The hydration free energies of ions exhibit an approximately quadratic dependence on the ionic charge, as predicted by the Born model. We analyze this behavior using second-order perturbation theory. The average and the fluctuation of the electrostatic potential at charge sites appear as the first coefficients in a Taylor expansion of the free energy of charging. Combining the data from different charge states (e.g., charged and uncharged) allows calculation of free-energy profiles as a function of the ionic charge. The first two Taylor coefficients of the free-energy profiles can be computed accurately from equilibrium simulations, but they are affected by a strong system-size dependence. We apply corrections for these finite-size effects by using Ewald lattice summation and adding the self-interactions consistently. An analogous procedure is used for the reaction-field electrostatics. Results are presented for a model ion with methane-like Lennard-Jones parameters in simple point charge water. We find two very closely quadratic regimes with different parameters for positive and negative ions. We also studied the hydration free energy of potassium, calcium, fluoride, chloride, and bromide ions. We find negative ions to be solvated more strongly (as measured by hydration free energies) compared to positive ions of equal size, in agreement with experimental data. We ascribe this preference of negative ions to their strong interactions with water hydrogens, which can penetrate the ionic van der Waals shell without direct energetic penalty in the models used. In addition, we consistently find a positive electrostatic potential at the center of uncharged Lennard-Jones particles in water, which also favors negative ions. Regarding the effects of a finite system size, we show that even using only 16 water molecules it is possible to calculate accurately the hydration free energy of sodium, if self-interactions are considered.

1. Introduction

A quadratic dependence on the ionic charge of the electrostatic free energy of solvation of a simple ion in aqueous solution is about the simplest reasonable possibility for that behavior. The Born model predicts that quadratic dependence. Several computer simulation calculations have shown that it is approximately correct for the simplest monovalent ions in water. Theoretical simplifications have been advanced to take advantage of such behavior.

If that quadratic behavior were correct with sufficient accuracy, it would indeed permit important simplifications of the difficult task of molecular calculations of solvation free energies owing to electrostatic interactions in complex solutions. The theoretical simplifications identified on that basis can be viewed either as perturbation theory through second order in the electrostatic interactions or as a Gaussian modeling of certain thermal fluctuations of those interactions. With the adoption of either view, these methods would have wide applicability and great simplicity. The question of the accuracy of the quadratic dependence on the charge of the free energy owing to electrostatic interactions deserves to be raised for its own sake and given a precise answer as general as possible.

This quadratic behavior is not a universal truth, and previous simulation calculations have given helpful information on the circumstances where this quadratic dependence can be expected to fail. However, previous simulation calculations are sufficiently disparate that a high precision answer to the question of the accuracy of second-order perturbation theory for the free energy owing to electrostatic interactions is not available. The disparate character of the available simulation results is largely caused by a lack of uniformity with respect to the treatment of finite-system-size effects on electrostatic interactions in aqueous solutions. It is not atypical for a finite-system-size correction and the electrostatic solvation free energy to be of similar size.

In contrast to the role of computer experiments in answering this question, laboratory experiments have been useful mostly for framing the question. The difficulty of using laboratory experiments for the present purpose resides in our inability to extract generally an electrostatic contribution from contributions of the other interactions present.

Because of these points, this work calculates the free energy owing to electrostatic interactions of simple, spherical ions in water by Monte Carlo methods and gives particular attention to the methodological issue of correction for finite system size. The molecular models used are simple, but they have been widely tested. Because the goal of this work is to address the question of quadratic dependence on charge of the electrostatic solvation free energy, these models are sufficiently realistic for the present purposes. However, we will compare our computed free energies with experimental results and thus provide information on how these models might be simply improved for prediction of electrostatic free energies.

Before proceeding with the technical developments, it is worthwhile to give some discussion of the idea for the present treatment of system-size effects on solvation free energies of ions. There is no generally valid recipe that allows a determin-
nations of the effects of a finite system size on the calculated physical quantity in computer simulations. What must generally be done is to analyze the observed size dependence empirically. If, as in the case for Coulomb interactions of long range, different procedures are available, then we should expect consistent thermodynamic limiting \((N \to \infty)\) results for different methods of treating the finite-size system. It is well understood that certain quantities involving integrals over the whole sample, such as the dipole-moment fluctuations, depend intrinsically on exterior conditions or constraints.\(^{11}\) Those conditions must then be properly understood theoretically. For the present problem involving the interactions and associated thermodynamics of an ion immersed in a dielectric liquid, a reasonable view is the following: Treatment of electrostatic interactions in a truly periodic format, e.g., by Ewald procedures, is consistent with the periodic boundary conditions that are nearly inevitable for other reasons. In periodic boundary conditions the interactions at the longest range that must be taken seriously occur at an appreciable fraction of the distance to the surface of the simulation cell. For typical simulated system sizes, ionic interactions at that longest range are large. Treatment of electrostatic interactions in a truly periodic format thoroughly tempers those large interactions. But a mathematical price for true periodicity of electrostatic interactions is a "self-interaction" associated with interactions with images and a uniform neutralizing charge background. For neutral systems this self-interaction can be sometimes ignored. For nonneutral systems, such as those studied here, there may be practical advantages of consistency obtained for explicit consideration of the self-interaction. We will account for these self-interactions explicitly in the calculations below.

This argument permits treatments of the ionic interactions other than Ewald summation. In fact, the work below tests a generalized reaction-field (GRF) method and also finds that consistent results can be obtained if self-interactions are treated on a similar basis.

2. Theoretical Methods

2.1. Calculation of the Free Energy of Charging. The various methods for computing free energies using computer simulations have been reviewed extensively.\(^{12-14}\) We start here from the potential distribution theorem for the excess chemical potential \(\mu^e\),\(^{15}\)

\[
\mu^e(q_i) - \mu^e(q_0) = -k_B T \ln[\exp(-\beta [u(q_i) - u(q_0)])]_{q_0},
\]

where \(q_0\) and \(q_1\) are the two charge states and \(\beta = 1/k_B T\); \(\langle \cdots \rangle_q\) denotes a thermal configuration-space average in the charge state \(q\); and \(u(q)\) is the configuration-dependent interaction energy of the ion in charge state \(q\) with the solution. Apart from finite-size corrections to be discussed later, \(u(q)\) is given by \(\phi(q)(\mathbf{r})\), where \(\phi(q)\) is the electrostatic potential at the charge position \(\mathbf{r}\).

