



## Theoretical analysis of solvent effects on nitrogen NMR chemical shifts in oxazoles and oxadiazoles

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### ABSTRACT

Using quantum chemistry methods we have evaluated the solvent effects on the  $^{14}\text{N}$  NMR chemical shifts in five oxa- and oxadiazoles dissolved in twelve solvents. These solvents differ in their polarity with the dielectric constants varying from 2 to 80. Moreover, three of them have a hydrogen-bond donor character. All possible hydrogen-bonding in the water solution with the oxygen and nitrogen (hydrogen-acceptor) centers in oxazoles (2) and oxadiazoles (3) have been considered in our studies. It has been shown that both the pure solvent and hydrogen-bonding effects are significant and result in  $^{14}\text{N}$  magnetic shielding increase. In water solutions the pure solvent effect is larger than the hydrogen-bonding effect. In addition, the solvent effect has been analyzed in terms of its direct and indirect contributions. It should be emphasized that our theoretical results for  $^{14}\text{N}$  chemical shifts in oxa- and oxadiazoles remain in a very good agreement with the accurate experimental data.

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### 1. Introduction

It is obvious that a solvent can significantly change the molecular properties of a solute due to mutual interactions. These interactions between the solvent and solute molecules may have pure electrostatic nature as well as a very specific character like for instance, hydrogen-bonding. Influence of such interactions on molecular properties may have direct and indirect character, the latter arising from changes in molecular geometry due to a solvent [1].

Among other properties, the nuclear magnetic shielding constant is also affected by interactions with a solvent [1]. Especially, the nitrogen magnetic shielding turned out to be very sensitive to a solvent [2]. The solvent effect on the nitrogen nuclear magnetic shielding has been investigated both experimentally [3–19] and theoretically [20–32]. In particular, the solvent effects on the  $^{14}\text{N}$  magnetic shielding in 5- and 6-membered hetero-aromatic compounds have been extensively studied experimentally by Witkowski et al. [3–9]. Those studies have shown that solvent effects on the nitrogen shielding are always significant. Their magnitude depends strongly on a solvent polarity and a character of possible hydrogen-bonding between a solvent molecule and hydrogen-bond-acceptors in a heterocyclic ring. One paper of the series mentioned above focused on solvent effects on the  $^{14}\text{N}$  shielding in oxazoles and oxadiazoles [9] and very high precision NMR measurements were reported there for a variety of solvents. That paper has been a motivation for our study. Having excellent

experimental data one might check them against theoretical results and examine accuracy of quantum chemical methods. Besides, the theoretical approach is often more flexible than the experimental one and allows an analysis of the NMR results in terms of different contributions which is not always possible in an experiment.

In this work, following Witkowski et al. [9], we have studied the  $^{14}\text{N}$  nuclear magnetic shieldings and chemical shifts of two oxazoles and three oxadiazoles in twelve solutions. These 5-membered heterocyclic compounds shown in Fig. 1 contain one oxygen and one (A,B) or two (C,D,E) pyridine-type nitrogen atoms. Both oxygen and nitrogen have a lone electron pair (oxygen two) and might form a hydrogen bond with an appropriate solvent.

Our main goal was to reproduce, by means of quantum chemical calculations, the experimental nitrogen NMR results [9] and to evaluate the magnitude of the hydrogen-bonding and pure solvent effects on  $^{14}\text{N}$  shieldings. In addition, the pure solvent effect has been analyzed in terms of its direct and indirect contributions. The presence of a solvent has been included in calculations via the Conductor-like Screening Model (COSMO) [33]. Since this model does not take into account any specific interactions, in order to deal with hydrogen-bonding we have constructed molecular models with explicit hydrogen-bond(s) involving water for all five compounds of interest.

### 2. Computational procedures

Most of the results obtained in this study will be compared with the corresponding experimental data reported in Ref. [9].

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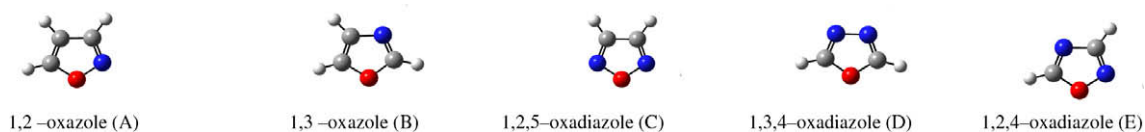


Fig. 1. Oxazoles and oxadiazoles structures.

The reference substance used in these NMR experiments was neat liquid nitromethane, the standard reference in the  $(^{14})^{15}\text{N}$  NMR spectroscopy. From a theoretical point of view it is inconvenient to use such a compound as a reference for oxa- and oxadiazoles considered here. First of all, it has completely different chemical nature and secondly, the calculated isotropic nitrogen shielding in nitromethane is strongly dependent on the method as well as the basis set used and ranges from  $-139$  to  $-269$  ppm [34]. Consequently, calculations of the corresponding chemical shifts according to

$$\delta^X = \sigma_{\text{Ref}}^X - \sigma^X \quad (1)$$

where  $\sigma_{\text{Ref}}^X$ ,  $\sigma^X$  denote the nuclear magnetic shielding constant for a nucleus  $X$  in the reference and in the system under study, respectively will likely suffer from substantial errors. In order to obtain better accuracy of the calculated nitrogen chemical shifts one may use as a reference the nitrogen nucleus in one of the discussed molecules A–E. This approach is often used in calculations and works well due to errors cancellation. We have chosen as our reference the  $\text{N}_4$  atom in 1,2,4-oxadiazole (E), the most shielded nitrogen nucleus in all five molecules studied and in all solvents considered in Ref. [9]. In this chemical shift scale the calculated values are defined according to Eq. (1) with  $\sigma_{\text{Ref}}^X = \sigma_{1,2,4\text{-oxadiazole}}^{\text{N}_4} = \sigma_{\text{E}}^{\text{N}_4}$ . The experimental chemical shifts referred to nitromethane (Table 1 in [9], note an opposite sign convention there) transfer to the 1,2,4-oxadiazole scale as

$$\begin{aligned} \delta_{\text{M}}^{\text{N},1,2,4\text{-oxadiazole}} &= \delta_{1,2,4\text{-oxadiazole}}^{\text{N}_4, \text{nitromethane}} - \delta_{\text{M}}^{\text{N}, \text{nitromethane}} \\ &= (\sigma_{1,2,4\text{-oxadiazole}}^{\text{N}_4} - \sigma_{\text{nitromethane}}^{\text{N}}) \\ &\quad - (\sigma_{\text{M}}^{\text{N}} - \sigma_{\text{nitromethane}}^{\text{N}}) \\ &= \sigma_{1,2,4\text{-oxadiazole}}^{\text{N}_4} - \sigma_{\text{M}}^{\text{N}} \end{aligned} \quad (2)$$

where  $\delta_{\text{M}}^{\text{N}, \text{Ref}}$  denotes the nitrogen chemical shift in a molecule  $\text{M}$  with respect to the reference and  $\sigma_{\text{M}}^{\text{N}}$  is the corresponding nitrogen shielding. Note that any references to nitromethane have been eliminated in this scale. The experimental results from Ref. [9] transferred to the new scale according to Eq. (2) are shown in Table

**Table 1**  
Experimental NMR nitrogen chemical shift (ppm) referred to  $\text{N}_4$  in 1,2,4-oxadiazole (molecule E).

