30 June 1995

ELSEVIER

Chemical Physics Letters 240 (1995) 253–260

CHEMICAL PHYSICS LETTERS

A new method for incorporating solvent effect into the classical, ab initio molecular orbital and density functional theory frameworks for arbitrary shape cavity

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Received 29 December 1994; in final form 3 February 1995

Abstract

A new method for calculating the solvation energy of an arbitrary shape solute is presented. In this method, the solvent is treated as a homogeneous dielectric medium with a cavity. The solvation energy is presented in the Hartree–Fock–Roothaan form, which can be incorporated into both molecular orbital and density functional theories, as well as in the classical theory using the distributed monopole approach. We found that this approach yields on the average of 10% additional CPU time compared to the gas-phase calculations and an accuracy of better than 2.0 kcal/mol for neutral polar solutes but somewhat larger for ions.

1. Introduction

Incorporating solvent effect into molecular orbital or density functional theory has recently been receiving much attention due to its importance in understanding mechanisms of enzymatic and chemical reactions in solution. Although much progress has been achieved in the semiempirical molecular orbital and classical approach, in this Letter, we focus our discussion on the developments of solvation models within the framework of either ab initio molecular orbital (MO) or density functional theory (DFT). There exist two different approaches for including solvent effect in quantum mechanical calculations [1]. One is the supermolecule approach where a finite number of solvent molecules are treated explicitly. The other is to utilize the dielectric continuum model to represent solvent electrostatic behavior by a single parameter, namely the dielectric constant ϵ. Within the dielectric continuum approach, only few methods existed for calculating solvation energy for general shape solute at an ab initio level [2–16] [2]. In particular, the polarizable continuum model (PCM) by Tomasi and co-workers [7] has been quite successful in studying many phenomena and properties of solvated systems in *arbitrary shape cavities*. Recent attempts [2,5,8] to incorporate solvent effect within the Poisson–Boltzmann formalism into density functional theory (DFT/PB) have been reported and the results are quite promising.

The above ab initio quantum mechanical methods

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[2] For reviews and more references see Refs. [17,18].

SSDI 0009-2614(95)00541-2

for calculating solvation energy share one common feature. That is the coupled iterative procedure for converging the SCF wavefunction in the presence of the solvent reaction field. That means the unperturbed (gas-phase) Hamiltonian was first solved. This wavefunction is then used to calculate the solvent reaction field by either solving the Poisson or Poisson–Boltzmann equation by the boundary element or finite difference method. The calculated solvent reaction field is then used as a perturbation for calculating a new wavefunction and then a new reaction field. The procedure is repeated until the solvent field or the total energy is converged. The nature of this coupled iterative procedure warrants that computational demand for calculating solvation energy either at the HF or DFT level will be several times more expensive compared to gas-phase calculations. Hoshi et al. [11] have proposed a different polarizable continuum model for an inhomogeneous dielectric medium, which can be directly incorporated into the molecular orbital theory and does not involve such coupled iterative procedure. However, practical implementation of this method has recently been reported only at the semiempirical MO level [19].

In this Letter, we present a new approach for incorporating solvent effect for an arbitrary shape solute into the molecular orbital or density functional theory. This work is motivated by the previous semiempirical MO model of Klamt and Schüürmann [20] which is based on a screening conductor theory and where the solute electrostatic potential is modeled by a distributed multipole method. The main advantage of the present method is that the solvent reaction field is included directly in the SCF procedure, and hence the solute electron density distribution and the solvent reaction field are converged simultaneously. This reduces the computational demand significantly. We have implemented this method so far into the HF and nonlocal DFT levels of theory. To check the consistency of our quantum mechanical results for solvation energies of 18 anions, 17 cations and 17 polar neutral molecules, we also present results from the classical treatment of our method within the distributed monopole approach. We found that the present method can provide comparable accuracy in solvation energy with the PCM model. This accuracy level, however, can be further improved by optimizing the cavity size.

