

# Nonconvergence of the Solute Potential in an Infinite Solvent and Its Implications in Continuum Models<sup>||</sup>

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The conventional way of computing the electrostatic potential at a solute charge in water,  $\Phi^\infty(Q)$ , includes contributions from an infinite number of water molecules.  $\Phi^\infty(Q)$  varies by as large as 20 kcal/mol depending on the summation scheme or dielectric boundary. Here we show that  $\Phi^\infty(Q)$  is *nonconvergent*. By computing  $\Phi(Q)$  as a sum of contributions from an interior, explicit water region, an intermediate, continuum water region, and an exterior, explicit water region using the same summation scheme, the two implicit water/explicit water surface effects cancel and  $\Phi(Q)$  converges to a single value, independent of the summation scheme.

An accurate evaluation of the solvent-induced electrostatic potential at a solute atom of charge  $Q$ ,  $\Phi(Q)$ , is required in computing ionic charging free energies or ligand binding free energies using the linear response approximation and in analyzing solute redox properties. Conventional calculations of  $\Phi^\infty(Q)$ , and thus the absolute/charging free energy, by both explicit water simulations and implicit water models assume that the water/vacuum surface potential is not correlated with  $\Phi^\infty(Q)$  and can be neglected. Thus, they include the electrostatic contributions from an *infinite* number of water molecules (approximated by a bulk dielectric constant in continuum models). In addition, they assume that there is a correct, unique  $\Phi^\infty(Q)$ . Here, we show that without a water/vacuum boundary  $\Phi^\infty(Q)$  does *not* converge to a single value. A corollary of this finding is that the continuum model cannot be used in an *infinite* solvent system with only *one* explicit water/implicit water interface to obtain an accurate, unique  $\Phi^\infty(Q)$ . However, as shown here, it can be used in a *finite* solvent system with *two* explicit water/implicit water interfaces to obtain a  $\Phi(Q)$  that converges to a single value for all summation schemes. This implies that  $\Phi(Q)$  cannot be determined only by the water orientations near the solute but is determined by the water orientation preferences at the solute/water interface *relative* to those at the water/vacuum interface. Consequently, the absolute solvation free energy cannot be evaluated separately from the water/vacuum surface free energy.

**Conventional Calculation of  $\Phi^\infty(Q)$  in an Infinite Solvent System.** The contributions from an infinite number of water molecules to  $\Phi^\infty(Q)$  can be evaluated in three ways. The first is by Ewald summation using *no* cutoff.<sup>1–3</sup> The second is by dividing the contributions into those from an explicit water region and those from a continuum water region; i.e.,

$$\Phi^\infty(Q) = \Phi^1(Q) + \Phi^2(Q) \quad (1)$$

$\Phi^1(Q)$  is evaluated by integrating the layer electrostatic potential,  $\Phi(Q, r)$ , from the solute atom to a given cutoff,  $R_{\text{cut}}$ :

$$\Phi^1(Q) = \int_0^{R_{\text{cut}}} \Phi(Q, r) \, dr \quad (2)$$

where  $\Phi(Q, r)$  is calculated by summing over all water *atoms* at a distance  $r$  from the solute center (particle or P-summation) or by summing over all water *molecules* whose molecular centers ( $M_X$ -centers) are at a radius  $r$  from the solute atom ( $M_X$ -summation, Figure 1).<sup>1,4</sup>  $\Phi^2(Q)$  is approximated by a Born term<sup>5</sup> corresponding to a sphere of radius  $R_{\text{cut}}$  and charge  $Q$  immersed in a continuum water of dielectric constant  $\epsilon_w$ .<sup>3,6–8</sup>

$$\Phi^2(Q) = \int_{R_{\text{cut}}}^\infty \Phi(Q, r) \, dr \approx 332 \left( \frac{1}{\epsilon_w} - 1 \right) \frac{Q}{R_{\text{cut}}} \quad (3)$$

The third way to evaluate the infinite-water potential contribution is by using a continuum model, in which  $\Phi^\infty(Q)$  is given by an analytical formula for a spherical solute<sup>5,9</sup> or by numerical solution to a Poisson equation for a nonspherical solute.<sup>10,11</sup>

