A Kirkwood-Buff derived force field for alkaline earth halide salts

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The activity and function of many macromolecules in cellular environments are coupled with the binding of divalent ions such as calcium or magnesium. In principle, computer simulations can be used to understand the molecular level aspects of how many important macromolecules interact with ions. However, most of the force fields currently available often fail to accurately reproduce the properties of divalent ions in aqueous environments. Here we develop classical non-polarizable force fields for the aqueous alkaline earth metal halides (MX_2), where $M = Mg^{2+}$, Ca^{2+} , Sr^{2+} , Ba^{2+} and $X = Cl^-$, Br^- , I^- , which can be used in bimolecular simulations and which are compatible with the Simple Point Charge/Extended (SPC/E) water model. The force field parameters are specifically developed to reproduce the experimental Kirkwood-Buff integrals for aqueous solutions and thereby the experimental activity derivatives, partial molar volumes, and excess coordination numbers. This ensures that a reasonable balance between ion-ion, ion-water, and water-water distributions is obtained. However, this requires a scaling of the cation to water oxygen interaction strength in order to accurately reproduce the integrals. The scaling factors developed for chloride salts are successfully transferable to the bromide and iodide salts. Use of these new models leads to reasonable diffusion constants and dielectric decrements. However, the performance of the models decreases with increasing salt concentration ($>4m$), and simulations of the pure crystals exhibited unstable behavior. *Published by AIP Publishing.* <https://doi.org/10.1063/1.5019454>

I. INTRODUCTION

Aqueous electrolyte solutions play a very important role in biological systems and in terrestrial and marine geology. Under physiological conditions, divalent ions are involved in many important processes such as nucleic acid and protein folding, the activation of enzymes, and cellular signal transduction.^{1,2} Divalent ions can bind strongly and selectively to biomolecules, leading to crucial structural and functional changes. For example, Mg^{2+} and Ca^{2+} ions act very differently in the context of blood clotting, where only Ca^{2+} ions can act as a cofactor.³ Likewise, magnesium ion channels are able to transport Mg^{2+} ions against a high background concentration of its major competitor, Ca^{2+} ions. The major determinants of Mg^{2+}/Ca^{2+} selectivity in magnesium ion channels are still unknown,⁴ although the degree of metal ion hydration, which correlates with the pore size and rigidity, is argued to be a major factor.⁴ However, any correlation between the size of the ions, their electronegativity, and/or coordination number with the regulation of enzyme activity in the presence of the ions is still not fully understood.⁵

In principle, one can use computer simulations as an atomistic microscope to help experimentalists to interpret and understand, with high spatial and temporal resolution, phenomena that are not accessible through conventional experimental techniques. However, an accurate and realistic

representation of ion solvation in aqueous solution is crucial to achieve this goal. A realistic computational model should accurately capture the relevant microscopic interactions between ions and water molecules. However, it remains non-trivial to achieve the required fine balance between the ion-ion, ion-water, and water-water interactions in a computational model. In particular, it is unclear how to include significant contributions from polarization effects, which may be very important in the case of multivalent metal ions, using conventional (efficient) non-polarizable force fields. For uncharged solutes, the average effect of electronic polarization by neighboring water molecules is often incorporated by simply increasing the dipole moment from the gas phase value.^{6,7} However, this is not an effective strategy for monatomic ions and, in our opinion, is also questionable for neutral molecules.

There are significantly more parameter sets available for monovalent ions compared to divalent.^{8,9} This is due, in part, to the inherent difficulty in modeling higher charged ions and their solvent interactions. The properties of water molecules bound to divalent cations can be drastically different from the bulk water properties.¹⁰ At least two significant issues arise when simulating ions with a high charge density.¹¹ The first is obtaining statistically significant data. To obtain convergence of ion-protein interactions, one may have to use concentrations higher than physiological conditions or employ free energy methods such as umbrella sampling. The second issue is the accuracy of the potentials employed for ions. Many non-polarizable force fields satisfactorily model monovalent ions such as Na^+ and K^+ in simulations. However, force fields developed using

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similar approaches struggle to model divalent and trivalent ions and often overestimate ion-protein and ion-peptide interactions.¹² Employing polarizable force fields,^{13,14} scaling the ion charges (or adjusting the background permittivity),^{6,15–17} and adjusting the ionic radii¹⁸ have all been used as potential strategies to overcome issues simulating high charge ions.

The treatment of Mg^{2+} ions in simulations is particularly problematic. Although Mg^{2+} ions play a very important role in the activity of nucleic acids, Hashem *et al.* reported that, when considering publications up to the year 2008, only 22 out of 113 RNA simulations used Mg^{2+} as one of the ions.¹⁹ This highlights the difficulty of modeling ions with high charge densities and is a major reason Mg^{2+} ions are avoided in RNA simulations. Due to a high charge density, the water molecules bound to Mg^{2+} ions display very long residence times compared to monovalent cations.²⁰ Therefore, many current molecular dynamics (MD) simulations fail to capture the desolvation processes of Mg^{2+} ions.²¹ Furthermore, MD simulations of Mg^{2+} ions with DNA have resulted in considerable artifacts when using the Assisted Model Building with Energy Refinement (AMBER)²² and Chemistry at Harvard Macromolecular Mechanics (CHARMM)²³ force fields.²⁴ Interestingly, the results can be improved by fine tuning the van der Waals interactions parameter for the ions to reproduce experimental salt solution osmotic pressures.²⁴

