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On finite-size effects in computer simulations using the Ewald potential

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We discuss the origin and relevance for computer simulations of a strong finite-size effect that appears when using the Ewald summation formula. It can be understood as arising from a volume-dependent shift of the potential in a finite, periodic box relative to the infinite volume limit. This shift is due to the fact that the ''zero of energy'' for a periodic system cannot be defined by letting the interacting particles be separated by an infinite distance; the correct definition corresponds to setting its $\boldsymbol{k}=\mathbf{0}$ Fourier mode to zero. The implications of this effect for computer simulations are discussed. © *1995 American Institute of Physics.*

I. INTRODUCTION

The correct and efficient treatment of the long-range electrostatic interactions in simulations of aqueous solutions continues to be an issue of intense research. The Ewald summation technique[1–3] appears to be a promising approach for the consistent treatment of these interactions. Several groups have discussed that the truncation of the electrostatic forces, either spherical or using the ''minimum image'' convention, results in severe modifications of the dielectric behavior.[4–8] There are indications that these modifications have quite noticeable effects on the behavior of aqueous solutions in computer simulations.[9–14]

In spite of this, the Ewald summation method has not been extensively applied to simulations of macromolecules in solution, where the preferred method continues to be spherical truncation of the Coulomb potential. With the rapid advances in computer technology and new, improved algorithms that speed the calculation of the long-range forces without sacrificing accuracy,[15–19] this situation may soon change. Thus, a discussion of the artifacts that affect the computer simulations is timely. In this paper we focus our attention on a finite-size effect, that is, an artifact that arises from the fact that the system being simulated is constrained to a finite volume, V. This effect can be quite strong and, although it disappears in the limit $V\rightarrow\infty$, the convergence to this limit is not particularly rapid. It should be noted, however, that volume dependencies affect any simulation of a finite system, and are not just an artifact of using the Ewald summation method, although the Ewald method lends itself to a more systematic theoretical treatment.

The effect described in this paper can be seen from two different perspectives: either as the result of the fact that constraining the system to a finite box introduces a volume-dependent natural scale for the interaction energy of a system of two ions; or as the dependence on the unit cell volume, V, of the electrostatic interaction energy of a pair of charges immersed in a continuum of dielectric ε (with periodic boundary conditions). These two views are expounded in Secs. III and IV. In a related paper[20] Del Buono *et al.* demonstrate by explicit computer simulations in water that this effect is not negligible.

The structure of the paper is as follows. In Sec. II we discuss the most general form of the electric potential in a periodic box of volume V and show that simple physical requirements lead to the (tinfoil) Ewald potential augmented by an ''extrinsic'' potential, proportional to the unit cell's dipole moment. This section does not contain new results but can shed new light on old results that are still not quite clear in the technical literature.[21] In Sec. III the classical electrostatics expression for the interaction energy of two point charges in a periodic box is discussed. It is shown that the interaction energy coincides with the potential only if the latter satisfies the condition that its volume average vanishes. This condition generalizes the usual ''zero potential at infinity'' rule in infinite systems. Section IV presents results of molecular dynamics simulations of two ions in an aqueous solution in order to illustrate the issue of volume dependence and its importance to computer simulations. We focus on the free energy of charging a system of two ions in a bath and show that, again, the condition of vanishing volume average arises quite naturally. Next we discuss a numerical example to put into perspective the size of the effect. Finally the relevance to computer simulations of aqueous solutions is discussed.

II. THE LATTICE SUMS

Since the seminal work of de Leeuw *et al.*[22,23] it has been known that the lattice summation method, that is, the summation of the potentials and forces produced by an infinite number of replicas of a system of charges (unit cell), produces not one but a whole family of potentials, which differ in a term proportional to the dipole moment $\mathbf{d}$ of the unit cell and take the form

$$\Phi(\mathbf{x})=\sum_{\mathbf{n}}\frac{\operatorname{erfc}(\alpha||\mathbf{x}-L\mathbf{n}||)}{||\mathbf{x}-L\mathbf{n}||}+\frac{1}{\pi}\sum_{\mathbf{k}\neq\mathbf{0}}\frac{\exp(-\pi^2||\mathbf{k}||^2/\alpha^2L^2+2\pi i/L\mathbf{x}\cdot\mathbf{k})}{L||\boldsymbol{k}||^2}+\frac{\lambda}{V}\mathbf{x}\cdot\mathbf{d}+\text{constant}. \tag{1}$$

Although for $\lambda \neq 0$ this potential is not periodic due to the term linear in $\mathbf{x}$, it nevertheless gives rise to a periodic electric field, which is the only constraint that can be imposed on physical grounds. The constant of proportionality, λ, can be related to the dielectric constant $\varepsilon_{\mathrm{rf}}$ of a medium surrounding a large sphere of replicas of the unit cell. In the limit of an infinite sphere a residual dependence on this dielectric constant remains, giving rise to this ''extrinsic'' potential.[24] Sometimes the choice of $\varepsilon_{\mathrm{rf}}$ is called the ''boundary condition,'' not to be confused with the fact that these models impose periodic boundary conditions on the particles. The value $\varepsilon_{\mathrm{rf}}=\infty$ (tinfoil or conducting boundary) is very special since it alone results in a potential that is periodic due to the absence of this dipolar term. All other choices necessarily break periodicity and their use in molecular dynamics simulations introduces some subtle questions. In what follows when we talk about the ''Ewald potential'' we mean that which results from the choice of tinfoil boundary conditions. If other ''boundary conditions'' are chosen another finite-size effect related to this dipolar term appears. This will not be discussed further in this paper.

In their excellent mathematical treatment de Leeuw *et al.*[22,23] were concerned with the calculation of the conditionally convergent (i.e., ill-defined) sum

$$\frac{1}{2}\sum_{\mathbf{n}}\sum_{i,j}\frac{q_i q_j}{\|\mathbf{x}_i-\mathbf{x}_j-L\mathbf{n}\|} \tag{2}$$

that defines the potential energy of a system of charges in a periodic box of side length L (notice that for $\mathbf{n}=\mathbf{0}$ the diagonal terms $i=j$ are dropped). Formally this sum can be rewritten as

$$\frac{1}{2}\sum_{i,j} q_i q_j \Phi(\mathbf{x}_i-\mathbf{x}_j), \tag{3}$$

where

$$\Phi(\mathbf{x})=\sum_{\mathbf{n}}\frac{1}{\|\mathbf{x}-L\mathbf{n}\|}. \tag{4}$$

It is this sum, or rather a regularization of it, that we will be concerned with.

First of all, note that if the system is electrically neutral we can add to Φ any constant term without changing the potential energy since

$$\sum_{i,j} q_i q_j c = c\left(\sum_i q_i\right)^2 = 0. \tag{5}$$

The second observation is that $\Phi(\mathbf{x}_i-\mathbf{x}_j)$ diverges as $1/\|\mathbf{x}_i-\mathbf{x}_j\|$ when $\mathbf{x}_i\to\mathbf{x}_j$. This short-distance divergence is well known and has nothing to do with the fact that the sum in Eq. (2) is ill-defined; it is just an artifact of using point charges, which have a divergent self-energy even in an infinite space. Thus the diagonal sum $i=j$ should be redefined to subtract this trivial divergence. In any case, the diagonal sum contributes only to the self-energy of the system and does not influence the dynamics.

