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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.

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

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[12,13], which essentially means that the charges of the ions and the waters are moving in an 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 Na^+-Cl^- pair in water and of a K^+-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 $\boldsymbol{\mu}$, the quadrupole $\boldsymbol{\Theta}$, the octupole $\boldsymbol{\Omega}$, and the hexadecapole $\mathbf{H}$, the spherical harmonic components μ_0, Θ_0, Θ_2, Ω_0, Ω_2, H_0, H_2, and H_4 are defined as.

$$\ddot{E}_0 = \ddot{E}_z \tag{1}$$

$$\begin{aligned}\Theta_0 &= \Theta_{zz}\\ \Theta_2 &= \frac{1}{2}\left(\Theta_{yy}-\Theta_{xx}\right)\end{aligned} \tag{2}$$

$$\begin{aligned}\Omega_0 &= \Omega_{zzz}\\ \Omega_2 &= \frac{1}{2}\left(\Omega_{yyz}-\Omega_{xxz}\right)\end{aligned} \tag{3}$$

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

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