We next analyze eq 1 utilizing a cumulant expansion\(^{16}\) with respect to \(\beta\),

\[
\langle \exp(-\beta \Delta u) \rangle_{q_0} = \exp \left[ \sum_{n=0}^{\infty} (-\beta)^n C_n \right]
\]

where \(\Delta u = u(q_1) - u(q_0)\). This defines the cumulants \(C_n\) of order \(n = 0, 1, 2\) as

\[
C_0 = 0
\]
\[
C_1 = \langle \Delta u \rangle_{q_0}
\]
\[
C_2 = \langle (\Delta u - \langle \Delta u \rangle_{q_0})^2 \rangle_{q_0}
\]

We can interpret eq \(2\) as a Taylor expansion in \(\Delta q = q_1 - q_0\) if we set \(\Delta u = \Delta q \phi + (q_1^2 - q_0^2)/2\), where \(\xi\) accounts for finite-size effects as a "self-interaction" to be discussed further below,

\[
\Delta \mu^e = \Delta q (\langle \phi \rangle_{q_0} + q \xi) - \frac{\beta}{2} \Delta q^2 \left[ (\langle \phi \rangle_{q_0}^2)_{q_0} - \frac{\xi}{\beta} \right] + ...
\]

(4)

where \(\Delta \mu^e = \mu^e(q_1) - \mu^e(q_0)\). The mean and the fluctuation of the electrostatic potential at the charge site \(q\) (corrected for finite-size effects) yield the derivatives of the free energy with respect to \(\Delta q\). The information about the derivatives can therefore be extracted from equilibrium simulations. In principle, higher-order cumulants could be used to obtain information about the other Taylor coefficients. However, as was observed by Smith and van Gunsteren,\(^4\) higher-order cumulants are increasingly difficult to extract from computer simulations of limited duration.

Therefore, we will evaluate \(C_1\) and \(C_2\) at a few discrete charge states and combine this information about the derivatives, either by constructing an interpolating polynomial or by using a \(\chi^2\) fit to a polynomial expression (or any other functional form) for the free energy as a function of \(\Delta q\). The \(\chi^2\) fit minimizes the mean square deviation of the observed data with respect to the coefficients \(\{a_k\}\) of the fitting function \(\Delta \mu^e(q; \{a_k\})\),

\[
\chi^2 = \sum_{i=m}^{n} \left[ \frac{\Delta \mu^e(q_i; \{a_k\}) - \Delta \mu^e_{\text{obs}}(q_i)}{\sigma_i} \right]^2 + \frac{[\Delta \mu^e(q; \{a_k\}) - \Delta \mu^e_{\text{obs}}(q_i)]^2}{\rho_i}
\]

(5)

where \(\sigma_i\) and \(\rho_i\) are the estimated errors (standard deviations) of the observed first and second derivatives \(\mu^e_{\text{obs}}\) and \(\mu^e_{\text{obs}}\) at charge state \(q_i\).

2.2. Long-Range Coulomb Interactions and Finite-Size Effects. To minimize finite-size effects on energetic properties of Coulombic systems, we adopt the following strategy:\(^{17}\) We use lattice summation for calculating the electrostatic interactions to account for the periodic boundary conditions employed in the computer simulations, and we consistently include the self-interactions arising from lattice summation. We point out that aside from formal consistency the numerical results can motivate this approach by demonstrating in a finite-size analysis that the deviations from the thermodynamic limit \((N \to \infty)\) are small.

The Coulomb energy of a periodically replicated system of charged \(q_i\) at positions \(r_i (i = 1, ..., N)\) can be expressed as

\[
U = \sum_{1 \leq i < j \leq N} q_i q_j \varphi_{\text{EW}}(\mathbf{r}_i - \mathbf{r}_j) + \frac{1}{2} \sum_{1 \leq i \leq N} q_i^2 \varphi_{\text{EW}}
\]

(6)

where \(r_i = r_i + \mathbf{n}, \mathbf{n}\), with the lattice vector \(\mathbf{n}\) chosen such that \(r_0 = 0\) is a vector in the unit cell. The effective, position-dependent potential \(\varphi_{\text{EW}}(\mathbf{r})\) is obtained by lattice summation using Ewald’s method,\(^{13,18,19}\)

\[
\varphi_{\text{EW}}(\mathbf{r}) = \sum_{\mathbf{n}} \frac{\text{erfc}(\eta|\mathbf{r}| + \mathbf{n})}{|\mathbf{r} + \mathbf{n}|} + \sum_{k=0}^{4\pi} \exp\left(-\frac{k^2}{4\eta^2} + ik \cdot \mathbf{r}\right) - \frac{\pi}{V \eta^2}
\]

(7)

where \(V\) is the volume of the box, \(\text{erfc}\) is the complementary error function, and \(k = |\mathbf{k}|\). The two lattice sums extend over real- and Fourier-space lattice vectors \(\mathbf{n}\) and \(\mathbf{k}\), respectively.
The self-term $\xi_{\text{EW}} = \lim_{r \to 0} [q_{\text{EW}}(r) - 1/r]$ is the Wigner potential.20–22 Using Green’s theorem and $\Delta(1/r) = -4\pi\delta(r)$, we find

$$\xi_{\text{EW}} = \lim_{r \to 0} \left[ q_{\text{EW}}(r) - \frac{1}{r} \right] = -\frac{1}{4\pi} \lim_{r \to 0} \int_{|r'| > r} d\mathbf{r}' \Delta q_{\text{EW}}(r) \tag{8}$$

The integration region is infinite and includes all background charge and lattice image charges,

$$\Delta q_{\text{EW}}(r) = -4\pi \sum_n \delta(r - n) - \frac{1}{V}$$

Equations 8 and 9 establish that $\xi_{\text{EW}}$ is the electrostatic potential in a Wigner lattice at a charge site owing to the lattice images and the neutralizing background. For Ewald summation in a cubic lattice the self-term is $\xi_{\text{EW}} = -2.837297/L$,21–23 where $L$ is the length of the cube.

It will be interesting to remember that $\xi_{\text{EW}}$ can also be expressed in terms of quantities associated with the primitive simulation cell

$$\xi_{\text{EW}} = -\frac{1}{4\pi} \lim_{r \to 0} \int_{|r'| > r} d\mathbf{r}' \Delta q_{\text{EW}}(r) - \frac{1}{4\pi} \int_{S_0} d\mathbf{r}' q_{\text{EW}}(r) \hat{n} \cdot \nabla \left( \frac{1}{r} \right)$$

The first term on the right is explicitly the interaction with the background density in the primitive simulation cell. The second term on the right is an integral over the surface of the primitive simulation cell. It describes electrostatic interactions of the central unit charge with a dipolar surface distribution $q_{\text{EW}}(\mathbf{r})\hat{n}$, where $\hat{n}$ is the surface normal pointing outward.

