Simulation study of ion pairing in concentrated aqueous salt solutions with a polarizable force field

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Abstract

The accuracy of empirical force fields is critical for meaningful molecular dynamics simulations of concentrated ionic solutions. Current models are typically developed on the basis of single ion properties such as the monohydrate energy in the gas phase, or the absolute hydration free energy at infinite dilution. However, the failure of these models to represent accurately the properties of concentrated solutions cannot be excluded. Here, these issues are illustrated for a polarizable potential based on classical Drude oscillators. To model accurately concentrated ionic solutions, the parameters of the potential functions are optimized to reproduce osmotic pressure data. The sodium-chloride potential of mean force in solution calculated from the empirically-adjusted model is consistent with the results from that calculated from ab initio CPMD simulations.

Keywords

solutions, salt, aqueous, concentrated, pairing, ion, study, simulation, field, polarizable, force, CMMB

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Simulation study of ion pairing in concentrated aqueous salt solutions with a polarizable force field†

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The accuracy of empirical force fields is critical for meaningful molecular dynamics simulations of concentrated ionic solutions. Current models are typically developed on the basis of single ion properties such as the monohydrate energy in the gas phase, or the absolute hydration free energy at infinite dilution. However, the failure of these models to represent accurately the properties of concentrated solutions cannot be excluded. Here, these issues are illustrated for a polarizable potential based on classical Drude oscillators. To model accurately concentrated ionic solutions, the parameters of the potential functions are optimized to reproduce osmotic pressure data. The sodium-chloride potential of mean force in solution calculated from the empirically-adjusted model is consistent with the results from that calculated from *ab initio* CPMD simulations.

1. Introduction

Computer simulations of atomic models are increasingly used to study a broad range of physical and biological processes. Ions play a fundamental role in many of these complex molecular systems, and for meaningful computer simulations studies, accurate force fields are absolutely critical. Modeling ions and strong electrolytes accurately is particularly challenging because of the long-range nature and strength of electrostatic interactions that are involved. The ion models widely used in molecular dynamics (MD) simulations are generally developed on the basis of single ion properties, such as the energy and geometry of the monohydrate ion in the gas phase and the absolute hydration free energy of the ion at infinite dilution.[1–5] It has been reported that ion models developed with this strategy can dramatically fail to represent accurately the properties of concentrated solutions, such as the solubility[3,4] and osmotic pressure.[6] Even if a model is optimized to match the gas-phase monohydrate energy and geometry, the hydration free energies in the bulk phase at infinite dilution, as well as dynamic transport properties, may be in good agreement with experimental data and high-level *ab initio* calculations,[5] but it is not guaranteed that the thermodynamic properties of concentrated solutions will be accurately represented.

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The thermodynamic properties of concentrated solutions depend sensitively on the propensity of ion pairs. However, exploiting this information to test, validate and improve the force fields is difficult because the available data provide only indirect information about ion pairing. Neutron and X-ray scattering yield the average structure factor of a solution and multiple experiments involving isotopic substitutions as well as extensive analysis are needed to extract individual solvent–solvent, ion–solvent, and ion–ion pair correlation functions.[7–9] The amount of ion pairing can indirectly be related to conductivity measurements,[10] although this involves additional assumptions. Ion-pairing in aqueous solution has been studied using a wide range of computational and theoretical methods, including classical force field molecular dynamics (MD)[6,11–14] and Monte Carlo (MC) simulations,[15,16] simple models based on a polarizable continuum,[17,18] and quantum mechanical Car–Parinello MD (CPMD) simulations.[19] Nevertheless, in spite of these efforts, our ability to assess computationally the accuracy of force field models of electrolyte solutions at very high concentrations remains fairly limited.

One experimental observable that is potentially of great interest to test, validate, and refine force field models used in computer simulations of concentrated ionic solutions is the osmotic pressure. It is one of the key thermodynamic properties that can be measured for a wide range of conditions and it offers a measure of the strength of the effective solvent-mediated interaction between ions in the solution. For non-ideal solutions the osmotic pressure is equal to $\Pi = \phi\Pi^*$, where ϕ is the osmotic coefficient defined with respect to the osmotic pressure Π^* for an ideal solution by the Van't Hoff equation $\Pi^* = cRT$ (c is the total concentration of mobile ions and R is the gas constant). Theoretical studies of thermodynamics of ion-pairing, such as activity coefficient and osmotic coefficients of electrolyte solutions have often been based on statistical mechanical frameworks such as the McMillan–Mayer (MM)[20] and Kirkwood–Buff (KB)[21] theories. Some studies have aimed at calculating Kirkwood–Buff Integrals (KBIs) directly using computer simulations.[22–29] Statistical mechanical integral equation theories, such as the mean spherical approximation (MSA)[30,31] or the hypernetted chain (HNC) equation[32] were used to derive pair correlation functions needed to calculate ϕ. The multicomponent reference interaction site model HNC (RISM-HNC) theory was used to incorporate effects arising from the molecular nature of water.[33] For a review see ref. 6.