The third observation is the following: the sum in Eq. (4) diverges. In their treatment de Leeuw *et al.* actually found that the divergence is independent of $\mathbf{x}$, and there is no effect for an electrically neutral system. Once this divergence is removed, what remains is conditionally convergent. We should mention that there seems to be some confusion about this point: the *only* requirement that needs to be made to obtain sensible results is that the system be electrically neutral and not, as has been mentioned in the literature,[21] that the net dipole moment vanish as well. If there is a net dipole moment the sum in Eq. (4) is conditionally convergent (not divergent), which means that there is not a unique answer. This nonuniqueness reflects the fact that some properties of a system depend not only on the intrinsic characteristics of the system but also on the shape and other boundary conditions. Due to its long-range nature, the electrostatic energy is a prime example of this dependence. A clear discussion of this point, albeit quite technical, can be found in (Ref. 24).

Since $\Phi(\mathbf{x}-\mathbf{u})$ is the electric potential produced by a unit charge at $\mathbf{u}$ (plus all its infinite copies), we might start by requiring that Φ satisfy Poisson's Eq. (Ref. 25):

$$\nabla^2\Phi(\mathbf{x}-\mathbf{u})=-4\pi\delta_p(\mathbf{x}-\mathbf{u}) \tag{6}$$

and that Φ be a periodic function: $\Phi(\mathbf{x}+L\mathbf{n})=\Phi(\mathbf{x})$ (here δ_p is the periodic Dirac δ function). This is, however, not consistent, as integrating both sides over the unit cell shows. The left-hand side gives identically zero, as can be seen by using Stoke's theorem to convert the volume integral to a surface integral and the fact that the electric field is periodic, while the right-hand side does not vanish. This is simply a consequence of the well-known fact that in a periodic system the net charge must vanish. We can easily satisfy the neutrality requirement by adding a homogeneous background charge density that exactly cancels the unit charge in Eq. (6) (Ref. 26–28):

$$\begin{aligned}\nabla^2\Phi(\mathbf{x}-\mathbf{u}) &= -4\pi\left(\delta_p(\mathbf{x}-\mathbf{u})-\frac{1}{V}\right)\\ &= -4\pi\sum_{\mathbf{k}\neq\mathbf{0}}\exp[(2\pi i/L)(\mathbf{x}-\mathbf{u})\cdot\mathbf{k}],\end{aligned} \tag{7}$$

where we have also written the right-hand side in Fourier space (here $V=L^3$).

With hindsight we can find a particular solution of Eq. (7): Ewald's potential with conducting, or tinfoil, boundary conditions,,[1,3,22,23] which corresponds to $\lambda=0$ in Eq. (1):

$$\begin{aligned}\Phi'_{\mathrm{Ew}}(\mathbf{x}) &= \sum_{\mathbf{n}}\frac{\mathrm{erfc}(\alpha\|\mathbf{x}-L\mathbf{n}\|)}{\|\mathbf{x}-L\mathbf{n}\|}\\ &\quad+\frac{1}{\pi}\sum_{\mathbf{k}\neq\mathbf{0}}\frac{\exp\left(-\pi^2\frac{\|\mathbf{k}\|^2}{\alpha^2L^2}+\frac{2\pi i}{L}\mathbf{x}\cdot\mathbf{k}\right)}{L\|\mathbf{k}\|^2}.\end{aligned} \tag{8}$$

As written this potential has a flaw: it depends on the arbitrary parameter α. This can be seen most easily by considering the mean value of Φ'_{Ew} over the unit cell V:

$$\frac{1}{V}\int_V d^3x\ \Phi'_{\mathrm{Ew}}(\mathbf{x}) = \sum_{\mathbf{n}} \frac{1}{V}\int_V d^3x\ \frac{\mathrm{erfc}(\alpha\|\mathbf{x}-L\mathbf{n}\|)}{\|\mathbf{x}-L\boldsymbol{n}\|}$$

$$= \frac{1}{V}\int d^3x\ \frac{\mathrm{erfc}(\alpha\|\mathbf{x}\|)}{\|\mathbf{x}\|} = \frac{1}{L}\frac{\pi}{(\alpha L)^2}\,.$$

Subtracting this mean value results in an α-independent potential,

$$\Phi_{\mathrm{Ew}}(\mathbf{x}) = \Phi'_{\mathrm{Ew}}(\mathbf{x}) - \frac{1}{L}\frac{\pi}{(\alpha L)^2} \tag{9}$$

which, furthermore, has the following property:

$$\frac{1}{V}\int_V d^3x\ \Phi_{\mathrm{Ew}}(\mathbf{x}) = 0. \tag{10}$$

Applying the Laplacian ∇^2 to Φ_{Ew} one verifies, after a few manipulations, that it is a solution of Eq. (7).

Thus we can write our sought-after potential Φ in the form

$$\Phi(\mathbf{x}) = \Phi_{\mathrm{Ew}}(\mathbf{x}) + \phi'(\mathbf{x}), \tag{11}$$

where now ϕ' satisfies the homogeneous Laplace's equation

$$\nabla^2\phi'(\mathbf{x}) = 0. \tag{12}$$

In Appendix A the most general solution of the homogeneous problem is derived. The general form found by de Leeuw *et al.*, Eq. (1), is recovered. In the remainder of the paper we choose the solution to the homogeneous problem equal to zero, which corresponds to setting $\lambda = 0$ in Eq. (1).

III. INTERACTION ENERGY OF TWO IONS: CONTINUUM ELECTROSTATICS APPROACH

If two ions are placed in a periodic box filled with a solvent and the separation between them is large compared with typical molecular correlation lengths, the free energy of the system is given by the classical continuum electrostatic energy. The effect of the solvent is merely to renormalize the vacuum interaction energy (dielectric screening), and the complicated many-body problem is reduced to a simpler two-body problem. In this section we focus on this interaction energy from the point of view of continuum electrostatics, and Sec. IV we present a microscopic treatment of the same quantity. For large enough separations, of course, both treatments should give the same results.

Let us therefore consider a system of two point charges, together with their respective neutralizing backgrounds, in a cubic box with periodic boundary conditions filled with a dielectric medium of dielectric constant ε. It will be shown that continuum electrostatics predicts that the interaction energy shows a rather strong finite-size effect, i.e., a dependence on the linear dimension L of the box. In what follows we set $\lambda = 0$ so that the electric field is derived from a well-defined periodic potential.