Equation 6 can also be used for a nonneutral system since charges are implicitly compensated by a homogeneous background in the Ewald formulation. This results in an expression for the energy difference $\Delta u$ between two configurations with different charge states $q_0$ and $q_1$ of an ion at position $\mathbf{r}$,

$$\Delta u = \Delta q_{\text{EW}}(r) + \frac{1}{2} \xi_{\text{EW}}(q_1^2 - q_0^2)$$

In the following, we will use this expression containing a self-interaction which is quadratic in the charge to calculate the free energy of charging; i.e., we assume that the self-interaction accounts for the finite-size corrections.24

In our calculations, we will also use a generalized reaction field (GRF).25,26 The GRF Coulomb interaction depends only on the distance $r$ of the charges and has a cutoff distance $r_c$,

$$q_{\text{GRF}}(r) = \frac{1}{p(r/c)} \Theta(r_c - r) + C$$

$\Theta$ is the Heaviside unit-step function; $p(x)$ is a screening polynomial:

$$p(x) = (1 - x)^5(1 + 8x/5 + 2x^2/5)$$

By analogy with the Ewald summation, we define the self-term for the GRF as the potential at the charge site, $\xi_{\text{GRF}} = \lim_{r \to 0} q_{\text{GRF}}(r) - 1/r$. The total energy of neutral systems, if defined as in eq 6, is independent of the constant $C$. However, in nonneutral systems $C$ affects the total energy. We define $C$ in analogy with the Ewald potential, which satisfies

$$\int_V d\mathbf{r} \ q_{\text{EW}}(\mathbf{r}) = 0$$

such that the average potential in the cell vanishes. If we require the normalization condition eq 14 also for the GRF interaction, we obtain $C = -\pi r_c^2/2V$. The GRF self-term is $\xi_{\text{GRF}} = -12/5r_c + C$. For $r_c = L/2$, the normalization condition eq 14 accounts for only a small additional correction, yielding $\xi_{\text{GRF}} = -24/5L - \pi/20L$.

It is interesting to make a connection with the correction method proposed by Sloth and Sørensen.27 These authors use the minimum-image Coulomb interaction. To eliminate the system-size dependence in their calculation of chemical potentials of restricted-primitive-model ions, they introduce a background neutralizing the test-particle charge. This is done by adding a constant $\xi_{1/r}$ to the bare Coulomb potential.28

$$\xi_{1/r} = -\frac{1}{V} \int_V d\mathbf{r} \ 1/r$$

This corresponds to enforcing eq 14 and adding a self-term $\xi_{1/r} = \lim_{r \to 0} q(r) - 1/r$ for the minimum-image interaction. $\xi_{1/r}$ is also precisely the first term on the right side of eq 10. It accounts for a large correction since $\xi_{1/r} \approx -2.38/L$.

3. Computer Simulations

We calculated the free energy of charging ions in water using Metropolis Monte Carlo simulations.13,30 The systems comprise a single ion and $N$ water molecules. For water we used the simple point charge (SPC) model.31 The ion–water interactions were described by Coulomb and Lennard-Jones (LJ) interactions. The Coulomb terms involve the partial charges of oxygens and hydrogens on SPC water. The LJ interactions act only between water oxygen and the ion. We studied the ions Na+, K+, Ca2+, F−, Cl−, and Br−. The LJ parameters for these ions were those of Straatsma and Berendsen.32 We also studied the charging of a model ion Me with methane LJ parameters as given by Jorgensen et al.33 Lorentz–Berthelot mixing rules were applied to obtain LJ parameters between water and Me. The LJ parameters are compiled in Table 1.

| ion   | $\epsilon$(kJ mol$^{-1}$) | $\sigma$(nm) |
|-------|--------------------------|--------------|
| Na+   | 0.200 546               | 0.285 000    |
| K+    | 0.006 070               | 0.452 000    |
| Ca2+  | 0.637 972               | 0.317 000    |
| F−    | 0.553 830               | 0.305 000    |
| Cl−   | 0.537 866               | 0.375 000    |
| Br−   | 0.494 464               | 0.383 000    |
| Me    | 0.893 228               | 0.344 778    |

The charge interactions in the simulations were calculated using the Ewald lattice summation (eqs 6 and 7) and the generalized reaction-field potential (eqs 12 and 13). In both cases, the real-space interactions were truncated on an atom basis using $L/2$ as the cutoff and applying the periodic boundary conditions on an atom basis. For the Ewald Fourier-space calculation, a cutoff of $k^2 \leq 38(2\pi/L)^2$ was used, resulting in 2 × 510 k vectors. To correct the background dielectric constant from infinity to $\varepsilon_{\text{GRF}} = 65$, a term $2\pi M^2/(2\varepsilon_{\text{GRF}} + 1)V$ was added to the potential energy (in both Ewald and GRF calculations), where $M$ is the net dipole moment of the water molecules. The real-space damping factor was set to $\eta = 5.6/L$. Electrostatic potentials at the ion sites were calculated using $q_{\text{EW}}$ and $q_{\text{GRF}}$. The potentials were calculated after each pass (one attempted move per particle) and stored for analysis. For each system 100 000 passes were used for averaging. Random configurations or configurations of previous runs were used as initial structures and always extensively equilibrated. The temperature was 298 K. The total number density was $\rho = 33.33$ nm$^{-3}$ in all simulations. Cubic boxes were used as simulation cells with
edges $L = [(N + 1)/\rho]^{1/3}$. The Monte Carlo move widths were chosen so that an approximate acceptance ratio of 0.5 was obtained.

In addition, thermodynamic integration (TI) was used to calculate directly the free energy of charging. Within 100 000 Monte Carlo passes, the charge of the ion was linearly changed from 0 to its full magnitude ($\pm e, 2e$, where $e$ is the elementary charge). The free-energy changes were then calculated as

$$
\mu^e(q_i) - \mu^e(q_0) = (q_i - q_0)n^{-1} \sum_{j=1}^{n} \phi_j + \xi(q_i^2 - q_0^2)/2 \tag{16}
$$

where the sum extends over $n = 100 000$ Monte Carlo passes and the last term is a finite-size correction. Equation 16 approximates the exact expression

$$
\mu^e(q_i) - \mu^e(q_0) = \int_{q_0}^{q_i} dq \left( \frac{\partial \mu(q)}{\partial q} \right)_q \tag{17}
$$

TI was also performed using the reverse path, i.e., decreasing the charge to 0.

We also performed Monte Carlo simulations of ion–water clusters comprising one ion and $N$ SPC water molecules (4 ≤ $N$ ≤ 256). The starting structure was a random configuration with the bulk density of water in a cubic box around the ion. The cluster was equilibrated for at least 50 000 passes (with an acceptance rate of about 0.5) and then averaged over 50 000 passes at 298 K. We used the bare Coulomb interaction 1/$R$ and did not apply a distance cutoff. No periodic boundary conditions were employed in the cluster simulations.

4. Results and Discussion

4.1. Charging of a Methane-like Lennard-Jones Particle. The free energy of charging a methane-like LJ particle in SPC water was determined from a series of simulations with $N = 128$ and 256 water molecules and with Ewald and GRF charge treatment. A range of charges from $-e$ to $+e$ was covered in steps of 0.25$e$ ($N = 128$) and $0.5e$ ($N = 256$). The results for the mean $m$ and the fluctuation $f$ of the potential at the ion site (with and without finite-size correction) are compiled in Table 2. In the calculations, the potential $\phi$ at the ion site ($r = 0$) is defined as

$$
\phi = \sum_{i=1}^{N} \sum_{j=1}^{3} q_i \cdot \varphi(r_{ij}) \tag{18}
$$

where the double sum extends over all water oxygen and hydrogen sites; $\varphi$ is either $\varphi_{\text{EW}}$ or $\varphi_{\text{GRF}}$. The mean $m$ and the fluctuation $f$ are calculated from 100 000 Monte Carlo passes as

$$
m = e\langle \phi \rangle \tag{19a}
$$

$$
f = \beta e^2 \langle (\phi - \langle \phi \rangle)^2 \rangle \tag{19b}
$$

The corrected values for mean and fluctuation are defined as $m_c = m + qe \xi$ and $f_c = f - e^2 \xi$. The Taylor expansion of the free energy of charging around a charge state $q$ assumes the following form:

$$
\Delta \mu^e = \left( \frac{\Delta q}{e} \right) m_c - \frac{1}{2} \left( \frac{\Delta q}{e} \right)^2 f_c + \ldots \tag{20}
$$

