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Effects of long-range electrostatic potential truncation on the free energy of ionic hydration

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The free energy of sodium ion hydration calculated from computer simulations employing both the molecular potential truncation and Ewald summation methods for evaluation of long-range electrostatic interactions disagree by 20%. The discrepancy between the free energies determined by both techniques is found to be methodological, resulting from an imbalance in the molecular potential truncation scheme that biases the interaction of the water–oxygen and hydrogens with the ion unequally. A simple physical model is proposed and an analytical expression derived to correct this discrepancy. © 1997 American Institute of Physics. [S0021-9606(97)51119-6]

Computer simulations of aqueous ion solvation provide experimentally inaccessible molecular detail on hydration energetics of critical interest to issues of protein activity and colloidal stability in solution. Evaluation of the electrostatic interaction between an ion and water is complicated by the fact that these forces are long ranged and extend beyond the length of a periodic simulation cell. Brute force direct calculation of the electrostatic potential arising from an infinite periodic distribution of charges is impractical, however. Numerous methods of varying theoretical accuracy for computing the long-range interaction have been proposed to alleviate this difficulty. Two of these methods routinely used in simulations of aqueous solvation are molecular potential truncation (MPT)¹ and Ewald summation (ES).² In MPT, the interaction between two molecules is assumed to be negligible and equal to zero when the molecules are separated by a specified cutoff distance. This assumption is questionable since the extent of the electrostatic potential is larger than typical cutoff radii. In ES, the long-range electrostatic potential summation is split into two rapidly convergent contributions: a short-range real space component, and long-range Fourier space component. For an electrically neutral system, the ES method accurately calculates the potential arising from an infinite periodic distribution of charges without approximation. However, when the simulation carries a net charge, such as an ion at infinite dilution in water, it is necessary to introduce a uniform background charge that dissipates the ionic charge and ensures convergence of the ES potential. Under these circumstances, both the MPT and ES methods introduce unphysical constructions and it is not clear *a priori* which method provides the more accurate representation of the thermodynamics of a charged system.

The difference between these methods is highlighted by recent calculations of the hydration free energy of sodium, μ^* , at ambient conditions.^{3–5} The use of periodic boundary conditions to mimic an infinite aqueous medium leads to system size dependent values of μ^* at infinite dilution.

Therefore, finite size effects must be corrected to yield the proper infinite dilution limiting value of μ^* . For the ES method, Hummer, Pratt, and Garcia found that these effects can be corrected by adding a self-term to the simulation potential which accounts for the interaction of the ion with its periodic images and the background neutralizing charge.³ From ES simulations of sodium ion hydration they calculated an infinite dilution μ^* of -97 kcal/mol that was independent of system size over a wide range. Wood developed a system size correction for the MPT method that accounts for the ion–water and water–water interactions beyond their cutoff radii.⁴ When applied to simulations of sodium hydration performed by Straatsma and Berendsen using the MPT method,⁵ Wood calculated an infinite dilution μ^* of -115 kcal/mol.⁴ Similar to the result of Hummer *et al.* this result was found to be independent of the simulation size and the cutoff radii used. The two free energies differ by $\sim 20\%$, although the potential energy models used in both studies were the same. It is important to reconcile this difference to understand when the approximations inherent to either method are reasonable. In this work we present a detailed analysis of the hydration free energy of the sodium ion test case with simulations performed using both the MPT and ES methods. The source of the discrepancy is found to be a difference in the extrinsic potential; that is the difference is due to effects at the boundary of the potential calculation which persist even in the limit of infinite system size.⁶ The extrinsic potential in the MPT method is shown to arise from the choice of site on the water molecule from which the truncation distance is measured.