While these approaches are useful, they do not provide a simple route for establishing a quantitative relationship between the force field used in a computer simulation and the osmotic pressure. It is largely to address this issue that we previously developed a simple and practical approach allowing the direct calculation of the osmotic pressure from all-atom MD simulations of concentrated aqueous solutions.[6] The basic concept is to introduce "virtual" walls to represent the effect of ideal semipermeable membranes, separating the high concentration region from the pure water region. The walls keep the solutes confined but the water molecules are allowed to pass through freely, permitting an equalization of their chemical potential throughout the entire system. The mean force per unit area exerted on the solutes by the virtual walls during the simulations directly reports the osmotic pressure.

In the present study, the Drude polarizable force field for K⁺, Na⁺ and Cl⁻ is tested by calculating the osmotic pressure over a wide range of concentrations. A polarizable force field is crucial for the realistic simulations of charged or highly polar species, and also for describing accurately the electrostatic properties of the hydrophobic region in protein and membranes. In the Drude force field, the induced electronic polarization is introduced by an auxiliary particle attached to each polarizable atom *via* a harmonic spring. The Drude ion models were previously developed to be consistent with the SWM4-NDP water model.[5,34] Here, the osmotic pressure of NaCl and KCl aqueous solution are calculated over a wide range of concentrations (up to 5 m) and compared with the experimental values.[35] The results show that the osmotic pressure depends sensitively on ion pair interactions, in agreement with previous studies.[36,37] The present study demonstrates that the

osmotic pressure is a powerful route for validating and parameterizing accurate atomistic force fields.

2. Methods

2.1. Classical Drude polarizable model

The present simulations of ionic solutions are based on the SWM4-NDP polarizable water model[34] and the set of polarizable models developed recently for the alkali-halide series.[5] The SWM4-NDP model correctly reproduces the static dielectric constant of liquid water, which makes it appropriate for simulating systems where water-mediated electrostatic interactions have dominant effects,[34] such as concentrated electrolyte aqueous solutions. The gas-phase experimental geometry of water is maintained rigidly, and the static charge distribution of the isolated molecule gives rise to a dipole of 1.85 D, in accord with experiment. In the classical Drude oscillator model, electronic induction is represented by introducing a mobile auxiliary charged particle attached to a polarizable atom *via* a harmonic spring of force constant k_D. The relative displacement of the atom–Drude pair gives rise to an electric dipolar moment. Assuming that the Drude particle carries a q_D and the atom carries an opposite charge $-q_D$, the molecular polarizability α is equal to q_D^2/k_D.[38] In the present models, the charge carried by the Drude particles is always negative, to mirror the physical effects of the electronic density around positively charged nuclei. An anharmonic restoring force was introduced to damp atom–Drude separations larger than 0.2 Å to prevent numerical instabilities with the highly polarizable anions.[5] Atomic dispersion and electronic overlap effects are represented in a pairwise additive way using the Lennard-Jones (LJ) 6–12 potential. The electrostatic interaction energy of a single monovalent ion with a water molecule is comprised of a sum of charge-charge Coulomb interactions running over all nuclei and Drude particles.

All dynamical simulations were performed by considering the dynamics of an extended Lagrangian in which a small mass and kinetic energy is attributed to the Drude particles. The equations of motion of the atom–Drude pair are separated into the global motion of the center-of-mass, and the relative internal motion of the oscillator (reduced mass). To ensure that the time course of the induced dipoles stays close to the self-consistent field (SCF) solution, the amplitude of the atom–Drude oscillations away from the local energy minimum is controlled with a low-temperature thermostat acting in the local center-of-mass reference frame of each atom–Drude pair.[38] The trajectories generated according to this extended Lagrangian are very close to those generated by the SCF regime of induced polarization.[38]

For the present study, MD trajectories were generated with the program CHARMM[39] and NAMD2.8.[40] In the simulations generated with the program CHARMM,[39] the two-temperature isothermal-isobaric ensemble was simulated using a Nosé–Hoover thermostat scheme[41,42] and the modified Anderson–Hoover barostat.[43] The simulations were propagated using the velocity-Verlet algorithm with a 0.5 fs time step. The internal geometry of the SWM4-NDP water molecule was kept rigidly fixed using the SHAKE/Roll and RATTLE/Roll algorithm.[44,45] Long-range electrostatic interactions were computed using particle mesh Ewald summation (PME).[46] A smooth real space cutoff is applied between 10 and 12 Å with an Ewald splitting parameter of 0.34 Å^{-1}, a fast-Fourier grid density of ≈ 1 Å^{-1}, and a sixth-order interpolation of the charge to the grid. The LJ potential is smoothed with a switching function with the same cutoff scheme, and a long range correction of the energy and pressure from the LJ potential is included.[47]

In the simulations generated with the program NAMD2.8,[40] a dual-Langevin scheme is employed to propagate the trajectory of the polarizable Drude model.[48] While the concept is similar to the dual Nosé–Hoover thermostat in the program

tions of the Drude model on massively parallel supercomputers, such as Blue-
Gene/P.[48] To ensure near-SCF conditions, the thermostat for the relative motion
of the Drude particles with respect to their parent atoms was set at a temperature
of 1 K with a damping coefficient of 0.1 ps^{-1}. The thermostat for the center-of-
mass was set at a temperature of 298 K with a damping coefficient of 0.05 ps^{-1}.
The geometry of the SWM4-NDP water molecule was maintained using SETTLE.[49]
A multiple time-step integration scheme was used, with 0.5 fs for the calculation of
the internal energy terms, and 1.0 fs for the calculation of the nonbonded LJ and
electostatics terms. The shorter time-step 0.5 fs time step is necessary for stable inte-
gration due to the anharmonic restoring force introduced to prevent the hyper-
polarization of anions at the finite concentrations.[5] The electrostatic interactions
were treated using PME.[46,50] A smooth real space cutoff is applied between 10
and 12 Å with grid density of ≈ 1 Å^{-1}, and a sixth-order interpolation of the charge
to the grid. The same cutoff is used for the LJ potential with a switching function.

