Published in final edited form as:

J Phys Chem B. 2016 November 10; 120(44): 11436–11448. doi:10.1021/acs.jpcb.6b09262.

Balancing the Interactions of Mg^{2+} in Aqueous Solution and with Nucleic Acid Moieties For a Polarizable Force Field Based on the Classical Drude Oscillator Model

Justin A. Lemkul and Alexander D. MacKerell Jr.*

Department of Pharmaceutical Sciences, School of Pharmacy, University of Maryland, Baltimore, MD 21201

Abstract

Mg^{2+} ions are important in biological systems, particularly in stabilizing compact RNA folds. Mg^{2+} is strongly polarizing, and representing its interactions in heterogeneous environments is a challenge for empirical force field development. To date, the most commonly used force fields in molecular dynamics simulations utilize a pairwise-additive approximation for electrostatic interactions, which cannot account for the significant polarization response in systems containing Mg^{2+} . In the present work, we refine the interactions of Mg^{2+} with water, Cl^- ions, and nucleic acid moieties using a polarizable force field based on the classical Drude oscillator model. By targeting gas-phase quantum mechanical interaction energies and geometries of hydrated complexes, as well as condensed-phase osmotic pressure calculations, we present a model for Mg^{2+} that yields quantitative agreement with experimental measurements of water dissociation free energy and osmotic pressure across a broad range of concentrations. Notable is the direct modeling of steric repulsion between the water Drude oscillators and Mg^{2+} to treat the Pauli exclusion effects associated with overlap of the electron clouds of water molecules in the first hydration shell around Mg^{2+} . Combined with the refined interactions with nucleic acid moieties, the present model represents a significant advancement in simulating nucleic acid systems containing Mg^{2+} .

Graphical abstract

*Corresponding Author. Mailing address: 20 Penn St., Room 633, Baltimore, MD, 21201, alex@outerbanks.umaryland.edu, Phone: (410) 706-7442, Fax: (410) 706-5017.

SUPPORTING INFORMATION AVAILABLE

One figure, showing individual MSD traces of Mg^{2+} diffusion using the Drude and CHARMM force fields, residue definitions for the RNA bases, and coordinates of the base- Mg^{2+} complexes, are provided. This material is made available free of charge via the Internet at <http://pubs.acs.org>.

INTRODUCTION

Atomistic MD simulations rely on accurate force fields to yield insights into important biological and physical processes. Systems containing ions, particularly divalent species such as Mg^{2+} , are a challenge for traditional fixed-charge (additive) force fields, which cannot explicitly account for the significant polarization and charge-transfer effects manifested by such species.^{1, 2, 3} Mg^{2+} has particular biological significance as it is required for many RNA sequences to adopt compact tertiary folds.^{4, 5} Owing to its small size and subsequent high charge density, Mg^{2+} can occupy tight turns in the RNA phosphodiester backbone and effectively shield the negative charges from the phosphates. Describing such interactions accurately using empirical force fields by balancing the interactions among water, ions, and biological moieties is an ongoing challenge.

In solution, Mg^{2+} is hydrated by six water molecules in an octahedral geometry;^{6, 7} these water molecules are tightly bound and undergo exchange on the μs time scale.⁸ Recent studies have shown that additive force fields for Mg^{2+} significantly overestimate the free energy barrier for dissociation of inner-shell water molecules from Mg^{2+} ,^{9, 10} thus molecular dynamics (MD) simulations using these force fields will be incapable of producing a proper representation of thermodynamic and kinetic properties for aqueous systems containing Mg^{2+} . Various approaches have been used to address the deficiencies in additive representations in Mg^{2+} -containing systems. The simplest of these was proposed by Allnér et al.,¹⁰ who refined the standard CHARMM Lennard-Jones (LJ) parameters of the Mg^{2+} ion to reproduce the free energy barriers of dissociation between water and dimethylphosphate (DMP), a model compound often used to represent the nucleic acid backbone. By doing so, it was possible to recover the experimentally determined free energy barrier for water dissociation and sample Mg^{2+} occupancy around the adenosine riboswitch. The RNA remained stable following the adjustment of the Mg^{2+} LJ parameters, but the simulation was only carried out for 10 ns after equilibration, which is orders of magnitude shorter than what would be necessary to determine the ability of the new parameters to undergo reversible exchanges between water and phosphate moieties. Saxena et al. have proposed multi-site models for Mg^{2+} , in which the charge of the ion is delocalized over six off-center virtual sites, corresponding to water ligand positions.^{11, 12} By tuning LJ

parameters and the magnitude of the partial charges assigned to each of these sites, it was possible to recover the osmotic pressure of MgCl_2 as a function of increasing concentration.¹¹ Bulk simulations of MgCl_2 of 100 ns confirmed that water molecules did not dissociate from the Mg^{2+} coordination shell, but these simulations were also too short to conclusively demonstrate μs -scale retention of water coordination.

Newer force fields that explicitly account for polarization effects show great promise in their ability to represent Mg^{2+} in aqueous solution. An early model of polarizable Mg^{2+} was produced using the AMOEBA force field,¹³ which includes atomic multipole moments and dipole induction to represent polarization response.¹⁴ By targeting the free energy of solvation and quantum mechanical (QM) Mg^{2+} monohydrate interaction energies, Jiao et al. produced a model that adequately reproduced the water coordination and solution structure of Mg^{2+} . However the authors noted that water molecules in the first solvation shell dissociated from Mg^{2+} on the sub-nanosecond scale, which is at odds with experimental data indicating that dissociation of these water molecules is at least 1000 times slower. The model of Jiao et al. was further refined by Piquemal et al., who used a Thole damping function to screen the interactions of Mg^{2+} with water.¹⁵ This refined model led to stable water coordination over 5 ns, an improvement over the model of Jiao et al. Using the Piquemal et al. model of polarizable Mg^{2+} , Kurnikov and Kurnikova determined that water dissociation still occurred two orders of magnitude too rapidly due to a low free energy barrier for dissociation.⁹ They proposed to solve this defect using a distance-dependent polarization response of water, in which the atomic polarizabilities are recomputed as a function of Mg^{2+} -oxygen distance during the simulation. This approach led to more accurate dissociation kinetics as a result of an improved free energy barrier.⁹

Another approach to treating explicit electronic polarization is the Drude oscillator model,^{16, 17} in which negatively charged particles are attached to the real atoms in a system via harmonic springs. These particles represent the electronic degrees of freedom in the system and model the dipole response of each atom as the local electric field varies over the course of an MD simulation. Charge is apportioned between the parent atom and the Drude oscillator according to the atomic polarizability, α :

$$\alpha = \frac{q_D^2}{k_D} \quad (1)$$

$$q_{\text{Tot}} = q_D + q_A \quad (2)$$

where q_D is the charge on the Drude oscillator, which is always assigned a negative sign consistent with its representation of the electronic degrees of freedom, q_A is the charge on the parent atom, and q_{Tot} is the total charge of the Drude-atom pair. The force constant for the harmonic bond between the Drude oscillator and its parent atom is k_D . The force field supports isotropic and anisotropic polarization,¹⁸ and Thole screening¹⁹ between neighboring intramolecular or intermolecular²⁰ dipoles. The presence of an explicit particle

representing the electronic degrees of freedom allows for “mechanical” polarization effects that can be exploited by applying LJ parameters to the Drude oscillators, as previously discussed.²¹ Details of this force field and its development history are reviewed elsewhere.¹⁶ Yu et al. previously parametrized a series of monovalent and divalent ions using the Drude oscillator model.²⁰ The present work is a refinement of those parameters, specifically for Mg^{2+} and its interactions with water, ions, and nucleic acid moieties. By targeting QM interaction energy calculations and bulk-phase osmotic pressure simulations, it will be shown that the simple Drude oscillator model yields good quantitative agreement with bulk-phase behavior of Mg^{2+} ions in aqueous solution, without the need for complex multipole expansions or time-consuming recalculations of atomic polarizability during the simulation.

