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Solvent effects on the nitrogen NMR chemical shifts in 1-methylazoles – a theoretical study

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We have investigated solvent effect on the nitrogen chemical shifts in a series of 1-methylazoles. The detailed results for 1-methylazoles – systems containing one (1-methylpyrrole), two (diazoles), three (triazoles) and four (tetrazoles) nitrogen atoms in the heteroaromatic ring – have been presented. We have examined twenty six popular DFT functionals to calculate the nitrogen magnetic shielding constants in gas phase and 12 different solvents within the Conductor-like Screening Model (COSMO), the Explicit Solvation Model (ESM), as well as their combination (ESM+COSMO) in the case of water solutions. The vibrational corrections for the analyzed systems have been also reported. Additionally, the solvent effect on the nitrogen chemical shifts has been analyzed in terms of its direct and indirect contributions. Our theoretical vibrationally corrected results properly reproduce the experimental data. In the calculations of N NMR chemical shifts, the best results have been achieved with the B97-2 functional with the mean absolute error as small as 3 ppm for a range exceeding 270 ppm in the tested azole systems.

Introduction

The nitrogen NMR spectroscopy (^{14,15}N) is one of the most powerful methods for molecular structure determination, especially for many biologically important compounds containing nitrogen atom(s) (e.g., over 80% of all drugs). The range of nitrogen chemical shifts for organic compounds exceeds 1000 ppm. For comparison, the range of changes in the chemical shifts is about 250 ppm and 15 ppm only in the carbon and proton NMR, respectively. The nitrogen chemical shifts are very sensitive to changes in electron density in the vicinity of the nitrogen atom. This indicates that solvent/substituent changes very often can induce significant effect on the nitrogen chemical shifts. Therefore, the N NMR spectroscopy is an excellent technique for the investigation of intra– and intermolecular interactions.

The solvent effect on the nitrogen nuclear magnetic shielding has been widely investigated both experimentally[1–16] and theoretically[17–23]. The extensive experimental studies have been conducted by Witanowski and Webb et al. to test the solvent effect on the nitrogen shielding in a large set of compounds. In those consistent studies, the structural and environmental effects have been examined in a systematic and controlled manner. The investigations have been carried out for dilute solutions where bulk susceptibility effect can be taken into account. These tests involved evaluation of impact of many solvents which differ in polarity (with the dielectric constants varying from 2 to 80), dipole moment values and their protic properties (the ability to form hydrogen bonds).

In recent years, the research focused on a number of classes of organic nitrogen compounds: nitroalkanes[12], aliphatic and aromatic nitroso compounds[5], nitramines[15], nitrosamines[16], cyanamides[6], amidines[24], aminoethers[9], oximes[10], urea derivative[13,14], heterocyclic nitrogen compounds, such as azoles[1], diazoles[2], triazoles[3], tetrazoles[4] oxa- and oxadiazoles[7], thia- and thiadiazoles[8] and azines[11,25]. The results of those studies clearly demonstrate that the medium effect on the nitrogen chemical shifts is always significant. The magnitude of the solvent effect depends strongly on the polarity of the solvent and its ability to form hydrogen bonds with the molecules of the solute.

In this work, we have investigated the solvent effect on N NMR chemical shifts in a series of 1-methylazole systems containing one (1-methylpyrrole itself), two (diazoles), three (triazoles) and four (tetrazoles) nitrogen atoms (see Figure 1). In these 5-membered compounds there are two different types of nitrogen atoms. The pyrrole-type nitrogen atom (denoted N1 in all heterocyclic rings) has one lone electron pair contributing to the aromaticity of the ring. The pyridine-type nitrogen atom also has one lone electron pair, this time directed outward from the ring, though. The presence of different types of atoms in the heteroaromatic ring can significantly modify the polarity/acidity/basicity of a heterocycle and may result in different (in nature and strength) interactions with solvents.

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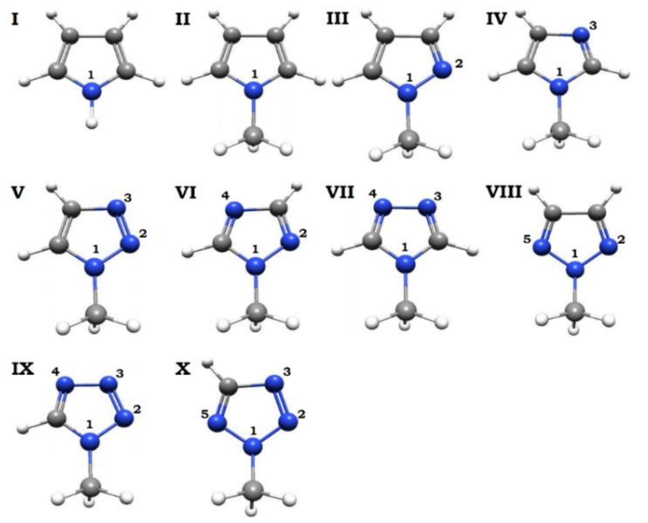

Figure 1 Azole systems: I – pyrrole, II – 1-methylpyrrole, III – 1-methyl-1,2-diazole, IV – 1-methyl-1,3-diazole, V – 1-methyl-1,2,3-tirazole, VI – 1-methyl-1,2,4-triazole, VII – 1-methyl-1,3,4-triazole, VIII – 1-methyl-1,2,5-triazole, IX – 1-methyl-1,2,3,4-tetrazole, X – 1-methyl-1,2,3,5-tetrazole.

The solvent effect on the nitrogen chemical shifts in the studied molecules cannot be easily estimated by comparing with the results in gas phase due to the lack of the latter. However, changes in the N NMR chemical shifts caused by the polar solvent can be evaluated with respect to, for example, cyclohexane – the nonpolar solvent. The NMR chemical shifts of the pyridine-type nitrogen atoms are much more sensitive to the presence of the solvent than pyrrole-type atoms. It can be seen from Table 1 containing the experimental data concerning solvent effects on the N NMR chemical shift [1–4]. The largest (absolute value) total solvent effect in water solutions, estimated here as a difference $\Delta\delta_{tot}=\delta_{H2O}-\delta_{cyclohexane}$, is observed for N3 and N4 atoms in 1-methyl-1,3,4-triazole (structure VII; $|\Delta\delta_{tot}| \approx 30$ ppm), while for the nitrogen atoms at the N1 position (pyrrole-type) the maximum $|\Delta\delta_{tot}|$ does not exceed 13 ppm (for pyrrole molecule I). Additionally, the directions of the solvent induced N NMR shifts ($\Delta\delta_{tot}$) are opposite. A similar trend can be observed for the solvent polarity effect, defined here as $\Delta\delta_{polar}=\delta_{DMSO}-\delta_{cyclohexane}$. In the case of the pyridine-type nitrogen the presence of polar solvent produces a deshielding effect ($\Delta\delta_{polar}>0$, except N5 in molecule X). Note that Witanowski et al. use the scale of the nitrogen chemical shifts which has the opposite sign[26] (as a nucleus resonates at lower frequency, i.e., it is more shielded, and it has a more negative chemical shift; to avoid them they adopted the negative sign of delta), thus according to Witanowski's convention the more positive chemical shifts, the more shielded the nucleus. For the pyrrole-type nitrogen atoms, a shielding effect is observed ($\Delta\delta_{polar}<0$). This is associated with the increased delocalization of an electron pair of the nitrogen atom at the N1 position. It can also be seen that the hydrogen bonding effect (estimated as $\Delta\delta_{Hbond}=\delta_{H2O}-\delta_{DMSO}$) is much stronger for the pyridine type atoms which can easily form hydrogen bonds. In this case the hydrogen bonding effect substantially predominates over the solvent polarity effect ($\Delta\delta_{Hbond} >> \Delta\delta_{polar}$). The largest value of the absolute hydrogen bonding effect ($|\Delta\delta_{Hbond}| \sim 18$ ppm) is observed for pyridine-type nitrogen atoms in III, IV and VII structures. For pyrrole-type nitrogen atoms this effect does not exceed 3 ppm. Furthermore, in tri- and tetrazoles the effect of a hydrogen bond formation is significantly stronger for the pyridine-type nitrogen atoms which are not directly adjacent to the pyrrole type nitrogen atom (for IX $\Delta\delta N2_{Hbond} \approx 1/4 \cdot \Delta\delta N3_{Hbond}$).

Theoretical approaches are frequently used to predict the solvent effect on the nitrogen NMR spectra of small molecules as well as large bio-molecules. The size of the molecular system often determines the level of theory used, and thus the accuracy of the results. For more accurate results it is necessary to include electron correlation effect. However, the cost of such calculations with high level quantum chemical methods is often too high to allow routine applications to chemically interesting large systems. The realistic alternative at present remains the density functional theory (DFT) approach.

The methodology mostly used in this study, based on the DFT calculations, has been previously successfully tested for analogous molecular systems (oxa- and oxadiazoles)[22]. Our former study of five- and six-membered nitrogen compounds indicates that commonly used DFT functionals (B3LYP, B3PW91) do not always have to be the best choice. Additionally, we have pointed out that the vibrational corrections (VCs) can be important for the nitrogen magnetic shielding constants. A systematic investigation of the zero-point vibrational corrections may help to identify the cases in which the VCs to the nitrogen magnetic shielding constants, and consequently to the chemical shifts are significant. It will hopefully be useful in the N NMR calculations for other molecular systems as well as increasingly more demanding interpretations of the experimental data. These facts justify the systematic studies in this area.

Computational details

In this work, as previously for oxazoles[22], we replaced nitromethane – the standard reference in the N NMR spectroscopy – by the most shielded nitrogen nucleus in the discussed set of molecules II-X. Thus, the theoretical chemical shifts δ^t ($\sigma_{reference}-\sigma_{sample}$) were calculated relative to the N1 atom in 1-methylpyrrole (structure II).

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Table 1 Estimated experimental solvent effects on nitrogen NMR chemical shifts [1–4]; $\Delta\delta_{tot}=\delta_{H_2O}-\delta_{cyclohexane}$ – total solvent effect, $\Delta\delta_{polar}=\delta_{DMSO}-\delta_{cyclohexane}$ – solvent polarity effect, $\Delta\delta_{Hbond}=\delta_{H_2O}-\delta_{DMSO}$ – hydrogen bonding effect*.

