J. Phys. Chem. A **2000,** *104,* 9600−9604

Solvent Effects on ^{15}N NMR Shielding of 1,2,4,5-Tetrazine and Isomeric Tetrazoles: Continuous Set Gauge Transformation Calculation Using the Polarizable Continuum Model

Marlon N. Manalo,[†] Angel C. de Dios,*[,†] and Roberto Cammi[‡]

Department of Chemistry, Georgetown University, 37th and O Streets, N.W., Washington, DC 20057-1227, and Dipartimento di Chimica Generale ed Inorganica, Università di Parma, viale delle Scienze, 43100 Parma, Italy

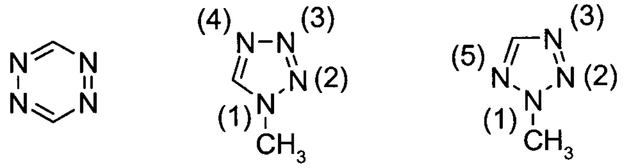
Received: April 21, 2000; In Final Form: August 1, 2000

Solvent-induced effects on nitrogen NMR shielding of 1,2,4,5-tetrazine and two isomeric tetrazoles are calculated using density functional theory combined with the polarizable continuum model and using the continuous set gauge transformation. Direct and indirect solvent effects on shielding are also calculated. It has been shown that the observed solvent-induced shielding variation is more strongly related to the intensity of the solvent reaction field rather than on the change of molecular geometry induced by the solvent.

Introduction

Ab initio calculation of nuclear magnetic shielding has become an indispensable aid in the investigation of molecular structure and accurate assignment of NMR spectra of compounds. Because most of the systems studied experimentally are in solution, the formulation of satisfactory theoretical models for solvated systems has been the object of continuously increasing interest.[1−13] Evaluation of the dependability of such models requires its rigorous application to various types of molecular systems and comparison of computed results with experimental data. Necessary improvements to the model are then made, or restriction of its application to some chemical systems is established, at the least.

The experimental study of solvent effects on nitrogen NMR shielding of azine[14−16]and azole[17−22] systems has been the focus of a series of papers published by Witanowski et al. The data from these works constitute a database of experimental nitrogen shieldings that can be utilized to evaluate the reliability of NMR calculations for systems in solution. In a recent study, Jaszuński et al. compare their experimental data with multiconfigurational self-consistent field (SCF) calculations and describe the solvent dependence of NMR properties of azoles using solvent response theory.[23] In the present report, the polarizable continuum model (PCM)[24−25] and continuous set gauge transformation (CSGT)[26] method are used to calculate nitrogen NMR shieldings of 1,2,4,5-tetrazine (I), 1-Me-1,2,3,4-tetrazole (II), and 1-Me-1,2,3,5-tetrazole (III) (Figure 1) in a wide range of solvents encompassing a broad spectrum of dielectric constant, ϵ. Solvent-induced effects on nitrogen shielding are then evaluated and compared with the experimental results of Witanowski et al.[16,22] The analysis presented here, however, only takes account of the shielding variation in terms of nonspecific solute−solvent interactions and does not include specific influences that may arise from hydrogen bonding, protonation, molecular association, ionic interactions, and aromaticity of solvent.[27] To study these latter types of interaction, it is necessary to introduce one or more explicit solvent molecules in all PCM calculations. The property parameters of organic solvents listed by Marcus in his review[28] may also be used for a more detailed examination of solvent effect on nuclear magnetic shielding.



I II III

Figure 1. Structures of 1,2,4,5-tetrazine (I), 1-Me-1,2,3,4-tetrazole (II), and 1-Me-1,2,3,5-tetrazole (III). The pyrrole-type nitrogens in the azoles are marked invariably as N-1.

PCM has proved useful in describing the effects of the solvent on some characteristics of the molecule in solution.[13,29−31] Recent theoretical studies using PCM include calculation of dipole polarizability and hyperpolarizabilities,[32] magnetic susceptibility and nuclear magnetic shielding,[11,12] and of course, solvent effects on NMR shielding of solutes.[33] In 1997, a new PCM method called the integral equation formulation,[34,35] was introduced. In this method, diverse types of dielectrics (standard isotropic liquids, intrinsically anisotropic media like liquid crystals and solid matrices, and ionic solutions) are treated in a single common approach. All PCM calculations in this report have been performed using this formalism as implemented in Gaussian 98.[36] The unavailability of PCM−gauge-invariant atomic orbital[11,12] in Gaussian 98 has restricted us to exploit PCM-CSGT[11] in nuclear shielding calculations.

