# Modeling Multibody Effects in Ionic Solutions with a Concentration Dependent Dielectric Permittivity

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We report a new strategy to parametrize effective ion-ion potentials for implicit solvent simulations of charged systems. The effective potential includes a pair term and a Coulomb term that by means of a concentration dependent dielectric permittivity takes into account multibody effects. We demonstrate that this approach allows us to accurately reproduce the solution osmotic properties and the ion coordination up to concentrations of 2.8 M aqueous NaCl.

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Ions in aqueous solutions play an important role in many biological and man-made systems [1,2]. The ions can be involved directly, for example, in interactions with proteins, or indirectly by screening interactions between charged molecules in solution. In both cases the behavior of the system depends strongly on the spatial distribution of the ions. To model the proper ion distribution large length scales are required because of the long-ranged nature of electrostatic interactions. As the system sizes prohibit the use of explicitly modeled solvent molecules one has to use effective potentials that implicitly take solvation into account. The most simple model is a combination of a Coulomb potential, using the relative dielectric permittivity of the pure solvent, with a short-ranged repulsive potential to model the excluded volume of the ions. For a single solute species at a fixed concentration more accurate potentials can be obtained by Boltzmann inversion of pair distributions functions. For ionic solutions, however, one cannot directly invert the distributions of the three ion pairs as they are not independent. One can approximate the effective interactions between the ions with pair potentials using McMillan-Mayer theory [3]. The potentials can be obtained through a reverse Monte Carlo procedure or the hypernetted-chain approximation, see Lyubartsev *et al.* [4,5] for studies on NaCl. The problems of this approach are that the potentials are not unique, (although one can define a best approximation), for each density of interest one has to perform long simulations to obtain accurate distributions, and one is limited to homogeneous systems.

Here we describe a method that avoids the disadvantages of Boltzmann inversion by splitting the procedure into two parts. We will use NaCl in aqueous solution as an example system. First we derive effective pair potentials for the three different ions pairs at high dilution. This we do by using atomistic simulations of a single ion pair in a box of explicit water molecules. The effective force is determined by fixing the distance between $Na^+$-$Cl^-$, $Na^+$-$Na^+$ and $Cl^-$-$Cl^-$ and measuring the constraint force. To account for multibody effects, certainly present at high ionic concentrations, a concentration dependent dielectric permittivity is introduced in a Coulomb term augmenting the long-ranged part of the effective pair potential. We demonstrate that to obtain these permittivities, in practice only a single simulation at a high salt concentration is required. We will show that the effective potential accurately reproduces the pair distribution functions of the explicit solvent simulations, as well as the experimentally measured osmotic coefficient. The latter result can also be achieved by replacing the short-ranged part of the effective potential with a simple repulsive potential. Extending this procedure to inhomogeneous systems would allow for the first time an accurate description using an implicit solvent.

We used the atomistic force-field parametrized by Weerasinghe and Smith (WS) [6], which should be used with the extended simple point charge (SPC/E) water model [7]. We chose this force field as it is the only one that has been parametrized with respect to the long-range structure of the solution. To obtain effective pair potentials between solvated molecules at infinite dilution one has to bias the sampling. The easiest way of doing this is by using a constraint. In this work we use the LINCS algorithm [8] implemented in the GROMACS package [9] to constrain the distance between two ions. Periodic boundary conditions are required to properly simulate ions in solution. The simulation setup consists of two ions in a rhombic dodecahedron unit cell with a periodic image distance of 3.5 nm filled with 1000 water molecules. The electrostatic interactions are treated with the particle-mesh Ewald method (PME) [10]. Thus, in effect, one does not measure the force between two ions at infinite dilution, but also the interactions with all periodic images. By simulating the same system with implicit solvent, where one knows the exact answer, we estimated that over the distance range we are interested in the error induced by the periodic setup is around $0.04k_BT$, and therefore negligible. We performed constrained simulations at 300 K for the three ion pairs in SPC/E water for up to 56 distances ranging from 0.23 to 1.2 nm. Each simulation was run 4 ns for distances below

