ION PARAMETRIZATION IN WATER-LIGAND SYSTEMS

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ABSTRACT

Metal ion-water-ligand interactions play myriad roles in biochemical, pharmaceutical, and medical sciences. For example, over 27% of all proteins have more than one metal binding site, according to the known PDB data up to the end of 2022. Because force field models are built on Newtonian mechanics and dynamics, they offer fast and detailed ways to simulate, analyze and visualize chemical processes at the level of atoms. The accuracy and transferability of force field models can be further improved using suitable Molecular Dynamics protocols or data analysis workflows. Nonetheless, the most significant challenge that force field models face is related to metal ions, specifically, simulating metal ion-ligand interactions in water or more complex systems such as metalloproteins. Various force field models have been developed and are in high demand. These force field models include the bonded, nonbonded, bonded non-bonded hybrid models featuring cationic dummy atoms and polarizable models featuring Drude oscillators with fluctuating charges.

In the past six years, the work covered by this dissertation was mainly focused on providing parameters and improving the performance of the nonbonded models, which are the most widely used force field models. First, it was discovered that the traditional 12-6 Lennard - Jones model has limited accuracy when describing metal ion–water systems. This makes it hard to reproduce different experimental properties simultaneously. Based on the physical origins of the 12-6 model, an augmented nonbonded model, named the 12-6-4 LJ-type nonbonded model, has been previously proposed. However, this 12-6-4 LJ-type nonbonded model was not compatible with various new water models, like OPC3, OPC, TIP3P-FB and TIP4P-FB. Therefore, 60 different ions (including 8 monovalent cations, 4 monovalent anions, 24 divalent cations, 18 trivalent cations, and 6 tetravalent cations) were re-parametrized for the four new water models to expand the compatibility of this 12-6-4 LJ-type nonbonded model with the new water models. Further testing on these parameters proved that the 12-6-4 model could simultaneously reproduce

hydration-free energies and ion-oxygen distances with high confidence levels.

Second, the parameters obtained were used in the investigation of ion diffusion and ligand exchange in water. Fifteen ions (3 monovalent anions, 4 monovalent cations, 5 divalent cations, and 3 trivalent cations) had their diffusion coefficients calculated in OPC3, OPC, TIP3P-FB, and TIP4P-FB water models using an automated workflow ISAIAH (Ion Simulation using AMBER for dIffusion Action when Hydrated). A total of 60 simulated diffusion coefficients were obtained, with values within $\pm 20\%$ of the experimental values.

Third, a pure programming contribution was needed by the AMBER molecular dynamics software package community. To improve the user-friendliness of implementing parameters for the 12-6-4 nonbonded model, modifications of the AMBER22 source code were conducted. These modifications allow users to add 12-6-4 potentials not only between two designated atom types but also between two single designated atoms, leading to specific interactions.

Fourth, with proper computational support from the AMBER source code about the atom-specific pairwise potentials, the 12-6-4 potentials were then transferred to ligand (imidazole and acetate) systems. To guarantee the accuracy of ion-ligand-water simulation, the polarizability of ligating atoms was further parametrized to keep both ion-water and ion-ligand interactions consistent with the experiment.

Fifth, the parameters designed for the ion-ligand-water system are applied to two protein systems. The first is an artificial protein TriCyt3 (PDB ID: 6WZC), which is used to test the robustness of the parametrization process for a protein that is totally unknown in evolution or homology models. The second is a membrane protein hZIP8 (PDB ID: 5TSA with a slight homology modification), which is used to test the transferability of these parameters in a complex environment that contains water, lipid, and protein with a variety of dielectric constants in the background. Copyright by ZHEN LI 2023 This dissertation is dedicated to my grandmother, Bao-He Shen, who took care of me from threemonth-eight-day old to middle school with unconditional love, as well as steadfast support.

