The Aqueous Solvation of Water: A Comparison of Continuum Methods with Molecular Dynamics

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Abstract: The calculation of the solvation properties of a single water molecule in liquid water is carried out in two ways. In the first, the water molecule is placed in a cavity and the solvent is treated as a dielectric continuum. This model is analyzed by numerically solving the Poisson equation using the DelPhi program. The resulting solvation properties depend sensitively on the shape and size of the cavity. In the second method, the solvent and solute molecules are treated explicitly in molecular dynamics simulations using Ewald boundary conditions. We find a 2-kcal/mol difference in solvation free energies predicted by these two methods when standard cavity radii are used. In addition, dielectric continuum theory assumes that the solvent reacts solely by realigning its electric moments linearly with the strength of the solute's electric field; the results of the molecular simulation show important nonlinear effects. Nonlinear solvent effects are generally of two types: dielectric saturation, due to solvent–solute hydrogen bonds, and electrostriction, a decrease in the solute cavity due to an increased electrostatic interaction. We find very good agreement between the two methods if the radii defining the solute cavity used in the continuum theory is decreased with the solute charges, indicating that electrostriction is the primary nonlinear effect and suggesting a procedure for improvement of continuum methods. The two methods cannot be made to agree when the atomic radii are made charge independent, but charge dependent cavity radii are shown to greatly improve agreement.

Introduction

Dielectric continuum methods based on the numerical solution of the Poisson equation provide estimates of solvation free energies. Because this approach is much faster than full molecular dynamics simulations, continuum theory (CT) has been applied to a wide variety of systems, from aqueous solutions of large solute molecules such as proteins and nucleic acids to small solutes such as atomic ions.[1] The widespread use of such continuum calculations makes it important to test them against simulations with explicit solvent molecules and against experimental data where available. Previous comparisons of continuum theory and molecular simulations have found good agreement for solvation energies, typically about 10%.[2,3] The focus of this paper will be to compare continuum theory with full molecular simulations of a small polar solute for equilibrium properties such as solvation energies, electrostatic potentials, and average electric fields from which the electrostatic forces can be calculated.

The solvation process studied here is the solvation of a single water molecule in liquid water. The free energy of solvation, ΔA_{sol}, of a water molecule can be decomposed into a three-step process: (1) removal of the gas-phase partial charges from the gas-phase water molecule (ΔA_{es}^{gas}); (2) insertion of the uncharged water molecule into the solvent making a hydrophobic cavity in the bulk water (ΔA_{cav}); and (3) charging the water solute to the desired liquid-phase charges (ΔA_{es}) (see Figure 1).[4] The free energy, ΔA_{es}^{gas}, for the first step is the self–energy for electronic polarization in the gas phase or the free energy difference between the isolated molecule with its gas-phase partial charges and with no partial charges. The free energy for the liquid-state charging step, ΔA_{es}, contains two parts, a self-energy for polarization in

$$\Delta A_{sol}$$
$$\mathrm{H_2O}(Q_H^{gas}, gas) \longrightarrow \mathrm{H_2O}(Q_H^{liq}, liq)$$
$$\Big\downarrow \Delta A_{es}^{gas} \qquad\qquad \Big\uparrow \Delta A_{es}$$
$$\mathrm{H_2O}(Q_H = 0, gas) \longrightarrow \mathrm{H_2O}(Q_H = 0, liq)$$
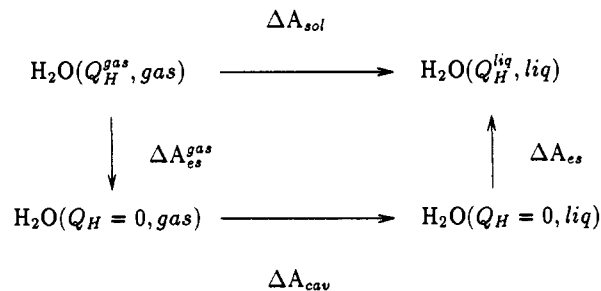$$\Delta A_{cav}$$

Figure 1. Thermodynamic cycle for the solvation of water in water.

the liquid phase and a solvent electrostatic contribution. The two polarization terms will not completely cancel since the gas-phase and solution charges are not necessarily (or generally) equal and also the polarization energy will depend on the medium. The two polarization-energies are commonly neglected (but see refs 4 and 5).

The solvent electrostatic contribution to the free energy is the focus of this paper and is the subject of comparison between the full molecular simulation and the continuum calculations. This step consists of reversibly charging the hydrogen charge, Q_H, on the solute water molecule from 0 to 0.5e (the oxygen charge, Q_O, equals $-2Q_H$) while keeping the solvent charges equal to the usual liquid-state values. (We are including charges higher than Q_H^{liq}—higher than is necessary for the evaluation of ΔA_{es} for H_2O—in order to look at the effects of high charge.) In the continuum approximation, all the solvent electrostatic properties are contained in the dielectric constant, ϵ. Setting ϵ equal to the same value given by the molecular potential used in the simulation, we can assure self-consistency.