Solvent effect	Molecule									
	I	II	III	IV	V	VI	VII	VIII	IX	X
	N1									
$\Delta\delta_{tot}$	-12.27	-8.30	-3.08	-9.67	-7.79	-4.79	-11.67	-0.19	-9.21	-4.65
$\Delta\delta_{polar}$	-14.60	-5.86	-4.28	-7.00	-7.18	-5.22	-9.18	-2.39	-8.63	-5.48
$\Delta\delta_{Hbond}$	+2.33	-2.44	+1.20	-2.67	-0.61	+0.43	-2.49	+2.20	-0.58	+0.83
			N2		N2	N2		N2,5	N2	N2
$\Delta\delta_{tot}$			+22.29		+19.98	+13.11		+10.88	+5.64	+9.41
$\Delta\delta_{polar}$			+4.51		+7.32	+2.33		+0.97	+1.93	+3.79
$\Delta\delta_{Hbond}$			+17.78		+12.66	+10.78		+9.91	+3.71	+5.62
				N3	N3		N3,4		N3	N3
$\Delta\delta_{tot}$				+24.06	+22.05		+30.71		+25.06	+15.06
$\Delta\delta_{polar}$				+6.02	+6.64		+12.33		+10.31	+4.84
$\Delta\delta_{Hbond}$				+18.04	+15.41		+18.38		+14.75	+10.22
						N4			N4	N5
$\Delta\delta_{tot}$						+15.81			+17.10	+4.47
$\Delta\delta_{polar}$						+4.08			+6.95	-0.51
$\Delta\delta_{Hbond}$						+11.73			+10.15	+4.98

*The values for the original experimental data referred to nitromethane

Also the original experimental chemical shits (referred to CH_3NO_2) (see Table 1S in Electronic Supplementary Information) were recalculated according to the following relation

$$\delta^{e}_{\text{sample}} = \delta^{\mathrm{CH_3NO_2}}_{\mathrm{N_1(II)}} - \delta^{\mathrm{CH_3NO_2}}_{\text{sample}} \tag{1}$$

The experimental chemical shifts transferred in such a manner are gathered in Table 2. These values have been used in our study as the reference, experimental data. Once again we emphasize that Witanowski et al. use the scale of the nitrogen chemical shifts with the opposite sign[26] which employs higher shielding for higher values of chemical shifts .

The equilibrium geometries of molecules II – X (see Figure 1) and the corresponding molecular models (III-X+H_2O, see Figure 2) were obtained at the DFT/B3LYP level of theory with 6-311G** basis set [27]. The subsequent frequency calculations proved that the obtained structures correspond to local minima. The calculations of the isotropic magnetic shielding constants (σ) were carried out at the DFT/B3LYP/6-311G** equilibrium geometries within the DFT/GIAO framework[28–31] with the same basis set and different DFT functionals: HFS , SVWN, SVWN5, HFB, BVWN, BVWN5, P86, BPW91, BLYP, BVP86, OPTX, OVWN, OVWN5, OP86, OPW91, OLYP, PW91, PBE, O3LYP, B3LYP, B3PW91, WAH, B97, B91-1, B97-2, HCTH. The references to the functionals are well known; the most important ones are reported, e.g., in our previous work [32]. For comparison we also examined the basic Hartee–Fock (HF) method.

The solvent effect was generally included by means of the conductor-like screening model (COSMO)[33–37] in which the medium is characterized by its static dielectric constant (ε). In our work, in addition to the gas-phase calculations the following solvents were considered: cyclohexane – c-hexane (2.02), dioxane (2.19), carbon tetrachloride – CCl_4 (2.23), benzene – C_6H_6 (2.25), dimethyl ether – Et_2O (4.34), chloroform – $CHCl_3$ (4.90), dichloromethane – CH_2Cl_2 (8.93), acetone – $(CH_3)_2CO$ (20.70), ethanol – EtOH (24.55), methanol – MeOH (32.63), DMSO (46.70), and water – H_2O (78.39). The values in parentheses refer to the dielectric constants. All calculations were carried out using the PQS quantum chemistry software[38,39].

Due to the limitations of the COSMO model in the proper description of the specific interactions, the appropriate super-molecule solvation models with explicit hydrogen-bond(s) involving water molecule(s) were also considered. For heterocycles containing three or more nitrogen atoms the appropriate number of water molecules were included to saturate all potential hydrogen binding sites (see Figure 2; the structures optimized at the B3LYP/6-311G**). Such a discrete solvation model (super-molecule scheme) is also known as Explicit Solvation Model (ESM). In order to obtain satisfactory results we also tested the combination of two solvent models. The initial hydrogen-bonding structures were also optimized at the B3LYP/6-311G** level of theory.

Table 2. Experimental nitrogen chemical shifts (in ppm) in azole molecules (II-X) referred to N1 in 1-methylpyrrole (II).

	II	III		IV		V			VI			VII		VIII		IX				X			
ref.: II	N1	N1	N2	N1	N3	N1	N2	N 3	N 1	N 2	N 4	N 1	N 3,4	N 1	N 2,5	N 1	N 2	N3	N4	N1	N2	N3	N5
c-hexane	0.00	53.91	169.50	10.17	123.69	85.69	214.61	227.68	59.12	156.24	112.28	9.19	188.19	102.12	187.22	75.64	226.77	258.50	191.96	128.20	238.60	193.89	162.10
dioxane	0.00	53.19	162.76	10.82	115.84	86.81	206.53	219.56	58.76	150.94	105.81	11.00	176.92	100.58	182.72	77.70	221.63	248.09	183.73	128.35	232.22	186.75	158.26
CCl_4	0.00	53.21	165.30	10.66	119.43	86.53	209.83	222.55	58.67	153.90	109.61	9.91	184.10	100.92	185.42	76.67	224.85	252.96	188.51	127.51	236.03	191.18	160.96
C_6H_6	0.00	53.16	164.31	10.32	117.47	86.36	208.37	221.52	58.59	152.33	107.53	10.37	180.17	100.72	183.90	76.94	223.51	250.84	186.26	127.91	234.52	189.12	159.61
Et_2O	0.00	53.38	166.37	10.57	119.56	86.47	209.57	222.90	59.17	153.17	108.64	10.22	182.41	101.10	184.75	77.15	224.20	252.73	187.68	128.54	235.57	190.35	160.23
$CHCl_3$	0.00	51.44	157.06	10.28	108.26	85.31	200.44	215.52	57.25	147.24	100.99	10.31	171.41	98.40	179.47	76.17	220.89	245.41	181.09	126.28	231.08	183.49	157.14
CH_2Cl_2	0.00	51.98	159.07	10.51	110.49	85.69	202.16	216.68	57.64	148.34	102.08	10.80	171.78	98.90	180.00	76.46	220.93	245.20	181.50	126.74	230.86	183.84	157.11
$(CH_3)_2CO$	0.00	52.85	161.31	11.13	114.20	86.84	205.18	218.51	58.97	150.37	104.63	11.91	174.95	99.84	182.00	78.26	221.43	246.63	182.75	128.43	231.86	185.89	158.50
EtOH	0.00	52.11	149.32	13.42	100.99	88.17	194.30	214.89	60.46	147.54	95.96	15.45	160.13	99.66	180.13	79.43	221.18	240.92	176.51	128.67	231.84	182.64	158.72
CH_3OH	0.00	51.63	146.89	15.16	97.63	88.07	191.40	213.53	60.09	145.81	94.09	15.16	158.27	99.02	178.17	79.38	221.02	239.65	175.02	128.59	230.69	179.96	158.02
DMSO	0.00	52.33	159.13	11.31	111.81	87.01	202.11	214.50	58.48	148.05	102.34	12.51	170.00	98.65	180.39	78.41	218.98	242.33	179.15	127.82	228.95	183.19	156.75
H_2O	0.00	48.69	138.91	11.54	91.33	85.18	184.26	199.40	55.61	134.83	88.17	12.56	149.18	94.01	168.04	76.55	212.83	225.14	166.56	124.55	220.89	170.53	149.33

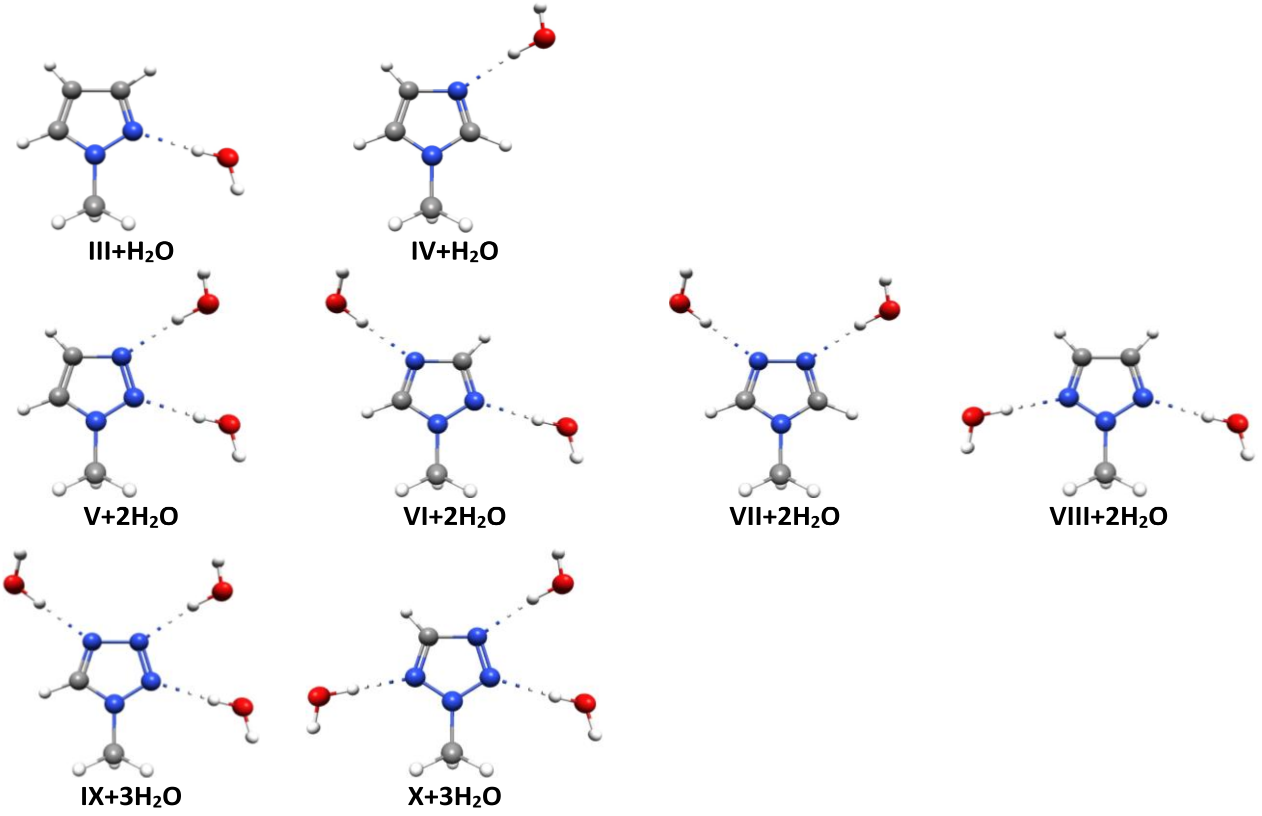

Figure 2 Azole-water clusters used in ESM model.

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Symbols δ^{e}_{ns}, where *n* refers to the nitrogen nucleus (n=1,…,24) and *s* refers to the solvent (*s*=1,…12), is used to denote experimental chemical shifts. Symbols δ^{t}_{fns}, where the additional index *f* refers to the functional employed in the calculations, is used to denote theoretical chemical shifts. The deviation of the calculated chemical shift from the experimental value is defined as $\Delta\delta_{fns}=|\delta^{e}_{ns}-\delta^{t}_{fns}|$.