1 nm and for 8 ns for distances above 1 nm. Integrating the constraint force from $r_m = 1.2$ nm downwards gives the effective potential with respect to $r_m$. Here one has to correct for the entropic volume contribution of $2k_B \log(r)$, because the volume sampled by the two ions rotating around each other scales as $r^2$. As beyond 1 nm the curve is very smooth we assume that the effective potential beyond is given by the Coulomb potential. The total effective potential can then be written as

$$V_p(r) = \begin{cases} \int_{r_m}^{r} [\langle f_c \rangle_s + \frac{2k_BT}{s}]ds + \frac{q_1 q_2}{4\pi\epsilon_0\epsilon_r r_m}, & r < r_m \\ \frac{q_1 q_2}{4\pi\epsilon_0\epsilon_r r}, & r \geq r_m \end{cases} \qquad (1)$$

where $f_c$ is the constraint force. To obtain the dielectric permittivity $\epsilon_r$ we performed 80 ns simulations of 1000 SPC/E water molecules, which resulted in $\epsilon_r = 71.9 \pm 0.6$. The effective potentials are shown in Fig. 1.

For all three ion pairs one can distinguish three to four minima, going from the contact pair to one and more solvent-shell separated configurations. The potential for the like-charged ions is always positive. The $\mathrm{Na}^+$-$\mathrm{Cl}^-$ effective potential has a narrow first minimum, that, although it is deeper than the second minimum, is relatively unimportant in solutions containing many ions. The population of the second minimum is always 5 to 8 times higher. This is because its volume is much larger due to its large width and the larger distance.

Using the above obtained effective ion-ion potentials we performed implicit solvent simulations using a relative dielectric permittivity of $\epsilon_r = 71.9$. We have done this using PME for 100 ion pairs at six salt concentrations ranging from 0.1 M to 4.5 M, corresponding to 555 to 11.1 water molecules per ion pair. What one observes is that due to the absence of multibody terms in the effective potential the $\mathrm{Na}^+$-$\mathrm{Cl}^-$ coordination is underestimated. To quantify this we look at the excess ion coordination, which is defined as

$$n_e(r) = \int_0^r 4\pi r^2 \rho[g(s) - 1]ds \qquad (2)$$

where $g(r)$ is the radial distribution function and $\rho$ is the number density of ion pairs. This measures how much the coordination differs from the ideal gas distribution. The results show that the effective pair potential already underestimates the $\mathrm{Na}^+$-$\mathrm{Cl}^-$ coordination significantly at a concentration of 1 M (Fig. 2).

The major multibody effect at higher NaCl concentrations arises from electrostriction of water. When three or more ions approach each other strong local electrostatic fields suppress orientation fluctuations of water molecules. It turns out that the multibody effects can be captured well by a concentration dependent effective dielectric permittivity $\epsilon_E(c)$, where $c$ is the salt molarity. It is determined from a part of the dipole fluctuation of a solution by considering the contribution of the water molecules only [11]. To determine $\epsilon_E(c)$ we have performed simulations of 40 ion pairs for 50 ns in SPC/E water; the results are shown in Fig. 3. The scaling factor for the electrostatic interactions $1/\epsilon_E$ can be fitted very well with a straight line (Fig. 3). This means that to determine $\epsilon_E(c)$ in practice it suffices to simulate two small systems, one consisting of pure water and one salt solution at a high concentration. We have also simulated potassium [12] iodide [13] (KI) + SPC/E water systems at 1.8 and 3.8 M and the results are close to the NaCl curve (Fig. 3). As $\mathrm{K}^+$ and $\mathrm{I}^-$ are significantly larger than $\mathrm{Na}^+$ and $\mathrm{Cl}^-$ respectively, this shows that the concentration dependence of $\epsilon_E$ is quite general, at least for solutions of monovalent ions.

