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Purisma, Enrico; Sulea, Traian

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Restoring Charge Asymmetry in Continuum Electrostatics Calculations of Hydration Free Energies

Enrico O. Purisima* and Traian Sulea

Biotechnology Research Institute, National Research Council of Canada, 6100 Royalmount Avenue, Montreal, Quebec, Canada H4P 2R2

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Implicit solvation models are symmetric with respect to charge inversion. On the other hand, explicit solvent simulations show significant asymmetry in hydration free energies with respect to charge reversal. It has not been obvious how implicit solvation models can be modified in a general way to address this serious shortcoming. We solve this problem by using the induced surface charge density (ISCD) obtained from a boundary element solution of the Poisson equation to derive a simple customized correction for the Born radius of each atom. This simple correction restores the charge asymmetry and reproduces the hydration free energies from free energy perturbation calculations with a high degree of fidelity. The induced surface charge density profile of an atom essentially provides a measure of the average preferred orientation of a water molecule in the first solvation shell, thereby allowing a proper assignment of the dielectric boundary. We refer to these modified radii as ISCD-corrected Born radii.

1. Introduction

The asymmetric response of water to positively and negatively charged solutes has been recognized for some time.^{1–4} Water molecules orient differently around anions and cations resulting in different effective Born radii and asymmetric dependence of the reaction field energies on solute charge. This asymmetry is not limited to molecules carrying a net charge. Recently, Mobley et al. have explored this issue in depth using charge-inverted pairs of neutral model systems.⁵ They show how the usual continuum electrostatics calculations fail miserably in capturing this asymmetry. In the conclusion of their paper, they state that “given that most of the asymmetries observed here are dominated by first solvation shell effects, there may be a way to improve implicit solvent models by including some explicit treatment of first solvation shell effects.” Kelly et al. have described an approach for capturing specific interactions of a solute with the first hydration shell in which a single water molecule is added where there is a high concentration of charge.⁶ However, it is not clear when such a water molecule would be needed or if just one molecule would be sufficient in general. We agree with Mobley et al. that the first solvation shell is the key to recovering charge asymmetry and higher accuracy but we find that an *implicit* treatment suffices and obviates the need for a more complex implicit–explicit hybrid model. In this paper, we present a proof of concept that charge asymmetry of hydration free energies can be handled in a simple, systematic, and transferrable way within a purely continuum electrostatics framework.

2. Methods

2.1. Model Systems. The model systems used are regular polygon “molecules” as described in Mobley et al.⁵ These are essentially *n*-sided planar bracelets consisting of three to eight carbon atoms with a bond length of 1.4 Å and various patterns of partial charges. In this work, we use two of their patterns: the distributed charge and the opposing charge scheme. In the distributed charge scheme, a charge of ± 1 is placed on one atom, and a neutralizing charge is distributed evenly among the remaining atoms. In the opposing charge scheme, the neutralizing charges are placed on two atoms symmetrically placed at the opposite ends of the molecule. The other atoms have zero partial charge. Using the terminology of Mobley et al.⁵ the bracelets with a full -1 charge on one atom are called N-bracelets. Those with a full $+1$ charge on one atom are called P-bracelets. Hydration free energies for all these bracelets have been calculated previously⁵ with free energy perturbation (FEP) methods, and we use those published values for our calibration and validation calculations. The electrostatic components of the FEP hydration free energies were obtained by subtracting the nonpolar components (D. Mobley, private communication) from the total FEP hydration free energy. It should be noted that these model systems were held rigid during the FEP calculations, permitting a direct comparison with single-structure continuum calculations.

2.2. Hydration Free Energy. Reaction field energies were calculated using the BRI BEM program, which solves the Poisson equation using a boundary element method.^{7,8} The solute and solvent dielectric constants were taken to be 1.0 and 78.5, respectively. The dielectric boundary was taken to be the solvent-excluded surface (also known as the molecular surface) as generated and triangulated using a marching tetrahedra algorithm and a solvent probe radius of 1.4 Å.^{9,10} The induced surface charge density (ISCD) distribution at the dielectric

* To whom correspondence should be addressed. E-mail: Enrico.Purisima@nrc.ca.

boundary was automatically obtained as part of the solution of the Poisson equation.