2.2. Single ion pair potential of mean force (PMF) simulation details

The 1D-PMF of single ion pair in bulk was calculated as a function of the cation–
anion separation, $r = \|\mathbf{r}_c - \mathbf{r}_a\|$, using umbrella sampling.[51] A total of 26 independent
biasing windows in which the two ions were harmonically restrained by the potential
$u_i(r) = k(r - R_i)^2/2$, were set up at different separation R_i and force constant k to
ensure good sampling and overlap of neighboring windows (0.2 Å increments
between 2.5 Å to 3.5 Å with force constant of 30 kcal mol^{-1}Å^{-2}, 0.25 Å increments
between 3.5 Å to 7.0 Å with force constant of 30 kcal mol^{-1}Å^{-2}, and 0.5 Å for the
rest with the force constant of 20 kcal mol^{-1}Å^2). The simulations were carried out
using the program CHARMM,[39] with one ion pair placed in a periodic cubic box
containing 395 explicit SWM4-NDP water molecules. The chloride ion was harmon-
ically restrained near the center of water box to prevent any significant drift of the
ion pair. Each window simulation of 500 ps was initially started from a configuration
with the ion near the restraint position and equilibrated for 50 ps. The results from
the 26 windows were unbiased using the weighted histogram analysis method
(WHAM),[52] with a bin size of 0.05 Å and a stringent tolerance of 0.0001 kcal
mol^{-1} on every point in the PMF. The radial PMF resulting directly from umbrella
sampling simulations biased by a simple distance restraint implicitly contains an
additional hidden term, $+2k_BT \ln(r)$, arising from the increasing volume element
in the configurational space at large ion–ion separation.[53] This can be seen by con-
verting the two Cartesian coordinates of the cation and anion, $\mathbf{r}_c$ and $\mathbf{r}_a$, into the
relative spherical coordinates in the biased Boltzmann configurational integral,
yielding the Jacobian $4\pi r^2$. To obtain the PMF that is a simple function of ion–
ion separation, we write $W(r) = W_{\text{radial}}(r) + 2k_BT\ln(r) + C$, where the constant C
is chosen such that $W(r) \to 0$ as $r \to \infty$. In practice, the offset constant was chosen
such that $W(r)$ matches the value expected in a dielectric continuum with $\varepsilon = 79$[34] at
an ion–ion distance of 7 Å.

2.3. Osmotic pressure simulation details

The osmotic pressure for KCl and NaCl aqueous solutions was calculated by intro-
ducing an idealized virtual semi-permeable membrane separating a salt solution
from pure water, according to a method described previously.[6] Here, the idealized
virtual semi-permeable membrane is made of two half-harmonic walls acting only
on the ions to keep them within the salt solution region. The water molecules can
freely cross the virtual semi-permeable membrane and move throughout the system.
Averaging the force acting on the ions from the half-harmonic walls under these
conditions directly yields the osmotic pressure in the system. The osmotic pressure
MD simulations were carried out with periodic boundary conditions using the

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program NAMD2.8.[40] The shape of the entire simulation cell is orthorhombic with dimension $96 \times 96 \times 96$ Å^3 and is comprised of approximately 150 000 atoms. The central region corresponds to a salt solution with dimensions $96 \times 96 \times 48$ Å^3. A flat-bottom half-harmonic planar restraint with a force constant of 10 kcal mol^{-1}Å^{-2} was applied to the ions at $z = \pm 24$ Å to keep them inside the region corresponding to the salt solution. The virtual walls acting on the ions were setup *via* a Tcl script in NAMD. No restraint was applied to the water molecules. The molality scale (m $\equiv$ mol kg^{-1}) is used throughout the manuscript to compare directly to the experimental osmotic pressure data. The atomic systems were first setup at different molarity concentrations (1, 2, 3, 4, and 5, mol l^{-1}), as in our previous simulations of nonpolarizable models,[6] and the effective molality concentrations of the solution were estimated after equilibration. After a 400 ps equilibrium run under NPT conditions at 298.15 K and constant area, 6 independent 800 ps simulations (different initial configuration and initial velocity) were carried out under NVT condition for each concentration and the coordinates of the ions were saved every 0.1 ps.