**$\Phi^\infty(Q)$  Varies by as Large as 20 (kcal/mol)/e Depending on the Summation Scheme or Dielectric Boundary.** The three ways of evaluating  $\Phi^\infty(Q)$  do not yield the same value. In simulations using periodic boundary conditions (PBCs) with all charges mapped into the simulation box, the Ewald-summed electrostatic potential at an *uncharged* atom in SPC water computed with conducting boundary conditions ( $\epsilon = \infty$ ) is similar to the respective potential computed using P-summation or  $M_{-\mu}$ -summation with the molecular center equal to the dipole center reflected about H–H ( $-\mu$ , Figure 1) and is equal to +10 (kcal/mol)/e.<sup>1,2,12</sup> However, the corresponding Ewald-summed potential computed using a vacuum boundary ( $\epsilon = 1$ ) depends on the  $M_X$ -center upon which PBCs are applied and converges to the  $M_X$ -summed potential, which ranges from  $-9$  to  $-10$  (kcal/mol)/e if the  $M_X$ -center is the water oxygen, and  $+10$  (kcal/mol)/e if the  $M_X$ -center is  $-\mu$ .<sup>1,12–14</sup> This shows that the

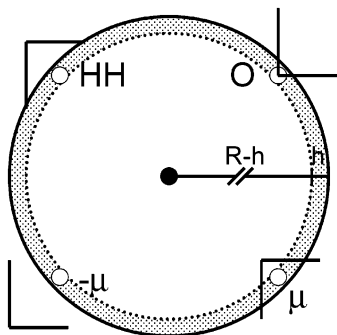
<sup>||</sup> Dedicated to Prof. John Tully on the occasion of his 60th birthday.

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**Figure 1.** Schematic diagram for computing  $\Phi^\infty(Q)$  at an atom of charge  $Q$  at the center of an infinite water system using a cutoff,  $R$ . All summation schemes include the same water atoms in the sphere of radius  $R - h$  but they select different water atoms in the region between  $R - h$  and  $R$ . In P-summation, atoms outside the cutoff are excluded. In  $M_O$  and  $M_{-\mu}$ -summation, the two water molecules shown on the right and left are included, respectively, whereas in  $M_\mu$  and  $M_{HH}$ -summation, only the water molecule on the bottom right and top left is included, respectively.

electrostatic contributions from an infinite number of water molecules to the potential at an uncharged solute atom,  $\Phi^\infty(0)$ , differs by as large as 20 (kcal/mol)/e depending on the summation scheme and  $M_X$ -center choice. The 20 (kcal/mol)/e difference between the P-summed and  $M_O$ -summed  $\Phi^\infty(0)$  has been found to be independent of the cutoff radius and solute charge.<sup>2</sup> The  $\Phi^\infty(Q)$  derived from continuum models can also differ significantly depending on how the dielectric boundary is defined; i.e., on which water atoms are assigned to an implicit solvent region.<sup>15</sup>

**$\Phi^\infty(Q)$  Does Not Converge to a Single Value.** For a solute of charge  $Q$  in an infinite bath of water molecules,  $\Phi^\infty(Q)$  can be written as a sum of two terms:

$$\Phi^\infty(Q) = \Phi^\infty(0) + [\Phi^\infty(Q) - \Phi^\infty(0)] \quad (4)$$