From the results of Table 2 we see that the finite-size corrections are of a magnitude similar to the uncorrected results $m$ and $f$. The uncorrected results of the different methods and system sizes are widely spread. If however the finite-size corrections are applied, we obtain consistent results for all methods and system sizes over the range of ion charges considered. With estimated errors (1 standard deviation, as calculated from block averages) of 4.0 and 30 kJ mol$^{-1}$ for $m_c$ and $f_c$, we find data of different methods within 2 standard deviations from each other. The only exception is the fluctuation $f_c$ for $q = -e$, where the two extreme values (Ewald, $N = 128$ and 256) differ by about 3 standard deviations. In the following, we will restrict the discussion to the corrected values $m_c$ and $f_c$.

Figure 1 shows the probability distribution $P(\phi)$ of the electrostatic energy $\phi$ at the site of a methane-like ion Me with charge $q = +e$ from Ewald summation with $N = 256$ ($\bigcirc, -, -$), $N = 128$ ($\bigtriangleup, -, -$), and GRF with $N = 256$ water molecules ($+, -, -$), respectively. The lines are Gaussian distributions. Also shown are Gaussian distributions corrected for finite-size effects, which are peaked near $\phi = 550$ kJ mol$^{-1}$; they agree closely in position and variance.

| $N$ | Coulomb | $q/e$ | $m$ | $f$ | $m_c$ | $f_c$ |
|-----|---------|------|-----|-----|------|------|
| 256 | EW      | -1.00| 670.3| 604 | 869.9| 804  |
| 128 | EW      | -1.00| 618.1| 664 | 862.9| 915  |
| 256 | GRF     | -1.00| 520.5| 493 | 869.1| 842  |
| 128 | GRF     | -0.75| 465.3| 730 | 653.6| 581  |
| 256 | EW      | -0.50| 324.0| 713 | 423.7| 913  |
| 128 | EW      | -0.50| 292.2| 698 | 417.8| 950  |
| 256 | GRF     | -0.50| 242.0| 568 | 416.5| 917  |
| 128 | EW      | -0.25| 141.3| 529 | 204.0| 780  |
| 256 | EW      | 0.00 | 38.0 | 367 | 38.0 | 567  |
| 128 | EW      | 0.00 | 37.3 | 341 | 37.3 | 592  |
| 256 | GRF     | 0.50 | 248.7| 581 | 248.7| 581  |
| 128 | EW      | 0.50 | 118.1| 332 | 243.6| 583  |
| 256 | GRF     | 0.75 | 205.9| 354 | 394.2| 605  |
| 256 | EW      | 1.00 | 348.8| 450 | 548.3| 650  |
| 128 | EW      | 1.00 | 298.9| 389 | 550.0| 640  |
| 256 | GRF     | 1.00 | 202.2| 296 | 550.9| 645  |

"Coulomb" refers to the treatment of the electrostatic interactions (Ewald or GRF). $N$ is the number of water molecules. The mean and the fluctuation are listed as $m = \langle \phi \rangle$ and $f = \beta e^2 \langle (\phi - \langle \phi \rangle)^2 \rangle$, both in units of kilojoules per mole. The corrected values are $m_c = m + qe \xi$ and $f_c = f - e^2 \xi$. The statistical errors of $m$ and $f$ are estimated from block averages as approximately 4.0 and 30 kJ mol$^{-1}$.
The Gaussian distributions corresponding to the corrected values $m_c$ and $f_c$ for mean and variance. The application of the finite-size corrections brings the three curves to very close agreement, yielding results that are approximately independent of system size and treatment of electrostatic interactions.

To further illustrate the importance of the finite-size correction, we calculated $\langle \phi \rangle$ from the pair correlations of the Ewald-summation simulation with $N = 256$ water molecules as

$$
\langle \phi \rangle(R) = 4\pi \rho_{H,O} \int_0^R \rho(r^2) q(r)[q_{00}(r) + 2q_{11}R_{11}(r)]
$$

$\rho_{H,O}$ is the water density, $q_0$ and $q_{11}$ are the oxygen and hydrogen charge, and $g_{00}$ and $g_{11}$ are the ion-oxygen and ion-hydrogen pair correlation functions. Figure 2 shows the results for the charge state $q = -e$ of the ion Me as a function of the integration cutoff $R$ for the bare Coulomb potential $q(r) = 1/r$ and $q_{GRF}$ with $r_c = L/2$. In both cases we included the finite-size correction as a constant. The integration of $1/r$ interaction extended into the corners of the cube, using the correct weights. As a reference, the Ewald result is shown as a straight line. All three methods converge to within 1 kJ mol$^{-1}$, which has to be compared with the estimated statistical error of 4 kJ mol$^{-1}$ of the data. The integrated $1/r$ interaction shows strong oscillations, and only in the corners of the cube does it approach its final value. The GRF interaction on the other hand contains a large self-term and within two oscillations reaches its limiting value.

This illustrates an important point regarding the correction of finite-size effects in the calculation of charge-related quantities. We achieve agreement between different methods of treating Coulomb interactions (Ewald summation, reaction field, bare Coulomb interaction) if we (i) normalize $q$ according to eq 14 and (ii) add a self-term $\xi = \lim_{r \to 0}[q(r) - 1/r]$ to the energy. Further demonstrations of the validity of these finite-size corrections will be given in the discussion of the results for sodium and fluoride ions in SPC water.

Figure 3 shows $m_c$ as a function of the charge. We observe two linear regimes with different characteristics for $q < 0$ and $q \geq 0$. Linear behavior of $m_c$ on the whole range of $q$ would reflect validity of the second-order perturbation theory. It would imply Gaussian statistics of $\phi$ and, correspondingly, that the coefficients in the Taylor expansion of order 3 and higher vanish. However, since we observe a transition in the linear behavior between charges of $-0.25e$ and 0, the statistics are only approximately Gaussian. We note that from the $\phi$ data of 100 000 passes it proved impossible to extract reliable information about the Taylor coefficients (cumulants) of order 3 and higher. The second Taylor coefficient $f_c$ can however be extracted accurately. Figure 4 shows $f_c$ as a function of $q/e$. Included in Figure 4 as lines are the values of $f_c$ estimated from the linear fits of $m_c$ for $q < 0$ and $q \geq 0$.