The properties of interest are the energy of the solute, the average electrostatic potential, and the field of the solvent at the solute charge sites. The electrostatic potential, ϕ, at position $r_{1\alpha}$ (where 1 labels the solute molecule and α labels the charge site)

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due to the solvent is given by

$$\phi(\mathbf{r}_{1\alpha}) = \sum_{j=2}^{N} \sum_{\beta=1}^{3} Q_{\beta}/|\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta}| \qquad (1)$$

The electrostatic potential energy of the solute is

$$\langle U_{es} \rangle = \sum_{\alpha=1}^{3} Q_{\alpha} \langle \phi_{\alpha} \rangle \qquad (2)$$

and the electric field is

$$\mathbf{E}(\mathbf{r}_{1\alpha}) = -\left\langle \frac{\partial \phi(\mathbf{r}_{1\alpha})}{\partial \mathbf{r}_{1\alpha}} \right\rangle \qquad (3)$$

where the brackets $\langle \cdots \rangle$ indicate an average over the solvent configurations. The free energy, ΔA_{es}, for the solute with a set of partial charges $\mathbf{Q}$ can be calculated by using the charging integral,

$$\Delta A_{es}(\mathbf{Q}) = \sum_{\alpha=1}^{3} Q_{\alpha} \int_{0}^{1} \langle \phi(\mathbf{r}_{1\alpha}) \rangle_{\lambda} \, d\lambda$$

$$= \int_{0}^{1} \langle U_{es} \rangle_{\lambda} / \lambda \, d\lambda \qquad (4)$$

where the angular brackets, $\langle \cdots \rangle_{\lambda}$, indicate an ensemble average with the solute charges equal to $\lambda \mathbf{Q}$.[6] Equation 4 is integrated numerically by performing simulations at 11 different hydrogen charges, ranging from 0 to 0.5.

Continuum theories assume that the solvent response to the solute is linear in the solute charge. Specifically, the potential, $\phi(\mathbf{r}_{1\alpha})$, is linear in the charge Q_{α} and therefore, from eq 4, $\Delta A_{es} \propto Q^2$. The results of the simulations will test the assumption of linear response. Specifically, continuum theory based on the Poisson equation is a linear theory in that it assumes that the orientations of the solvent molecules respond linearly to the electric field of the solute.[7] In real molecular liquids, nonlinear responses not described by the Poisson equation arise from many factors including the formation of solute–solvent hydrogen bonds and electrostriction, the decrease in the excluded volume of the solute due to the increased solute–solvent Coulombic interaction. Strong hydrogen bonds prevent the solvent from further responding to the solute causing dielectric saturation which decreases the solvation energy. On the other hand, electrostriction increases the solvation energy.

Methods

The water potential used here is the SPC potential, characterized by an OH bond length of 1 Å, an HOH bond angle of 109.47°, charges on the hydrogens and oxygen equal to 0.41e and –0.82e, respectively, and a Lennard-Jones interaction between oxygen atoms with a well depth, ϵ/k_B, equal to 78.2 K and a radius, σ, equal to 3.166 Å.[8] The molecular dynamics simulations were performed on the Connection Machine CM-5 with use of a direct N^2 method,[9] with 511 *solvent* molecules and 1 *solute* molecule. Periodic boundary conditions, using the Ewald sum for the long-ranged electrostatic potentials, a time step of 1 fs, and the SHAKE algorithm for enforcing bond constraints, are used.[10] The simulations are done in the canonical (constant T, V, N) ensemble by coupling to a

Nosé thermostat[10,11] and are at a density of 1 g/cm³ and a temperature of 300 K. Each data point at a given charge represents a 40-ps simulation.[12] The electrostatic potential with periodic boundary conditions is

$$\phi(\mathbf{r}_{1\alpha}) = {\sum_{\mathbf{n}}}' \sum_{j=1}^{N} \sum_{\beta} Q_{\beta}/|\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta} + \mathbf{n}| \qquad (5)$$

where the prime on the sum over periodic images $\mathbf{n}$ indicates that for $\mathbf{n} = 0$ the term $j = 1$ is omitted. In the standard Ewald evaluation of eq 5, the energy is written as a sum of four terms,

$$\phi(\mathbf{r}_{1\alpha}) = \sum_{j=2}^{N} \sum_{\beta} Q_{\beta} \, \mathrm{erfc}(\kappa|\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta}|)/|\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta}|$$

$$+ \sum_{j=1}^{N} \sum_{\beta} Q_{\beta} \frac{4\pi}{L^3} \sum_{\mathbf{G} \neq 0} \frac{1}{G^2} e^{-G^2/4\kappa^2} \cos(\mathbf{G} \cdot (\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta}))$$