The free energy associated with charging an ion at infinite dilution in aqueous solution from a charge of 0 to q is^{5,7}

$$\mu^* = \int_0^q \langle \Phi \rangle_\lambda d\lambda, \quad (1)$$

where $\langle \Phi \rangle_\lambda$ is the average solvent-induced electrostatic potential at the center of the ion with charge λ . The simplest

reasonable relationship between λ and $\langle\Phi\rangle_\lambda$ is linear, as predicted by the continuum Born model.⁸ Numerous simulation studies of ion hydration using explicit water molecules have verified that this relationship holds approximately over a wide range of λ .^{3,5,9,10} If $\langle\Phi\rangle_\lambda$ is assumed to have a quadratic dependence on λ to account for slight deviations from linearity, Eq. (1) can be integrated immediately giving

$$\mu^* = q/6(\langle\Phi\rangle_0 + 4\langle\Phi\rangle_{q/2} + \langle\Phi\rangle_q). \quad (2)$$

While this expression does not necessarily give the most accurate estimate of μ^* ,⁷ Eq. (2) is satisfactory for our purposes here. The average electrostatic potential obtained from computer simulations employing periodic boundary conditions, $\langle\Phi_{\text{SIM}}\rangle_\lambda$, does not correspond to the potential used in Eq. (2) but must be corrected, as stated above, to remove artificial system size effects. Previous work has suggested that this correction for both the MPT and ES methods is a linear function of λ ,^{3,4}

$$\langle\Phi\rangle_\lambda = \langle\Phi_{\text{SIM}}\rangle_\lambda + \xi\lambda. \quad (3)$$

The proportionality constant ξ for the correction depends on the method used to evaluate electrostatic interactions and the periodic box size.

Wood's derivation of the correction for MPT simulations, ξ_{MPT} , uses a dielectric continuum model for the free energy difference between the periodic truncated system and the system at infinite dilution.⁴ ξ_{MPT} , as mentioned above, corrects for periodicity and errors introduced from the truncation of both ion–water and water–water interactions. ξ_{MPT} therefore depends not only on the size of the central simulation cell, but on the ion (I)–water(W), r_{IW} , and water–water, r_{WW} , cutoff radii. ξ_{MPT} is not a simple function of these variables, however. Details on the calculation of ξ_{MPT} are presented in the article by Wood.^{4,11} The ES correction, ξ_{ES} , is simpler than that for the MPT method and has been shown to be $\xi_{\text{ES}} = -2.837\,297e/4\pi\epsilon_0 L$,³ where e is the fundamental electrostatic charge, ϵ_0 is the permittivity of a vacuum, and L is the length of the periodic cubic simulation cell. ξ_{ES} is the self-term and accounts for the interactions of the ion with its periodic images and the uniform background neutralizing charge.

We have performed canonical ensemble Monte Carlo (MC) simulations of sodium ion hydration using both the MPT and ES methods to evaluate the electrostatic energy.¹² The simulations consisted of 255 simple point charge (SPC) water molecules¹³ hydrating one sodium ion modeled using the Lennard-Jones potential parameters used by Straatsma and Berendsen.⁵ For this simulation size, μ^* was previously found to have converged to its infinite dilution value using both methods. The simulations were carried out at ambient conditions of 25 °C and a water density of 0.997 g/cm³ ($L = 19.7308$ Å). Three sodium charge states of $0e$, $+e/2$, and $+1e$ were considered. At each charge state $\langle\Phi\rangle_\lambda$ was calculated and μ^* was computed by Eq. (2) once all three simulations were completed. Each charge state was equilibrated for 5×10^4 cycles (1 cycle = one attempted MC move on each molecule), followed by 2×10^5 cycles for thermodynamic averaging. The averages were grouped into five blocks of

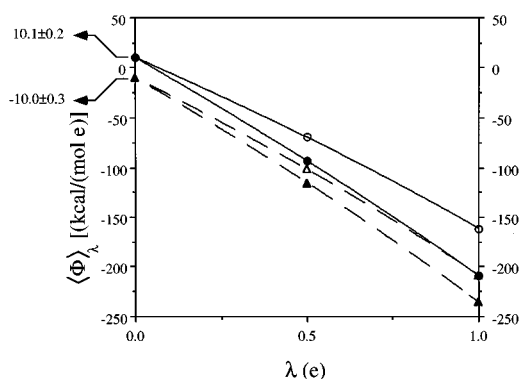


FIG. 1. Plot of $\langle\Phi\rangle_\lambda$ as a function of λ for the free energy simulations. The dashed lines (---) are the MPT results and the full lines (—) are the ES results. The open (Δ) and closed (\blacktriangle) triangles denote the MPT results before and after the finite simulation size correction has been applied. The open (\circ) and closed (\bullet) circles denote the ES results before and after the finite simulation size correction has been applied.