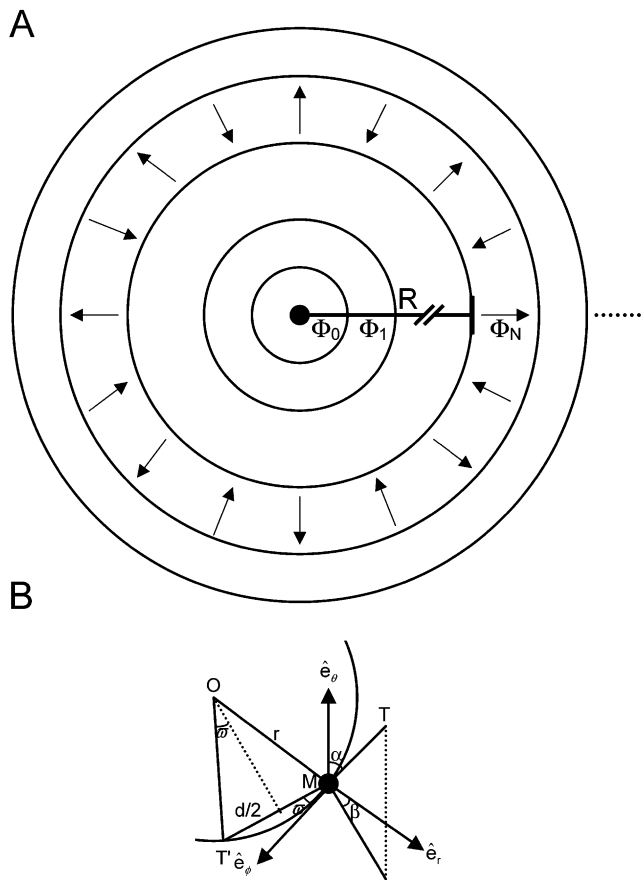
The first term is the electrostatic potential at an uncharged solute. The second term is the electrostatic potential due to polarization of the water molecules upon charging the solute from zero to charge  $Q$ . We show below that although  $\Phi^\infty(Q) - \Phi^\infty(0)$  converges to a single value,  $\Phi^\infty(0)$  does not, and hence  $\Phi^\infty(Q)$  is nonconvergent.

**$\Phi^\infty(0)$  Does Not Converge to a Single Value.**  $\Phi^\infty(0)$  can be evaluated by summing  $\Phi_n^{\text{out}}$  and  $\Phi_n^{\text{in}}$ , the electrostatic potential contribution from water molecules with their average dipoles pointing in the outward ( $\hat{r}$ ) and inward ( $-\hat{r}$ ) direction, respectively, in each spherical layer  $n$ , from  $n = 1$  to  $\infty$  (Figure 2):

$$\Phi^\infty(0) = \sum_{n=1}^{N-1} (\Phi_n^{\text{out}} + \Phi_n^{\text{in}}) + \Phi_N^{\text{out}} + \Phi_N^{\text{in}} + \Phi_{N+1}^{\text{out}} + \Phi_{N+1}^{\text{in}} + \dots \quad (5)$$

Water molecules in layer  $n$  ( $n \geq N$ ) are far from the solute and are randomly oriented relative to an uncharged solute and can thus be approximated by point dipoles or two-point linear dipoles, as shown in previous works.<sup>4,16</sup> The average dipole of such randomly oriented water molecules in the annular space between  $r$  and  $r + dr$  in the direction  $\hat{r}$  (see Figure 2B) is given by

$$\langle \mu^{\text{out}} \rangle = -\langle \mu^{\text{in}} \rangle = \frac{\mu r^2 \int_0^\pi \sin \alpha \, d\alpha \int_{-\pi/2-\varpi_r}^{\pi/2+\varpi_r} \cos \beta \, d\beta}{4\pi r^2 \, dr \, \rho \frac{2\pi r^2}{2\pi r^2}} \hat{r} \quad (6)$$



**Figure 2.** (A) Schematic diagram for computing the electrostatic potential,  $\Phi^\infty(Q)$ , at a solute atom of charge  $Q$  at the center of an infinite water system. (B) Schematic diagram for computing the average dipole of randomly oriented water molecules in the annular space between  $r$  and  $r + dr$  in the direction  $\hat{r}$ .  $M(r, \theta, \phi)$  is the center of a water molecule,  $T$  is the dipole tip, and  $T'$  is the point at which  $T$  intersects the sphere of radius  $r$ . The new coordinate system at  $M$  is  $\hat{e}_r = \sin \theta \cos \phi \hat{x} + \sin \theta \sin \phi \hat{y} + \cos \theta \hat{z}$ ,  $\hat{e}_\theta = \cos \theta \cos \phi \hat{x} + \cos \theta \sin \phi \hat{y} - \sin \theta \hat{z}$ , and  $\hat{e}_\phi = -\sin \phi \hat{x} + \cos \phi \hat{y}$ .  $\varpi$  is the angle between the plane with the normal vector  $\hat{e}_r$  and  $MT'$ .

and the corresponding electrostatic contribution is given by

$$\Phi^{\text{out}}(r) \, dr = -\Phi^{\text{in}}(r) \, dr = \frac{2\pi r^2 \, dr \, \rho \mu \cos \varpi_r}{r^2} = 2\pi \rho \mu \cos \varpi_r \, dr \quad (7)$$