As reviewed by Auffinger,²⁵ no MD simulations of Ca^{2+} , Sr^{2+} , and Ba^{2+} ions with RNA molecules are available in the literature up to 2012, despite these ions being present in experimental crystallographic structures.²⁶ Many MD simulations have appeared in the literature where the crystallographic biomolecular structure originally contained Ca^{2+} , Sr^{2+} , or Ba^{2+} ions, but these were subsequently replaced with Mg^{2+} ions in the simulations. Alternatively, Mg^{2+} ions are simply ignored or replaced with two monovalent Na^+ ions in many biomolecular MD studies. Although including divalent ions in MD simulations is a challenging task, it is clearly necessary to perform realistic simulations. A recent study shows that the AMBER and CHARMM force fields for Ca^{2+} ions form artificial clusters in MD simulations containing chloride, acetate, and phosphate ions.²⁷ These salt solutions also fail to reproduce experimental osmotic pressures. The same work indicated that Ca^{2+} ions mediated DNA-DNA interactions leading to strong inter-DNA attractions in MD simulations. The net interaction between double strand DNA molecules observed under typical experimental conditions containing monovalent alkaline or divalent alkaline earth ions has been reported to be repulsive.^{28,29} Hence, the failure to capture the correct solvation of Ca^{2+} ions by the standard force fields, leading to an artificial attraction between the Ca^{2+} ions and the phosphate groups in the DNA molecules, was implicated as being directly responsible for the inconsistency of the simulated osmotic pressure. However, there are experimental studies reporting that DNA molecules can display attractive forces in the presence of some transition metal ions (such as manganese, cadmium, cobalt hexamine), high valance cations, or depending on the exact solution conditions such as DNA length, concentration, etc.^{29,30}

Due to the problems modeling the strong solvation shells around Mg^{2+} ions, a refined dummy atom model has also been proposed.³¹ In this model, a single Mg^{2+} ion is represented as an octahedron with a metal at the center carrying a -1.0 charge covalently bound by six dummy atoms possessing a $+0.5$ charge. This approach attempted to optimize the AMBER ff03 force field to obtain better performance for experimental geometries and thermodynamic properties such as the solvation free energy. However, Saxena *et al.* reported that multi-site models of the Ca^{2+} and Mg^{2+} ions in the CHARMM force field overestimate the attraction between the cation and chloride ions resulting in unusual ion-ion pairing and clustering in the MD simulations.^{32,33} This also leads to osmotic pressures for salt solutions that were inconsistent with the experimental results.^{32,33}

The pioneering work of Johan Aqvist highlighted that the solvation free energy of the ions at infinite dilution can be used as a critical property in the parameterization of alkaline and alkaline earth ions.³⁴ Most of the commonly used ion force field parameters are typically optimized using single ion properties and the experimental data for the crystalline state. Hence, they cannot necessarily reproduce experimental thermodynamic properties at finite concentrations.^{34–37} Luo and Roux reported that the thermodynamic stability of concentrated salt solutions depends sensitively on ion pairing propensity.¹⁸ This study also demonstrated that using gas phase derived ion pair distances fails to reproduce the experimental osmotic pressures at high concentrations for both NaCl and KCl salt solutions. However, breaking the standard combination rules by fine tuning ion pair distances appeared to be a way to solve this problem. Mamatkulov *et al.* reported that widely used divalent ion force field parameters can only reproduce the experimental solvation free energy, and the first peak of water ion radial distribution function, with reasonable accuracy at low salt concentrations.³⁷ Furthermore, this study emphasized the necessity of improving existing divalent ion parameters as none of the widely used force fields, such as AMBER,²² CHARMM,²³ or Groningen Molecular Simulation (GROMOS),³⁸ are capable of describing the ion specific effect of divalent cations in ion channels.

Therefore, there is a clear desire to develop a force field for the alkaline earth ions that can reproduce the correct activities, osmotic pressures and solvation properties in aqueous solutions at finite concentrations. Any new force field has to be able to capture the fine balance between ion-ion, ion-water, and water-water interactions. The Kirkwood-Buff (KB) theory of solutions has been used successfully to generate models for the alkali halides that provide the correct thermodynamic and solvation properties in MD simulations.^{8,9} The models are termed Kirkwood-Buff derived force fields (KBFFs) and were developed to reproduce the experimental KB integrals (KBIs) and thereby the solution activities, as a function of salt concentration. This represents a rigorous approach that quantifies the solute-solute, solute-solvent, and solvent-solvent distributions and can thereby evaluate the ability of a force field to reproduce the distributions, implying some degree of confidence in the underlying interactions. Furthermore, the models can reasonably reproduce other experimental properties such as diffusion constants, dielectric decrements, and excess heats of mixing.

In doing so, we essentially ignore single ion (infinitely dilute) properties, such as free energies of solvation, in favor of reproducing the finite concentration behavior of the solutions. The same approach used to parameterize the alkali halide models is used here to develop parameters for the alkaline earth halides that are compatible with the existing KBFF models. We provide parameters for the alkaline earth metal halides (MX_2), where $\text{M} = \text{Mg}^{2+}$, Ca^{2+} , Sr^{2+} , Ba^{2+} and $\text{X} = \text{Cl}^-$, Br^- , I^- , for future use in biomolecular simulations. We have avoided the Be^{2+} and Ra^{2+} ions in this parametrization as these ions are not common in biological systems. Furthermore, the fluoride salts were not studied as they are mostly insoluble.

II. EXPERIMENTAL ANALYSIS AND MD SIMULATIONS

A. Experimental KB inversion analysis

The KB theory provides a link between the thermodynamic properties of a solution mixture and the underlying molecular distributions.³⁹ Molecular distributions are easily obtained from a simulation. These distributions can be used, via the equations of the KB theory, to provide several thermodynamic properties of the mixture. The properties can then be compared with experimental data to determine the quality of the model. Alternatively, one can extract information concerning the molecular distributions from the appropriate experimental thermodynamic data and compare directly with simulations. This is the KB inversion approach.⁴⁰