2. Theory

Consider a molecule with the charge density

$$\sum_i z_i \delta(\boldsymbol{r} - \boldsymbol{R}_i) - \rho(\boldsymbol{r}) \tag{1}$$

situated inside the arbitrary shape cavity conductor. Here z_i and $\boldsymbol{R}_i$ are values and positions of N nuclear charges, and $\rho(\boldsymbol{r})$ is electronic density. The solvent reaction field is represented by the charge density $\sigma(\boldsymbol{r})$ on the surface (S) of the cavity such that the total electrostatic potential on the surface is zero

$$\sum_i \frac{z_i}{|\boldsymbol{r} - \boldsymbol{R}_i|} - \int_V \frac{\rho(\boldsymbol{r}')}{|\boldsymbol{r} - \boldsymbol{r}'|}\, \mathrm{d}^3 r' + \int_S \frac{\sigma(\boldsymbol{r}')}{|\boldsymbol{r} - \boldsymbol{r}'|}\, \mathrm{d}^2 r' = 0, \tag{2}$$

where $\boldsymbol{r}$ is on S. In the present study, the cavity boundary is approximated by M surface elements (tesserae with areas S_u) by a boundary element method. Surface density at each tessera is then approximated as a point charge, $\{q_u\}$, located at the center of that tessera, $\{\boldsymbol{t}_u\}$. From the above approximations, we can define the following matrix elements [20]:

$$A_{uv} = \frac{1}{S_u S_v} \int_{S_u} \int_{S_v} \frac{1}{|\boldsymbol{r} - \boldsymbol{r}'|}\, \mathrm{d}s\, \mathrm{d}s'$$

$$\approx \frac{1}{|\boldsymbol{t}_u - \boldsymbol{t}_v|}, \quad \text{for } u \neq v, \tag{3a}$$

$$A_{uu} = 1.07 \sqrt{\frac{4\pi}{S_u}}, \tag{3b}$$

$$B_{ui} = \frac{1}{S_u} \int_{S_u} \frac{1}{|\boldsymbol{r} - \boldsymbol{R}_i|}\, \mathrm{d}s \approx \frac{1}{|\boldsymbol{t}_u - \boldsymbol{R}_i|}, \tag{4}$$

$$c_u = -\frac{1}{S_u} \int_V \int_{S_u} \frac{\rho(\boldsymbol{r})}{|\boldsymbol{r} - \boldsymbol{r}'|}\, \mathrm{d}^2 r'\, \mathrm{d}^3 r$$

$$\approx -\int \frac{\rho(\boldsymbol{r})}{|\boldsymbol{r} - \boldsymbol{t}_u|}\, \mathrm{d}^3 r, \tag{5}$$

and Eq. (2) yields a solution

$$\boldsymbol{q}^0 = -\mathbf{A}^{-1}(\mathbf{B}z + \mathbf{c}), \tag{6}$$

where $\boldsymbol{q}^0$ and z are the vectors of surface and nuclear charges respectively; $\mathbf{A}$, $\mathbf{B}$, and $\mathbf{c}$ are $M \times M$,

$M \times N$, and $M \times 1$ matrices defined above. In the case of a dielectric continuum, the *total* surface charge is determined by scaling the screening conductor total surface charge by a factor of $f = (\epsilon - 1)/\epsilon$ according to the Gauss theorem. In this work, we adopt the same scaling factor for the surface charge distribution,

$$\mathbf{q} = \frac{(\epsilon - 1)}{\epsilon}\mathbf{q}^0 = -f\mathbf{A}^{-1}(\mathbf{B}z + \mathbf{c}). \tag{7}$$

Alternatively, these surface charges can be determined by variationally minimizing the solvation energy

$$E_s(\mathbf{q}) = z^\dagger \mathbf{B}^\dagger \mathbf{q} + \mathbf{c}^\dagger \mathbf{q} + \frac{1}{2f}\mathbf{q}^\dagger \mathbf{A}\mathbf{q}, \tag{8}$$

(the dagger denotes matrix transposition) with respect to $\mathbf{q}$ (see also Ref. [20]).

Such scaling would yield error of order ϵ^{-1} in the solvation energy. For aqueous solution, the error is about 1% in the solvation energy, which is comparable to or less than errors from other sources such as the boundary element approximation and the uncertainty in atomic radii. In a separate study [21], we showed that surface charges determined from Eqs. (6) and (7) converge much faster with respect to the number of surface elements M than surface charges calculated from the normal component of the total electric field on the boundary as adopted in the PCM model. Due to this rapid convergence, our method requires several thousand times less CPU time to reach the same accuracy in $\mathbf{q}$ and E_s than the PCM model, and also it can give reasonably accurate solvation energy for a solvent with a dielectric constant as low as 20.