We have fitted the $m_c$ and $f_c$ data by a model with two Gaussian regimes. Included in Figures 3 and 4 is a $\chi^2$ fit of the whole set of derivative data (38 data points) to

$$
\mu_c^x(q) - \mu_c^x(0) = (a_c + b_c q^2)[1 + \tanh(c + dq)]/2 + (a_c + b_c q^2)(1 - \tanh(c + dq))/2
$$

where $\chi^2$ is defined as in eq 5 with parameters $a_c, b_c, a_c, b_c, c,$ and $d$. This model can nicely reproduce the data. We find a transition at $q = c/d \approx -0.2e$ between the two regimes of approximately Gaussian behavior with a quadratic $q$ dependence. We ascribe this transition to differences in the structural organization of water molecules near negatively and positively charged ions. A possible explanation for the observed behavior is that for positive ions, the oxygen atom of water is pointing toward the LJ particle. The strongly repulsive forces of the
TABLE 3: Free Energy (in kJ mol⁻¹) of Charging the Methane-like Lennard-Jones Particle Me from 0 to ±e⁺

| function | Δμe⁺(0→+e⁺) | Δμe⁻(0→−e⁻) |
|----------|--------------|--------------|
| p2       | −246         | −454         |
| p₄       | −253         | −431         |
| p₆       | −250         | −431         |
| p₈       | −250         | −431         |
| p₁₀      | −250         | −431         |
| tanh     | −250         | −430         |

* The free energy was calculated from fitting to polynomials pₙ of degree n and a tanh-weighted model of two Gaussian regimes (eq 22).

$r^{-12}$ interaction prevent large fluctuations of $\phi$ because of the restricted oxygen motions. The hydrogens are pointing away so that rearranging them has only a comparably small effect on $\phi$. For negative ions, the structures with one of the hydrogens pointing toward the ion will dominate. Because of the symmetry between the water hydrogens and the finite life time of the hydration shell, transitions will occur which could explain the larger fluctuations in the negative charage range.

Similarly, a transition to a different Gaussian behavior for highly-charged positive ions was observed by Jayaram et al.² These authors studied the free energy of charging of a sodium ion in the charge range 0 to 3e. When increasing the ion charge, a transition occurs to a more weakly decreasing quadratic free-energy regime at a charge of about 1.1e. This transition has also been discussed by Figueirido et al.³⁴

We also find a nonvanishing potential at the methane site even at zero charge.⁵ In a dipolar solvent, $\langle \phi_q \rangle_{q=0}$ is zero because of charge-reversal symmetry. However, the asymmetry of the charge distribution on the water molecule gives rise to a positive potential for $q = 0$; this is primarily caused by the hydrogens penetrating the LJ sphere of the methane particle, since they do not have a protecting repulsive shell in the model used. As a consequence, there is a small charge region in which increasing the charge costs free energy. A positive potential at the center of an uncharged particle was also observed by Rick and Berne.³⁵

As a consequence of both the positive potential at zero charge and the larger potential fluctuations for negative ions, negative ions are more stably solvated compared to positive ions. Table 3 compiles the free energies of charging as calculated from fitted polynomials $p_n$ of degree $n$ to the derivative data $m_e$ and $f_e$. Except for the simple Gaussian model $p_2$, different fitting functions give consistent results for the free energies of charging. For ions with charge $+e$ and $−e$ we find $\Delta \mu_{\text{ex}} = −250$ and $−431$ kJ mol⁻¹. Interpreted within a Born model for the free energy, i.e.

$$\Delta \mu_{\text{ex}}^{\text{Born}} = −(1 − 1/\epsilon)q^2 / 2R$$

we obtain Born radii $R_+ = 0.27$ nm and $R_- = 0.16$ nm. (A value of $\epsilon = 80$ is used for the dielectric constant, but this hardly affects the results.) The difference between $R_+$ and $R_-$ is somewhat smaller if we use the actual coefficients of the $q^2$ term in the free-energy expansion, as obtained from eq 22 giving 0.23 and 0.16 nm for the Born radii of positive and negative ions. We emphasize the model character of the interaction potentials used in this study. A repulsive shell of the hydrogen atom might reduce the free energy difference between positive and negative ions. The favoring of negative ions however should persist.

The lower free energy of negative ions compared to positive ions of equal size agrees with the experimental observations. The hydration free-energy data compiled by Marcus³⁶ for alkali metal and halide ions show a power-law dependence with respect to the ion radius. Using these fitted curves, we find

$$\Delta f_q = (1 − 1/\epsilon)q^2 / 2R$$

A positive potential at the center of an uncharged particle was also observed by Rick and Berne.³⁵

The energetic differences in the hydration of positive and negative ions go along with differences in the structural organization of water molecules in the hydration shell. Figure 5 shows the ion–water pair correlation functions for different ionic charges. Going from $q = 0$ to positive charges does not change the qualitative properties of the ion–oxygen and ion–hydrogen correlation functions $g_{\text{OH}}$ and $g_{\text{HO}}$. An increase of the ionic charge results in a higher first peak. However, going from charge $q = 0$ to negative charges affects strongly the structural organization of the first hydration shell. Already at $q = −0.5e$ $g_{\text{OH}}$ shows the buildup of a second peak at about $r = 0.2$ nm distance. This peak reaches a value of almost 5 at $q = −e$, compared to $g_{\text{OH}}$ essentially being zero in this distance region for charge $q = 0$. This strong interaction of the negatively charged ion with the hydrogens of water in turn affects the ion–oxygen correlation functions. Despite the negative charge of both the ion and oxygen site, $g_{\text{HO}}$ has a first peak with a height of about 5 for $q = −e$ compared to only 3 for $q = +e$. The strong charge repulsion between water oxygen and the ion with $q = −e$ is overcome by a large attraction caused by a water hydrogen pointing toward the ion and penetrating the ionic van der Waals shell without energetic penalty.

4.2. Free Energy of Charging of the Ions Na⁺, K⁺, Ca²⁺, F⁻, Cl⁻, and Br⁻. Using the LJ parameters of Straatsma and Berendsen³² (see Table 1), we computed solvation free energies of different 150 and 240 kJ mol⁻¹ for the solvation free energy between negative and positive ions of the size of potassium and sodium, respectively. The LJ particle Me studied here has a van der Waals radius between those of K⁺ and Na⁺. The calculated free energy required to go from $−e$ to $+e$ is 180 kJ mol⁻¹, which is indeed bracketed by the experimental data.

The revised Born model by Latimer et al.³⁹ also yields lower free energies for negative ions. For alkali metal and halide ions, it uses effective Born radii $R = r_p + \Delta$, where $r_p$ is the Pauling radius and $\Delta$ is 0.085 and 0.010 nm for cations and anions. This smaller effective-radius correction for anions in eq 23 results in considerably lower free energies of negative ions compared to positive ions of equal size, in agreement with our calculations. The difference of the effective Born-radius correction as defined by Latimer et al.⁴⁰ is 0.075 nm, which agrees with what we find for the Me ion.