equal size for statistical analysis of the results. For the MPT simulations, water–water interactions were cutoff when the oxygens of neighboring water molecules were separated by 9 Å or more ($r_{\text{WW}} = 9$ Å) and ion–water interactions were cut-off when the ion and water oxygen were separated by 9 Å or more ($r_{\text{IW}} = 9$ Å). ξ_{MPT} equals -27.3 kcal/(mol e) for these simulation conditions, calculated using the equations presented by Wood.⁴ Following the work of Hummer *et al.*³ the ES damping factor was chosen as $5.6/L$ for evaluation of the short-range real space component of the ES method. Likewise, the long-range Fourier space component was truncated spherically at $k^2 \leq 38(2\pi/L)^2$ employing 1020 reciprocal lattice \mathbf{k} vectors. Unlike the previous study, the sum was evaluated with an infinite background dielectric constant (conducting boundary conditions) instead of the dielectric constant of SPC water ($\epsilon = 65$).³ For the simulation cell size used here ξ_{ES} equals -47.8 kcal/(mol e).

The simulation results of $\langle\Phi\rangle_\lambda$ as a function of λ before and after the electrostatic correction has been applied are shown in Fig. 1. As expected from the Born prediction,⁶ $\langle\Phi\rangle_\lambda$ is nearly linear with λ . The corrected hydration free energy for the MPT simulations is -118.1 ± 0.6 kcal/mol (errors reported as one standard deviation) in good agreement with Straatsma and Berendsen's result.^{4,5} The corrected free energy for the ES simulations is -95.7 ± 0.6 kcal/mol, likewise in good agreement with the result of Hummer *et al.*³ It is interesting to note is that before the electrostatic correction is applied, $\langle\Phi\rangle_\lambda$ values for the two methods have differing slopes. After the correction is applied the values of $\langle\Phi\rangle_\lambda$ evaluated by the two methods are essentially parallel to one another. The first derivative of $\langle\Phi\rangle_\lambda$ with respect to λ has been shown to be^{3,7,10}

$$\frac{\partial\langle\Phi\rangle_\lambda}{\partial\lambda} = -\frac{(\langle\Phi^2\rangle_\lambda - \langle\Phi\rangle_\lambda^2)}{k_B T}, \quad (4)$$

where k_B is Boltzmann's constant, T is the temperature, and $(\langle\Phi^2\rangle_\lambda - \langle\Phi\rangle_\lambda^2)$ is the fluctuation in the electrostatic potential at the center of the charge site. The uncorrected and

corrected values of $\partial\langle\Phi\rangle_\lambda/\partial\lambda$ for the MPT results, obtained by linear regression of the simulation data, are -199 ± 2 kcal/(mol e^2) and -226 ± 2 kcal/(mol e^2), respectively. Similarly, the uncorrected and corrected values of $\partial\langle\Phi\rangle_\lambda/\partial\lambda$ for the ES simulation data are -172 ± 2 kcal/(mol e^2) and -220 ± 2 kcal/(mol e^2), respectively. Hence, the finite size correction brings the fluctuations in $\langle\Phi\rangle_\lambda$ for both methods into closer agreement with one another. The difference between the sodium hydration free energies can be attributed to the constant shift down in $\langle\Phi\rangle_\lambda$ for the MPT result relative to the ES result. We thus proceed to examine this difference more closely. When the sodium ion is an uncharged solute ($\lambda=0e$), $\langle\Phi\rangle_0$ is -10.0 ± 0.3 kcal/(mol e) and 10.1 ± 0.2 kcal/(mol e) for the MPT and ES simulations, respectively. Similar values of $\langle\Phi\rangle_0$ for the MPT¹⁰ and ES³ methods have been reported. The difference between $\langle\Phi\rangle_0$ evaluated by these methods is -20.1 ± 0.3 kcal/(mol e). If the difference is assumed to be independent of λ a free energy difference of -20.1 ± 0.3 kcal/mol at full ionic charge results. This contribution dominates the observed free energy difference of -22.4 ± 0.9 kcal/mol. Therefore, if the origin of the difference in $\langle\Phi\rangle_0$ can be determined, the discrepancy between the MPT and ES hydration free energies can be resolved.

