On Finite-Size Corrections to the Free Energy of Ionic Hydration

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Efforts to compare thermodynamic predictions of simulations with experiment have been thwarted by the approximations used in modeling the long-range electrostatic interactions. In a recent article Hummer et al. proposed an explicit formula that accounts for most of the finite-size effect in simulations of ion charging using periodic boundary conditions. In this Letter we have verified the numerical results of Hummer et al. and we provide a simple theoretical argument that explains why the solvent polarization free energy contains a contribution that largely cancels the lattice self-energy. The cancellation depends on the fact that the solvent is a high dielectric. We propose a finite size correction formula that can be applied in both the low and high dielectric limits.

The study of the molecular features of ion hydration by computer simulations remains an active research area.[1−8] Efforts to (quantitatively) compare thermodynamic predictions of simulations with experiment have been thwarted by the approximations used in modeling the long-range electrostatic interactions which dominate this problem. In a recent article Hummer et al.[5] proposed an explicit formula that accounts for most of the finite-size effect in simulations of ion charging using periodic boundary conditions. It is well-known that the solution of Poisson's equation under periodic boundary conditions leads to a self-energy term; that is, the total energy of a single ion is not zero but rather

$$^1/_2\zeta_{EW}q^2 \quad (1)$$

where, for a cubic lattice of periodicity L, ζ_{EW} is proportional to $1/L$.[5,7] However, in molecular mechanics simulations what is typically computed is the contribution of the solvent to the free energy of charging, and the self-energy is not included. What Hummer et al. proposed was to include it in the final formula, that is, that the free energy change in charging the ion from q_0 to q_1 be computed as

$$\Delta F_{total}(q_0 \rightarrow q_1) = \Delta F_{sim}(q_0 \rightarrow q_1) + {}^1/_2\zeta_{EW}\,(q_1^2 - q_0^2) \quad (2)$$

Here ΔF_{sim} is the free energy change due to the polarization of the solvent obtained from the simulation according to the usual procedure.[5,7] Equation 2 gives the *total* free energy of charging the ion, in a finite volume, from q_0 to q_1. They carried out several Monte Carlo simulations where the free energy of charging diverse ions in systems with different periods (but all cubic) were computed. Their results are quite impressive and imply that the total free energy of charging the ion is only weakly dependent on the simulation volume.

We have calculated the charging free energy of a chloride ion in aqueous solution using both the free energy perturbation (FEP) method (see Table 1)[9] and the linear response approximation (see Table 2)[10,11] using the molecular mechanics package IMPACT.[12] The results from both methods are in good accord, implying that the molecular nature of the solvent does not introduce strong nonlinearities.[2,5,11] The corrections were applied as suggested by Hummer et al., using eq 2. These corrections have the effect of subtracting most, if not all, the effect of having a finite simulation volume.

TABLE 1: Charging Free Energy of a Chloride Ion in Aqueous Solution Using FEP[a]

N_{H_2O}	L (Å)	ΔF_{sim}	ΔF_{total}
25	9.322	−45 (2)	−96
270	19.8	−70 (2)	−94

[a] L is the size of the simulation box; the units of ΔF are kcal/mol.

TABLE 2: Charging Free Energy of a Chloride Ion in Aqueous Solution Using Linear Response[a]

N_{H_2O}	t (ns)	V	V^{corr}	ΔV^2	$\Delta V^{2,corr}$	ΔF_{total}
25	3	88.7 (0.2)	189.7	56 (2)	116	−92
270	3	138.4 (0.2)	185.9	84 (2)	112	−91

[a] V, V^{corr}, ΔV^2, and $\Delta V^{2,corr}$ are the electrostatic potentials at the ion site and electrostatic potential correlation functions without and with the finite-size correction. The units of V and ΔF are kcal/mol.