Solvent	Molecule A	Molecule B	Molecule C	Molecule D	Molecule E	
					$\text{N}_2$	$\text{N}_4$
$\text{H}_2\text{O}$	132.99	10.39	172.32	57.93	121.51	0.00
DMSO	140.31	14.83	171.78	62.24	121.58	0.00
$\text{CH}_3\text{OH}$	138.28	9.71	175.62	60.70	124.61	0.00
$\text{C}_2\text{H}_5\text{OH}$	138.50	10.25	175.48	61.26	125.06	0.00
$(\text{CH}_3)_2\text{CO}$	142.60	15.05	173.48	64.19	123.04	0.00
$\text{CH}_2\text{Cl}_2$	141.35	13.54	174.57	64.03	123.21	0.00
$\text{CHCl}_3$	139.85	12.34	175.44	63.94	123.68	0.00
$(\text{C}_2\text{H}_5)_2\text{O}$	145.08	15.22	175.42	66.05	124.21	0.00
$\text{C}_6\text{H}_6$	143.57	15.14	174.80	65.77	123.99	0.00
$\text{CCl}_4$	143.98	14.70	176.24	66.62	124.39	0.00
Dioxane	143.62	15.29	174.29	64.91	123.36	0.00
Cyclohexane	146.26	15.58	177.44	68.76	125.70	0.00
Gas phase*	113.94*	17.02*	182.44*	73.80*	130.29*	0.00

\* Semiempirical values from Ref. [42] deduced on the basis of structural properties of the oxa- and oxadiazoles.

1. These values have been used in our study as the reference, experimental data.

All calculations reported in this paper have been performed with the PQS *ab initio* package [35]. This includes calculations of the nitrogen isotropic magnetic shielding and geometry optimization of all five oxa- and oxadiazoles A–E (Fig. 1) as well as the corresponding hydrogen-bonding models. Molecular models with hydrogen-bonding involving water have been constructed for all five compounds of interest. For each one we have considered two different types of the hydrogen-bonded system. The first one contains one (oxazoles) or two (oxadiazoles) water molecules connected to the nitrogen atom(s) only, while in the second type an additional water molecule forms a hydrogen bond with the oxygen atom also. These models (A – E +  $n\text{H}_2\text{O}$ ) are shown in Fig. 2.

Geometry optimization for all 15 molecular systems has been carried out using Density Functional Theory (DFT) with the B3LYP exchange-correlation potential [36] and the 6-31G(d,p) basis set [37]. Geometry of the A–E molecules has been optimized for the gas phase (isolated systems) as well as for the liquid phase in the presence of twelve solvents using the COSMO model [33]. Geometry of the hydrogen-bonding systems A – E +  $n\text{H}_2\text{O}$  in the water solutions has also been optimized with COSMO. Geometry changes due to the solvents are small in all cases. The largest change occurs in 1,2-oxazole (A) in aqueous solution where the N–O bond elongates from 1.396 to 1.403 Å. The geometrical parameters for all optimized structures are available from the authors upon request.

The nitrogen magnetic shielding has been calculated using the Gauge Including Atomic Orbitals (GIAO) method [38]. The precise level of theory used has been selected based on the best agreement with the experimental results from Table 1. We have examined basic Hartree–Fock (HF) and DFT methods with 26 popular exchange-correlation potentials (see the PQS manual [35] for corresponding Refs.) using the 6-31G-(d,p) basis set. This triple- $\zeta$  polarized basis set is usually good enough in the NMR chemical shift calculations at these levels. The statistical results of our calculations are presented in Table 2. It can be seen that in this case the performance of the HF method is the worst while the DFT/O3LYP results are the best. Thus, we have chosen the DFT/O3LYP [39] method with the 6-31G(d,p) basis set for all nitrogen magnetic shielding calculations undertaken in this study.

### 3. Results and discussion

As mentioned above, among the 26 tested DFT potentials and the HF method the best overall agreement with experiment for the molecules A–E in 9 solvents (the hydrogen-bond-donor solvents  $\text{H}_2\text{O}$ ,  $\text{CH}_3\text{OH}$  and  $\text{C}_2\text{H}_5\text{OH}$  have been excluded) has been obtained with the DFT/O3LYP method. The mean absolute error (MAE) in this case was only 1.88 ppm compared to an error of 29.13 ppm with the HF method (Table 2). This shows that, as expected, electron correlation is very important for the molecules considered in this study. Surprisingly, the WAH [40] potential, an especially modified B3LYP potential for magnetic shieldings, does not show any improvement over standard B3LYP, both having a mean absolute error of about 7.5 ppm.

Besides the method, there is another important issue affecting the accuracy of calculated magnetic shieldings and chemical shifts.

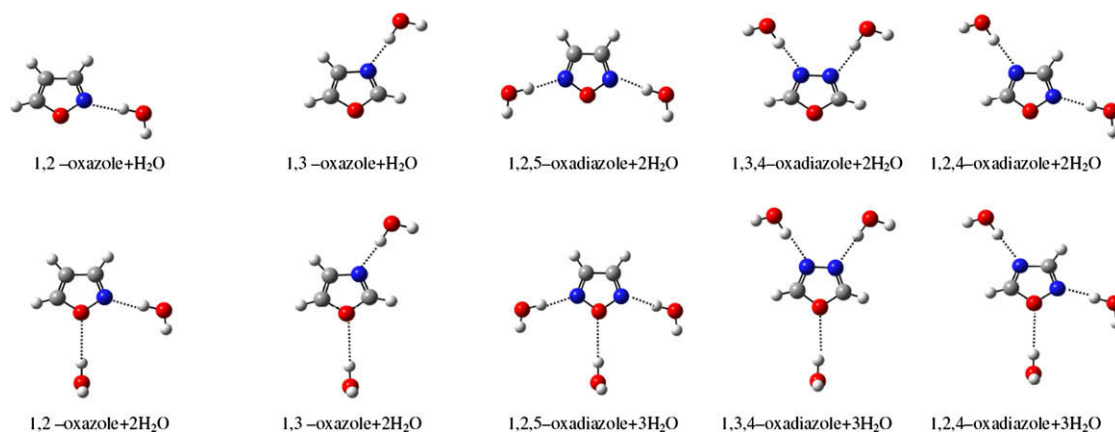


Fig. 2. Hydrogen-bonding models.

