Multipole Moments of Water Molecules and the Aqueous Solvation of Monovalent Ions

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Abstract

The differences in solvation of ions in water play important roles in biology and chemistry, such as the kosmotropic and chaotropic properties of different ions. However, the differences in certain properties of ions in aqueous solutions have been difficult to capture in atomistic computer simulations. Given the uniqueness of water as a liquid, this may be due to oversimplifications in empirical potential energy functions used to describe water in these simulations. Recently, a single-site multipole (SSMP) non-polarizable model of water, which uses multipoles from a quantum mechanical calculation, has been shown to model the properties of liquid water over a range of temperatures and pressures with remarkable accuracy compared to both nonpolarizable and polarizable multi-site models. Thus, it appears to capture features of the average electrostatic potential that other models lack. Here, the ability of SSMP to model the structure of the hydration shell of monovalent ions is investigated. Although only multipoles up to the octupole are needed for water-water interactions, it is shown to be necessary to include the hexadecapole for interactions with charged species, so that the multipole expansion energies are all truncated at order $1/r^5$. More importantly, it is shown that solvation of cations in SSMP water leads to agreement of the orientational distribution of water molecules with *ab initio* molecular dynamics results, unlike typical multi-site models. The additional orientation seen in SSMP water may lead to an understanding of the differences in the kosmotropic and chaotropic properties of sodium and potassium ions.

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Keywords: Ion hydration shell; multipole models; non-polarizable water models; molecular dynamics simulations; sodium chloride; potassium chloride

1. Introduction

Water is the most important solvent for biological and chemical systems on this planet. Therefore, accurate descriptions of liquid water and aqueous solutions are crucial in our understanding of many physical, chemical, and biochemical problems. For instance, simple salts are important for the structure, dynamics, and function of biological macromolecules, including the stability and activity of proteins [1, 2]. For atomistic computer simulations of biological macromolecules, explicit water models are generally considered to be the most accurate method for treating solvent effects, which requires adding neutralizing salts since Ewald methods are generally preferred for handling long-range electrostatic interactions. However, there are indications that current models do not represent ions in water accurately enough to make critical distinctions between important biological ions such as sodium and potassium.

While most potential energy functions for ions do well for free energies of hydration, two problems have recently been noted. In particular, the hydration number of cations is overpredicted in most potential energy functions [3] and the anomalous water diffusion in salt solutions is not even qualitatively predicted by most nonpolarizable and polarizable force fields [4], while *ab initio* molecular dynamics (AIMD) simulations give good agreement with experiment for both the hydration [3] and diffusion [5]. The hydrogen bonding properties of water were pointed out as a source of discrepancies between classical simulations and experiment [5]. However, when the main object of interest is a macromolecular solute as is often the case for biological problems, a balance between accuracy and efficiency of the water model must be considered, thus making AIMD simulations impractical and the search for better empirical models essential.

Recently, some new ideas have come forward in the search for empirical potentials for ions. There are indications that charge transfer may be important for ion-water interactions [6],

since accounting for charge transfer in polarizable models was attributed for giving good diffusion properties [7, 8]. While adding charge transfer may eventually prove necessary, there are also some indications that pair-wise additive approaches can work. For example, a pair-wise approach that also leads to good diffusion behavior uses charge scaling for ions described by more modern force fields [9-12] and reduced dielectric water models [12, 13], which essentially means that the charges of the ions and the waters are moving in a electronic continuum. However, our ultimate goal is to make a solvent force field compatible with current biomolecular force fields that do not use charge scaling. Thus, our focus here is on the water model in the ion-water interaction, while future work will be in the ion parameterization, whereby charge transfer effects are included in the short-range forces such as in the Lennard-Jones potential is possible.

A good description of the electrostatics is the most important determinant of the accuracy of an empirical water model. Although much recent effort has been made in introducing polarizability, considerable evidence indicates nonpolarizable models that account for the average polarization in the condensed phase are sufficient for many problems [14, 15]. Moreover, simple polarizable models have struggled to achieve the same agreement with experiment as the best nonpolarizable models [15], and understanding what makes good nonpolarizable models could lead to better polarizable models. Thus, the focus here is on nonpolarizable pair-wise additive models. Typically, the molecular charge distribution is represented using “partial charges” even though partial charges located on sites can only qualitatively describe electron density. For water, good liquid state properties require “dummy” sites in addition to sites on the nuclei [15, 16]. Alternatively, the electrostatic potential due to a charge distribution can be described by a multipole expansion outside of the charge distribution, which becomes exact in the limits of infinite distances *or infinite order of multipoles* [17, 18]. For electrostatic interactions between water molecules, multipoles up to the octupole appear to

be necessary and sufficient because the octupole is the first moment that breaks the tetrahedral symmetry of the positive charge from the hydrogens and the negative charge from the p -orbital density perpendicular to the molecular plane [19-21]. Interestingly, the soft-sticky dipole-quadrupole-octupole (SSDQO) model [20], a single-site multipole model for water that uses an approximate $1/r^5$ term in the interaction energy, predicts accurate properties of water as a function of temperature and pressure [22] as well as the minimum in the partial molar volume of ethanol in ethanol-water mixtures [23], when the SSDQO1 parameters [22] are used. The dipole and quadrupole mimic hydrogen bonding [24], while the octupole distinguishes between solvation of cations and anions [19, 25]. In effect, *the multipole representation up to octupoles allows a better description of the charge distribution than a partial charge representation using up to five sites.*

