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SOLVENT EFFECT ON ^{14}N NMR SHIELDING OF GLYCINE, SERINE, LEUCINE, AND THREONINE: COMPARISON BETWEEN CHEMICAL SHIFTS AND ENERGY VERSUS DIELECTRIC CONSTANT

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ABSTRACT. The polarizable continuum model (PCM) is employed to describe the system in the condensed phase. The performance of DFT and PCM in describing high order nonlinear mixed electric and magnetic effects in condensed phase are described. In this paper we consider the effect of 10 solvents with a wide range of dielectric constants on 4 amino acids. NMR shielding values (ppm), isotropic and anisotropic effects, energy interaction between solute and solvent, and the effect of hydrogen bond on shielding are described. Direct and indirect solvent effects on shielding are also calculated. 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.

KEY WORDS: Solvent effect, ^{14}N NMR shielding, Solvent-induced shielding, Polarizable continuum model, Amino acids

INTRODUCTION

For the past half century, quantum chemistry has made significant progress in predicting properties of gas phase processes. Theoretical efforts recently have been turning toward solution chemistry. Some progress has been made in developing predictive models for equilibrium and spectroscopic properties of molecules in solution. The advantage of approaches with explicit solvent is that they provide detailed salvation structure enabling one to elucidate specific roles of solvent in reaction mechanism.

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. The polarizable continuum model (PCM) and continues set of gauge transformations (CSGT) method are used to calculate the nitrogen atom NMR shielding of amino acids in a wild range of solvents encompassing a broad spectrum of dielectric constant, ϵ. Direct and indirect solvent effects on shielding are also calculated [1].

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. PCM has proved useful in describing the effects of the solvent on some characteristics of the molecule in solution. All PCM calculations in this report have been performed using this formalism as implemented in Gaussian 98 [2]. Direct effects involve perturbation of the solvent on the electric waved 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 [3]. The PCM cavity is defined by using the Pauling radius for each solute atom. The relative stability of tautomers of amino acids is of fundamental importance to the structure of DNA. The occurrence of rare tautomers has been put forward as a possible mechanism of

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spontaneous mutation [4, 5]. This tautomerization is highly sensitive to environmental effects such as solvent polarity or transition to the gas phase. The solvent dependence of tautomeric equilibria has also been the subject of many experimental studies. Solvents with large dielectric constants favor the more polar tautomers.

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. The solvation effect is taken into account via the self-consistent reaction field (SCRF) method. The solute is placed into a cavity within the solvent. SCRF approaches differ in how they define the cavity and the reaction field. Properties measured in low-pressure gases and those derived from measurements in the liquid phase differ as molecular interactions perturb the intrinsic polarizabilities, in the so-called solvent effect. A dielectric continuum model with the solvated molecule placed in a spherical cavity and surrounded by a linear, homogeneous, polarizable dielectric medium was employed for the description of the condensed phase. The system (usually indicated as the solute) is described as a quantum mechanical charge distribution within a volume, the so-called solute cavity, modelled on the molecular shape of the solute and the environment (or the solvent) as a continuum dielectric. The solute polarizes the dielectric and the dielectric polarization in turn generates an electrostatic field at the solute which modifies the original charge distribution [6].

B3LYP/DFT can perform in the calculation of the magnetizability tensor with respect to other more expensive and complete ab initio approaches, such as complete active space self-consistent field [7]. This is an extremely satisfactory result considering the numerous approximations, e.g. the relatively limited basis set, the in principle unsophisticated treatment of electron correlation, the neglect of vibrational contributions, the uncertainty arising from the neglect of intermolecular interactions in the theoretical treatment and that inherent in the extrapolation made to zero gas density in the experiment.

Solvent can also change the reaction mechanism as seen in the keten-imid [8] cycloaddition in which the two step mechanism is preferred in solution while the concerted mechanism was predicted for the gas phase. In general the combined QM/MM approach [9-12] in conjunction with molecular dynamics or Monte Carlo free-energy simulations would be the best way to provide accurate and detailed picture of reactions in solution.