The statistical assessment of the discussed DFT functionals in a given solvent was made by determining the mean absolute errors (MAE). Depending on the considered statistics the following MAEs were calculated:

$$\mathrm{MAE}_{fs} = \frac{1}{24}\sum_{n=1}^{24}\Delta\delta_{fns},$$

which denotes the mean error for all nuclei for a given DFT functional in a given solvent,

$$\mathrm{MAE}_{f} = \frac{1}{12}\sum_{s=1}^{12}\mathrm{MAE}_{fs},$$

which denotes the mean error for all nuclei and all solvents for a given functional. For the pyrrole- and pyridine-type nitrogen atoms the mean absolute errors $\mathrm{MAE}_{fs}^{\mathrm{pyrrole}}$, $\mathrm{MAE}_{f}^{\mathrm{pyrrole}}$ and $\mathrm{MAE}_{fs}^{\mathrm{pyridine}}$, $\mathrm{MAE}_{f}^{\mathrm{pyridine}}$, where summations run over the number of a given atom type, where also calculated separately. The results for the standard COSMO calculations are presented in Table 3.

To fully rely on the calculated chemical shifts the vibrational corrections (VCs) to the shielding constants of nitrogen atoms were also estimated. We used the following formula[40–42]

$$\Delta\sigma = \frac{1}{4}\sum_{K}^{3N-6}\frac{1}{\omega_K}\left[\left(\frac{d^2\sigma}{dQ_K^2}\right)_e - \frac{1}{\omega_K}\left(\frac{d\sigma}{dQ_K}\right)\sum_{L}^{3N-6}\frac{F_{eKLL}}{\omega_L}\right] \qquad (2)$$

where ω denotes the harmonic frequency, *Q* – the normal coordinate, *F* – the cubic force constant. Indices *K* and *L* refer to normal modes of vibrations, and subscript *e* indicates that the value is to be computed at the equilibrium geometry. In the following the terms are named 2nd and 1st order term with respect to shielding, respectively. The first and second shielding constant derivatives and the cubic force constants were first obtained in the Cartesian coordinates, and then transformed to normal coordinate representation after solving the vibrational problem. We used our home-made routines. The first- and the second derivatives of the NMR shielding constants with respect to the nuclear Cartesian coordinates were calculated by the numerical differentiation of the shielding constants. The third energy derivatives (cubic force constants) were also calculated numerically as the second derivatives of the energy gradient. This procedure requires $18N^2+1$ single-points shielding constants calculations, and $18N^2-12N+5$ single-point gradient calculations. In both cases the Cartesian step of 0.05 a.u. was applied. Then, the vibrational problem was solved, and the transformation matrix **L** from normal (**Q**) to Cartesian (ρ) coordinates (ρ=**LQ**) was found. The **L** matrix was used in the transformation procedure, and the VCs were calculated according to eqn. (2).

Results and discussion

Performance of various DFT functionals

The results of the statistical assessment for the tested DFT functionals and HF SCF method are listed in Table 3 (Part A). For the vast majority of the DFT functionals the mean error MAE_f calculated without the vibrational corrections estimated for all solvents does not exceed 6 – 7 ppm. The exceptions are functionals: OP* ($\mathrm{MAE}_f \approx 12-13$ ppm), OV* ($\mathrm{MAE}_f \approx 10$ ppm), OLYP, HCTH ($\mathrm{MAE}_f \approx 10.5$ ppm) and WAH ($\mathrm{MAE}_f \approx 15.6$ ppm). The lowest discrepancies (about 3-4 ppm) between the theoretical and experimental data were obtained for the two hybrid functional groups: B3*(B3LYP and B3PW91) and B97*(B97, B97-1 and B97-2).

It is also worth noting that for all DFT functionals, the errors estimated for the pyrrole-type nitrogen atoms $\mathrm{MAE}^{\mathrm{pyrrole}}$ are significantly lower than $\mathrm{MAE}^{\mathrm{pyridine}}$ calculated for the pyridine-type nitrogen atoms. In azoles possessing different types of nitrogen atoms, the accuracy of the chemical shifts of the pyrrole-type nitrogen atoms is 3-4 times higher than for the pyridine-type ones. Additionally, it is evident from Table 3, that the HF SCF approach is not suitable for the determination of the nitrogen chemical shifts in the analyzed molecules. Each of the DFT functionals gives much better results. This is what could be expected due to the importance of the electron correlation for the analyzed molecular systems.

Vibrational correction to the nitrogen shielding

As will be shown the VCs for different types of nitrogen atoms (pyrrole- and pyridine-type) differ significantly. Thus, the inclusion of vibrational effects seems to be necessary. The calculations of the VCs for nitrogen atoms in all 10 molecules and in all 12 solvents (plus gas phase), for all 26 density functionals (plus HF SCF; this gives an overall number of 27×13×10=3510 combinations) are obviously not practical. Note that even for the smallest system (IX or X; 10 atoms) 1801 single-point shielding constants, and 1685 single-point gradient calculations are required. Therefore some simplification of the procedure was needed.

First, the VCs to the magnetic shielding constants are not expected to depend significantly on the computational level. Indeed, the gas phase calculations for III carried out using B3LYP, B3PW91, and randomly chosen PBE functionals reveal that only minor changes, well below 1 ppm, are observed when comparing VCs for a given type of nitrogen atom (pyrrole- and pyridine-type).

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Table 3 Accuracy of the HF SCF and DFT calculations of the nitrogen NMR chemical shifts.

	MAE_{fs}												MAE		
	c-hexane	dioxane	CCl_4	C_6H_6	Et_2O	$CHCl_3$	CH_2Cl_2	$(CH_3)_2CO$	EtOH	MeOH	DMSO	H_2O	MAE_f	$\mathrm{MAE}_f^{\mathrm{pyrrole}}$	$\mathrm{MAE}_f^{\mathrm{pyridine}}$
Part A: MEAs **without** the vibrational corrections															
HF SCF	30.44	34.58	31.93	33.18	28.00	32.34	29.48	26.34	29.74	30.65	27.41	36.90	30.91	13.69	39.53
DFT/HFS	6.65	5.22	5.53	5.13	8.74	5.40	7.00	10.35	8.20	8.01	9.10	5.23	7.04	4.32	8.41
DFT/SVWN	4.86	3.74	3.75	3.69	6.73	3.86	5.19	8.29	6.20	6.06	7.03	4.79	5.35	3.11	6.47
DFT/SVWN5	4.99	3.86	3.87	3.79	6.87	3.95	5.32	8.44	6.37	6.21	7.18	4.82	5.47	3.20	6.61
DFT/HFB	7.08	4.50	5.50	4.90	9.02	4.84	7.03	10.35	7.66	7.19	9.08	4.18	6.78	3.61	8.37
DFT/BVWN	5.02	2.80	3.50	2.99	6.88	2.99	4.97	8.17	5.46	5.13	6.87	3.88	4.89	2.37	6.15
DFT/BVWN5	5.16	2.90	3.65	3.09	7.04	3.11	5.10	8.33	5.63	5.29	7.03	3.84	5.01	2.45	6.30
DFT/P86	8.41	5.09	6.80	5.74	10.35	5.72	8.34	11.66	8.42	7.79	10.36	4.10	7.73	3.84	9.68
DFT/BLYP	8.12	4.85	6.51	5.47	10.06	5.45	8.06	11.38	8.11	7.50	10.08	3.98	7.46	3.78	9.31
DFT/BVP86	5.14	3.40	3.89	3.38	7.10	3.47	5.13	8.42	6.05	5.86	7.12	4.20	5.26	2.80	6.50
DFT/BPW91	8.34	5.03	6.73	5.68	10.27	5.66	8.26	11.58	8.34	7.72	10.28	4.07	7.66	3.80	9.59
DFT/OPTX	13.82	9.62	12.19	10.93	15.47	10.77	13.30	16.51	12.94	12.07	15.17	6.30	12.42	6.12	15.58
DFT/OVWN	11.77	7.47	10.12	8.87	13.38	8.68	11.18	14.38	10.62	9.74	13.02	4.50	10.31	4.84	13.05
DFT/OVWN5	11.92	7.63	10.27	9.03	13.54	8.84	11.34	14.54	10.80	9.92	13.19	4.64	10.47	4.94	13.24
DFT/OP86	15.05	10.75	13.40	12.16	16.69	11.98	14.50	17.71	14.02	13.14	16.36	6.94	13.56	6.45	17.12
DFT/OPW91	14.75	10.45	13.10	11.86	16.39	11.69	14.20	17.42	13.69	12.81	16.07	6.69	13.26	6.40	16.69
DFT/OLYP	11.98	7.69	10.33	9.09	13.63	8.93	11.46	14.67	10.97	10.09	13.32	5.19	10.61	5.33	13.25
DFT/O3LYP	7.33	4.58	5.72	4.98	9.27	4.96	7.26	10.58	7.60	7.13	9.28	4.14	6.90	3.73	8.49
DFT/PW91	8.51	5.32	6.90	5.92	10.42	5.88	8.39	11.71	8.54	7.98	10.40	4.40	7.86	4.25	9.67
DFT/PBE	6.55	3.23	4.93	3.85	8.37	3.74	6.28	8.45	6.34	5.32	7.30	3.37	5.64	2.87	7.03
DFT/B3LYP	2.83	6.63	4.04	5.29	2.09	5.07	2.59	2.51	3.24	3.98	2.29	10.05	4.22	1.35	5.65
DFT/B3PW91	1.78	4.31	1.87	2.92	2.74	2.57	1.72	3.93	2.52	2.68	2.99	7.47	3.12	1.21	4.08
DFT/WAH	17.37	13.26	15.80	14.56	18.99	14.26	16.76	20.02	16.48	15.60	18.71	8.75	15.88	6.83	20.40
DFT/B97	1.65	3.96	1.68	2.55	2.77	2.30	1.73	4.01	2.56	2.66	2.95	7.35	3.01	1.06	3.99
DFT/B91-1	1.92	4.78	2.27	3.41	2.32	3.20	1.83	3.28	2.43	2.71	2.62	8.27	3.25	1.06	4.35
DFT/B97-2	2.81	2.40	1.78	1.70	4.64	1.27	2.79	5.96	3.36	3.13	4.69	5.33	3.32	1.46	4.26
DFT/HCTH	11.82	7.53	10.17	8.93	13.48	8.78	11.30	14.52	10.79	9.91	13.17	5.05	10.45	5.33	13.02
Part B: MEAs **with** vibrational corrections															
HF SCF	32.28	36.42	33.77	35.01	29.63	34.17	31.23	27.97	31.58	32.49	29.03	38.73	32.69	14.40	42.33
DFT/HFS	5.19	5.03	4.63	4.67	6.90	4.87	5.45	8.51	7.48	7.39	7.26	5.52	6.08	4.29	6.77
DFT/SVWN	3.73	4.01	3.20	3.35	4.88	3.60	3.89	6.45	5.78	5.78	5.19	5.92	4.65	3.01	5.26
DFT/SVWN5	3.83	4.08	3.32	3.44	5.03	3.69	3.99	6.60	5.92	5.92	5.35	5.88	4.75	3.10	5.37
DFT/HFB	5.26	4.02	4.00	3.82	7.20	3.78	5.20	8.54	6.61	6.45	7.29	4.49	5.55	3.64	6.38
DFT/BVWN	3.17	2.95	2.27	2.30	5.05	2.43	3.19	6.33	4.74	4.65	5.03	5.19	3.94	2.27	4.61
DFT/BVWN5	3.30	2.97	2.39	2.40	5.20	2.52	3.32	6.49	4.88	4.79	5.19	5.09	4.04	2.36	4.72
DFT/P86	6.57	4.32	4.98	4.25	8.51	4.33	6.50	9.82	7.01	6.83	8.53	4.12	6.31	3.82	7.50
DFT/BLYP	6.28	4.12	4.68	4.06	8.22	4.12	6.22	9.54	6.73	6.56	8.25	4.04	6.07	3.74	7.15
DFT/BVP86	3.56	3.43	2.85	2.89	5.26	3.02	3.58	6.58	5.45	5.39	5.28	5.32	4.38	2.73	5.03
DFT/BPW91	6.50	4.27	4.91	4.19	8.44	4.27	6.43	9.74	6.94	6.76	8.45	4.10	6.25	3.77	7.42
DFT/OPTX	11.98	7.84	10.37	9.13	13.64	8.94	11.46	14.68	11.16	10.30	13.39	5.79	10.72	6.16	13.16
DFT/OVWN	9.93	5.71	8.28	7.04	11.55	6.84	9.34	12.54	8.84	8.07	11.19	4.36	8.64	4.80	10.64
DFT/OVWN5	10.09	5.85	8.43	7.19	11.70	7.00	9.50	12.70	9.02	8.24	11.35	4.46	8.79	4.91	10.82
DFT/OP86	13.22	8.95	11.58	10.32	14.85	10.15	12.66	15.88	12.24	11.36	14.53	6.13	11.82	6.45	14.69
DFT/OPW91	12.92	8.63	11.26	10.02	14.55	9.85	12.37	15.58	11.91	11.03	14.23	5.96	11.53	6.38	14.27
DFT/OLYP	10.14	6.15	8.50	7.25	11.80	7.10	9.62	12.83	9.21	8.66	11.48	5.03	8.98	5.31	10.90
DFT/O3LYP	5.49	4.06	4.04	3.94	7.43	3.96	5.42	8.74	6.55	6.38	7.44	4.48	5.66	3.68	6.53
DFT/PW91	6.67	4.64	5.07	4.52	8.58	4.63	6.56	9.87	7.26	7.09	8.56	4.42	6.49	4.21	7.55
DFT/PBE	4.71	2.64	3.09	2.44	6.53	2.48	4.44	6.61	5.15	4.51	5.47	4.19	4.35	2.79	5.02
DFT/B3LYP	4.48	8.46	5.86	7.10	2.69	6.85	4.17	2.10	4.93	5.80	2.72	11.40	5.55	1.40	7.47
DFT/B3PW91	2.32	6.17	3.52	4.75	1.82	4.35	2.01	2.47	2.97	3.64	1.81	8.86	3.73	1.20	4.83
DFT/WAH	15.58	11.47	14.02	12.78	17.21	12.46	14.94	18.23	14.70	13.82	16.93	7.29	14.12	6.99	17.97
DFT/B97	2.06	5.83	3.16	4.38	1.76	4.08	1.89	2.46	2.84	3.48	1.78	8.80	3.54	1.07	4.61
DFT/B91-1	2.67	6.65	4.01	5.23	1.84	4.99	2.45	2.09	3.40	4.13	1.92	9.70	4.09	1.12	5.42
DFT/B97-2	1.63	4.23	1.69	2.70	2.90	2.20	1.37	4.13	2.52	2.62	3.04	6.80	**2.98**	1.41	**3.62**
DFT/HCTH	9.98	6.04	8.34	7.09	11.64	6.94	9.47	12.68	9.07	8.53	11.34	4.94	8.84	5.30	10.68

