in the latter is increased by acidic solvents.

One further shortcoming is the inaccurate description of values at the low end of the acidity scale and the high end of the basicity scale. This could be circumvented by measuring the shieldings of six additional solvents, namely: butan-1-ol (SA = 0.314, SB = 0.809), heptan-1-ol (SA = 0.302, SB = 0.912), decan-1-ol (SA = 0.259, SB = 0.912), 3-methylbutan-2-ol (SA = 0.196, SB = 0.893), 2-methylpropanol (SA = 0.145, SB = 0.928) and pentan-3-ol (SA = 0.100, SB = 0.950). The SPP, SA and SB values for two hundred solvents including the previous ones are compiled elsewhere.[22] The strong influence of the basicity of pyridine-type nitrogens on the interaction of these compounds with solvents also makes it advisable to more accurately cover the acidity region between methanol (SA = 0.605) and trifluoroethanol (SA = 0.893); this could be accomplished by using binary mixtures of the two solvents. In fact, characterizing binary solvent mixtures within the framework of the pure solvent scales poses no special problem.[37,39,40]

Conclusions

As shown in this work, careful analysis of the solvent effect provides interesting structural information with a view not only to understanding the behaviour of solutes towards different molecular moieties, but also to approximating intrinsic data for the solutes in the gas phase and hence, for example, to establishing the basicity sequence for the different nitrogen sites in a heterocyclic compound.

Acknowledgements

The author is grateful to Spain's DGICYT for funding this research within the framework of Project PB98-0063.