In addition, the computational efficiency of a water model is especially important when a macromolecular solute is the focus of interest, since most of the computer time is spent on the water. On one hand, a multipole expansion of the interaction energy gains in efficiency for a complex charge distribution if a single site is used on each molecule since only one distance is calculated between the molecules, while a model with n partial charges per molecule requires n^2 distances. On the other hand, multipole expansions can also lose in efficiency because higher-order tensor multiplications are required. The implementation of MPOLE [26], a computationally fast method for multipole interactions that uses spherical harmonic multipoles within a particle mesh Ewald (PME) framework [27], into the CHARMM molecular mechanics/dynamics program [28] affords the opportunity for exploring accurate and efficient multipole models of water in biological simulations.

Recently, a new single-site multipole (SSMP) model for liquid water has been developed for use with MPOLE, which exhibits even better temperature and pressure dependency of liquid

properties that meet or exceed 4- and 5-site models, but with the computational efficiency of 3-site models [29]. Like SSDQO1, the dipole, quadrupole, and octupole tensors and a van der Waals sphere are all located on a single site in SSMP. However, while SSDQO1 uses multipoles as well as Lennard-Jones parameters that were optimized for standard temperature and pressure (STP) properties of liquid water, SSMP uses multipoles based on QM/MM calculations [30] and only the Lennard-Jones parameters are optimized. The good results for SSMP can be attributed to having both a large quadrupole and a good description of the charge out of the molecular plane, which can be characterized as p -orbital rather than sp^3 -hybridized [30]. These characteristics are found independently in the best site models but not together in one model; *i.e.*, the TIP4P-type [31] models have large quadrupoles due to the “M” site but no out-of-plane charge and the TIP5P-type [32] models have out-of-plane charge due to the two “L” sites but a very small quadrupole.

In developing the SSMP model, the importance of truncating in power of distance rather than order of multipole has recently been demonstrated for water since the higher order multipoles are large [33]. In practical terms, since the MPOLE module truncates in order of multipole, a dipole-octupole term has been added to the implementation in CHARMM. However, it remains to be seen whether a monopole-hexadecapole $1/r^5$ term is needed for interactions between a charge, such as a partial charge on a molecule or the net charge of an ion, and a water molecule. This term was needed for good water structure around sodium when the approximate multipole model SSDQO with multipoles corresponding to SPC/E [34] were used [21], although apparently less so when the SSDQO1 multipoles with a large quadrupole were used [35]. Thus, it is important to investigate the effects of the monopole-hexadecapole term.

Simulations are performed here of a $\text{Na}^+\text{-Cl}^-$ pair in water and of a $\text{K}^+\text{-Cl}^-$ pair in water to examine the effects of multipoles on the structure of water around ions. These two ion pairs are

examined because of their biological importance, and the simulations are at very low concentrations (0.0136 M). Since the emphasis is on the water model in the ion-water interactions rather than the ion parameters, the ion parameter set optimized for TIP4P-Ew [36] in ref. [37] was used because TIP4P-Ew is a reasonable water model for biomolecular simulations. First, molecular dynamics simulations of these two ion pairs in TIP4P-Ew water and in a single-site multipole model with the multipole moments and Lennard-Jones parameters of TIP4P-Ew, referred to here as MP:TIP4P-Ew, are compared. This allows testing of the effects of including hexadecapoles in the ion-water interaction against a case where the charge distribution is known; i.e., the TIP4P-Ew charge distribution. This hexadecapole *only* appears in solute-water interactions, not in water-water interactions since water has no monopoles. Next, simulations of the same two ion pairs in SSMP water are compared with the simulations in TIP4P-Ew water to assess how well the two models perform compared to experimental and AIMD results from the literature. In addition, the differences between the hydration shells of SSMP and TIP4P-Ew are discussed in terms of how they could affect the properties of ions in aqueous solution.

2. Theory and methods

2.1. Multipolar Model for Ion-Water Interactions

The multipole parameters utilized here are defined in a molecular coordinates system centered on the water oxygen with the positive z -axis pointing towards the hydrogens and the y -axis parallel to the molecular plane. A monopole, or charge, is referred to as q , and in terms of the traceless Cartesian multipole tensors for the dipole μ , the quadrupole Θ , the octupole Ω , and the hexadecapole H , the spherical harmonic components μ_0 , Θ_0 , Θ_2 , Ω_0 , Ω_2 , H_0 , H_2 , and H_4 are defined as

$$m_0 = m_z \quad (1)$$

$$\begin{aligned} Q_0 &= Q_{zz} \\ Q_2 &= \frac{1}{2} (Q_{yy} - Q_{xx}) \end{aligned} \quad (2)$$

$$\begin{aligned} W_0 &= W_{zzz} \\ W_2 &= \frac{1}{2} (W_{yyz} - W_{xxz}) \end{aligned} \quad (3)$$

$$\begin{aligned} H_0 &= H_{zzzz} \\ H_2 &= \frac{1}{2} (H_{yyzz} - H_{xxzz}) \\ H_4 &= \frac{1}{8} (H_{xxxx} - 6H_{xxyy} + H_{yyyy}) \end{aligned} \quad (4)$$

