

Perspective on Foundations of Solvation Modeling: The Electrostatic Contribution to the Free Energy of Solvation

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1. Introduction

Solvation effects are essential components of all liquid-state chemistry, and it is impossible to understand liquid-phase organic, biological, or inorganic chemistry without including them. The Nobel-Prize-winning gas-phase quantum mechanical electronic structure methods of Pople¹ and Kohn et al.² require the additional inclusion of solvent for reliably addressing problems in liquid-phase chemistry. Methods that include the solvent implicitly are especially powerful because they allow one to retain the minimal representation of the solute, thereby facilitating progress with quantum mechanical calculations at the same high levels as those used in the gas phase,^{3,4} and because they allow one to model the solvent with the correct bulk permittivity. Reliable calculations of solutes in solution must take account of electrostatics, cavitation, dispersion, and solvent structure, but solvation effects are frequently dominated by electrostatics. Therefore, achieving a solid understanding of electrostatic solvation effects is an excellent starting point for understanding solvation and improving solvation models.

Thermodynamically, there is no unique way to separate electrostatic from nonelectrostatic contributions to the free energy of solvation;⁵ only their sum is a state function.⁶ Nevertheless, one might try to *define* the electrostatic contribution in a way that most practitioners would find reasonable and definitive and to use that as a starting point for physical analysis. It is already known, however, that various successful solvation models make this partition differently.⁷ This is sometimes attributed to their use of different parameters, especially the atomic radii. If the atomic radii were the only issue, one might try to define them in some unambiguous way, for example, from radial distribution functions,⁸ and thereby establish a useful working

definition of the electrostatic contribution to equilibrium solvation effects in terms of the static relative permittivity and systematically defined atomic radii.

The first subject of the present contribution is to examine popular implicit solvation models with a view to understanding if the above procedure has merit. After that, we draw some general conclusions about solvation modeling.

In section 2, we summarize the relevant theoretical background. In section 3, we summarize five methods for estimating the electrostatic contribution to the free energy of solvation, and in section 4, we compare calculations (especially designed for this perspective) carried out with these methods. Section 5 contains discussion, and section 6 gives the principal conclusions.

2. Theory

In the electrostatic theory of dielectric media (i.e., nonconducting media), the medium is associated with a relative permittivity ϵ , which is a scalar constant for isotropic homogeneous media and a scalar function of position for isotropic nonhomogeneous media. The charges of the medium (called bound charges) do not appear explicitly, and the charge density per unit volume of explicitly treated objects in the medium is called the free charge density ρ_f . In a linear isotropic homogeneous medium, the scalar electric potential Φ satisfies Poisson's equation:

$$\epsilon \nabla^2 \Phi = -4\pi \rho_f \quad (1)$$

For a nonhomogeneous medium, ϵ depends on position. For such a medium eq 1 is replaced by⁹

$$\nabla \cdot (\epsilon \nabla \Phi) = -4\pi \rho_f \quad (2)$$

which will be called the nonhomogeneous Poisson equation (NPE). In the application considered in this article, ρ_f is the solute charge density. Implicit solvation models (sometimes called continuum solvation models or implicit or continuum

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solvent models) represent a solvated molecule at an atomic level of detail inside a molecule-sized (and usually molecule-shaped) cavity surrounded by a dielectric medium that represents the solvent. The relative permittivity is equated to the bulk static solvent value ϵ_s outside the cavity and to a smaller value inside the cavity. The smaller value is usually taken as unity (the relative permittivity of empty space), which is appropriate if the solute polarization is treated explicitly. Although models that treat the solute by unpolarized molecular mechanics are sometimes used, the rest of this article is concerned with models that treat the solute as polarizable and quantum mechanical. One then solves the NPE coupled to the quantal description of the solute to obtain the electric potential due to the polarized dielectric continuum and the polarization of the solute; this potential, called the reaction field φ , equals the total potential Φ minus the electrostatic potential¹⁰ $\Phi^{(0)}$ of the gas-phase molecule.

From the reaction field, one calculates the free-energy change corresponding to the solvation process. If we approximate the solute as rigid, the electrostatic contribution to the free energy of solvation is given by¹¹

$$\Delta G_{EP} = \langle \Psi | H^{(0)} - \frac{e}{2} \varphi | \Psi \rangle + \frac{e}{2} \sum_k Z_k \varphi_k - \langle \Psi^{(0)} | H^{(0)} | \Psi^{(0)} \rangle \quad (3)$$

where e is the atomic unit of charge, φ_k is the reaction field evaluated at atom k , Z_k is the atomic number of atom k , $H^{(0)}$ and $\Psi^{(0)}$ are the solute electronic Hamiltonian and electronic wave function, respectively, in the gas phase, and Ψ is the polarized solute electronic wave function in solution. This equation includes the polarization of the solvent by the solute and the distortion of the solute that is induced by this polarization effect. If the charge density (the sum of the electronic charge density $e|\Psi|^2$ and the nuclear charges) is represented by a set of nuclear-centered partial charges q_k , then

$$-\langle \Psi | e\varphi | \Psi \rangle + e \sum_k Z_k \varphi_k = \sum_k q_k \varphi_k \quad (4)$$

which is always negative (favorable to the solvation process) if the model is accurate.

A key issue in all implicit solvation models is the boundary between the solute cavity where $\epsilon < \epsilon_s$ and the solvent continuum where $\epsilon = \epsilon_s$. In modern models, the boundary is defined to enclose a superposition of atom-centered spheres with radii ρ_k , which are called intrinsic Coulomb radii. The boundary that encloses this superposition of spheres may be defined to precisely enclose these spheres and nothing else,^{12,13} which is called the solvent-accessible surface (SAS), or it may also enclose the regions not touched by a certain-size ball (whose radius is called the solvent radius or probe radius) rolling on the SAS;¹⁴ the latter is called the solvent-excluding surface or Connolly's molecular surface. The intrinsic Coulomb radii may be the van der Waals radii of the atoms, scaled van der Waals radii, van der Waals radii augmented by a solvent radius, or freely adjustable parameters. (Some models use spheres, ellipsoids, or isodensity surfaces of the solute electron density as the boundary, but

such cavity boundaries are either unrealistic or numerically troublesome and will not be considered here.)