From the formula

$$E = E_0 + E_S + E_{n-n} \tag{9}$$

for the total energy of the solute in a dielectric medium, where E_0 is the total electronic energy of the solute, E_{n-n} is the nuclear–nuclear repulsion term, we can derive the Fock matrix elements for a system in a dielectric medium. In particular,

$$F_{\mu\nu} = \frac{\partial E}{\partial P_{\mu\nu}} = F^0_{\mu\nu} - f\left(z^\dagger \mathbf{B}^\dagger \mathbf{A}^{-1} \frac{\partial \mathbf{c}}{\partial P_{\mu\nu}} + \mathbf{c}^\dagger \mathbf{A}^{-1} \frac{\partial \mathbf{c}}{\partial P_{\mu\nu}} \right), \tag{10}$$

where $F^0_{\mu\nu}$ is the gas-phase Fock matrix element,

$$\frac{\partial \mathbf{c}}{\partial P_{\mu\nu}} = \frac{\partial}{\partial P_{\mu\nu}}\left(\sum_{\mu\nu} P_{\mu\nu} L^u_{\mu\nu} \right) = \mathbf{L}_{\mu\nu}, \tag{11}$$

$P_{\mu\nu}$ is the density matrix element, and

$$L^u_{\mu\nu} = -\left\langle \mu \left| \frac{1}{\boldsymbol{r} - \boldsymbol{t}_u} \right| \nu \right\rangle. \tag{12}$$

Thus,

$$H^S_{\mu\nu} = -fz^\dagger \mathbf{B}^\dagger \mathbf{A}^{-1} \mathbf{L}_{\mu\nu} \tag{13}$$

and

$$G^S_{\mu\nu} = -f\mathbf{c}^\dagger \mathbf{A}^{-1} \mathbf{L}_{\mu\nu} \tag{14}$$

are the solvent contributions to the one and two electron terms of the Fock matrix, respectively. The total electrostatic energy of the whole system (solute + surface charges) is then given by

$$E = \tfrac{1}{2}\sum_{\mu\nu} P_{\mu\nu}(H_{\mu\nu} + G_{\mu\nu}) - \tfrac{1}{2} fz^\dagger \mathbf{B}^\dagger \mathbf{A}^{-1} \mathbf{B}z + E_{n-n}, \tag{15}$$

and the free energy of solvation can be approximately calculated as

$$\Delta G_S = (E + \Delta G_{CD}) - E^0, \tag{16}$$

where E^0 is the total energy of the molecule in vacuum, and ΔG_{CD} is the nonelectrostatic contribution (dispersion and cavity formation terms). In this study, we estimated the dispersion and cavity contributions, ΔG_{CD}, to the free energy of hydration from a linear interpolation of the free energies of hydration for linear-chain alkanes as a function of surface area (A),

$$\Delta G_{CD}(\text{kcal/mol}) = 1.321 + 0.0067639A(\text{Å}^2). \tag{17}$$

This approach is similar to that in the previous study by Sitkoff, Sharp and Honig [22].

We have implemented the present solvation model into both the MO theory at the HF level and the nonlocal DFT method by modifying the GAUSSIAN 92/DFT [23] program. However our implementation also allows solvation energy to be calculated from other ab initio methods available within the GAUSSIAN 92/DFT program such as the MPn, CCSD, and CI methods.

For classical treatment of the present method, the gas-phase solute electrostatic potential is represented

by a set of partial charges located at the nuclei. In this study, these partial charges were calculated by using the CHELPG [24] method. The classical electrostatic solvation energy is then equal to the second term in Eq. (16), where the nuclear charge vector is replaced by the partial charge vector.

3. Computational details

To check the accuracy of the present method, we have calculated free energies of hydration for 17 anions, 18 cations and 17 polar neutral molecules. In this study, we used the solvent excluding surface [25] with the solvent sphere of radius 1.4 Å to define the cavity boundary. The solvent excluding surface has been found to give more accurate correlations between thermodynamic properties of solvated systems and their cavity size [26]. We used the program GEPOL93 [27] to generate surface elements with 60 points per each atomic sphere for solvation calculations. The atomic radii used to define the cavity are 1.16 Å for hydrogen, 1.5 Å for hydrogen-bonding nitrogen, 2.2 Å for non-hydrogen-bonding nitrogen, 1.4 Å for oxygen, 2.3 Å for carbon, 1.7 Å for aromatic carbon, 1.97 Å for sulfur, 2.35 Å for phosphorus, 1.423 Å for fluorine, and 1.937 Å for chlorine. These radii are modified slightly from those of Rashin et al. [8], though they were not optimized for the present solvation model in this study. Thus, we can further improve the accuracy of the present solvation model by optimizing the atomic radii. Such step is currently under investigation in our lab.