The electrostatic interaction energy between an ion of charge q and a water molecule with moments $\boldsymbol{\mu}$, $\boldsymbol{\Theta}$, $\boldsymbol{\Omega}$, and $\mathbf{H}$, to order $1/r^5$ is given by

$$U_{i-w} = -\frac{q\boldsymbol{\mu} \cdot \mathbf{n}}{r^2} + \frac{q\boldsymbol{\Theta} : \mathbf{n}^{(2)}}{r^3} - \frac{q\boldsymbol{\Omega} \setminus \mathbf{n}^{(3)}}{r^4} + \frac{q\mathbf{H} :: \mathbf{n}^{(4)}}{r^5} + \dots \quad (5)$$

where $\mathbf{r} = r\mathbf{n}$ is the internuclear vector from the ion to the water, the dyadic products are denoted by $[\mathbf{n}^{(2)}]_{ij} = n_i n_j$, $[\mathbf{n}^{(3)}]_{ijk} = n_i n_j n_k$, and $[\mathbf{n}^{(4)}]_{ijkl} = n_i n_j n_k n_l$, and the matrix contractions are denoted by $\mathbf{A} \cdot \mathbf{B} = \sum_i A_i B_i$, $\mathbf{A} : \mathbf{B} = \sum_{ij} A_{ij} B_{ij}$, $\mathbf{A} \setminus \mathbf{B} = \sum_{ijk} A_{ijk} B_{ijk}$, and $\mathbf{A} :: \mathbf{B} = \sum_{ijkl} A_{ijkl} B_{ijkl}$. The first term will be referred to as the $q\text{-}\boldsymbol{\mu}$ term, the second as the $q\text{-}\boldsymbol{\Theta}$ term, the third as the $q\text{-}\boldsymbol{\Omega}$ term, and the final as the $q\text{-}\mathbf{H}$ term. The water-water interaction energy between two water molecules i and j to order $1/r^5$ is given by

$$\begin{aligned} U_{ij}(\mathbf{r}) &= \frac{1}{r^3} [m_i \cdot m_j - 3(\mathbf{n} \cdot m_i)(m_j \cdot \mathbf{n})] \\ &+ \frac{1}{r^4} [-2m_i \cdot Q_j \cdot \mathbf{n} + 2\mathbf{n} \cdot Q_i \cdot m_j + 5(\mathbf{n} \cdot m_i)(Q_j : \mathbf{n}^{(2)}) - 5(\mathbf{n}^{(2)} : Q_i)(m_j \cdot \mathbf{n})] \\ &+ \frac{1}{3r^5} [2Q_i : Q_j - 20(\mathbf{n} \cdot Q_i) \cdot (Q_j \cdot \mathbf{n}) + 35(\mathbf{n}^{(2)} : Q_i)(Q_j : \mathbf{n}^{(2)}) \\ &\quad + 9m_i \cdot (W_j : \mathbf{n}^{(2)}) + 9(\mathbf{n}^{(2)} : W_i) \cdot m_j - 21(\mathbf{n} \cdot m_i)(W_j \setminus \mathbf{n}^{(3)}) - 21(\mathbf{n}^{(3)} \setminus W_i)(m_j \cdot \mathbf{n})] \\ &+ \dots \end{aligned} \quad (6)$$

The multipole expansion truncated at order of octupoles as in the MPOLE module is given in ref. [33].

$\begin{matrix} j \\ i \end{matrix}$	q	μ	Θ	Ω	H
q	qq/r	$q\mu/r^2$	$q\Theta/r^3$	$q\Omega/r^4$	qH/r^5
μ	$q\mu/r^2$	$\mu\mu/r^3$	$\mu\Theta/r^4$	$\mu\Omega/r^5$	$\mu H/r^6$
Θ	$\Theta q/r^3$	$\Theta\mu/r^4$	$\Theta\Theta/r^5$	$\Theta\Omega/r^6$	$\Theta H/r^7$
Ω	$\Omega q/r^4$	$\Omega\mu/r^5$	$\Omega\Theta/r^6$	$\Omega\Omega/r^7$	$\Omega H/r^8$
H	Hq/r^5	$H\mu/r^6$	$H\Theta/r^7$	$H\Omega/r^8$	HH/r^9

Fig. 1.

Multipole interaction terms between particles i and j . Terms included in the SSMP $1/r^5$ truncation scheme are outlined by a thick black line while terms included in an octupole truncation are outlined by a thick dashed line.

The terms involved in the multipole expansion are illustrated in Fig. 1. Terms appearing in a truncation at order of multipole are within a square box while those in a truncation in power of $1/r$ are within an upper left triangle. Since the MPOLE algorithm truncates according to multipole order, terms in the green area are calculated via MPOLE; i.e., up to the quadrupole. The terms in the yellow area are calculated separately and added in. Note that if MPOLE were used to calculate terms up to the octupole, then the unshaded terms could be subtracted out by calculating them separately but this is less efficient because it involves higher order tensor operations and the qH terms would still need to be calculated separately.

Table 1.

Charge and Lennard-Jones parameters for ions and water models.