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However, the VC values for different types of nitrogen atoms differ by more than 4 ppm. Second, the solvent effect on VCs was studied. We have chosen the representative molecules (II, IV, VI, and X) from each group of azoles (i.e., azole, as well as diazoles, triazoles, and tetrazoles), and carried out the VCs calculations in gas phase and in representative solvents. The solvents (CCl_4, $CHCl_3$, CH_2Cl_2, EtOH, and DMSO) were chosen to cover a wide range of electrical permittivity values. Again changes in VCs lower than 1 ppm for a given nitrogen atom were found when comparing results corresponding to different e value. Therefore it seems reasonable to relay on VCs computed for all molecules individually and in gas phase. Thus, our corrections used to calculate final chemical shifts were obtained for all systems in gas phase using B3LYP functional. They are gathered in Table 4 where – in addition to total corrections – first and second order terms as well as the uncorrected magnetic shielding constants are also included.

The effects of vibrational corrections are significant for the magnetic shielding constants of both types of nitrogen atoms and constitute a significant part of the total (vibrationally corrected) value. However, when evaluating the chemical shifts, the VCs tend to cancel, leaving only relatively small corrections. Thus the vibrational corrections to the chemical shifts of the pyrrole-type nitrogen atoms do not exceed ± 0.4 ppm. For the pyridine-type nitrogen atoms these corrections $\Delta\delta_{\mathrm{tot}}$ are slightly larger and comprised between -1.5 to +4 ppm.

The nitrogen chemical shifts were corrected by using estimated gas-phase vibrational corrections. The corresponding mean absolute errors (MAE) for all DFT functionals as well as for HF SCF method are shown at the bottom of Table 3 (Part B) and can be compared to MAEs for uncorrected values of nitrogen chemical shifts from Table 3 (Part A). Inclusion of the vibrational corrections generally improves the agreement between the DFT theoretical results and the experimental data. The exceptions are the previously chosen DFT functionals: B3LYP, B3PW91, B97 and B97-1 for which discrepancies with the experiment are slightly larger. Only for B97- 2 functional from this selected group the reduction of the mean absolute error (MAE_f) calculated for the tested set of azoles in all solvents is observed. However, there are four solvents (water, dioxane, ether and $CHCl_3$) for which the agreement with the experimental data is slightly worse than for uncorrected values. Interestingly, in the case of the following DFT functionals: OP*, OV*, OLYP, WAH and HCTH, taking into account the vibrational corrections results in a decrease of the mean absolute errors in all considered solvents – even in water.

Table 4 Magnetic shielding constants and their vibrational corrections of the pyrrole- and pyridine-type nitrogen atoms (in ppm) for all molecules considered in this work in gas phase. 1st and 2nd order (with respect to the shielding), as well as total corrections (in ppm) are given. Uncorrected magnetic shielding constants are also reported.

Pyrrole-type nitrogen atoms					Pyridine-type nitrogen atoms				
	σ	Vibrational correction				σ	Vibrational correction		
		2nd	1st	tot			2nd	1st	tot
II N1	87.50	-6.86	-0.83	-7.69					
III N1	33.53	-6.84	-0.75	-7.59	III N2	-90.38	-8.30	-3.43	-11.73
IV N1	77.20	-6.59	-0.82	-7.41	IV N3	-44.96	-7.68	-3.17	-10.85
V N1	-0.34	-5.60	-2.27	-7.86	V N2	-153.90	-6.25	-4.29	-10.54
					V N3	-136.46	-6.16	-4.34	-10.50
VI N1	27.80	-5.45	-2.06	-7.51	VI N2	-77.70	-7.53	-4.21	-11.74
					VI N4	-32.75	-6.97	-3.23	-10.20
VII N1	78.77	-8.27	0.95	-7.33	VII N3	-118.58	-6.54	-2.89	-9.43
					VII N4	-118.58	-6.54	-2.89	-9.43
VIII N1	-109.43	-5.70	-2.02	-7.71	VIII N2	-109.43	-6.43	-4.61	-11.04
					VIII N5	-109.43	-6.43	-4.60	-11.03
XI N1	9.99	-6.75	-0.70	-7.44	IX N2	-150.36	-6.51	-3.97	-10.48
					IX N3	-186.71	-3.07	-3.08	-6.15
					IX N4	-118.63	-7.35	-4.14	-11.49
X N1	-43.07	-4.60	-3.42	-8.03	X N2	-166.59	-5.22	-5.20	-10.42
					X N3	-116.49	-5.88	-4.39	-10.26
					X N5	-83.14	-6.52	-4.67	-11.20

For B97-2 functional the MAEs for uncorrected and corrected chemical shifts are comparable for the pyrrole-type nitrogen atoms, whereas inclusion of the VCs results in the noteworthy reduction of the errors for the pyridine-type nitrogen atoms (4.26 vs 3.62 ppm). From now on B97-2 functional becomes the method of choice on which further discussion will be based. The theoretical nitrogen chemical shifts (uncorrected and corrected) for the DFT/B97-2 method are presented in Table 5. Unless otherwise stated, we will refer to the vibrationally corrected values.

Solvent effects on the nitrogen chemical shift

For all discussed solvents the experimental chemical shifts increase in the following orders:

$$\delta_{\mathrm{N}_1^{\mathrm{VII}}} \leq \delta_{\mathrm{N}_1^{\mathrm{IV}}} < \delta_{\mathrm{N}_1^{\mathrm{III}}} < \delta_{\mathrm{N}_1^{\mathrm{VI}}} < \delta_{\mathrm{N}_1^{\mathrm{IX}}} < \delta_{\mathrm{N}_1^{\mathrm{V}}} < \delta_{\mathrm{N}_1^{\mathrm{VIII}}} < \delta_{\mathrm{N}_1^{\mathrm{IX}}}$$

and

$$\delta_{\mathrm{N}_4^{\mathrm{VI}}} < \delta_{\mathrm{N}_3^{\mathrm{IV}}} < \delta_{\mathrm{N}_2^{\mathrm{VI}}} < \delta_{\mathrm{N}_5^{\mathrm{X}}} \leq \delta_{\mathrm{N}_2^{\mathrm{III}}} < \delta_{\mathrm{N}_{2,5}^{\mathrm{VIII}}} \leq \delta_{\mathrm{N}_{3,4}^{\mathrm{VII}}} < \delta_{\mathrm{N}_4^{\mathrm{IX}}} \leq \delta_{\mathrm{N}_3^{\mathrm{X}}} < \delta_{\mathrm{N}_2^{\mathrm{V}}} < \delta_{\mathrm{N}_2^{\mathrm{IX}}} \leq \delta_{\mathrm{N}_3^{\mathrm{V}}} < \delta_{\mathrm{N}_2^{X}} < \delta_{\mathrm{N}_3^{\mathrm{IX}}}$$

for the pyrrole- and pyridine-type nitrogen atoms, respectively.