METHODS

Quantum Mechanical Calculations

The refinement of Mg^{2+} interactions was carried out in two parts, targeting QM interaction energies and geometries of Mg^{2+} -containing complexes. To refine Mg^{2+} -water interactions, one water molecule from a pre-optimized $[\text{Mg} \cdot (\text{H}_2\text{O})_6]^{2+}$ complex was translated along the x -axis at Mg^{2+} -O distances ranging from 1.8 to 6.0 Å in intervals of 0.1 Å, while the other atoms (Mg^{2+} and five water molecules) were constrained in their octahedral coordination geometry. Using Gaussian09,²² single-point QM interaction energies were then calculated between the translated water molecule and the remaining $[\text{Mg} \cdot (\text{H}_2\text{O})_5]^{2+}$ complex using MP2/6-311++G(2df,2pd) and MP2/6-311++G(3df,3pd) model chemistries to check for basis set dependency, given the strongly polarizing nature of Mg^{2+} . Counterpoise correction²³ for basis set superposition error (BSSE)²⁴ was applied. This approach improves upon the original parametrization of Mg^{2+} -water interactions, which focused primarily on the Mg^{2+} monohydrate,²⁰ by explicitly accounting for water-water interactions in the first hydration shell around Mg^{2+} . As will be shown below, the previous parameters for Mg^{2+} -water interactions resulted in an inadequate description of the binding affinity in bulk solution, requiring adjustment.

The balance of water-mediated (outer shell) and direct (inner shell) interactions between RNA moieties and Mg^{2+} is of particular importance in describing the association of Mg^{2+} with RNA. To this end, we constructed hydrated Mg^{2+} complexes that were ligated both directly and indirectly by RNA base atoms or DMP to ensure that the force field would accurately reflect the most common interactions in aqueous RNA systems containing Mg^{2+} . Inner-shell (direct) coordination complexes were constructed by deleting one water molecule from a $[\text{Mg} \cdot (\text{H}_2\text{O})_6]^{2+}$ octahedral complex and positioning the ligating base or DMP atom at the position of the oxygen atom from the deleted water molecule (Figure 1A). Outer-shell (indirect) coordination complexes were prepared by positioning the ligating base or DMP atom 3 Å away from the oxygen of one water molecule, linearly along the O-H bond to represent an ideal hydrogen-bonded geometry (Figure 1B). These complexes were all subsequently optimized in Gaussian09²² using the B3PW91/LANL2DZ model chemistry,^{25, 26} which was recently used for balancing ion-protein interactions in the Drude force field.²⁷ The geometries from QM optimization were used as target data for refining specific nonbonded terms between selected RNA atoms and Mg^{2+} .

To validate the parameters derived by targeting QM geometries, we utilized an approach based on previous efforts to balance monovalent ion interactions with DNA.²⁸ One-dimensional energy surfaces of Mg^{2+} ions as a function of distance from ligating atoms in RNA bases and DMP were constructed by placing Mg^{2+} ions at distances ranging from 1.0 Å to 3.5 Å from the heavy atom of interest, considering both in-plane (Figure 1C) and out-of-plane interactions with bases, as well as interactions with one or two DMP oxygen atoms (Figure 1D,E). DMP was built with α and ζ torsions fixed at values found in canonical A-RNA (291° and 287°, respectively). Configurations were generated at intervals of 0.1 Å. In-plane interactions with bases were carried out for every planar N or O atom in each base, except NH groups, which were assessed only by out-of-plane interactions. Exocyclic amino groups on adenine, guanine, and cytosine were similarly assessed using out-of-plane scans. Initial geometries were generated with the CHARMM program,²⁹ with single-point interaction energy calculations carried out with Gaussian09,²² using the MP2/6–311++G(2df,2pd) model chemistry, including counterpoise correction²³ for BSSE.²⁴ Since the magnitudes of these interaction energies is likely considerably larger *in vacuo* relative to those in aqueous solution, the computed QM interaction energies did not serve as target data as they did in the case of monovalent ions.²⁸ Rather, the distance and magnitude of the energy minima were only used as validation for the parameters derived using the DFT-optimized hydrated complexes described above.

Force Field Parameter Optimization

The LJ parameters (well depth, ϵ , and radius, $R_{\text{min}}/2$) of the Mg^{2+} ion were previously optimized to reproduce solvation free energies and coordination geometries,²⁰ therefore making adjustments directly to the ion LJ parameters was undesirable as doing so would likely result in an imbalance among interactions with water and existing moieties in the Drude-2013 force field.^{16, 28, 30, 31} Instead, we parametrized interactions with Mg^{2+} using pair-specific LJ terms (called NBFIX in CHARMM), including terms between the water Drude oscillators and Mg^{2+} . Additionally, for some interactions, through-space Thole dipole screening factors (NBTHOLE) were applied for some atom pairs (see Results and Discussion), as was done previously in the parametrization of monovalent and divalent ions in the force field.²⁰

The use of NBFIX and NBTHOLE overcomes limitations present in most classical MD force fields due to LJ interactions being calculated using predefined combination rules that describe the interactions between two atom types, yielding values of ϵ and R_{min} that are used in the LJ equation. NBFIX terms override those combination rules to allow for pair-specific (off-diagonal) assignment of LJ terms, without reparametrization of the individual atom type LJ terms, which may result in imbalances in the remainder of the force field. LJ terms are typically derived in homogeneous media, such as crystals or pure liquids, therefore use in heterogeneous environments, in which the LJ interactions between atoms that have not been tested specifically occur, may expose deficiencies in the standard combination rules.³² Use of NBFIX addresses this issue by allowing for specific LJ terms to be assigned to atom type pairs for which deficiencies have been identified. Similarly, the use of NBTHOLE allows for pair-specific dipole screening that can be used to optimize the atomic dipole-dipole interactions between specific atom pairs. It is used to reduce the strength of cation-

anion attraction in the present study. Neighboring dipoles from Drude-atom pairs have their Coulombic interactions multiplied by a function, $S(r_{ij})$, proposed by Thole,¹⁹ and the same form is used for the through-space NBTHOLE screening:

$$S(r_{ij}) = 1 - \left(1 + \frac{r_{ij}t_{ij}}{2(\alpha_i\alpha_j)^{1/6}} \right) \exp \left[\frac{-r_{ij}t_{ij}}{(\alpha_i\alpha_j)^{1/6}} \right] \quad (3)$$

in which r_{ij} is the distance between atoms i and j , α_i and α_j are the atomic polarizabilities of atoms i and j , and t_{ij} is the screening constant applied to that interaction. It is the value of t_{ij} that is parametrized in the present work for the atom pairs listed below, and allows the screening of specific interaction without having to reparametrize individual atomic polarizabilities, which may lead to intramolecular and intermolecular imbalances in the remainder of the force field. The availability of algorithms such as NBFIX and NBTHOLE, in concert with explicit representation of electronic degrees of freedom in the Drude oscillator model, allows for considerable flexibility in developing the force field. In addition, effects such as steric repulsion between Drude oscillators and atoms (based on the Pauli exclusion effect) can be parametrized directly in the model using NBFIX to further balance polarization effects in heterogeneous environments.