Species	Site	q (e)	σ (Å)	ϵ (kcal/mol)
Na ⁺ for TIP4P-Ew	Na ⁺	+1.0	2.1845	0.1684
K ⁺ for TIP4P-Ew	K ⁺	+1.0	2.8331	0.2795
Cl ⁻ for TIP4P-Ew	Cl ⁻	-1.0	4.9178	0.01166
TIP4P-Ew	O	0.0	3.16435	0.16275
TIP4P-Ew	H	0.52422	N/A	N/A
TIP4P-Ew	M	-1.04844	N/A	N/A
MP:TIP4P-Ew	O	0.0	3.16435	0.16275
SSMP	O	0.0	3.275	0.106

2.2. Computational methods

Molecular dynamics (MD) simulations were performed using the molecular mechanics package CHARMM development version c41 [28]. The procedure mostly followed the default protocol in CHARMMing [38]; pertinent details including changes from the default protocols are noted here. The water molecules were represented by either SSMP [29], MP:TIP4P-Ew, or TIP4P-Ew [36]. Sodium, potassium, and chloride ions were represented using parameters optimized for TIP4P-Ew [37]. The force field parameters are given in Table 1 and Table 2.

Table 2.

Multipole parameters for SSMP and MP:TIP4P-Ew water.

Model	μ_0 (D)	Θ_0 (DÅ)	Θ_2 (DÅ)	Ω_0 (DÅ ²)	Ω_2 (DÅ ²)	H_0 (DÅ ³)	H_2 (DÅ ³)	H_4 (DÅ ³)
SSMP	2.28	0.11	2.46	-1.33	1.61	-1.43	1.13	0.90
MP:TIP4P-Ew	2.321	0.207	2.164	-1.533	2.113	-1.759	1.340	0.904

The nonbonded interactions were handled as follows. Pair and image lists were generated out to 12 Å and updated heuristically. The van der Waals interactions were turned off using the CHARMM switching function from 8 to 10 Å. The electrostatic interactions for simulations using either SSMP or MP:TIP4P-Ew were calculated using MPOLE, which uses PME with a β -spline of order 6, a κ value of 0.55 Å^{-1} , 100 k -vectors in each Cartesian direction, and a real space truncation at 7 Å. In addition, the predominantly short-ranged charge-octupole, dipole-octupole, and charge-hexadecapole interactions are treated on a pair-wise basis in real space at short range and are smoothly reduced to zero between 5 Å and 7 Å using the CHARMM switching function. The electrostatic interactions for simulations with TIP4P-Ew were calculated using PME with a β -spline coefficient of 6, a κ value of 0.34 Å^{-1} , 100 k -vectors in each Cartesian direction, and a real space truncation at 10 Å. The limits of the integration of the radial distribution to determine the coordination numbers of the ions were chosen to match those of Soper [39], which were 3.20 Å for $\text{Na}^+\text{-O}$, 3.45 Å for $\text{K}^+\text{-O}$, and 3.80 Å for $\text{Cl}^-\text{-O}$.

Cubic simulation boxes were prepared from equilibrated boxes of pure water with 4096 water molecules and a side length of $L_0 = 49.81 \text{ Å}$. A single ion pair of NaCl or KCl replaces two water molecules, so the final number of water molecules in each box is 4094 and the concentration is 0.0135 M. The simulations employed the leapfrog Verlet algorithm [40] with a time step of 1 fs. Initially, the ion pair is harmonically restrained to remain at the positions $(-L_0/4, 0, 0)$ and $(+L_0/4, 0, 0)$ with a force constant of 200 kcal/mol/Å^2 . After heating from 98 K to 298 K in 5 K increments for 100 ps in the NVT ensemble, the systems were allowed to run unperturbed except for the harmonic restraints on the ion pair in the NPT ensemble at a pressure of 1 atm and temperature of 298 K using the Nosé-Hoover algorithm [41, 42] for 1 ns to equilibrate the density. Then, the ion pair is constrained at the positions $(-L_0/4, 0, 0)$ and $(+L_0/4,$

0, 0) and the systems were allowed to run unperturbed in the *NVT* ensemble at a temperature of 298 K for a further 1 ns of equilibration and 4 ns of production. However, since the equilibrated density of MP:TIP4P-Ew at 1 atm was found to be substantially higher than that for TIP4P-Ew, the simulations for MP:TIP4P-Ew were at the average volume for TIP4P-Ew water in the *NVT* ensemble.

Fig. 2.

Diagram of hydrogen directions (solid arrows) and lone pair directions (dashed arrows).

3. Results and discussion

The simulations are (1) to assess the importance of including the charge-hexadecapole $1/r^5$ term in describing electrostatic interactions between monovalent ions and water using multipole expansion and (2) to assess how well the SSMP model describes aqueous solvation of monovalent ions. While there have been recent attempts to improve the quality of the ion force field as described in the introduction, the simulations here do not address assessing the parameterization of the ions; instead they focus on the water contributions to the ion-water interactions.