In general we can expand $\mathbf{E}$ as a Fourier series

$$\mathbf{E}(\mathbf{x}) = \sum_{\mathbf{k}\neq\mathbf{0}} \mathbf{E}_{\mathbf{k}}\, e^{(2\pi i/L)(\mathbf{x}\cdot\mathbf{k})} \tag{13}$$

excluding, as discussed above, the $\mathbf{k}=\mathbf{0}$ term. The other terms can all be obtained from Eq. (7):

$$-4\pi^2\frac{\|\mathbf{k}\|^2}{L^2}\,\phi_{\mathbf{k}} = -4\pi\rho_{\mathbf{k}} \Rightarrow \phi_{\mathbf{k}} = \frac{L^2\rho_{\mathbf{k}}}{\pi\|\mathbf{k}\|^2}\,, \tag{14}$$

together with the Fourier space version of $\mathbf{E} = -\nabla\phi$:

$$\mathbf{E}_{\mathbf{k}} = -\frac{2\pi i}{L}\mathbf{k}\ \phi_{\mathbf{k}}. \tag{15}$$

The term $\phi_{\mathbf{0}}$ is not fixed by Eq. (7); since it does not contribute to the physical observables (like $\mathbf{E}$) this term is completely arbitrary. In particular, the Ewald potential Φ_{Ew} corresponds to $\phi_{\mathbf{0}} = 0$.

Consider now a system consisting of two charge distributions, ρ_1 and ρ_2, which are well separated, i.e., ρ_j is zero outside of a small neighborhood of points $\mathbf{u}_j$, and the two neighborhoods do not overlap. The energy of the system can be written (assuming a medium with dielectric constant ε)

$$E = \frac{\varepsilon}{8\pi}\int_V d^3x\ \|\nabla\phi\|^2, \tag{16}$$

where ϕ satisfies the equation

$$\nabla^2\phi(\mathbf{x}) = -\frac{4\pi}{\varepsilon}(\rho_1(\mathbf{x}) + \rho_2(\mathbf{x})). \tag{17}$$

For simplicity we assume that

$$Q_j = \int_V d^3x\ \rho_j \neq 0, \quad Q_1 + Q_2 = 0, \tag{18}$$

otherwise a further neutralizing background must be added to Eq. (17). We want to extract from the total energy E the interaction piece. In an infinite system ($L=\infty$) this is done by subtracting from E the terms

$$E_j = \frac{\varepsilon}{8\pi}\int_V d^3x\ \|\nabla\phi_j\|^2, \tag{19}$$

where

$$\nabla^2\phi_j(\mathbf{x}) = -\frac{4\pi}{\varepsilon}\,\rho_j(\mathbf{x}). \tag{20}$$

In a periodic box, as discussed previously, this equation must be replaced by

$$\nabla^2\phi_j(\mathbf{x}) = -\frac{4\pi}{\varepsilon}\left(\rho_j(\mathbf{x}) - \frac{Q_j}{V}\right). \tag{21}$$

Subtracting $E_1 + E_2$ from E we obtain the interaction energy, E_{int}

$$E_{\mathrm{int}} = \frac{\varepsilon}{4\pi}\int_V d^3x\ \nabla\phi_1\cdot\nabla\phi_2\,. \tag{22}$$

Integrating by parts and using Eq. (21) we can rewrite this as

$$E_{\mathrm{int}} = \int_V d^3x\ \left(\rho_1(\mathbf{x}) - \frac{Q_1}{V}\right)\phi_2(\mathbf{x})$$

$$= \int_V d^3x\ \rho_1(\mathbf{x})\left(\phi_2(\mathbf{x}) - \frac{1}{V}\int_V d^3y\ \phi_2(\mathbf{y})\right). \tag{23}$$

Notice that

$$\frac{1}{V}\int_V d^3y\ \phi_2(\mathbf{y}) \tag{24}$$

is nothing more than the $\mathbf{k}=\mathbf{0}$ term in the Fourier decomposition, sometimes called the *zero mode*. This simple argument shows that to calculate the electrostatic interaction energy between two charge distributions the $\mathbf{k}=\mathbf{0}$ Fourier mode of the potential must be removed.

Specializing to the case of two point charges, of charges $+q$ and $-q$, situated at $\mathbf{u}_1$ and $\mathbf{u}_2$, respectively, we find

$$E_{\rm int}=-\frac{q^2}{\varepsilon}\,\Phi_{\rm Ew}(\mathbf{u}_1-\mathbf{u}_2), \tag{25}$$

where $\Phi_{\rm Ew}$ is defined by Eq. (9) so that its integral over the unit cell vanishes identically.

IV. INTERACTION ENERGY OF TWO IONS: FREE ENERGY APPROACH

In this section we show again, but from a statistical mechanics perspective, that the interaction energy of two ions in solution coincides with the potential if and only if the latter satisfies that its volume average vanishes.

Consider two ions of charges q_1 and q_2 immersed in a molecular solvent inside a box of volume V. Under very general conditions it is possible to write the free energy of solvation of the ions as a quadratic function of the charges (see Appendix B and Ref. 29):

$$F_{\rm solv}(q_1,q_2)=F_{\rm solv}(q_1)+F_{\rm solv}(q_2)+q_1q_2\Phi(\mathbf{x}_1-\mathbf{x}_2) +q_1q_2W(\mathbf{x}_1-\mathbf{x}_2), \tag{26}$$

where $F_{\rm solv}(q)$ is the free energy of solvation of one ion immersed in the solvent when the charge in the other is set to zero (there is still a dependence on the cavity produced by the other ion, but it is negligible at large separations of the charges). Here $\mathbf{x}_i$ ($i=1$ and 2) are the positions of the ions inside the box and Φ is the interaction energy in the absence of solvent. The quantity $W(\mathbf{x}_1-\mathbf{x}_2)$ is the solvent contribution to the effective interaction energy and can be written as (Appendix B)

$$W(\mathbf{x}_1-\mathbf{x}_2)=-\frac{1}{\beta}\frac{\partial^2\ln Z}{\partial q_1\partial q_2}=-\beta(\langle\phi_{\rm solv}(\mathbf{x}_1)\phi_{\rm solv}(\mathbf{x}_2)\rangle -\langle\phi_{\rm solv}(\mathbf{x}_1)\rangle\langle\phi_{\rm solv}(\mathbf{x}_2)\rangle), \tag{27}$$

where $\phi_{\rm solv}(\mathbf{x})$ is the total electrostatic potential produced by the solvent atoms at the position $\mathbf{x}$. The mean values are computed with the ionic charges set to zero. As written, W depends on the size of the ionic cavities; however, this dependence is expected to be of short range. If the separation $\|\mathbf{x}_1-\mathbf{x}_2\|$ between the ions is larger than the corresponding short-range correlation length, it should be a good approximation to replace the mean values in Eq. (27) by mean values computed for zero charge and *in the absence of any cavity*, which we will denote by the subscript ''nc''

$$W(\mathbf{x}_1-\mathbf{x}_2)\simeq-\beta(\langle\phi_{\rm solv}(\mathbf{x}_1)\phi_{\rm solv}(\mathbf{x}_2)\rangle_{\rm nc} -\langle\phi_{\rm solv}(\mathbf{x}_1)\rangle_{\rm nc}\langle\phi_{\rm solv}(\mathbf{x}_2)\rangle_{\rm nc}). \tag{28}$$