We present here the theoretical study of solvent-induced effects on nitrogen NMR shielding of compounds I, II, and III. The diversity of nitrogen atoms in these molecules makes them good candidates for a preliminary investigation of the influence of solvent polarity on nuclear magnetic shielding. Direct and indirect contributions to the total solvation effect are also examined. Direct effects involve perturbation of the solvent on the electronic wave function of the solute held at fixed geometry; indirect effects are due to the relaxation of the solute geometry under the influence of the solvent.[11,12] The same convention adopted by Witanowski et al.[16] is used to describe trends in shielding data; thus, a positive solvent effect indicates an increase in nuclear shielding. The results reported in this work can be considered to provide a good assessment of the ability of PCM to predict the NMR properties of molecules in solution.

---

* To whom correspondence should be addressed. Fax: (202) 687-6209; e-mail: angel@bouman.chem.georgetown.edu.

[†] Georgetown University.

[‡] Universitá di Palma.

10.1021/jp001525g CCC: $19.00

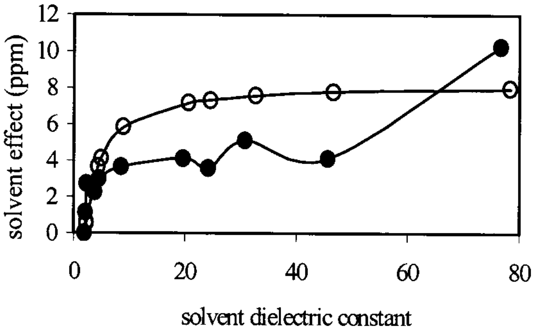


Figure 2. Dependence of experimental (●) and theoretical (○) solvent effect on the nuclear magnetic shielding of ^{15}N in 1,2,4,5-tetrazine (compound I) with solvent dielectric constant.

Computational Details

Gas-phase geometry optimization and shielding calculations are performed on an IBM/RS6000 model 3CT workstation using Gaussian 94[37] whereas solution-phase computations are performed with Gaussian 98 on an Origin 2000 workstation (Silicon Graphics). Charge normalization in the PCM calculations is achieved by scaling the calculated charge on each tessera by a constant factor. The PCM cavity is defined by using the Pauling[36] (Merz–Kollman) radius for each solute atom. The model chemistry used for all calculations is B3LYP/6-311++G-(2d,2p).[38] This corresponds to the approximation method that makes use of Becke-style 3-parameter density functional theory[39] with the Lee–Yang–Parr correlation functional.[40] The triple-ζ basis set adds three sizes of s and p functions to the atoms and puts two d and two p functions on heavy atoms and hydrogens, respectively, as well as diffuse functions on both. Therefore, compound I is given 182 basis functions, whereas II and III are given 202 basis functions each. Experimental data used for comparison are taken from the published work of Witanowski et al.[16,22] Relative solvent effects are calculated using the corresponding nuclear shielding in cyclohexane as reference. Direct ($\Delta\sigma_{dir}$) and indirect ($\Delta\sigma_{ind}$) solvent effects are obtained with a slight modification of the method used by Cammi et al.[12] Instead of deriving $\Delta\sigma_{ind}$ from the difference of the PCM-optimized shielding and the PCM shielding of the molecule held at the geometry optimized in vacuo, it is obtained from the shielding calculated in vacuo for a molecule that is geometry-optimized in solution. Thus,

$$\Delta\sigma_{dir} = \sigma_{sol}(R_v) - \sigma_{cyc}(R_v) \quad (1)$$

$$\Delta\sigma_{ind} = \sigma_{vac}(R_s) - \sigma_{vac}(R_{cyc}) \quad (2)$$

where $\sigma_{sol}(R_v)$ is the value of the nuclear shielding computed in solution but with the solute in the geometry optimized in vacuo, and $\sigma_{vac}(R_s)$ is the value of the nuclear shielding in vacuo but with the solute geometry optimized in solution. $\sigma_{cyc}(R_v)$ and $\sigma_{vac}(R_{cyc})$ are the corresponding parameters for calculations with cyclohexane. The percentage contribution of these effects to the total solvation effect is determined in each case. The tensor components ($\sigma_{11,}$ $\sigma_{22,}$ and σ_{33}) of the nitrogen NMR shielding of 1,2,4,5-tetrazine are also calculated to examine the theoretical dependence of each of these principal components on the solvent.