Other implicit solvent models do not start with the NPE, and it is instructive to classify implicit solvation models into two groups, those that solve the NPE numerically, for example, by finite differences¹⁵ or by boundary element methods based on integral equations,¹⁶ and those that employ a starting point based on Coulomb's law, for example, single-center multipolar expansions^{17,18} or the generalized Born (GB) approximation.^{19–27} The Coulomb's law models represent the solute as a collection of point charges^{19–27} (the distributed monopole approximation), almost always located at the nuclei, or as a set of point multipoles at the center of the molecule.^{17,18} Most NPE solvers use the continuous electron density of the solute, without approximating it by charges or multipoles. One may label such solvers as density-based NPE solvers. However, at least one NPE solver, which is called the Poisson–Boltzmann solver (PBS),²⁸ uses an iterative two-step approach in which the first step of each iteration (the calculation of an apparent surface charge that represents the field due to the polarized dielectric medium) uses a distributed monopole representation $\{q_k\}$ of the solute charge density, and the second step (the calculation of the interaction of the apparent surface charge with the solute electron density) uses the continuous density distribution of the solute.

In practice the NPE solvers approximate the reaction field at an arbitrary position \mathbf{r}_K within the cavity as

$$\varphi_K = \sum_m \frac{q_m}{|\mathbf{r}_K - \mathbf{r}_m|} \quad (5)$$

where \mathbf{r}_m is the coordinate of an element m of surface area on the solute–solvent boundary (these elements are called tesserae), and q_m is the apparent surface charge on element m . In contrast, the GB approximation is equivalent to approximating the reaction field distribution as

$$\varphi_k = \sum_{k'} \frac{q_{k'}}{|\mathbf{r}_k - \mathbf{r}_{k'}|} f_{kk'} \quad (6)$$

where \mathbf{r}_k and $\mathbf{r}_{k'}$ are evaluated only at atomic positions, and $f_{kk'}$ is a function to be specified. The value of a single term in eq 6 (excluding $q_{k'}$) is called a Coulomb integral. The most successful function $f_{kk'}$ for approximating the Coulomb integrals is the dielectric descreening approximation,²⁶ which yields

$$f_{kk'} = - \left(1 - \frac{1}{\epsilon_s} \right) \frac{r_{kk'}}{\sqrt{r_{kk'}^2 + \alpha_k \alpha_{k'} \exp(-r_{kk'}^2/d\alpha_k \alpha_{k'})}} \quad (7)$$

where

$$r_{kk'} \equiv |\mathbf{r}_k - \mathbf{r}_{k'}| \quad (8)$$

and d is a parameter and α_k is the shielded atomic radius of atom k ; α_k represents an appropriately weighted average distance of atom k from the solvent. The number of elements m in eq 5 is in principle increased to convergence, whereas the number of terms k' in eq 6 is equal to the number of atoms in the solute. A relation connecting eqs 5–8 is that^{4,29}

$$\sum_m q_m = - \left(1 - \frac{1}{\epsilon_s} \right) \sum_k q_k \quad (9)$$

In sections 3 and 4, we consider calculations with various NPE solvers and compare them to GB calculations. (We do not include calculations with one-center multipole expansions among our test calculations in this article because for large molecules this method is slowly convergent with respect to the number of multipole moments.)

3. Computational Methods

The NPE coupled to a quantum simulation of a rigid solute was solved using four implicit solvent models implemented in four popular quantum chemical program packages:

- (1) The Integral Equation Formalism Polarizable Continuum Model of *Gaussian 03*,³⁰ namely, IEFPCM^{29,31–33}
- (2) The conductor-like PCM model in the *GAMESS* computer package,^{34–36} namely, C-PCM^{37–43}
- (3) The PBS algorithm^{28,44} in the *Jaguar* computer package⁴⁵
- (4) The Generalized Conductor-like Screening Model (GCOSMO) as implemented in *NWChem*.⁴⁶

There are various ways to implement a conductor-like model, and the various later implementations^{4,38,40,47–50} should not be confused with the original³⁷ COSMO method. In this article, GCOSMO refers to the default implementation of the conductor-like method in the *NWChem*, version 4.7, computer package.⁴⁶ This implementation uses the GCOSMO dielectric screening factor³⁸ for the conductor-like apparent surface charge.

Except for intrinsic Coulomb radii, solvent radii, and ϵ_s , which are specified in section 4, all NPE calculations were carried out with the default numerical parameters and cavity definitions of the respective programs. We varied tesserae surface areas from 0.01 to 0.4 Å² and found no significant dependence of the solvation free energy on this parameter (see the Supporting Information for more details). In the case of large intrinsic Coulomb radii (>5 Å) with IEFPCM/*Gaussian 03*, in order to improve the convergence of the self-consistent reaction field, we set the average area of the tesserae generated on each sphere in the cavity surface to 0.4 Å² (instead of the default value of 0.2 Å²).

The GB calculations were carried out with a locally modified version⁵¹ of *Gaussian 03*.³⁰ The locally modified version is based on algorithms described previously.^{13,52–55} The solute is again considered to be rigid. The Coulomb integrals in the electrostatic polarization formula are approximated with the dielectric descreening approximation of eq 7, with the parameter d set equal to 3.7, which is the value used in the SM6⁵⁶ and SM8⁵⁷ solvation models. The shielded Coulomb radius of atom k is computed by a three-dimensional integration over the entire region outside the atomic sphere defined by the intrinsic Coulomb radius ρ_k of that atom.^{13,26} (A pairwise approximation that has been used in some past work⁵⁸ is not used in the present article.)