3. Results and discussion

Fig. 1(a) and 1(b) show the calculated osmotic pressure for the NaCl and KCl aqueous solutions using the Drude polarizable force field with standard LJ parameters. Without any additional adjustments, the force field for KCl is able to reproduce the experimental osmotic pressure quite well, with a slight deviation from the experimental value at higher concentrations (above 2 m). For the NaCl solution, however, the osmotic pressure is systematically underestimated, even at concentrations as low as 1 m. Although the discrepancy is larger than previously observed for the nonpolarizable NaCl ion models, the analysis showing that such a systematic
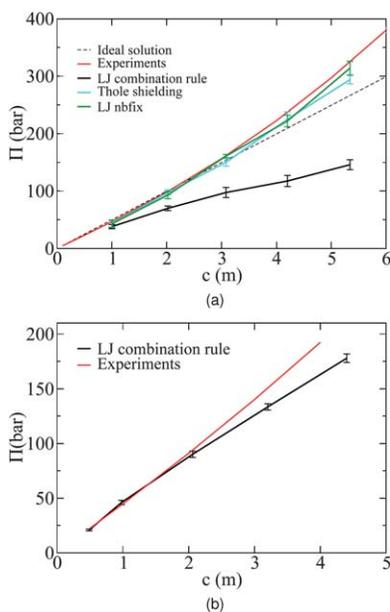
Fig. 1 The osmotic pressure as a function of the NaCl (a) and KCl (b) salt concentration. The red line is experimental values; the black line is obtained from MD simulations with the Lorentz–Berthelot combination rule. In (a), the cyan line is from simulations with adjusted Na–Cl R_{min} 4.09 Å LJ parameters using NBFIX; the green line is from simulations with a Thole shielding screening parameter t_{ij} 2.10. The error bars were estimated from the variance amongst 6 independent 800 ps simulations.

underestimation of the osmotic pressure in electrolyte solution reflects an excess of ion pairing[6] remains valid. A simple explanation is that the osmotic pressure is directly affected by the actual concentration of mobile species in solution, cations and anions. For example, if all cations and anions were bound together to form stable pairs, the resulting osmotic pressure would be roughly reduced by a factor of two compared to a fully dissociated electrolyte solution. Thus, excessive ion pairing caused by inaccuracies in the force field model results in an underestimated osmotic pressure. To improve the accuracy of the model, it is necessary to alter and optimize the potential function. This is possible by using the experimental osmotic pressure as target data.

The origin of the problem with the model with standard LJ parameters starts with the over-binding of the Na–Cl pair in vacuum. Within the Drude polarizable force field, the potential energy between two ions is written as a sum of Coulombic interactions summed over all charges (from the atom and the Drude particles), and a Lennard-Jones (LJ) 6–12 potential to account for the core–core repulsion and the van der Waals dispersive attraction between the two atoms. The default parameters of the LJ potential for the interactions between two ions i and j, that is, R_{min}^{ij} and E_{min}^{ij}, are generated with the standard Lorentz–Berthelot combining rule. The latter uses the arithmetic mean for

$$R_{min}^{ij} = (R_{min}^{ii} + R_{min}^{jj})/2$$

and the geometric mean for the well depth $E_{min}^{ij} = \sqrt{E_{min}^{ii} E_{min}^{jj}}$. Fig. 2(a) shows the potential energy of an NaCl ion pair in vacuum as a function of distance. The energy minimum obtained from the Drude model with default LJ parameters is 25 kcal mol^{-1} lower than the *ab initio* value. The *ab initio* quantum chemical computation
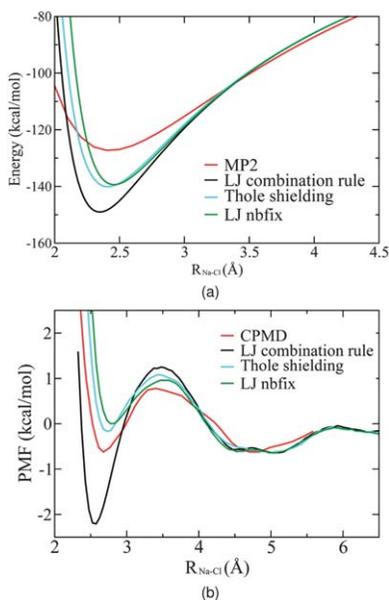
Fig. 2 (a) Potential energy of NaCl ion pair in vacuum as a function of distance. The *ab initio* quantum chemical computation is carried out at MP2/aug-cc-pVDZ level (BSSE corrected) using Gaussian03 (54). (b) Potential of mean force (PMF) of the single ion pair in bulk calculated from MD simulation with different Na–Cl pair parameters. The PMF from CPMD simulation is taken from ref. 19.

Therefore, there is considerable over-binding of the cation–anion pair in vacuum according to the polarizable Drude model with default LJ parameters.

The over-binding of Na^+ and Cl^- in vacuum represents a failure of the complete model, with default LJ parameters. It is important to realize, however, that the LJ 6–12 potential is only an approximation to the quantum mechanical cation–anion interactions, and the usage of the Lorentz–Berthelot combination rule is merely a convenient route for generating pairwise parameters between unlike atoms.[55] The LJ parameters of the model were previously optimized to reproduce accurately single-ion properties such as the geometry and energy of the monohydrate, and the solvation free energy in bulk water at infinite dilution.[5] Thus, the current model is not constrained by any experimental information at finite concentrations where ion–ion interactions become important. For example, it is perfectly reasonable to imagine that by increasing the radius, R_{min}^{ij}, the cation and anion will be pushed further apart, decreasing the favorable association that leads to an excess of ion pairing and an under-estimated osmotic pressure. Ultimately, several different methods may be considered to alter and improve the polarizable Drude model. In the following, two different methods were considered.