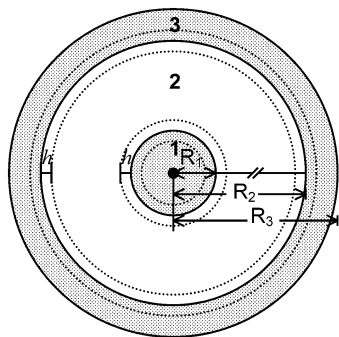
where

$$\varpi_r = \sin^{-1} \frac{d}{2r} \quad (8)$$

In eqs 6–8,  $r$  is the distance from the solute atom to the dipole center,  $\rho$  is the bulk water density,  $\mu$  is the magnitude of the water dipole,  $d$  is the maximum distance between the dipole center and its tip, and the angles are defined as shown in Figure 2B. As water molecules in each layer  $n$  ( $n \geq N$ ) are far from the uncharged solute ( $r \gg d$ ),  $\cos \varpi_r \approx 1$  and  $\Phi^{\text{out}}(r) = \Phi = 2\pi \rho \mu = -\Phi^{\text{in}}(r)$ . Therefore, eq 5 can be approximated by

$$\Phi^\infty(0) \approx \sum_{n=1}^{N-1} (\Phi_n^{\text{out}} + \Phi_n^{\text{in}}) + \int_R^{R+dr} \Phi \, dr - \int_R^{R+dr} \Phi \, dr + \int_{R+dr}^{R+2dr} \Phi \, dr - \int_{R+dr}^{R+2dr} \Phi \, dr + \dots \quad (9)$$

Because  $\lim_{r \rightarrow \infty} \Phi \, dr \neq 0$ , the alternating infinite series in eq



**Figure 3.** Schematic diagram for computing the electrostatic potential at a solute atom of charge  $Q$  at the center of a macroscopic water cluster, which is divided into three regions, defined by spheres of radius  $R_1$ ,  $R_2$ , and  $R_3$ , respectively.  $h$  is the maximum distance between any two molecular centers used in the different summation schemes.

9 is divergent. This is also evident by rewriting eq 9 in terms of the well-known divergent infinite series (eq 10):<sup>17</sup>

$$\Phi^\infty(0) \approx \sum_{n=1}^{N-1} (\Phi_n^{\text{out}} + \Phi_n^{\text{in}}) + \Phi \, dr \sum_{n=0}^{\infty} (-1)^n \quad (10)$$

$\Phi^\infty(Q) - \Phi^\infty(0)$  Converges to a Single Value. For a given charge  $Q$  at the origin, the average dipole of water molecules in the annular space between  $r$  and  $r + dr$  in the  $\hat{r}$  direction is given by<sup>18</sup>

$$\langle \mu \rangle = 4\pi r^2 \, dr \, \rho \frac{\mu^2}{3k_B T} \frac{Q}{r^2} = \frac{4\pi \rho \mu^2 Q \, dr}{3k_B T} \hat{r} \quad (11)$$

where  $k_B$  is Boltzmann's constant and  $T$  is the temperature. The electrostatic contribution from this average dipole (eq 11) to the potential at charge  $Q$  is given by

$$\Phi_n(Q) - \Phi_n(0) = \frac{4\pi \rho \mu^2 Q \, dr}{3k_B T r^2} \propto \frac{1}{r^2} \quad (12)$$

From eq 12,  $\Phi^\infty(Q) - \Phi^\infty(0) = \sum_{n=1}^{\infty} (\Phi_n(Q) - \Phi_n(0))$  is convergent, but because  $\Phi^\infty(0)$  is divergent,  $\Phi^\infty(Q)$  by eq 4 is also divergent.