Table 2

Accuracy of the Hartree–Fock and DFT calculations of the nitrogen NMR chemical shift in the five molecules A–E in solution. Mean absolute errors (MAE) (ppm) for Hartree–Fock and 26 different DFT potentials over a range of 12 solvents\*.

Method**	Solvent									
	DMSO	(CH <sub>3</sub> ) <sub>2</sub> CO	CH <sub>2</sub> Cl <sub>2</sub>	CHCl <sub>3</sub>	(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	C <sub>6</sub> H <sub>6</sub>	CCl <sub>4</sub>	Dioxane	Cyclohexane	Average MAE
HF SCF	26.68	25.91	27.86	29.79	28.02	31.38	30.81	31.85	29.87	29.13
DFT/HFS	2.78	2.98	2.74	3.32	3.07	3.17	2.97	3.40	2.86	3.03
DFT/SVWN	2.82	3.02	2.76	2.88	3.05	2.94	2.74	3.17	2.80	2.91
DFT/SVWN5	2.81	3.01	2.75	2.92	3.04	2.98	2.77	3.21	2.79	2.92
DFT/HFB	2.48	2.69	2.45	3.34	2.77	2.72	2.53	2.94	2.55	2.72
DFT/BVWN	2.50	2.70	2.44	2.85	2.74	2.50	2.29	2.90	2.47	2.60
DFT/BVWN5	2.49	2.69	2.43	2.91	2.73	2.53	2.33	2.87	2.47	2.61
DFT/BP86	3.03	3.23	2.98	2.36	3.30	2.80	2.74	3.00	3.07	2.94
DFT/BPW91	3.13	3.33	3.08	2.39	3.40	2.89	2.84	3.09	3.17	3.03
DFT/BLYP	2.47	2.67	2.42	3.25	2.72	2.86	2.66	3.09	2.48	2.73
DFT/BVP86	3.03	3.24	2.99	2.35	3.30	2.80	2.74	3.00	3.08	2.95
DFT/OPX	5.22	6.32	5.49	4.80	6.14	4.91	5.01	4.85	5.95	5.41
DFT/OVWN	5.04	6.12	5.23	4.41	5.83	4.54	4.63	4.46	5.54	5.09
DFT/OVWN5	5.02	6.11	5.23	4.41	5.83	4.55	4.65	4.48	5.55	5.09
DFT/OP86	7.39	8.49	7.25	6.18	8.26	6.28	6.87	6.19	8.03	7.22
DFT/OPW91	7.55	8.65	7.40	6.33	8.41	6.42	7.01	6.32	8.17	7.36
DFT/OLYP	4.95	6.04	5.17	4.36	5.79	4.52	4.61	4.44	5.53	5.05
DFT/PW91	3.08	3.28	3.04	2.38	3.35	2.84	2.79	3.05	3.12	2.99
DFT/PBE	3.27	3.52	3.23	2.55	3.55	3.06	3.00	3.26	3.33	3.20
DFT/O3LYP	2.18	1.84	1.45	1.79	1.74	2.22	1.55	2.67	1.50	1.88
DFT/B3LYP	6.60	5.58	7.00	8.28	6.28	8.63	8.04	9.04	6.93	7.38
DFT/B3PW91	4.51	3.50	4.69	5.97	3.96	6.29	5.70	6.70	4.59	5.10
DFT/WAH	7.76	8.85	7.60	6.54	8.59	6.59	7.18	6.37	8.34	7.53
DFT/B97	4.29	3.27	4.44	5.68	3.67	5.95	5.36	6.36	4.24	4.81
DFT/B97-1	4.95	3.94	5.22	6.48	4.47	6.76	6.17	7.18	5.06	5.58
DFT/B97-2	3.23	2.46	3.39	4.64	2.62	4.89	4.30	5.30	3.18	3.78
DFT/HCTH	4.35	5.44	4.58	3.76	5.15	3.90	3.99	3.82	4.86	4.43

\* For each method:  $MAE = \frac{\sum_{i=1}^N |\delta_{N_i}^{calc} - \delta_{N_i}^{ref}|}{N}$ , Average =  $\frac{\sum_{i=1}^N MAE_i}{N}$ .

\*\* See the PQS manual [35] for corresponding references.

Very often the nuclear magnetic shielding strongly depends on the molecular geometry and therefore can be sensitive to nuclear motion. Rovibrational effects should then be taken into account [43,44]. We have estimated the importance of these effects in the present case. We have calculated approximate zero-point vibrational corrections (ZPVC) to the nitrogen magnetic shielding in 1,2-oxazole and in 1,2,4-oxadiazole, our reference. ZPVC values have been calculated around the equilibrium geometry using a perturbational approach [44]. These calculations require both first and the second derivatives of the magnetic shielding and third-order energy derivatives (cubic force constants) with respect to the normal coordinates (cf. Eq. (10.21) in Ref. [44]). These derivatives have been calculated numerically with respect to the internal coordinates first and then transformed to the normal coordinates after solving the vibrational eigen-problem. We have made, however, two important

simplifications. The derivatives of the nitrogen magnetic shieldings have been calculated with respect to a *limited subset* of the internal coordinates. We have chosen two bonds the nitrogen atom is involved in as well as the valence angle they form. The remaining derivatives were set to zero since motions of all other distant nuclei as well as the out-of-plane motion of the nitrogen atom should not influence the nitrogen magnetic shielding constant significantly. Our second approximation concerned the cubic force constants. We have calculated *only diagonal* third order energy derivatives with respect to all internal coordinates. Off-diagonal cubic force constants were again set to zero since they are expected to be much smaller than the diagonal terms. Once all these derivatives were transformed to the normal coordinates the final ZPV correction was calculated. We obtained the following ZPV corrections for the nitrogen shielding constant: 4.60 ppm in 1,2-oxazole and

6.93 ppm in 1,2,4-oxadiazole (N4). This gives a contribution to the chemical shift of 2.33 ppm. Thus we conclude that in the present case ZPV corrections, although quite significant for the nitrogen shielding, are not so important for the relative chemical shifts.