First, we developed pair-specific LJ parameters between Na^+ and Cl^-. This is perhaps the simplest correction to the model, as it keeps all other features of the potential function unchanged. To override the values generated from the standard combination rule, the pair-specific LJ parameters are assigned using the NBFIX option of the CHARMM parameter file. Importantly, the LJ parameters controlling the direct interaction between the ions and water remain untouched by the NBFIX option. A second approach was to introduce a shielding function to alter the bare Coulombic interactions between the cation and the anion,

$$\left(\frac{q_i q_j}{r_{ij}}\right) \rightarrow \left(\frac{q_i q_j}{r_{ij}}\right) S(r_{ij}) \tag{1}$$

where $S(r_{ij})$ is a screening function given by,

$$S(r_{ij}) = 1 - \left(1 + \frac{r_{ij} t_{ij}}{2(\alpha_i \alpha_j)^{1/6}}\right) e^{-r_{ij} t_{ij}/(\alpha_i \alpha_j)^{1/6}} \tag{2}$$

where α_i and α_j are the polarizability of atom i and atom j, respectively, and t_{ij} is the Thole parameter modulating the strength of the electrostatic screening for the ij pair. This functional form is consistent with the general idea that the Coulomb interaction between delocalized clouds of electronic charges does not diverge as $1/r$ at short distances. It was first introduced by Thole to account for intramolecular polarization.[56] In the Drude polarizable force field, the $S(r)$ shielding function has been utilized to treat the intramolecular 1–2 and 1–3 bonded interactions.[57] More recently, it was used to "tame" the very strong electrostatic interactions between divalent ions (Zn^{2+}, Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+}) and the induced dipole component of the oxygen of the water molecules.[5] Such shielding is unnecessary for the interactions of monovalent ions with the water molecules, but it could be needed to treat accurately the cation–anion pairs. Here, a pair-specific Thole parameter was introduced between Na^+ and Cl^- using the option NBTHOLE of the CHARMM potential function parameter file.

Using either the pair-specific LJ parameter (NBFIX) modification and the Thole shielding (NBTHOLE), it ought to be possible to correct for the over-binding of the Na–Cl pair. However, in trying to optimize and improve the force field parameters, it is difficult to rely directly on the *ab initio* data in vacuum in a meaningful way. The interactions of the ions in vacuum is simply too different from the effective interactions in bulk solution, and the impact of any modifications to the vacuum interaction on the thermodynamic properties in the bulk is difficult to predict. A more productive

route to assess the default model is to start from considerations of the effective solvent-
mediated potential of mean force (PMF) of the single ion pair in bulk water. Here,
a key piece of information is provided by the PMF between an Na^+ and a Cl^- in
bulk water previously calculated by Kuyucak and co-workers using CPMD simula-
tions.[19] In Fig. 2(b), the PMF from the Drude model with default LJ parameters is
compared with the PMF calculated from CPMD simulations. While the two PMFs
are in near-quantitative agreement at large and moderate distances they differ strongly
at short distances (*i.e.*, less than 3 Å) in the region where the core repulsion begins to be
important. The discrepancy at short distances affects the depth of the first free energy
well in the PMF, which corresponds to the situation where the cation and anion form
a contact pair. As shown in Fig. 2(b), the Drude model with default LJ parameters
gives the first minimum of NaCl PMF 1.6 kcal mol^{-1} deeper than the first minimum
obtained from CPMD.[19] Obviously, the depth of the first free energy well directly
affects the propensity for cation–anion association.

To clarify the features of the model having the most direct impact on ion pairing,
it is useful to separate the total PMF from the default model into a long-range and
short-range contributions,

$$W_{lr}^{MD}(r) = \Delta W_{lr}^{MD}(r) + U_{LJ}(r) \qquad (3)$$

where $\Delta W_{lr}^{MD}(r)$ represents all the long-range electrostatic contributions along with
the effects of solvent, other than the cation–anion short-range repulsion and van der
Waals dispersion, which are modeled by the LJ potential, $U_{LJ}(r)$, with default
parameters generated from the standard combining rule. The function $W_{lr}^{MD}(r)$ ex-
tracted from the PMF that was calculated from the simulations with the default
LJ parameters for NaCl is shown in Fig. 3(a). This contribution to the PMF bears
some similarities with the indirect cavity potential that is sometimes considered in
integral equation studies.[33] At moderate distances, the oscillations in $\Delta W_{lr}^{MD}(r)$
reflect the complexity of the hydration shell around the cation and anion. At short
distances, in the region where the core repulsion begins to be important, the function
$\Delta W_{lr}^{MD}(r)$ becomes strongly attractive. This strong attraction is compensated by the
short-range repulsion, which essentially controls the depth of the free energy well in
the PMF at ion–ion contact. It is worth pointing out that the steepness of the cavity
potential largely undermines our ability to be accurately predictive about the
opposing short-range repulsive core potential, a problem noted long ago by Dang
et al.[58] For this reason, relying on the osmotic pressure data to adjust empirically
the force field is absolutely necessary and unavoidable to obtain accurate models.