Quantum mechanical calculations of dielectric screening energies were carried out at both the HF and nonlocal DFT levels. For DFT calculations, we used the combinations of the Becke's three-parameter exchange [28] and Lee–Yang–Parr correlation [29] (B3LYP) functionals. Geometries of all molecules were optimized at the HF/6-31G* level. Partial charges used in classical calculations of hydration energy were also calculated at this level.

4. Results and discussion

4.1. Neutral molecules

Calculated hydration energies for 17 polar molecules with different functional groups are listed in Table 1 with available experimental data [30,31]. Correlation plot between the calculated and experimental results is shown in Fig. 1. Also shown in Fig. 1 are hydration energies calculated from the PCM self-consistent reaction field (SCRF)/6-31G* level with optimized cavity size for that model [33]. Notice that our DFT results yield a good agreement with experimental data and about the same level of accuracy as the optimum cavity size PCM model. The HF hydration energies are consistently too low by about 1 kcal/mol. The RMS differences between the present classical, HF and B3LYP results for hydration energy and the experimental data are within the uncertainty of ±2 kcal/mol. Furthermore, the dipole moment of water in aqueous solution is predicted to be 2.48 D at the B3LYP level as compared to the experimental value of 2.4 D. The consistency between classical and quantum mechanical treatments of our solvation model as well as their accuracy are particularly encouraging. It raises new possibilities for studying properties of solvated biologi-

Table 1
Calculated and experimental free energies of hydration (kcal/mol) for neutral molecules [a]

Compound	ΔG_{CD}	ΔG_S^C	ΔG_S^{HF}	ΔG_S^{B3LYP}	ΔG_S^{exp}
HF	1.52	−5.7	−7.2	−6.2	−5.6
H_2O	1.54	−8.8	−10.5	−9.4	−6.3
NH_3	1.59	−6.9	−7.7	−7.1	−4.3
CH_3Cl	1.87	−0.2	−1.1	−0.7	−0.6
CH_3OH	1.80	−4.4	−5.5	−4.5	−5.1
CH_3SH	1.89	−0.5	−2.3	−2.2	−1.2
CH_3CN	1.92	−4.6	−5.6	−4.7	−3.9
CH_3NH_2	1.83	−3.8	−4.8	−4.2	−4.6
CH_3COOH	1.95	−8.0	−8.5	−6.7	−6.7
CH_3OCH_3	2.01	−0.4	−1.7	−0.9	−1.9
CH_3CONH_2	1.97	−9.7	−11.7	−9.6	−9.7
CH_3COCH_3	2.07	−4.1	−5.1	−3.4	−3.0
CH_3COOCH_3	2.14	−4.3	−5.0	−3.4	−3.3
C_5H_5N	2.00	−4.2	−6.3	−4.7	−4.7
C_6H_5OH	2.09	−7.3	−9.0	−7.2	−6.6
HPO_3	1.84	−11.9	−13.7	−8.9	−18.6 [b]
$H_4P_2O_7$	2.27	−34.8	−36.4	−30.7	−20.0 [b]
RMS difference [c]		1.2	2.0	1.1	

[a] ΔG_{CD} stands for cavity formation and dispersion terms. The superscript C on the ΔG_S term is for classical, HF for Hartree–Fock and B3LYP for the nonlocal density functional method. Experimental data (expt) are from Refs. [30,31].
[b] Calculated at SCRF HF/6-311++G** level [32].
[c] With respect to experimental data only.

cal systems such as to calculate free energy of solvation for large biological systems or to reduce the number of water molecules required to completely solvate the system and bypass the periodic boundary conditions in classical molecular dynamics simulations.

4.2. Ions

Calculated and experimental hydration energies for 17 cations and for 18 anions are listed in Tables 2 and 3, respectively. The correlation plots between calculated and experimental data [34] are shown in Fig. 2 for cations and in Fig. 3 for anions, respectively. These results indicate that the present solvation model can provide comparable accuracy with the optimum cavity-size SCRF/PCM method [35]. Quantitatively, the RMS differences between the calculated and experimental solvation energies for ions are larger compared to the neutral case, in particular, ranging from 3.4 to 4.4 kcal/mol for cations and from 5.3 to 8.4 kcal/mol for molecular anions. Such large differences are also observed for other solvation models. For cations, classical, HF and B3LYP solvation methods yield correct trends in solvation energies of different methyl substituted cations. This is quite encouraging, though larger differences with experimental data were found for H_3O^+ and its substituted ions as compared to those of NH_4^+, PH_4^+, SH_3^+ and their substituted ions. Such differences are due to the uncertainty in the cavity size. The present results for atomic anions are of particular interest. The classical approach grossly overestimates the hydration energies of atomic anions whereas the quantum mechanical approach shows strong dependence on the basis set used. For instance, adding diffuse functions allows the solute electrons to move outside the cavity, consequently, it lowers the solvation energy. The basis set dependent effects had also been observed in previous studies [8,35] and require more investigation.