To describe directions in the molecular frame of a water molecule, vectors are defined from the origin to a tetrahedron placed symmetrically about the origin such that two of its

vertices lie in the positive z -direction and the y - z plane while the other two lie in the negative z -direction and the x - z plane. The vectors from the origin to the first two vertices define the “hydrogen” directions while those from the origin to the second two vertices define the “lone pair” directions (Fig. 2). Radial distribution functions $g(r)$, coordination numbers of the first hydration shell n , and the orientational probability of θ , the angle between the water dipole vector and the ion-water internuclear vector, of water in the first hydration shell (Fig. 3) are examined. Fig. 3 also illustrates typical orientations found in the simulations. The quantities are identified by subscripts “ ab ”, where a is the ion and b is the water atom; in addition, “+” and “−” are used to refer to the general cases of cations and anions, respectively. The first hydration shell around an ion was defined as all water within a distance of 3.20 Å for Na^+ -O, 3.45 Å for K^+ -O, and 3.80 Å for Cl^- -O.

Fig. 3.

Orientations of water relative to the ion with r_{qO} and θ and μ labeled for (a) linear hydrogen bond orientation typical around an anion (green) and (b) dipole orientation or (c) lone-pair orientation typical around a cation (purple).

3.1. Importance of the q -**H** term.

First, the importance of the q -**H** term is assessed by comparing simulations of ions in MP:TIP4P-Ew against those of ions in TIP4P-Ew. While an infinite expansion in multipoles should give complete agreement between MP:TIP4P-Ew and TIP4P-Ew, here the water-water interaction for MP:TIP4P-Ew uses moments up to the octupole of TIP4P-Ew and so it reproduces TIP4P-Ew only qualitatively (Fig. S1 and S2 in supplementary data; also see comparison of MP:SPC/E vs SPC/E in ref. [33]). However, the focus here is on the ion-water

structure, and it should be adequate for examining effects of truncating the interaction energy after the $q\text{-}\Omega$ term versus after the $q\text{-}\mathbf{H}$ term (Eq. 5).

Table 3.

Coordination numbers for NaCl and KCl in aqueous solution.

Water Model	<u>NaCl in solution</u>		<u>KCl in solution</u>	
	n_{NaO}	n_{ClO}	n_{KO}	n_{ClO}
MP:TIP4P-Ew, without $q\text{-}\Omega$	6.5	7.5	7.9	7.4
MP:TIP4P-Ew, with $q\text{-}\mathbf{H}$	5.9	7.4	7.3	7.4
TIP4P-Ew	5.9	6.8	6.7	6.8
SSMP, without $q\text{-}\Omega$	6.0	7.1	7.0	7.1
SSMP, with $q\text{-}\mathbf{H}$	5.8	7.1	6.7	7.1
AIMD (0.88 M) [43]	5.2 ± 0.1	NA	7.1 ± 0.4	NA
AIMD (0.88 M) [3]	5	NA	6	NA
Exp (0.7 M) [39]	5.3 ± 0.8	6.9 ± 1.0	6.0 ± 1.2	7.0 ± 1.1

From the $g(r)$ for water around the ions in the NaCl aqueous solutions (Fig. 4a), MP:TIP4P-Ew appears able to model the solvation structure around the ions in agreement with TIP4P-Ew if the $q\text{-}\mathbf{H}$ term is included, but excluding this term gives poorer agreement around Na^+ . In particular, without the $q\text{-}\mathbf{H}$ term, the second peak in g_{NaO} is somewhat less peaked than that in TIP4P-Ew and, more disturbingly, the first peak in g_{NaH} is split into two peaks while it is a single peak in TIP4P-Ew. Examining the coordination numbers (Table 3), including the $q\text{-}\mathbf{H}$ term gives values in reasonable agreement with TIP4P-Ew especially around Na^+ , but excluding the $q\text{-}\mathbf{H}$ term results in values that are consistently too large.

In addition, from the orientational distribution of θ for water molecules in the first solvation shell (Fig. 4b), it is apparent that the $q\text{-}\mathbf{H}$ term contributes significantly to the orientation of water molecules around both Na^+ and Cl^- . While TIP4P-Ew predicts the water

molecules to form a linear hydrogen bond to Cl^- (Fig. 3a) as generally accepted, lack of the $q\text{-H}$ term leads to a tendency to tilt beyond a linear hydrogen bond. In addition, while TIP4P-Ew predicts the water molecules to adopt a dipolar orientation with respect to Na^+ (Fig. 3b), lack of the $q\text{-H}$ term leads to an overpopulation of water molecules around Na^+ with the ion located in a bent orientation of the dipole vector and a slight population with their dipole vector nearly perpendicular to the internuclear vector. The inclusion of the $q\text{-H}$ term seems to lead to a slight overcorrection since the simulations with SSMP show more in a dipolar orientation with respect to the Na^+ compared to the distributions in TIP4P-Ew. However, overall the inclusion of the $q\text{-H}$ term gives reasonable agreement with TIP4P-Ew.

(a)

(b)

Fig. 4.

Comparisons of (a) radial distribution functions of $\text{Na}^+\text{-O}$, $\text{Na}^+\text{-H}$ (shifted upwards by 2), $\text{Cl}^-\text{-O}$ (shifted upwards by 4), and $\text{Cl}^-\text{-H}$ (shifted upwards by 6) and (b) orientational probability of the first shell of water around Cl^- (left peak, squares) and Na^+ (right peak, circles) for MP:TIP4P-Ew (blue lines and solid symbols), MP:TIP4P-Ew without the $q\text{-H}$ term (blue dashed lines and open symbols), and TIP4P-Ew (green line and solid symbols).