$$- \frac{2\pi}{3L^3} \sum_{j=1}^{N} \sum_{\beta} Q_{\beta} (\mathbf{r}_{1\alpha} - \mathbf{r}_{j\beta})^2$$

$$- \sum_{\beta} Q_{\beta} \, \mathrm{erf}(\kappa|\mathbf{r}_{1\alpha} - \mathbf{r}_{1\beta}|)/|\mathbf{r}_{1\alpha} - \mathbf{r}_{1\beta}| \qquad (6)$$

where κ is a parameter in the Ewald sum chosen for computational convenience to be $6/L$, L is the length of the primary simulation cell, and $\mathbf{G}$ is a recriprocal lattice vector of the periodic simulation cells.[10]

In the continuum calculations, the solute is characterized by a molecular cavity defined by spheres around each charge site and a dielectric continuum outside this cavity. The potential, ϕ, can then be found by solving the Poisson equation

$$\nabla \cdot \epsilon(\mathbf{r}) \nabla \phi(\mathbf{r}) + 4\pi \rho(\mathbf{r}) = 0 \qquad (7)$$

where $\epsilon(\mathbf{r})$ is a position-dependent dielectric constant, equal to 1 inside the solute cavity and 65 outside (65 is the dielectric constant of the SPC water model,[13,14] and $\rho(\mathbf{r})$ is the charge density. Equation 7 is solved using the DelPhi program, which discretizes space on a cubic grid (with $65 \times 65 \times 65$ points).[15] This approach is thus based on a finite-difference solution of the Poisson equation. The calculations reported here use focusing boundary conditions, in which successive calculations are done, each with a finer mesh, using the previous coarser grid results to correct for the long-range boundary effects. At the highest resolution, 80% of the grid points are inside the solute cavity, corresponding to a grid spacing of about 0.034 Å. The water molecule geometry is the SPC geometry. The oxygen cavity radius, r_O, is set equal to 1.77 Å and the hydrogen cavity radius is 0.8 Å. The oxygen radius is about $2^{-5/6}\sigma$, one-half the minimum of the Lennard-Jones potential. This is the standard method for choosing radii in DelPhi calculations.[2,4]

Results and Discussion

The free energies corresponding to the molecular dynamics (MD) simulations and to the CT calculations are shown in Figure 2. At the charge value of SPC water ($Q_H = 0.41$), the MD and CT yield -8.4 ± 0.5 and -10.5 kcal/mol, respectively, for ΔA_{es}. The reported error bars are two standard deviations. This difference of about ± 2 kcal/mol between the two methods is comparable to the agreement between the CT and molecular free energy calculations (using the TIP4P water potential) for several solutes (but not water).[2] The charge dependence for the simulation data is not quadratic, as can be seen by the poorness of a quadratic fit (the dotted line).

Previous calculations for SPC and also TIP4P water embedded in a dielectric continuum find $\Delta A_{es} = -10.96$ and -10.89 kcal/mol, respectively.[16] These calculations use an oxygen cavity radius

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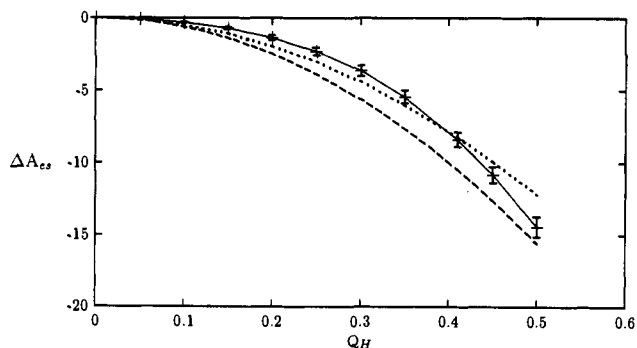(10) Allen, M. P.; Tildesley, D. J. *Computer Simulation of Liquids*; Oxford University Press: Oxford, 1987.

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Figure 2. Free energy, ΔA_{es}, from MD simulations (solid line) and DelPhi continuum calculations (dashed line) as a function of solute charge (in kcal/mol). The dashed line is a quadratic fit to the simulation data.
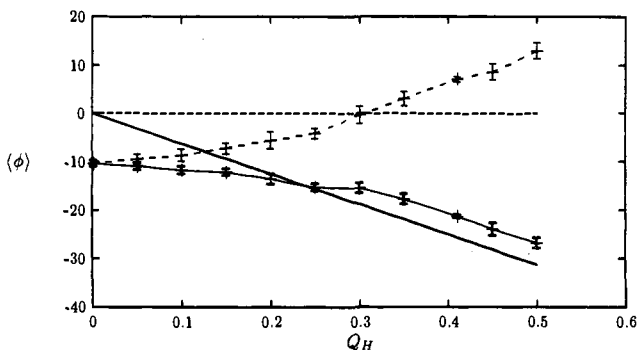