We can then correct the effective potential for the salt concentration by adding a purely Coulombic term:

$$V_c(r, c) = V_p(r) + \frac{q_1 q_2}{4\pi\epsilon_0}\left(\frac{1}{\epsilon_E(c)} - \frac{1}{\epsilon_r}\right)\frac{1}{r}. \qquad (3)$$

With the correction we obtain the correct coordination up

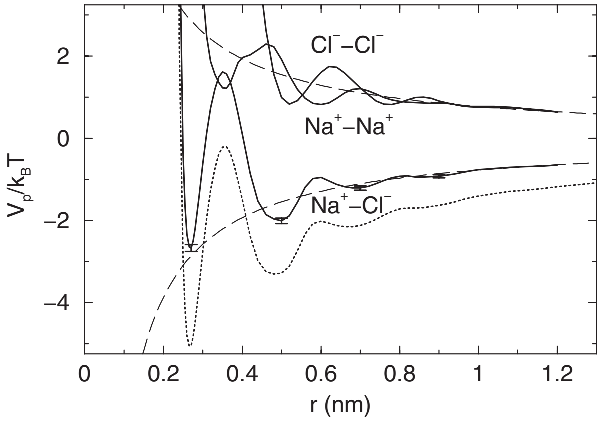

FIG. 1. The effective potential for single ion pairs with the WS force field (solid lines), $V_s(r, c)$ for $c = 2.8$ M (dotted line), and pure Coulomb curves with $\epsilon_r = 72$ (dashed lines).

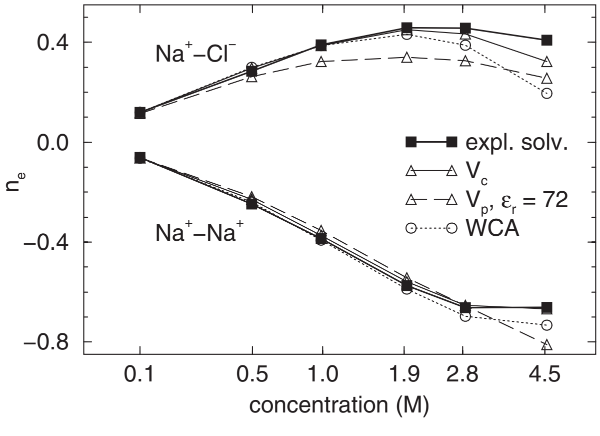

FIG. 2. The excess coordination $n_e$ [Eq. (2)] up to 0.8 nm for the explicit solvent and three implicit solvent simulations. The $\mathrm{Cl}^-$-$\mathrm{Cl}^-$ coordination is nearly identical to the $\mathrm{Na}^+$-$\mathrm{Na}^+$ coordination (results not shown).

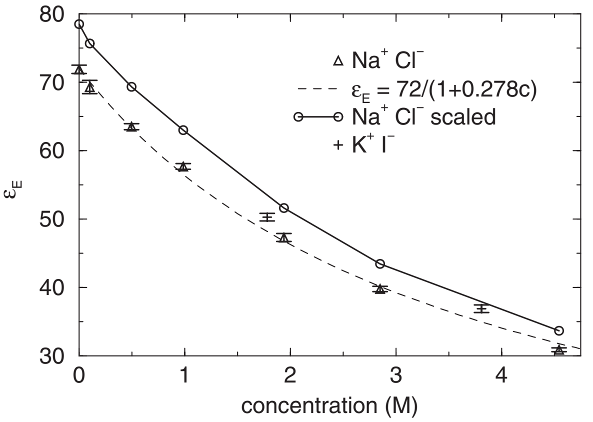

FIG. 3. The NaCl concentration dependent dielectric permittivity $\epsilon_E$ for the WS force field, a fit and $\epsilon_E$ scaled to 78.5 at zero concentration which is used for the WCA model. Also shown are a 1.8 and 3.8 M KI solution.