From the radial distribution functions for the ions in the KCl aqueous solutions (Fig. 5a), MP:TIP4P-Ew also appears able to model the solvation structure around the ions in agreement with TIP4P-Ew if the q -**H** term is included, but excluding this term also gives a split first peak in g_{KH} around K^+ similar to the Na^+ case. Examining the coordination numbers (Table 4), including the q -**H** term gives values that are somewhat too large compared to in TIP4P-Ew, but excluding the q -**H** term results in values that are even worse, also similar to the NaCl solutions. From the orientational distribution of first solvation shell θ (Fig. 5b), the effects of the q -**H** term mirror the results for the NaCl in solution. However, one interesting difference is that even with the inclusion of the q -**H** term, MP:TIP4P-Ew yields *fewer* water molecules in the dipole orientation with respect to K^+ compared to the results for TIP4P-Ew.

(a)

(b)

Fig. 5.

Comparisons of (a) radial distribution functions of $\text{K}^+\text{-O}$, $\text{K}^+\text{-H}$ (shifted upwards by 2), $\text{Cl}^-\text{-O}$ (shifted upwards by 4), and $\text{Cl}^-\text{-H}$ (shifted upwards by 6) and (b) orientational probability of the first shell of water around Cl^- (left peak, squares) and K^+ (right peak, circles) for MP:TIP4P-Ew (blue lines and solid symbols), MP:TIP4P-Ew without the $q\text{-H}$ term (blue dashed lines and open symbols), and TIP4P-Ew (green lines and solid symbols).

To examine the origin of the split first peak of g_{+H} when the $q\text{-H}$ term is omitted, the orientational distributions of each peak are calculated separately. For the water molecules in the first solvation shell, “inner” and “outer” hydrogens are defined as less than or more than 3.0 Å from the sodium ion and less than or more than 3.4 Å from the potassium ion (*i.e.*, based on the minimum in the split peak of g_{+H} for MP:TIP4P-Ew) and then the orientational distributions of the water molecules are calculated separately (Fig. 6, see also Fig. S3 and S4 in supplementary data for both ions and with and without the $q\text{-H}$ term). As suggested by the observation that the distributions of both the inner and outer hydrogens have a peak at $\theta = \sim 40^\circ$, analysis of the simulations shows that the split peak of g_{+H} arises mainly from water molecules oriented at $\theta = \sim 40^\circ$ with one hydrogen predominantly along the internuclear vector pointing away from the ion and the other pointing diagonally towards the ion. This can be understood by the symmetries of the spherical harmonics in the multipole expansion of the water potential. The Ω_2 term makes the potential more positive in the hydrogen directions, which is a better description of the electrostatic potential due to the hydrogens, but also makes the potential more negative in the $y\text{-}z$ plane in the negative z -direction, which is unphysical and leads to the split peak with one hydrogen nearer and one hydrogen further. The H_2 term corrects for this by making the potential in the negative z -direction more positive in the $y\text{-}z$ plane and more negative in the $x\text{-}y$ plane. In other words, the H_2 term disfavors the $\theta = \sim 40^\circ$ orientation that gives rise to the split peak in g_{+H} . In addition, some of the water appears to be oriented with their dipole vectors almost perpendicular to the internuclear vector; these are apparently due to interacting with the $\theta = \sim 40^\circ$ orientation water molecules.

Fig. 6.

Comparisons of orientational distribution of MP:TIP4P-Ew waters *without* the $q\text{-H}$ term from the inner $g(r)$ peak for $\text{Na}^+\text{-H}$ (small solid circles), from the outer $g(r)$ peak for $\text{Na}^+\text{-H}$ (large solid circles) and from both peaks (blue dashed line, no symbols). The molecular inset illustrates the dominant orientation.

The lack of dipolar oriented water molecules when the $q\text{-}\mathbf{H}$ term is omitted can also be understood by the symmetries of the spherical harmonics in the multipole expansion. In the positive z -direction, the Ω_0 term corrects the positive potential from the dipole μ_0 by spreading it into the x - y plane, which is a better description of the electrostatic potential due to the hydrogens, but in the negative z -direction, it also spreads the negative potential from μ_0 into the x - y plane, which overestimates the separation of p -orbital density perpendicular to the z -axis. The H_0 term corrects for this by further enhancing the spread in the x - y plane in the positive z -direction while decreasing the spread in the x - y plane in the negative z -direction, thus improving the description of both the hydrogens and the p -orbital density. In other words, the H_0 term will concentrate the negative electrostatic potential downward in the negative z -direction and thus favor a dipolar orientation with respect to a cation. However, the effects of the H_0 term is less important for water-water interactions since it is rare for two water molecules to be aligned in a head to tail configuration in the pure liquid.