Figure 3. The average electrostatic potential, $\langle\phi\rangle$ (in kcal/(mol e)), at the hydrogen (solid lines) and oxygen (dashed lines) position, comparing the MD simulations (the lines showing data points and error bars) with DelPhi continuum results (no point symbols).

of 1.5 Å and a hydrogen cavity radius of 1.16 Å. The sensitivity of the CT results to these input parameters will be discussed below. Other CT calculations by Sharp et al.[4] for the TIP4P geometry, which include polarizability of the solute, find ΔA_{es} = -9.3 kcal/mol. There have been calculations of ΔA_{sol} from molecular simulations, but the electrostatic part, ΔA_{es}, was not reported so there is no other molecular simulation with which to compare.[17]

Figure 3 shows the average electrostatic potentials, $\langle\phi\rangle$. The MD and CT results are qualitatively different in two respects: (1) $\langle\phi_H\rangle$ and $\langle\phi_O\rangle$ from the MD simulations are not linear in charge and (2) $\langle\phi_H\rangle$ and $\langle\phi_O\rangle$ from MD are not zero at zero charge, whereas the ϕ's from the CT calculations are linear in charge and zero at zero charge. As is well-known, molecular water solvates a small uncharged solute by forming a clathrate cage around the uncharged sphere.[18] For realistic water potentials, the electrostatic potential is not zero inside the cage because fluctuations of the water molecules that form the clathrate cage are known to bring the hydrogen atoms closer to the cage than the oxygen atoms. This is apparent from the charge distribution function (see below). Since the positive charges can get closer than the negative charges there is a net electrostatic potential inside the sphere. However, it is the spatial dependence and not the exact value of ϕ that is important because (1) properties such as the electric field and the energy are invariant with respect to an additive constant in ϕ and (2) the exact value of $\langle\phi\rangle$ is strongly dependent on the choice of boundary conditions used in the Ewald sum. In the Ewald summation, the periodically replicated system must be surrounded by a medium; in eq 6 the medium is taken to be an insulator (this boundary term is the third term on the right-hand side of the equation). If the surrounding medium is taken to be a conductor, then this term vanishes.[10] The boundary

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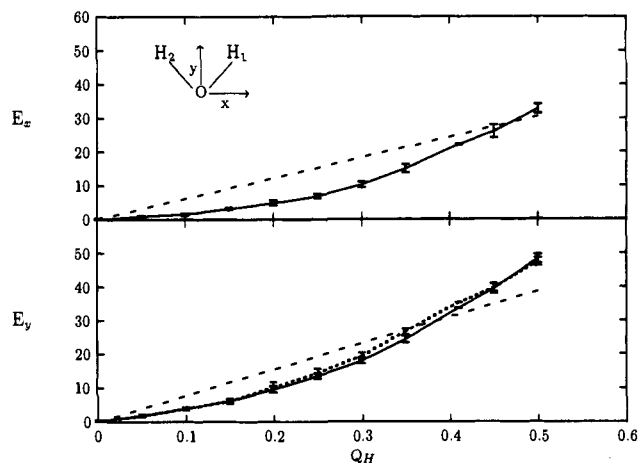

Figure 4. Electric field, E (kcal/(mol e Å)), in the x direction at the H_1 hydrogen atom (top) and in the y direction at the hydrogen and oxygen atoms (bottom) comparing MD simulation (solid (H) and dashed lines (O)) and DelPhi continuum calculations (dashed lines). In the continuum model E_y at the H and O sites are equal; for the simulation there is a small difference (see text). See the upper left-hand corner for the definition of the coordinate system.

conditions have only a slight influence on most properties; however, for the electrostatic potential the boundary conditions give rise to a large constant term.

The electric field, E, arising from the solvent at each solute site is shown in Figure 4. The geometry of the water molecule is shown in the upper left corner of Figure 4. The top panel shows the x component of the field, E_x, at the position of the hydrogen H_1, E_x at the other hydrogen is minus the field at H_1, and E_x at the oxygen is zero. The bottom panel shows the y component of the field at the oxygen and hydrogen positions. Since there is no net force on the molecule and for the continuum solvent all forces are Coulombic then

$$\sum_{\alpha} Q_{\alpha} E(r_{1\alpha}) = 0$$

and the y component of the field at the oxygen site and hydrogen sites must be equal. For the SPC simulations, there is an additional force on the oxygen atom due to the nonbonded Lennard-Jones interaction which has a small nonzero component in the y direction (at Q_H = 0.41, it is 1.47 kcal/(mol Å)) so the net force is zero but the electrostatic fields do not exactly balance. The field from the MD simulation is not linear in charge, unlike the CT field. This is consistent with the simulation results for the electrostatic potential, ϕ, being nonlinear and the free energy, ΔA_{es}, being non-quadratic (Figures 3 and 4). A non-quadratic charge dependence was reported by Jayaram et al.[3] for the solvation of a spherical cation.