In all five methods, the calculations are iterated to self-consistency of the solute electron density with the reaction field due to the solvent, and reported electrostatic solvation energies include the reorganization costs of distorting the

solute and polarizing the solvent. (For four of the methods, the solute distortion cost is broken out in tables presented in the Supporting Information.)

In the example calculations presented in this article, in all five methods, the solute cavity is determined from the same intrinsic Coulomb radii ρ_k that depend only on the atomic numbers Z_k of the atoms; these parameters are called R_Z .

All solvation free energies, ΔG_s , in this paper are the electrostatic contribution only. That is, the cavity, dispersion, solvent structure, repulsion, and liberation components are not included because our goal in this perspective is to compare alternative approaches to the electrostatic contribution. We note that to better illustrate the physics we present results for solute cavities of various sizes, some quite different from those that would be produced using the default atomic radii for specific models. We adopt this strategy because examining the behavior of the models over a large range of parameter space, including intentionally unphysical values, provides insight into the way they work. Analysis of the accuracy of these models with their default settings has been presented elsewhere.^{7,56,57}

4. Results

Nine atomic species ($\text{Ne}^{0,\pm}$, $\text{Na}^{0,\pm}$, $\text{Cl}^{0,\pm}$) and nine molecular species ($\text{C}_2\text{H}_4^{0,\pm}$, C_2H_6 , CH_3OH , CH_3OH_2^+ , CH_3O^- , CH_2CHO , and CH_2CF_2) were studied as model systems with the solvent relative permittivity ϵ_s set equal to the aqueous value of 78.4. Electrostatic calculations were performed with the solvent radius set to zero, in which case the solvent-excluded surface reduces to the SAS. The solute was treated by Hartree–Fock theory with the 6-31G(d)⁵⁹ basis set. In the case of open-shell electronic systems (Ne^\pm , Na , Cl , and C_2H_4^\pm) we employed either restricted open-shell Hartree–Fock (GCOSMO/*NWChem*) or spin-unrestricted Hartree–Fock wave functions (for all other models). We use the Hartree–Fock method in calculations of electrostatic energies of solvation because it is available in all four of the tested programs. We also tested the M05-2X density functional⁶⁰ available in *Gaussian 03*,³⁰ *Jaguar*,⁴⁵ and *NWChem*.⁴⁶ The results obtained by density functional theory were nearly identical to those obtained by Hartree–Fock theory (see the Supporting Information for such a comparison). Electrostatic contributions to the free energies of solvation of molecular species were computed at gas-phase geometries optimized with the M06-2X density functional⁶⁰ and the 6-31+G(d,p) basis set⁵⁹ except that, for the C_2H_4^\pm calculations, we used the M06-2X/6-31+G(d,p) geometry of the neutral molecule.

Tables 1–3 give results for atoms and monatomic ions. In each case, we considered several sets of atomic radii. For atoms and monatomic ions, the GB result reduces to the original Born formula:⁶¹

$$\Delta G_{\text{EP}} = -\frac{1}{2} \left(1 - \frac{1}{\epsilon_s} \right) \frac{q_k^2}{R_Z} \quad (10)$$

which is the exact classical result for the case where the solute is a conducting sphere of radius R_Z . Tables 4–6 give results for molecules and molecular ions. In these cases, we

Table 1. Electrostatic Free Energies of Solvation for Ne, Ne⁺, and Ne[−]

R_{Ne} (Å)	ΔG_{S} (kcal/mol)				
	GB	C-PCM	GCOSMO	IEFPCM	PBS
Ne					
0.85	0.0	−3.8	0.0	−3.8	0.0
1.00	0.0	−0.5	0.0	−0.5	0.0
1.15	0.0	−0.1	0.0	−0.1	0.0
≥1.30	0.0	0.0	0.0	0.0	0.0
Ne ⁺					
0.85	−192.8	−231.7	−213.0	−231.3	−215.0
1.00	−163.9	−177.4	−171.6	−177.2	−173.1
1.15	−142.5	−147.2	−145.4	−147.2	−146.7
1.30	−126.1	−127.7	−127.2	−127.6	−128.5
1.54 ^a	−106.4	−106.8	−106.8	−106.7	−107.9
1.848 ^b	−88.7	−88.8	−88.8	−88.8	−89.9
2.00	−82.0	−82.0	−82.0	−82.0	−83.0
4.00	−41.0	−41.0	−41.0	−41.0	−41.5
10.00	−16.4	−16.4	−16.4	−16.4	−16.6
Ne [−]					
0.85	−192.8	−107.9	−148.0	−110.5	−138.6
1.00	−163.9	−129.8	−151.1	−134.3	−144.2
1.15	−142.5	−130.6	−140.8	−134.7	−136.6
1.30	−126.1	−122.5	−127.2	−125.2	−125.3
1.54 ^a	−106.4	−106.0	−107.6	−107.3	−107.5
1.848 ^b	−88.7	−88.7	−89.3	−89.2	−89.8
2.00	−82.0	−82.0	−82.3	−82.3	−83.0
4.00	−41.0	−41.0	−41.0	−41.0	−41.5
10.00	−16.4	−16.4	−16.4	−16.4	−16.6

^a van der Waals radius according to Bondi. ^b 1.2 × Bondi's radius.

considered several sets of radii obtained by scaling the radii used in the SM6⁵⁶ and SM8⁵⁷ aqueous solvation models by the formula

$$R_Z = MR_Z^{\text{SM8}} \quad (11)$$

where M is a scaling factor. The other two sets of R_Z values correspond to using the van der Waals radii of Bondi⁶² and the same Bondi radii scaled by a factor of 1.2. We chose 1.2 × Bondi because previous recommendations based on COSMO-RS calculations suggested that the optimal radii are about 1.17–1.2 times the Bondi radii.^{63,64} The last set of R_Z values is to set all $R_Z = 10$ Å.