Water has been shown to adopt preferential orientations in the first hydration shell of an uncharged solute and becomes uncorrelated in subsequent hydration shells.¹⁴ Hence, the nonzero electrostatic potential in the interior of the solute reflects the asymmetric distribution of water orientations in the first hydration shell. To investigate the origin of the observed differences in $\langle\Phi\rangle_0$, we have calculated potential contributions using both the MPT and ES methods from water configurations generated during the ES simulation of the uncharged Lennard-Jones sodium. The individual water-oxygen and hydrogen site contributions to the solvent-induced electrostatic potential were determined in 0.1 Å shells centered around the solute. The MPT interaction was calculated out to 9 Å as in the MPT free-energy simulations. $\langle\Phi\rangle_0$ was evaluated by integrating the individual water-oxygen and water-hydrogen contributions radially out from the center of the solute and summing them. The cumulative values of $\langle\Phi\rangle_0$ as a function of the radial distance from the center of the solute are shown in Fig. 2. Only the real space contributions to the ES method can be easily analyzed in this manner, so 0.6 ± 0.2 kcal/(mol e) has been added to the ES result to account for the average Fourier space contribution to $\langle\Phi\rangle_0$. The real space component quickly converges after the first hydration shell to the final ES result for $\langle\Phi\rangle_0$ of 10.1 ± 0.2 kcal/(mol e). The MPT result, on the other hand, does not converge as quickly as the real space ES result, but approaches the ES value at intermediate separations after the first solute hydration shell. For the MPT calculation $\langle\Phi\rangle_0$ in the vicinity of the cutoff sharply dips down and back up to a final value of -8.9 ± 0.2 kcal/(mol e). Using water configurations generated by the ES simulation, $\langle\Phi\rangle_0$ calculated using the MPT method has a value close to that calculated from the explicit MPT simulation. This result suggests that water structures around an uncharged solute generated by MPT and

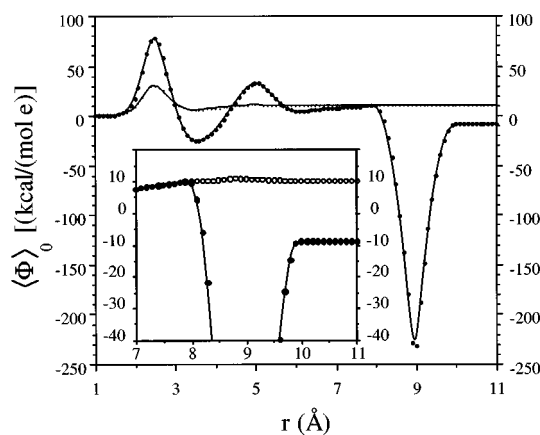


FIG. 2. Plot of the combined water-oxygen and hydrogen cumulative contributions to $\langle\Phi\rangle_0$ as a function of the radial distance from the center of the uncharged sodium ion. The line (—) is the ES result and the closed circles (●) are the MPT result evaluated from water configurations generated during the ES simulation. The inset figure shows the MPT result in the vicinity of the cutoff radius, $r_{IW}=9$ Å, before (●) and after (○) the $\Delta\Phi_{MPT}$ correction has been applied.

ES simulations are virtually indistinguishable and that the difference in $\langle\Phi\rangle_0$ between the two methods is methodological. It is shown below that the spurious dip in $\langle\Phi\rangle_0$ can be attributed to an imbalance of the water-oxygen and hydrogen interactions with the solute in the vicinity of the potential cutoff.