Table 2
Calculated and experimental free energies of hydration (kcal/mol) for molecular cations [a]

Compound	ΔG_{CD}	ΔG_S^C	ΔG_S^{HF}	ΔG_S^{B3LYP}	ΔG_S^{exp}
NH_4^+	1.73	−74.1	−74.6	−74.5	−77
$MeNH_3^+$	1.90	−65.0	−66.7	−66.8	−68
$Me_2NH_2^+$	2.05	−58.9	−60.7	−60.7	−61
Me_3NH^+	2.18	−54.0	−55.7	−55.8	−57
$MeCONH_3^+$	2.05	−66.1	−69.0	−67.0	−64
$C_6H_5NH_3^+$	2.20	−58.7	−64.3	−63.2	−66
PH_4^+	1.80	−67.6	−69.6	−69.8	−71
$MePH_3^+$	1.97	−60.4	−62.7	−62.4	−64
$Me_2PH_2^+$	2.13	−55.2	−57.3	−56.8	−55
Me_3PH^+	2.28	−51.6	−53.3	−52.6	−50
H_3O^+	1.58	−96.1	−98.5	−98.5	−102
$MeOH_2^+$	1.83	−73.8	−76.4	−77.0	−83
Me_2OH^+	2.02	−60.9	−62.7	−62.9	−68
$C_6H_5OH_2^+$	2.12	−68.3	−76.8	−76.0	−67
SH_3^+	1.69	−81.7	−86.2	−85.8	−85
$MeSH_2^+$	1.91	−66.9	−71.2	−70.9	−72
Me_2SH^+	2.09	−57.2	−60.8	−60.4	−59
RMS difference		4.4	3.8	3.4	

[a] Abbreviations are the same as for Table 1. Experimental data are from Ref. [34]

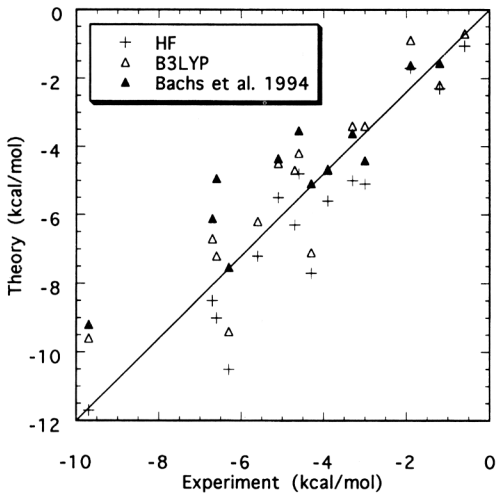

Fig. 1. Comparison between calculated and experimental free energies of hydration for neutral molecules. Bachs et al. 1994 is Ref. [33].

4.3. Computational demands

Since solvent effect is included directly in the Fock matrix, the CPU time required to converge the solvation energy calculation using the present method is substantially less than that using the coupled iterative procedure. In fact, we found that on the average

Table 3
Calculated and experimental free energies of hydration (kcal/mol) for atomic and molecular anions [a]

Compound	ΔG_{CD}	ΔG_S^C	ΔG_S^{HF}	ΔG_S^{B3LYP}	ΔG_S^{exp}
atomic anions					
H^-	1.43	−139.9	−111.3	−111.7	−87
(6-31 + G*)			−80.4	−78.1	
F^-	1.49	−113.7	−111.1	−111.1	−105
(6-31 + G*)			−102.0	−97.7	
Cl^-	1.64	−83.0	−77.4	−77.6	−75
(6-31 + G*)			−73.0	−71.0	
molecular anions					
OH^-	1.51	−118.2	−113.8	−112.1	−104
SH^-	1.66	−82.1	−75.6	−75.9	−74
NH_2^-	1.56	−110.9	−103.6	−102.0	−93
PH_2^-	1.80	−67.9	−65.2	−65.5	−65
HO_2^-	1.60	−106.0	−101.4	−101.5	−99
NO_2^-	1.76	−76.4	−75.3	−73.7	−70
N_3^-	1.75	−78.2	−72.7	−72.5	−72
HC_2^-	1.80	−77.7	−77.3	−76.8	−71
CH_3O^-	1.78	−83.0	−87.7	−78.5	−93
CH_3S^-	1.89	−75.2	−74.0	−73.6	−77
NO_3^-	1.77	−75.4	−71.1	−70.7	−63
CH_2CN^-	1.85	−74.1	−69.5	−68.7	−73
$CH_3CO_2^-$	1.94	−78.3	−77.2	−74.4	−75
$CH_3COCH_2^-$	2.00	−76.7	−74.2	−72.1	−79
$C_6H_5O^-$	2.07	−72.0	−71.0	−66.0	−70
RMS difference [b]		8.4	5.3	6.2	