Parametrization of NBFIX and NBTHOLE terms was carried out using a Monte-Carlo/simulated annealing (MC/SA) protocol. The NBFIX parameters (ϵ and $R_{\min}$) were allowed to vary freely in the ranges of $-0.250 < \epsilon < -0.001$ kcal mol⁻¹ and $2.0 < R_{\min} < 5.0$ Å. The initial value of the NBTHOLE term was 2.6, which is a default value for the sum of atom-based Thole terms in the Drude-2013 force field;¹⁶ this value was allowed to vary from 0.5 to 3.0, a range of values typically used to screen ion interactions. Target data for the fitting protocol were the minimum distances between the ligating atom on the nucleic acid base or DMP and the Mg²⁺ ion, as well as a characteristic angle that was established for each complex (see below). These target data were used to define the error function for MC/SA fitting, which included the root-mean-square difference (RMSD) between all of the relevant distances and angles. The initial temperature for MC/SA was set to 500 K; new parameter sets were accepted if the RMSD decreased or if the Metropolis criterion was accepted. The temperature was scaled down by a factor of 0.75 every 200 steps.

The optimized geometries were chosen as target data due to the importance of balancing inner- and outer-shell coordination, using quantities that have magnitudes that should not significantly differ *in vacuo* and in bulk solution, unlike *in vacuo* interaction energies, which are very large in the case of divalent ion complexes. Obtaining agreement across the different inner- and outer-shell ligated complexes is an implicit indicator that the balance of the energetics is suitably accurate. Parameter optimization was attempted using NBFIX and NBTHOLE independently, and the two terms were combined only when suitable agreement could not be achieved by using only one.

Initial simulations using the ion parameters by Yu et al.²⁰ (part of the Drude-2013 force field)¹⁶ showed an overly strong attraction between Mg²⁺ and Cl⁻ that led to incorrect solution structure and aberrantly low osmotic pressure (see below), motivating the present

refinement of specific pairwise interactions between the ions. Initial attempts to use an NBFIX term for the Mg^{2+} - Cl^- interaction used the method proposed by Luo and Roux.³³ Targeting the osmotic pressure (see below) of a 1 M MgCl_2 solution with the combination rule value of ϵ constant ($-0.05999 \text{ kcal mol}^{-1}$) constrained while varying $R_{\min}$ was unsuccessful, as an unphysically large $R_{\min}$ would be required to correct the strong attraction. Given the large electrostatic and dipole interaction between Mg^{2+} and Cl^- , we instead varied the value of the NBTHOLE screening factor using values of 1.0, 1.2, 1.4, 1.6, 1.8, and 2.0, and extrapolating to the NBTHOLE value that would lead to agreement with experimental data.^{34, 35} This NBTHOLE value was subsequently evaluated using osmotic pressure calculations over a range of MgCl_2 concentrations (see below).

General MD Simulation Protocol

For all MD simulations, equations of motion were integrated using the extended Lagrangian integration scheme for Drude polarizable systems.³⁶ Temperature was regulated using a dual Nosé-Hoover thermostat approach,³⁷ with the temperature of the real atoms coupled at 298 K ($\tau = 0.1 \text{ ps}$) and the relative temperature of the Drude oscillators at 1 K ($\tau = 0.005 \text{ ps}$). Pressure was maintained at 1 atm. Simulations in CHARMM used a modified Andersen-Hoover barostat³⁸ (with a relaxation time of 0.1 ps), while those in NAMD used the Langevin piston method³⁹ (with an oscillation period of 200 fs and a damping time of 100 fs), and those in OpenMM⁴⁰ used a Monte Carlo barostat with pressure changes attempted every 25 integration time steps. Periodic boundary conditions were applied in all dimensions and electrostatic interactions were evaluated using the particle mesh Ewald (PME) method,⁴¹ with a real-space cutoff of 12 Å and a splitting parameter, κ , of 0.34 Å^{-1} . van der Waals interactions were computed by switching the LJ potential to zero from 10 – 12 Å. Bonds involving hydrogen atoms were fixed using the SHAKE algorithm,⁴² allowing an integration time step of 1 fs, and a so-called “hard wall” constraint⁴³ was placed on Drude oscillators at a distance of 0.2 Å to prevent polarization catastrophe. The water model used for all polarizable simulations was SWM4-NDP,⁴⁴ and for simulations carried out with the additive CHARMM force field, the water model was the CHARMM-modified TIP3P model.^{45, 46, 47}

Potential of Mean Force Calculations

To compute the free energy profiles of water dissociating from the first hydration shell around a Mg^{2+} ion, we applied umbrella sampling to compute potential of mean force (PMF) profiles. The reaction coordinate was defined as the distance, ξ , between Mg^{2+} and the O atom of one inner-shell water molecule. Initial configurations were constructed from 1.8 – 10 Å in intervals of 0.2 Å in a 30-Å cubic box, totaling 42 windows for each system. Similar to the protocol applied by Callahan et al.,⁴⁸ distance-dependent harmonic force constants were applied, $480 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ within 2.2 Å, $240 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ from 2.4 – 4.8 Å, and $120 \text{ kcal mol}^{-1} \text{ Å}^{-2}$ from 5.0 Å and beyond. Umbrella sampling simulations were carried out in CHARMM,²⁹ using the MMFP module to enforce the harmonic restraints. Each window was energy-minimized and equilibrated for 100 ps under an NPT ensemble. Following equilibration, interatomic distances were collected over 500 ps in each window. Restraint distances were de-biased using the WHAM algorithm⁴⁹ to construct PMF profiles. An entropy correction of $2RT\ln(\xi)$ was applied to each window in the resulting PMF

profiles to account for the sampling of a larger spherical volume as a function of ξ . Error bars for the activation barriers in each PMF profile were calculated by splitting the simulations into two equal blocks of 250 ps and taking the standard deviation of the peak heights.

Hydration Free Energy of the Mg^{2+} Ion

Parametrization of monoatomic ions in the Drude force field²⁰ focused on hydration free energies (G_{hydr}), and to this end, after reparametrizing Mg^{2+} - water interactions, we computed G_{hydr} of Mg^{2+} at infinite dilution using CHARMM,²⁹ following the method of Deng and Roux.⁵⁰ The total G_{hydr} was computed from the following terms:

$$\Delta G_{\text{hydr}} = \Delta G_{\text{rep}} + \Delta G_{\text{disp}} + \Delta G_{\text{elec}} \quad (4)$$

in which G_{rep} and G_{disp} are the repulsive and dispersive components of the LJ potential and G_{elec} is the electrostatic contribution to G_{hydr} . The separation of G_{rep} and G_{disp} is done according to the Weeks-Chandler-Andersen (WCA) theory of liquid perturbation,⁵¹ allowing a decomposition of the total nonpolar solvation energy into attractive (G_{disp} , strictly negative) and repulsive (G_{rep} , strictly positive) contributions. The transformation of each component of G_{hydr} was carried out separately, with G_{disp} and G_{elec} transformed linearly from $\lambda = 0$ to $\lambda = 1$ in uniform increments of 0.1. The G_{rep} term was transformed using a soft-core potential⁵⁰ to avoid numerical singularities with $\lambda = 0, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9$, and 1.0.

The starting configuration for each system was a single Mg^{2+} ion centered in a box of 250 SWM4-NDP water molecules.⁴⁴ For each λ state, the system was energy-minimized and subsequently equilibrated for 50 ps under an NPT ensemble (temperature of 298 K and 1 atm of pressure). Data collection was then carried out for 100 ps in each λ window. The final G_{rep} and G_{disp} values were obtained by de-biasing the results with WHAM⁴⁹ and G_{elec} was obtained by thermodynamic integration (TI). A long-range correction (LRC) term was computed to account for the finite truncation of LJ interactions. A single simulation of 300 ps was carried out in the fully interacting state using the truncation scheme described above. The configurations in this trajectory were subsequently evaluated with a longer van der Waals cutoff of 30 Å and the ensemble-average difference in energy was taken as the LRC.