Before continuing, it should be pointed out that the convergence behavior of $\langle\Phi\rangle_0$ in Fig. 2 for the MPT method depends on how the individual water contributions to the potential are integrated. If contributions to $\langle\Phi\rangle_0$ are integrated on a per molecule basis from the position of the water oxygen,¹⁰ rather than a per charge basis from the positions of the individual water sites as presented in Fig. 2, the dip disappears and the potential smoothly converges to -8.9 ± 0.2 kcal/(mol e). The smooth convergence of $\langle\Phi\rangle_0$ to the negative value is erroneous. In reality, it is the distribution of charge density and not the distribution of water molecules that determines the net electrostatic potential.

The correlation of water molecules far away from a central solute molecule is uniform. If r_{IW} for the MPT method is large, then the radial distribution of water-oxygens, $g_{IO}^{MPT}(r)$, that contribute to $\langle\Phi\rangle_0$ in the vicinity of the cutoff is a step function with a value of 1 for separations below r_{IW} and 0 above r_{IW} ,

$$g_{IO}^{MPT}(r) = \begin{cases} 1 & r < r_{IW} \\ 0 & r > r_{IW} \end{cases} \quad (5a)$$

While water-oxygens in the MPT method must be within r_{IW} of the solute to interact with it, the pendant hydrogen sites are not so constrained. When an oxygen is inside r_{IW} , the hydrogen sites can extend outside of r_{IW} by the oxygen-hydrogen bond length, r_{OH} , and still interact with the solute. Similarly, when a water-oxygen is outside r_{IW} , the hydrogen sites can extend inside r_{IW} without interacting with the solute. Consequently, the radial distribution of water-

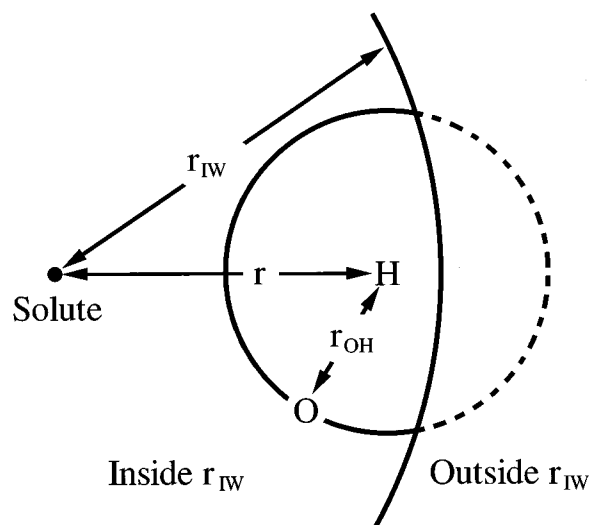


FIG. 3. Schematic illustration of the geometry required to derive $g_{\text{IH}}^{\text{MPT}}(r)$, Eq. (5b). The water–oxygen–solute electrostatic potential cutoff describes a sphere of radius r_{IW} centered on the solute. One of the water–hydrogens is located at a distance r relative to the solute. The location of the second hydrogen is unimportant for the derivation. The oxygen–hydrogen bond length describes a sphere of radius r_{OH} centered on the hydrogen site shown explicitly in the illustration. The solid portion of this sphere represents water orientations in which the oxygen is inside of r_{IW} and the hydrogen interacts with the solute. The dashed portion of this sphere represents water orientations in which the oxygen is outside of r_{IW} and the hydrogen does not interact with the solute.