The reaction field energies were calculated in two passes. First, all the atoms in the molecule were assigned a Born radius equal to the force-field radius used in the FEP simulation,⁵ 1.908 Å, corresponding to the minimum of the Lennard-Jones potential of the atom. Then the ISCD distribution was calculated, and average surface charge densities, σ_i , were obtained for each atom. This was done by assigning surface patches to the nearest atom and averaging the ISCDs of the patches. The atomic Born radii were then adjusted according to the sign and magnitude of the atom's ISCD.

$$r = \begin{cases} r_0 - c_+ \sigma & \text{if } \sigma \geq 0 \\ r_0 - c_- \sigma & \text{if } \sigma < 0 \end{cases} \quad (1)$$

There are separate coefficients for positive and negative induced surface charge densities. The two coefficients were fitted to a training set to be described next.

2.3. Parameter Fitting. The distributed and opposing charge hexagonal N- and P-bracelets were used for the calibration step. Pairs of values of c_+ and c_- coefficients were systematically scanned in 0.5 unit increments, and the reaction field energies for the hexagonal bracelets were calculated using the corresponding modified radii calculated with eq 1. We sought to minimize the following objective function.

$$\text{Err}(c_+, c_-) = \sum_i \left| \Delta G_i^{\text{FEP}} - \Delta G_i^{\text{RF}}(c_+, c_-) \right| \quad (2)$$

The sum is over all four types of hexagonal bracelets. ΔG^{FEP} is the electrostatic hydration free energy from FEP simulations. ΔG^{RF} is the reaction field energy from the continuum model. The optimum value obtained for (c_+, c_-) was (15.5, 11.5). These coefficients were used to calculate the absolute hydration free energies of the rest of the bracelets.

We see from eq 1 that when the charge density is positive, the original Born radius, r_0 , is reduced in proportion to the magnitude of the charge density. When the charge density is negative, the original Born radius is increased proportionately. This is meant to reflect the orientation of the nearby water molecules in the first solvation shell and to adjust the dielectric boundary accordingly. We shall refer to the new radii as ISCD-corrected Born radii. The reaction field energies were then recalculated using the ISCD-corrected Born radii and used for further analysis.

3. Results and Discussion

3.1. Induced Surface Charge Density and Radius Correction. Table 1 lists the induced surface charge density for each of the atoms in the distributed charge hexagonal N- and P-bracelets as well as the adjusted radii using our optimized parameters. We note the large dynamic range in the charge densities. Although qualitatively related to the atomic partial charges, there is no simple relationship between the magnitudes of an atom's ISCD and its partial charge. Neither do the signs of an atom's partial charge and its ISCD even have to match. The ISCD is very much a molecular property rather than an atomic one. We also note that the adjusted radii can vary quite a bit from the initial nominal van der Waals radius of 1.908 Å.

One related approach in the literature for defining cavity radii is to make them dependent on the atomic partial charges.^{11,12}

TABLE 1: Induced Surface Charge Density and Corrected Radii

N-bracelet			P-bracelet		
q	σ	R	q	σ	R
-1.0	0.0206	1.59	1.0	-0.0206	2.15
0.2	0.0019	1.88	-0.2	-0.0019	1.93
0.2	-0.0072	1.99	-0.2	0.0072	1.80
0.2	-0.0087	2.01	-0.2	0.0087	1.77
0.2	-0.0073	1.99	-0.2	0.0073	1.79
0.2	0.0022	1.87	-0.2	-0.0022	1.93

Shown are the values for distributed charge N- and P-hexagonal bracelets. The column headings are as follows: q , the atomic partial charge; σ , the average induced surface charge density of the atom (electron unit/Å²); R , the corrected Born radius (Å). The initial radius for all the atoms was 1.908 Å.