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Table 5 Theoretical (DFT/B97-2) values of the uncorrected and vibrationally corrected nitrogen chemical shifts.

	gas	c-hexane	dioxane	CCl_4	C_6H_6	Et_2O	$CHCl_3$	CH_2Cl_2	$(CH_3)_2CO$	EtOH	MeOH	DMSO	H_2O
Part A: Values without the vibrational corrections													
III N1	52.32	51.72	51.63	51.58	51.61	51.08	50.98	50.71	50.44	50.36	50.27	50.25	50.25
III N2	171.32	163.63	162.71	162.68	162.63	157.30	156.52	153.55	151.15	150.76	150.20	149.98	149.31
IV N1	10.25	10.77	10.80	10.77	10.81	11.26	11.28	11.64	11.85	11.85	11.88	11.89	12.02
IV N2	126.75	117.26	116.20	116.09	116.02	109.24	108.29	104.50	101.50	101.02	100.39	100.05	99.30
V N1	85.56	85.82	85.86	85.83	85.87	86.09	86.13	86.36	86.46	86.45	86.48	86.49	86.59
V N2	233.09	225.10	224.14	224.06	224.00	218.21	217.32	214.04	211.36	210.96	210.41	210.09	209.42
V N3	216.28	207.48	206.44	206.35	206.29	199.92	198.98	195.37	192.51	192.05	191.42	191.11	190.37
VI N1	57.96	57.57	57.52	57.49	57.52	57.21	57.18	57.08	56.94	56.88	56.81	56.81	56.81
VI N2	159.15	152.50	151.69	151.68	151.64	147.17	146.53	144.13	142.23	141.94	141.52	141.35	140.77
VI N4	115.25	106.98	106.03	105.95	105.89	100.24	99.40	96.33	93.90	93.53	93.01	92.73	92.15
VII N1	8.83	10.01	10.11	10.09	10.14	10.89	11.15	11.76	12.19	12.23	12.28	12.34	12.41
VII N3,4	197.69	185.64	184.26	184.14	184.04	175.50	174.21	169.41	165.59	165.01	164.27	163.80	162.84
VIII N1	99.10	97.83	97.72	97.63	97.65	96.57	96.43	95.86	95.34	95.23	95.13	95.04	94.98
VIII N2,5	191.13	185.03	184.29	184.26	184.23	180.08	179.45	177.21	175.48	175.13	174.79	174.61	174.11
IX N1	75.38	76.23	76.31	76.32	76.36	77.04	77.16	77.63	77.97	77.96	78.00	78.06	78.17
IX N2	230.54	224.90	224.84	224.28	224.27	220.89	220.34	218.59	217.13	216.91	216.58	216.43	216.04
IX N3	264.84	258.66	254.47	257.42	257.36	250.31	249.22	245.22	242.02	241.56	240.94	240.51	239.78
IX N4	198.66	186.85	188.83	185.83	185.77	180.08	179.22	176.16	173.68	173.35	172.83	172.52	171.93
X N1	127.23	126.81	126.76	126.74	126.76	126.47	126.44	126.38	126.26	126.22	126.15	126.18	126.14
X N2	246.32	239.60	238.73	238.73	238.75	234.09	233.47	230.83	228.84	228.52	228.03	227.86	227.26
X N3	196.82	188.61	187.62	187.63	187.51	181.88	181.00	177.95	175.44	175.06	174.52	174.28	173.60
X N5	165.05	160.11	159.49	159.52	159.48	156.30	155.82	154.22	152.92	152.72	152.37	152.30	151.83
Part B: Values with the vibrational corrections													
III N1	52.22	51.62	51.53	51.48	51.51	50.98	50.88	50.61	50.34	50.26	50.17	50.15	50.15
III N2	175.36	167.67	166.75	166.72	166.67	161.34	160.56	157.59	155.19	154.80	154.24	154.02	153.35
IV N1	9.97	10.49	10.52	10.49	10.53	10.98	11.00	11.36	11.57	11.57	11.60	11.61	11.74
IV N2	129.91	120.42	119.36	119.25	119.18	112.40	111.45	107.66	104.66	104.18	103.55	103.21	102.46
V N1	85.28	85.54	85.58	85.55	85.59	85.81	85.85	86.08	86.18	86.17	86.20	86.21	86.31
V N2	235.94	227.95	226.99	226.91	226.85	221.06	220.17	216.89	214.21	213.81	213.26	212.94	212.27
V N3	219.09	210.29	209.25	209.16	209.10	202.73	201.79	198.18	195.32	194.86	194.23	193.92	193.18
VI N1	57.78	57.39	57.34	57.31	57.34	57.03	57.00	56.90	56.76	56.70	56.63	56.63	56.63
VI N2	163.20	156.55	155.74	155.73	155.69	151.22	150.58	148.18	146.28	145.99	145.57	145.40	144.82
VI N4	117.76	109.49	108.54	108.46	108.40	102.75	101.91	98.84	96.41	96.04	95.52	95.24	94.66
VII N1	8.47	9.65	9.75	9.73	9.78	10.53	10.79	11.40	11.83	11.87	11.92	11.98	12.05
VII N3,4	199.43	187.38	186.00	185.88	185.78	177.24	175.95	171.15	167.33	166.75	166.01	165.54	164.58
VIII N1	99.12	97.85	97.74	97.65	97.67	96.59	96.45	95.88	95.36	95.25	95.15	95.06	95.00
VIII N2,5	194.48	188.38	187.64	187.61	187.58	183.43	182.80	180.56	178.83	178.48	178.14	177.96	177.46
IX N1	75.13	75.98	76.06	76.07	76.11	76.79	76.91	77.38	77.72	77.71	77.75	77.81	77.92
IX N2	233.33	227.69	227.63	227.07	227.06	223.68	223.13	221.38	219.92	219.70	219.37	219.22	218.83
IX N3	263.30	257.12	252.93	255.88	255.82	248.77	247.68	243.68	240.48	240.02	239.40	238.97	238.24
IX N4	179.48	167.67	169.65	166.65	166.59	160.90	160.04	156.98	154.50	154.17	153.65	153.34	152.75
X N1	127.57	127.15	127.10	127.08	127.10	126.81	126.78	126.72	126.60	126.56	126.49	126.52	126.48
X N2	249.05	242.33	241.46	241.46	241.48	236.82	236.20	233.56	231.57	231.25	230.76	230.59	229.99
X N3	199.38	191.17	190.18	190.19	190.07	184.44	183.56	180.51	178.00	177.62	177.08	176.84	176.16
X N5	168.56	163.62	163.00	163.03	162.99	159.81	159.33	157.73	156.43	156.23	155.88	155.81	155.34

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These trends are properly reproduced by the DFT method within the COSMO model. The lowest shieldings are observed for the nitrogen atoms directly bound to two carbon atoms in the heterocyclic ring. The neighbourhood of other nitrogen atom(s) results in an increase of the chemical shifts (for the most shielded nitrogen atom $\mathrm{N}_3^{\mathrm{IX}}$ the experimental chemical shifts $\delta_{\mathrm{N}_3^{\mathrm{IX}}}$ varies from 220 to 270 ppm depending on the solvent).

The relationship between the experimental and theoretical data obtained within the COSMO model was examined using linear regression analysis[43]. The linear regression parameters (a – slope, b – intercept) were determined for each discussed solvent according to the relation: $\delta^e = a \cdot \delta^t + b$. The correlation coefficients (R^2) and the standard regression errors S_{xy} were also determined. The results for the vibrationally corrected nitrogen chemical shifts obtained using B97-2 functional are presented in Figure 3. Generally, for all solvents the correlation between the experimental and the theoretical data is very good. The correlation coefficients are very close to 1.000. This means a strong correlation between these data sets.

Direct and indirect solvent effects

The total theoretical solvent effects $\Delta\sigma_{total}$ can be also analyzed in terms of their direct and indirect contributions[44,45] ($\Delta\sigma_{\mathrm{total}} = \Delta\sigma_{\mathrm{direct}} + \Delta\sigma_{\mathrm{indirect}}$). The direct effect, defined here as [22]

$$\Delta\sigma_{\mathrm{direct}} = \sigma_{\mathrm{solution}}(\mathrm{R}_{\mathrm{solution}}) - \sigma_{\mathrm{vaccum}}\ (\mathrm{R}_{\mathrm{solution}})$$

involves the solvent effect on the electronic wave function of a solute held at fixed geometry in a solvent. The indirect effect is due to the relaxation of the solute geometry under the influence of the solvent and it can be expressed as [22]

$$\Delta\sigma_{\mathrm{indirect}} = \sigma_{\mathrm{vaccum}}(\mathrm{R}_{\mathrm{solution}}) - \sigma_{\mathrm{vaccum}}(\mathrm{R}_{\mathrm{vaccum}})$$

Obviously, in the experiment the total effect is observed. The $\Delta\sigma_{\mathrm{direct}}$ and $\Delta\sigma_{\mathrm{indirect}}$ values for the pyrrole- and pyridine-type nitrogen atoms as a function of solvent dielectric constants are presented in Figure 4.

For both types of the nitrogen atoms the absolute value of direct effect significantly predominates the indirect effect ($|\Delta\sigma_{\mathrm{direct}}| >> |\Delta\sigma_{\mathrm{indirect}}|$) and consequently determines the total effect value. The direct and total effects for all pyridine-type nitrogen atoms are positive and increase with the dielectric constant of the solvent. On the contrary, for the pyrrole-type nitrogen atoms $\Delta\sigma_{\mathrm{direct}}$ and $\Delta\sigma_{\mathrm{total}}$ are negative and decrease with ε. In most cases for both nitrogen atoms, the indirect effect increases/decreases monotonically with the solvent dielectric constant, depending on the nitrogen atom type. The exceptions are N3 in 1-methyl-1,2,3,4-tetrazole (structure IX) and N2 in 1-methyl-1,2,3-triazole (structure V), for which the effect practically does not depend on ε.

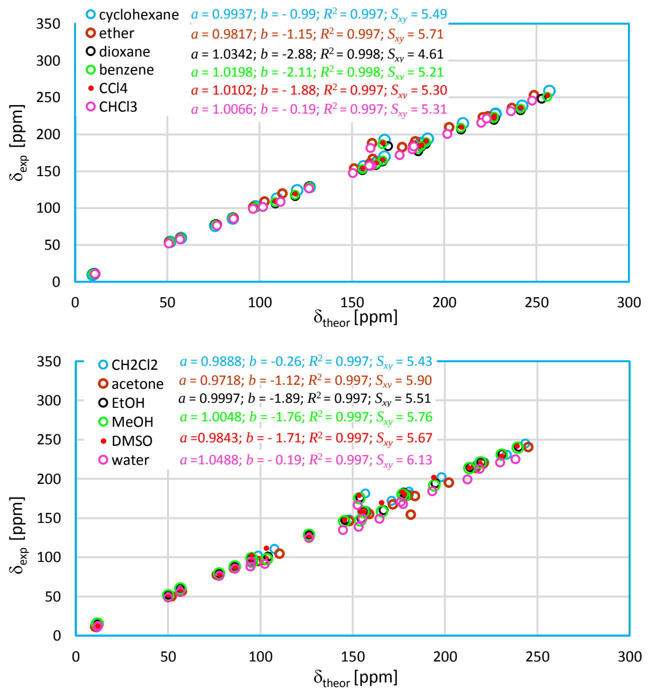

Figure 3 Experimental vs theoretical (DFT/B97-2) nitrogen chemical shifts and the linear regression parameters calculated for all solvents.