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LIST OF ABBREVIATIONS

AMBER	Assisted Model Building with Energy Refinement
AUE	Average Unsigned Error
CDAM	Cationic Dummy Atom Model
СНА	Charge hydration asymmetry
CHARMM	Chemistry at Harvard Macromolecular Mechanics
СМ	Compromise
CN	Coordination number
CPMD	Car-Parrinello molecular dynamics
FF	Force field
GAFF	General AMBER force field
GROMACS	Groningen machine for chemical simulations
GROMOS	A force field in the GROMACS software package
HFE	Hydration free energy
hZIP8	Human-sourced Zrt/Irt-like Protein
INPCRD	Input Coordination (a file format recognized by AMBER)
IOD	Ion-oxygen distance
ISAIAH	Ion Simulation using AMBER for dIffusion Action when Hydrated
KB	Kirkwood-Buff
LAMMPS	Large-scale atomic/molecular massively parallel simulator
LEaP	Low Energy atom Preparer.
LJ	Lennard-Jones
MC	Monte Carlo

MD	Molecular dynamics
MM	Molecular mechanics
MOF	Metal-Organic Framework
NAMD	Nanoscale molecular dynamics
NGC	Noble gas curve
OPLS-AA	Optimized potentials for liquid simulations - all-atom
PBC	Periodic boundary condition
PDB	Protein databank
PME	Particle mesh Ewald
PRMTOP	Parameter and Topology (a file format recognized by AMBER)
QM	Quantum mechanics
QMCF	quantum mechanical charge field
QMSP	Quantum scaling principle
RDF	Radial distribution function
RESP	Restrained electrostatic potential
Sander	Simulated Annealing with NMR-Derived Energy Restraints
TI	Thermodynamic integration
TyiCyt3	Trimerized Cytosolic Protein 3
VDW	van der Waals
ZAFF	Zinc AMBER force field

CHAPTER 1: INTRODUCTION

1.1 Recent Advances in Ion Models for Simulations

In many chemistry-related fields, such as protein science, geological science, circuit engineering, and battery industry, charged ionic species play myriad roles.¹⁻³ As described in **Figure 1**, among all the 118 chemically meaningful elements in the periodic table, 53 elements are very common in daily life (e.g., rare earth elements in the circuit, metals in material), which functions by being ionized to produce charged species, let alone those who form ions by forming multi-atom molecules (e.g., Ammonium, Phosphate). Abundance-wise, about a quarter of the earth's geological material (rock, lava) is made of metallic elements such as Aluminum, Iron, Calcium, Sodium, Titanium, etc. In the biochemistry realm, approximately 30% of the structures in the protein databank (PDB) contain at least one metal ion.⁴⁻⁶ Among these structures, many metal ions like Calcium, Zinc, Iron, and Magnesium can stably form complexes in the protein pocket by interacting with several negatively charged amino acid side chains. Such metal-organic framework (MOF) can serve as structural supports due to strong Coulombic forces, as well as catalytic centers due to significant electron transferability.⁷⁻⁸ Finally, industry-wise, almost all large-scale industrial procedures rely deeply on catalysis, and most catalyzes are ion-related and cannot be replaced by any other non-ionic materials.



Figure 1. Common ions as displayed in the period table of elements.

Thus, a good model of describing ion behavior has always been highly demanded over the decades. Multiple theoretical approaches have been developed and utilized by the community in simulating systems with charged ionic species. For example, *ab initio* quantum mechanics (QM) methods have been known for its strong accuracy of reproducing experimental free energies and geometries if the basis sets and methods are properly selected.^{2, 9} In contrast, the molecular mechanics (MM) method¹⁰⁻²⁴ and the combined QM/MM method²⁵⁻²⁷ both offered a compromise between simulation speed and accuracy. Such a compromise allows the object system to be large scales like proteins, DNAs, lipid membranes, or even part of a cell. As the key back-end support of modern MM and QM/MM methods, a well-designed forcefield (FF) can help improve the performance of MM calculation significantly. Recent rapid advances in the *ab initio* physics-based force fields have significantly enhanced the speed of QM,²⁸, but the sizes of its simulation systems still need time to catch up with the ones done by MM and QM/MM.

Generally, forcefields use analytical functions to iterate between the energy and geometry of a system. **Figure 2** shows a typical workflow of how MM and forcefield corporate to run molecular dynamics.²⁹ Because the forcefields can be flexibly optimized as a mechanical structure not involving molecular orbitals, MM has significant speed advantages over the QM-based methods, meanwhile maintaining its physical meaningfulness. Also, MM is a cut-edge tool at its extensivity since it can be seamlessly combined with Monte Carlo (MC) method for studying probability-based systems at the atomic levels.³⁰



Figure 2. Illustration of the relationship between forcefield and molecular dynamics engine in a typical MM or QM/MM computational system.