Figure 5. Pair correlation functions $g_{\text{OH}}$ (top panel) and $g_{\text{HO}}$ (bottom panel) of the Me ion with water oxygen and hydrogen. The $g(r)$ curves are shifted vertically according to the ionic charge by $q\epsilon$, i.e., by 1 for $q = +e$, 0.5 for $q = 0.5e$, etc. The $g(r)$ curves of Ewald summation and GRF simulations with $N = 256$ water molecules are shown with solid and dashed lines, respectively.
TABLE 4: Results for the Mean $m_e$ and Fluctuation $f_e$ of the Potential (with Finite-Size Corrections Included) at the Position of Sodium, Potassium, Calcium, Fluoride, Chloride, and Bromide Ions at Different Charge States $q^a$

| ion  | $q/e$ | $m_e$  | $f_e$  |
|------|-------|--------|--------|
| Na   | 0.00  | 39.0   | 891    |
| Na   | 0.50  | −395.6 | 956    |
| Na   | 1.00  | −885.1 | 970    |
| K    | 0.00  | −386.6 | 682    |
| K    | 0.50  | −282.1 | 690    |
| K    | 1.00  | −662.6 | 772    |
| Ca   | 0.00  | 41.0   | 662    |
| Ca   | 1.00  | −653.6 | 789    |
| Ca   | 2.00  | −1367.6| 667    |
| F    | 0.00  | 35.7   | 718    |
| F    | −0.50 | 587.6  | 1381   |
| F    | −1.00 | 1167.3 | 961    |
| Cl   | 0.00  | 36.2   | 550    |
| Cl   | −0.50 | 378.2  | 819    |
| Cl   | −1.00 | 794.1  | 773    |
| Br   | 0.00  | 37.3   | 545    |
| Br   | −0.50 | 369.2  | 758    |
| Br   | −1.00 | 772.7  | 773    |

$^a$ The data were calculated from Monte Carlo simulations using $N = 128$ water molecules and Ewald summation over 100 000 passes. The mean and the fluctuation are listed as $m_e = \langle e(\phi) + q \xi \rangle$ and $f_e = \beta e^2 \langle (\phi - \langle \phi \rangle)^2 \rangle - e^2 \xi$, both in units of kilojoules per mole. The statistical errors of $m_e$ and $f_e$ are estimated from block averages to be approximately 4.0 and 30 kJ mol$^{-1}$.

of ions representing Na$^+$, K$^+$, Ca$^{2+}$, F$^-$, Cl$^-$, and Br$^-$. Again, we emphasize the model character of this study. Its purpose is not to provide accurate theoretical values for the free energies but rather to characterize the theory. We can expect to obtain accurate values only after considerable improvement of the currently rather crude descriptions of the interaction potentials used here and similarly in most other studies. Some of that work has indeed been guided by using free energies of hydration.$^{38,39}$ However, controversies about certain technical aspects, primarily regarding the correct treatment of long-range interactions, need to be resolved to obtain conclusive results.$^{40,41}$

We extensively studied the solvation free energy of the sodium cation using the model described in section 3. Monte Carlo simulations using $N = 128$ water molecules were carried out for charges $0$, $0.5e$, and $1.0e$ to calculate the mean $m_e$ and the fluctuation $f_e$ of the electrostatic potential $\phi$ at the ion site. As in the previous calculations, 100 000 passes were used for averaging. The results are listed in Table 4. As for the uncharged methane, the potential at the uncharged sodium site is slightly positive. The decrease of $m_e$ with increasing charge is stronger than linear, and, correspondingly, the fluctuation $f_e$ increases slightly with the charge. This indicates that a simple Gaussian model using an expansion around the uncharged particle is of limited utility.

We use the information about the derivatives to calculate the free energy of charging using polynomial fits. The results for the sodium ion using polynomials of degrees 2, 4, and 6 are compiled in Table 5. Also included in Table 5 are results obtained from TI, as described in section 3. TI was performed using Ewald summation and $N = 8$, 16, 32, 64, and 256 water molecules as well as using the GRF Coulomb interaction and $N = 32$, 64, and 128 water molecules. We observe excellent agreement of the free-energy data from polynomial fits and TI, except for the $p_2$ fit which cannot fully account for the increasing potential fluctuations with increasing charge. The TI data of charging from 0 to $+e$ and uncharging from $+e$ to 0 show variations of about 5 kJ mol$^{-1}$. Regarding the system-size dependence, Ewald summation gives accurate results even for as few as $N = 16$ water molecules. The GRF shows a more pronounced system-size dependence with the $N = 64$ data.

TABLE 5: Results for the Free Energy $\mu^e$ (kJ mol$^{-1}$) of Charging the Sodium Cation from $q = 0$ to $+e$ in SPC Water$^a$

| method | Coulomb | $N$ | $\mu_{self}^e$ | $\mu^e$ |
|--------|---------|----|----------------|--------|
| $p_2$  | EW      | 128| −126           | −415   |
| $p_4$  | EW      | 128| −126           | −407   |
| $p_6$  | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |
| TI$^f$ | EW      | 128| −126           | −407   |

$^a$ $\mu^e$ includes the finite-size corrections which are listed as $\mu_{self}^e$. The free energies were calculated from polynomial fits to the derivative data of Table 4 (polynomials $p_n$ of degree $n$). Also included are results of thermodynamic integration (TI). Linear charging paths from 0 to $+e$ and from $+e$ to 0 are denoted by upward ($\uparrow$) and downward ($\downarrow$) arrows, respectively. Ewald (EW) and generalized reaction-field (GRF) interactions were used for the charges.

TABLE 6: Results for the Free Energy $\mu^e$ (kJ mol$^{-1}$) of Charging the Potassium, Calcium, Fluoride, Chloride, and Bromide Ions from $q = 0$ to $+e$ in SPC Water$^a$

| ion  | $p_2$ | $p_4$ | $p_6$ | TI$^f$ | TI$^f$ |
|------|-------|-------|-------|--------|--------|
| K$^+$| −297  | −293  | −295  | −291   | −294   |
| Ca$^{2+}$| −1317 | −1315 | −1316 | −1311 | −1327 |
| F$^-$| −594  | −590  | −590  | −590   | −594   |
| Cl$^-$| −401  | −392  | −392  | −389   | −394   |
| Br$^-$| −393  | −382  | −382  | −379   | −382   |

$^a$ $\mu^e$ includes finite size corrections. Details as in Table 5.

(cutoff $r_c = 0.62$ nm) being slightly too low. These results indicate that the free energy of charging is unexpectedly insensitive to the system size if the electrostatic interactions are treated appropriately. In particular, it is important to apply the correct finite-size corrections. For Ewald summation with $N = 16$, for instance, the finite-size correction accounts for about 60% of the free energy. Without the self-terms the Ewald results for $N = 256$ and $N = 16$ differ by about 63 kJ mol$^{-1}$; with the self-terms included the difference is only 5 kJ mol$^{-1}$.

Table 6 lists the results of polynomial fits of the free energy to the derivative data for the other ions studied (K$^+$, Ca$^{2+}$, F$^-$, Cl$^-$, and Br$^-$). Also included are results of TI calculations using Ewald summation and $N = 128$ water molecules. Except for the polynomial fit of degree 2, we obtain consistent results from the derivative data and TI. The $p_2$ results are always somewhat too negative, but this is more apparent for the negative ions. The two TI data per ion typically bracket the $p_2$ and $p_6$ results for the free energy.

