Accurate First Principles Calculation of Molecular Charge Distributions and Solvation Energies from Ab Initio Quantum Mechanics and Continuum Dielectric Theory

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Abstract: In this paper, we combine high-level ab initio quantum chemical calculations with a continuum description of the solvent to obtain accurate solvation free energies of organic solutes in water. By using correlated wave functions at the generalized valence bond/perfect pairing (GVB-PP) level, we are able to efficiently produce accurate gas-phase charge distributions. These are then used to obtain solvation energies in a self-consistent formalism which cycles through quantum chemical calculations in the solvent reaction field and continuum electrostatic calculations utilizing polarized solute charges. An average error of 0.6 kcal/mol for solvation energies is obtained for 29 molecules. A systematic discrepancy between theory and experiment is obtained for the difference in solvation free energy between several methylated and unmethylated primary amines and amides. This poses a major puzzle in theoretical modeling of solvation effects.

I. Introduction

The determination of molecular structure, energetics, and charge distributions in solution is fundamental to the application of molecular modeling methods to realistic chemical systems. Potential energy functions are frequently parameterized against solution properties or are fit to gas-phase quantum mechanical calculations. However, the change in molecular charge distribution in going from the gas phase to solution has not until recently been taken into account in treatments of solvation free energies. This is the goal of the present paper.

The development during the past decade of efficient electronic structure codes capable of carrying out both SCF and correlated calculations on large molecules (50−100 atoms) with reasonable basis sets (e.g., GAUSSIAN 92,[1] various density functional codes such as DGAUSS,[2] and the PSGVB program[3]) in principle greatly expands the potential applications of ab initio quantum chemical methods in the development of molecular modeling potentials. To exploit the power of these codes, however, it is necessary to directly attack the problem of solution-phase quantum chemical calculations; the most highly accurate gas-phase results are of limited utility in the development of transferable condensed-phase potentials without corrections for polarization effects.

Continuum solvent models which account for the details of molecular shape have proved to be remarkably accurate in the description of a variety of chemical and biochemical phenomena.[4] An important step has been the development of programs which yield numerical solutions of the Poisson−Boltzmann (PB) equation for molecules of arbitrary shape and charge distribution.[5,6] The ability of the Born model, using realistic atomic radii, to reproduce the solvation free energies of ions[7] and the similar success of numerical PB methods in the calculation of solvation enthalpies[8] and free energies[9−11] of small organic molecules have demonstrated that accurate results can be obtained even if water is represented as a dielectric continuum. Thus, the integration of continuum solvent models with state of the art ab initio methods opens up the possibility of carrying out accurate quantum mechanics in solution and near interfaces, even accounting for variations in ionic strength. While several pioneering papers along these lines have been reported in the literature[12−14] (and our method has many features in common with algorithmic elements in several of these papers), the

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quantity and quality of results presented have not yet established the utility of such a methodology by comparison with a substantial data base of experimental results.

In the present paper, we describe a very efficient and reliable computational scheme for determining quantum chemical wave functions, charge distributions, and energies in the reaction field of a dielectric continuum solvent, obtained by linking the PSGVB electronic structure code[3] with the DelPhi program[15] which yields numerical solutions to the PB equation. When computed solvation energies are compared with experiment for 29 molecules of various types, exceptionally good agreement is found, employing a small number of adjustable parameters.

A key issue in molecular modeling is the determination of accurate charge distributions in the gas phase and in solution. We show below that the generalized valence bond (GVB) electron correlation method[44] is extremely well suited to the calculation of charge distributions, uniformly reducing the large errors in the dipole moment (~0.5 D in unfavorable cases)[16] present in gas-phase Hartree–Fock calculations to, in most cases, substantially less than half this size while requiring only a modest increase in computational cost.

The paper is organized as follows. Section II describes the computational methodology, providing a brief overview of PSGVB and DelPhi and explains in detail how the codes are connected to generate a self-consistent calculation of quantum chemistry in a reaction field. The Results section presents gas-phase dipole moment calculations, compares calculated and experimental solvation energies, and displays solution-phase charge distributions, dipole moments, and internal quantum mechanical polarization energies. In the Conclusion, we contrast our method with other approaches and suggest future research directions.

II. Computational Methods

A. Quantum mechanical calculations.

PSGVB is an ab initio electronic structure package which uses a synthesis of standard Gaussian orbital methods with grid-based numerical techniques to obtain accurate solutions to the Hartree–Fock, GVB, and other ab initio electronic structure equations.[3] In a recent publication, detailed timing and accuracy comparisons with GAUSSIAN 92 are reported; these show that for 30–50 atom molecules, PSGVB is on the order of 3–6.5 times faster (depending upon what sort of computer is used and the basis set) for comparable accuracy in Hartree–Fock calculations;[17] for GVB calculations, the timing advantage is much more than an order of magnitude for systems of this size, and substantial even for small molecules. Until recently, the human effort in constructing initial guesses for the wave function and obtaining MCSCF convergence has rendered automated use of the GVB methodology problematic. However, the recent development of new initial guess and convergence algorithms[18,19] has solved these problems, and the calculation of GVB wave functions is now straightforward for an arbitrary molecule and a large number of GVB electron pairs.

B. PB Calculations. DelPhi is a program which solves the Poisson–Boltzmann (PB) equation using a finite difference formulation of the problem on a cubical mesh and an efficient successive overrelaxation algorithm to achieve convergence of the resultant linear equation system.[15] Standard representations of the Laplacian are employed; the crucial issues concern treatment of the boundary between the solvent and the solute where, in dielectric continuum theory, there is a discontinuity in the dielectric constant.