The value of G_{hydr} from this transformation does not reflect the real G_{hydr} obtained experimentally for ions, as it does not include the contribution from the phase potential attributed to crossing a vacuum-water interface. Thus, the computed G_{hydr} from the simulations corresponds to an “intrinsic” bulk-phase value that is independent of the phase potential. The “real” G_{hydr} is calculated according to:

$$\Delta G_{\text{hydr}}^{\text{real}} = \Delta G_{\text{hydr}}^{\text{intr}} + zF\Phi \quad (5)$$

in which z is the charge on the ion, F is the Faraday constant ($23.06 \text{ kcal mol}^{-1} \text{ V}^{-1}$) and Φ is the electrostatic Galvani potential at the vacuum-liquid interface. For the SWM4-NDP water, the value of Φ is -545 mV ,⁴⁴ and the total correction due to the interface potential in the case of Mg^{2+} becomes $-25.2 \text{ kcal mol}^{-1}$. Additionally, to compare our results with those tabulated in experimental studies in standard state (1 M concentration) an entropy correction must be included, corresponding to the volume change that arises from an ion in the ideal gas state at 1 atm with a molar volume of $24.465 \text{ L mol}^{-1}$ being compressed into solution. This value corresponds to $-k_B T \ln (1/24.465) = 1.9 \text{ kcal mol}^{-1}$ per ion.

Self-Diffusion Coefficient of Mg^{2+}

The dynamic transport of the Mg^{2+} ion is sensitive to its interactions with water, thus an important test of the present refinement of Mg^{2+} -water interactions is the ability of the force field to reproduce the self-diffusion coefficient of Mg^{2+} at infinite dilution. To this end, one Mg^{2+} ion was placed in the center of each of three cubic boxes, with initial cell lengths of 30, 40, and 50 Å, which were subsequently filled with SWM4-NDP water.⁴⁴ Such an approach was suggested by Yeh and Hummer to correct for system size dependence of the observed self-diffusion coefficients.⁵² The systems were energy minimized and ten independent simulations were carried out in CHARMM,²⁹ starting from different random initial velocities. Each replicate was carried out for 300 ps under an NPT ensemble, with the first 100 ps discarded as equilibration. Coordinates were saved every 0.1 ps and the self-diffusion coefficient, D , of Mg^{2+} was obtained from linear region of the mean-square displacement:

$$D = \lim_{t \rightarrow \infty} \left\langle \frac{1}{N} \sum_{i=1}^N [\vec{r}_{o,i}(t) - \vec{r}_{o,i}(0)]^2 \right\rangle \quad (6)$$

Molecular Dynamics Simulations of Bulk MgCl_2 Solution

To assess solution structure, water dipole moments, and hydration shell exchange kinetics, we carried out a 1- μs NPT simulation of a 1 M aqueous MgCl_2 solution using OpenMM⁴⁰ with the extended Lagrangian integration scheme.³⁶ The simulation system was a 30-Å cube containing 16 Mg^{2+} , 32 Cl^- , and 964 SWM4-NDP water molecules. Snapshots were recorded at 100-ps intervals for analysis. Simulation methods were the same as described above.

Osmotic Pressure Calculations

A useful method for assessing the quality of intermolecular interactions in aqueous solution is to compute the osmotic pressure of solutions at varying solute concentration. Osmotic pressure calculations have previously been used to fine-tune the interactions of electrolyte solutions containing monoatomic and polyatomic ions.^{28, 33, 53} MD simulations can be used to calculate osmotic pressure by constructing virtual semipermeable membranes in the simulation system using a method developed by Luo and Roux.³³ In this approach, a cubic volume is constructed with a given concentration of solute and filled with water. This cubic cell is centered at the coordinate origin in a rectangular box that is twice as long in the z -

dimension. The remaining volume is filled with water. Virtual semipermeable membranes are constructed using a half-harmonic potential in the x - y plane at values of $\pm z_{wall}$, which define the upper and lower bounds of the solute-containing central region. A half-harmonic potential, with a force constant k , is applied to solute atoms, but water molecules are free to pass through these planes. Pressure coupling is applied along the z -axis but the x - y plane has a fixed cross-sectional area, A . The osmotic pressure is calculated from the ensemble average of the total force acting on the restrained solute atoms, divided by the area of the semipermeable membrane and averaged over the two walls:

$$\langle F_{wall} \rangle = k \left(\frac{1}{N} \right) \sum_N \sum_i \left(|z_i - z_{wall}| \right) \quad (7)$$

where i is the index of all ions in the system and N is the number of simulation steps. The force imposed by the semipermeable membrane is only enforced when $|z_i| > |z_{wall}|$, otherwise it is zero.

We constructed several aqueous MgCl_2 systems with increasing concentration (Table 1). Solutions were initially built in $30\text{-}\text{\AA}$ cubic boxes, and slabs of water of equal volume were added along the z -axis, yielding a system with initial dimensions of $30 \times 30 \times 60\text{ }\text{\AA}$, centered at the coordinate origin (Figure 2). Thus, z_{wall} was set to $\pm 15\text{ }\text{\AA}$. The force constant in Eq. 7, k , was set to $10\text{ kcal mol}^{-1}\text{ }\text{\AA}^{-2}$. Simulations were carried out in NAMD using the extended Lagrangian integration method,³⁶ implemented in NAMD as Langevin dynamics.⁵⁴ The virtual semipermeable membranes were set up using the Tcl scripting feature in NAMD. Pressure coupling was applied along the z -axis while the x - and y -dimensions were fixed to maintain a constant area ($900\text{ }\text{\AA}^2$) for each semipermeable membrane. Langevin damping was used to maintain temperature at 298 K with a 5.0 ps^{-1} friction coefficient on real atoms, and pressure was maintained at 1 atm using the Langevin piston method³⁹ with a 200-ps oscillation period and a 100-fs decay time. The Drude oscillator relative thermostat was set to 1 K and maintained with a 20.0 ps^{-1} friction coefficient. The LJ potential was switched to zero from $10 - 12\text{ }\text{\AA}$ and electrostatic forces were evaluated using the particle mesh Ewald method,⁴¹ with a real-space cutoff of $12\text{ }\text{\AA}$ and a Fourier grid spacing of $1\text{ }\text{\AA}$. Following a 1-ns equilibration time, five independent simulations were carried out at each concentration (Table 1) for 10 ns with coordinates saved every 0.5 ps . Osmotic pressure values were subsequently calculated according to Eq. 7 using CHARMM.²⁹ The concentration of the central cubic region was converted from molarity, M , to molality, m , by counting the number of water molecules within $\pm z_{wall}$ and taking the average over time.