This has led to improved accuracy of calculated hydration free energies, especially for anions, in a method such as CD-COSMO (charge-dependent conductor-like screening model) for a limited test set.¹² We believe that the use of charge-dependent radii can be helpful but may not be as general and easy to parametrize as ISCD-corrected radii. As seen in Table 1, even atoms with identical partial charges may have differing effective Born radii.

3.2. Parameter Transferability. As a test of transferability, we used the parameters optimized for the hexagonal bracelets to calculate the hydration free energies for the whole set of model compounds. Figure 1 shows significant asymmetry in the calculated hydration free energies for the N- and P-bracelets. For both the distributed and opposing charge schemes, the N-bracelets have lower energies than their corresponding P-bracelet. This is largely because the ISCD-corrected radii result in a reduced radius for the -1 charge in the N-bracelet, in contrast to the increased radius for the +1 charge in the P-bracelet. Of course, the opposite change in radius is observed for the other smaller partial charges in the bracelet, opposing part of the change in reaction field energy experienced by the ± 1 partial charge. However, the magnitude of the ± 1 partial charges and the consequent greater adjustment in their radii make them the dominant source of asymmetry in the reaction field energies.

Figure 2a shows a scatter plot of the implicit versus explicit solvation model (taken from ref 5) for all the bracelets. There is very good agreement between the continuum solvation results and the FEP simulations, confirming the transferability of the optimized parameters. For comparison, Figure 2b shows an analogous scatter plot in which the atomic radii are unmodified from their original values of 1.908 Å. The binding free energies with the unmodified radii show correlation with the FEP values but have absolutely no charge asymmetry, as expected. It is interesting to note that even with the uncorrected Born radii, there is already reasonably good agreement between continuum model and FEP results for the P-bracelets. The N-bracelets, on the other hand, have hydration free energies consistently underestimated by a fixed-radius continuum model. This can be understood in terms of the average orientation of a water molecule in the first hydration shell. Consider the average orientation of a water molecule in three situations: near a sphere with a +1, -1, and 0 partial charge, respectively. In the case of the 0 partial charge, the O-H bond of a water molecule will most likely be tangential to the solute's surface to preserve intermolecular hydrogen bonds. In the case of the +1 partial charge, the O-H bond will tend to be directed away from the solute. We see that in going from a 0 to +1 partial charge, the distance of the closest atomic charge center of the water molecule to the solute atom is essentially unchanged. In contrast,

Figure 1. Asymmetry for distributed and opposing charge bracelets. Asymmetry in hydration free energies. The hydration free energies are from implicit solvation calculations using the ISCD-corrected Born radii. (a) Distributed charge bracelets. (b) Opposing charge bracelets.

in going from a 0 to a -1 partial charge, the water hydrogen swings toward the solute, and the distance of the closest water charge center is significantly reduced. Hence, we expect the dielectric boundary (i.e., the Born radius) to be more drastically modified with the -1 partial charge than with the $+1$ partial charge. In addition, mathematically, the same magnitude of incremental change in Born radius affects the reaction field energy more when the radius is reduced than when it is increased.

A reviewer suggested that simply setting the radius for atoms with a $+1$ or -1 partial charge to 2.15 and 1.59 Å, respectively, while keeping the other atoms fixed at their original 1.908 Å radii would be sufficient in reproducing the charge asymmetry behavior. After all, as mentioned above, we expect the atoms with the ± 1 partial charges to have the dominant effect in charge asymmetry. Indeed, we find that using just those three values for the radii yields generally good agreement with FEP results, albeit with somewhat degraded agreement for the opposing charge bracelets (see Supporting Information for more details). However, in real molecules, one has a continuum of partial charges and it would not be straightforward generalizing this specific strategy of assigning radii for ± 1 partial charges. In the following section, we examine the application of ISCD-corrected Born radii to more realistic molecules.