The PCM model has several weaknesses. In particular it dose not provide any information on the solvent structure. In addition the size and shape of cavity have no rigorous definitions. However, there are also several important advantages. First, one can select a designed level of quantum mechanical theory from a wide range of ab initio molecular orbital (MO) and density functional theory (DFT) levels that are sufficiently accurate for modelling bond breaking and forming processes. Second the reaction coordinate is uniquely defined because solvent effects from the continuum medium are effectively included in the solute Hamiltonian and do not increase the dimensionality of the system. Although these self-consistent reaction field studies provide useful insight, their accuracy is often questionable due to the uncertainty in the cavity size and shape for variable geometry of the reacting system.

EXPERIMENTAL

The ab initio molecular orbital calculations were carried out with the GAUSSIAN 98 [2] program. Geometry optimizations in the gas phase for all four amino acids were performed at the Hartree-fock (HF) level with a locally dense basis set 6-311++G(d, p).The unavailability of PCM-gauge invariant atomic orbital in GAUSSIAN 98 has restricted us to exploit PCM-CSGT in nuclear shielding calculations. A positive solvent effect indicates an increase in nuclear shielding. The model chemistry used for shielding calculations is B3LYP/6-311++G (d, p). This

corresponds to the approximation method that makes use of Becke-Style 3-parameter density functional theory [13] with the Lee-Yang-Paar correlation function [14]. The triple-ξ basis set adds three sizes of S and P functions on heavy atoms and hydrogen, respectively, as well as diffuse functions on both. 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 Manalo *et al.* [1]:

$$\Delta\sigma_{dir} = \sigma_{sol}(R_V) - \sigma_{cyc}(R_V)$$

$$\Delta\sigma_{ind} = \sigma_{vac}(R_S) - \sigma_{vac}(R_{cyc})$$

RESULTS AND DISCUSSION

In Table 1 the effect of solvent on four amino acids is shown. It can be seen that in solvents that have OH group and can form hydrogen bond shielding is decreased (water, methanol, and ethanol) except for thr (threonin) that has an OH and CH_3 group on C^{β} that could produce steric and inductive inhibition for hydrogen bonding with carbonyl group.

Table 1A. The ^{14}N NMR isotropic shielding in different solvents with optimized molecule in vaccum (ppm).

		Isotropic shielding (ppm)			
Solvent	ϵ	gly	ser	leu	thr
Water	78.39	235.926	226.902	218.407	249.417
DMSO	46.8	238.409	230.597	219.302	237.704
Nitromethane	38.2	238.409	230.571	219.313	237.569
Methanol	32.63	235.889	227.214	218.502	248.581
Ethanol	24.55	235.869	227.374	218.552	248.121
Acetone	20.7	238.367	230.447	219.362	236.957
Dichloroethane	10.36	238.297	230.177	219.456	235.688
Dichloromethane	8.93	238.278	230.091	219.483	235.299
THF	7.58	238.254	229.981	219.516	234.811
Aniline	6.89	238.238	229.907	219.537	234.494

Table 1B. The ^{14}N NMR anisotropic shielding in different solvents with optimized molecule in vaccum (ppm).

		Anisotropic shielding (ppm)			
Solvent	ϵ	gly	ser	leu	thr
Water	78.39	51.689	55.094	63.909	60.597
DMSO	46.8	43.702	48.335	38.939	51.643
Nitromethane	38.2	49.137	48.333	38.858	51.639
Methanol	32.63	51.339	54.517	62.206	60.118
Ethanol	24.55	51.158	54.222	61.289	59.864
Acetone	20.7	49.112	48.327	38.496	51.618
Dichloroethane	10.36	49.093	48.315	37.775	51.567
Dichloromethane	8.93	49.098	48.312	37.562	51.549
THF	7.58	49.106	48.309	37.299	51.526
Aniline	6.89	49.113	48.306	37.132	51.511

Table 1C. The ^{14}N NMR η shielding in different solvents with optimized molecule in vaccum (ppm).