Interestingly, there is no simple trend for the free energy of charging of monovalent cations with the ion size (as measured by $\sigma$ of the LJ interaction). The positive ions Na$^+$ and K$^+$ as well as the negative ions F$^-$, Cl$^-$, and Br$^-$ show the expected increase of $\Delta \mu^e$ with increasing $\sigma$. However, only the negatively charged methane-like LJ particle Me$^-\ast$ fits into this ordering. The positively charged Me$^+$ has a less negative $\Delta \mu^e$ than K$^+$, even though the van der Waals diameter $\sigma$ of K$^+$ is considerably larger. However, the LJ interaction of the K$^+$ ion

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is more shallow than that of Me\textsuperscript{+} with the LJ ε values differing by a factor of about 150.

We also calculated the excess chemical potential of inserting uncharged LJ particles in SPC water at density ρ = 33.33 nm\textsuperscript{-3} at temperature T = 298 K. This was done using test-particle insertion.\textsuperscript{15,42–50} A set of 5000 SPC water configurations was used of a simulation run extending over 500 000 Monte Carlo passes. The simulation was performed using N = 256 water molecules and GRF Coulomb interaction with a cutoff of r\textsubscript{c} = 0.9 nm. We calculated (exp(−βu)) using 100 test particles per configuration, where u is the interaction energy of a LJ test particle with the water molecules. For the LJ interaction, a spherical cutoff distance of L/2 = 0.9865 nm was used. A cutoff correction for the r\textsuperscript{−6} term was applied, assuming homogeneous water density beyond the cutoff. The excess chemical potential is calculated as

\[ \mu^e = -k_B T \ln \langle \exp(-\beta u) \rangle \]  

(24)

Results are listed in Table 7. We find positive values for μ\textsuperscript{ex} between 9 and 25 kJ mol\textsuperscript{−1}, favoring the gaseous state. Adding μ\textsuperscript{ex} to the free energy of charging, we obtain single-ion free energies of hydration.

Experimental data for single-ion free energies of hydration have been compiled by, for instance, Friedman and Krishnan,\textsuperscript{51} Conway,\textsuperscript{52} and most recently Marcus.\textsuperscript{36} The first two references report values for the standard molar Gibbs free energy ∆G\textsuperscript{µ}, i.e., for a hypothetical transfer from a 1-atm gas state to a 1 mol/L solution. Marcus lists values for ∆G\textsuperscript{µ} which is the Gibbs free energy of bringing an ion from an empty box into solution. The theoretical calculations determine the excess free energy of hydration, i.e., the transfer from an ideal gas of given density to solution of equivalent solute density. This process corresponds to that used by Marcus, so that ∆G\textsuperscript{µ} is the experimental equivalent of the theoretical free energy that we have referred to as μ\textsuperscript{ex}, disregarding volume contributions. Because Marcus used ∆G\textsuperscript{µ} for the experimental free energies of hydration, we will retain that notation here for those quantities. Conversion from ∆G\textsuperscript{µ} to ∆G\textsuperscript{µ} requires adjustment for the differences in standard states: we add to ∆G\textsuperscript{µ} the free energy of an ideal gas going from a pressure p\textsubscript{0} corresponding to a density of 1 mol/L to a pressure p\textsubscript{1} = 1 atm, which is k\textsubscript{B} T ln(p\textsubscript{1}/p\textsubscript{0}), i.e., ∆G\textsuperscript{µ} = ∆G\textsuperscript{µ} + 7.92 kJ mol\textsuperscript{−1}.\textsuperscript{53} Another correction accounts for differing values for the reference ion H\textsuperscript{+}. We take the most recent value by Marcus\textsuperscript{36} ∆G\textsuperscript{µ}[H\textsuperscript{+}] = −1050 ± 6 kJ mol\textsuperscript{−1} and adjust the other values [−1098\textsuperscript{53} and −1074 ± 17 kJ mol\textsuperscript{−1}\textsuperscript{52}] accordingly.

Results for the calculated free energy of ionic hydration μ\textsuperscript{ex} = μ\textsuperscript{ex}(q=0) + ∆F\textsuperscript{exp}(q→0) and the experimental values ∆G\textsuperscript{µ} are compiled in Table 8. For the calculated values we use those obtained from a fit of a sixth-order polynomial p\textsubscript{b} to the derivative data, as listed in Table 6. The experimental data were adjusted as described above. The experimental data for cations show little variation between the three sources. However, the anion data vary by as much as 70 kJ mol\textsuperscript{−1}, with the Conway data\textsuperscript{36} bracketed by the those of refs 36 and 51, but generally closer to the data of Marcus.\textsuperscript{36}

The calculated free energy data for cations do not show a clear trend. The results for Na\textsuperscript{+} and K\textsuperscript{+} are too low and too high by about 10%, respectively. The hydration free energy of Cs\textsuperscript{+} is too high by about 15%. The anions on the other hand show a clear tendency with the magnitudes of the calculated free energies generally being too large. The relative errors are 26, 10, and 15% for F\textsuperscript{−}, Cl\textsuperscript{−}, and Br\textsuperscript{−}, respectively, compared to the data of Marcus. These significantly too negative values of the hydration free energy of anions might be a consequence of the unprotected hydrogen atoms in the water−ion interaction model used. The positively charged hydrogen atom can penetrate the LJ shell of the ions without a direct energetic penalty. The interaction with the negative point charge at the center of the ion strongly binds the water molecule, resulting in a large enthalpic contribution to the free energy of hydration. But also effects of nonadditive interactions might play a considerable role.\textsuperscript{54}

Also included in Table 8 are computer simulation results by Straatsma and Berendsen.\textsuperscript{32} These authors used thermodynamic integration in conjunction with isothermal−isobaric molecular dynamics simulations to compute hydration free energies of ions. The interaction potentials used here are identical with those of Straatsma and Berendsen, except for the treatment of the electrostatic interactions. We used Ewald summation, whereas Straatsma and Berendsen used a spherical cutoff and a Born-type correction for finite-size effects. These authors (and others\textsuperscript{39}) argue that the application of a Born-type correction is rather crude, approximating the solvent molecules beyond the cutoff by a dielectric continuum. Nevertheless, in the absence of a better alternative it has been widely adopted. Migliore et al.\textsuperscript{55} calculated the free energy of ionic hydration based on a perturbation formula from Monte Carlo simulations using MCY water and \textit{ab initio} ion−water potentials. These authors also used a spherical cutoff. Table 8 includes the results of Migliore et al., who did not apply a finite-size correction.

Qualitatively, our free-energy data agree with those of Straatsma and Berendsen\textsuperscript{32} and Migliore et al.\textsuperscript{55} We observe the same ordering of the free energies with respect to ion size. The quantitative agreement is however poor. Our values for the cations Na\textsuperscript{+} and K\textsuperscript{+} are closer to the experimental data of Marcus. The cation free energies of Straatsma and Berendsen (with Born correction) are consistently more negative than those of our calculations. On the other hand, our anion free energies are significantly more negative than those of Straatsma and Berendsen.