Although the separation given in eqn (3) is trivially satisfied by construction, it
seems plausible on physical grounds that the indirect cavity potential contribution
to the PMF should be fairly insensitive to the details of the short-range contribution
of the model. This suggests that the function $\Delta W_{lr}^{MD}(r)$ evaluated from the default
model could be used to extract the short-range cation–anion repulsive potential
that is needed to best-match the PMF from CPMD. Following this argument, one
may write,

$$U_{sr}^{CPMD}(r) \equiv W^{CPMD}(r) - \Delta W_{lr}^{MD}(r) \qquad (4)$$

where $\Delta W_{lr}^{MD}(r)$ is the long-range contribution shown in Fig. 3(a). The short-range
potential $U_{sr}^{CPMD}(r)$ extracted from the CPMD simulations *via* eqn (4) is shown in
Fig. 3(b). The function $U_{sr}^{CPMD}(r)$ can then be used as a "target" to help design an
optimal model for Na^+ and Cl^- that is able to reproduce the PMF from *ab initio*
$W^{CPMD}(r)$. The default value of the LJ parameter R_{min}^{ij} for the Na–Cl pair is 3.94
Å. By visual inspection of Fig. 3(b), the pair-specific radius R_{min}^{ij} must be adjusted
to 4.03 Å to match the short-range repulsion extracted from the PMF calculated
from CPMD. Further simulations showed that the experimental osmotic pressure
were obtained with a Na–Cl R_{min}^{ij} of 4.09 Å. As shown in Fig. 1(a), R_{min}^{ij} 4.09 Å
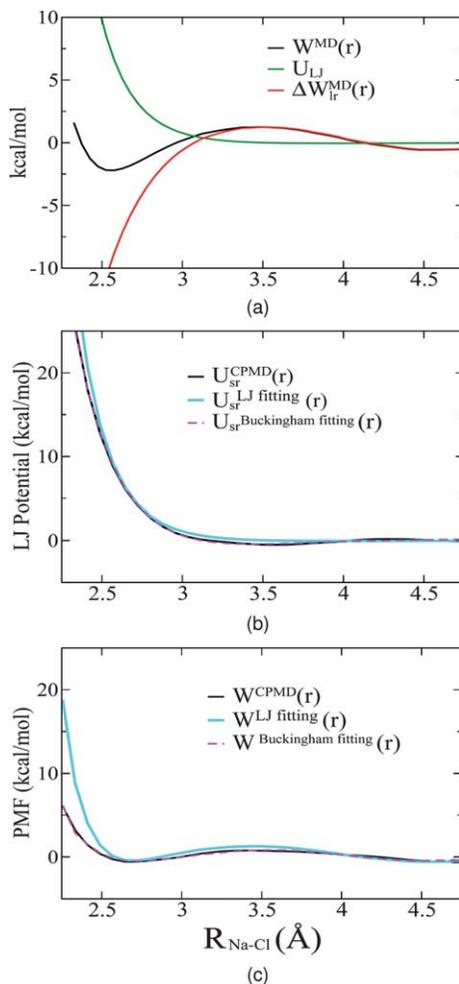
Fig. 3 (a) The $\Delta W(r)$ (red line) is extracted from the default PMF profile (black line) subtracted by the default LJ pair potential (green line); (b) the black line is the target LJ potential needed to fit the CPMD PMF; the cyan line is the fitted LJ potential using the standard 6–12 potential giving an estimation of R_{min} as 4.03 Å (the default value is 3.94 Å); the magenta line corresponds to the Buckingham potential fitting; (c) the black line is the PMF calculated from CPMD; the cyan line is the PMF from the LJ potential fitting; the magenta line is the PMF from the Buckingham potential fitting.

can reproduce the experimental osmotic pressure very well for a broad range of concentrations, up to the solubility limit of 6 m. Fig. 2(a) shows the Na–Cl potential with this empirically adjusted pair-specific LJ parameters. The energy minimum for the ion pair in vacuum is increased by 10 kcal mol^{-1}, but is still about 15 kcal mol^{-1} less than the *ab initio* value. Alternatively, it is also possible to derive an accurate model with Na–Cl Thole shielding. This was achieved by trying to match the vacuum energy and PMF calculated from the optimized NBFIX model (with $R_{min}^{ij} = 4.09$ Å). Following this procedure, an optimal value of 2.10 was obtained for the Thole shielding parameter t_{ij}. All pair-specific parameter results are summarized in Table 1.

Based on the above results, it is clear that the two approaches, the pair-specific LJ parameter modification and the Thole shielding, can both be utilized to empirically

Table 1 LJ parameter of ions and pair-specific parameters

Ion	$\frac{1}{2}R^{ii}_{min}$ (Å)	$\frac{1}{2}E^{ii}_{min}$ (kcal/mol)
Na$^+$	1.4616800	−0.0315100
Cl$^-$	2.4811139	−0.0719737
Na$^+$–Cl$^-$	R^{ij}_{min} (Å)	t_{ij}
Combination rule	3.94	—
LJ NBFIX	4.09	—
Thole shielding	3.94	2.10