### 3.1. Nitrogen chemical shifts

The absolute nitrogen magnetic shieldings in the molecules A–E calculated with the DFT/O3LYP/6-311G(d,p) method are reported in Table 3 for 12 solvents and the gas phase. In the case of water, the results for two sets of hydrogen-bonding models for the molecules A–E, are also included. These results will be used later to evaluate and discuss the solvent and hydrogen-bonding effects on the nitrogen magnetic shielding. First, however, we like to discuss the accuracy of our calculations. To this end we converted the absolute shieldings from Table 3 to our chemical shift scale with respect to N<sub>4</sub> in 1,2,4-oxadiazole (E). These results are compared to the experimental values (Table 1) in Tables 4a and 4b shows the corresponding differences. The largest absolute errors, up to 6.36 ppm for 1,3,4-oxadiazole (D), occur for the water solution when the hydrogen-bonds are not included in calculations. Also for two other hydrogen-bond-donor solvents (methanol and ethanol) absolute errors are quite large, in particular for 1,3,4-oxadiazole (D) again (3.93 and 3.56 ppm). Remarkable improvement is obtained when hydrogen-bonds are included in the calculations for water solutions. For the molecule D the error of 6.36 ppm is reduced to only 0.84 ppm and for the molecule A from 4.85 to –0.32 ppm. Among all 12 solvents the results for the hydrogen-bonding molecular models A–E + nH<sub>2</sub>O in water show overall the best agreement with the experimental data, with an average error of 0.97 ppm. The largest errors occur for DMSO, benzene and dioxane. However, the average errors (2.21, 2.25 and 2.72 ppm, respectively), are not very large. On the other hand, across all solvents, the most accurate results are obtained for 1,3-oxazole (B) with an average error of 1.45 ppm and the worst results for 1,3,4-oxadiazole (D) which has a 3.14 ppm error.

The correlation between the experimental and the calculated nitrogen chemical shifts has also been analyzed in terms of a linear regression  $\delta_{\text{exp}} = a \delta_{\text{calc}} + b$ . These results for each solvent are presented in Table 5. First of all, the hydrogen-bonding effect can be easily noticed. If specific hydrogen bonds are not taken into account in calculations then for the solvents H<sub>2</sub>O, CH<sub>3</sub>OH and C<sub>2</sub>H<sub>5</sub>OH, the linear regression parameters are noticeably poorer. In particular, the intercept (b) has value of –4.15, –4.37 and

–3.79, respectively. For the hydrogen-bonded models A–E + nH<sub>2</sub>O with H<sub>2</sub>O connected to all hydrogen-acceptors (oxygen and all nitrogen nuclei) the intercept parameter decreases in absolute value from –4.15 to –1.75 and the correlation coefficient (*R*) reaches the theoretical limit of 1.0000. Overall, the correlation between the experimental and the calculated shifts is very satisfactory.

For the molecules A–E the calculated nitrogen shielding increases in the following order: C < A < E<sub>N<sub>2</sub></sub> < D < B < E<sub>N<sub>4</sub></sub>

This order is the same in the gas phase and in each of the twelve considered solvents. The same order was found in the NMR experiment [9]. The less shielded nitrogen nuclei (lowest magnetic shielding) are those directly bonded to the oxygen atom, i.e. N<sub>2</sub> and N<sub>5</sub> in C, N<sub>2</sub> in A and N<sub>2</sub> in E. This can be explained by migration of the electronic charge from the nitrogen atoms toward the oxygen atom in the aromatic ring. This is rather a short range effect because nitrogen atoms separated from oxygen (N<sub>3,4</sub> in D, N<sub>3</sub> in B and N<sub>4</sub> in E) in the aromatic ring are much more shielded. The attraction of the electronic charge in a ring by oxygen has been confirmed in the additional testing calculations. We have replaced the oxygen atoms in A–E by N–H making corresponding diazoles and triazoles (without relaxing geometry). In all cases the magnetic shielding of the nitrogen atoms of interest increased significantly. For instance, the magnetic shielding of N<sub>2</sub> changed from –156.5 ppm in 1,2-oxazole to –82.3 ppm in 1,2 diazole (in the gas phase).

### 3.2. Solvent effect on the nitrogen shielding

The total solvent effect can be defined as the difference between the magnetic shielding in a given solvent and in the gas phase. From the theoretical point of view it can be written as

$$\Delta\sigma_{\text{total}}^{\text{N}} = \sigma_{\text{solution}}^{\text{N}}(R_{\text{solution}}) - \sigma_{\text{gas phase}}^{\text{N}}(R_{\text{gas phase}}) \quad (3)$$

where  $R_{\text{solvent}}$  and  $R_{\text{gas phase}}$  denote the molecular geometry (optimized) in the presence of a solvent and in the gas phase, respectively. The total solvent effect may be further partitioned into *direct* and *indirect* contributions [1,21,25], the latter arising from molecular geometry changes due to a solvent

$$\Delta\sigma_{\text{total}}^{\text{N}} = \sigma_{\text{direct}}^{\text{N}} + \Delta\sigma_{\text{indirect}}^{\text{N}} \quad (4)$$

$$\Delta\sigma_{\text{direct}}^{\text{N}} = \sigma_{\text{solution}}^{\text{N}}(R_{\text{solution}}) - \sigma_{\text{gas phase}}^{\text{N}}(R_{\text{solution}}) \quad (5)$$

$$\Delta\sigma_{\text{indirect}}^{\text{N}} = \sigma_{\text{gas phase}}^{\text{N}}(R_{\text{solution}}) - \sigma_{\text{gas phase}}^{\text{N}}(R_{\text{gas phase}}) \quad (6)$$

**Table 3**  
Calculated nitrogen magnetic shielding constants at the DFT/O3LYP//GIAO/6-311G(d,p) level.

Solvent	Molecule A	Molecule B	Molecule C	Molecule D	Molecule E	
					N <sub>2</sub>	N <sub>4</sub>
H <sub>2</sub> O <sup>a</sup>	–122.12	–5.49	–161.05	–54.90	–112.86	5.54
H <sub>2</sub> O <sup>b</sup>	–127.27	–6.37	–165.76	–53.37	–117.28	5.40
H <sub>2</sub> O	–139.70	–14.28	–175.16	–66.14	–125.86	–1.86
DMSO	–139.98	–14.46	–175.42	–66.43	–126.09	–2.00
CH <sub>3</sub> OH	–140.28	–14.62	–175.66	–66.72	–126.29	–2.09
C <sub>2</sub> H <sub>5</sub> OH	–140.61	–14.86	–175.92	–67.04	–126.53	–2.22
(CH <sub>3</sub> ) <sub>2</sub> CO	–140.83	–14.98	–176.11	–67.28	–126.70	–2.32
CH <sub>2</sub> Cl <sub>2</sub>	–142.70	–16.11	–177.61	–69.13	–128.03	–3.04
CHCl <sub>3</sub>	–145.05	–17.57	–179.51	–71.50	–129.87	–3.95
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	–146.24	–17.86	–179.92	–72.72	–130.58	–4.50
C <sub>6</sub> H <sub>6</sub>	–149.80	–20.57	–183.36	–76.47	–133.49	–6.11
CCl <sub>4</sub>	–149.86	–20.62	–183.41	–76.53	–133.54	–6.14
Dioxane	–149.99	–20.70	–183.49	–76.66	–133.63	–6.19
Cyclohexane	–150.57	–21.09	–184.01	–77.26	–134.05	–6.49
Gas phase	–156.50	–24.96	–188.89	–83.37	–139.01	–9.45

<sup>a</sup> Hydrogen-bonding models: A,B + H<sub>2</sub>O, C–E + 2H<sub>2</sub>O.