By translation invariance the averages $\langle\phi_{\rm solv}(\mathbf{x})\rangle_{\rm nc}$ are position independent and, moreover, vanish in most cases. We will keep them, however, for the sake of generality. If the simulation volume V were infinite we would expect this correlation function to decay to zero as $\|\mathbf{x}_1-\mathbf{x}_2\|$ approaches infinity. From continuum electrostatics,[25] we expect the decay to be given by the asymptotic formula

$$W(\mathbf{x}_1-\mathbf{x}_2)\simeq\left(\frac{1}{\varepsilon}-1\right)\frac{1}{\|\mathbf{x}_1-\mathbf{x}_2\|}, \tag{29}$$

where ε is the solvent dielectric constant. Note that the physical decay of the correlations selects a ''natural'' scale for the interaction energy: it should be zero at infinite separation. In a finite, periodic box, continuum electrostatics leads us to expect that the Coulomb potential in Eq. (29) should be replaced by its appropriate periodic version: the Ewald potential

$$W(\mathbf{x}_1-\mathbf{x}_2)\simeq\left(\frac{1}{\varepsilon}-1\right)\Phi_{\rm Ew}(\mathbf{x}_1-\mathbf{x}_2). \tag{30}$$

In the infinite volume case we require that the potential go to zero at infinite separation. Since the ions in a finite box cannot be separated to an infinite distance, what is the equivalent ''natural'' scale for the interaction energy? A simple argument provides an answer, which is borne out by a further analysis. The interaction energy is that part of the energy that depends on the positions of both ions; therefore, any part of the potential in Eq. (30) that does not depend on the positions of the ions must be removed. One way to do this is to set the $\mathbf{k}=\mathbf{0}$ Fourier component of the potential to zero. All other modes depend in an essential way on the positions of the ions and are left untouched. Thus we are led to the conclusion that the natural choice for periodic boundary conditions is that which has no $\mathbf{k}=\mathbf{0}$ Fourier mode. A more rigorous way to arrive at this same conclusion is to observe that the integral over the simulation box vanishes (see Appendix B):

$$\frac{1}{V}\int_V d^3u\ (\langle\phi_{\rm solv}(\mathbf{u})\phi_{\rm solv}(\mathbf{0})\rangle_{\rm nc} -\langle\phi_{\rm solv}(\mathbf{u})\rangle_{\rm nc}\langle\phi_{\rm solv}(\mathbf{0})\rangle_{\rm nc})=0. \tag{31}$$

This integral is in fact the $\mathbf{k}=\mathbf{0}$ Fourier mode of this two-point correlation function.

Since the Fourier modes depend on the simulation volume, the requirement that the $\mathbf{k}=\mathbf{0}$ mode be zero introduces a subtle volume dependence. Section V shows with an example that this dependence can be large.

V. INTERACTION ENERGY OF TWO IONS: EXPLICIT SIMULATION

In this section we present the results of molecular dynamics simulations of two ions in aqueous solution using the Ewald summation method. After evaluating the charging free energy the volume dependence is discussed.

In a large dielectric medium the contribution of the solvent to the free energy of charging, Eq. (30), almost exactly cancels the direct interaction energy (i.e., interaction in the

absence of solvent). In order to correctly model the dielectric response of the solvent in molecular simulations this balance needs to be accurately evaluated.

From Eq. (26), the free energy of solvation of two charged particles can be related to several terms that are easily identifiable with particular interactions within the system. The first two terms represent the free energy of solvation of each ion in solution when the other ion has a charge of zero; the second term is the direct interaction contribution, and the last term is related to the solvent dielectric shielding. This last term is what will be obtained from simulations. There are at least two ways in which the solvent dielectric shielding contribution can be explicitly evaluated: one is in the absence of the charges through a solvent correlation function [see Eq. (27)]; the other is in presence of the charges by relating the dielectric shielding to the average electrostatic potentials of the systems with two and one charged particles (see Appendix B). The simulations discussed in this section were designed to use the second approach.

Two oppositely charged chloridelike ions were situated on an axis perpendicular to two faces of the unit cell 10 Å apart in a 32 Å cubic box with 1103 SPC water molecules (the orientation is important as the Ewald potential is not isotropic, see Fig. 1). Three 200 ps molecular dynamics simulations were performed at room temperature for systems with the two charged particles, and systems with only one of the particles charged. The average electrostatic potentials due to the solvent were evaluated at the cavity sites and the free energy of charging was calculated from the difference of the average potentials using the formula

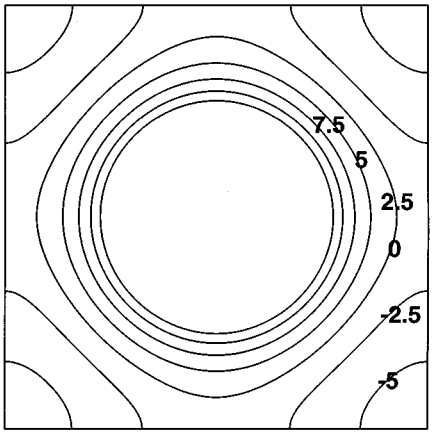

FIG. 1. Contour plot of the Ewald potential. The labels correspond to the levels in kcal/mol au, for a simulation box of 32 Å. The contours lie all in the plane $z=0$.

$$\Delta F_{0\to q,0\to -q}=\tfrac{1}{2}(\langle \phi_{\mathrm{solv}}(\mathbf{x}^{+})\rangle_{q,-q}-\langle \phi_{\mathrm{solv}}(\mathbf{x}^{-})\rangle_{q,-q}), \tag{32}$$

where $\mathbf{x}^{+}$ and $\mathbf{x}^{-}$ are, respectively, the positions of the positive and negative ions (see Appendix B). More details about