In most PB-based calculations of solvation energies the dielectric interface between solvent and solute is taken to be the molecular surface, which is the contact surface between the van der Waals envelope of the solute and a probe solvent molecule[20] (in the present paper, where we study aqueous solutions, a probe radius of 1.4 Å was employed). Atomic radius parameters for each atom type (analogous to the Born radius in simple dielectric theories of ionic solvation) are described below. In previous calculations of small molecule solvation free energies using the PB equation, the interior of the solute is generally assigned an "internal dielectric constant" of about 2, a value which accounts for the electronic polarizability of the solute.[21,22] However, in this work the internal dielectric constant in the PB calculations is set equal to unity, as molecular polarizability is treated explicitly with the quantum chemical calculations. All regions outside of the molecular surface are assigned the experimental solvent dielectric (e.g., $\epsilon = 80$ for aqueous solution).

The accuracy of the PB solutions obtained depends upon the resolution of the grid on which the equation is solved. In the calculations below, a scale of 3.0 grids/Å was used. Numerical tests in which the grid scale was doubled demonstrate that the solvation energy is calculated to an absolute accuracy of 0.1 kcal/mol, which is more than adequate for the purpose of this paper. Consequently, in what follows the possibility that disagreement with experiment arises from insufficient resolution the Poisson–Boltzmann calculation can be ignored. We note that, in a recent publication, convergence problems with DelPhi were reported;[46] our investigations indicate that these problems were due to the use of a very early version of the program. In a future publication, recent developments in algorithms and issues such as accuracy and convergence in the DelPhi program will be examined in detail.[47]

It is most convenient to represent the molecular charge distribution in the current version of DelPhi via a set of point charges (as opposed to a continuous distribution of charge) at the atomic centers. Therefore, we utilize electrostatic potential fitting (ESP)[23] routines in PSGVB to produce partial atomic charges by fitting the long-range Coulomb field from the quantum chemical wave function using a least-squares criterion. In implementing ESP fitting, one has to choose atomic radii which define the innermost points used to fit the Coulomb potential. We have defined the default values in PSGVB to be the van der Waals radii in the DREIDING force field of Mayo, Olafson, and Goddard.[24] This definition may not be optimal; however, it was not adjusted to improve agreement with experiment for calculation of solvation energies.

One accuracy check that we have made with regard to the validity of the ESP fitting procedure is to compare the gas- and solution-phase dipole moments calculated via ESP fitting with those determined directly from the quantum chemical wave functions. For the molecules studied to date these differ by a maximum of about 0.03 D, but in most cases by less than 0.02 D. A second test was carried out by computing the electrostatic energy of interaction of the reaction field (surface charges) with the molecular charge distribution in two ways; firstly via interaction with the ESP-derived point charges and secondly from integration over the actual quantum chemical wave function (the latter is what is reported in the results below). Differences on the order of a few tenths of kilocalories per mole were the largest observed, suggesting that, from the point of view of the surface charges, the atomic point charge representation is a reasonable fascimile of the actual distribution.

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C. Self-Consistent Quantum Chemistry in Solution. The first step in the determination of a solvation free energy is to carry out a gas-phase quantum chemistry calculation with PSGVB. The ESP fitting program is then run, and a set of atomic point charges is obtained. These charges are passed to DelPhi which then solves the PB equations as described above.

The reaction field in a continuum solvent model can be defined as the difference field between a uniform-dielectric PB calculation and a two-dielectric PB calculation. This field can be exactly represented as due to a set of source terms (charges) at the dielectric boundary, calculated as the divergence of the field at the surface. In our calculation, the number of such points is roughly proportional to the surface area (Å^2) divided by the square of the grid spacing (Å), typically a few hundred for a small molecule at accurate grid scales. This set of point charges is calculated in DelPhi and then passed to PSGVB, which solves the electric structure equations in the electrostatic field of the point charges, i.e., in the presence of the reaction field. The latter step is computationally trivial (and highly accurate) because the surface charges are easily included in the one-electron Hamiltonian as matrix elements (essentially, electron–nuclear attraction integrals, although each individual point charge may of course be positive or negative) between two Gaussian basis functions which can be evaluated analytically.

The Hamiltonian in solution is given by $H^o + H' + H''$ where H^o is the gas-phase Hamiltonian, H' is the sum of one-electron integrals over the surface charges defined above, and H'' is the sum of Coulomb interactions between those surface charges and the nuclear charges (the atomic number of each element, not the ESP-fit charges). The electrostatic free energy of solvation is given by

$$\Delta G^{es} = \langle \psi^s | H^o | \psi^s \rangle - \langle \psi^g | H^o | \psi^g \rangle + \frac{1}{2}[\langle \psi^s | H' | \psi^s \rangle + H''] \quad (1)$$

where ψ^s is the solvated solute wave function, ψ^g is the gas-phase solute wave function and the factor of $^1/_2$ accounts for the free energy associated with polarizing the solvent (see, e.g., the discussion in Szafran et al.[25]).

The PSGVB and DelPhi calculations are iterated until convergence is achieved, i.e., until the total energy of two runs agrees to within a preset tolerance; the solvation energy is obtained as the difference between the gas-phase and solution-phase quantum chemical energies. For a tolerance of 0.1 kcal/mol, we found that convergence was obtained in six iterations in all cases studied to date. The iterations beyond the initial gas-phase one are computationally inexpensive because one can restart the calculation from the previous run and use Fock matrix updating (and hence inexpensive grids in the PSGVB convergence scheme); computation of solvation energies typically requires on the order of twice the effort to carry out a gas-phase calculation. The computational cost of a GVB calculation for the largest and most highly correlated molecule studied here (*N*-methylacetamide) is 37 min on an IBM 580 workstation.