hydrogens that contribute to $\langle \Phi \rangle_0$ in the vicinity of cutoff, $g_{\text{IH}}^{\text{MPT}}(r)$, does not end abruptly like the oxygen distribution, but gradually decreases from 1 to 0 between $r_{\text{IW}} - r_{\text{OH}}$ and $r_{\text{IW}} + r_{\text{OH}}$. The geometry relevant for determining $g_{\text{IH}}^{\text{MPT}}(r)$ in the neighborhood of r_{IW} is illustrated in Fig. 3. Consider a water molecule with one of its hydrogen sites located a distance r from the solute. The solute may be charged or not, as long as the water molecule is effectively uncorrelated with it. The probability of observing a solute–oxygen separation less than r_{IW} , and hence the probability that the water molecule interacts with the solute, is equal to the fractional surface area of the sphere of radius r_{OH} centered on the hydrogen site that is inside the sphere of radius r_{IW} centered on the solute. $g_{\text{IH}}^{\text{MPT}}(r)$ is thereby given as

$$g_{\text{IH}}^{\text{MPT}}(r) = \begin{cases} 1 & r < r_{\text{IW}} - r_{\text{OH}} \\ \frac{1}{2} + \frac{r_{\text{IW}}^2 - r_{\text{OH}}^2 - r^2}{4r_{\text{OH}}r} & r_{\text{IW}} - r_{\text{OH}} < r < r_{\text{IW}} + r_{\text{OH}} \\ 0 & r > r_{\text{IW}} + r_{\text{OH}} \end{cases} \quad (5b)$$

The combined oxygen and hydrogen distributions describe a shell of charge separation at the truncation boundary.

From the expressions for $g_{\text{IO}}^{\text{MPT}}(r)$ and $g_{\text{IH}}^{\text{MPT}}(r)$ the increment in the MPT electrostatic potential, $\Delta\Phi_{\text{MPT}}$, attributed to the distribution of water molecules at the cutoff boundary can be calculated. $\Delta\Phi_{\text{MPT}}$ is given as

$$\Delta\Phi_{\text{MPT}} = \frac{\rho_{\text{W}}}{4\pi\epsilon_0} \left\{ \int_{r_{\text{IW}} - r_{\text{OH}}}^{r_{\text{IW}} + r_{\text{OH}}} [q_{\text{O}}g_{\text{IO}}^{\text{MPT}}(r)/r + 2q_{\text{H}}g_{\text{IH}}^{\text{MPT}}(r)/r] dr \right\} \quad (6a)$$

$$= -\frac{\rho_{\text{W}}q_{\text{H}}r_{\text{OH}}^2}{3\epsilon_0}, \quad (6b)$$

where ρ_{W} is the bulk density of water, and q_{O} and q_{H} are the electrostatic charges on the oxygen and hydrogen sites, respectively ($q_{\text{O}} = -2q_{\text{H}}$). The present derivation assumes a spherical truncation geometry for which the ion–water electrostatic interaction is abruptly turned off at the cutoff radius. It can be easily shown, through application of Gauss’s law,¹⁵ that the analytical result, Eq. (6b), is applicable to both non-spherical truncation geometries (i.e., cubic⁹) and potentials that are turned off with a switching function near the truncation boundary. For SPC water r_{OH} is 1 Å and q_{H} is $+0.41e$.¹³ With these parameters and the simulation density of water, $\Delta\Phi_{\text{MPT}}$ is calculated as -19.0 kcal/(mol e). This value is in excellent agreement with the observed difference between $\langle \Phi \rangle_0$ evaluated by the ES and MPT methods from explicit ES simulations. The analytical expression for $\Delta\Phi_{\text{MPT}}$ indicates that the difference in $\langle \Phi \rangle_0$ evaluated by the two methods is independent of r_{IW} . The MPT method assumes that for large cutoff radii the water molecules r_{IW} away from the solute appear as randomly oriented point dipoles that can be neglected in the potential calculation. While this assumption seems reasonable, our analysis demonstrates that when the potential cutoff is based on the ion–oxygen separation, convergence to the point dipole limit is counterbalanced by the total number of molecules at r_{IW} . Furthermore, as long as r_{IW} is chosen to be large enough, $\Delta\Phi_{\text{MPT}}$ will be independent of the ion charge state. The values of $\langle \Phi \rangle_{\lambda}$ determined from a simulation that uses the MPT method then will be shifted down from the ES results by a constant amount consistent with the observed shift in Fig. 1.