**Summation-Scheme Independent Calculation of  $\Phi(Q)$  in a Finite Solvent System.** The above results imply that an infinite solvent system (with no water/vacuum boundary) cannot be used to evaluate  $\Phi(Q)$ . To incorporate the water/vacuum interface potential, a simulation of a finite water cluster of *microscopic* dimension (say containing 1024 water molecules as in ref 1) is inadequate because artificial boundary forces, which are usually parametrized for bulk solvent, would not yield the correct dynamics of water molecules near the water/vacuum interface, whereas without such solvent boundary forces, water molecules could escape into vacuum and equilibrium would not be attained. Hence to evaluate  $\Phi(Q)$ , we have employed a finite water cluster of *macroscopic* dimension (say of radius  $R_3 = 1$  m, Figure 3) to mimic experimental conditions. The *macroscopic* size is achieved by choosing  $R_1$  and  $R_2$  in Figure 3 to be far enough from the solute and water/vacuum interface, respectively, so that water molecules in region 2 are totally random relative to an *uncharged* solute and can be treated as a continuous medium. Water molecules near the solute in region 1 and near the water/vacuum interface in region 3 are treated explicitly.  $\Phi(Q)$  is then computed by summing the electrostatic contributions from the explicit water molecules in regions 1 and 3 as

well as the implicit solvent in region 2 as follows:

$$\Phi(Q) = \int_0^{R_1} \Phi(r) \, dr + \int_{R_1}^{R_2} \Phi(r) \, dr + \int_{R_2}^{R_3} \Phi(r) \, dr \quad (13a)$$

$$= \Phi^1(Q) + \Phi^2(Q) + \Phi^3 \quad (13b)$$

The  $\Phi^1(Q)$  contribution can be evaluated by P-summation or  $M_X$ -summation from simulations of a solvated solute using eq 2. The  $\Phi^2(Q)$  contribution can be estimated from the difference between two Born terms:

$$\Phi^2(Q) = \int_{R_1}^{\infty} \Phi(r) \, dr - \int_{R_2}^{\infty} \Phi(r) \, dr \approx 332 \left( \frac{1}{\epsilon_w} - 1 \right) \left( \frac{Q}{R_1} - \frac{Q}{R_2} \right) \quad (14)$$

For  $R_2 \gg R_1$ ,  $Q/R_2$  is negligible compared to  $Q/R_1$ , thus  $\Phi^2(Q)$  can be approximated by eq 3. The  $\Phi^3$  contribution can be evaluated by P-summation or  $M_X$ -summation from simulations of a water sphere in a vacuum box according to

$$\Phi^3 = \int_r^{R_3} \Phi(r) \, dr \quad (15)$$

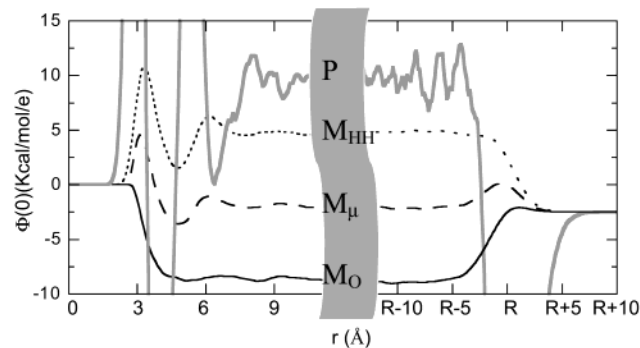
where  $r \geq R_2$ , and the integration is performed by starting from the water/vacuum boundary ( $R_3$ ) to the center of the water sphere.

To see why the scheme described above (Figure 3) yields a converged, summation-independent  $\Phi(0)$ , we rewrite  $\Phi(0)$  in eq 13a as a sum of integrals that are either independent of or dependent on a given summation scheme,  $x$  (Figure 3):

$$\begin{aligned} \Phi(0) = & \int_0^{R_1-h} \Phi(r) \, dr + \int_{R_1-h}^{R_1} \Phi(r) \, dr + \int_{R_1}^{R_1+h} \Phi(r) \, dr + \\ & \int_{R_1+h}^{R_2-h} \Phi(r) \, dr + \int_{R_2-h}^{R_2} \Phi(r) \, dr + \int_{R_2}^{R_2+h} \Phi(r) \, dr + \\ & \int_{R_2+h}^{R_3} \Phi(r) \, dr \quad (16) \end{aligned}$$