RESULTS AND DISCUSSION

Nonbonded Parameters

The optimized set of pair-specific nonbonded parameters for Mg^{2+} -water and Mg^{2+} -nucleic acid interactions is listed in Table 2. Most of these interactions required the use of both pair-specific LJ (NBFI) and through-space Thole dipole screening (NBTHOLE) with specific atoms and Mg^{2+} to achieve good agreement with the DFT-optimized inner- and outer-shell

coordinated complex geometries (Tables 3 and 4). In two cases, it was necessary to assign NBFIX terms to lone pairs and Drude oscillators. The general LPDNA1 type refers to any lone pair on nucleic acids; these occur on hydrogen bonding groups such as carbonyl oxygen, aromatic nitrogen, and hydroxyl oxygen atoms. The NBFIX applied to the SWM4-NDP Drude oscillator (type DOH2) is a special case; it is assigned a unique type in the Drude force field that allows for such flexibility in describing heterogeneous interactions. We note the use of an NBFIX between the water Drude oscillator and Mg^{2+} represents steric repulsion that is effectively modeling the Pauli exclusion effect where the overpolarization of the water (see below) corresponds to a distortion of its electron cloud that leads to overlap with the electron cloud of Mg^{2+} .²¹

The application of an NBFIX to the interaction of Mg^{2+} and the Drude oscillator of water (MAGD-DOH2) was needed due to the observation that water molecules frequently dissociated from $[\text{Mg} \cdot (\text{H}_2\text{O})_6]^{2+}$ complexes in bulk solution in < 10 ns using the Drude-2013 force field¹⁶ (data not shown). As the off-rate for inner-shell water molecules is $6.7 \times 10^5 \text{ s}^{-1}$ in bulk solution,⁸ such exchanges should only occur on the μs scale. The interaction energy of Mg^{2+} and a single water molecule is somewhat overestimated in the Drude-2013 force field relative to QM interaction energies,²⁰ yet the interaction energy of water binding to a higher-order complexes is too weak by approximately $1.5 \text{ kcal mol}^{-1}$ in the fully hydrated octahedral complex.²⁰ Careful analysis revealed that the strong dipole response between the individual waters and Mg^{2+} led to excess dipole-dipole repulsion between the water molecules in the octahedral complex, thereby reducing the affinity of each water in an octahedral $[\text{Mg} \cdot (\text{H}_2\text{O})_6]^{2+}$ complex. The previous parametrization did not adequately account for cooperative polarization effects that have subsequently been found to be of particular importance in coordinated ion complexes.²⁷ The application of an NBFIX term between Mg^{2+} and the water Drude oscillator damps the water dipole moment very slightly and reduces the repulsion between neighboring water molecules. Doing so has the effect of improving the *in vacuo* interaction energy (Figure 3), yielding a difference at the energy minimum of less than $0.3 \text{ kcal mol}^{-1}$ with respect to the MP2/6-311++G(2df,2pd) surface and 0 kcal mol^{-1} with respect to the MP2/6-311++G(3df,3pd) surface. As will be shown below, the solution structure and the free energy barrier for water dissociation in bulk solution are also improved as a result. Given the close agreement between the two QM calculations, the 6-311++G(2df,2pd) basis set will be used in additional validation calculations presented below. We note that this is the same basis set utilized by Yu et al. in the original derivation of the Drude monovalent and divalent ion series,²⁰ as well as in work by Savelyev and MacKerell in tuning monovalent cation interactions with nucleic acid moieties.²⁸ The present results confirm that such a basis set is appropriate for these calculations given that there is no basis set dependency in the results.

Hydration Free Energy of the Mg^{2+} Ion

Following the introduction of the MAGD-DOH2 NBFIX, we computed the absolute G_{hydr} of Mg^{2+} at infinite dilution; this “intrinsic” G_{hydr} was $-412.24 \text{ kcal mol}^{-1}$. After accounting for interface potential contributions, entropy change upon solvation (see Methods), and LRC due to truncation of the LJ potential (which only amounts to $-0.02 \text{ kcal mol}^{-1}$), the final value of the real G_{hydr} produced by the new parameter set is -435.6 kcal

mol⁻¹, which is slightly reduced in magnitude compared to the previous force field, which yielded a G_{hydr} of -449.2 kcal mol⁻¹ (in good agreement with the value of -447.2 kcal mol⁻¹ reported by Yu et al.²⁰). We confirmed that the G_{hydr} value using the new parameters was adequately converged by repeating the free energy calculations using a sampling time of 200 ps per λ state. The resulting value was -436.4 kcal mol⁻¹, a difference of only 0.02%. The new value is in better agreement with available experimental data, though there is considerable spread in these values (-442.08, -434.99, and -437.38 kcal mol⁻¹).^{55, 56, 57} Whereas the previous force field parameters were somewhat too favorable compared to the experimental values, the new force field, differing only by the introduction of a MAGD-DOH2 NBFIX in this context, yields a value within the experimental range. Thus the improved agreement of gas-phase interaction energy gives rise to better agreement with condensed-phase thermodynamic properties.

Free Energy Profile of Water Dissociation from Mg²⁺

The slow exchange of water molecules from the first hydration shell around Mg²⁺ is due to a large activation barrier of 9.9 kcal mol⁻¹.⁸ It has recently been determined that several commonly used additive force field parameter sets overestimate this free energy barrier.¹⁰ Conversely, polarizable models using the AMOEBA force field underestimate the dissociation barrier, leading to rapid exchange of inner-shell water molecules.¹³ To assess the quality of our newly refined parameters for Mg²⁺-water interactions, we computed the PMF of water dissociation as a function of the linear distance between the Mg²⁺ ion and the oxygen atom of one inner-shell water, comparing the new force field parameters to the ion parameters in the additive CHARMM⁵⁸ and Drude-2013 polarizable force fields.²⁰ The PMF profiles (Figure 4) confirm the previous observation¹⁰ that CHARMM36 overestimates the free energy barrier, with a value of 13.1 ± 0.2 kcal mol⁻¹. In contrast, the Drude-2013 force field¹⁶ (which includes ion parameters from Yu et al.²⁰) underestimated the free energy barrier (4.7 ± 0.7 kcal mol⁻¹), comparable to the value produced by the AMOEBA force field.^{9, 13, 15} The application of the NBFIX described above to Mg²⁺-water interactions yields a value 10.4 ± 0.3 kcal mol⁻¹, in good agreement with the experimental activation barrier. This outcome indicates that not only are the *in vacuo* interaction energies improved by this refinement, but the condensed-phase thermodynamics of Mg²⁺-water interactions are more accurate than the additive CHARMM36 force field and the previous Drude-2013 Mg²⁺ parameters,²⁰ thus the dynamics of hydrating waters will be more accurately modeled by the refined Drude force field than these other force field models.

Self-Diffusion Coefficient of Mg²⁺

The diffusion of an ion through bulk water provides an assessment of the strength of its interactions with surrounding solvent molecules. To this end, we computed the self-diffusion coefficient, D , of a Mg²⁺ ion at infinite dilution in 30-, 40-, and 50-Å cubic boxes of SWM4-NDP water.⁴⁴ This approach allows the observed value of D (called D_{PBC}), which is dependent on the system size, to be corrected via a linear fit against the inverse cell length ($1/L$) to achieve the size-independent self-diffusion coefficient, D_0 .⁵² The linear region of each MSD trace (Figure S1 in the Supporting Information) was from approximately 25 – 125 ps in each simulation, and this time interval was used for calculation of D_{PBC} . Values of D_{PBC} for the present Drude Mg²⁺ model are listed in Table 3 and are plotted as a function of

1/L in Figure 5. Extrapolating back to an infinitely large system to obtain D_0 yields a value of $0.89 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, in good agreement with the experimental value of $0.81 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$.⁵⁹ The previous Mg^{2+} parameters by Yu et al.²⁰ produced a value of $D = 0.71 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, though the authors indicated that the value was independent of system size. In the present work, we do find that the results using the new parameters have a system size dependence that may have been present but undetected in the previous parameter set due to the large error bars associated with D_{PBC} in each system. We note that the system size dependence is also observed in the case of the CHARMM additive ion parameters (Table 3) and as such this is not a phenomenon inherent to only the polarizable model. Ultimately, the introduction of the MAGD-DOH2 NBFIX did not substantially alter the transport properties of the ion through bulk water relative to the previous parameters,²⁰ although the increase in D does improve on the agreement with the experimental value.