<sup>b</sup> Hydrogen-bonding models: A,B + 2H<sub>2</sub>O, C–E + 3H<sub>2</sub>O.

**Table 4a**

The DFT/O3LYP/GIAO/6-31(d,p) calculated ( $\delta_N^t$ ) and experimental ( $\delta_N^e$ ) nitrogen chemical shifts (ppm) referred to N<sup>4</sup> in 1,2,4-oxadiazole (molecule E) as a function of the dielectric constant  $\epsilon$ .

Solvent	$\epsilon$	Molecule A		Molecule B		Molecule C		Molecule D		Molecule E	
		$\delta_N^t$	$\delta_N^e$	$\delta_N^t$	$\delta_N^e$	$\delta_N^t$	$\delta_N^e$	$\delta_N^t$	$\delta_N^e$	$\delta_N^t$	$\delta_N^e$
H <sub>2</sub> O**		127.66		11.03		166.59		60.44		118.40	
H <sub>2</sub> O***	78.39	132.67	132.99	11.77	10.39	171.16	172.32	58.77	57.93	122.68	121.51
H <sub>2</sub> O		137.84		12.42		173.30		64.29		124.00	
DMSO	46.70	137.98	140.31	12.46	14.83	173.43	171.78	64.43	62.24	124.09	121.58
CH <sub>3</sub> OH	32.63	138.19	138.28	12.53	9.71	173.57	175.62	64.63	60.70	124.20	124.61
C <sub>2</sub> H <sub>5</sub> OH	24.55	138.39	138.50	12.64	10.25	173.70	175.48	64.82	61.26	124.31	125.06
(CH <sub>3</sub> ) <sub>2</sub> CO	20.70	138.52	142.60	12.66	15.05	173.80	174.60	64.96	64.19	124.38	123.04
CH <sub>2</sub> Cl <sub>2</sub>	8.93	139.67	141.35	13.07	13.54	174.58	174.57	66.09	64.03	124.99	123.21
CHCl <sub>3</sub>	4.90	141.09	139.85	13.62	12.34	175.56	175.44	67.54	63.94	125.92	123.68
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	4.34	141.74	145.08	13.37	15.22	175.43	175.42	68.22	66.05	126.08	124.21
C <sub>6</sub> H <sub>6</sub>	2.25	143.69	143.57	14.46	15.14	177.25	174.80	70.36	65.77	127.38	123.99
CCl <sub>4</sub>	2.23	143.72	143.98	14.48	14.70	177.27	176.24	70.39	66.62	127.40	124.39
Dioxane	2.22	143.80	143.62	14.51	15.29	177.30	174.29	70.47	64.91	127.44	123.36
Cyclohexane	2.02	144.08	146.26	14.59	15.58	177.52	177.44	70.76	68.76	127.56	125.70
Gas phase	—	147.05	113.94*	15.51	17.02*	179.44	182.44†	73.92	73.80†	129.56	130.29*

\* Semiempirical values from Ref. [42] deduced on the basis of structural properties of the oxa- and oxadiazoles.

\*\* Hydrogen-bonding models: A,B + H<sub>2</sub>O, C-E + 2H<sub>2</sub>O.

\*\*\* Hydrogen-bonding models: A,B + 2H<sub>2</sub>O, C-E + 3H<sub>2</sub>O.

**Table 4b**

Differences  $\delta_N^t - \delta_N^e$  and average absolute errors (ABS) (ppm).

Molecule	A	B	C	D	E	Average (ABS)
H <sub>2</sub> O <sup>a</sup>	-5.33	0.64	-5.73	2.51	-3.11	3.46
H <sub>2</sub> O <sup>b</sup>	-0.32	1.38	-1.16	0.84	1.17	0.97
H <sub>2</sub> O	4.85	2.03	0.98	6.36	2.49	3.34
DMSO	-2.33	-2.37	1.65	2.19	2.51	2.21
CH <sub>3</sub> OH	-0.09	2.82	-2.05	3.93	-0.41	1.86
C <sub>2</sub> H <sub>5</sub> OH	-0.11	2.39	-1.78	3.56	-0.75	1.72
(CH <sub>3</sub> ) <sub>2</sub> CO	-4.08	-2.39	0.32	0.77	1.34	1.78
CH <sub>2</sub> Cl <sub>2</sub>	-1.68	-0.47	0.01	2.06	1.78	1.20
CHCl <sub>3</sub>	1.24	1.28	0.12	3.6	2.24	1.70
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	-3.34	-1.85	0.01	2.17	1.87	1.85
C <sub>6</sub> H <sub>6</sub>	0.12	-0.68	2.45	4.59	3.39	2.25
CCl <sub>4</sub>	-0.26	-0.22	1.03	3.77	3.01	1.66
Dioxane	0.18	-0.78	3.01	5.56	4.08	2.72
Cyclohexane	-2.18	-0.99	0.08	2.00	1.86	1.42
Average (ABS)	1.87	1.45	1.46	3.14	2.14	

<sup>a</sup> Hydrogen-bonding models: A,B + H<sub>2</sub>O, C-E + 2H<sub>2</sub>O.

<sup>b</sup> Hydrogen-bonding models: A,B + 2H<sub>2</sub>O, C-E + 3H<sub>2</sub>O.

**Table 5**

Correlation between the experimental and the calculated nitrogen chemical shifts for the molecules A–E. Parameters of the linear regression  $\delta_{\text{exp}} = a \delta_{\text{calc}} + b$ , standard errors ( $S_{xy}$ ) and correlation coefficients ( $R$ ).