improve the model in order to reproduce the experimental osmotic pressure data in a broad concentration range. It is worth pointing out that the optimized models obtained here are not concentration dependent and that the models are, thus, transferable to any finite concentrations. From this point of view, the current strategy departs from approaches based on a concentration-dependent dielectric constant used to account for the many-body interactions in implicit solvent models.[14,36,59] However, comparing the PMF and also the interaction energy in vacuum with the corresponding *ab initio* data (Fig. 2(a) and 2(b)), the electrostatic Thole shielding strategy produces the energy minimum at a similar position as the *ab initio* data, while increasing the radius (R_{min}) has pushed the energy minimum about 0.6 Å further apart in both vacuum energy and bulk phase PMF profiles. Also, it is known that the classical Drude model does not allow charge transfer between atoms at the short distance. This approximation may cause the electrostatic interaction at short distances to be too favorable, which causes the excess ion pairing. In both cases, the Thole shielding strategy seems more reasonable and precise than LJ parameter modification for the Drude ion pair parameters. As observed in Fig. 3(b), it is of interest to note that the Buckingham potential is able to reproduce accurately the target short-range cation–anion repulsion better than a standard LJ 6–12 potential, particularly for distances shorter than 2.75 Å. This is expected, as it is well understood that the r^{-12} repulsion from the LJ potential is much too steep at short distances and that the exponential functional form of the Buckingham potential is a better physical model for the core repulsion. Nevertheless, the LJ potential, which remains a simple and popular approximation that is widely used in the field of biomolecular simulations, can also yield reasonably accurate results for the concentrated ionic solutions.

The osmotic pressure of concentrated electrolyte solution appears to result from a delicate balance of strongly attractive and repulsive interactions. A useful framework to deepen our understanding of these systems is provided by the McMillan–Mayer (MM) theory.[60] According to MM theory, the osmotic virial series for a non-ideal solution can be expressed as,

$$\Pi = (1 + B^{tot}_2 c + \ldots)cRT \qquad (5)$$

where c is the concentration of dissociated ionic species and B^{tot}_2 is the second osmotic coefficient. The latter is related to the effective inter-particle potential *via*,

$$B^{tot}_2 = -\frac{1}{2}\sum_{ij}\int d\mathbf{r}\left[e^{-W_{ij}(r)/k_BT} - 1\right] \qquad (6)$$

where $W_{ij}(r)$ is the PMF between ion i and j (the indices run over the cation and anion). The osmotic virial coefficient B^{tot}_2 is, thus, directly related to the Na–Cl, Na–Na and Cl–Cl inter-ionic PMFs. Long-range ionic screening is ignored in this discussion focused on the direct ion–ion PMF. The running integrals for the second

osmotic coefficient B_2^{tot} are shown in Fig. 4 for a few different models. It is observed that the coefficient B_2^{tot} determined from the default model based on the LJ parameters determined from the combination rule is extremely large, with an estimated value at a distance of 6.5 Å of -420 Å^3. In contrast, the second osmotic coefficient B_2^{tot} for the two optimized models remain much smaller. Their estimated value at a distance of 6.5 Å the running integral for the model with an optimized pair-specific LJ parameters (NBFIX) yields -74 Å^3, and the model with the optimized cation–anion Thole shielding yields -54 Å^3 (Fig. 4(b)). It is interesting to note that the Na–Cl contribution from the two optimized models are both very close to the CPMD estimates, further strengthening the present optimized models for NaCl aqueous solutions at finite concentration.

While eqn (6) is truly valid only at low concentration c, it can nevertheless serve as a useful guide to highlight the large opposing contributions that are at play in the electrolyte. An important observation is that the osmotic pressure of the NaCl solution does not markedly deviate from the ideal relation, $\Pi = cRT$ (see Fig. 1(a)). For this reason, it is imperative that the second osmotic coefficient B_2^{tot} in eqn (6) be relatively small. The indirect implication is that the contribution from the cation–anion pair and that from the like-charged ion pairs (Na–Na, Cl–Cl) must almost cancel each other out. The near-ideal behavior of the NaCl aqueous solution implies that
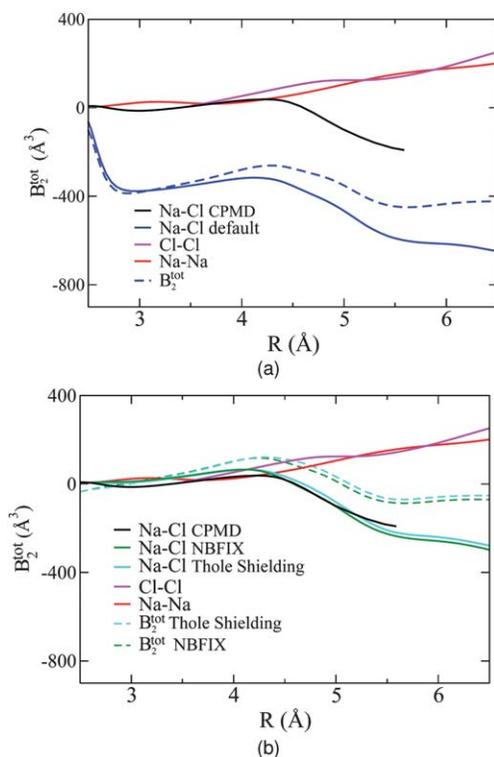
Fig. 4 The second virial coefficient B_2 as a function of ion pair distance. (a) The black line is B_2 from CPMD PMF; the blue solid line is B_2 of Na–Cl ion pairs from LJ combination rule; the blue dashed lines are the sum of B_2 from all ion pairs; the red line is B_2 of Na–Na pairs and the magenta line is B_2 of Cl–Cl pairs, calculated from the radial distribution of like-charged ion pairs in bulk solution (see supplementary material†). (b) The black, red and magenta lines are the same as in (a); the green and cyan solid lines are B_2 coefficients of Na–Cl pairs from LJ nbfix and Thole shielding respectively; the green and cyan dashed lines are the sum of B_2 from all ion pairs from LJ nbfix and Thole shielding respectively.