At the heart of the KB theory are the KB integrals (KBIs) defined by

$$G_{ij} \equiv 4\pi \int_0^\infty [g_{ij}(r) - 1] r^2 dr, \quad (1)$$

where $g_{ij}(r)$ is the center of mass based pair correlation function between species i, j , and r is the intermolecular separation. The KB integrals (G_{ij}) quantify the solute-solute, solute-solvent, and solvent-solvent distributions in a solution. Three types of KB integrals (G_{cc} , G_{ww} , $G_{cw} = G_{wc}$) are sufficient to describe all the relevant distributions in a binary solution consisting of water (w) and an ionic cosolvent (c). For salts, the cations and anions are treated as indistinguishable in this type of approach.^{8,41} The three KB integrals, together with the corresponding number densities (ρ_c and ρ_w), are used to determine several different thermodynamic quantities. In addition, the KB inversion procedure was used—together with the composition dependent experimental data for the isothermal compressibility, the partial molar volumes, and the cosolvent activity—in order to extract the corresponding three experimental KB integrals.^{40,42} The relationships between the KBIs and the experimental data required for this study are given by⁴²

$$\begin{aligned} 1 + N_{cc} &= \rho_c RT \kappa_T + \rho_w^2 \frac{\bar{V}_w^2}{\mu_{cc}}, \\ 1 + N_{ww} &= \rho_w RT \kappa_T + \rho_w \rho_c \frac{\bar{V}_c^2}{\mu_{cc}}, \\ N_{wc} &= \rho_c RT \kappa_T + \rho_w \rho_c \frac{\bar{V}_w \bar{V}_c}{\mu_{cc}}, \end{aligned} \quad (2)$$

where $N_{ij} \equiv \rho_j G_{ij}$ is the excess coordination number, R is the gas constant, T is the absolute temperature, κ_T is the isothermal compressibility, $\bar{V}_i$ is the partial molar volume of species i , and μ_{cc} is a chemical potential derivative defined by

$$\mu_{cc} \equiv \frac{1}{RT} \left(\frac{\partial \mu_c}{\partial \ln m_c} \right)_{T,p} = 1 + \left(\frac{\partial \ln \gamma_c}{\partial \ln m_c} \right)_{T,p}, \quad (3)$$

where γ_c is the mean molal activity coefficient of the salt and m_c is the ion molality of the salt. The ion molality is related to the traditional salt molality (m_s) by $m_c = \nu m_s$, where ν is the total number of ions in the formula unit.

The experimental activity coefficients and densities for alkaline earth metal halides solutions (MX_2), with $\text{M} = \text{Mg}^{2+}$, Ca^{2+} , Sr^{2+} , Ba^{2+} and $\text{X} = \text{Cl}^-$, Br^- , I^- , were obtained from the literature.^{43,44} The experimental activity derivatives were then fitted to the Pitzer equation.^{45,46} For a single electrolyte, $M_{v+} X_{v-}$, the Pitzer equation is given by⁴⁷

$$\ln \gamma_c = |q_+ q_-| f^\gamma + m_s \left(\frac{2\nu_+ \nu_-}{\nu} \right) B^\gamma + m_s^2 \left(\frac{2(\nu_+ \nu_-)^{3/2}}{\nu} \right) \frac{3C^\phi}{2}, \quad (4)$$

where

$$\begin{aligned} f^\gamma &= -A_\phi \left[\frac{\sqrt{I/m^0}}{1 + b\sqrt{I/m^0}} + \frac{2}{b} \ln(1 + b\sqrt{I/m^0}) \right], \\ B^\gamma &= 2\beta^{(0)} + \frac{2\beta^{(1)}}{\alpha^2 I/m^0} \left[1 - \exp(-\alpha\sqrt{I/m^0}) \right] \\ &\quad \times \left(1 + \alpha\sqrt{I/m^0} - \frac{1}{2}\alpha^2 I/m^0 \right), \end{aligned} \quad (5)$$

with

$$\begin{aligned} A_\phi &= \frac{\sqrt{2\pi N_A d_0}}{3} \left(\frac{e^2}{4\pi \epsilon_0 D k_B T} \right)^{3/2}, \\ I &= \frac{1}{2} \sum_{i=1}^{\nu} m_i q_i^2. \end{aligned} \quad (6)$$

Here, I is the ionic strength on the molality scale, q is the formal charge, $\nu = \nu_+ + \nu_-$, $m^0 = 1 \text{ mol kg}^{-1}$ is the standard molality, while N_A , d_0 , e , D , k_B , and ϵ_0 are the Avogadro number, the density of the pure solvent, the charge on an electron, the dielectric constant, the Boltzmann constant, and the vacuum permittivity, respectively. Using values of $\alpha = 2 \text{ (kg/mol)}^{1/2}$ and $b = 1.2 \text{ (kg/mol)}^{1/2}$, the remaining parameters, $\beta^{(0)}$, $\beta^{(1)}$, and C^ϕ , were used to fit the experimental activity data using the Pitzer equation. The activity derivatives required for Eqs. (2) and (3) were then obtained directly from Eq. (4).

The experimental partial molar volumes were obtained from the experimental densities using previously established standard approaches.^{39,43} The experimental compressibility of the salt solution was assumed to follow

$$\kappa_T = \phi_w \kappa_{T,w}^0 + \phi_c \kappa_{T,c}^0 = \phi_w \kappa_{T,w}^0, \quad (7)$$

where $\kappa_{T,i}^0$ is the compressibility of pure species i and ϕ_i is the volume fraction of that species. The compressibility of pure water was taken to be $4.6 \times 10^{-5} \text{ bar}^{-1}$,⁴⁸ while the compressibility of salt crystals was taken to be zero. More details concerning the KB inversion procedure, and how to obtain the KBIs using experimental data, are provided in our earlier studies.^{8,9,49}

B. Parameterization of the alkaline earth metal ions

The solutions studied here are composed of just ions and water molecules. The compatible water model for the KBFF force field is considered to be the Simple Point Charge/Enhanced (SPC/E) model.⁵⁰ Since KBFF parameters for Cl^- , Br^- , and I^- have already been developed,⁹ we only need to parameterize the metal cations in the present work. As the ions considered here are monatomic species, and the water model is rigid, only the non-bonded interactions contribute to the potential energy of a given system via the usual Coulomb and Lennard-Jones (LJ) potentials for the electrostatic and van der Waals interactions, respectively,

$$E_{elec} = \frac{1}{4\pi\epsilon_0} \sum_{i<j} \frac{q_i q_j}{r_{ij}},$$

$$E_{VDW} = \sum_{i<j} 4\epsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]. \quad (8)$$