What makes MM even more powerful is its compatibility with multiple types of forcefield models specially designed for charged ionic species. For example, there are many ways to describe the local interactions of an ion coordinated by its surrounding atoms. The most popular models that have been used widely are bonded model,^{19, 31-32} nonbonded model,³³, and the cationic dummy atom model.³⁴ The bonded model, as the name suggests, builds "virtual" bonds between the ion and its surrounding atoms by defining bond-like terms, such as bond length, strength, bond-involving angles and torsions as well as charge and van der Waals (VDW) potential if necessary. However, bonded model has its own drawback, that is, its inability to simulate the breaking and reforming of chemical bonds, since the bond, angle, and torsion terms all use spring-like models to describe their potentials, while broken bonds will violate such a harmonic model.¹⁹ To solve this problem, the nonbonded models are commonly used. This type of model regards the central ion as a point charge, which only has Coulombic charge and VDW terms to describe the forces and potentials surrounding the ion of interest. This simplification is compatible with bond-breaking reforming processes and thus can make the simulation of ion exchange possible. However, because

there only exists two types of interactions, charge and VDW, in the nonbonded model, it usually faces challenges of underestimating the ion-ligand binding free energy, especially for those smallradius or high charge/size ratio ions³³, since they usually have strong polarization effect onto the coordinating atoms, leading to a bond-like behavior which can be described by neither charge nor VDW terms. Another very popular model that resolves both the issues of bond breaking/reforming and energy underestimation is called the cationic dummy atom model (CDAM). CDAM combines the advantages of both bonded and nonbonded models by considering the ion as a "pre-polarized" charged specie. CDAM arbitrarily assigns dummy charge points in a pre-defined pattern (tetrahedral, octahedral, etc.) surrounding the ion of interest by covalent bonds, and these cationic dummy atoms only have Coulombic charges to describe charge interactions, while the central ion has the full VDW terms and the rest of charges. For example, an Mg²⁺ ion can be described as a central ion containing the VDW terms a charge of +0.8, which is also surrounded by six dummy atoms, each containing a charge of +0.2. Such a combination of covalent-bonded and nonbonded charge/VDW terms can guide the surrounding atoms to form a coordination shell based on the predefined cationic dummy atom pattern.¹⁸ This seems to be the ultimate solution, but nonetheless cannot describe another common phenomenon in ion-ligand simulation, that is the flexible coordination number of ions in different environments (e.g., from high dielectric constant, aqueous surrounding to low dielectric constant, hydrophobic cavity of a protein).³⁴ There are still a few models possible to solve all the three problems (bond breaking, energy underestimation, coordination number change) at once, such as reactive forcefields and polarizable force fields, but these forcefields require long computing time and intricate parameter training processes. Any mistake in the parametrization phase will cause overfitting and hence affect the model transferability between various systems.³⁵⁻⁴¹

1.2 The 12-6-4 Nonbonded Model and Parametrization

Because there is no spring-like bonded term in the nonbonded model, the equation describing such an interaction is represented by both Coulombic and Lennard-Jones (LJ) terms as presented in Equation (1).

$$U_{12-6}(r_{ij}) = \frac{e^2 Q_i Q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6}$$
$$= \frac{e^2 Q_i Q_j}{r_{ij}} + \varepsilon_{ij} \left[\left(\frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{min,ij}}{r_{ij}} \right)^6 \right]$$
$$= \frac{e^2 Q_i Q_j}{r_{ij}} + 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right]$$
(1)

Herein, the first term is the electrostatic term, where *e* is the unit proton charge. Q_i and Q_j represent the charge of metal *i* and partial charges of the chelating atom *j*, respectively. r_{ij} is the distance between atoms *i* and *j*. Regarding the VDW term, $R_{min,ij}$ is the distance at which the VDW potential energy between atoms *i* and *j* has a minimum. σ_{ij} is the distance where the VDW potential energy between these two atoms equals to zero. And ε_{ij} is the well depth of the VDW interaction. For the VDW terms, the Lorentz-Berthelot combining rules, as presented in Equations (2) and (3), were used, which is consistent with the AMBER⁴² and CHARMM⁴³ force fields, as well as many previous studies.^{33, 44-52}

$$R_{min,ij} = \frac{R_{min,ii} + R_{min,jj}}{2} = R_{min,i} + R_{min,j}$$
(2)

$$\varepsilon_{ij} = \sqrt{\left(\varepsilon_i \times \varepsilon_j\right)} \tag{3}$$

Herein $R_{min,ii}$ and $R_{min,jj}$ are the VDW diameters of atoms *i* and *j*, while $R_{min,i}$ and $R_{min,j}$ are the VDW radii of atoms *i* and *j*.