The indirect effect is associated with the molecular geometry changes due to solvation. The heterocyclic rings are quite rigid structures and the solvent effect on the geometrical parameters is relatively low (see Table 2SA and Table 2SB Supplementary Materials – the solvent effects on the geometrical parameters of 1-methyl-1,2,3,4-tetrazole). This justifies the fact that the absolute values of the indirect effects are several times smaller than the direct effects. Therefore, in the case of the solvent effects on the magnetic shielding constants, the gas-phase optimized molecular geometry used in the calculations should not introduce the substantial errors. Much more important is to determine the NMR parameters in the presence of a solvent.

COSMO model

The theoretical (DFT/B97-2/COSMO with vibrational corrections) solvent effects for the pyrrole- and pyridine-type nitrogen atoms were estimated with respect to cyclohexane ($\Delta\sigma_s^t$=$\sigma_{\mathrm{solvent}}$-$\sigma_{\mathrm{cyclohexane}}$) due to the lack of the experimental gas-phase data, and are gathered in Table 6 and Table 7.

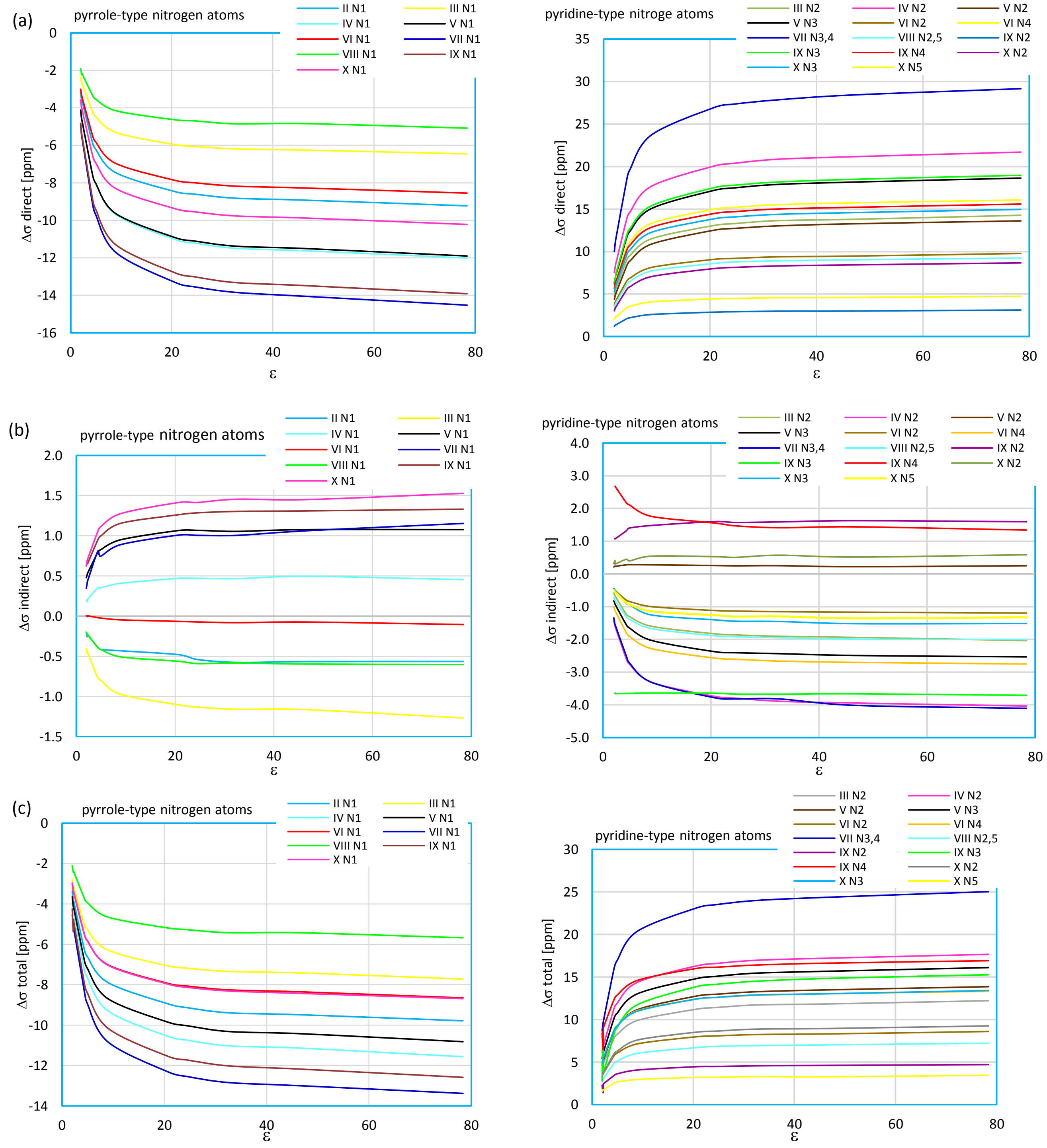

Figure 4 (a) Direct $\Delta\sigma_{direct}$, (b) indirect $\Delta\sigma_{indirect}$, and (c) total $\Delta\sigma_{total}$ theoretical (DFT/B97-2) solvent effects on the nitrogen shielding as a function of the dielectric constant ε.

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Table 6 Solvent effects for the pyrrole-type nitrogen atoms calculated with respect to cyclohexane.

	dioxane	CCl_4	C_6H_6	Et_2O	$CHCl_3$	CH_2Cl_2	$(CH_3)_2CO$	EtOH	MeOH	DMSO	H_2O
ε→	2.19	2.23	2.25	4.34	4.90	8.93	20.70	24.55	32.63	46.70	78.39
$\Delta\sigma^{tr}$											
N1II	-0.43	-0.35	-0.46	-0.46	-0.38	-0.53	-0.32	-0.51	-0.43	-0.35	-0.46
N1III	-0.45	-0.32	-0.45	-0.46	-0.37	-0.53	-0.25	-0.53	-0.45	-0.32	-0.45
N1IV	-0.45	-0.35	-0.49	-0.50	-0.40	-0.58	-0.27	-0.58	-0.45	-0.35	-0.49
N1V	-2.86	-2.22	-3.34	-3.12	-2.49	-3.74	-1.60	-3.67	-2.86	-2.22	-3.34
N1VI	-3.21	-2.48	-3.72	-3.52	-2.82	-4.35	-1.82	-4.14	-3.21	-2.48	-3.72
N1VII	-4.51	-3.51	-5.38	-5.04	-4.01	-6.26	-2.54	-5.91	-4.51	-3.51	-5.38
N1VII	-5.57	-4.29	-6.65	-6.21	-4.93	-7.75	-3.08	-7.30	-5.57	-4.29	-6.65
N1IX	-5.76	-4.41	-6.84	-6.39	-5.07	-7.99	-3.16	-7.49	-5.76	-4.41	-6.84
N1X	-6.02	-4.57	-7.12	-6.67	-5.26	-8.28	-3.31	-7.78	-6.02	-4.57	-7.12
$\Delta\delta^{e*}$											
N1II	-3.50	-1.05	-2.31	-1.57	-4.39	-4.45	-3.83	-3.05	-3.82	-5.86	-8.30
N1III	-2.78	-0.35	-1.56	-1.04	-1.92	-2.52	-2.77	-1.25	-1.54	-4.28	-3.08
N1IV	-4.15	-1.54	-2.46	-1.97	-4.50	-4.79	-4.79	-6.30	-8.81	-7.00	-9.67
N1V	-4.62	-1.89	-2.98	-2.35	-4.01	-4.45	-4.98	-5.53	-6.20	-7.18	-7.79
N1VI	-3.14	-0.60	-1.78	-1.62	-2.52	-2.97	-3.68	-4.39	-4.79	-5.22	-4.79
N1VII	-5.31	-1.77	-3.49	-2.60	-5.51	-6.06	-6.55	-9.31	-9.79	-9.18	-11.67
N1VII	-1.96	0.15	-0.91	-0.55	-0.67	-1.23	-1.55	-0.59	-0.72	-2.39	-0.19
N1IX	-5.56	-2.08	-3.61	-3.08	-4.92	-5.27	-6.45	-6.84	-7.56	-8.63	-9.21
N1X	-3.65	-0.36	-2.02	-1.91	-2.47	-2.99	-4.06	-3.52	-4.21	-5.48	-4.65
$\mathbf{Diff_s} = \Delta\sigma_s^t - \Delta\delta_s^{e*}$											
N1II	3.07	0.60	1.86	-1.29	1.18	-0.06	-1.74	-2.71	-2.20	-0.25	1.89
N1III	2.43	0.03	1.21	-1.18	-0.56	-0.99	-1.52	-3.16	-3.03	-0.37	-1.87
N1IV	3.69	1.09	1.97	-1.37	0.78	-0.59	-1.86	-0.54	1.69	-0.23	2.01
N1V	4.16	1.43	2.48	-0.77	0.49	-0.59	-1.23	-0.86	-0.47	0.40	0.61
N1VI	2.76	0.23	1.38	-0.87	-0.30	-1.04	-1.25	-0.68	-0.47	-0.13	-0.86
N1VII	4.78	1.24	2.91	-1.14	1.16	-0.20	-1.20	1.32	1.51	0.74	2.85
N1VII	1.64	-0.40	0.64	-1.05	-1.15	-1.31	-1.53	-2.57	-2.59	-0.93	-3.38
N1IX	5.05	1.55	3.03	-0.59	0.78	-0.64	-0.85	-0.65	-0.22	0.69	0.86
N1X	3.27	-0.02	1.62	-0.60	-0.37	-1.08	-0.95	-1.66	-1.15	0.00	-1.09
$\vert MAE_{Diff}\vert$											
	3.43	**0.73**	**1.90**	**0.98**	**0.75**	**0.72**	**1.35**	**1.57**	**1.48**	**0.42**	**1.71**

*The values for the original experimental data referred to nitromethane

Table 7 Solvent effects for the pyridine-type nitrogen atoms calculated with respect to cyclohexane.