A related method for correcting D_{PBC} is based on the shear viscosity of the liquid:⁵²

$$D_0 = D_{PBC} + \frac{2.837297 k_B T}{6\pi\eta L} \alpha \quad (8)$$

where k_B is the Boltzmann constant, T is the absolute temperature (298 K), η is the solvent viscosity, and L is the box length. The α scaling term was introduced by Yeh and Hummer in a study including monovalent ions⁶⁰ that showed such a correction was necessary for charged species, and that α should be set to 0.88 in this case. To perform this calculation of an infinitely dilute solution of one Mg^{2+} , the shear viscosity of the system, η , is set to that of the solvent, SWM4-NDP water (0.70 cP).⁴⁴ Using this approach yields a slightly smaller value for $D_0 = (0.78 \pm 0.10) \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$, still in good agreement with the experimental value and consistent with the approach above of using a linear fit of D_{PBC} to calculate D_0 given the error bars of the individual data points. These error bars are due to the considerable variability in D_{PBC} values from different simulations (Figure S1 in the Supporting Information), reflecting a general difficulty in obtaining converged results for these microscopic properties, relative to experiments, as the simulations analyze only a single particle over a short time period. It is difficult to compare the precision of our present results in the context of previous studies on ion diffusion using polarizable models, as error bars are not frequently reported,^{13, 20} though we suspect similar difficulties were observed.

MgCl₂ Solution Structure and Dynamics

The structure of a solution can be described by the radial distribution function (RDF) between pairs of atoms. The RDF of a 1 M MgCl_2 system over a 1- μs simulation is shown in Figure 6. The two peaks in the $\text{Mg}^{2+}\text{-O}_{\text{wat}}$ RDF are located at 2.1 and 4.3 Å, corresponding to the first and second hydration shells around each Mg^{2+} ion. The positions of these peaks are in good agreement with the values observed in experimental X-ray diffraction experiments on MgCl_2 solutions⁶¹ and coincide with the minima in the PMF profile (Figure 4). The $\text{Cl}^-\text{-O}_{\text{wat}}$ RDF shows a single peak at 3.1 Å, also corresponding to its first hydration shell and also in good agreement with X-ray diffraction data.⁶¹ The peaks between Mg^{2+} and Cl^- ions are beyond 4.9 Å, indicating that the ions are generally separated by two or more hydration shells. Experimentally, a broad peak between 4.0 – 5.0 Å is observed and is

attributed to a combination of these ion-ion and ion-water distances,⁶¹ thus the structure of the MgCl_2 solution is in good agreement with available experimental data.

Over the course of the 1- μs simulation, we observed no exchanges of inner-shell hydrating waters around Mg^{2+} and the hydration number of each Mg^{2+} ion remained constant at the expected value of 6. This simulation is the longest of its kind in assessing the stability of Mg^{2+} -water coordination, exceeding previous additive (~ 100 ns)¹¹ and polarizable AMOEBA (5 – 10 ns)^{9, 13, 15} simulations. As the off-rate for water molecules in the first hydration shell around Mg^{2+} is $6.7 \times 10^5 \text{ s}^{-1}$,⁸ water exchange is expected to take place on the order of 1.5 μs . Our observation that no dissociation occurred in 1 μs is consistent with this behavior and derives from the good agreement with the experimental free energy barrier obtained using the refined Drude force field parameters.

Water Dipole Moments in MgCl_2 Solutions

As additive water models are typically kept rigid, such that the internal geometry of the water molecules cannot vary over time, their dipole moments are fixed. Thus, a water molecule in the first Mg^{2+} hydration shell has the same dipole moment as a bulk water molecule. An advantage of polarizable force fields is the ability to observe dipole response as a function of distance from strongly polarizing ions and other species. In the development of the first AMOEBA Mg^{2+} model, Jiao et al. noted water dipole moments on the order of ~ 3.5 D in the first hydration shell, whereas bulk water molecules had dipole moments on the order of 2.8 D.¹³ In our Drude model, water dipole moments in the inner shell around Mg^{2+} are 2.94 ± 0.11 D on average, while bulk water molecules have dipole moments of 2.48 ± 0.18 D (Figure 7), as expected for the SWM4-NDP model.⁴⁴ Thus we see a similar behavior to that observed by Jiao et al., in that the inner-shell waters become more polarized as a function of their proximity to Mg^{2+} . The response in the Drude model is less than that of the Jiao et al. AMOEBA model, but as we have shown, over-polarization of water leads to repulsion among coordinating waters and spurious dissociation, which was observed in the case of the AMOEBA model^{9, 13} to an even greater degree than we observed with the Drude-2013 parameters. Thus, obtaining a proper dipole response between Mg^{2+} and its inner-shell waters is a critical component of correctly modeling the hydration shell structure and the thermodynamics of water exchange.

Osmotic Pressure of MgCl_2 Solutions

The osmotic pressure of MgCl_2 as a function of increasing concentration using the refined Drude force field parameters is shown in Figure 8. Two problems were identified when using the Drude-2013 force field to represent MgCl_2 solutions that contributed to underestimated osmotic pressure. The first was a tendency for water molecules in the first hydration shell of Mg^{2+} to dissociate abnormally rapidly, leading to contact ion pairing that is not observed in MgCl_2 solutions below 3 M concentration.⁶¹ This deficiency was due to excess water-water dipole repulsion within the first hydration shell and was mitigated by the introduction of the MAGD-DOH2 NBFIX in the present work (see above). The second problem arose from a large polarization response between Mg^{2+} and Cl^- , which resulted in strong attraction via water-mediated interactions. This behavior led to the formation of hydrated clusters of Mg^{2+} and Cl^- ions (Figure 8, inset) that did not form contact ion pairs but Cl^- displaced water

molecules in the second hydration shell around Mg^{2+} , forming inseparable, water-mediated inclusions with reduced diffusion and thus depressed osmotic pressure. The application of the NBTHOLE term between the ions (Table 2) led to a diffuse distribution of ions (Figure 7) that produced better agreement with osmotic pressure values over a broad range of concentrations. We note that at concentrations exceeding 1 M, the Drude model produces osmotic pressure values that are somewhat larger than the experimental data (Figure 8), though below this concentration the agreement is nearly perfect.

Interactions of Mg^{2+} with Nucleic Acid Moieties

A complete, balanced force field for nucleic acids requires an assessment of the interactions of Mg^{2+} ions with nucleic acid moieties, particularly in the case of RNA, for which Mg^{2+} is often required for stability of complex tertiary, folded structures.^{62, 63, 64} To this end, we performed DFT optimizations of inner- and outer-shell hydrated Mg^{2+} complexes, coordinated by nucleobase atoms and DMP as a model of the phosphodiester backbone. The Drude-2013 nucleic acid force field,^{31, 65} in concert with the Drude Mg^{2+} parameters by Yu et al.²⁰ led to very strong attraction between these nucleic acid functional groups and Mg^{2+} , manifesting in aberrantly short interaction distances and distorted coordination geometries (Tables 4 and 5). This behavior would likely lead to instability in MD simulations, as was previously observed in the case of monovalent ions like Na^+ and K^+ ,²⁸ and as such, specific interactions must be addressed towards achieving the goal of a fully functional nucleic acid force field that allows for interactions with Mg^{2+} . To correct the overly strong interactions, we used the DFT geometric parameters listed in Tables 4 and 5 as target data to optimize the nonbonded interactions between the ligating nucleic acid atoms and Mg^{2+} through the use of NBFIX and NBTHOLE terms (Table 2).