Any conclusions regarding the validity of dielectric continuum theory are of course dependent on the input parameters, particularly on the radii, r_O and r_H. The values for the ΔA_{es}, the x and y components of the electric field, and the Coulomb energy, $\langle U_{es}\rangle$, are given in Table 1. (From the fact that the electrostatic potential $\langle\phi\rangle$ is linear in charge, it follows from eqs 2 and 4 that $\Delta A_{es} = \langle U_{es}\rangle/2$ for the continuum results.) Also shown on Table 1 are the SPC simulation results and the results of two approximate models (see below). Some cavity radii give accurate estimates for the free energy, but it is not possible for continuum theory to simultaneously predict values of ΔA_{es}, $\langle U_{es}\rangle$, and the electric field, E, to within 20%. In addition, the charge dependence of $\langle U_{es}\rangle$ and E must be linear and ΔA_{es} must be quadratic, in contrast to the results of the simulation. There are sets of radius parameters which will give the best quadratic fit to the simulation free energy. Two such sets are (r_O = 1.88 Å, r_H = 0.80 Å) and (r_O = 1.83

Table 1. Comparison of the MD Simulation Results (First Row) with Continuum Theory (CT) Results for a Variety of Cavity Radii (r_O, r_H), the Scaled Radius CT Results, and Semicontinuum Results with n Explicit Neighbors[a]

	ΔA_{es}	$\langle U_{es} \rangle$	$E_x(r_{H1})$	$E_y(r_{H1})$
simulation	−8.4(5)	−23.32(6)	22.2(1)	33.6(1)
CT ($r_O = 1.77$, $r_H = 0.80$)	−10.5	−21.0	25.	32.
($r_O = 1.88$, $r_H = 0.80$)	−8.2	−16.4	17.	25.
($r_O = 1.83$, $r_H = 1.00$)	−8.2	−16.4	14.	25.
($r_O = 1.80$, $r_H = 1.00$)	−8.6	−17.2	15.	26.
($r_O = 1.70$, $r_H = 1.10$)	−8.7	−17.4	12.	27.
($r_O = 1.50$, $r_H = 1.16$)	−10.1	−20.2	12.	31.
scaled radius CT	−8.4	−23.6	26.	35.
semicontinuum ($n = 4$)	−11.3(3)	−26.1(1)	26.1(7)	39.2(4)
($n = 6$)	−10.3(4)	−25.2(4)	24.0(7)	37.6(5)
($n = 8$)	−9.7(5)	−24.2(2)	22.9(3)	36.1(2)

[a] The properties listed are the free energy, ΔA_{es}, the Coulomb energy, $\langle U_{es} \rangle$, both in kcal/mol, and the x component, E_x, and y component, E_y, of the electric field in kcal/(mol e Å) (see Figure 4) for a solute with Q_H = 0.41. The numbers in parentheses are two standard deviation error estimates.
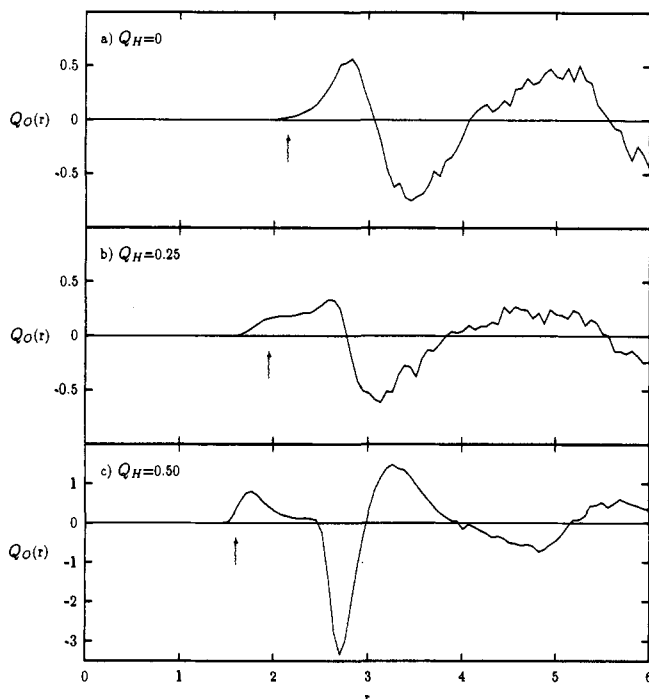

Figure 6. As for Figure 4, but comparing MD simulation (solid lines), DelPhi continuum results with fixed radii (dashed lines), and scaled radii continuum results (dotted lines).