The numerical results demonstrate that the total free energy of charging an ion, eq 2, does not depend strongly on the simulation volume. In contrast, the self-energy term (the second term in eq 2) has a very strong dependence: it goes from about 51 kcal/mol for a 9 Å box to 24 kcal/mol for a 20 Å box. This implies that the solvent contribution, ΔF_{sim} ($q_0 \rightarrow q_1$), must also show a marked dependence on the simulation volume which effectively cancels the lattice self-energy of the ion.

In this Letter we have verified the numerical results of Hummer et al.[5] and we provide a simple theoretical argument that explains why the solvent polarization free energy contains a contribution that largely cancels the lattice self-energy. Our argument also shows that this cancellation depends on the fact that the solvent is a good dielectric. It is interesting to note that the Born charging free energy formula for an ion in an unbounded medium results from a corresponding cancellation between the self-energy of the ion and the polarization free energy of the solvent.

Consider a spherical ion of radius a in a finite (cubic) simulation box of side L. If we ignore the molecular nature of the solvent, there are only two length scales in the problem (a and L), and therefore, by dimensional analysis, the total free energy of charging an ion can be written as

$$\Delta F_{total}(q_0 \rightarrow q_1) = (q_1^2 - q_0^2)\left(\frac{b}{a} + c_0\frac{1}{L} + c_1\frac{a}{L^2} + ...\right) \quad (3)$$

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The first term in the expansion, b/a, is essentially the Born term. Although we don't know the complete expansion, the strongest L-dependent term, c_0/L, has a very small coefficient—thus the total free energy is only weakly dependent on L, in accord with Hummer et al.'s and our results.

The term c_0/L can be calculated explicitly: it is the (finite part) of the total free energy of charging a *pointlike* ion ($a = 0$) from $q_0 = 0$ to $q_1 = 1$. This quantity is easy to compute since we can use classical electrostatics of point charges. After the r^{-1} divergence is subtracted, the remaining contribution to the free energy is simply the vacuum lattice term divided by ϵ, that is

$$\frac{c_0}{L} = \frac{1}{2}\zeta_{\mathrm{EW}}\frac{1}{\epsilon} \tag{4}$$

For aqueous solutions, ϵ is around 70 and therefore this term goes only from about 0.73 kcal/mol for a 9 Å box to 0.34 for a 20 Å box, a quite negligible change compared with the calculated free energies.

This result implies, however, that an entirely different situation occurs when the dielectric constant of the solvent is low. In particular, if $\epsilon = 1$, that is, there is no solvent, we recover the vacuum lattice term. In this case it is not true that $\Delta F_{\mathrm{total}}$ is only weakly dependent on the simulation volume! This leads us to propose that the total free energy of charging, eq 2, be corrected by subtracting the c_0/L dependence:

$$\begin{aligned}\Delta F_{\mathrm{corr}}(q_0 \rightarrow q_1) &= \Delta F_{\mathrm{total}}(q_0 \rightarrow q_1) - \frac{c_0}{L} \\ &= \Delta F_{\mathrm{sim}}(q_0 \rightarrow q_1) + \frac{1}{2}\zeta_{\mathrm{EW}}\left(1 - \frac{1}{\epsilon}\right)(q_1^2 - q_0^2)\end{aligned} \tag{5}$$

Notice that for aqueous solvation ϵ is around 70 and the term in parentheses is very close to 1, so that our corrected free energy is numerically quite similar to Hummer et al.'s. It differs, however, if the dielectric constant of the solvent is low. Equation 5 has the desirable property that it approaches the thermodynamic limit, as $L \rightarrow \infty$, more rapidly than does eq 2 for any solvent dielectric, although the finite size correction term will depend explicitly on the thermodynamic state of the system through the dependence on ϵ.

The argument presented above does not, however, allow us to predict the quite surprising fact that boxes of water with as few as 25 water molecules (see Tables 1 and 2) or even 16 molecules[5] are "large" enough to obtain a very good approximation to the thermodynamic limit. For this a knowledge of the other terms in the expansion is necessary. It is expected, however, that all of them will be inversely proportional to ϵ.

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