Hence, only 3 parameters, the charge of the ion (q), the Lennard-Jones interaction length (σ), and the interaction strength (ϵ), are required to model an ion in this type of simple, but common, force field. Since the charge of an ion is fixed, just two adjustable parameters, σ and ϵ , for each ion are required in the KBFF models. In our previous study of alkali metal salts, we observed that the experimental KBIs could not be reproduced by adhering to the usual combination rules for ϵ ,⁹ and we rationalized this in terms of strong polarization effects that are difficult to capture in non-polarizable force fields. Fortunately, a simple scaling of the cation-water ϵ parameter provided a significant improvement in the agreement between simulated and experimental KBIs. Hence, we have adopted the same approach here.^{8,9}

Geometric combination rules were used for both the σ and ϵ parameters. The cation-water oxygen (+o) interaction strength was then modified using a simple scaling factor such that

$$\epsilon_{+o} = s\sqrt{\epsilon_{++}\epsilon_{oo}}, \quad (9)$$

where s is the cation specific scaling factor and is >0 . It should be noted that this strategy not only changes the ion-water interaction well depth but also modifies the repulsive

wall of the LJ potential. A value of $0 < s < 1$ allows water molecules to approach closer to the cation, thereby increasing the degree of solvation. This represents a simple modification to account for strong polarization effects close to the cations.

In the first step of the parameterization process, two pieces of experimental data were used to determine the σ and ϵ parameters for the alkaline earth metal cations. These were the ionic radii consistent with the crystal lattice unit dimensions and the experimental ion-water contact distances.^{51,52} A set of crystal structure and aqueous salt solution MD simulations were performed (see Sec. IIC). The values of ϵ_{++} and σ_{++} were then varied to obtain the correct experimental lattice dimensions and water-cation contact distances for 1 M aqueous metal chloride salt solutions. The cation-water interaction strength was then further scaled by different s factors in an attempt to reproduce the experimental KBIs, while maintaining a reasonable cation-water contact distance. After some iteration, a set of parameters producing the best agreement with the experimental data were obtained and are displayed in Table I. Once the scaling factors were established for the alkaline earth metal chlorides, a series of simulations were performed to analyze the ability of the scaling factors to model the corresponding bromide and iodide salts.

C. MD simulation and analysis details

Classical MD simulations were performed using version 4.6 of the GROMACS software,⁵³ using the SPC/E water model.⁵⁰ All simulated systems were maintained in the isothermal isobaric ensemble at 300 K temperature and 1 bar pressure using the Berendsen pressure and temperature coupling approaches.⁵⁴ Here, the temperature and pressure are weakly coupled to a bath with relaxation times of 0.1 ps and 0.5 ps, respectively. A 2 fs time step was used to integrate the equations of motion, and all bonds were constrained with the SETTLE algorithm.⁵⁵ The particle mesh Ewald (PME) approach was used to model electrostatic interactions with a 1.0 nm cutoff distance for real space calculations⁵⁶ and a 1.5 nm cutoff distance for the van der Waals interactions. All the simulations were performed in ≈ 10 nm length cubic boxes. A random initial configuration of ions and water molecules was generated at a fixed target molality for each salt

TABLE I. Lennard-Jones parameters (σ and ϵ), scaling factors (s), and atomic charges (q) for aqueous alkaline earth salt solutions for the KBFF models. Geometric combination rules are used for σ and ϵ , while ϵ_{+o} was scaled according to Eq. (9). The water model corresponds to the SPC/E model.

Model	Atom	σ_{ii} (nm)	ϵ_{ii} (kJ/mol)	ϵ_{+o} (kJ/mol)	s	q lel	References
KBFF	Mg^{2+}	0.2100	0.7500	0.0699	0.1	2	
	Ca^{2+}	0.2900	0.4700	0.3871	0.7	2	
	Sr^{2+}	0.3100	0.5000	0.5704	1.0	2	
	Ba^{2+}	0.3800	0.2000	0.4329	1.2	2	
	Cl^-	0.4400	0.4700			-1	8
	Br^-	0.4760	0.3000			-1	9
	I^-	0.5350	0.2000			-1	9
SPC/E	O	0.3166	0.6506			-0.8476	50
	H	0.0000	0.0000			0.4238	50

simulation. Energy minimization using the steepest descent method was performed followed by 2 ns of equilibration before the production run. Production runs of 15 ns were used to calculate ensemble averages from configurations saved every 0.1 ps.

Anisotropic MD simulations of all the salt crystals were performed at 300 K and 1 bar where only the crystal x , y , and z box lengths could vary (the unit cell angles were fixed). Roughly 5 nm length crystals were generated using the unit cell dimensions and symmetry group operations provided by the crystallography open database.⁵² Unfortunately, the MgCl_2 , MgBr_2 , MgI_2 , and CaI_2 crystals, which have non-orthogonal crystal structures (angles of 90° , 90° , 120°), were not stable in the MD simulations (the densities decreased by 20% or so and significant mixing of the ions occurred). Therefore, orthogonal crystals (90° , 90° , 90°) of these salts were also simulated and used for an approximate analysis of the heats of mixing.