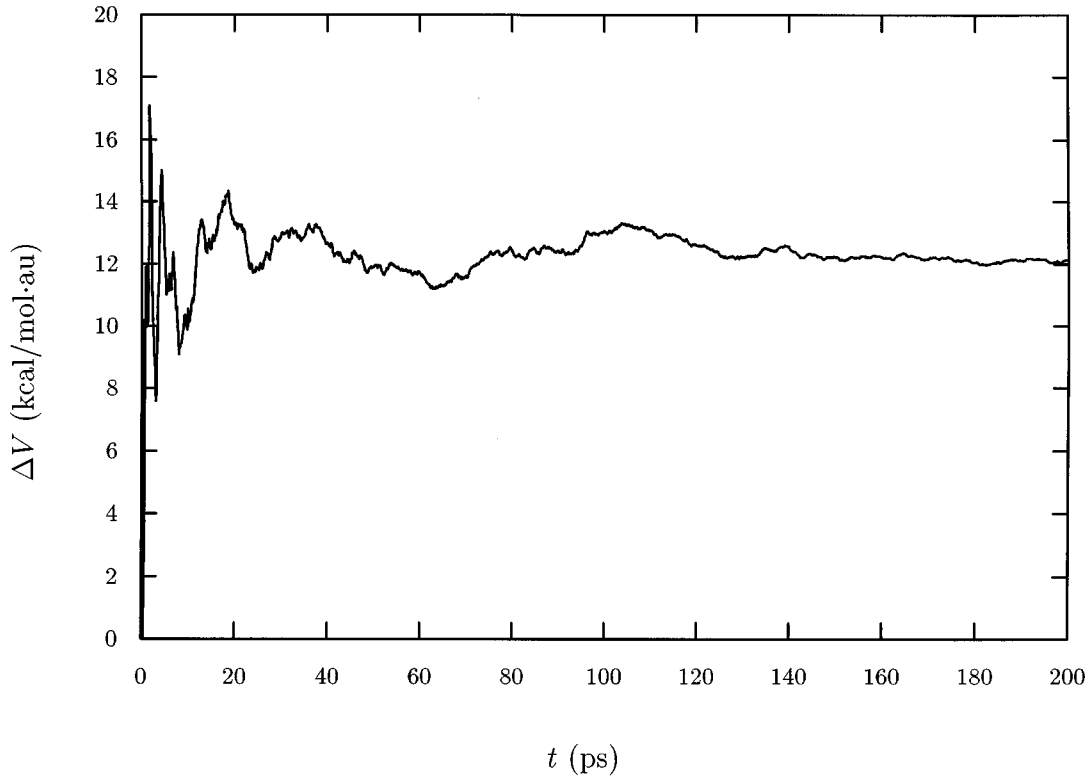

FIG. 2. Running average of the difference in the electrostatic potential produced by the solvent in the charged and uncharged states.

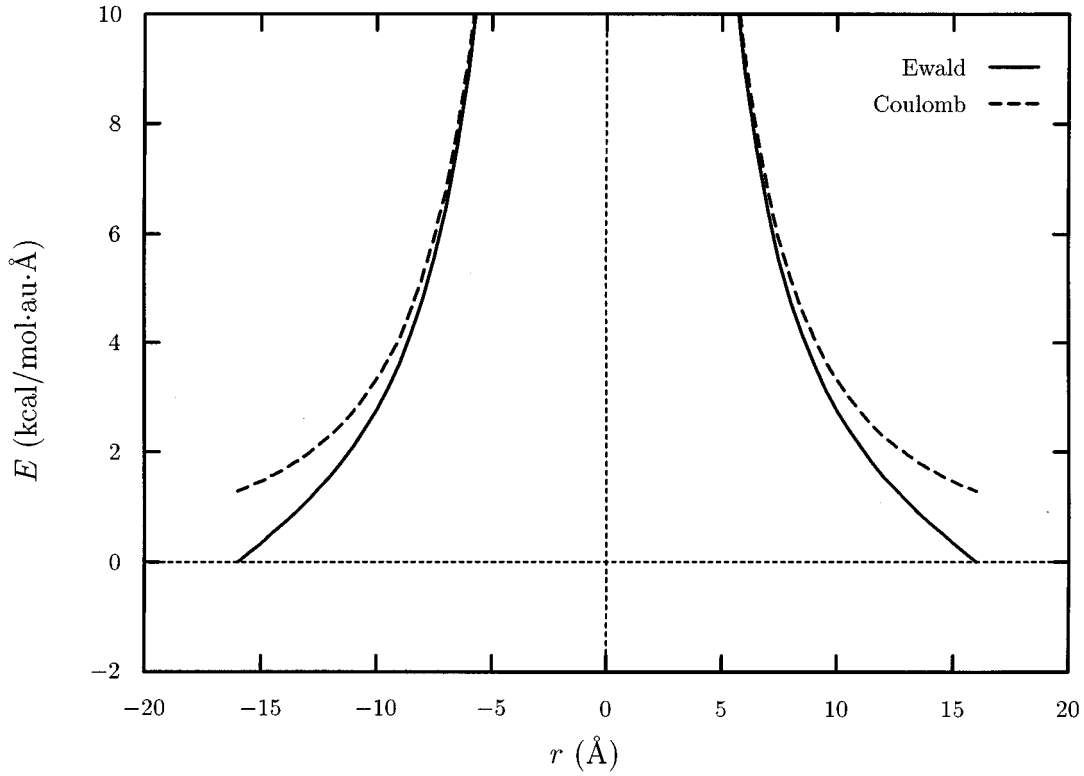

FIG. 3. Comparison between Ewald (full curve) and Coulomb (dashed curve) fields for a unit charge at the origin in a box of side length 32 Å.

the methodology and additional studies of the effect of the truncation scheme on the dielectric shielding can be found in a related paper.[20]

Figure 2 shows the running average of the difference between the electrostatic potentials due to the solvent at the ionic positions. In order to obtain the free energy of charging due to the solvent the number obtained is divided by two, yielding -6.1 kcal/mol. The direct interaction energy of the ions in the absence of the solvent is -6.12 kcal/mol; therefore the near cancellation of the direct interaction by the interaction with the solvent is observed, as is expected for a high dielectric solvent (water).

It is relevant at this point to make a comparison between the finite volume direct interaction energy in the absence of solvent, -6.12 kcal/mol, and the infinite volume direct interaction energy, -32.77 kcal/mol. What produces this large difference? If we compare the fields produced by the Coulomb and Ewald potentials (Fig. 3), a much smaller difference is found. On the other hand, the numbers just quoted refer to the (unmodified) Coulomb and the particular Ewald potential that satisfies the condition of vanishing volume average (no zero mode). These are compared in Fig. 4. The Ewald potential is shifted down by a considerable amount with respect to the Coulomb potential. Besides this shift there are other differences that appear because of the requirement of periodicity (note that the Coulomb potential does not meet the boundaries smoothly). These distortions are also of interest and will be the subject of a future publication.

We can estimate the importance of this shift downward with respect to the Coulomb potential as a function of the simulation volume as follows. Neglecting, to a first approximation, the distortions mentioned in the previous paragraph, the amount of this shift should be given by the zero mode, or volume average, of the Coulomb potential. Actually, since the Coulomb potential is not periodic this computation is ill-defined; however, we can replace it by its simplest periodic extension, the ''minimum image'' potential. Its volume average is easy to calculate and we obtain

$$\frac{1}{V}\int_V d^3x\,\frac{1}{\|\mathbf{x}\|}=\frac{2}{L}\int_0^1 dx\int_0^1 dy\int_0^1 dz\,\frac{1}{\sqrt{x^2+y^2+z^2}}$$
$$\simeq \frac{2}{L}(1.19), \tag{33}$$

where L is the linear dimension of the simulation box ($V=L^3$) (for the exact expression see Ref. 26). For the case considered above ($L=32$ Å) this gives about 24 kcal/mol, a substantial portion of the difference ($32.77-6.12=26.65$) between the infinite volume limit and the correct finite volume answer. This justifies, *a posteriori*, the neglect of the shape distortions as a first approximation. Thus, to a large extent, we can say that the Ewald potential, Eq. (9), is ''just'' the Coulomb potential but shifted down to guarantee that its mean value over the finite box is zero. This shift introduces a volume dependence that, as we have seen, is not negligible.