Overall, the simulations of both ion pairs in MP:TIP4P-Ew appear to give the best agreement with simulations of the ion pairs in TIP4P-Ew when the ion-water multipole interaction energy (Eq. 5) is truncated after the $q\text{-}\mathbf{H}$ term. Therefore, the $q\text{-}\mathbf{H}$ term appears to be essential for the ion-water interaction energy. However, adding a hexadecapole to the water-water interaction at the lowest power of $1/r$ (i.e., a $\mu\text{-}\mathbf{H}$ $1/r^6$ term) is not recommended since this would entail also adding a $\Theta\text{-}\mathbf{\Omega}$ term as well as a $q\text{-}2^5$ -pole term in the ion-water interaction energy. We caution that adding only certain terms at a given power of $1/r$ for water can lead to greater error since the multipoles are all of approximately the same magnitude and so there can be significant cancellation. The $1/r^5$ truncation scheme needed for charge-water as well as water-water interactions is available in the CHARMM developmental code.

Fig. 7.

Comparisons of (a) radial distribution functions of $\text{Na}^+\text{-O}$, $\text{Na}^+\text{-H}$ (shifted upwards by 2), $\text{Cl}^-\text{-O}$ (shifted upwards by 4), and $\text{Cl}^-\text{-H}$ (shifted upwards by 6) and (b) orientational probability of the first shell of water around Cl^- (left peak, squares) and Na^+ (right peak, circles) for SSMP (red lines and solid symbols), SSMP without the $q\text{-H}$ term (red dashed lines and open symbols), TIP4P-Ew (green lines and solid symbols), and AIMD (black) from ref. [43].

3.2. Assessment of the SSMP water model for the structure of the hydration shell of ions.

Next, the SSMP water was assessed for its ability to reproduce the solvation structure for ions in aqueous solution using the same ion parameters as in the previous calculations for TIP4P-Ew. The radial distribution functions for the ions in the NaCl aqueous solutions (Fig. 7a) using the SSMP model with the q -**H** term appear very similar to those for TIP4P-Ew. Without the q -**H** term, the first peak in SSMP is broadened although not so clearly split as in MP:TIP4P-Ew. The coordination numbers (Table 3) for SSMP with the q -**H** term are also quite similar to TIP4P-Ew; although the value around Cl^- appears too large, this may be a property of the multipole interaction energy since this was also observed for MP:TIP4P-Ew. Although there is little data from experiment or AIMD simulations at low concentrations, values for both SSMP and TIP4P-Ew appear to be a little high.

Interestingly, from the orientational distribution of first solvation shell θ (Fig. 7b), SSMP appears to have an even greater population of water molecules with a lone pair pointing to the Na^+ and a lesser population in a dipolar orientation than TIP4P-Ew. Recent AIMD simulations also show this broader range of θ [5, 43, 44]. In addition, the lack of the q -**H** term appears to overestimate the population of waters with the lone pair pointing toward the Na^+ .

From radial distribution functions for the ions in the “infinite” dilution KCl aqueous solutions (Fig. 8a), SSMP appears to give solvation structure similar to TIP4P-Ew, although the lack of the q -**H** term does not appear to be as important as for MP:TIP4P-Ew. Also, the trends for the coordination numbers (Table 3) and the orientational distribution of first solvation shell θ (Fig. 8b) mirror the results for the NaCl solutions.

Fig. 8.

Comparisons of (a) radial distribution functions of $\text{K}^+\text{-O}$, $\text{K}^+\text{-H}$ (shifted upwards by 2), $\text{Cl}^-\text{-O}$ (shifted upwards by 4), and $\text{Cl}^-\text{-H}$ (shifted upwards by 6) and (b) orientational probability of the first shell of water around Cl^- (left peak, squares) and K^+ (right peak, circles) for SSMP (red lines and solid symbols), SSMP without the $q\text{-H}$ term (red dashed lines and open symbols), TIP4P-Ew (green lines and solid symbols), and AIMD (black) from ref. [43].

Overall, the simulations of both ion pairs in SSMP (with the q - $\mathbf{H}$ term) and TIP4P-Ew give similar results for the ion-water radial distribution functions and coordination numbers, although the coordination numbers appear to be somewhat high compared to existing experimental data and AIMD simulations, although both were at much higher concentrations than the simulations where the coordination numbers should decrease. The most notable difference between SSMP and TIP4P-Ew is in the distribution of θ , the angle between the dipole vector and the ion-water internuclear vector within the first solvation shell. The preference for the dipole orientation appears to be a characteristic of three- and four-site models [35], not just TIP4P-Ew, presumably because of the lack of out-of-plane charge. Moreover, the broader distribution of θ predicted by SSMP is in good agreement with AIMD simulations. We also note that the same Lennard-Jones parameters for the ions were utilized in both the SSMP and the TIP4P-Ew simulations, even though the Lennard-Jones parameters were optimized for use with TIP4P-Ew. Given the discrepancies in the coordination numbers for SSMP with experiment and AIMD, future research will be on optimizing Lennard-Jones parameters for these ions in SSMP water. The broader distribution of angles between the dipole vector and the ion-water internuclear vector is relatively independent of the Lennard-Jones parameters since the angular distribution is driven by the asymmetries in the electrostatic potential, which will be maintained since the SSMP model will be used.