Center of mass radial distribution functions were determined and used to calculate the corresponding KBIs by averaging the integral values in Eq. (1) between 1.5 and 2.0 nm. For some of the systems, the accuracy of the KBI values was verified by calculating the integrals using the equivalent particle fluctuation approach (results not shown).⁵⁷ No significant differences were observed. The simulated KBIs were then used to calculate the activity derivatives, excess coordination numbers, and partial molar volumes. Translational self-diffusion coefficients were calculated using the mean square fluctuation approach and no system size corrections were applied.^{58,59} Dielectric coefficients were calculated by a dipole fluctuation analysis.^{60,61} The enthalpy of mixing was determined from the average potential energies of a molecule in the solution compared with those of the pure salt crystal and pure water. Mean residence times for waters and anions around each cation were also calculated using a time correlation function approach.⁶²

III. RESULTS AND DISCUSSION

Many of the widely used force fields for biomolecular simulations fail to reproduce the experimental KB integrals in computer simulations.^{8,49,63} As an example, the results for CaCl_2 salt solutions using a variety of force fields are displayed in Fig. 1. While all the force fields, except for CHARMM, performed well at high (4m) salt concentrations, the results differ at low salt concentrations. In particular, large deviations between the G_{cc} values were observed and imply that the ion-ion distribution is not correctly captured by the force fields, with one force field providing the wrong sign. Hence, the balance between the ion-ion, ion-water, and water-water interactions is incorrect. The KBFF models attempt to fix this issue using the KBIs as a guide. We note that, while this manuscript was under review, a new CHARMM version was reported to be capable of reproducing experimental osmotic pressures over a wide range of CaCl_2 concentrations (after tuning of the LJ parameters).⁶⁴

The experimental excess coordination numbers for the aqueous magnesium halides and aqueous metal chloride solutions are displayed in Fig. 2. This is the primary data used in

FIG. 1. Comparison of the experimental and simulated KBIs for aqueous CaCl_2 salt solutions using four different force fields (KBFF,⁶⁵ AMBER99,⁶⁵ CHARMM27,⁶⁶ and OPLSAA⁶⁷) at 300 K. The KBFF simulations were performed with the SPC/E water model, while all other force fields used the TIP3P water model. Lines correspond to the KB analysis of the experimental data (see the text), and the symbols represent the simulations.

the current parametrization process. The data show systematic trends between different salts at low to medium concentrations that provide information concerning the underlying molecular distributions. Positive values for the excess coordination numbers indicate a net overall attraction between the two species, while negative numbers indicate a net overall repulsion. The positive values for the ion-ion excess coordination numbers (N_{cc}) at low concentrations arise from the Debye-Huckel limiting behavior. However, the ion-ion excess coordination numbers decrease for moderate salt concentrations, and the changes depend upon the particular salt. The experimental data indicate that the overall ion-ion distribution becomes less attractive as one increases the anion or cation size. This is accompanied by a corresponding decrease in the ion-water distribution and an increase in the water-water distribution.

The radial distribution functions (rdfs) obtained from simulations of 1m magnesium halide solutions using the KBFF models are displayed in Fig. 3, with the results for 1m alkaline earth chloride solutions shown in Fig. 4. The rdfs and corresponding coordination numbers for all salts are provided in the [supplementary material](#). As expected, the cation-anion rdfs display a gradual increase in the excluded volume as the size of the anion increases. The water-water and the cation-water distributions, and the corresponding first shell coordination numbers, are not significantly affected by changing the anion from chloride to bromide or iodide, even at high concentrations (see [supplementary material](#)). In addition, the number of water molecules directly interacting with an anion is independent of the cation. The cation-anion rdfs display several peaks. A peak arising from the contact ion pair is not present for the Mg^{2+} ion; rather, the first peak corresponds to a solvent-separated ion pair. An experimental study published in 2010 reported that, even at high concentrations (4.7m), there is no clear spectroscopic evidence to claim the occurrence of contact ion pairs in aqueous MgCl_2 solutions.⁶⁸ The simplest reason for this behavior is the high charge density on the metal that leads to a number of strongly bound water molecules surrounding the

FIG. 2. Experimental excess coordination numbers for aqueous alkaline earth halide salt solutions as a function of salt molality at 298 K and 1 atm.

Mg^{2+} ion that simply cannot be substituted for an anion. The Ca^{2+} salts displayed a small peak for the contact ion pair, while for Sr^{2+} and Ba^{2+} ions the contact ion pairs are more prominent. However, all the cations display sizeable peaks corresponding to solvent separated ion pairs. The cation-water distribution is affected when the size of the cation increases, leading to a lower degree of solvation.

All the rdfs converged to unity beyond 1 nm. The first shell coordination numbers, the distance to the first rdf maximum (contact distance), and the distance to the first rdf minimum (first solvation shell) were calculated from the corresponding rdfs and are provided in the [supplementary material](#). As expected, the hydration shells increase as the cation or anion size increases. The coordination numbers are relatively insensitive to the concentration of the salt solutions. The higher concentrations increase the degree of ion pair formation. However, no strong (excessive) aggregation or crystallization was observed in the simulations.

Several X-ray diffraction studies have shown that the magnesium to water oxygen contact distance is about 0.209 nm and the average metal coordination number is 6.^{51,69,70} In the present study, the magnesium to water contact distance is 0.185 nm and the coordination number is 5.9. A slightly smaller contact distance was required to help reproduce the KBIs. The coordination number is also consistent with many other MD simulations reported in the literature.^{71–73} The experimental ion to water oxygen distance for the second hydration shell is reported as 0.413 nm, compared to 0.406 nm in the present study.⁷⁴

The calcium ion to water distance is 0.245 nm and the coordination number is 7.8 in the present study. For comparison, the water coordination number around the Ca^{2+} ions was reported as 7.3 in a MD simulation using a polarizable potential.^{71,72} The neutron spectroscopic studies have reported the calcium ion to water oxygen distance as 0.24 nm.^{70,71} However, the coordination number can vary between 7 and 10

FIG. 3. Radial distribution functions as a function of distance (nm) obtained from simulations of 1m magnesium halide salt solutions at 300 K. The cation, anion, and the water oxygen are denoted by +, -, and O, respectively.