Therefore, only two parameters (A_{ij} , B_{ij}), namely ($R_{min,ij}$, ε_{ij}) or essentially (σ_{ij} , ε_{ij}) need to go

through the parametrization process in the 12-6 LJ nonbonded model. Although the parametrization process is rather simple, such a model is still facing many challenges. First, the coordination of the metal ion is flexible due to ligand exchange and switching of strong/weak field ligands under many circumstances,^{27, 41, 53-56} the coordination number (CN) usually cannot be simulated correctly by 12-6 LJ nonbonded model. Second, this model oversimplifies the interactions between the central ion and its coordinating atoms by merely considering Coulombic and VDW potentials. Other common phenomena in charged systems, like charge transfer, polarization, or even covalent-like coordination bonds between d orbitals, are omitted. This omission is likely a result of not considering the uneven distribution of the charge surrounding the ion. Moreover, the electronic cloud is not ideally spherical due to some effects like Jahn-Teller distortion.⁵⁷ And such a non-spherical electron distribution is dynamic as well, depending on changes in the ion's environment. Nevertheless, even though the 12-6 nonbonded model is not the most accurate one to describe metal ion interactions, it is still widely used due to its simplicity, computational efficiency, and transferability between various molecular environments.^{15, 21, 58} Moreover, some light modification on the 12-6 LJ nonbonded model are also conducted. For example, the charge scaling model adds a dynamic fudge factor on the point charge to simulate the charge transfer effect, meanwhile still maintaining the basic architecture of 12-6 LJ potential. In metal ion simulations, such a slight modification has shown promising improvements in terms of accuracy without negatively affecting the computational speed.⁵⁹⁻⁶³ Still, slight modifications cannot resolve all the challenges. For instance, the ion-induced dipole interactions, described in Figure 3,⁴⁴, cannot be simulated by the 12-6 LJ model regardless of the charge value scaling. The result of ignoring ion-induced dipole is that the energetic hydration free energy (HFE) and geometric ion-oxygen distance (IOD) features cannot be reproduced at the same time, especially

when the ion charge is large.⁴⁶ In many cases, when a charged ion is in an aqueous environment, if the IOD matches the experimental value, the HFE, however, can be about twenty kcal/mol less negative than the experimental value.³³ Vice versa, reproducing experimental HFE will yield IOD values about 0.3 Å shorter than target values.³³ To resolve this issue in a non-trivial way, an augmentation on the current 12-6 LJ model is needed. Therefore, by adding a C_4 term⁶⁴ with proper optimization and parametrization, a new 12-6-4 LJ-type nonbonded model is hence able to account for the ion-induced dipole interaction in a highly charged system.⁴⁴ and eventually reproduce the energetic HFE and geometric IOD of an ion simultaneously.^{44, 47} Further applications have proved that the 12-6-4 LJ-type nonbonded model is compatible with not only aqueous but more heterogeneous systems, such as nucleic acid and metalloproteins in a saline solution.⁶⁵⁻⁶⁶ The numeric difference between the 12-6 and 12-6-4 models can be compared between expressions in Equations (1) and (4).

$$U_{12-6-4}(r_{ij}) = \frac{e^2 Q_i Q_j}{r_{ij}} + \frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} - \frac{C_4^{ij}}{r_{ij}^4}$$
$$= \frac{e^2 Q_i Q_j}{r_{ij}} + \varepsilon_{ij} \left[\left(\frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{min,ij}}{r_{ij}} \right)^6 \right] - \frac{C_4^{ij}}{r_{ij}^4}$$
$$= \frac{e^2 Q_i Q_j}{r_{ij}} + 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] - \frac{C_4^{ij}}{r_{ij}^4}$$
(4)



Figure 3. Intermolecular forces: exist in a charged ionic system. Green arrows represent the interactions included in the 12-6 LJ nonbonded model, while red ones represent ones not included; the size of the arrows represents their contributions to potential energy in an arbitrary pattern.