In studying the tables, it is instructive to have an idea of what radii would be most physical for practical calculations. The optimum scaling factor for the radii depends to some extent on how they are optimized, but the following comments might be useful. The scale factor of 1.0 is by definition optimal for the GB algorithm when optimized against the SM6 aqueous training set.⁵⁶ Optimizing M with IEFPCM against all 2821 data points in the SM8 aqueous and nonaqueous training set⁵⁷ yields $M = 1.08$. If, instead of scaling the aqueous SM8 radii (which are the same as the SM6 radii), we scale the Bondi radii and optimize the scale factor against the 2821 data points in the SM8 aqueous and nonaqueous training set, the optimum is found to be 1.08 × Bondi. (In each of these optimizations, we simultaneously optimized a set of SM8-like atomic surface tensions.) When one takes account of these optimizations and when one compares the SM8 radii to the Bondi radii, one finds that the physical region of the tables is between $M = 1$ and $M = 1.3$ and between the Bondi row and the 1.2 × Bondi row.

Table 2. Electrostatic Free Energies of Solvation for Na, Na⁺, and Na[−]

R_{Na} (Å)	ΔG_{S} (kcal/mol)				
	GB	C-PCM	GCOSMO	IEFPCM	PBS
Na					
1.00	0.0	−51.1	0.0	−51.0	0.0
1.15	0.0	−31.3	0.0	−31.3	0.0
1.30	0.0	−19.4	0.0	−19.3	0.0
1.65	0.0	−6.1	0.0	−6.1	0.0
2.00	0.0	−1.8	0.0	−1.8	0.0
2.27 ^a	0.0	−0.7	0.0	−0.7	0.0
2.724 ^b	0.0	−0.1	0.0	−0.1	0.0
≥3.00	0.0	0.0	0.0	0.0	0.0
Na ⁺					
1.00	−163.9	−170.8	−167.2	−170.6	−170.2
1.15	−142.5	−144.6	−143.5	−144.6	−145.7
1.30	−126.1	−126.7	−126.4	−126.5	−128.1
1.65	−99.3	−99.4	−99.4	−99.4	−100.7
2.00	−82.0	−82.0	−82.0	−81.9	−83.0
2.27 ^a	−72.2	−72.2	−72.2	−72.2	−73.1
2.724 ^b	−60.2	−60.2	−60.2	−60.2	−60.9
4.00	−41.0	−41.0	−41.0	−41.0	−41.5
10.00	−16.4	−16.4	−16.4	−16.4	−16.6
Na [−]					
1.00	−163.9	−5.1	17.7	−5.1	23.1
1.15	−142.5	0.0	−3.8	0.0	0.5
1.30	−126.1	−2.4	−18.2	−2.4	−14.6
1.65	−99.3	−17.3	−37.0	−17.3	−34.5
2.00	−82.0	−29.9	−45.1	−29.8	−43.4
2.27 ^a	−72.2	−35.8	−47.5	−35.8	−46.2
2.724 ^b	−60.2	−40.4	−47.6	−40.4	−46.9
3.00	−54.6	−41.2	−46.4	−41.2	−46.0
4.00	−41.0	−38.2	−39.5	−38.2	−39.7
5.00	−32.8	−32.4	−32.6	−32.4	−33.0
10.00	−16.4	−16.4	−16.4	−16.4	−16.6

^a van der Waals radius according to Bondi. ^b 1.2 × Bondi's radius.

When M is increased to greater than ~1.4, the cavity becomes more and more unphysical, but calculations with such M values are included to show how the algorithms respond when the cavity encloses larger and larger fractions of the solute charge density. Similarly, when M gets significantly smaller than 1.0, the cavity again becomes unrealistic, and calculations with such values of M show what happens when the amount of charge outside the cavity gets even larger than it is for realistic cavities.

5. Discussion

The tables show a number of interesting features, especially when one considers that they all correspond in some sense to the same electrostatic problem. Consider first the monatomic species in Tables 1–3. The C-PCM and IEFPCM algorithms yield very similar results for all neutral atoms and cations with all radii examined, except for very small (unphysical) radii. For large atomic radii, these two methods and the GCOSMO method agree precisely with the Born formula for ions, which is comforting; however, the PBS result is always larger by a factor of 1.0182 because *Jaguar*, for reasons unexplained in the original articles,^{28,44} premultiplies all radii by 0.9821. For anions with small radii, the GCOSMO and PBS algorithms sometimes yield unphysical positive results. Even for the Bondi radii, the deviations of the various algorithms from one another are as large as 36.4

Table 3. Electrostatic Free Energies of Solvation for Cl, Cl⁺, and Cl[−]

R_{Cl} (Å)	ΔG_{S} (kcal/mol)				
	GB	C-PCM	GCOSMO	IEFPCM	PBS
Cl					
1.00	0.0	−66.9	−8.1	−66.7	0.0
1.15	0.0	−23.2	−6.4	−23.2	0.0
1.30	0.0	−9.7	−4.9	−9.7	0.0
1.65	0.0	−2.5	−2.3	−2.6	0.0
1.75 ^a	0.0	−1.9	−1.9	−1.9	0.0
2.10 ^b	0.0	−0.9	−0.9	−0.9	0.0
≥4.00	0.0	0.0	0.0	0.0	0.0
Cl ⁺					
1.00	−163.9	−367.0	−258.3	−365.7	−235.6
1.15	−142.5	−239.2	−197.0	−239.2	−178.6
1.30	−126.1	−175.8	−158.1	−175.6	−144.8
1.65	−99.3	−112.3	−109.5	−112.3	−104.2
1.75 ^a	−93.7	−102.8	−101.2	−102.8	−97.2
2.10 ^b	−78.1	−81.2	−80.9	−81.2	−79.5
4.00	−41.0	−41.1	−41.1	−41.1	−41.5
10.00	−16.4	−16.4	−16.4	−16.4	−16.6
Cl [−]					
1.00	−163.9	−6.0	−29.6	−5.9	−17.1
1.15	−142.5	−36.0	−69.4	−36.0	−61.9
1.30	−126.1	−60.5	−86.1	−60.5	−81.9
1.65	−99.3	−81.2	−89.7	−81.2	−89.0
1.75 ^a	−93.7	−81.5	−87.3	−81.4	−87.1
2.10 ^b	−78.1	−75.3	−76.7	−75.3	−77.3
4.00	−41.0	−41.0	−41.0	−41.0	−41.5
10.00	−16.4	−16.4	−16.4	−16.4	−16.6