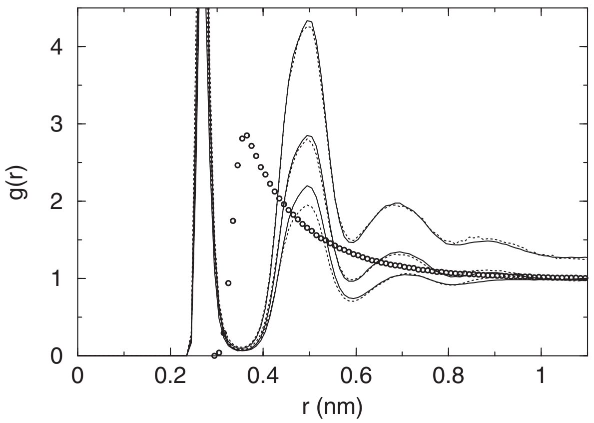

FIG. 4. The Na$^+$-Cl$^-$ radial distribution function for the explicit solvent (solid lines) and implicit solvent (dotted lines) WS systems at concentrations of $c = 0.1$, 1, and 4.5 M, upper, middle, and lower curves, respectively. The circles show the WCA model at 1 M.

to a concentration of 2.8 M (Fig. 2). The radial distribution functions match perfectly (Fig. 4). Only at 4.5 M we start to see an underestimation of the Na$^+$-Cl$^-$ coordination. Such a superposition has been demonstrated for finite concentrations before for Na$^+$-Na$^+$ interactions, by empirically fitting $\epsilon_r$ at each concentration to obtain the best possible overlap of the short-range potentials [14]. We have shown that this superposition also works for a NaCl solution, which contains the much stronger interacting Na$^+$-Cl$^-$ pairs, but more importantly that it has a physical basis in the $\epsilon_E(c)$ determined from dipole fluctuations.

We compared the "sophisticated" effective potential with a simpler Coulomb plus a Weeks-Chandler-Andersen (WCA) potential [15]:

$$V_s(r, c) = \begin{cases} \frac{q_1 q_2}{4\pi\epsilon_0\epsilon_E(c)r} + k_B T[4(\frac{\sigma}{r})^{12} - 4(\frac{\sigma}{r})^6 + 1], & r < 2^{1/6}\sigma \\ \frac{q_1 q_2}{4\pi\epsilon_0\epsilon_E(c)r}, & r \geq 2^{1/6}\sigma \end{cases}. \tag{4}$$

For $\sigma$ we used the WS force-field values: 0.33 nm for Na$^+$-Cl$^-$, 0.25 nm for Na$^+$-Na$^+$ and 0.44 nm for Cl$^-$-Cl$^-$. Note that the values for the like-charged ion pairs have little influence on the results. We simulated this model under the same conditions as the effective potential simulations, but with the dielectric permittivity scaled using reference value of 78.5 at infinite dilution (Fig. 3). Although the radial distribution functions are completely different (Fig. 4), the Na$^+$-Cl$^-$ coordination matches the WS model perfectly up to a concentration of 1.9 M (Fig. 2). At 2.8 M it slightly underestimates the atomistic values. Apparently the detailed minima and maxima of the effective potential are not important for the ion coordination.

With effective potentials between ions, one can determine the osmotic pressure or osmotic coefficient, which is difficult for simulations with explicit solvent. The osmotic coefficient $\phi$ is defined as the pressure divided by the ideal gas pressure:

$$\phi = \frac{P}{P_{\text{ideal}}} = \frac{K - \Xi}{K} = 1 - \frac{\Xi}{K} \tag{5}$$

where $K$ is the kinetic energy and $\Xi$ is the virial. This quantity allows for a direct comparison of computer models with experiment. It is also frequently used in the study of polyelectrolytes, as it is often the only experimentally accessible quantity that contains information on the spatial distribution of the ions [16,17]. Therefore it is important that an effective potential reproduces the osmotic coefficient. The values as a function of concentration are shown for the different models as well as experiment [18] in Fig. 5. The WS model nicely follows the experimental trend, but is slightly too low over the whole concentration range. We also tried the WS force field in combination with the SPC water model [19]. Because of the too low dielectric permittivity of 65.5, the osmotic coefficient is slightly underestimated at lower concentrations and significantly overestimated at higher concentrations (results not shown). Note that if one uses a fixed dielectric permittivity the osmotic coefficient is far off at higher concentrations (Fig. 5). The WCA model is closer to the experiment, which is surprising for such a simple model. At low concentrations this improvement is due to the correction for the dielectric permittivity.