To confirm that the difference in $\langle \Phi \rangle_0$ is attributed to the biasing of ion–oxygen and ion–hydrogen interactions at the cutoff, we have subtracted the cumulative integral for $\Delta\Phi_{\text{MPT}}$, Eq. (6a), between $r_{\text{IW}} - r_{\text{OH}}$ and $r(r_{\text{IW}} - r_{\text{OH}} < r < r_{\text{IW}} + r_{\text{OH}})$ from the MPT values of $\langle \Phi \rangle_0$ presented in Fig. 2. The corrected results for $\langle \Phi \rangle_0$ are shown in the inset to Fig. 2. After the present correction is applied the anomalous dip in $\langle \Phi \rangle_0$ disappears and the MPT result converges to 10.1 ± 0.2 kcal/(mol e) in excellent agreement with the ES value. Subtracting $\Delta\Phi_{\text{MPT}}$ from the MPT free energy simulations yields an improved value for the free energy of -99.1 ± 0.6 kcal/mol compared to the ES simulation result of -95.7 ± 0.6 kcal/mol.

In conclusion, we have identified the origin of the hydration free energy differences of the sodium ion calculated using the MPT and ES methods to evaluate the long-range electrostatic energy. The discrepancy between these methods was traced to the unequal biasing of water–oxygen and water–hydrogen interactions with the solute at the potential cutoff in the MPT method. An analytical expression was

developed that corrects this imbalance assuming that the water molecules are randomly oriented with respect to the solute in the neighborhood of the truncation boundary. Rather than truncating the ion–water interaction based on the ion–oxygen distance, our results suggest that truncation based on an uncharged auxiliary site could be used to eliminate the extrinsic potential difference between the two methods. The auxiliary site must be chosen so that the distances from the site to the oxygen and from the site to either hydrogen are equal. This ensures that the distribution of interacting oxygens and hydrogens on either side of the truncation boundary are equal and cancel in the evaluation of the extrinsic potential increment, $\Delta\Phi_{\text{MPT}}$. Setting the extrinsic potential of the MPT and ES methods equal to each other enables the free energies evaluated by both techniques to be compared properly. After this correction is made, we obtain sodium ion hydration free energies of -99.1 ± 0.6 kcal/mol and -95.7 ± 0.6 kcal/mol for the MPT and ES methods which compare favorably and give us confidence that the simulations are producing the correct infinite dilution behavior by either method. Experimentally, however, the free energy of a single ion cannot be measured independently since real systems are required to satisfy the constraint of electroneutrality. This extrinsic potential therefore cannot be measured experimentally since ion hydration free energies must be referenced to a single ion, typically H^+ for aqueous solutions.¹⁶

The assumption that water–oxygens and hydrogens are uniformly distributed on either side of r_{IW} is strictly true only in the limit of an infinite cutoff. Our analysis indicates that for finite r_{IW} this is a good approximation around an uncharged solute. For an ion though this approximation will breakdown. Previous theoretical¹⁷ and simulation¹ work has found that truncation of the electrostatic potential disrupts the radial distribution of water–oxygens and water–hydrogens around an ion in the vicinity of r_{IW} . Furthermore, the distribution of water in hydration shells close to the ion are sensitive to the choice of r_{IW} .¹ Similar irregularities in the ion–water pair structure for the charged sodium states were observed during the MPT simulations performed here. ES simulations of charged solutes, on the other hand, do not present these structural anomalies.³ The remaining difference between the MPT and ES values for μ^* can most likely be attributed to this structural problem. While this effect ap-

pears to be small for the thermodynamic results presented here, it will be exacerbated for small r_{IW} and high ionic charges.

Note added in proof. After this work had been submitted for publication we received a preprint in which related material was presented.¹⁸

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¹¹It should be noted that in Wood's method the MPT Hamiltonian is considered to be a short-ranged potential that is easily simulated. Corrections are applied for the difference between the short- and long-range Hamiltonians. An alternate method is to consider the MPT system as a Coulomb system that needs "surface" corrections at the truncation distance, yielding essentially a reaction field Hamiltonian (see Ref. 6).

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