D. Nonpolar Contributions. The above procedure evaluates only the electrostatic contribution to the solvation energy. The total solvation free energy can be written as[4]

$$\Delta G^t = \Delta G^{es} + \Delta G^{np} \quad (2)$$

where ΔG^{np} is the solvation energy of a nonpolar solute of identical size and shape to the actual solute and will be positive. We evaluated this term in the present paper by fitting a straight line to the experimental vacuum to water solvation free energies obtained from Ben-Naim and Marcus[26] for a series of linear and branched alkanes (methane through octane, isobutane, isopentane, neopentane, isohexane, 3-methylpentane, neohexane, 2,4-dimethylpentane, isooctane, and 2,2,5-trimethylhexane). The experimental transfer energies are plotted in Figure 1 as a function of accessible surface area, *A*, where *A* was obtained via a newly developed fast numerical algorithm.[27] There is a good correlation between free energy and surface area for these molecules which is given

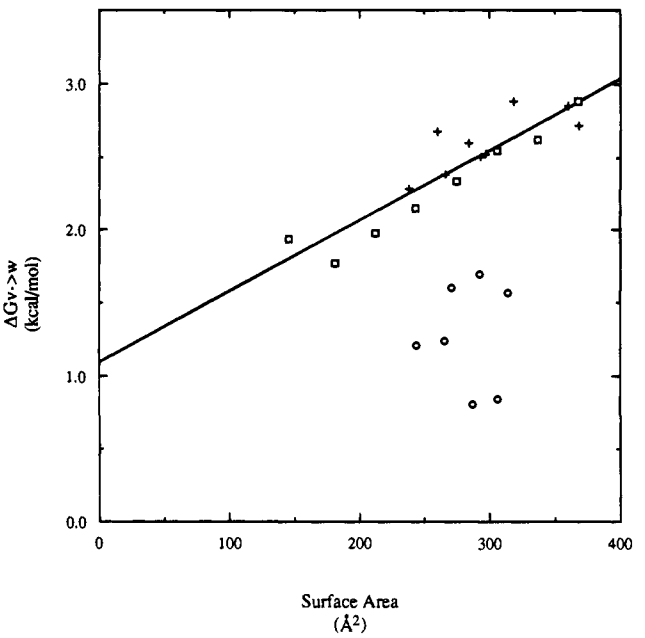

Figure 1. Dependence of experimental vacuum to water solvation free energies on calculated solvent-accessible surface area for hydrocarbons of varying shapes: linear alkanes (□), branched alkanes (+), cyclic alkanes (○). Experimental data are from Ben-Naim and Marcus.[26] The solid line is the least-squares fit line to straight and branched alkanes only: $\Delta G(v \rightarrow w) = 0.005A + 1.092$. The correlation constant is 0.822.

by

$$\Delta G^{np} = 1.09 + 0.005A \quad (3)$$

where ΔG^{np} is in units of kilocalories per mole and *A* is in square angstroms.

Figure 1 also plots solvation free energies of cyclic hydrocarbons (cyclopentane through cyclooctane, methylcyclopentane, methylcyclohexane, and 1,2-dimethylcyclohexane, data obtained from Ben-Naim and Marcus[26]) which clearly do not fall on the same line; indeed there is no obvious correlation between free energy and surface area for this class of molecules.[46] The source of this behavior is not at present understood. One problem associated with the use of hydrocarbons to obtain ΔG^{np} is that these molecules have small partial charges at atomic centers so that the implicit assumption that $\Delta G^{es} = 0$ is not strictly valid. However, the largest values of ΔG^{es} we have calculated for alkanes are on the order of only −0.3 kcal/mol. ΔG^{es} for branched alkanes are somewhat larger (−0.9 kcal/mol) but are less reliable due to problems with ESP fitting to buried atoms in hydrocarbons.[28] We have ignored the electrostatic contributions from hydrocarbons in the calculations presented below.

A further factor ignored in this section is possible volume-dependent contributions to solubility.[29,30] However, since volume and area are well-correlated for small solutes, it is reasonable to incorporate all volume effects into the surface area-dependent term given in eq 3.

III. Results

A. Gas-Phase Dipole Moments. The use of an electronic structure method sufficiently accurate to produce reliable gas-phase charge distributions is essential in developing a physically meaningful solution-phase methodology. This is particularly true if one wants to use the solution-phase charges for purposes other than the computation of the isolated molecule solvation energy (e.g., binding of a drug molecule to a protein). One can perhaps compensate for inadequate charges in a solvation

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Table 1. Gas-Phase Dipole Moments (D)[a]

molecule	HF	GVB	exptl[b]
water	2.19	2.09	1.85
methanol	1.93	1.81	1.70
ethanol	1.77	1.67	1.69
acetic acid	1.94	1.56	1.74
acetone	3.23	2.70	2.88
cis-N-methylacetamide	4.50	3.96	—[d]
trans-N-methylacetamide	4.28	3.78	3.73[c]
acetamide	4.30	3.81	3.76
2-propanol	1.53	1.45	1.66
phenol	1.43	1.36	1.45
toluene	0.29	—	0.36
2-pentanone	3.24	2.70	—[d]
ethylbenzene	0.20	—	0.59
3,5-dimethylpyridine	2.61	—	—[d]
4-methylpyridine	2.62	—	—[d]
4-methyl-2-pentanone	3.24	2.69	2.70
methanethiol	1.77	1.70	1.53
ethanethiol	1.78	1.71	1.58
dimethyl sulfide	1.79	1.74	1.50
methyl ethyl sulfide	1.73	1.68	1.56
diethyl sulfide	1.66	1.60	1.54
methylamine	1.52	1.48	1.31
dimethylamine	1.12	1.09	1.03
trimethylamine	0.76	0.73	0.61
ethylamine	1.46	1.41	1.22
n-propylamine	1.55	1.50	1.17
n-butylamine	1.52	1.47	1.44
diethylamine	0.97	0.94	0.92
max error	0.55	0.33	
mean error	0.24	0.13	