Where the 12-6-4 model has an added r^{-4} term to represent the ion-induced dipole interactions.⁴⁴⁻⁴⁶ From the waterside, 4 water models (OPC3,⁶⁷ OPC,⁶⁸ TIP3P-FB, and TIP4P-FB⁶⁹) are used in both the parametrization and application research, and the C_4 term between a divalent ion and the water oxygen in the new water models (represented by C_4^{m-w}) are hence taken from the parametrization studies.⁴⁷⁻⁴⁹ Physically and mathematically, C_4 is proportional to the polarizability of the particle which is interacting with the metal ion.⁴⁴ Therefore, the C_4 terms between the ion and non-water-oxygen ligands (denoted as l) are calculated using Equation 5. Where in Equation (5), α_w is the water oxygen polarizability (default 1.444 Å³), while α_l is the polarizability of ligand l.

$$C_4^{m-l} = C_4^{m-w} \times \frac{\alpha_l}{\alpha_w} \tag{5}$$

For special cases, if the system has multiple ions and will have a crossover effect on C_4 , the C_4 term between each two ions (denoted as *i* and *j*) is calculated using Equation 6. Herein α_i and α_j are the polarizabilities of ions *i* and *j*, respectively.

$$C_4^{i-j} = C_4^{i-w} \times \frac{\alpha_j}{\alpha_w} + C_4^{j-w} \times \frac{\alpha_i}{\alpha_w}$$
(6)

To increase user-friendliness, the library file storing all polarizabilities of atoms and ions is available at "\$AMBERHOME/dat/leap/parm/lj_1264_pol.dat" in the AMBER 2022 software package.⁷⁰

Given the capability of the 12-6-4 model to represent the interactions between metal ions and their environment, previous works have successfully parametrized charged ion species (8 M(I) ions, 4 M(-I) ions, 24 M(II) ions, 18 M(III) ions and 6 M(IV) ions)⁴⁴⁻⁴⁶ in conjunction with three water models (TIP3P,⁷¹ SPC/E,⁷² and TIP4PEW⁷³). For the ions with higher charges, larger errors were observed in the 12-6 model than for the lower-charged ones, which is likely a result of the strong dipole-inducing ability of the higher-charged ions.^{33, 45-46} In contrast, the 12-6-4 model could simultaneously reproduce the experimental HFE and IOD values for all of the highly charged metal ions.⁴⁵ Note here that HFE and IOD values are both aqueous properties, so all the 60 ions are in conjunction with all the four new water models (OPC3,⁶⁷ OPC,⁶⁸ TIP3P-FB, and TIP4P-FB⁶⁹) because these water models have demonstrated significant improvements in simulating biological systems and a strong correlation exists between the ion parameters and the water models. Regarding the features of each water model, OPC3 and OPC water models were designed to simulate the bulk properties, like density, heat capacity, boiling point, and diffusion coefficient of water. By using either of these two, the HFEs of the small molecule of interest can be reproduced within a range of ± 1 kcal/mol compared to the experimental values.⁷⁴ Likewise, the TIP3P-FB and TIP4P-FB models can accurately reproduce the liquid bulk properties but are also able to maintain

it over a wide range of temperatures because of its including the force balance consideration when parametrizing these models.⁶⁹ Because ion parameters are highly dependent on water modes, and no former parameters have been prepared for the simulation of highly charged ionic systems in conjunction with these four new water models, the parametrization was therefore performed on both 12-6 and 12-6-4 nonbonded models for these highly charged ions in new water models using the particle mesh Ewald (PME) method. Parameters obtained from this procedure can successfully reproduce experimental HFE and IOD values and showed great agreement while being compared to the quantum mechanical (QM) data.⁷⁵⁻⁷⁶

1.3 Diffusion Coefficient Calculation Using 12-6-4 Parameters

As a basic property of many liquids, diffusion coefficient is a key feature of evaluating its possible function engineering and utility in daily life. Many fluids, including water, have already had their diffusion coefficient been extensively studied by both experiment operation and theoretical calculation. However, for water systems with transition metal ions, there exists a huge amount of experimental data which has not been theoretically studied. Hence, high-confidence predictions for challenging systems like radioactive or biohazardous can't be accomplished using the current computation models. To resolve this issue and close the gap, a workflow named ISAIAH (Ion Simulation using AMBER for dIffusion Action when Hydrated) was developed to achieve accurate simulations on the diffusion coefficients of 15 monoatomic ions varying their charges from -1 to +3 in four new water models that has just been parametrized.⁴⁷⁻⁴⁹ The simulation results generated by ISAIAH indicated a good agreement with experimental values.⁷⁷ This leads the project to further investigate the diffusion coefficient of 239 Pu⁴⁺ in water (no experimental data available) from a theoretical perspective. Among all the force field parameter sets, the ones parametrized using the 12-6-4 LJ-type nonbonded model showed an overall lower Average Unsigned Errors (AUE) of ions with various radii and electron configurations relative to 12-6 LJ parameters that can only reproduce either HFE or IOD independently. This observation proves the fact that diffusion is a fluidic phenomenon affected by both HFE and IOD between solute and solvent molecules. The main equations used in this research are mainly displayed by Equation (7) and (8) as below. The code for running ISAIAH is available at https://github.com/lizhen62017/ISAIAH.