Overall, the application of NBFIX and NBTHOLE terms obtained from MC/SA fitting yielded considerable improvement across all coordination complexes, though the effect was less prominent in the case of the outer-shell complexes. The force field used in the present calculations applies the NBFIX and NBTHOLE terms listed in Table 2 in concert with a refined version of the Drude-2013 DNA force field^{28, 31} with updated base LJ and electrostatic parameters that includes RNA (Lemkul and MacKerell, manuscript in preparation). Topologies and nonbonded parameters for these bases are provided in the Supporting Information. It is clear that balancing interactions in systems including divalent ions like Mg^{2+} requires careful consideration of heterogeneous interactions that will occur in nucleic acid systems, and obtaining a balance in the coordination of Mg^{2+} ions (direct and indirect) is critical to producing a proper model for RNA simulations.

To further validate the optimized NBFIX and NBTHOLE parameters for nucleic acid- Mg^{2+} interactions, we performed single-point, *in vacuo* interaction energy calculations of base- Mg^{2+} and DMP- Mg^{2+} binary systems as a function of distance between Mg^{2+} and the coordinating atom. No water molecules were present in these calculations. Whereas such calculations were used previously to balance the interactions of monovalent ions with nucleic acid moieties,²⁸ the magnitude of the interaction energies in Mg^{2+} systems is considerably larger than, and likely not relevant to, solution interactions. Thus we approached the parametrization using hydrated complexes and only use these single-point

energies as validation that the physical model is reasonable. As with the DFT optimizations of Mg^{2+} hydrates, the Drude-2013 force field, including the Yu et al. ion parameters,^{20, 31, 65} generally overestimates the interaction of Mg^{2+} with each of the nucleic acid moieties, leading to energy minima that occur at very short distances (Table 6). The newly developed NBFIX and NBTHOLE parameters considerably improve both the position and magnitude of each energy minimum. As such, these new parameters represent a better representation of ion-nucleic acid interactions that will avoid over-polarization problems and instability in systems of hydrated nucleic acids.

CONCLUSIONS

In this study, we have presented a refinement of interactions between Mg^{2+} and water, Cl^- ions, and nucleic acid moieties using a polarizable force field based on the classical Drude oscillator model. By tuning pair-specific LJ interactions (NBFIX) and dipole screening (NBTHOLE), the new model for Mg^{2+} better reproduces a variety of condensed-phase properties of Mg^{2+} in solution than the previous parameter set, including hydration free energy, the free energy barrier for inner-shell water dissociation, self-diffusion coefficient, osmotic pressure, and solution structure. Notable in this effort is the avoidance of over-polarization of inner-shell waters that has been associated with poor dissociation kinetics in other polarizable force fields.^{9, 13} Tuning the interactions of Mg^{2+} with nucleic acid moieties to reproduce DFT-optimized geometries of hydrated Mg^{2+} clusters improved the coordination of Mg^{2+} in both inner- and outer-shell complexes, a phenomenon that will be important in the development of a comprehensive force field for nucleic acids. Important in this effort is the excellent agreement of the MgCl_2 osmotic pressures. Even in low millimolar bulk MgCl_2 solution, RNA will condense Mg^{2+} ions by virtue of its polyanionic nature,^{4, 5} yielding a higher effective concentration in the vicinity of the RNA. Thus, a proper description of ion-ion, ion-water, and ion-RNA interactions is necessary; the present results suggest the model achieves such a balance on the small molecule level, though it must be tested in the context of full-length nucleic acids. Efforts are ongoing to validate this force field.

These outcomes were achieved using the Drude oscillator model, which is a conceptually simple representation of explicit polarization, and does not require expensive calculations of higher-order multipoles^{13, 14, 15} or complex, dynamic reparametrization of atomic polarizabilities during the simulation,⁹ as has been proposed previously as a solution to over-polarization problems. However, the model yields a level of accuracy comparable to that of multipole and induced dipole-based models, as evidenced by the present study. Of specific note is that the use of Drude oscillators allows for the “steric” treatment of electronic polarization effects,²¹ in which overlap of electron clouds associated with the Pauli exclusion effect may be modeled via LJ interactions between the electronic degrees of freedom (i.e. the Drude oscillators) and surrounding atoms. Such a treatment is not accessible to polarizable force fields based on induced dipoles or fluctuating charge models. Moreover, the Drude model is computationally more efficient than either of these approaches and produces a wide range of correct behavior in heterogeneous systems.¹⁶ We anticipate that this new model will yield new insights into nucleic acid-ion interactions as well as properties of Mg^{2+} in solution.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Financial support for this work was provided by the National Institutes of Health, grants F32GM109632 (to J.A.L.), GM070855, and GM051501 (to A.D.M.). Computing time was provided by the Computer-Aided Drug Design Center at the University of Maryland, Baltimore, and by the National Science Foundation XSEDE project. The authors thank Dr. Ashley McDonald for helpful discussions regarding QM calculations on Mg^{2+} -containing systems.

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Figure 1.

Interaction orientations of uracil and DMP with Mg^{2+} ions. (A) Inner-shell (B) outer-shell coordination of Mg^{2+} hydrates by the uracil O2 atom. (C) In-plane configurations of Mg^{2+} as a function of distance from the uracil O2 atom. (D) Monodentate and (E) bidentate oxygen coordination of Mg^{2+} by DMP. In all panels, atoms are colored by element (C = gray, H = white, N = blue, O = red, P = orange, and Mg^{2+} = green).

Figure 2. Schematic of the osmotic pressure calculations. Water molecules are drawn as blue lines, and Mg^{2+} and Cl^{-} ions are shown as purple and green spheres, respectively. The solution in the central 30-Å cubic region contains 1 M MgCl_2 . The vertical, black dashed lines represent virtual half-harmonic walls that restrict Mg^{2+} and Cl^{-} ions to the central volume but are permeable to water molecules.

Figure 3. One-dimensional interaction energy surfaces for water dissociation from a $[\text{Mg} \cdot (\text{H}_2\text{O})_6]^{2+}$ complex. Two different basis sets were compared to check the robustness of the target data. The previous force field (Drude-2013) is compared to the parameters developed in the present work (Drude-New), including an NBFIX on the DOH2 atom type.

Figure 4.
Potential of mean force profiles for the dissociation of one inner-shell water molecule from Mg²⁺ at infinite dilution.

Figure 5.

Apparent self-diffusion coefficients (D_{PBC}) of Mg^{2+} as a function of inverse cell length. The y-intercept corresponds to the size-independent value of D_0 .

Figure 6. RDF of ion-ion and ion-water atom pairs in a 1 M MgCl_2 solution, computed from snapshots saved at 100-ps intervals over a 1- μs MD simulation using the Drude force field parameters derived in the present work.

Figure 7.
Water dipole moment distributions from a 1- μ s MD simulation of a 1 M MgCl_2 solution.

Figure 8.

Osmotic pressure of MgCl_2 solutions as a function of concentration. Inset: Water-mediated inclusions that arose in the Drude-2013 force field at 1 M (1.012 m) concentration that led to impaired diffusion and depressed osmotic pressure values. Mg^{2+} and Cl^- ions are shown as purple and green spheres, respectively, and water molecules are drawn as blue sticks.

Table 1

Properties of the MgCl_2 osmotic pressure systems. The value of $\langle N_{\text{water}} \rangle$ is the time average number of water molecules within $\pm z_{\text{wall}}$.

Concentration, M	Concentration, m	N_{Mg}	N_{Cl}	$\langle N_{\text{water}} \rangle$
0.125	0.124	2	4	896
0.25	0.249	4	8	893
0.5	0.500	8	16	888
1.0	1.012	16	32	877
1.5	1.536	24	48	867
2.0	2.076	32	64	855

Table 2

Pair-specific LJ parameters (NBFIX) and through-space screening (NBTHOLE) for Mg^{2+} with the indicated atom types in the Drude force field.