		η shielding (ppm)			
Solvent	ϵ	gly	ser	leu	thr
Water	78	-0.077	0.304	1.383	0.505
DMSO	47	-0.252	0.281	2.013	0.531
Nitromethane	38	-0.252	0.282	2.024	0.532
Methanol	33	-0.097	0.291	1.427	0.517
Ethanol	25	-0.108	0.284	1.451	0.523
Acetone	21	-0.261	0.287	2.071	0.541
Dichloroethane	10	-0.271	0.298	2.172	0.555
Dichloromethane	8.9	-0.279	0.301	2.203	0.561
THF	7.6	-0.283	0.306	2.243	0.565
Aniline	6.9	-0.286	0.309	2.269	0.568

Table 2A. The ^{14}N NMR isotropic shielding in vaccum with optimiezd molecule in different solvents (ppm).

		Isotropic shielding (ppm)			
Solvent	ϵ	gly	ser	leu	thr
Water	78.39	226.726	222.015	207.237	210.141
DMSO	46.8	226.73	222.016	207.233	210.138
Nitromethane	38.2	226.725	222.016	207.233	210.138
Methanol	32.68	226.725	222.016	207.239	210.138
Ethanol	24.55	226.725	222.016	207.238	210.138
Acetone	20.7	226.725	222.016	207.237	210.138
Dichloroethane	10.36	226.725	222.016	207.241	210.138
Dichloromethane	8.93	226.725	222.016	207.236	210.138
THF	7.58	226.725	222.016	207.237	210.138
Anilline	6.89	226.725	222.016	207.237	210.138

Table 2B. The ^{14}N NMR anisotropic shielding in vaccum with optimized molecule in different solvents (ppm).

		Anisotropic shielding (ppm)			
Solvent	ϵ	gly	ser	leu	thr
Water	78.39	39.612	44.123	43.131	36.008
DMSO	46.80	39.614	44.126	43.124	36.001
Nitromethane	38.20	39.614	44.125	43.128	36.004
Methanol	32.68	39.614	44.125	43.131	36.004
Ethanol	24.55	39.614	44.125	43.132	36.004
Acetone	20.70	39.614	44.125	43.131	36.004
Dichloroethane	10.36	39.614	44.125	43.132	36.004
Dichloromethane	8.93	39.614	44.125	43.132	36.004
THF	7.58	39.614	44.125	43.131	36.004
Anilline	6.89	39.614	44.125	43.131	36.004

In anisotropic effect this trend is inversed that means for solvents consist OH group greater shielding values observe. In solvent effect studies, it is more advisable to carry out shielding calculations in solution even with a fixed (gas-phase-optimized) solute geometry than to perform shielding computations in vacuo for a solute whose geometry is optimized in solution. This matter can be seen from Table 3 that the mean relaxation of solute geometry under the

influence of the solvent cannot be a suitable scale for investigation of solvent effect. The data in Table 4 indicate irregular variations concerning relative energy versus dielectric constant where the energy variations are calculated as the result of two levels of regular changes: a) energy variations with solvents that have no hydrogen bonded to oxygen and b) energy variations with solvents that have hydrogen bonded to oxygen. The factors such as polarizability and dipole moment can generate deviations. It is apparent that for a more accurate prediction of solvent effects on shielding and relative stabilities, it is necessary to consider specific solute-solvent interactions by introducing are or several solvent molecules in the calculations.

Table 3. Values of Δσ dir and Δσ ind (ppm) calculated for 4 amino acids.