$$MSD = \frac{\sum_{i=0}^{N} |x_{i+1} - x_i|^2}{(N-1)}$$
(7)

$$D = \lim_{t \to \infty} \frac{MSD}{6t}$$
(8)

1.4 Pairwise Interaction

During the parametrization process, it has been brought to notice that applying 12-6-4 LJ interaction between two specific atoms IS hard to be achieved in AMBER because of the nature that in AMBER forcefield,⁷⁸⁻⁷⁹ the program assigns all the nonbonded interactions in an atom-type-specific pattern. As described in **Figure 4**, if the C_4 interaction was assigned between the atom types Zn^{2+} (zinc ion) and OW (water oxygen), it will be calculated among all the zinc ions and all the water molecules in the whole system. This will cause an inability to focus on small local areas where the long-distance C_4 interactions can be excluded because the induced dipole phenomenon is supposed to decay fast as a function of interatomic distance. Therefore, to resolve this issue, the AMBER code was rewritten from an atom-type specific way of implementing C_4 interactions on specific atom pairs to avoid background C_4 interference. Using **Figure 4** as an example again, the users can specifically apply C_4 between the central zinc ion and only the five atoms in its vicinity. Meanwhile, another atom in the whole protein with the same atom type will not be affected at all.

To achieve this, the source code of the AMBER program needs to be modified, especially three parts: LEaP, which functions as the molecule builder, Sander, which functions as the CPU-driven MD engine, and PMEMD.cuda, which functions as the GPU-driven MD engine. The overview of this project is illustrated in **Figure 5**, where both the construction ideas of LEaP (molecule building tool) and Sander/PMEMD (MD engine) are displayed. The code for running tLEaP, Sander and PMEMD (CPU only) is available at AmberTools23, while the PMEMD.cuda (GPU engine) code can be tested at https://github.com/lizhen62017/C4Pairwise.



Figure 4. Indication of pairwise C4 implementation.



Figure 5. Programming overview of the atom-type specific C_4 interactions. The upper panel shows the construction of LEaP, while the lower panel shows the construction of Sander and PMEMD.

1.5 Ion Imidazole Interaction

The interactions between a charged ionic species and small molecules provide pivotal information to both simulations on the ion-water system and the ion-protein system. It has been proved in the previous chapters that the 12-6-4 Lennard-Jones (LJ)-type nonbonded model is highly successful in simulating ion-containing systems due to the system's ability to account for the induced dipole effect. Combining the 12-6-4 LJ nonbonded model with the potential of the mean force (PMF) method, a parametrization process on atom polarizabilities was conducted. The polarizabilities are for the metal-chelating nitrogen on two kinds of imidazole molecules resembling different charged states of Histidine in a real protein case. The two Histidine types are delta nitrogen protonated (HID) and epsilon nitrogen protonated (HIE), where the coordinating, unprotonated nitrogens of each time are believed to have a higher polarizability due to their having lone-paired electrons. After being parametrized against experimental values, the 11 metal ions (Ag(I), Ca(II), Cd(II), Co(II), Cu(I), Cu(II), Fe(II), Mg(II), Mn(II), Ni(II), and Zn(II)) in conjunction with three common water models (TIP3P, SPC/E, and OPC) indicate a strong trend on their parameter according to electronic configurations. It was also shown that the standard 12-6 and default 12-6-4 models for ion-water systems are unable to accurately model these interactions and, therefore, suggest that the ion-imidazole complex should be unstable, which is different from the experimental observations. The results further extended the flexibility and the reliability of the 12-6-4 LJ-type nonbonded model, which can accurately reproduce three-component interactions between an ion, one or more ligand molecules, and solvent by tuning the polarizability of the ligand's chelating atom. Moreover, the transferability of this model was rigorously tested to show the capability of describing ionligand interactions in various environments.⁸⁰

1.6 Protein Interaction

With the metal imidazole interaction showing high accuracy and confidence in reproducing the binding free energy, a similar model was then used on imidazole and acetate-containing proteins. The first protein to be tested was a purely imidazole-metal-centered artificial protein. This is of major importance since, unlike ZIP8 and ZIP4, the artificial protein TriCyt3 was designed *de novo* and thus does not have any homology model for comparison in the current database. This leaves little space for a machine-learning-based force field and is a strong test on the pure-physics-based model.