3.3. *N,N*-Dimethylaniline and Nitrobenzene. As a further test of restoring charge asymmetry, we examined a pair of

Figure 2. Scatter plot, implicit versus explicit solvation. FEP⁵ versus implicit solvation. Red symbols, N-bracelets; blue symbols, P-bracelets. The dashed line represents perfect agreement between the electrostatic FEP hydration free energies and implicit solvation calculations. The electrostatic FEP values were obtained by subtracting the nonpolar FEP hydration free energy (D. Mobley, private communication) from the total FEP hydration free energy. (a) Implicit solvation for both the distributed and opposing charge bracelets calculated with ISCD-corrected Born radii. (b) Implicit solvation for opposing charge bracelets with Born radii fixed at 1.908 Å. The numbers beneath the symbols refer to the number of atoms in the bracelet.

molecules that provide an approximate real example of charge reversal and hydration asymmetry: *N,N*-dimethylaniline and nitrobenzene. In these two molecules, the C–NC₂ and C–NO₂ groups are roughly isosteric and have partial charge distributions that are reversed with respect to sign. Mobley et al. used free energy perturbation calculations on simplified models of *N,N*-dimethylaniline and nitrobenzene and demonstrated that starting with either molecule and reversing the partial charges of the side group described above always resulted in the *N,N*-dimethylaniline-like molecule having the more negative hydration free energy for a given charge-reversal pair.⁵ (*N,N*-dimethylaniline-like means that N has a negative partial charge.) This was attributed to the charge asymmetry of hydration free energies, with the *N,N*-dimethylaniline and nitrobenzene behaving like the N- and P-bracelets, respectively. We carried out the analogous calculations using continuum electrostatics with ISCD-corrected Born radii using the same parameters obtained from the hexagonal bracelets and obtained results consistent with the FEP calculations. Details of the calculations and results can be found in the Supporting Information.

3.4. Beyond Linear Radius Correction. Equation 1 assumes a linear dependence of the Born radius correction on the induced surface charge density. Clearly, that approximation has its limitations. We expect the correction to level off at some point or even reverse in the case of a negative ISCD. At moderately large negative ISCD, the Born radius is larger than the Lennard-Jones radius because this reflects the orientation of the first solvation shell water molecule with the water hydrogen atoms pointing away from the surface. However, as the ISCD becomes even more negative (i.e., the solute electrostatic potential in that region becomes more positive), the water molecule will be drawn closer to the solute molecular surface, and the effective Born radius should decrease. For a positive ISCD, the decrease in radius with increasingly positive ISCD cannot go on indefinitely, either, and must level off, since the van der Waals repulsion will start to become significant. A nonlinear functional form for the ISCD correction would be more appropriate and will be the subject of a future study. However, the nonlinearity may not be significant for the normal range of partial charges observed in real molecules. With the model systems studied here, it does not seem to be a major issue. Also of interest will be the dependence of the optimized parameters in eq 1 on the well depth of the Lennard-Jones potential. The (c_+ , c_-) coefficients may have to be made dependent on the atomic Lennard-Jones parameters, as well.

4. Conclusion

The presence of charge asymmetry in hydration free energies complicates the problem of properly parametrizing implicit solvation models. In particular, the use of universal Born radii for designated atom types becomes problematic. We have shown that the use of the induced surface charge density provides a simple and efficient strategy for defining ISCD-corrected Born radii that restores the charge asymmetry for continuum models. We believe that this reflects the ability of the method to recover some of the molecular details of the first hydration shell (i.e.,

the average orientation of water molecules in the layer) while remaining within a continuum framework. This has led to remarkable accuracy of implicit solvation calculations on model systems vis-à-vis FEP hydration free energies. We expect that the same strategy will facilitate the development of robust and transferable parameters for implicit solvation models of hydration free energies of real molecules.

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Supporting Information Available: Three figures on the ability of a two-radii model to reproduce charge asymmetry; two tables of computed hydration free energies for various models of nitrobenzene and *N,N*-dimethylaniline. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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