Δσ dir				Δσ ind			
gly	ser	leu	thr	gly	ser	leu	thr
-2.058	-1.222	-1.484	21.669	3.50E-03	1.20E-03	0	0
42.511	2.473	-0.585	9.956	0	1.90E-03	-3.60E-03	-2.00E-04
0.425	2.446	-0.578	9.821	0	2.20E-03	-4.00E-03	0
-2.095	-0.909	-1.388	20.833	0	2.20E-03	2.20E-03	0
-2.115	-0.749	-1.338	20.371	0	2.20E-03	1.10E-03	0
0.383	2.323	-0.529	9.2084	0	2.20E-03	0.00E+00	0
0.313	2.053	-0.435	7.941	0	2.20E-03	3.20E-03	0
0.294	1.968	-0.407	4.552	0	2.20E-03	-6.00E-04	0
0.271	1.857	-0.374	7.062	0	2.20E-03	0.00E+00	0
0.254	1.783	-0.353	6.745	0	2.20E-03	0.00E+00	0

Table 4. Solvent effect on energy values (kJ/mol) of four amino acids with respect to gas phase value.

Solvent	ϵ	gly	ser	leu	thr
Water	78.39	-1195.103	-2631.832	-1855.757	-2635.659
Dmso	46.8	-1195.063	-2631.695	-1855.713	-2635.541
Nitromethane	38.2	-1195.061	-2631.689	-1855.711	-2633.239
Methanol	32.63	-1195.111	-2631.804	-1855.777	-2633.379
Ethanol	24.55	-1195.099	-2631.779	-1855.759	-2633.354
Acetone	20.7	-1195.063	-2631.697	-1855.721	-2633.246
Dichloroethane	10.36	-1195.058	-2631.687	-1855.712	-2633.232
Dichloromthane	8.93	-1195.069	-2631.713	-1855.731	-2633.258
THF	7.58	-1195.054	-2631.675	-1855.709	-2633.227
Anillin	6.89	-1195.027	-2631.623	-1855.667	-2633.172
Cyclohexane	2.023	-1195.076	-2496.231	-1855.762	-2633.279

CONCLUSIONS

The present work provides a brief assessment of the reliability of the polarizable continuum model in describing the influence of solvents on nuclear magnetic shielding for amino acids. The approach used however does not take into account the consequence of specific solute-solvent interactions. We can discuss the effect of variable solvent on amino acids and whenever special reaction must be done, for example, synthesis of a kind of protein in a particular solvent, reaction of proteins with other molecules in certain type of solvent, hydrolysis of protein, etc. these information are useful.

REFERENCES

1. Manalo, M.; Cammi, R. *J. Phys. Chem.* **2000**, A, 104, 9600.
2. 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 98*, Revision A.7, Gaussian, Inc.: Pittsburgh PA; **1998**.
3. Fazaeli, R; Monajjemi, M. *J. Mol. Struct. (Theochem)* **2002,** 581, 51.
4. Saenger, W. *Priciples of Nucleic Acid Structure*, Springer: New York; **1984**.
5. Blackborn, G.M. *Nucleic Acids in Chemistry and Biology*, Oxford University Press: Oxford; **1996**.
6. Tomasi, J; Cammi, R. *J. Chem. Phys.* **2003**, 118, 10712.
7. Tomasi, J; Cammi, R. *Chem. Phys. Lett*. **2001**, 346, 251.
8. Assfeld, X; Sordo, J.A. *J. Mol. Struct. (Theochem)* **1993**, 106, 193.
9. Gao, J. in *Reviews in Computational Chemistry*, Vol. 7, Lipkowitz, K.B.; Boyd, D.B. (Eds.); VCH: New York; **1996**; p 119.
10. Singh, U.C.; Kollman, P.A. *J. Comput. Chem*. **1986**, 7, 718.
11. Field, M.J. in *Computer Simulation of Biomolecular Systems: Theoretical and Experimental Applications*, Vol. 2, van Gunsteren, W.F.; Weiner, P.K.; Wilkinson, A.J. (Eds.); ESCOM: Leiden; **1993**; p 82.
12. Field, J.J.; Bash, P.A.; Karplus, M. *J. Comp. Chem.* **1990**, 11, 700.
13. Becke, A.D. *J. Chem. Phys.* **1993**, 98, 5648.
14. Lee, C.; Yang, W.; Parr, R.G. *Phys. Rev*. **1998**, B37, 785.