[a] Calculations done with the 6-31G** basis set. In the GVB column, only heteroatom bonds were correlated. The dash indicates no heteroatom bonds in the molecule or C−N bonds in pyridine not correlated. [b] Experimental values from the *CRC Handbook of Chemistry and Physics*, 65th ed., and from the *Table of Experimental Dipole Moments*, v. 1−3, by A. L. McClellan. [c] Experimental value from a mix of cis and trans. Trans is the lower energy conformation, so it should dominate the population of isomers. [d] No experimental data available.

model by adjusting other parameters like the atomic radii; however, this makes the model difficult to interpret physically and makes it unlikely that the charge parameters can be easily employed in other contexts.

In Table 1, we compare experimental gas-phase dipole moments with gas-phase dipole moments computed via HF and GVB-PP (perfect pairing) calculations for 29 small molecules representing a variety of functional groups. Molecular structures were built and energy minimized using the Insight/Discover molecular modeling package (Biosym Technologies, Inc.). The ab initio calculations were performed using the 6-31G** basis set. The results show that both the maximum and average error in dipole moment are dramatically reduced for the GVB relative to the HF calculations. It is well known that Hartree−Fock theory makes substantial errors in calculating dipole moments, often in excess of 0.5 D. However, we are not aware of any previous systematic studies on a wide variety of molecules to establish the level of electron correlation required to produce adequate corrections to these errors. The results in Table 1 are for correlation only between bonds to heteroatoms (N, S, and O), the charge distribution of lone pairs, C−H and C−C bonds being relatively unaffected by correlation of their electron pairs (note that this observation would not apply to total energies).

It is important to address the question of what is sufficient charge distribution accuracy for the method we are developing. Moreover, it should be noted that accurate calculation of the dipole moment is not a guarantee that the entire charge distribution is adequate, though it certainly suggests that this is the case. In this regard, the criterion adopted here is that the systematic error in solvation energies induced by the charges be smaller than the uncertainties inherent in the dielectric continuum theory (i.e., atomic radius values). To test this criterion, additional studies utilizing an extended triple ζ double polarization basis set (as opposed to the 6-31G** basis) were carried out. While the gas-phase dipole moments displayed some improvement (most dramatically for water whose dipole moment was reduced from 2.09 to 1.92 D), the computed solvation energies (reoptimizing parameters for this basis set) failed to yield an average error in better agreement with experimental data, with the exception of very small molecules like water. It is likely that this small molecule result is due to the unavailability of basis functions from non-nearest-neighbor atoms in a triatomic to compensate for deficiencies in the double ζ plus polarization basis, a problem remedied by the larger basis; however, the effect is much smaller even for molecules with 5−10 atoms.

The computational cost for this accuracy, using GVB-PP (perfect pairing) methods as implemented in PSGVB, scales as N^3; furthermore, the prefactor is relatively small because of the special properties of GVB Hamiltonians. On the basis of scattered results in the literature, it seems likely that high-level correlation methods such as MP2 would produce sufficiently accurate charge distributions by the above criterion. However, the computational effort for MP2 scales as N^5, where N is the basis set size; for this reason, we rejected it and other wave function-based correlation methods (higher order MP, coupled cluster, CASSCF, etc.) with equal or worse scaling. Density functional theory scales as N^2−N^3 and has proven to be remarkably accurate for bond energies if one employs nonlocal gradient corrections; however, its performance for charge distributions is at present not well studied. While we did not carry out such calculations here, we consider this to be a promising alternative to the GVB-PP method.

B. Calculation of Solvation Free Energies. 1. Comparison with Experimental Values. Solvation free energies for the 29 molecules were calculated for Hartree−Fock and GVB-PP (correlating heteroatom bonds only) wave functions by the methods described above. The molecules contain a wide variety of functional groups: carbonyl groups, carboxylic acids, several types of amines, and several sulfur compounds. The calculated and experimental solvation energies are displayed in Table 2. The parameters of the model are the atomic radii described previously. For O, N, C, and S, we used the values 1.6, 1.6, 1.9, and 1.9 Å, respectively. These values were obtained from the PARAM19 parameter set of the CHARMM[31] force field as extracted from the X-PLOR program.[32] For aromatic ring moieties, the aromatic carbon parameter values of the OPLS force field,[33] 1.99 Å for carbon and 1.36 Å for hydrogen, were used. None of these parameters were subsequently adjusted to improve agreement with experimental data.