[a] Abbreviations are the same as in Table 1. For atomic anions results obtained with the 6-31 + G* basis set are also presented. Experimental data are from Ref. [34].
[b] Only for molecular anions.

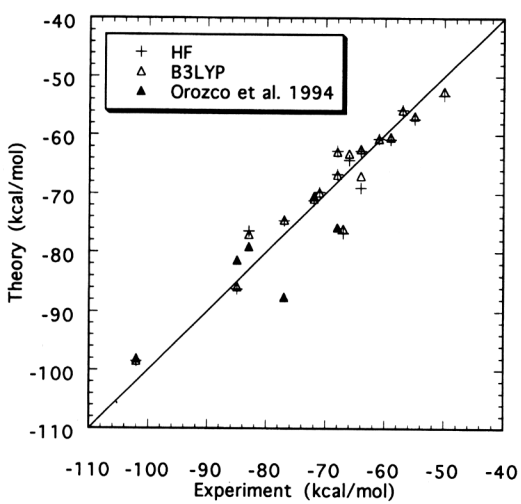

Fig. 2. Comparison between calculated and experimental free energies of hydration for cations. Orozco et al. 1994 is Ref. [35].

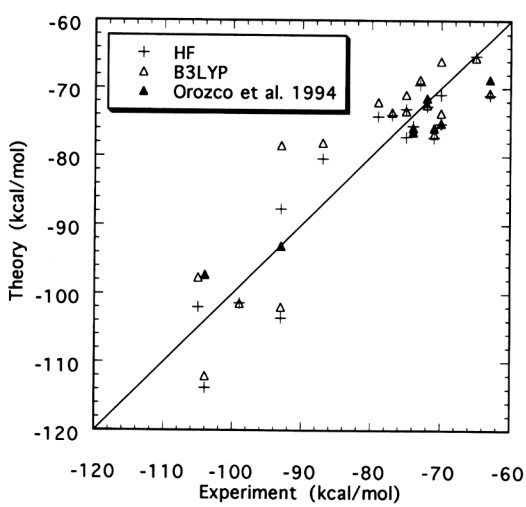

Fig. 3. Comparison between calculated and experimental free energies of hydration for anions. Orozco et al. 1994 is Ref. [35].

of all test cases, the solvation energy calculations are about 10% longer in CPU time compared to the gas-phase calculations. Due to the localizing electric field created by the surface charges, solute wavefunction sometimes converges faster (with a smaller number of SCF cycles) than if it is in vacuum. As a result, we found that calculations for solvated molecules sometimes required less CPU time that that for free molecules.

5. Conclusion

We have introduced a new approach for incorporating solvent effects into the classical, ab initio molecular orbital and nonlocal density functional theory frameworks. The present method can provide accurate solvation energy for systems in a dielectric medium with a high dielectric constant such as water and is in comparable accuracy with the well-known PCM method though computational demand is significantly less. Hydration energies for a number of ions and neutral polar molecules calculated at the classical, HF and B3LYP levels of theory are in good agreement with experimental data. The results so far are very encouraging, however, more work is required. In particular, the effects of basis set and different DFT functionals on the solvation energy are currently under investigation. In addition, optimization of the cavity size to improve the accuracy of the present method as well as implementation of analytical gradients to study the solvent effects on the structure and spectroscopic properties of a solute in aqueous environment, and incorporation of more accurate treatments for the dispersion and cavity formation terms are also being developed in our lab.

Acknowledgement

This work is supported by the National Science Foundation through a Young Investigator Award to TNT. TNT would like to thank Dr. Jack Simons for helpful discussion and Dr. J.L. Pascaul-Ahuir for assistance with the GEPOL93 program.

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