there is an underlying balance in the Na–Na, Cl–Cl and Na–Cl pairs in this system.
For the present model, the contributions for like-charged ion pairs are on the order
of +200 Å³ and +230 Å³ for Na–Na and Cl–Cl, respectively (these estimates were
obtained from the radial distribution function directly extracted from the unbiased
simulations of the NaCl salt solution; see Supplementary Information†). As the
latter are dominated by the long-range Coulombic repulsion, these values are ex-
pected to be fairly insensitive to the details of the models. Thus, the total contribu-
tion from the like-charge pairs can be used to set an empirical upper-bound on the
Na–Cl contribution. This means in practice that the Na–Cl contribution should not
considerably exceed −430 Å³ to be in agreement with the near-ideal solution exper-
imental osmotic pressure. This shows that the estimated contribution for the Na–Cl
pair of the default model based on the LJ parameters determined from the combina-
tion rule, which amounts roughly to −840 Å³, is clearly much too large due to over-
binding of the cation–anion pair. This cannot be compensated by the opposite
Na-Na and Cl–Cl repulsive contributions, hence resulting in an osmotic pressure
that deviates strongly from an ideal solution. Despite the limitations of the BLYP
density functional theory used in the CPMD simulations,[19] it is comforting to
note the relatively good agreement with the PMF calculated from the optimized
Drude force field that was empirically adjusted to match the osmotic pressure
data. The good accord between the two optimized models, as well as with the
CPMD calculations, is a strong indication that the association of Na⁺ and Cl⁻ in
aqueous solution should be consistent with these 3 different approaches.

4.   Conclusion

The osmotic pressure simulation is used to validate the polarizable classical Drude
oscillator ionic parameters at finite concentrations. The ion models were previously
optimized in conjunction with the polarizable SWM4-NDP water model, to be accu-
rate in the infinite dilution limit.[5] However, there's no guarantee that the model is
accurate at finite concentrations. The osmotic pressure MD simulation method
offers a direct way to measure the thermodynamic properties of electrolyte solution
at a wide range of concentrations, up to the solubility limit. In this study, the osmotic
pressure of NaCl and KCl aqueous solutions are calculated from all-atom MD simu-
lations for a variety of concentrations. It was found that the NaCl parameters under-
estimate the osmotic pressure significantly even at 1 m. Two sets of pair-specific
parameters, electrostatic Thole shielding and the pairwise LJ parameter, are intro-
duced to modify the ion pair potential in order to reproduce the experimental
osmotic pressure for a wide range of concentrations. The fitting procedure is done
carefully and hierarchically, from vacuum pair potentials, single ion pair PMFs in
bulk to the osmotic pressure at finite concentrations. The fitting results show that
the experimental osmotic pressure can be reproduced by either increasing the LJ
radius by 0.15 Å from the default combination rule or by assigning a Thole shielding
factor of 2.10. The PMF profiles of a single ion pair in the bulk and the ion pair
interaction energy in vacuum show that the electrostatic Thole shielding strategy
is able to shift the magnitude of the interaction energy and preserve the position
of the energy-well at the same time, while increasing the pair-specific LJ radius
(R_{min}) pushes the most favorable interaction position further apart in both vacuum
energy and bulk phase PMF profiles. Also, introducing the electrostatic Thole
shielding at short distances seems more reasonable to take into account the lack
of the charge transfer effect between atoms in the Drude polarizable models.

The second virial coefficients B_2^{ij}, which are directly related to the pair interactions,
were also calculated from the ion pair PMF profiles. It is clear that the B_2^{ij} coefficients
from the fitted pair-specific parameters are very close to the CPMD data, and much
smaller than the one from the default Drude model. The sum of the B_2^{ij} coefficients of
Na–Cl, Na–Na and Cl–Cl ion pairs is close to zero with the pair-specific parameters,
but around −400 Å³ with the default Drude parameters. The fact that B_2^{tot} is small

suggests that the non-ideal contributions from the like-charged ion pairs and unlike-charged ion pairs cancelled each other out. It is again consistent with the fact that the osmotic pressure of NaCl solution is very close to the ideal solution.

This work illustrated the important role of the osmotic pressure simulation in validating and calibrating the empirical force field under realistic conditions. Small adjustments of the pair-specific interactions can improve the thermodynamic properties of electrolyte solution at finite concentrations significantly. Relying on the experimental osmotic pressure data to adjust empirically the force field gets around the problems arising from our limited ability to accurately predict these interactions from first principles. It is worth pointing out that the osmotic pressure MD simulation method can be used for a large variety of molecular fragments to validate and adjust the empirical force field for lipids or other biomolecular systems. It offers a novel strategy for advanced parameterization.

Acknowledgements

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