Figure 5. Solvent charge distribution (determined from the MD simulations) about the solute oxygen site for (a) $Q_H = 0$, (b) $Q_H = 0.25$, and (c) $Q_H = 0.50$. The arrows indicate the optimized oxygen cavity radius.

Å, r_H = 1.00 Å) which will give the free energy curve shown by the dotted line of Figure 2.

The solvent reorganization that results from increasing the charge of the solute molecule is reflected in the radial distribution of charge, defined by

$$Q_\alpha(r) = \frac{4\pi}{3}\rho r^2 \sum_{\beta=1}^{3} Q_\beta g_{\alpha\beta}(r) \qquad (8)$$

where ρ is the bulk density of the solvent, the factor of 3 in the dominator is introduced to reflect that there are three atomic sites, and $g_{\alpha\beta}$ is the pair correlation function between the atomic sites α on the solute and β on the solvent molecules.[19] Figure 5 shows $Q_O(r)$—the radial distribution of charge as a function of distance from the solute oxygen site—for three values of the solute charge: Q_H = 0, 0.25, and 0.50. The distribution functions oscillate between positive hydrogen atom peaks and negative
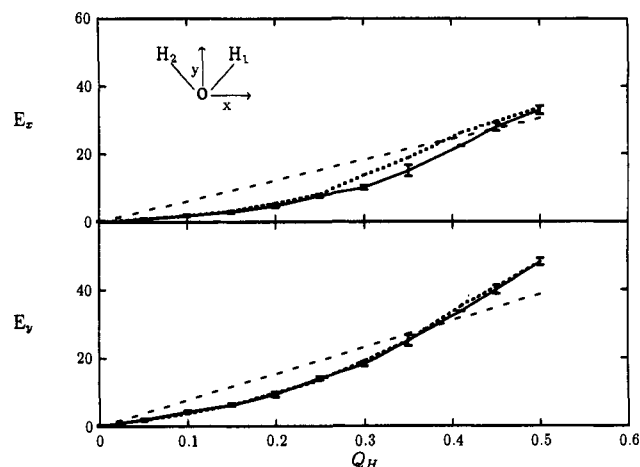
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oxygen atom peaks. As the charges on the solute are increased, the first peak moves in. In addition, a peak grows in at a O–H hydrogen bond distance of 1.8 Å. This hydrogen bond peak is faintly visible at Q_H = 0.25 and is prominent at Q_H = 0.50.

We focus on two of the possible explanations of the breakdown of dielectric continuum models: (1) dielectric saturation, in which the orientational ordering (from hydrogen bonds) of the first solvation shell decreases the dielectric response of the solvent, and (2) electrostriction, in which the solvent molecules come into closer contact with the solute molecule as its polarity is increased, and which thus leads to a decrease in the solute cavity as solute charge is increased. Dielectric saturation effects decrease the solvation energy whereas electrostrictive effects increase the solvation energy. Both of these solvent responses are visible in Figure 5. We will take two approaches to understanding the differences in the MD simulation free energies and the continuum free energies. In one, we will scale the cavity size with solute charge in the continuum model. In the other, we will explicitly include first shell waters in the CT calculations.

Scaled Radius. From Figure 5, for Q_H = 0 the cavity is larger than $2^{-5/6}\sigma$ (=1.78 Å), since the solvent peak does not start until after 2 Å, and the CT results, which use 1.77 Å as a cavity radius, therefore overestimate the free energy at low charges (see Figure 2). This raises a question as to whether the differences between the simulation and CT calculations are due to the approximation of a continuum solvent or just an inconsistent choice of cavity size. Estimates of the cavity size can perhaps be found from an examination of the liquid structure, although assigning a sharp solute/solvent boundary from a continuous distribution is ambiguous. A simple heuristic method is to find the radius which gives the best value for the Coulomb energy, $\langle U_{es} \rangle$. For each value of Q_H the optimal oxygen radius is found (the hydrogen radius is set equal to a constant value of 0.8 Å) and the free energy is calculated from eq 4. The resulting $\langle U_{es} \rangle$ and ΔA_{es} are in almost exact agreement with the simulation values (see Table 1). Of course, this agreement is by construction and with one adjustable parameter it is a trivial accomplishment to fit the simulation energies. However, this method also gives good values for the electric fields, which is not by construction (see Figure 6). The optimized oxygen radius is shown for each value of the hydrogen charge in Figure 7 (there is no optimized value at Q_H = 0 since at this point $\langle U_{es} \rangle$ = 0). The oxygen radius shows a strong charge dependence—the radius varies by 30% over the range of charges—and this dependence is approximately linear with a slope of about 1.2 Å/e. There is some uncertainty in the radius for low values of the charge since the energy is small and variations of ±0.1 Å in r_O give rise to energies which are all within the error bars of the simulation. The values of the scaled