^a van der Waals radius according to Bondi. ^b 1.2 × Bondi's radius.

kcal/mol, and for radii smaller than the Bondi radii, the deviations are very unsystematic. One should notice the distinction between the model problem of a cavity with a well-defined boundary, where ϵ is discontinuous and there is no solute charge outside the cavity, and a real atom with a nebulous boundary and a solute charge distribution that decreases exponentially to zero far from the nucleus rather than exactly to zero at a boundary. In some methods, the wave function has been constrained to go to zero at the cavity boundary,⁶⁵ and the radius was then variationally optimized. We do not consider such methods here, in part because the great majority of calculations in current use do not employ this constraint, and in part because this procedure does not give realistic results for anionic solutes.⁶⁵

For molecules (Tables 4–6), the clearest trend is that, for a given set of radii, the GB method yields much smaller (less-negative) free energies of solvation than the NPE solvers for neutral molecules (as also found previously⁷), but the GB free energy of solvation is not necessarily less negative for ions. This cannot be attributed to radii, since the radii are the same, and they do not yield this kind of difference for atomic species. For Bondi radii, the various methods differ by up to 5.2 kcal/mol for neutrals, 10.2 kcal/mol for cations, and 5.5 kcal/mol for anions. Even for radii 15% larger than the SM6–SM8 radii, the deviations are up to 4.9 kcal/mol for neutrals, 8.3 kcal/mol for cations, and 4.4 kcal/mol for anions. Even with $M = 4$, some deviations remain as large as 1.2 kcal/mol.

Whereas the GB approximation must give 0 for a neutral atom, it need not give 0 for a neutral molecule. The experimental solvation free energies of C₂H₄, C₂H₆, and

CH₃OH in water are⁶⁶ +1.3, +1.8, and −5.1 kcal/mol, respectively. If, just for the sake of argument, we approximate the cavity, dispersion, and solvent structure contributions as being approximately equal for C₂H₄ and C₂H₆, then ΔG_{EP} should be about 0.5 kcal/mol more negative for C₂H₄ than for C₂H₆. For $M \leq 1.30$, Tables 4 and 5 show much larger differences for the NPE solvers. Similarly, ΔG_{EP} should probably be at most 3–4 kcal/mol more negative for CH₃OH than for C₂H₆, but Table 5 shows much greater differences for the NPE solvers for $M \leq 1.15$ and for GB for $M \leq 0.85$.

A large part of the complication in comparing different approaches to the electrostatic problem must be attributed to outlying charge effects.⁶⁷ These arise from the fact that the Poisson solvers other than IEFPCM (and methods equivalent to it—see next paragraph) assume that the entire solute charge distribution lies within the solute cavity, but the electron density used in the NPE solvers has tails that lie outside the cavity. The GB algorithm and the first step of each iteration in the PBS algorithm assume nuclear-centered charges and therefore have no outlying charge, but there is a related error due to approximating the real charge distribution by distributed monopoles that lie entirely within the cavity. The Born formula itself is not valid for real atomic ions; one reason is that their charge is not confined to a finite cavity.

The IEFPCM method includes an approximate treatment of outlying charge that is equivalent^{28,68} to the approximate SS(V)PE method⁶⁹ of Chipman, but it seems unlikely that this accounts for the entire difference from the GCOSMO algorithm. For example, it has been noted that numerical aspects of the solution of the Poisson equation lead to outlying charge artifacts even for nuclear-centered charges;²⁹ perhaps for this reason it is sometimes called “escaped charge.”

The comparison of calculated solvation energies for C₂H₄⁺ and C₂H₄[−] for a given set of radii is very complex. For example, for $M = 1.30$, C₂H₄[−] is better solvated, whereas for $M \leq 1.00$, C₂H₄⁺ is better solvated with NPE methods, but C₂H₄[−] is better solvated in the GB approximation. Note that a loss of outlying charge decreases the intracavity (negative) charge of an anion and *increases* the intracavity (positive) charge of a cation, which rationalizes the behavior of the NPE solvers. In the GB case, the unit nature of the total charge is unaffected by the choice of cavity size. However, the individual partial atomic charges appearing in eq 6 need not be the same for the anion and the cation, so that different solvation free energies are possible, effectively recognizing higher moments than the molecular monopole by use of an atom-centered monopole expansion of the charge distribution.

We note that GB and NPE methods have been compared previously for the same sets of radii,^{7,70,71} but some of the key issues *vis-a-vis* the GB method that are evident in Tables 1–6 were not brought out in those studies, and the comparison with more than one NPE solver also brings new insight. Furthermore, we note that we do not consider the GB approximation to be an approximation to the model problem solved by the NPE solvers (with its unrealistic or arbitrary

Table 4. Electrostatic Free Energies of Solvation for C_2H_4 , C_2H_4^+ , and C_2H_4^-