Results and Discussion

The variation of experimental and calculated solvent effects with solvent dielectric constant for 1,2,4,5-tetrazine is shown in Figure 2. It can be seen that the PCM calculations reproduce the main aspects of the experimental outcome: both the sign of the solvent effect and the relative strength. The standard approach of the PCM (without any explicit solvent molecules), as is used here, appears to be a good first step in the theoretical investigation of the effect of solvent on nuclear magnetic shielding. A more favorable agreement between experiment and calculation can be seen for compounds II and III (Figures 3 and 4). The range of theoretical solvent-induced nitrogen shielding variation is quite significant for all three compounds: about 8 parts per million (ppm) for (I); as high as 14 ppm for pyridine-type nitrogens and 8 ppm for pyrrole-type nitrogens in compounds II and III. These values compare well with the experimental data of Witanowski et al.[16,22] The MCSCF calculations of Jaszuński et al.,[23] on the other hand, undervalue the range of solvent effect on the pyridine-type nitrogens of both II and III by a significant amount. It is interesting to note that the observed disparity between calculation and experiment in Figures 2 through 4 is observed only for solvents that are either aromatic (benzene) or capable of forming very strong hydrogen bonds (ethanol, methanol, and water). The magnitude of the shielding due to the ring current in benzene has been calculated by Johnson and Bovey[41] and was found to be as high as +4 ppm in the direction normal to the plane of the ring and −2 ppm along this plane. These translate to aromatic-induced solvent effects of about +0.5 ppm.[41] In the case of solvent-to-solute hydrogen bonding effects, Witanowski et al.[22] have found that pyrrole-type nitrogens exhibit insignificant deshielding upon the formation of a hydrogen bond at a pyridine-type nitrogen as an acceptor. Consequently, the hydrogen-bonded pyridine-type nitrogen becomes more shielded by about +2 to +10 ppm. A gas-phase computation that involves one explicit water molecule hydrogen-bonded to a pyridine-type nitrogen has shown similar trends. In this additional computation, a water molecule is added such that one of its hydrogen atoms lies 1.5 Å from N-3 of 1-Me-1,2,3,4-tetrazole, with all the atoms of the water molecule lying on the same plane as the tetrazole ring,

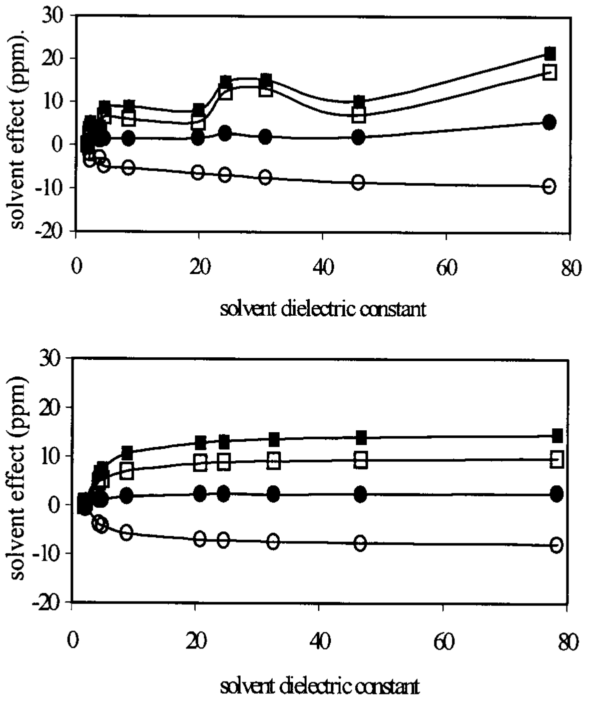


Figure 3. Dependence of experimental (top) and theoretical (bottom) solvent effect on the nuclear magnetic shielding of ^{15}N in 1-Me-1,2,3,4-tetrazole (compound II) with solvent dielectric constant: (○) N1; (●) N2; (■) N3; (□) N4.