FIG. 4. Radial distribution functions as a function of distance (nm) obtained from simulations of 1M alkaline earth metal chloride salt solutions at 300 K. The cation, anion, and the water oxygen are denoted by +, -, and O, respectively.

depending on the studies.^{51,70,73,75,76} The experimental second hydration shell distance for the calcium ion was reported to be 0.450–0.460 nm,^{70,71} compared to 0.466 nm in this study. A X-ray absorption fine structure (XAFS) spectroscopic study of a 6M calcium chloride solution found that the coordination number is 7.2 and the cation to water contact distance is 0.244 nm.⁷⁷ Furthermore, this study claims that there is no evidence for the formation of a significant number of the ion pairs at high concentrations and that solvent separated ion pairs, rather than contact ion pairs, are responsible for the unusual (high solubility) thermodynamic behavior of CaCl_2 solutions. Another experimental study of 6M CaCl_2 solutions reported a value of 0.26 for the coordination number of contact ion pairs at a distance of 0.271 nm and a coordination number of 3.4 for solvent separated ion pairs at a distance of 0.498 nm.⁷⁸ The values reported for CaCl_2 ion pairs in the [supplementary material](#) suggest a very small peak at 0.285 nm for the ion pair and a prominent peak at 0.485 nm for the solvent separated ion pair.

A molecular dynamics simulation study of the solvation of Mg^{2+} and Ca^{2+} ions using polarizable atomic multipole potentials reported that divalent ions perturb the structure and the dipole moment of the first solvation shell of water molecules.⁷² This study also indicated that the structure of the first solvation shell is enhanced compared to that of the surrounding monovalent ions. Average coordination numbers for Mg^{2+} and Ca^{2+} ions of 6 and 7.3, respectively, were reported at infinite dilution.⁷² The present MD study supports this claim, as reflected by the sharp first peak and the prominent separation between the first and second peaks in the +/-O rdfs.

In the current MD simulations, the strontium ion to water contact distance is 0.256 nm and the coordination numbers are close to 8 for both 1M and 2M concentrations. X-ray diffraction, neutron scattering, and other spectroscopic studies have reported the strontium ion to water oxygen distance in the range of 0.256–0.269 nm and a coordination number in the range of 6.7–10.3.^{51,70,79–81} An experimental and MD simulation study performed using X-ray adsorption near edge structure

FIG. 5. Excess coordination numbers as a function of magnesium halide salt molality at 300 K. The lines are obtained from the experimental KBI analysis. The symbols are from simulations performed using the KBFF models.

FIG. 6. Excess coordination numbers as a function of alkaline earth metal chloride salt molality at 300 K. The lines are obtained from experimental KBI analysis. The symbols are from simulations performed using the KBFF models.

(XANES) spectroscopy reported that the strontium ion to water oxygen distance is 0.26 nm and the coordination number is 8 at 3.5m.⁸² The study also reported that the hydration shells of the Sr^{2+} ion seem to be flexible in nature with a fast ligand exchange rate between the first and second hydration shells. The second hydration shell distance of the strontium ion and the water molecule was reported to be 0.494 nm,⁷⁰ compared to the current value of 0.475 nm.

The barium ion to water distance is reported as 0.29 nm with a coordination number of 9.5 in several experimental studies.^{51,70} In the present study, the barium ion to water contact distance is 0.285 and the coordination number is close to 8. We conclude that the present simulations provide very reasonable values for the first shell structure and coordination numbers for the alkaline earth cations.

The simulated and experimental excess coordination numbers are displayed in Fig. 5 for magnesium halide solutions and in Fig. 6 for the alkaline earth chloride solutions. The excess coordination numbers for the other calcium halides,

the strontium halides, and the barium halides are provided in the [supplementary material](#). The KBFF models quantitatively reproduce the experimental data indicating that the parametrization procedure was successful. The only possible exception is the result for MgCl_2 solutions at high (6m) concentrations. The correct trends are reproduced in all the alkaline earth halide salt solutions. As displayed in Fig. 5, the ion-ion interactions are less affected compared to the ion-water interactions when the halide ion is changed for a given alkaline earth metal ion, which is in agreement with the experimental data. This suggests that changes in the ion-water and water-water distributions determine the solution behavior to a large extent, as discussed in our earlier publication of alkali halide solutions.⁹ The transferability of LJ parameters and scaling factors from the magnesium chloride salts to the corresponding bromides and iodides appears to be successful.

Our major aim in developing the KBFF models is to reproduce the experimental KBIs, thereby ensuring a reasonable

FIG. 7. Activity derivatives for magnesium halide salts as a function of salt molality at 300 K. Lines are obtained from the KB analysis of the experimental data, and the symbols are for the KBFF models.

FIG. 8. Activity derivatives for alkaline earth metal chloride salts as a function of salt molality at 300 K. Lines are obtained from the KB analysis of the experimental data, and the symbols are for the KBFF models.

balance between the ion-ion, ion-water, and water-water distributions and (presumably) their interactions. Of course, since the KBIs are an integral over the pair distribution function (or rdf), it is possible that many distributions could result in the same value for the integral, rendering our parameter set non-unique. While this is a theoretical possibility, because the charges on these ions are not free to vary and because reasonable values for the sizes of the cations are known, we believe that the number of possible parameter sets that reproduce the integrals subject to these additional constraints is quite limited for these types of systems. Indeed, we often struggle to find a single satisfactory parameter set, rather than have to choose between multiple equally satisfactory sets.

One of the more important properties of a salt solution is the activity. Unfortunately, the KB theory does not provide activities (chemical potentials). It does, however, provide concentration derivatives of the salt activity (a_c). In our previous work, we have focused on the derivatives of the solute chemical potential with respect to the number density (molarity) as

defined by

$$a_{cc} \equiv \frac{1}{RT} \left(\frac{\partial \mu_c}{\partial \ln \rho_c} \right)_{T,p} = \left(\frac{\partial \ln a_c}{\partial \ln \rho_c} \right)_{T,p} = \frac{1}{1 + \rho_c (G_{cc} - G_{cw})}. \quad (10)$$

A comparison of the simulated and experimental activity derivatives are displayed in Figs. 7 and 8. The activity coefficient derivatives for calcium halides, strontium halides, and barium halides are displayed in the [supplementary material](#). The KBFF models can reproduce the correct experimental activity derivatives, and thereby the correct activities. However, at higher concentrations, the simulated activity derivative for magnesium halides deviated from the experimental values, and the statistical noise for calcium chloride at high concentrations was such that a firm conclusion concerning the quality of the model in this region is difficult. The results for the calcium, strontium, and barium halides are in excellent agreement with the experimental data (see the [supplementary material](#)). It should be noted that many force fields for

FIG. 9. Partial molar volumes ($\text{cm}^3 \text{mol}^{-1}$) of the salt (black) and water (red) for magnesium halide salts as a function of salt molality at 300 K. Lines represent the experimental data, and the symbols are for the KBFF models.