M	R_{H} (Å)	R_{C} (Å)	ΔG_{S} (kcal/mol)				
			GB	C-PCM	GCOSMO	IEFPCM	PBS
C_2H_4							
0.85	0.87	1.33	−0.7	−5.6	−5.1	−5.6	−3.8
1.00	1.02	1.57	−0.3	−3.6	−3.7	−3.6	−3.0
1.15	1.17	1.81	−0.2	−2.3	−2.3	−2.3	−2.1
Bondi	1.20	1.70	−0.2	−2.2	−2.3	−2.2	−2.0
1.30	1.33	2.04	−0.1	−1.5	−1.7	−1.4	−1.2
1.2 × Bondi	1.44	2.04	−0.1	−1.2	−1.2	−1.2	−1.0
1.65	1.68	2.59	0.0	−0.5	−0.4	−0.5	−0.4
2.00	2.04	3.14	0.0	−0.2	−0.2	−0.2	−0.2
3.00	3.06	4.71	0.0	0.0	0.0	0.0	0.0
n.a.	10.00	10.00	0.0	0.0	0.0	0.0	0.0
C_2H_4^+							
0.85	0.87	1.33	−88.7	−109.0	−101.9	−109.0	−104.8
1.00	1.02	1.57	−80.1	−88.8	−88.6	−88.8	−87.7
1.15	1.17	1.81	−73.0	−77.2	−78.1	−77.1	−77.5
Bondi	1.20	1.70	−74.3	−79.3	−81.1	−79.7	−78.9
1.30	1.33	2.04	−66.9	−69.3	−71.7	−69.3	−68.3
1.2 × Bondi	1.44	2.04	−65.6	−67.7	−69.9	−67.7	−67.8
1.65	1.68	2.59	−55.8	−56.6	−56.5	−56.7	−56.3
2.00	2.04	3.14	−47.2	−47.6	−47.9	−47.8	−48.6
3.00	3.06	4.71	−32.5	−32.7	−33.0	−32.7	−33.1
4.00	4.08	6.28	−24.8	−24.9	−24.8	−24.9	−23.7
5.00	5.10	7.85	−20.1	−20.1	−20.0	−20.1	−20.3
n.a.	10.00	10.00	−14.9	−14.9	−14.8	−14.9	
C_2H_4^-							
0.85	0.87	1.33	−96.1	−74.6	−89.4	−74.5	−85.3
1.00	1.02	1.57	−84.2	−78.8	−86.5	−78.7	−80.8
1.15	1.17	1.81	−75.5	−75.5	−79.9	−75.3	−77.0
Bondi	1.20	1.70	−77.9	−77.6	−82.9	−77.6	−80.3
1.30	1.33	2.04	−68.5	−69.8	−73.0	−69.8	−69.0
1.2 × Bondi	1.44	2.04	−67.5	−69.7	−72.9	−69.7	−69.9
1.65	1.68	2.59	−56.4	−57.1	−56.8	−57.4	−56.7
2.00	2.04	3.14	−47.6	−47.9	−48.2	−48.1	−48.5
3.00	3.06	4.71	−32.6	−32.8	−33.1	−32.8	−33.1
4.00	4.08	6.28	−24.9	−24.9	−24.8	−24.9	−23.7
5.00	5.10	7.85	−20.1	−20.1	−20.0	−20.1	−20.3
n.a.	10.00	10.00	−14.9	−14.9	−14.8	−14.9	

solute–solvent boundary) but rather to be a separate approximation to the physical problem of a molecule in a real solution.

For a given atomic radius, the amount of outlying charge is larger for an anion than a cation. This explains why there are larger deviations between NPE solvers and the GB equation for large R for anions than for cations in Tables 1–3. But it is unlikely that the NPE result is meaningful when there is outlying charge because charge transfers to the solvent, if present, should be treated quantum mechanically, not by dielectric continuum models.

From one point of view, the NPE solvers and the multipole expansion methods may seem more fundamental than the generalized Born approximation because the NPE is equivalent to one of Maxwell's four equations and is exact in classical electrostatics, and multipole expansions are exact when converged. However, there are also contrary considerations:

1. As illustrated above, the NPE solvers in current use in molecular quantum chemistry codes give quite different results for many realistic situations, even when employed with the same atomic radii as parameters, and even when the continuous electron density is not replaced by a point charge representation. Hence, they do not necessarily represent the correct solution even to the idealized

nonhomogeneous dielectric problem. We have attributed a significant part of this deviation to outlying charge. In this regard, we should also note that the interaction of a test charge with a charge distribution (such as the charge distribution of a solute) can be precisely represented by a multipole expansion only when the test charge lies outside the charge distribution, but due to atomic tails, this is never actually satisfied; therefore, the multipole expansion methods also suffer from outlying charge inconsistencies at the step where they represent the solute charge distribution as a multipole expansion on a finite cavity surface. An additional contributor to the differences between the various NPE solutions is that the default tesserae in the implementation of GCOSMO in *NWChem* are farther from convergence than those employed in the default implementation of IEFPCM in *Gaussian 03* or the default implementation of C-PCM in *GAMESS*.

2. Even if the Poisson equation were solved correctly for the situation of ϵ equals unity in an interior region and ϵ equals the bulk relative permittivity in an exterior region representing the solvent, this is not an exact model of a real solution. Actually, the permittivity changes gradually over a fluctuating region with a width of at least a few tenths of an Ångström and maybe even a width of one or two solvent

Table 5. Electrostatic Free Energies of Solvation for C₂H₆, CH₃OH, CH₃OH₂⁺, and CH₃O[−]