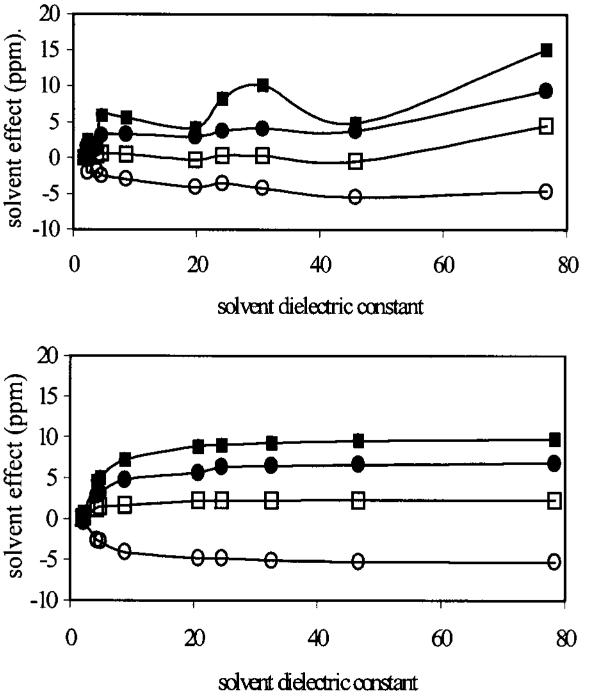


Figure 4. Dependence of experimental (top) and theoretical (bottom) solvent effect on the nuclear magnetic shielding of ^{15}N in 1-Me-1,2,3,5-tetrazole (compound III) with solvent dielectric constant: (○) N1; (●) N2; (■) N3; (□) N5.

TABLE 1: PCM-CSGT Nitrogen NMR Shielding (ppm) for 1,2,4,5-Tetrazine

solvent	ϵ	σ
cyclohexane	2.023	−178.3
carbon tetrachloride	2.228	−177.7
benzene	2.247	−177.7
diethyl ether	4.335	−174.6
chloroform	4.900	−174.1
methylene chloride	8.930	−172.4
acetone	20.70	−171.1
ethanol	24.55	−170.9
methanol	32.63	−170.7
dimethyl sulfoxide	46.70	−170.5
water	78.39	−170.3

and a linear arrangement between N-3 and the OH atoms of water is assumed. This supermolecule calculation fortuitously yields a shielding effect of about 24 ppm, in very good agreement with the observed solvent-induced shift in water. Furthermore, the calculations show that while the pyridine-type N becomes shielded, the pyrrole type N becomes deshielded by about −2 ppm. Thus, it is apparent that for a more accurate prediction of solvent effects on shielding, it is necessary to consider specific solute−solvent interactions by introducing one or several solvent molecules in the calculations.

Table 1 lists the PCM-CSGT nitrogen NMR shieldings calculated for compound I in a range of solvents available in Gaussian 98. The increase in shielding with an increase in ϵ is again consistent with the experimental and Solvaton calculation data of Witanowski et al.[16] Calculated PCM-CSGT shielding data for compounds II and III are given in Tables 2 and 3, respectively. Similar to the nitrogens of I, there is a shielding effect on the pyridine-type nitrogens of II and III with the increasing polarity of the solvent used. The opposite effect is observed for the pyrrole-type nitrogens (N-1). These results are in good agreement with the experimental data of Witanowski et al.[22] The MCSCF data of Jaszuński et al. on N-2 of compound II,[23] however, opposes that of the experiment. Witanowski et al. have attributed these trends to the delocalization of the lone pair electrons of N-1 into the π-electron system of the aromatic ring, as influenced by either solvent polarity or some form of specific solvent-to-solute interaction. The magnitude of the deshielding effect is larger for II, where N-1 is at one end of the chain of four nitrogens, than for III, where N-1 is located within the chain, and the electron-withdrawing effect of N-5 competes with those exerted by N-2 and N-3.[22]

TABLE 2: PCM-CSGT Nitrogen NMR Shielding (ppm) for 1-Me-1,2,3,4-Tetrazole

solvent	ϵ	N(1)	N(2)	N(3)	N(4)
cyclohexane	2.023	5.2	−145.4	−179.0	−104.7
carbon tetrachloride	2.228	4.7	−145.2	−178.0	−104.1
benzene	2.247	4.7	−145.2	−177.9	−104.0
diethyl ether	4.335	1.4	−144.3	−172.3	−100.0
chloroform	4.900	1.0	−144.1	−171.4	−99.5
methylene chloride	8.930	−0.6	−143.6	−168.4	−97.6
acetone	20.70	−1.8	−143.0	−166.1	−96.0
ethanol	24.55	−2.0	−143.0	−165.8	−95.8
methanol	32.63	−2.2	−143.0	−165.3	−95.6
dimethyl sulfoxide	46.70	−2.4	−142.9	−164.9	−95.3
water	78.39	−2.7	−142.9	−164.5	−95.0