We experimented with a number of other sets of O, C, N, and S parameters, primarily those from the OPLS[34] and Amber[35] force fields. In general, the results obtained with these two alternative choices are not qualitatively different; quantitatively, one can compensate somewhat for the minor alterations by reparametrizing the hydrogen radius. We selected the CHARMM

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Table 2. Solvation Free Energy Data[a]

	ΔG_{el}					ΔG_{tot}					
		ΔG_{pol}									
molecule	$\Delta G_{\mu_{vac}}$	$\Delta G_{\Delta\mu}$	ΔG_{reorg}	$\Delta G_{el,tot}$	ΔG_{np}	HF	GVB	exptl[b]	$\Delta G_{pol}/\Delta G_{el,tot}$	$\Delta G_{pol}/\Delta G_{tot}$	μ_{aq}/μ_{vac}
water	−7.8	−2.4	1.2	−9.0	1.7	−8.3	−7.3	−6.3	0.13	0.16	1.14
methanol	−5.9	−1.9	0.8	−7.0	1.9	−5.8	−5.2	−5.1	0.17	0.23	1.22
ethanol	−5.5	−1.8	0.8	−6.5	2.1	−5.1	−4.5	−5.0	0.16	0.23	1.30
acetic acid	−7.9	−2.3	0.9	−9.4	2.1	−9.5	−7.3	−6.7	0.15	0.20	1.31
acetone	−5.0	−2.9	1.3	−6.6	2.2	−6.9	−4.5	−3.9	0.24	0.36	1.37
cis-N-methylacetamide	−8.5	−4.6	2.2	−11.0	2.3	−11.3	−8.7	−10.1	0.22	0.28	1.33
trans-N-methylacetamide	−8.4	−5.5	2.6	−11.3	2.3	−11.6	−9.0	−10.1	0.26	0.32	1.41
acetamide	−10.4	−5.3	2.6	−13.1	2.1	−13.6	−11.0	−9.7	0.21	0.25	1.35
2-propanol	−5.6	−1.7	0.7	−6.6	2.2	−5.1	−4.4	−4.8	0.15	0.22	1.29
phenol	−7.0	−2.2	0.8	−8.4	+2.4	−6.4	−5.9	−6.6	0.16	0.23	1.37
toluene	−2.7	−0.7	0.2	−3.3	2.5	−0.8	−[c]	−0.8	0.16	0.62	1.49
2-pentanone	−4.7	−2.6	1.1	−6.2	2.4	−6.1	−3.7	−3.5	0.24	0.40	1.38
ethylbenzene	−2.6	−0.7	0.2	−3.1	2.6	−0.5	−[c]	−0.8	0.17	1.10	1.67
3,5-dimethylpyridine	−5.4	−3.0	1.5	−6.9	2.6	−4.3	−[c]	−5.5	0.22	0.36	1.42
4-methylpyridine	−5.9	−3.3	1.7	−7.6	2.5	−5.1	−[c]	−4.9	0.22	0.32	1.43
4-methyl-2-pentanone	−5.0	−2.6	1.2	−6.5	2.6	−6.2	−3.9	−3.1	0.22	0.36	1.37
benzene	−2.7	−0.7	0.2	−3.2	2.4	−0.8	−[c]	−0.9	0.16	0.65	1.08
methanethiol	−2.8	−1.7	0.8	−3.8	2.0	−2.1	−1.8	−1.2	0.25	0.52	1.34
ethanethiol	−2.8	−1.7	0.8	−3.7	2.1	−1.8	−1.6	−1.2	0.25	0.60	1.39
dimethylsulfide	−2.8	−1.6	0.7	−3.6	2.1	−1.7	−1.5	−1.5	0.24	0.58	1.37
methyl ethyl sulfide	−2.9	−1.8	0.9	−3.8	2.3	−1.7	−1.5	−1.4	0.23	0.59	1.47
diethyl sulfide	−2.7	−1.8	0.9	−3.6	2.5	−1.3	−1.2	−1.4	0.25	0.76	1.54
methylamine	−5.5	−1.9	0.9	−6.3	1.9	−4.9	−4.3	−4.5	0.15	0.22	1.24
dimethylamine	−4.1	−1.4	0.7	−4.8	2.1	−3.1	−2.7	−4.3	0.14	0.25	1.32
trimethylamine	−3.0	−0.9	0.5	−3.5	2.2	−1.4	−1.2	−3.2	0.14	0.40	1.30
ethylamine	−5.8	−2.0	1.0	−6.8	2.1	−5.2	−4.7	−4.5	0.15	0.21	1.30
n-propylamine	−5.8	−2.1	1.0	−6.9	2.2	−5.2	−4.6	−4.4	0.15	0.23	1.29
n-butylamine	−5.7	−2.1	1.1	−6.7	2.4	−4.8	−4.3	−4.4	0.15	0.24	1.28
diethylamine	−3.6	−1.2	0.5	−4.3	2.4	−2.1	−1.9	−4.1	0.16	0.36	1.50
					max:	3.9	2.2		0.26	1.10	1.67
					mean:	1.1	0.6		0.19	0.39	1.35

[a] Calculations done with the 6-31G** basis set. All data are for GVB calculations with only heteroatom bonds correlated unless otherwise noted. ΔG_{el} = electrostatic solvation free energy; $\Delta G_{\mu_{vac}}$ = solvation free energy for a nonpolarizable solute having the gas-phase charge distribution; $\Delta G_{\Delta\mu}$ = change in solvation energy due to polarization of the solute dipole from μ_{vac} to μ_{aq}; ΔG_{reorg} = change in solute self-energy due to polarization of the electron cloud; ΔG_{pol} = polarization free energy, given by the sum of $\Delta G_{\mu_{vac}}$ and ΔG_{reorg}; $\Delta G_{el,tot}$ = total solvation energy, given by the sum of $\Delta G_{\mu_{vac}}$ and ΔG_{pol}; ΔG_{np} = nonpolar contribution, calculated as described in the text; ΔG_{tot} = total solvation energy, given by the sum of $\Delta G_{el,tot}$ and ΔG_{np}. Energies are in kilocalories per mole. [b] Experimental values: Wolfenden, R.; Andersson, L.; Cullis, P. M.; Southgate, C. C. *Biochemistry* **1981**, *20*, 849. Wolfenden, R. *Biochemistry* **1978**, *17*, 199. Cabani, S.; Gianni, P.; Mollica, V.; Lepori, L. *J. Soln. Chem.* **1981**, *10*, 563. [c] Results are the same as for the HF calculation; no heteroatom bonds present in the molecule or C−N bonds in pyridine not correlated.