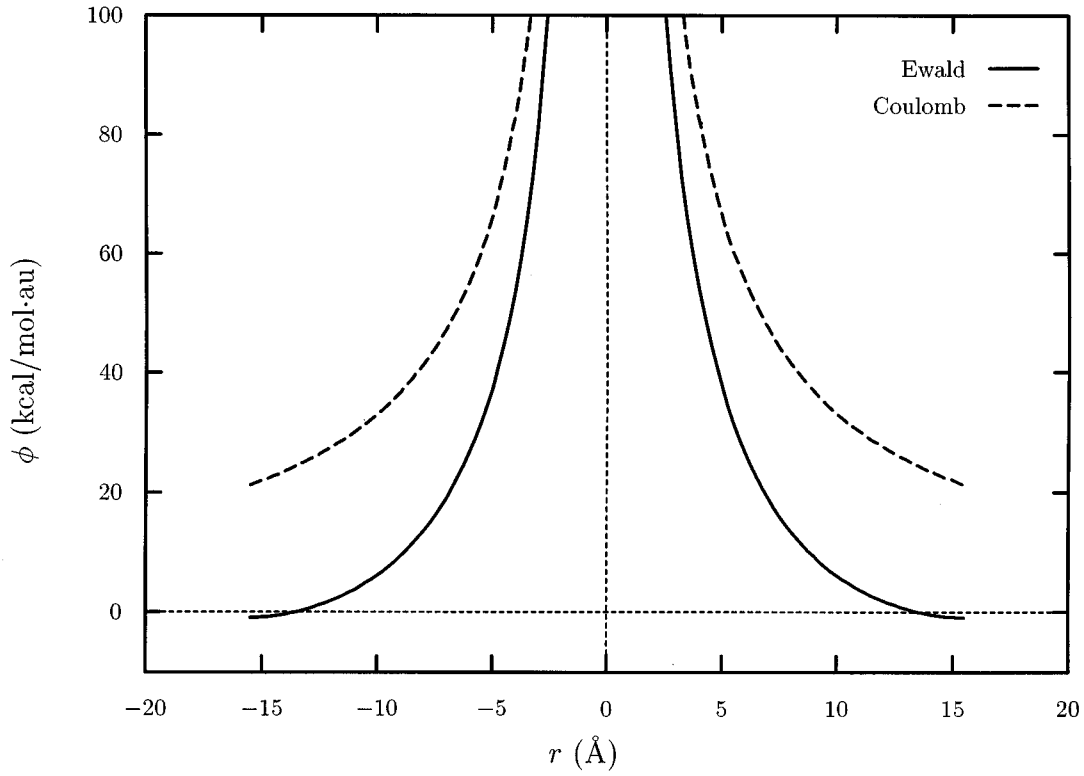

FIG. 4. Comparison between Ewald (full curve) and Coulomb (dashed curve) potentials for a unit charge at the origin in a box of side length 32 Å.

VI. DISCUSSION

In the previous sections we have seen how a strong finite-size effect arises, which shifts the interaction energy of two point charges by a non-negligible amount for the size of boxes that are customary at present. We have also discussed why it is mostly due to a shift downwards of the Ewald with respect to the Coulomb potential.

As shown by Del Buono *et al.*,[20] when this effect is taken into account different calculations of the dielectric response give results that are consistent with each other and with experimental observations. This is expected for intensive quantities, like the dielectric constant, which are not strongly dependent on the shape of the sample.[30,31] For the calculation of extensive quantities, however, the finite size effects described in this paper can produce results that are not directly comparable with experiment. A particularly interesting example is provided by the calculation of pK_a values,[14,32–35] or rather, the shift, of titratable residues in biological macromolecules. Since these shifts can be related to the interaction energy of the set of titratable residues,[32] we expect a dependence on the size of the simulation box.

The constant field in Eq. (1) introduces problems for the consistent simulation of the system unless $\lambda = 0$. The problems arise because of the fact that the system ''remembers'' the unit cell from which it was constructed by infinite replication, and, as a consequence, this field does not depend continuously on the position of the charges: there is a finite jump whenever a charge crosses the boundaries of the unit cell. It is interesting to notice that if, instead of point charges, point dipoles are used, these discontinuities do not arise, since the total dipole moment is independent of the position of the dipoles.[36] However, in simulations using explicit atom models these jumps are bound to occur and it is not clear what the correct implementation of the dynamics is in that case. Until this point is clarified it seems best to set $\lambda = 0$ (see, however, Ref. 37 for a possible solution).

The appearance of strong finite-size effects is not surprising, given the long-range nature of the electrostatic forces. Many earlier simulations were focused either on radial distribution functions, $g(r)$, which show remarkable insensitivity to the detailed treatment of the electrostatic forces, or on the computation of the dielectric constant, which is an intrinsic measure of the response of the solvent and not affected by these finite-size effects. It is well known, however, that the Kirkwood G_K factor, and its detailed relation to the dielectric constant of the medium, is strongly dependent on the choice of boundary conditions.[4] Nowadays many simulations, particularly those concerned with biological molecules, attempt to compute (differential) free energies, and it is reasonable to expect that these calculations will be dependent on the size of the simulation box through the volume dependence of the electrostatic potential. How strong this dependence really is in a realistic simulation is a question that we will attempt to answer in the future.

After this work was completed we received a preprint by Hummer, Pratt, and García[38] where a related finite-size effect was reported that affects the calculation of free energies of hydration of single ions.

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APPENDIX A

In this Appendix we derive the most general form of a solution to the homogeneous equations

$$\nabla\cdot\mathbf{E}=0 \quad \text{and} \quad \nabla\times\mathbf{E}=0 \tag{A1}$$

for the electrostatic field in a periodic box of linear dimension L.

Algebraic topology[39,40] can be used to prove that the only *periodic* solutions to Eq. (34) are constant fields. Note that if

$$-\nabla\phi'(\mathbf{x})=\mathbf{E}_0, \tag{A2}$$

for a constant $\mathbf{E}_0$, then ϕ' must have the form

$$\phi'(\mathbf{x})=-\mathbf{x}\cdot\mathbf{E}_0+\mathbf{x}\text{-independent terms} \tag{A3}$$

which is not a periodic potential.