Solvent	$a$ (Slope)	$b$ (Intercept)	$S_{xy}$	$R$
H <sub>2</sub> O	1.0079	-4.15	2.48	0.9994
H <sub>2</sub> O <sup>a</sup>	1.0519	-2.83	2.08	0.9996
H <sub>2</sub> O <sup>b</sup>	1.0137	-1.75	0.74	1.0000
DMSO	0.9866	1.04	2.67	0.9993
CH <sub>3</sub> OH	1.0344	-4.37	1.29	0.9999
C <sub>2</sub> H <sub>5</sub> OH	1.0304	-3.79	1.27	0.9999
(CH <sub>3</sub> ) <sub>2</sub> CO	0.9944	1.39	2.65	0.9993
CH <sub>2</sub> Cl <sub>2</sub>	1.0035	-0.70	1.80	0.9997
CHCl <sub>3</sub>	1.0091	-2.65	1.35	0.9998
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	0.9995	0.28	2.74	0.9993
C <sub>6</sub> H <sub>6</sub>	0.9913	-1.05	2.47	0.9994
CCl <sub>4</sub>	0.9995	-1.41	2.14	0.9996
Dioxane	0.9895	-1.29	2.97	0.9992
Cyclohexane	1.0011	-0.27	2.09	0.9996

<sup>a</sup> Hydrogen-bonding models: A,B + H<sub>2</sub>O, C-E + 2H<sub>2</sub>O.

<sup>b</sup> Hydrogen-bonding models: A,B+2H<sub>2</sub>O, C-E + 3H<sub>2</sub>O.

A similar, but not identical, definition of direct and indirect solvent effects on nuclear magnetic shielding has been introduced by Cammi et al. [21,25]. Our definition requires two calculations of a

shielding in the gas phase and one in the solution, while another needs one gas phase and two solvent calculations. It is perhaps worth mentioning that the indirect solvent effect can always be estimated via calculations of the shielding derivatives with respect to certain geometrical parameters [43]. In this case, however, the calculations of the shielding derivatives would be even more expensive than direct calculations according to Eqs. (4)–(6) and still would provide only an estimate of the indirect effects.

We have calculated the solvent effects on the nitrogen shielding constant according to Eqs. (3)–(6). These results are shown in Table 6a. It should be emphasized that hydrogen bonding is not taken into account and therefore in the following discussion the three solvents: H<sub>2</sub>O, CH<sub>3</sub>OH and C<sub>2</sub>H<sub>5</sub>OH should be viewed just as continuum media with a given dielectric constant  $\epsilon$ .

In all cases the presence of the solvent increases the nitrogen magnetic shielding. The results presented in Table 6a show a strong dependence of the shielding increment on the solvent polarity. Going from cyclohexane ( $\epsilon \sim 2$ ) to water ( $\epsilon \sim 78$ ) the total solvent effect increases by a factor of 2.6–2.8 for all five molecules. The largest increment (about 17 ppm) occurs in water for 1,2-oxazole and 1,3,4-oxadiazole (A,D). For these two molecules the total solvent effect on the nitrogen shielding is very similar for all 12 solvents despite of the fact that nitrogen is connected to oxygen in 1,2-oxazole only. For 1,2,5- and 1,2,4-oxadiazoles (C,E) the increment in the N<sub>2</sub> nitrogen (connected to oxygen) shielding is also essentially the same in all 12 solvents. The smallest solvent effect is observed in 1,2,4-oxadiazole (E) and 1,3-oxazole (B) for the nitrogen nuclei which are not bonded to oxygen (N<sub>4</sub> and N<sub>3</sub>, respectively).

Partitioning of the total solvent effect into the direct and indirect contributions (Eqs. (4)–(6)) shows that these two are always of an opposite sign. For the molecules considered in this study the direct solvent effect is positive and 5–10 times larger in magnitude than the indirect effect (negative). The largest (in absolute value) indirect solvent effect occurs for 1,2-oxazole (A) in aqueous solution. Its magnitude -4.50 ppm resulting from the geometry relaxation due to the solvent reflects the N–O bond elongation from 1.396 to 1.403 Å. The relatively small indirect solvent effects on the nitrogen shielding for oxa- and oxadiazoles are not a surprise because these molecules have rigid structures and so geometry changes due to solvation are very small.

The direct, indirect and total solvent effects on the nitrogen shielding are plotted in Fig. 3 as a function of the solvent dielectric

**Table 6a**  
Calculated direct ( $\Delta\sigma_{\text{dir}}$ ), indirect ( $\Delta\sigma_{\text{ind}}$ ) and total ( $\Delta\sigma_{\text{tot}}$ ) solvent effects on the nitrogen magnetic shielding constant. (hydrogen bonds not included in calculations).

Solvent	$\epsilon^*$	Molecule A			Molecule B			Molecule C			Molecule D			Molecule E			Molecule F		
		$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$	$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$	$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$	$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$	$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$	$\Delta\sigma_{\text{dir}}$	$\Delta\sigma_{\text{ind}}$	$\Delta\sigma_{\text{tot}}$
H <sub>2</sub> O	78.39	21.30	-4.50	16.80	13.67	-2.99	10.68	15.64	-1.91	13.73	20.42	-3.19	17.23	16.42	-3.27	13.15	9.81	-2.22	7.59
DMSO	46.70	20.97	-4.45	16.52	13.44	-2.94	10.50	15.36	-1.89	13.47	20.09	-3.15	16.94	16.18	-3.26	12.92	9.64	-2.19	7.45
CH <sub>3</sub> OH	32.63	20.57	-4.35	16.22	13.24	-2.90	10.34	15.07	-1.84	13.23	19.73	-3.08	16.65	15.90	-3.18	12.72	9.51	-2.15	7.36
C <sub>2</sub> H <sub>5</sub> OH	24.55	20.18	-4.29	15.89	12.97	-2.87	10.10	14.77	-1.80	12.97	19.34	-3.01	16.33	15.61	-3.13	12.48	9.35	-2.12	7.23
(CH <sub>3</sub> ) <sub>2</sub> CO	20.70	19.89	-4.22	15.67	12.77	-2.79	9.98	14.55	-1.77	12.78	19.05	-2.96	16.09	15.40	-3.09	12.31	9.22	-2.09	7.13
CH <sub>2</sub> Cl <sub>2</sub>	8.93	17.49	-3.69	13.80	11.32	-2.47	8.85	12.79	-1.51	11.28	16.82	-2.58	14.24	13.69	-2.71	10.98	8.26	-1.85	6.41
CHCl <sub>3</sub>	4.90	14.50	-3.05	11.45	9.48	-2.09	7.39	10.59	-1.21	9.38	13.98	-2.11	11.87	11.48	-2.34	9.14	7.00	-1.50	5.50
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	4.34	12.95	-2.69	10.26	8.98	-1.88	7.10	10.01	-1.04	8.97	12.52	-1.87	10.65	10.33	-1.90	8.43	6.34	-1.39	4.95
C <sub>6</sub> H <sub>6</sub>	2.25	8.45	-1.75	6.70	5.63	-1.24	4.39	6.15	-0.62	5.53	8.19	-1.29	6.90	6.86	-1.34	5.52	4.27	-0.93	3.34
CCl <sub>4</sub>	2.23	8.37	-1.73	6.64	5.57	-1.23	4.34	6.09	-0.61	5.48	8.12	-1.28	6.84	6.79	-1.32	5.47	4.23	-0.92	3.31
Dioxane	2.22	8.19	-1.68	6.51	5.46	-1.20	4.26	5.98	-0.58	5.40	7.95	-1.24	6.71	6.66	-1.28	5.38	4.16	-0.90	3.26
Cyclohexane	2.02	7.46	-1.53	5.93	4.97	-1.10	3.87	5.43	-0.55	4.88	7.22	-1.11	6.11	6.07	-1.11	4.96	3.80	-0.84	2.96