FIG. 10. Partial molar volumes ($\text{cm}^3 \text{mol}^{-1}$) of the salt (black) and water (red) for alkaline earth metal chloride salts as a function of salt molality at 300 K. Lines represent the experimental data, and the symbols are for the KBFF models.

alkaline earth ions fail to reproduce the correct thermodynamic properties.³⁷

The simulated and experimental partial molar volumes of the salts and water as a function of concentration for the magnesium halide salts and alkaline earth metal chloride salts are displayed in Figs. 9 and 10. The simulated and experimental partial molar volumes and densities for calcium halides, strontium halides, and barium halides are provided in the [supplementary material](#). The simulated values follow the experimental trends with an increase in the salt concentration resulting in an increase of the partial molar volume of the salt, with a slight decrease in the partial molar volume of the water. Magnesium iodide at low concentrations displayed anomalous behavior. The partial molar volumes of the ions are clearly related to the LJ σ parameter for the cations. One could improve the agreement with experiment for the partial molar volumes, and thereby the density, by adjusting these values. However, one then has to sacrifice agreement with experiment

for the cation-water contact distance. We have chosen to prioritize the contact distance in this study. It should be noted that the density data used to determine the partial molar volumes were scarce for low salt ($<0.5\text{m}$) concentrations. Hence, the salt partial molar volumes do not follow the expected trends in this region. The data for the higher concentrations considered here are, however, in agreement with previous studies.⁸³

The excess coordination numbers and activity derivatives were used in the parameterization process for the KBFF models. Hence, the agreement with experiment for these properties is, to some degree, expected. Therefore, some properties of salt solutions that were not used in the parametrization process—namely, the self-diffusion coefficient, dielectric constant, heats of mixing, and water residence times—have also been investigated in this study. The self-diffusion coefficients are displayed in Figs. 11 and 12. The simulated and experimental self-diffusion coefficients for calcium halides, strontium

FIG. 11. Ion and water self diffusion constants ($10^{-9} \text{m}^2 \text{s}^{-1}$) for magnesium halide salts as a function of salt molality at 300 K. The lines represent the experimental diffusion constant data,⁸⁶ and the symbols correspond to the KBFF models.

FIG. 12. Ion and water self diffusion constants ($10^{-9} \text{ m}^2 \text{ s}^{-1}$) for alkaline earth metal chloride salts as a function of salt molality at 300 K. The lines represent the experimental diffusion constant data,⁸⁶ and the symbols correspond to the KBFF models.

halides, and barium halides are displayed in the [supplementary material](#). In all cases, an increase in the salt concentration lowers the self-diffusion coefficient of the cation, anion, and water molecules. As reported in the experimental studies, the self-diffusion coefficients of alkaline earth cations are independent of the molar mass.⁸⁴ Furthermore, the self-diffusion coefficients of the halide ions also do not display any correlation with the size of the ion. These trends appear to be correctly reproduced in the MD simulations, with almost quantitative agreement for the cations in many cases. In the present study, the diffusion constants of the halide ions were slightly underestimated in the simulations. The halide parameters used in this study are taken from our previous work for alkali halides, which also displayed the same trend.⁹ Therefore, the parameterization of halide ions to reproduce reasonable diffusion coefficients for both alkali halides and alkaline earth halides appears to be a challenging task. A previous MD study of ions using a polarizable force field reported the self-diffusion coefficients for Mg^{2+} and Ca^{2+} ions at infinite dilution of 0.3 and

$0.8 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$, respectively, which is too low for Mg^{2+} , but in good agreement with experiment for Ca^{2+} .⁷² Other non-polarizable force field studies have reported lower self-diffusion coefficients at infinite dilution for Mg^{2+} and Ca^{2+} ions.⁸⁵ In comparison, the KBFF models appear to agree (on extrapolation) with the experimental values of 0.71 and $0.79 \times 10^{-9} \text{ m}^2 \text{ s}^{-1}$ for Mg^{2+} and Ca^{2+} ions at infinite dilution, respectively.⁸⁶

The dielectric decrements for the magnesium halide salts and for the alkaline earth metal chloride salts as a function of salt concentration are provided in Figs. 13 and 14. The simulated and experimental dielectric decrements for calcium halides, strontium halides, and barium halides are provided in the [supplementary material](#). Note that ϵ_0 refers to the dielectric constant of pure water and not the vacuum permittivity. The dielectric constant for the SPC/E water model is 63 and is significantly lower than the experimental dielectric constant of pure water which is 78.⁸⁸ Therefore, it is more convenient to use the dielectric decrements, instead of the absolute

FIG. 13. Dielectric decrements ($\epsilon - \epsilon_0$) for the magnesium halide salts as a function of salt molality at 300 K. Lines are for the experimental data,⁸⁷ and the symbols are for the KBFF models.

FIG. 14. Dielectric decrements ($\epsilon - \epsilon_0$) for the alkaline earth metal chloride salts as a function of salt molality at 300 K. Lines are for the experimental data,⁸⁷ and the symbols are for the KBFF models.

dielectric constants, to compare the experimental and simulated results for salts. All salts resulted in a decrease in the dielectric constant with increasing salt concentration. This is due to the presence of the ions restricting the rotational and collective motion of the water molecules. At low concentrations, this decrease was in quantitative agreement with the available experimental data. However, at higher concentrations, the simulated values appear to overestimate the experimental dielectric decrement values.