TABLE 3: PCM-CSGT Nitrogen NMR Shielding (ppm) for 1-Me-1,2,3,5-Tetrazole

solvent	ϵ	N(1)	N(2)	N(3)	N(5)
cyclohexane	2.023	−48.0	−158.3	−105.8	−74.6
carbon tetrachloride	2.228	−48.3	−157.9	−105.1	−74.3
benzene	2.247	−48.4	−157.8	−105.0	−74.3
diethyl ether	4.335	−50.6	−155.4	−101.2	−73.3
chloroform	4.900	−50.8	−155.1	−100.7	−73.1
methylene chloride	8.930	−52.1	−153.5	−98.5	−72.9
acetone	20.70	−52.7	−152.6	−96.9	−72.4
ethanol	24.55	−52.8	−152.0	−96.8	−72.4
methanol	32.63	−53.0	−151.8	−96.5	−72.3
dimethyl sulfoxide	46.70	−53.2	−151.7	−96.2	−72.3
water	78.39	−53.2	−151.5	−96.0	−72.3

TABLE 4: Values of $\Delta\sigma_{\mathrm{dir}}$ and $\Delta\sigma_{\mathrm{ind}}$ (ppm) Calculated for 1,2,4,5-Tetrazine

solvent	ϵ	$\Delta\sigma_{\mathrm{dir}}$	$\Delta\sigma_{\mathrm{ind}}$
cyclohexane	2.023	0.0	0.0
carbon tetrachloride	2.228	0.6	−0.0
benzene	2.247	0.6	−0.0
diethyl ether	4.335	3.6	−0.0
chloroform	4.900	4.1	−0.0
methylene chloride	8.930	5.7	−0.0
acetone	20.70	7.0	0.0
ethanol	24.55	7.1	0.0
methanol	32.63	7.4	0.0
dimethyl sulfoxide	46.70	7.6	0.0
water	78.39	7.8	0.0

As mentioned earlier, the total solvation effect consists of two distinct contributions: $\Delta\sigma_{\mathrm{dir}}$ and $\Delta\sigma_{\mathrm{ind}}$. The former contribution is directly related to the intensity of the solvent reaction field used in the PCM calculation, whereas the latter is due to the relaxation of the molecular geometry of the solute brought about by the solvent. Tables 4, 5, and 6 list $\Delta\sigma_{\mathrm{dir}}$ and $\Delta\sigma_{\mathrm{ind}}$ calculated for compounds I, II, and III, respectively. Scrutiny of these data reveals that $\Delta\sigma_{\mathrm{dir}}$ is much more consistent with the trend followed by the theoretical and experimental solvent effect as the solvent dielectric constant is increased. A more crucial consequence when only $\Delta\sigma_{\mathrm{ind}}$ is considered is that a shielding effect is obtained for N-1 of both compounds II and III instead of the actual deshielding effect observed in experiment. Moreover, anomalous results are found for N-4 of compound II and N-3 and N-5 of compound III. Thus, in solvent effect studies, it is more advisable to carry out shielding calculations in solution even with a fixed (gas-phase-optimized)

TABLE 5: Values of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ (ppm) Calculated for 1-Me-1,2,3,4-Tetrazole

	$\Delta\sigma_{dir}$				$\Delta\sigma_{ind}$			
ϵ	N(1)	N(2)	N(3)	N(4)	N(1)	N(2)	N(3)	N(4)
2.023	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2.228	−0.7	0.1	1.0	0.8	0.1	−0.0	0.1	−0.1
2.247	−0.7	0.2	1.0	0.8	0.2	0.0	0.1	−0.1
4.335	−4.4	0.7	6.4	5.1	0.4	0.3	0.4	−0.4
4.900	−4.8	0.8	7.2	5.7	0.5	0.3	0.5	−0.4
8.930	−6.6	1.4	10.1	7.8	0.6	0.2	0.7	−0.8
20.70	−8.0	1.7	12.3	9.5	0.8	0.3	0.7	−0.9
24.55	−8.2	1.8	12.6	9.7	0.8	0.3	0.7	−0.9
32.63	−8.4	1.8	13.0	10.0	0.8	0.2	0.8	−1.0
46.70	−8.7	1.7	13.5	10.3	0.8	0.4	0.8	−1.0
78.39	−9.0	1.8	13.9	10.6	0.8	0.4	0.8	−1.0

TABLE 6: Values of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ (ppm) Calculated for 1-Me-1,2,3,5-Tetrazole