If  $R_1$  and  $R_2$  are the cutoffs used to compute  $\Phi^1(0)$  and  $\Phi^3$ , respectively, any discrepancy among the P-summed and  $M_X$ -summed  $\Phi^1(0)$  or  $\Phi^3$  will arise from water molecules in the annular space between  $R_1 - h$  and  $R_1$  or between  $R_2$  and  $R_2 + h$  (see Figure 1). Hence the various summation schemes include the same water atoms in the sphere of radius  $R_1 - h$  and yield the same value  $A$  for the first integral: i.e.,  $\int_0^{R_1-h} \Phi(r) \, dr = A$ . Likewise, they yield the same value  $C$  for the last integral; i.e.,  $\int_{R_2+h}^{R_3} \Phi(r) \, dr = C$ . Water molecules that are far from the solute center and the water/vacuum interface in the annular space between  $R_1 - h$  and  $R_1 + h$  and between  $R_2 - h$  and  $R_2 + h$  are randomly oriented relative to an *uncharged* solute, hence their potential contributions in these two regions are equal to zero; i.e.,  $\int_{R_1-h}^{R_1} \Phi(r) \, dr + \int_{R_1}^{R_1+h} \Phi(r) \, dr = 0$  and  $\int_{R_2-h}^{R_2} \Phi(r) \, dr + \int_{R_2}^{R_2+h} \Phi(r) \, dr = 0$ . The various summation schemes select different water atoms in the annular space between  $R_1 - h$  and  $R_1$  (see Figure 1), and therefore the value of the second integral depends on the summation scheme  $x$ ; i.e.,  $\int_{R_1-h}^{R_1} \Phi(r) \, dr = a(x)$  and, because  $\int_{R_1-h}^{R_1} \Phi(r) \, dr + \int_{R_1}^{R_1+h} \Phi(r) \, dr = 0$ ,  $\int_{R_1}^{R_1+h} \Phi(r) \, dr = -a(x)$ . Likewise,  $\int_{R_2-h}^{R_2} \Phi(r) \, dr = a(x)$  and  $\int_{R_2}^{R_2+h} \Phi(r) \, dr = -a(x)$ . Water molecules in the annular space between  $R_1 + h$  and  $R_2 - h$  are randomly oriented relative to an *uncharged* solute, hence  $\int_{R_1+h}^{R_2-h} \Phi(r) \, dr = 0$ . Therefore, although the electrostatic potential contribution from each region depends





**Figure 4.** Net electrostatic potential at an uncharged TIP3P oxygen as a sum of  $\Phi^1(0)$  (left curve) and  $\Phi^3$  (right curve) for each summation scheme.  $r$  is the distance from the solute atom, whereas  $R$  is the position of the water/vacuum interface. The gray solid, black dotted, black dashed, and black solid lines correspond to P-,  $M_{HH}$ -,  $M_\mu$ -, and  $M_O$ -summed potentials, respectively. The  $\Phi^1(0)$  contribution was computed from a 500 ps simulation of an uncharged TIP3P oxygen hydrated by 1558 TIP3P<sup>19,20</sup> water molecules centered in a  $36 \times 36 \times 36 \text{ \AA}^3$  box using eq 2. The  $\Phi^3$  contribution was calculated from a nanosecond simulation each of a 15.5, 18.6, or 20.0  $\text{\AA}$  radius sphere containing 522, 902, or 1119 water molecules centered in a vacuum cubic box of length 60, 70, or 80  $\text{\AA}$  using eq 15. The simulations were carried out at a mean temperature of 300 K using PBCs with particle-mesh Ewald summation.<sup>21</sup> The P-,  $M_{HH}$ -,  $M_\mu$ -, and  $M_O$ -summed  $\Phi^1(0)$  values averaged from  $r$  equal to 10–15  $\text{\AA}$  in Figure 4 are +9.4, +4.7, –2.0, and –8.6 (kcal/mol)/e, respectively, whereas the corresponding average  $\langle\Phi^3\rangle$  values are –11.7, –7.0, –0.1, and +6.8 (kcal/mol)/e, respectively. Details of the simulations are reported in a subsequent paper (Yang & Lim, manuscript in preparation).