References

1 R. W. Taft, F. Anvia, M. Taagepera, J. Catalán and J. Elguero, *J. Am. Chem. Soc.*, 1986, **108**, 3237.
2 J. Catalán, J. Palomar and J. L. G. de Paz, *Int. J. Mass Spectrom. Ion Processes*, 1988, **175**, 51 and references therein.
3 J. E. Bartmess, J. A. Scott and R. T. McIver, *J. Am. Chem. Soc.*, 1979, **101**, 6047.
4 J. Catalán, R. M. Claramunt, J. Elguero, J. Laynez, M. Menéndez, F. Anvia, J. H. Quian, M. Taagepera and R. W. Taft, *J. Am. Chem. Soc.*, 1988, **110**, 4105.
5 L. Nygaard, J. F. Nielsen, J. Kirchheiner, G. Maltrsen, J. Rastrup-Andersen and G. O. Sørensen, *J. Mol. Struct.*, 1969, **4**, 49.
6 W. D. Krugh and L. P. Gold, *J. Mol. Spectrosc.*, 1974, **49**, 423.
7 J. Catalán, J. L. G. de Paz, M. Yañez and J. Elguero, *Chem. Scr.*, 1984, **24**, 84.
8 M. Witanowski, W. Sicinska, Z. Grabowski and G. A. Webb, *J. Magn. Reson., Ser. A*, 1993, **104**, 310.
9 M. Witanowski, W. Sicinska, Z. Biedrzycka and G. A. Webb, *J. Magn. Reson., Ser. A*, 1994, **109**, 177.
10 M. Witanowski, W. Sicinska, Z. Biedrzycka, Z. Grabowski and G. A. Webb, *J. Magn. Reson., Ser. A*, 1995, **112**, 66.
11 M. Witanowski, Z. Biedrzycka, W. Sicinska and Z. Grabowski, *J. Magn. Reson.*, 1998, **131**, 54.
12 M. Witanowski, W. Biedrzycka, W. Sicinska, Z. Grabowski and G. A. Webb, *J. Magn. Reson., Ser. A*, 1996, **120**, 148.
13 M. Witanowski, W. Sicinska, Z. Biedrzycka, Z. Grabowski and G. A. Webb, *J. Chem. Soc., Perkin Trans. 2*, 1996, 619.
14 M. Witanowski, W. Sicinska, S. Biernat and G. A. Webb, *J. Magn. Reson.*, 1991, **91**, 289.
15 M. Witanowski, W. Sicinska and G. A. Webb, *J. Magn. Reson.*, 1992, **98**, 109.
16 M. Witanowski, Z. Biedrzycka, W. Sicinska, Z. Grabowski and G. A. Webb, *J. Magn. Reson.*, 1997, **124**, 127.
17 M. Witanowski, W. Sicinska, Z. Grabowski and G. A. Webb, *Magn. Reson. Chem.*, 1990, **28**, 988.
18 J. Catalán, V. López, P. Pérez, R. Martín-Villamil and J. G. Rodríguez, *Liebigs Ann. Chem.*, 1995, 241.
19 J. Catalán, C. Díaz, V. López, P. Pérez, J. L. G. de Paz and J. G. Rodríguez, *Liebigs Ann. Chem.*, 1996, 1785.
20 J. Catalán and C. Díaz, *Liebigs Ann./Recl.*, 1997, 1941.
21 J. Catalán and C. Díaz, *Eur. J. Org. Chem.*, 1999, 885.
22 J. Catalán, *Solvent Effects Based on Pure Solvent Scales* in *Handbook of Solvents*, ed. G. Wypych, ChemTec Publishing, Toronto, 2001, 583.
23 M. J. Kamlet and R. W. Taft, *J. Am. Chem. Soc.*, 1976, **98**, 377.
24 R. D. Duthaler and J. D. Roberts, *J. Am. Chem. Soc.*, 1978, **100**, 4969.
25 M. Jaszunski, K. V. Mikkelsen, A. Rizzo and M. Witanowski, *J. Phys. Chem. A*, 2000, **104**, 1466.
26 M. N. Manalo, A. C. de Dios and R. Cammi, *J. Phys. Chem. A*, 2000, **104**, 9600.
27 J. Catalán, J. Gómez, A. Couto and J. Laynez, *J. Am. Chem. Soc.*, 1990, **112**, 1678.
28 P. Mauret, J. P. Fayet and M. Fabre, *Bull. Soc. Chim. Fr.*, 1975, 1675.
29 M. H. Kaufman, F. M. Ernsberger and W. S. McEwan, *J. Am. Chem. Soc.*, 1956, **78**, 4197.
30 J. Catalán, J. L. M. Abboud and J. Elguero, *Adv. Heterocycl. Chem.*, 1987, **41**, 187.
31 D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution: Supplement 1972*, Butterworths, London, 1972; D. Perrin, *Dissociation Constants of Organic Bases in Aqueous Solution*, Butterworths, London, 1965.
32 A. L. McClellan, *Tables of Experimental Dipole Moments*, Rahara Enterprises, El Cerrito, CA, 1963, Vol. 1; A. L. McClellan, *Tables of Experimental Dipole Moments*, Rahara Enterprises, El Cerrito, CA, 1973, Vol. 2; A. L. McClellan, *Tables of Experimental Dipole Moments*, Rahara Enterprises, El Cerrito, CA, 1989, Vol. 3.
33 S. G. Lias, J. F. Liebman and R. D. Levin, *J. Phys. Chem. Ref. Data*, 1984, **13**, 695.
34 J. Catalán, J. L. G. de Paz, M. Yañez, F. Amat-Guerri, R. Houriet, E. Rolli, R. Zehringer, P. Oelhafen, R. W. Taft, F. Anvia and J. H. J. Qian, *J. Am. Chem. Soc.*, 1988, **110**, 2699.
35 J. Catalán, *New J. Chem.*, 1995, **19**, 1233.
36 J. Catalán, J. C. del Valle, C. Díaz, J. Palomar, J. L. G. de Paz and M. Kasha, *Int. J. Quantum Chem.*, 1999, **72**, 421.
37 J. Catalán, C. Díaz and F. García-Blanco, *J. Org. Chem.*, 1999, **64**, 6512.
38 M. Witanowski, L. Stefaniak and G. A. Webb, *Annu. Rep. NMR Spectrosc.*, 1993, **25**, 1.
39 J. Catalán, C. Díaz and F. García-Blanco, *J. Org. Chem.*, 2000, **65**, 3409.
40 J. Catalán, C. Díaz and F. J. García-Blanco, *J. Org. Chem.*, 2000, **65**, 9226.