	$\Delta\sigma_{dir}$				$\Delta\sigma_{ind}$			
ϵ	N(1)	N(2)	N(3)	N(5)	N(1)	N(2)	N(3)	N(5)
2.023	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2.228	−0.5	0.4	0.7	0.2	0.1	0.0	−0.0	−0.0
2.247	−0.5	0.4	0.8	0.3	0.1	0.0	−0.0	−0.0
4.335	−3.0	2.7	4.7	1.5	0.4	0.0	−0.3	−0.2
4.900	−3.3	3.0	5.2	1.7	0.6	−0.0	−0.4	−0.2
8.930	−4.8	4.5	7.6	2.0	0.7	0.1	−0.6	−0.4
20.70	−5.8	5.5	9.3	2.3	1.0	0.4	−0.8	−0.4
24.55	−6.0	5.7	9.5	2.4	1.0	0.5	−0.8	−0.4
32.63	−6.1	5.8	9.7	2.4	1.0	0.4	−0.8	−0.4
46.70	−6.3	6.0	10.0	2.5	1.0	0.4	−0.8	−0.4
78.39	−6.4	6.2	10.3	2.5	1.1	0.4	−0.9	−0.5

TABLE 7: Contribution (%) of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ to Total Solvent Effect on Nitrogen NMR Shielding of 1,2,4,5-Tetrazine

ϵ	$\Delta\sigma_{dir}$	$\Delta\sigma_{ind}$
2.023	96.3	3.7
2.228	96.3	3.7
2.247	96.3	3.7
4.335	98.4	1.6
4.900	98.6	1.4
8.930	99.4	0.6
20.70	100.0	0.0
24.55	99.8	0.2
32.63	99.7	0.3
46.70	99.6	0.4
78.39	99.6	0.4

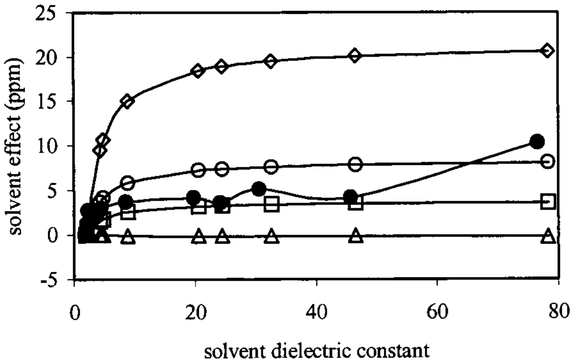


Figure 5. Dependence of the solvent effect on the tensor components, σ_{11} (◇), σ_{22} (□), and σ_{33} (□) of the nuclear magnetic shielding of ^{15}N in 1,2,4,5-tetrazine (compound I) with solvent dielectric constant. The plots for the experimental (●) and theoretical (isotropic) (○) solvent effect are shown for comparison.

TABLE 8: Contribution (%) of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ to Total Solvent Effect on Nitrogen NMR Shielding of 1-Me-1,2,3,4-Tetrazole

	$\Delta\sigma_{dir}$				$\Delta\sigma_{ind}$			
ϵ	N(1)	N(2)	N(3)	N(4)	N(1)	N(2)	N(3)	N(4)
2.023	93.8	99.5	94.8	93.1	6.2	0.5	5.2	6.9
2.228	92.0	99.5	94.8	92.1	8.0	0.5	5.2	7.9
2.247	91.4	97.0	94.8	92.3	8.6	3.0	5.2	7.7
4.335	91.8	83.7	95.2	93.0	8.2	16.3	4.8	7.0
4.900	91.5	83.0	94.8	93.2	8.5	17.0	5.2	6.8
8.930	91.1	86.4	94.7	92.3	8.9	13.6	5.3	7.7
20.70	90.8	84.0	95.3	92.8	9.2	16.0	4.7	7.2
24.55	90.9	84.1	95.3	92.9	9.1	15.9	4.7	7.1
32.63	91.0	86.4	94.9	92.6	9.0	13.6	5.1	7.4
46.70	90.7	81.9	95.1	92.7	9.3	18.1	4.9	7.3
78.39	90.7	82.2	95.2	92.9	9.3	17.8	4.8	7.1

TABLE 9: Contribution (%) of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ to Total Solvent Effect on the Nitrogen NMR Shielding of 1-Me-1,2,3,5-Tetrazole