The explicit form of $\mathbf{E}_0$ given by de Leeuw *et al.*[22] can be recovered by the following argument. First, we make the natural assumption that $\mathbf{E}_0$ depends only on the distribution of charge inside the unit cell, that is, we assume there are no charges ''at infinity.'' Moreover, we assume this dependence is linear and that the ''charges inside the unit cell'' include the homogeneous background (if present). Introducing the Green's function $\mathbf{G}(\mathbf{x},\mathbf{u})$ we can then write

$$\mathbf{E}_0=\int_V d^3u\ \mathbf{G}(\mathbf{x},\mathbf{u})\left(\rho(\mathbf{u})-\frac{1}{V}\int_V d^3v\ \rho(\boldsymbol{v})\right). \tag{A4}$$

Below we will see how the form of $\mathbf{G}(\mathbf{x},\mathbf{u})$ is constrained by the requirement that $\mathbf{E}_0$ be constant; in the end we will recover the expression obtained by de Leeuw *et al.*

Notice that since

$$\int_V d^3u\left(\rho(\mathbf{u})-\frac{1}{V}\int_V d^3v\ \rho(\boldsymbol{v})\right)=0 \tag{A5}$$

for any charge distribution ρ, we are free to add to $\mathbf{G}(\mathbf{x},\mathbf{u})$ an arbitrary $\mathbf{u}$-independent term. Furthermore, because of translational invariance, $\mathbf{G}$ can only depend on relative coordinates: $\mathbf{G}(\mathbf{x},\mathbf{u})=\mathbf{G}(\mathbf{x}-\mathbf{u})$. Taking derivatives with respect to x^j on both sides of Eq. (A4), one can prove that $\mathbf{G}$ must be of the form

$$\mathbf{G}(\mathbf{x},\mathbf{u})=\frac{\lambda}{V}(\mathbf{x}-\mathbf{u})+\mathbf{G}_0. \tag{A6}$$

Here we have again assumed that the symmetries of the cubic unit cell are preserved; otherwise a slightly more general, albeit still linear, form for $\mathbf{G}$ is obtained. The factor of $1/V$ is present to make λ dimensionless. The constant $\mathbf{G}_0$ drops from the integral, as does the term proportional to $\mathbf{x}$, and we are left with the final result:

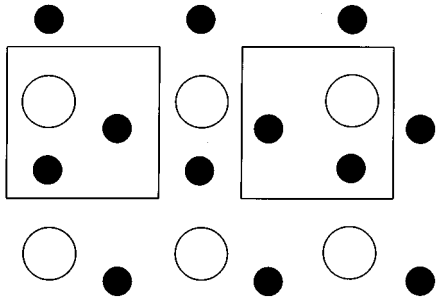

FIG. 5. Two choices of unit cell in a periodic system.

$$\mathbf{E}_0=-\frac{\lambda}{V}\int_V d^3u\ \mathbf{u}\left(\rho(\mathbf{u})-\frac{1}{V}\int_V d^3v\ \rho(\boldsymbol{v})\right). \tag{A7}$$

In particular, for a collection of charges $\{q_\alpha\}$ at positions $\{\mathbf{u}_\alpha\}$, this expression becomes

$$\mathbf{E}_0=-\frac{\lambda}{V}\sum_\alpha q_\alpha(\mathbf{u}_\alpha-\mathbf{u}_0), \tag{A8}$$

where $\mathbf{u}_0$ is the center of the unit cell, given by

$$\mathbf{u}_0=\frac{1}{V}\int_V d^3u\ \mathbf{u}. \tag{A9}$$

(Notice that if $\Sigma_\alpha q_\alpha=0$ the sum in Eq. (A8) is independent of $\mathbf{u}_0$.) Thus $\mathbf{E}_0$ is proportional to the dipole moment of the unit cell with respect to its center. The only remaining freedom lies in the choice of λ which, as shown by de Leeuw *et al.*, is strongly dependent on the regularization procedure.

Even though $\mathbf{E}_0$ cannot be written as the gradient of a periodic function we can write $\mathbf{E}_0=-\nabla\phi_{\text{ext}}$, where the ''extrinsic'' potential is given by

$$\phi_{\text{ext}}(\mathbf{x})=\frac{\lambda}{V}\sum_\alpha q_\alpha(\mathbf{x}-\mathbf{u}_0)\cdot(\mathbf{u}_\alpha-\mathbf{u}_0). \tag{A10}$$

Under the condition that $\Sigma_\alpha q_\alpha=0$, ϕ_{ext} can be rewritten, up to an $\mathbf{x}$-independent term, in the form

$$\phi_{\text{ext}}(\mathbf{x})=\frac{\lambda}{2V}\sum_\alpha q_\alpha\|\mathbf{x}-\mathbf{u}_\alpha\|^2. \tag{A11}$$

Interestingly, written in this way it takes the same form as the quadratic term in the expansion of the Ewald potential around the source

$$\Phi_{\text{Ew}}(\mathbf{x}-\mathbf{u})=c+\frac{1}{\|\mathbf{x}-\mathbf{u}\|}+\frac{2\pi}{3V}\|\mathbf{x}-\mathbf{u}\|^2 + \text{higher-order terms}. \tag{A12}$$

This observation can be used to explain the results recently reported by Roberts and Schnitker[41] and will be the subject of a future publication.

It is important to realize that Eq. (A7) only makes sense after a unit cell has been chosen, which is then replicated ad infinitum: different choices for the unit cell will give different total dipole moments. Figure 5 shows schematically how the choice of unit cell in a periodic system influences the

dipole moment. The white circles represent positively charged atoms and the black circles correspond to the negative charges. As Fig. 5 shows, one can select different unit cells where the white circles are on different sides with respect to the black circles, therefore changing the dipole moment with respect to the center of the unit cell. Thus, if $\lambda \neq 0$ the system ''remembers'' the unit cell from which it was constructed by infinite replication. This memory of the unit cell complicates the dynamics and it is not clear to us what the correct treatment is.

We should also stress that our derivation of Eq. (A7) is independent of any regularization (as long as the regularization respects the symmetries of the unit cell, see above): only the value of λ can be regularization dependent, as shown in some specific examples by de Leeuw *et al.*[22]

APPENDIX B

In this appendix we derive some identities for the derivatives of the free energy of a system of charges with respect to those charges.

Consider a system of N fixed charges, $\{q_\alpha, \mathbf{x}_\alpha\}$, immersed in a solvent, constrained to a periodic box of linear dimension L. We do not need to assume that the fixed charges are pointlike. Instead, the interaction with the solvent is taken to consist of an electrostatic piece plus a van der Waals-like short-range repulsion. The partition function for the system can be decomposed into the product of a solvent-independent piece and the ''reduced'' partition function

$$Z \equiv Z(\{q_\alpha, \mathbf{x}_\alpha\}) = \int \prod_j du_j \exp\left(-\beta \sum_{\alpha,j} V_{\alpha,j}(\mathbf{x}_\alpha, \mathbf{u}_j) - \beta H(\{\mathbf{u}\}) \right), \tag{B1}$$

where the sum over α is over the N fixed charges and that over j is over the solvent atoms. The potential $V_{\alpha,j}$ gives the interaction energy between the charge q_α and the jth solvent atom, which we take to have the form

$$V_{\alpha,j}(\mathbf{x}_\alpha, \mathbf{u}_j) = q_\alpha q_j \, \Phi(\mathbf{x}_\alpha - \mathbf{u}_j) + \Psi^{\mathrm{sr}}_{\alpha,j}(\mathbf{x}_\alpha - \mathbf{u}_j) \tag{B2}$$

where Ψ^{sr} is the short-range (van der Waals) interaction and Φ is the electrostatic potential of a unit charge. For the sake of notational simplicity we define

$$\phi_{\mathrm{solv}}(\mathbf{x}) = \sum_j q_j \Phi(\mathbf{x} - \mathbf{u}_j). \tag{B3}$$

The Hamiltonian H contains all the energy terms that depend only on the solvent degrees of freedom.