<i>M</i>	<i>R</i> _H (Å)	<i>R</i> _C (Å)	<i>R</i> _O (Å)	Δ <i>G</i> _S (kcal/mol)				
				GB	C-PCM	GCOSMO	IEFPCM	PBS
C ₂ H ₆								
0.85	0.87	1.33		−0.4	−2.6	−3.2	−2.6	0.2
1.00	1.02	1.57		−0.1	−1.1	−0.7	−1.1	0.0
1.15	1.17	1.81		−0.1	−0.5	−0.5	−0.5	0.0
Bondi	1.20	1.70		−0.1	−0.4	−0.4	−0.4	0.0
1.30	1.33	2.04		0.0	−0.3	−0.5	−0.3	0.0
1.2 × Bondi	1.44	2.04		0.0	−0.2	−0.3	−0.2	0.0
1.65	1.68	2.59		0.0	−0.1	−0.1	−0.1	0.0
≥2.00	2.04	3.14		0.0	0.0	0.0	0.0	0.0
CH ₃ OH								
0.85	0.87	1.33	1.29	−6.2	−18.0	−17.7	−18.0	−14.8
1.00	1.02	1.57	1.52	−3.5	−10.9	−11.3	−10.9	−9.4
1.15	1.17	1.81	1.75	−2.2	−6.8	−7.1	−6.8	−6.0
Bondi	1.20	1.70	1.52	−2.9	−8.1	−8.1	−8.0	−7.4
1.30	1.33	2.04	1.98	−1.5	−4.5	−4.9	−4.5	−4.0
1.2 × Bondi	1.44	2.04	1.82	−1.6	−4.7	−4.7	−4.6	−4.3
1.65	1.68	2.59	2.51	−0.7	−2.0	−2.0	−2.0	−1.8
2.00	2.04	3.14	3.04	−0.4	−1.0	−1.1	−1.0	−1.0
3.00	3.06	4.71	4.56	−0.1	−0.3	−0.3	−0.3	−0.3
4.00	4.08	6.28	6.08	0.0	−0.1	−0.1	−0.1	−0.1
5.00	5.10	7.85	7.60	0.0	−0.1	−0.1	−0.1	−0.1
n.a.	10.00	10.00	10.00	0.0	0.0	0.0	0.0	0.0
CH ₃ OH ₂ ⁺								
0.85	0.87	1.33	1.29	−92.9	−116.6	−116.4	−116.5	−106.9
1.00	1.02	1.57	1.52	−82.8	−95.5	−95.7	−95.5	−90.8
1.15	1.17	1.81	1.75	−75.1	−82.7	−83.4	−82.7	−79.8
Bondi	1.20	1.70	1.52	−76.6	−84.5	−86.8	−84.4	−80.8
1.30	1.33	2.04	1.98	−68.7	−73.7	−76.3	−73.7	−72.5
1.2 × Bondi	1.44	2.04	1.82	−67.6	−71.9	−72.9	−71.8	−70.5
1.65	1.68	2.59	2.51	−57.0	−59.4	−60.6	−59.5	−58.8
2.00	2.04	3.14	3.04	−48.1	−49.5	−50.4	−49.5	−49.8
3.00	3.06	4.71	4.56	−33.0	−33.4	−33.4	−33.4	−32.8
4.00	4.08	6.28	6.08	−25.1	−25.3	−25.3	−25.3	−24.3
5.00	5.10	7.85	7.60	−20.3	−20.4	−20.4	−20.4	−20.4
n.a.	10.00	10.00	10.00	−14.8	−14.8	−14.8	−14.8	−14.8
CH ₃ O [−]								
0.85	0.87	1.33	1.29	−103.2	−94.5	−106.5	−94.5	−101.3
1.00	1.02	1.57	1.52	−88.7	−87.8	−93.4	−87.7	−90.9
1.15	1.17	1.81	1.75	−78.5	−79.4	−82.9	−79.3	−80.6
Bondi	1.20	1.70	1.52	−86.3	−88.1	−91.8	−88.2	−89.8
1.30	1.33	2.04	1.98	−70.7	−71.9	−73.6	−71.9	−72.7
1.2 × Bondi	1.44	2.04	1.82	−73.2	−76.3	−78.4	−76.2	−77.0
1.65	1.68	2.59	2.51	−57.6	−58.5	−59.9	−58.6	−57.4
2.00	2.04	3.14	3.04	−48.5	−49.1	−50.2	−49.2	−49.6
3.00	3.06	4.71	4.56	−33.2	−33.5	−33.5	−33.5	−33.9
4.00	4.08	6.28	6.08	−25.3	−25.4	−25.4	−25.4	−24.9
5.00	5.10	7.85	7.60	−20.4	−20.5	−20.4	−20.5	−20.7
n.a.	10.00	10.00	10.00	−15.2	−15.2	−15.3	−15.2	−15.3

Table 6. Electrostatic Free Energies of Solvation for CH₂CHCHO and CH₂CF₂

<i>M</i>	<i>R</i> _H (Å)	<i>R</i> _C (Å)	Δ <i>G</i> _S (kcal/mol)				
			GB	C-PCM	GCOSMO	IEFPCM	PBS
CH ₂ CHCHO							
Bondi	1.20	1.70	−4.3	−10.3	−10.6	−10.4	−9.3
1.2 × Bondi	1.44	2.04	−2.7	−6.0	−6.1	−6.0	−5.6
CH ₂ CF ₂							
Bondi	1.20	1.70	−0.6	−3.3	−3.9	−3.3	−2.7
1.2 × Bondi	1.44	2.04	−0.4	−1.5	−1.9	−1.5	−1.2

shells. (Some workers have used a three-parameter smooth function instead of a discontinuous one for the permittivity,^{72,73} but the uncertainty in the shape and parameters remains.) The shape and size of the region where the permittivity differs from the bulk value are not known, and the correct

value or function to use for the permittivity in this region is also not known, and these uncertainties make the electrostatic contribution quite uncertain. It is not clear that it is worthwhile to expend the effort to solve a partial differential equation accurately when there are significant uncertainties

in the parameters of the differential equation and the results depend strongly on these parameters.

3. Even if the parameters governing the spatial dependence of the solvent permittivity were known, and even if the Poisson equation were easy to solve, it is not strictly valid to use an equation of macroscopic electrostatics on an atomic scale. Just as macroscopic thermodynamics breaks down at the nanoscale, so does macroscopic electrostatics.