3.3. Orientation of SSMP water in the first hydration shell of ions.

Finally, the orientations found in the first hydration shell using SSMP are examined further. As in the analysis for Fig. 6, the orientational distributions of waters are separated into those with their hydrogens closer (inner) and further (outer) from the ion based on the same distances, although the first peak of $g_{\text{+H}}$ is not split (Fig. 7a and 8a). As might be expected, the water molecules in the lone pair orientation (Fig. 3c) have their hydrogens closer to the ion while

those in the dipole orientation (Fig. 3b) have their hydrogens further from the ion, although this does not lead to broadening of the g_{+H} peak compared to TIP4P-Ew in either NaCl or KCl solutions (Fig. 7a and 8a). Interestingly, comparisons of the inner and outer distributions in NaCl (Fig. 9a) with those in KCl (Fig. 9b) indicate that while the probability of the lone pair orientation is almost the same, the probability of the dipole orientation is much smaller around K^+ . This suggests that the chaotropic properties of Na^+ may be due to the dipole oriented waters, while the weakly kosmotropic properties of K^+ may arise because the lone pair oriented waters predominate over weakly dipole oriented waters.

Fig. 9.

Comparisons of orientational distribution contributions of SSMP waters with the $q\text{-H}$ term around (a) Na^+ and (b) K^+ from the inner $g(r)$ peak for $+H$ (small solid circles), from the outer $g(r)$ peak for $+H$ (large solid circles) and from both peaks (red solid line, no symbols). Distribution from AIMD simulations (black) from ref. [43] is also shown.

4. Conclusions

Molecular dynamics simulations of Na^+ , K^+ , and Cl^- in nonpolarizable, pair-wise additive models of water have been used to investigate how well single-site multipole models of water are able to reproduce structural observations about the hydration of monovalent ions from experiment or AIMD simulations. For water-water interactions, these multipole models truncate the multipole expansion of the interaction energy after the $1/r^5$ term, which includes dipoles, quadrupoles, and octupoles. These studies were performed using Lennard-Jones parameters for the ions that were optimized for the TIP4P-Ew model. Additionally, more recent ion parameters have been developed for pairwise-additive force fields [9-12]. Since the SSMP model appears to reproduce the orientational structure of water in AIMD simulations by including the effect of the out-of-plane charge, future work includes optimization of the Lennard-Jones parameters of the ions for SSMP to better reproduce experimental and AIMD coordination numbers as well as other solution properties. In particular, since the SSMP model is meant for use with current biomolecular force fields, the electronic continuum assumption used in the development of recent ion parameters [12, 13] can not be used.

It should be noted that these conclusions are based on the importance of higher multipoles for multipole models of water. The SSMP model includes the average effects of polarization since the multipoles were obtained from a QM/MM calculation in which a QM water was polarized by four MM neighbors [30] into all of the multipoles, so the multipole representation here includes both permanent and induced effects. These effects increase the magnitude of permanent spherical multipole moments by $\sim 10\%$ to $\sim 30\%$ even for the hexadecapole, which indicate that polarization effects beyond the dipole may be important in polarizable site models as well.

The first conclusion is that the ion-water interaction energy must include the charge-hexadecapole $1/r^5$ term. The major contribution of this term appears to be in the orientation of water molecules with respect to the internuclear vector around cations. In particular, while it has been recognized that it is necessary to include the octupole in multipole expansion of the potential for water for ion-water interactions, this work shows that it is also necessary to include the hexadecapole, but only for ion-water interactions and not for water-water interactions. In particular, this is critical for implementation of multipole water models for use with partial charge descriptions of a solute in typical biomolecular force fields such as CHARMM, Amber, GROMACS, OPLS, etc.

The second conclusion is that the SSMP (single-site multipole) water model, which is based on the multipoles from a quantum mechanical calculation of a water molecule in a liquid-like cluster, gives a better description of the orientation of water molecules with respect to the internuclear vector found in AIMD simulations than models lacking out-of-plane charge. In particular, the multipoles in SSMP characterized the *p*-orbital nature of the out-of-plane charge, which is not accounted for in three- and four-site models and differs from the “lone pair” type out-of-plane charge in common five-site models. Since three-, four-, and five-site models have been shown to give significantly different orientational distributions than AIMD [35], SSMP appears to represent the electrostatic potential of a water molecule probed by monovalent ions more accurately than these site models. Since SSMP has good temperature and pressure dependence for pure liquid properties, optimization of the Lennard-Jones parameters of ions for SSMP affords the opportunity to study temperature and pressure dependence for aqueous ionic solutions.

Finally, the prediction of water in the lone pair orientation in the first hydration shell of monovalent cations by SSMP and AIMD may be key to understanding the molecular origins of

the kosmotropic and chaotropic properties of these ions. The results here are suggestive that the relative populations of water in the lone pair versus dipolar orientations may play a role.

Acknowledgments

TI is grateful for support from the National Science Foundation through Grant No. CHE-1464766 and from the McGowan Foundation. JMR acknowledges support from the Department of Energy/National Nuclear Security Administration through Grant No. DE-NA-0002006 for the Carnegie/DOE Alliance Center (CDAC) and from the Alfred P. Sloan Foundation through the Deep Carbon Observatory. This work used time on the LoBoS cluster at the Laboratory for Computational Biology, National Heart, Lung, and Blood Institute, National Institutes of Health, which was generously provided by Dr. Bernard R. Brooks. The authors also thank Drs. Frank C. Pickard IV, Andrew C. Simmonett, and Russell J. Hemley for many helpful discussions.

Appendix A. Supplementary data.

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