	dioxane	CCl_4	C_6H_6	Et_2O	$CHCl_3$	CH_2Cl_2	$(CH_3)_2CO$	EtOH	MeOH	DMSO	H_2O
$\varepsilon\rightarrow$	2.19	2.23	2.25	4.34	4.90	8.93	20.70	24.55	32.63	46.70	78.39
$\Delta\sigma^{tr}$											
III N2	0.49	0.49	0.54	3.47	3.90	5.57	6.91	7.10	7.41	7.53	7.91
IV N2	0.63	0.73	0.79	5.17	5.75	8.25	10.20	10.48	10.86	11.10	11.55
V N2	0.52	0.59	0.64	4.03	4.56	6.55	8.17	8.37	8.67	8.89	9.26
V N3	0.61	0.68	0.74	4.70	5.29	7.60	9.40	9.66	10.04	10.26	10.69
VI N2	0.37	0.37	0.40	2.46	2.75	3.86	4.70	4.79	4.96	5.03	5.31
VI N4	0.52	0.59	0.64	3.88	4.37	6.14	7.52	7.69	7.95	8.14	8.42
VII N3,4	0.95	1.05	1.15	7.29	8.22	11.72	14.48	14.86	15.36	15.73	16.39
VIII N2,5	0.30	0.32	0.35	2.09	2.36	3.31	3.98	4.13	4.22	4.31	4.50
IX N2	-0.38	0.17	0.17	1.15	1.34	1.80	2.20	2.22	2.30	2.35	2.44
IX N3	3.75	0.79	0.85	5.49	6.22	8.93	11.07	11.34	11.71	12.03	12.46
IX N4	-2.42	0.57	0.62	3.91	4.42	6.18	7.60	7.74	8.00	8.22	8.51
X N2	0.44	0.42	0.40	2.65	2.92	4.26	5.20	5.32	5.55	5.62	5.93
X N3	0.56	0.53	0.64	3.87	4.39	6.15	7.60	7.78	8.08	8.21	8.60
X N5	0.19	0.15	0.18	0.96	1.08	1.38	1.63	1.63	1.73	1.70	1.87
$\Delta\delta^{e*}$											
III N2	3.24	3.15	2.88	1.56	8.05	5.98	4.36	17.13	18.79	4.57	22.29
IV N2	4.35	3.21	3.91	2.56	11.04	8.75	5.66	19.65	22.24	6.02	24.06
V N2	4.62	4.08	3.85	3.21	7.77	6.55	5.34	9.74	10.33	7.32	19.98
V N3	4.58	3.73	3.93	3.47	9.78	8.00	5.60	17.26	19.39	6.64	22.05
VI N2	1.80	1.29	1.60	1.50	4.61	3.45	2.04	5.65	6.61	2.33	13.11
VI N4	2.97	1.62	2.44	2.07	6.90	5.75	3.82	13.27	14.37	4.08	15.81
VII N3,4	7.77	3.04	5.71	4.21	12.39	11.96	9.41	25.01	26.10	12.33	30.71
VIII N2,5	1.00	0.75	1.01	0.90	3.36	2.77	1.39	4.04	5.23	0.97	10.88
IX N2	1.64	0.87	0.95	1.00	1.49	1.39	1.51	2.54	1.93	1.93	5.64
IX N3	6.91	4.49	5.35	4.20	8.70	8.85	8.04	14.53	15.03	10.31	25.06
IX N4	4.73	2.40	3.39	2.71	6.48	6.01	5.38	12.40	13.12	6.95	17.10
X N2	2.88	1.52	1.77	1.46	3.13	3.29	2.91	3.71	4.09	3.79	9.41
X N3	3.64	1.66	2.46	1.97	6.01	5.60	4.17	8.20	10.11	4.84	15.06
X N5	0.34	0.09	0.18	0.30	0.57	0.54	-0.23	0.33	0.26	-0.51	4.47
$\mathbf{Diff}_s = \boldsymbol{\Delta\sigma_s^t - \Delta\delta_s^{e*}}$											
III N2	-2.75	-2.66	-2.34	1.91	-4.15	-0.41	2.55	-10.03	-11.38	2.96	-14.38
IV N2	-3.72	-2.48	-3.12	2.61	-5.29	-0.50	4.54	-9.17	-11.38	5.08	-12.51
V N2	-4.10	-3.49	-3.21	0.82	-3.21	0.00	2.83	-1.37	-1.66	1.57	-10.72
V N3	-3.97	-3.05	-3.19	1.23	-4.49	-0.40	3.80	-7.60	-9.35	3.62	-11.36
VI N2	-1.43	-0.92	-1.20	0.96	-1.86	0.41	2.66	-0.86	-1.65	2.70	-7.80
VI N4	-2.45	-1.03	-1.80	1.81	-2.53	0.39	3.70	-5.58	-6.42	4.06	-7.39
VII N3,4	-6.82	-1.99	-4.56	3.08	-4.17	-0.24	5.07	-10.15	-10.74	3.40	-14.32
VIII N2,5	-0.70	-0.43	-0.66	1.19	-1.00	0.54	2.59	0.09	-1.01	3.34	-6.38
IX N2	-2.02	-0.70	-0.78	0.15	-0.15	0.41	0.69	-0.32	0.37	0.42	-3.20
IX N3	-3.16	-3.70	-4.50	1.29	-2.48	0.08	3.03	-3.19	-3.32	1.72	-12.60
IX N4	-7.15	-1.83	-2.77	1.20	-2.06	0.17	2.22	-4.66	-5.12	1.27	-8.59
X N2	-2.44	-1.10	-1.37	1.19	-0.21	0.97	2.29	1.61	1.46	1.83	-3.48
X N3	-3.08	-1.13	-1.82	1.90	-1.62	0.55	3.43	-0.42	-2.03	3.37	-6.46
X N5	-0.15	0.06	0.00	0.66	0.51	0.84	1.86	1.30	1.47	2.21	-2.60
$\|MAE_{Diff}\|$											
	3.14	**1.75**	**2.24**	**1.43**	**2.41**	**0.42**	**2.95**	**4.03**	**4.81**	**2.68**	**8.70**

*The values for the original experimental data referred to nitromethane

The experimental solvent effects, calculated from the observed chemical shifts[1–4] are denoted $\Delta\delta_s^{*e}$. Note that differences $\Delta\sigma_s^t$ and $\Delta\delta_s^{*e}$ can be compared with each other since in the latter case the reference is cancelled. The tables contain also the differences between the experimental and theoretical data ($\mathrm{Diff}_s = \Delta\sigma_s^t - \Delta\delta_s^{*e}$) and their mean absolute values ($|\mathrm{MAE_{Diff}}|$). Note, that the experimental solvent effects determined for DMSO and for water which are included in Tables 6 and 7, are defined in the same way as the solvent polarity effect and the total solvent effect for water solution (see Table 1 for comparison). The nature and strength of the solvent impact on the nitrogen chemical shifts depend on the type of nitrogen atom and the properties of the solvent. The directions of the solvent induced N NMR shifts are opposite for the two types nitrogen atoms. The presence of solvent results in a decrease/increase of the nitrogen shielding for the pyrrole-/pyridine-type nitrogen atoms (the exception is $\mathrm{N}_5^{\mathrm{X}}$ for which $\Delta\delta^*_{(CH_3)_2CO} < 0$ and $\Delta\delta^*_{DMSO} < 0$). This experimental trend is properly reproduced by the COSMO model.

Generally, the solvent effect on the chemical shifts of the pyrrole-type nitrogen atoms are slightly better described by the theoretical approaches used in this work. This applies particularly to the solvent polarity effect – the calculated and experimental values agree to within 0.4 ppm on average. The satisfactory theoretical description was obtained also for CCl_4, $CHCl_3$ CH_2Cl_2 and Et_2O. The largest differences between the theoretical and experimental data can be found for dioxane. The $|\mathrm{MAE_{Diff}}|$ values for the remaining solvents are comparable and oscillate between 1-2 ppm.

For the pyridine-type of nitrogen atoms discrepancies between the estimated theoretical and experimental solvent effects are much more evident. The best agreement was obtained for CH_2Cl_2 – a solvent with a moderate polarity ($\varepsilon \approx 9$), whereas the protic solvents effects are much less reproduced. For DMSO ($\varepsilon \approx 45$) and dioxane ($\varepsilon \approx 2$), the two solvents with significantly different dielectric constants, the similar (in the absolute values) differences between theory and experiment can be observed (~3 ppm on average). The solvent polarity effects, i.e., DMSO solvent effects are noticeably overestimated whereas for dioxane, the calculated solvent effects are considerably underestimated.

In the experiment there is no evident relationship between the magnitude of the solvent effect and its dielectric constant (ε) while the theoretical solvent effect for a given nitrogen atom increases smoothly with ε. This is a typical feature of the COSMO model (and its main weakness) which takes into account only dielectric constant of the solvent. The solvents in this work differ substantially in many properties. These properties (e.g., as characterized by α, β – hydrogen acceptor/ hydrogen donor strength of the solvent, π^* – solvatochromic parameter, i.e., index of solvent dipolarity/polarizability, which measures the ability of the solvent to stabilize a charge or a dipole by virtue of its dielectric effect[46]) may markedly change the solute-solvent interactions and contribute to the nitrogen shielding. The mean absolute errors in calculations of the pyrrole and pyridine-type nitrogen chemical shifts in different solvents are presented in Figure 5.

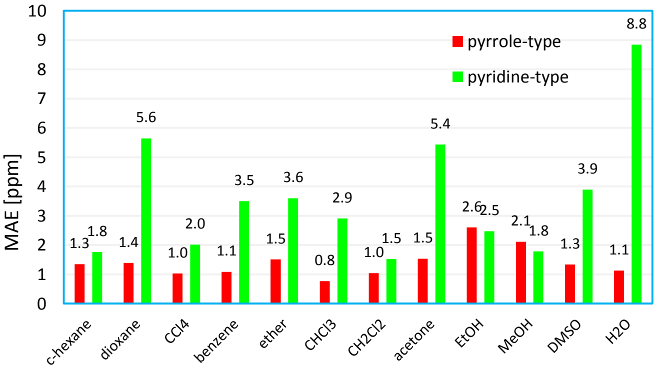

Figure 5. Mean absolute errors (in ppm) in the calculations of pyrrole- and pyridine-type nitrogen chemical shifts in different solvents using B97-2 functional.

In the case of the pyrrole-type nitrogen atoms the MAEs are comparable and practically independent on the solvent dielectric constant. The MAE values are about 1-2 ppm for B97-2 functional. The situation is slightly different in the case of the pyridine-type nitrogen atoms. In general, the MAEs for water are considerably larger than for aprotic solvents and they are about 10 ppm. This indicates that standard dielectric continuum solvent models may not be sufficiently accurate here. Thus, despite a good statistical correlation ($R^2 = 0.997$) and the slope of linear regression very close to 1.000, there still remains some inconsistencies in the calculated nitrogen shifts.