radii on the basis of a marginally better performance in terms of the largest single error. However, the correct approach is clearly to fully optimize the atomic radii over a larger data base, which would by definition yield a smaller mean square error than the present procedure of heuristically selecting among three parameter sets. We intend to carry this out in a subsequent publication.

We did find it necessary to optimize the radius of nonaromatic hydrogens, arriving at a value of 1.15 Å. Thus, our results for the 29 molecules are obtained with the use of a single fully adjustable parameter, in addition to the heuristic selection procedure described above for the remaining radii. As shown in Table 2, the method produces solvation energies in good agreement with experimental values. The GVB results are considerably improved over the HF results, in terms of both the maximum error and the average error, which is 0.6 kcal/mol. HF systematically overestimates the solvation energy due to the fact that its dipole moments are too large (but note that this effect is not obviously systematic and hence is nontrivial to scale out).

The GVB results are in fact qualitatively better than the average and maximum errors in Table 2 convey. The *only* compounds with errors greater than 1.0 kcal/mol (other than water, for which the error can be reduced by use of a better basis set, as discussed above) are amine and amide compounds with one or more methyl or ethyl groups replacing hydrogens in a $-NH_2$ moiety, *N*-methylacetamide, dimethylamine, trimethylamine, and diethylamine, which are systematically too low by 1−2.5 kcal/mol. The corresponding compounds with a methyl group replaced by a hydrogen (acetamide, methylamine, and ethylamine) are in good agreement with experiment, as are all of the remaining compounds of quite different chemical composition. Experimentally, it appears that replacing a polar hydrogen by a methyl group does not lead to a net decrease in the electrostatic component of the solvation energy as one might expect; in fact, for *N*-methylacetamide, it actually leads to an increase. This result is highly counterintuitive, and its source is at present unclear.

It is important to note that the ~2 kcal/mol difference between the methylated and unmethylated amines cannot be reconciled in any reasonable fashion by adjusting the atomic radii. In order to increase the relative solvation free energy of the methylated form, one would have to make the hydrogen radius for a methyl group *smaller* than it is for a polar hydrogen on an amine, which is physically unreasonable (and also would cause difficulties in solvation calculations for other molecules with methyl groups). Furthermore, several groups have recently carried out explicit solvent simulations[45] and uniformly find an energy difference on the order of 2 kcal/mol despite the use of different force fields and simulation codes. This suggests that the problem does not lie in the assumptions of dielectric continuum theory or in the details of the solute model. This surprising

discrepancy between theory and experiment is clearly deserving of further study.

It is of interest to note that the calculations successfully reproduce the equal solvation energies of *cis*- and *trans*-N-methylacetamide. As has been pointed out previously,[36,37] this requires that one use different charges for each species, in our case computed by GVB methods. In fact, our calculations show substantial differences in the charge sets between the cis and trans conformations in both the gas phase and the solution phase. The near equality of solvation energies is therefore a fortuitous cancellation of effects which can be fully explained within the continuum electrostatic model.

2. Effects of the Solvent on Solute Electronic Structure and Energy. Upon solvation, the solute charge distribution is polarized due to the surrounding water molecules (represented here by the high dielectric continuum). In Table 2 the ratio of solution-phase to vacuum-phase dipole moments is displayed. The solution-phase dipole moments typically are increased by 30−40% from the gas-phase values. This range of values is qualitatively in accord with previous estimates based entirely on continuum theory.[21] Table 3 contains the ESP-fitted gas-phase and solution-phase charges obtained from PSGVB for several example molecules. The electrons redistribute over the molecules in a complicated manner, as the ratio of solution-phase ESP charges shows.

Also in Table 3, we compare the PSGVB charges with charges from the OPLS force field. While the charges from the two methods correlate well on a linear plot (correlation coefficients of 0.92 and 0.93 for the vacuum- and solution-phase PSGVB charges versus OPLS, respectively), the values of the charges differ significantly; PSGVB charges are on average 1.13 or 1.26 times greater than the OPLS charges, in the vacuum and solution phases respectively. In the free energy perturbation calculations used by Jorgensen and co-workers in the parametrization of OPLS,[34] there is no internal polarization term (discussed in more detail below); consequently, the OPLS charges are smaller because this term has been removed and no longer cancels a part of the electrostatic solvation energy. Both methods can yield reasonable agreement with experiment, despite these differences and the differences in the values of the charges (which are not significant) because the solvent−solute interface (atomic Born radii in the PSGVB/DelPhi model, van der Waals parameters in the case of OPLS) is parametrized to reproduce experimental data, a successful procedure at least for small molecule test cases.