The excess enthalpies of mixing were also determined in this study. The enthalpies are sensitive measures of the mixing thermodynamics. However, we could not find the corresponding experimental excess enthalpies of mixing for alkaline earth metal halides at finite concentrations. Infinite dilution enthalpies are available⁸⁹ but are statistically challenging to determine from simulations. Therefore, the excess enthalpies are only reported in the [supplementary material](#). All the alkaline earth halide salts displayed a favorable excess enthalpy of mixing in the MD simulations. However, these values will be affected by the crystal lattice energy which is problematic for the current models (see below).

We have also simulated a variety of salt crystal structures. Unfortunately, all the non-orthogonal crystal forms were unstable during our simulations. It is unclear, and beyond the scope of the present study, why the current models performed poorly for these structures. This could be a general problem simulating ionic crystals with simple LJ plus Coulomb models, although our previous study of alkali halide salt crystals resulted in no such problems.^{8,9} For comparison, we have also simulated the orthogonal crystal structures for MgCl_2 , MgBr_2 , MgI_2 , and CaI_2 despite the non-orthogonal (90° , 90° , 120°) crystal forms being observed experimentally. The crystal simulation potential energies per molecule, densities, and unit cell dimensions are compared to the experimental values in the [supplementary material](#). It appears that the KBFF models would not be a good choice for crystal or solubility studies.

As outlined in the Introduction, the strong solvation shells appearing around alkaline earth cations can lead to problems

when simulating these systems. To investigate the nature of the ion solvation in more detail, we have determined the mean residence time of waters and anions around alkaline earth cations using a time correlation function approach fitted to a simple exponential model.⁶² The values for all salts and salt concentrations are provided in Table II. It is interesting to note that the MgI_2 water mean residence time decreases as the salt concentration increases, whereas the residence time increases with increasing salt concentration for all other systems studied here. However, it is difficult to explain this result. Here, we focus on the infinitely dilute salt water residence times. A single salt molecule of each alkaline earth chloride was simulated in

TABLE II. Simulated water and anion residence times (ps) around the cation in MX_2 salt solutions at 300 K. ND: Not determined (no single exponential decay observed).

m_s	Water			Anion		
	MgCl_2	MgBr_2	MgI_2	MgCl_2	MgBr_2	MgI_2
1	1158	1102	1106	...	...	...
2	1227	1176	1026	...	...	...
4	1443	1236	960	...	...	...
6	1768	...	...	...	...	...
m_s	Water			Anion		
	CaCl_2	CaBr_2	CaI_2	CaCl_2	CaBr_2	CaI_2
1	256	263	242	66	47	7
2	278	280	263	99	47	13
4	391	369	...	264	ND	...
6	685	609	...	956	ND	...
m_s	Water			Anion		
	SrCl_2	SrBr_2	SrI_2	SrCl_2	SrBr_2	SrI_2
1	318	318	309	464	217	29
2	370	367	379	501	258	50
m_s	Water			Anion		
	BaCl_2	BaBr_2	BaI_2	BaCl_2	BaBr_2	BaI_2
1	151	151	157	274	145	39
2	154	167	163	361	187	52

water for 100 ns. Mean residence times for water around magnesium, calcium, strontium, and barium ions were determined to be 1064 ± 358 , 252 ± 25 , 288 ± 21 , and 150 ± 12 ps, respectively. The experimentally measured residence time of water around Mg^{2+} ions is 6.7×10^{-5} s, four orders of magnitude longer than our simulated values.^{90,91} Longer residence times than the KBFF models have been observed in previous simulations,⁷³ but they remain many orders of magnitude faster than experiment. It appears that simple classical LJ plus Coulomb models are insufficient to capture the hydration dynamics of magnesium cations. Clearly, the long water residence times for Mg^{2+} may hamper the sampling processes required for correctly simulating many biological systems—when a force field that actually reproduces the experimental water residence time would be used. For Ca^{2+} , Sr^{2+} , and Ba^{2+} ions, the experimental water residence times around the cation were reported as 3.1, 2.5, and 1.2 ns, respectively,⁷³ which are all one order of magnitude longer than our simulated values. The calculated mean residence times of water around alkaline earth ions using computer simulations do cover a broad range.^{92–94} The current values are competitive, but there is clear room for improvement.

As mentioned in the Introduction, we have not determined the free energy of solvation for the current ion models at infinite dilution. We have chosen to focus on the properties of salt solutions at finite concentrations in an effort to develop and validate the models. The single ion free energies of solvation can be determined relatively easily and would represent useful reference values. Indeed, one would imagine that these values could be used to obtain the scaling parameters for the cation-water interactions as the solvation will be sensitive to the cation-water size parameters. Here, we have chosen to be consistent with our previous salt solution models that have not therefore focused on the solvation free energies.

IV. CONCLUSIONS

In this study, we have developed a series of models for aqueous alkaline earth halide salt solutions by attempting to reproduce the experimentally derived Kirkwood-Buff integrals using molecular dynamics simulations and a simple classical force field. It was demonstrated that the parameters developed for chloride salts are transferable to bromides and iodide salts. Breaking the standard combination rules when determining the cation-water interactions appears to be a reasonable way to include implicit polarization effects in non-polarizable force fields for cations with high charge densities. The models perform very well for low to medium salt concentrations. However, larger deviations from experiment are observed for high salt concentrations of some salt solutions. Furthermore, some of the salt parameters are clearly not suitable for salt crystal simulations, as unstable crystal structures are obtained. The KBFF models should be viewed as providing a reasonable balance between solute-solute, solute-solvent, and solvent-solvent interactions, as inferred by the resulting distributions and KBIs. The models provide the correct salt activity derivatives and reasonably reproduce experimental densities, diffusion constants, and dielectric decrements. Of course, the

ultimate test is the performance of the models for systems where the cations can interact with functional groups representative of proteins and nucleic acids. We are in the process of studying such systems.

SUPPLEMENTARY MATERIAL

See [supplementary material](#) for data of the simulated densities, potential energies, first shell coordination numbers, rdfs, excess coordination numbers, activity derivatives, partial molar volumes, diffusion constants, dielectric decrements, and enthalpies of mixing and crystal densities for all concentrations and all salts studied here.

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