	$\Delta\sigma_{dir}$				$\Delta\sigma_{ind}$			
ϵ	N(1)	N(2)	N(3)	N(4)	N(1)	N(2)	N(3)	N(4)
2.023	86.6	95.7	92.5	75.6	13.4	4.3	7.5	24.4
2.228	86.6	95.4	93.0	77.2	13.4	4.6	7.0	22.8
2.247	86.7	95.5	93.0	77.2	13.3	4.5	7.0	22.8
4.335	87.6	94.8	94.7	78.6	12.4	5.2	5.3	21.4
4.900	86.8	95.7	94.3	80.1	13.2	4.3	5.7	19.9
8.930	86.8	94.8	94.2	80.9	13.2	5.2	5.8	19.1
20.70	85.5	96.6	94.9	85.4	14.5	3.4	5.1	14.6
24.55	85.5	91.7	94.4	84.4	14.5	8.3	5.6	15.6
32.63	85.8	92.1	94.4	84.0	14.2	7.9	5.6	16.0
46.70	86.0	92.3	94.6	84.0	14.0	7.7	5.4	16.0
78.39	85.4	92.3	94.4	83.9	14.6	7.7	5.6	16.1

solute geometry than to perform shielding computations in vacuo for a solute whose geometry is optimized in solution.

The previous statement becomes more well-argued if we quantify the contribution of $\Delta\sigma_{dir}$ and $\Delta\sigma_{ind}$ to the total solvent effect. Tables 7, 8, and 9 report the percentage of each contribution to the total solvation effect on nitrogen NMR shieldings of the compounds studied. For compound I, $\Delta\sigma_{dir}$ amounts to no less than 96% of the total solvent effect; at least 82% for compound II and 75% for compound III. No significant trend is observed with regard to the dependence of this contribution on the dielectric constant of the solvent or the chemical nature of the nitrogen concerned.

The effect of solvent on the principal components of the shielding tensor for 1,2,4,5-tetrazine is also analyzed and plotted in Figure 5. The solvent has the most influence on the least-shielded component, σ_{11}, which lies parallel to the nitrogen−nitrogen bonds. For example, in water, there is an increase in shielding of σ_{11} by as much as 20 ppm. This is not unexpected because this tensor component is perpendicular to the π-electron system of the aromatic ring that experiences solvent polarization. On the other hand, there appears to be a rather weak deshielding effect on σ_{33}. This tensor component is normal to the ring, as is usually the case for aromatic compounds. The influence of increasing ϵ on σ_{22} is more remarkable because, with the exception of water, it closely parallels that of the experiment, differing by just an average of about 1 ppm. This component lies along the plane of the ring but perpendicular to the nitrogen−nitrogen bonds. Examination of the tensor components gives no new information that would explain certain discrepancies between theoretical and experimental results. However, it is apparent from such analysis that the introduction of explicit solvent molecules in the calculation would give varying results depending on the relative orientation of the solute and solvent molecules used in the calculation. This consideration is important when looking at solvent effects arising from specific solute−solvent interactions.

Conclusions

The present work provided a brief assessment of the reliability of the polarizable continuum model in describing the influence of solvent on nuclear magnetic shielding, in this case, the nitrogen shielding of 1,2,4,5-tetrazine and two isomeric tetrazoles. The results presented show that PCM, in its simplest application, is able to reproduce the key aspects of solvent effect: its magnitude and sign. The approach used, however, does not take into account the consequences of specific solute–solvent interactions. Analyses of direct and indirect contributions to the total solvent effect show that the intensity of the reaction field determines shielding variation more than solute geometry does. This can serve as an important consideration when doing a large number of calculations to investigate solvent effects on nuclear magnetic shielding.

Acknowledgment. This work was supported in part by a CAREER Award from the National Science Foundation under grant CHE-9874424. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

References and Notes

(1) Raynes, W. T.; Buckingham, A. D.; Bernstein, H. J. *J. Chem. Phys.* **1962**, *36*, 3481.

(2) Gruninger, J.; Hameka, H. F. *J. Chem. Phys.* **1968**, *48*, 4878.

(3) Batchelor, J. G. *J. Am. Chem. Soc.* **1975**, *97*, 3410.

(4) Riley, J. P.; Raynes, W. T. *Mol. Phys.* **1976**, *32*, 569.

(5) Sadlej, A. J.; Raynes, W. T. *Mol. Phys.* **1978**, *35*, 101.

(6) Zaucer, M.; Azman, A. *Z. Naturforsch.* **1979**, *34A*, 1279.

(7) Mikkelsen, K. V.; Ågren, H.; Jensen, H. J. Aa.; Helgaker, T. *J. Chem. Phys.* **1988**, *89*, 3086.

(8) Packer, M. J.; Raynes, W. T. *Mol. Phys.* **1990**, *69*, 391.

(9) Augspurger, J.; Pearson, J.; Oldfield, E.; Dykstra, C. E.; Park, K. D.; Schwartz, D. *J. Magn. Reson.* **1992**, *100*, 342.