Hydrogen bonding effects on the nitrogen chemical shifts

The appropriate solvation models with hydrogen bonds included explicitly were examined (see Figure 2). Our previous experience[22] have shown that the combined cluster/continuum models yielded the most reasonable values of the NMR spectroscopic parameters. So, in this work, both models (ESM and ESM+COSMO) were used

The absolute errors (AE) for the pyrrole- and pyridine-type nitrogen atoms are shown in Figure 6. In the case of pyridine-type nitrogen atoms, inclusion of the explicit water molecules only does not provide significant improvement – in half cases the AE value computed with ESM increases as compared with the standard COSMO calculations. The combination of both models generally leads to reduction of AEs in a vast majority of cases. The exceptions are V N2, VIII N 2,5, X N2. For pyrrole-type nitrogen atoms the ESM results (i.e., without any polarity solvent effects) are significantly worse than the standard COSMO values of the nitrogen chemical shifts in all but one cases. The use of the combined models (ESM+COSMO) does not produce any significant improvement of the results – AEs are comparable with the standard COSMO calculations. This indicates that while the hydrogen-bonding effect is important mainly for the pyridine-type nitrogen atoms, the solvent polarity effects are essential for both types of nitrogen atom.

Table 8 shows the experimental and the theoretical (DFT/B97-2) hydrogen bonding effect estimated as the difference $\Delta\sigma_{Hbond}=\sigma_{H2O}-\sigma_{DMSO}$ calculated for all solvation models (i.e. COSMO, ESM, and ESM+COSMO).

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Table 8 Estimated solvent effects (total and hydrogen bonding effects) for the pyrrole- and pyridine-type nitrogen atoms

Pyrrole-type nitrogen atoms										
		II	III	IV	V	VI	VII	VIII	IX	X
		N1								
$\Delta\sigma_{Hbond}$	COSMO	-0.30	-0.30	-0.42	-0.39	-0.30	-0.38	-0.25	-0.41	-0.26
	ESM		4.86	10.26	5.06	5.22	10.84	-2.07	5.84	3.51
	ESM+COSMO		0.67	-1.34	-0.87	-0.71	-2.68	0.06	-2.22	6.54
	EXP*	**-2.44**	**+1.20**	**-2.67**	**-0.61**	**+0.43**	**-2.49**	**+2.20**	**-0.58**	**+0.83**
$\Delta\sigma_{tot}$	COSMO	-6.41	-4.95	-7.66	-7.18	-5.65	-8.82	-3.57	-8.35	-5.74
	ESM		0.22	3.03	-1.72	-0.13	2.40	-5.39	-2.10	-1.97
	ESM+COSMO		-3.97	-8.57	-7.65	-6.06	-11.12	-3.25	-10.16	1.06
	EXP*	**-8.30**	**-3.08**	**-9.67**	**-7.79**	**-4.79**	**-11.67**	**-0.19**	**-9.21**	**-4.65**

Pyridine-type nitrogen atoms															
		III	IV	V		VI		VII	VIII	IX			X		
		N2	N3	N2	N3	N2	N4	N3,4	N2,5	N2	N3	N4	N2	N3	N5
$\Delta\sigma_{Hbond}$	COSMO	0.38	0.45	0.37	0.43	0.28	-2.40	0.65	0.20	0.09	0.43	0.29	0.30	0.38	0.17
	ESM	5.54	-4.05	9.33	-0.72	5.00	-7.58	-4.67	6.96	5.58	8.99	-5.52	0.60	1.42	4.62
	ESM+COSMO	14.81	12.05	18.17	15.30	11.37	6.35	16.15	12.53	11.70	17.11	9.91	11.02	11.08	7.51
	EXP*	**17.78**	**18.04**	**12.66**	**15.41**	**10.78**	**11.73**	**18.38**	**9.91**	**3.71**	**14.75**	**10.15**	**5.62**	**10.22**	**4.98**
$\Delta\sigma_{tot}$	COSMO	7.91	11.55	9.26	10.69	5.31	5.73	16.38	4.51	2.44	12.46	8.51	5.93	8.60	1.87
	ESM	13.07	7.05	18.22	9.54	10.03	0.55	11.06	11.27	7.93	21.02	2.70	6.22	9.63	6.32
	ESM+COSMO	22.34	23.14	27.06	25.56	16.41	14.49	31.88	16.84	14.05	29.14	18.13	16.64	19.29	9.21
	EXP*	**22.29**	**24.06**	**19.98**	**22.05**	**13.11**	**15.81**	**30.71**	**10.88**	**5.64**	**25.06**	**17.1**	**9.41**	**15.06**	**4.47**

*The values for the original experimental data referred to nitromethane

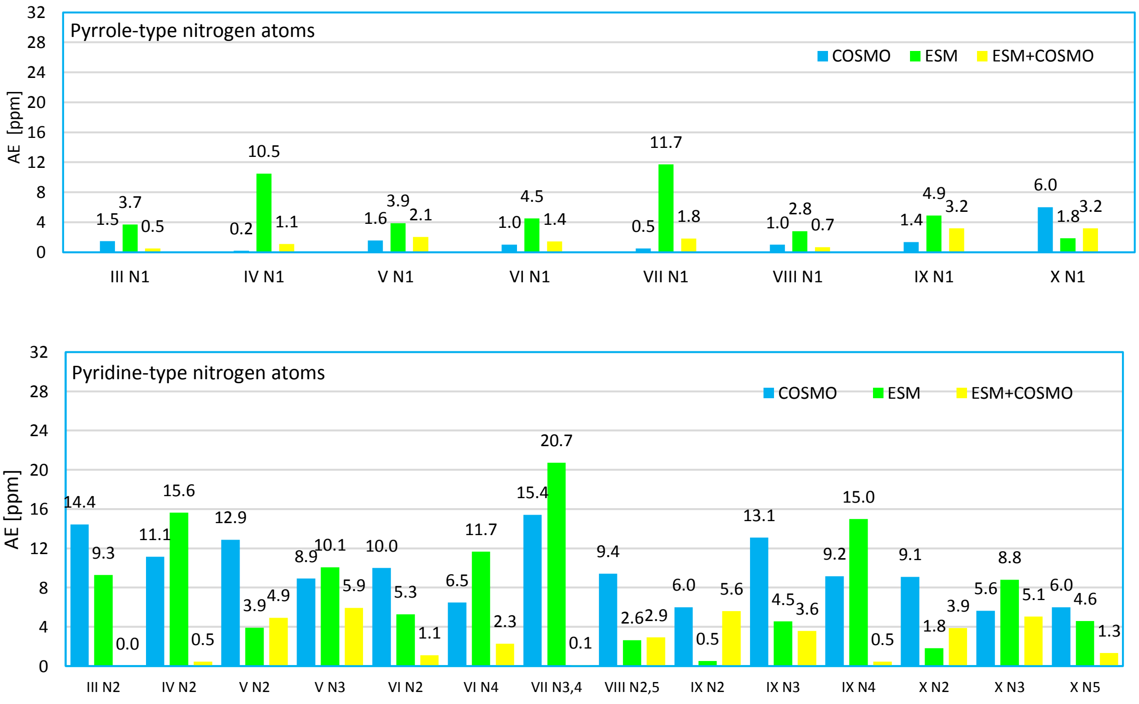

Figure 6. Absolute errors (in ppm) in the calculations of the chemical shifts for pyrrole-type and pyridine-type nitrogen chemical shifts in water using DFT/B97-2 functional.

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It also presents the total solvent effect in water solution expressed as before as $\Delta\sigma_{tot}=\sigma_{H2O}-\sigma_{cyclohexane}$.

It is evident that the hydrogen bonding effects are more important for the pyridine-type than for the pyrrole-type nitrogen atoms. The standard COSMO model reproduces only a minuscule part of the experimental hydrogen bonding effect (only a few tenths of a ppm). Similarly as for oxazoles, the best results were obtained for the combination of the COSMO and ESM models. In particular, it can be seen for the pyridine-type nitrogen atoms capable of producing potential hydrogen bonds with the protic solvent molecule(s). Generally, the estimated theoretical values of $\Delta\sigma_{Hbond}$ are comparable with the experimental values (except for N2 in tetrazoles, structures IX and X).

The limitation of the solvent models employed results in the deviation between the theoretical and experimental data.

Concluding remarks

In the present study we have theoretically examined the solvent effects on the nitrogen chemical shifts in the series of 1-methylazoles containing two significantly different nitrogen atoms, i.e., pyrrole- and pyridine-type. The N NMR spectra in the presence of a solvent environment were calculated with the COSMO model. Additionally, in the case of water solutions, a super-molecule approach ESM as well as its combination with the COSMO model were applied. We have reported also the vibrational corrections for the nitrogen atoms in the analyzed systems. While the vibrational correction to the magnetic shielding constants were found to be significant for both types of nitrogen atoms, the vibrational effect on chemical shifts was relatively small as compared with the overall range of the investigated chemical shifts.

For DFT/B97-2 method we have obtained the best agreement with the experimental chemical shifts (an average error below 3 ppm). In the case of all analyzed solvents strong correlation between the theoretical and experimental data sets was found. The solvent effect on the nitrogen chemical shifts, as defined by the difference between chemical shifts in a given solvent and in (nonpolar) cyclohexane, are well reproduced by the COSMO model. The calculated mean absolute error for the pyrrole-type nitrogen atoms is lower than 2 ppm in all but one cases (dioxane). In the case of pyridine-type nitrogen atoms the error is somewhat larger; still it does not exceed 4 ppm in the vast majority of cases. The lowest value of mean absolute error was obtained for CH_2Cl_2 for both types of nitrogen atoms. In addition, we showed that the geometric effect on the nitrogen chemical shifts due to the presence of a solvent is insignificant as compared with the effect of solvent on the nitrogen shielding. In the case of water solution the most accurate results were obtained for the combination of the COSMO and ESM models. In particular, this can be seen for the pyridine-type nitrogen atoms.

Our results reproduce properly all experimentally observed trends and confirm the different solvent effects (in the nature and strength) on the shielding of both type nitrogen atoms.

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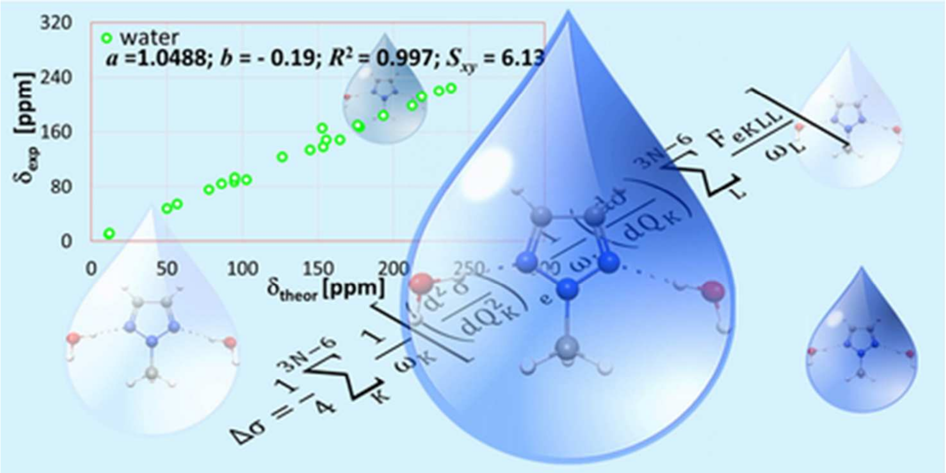

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