In contrast to the NPE solvers, the generalized Born approximation simplifies the treatment of charge distributions by replacing the continuous charge density of the solute by a set of atom-centered partial charges for all stages of the calculation. This eliminates the incorrect treatment of outlying charge but at the cost of incorrectly eliminating the outlying charge itself. Furthermore, the GB method introduces errors due to the fact that certain types of charge distributions may be poorly described by atom-centered monopoles, for example, the local charge distributions about atoms with lone pairs.⁷⁴

One way to try to ascertain the correct partition of solvation effects into electrostatic and nonelectrostatic terms is to consider the change in observable or potentially observable properties of solutes. For example, the change in solute dipole moment is mainly a response to the electrostatic interaction with the solvent, so that if two models give different electrostatic contributions to the solvation process, the one that predicts a more accurate solute dipole moment in solution might (other factors being equal) be judged to be the more reasonable one (although actual calculations of this response property show more complex relationships than one might have expected between predicted electrostatic contributions to free energy of solvation and predicted changes in dipole moments⁷). Unfortunately, the molecular dipole moment is not well-defined for a molecule immersed in a solvent, even in the absence of charge transfer (although considerable effort has gone into methods for obtaining physically reasonable values^{75–77}), and charge transfer to and from the solvent complicates this further.⁷⁸ Perhaps there are observables, for example, in vibrational spectroscopy or in NMR spectroscopy, that will eventually give useful information of this type, but so far the consideration of molecular properties in solution has not yielded any firm conclusions about the best way to approximate the electrostatic effect.

Some studies have shown good agreement between explicit and implicit solvent models for free energies of solvation,^{79–86} and other studies have found differences that were interpreted in terms of deficiencies in the GB type of treatment.⁸⁷ Thus, one might consider defining the electrostatic contribution statistical-mechanically from explicit calculations, but there are difficulties with this as well. In addition to the fundamental difficulty^{5,6} mentioned in the Introduction, there are uncertainties due to the molecular mechanics representation of the solvent. Furthermore, the partial charges that control electrostatic terms in molecular mechanics are sometimes not optimized separately from the short-range van der Waals terms. Thus, the electrostatic and nonelectrostatic terms are not separately meaningful in a quantitative sense.

In light of the intrinsic uncertainties in apportioning the solvation free energy into electrostatic and nonelectrostatic terms, either thermodynamically or by well-defined model problems, another strategy may be considered. First, recognizing that there is some arbitrariness, one defines the bulk electrostatic contribution in a physically reasonable way. Since, for any physical definition of the electrostatic contribution, electrostatics will dominate the solvation energy of ions, the reasonableness of this definition may be judged by its success for ionic solutes. If this definition is based on algorithms such as the NPE or GB ones, it will fully include the long-range interaction of the solute with bulk solvent, for which it is reasonable to use the bulk permittivity. All remaining contributions to the solvation free energy are then of short-range, and they include cavitation, dispersion (the $|\mathbf{r} - \mathbf{r}_k|^{-6}$ dependence of dispersion is of shorter range than the $|\mathbf{r} - \mathbf{r}_k|^{-4}$ dependence of electrostatic polarization), and solvent structural considerations that cause the short-range response of the solvent to differ from the defined bulk electrostatic contributions. The solvent structural component has two kinds of contributions, which one may label as short-range (or nonbulk) electrostatic contributions and nonelectrostatic contributions. The nonelectrostatic contributions include effects such as the solvent entropic components of the hydrophobic effect and the partial covalent character of hydrogen bonds. The short-range electrostatic contributions include all of the deviations of the electrostatics from the assumed bulk model, such as the inexactness of the solute charge model (whether the solute charge distributions are modeled by wave functions or partial charges, there is in practice a residual inaccuracy, for example due to basis sets or fixed solute geometries, and this may have a systematic component) and the inexactness of the solvent permittivity model (including assumed values for intrinsic Coulomb radii). Since the short-range effects are primarily associated with physical effects in the first solvation shell and the inexactness and uncertainties of the bulk electrostatic model in the first solvation shell, they can be modeled in terms of short-range analytic forms such as surface tensions associated with the SAS. Such a strategy has already been used for solvation modeling, and it has led to more accurate models than those for which the electrostatic and nonelectrostatic terms were determined separately.^{56,57}

6. Conclusions

There is no unique way to define the electrostatic contribution to the free energy of solvation, and methods currently in use can give very different answers for the same idealized problem of a molecular solute in a continuum dielectric medium. Although the electrostatic component of the free energy of solvation is not well-defined in thermodynamics, one might hope to define it by statistical mechanics. However, current methods based on the nonhomogeneous Poisson equation have uncertainties due to the definition, size, and shape of the solute cavity; the assumed way in which the permittivity changes at and near the solute–solvent boundary; and the portion of the solute charge that lies outside the cavity. The generalized Born approximation has different but equally serious approximations.

The electrostatic contribution to solvation, like the electrostatic contribution to any molecular modeling problem, cannot be considered in isolation from the whole model. Therefore, the “electrostatic” and “nonelectrostatic” terms should be considered as “bulk-electrostatic” and “non-bulk-electrostatic” terms, and the latter should account not only for cavity, dispersion, solvent structure, repulsion, and liberation, but also for deviations of the “true” electrostatics from those corresponding to the bulk model assumed in the bulk-electrostatic terms. This deviation is sensitive to the solvent structure in the first solvation shell, and it can be considered to be part of the solvent structure contribution to the nonbulk-electrostatic terms. The validity of a model can be judged by the usefulness of the whole model in predicting and correlating experimental observables, but not by any supposed rigor in the electrostatic part of the formulation.

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Supporting Information Available: Intramolecular and intermolecular contributions to the free energy of solvation for the case of a rigid solute; electrostatic components of the free energies of solvation for CH_3OH_2^+ and CH_3O^- calculated using the Hartree–Fock method and using the M05-2X density functional; electrostatic components of the free energies of solvation for CH_3OH_2^+ calculated by IEFPCM/Gaussian 03 using tesseræ of different sizes. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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