on the summation scheme used,

$$\Phi^1(0,x) = \int_0^{R_1-h} \Phi(r) dr + \int_{R_1-h}^{R_1} \Phi(r) dr = A + a(x) \quad (17a)$$

$$\Phi^2(0,x) = \int_{R_1}^{R_1+h} \Phi(r) dr + \int_{R_1+h}^{R_2-h} \Phi(r) dr + \int_{R_2-h}^{R_2} \Phi(r) dr = -a(x) + 0 + a(x) \quad (17b)$$

$$\Phi^3(x) = \int_{R_2}^{R_2+h} \Phi(r) dr + \int_{R_2+h}^{R_3} \Phi(r) dr = -a(x) + C \quad (17c)$$

the net contribution is summation-scheme independent when the same summation scheme is used to compute  $\Phi^1(0)$  and  $\Phi^3$ :

$$\Phi(0) = \Phi^1(0,x) + \Phi^2(0,x) + \Phi^3(x) = A + C \quad (18)$$

**$\Phi(0)$  Converges to a Single Value, Independent of the Summation Scheme.** When  $\Phi^1(0)$  and  $\Phi^3$  are computed using the same summation scheme  $x$ ,  $\Phi(0)$  (eq 18) converges to  $-2.1 \pm 0.2$  (kcal/mol)/e for all summation schemes (Figure 4). If the  $\Phi^3$  potential is neglected,  $\Phi(0) = \Phi^1(0,x)$  (eq 17a) is summation-scheme dependent and ranges from –8.6 to +9.4 (kcal/mol)/e (Figure 4, left), as found in previous works.<sup>1,4,12</sup> In analogy to  $\Phi^1(0,x)$ , the magnitude and sign of  $\Phi^3(x)$  (eq 17c) also depend on the summation scheme and vary from  $-11.7 \pm 1.2$  to  $+6.8 \pm 0.1$  (kcal/mol)/e (Figure 4, right). These results imply that  $\Phi(0)$  cannot be determined only by the orientations of water molecules near the solute. Instead, it is determined by comparing the water orientation preferences at the solute/water interface to that at the water/vacuum interface.

If  $\Phi^3$  is computed using summation scheme  $y$  instead of  $x$ ,  $\Phi(0) (= \Phi^1(0,x) + \Phi^3(y) = A + a(x) - a(y) + C)$  depends on the summation scheme and varies significantly. For example,  $\Phi(0)$  given by the sum of  $M_O$ -summed  $\Phi^1(0)$  (–8.6 (kcal/mol)/

e) and P-summed  $\Phi^3$  (–11.7 (kcal/mol)/e) is –20.3 (kcal/mol)/e, whereas the sum of P-summed  $\Phi^1(0)$  (9.4 (kcal/mol)/e) and  $M_O$ -summed  $\Phi^3$  (6.8 (kcal/mol)/e) is 16.2 (kcal/mol)/e.

**Implications for Continuum Models.** The above results show that a continuum model cannot be used in an infinite solvent system with only one explicit water/implicit water interface. However, it can be used in a finite solvent system with two explicit water/implicit water interfaces. In the conventional continuum model, water molecules in the annular region between  $R_1$  and  $R_2$  are replaced by a macroscopic dielectric constant  $\epsilon$  and do not contribute to  $\Phi(0)$ . However, if the electrostatic potential contributions from water molecules in the annular regions from  $R_1$  to  $R_1 + h$  and from  $R_2 - h$  to  $R_2$  cannot be canceled, then  $\Phi^2(0) \neq 0$ . This implies that in the conventional continuum model,  $\int_{R_1}^{R_1+h} \Phi(r) dr + \int_{R_2-h}^{R_2} \Phi(r) dr$  is assumed to be zero. Equation 18 shows that this is the case only if the same summation scheme is used to assign which water atoms belong to the explicit vs implicit water region at the cutoff spheres  $R_1$  and  $R_2$ . However, if summation schemes  $x$  and  $y$  are used to compute  $\Phi^1(0)$  and  $\Phi^3$ , respectively, then eq 18 is given by

$$\begin{aligned} \Phi(0) &= A + a(x) - a(x) + 0 + a(y) - a(y) + C \\ &= \Phi^1(0,x) + \Phi^2(0,x,y) + \Phi^3(y) \end{aligned} \quad (19)$$

In this case,  $\Phi^2(0,x,y) = a(y) - a(x) \neq 0$ . If the summation scheme used at  $R_1$  or  $R_2$  is not defined and  $\int_{R_1}^{R_1+h} \Phi(r) dr + \int_{R_2-h}^{R_2} \Phi(r) dr$  cannot be evaluated, then explicit water molecules between  $R_1$  and  $R_2$  cannot strictly be represented by  $\epsilon_w$ .

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