As described by Gao and Xia,[38] the contribution to solvation free energy due to the polarization of the electron cloud can be decomposed into two opposing terms, which are displayed in Table 2. Prior to polarization, the solute interacts with the solvent according to its gas-phase electron distribution ($\Delta G_{\mu vac}$). As polarization occurs, the electrons redistribute to achieve a more favorable interaction with the solvent, producing a gain in solvation energy ($\Delta G_{\Delta\mu}$). Concurrently, the distortion of the electron cloud leads to an altered interaction of the electrons with nuclei and with each other, contributing an unfavorable decrease in solvation energy (ΔG_{reorg}). It is of interest that the reorganization penalty is equal to about half the gain in solute−solvent interaction energy due to the redistribution of electrons, as is expected from classic linear response theory.[39] For the molecules studied here, the net polarization contribution is in the range of −1 to −3 kcal/mol, or about 20% of the total electrostatic energy, in close agreement with other recently reported values.[21,38,40]

IV. Discussion

We have shown that ab initio quantum mechanics can be combined with a dielectric continuum theory which accounts for detailed molecular shape to yield solvation energies that agree with experiment with an average error of 0.6 kcal/mol, a highly satisfactory performance for many applications. Improved results can undoubtedly be obtained by adjustment of the atomic radii to fit a larger experimental data basis; such work is currently in progress. An alternative approach is to utilize the quantum chemical electron density directly to define the dielectric boundary and to represent the charge distribution in DelPhi. We are also pursuing efforts in this direction, which may be necessary for more complicated molecules (e.g., transition metals).

Recently, Cramer and Truhlar[41] have developed a method (the AMSOL program) for calculating solvation energies utilizing semiempirical quantum chemistry methods (AM1)[42] and a solvent model derived from the generalized Born (GB) approach of Still and co-workers.[43] Their results for solvation energies of a large group of molecules are quite reasonable, and their computational costs are relatively low. However, the AMSOL program uses a relatively large number of adjustable parameters, on the order of 10 per atom in the recently derived SM2 and SM3 parameter sets. These involve atomic radii and a variety of surface area-dependent terms as well as parameters used to account for solvent effects on one- and two-center integrals. The only fully adjustable parameter used to fit the experimental solvation free energies of the molecules studied in this work is the hydrogen radius, although one could argue that CHARMM radii and the OPLS aromatic radii were chosen on the basis of their performance.

The single surface area coefficient (surface tension, eq 3) used in the present work of 5 (cal/mol)/Å^2 is fit to the experimental solubilities of linear and branched alkanes but is applied uniformly to all atoms of the solute. It should be emphasized that this value was not adjusted to improve agreement for the molecules listed in Table 2; that is, it was obtained from an independent data set. Thus, a polar heteroatom such as nitrogen is assigned the same positive surface tension as a carbon atom, even though the polar group clearly interacts favorably with water. In our approach, this favorable interaction is accounted for entirely in the electrostatic term. Cramer and Truhlar suggested that their adjustable surface tension parameters compensate for deficiencies in their partial charges (due to the use of the AM1 method and a Mulliken population analysis) and for deficiencies in the solvation model (for example, inadequate representation of hydrogen bonding with continuum electrostatics).[41] Indeed, a significant fraction of the electrostatic contribution to solvation is included in their surface area-dependent terms and not in their electrostatic model. The fact

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Table 3. Atomic Charges (−e units)[a]

		PSGVB−DelPhi						
		vacuum		aqueous				
molecule	atom[b]	all-atom	united	all-atom	united	OPLS[c]	q_{aq}/q_{vac}	μ_{aq}/μ_{vac}
methanol	C	0.209	0.239	0.225	0.274	0.265	1.08	1.14
	H	−0.012		−0.001			0.04	
	H	0.054		0.050			0.92	
	H	−0.012		−0.001			0.04	
	O	−0.643	−0.643	−0.739	−0.739	−0.700	1.15	
	H	0.404	0.404	0.465	0.465	0.435	1.15	
methylamine	C	0.396	0.274	0.442	0.315	0.200	1.12	1.24
	H	−0.020		−0.027			1.36	
	H	−0.019		−0.027			1.38	
	H	−0.084		−0.074			0.88	
	N	−0.997	−0.997	−1.152	−1.152	−0.900	1.16	
	H	0.362	0.362	0.419	0.419	0.350	1.16	
	H	0.362	0.362	0.419	0.419	0.350	1.16	
dimethylamine	C	−0.016	0.163	−0.010	0.194		0.63	1.32
	H	0.053		0.057			1.08	
	H	0.038		0.055			1.45	
	H	0.088		0.092			1.05	
	N	−0.696	−0.696	−0.814	−0.814		1.17	
	H	0.371	0.371	0.427	0.427		1.15	
acetone	C	−0.523	−0.125	−0.547	−0.107	0.062	1.05	1.37
	H	0.129		0.151			1.17	
	H	0.129		0.151			1.17	
	H	0.140		0.138			0.98	
	C	0.758	0.758	0.823	0.823	0.300	1.09	
	O	−0.509	−0.509	−0.609	−0.609	−0.424	1.20	
acetamide	C	−0.551	−0.117	−0.568	−0.092	0.000	1.03	1.35
	H	0.142		0.168			1.18	
	H	0.143		0.168			1.18	
	H	0.148		0.140			0.94	
	C	0.891	0.891	0.935	0.935	0.500	1.05	
	O	−0.605	−0.605	−0.727	−0.727	−0.500	1.20	
	N	−1.028	−1.028	−1.046	−1.046	−0.850	1.02	
	H	0.421	0.421	0.464	0.464	0.425	1.10	
	H	0.438	0.438	0.466	0.466	0.425	1.06	
trans-N-methylacetamide	C (C)	−0.544	−0.126	−0.565	−0.102	0.000	1.04	1.41
	H	0.131		0.158			1.20	
	H	0.156		0.148			0.95	
	H	0.131		0.157			1.20	
	C	0.742	0.742	0.798	0.798	0.580	1.08	
	O	−0.547	−0.547	−0.674	−0.674	−0.530	1.23	
	N	−0.513	−0.513	−0.530	−0.530	−0.550	1.03	
	H	0.312	0.312	0.358	0.358	0.300	1.15	
	C (N)	−0.225	0.132	−0.222	0.149	0.200	0.99	
	H	0.121		0.146			1.21	
	H	0.118		0.113			0.95	
	H	0.118		0.113			0.96	
cis-N-methylacetamide	C (C)	−0.448	−0.058	−0.470	−0.033	0.000	1.05	1.33
	H	0.127		0.152			1.20	
	H	0.136		0.133			0.98	
	H	0.127		0.152			1.20	
	C	0.742	0.742	0.796	0.796	0.530	1.07	
	O	−0.602	−0.602	−0.726	−0.726	−0.530	1.21	
	N	−0.529	−0.529	−0.544	−0.544	−0.550	1.03	
	H	0.323	0.323	0.355	0.355	0.350	1.10	
	C (N)	−0.191	0.124	−0.213	0.153	0.200	1.12	
	H	0.133		0.154			1.16	
	H	0.091		0.106			1.16	
	H	0.091		0.106			1.16	
acetic acid	C	−0.342	−0.021	−0.391	−0.017	0.080	1.14	1.31
	H	0.114		0.135			1.18	
	H	0.093		0.104			1.12	
	H	0.114		0.135			1.18	
	C	0.765	0.765	0.844	0.844	0.550	1.10	
	=O	−0.535	−0.535	−0.620	−0.620	−0.500	1.16	
	O	−0.633	−0.633	−0.682	−0.682	−0.580	1.08	
	H	0.425	0.425	0.475	0.475	0.450	1.12	