The aim of molecular mechanics simulations is to compute one or several averages with respect to the Boltzmann probability distribution giving rise to Eq. (B1). In this Appendix we will be concerned with averages that can be obtained as derivatives of Z with respect to the charges. One can also consider, of course, derivatives with respect to the coordinates of the fixed charges (see Refs. 13 and 20).

Taking a logarithmic derivative of Z with respect to q_α we obtain

$$\frac{\partial \ln Z}{\partial q_\alpha} = -\beta \, \frac{\int \Pi_j du_j \exp(-\beta \Sigma_{\alpha,j} V_{\alpha,j}(\mathbf{x}_\alpha, \mathbf{u}_j) - \beta H(\{\mathbf{u}\})) \; \phi_{\mathrm{solv}}(x_\alpha)}{\int \Pi_j du_j \exp(-\beta \, \Sigma_{\alpha,j} V_{\alpha,j}(\mathbf{x}_\alpha, \mathbf{u}_j) - \beta \, H(\{\mathbf{u}\}))} = -\beta \, \langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_q, \tag{B4}$$

where the subscript q is meant to indicate that this mean value is to be computed in the presence of the N charges.

From Eq. (B4) and the relation $\ln Z = -\beta F$ between the free energy and the partition function it follows that the free energy of charging one ion immersed in the solvent is given by

$$\Delta F_{q_i \to q_f} = \int_{q_i}^{q_f} dq \, \langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_q, \tag{B5}$$

with a simple extension to the case of several ions in solution. If the response to a charging process is linear,[29] that is, electrostriction and dielectric saturation effects are negligible, then the mean values $\langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_q$ are linear in q and therefore the free energy change can be written simply in terms of the mean values at the end points

$$\Delta F_{q_i \to q_f} = \frac{q_f - q_i}{2} (\langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_{q_f} + \langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_{q_i}). \tag{B6}$$

The second derivatives of the free energy also have a simple form:

$$\frac{\partial^2 \ln Z}{\partial q_\alpha \partial q_\beta} = -\beta \, \frac{\partial \langle \phi_{\mathrm{solv}}(\mathbf{x}_\beta) \rangle_q}{\partial q_\alpha} = \beta^2 (\langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \phi_{\mathrm{solv}}(\mathbf{x}_\beta) \rangle_q - \langle \phi_{\mathrm{solv}}(\mathbf{x}_\alpha) \rangle_q \langle \phi_{\mathrm{solv}}(\mathbf{x}_\beta) \rangle_q). \tag{B7}$$

The higher derivatives of $\ln Z$ with respect to the charges can be treated along the same lines but they are not needed in what follows.

Note that in Eq. (B7) there is a hidden dependence on the positions and values of all charges, not just those indexed by α and β, because of the $V_{\lambda,j}$ terms in the Boltzmann weights. This dependence is expected to disappear when $\mathbf{x}_\alpha$ and $\mathbf{x}_\beta$ are both far from all the other charges and from each other. In this regime the correlation function in Eq. (B7) should be independent of the value of the charges as well as the fact that they are not pointlike. Thus in this limit this correlation function can be computed by setting $V_{\lambda,j}$ to zero, that is, in the presence of the pure solvent. Since these now are independent of the details of the system and only depend on the solvent degrees of freedom, which are integrated out, we can write down some general relations.

Let us denote by $\langle \cdots \rangle_{\rm nc}$ the mean values obtained by dropping these terms, i.e.,

$$\langle A \rangle_{\rm nc} = \frac{\int \Pi_j du_j \; A \; \exp(-\beta H(\{\mathbf{u}\}))}{\int \Pi_j du_j \; \exp(-\beta H(\{\mathbf{u}\}))} \; . \tag{B8}$$

Since the exponents do not depend on the positions of the fixed charges, the order of operation of derivatives, integrals, and Boltzmann averaging can be interchanged:

$$\frac{\partial}{\partial x_j} \langle \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc} = \left\langle \frac{\partial \phi_{\rm solv}(\mathbf{x})}{\partial x_j} \right\rangle_{\rm nc} , \tag{B9}$$

$$\int d^3x \; \langle \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc} = \left\langle \int d^3x \; \phi_{\rm solv}(\mathbf{x}) \right\rangle_{\rm nc} . \tag{B10}$$

In the same way we obtain the relation

$$\begin{aligned} \int d^3x \; & (\langle \phi_{\rm solv}(\mathbf{0}) \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc} - \langle \phi_{\rm solv}(\mathbf{0}) \rangle_{\rm nc} \langle \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc}) \\ &= \left\langle \phi_{\rm solv}(\mathbf{0}) \int d^3x \; \phi_{\rm solv}(\mathbf{x}) \right\rangle_{\rm nc} \\ &\quad - \langle \phi_{\rm solv}(\mathbf{0}) \rangle_{\rm nc} \left\langle \int d^3x \; \phi_{\rm solv}(\mathbf{x}) \right\rangle_{\rm nc} . \end{aligned} \tag{B11}$$

Since

$$\begin{aligned} \int_V d^3x \; \phi_{\rm solv}(\mathbf{x}) &= \sum_j \; q_j \int_V d^3x \; \Phi(\mathbf{x} - \mathbf{u}_j) \\ &= \left(\sum_j \; q_j \right) \int_V d^3x \; \Phi(\mathbf{x}) \end{aligned} \tag{B12}$$

is independent of the position of the solvent atoms it follows that

$$\begin{aligned} & \left\langle \phi_{\rm solv}(\mathbf{0}) \int d^3x \; \phi_{\rm solv}(\mathbf{x}) \right\rangle_{\rm nc} \\ &\quad = \langle \phi_{\rm solv}(\mathbf{0}) \rangle_{\rm nc} \left\langle \int_V d^3x \; \phi_{\rm solv}(\mathbf{x}) \right\rangle_{\rm nc} . \end{aligned} \tag{B13}$$

From this it follows that

$$\int_V d^3x \; (\langle \phi_{\rm solv}(\mathbf{0}) \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc} - \langle \phi_{\rm solv}(\mathbf{0}) \rangle_{\rm nc} \langle \phi_{\rm solv}(\mathbf{x}) \rangle_{\rm nc}) = 0. \tag{B14}$$

The mean values

$$\langle \phi_{\rm solv}(\mathbf{x}_1) \phi_{\rm solv}(\mathbf{x}_2) \cdots \phi_{\rm solv}(\mathbf{x}_N) \rangle_{\rm nc} \tag{B15}$$

are independent of any details of the fixed charges, since they are computed in the presence of the pure solvent.

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