Atom types	Species	NBFIX		NBTHOLE
		ϵ (kcal mol ⁻¹)	$R_{\min}$ (Å)	t_{ij}
ND2B1-MAGD	Cyt, Gua amine	-0.10818	3.10817	1.343
ND2R5E-MAGD	Ade, Gua N7	-0.16925	2.68762	1.384
ND2R6B-MAGD	Ade, Cyt, Gua N3; Ade N1	-0.09031	3.13208	1.173
ND2R6C/ND2R6D-MAGD	Cyt, Thy, Ura N1	-0.06991	3.37008	1.491
OD2C1B-MAGD	Cyt, Gua, Ura, Thy carbonyl	-0.28833	2.43438	1.109
LPDNA1-MAGD	Lone pairs	-0.16504	2.20163	
OD2C2C-MAGD	Phosphate non- bridging O	-0.31211	2.59990	1.449
OD30BN/OD30BR-MAGD	O3'	-0.40592	4.40157	1.151
CLAD-MAGD	Chloride anion			0.660
DOH2-MAGD	Water O	-0.07500	2.65500	

Table 3

Values of $D_{PBC} (\times 10^{-5} \text{ cm}^2 \text{ s}^{-1})$ for Mg^{2+} using the present Drude model and the CHARMM additive force field⁵⁸ for comparison.

Cell Length (Å)	Drude	CHARMM
30	0.47 ± 0.40	1.36 ± 0.99
40	0.70 ± 0.58	2.12 ± 1.28
50	0.60 ± 0.45	1.77 ± 1.81
D_θ (Linear fit)	0.89	2.71

Table 4

Geometric parameters of B3PW91/LANL2DZ-optimized inner-shell coordinated complexes and the obtained geometries using the Drude force field before and after refinement. Distances are calculated between the indicated atoms and the Mg^{2+} ion in each complex. Characteristic angles of each complex are listed.

Atom	Angle, θ	QM			Drude-2013			Drude-New		
		r (Å)	θ (°)		r (Å)	θ (°)		r (Å)	θ (°)	
Ade-N1	C4-N1-Mg	2.20	164.63		1.75	149.82		2.14	157.99	
Ade-N3	C6-N3-Mg	2.15	172.21		1.76	179.14		2.15	174.04	
Ade-N7	C4-N7-Mg	2.20	161.91		1.66	175.07		2.08	165.35	
Gua-N3	C6-N3-Mg	2.20	166.16		1.84	174.77		2.22	171.49	
Gua-N7	C4-N7-Mg	2.21	161.73		1.70	177.07		2.03	171.81	
Gua-O6	C6-O6-Mg	2.04	145.88		1.93	135.78		1.95	140.93	
Cyt-N3	C6-N3-Mg	2.28	170.17		1.84	174.92		2.20	170.07	
Cyt-O2	C2-O2-Mg	2.04	139.91		1.95	129.25		1.92	148.51	
Ura-O2	C2-O2-Mg	2.01	157.47		1.96	128.18		1.96	167.62	
Ura-O4	C4-O4-Mg	1.99	173.43		1.94	132.55		1.90	171.71	
DMP-O1	P-O1-Mg	2.02	124.21		1.78	114.23		1.93	120.00	
<hr/>										
		Avg. Err.			-0.29			-0.08		
		AUE			0.29			14.96		
		RMSD			0.35			18.13		
								0.09		
								6.12		

Table 5

Geometric parameters of B3PW91/LANL2DZ-optimized outer-shell coordinated complexes and the obtained geometries using the Drude force field before and after refinement. Distances are calculated between the indicated atoms and the Mg^{2+} ion in each complex. Characteristic angles of each complex are listed.

Atom	Angle, θ	QM			Drude-2013			Drude-New		
		r (Å)	θ (°)		r (Å)	θ (°)		r (Å)	θ (°)	
Ade-N1	C4-N1-Mg	4.15	144.20		3.72	160.81		3.96	164.38	
Ade-N3	C6-N3-Mg	4.15	144.32		4.09	164.06		4.29	144.91	
Ade-N7	C4-N7-Mg	4.25	136.29		3.60	139.46		3.70	154.04	
Gua-N3	C6-N3-Mg	4.32	131.22		4.22	141.14		4.37	131.95	
Gua-N7	C4-N7-Mg	4.59	144.56		4.00	163.34		3.93	167.32	
Gua-O6	C6-O6-Mg	3.83	136.65		3.76	139.66		3.88	143.21	
Cyt-N3	C6-N3-Mg	4.27	144.14		4.10	151.19		5.07	131.25	
Cyt-O2	C2-O2-Mg	3.68	154.65		3.66	114.47		3.74	135.29	
Ura-O2	C2-O2-Mg	3.78	175.40		3.93	172.85		4.03	170.41	
Ura-O4	C4-O4-Mg	3.68	173.11		3.86	178.36		3.95	179.23	
DMP-O1	P-O1-Mg	3.94	92.54		3.63	96.41		3.68	97.38	
DMP-O2	P-O2-Mg	3.46	110.70		3.39	106.43		3.46	106.21	
Avg. Err.			-0.18			3.37		0.00	3.15	
AUE			0.23			11.20		0.27	10.11	
RMSD			0.31			15.46		0.37	12.69	

Table 6

Positions and magnitudes of interaction energy minima for *in vacuo* single-point interaction energy calculations of Mg^{2+} with nucleic acid moieties. QM interaction energies were calculated using the MP2/6–311++G(2df,2pd) model chemistry.

Atom	QM		Drude-2013		Drude-New	
	$r_{\min}$ (Å)	$U_{\min}$ (kcal mol ⁻¹)	$r_{\min}$ (Å)	$U_{\min}$ (kcal mol ⁻¹)	$r_{\min}$ (Å)	$U_{\min}$ (kcal mol ⁻¹)
Ade-N1	2.0	-115.97	1.8	-209.32	2.0	-120.97
Ade-N3	2.0	-118.86	1.8	-201.96	2.0	-118.09
Ade-N7	2.0	-105.35	1.6	-179.93	1.9	-90.53
Ade-N6 oop ^a	2.1	-82.38	1.6	-217.37	2.0	-95.74
Gua-N3	2.0	-94.27	1.8	-129.72	2.0	-77.79
Gua-N7	2.0	-148.99	1.7	-195.06	1.9	-143.47
Gua-O6	1.8	-147.50	1.8	-165.27	1.8	-147.58
Cyt-N3	2.0	-128.49	1.8	-164.59	2.0	-123.25
Cyt-N4 oop	2.2	-67.08	1.6	-162.82	2.1	-55.55
Cyt-O2	1.9	-151.79	1.8	-177.48	1.7	-159.55
Ura-N3 oop	2.2	-55.70	1.7	-141.79	2.2	-51.87
Ura-O2	1.8	-113.84	1.8	-116.89	1.8	-93.79
Ura-O4	1.8	-123.12	1.8	-137.27	1.8	-121.91
DMP-mono ^b	1.8	-308.19	1.7	-329.03	1.8	-281.23
DMP-bj ^c	2.3	-347.72	2.0	-430.33	2.2	-338.31
Avg. Err.						
-0.24						
AUE						
0.24						
RMSD						
0.30						
67.88						
0.08						
12.06						

^a Out-of-plane scans are denoted by “oop.”

^b Monodentate scan (see Figure 1D)

^c Bidentate scan (see Figure 1E)