\*  $\epsilon$ : Dielectric constant.

constant. The calculated nitrogen shielding increases smoothly in each molecule with increasing dielectric constant. The opposite trend is of course true for the nitrogen chemical shift: it decreases with increasing solvent dielectric constant. This is shown in Table 4a. In general, the experimental results from Table 1 (and 4a) exhibit the same kind of behavior. However, this is true only for solvents with significantly different dielectric constants. Among solvents with similar dielectric constants very often the larger chemical shift corresponds to the smaller  $\epsilon$  values. For example, the experimental nitrogen chemical shifts in all five molecules (A–E) are bigger in (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O with  $\epsilon = 4.3$  than in CHCl<sub>3</sub> with  $\epsilon = 4.9$ . This is not reproduced in our calculations. A similar situation occurs in the case of dioxane, CCl<sub>4</sub> and C<sub>6</sub>H<sub>6</sub> with essentially the same dielectric constants of ca. 2.2. In this case the experimental nitrogen chemical shifts differ even by 2 ppm (C) while the calculated values are practically the same for each molecule. These discrepancies can be explained by deficiency of the COSMO model used for the calculations in solutions. This model relies essentially on only one physical parameter describing a solvent, namely on its dielectric constant. Thus, for the solvents with roughly the same  $\epsilon$  the calculated magnetic shieldings are also the same regardless of other important differences among solvents such as, for instance, their dipole moments and polarizabilities. These properties, not taken into account in calculations, in reality influence interactions between the solvent and the solute molecules. It should be mentioned that there are other (than a dielectric constant) parameters characterizing solvent properties. For example, the so-called  $\pi^*$  scale of solvent polarities which takes into account also dipole moments and polarizabilities [41]. According to the  $\pi^*$  scale dioxane, CCl<sub>4</sub> and C<sub>6</sub>H<sub>6</sub> (having the same  $\epsilon = 2.2$ ) are quite different with  $\pi^*$  being 0.55, 0.29 and 0.59, respectively. Also the other solvents mentioned above, (C<sub>2</sub>H<sub>5</sub>)<sub>2</sub>O ( $\epsilon = 4.3$ ) and CHCl<sub>3</sub> ( $\epsilon = 4.9$ ), differ far more in their  $\pi^*$  values: 0.76 and 0.27, respectively.

The solvent effect calculated according to Eq. (3) (Table 6a) can not be directly compared with the experimental data because of the lack of gas phase measurements. However, instead of the gas phase as a reference one might use any low polarity solvent, e.g., cyclohexane. The calculated and experimental solvent effects on the nitrogen shielding, referred to cyclohexane, are reported in Table 6b. It can be seen that the accuracy of the calculated shielding increment varies with the solvent dielectric constant. For very polar solvents with  $\epsilon > 20$  ((CH<sub>3</sub>)<sub>2</sub>CO, DMSO, H<sub>2</sub>O) the calculated values are overestimated as compared to experiment. In some cases these discrepancies are large, e.g., 6.6 vs. 2.7 ppm for 1,3-oxazole in DMSO. On the other hand, for non polar solvents with ( $\epsilon \sim 2$ ) the calculated shielding increments are very much underestimated, sometimes by an order of magnitude, e.g., 0.52 vs. 5.26 ppm for 1,2,5-oxadiazole in dioxane. The best agreement between theory and experiment is achieved for CH<sub>2</sub>Cl<sub>2</sub>, a solvent with moderate polarity ( $\epsilon \sim 9$ ). The unreliable results for the shielding increment for non polar solvents should not be a surprise. The COSMO model used in our calculations is based on a conductor type of approximation and therefore is not expected to perform well for solvents with small dielectric constants [33].

### 3.3. Hydrogen bonding effect on the nitrogen shielding

Three solvents used in this study (H<sub>2</sub>O, CH<sub>3</sub>OH and C<sub>2</sub>H<sub>5</sub>OH) can form hydrogen bonds with oxa- and oxadiazoles (A–E). However, as mentioned in Section 3, we have considered hydrogen bonding in water solutions only. The two sets of hydrogen-bonding models A–E + nH<sub>2</sub>O are shown in Fig. 2. The best agreement between the experimental and the calculated nitrogen chemical shifts (see Section 4.1) has been obtained for the molecules A–E with water attached to all possible hydrogen-bond acceptors, i.e. to both

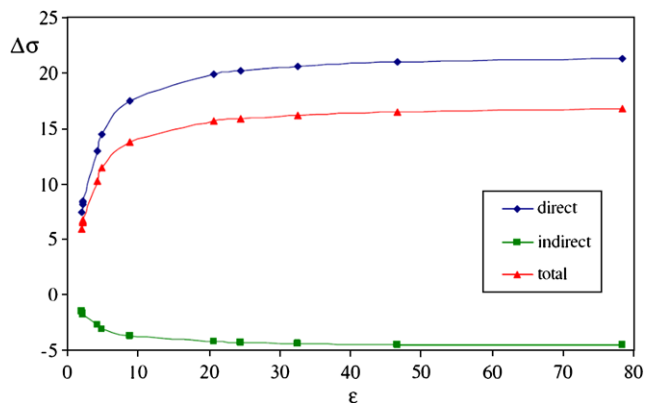


Fig. 3. Direct, indirect and total solvent effects on the nitrogen shielding as a function of the dielectric constant in 1,2-oxazole.

nitrogen and oxygen atoms. The results obtained for these molecular models will be discussed here.