### Table 7: Results for the Excess Chemical Potential μ\textsuperscript{ex} (kJ mol\textsuperscript{−1}) of Transferring an Uncharged LJ Particle from Ideal Gas into SPC Water\textsuperscript{a}

| LJ particle | μ\textsuperscript{ex} | LJ particle | μ\textsuperscript{ex} |
|-------------|-----------------------|-------------|-----------------------|
| Na          | 9.2(1)                | Cl          | 21(3)                 |
| K           | 23.7(5)               | Br          | 24(3)                 |
| Ca          | 10.2(3)               | Me          | 10.2(9)               |
| F           | 9.7(2)                |             |                       |

\textsuperscript{a} The LJ parameters are those of Table 1. Errors are estimated from block averages.

### Table 8: Results for the Calculated Free Energy of Ionic Hydration (kJ mol\textsuperscript{−1}) Compared with Experimental Data\textsuperscript{a}

| ion        | ∆G\textsuperscript{µ} | μ\textsuperscript{ex} |
|------------|------------------------|------------------------|
| Na\textsuperscript{+} | −398                   | −365                   |
| K\textsuperscript{+}    | −271                   | −295                   |
| Ca\textsuperscript{2+}  | −1306                  | −1505                  |
| F\textsuperscript{−}    | −580                   | −465                   |
| Cl\textsuperscript{−}   | −371                   | −340                   |
| Br\textsuperscript{−}   | −358                   | −315                   |

\textsuperscript{a} The experimental data were adjusted to give ∆G\textsuperscript{µ} = −1050 kJ mol\textsuperscript{−1} for H\textsuperscript{+}, as used by Marcus.\textsuperscript{36} Also included are computer simulation results by Straatsma and Berendsen\textsuperscript{32} and Migliore et al.\textsuperscript{55} Experimental data of Marcus.\textsuperscript{36,56} Experimental data of Friedman and Krishnan.\textsuperscript{51} Experimental data of Conway.\textsuperscript{52} Computer simulation data of Straatsma and Berendsen calculated using molecular dynamics of N = 216 water molecules.\textsuperscript{32} The results contain a Born-type correction applied by the authors to their raw data. Computer simulation data of Straatsma and Berendsen without the Born correction.\textsuperscript{32} Computer simulation data of Migliore et al. calculated using molecular dynamics of N = 342 water molecules.\textsuperscript{55}
The integration shows that the LJ contributions are strongly weighted with 218 water molecules and Ewald summation as a function of $\nu$, also agrees with the value $1077$ kJ mol$^{-1}$ of the fluoride ion with the SPC water. We observe two almost Gaussian regimes separated in eq 21, adding the LJ interaction potentials for anion $\phi_e$ and Br$^-$ to approximately 0, indicating that the calculated bulk values are the correct limits for $N \to \infty$.

From the cluster-size dependence of the solvation energy and the mean and variance of the electrostatic potential, it is important to include the self-interactions in the Coulomb energy.

5. Conclusions

We have shown that free energies can be accurately calculated from equilibrium simulations by extracting derivative information with respect to a coupling parameter. We have studied the free energy of electrostatic charging in water, which accounts for most of the free energy of ionic solvation for typical ion sizes. The choice of the ionic charge as coupling parameter results in free-energy expressions involving cumulants of the electrostatic potential $\phi$ at the charge sites. We find that the statistics of $\phi$ are approximately Gaussian. This means that only the first and second moment of the distribution can be calculated accurately, with higher moments dominated by the poorly sampled tails. Correspondingly, only information about the first and second derivative of the free energy can be calculated accurately for any given charge state. The information for different charge states (e.g., uncharged and fully charged) can then be combined using interpolation or polynomial fitting.

We have studied a methane-like Lennard-Jones particle in SPC water. We observe two almost Gaussian regimes separated by $q = 0$ with different characteristics. Negative ions are more stably solvated compared to positive ions of equal size, in agreement with the experimental data. The system shows further asymmetry, since the average electrostatic potential at the position of the uncharged particle is positive. This means that increasing the ion charge first costs energy. We relate these asymmetries of the energetics (lower free energy of negative ions, positive potential) to the structural asymmetry of the water molecule. The hydrogen atoms can penetrate the ionic van der Waals shell, whereas the oxygen atom is better protected. For the uncharged particle, this results in a net positive potential, and the point charge at the center of negative ions exerts strong electrostatic interactions with the tightly bound hydrogen of water.

However, particularly for small anions this effect might be exaggerated by the interaction potentials used. This potential model does not give a protective van der Waals sphere to the charge on the hydrogen atom. In principle, this is a fundamental difficulty, but in computer simulations, the heights of energetic barriers usually exclude the singularity. The development of interaction potentials for anion–water interactions nevertheless has to account for these problems. The strong interactions with the hydrogens “pull” the water closer, and the first maxima of at $R = 0.9$ nm (which is the cutoff Straatsma and Berendsen used) and do not apply a finite-size correction, we obtain a value of $-867$ kJ mol$^{-1}$ in much closer agreement with Straatsma and Berendsen’s. This indeed indicates that the treatment of the electrostatic interactions (Ewald summation versus spherical cutoff) is the major source of the discrepancy.

Also included in Figure 6 are the results for the mean and the variance of the electrostatic potential at the ion site. Figure 6 shows differences with respect to the bulk value. The differences of the mean values $\Delta \phi$ closely follow the solvation-energy differences $\Delta u_e$ and can also be fitted to a third-order polynomial in $N^{-1/3}$. The differences of the fluctuation $\Delta (\Delta \phi^2)$ depend linearly on $N^{-1/3}$ for $N$ between 8 and 256. Both fitted curves extrapolate to approximately 0, indicating that the calculated bulk values are the correct limits for $N \to \infty$.

The integration shows that the integration of $1/\rho_\nu$ weighted with the pair correlation functions obtained from Ewald summation
the ion–oxygen pair correlation function is already in the strongly repulsive region, reducing the effective ion radius.

We have also studied the charging of sodium, potassium, calcium, fluoride, chloride, and bromide ions. The agreement with the available experimental data for solvation free energies is only qualitative, reproducing the trends with ionic size. The quantitative data are not in satisfactory agreement with the experimental results, even conceding quite substantial discrepancies between different compilations of the experimental data for certain ions. We observe typical errors of about 10–15% for the free energies of ionic solvation compared to the experimental data of Marcus.36 This clearly indicates the further need to develop quantitatively reliable descriptions of ion–water interactions.

However, to allow for valid comparisons of data obtained from computer simulations with experimental results, it is crucial to eliminate systematic errors in the simulation methods. An important part of this study was devoted to analyzing the effect of finite system sizes on the free energy of charging. We could clearly establish that Ewald summation (and, similarly, the generalized reaction-field method) accounts for finite-size effects by adding a term that corrects for self-interactions. We showed that even for systems with only \( N = 16 \) water molecules it is possible to obtain accurate estimates of the solvation free energy of the sodium ion. For typical system sizes of a few hundred water molecules, these finite-size corrections are substantial in magnitude. Neglecting them yields results of little quantitative validity. Similar conclusions were drawn for the hydration of water, a polar molecule.36

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