Table 3 (Continued)

		PSGVB−DelPhi						
		vacuum		aqueous				
molecule	atom[b]	all-atom	united	all-atom	united	OPLS[c]	q_{aq}/q_{vac}	μ_{aq}/μ_{vac}
ethanethiol	C	−0.041	0.106	−0.077	0.100	0.000	1.86	1.39
	H	0.063		0.069			1.10	
	H	0.022		0.039			1.79	
	H	0.063		0.069			1.10	
	C	−0.214	0.019	−0.182	0.077	0.180	0.85	
	H	0.117		0.130			1.11	
	H	0.116		0.129			1.11	
	S	−0.319	−0.319	−0.429	−0.429	−0.450	1.34	
	H	0.194	0.194	0.252	0.252	0.270	1.30	
benzene[d]	C	−0.130	−0.130	−0.146	−0.146	−0.115	1.12	1.00
	H	0.130	0.130	0.146	0.146	0.115	1.12	
phenol	CD1	−0.016	−0.016	−0.027	−0.027	−0.115	1.71	1.37
	CE1	−0.429	−0.429	−0.447	−0.447	−0.115	1.04	
	CZ	0.496	0.496	0.516	0.516	0.150	1.04	
	CE2	−0.332	−0.332	−0.370	−0.370	−0.115	1.11	
	CD2	−0.062	−0.062	−0.072	−0.072	−0.115	1.16	
	CG	−0.249	−0.249	−0.276	−0.276	−0.115	1.11	
	HD1	0.132	0.132	0.150	0.150	0.115	1.14	
	HE1	0.177	0.177	0.206	0.206	0.115	1.16	
	HE2	0.189	0.189	0.201	0.201	0.115	1.07	
	HD2	0.140	0.140	0.158	0.158	0.115	1.13	
	HG	0.146	0.146	0.163	0.163	0.115	1.12	
	O	−0.612	−0.612	−0.681	−0.681	−0.585	1.11	
	H	0.419	0.419	0.477	0.477	0.435	1.14	

[a] ESP-fit charges obtained from PSGVB-DelPhi calculations using the 6-31G** basis set and GVB pair correlation between heteroatoms unless otherwise noted. Vacuum charges are from the gas-phase solute wave function; aqueous charges are from the final, fully converged wave function when solvent effects are included. United atom charges were obtained by summing the heavy atom and attached hydrogen atom charges. Symbols: q_{vac}, q_{aq}, vacuum and aqueous ESP-fit atomic charges from PSGVB−DelPhi; μ_{vac}, μ_{aq}, vacuum and aqueous solute dipole moments from PSGVB−DelPhi. [b] Hydrogen atoms appear immediately below the heavy atoms to which they are bonded. [c] Obtained from Jorgensen, W. L.; Tirado-Rives, J. J. *J. Am. Chem. Soc.* **1988**, *110*, 1657 or from a list of OPLS parameters for biochemical systems kindly provided by Dr. Jorgensen (OPLS charges for dimethylamine were not available). [d] No heteroatoms present; calculation done at the HF level.

that we have obtained results in good agreement with experiment using a single positive surface tension value for all atoms suggests that extensive parametrization of surface tension values may not be required if an accurate ab initio description of the solute is employed.

The ultimate evaluation of the validity of various continuum dielectric/quantum chemical solvation models will involve prediction of solvation energies for more complex systems (e.g., large drug molecules, amino acids and peptides, transition-metal complexes) and utilization of the solution-phase charge distributions for other calculations. A significant advantage of using correlated ab initio quantum chemical methods is that reparameterization to treat such complex systems is not required. We believe that, in this paper, we have demonstrated that the approach described above is a very good start toward attacking these important problems.

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