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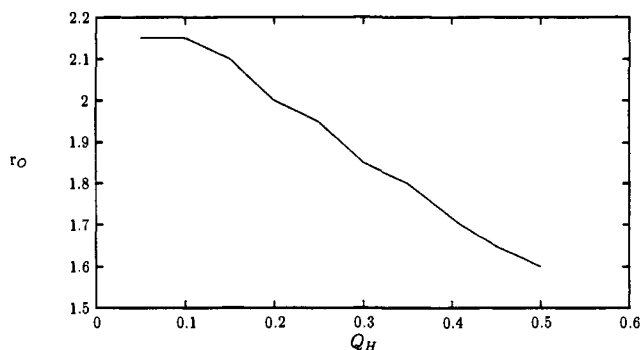*J. Am. Chem. Soc., Vol. 116, No. 9, 1994* 3953

Figure 7. Optimized oxygen cavity radius, r_O, as a function of solute charge.
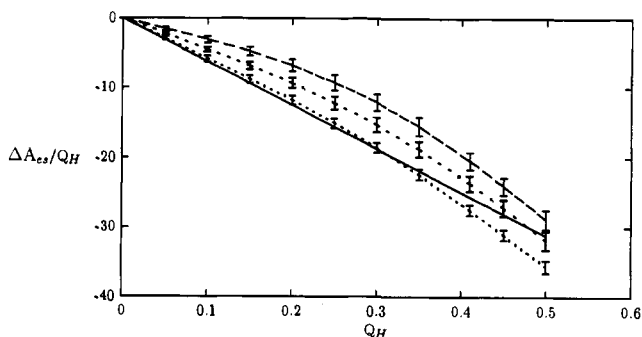

Figure 8. Free energy divided by hydrogen charge, Q_H, for the full MD simulation (long-dashed line), semicontinuum with 4 neighbors (dotted line), semicontinuum with 8 neighbors (short-dashed line), and the continuum theory (solid line).

r_O are shown by the arrows on Figure 5 indicating that these radii are consistent with the liquid structure. The arrow on the $Q_H = 0$ plot is the radius for $Q_H = 0.05$.

Semicontinuum Methods. In this model the nearest neighbor solvent water molecules are treated explicitly and the rest are treated as a continuum. This method could include both dielectric saturation effects as the first solvation shell orders around the solute and electrostriction effects as the first solvation shell moves closer to the solute. The focus of this analysis is to see if we can explain the nonlinear effects seen in the simulation in terms of reorganization of the local solvation shell. This method is implemented as follows. Configurations generated from the SPC simulation are taken and the coordinates of the solute plus its n nearest neighbors are input into the DelPhi program. This is done for about 300 configurations, each taken 0.1 ps apart. The energy and fields on the central solute will now be a sum of a part coming from the n explicit nearest neighbors and the dielectric continuum. This model is similar to previous semicontinuum methods, although here (1) we are averaging over configurations of the first shell molecules and *not* using thermodynamic data for the first shell contribution as is done in the other studies and (2) we are taking an arbitrary surface for regions beyond the first shell (as defined by the radii of the first shell atoms) and *not* a spherical shell.[20,21] Another semicontinuum study by Rashin and Bukatin includes one first shell water inside the continuum and thermodynamic properties are found by integrating numerically over the solute and single solute water coordinates and then extrapolating to a full hydration shell.[22] We are treating the number of explicit water molecules, n, as a variable, ranging from 4 to 8, in order to measure how many solvent molecules are strongly influenced by the solute.

Figure 8 compares the results of the full simulation, the continuum theory (with $r_O = 1.77$ Å and $r_H = 0.80$ Å), and the
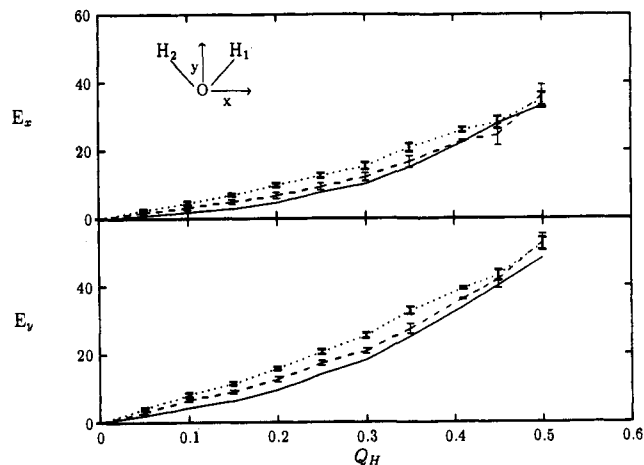
(20) Pitzer, K. S. *J. Am. Chem. Soc.* **1972**, *94*, 1476.
(21) Pitzer, K. S. *J. Phys. Chem.* **1983**, *87*, 1120.
(22) Rashin, A. A.; Bukatin, M. A. *J. Phys. Chem.* **1991**, *95*, 2942–2944.