(10) Mikkelsen, K. V.; Jørgensen, P.; Jensen, H. J. Aa. *J. Chem. Phys.* **1994**, *100*, 6597.

(11) Cammi, R. *J. Chem. Phys.* **1998**, *109*, 3185.

(12) Cammi, R.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1999**, *110*, 7627.

(13) Cammi, R.; Mennucci, B. *J. Chem. Phys.* **1999**, *110*, 9877.

(14) Witanowski, M.; Sicinska, W.; Biernat, S. *J. Magn. Reson.* **1991**, *91*, 289.

(15) Witanowski, M.; Sicinska, W. *J. Magn. Reson.* **1992**, *98*, 109.

(16) Witanowski, M.; Biedrzycka, Z.; Sicinska, W.; Grabowski, Z.; Webb, G. A. *J. Magn. Reson.* **1997**, *124*, 127.

(17) Witanowski, M.; Sicinska, W.; Grabowski, Z.; Webb, G. A. *J. Magn. Reson.* **1993**, *104*, 310.

(18) Witanowski, M.; Sicinska, W.; Biedrzycka, Z.; Webb, G. A. *J. Magn. Reson. A* **1994**, *109*, 177.

(19) Witanowski, M.; Sicinska, W.; Biedrzycka, Z.; Grabowski, Z.; Webb, G. A. *J. Magn. Reson. A* **1995**, *112*, 66.

(20) Witanowski, M.; Biedrzycka, Z.; Sicinska, W.; Grabowski, Z.; Webb, G. A. *J. Magn. Reson. A* **1996**, *120*, 148.

(21) Witanowski, M.; Sicinska, W.; Biedrzycka, Z.; Grabowski, Z.; Webb, G. A. *J. Chem. Soc., Perkin Trans. 2* **1996**, 619.

(22) Witanowski, M.; Biedrzycka, Z.; Sicinska, W.; Grabowski, Z. *J. Magn. Reson.* **1998**, *131*, 54.

(23) Jaszuński, M.; Mikkelsen, K. V.; Rizzo, A.; Witanowski, M. *J. Phys. Chem. A* **2000**, *104*, 1466.

(24) Miertus, S.; Scrocco, E.; Tomasi, J. *Chem. Phys.* **1981**, *55*, 117.

(25) Miertus, S.; Tomasi, J. *Chem. Phys.* **1982**, *65*, 239.

(26) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223.

(27) Ando, I.; Webb, G. A. *Theory of NMR Parameters*; Academic Press: London, 1983.

(28) Marcus, Y. *Chem. Soc. Rev.* **1993**, *22*, 409.

(29) Olivares del Valle, F. J.; Aguilar, M. A.; Tolosa, S. *J. Mol. Struct. (THEOCHEM)* **1993**, *279*, 223.

(30) Tomasi, J.; Persico, M. *J. Comput. Chem.* **1994**, *94*, 2027.

(31) Cramer, C. J.; Truhlar, D. G. *Chem. Rev.* **1999**, *99*, 2161.

(32) Cammi, R.; Cossi, M.; Tomasi, J. *J. Chem. Phys.* **1996**, *104*, 4611.

(33) Zhan, C.-G.; Chipman, D. M. *J. Chem. Phys.* **1999**, *110*, 1611.

(34) Cancès, E.; Mennucci, B.; Tomasi, J. *J. Chem. Phys.* **1997**, *107*, 3032.

(35) Mennucci, B.; Cancès, E.; Tomasi, J. *J. Phys. Chem. B* **1997**, *101*, 10506.

(36) Gaussian 98, Revision A.7. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1998.

(37) Gaussian 94, Revision C.2. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Robb, M. A.; Cheeseman, J. R.; Keith, T.; Petersson, G. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewski, V. G.; Ortiz, J. V.; Foresman, J. B.; Cioslowski, J.; Stefanov, B. B.; Nanayakkara, A.; Challacombe, M.; Peng, C. Y.; Ayala, P. Y.; Chen, W.; Wong, M. W.; Andres, J. L.; Replogle, E. S.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Binkley, J. S.; Defrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, M.; Gonzalez, C.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 1995.

(38) Foresman, J. B.; Frisch, Æ. *Exploring Chemistry with Electronic Structure Methods*, 2nd ed.; Gaussian, Inc.: Pittsburgh, PA, 1996.

(39) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

(40) Lee, C.; Yang, W.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785.

(41) Johnson, C. E.; Bovey, F. A. *J. Chem. Phys.* **1958**, *29*, 1012.