The properties of the WCA model depend, apart from $\epsilon_E(c)$, mainly on the parameter $\sigma$ for Na$^+$-Cl$^-$, the $\sigma$ for the like-charged pairs has little influence as they repel each other. To show the influence of $\sigma$ for Na$^+$-Cl$^-$ we performed simulations with values of 0.32 and 0.34 nm and the

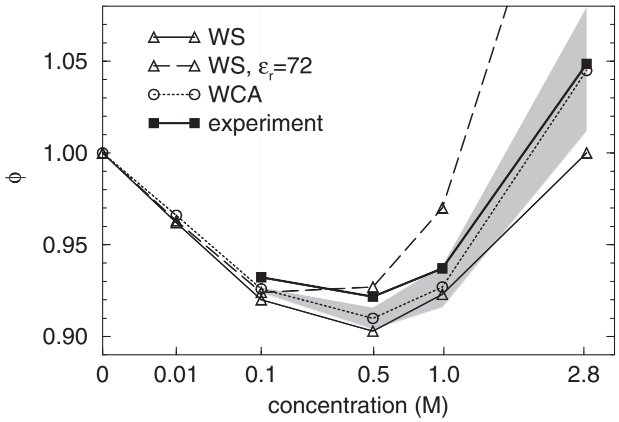

FIG. 5. The osmotic coefficient as a function of the cube root of the salt concentration for the models and experiment [18] as indicated. All models use a concentration dependent dielectric permittivity, except for the $\epsilon_r = 72$ curve. The boundaries of the gray region indicate the results for the WCA model with $\sigma = 0.32$ nm (bottom) and $\sigma = 0.34$ nm (top) for the $\mathrm{Na}^+$-$\mathrm{Cl}^-$ interaction.

range of the osmotic coefficient in between these values is drawn in gray in Fig. 5. As expected the results at high concentrations are sensitive to $\sigma$. The value of 0.33 nm, which gives the best correspondence with WS for the coordination, also gives the best osmotic coefficient.

We have shown that multibody effects between solvated ions, which start playing a role already at a concentration of 0.5 M, can be captured accurately by the use of a concentration dependent dielectric permittivity $\epsilon_M(c)$. As $1/\epsilon_M$ depends linearly on the concentration, it can be determined from a single simulation of a small, concentrated salt solution, assuming that the dielectric permittivity of the water model is known. This method is much simpler than the complicated procedure of inverting coupled radial distribution functions. For a range of concentrations it is also more efficient as one only needs to determine the three effective potentials once. Based on these effective potentials the ion-ion correlation functions of the explicit solvent simulations and the experimental osmotic coefficients are reproduced up to 2.8 M. Moreover, when one is not interested in spatial resolutions on the order of a few angstroms, a WCA potential performs just as well, as the excellent agreement with the experimental osmotic coefficients shows. In addition, even the ion coordination matches the WS results up to 1.9 M. There is only one important parameter left, namely, the distance of closest approach of the cation and anion, which is set by the WCA $\sigma$, and which can be determined by matching the ion coordination at a single concentration. This provides an extremely efficient way to simulate the thermodynamic properties of electrolyte solutions. For the important case of inhomogeneous systems that contain, for example, charged macromolecules or membranes, we suggest that the use of a local concentration dependent dielectric permittivity will enhance greatly the accuracy of large-scale implicit solvent simulations.

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