Figure 9. As for Figure 4, but comparing simulation (solid lines) results with semicontinuum results for 4 (dotted lines) and 8 neighbors (dashed line).

semicontinuum results with 4 and 8 neighbors. This figure gives ΔA_{es} divided by Q_H versus Q_H. The semicontinuum results and the full md simulation exhibit a similar nonlinear dependence on $\Delta A_{es}/Q_H$ on Q_H, although the deviations from linearity are not as great for the semicontinuum model. This means that the nonlinear effect is largely local, as is also supported by the scaled radius analysis. At low charges the $n = 4$ semicontinuum results are essentially the same as the pure continuum results, implying that we have not included enough explicit neighbors. At high charges the semicontinuum results are different from the continuum results. The free energy at a given charge depends on values of the potential at lower charges, through eq 4. Continuum theory with radii $r_O = 1.77$ Å and $r_H = 0.8$ Å overestimates $\langle U_{es} \rangle$ at low charges (because the oxygen radius is too small, see the preceding section) and underestimates it at higher charges (see Table 1). The $n = 4$ semicontinuum results also overestimate the potential energy at low charges (because it has not included enough neighbors and is similar the pure continuum results), and at higher charges, it does not have the same fortuitous and compensating underestimation of $\langle U_{es} \rangle$ (because at higher charges four solvating waters can more adequately describe the local environment). Therefore, the continuum theory gives better estimates of the free energy at high charge than the $n = 4$ semicontinuum method. For other properties, such as $\langle U_{es} \rangle$ (Table 1) and the electric fields (Table 1 and Figure 9), the semicontinuum methods are closer to the simulation results and as n increases, the agreement improves. At $Q_H = 0.41$ the first solvation shell contains 5 neighbors as measured by integrating the g_{OO} out to the first minimum. At $Q_H = 0$, the first solvation shell is broader and contains more molecules (about 16). By including up to 8 explicit neighbors in the semicontinuum model we are then including all the first shell solvent molecules of the higher charge solute, but only some of the first shell molecules of the lower charge solute. At the highest charges, above 0.41, the semicontinuum results are the same for 4 and 8 neighbors, so at these charges there is strong tetrahedral ordering and 4 nearest neighbors are enough to describe the local structure.

Conclusion

The simple example of solvation presented here is that of a single water molecule with partial charges on the atomic sites which are varied between zero and values greater than the charges for water (a partial charge on the hydrogen atoms equal to 0.50e). The continuum theory (CT) calculation by definition shows a simple quadratic dependence on charge for the free energy, ΔA_{es}, and a linear dependence for electrostatic potential, ϕ, and the electric fields, E. From the MD simulations, the charge depen-

dence of ΔA_{es} is definitely non-quadratic and that of $\langle \phi \rangle$ and $\mathbf{E}$ nonlinear (see Figures 2, 3, and 4). The MD simulations then indicate that some type of solvent reorganization other than the reorientation of the electric moments of the solvent molecules is occurring as the solute is charged. Because these effects are important and because they are not included in the CT calculations, continuum theory cannot simultaneously predict free energies, potential energies, and electric fields to within 20% no matter what radius parameters are used (see Table 1). There are sets of radius parameters which will predict the free energies shown by the dotted line in Figure 2, which represents the best quadratic fit to the simulation free energy.

Two simple models are suggestive of the types of solvent reorganizations that are important to this solvation process. These models also provide a method to improve continuum theory. In one model, the size of the solute cavity is charge dependent (scaled radius) and in the other model the system inside the dielectric continuum contains the solute together with explicit neighboring solvent molecules (semicontinuum). The energies and free energies for all of the different methods (MD simulation, pure continuum theory, scaled radius, and semicontinuum) are summarized in Table 1. As can be seen from this table and also from Figure 6, the scaled radius method provides a good estimate of the free energy and the electric fields. The agreement between the scaled radius and MD simulation results for the Coulomb energy, $\langle U_{es} \rangle$, is by construction since $\langle U_{es} \rangle$ is used to determine the scaled radius. The success of the scaled radius calculations suggests that electrostriction plays a more important role than dielectric saturation of close-lying solvent molecules in explaining the deviations of the continuum model from the full molecular solvent. The oxygen radius used in the scaled radius method varies by a large amount (30%) with the charges of the solvent (see Figure 7). This large decrease in the solute cavity is also seen in the liquid correlation functions from the simulation (see Figure 5).

In conclusion, simple continuum theory, as usually implemented in DelPhi calculations, is not capable of determining free energies to better than 2 kcal/mol accuracy and gives inaccurate predictions of electrostatic potentials and electric fields. We believe that continuum theory can be improved to give better than 1 kcal/mol accuracy by adopting charge dependent radii to allow for electrostrictive effects. It remains to invent a theoretical model that predicts how site radii should be scaled with charge.