The hydrogen-bonding (HB) effect on the nitrogen magnetic shielding in a molecule M dissolved in water is given as the difference between the magnetic shielding in (M + nH<sub>2</sub>O) and in M, both calculated in the presence of water

$$\Delta\sigma_{\text{HB}}^{\text{N,M}} = \sigma_{\text{water}}^{\text{N,m+nH}_2\text{O}} - \sigma_{\text{water}}^{\text{N,m}} \quad (7)$$

The results obtained according to Eq. (7) using the corresponding values from Table 3 are reported in Table 7. It can be seen that hydrogen-bonding always increases the nitrogen magnetic shielding. Our calculations show that hydrogen-bonds between water and the nitrogen atoms are the most important. As shown in Table 3 these bonds change the nitrogen shielding in A–E by 17.6, 8.8, 14.1, 11.2, 13.0 and 7.4 ppm, respectively. However, hydrogen-bonds involving the oxygen atom from aromatic ring also contribute significantly to the total hydrogen-bonding effect reducing it by up to 5 ppm (Table 3). This is contrary to the results of the semi-empirical calculations reported in [9] according to which, the oxygen involving hydrogen-bonds are not very important for the total effect.

The magnitude of the shielding increment due to hydrogen-bonding is smaller than pure solvent effect (Tables 6a and 6b), however, the direction is the same so the two effects reinforce.

Molecules	D	> A	> C	> E <sub>N<sub>2</sub></sub>	> B	> E <sub>N<sub>4</sub></sub>
HB	12.77	12.43	9.40	8.58	7.91	7.26
Solvent	17.23	16.80	13.73	13.15	10.68	7.59
Total	30.00	29.23	23.13	21.73	18.59	9.58

Table 6b

Calculated ( $\Delta\sigma_{\text{N}}^{\text{c}}$ ) and experimental ( $\Delta\sigma_{\text{N}}^{\text{e}}$ ) solvent effects on the nitrogen magnetic shielding (ppm) with respect to cyclohexane  $\Delta\sigma = \sigma^{\text{Solvent}} - \sigma^{\text{cyclohexane}}$ .

Solvent	$\epsilon$	Molecule A		Molecule B		Molecule C		Molecule D		Molecule E			
										N <sub>2</sub>		N <sub>4</sub>	
		$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$	$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$	$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$	$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$	$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$	$\Delta\sigma_{\text{N}}^{\text{c}}$	$\Delta\sigma_{\text{N}}^{\text{e}}$
H <sub>2</sub> O <sup>a</sup>	78.39	23.30	21.46	14.72	13.38	18.25	13.31	23.89	19.02	16.77	12.38	11.89	8.19
DMSO	46.70	10.59	7.92	6.63	2.72	8.59	7.63	10.83	8.49	7.96	6.09	4.49	1.97
(CH <sub>3</sub> ) <sub>2</sub> CO	20.70	9.74	5.84	6.11	2.71	7.90	6.14	9.98	6.75	7.35	4.84	4.17	2.18
CH <sub>2</sub> Cl <sub>2</sub>	8.93	7.87	7.30	4.98	4.43	6.40	5.26	8.13	7.12	6.02	4.88	3.45	2.39
CHCl <sub>3</sub>	4.90	5.52	8.65	3.52	5.48	4.50	4.24	5.76	7.06	4.18	4.26	2.54	2.24
(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> O	4.34	4.33	2.58	3.23	1.76	4.09	3.42	4.54	4.11	3.47	2.89	1.99	1.40
C <sub>6</sub> H <sub>6</sub>	2.25	0.77	3.89	0.52	1.64	0.65	3.84	0.79	4.19	0.56	2.91	0.38	1.20
CCl <sub>4</sub>	2.23	0.71	2.44	0.47	1.04	0.60	1.36	0.73	2.30	0.51	1.47	0.35	0.16
Dioxane	2.22	0.58	4.75	0.39	2.40	0.52	5.26	0.60	5.96	0.42	4.45	0.30	2.11

<sup>a</sup> Hydrogen-bonding models: A, B + 2H<sub>2</sub>O, C–E + 3H<sub>2</sub>O.

Table 7

Hydrogen-bonding effect on the nitrogen shielding in ppm. (Experimental values from Ref. [9]).

Molecule	$\sigma_{\text{N}}^{\text{H}_2\text{O}} - \sigma_{\text{N}}^{\text{H}_2\text{O}}$	$\sigma_{\text{N}}^{\text{H}_2\text{O}} - \sigma_{\text{N}}^{\text{DMSO}}$	
	Calculated	Calculated	Experimental
A	12.4	12.7	13.5
B	7.9	8.1	10.6
C	9.4	9.7	5.7
D	12.8	13.1	10.6
E (N <sub>2</sub> )	8.6	8.8	6.3
E (N <sub>4</sub> )	7.3	7.4	6.2

The hydrogen-bonding effect can also be estimated by the difference between the corresponding magnetic shieldings in water and DMSO solutions [9]. The dielectric constant of DMSO is big enough and there is no hydrogen-bond-donor center. This way one can make a comparison with the experimental data. These estimates are also included in Table 7.

Estimates of the hydrogen-bonding effect from the shielding differences ( $\sigma_{\text{H}_2\text{O}} - \sigma_{\text{DMSO}}$ ) remain very close to the exact theoretical values given above. They also agree quite well with the corresponding experimental values except for 1,2,5-oxadiazole (C) where the theoretical and experimental estimates are 9.66 and 5.68 ppm, respectively.

#### 4. Conclusions

In this study we have calculated the nitrogen magnetic shielding in two oxazoles and three oxadiazoles (A–E) for which experimental results in a variety of solvents were available. The presence of a solvent has been included in the calculations via the COSMO model. In order to obtain the best agreement with the experimental data we have examined twenty six popular DFT potentials and the Hartree–Fock method. The highest accuracy has been obtained using the DFT/O3LYP method which had an average error of about 2 ppm. Our calculations reproduced all the experimentally observed trends.

The solvent effect on the nitrogen shielding constant in the molecules investigated in this study is always positive and its magnitude depends strongly on the solvent polarity. The total solvent effect is dominated by its direct contribution. The indirect part (arising from geometry relaxation in the presence of the solvent) is much smaller and for the molecules and solvents studied in this work is always negative.

Solvent effects calculated with respect to cyclohexane instead of the gas phase can be compared with the experimental data. This comparison shows that the COSMO model overestimates solvent effects for very polar solvents and underestimates them for non

polar solvents. The most accurate results have been obtained for solvents with medium polarity. Discrepancies between predicted and experimental magnitudes of a solvent effect can be related to weaknesses of the COSMO model which has been designed for very polar solvents (conductor like).

Finally, we have calculated hydrogen-bonding effects on the nitrogen shielding for all five molecules A–E in aqueous solution. The formation of hydrogen-bonds always increases the magnetic shielding of all nitrogen atoms. Hydrogen bonds involving both nitrogen and oxygen contribute significantly to the total hydrogen-bonding effect, however, the former are more important. While hydrogen-bonds between water and nitrogen atoms increase the nitrogen shielding, hydrogen-bonds involving oxygen reduce it.

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