The result indicated a considerate agreement between experimental and simulation free energies. With tuned c4 values and added repulsion between ligands, the simulation can successfully reproduce 90% of the experimental value. The leftover differences showed a concerning disagreement between PMF and TI but can be explained by the nature of these two methods. Because PMF is a method to measure the free energy change while pulling away a ligand from the ion-ligand complex, TI is a method to measure the energy change from one ion to a dummy, as displayed in **Figure 6**. Unlike PMF, no ligand exchange process happens during TI, which will not cause sampling issues as PMF does. Further investigation is needed to resolve this disagreement.

The second protein to be simulated was ZIP8, a Zrt-/Irt-like protein (ZIP) metal transporter with multiple natural substrates because the engineering of transporters to alter substrate specificity as desired holds great potential for applications, including metabolic engineering.

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Figure 6. Illustration of TI process. Note here the dummy atom does not carry any charge, making it different from the dummy atom in CDAM.

However, the lack of knowledge on molecular mechanisms of substrate specificity hinders designing effective strategies for transporter engineering. The simulation using modified polarizability onto histidine, aspartate, and glutamate uncovered the determinants of substrate specificity. Using the mutate zinc-preferring ZIP4 as the primary object for simulation, a zinc-specific quadruple variant was created that exhibited largely reduced transport activities towards Cd(II), Fe(II), and Mn(II) whereas increased activity toward Zn(II). Analysis of the computational studies revealed a conditional selective filter which functions only when the transporter adopts the outward-facing conformation. The demonstrated approach for transporter engineering and the gained knowledge about substrate specificity will facilitate engineering and mechanistic studies of other transporters.

CHAPTER 2: PARAMETERIZATION OF THE 12-6-4 NONBONDED MODEL

2.1 Overview

Because many charged ionic species not only serve important roles in chemical processes but are also frequently found in rare-earth chemistry and materials research, computer simulation tools are crucially needed to scientifically investigate these unique ionic behaviors. In order to achieve meaningful and reproducible simulation results, reliable parameters are hence required. In the earlier work, the 12-6 and 12-6-4 nonbonded models are having their related parameters successfully determined for 60 ions (4 M(-I), 8 M(I), 24M(II), 18 M(III) and 6 M(IV)) in conjunction with three well-established water models (SPC/E, TIP3P, and TIP3P_{EW}).⁴⁴⁻⁴⁶ Moreover, it has been claimed that there are four new water models (OPC3,⁶⁷ OPC,⁶⁸ TIP3P-FB, and TIP4P-FB⁶⁹) that perform similarly to or significantly better than the earlier water models in the same category (3-point or 4-point water models, respectively). The parameters of these related water models are presented in Table 1.

Water model	Q(O) or Q(M) (<i>e</i>)	Q(H) (e)	r(O-H) (Å)	Н-О-Н (°)	r(O-M) (Å)	R _{min} /2 for O (Å)	ε for O (kcal/mol)
TIP3P	-0.834	+0.417	0.9572	104.52	N/A	1.7683	0.1520
SPC/E	-0.8476	+0.4238	1.0	109.47	N/A	1.7767	0.1553
TIP4P	-1.04	+0.52	0.9572	104.52	0.15	1.7699	0.1550
TIP4P-Ew	-1.04844	+0.52422	0.9572	104.52	0.125	1.775931	0.16275
OPC3	-0.8952	+0.4476	0.9789	109.47	N/A	1.7814990	0.163406
OPC	-1.3582	+0.6791	0.8724	103.6	0.1594	1.777167268	0.2128008130
TIP3P-FB	-0.84844	+0.42422	1.0118	108.15	N/A	1.7835723	0.155866
TIP4P-FB	-1.05174	+0.52587	0.9572	104.52	0.10527	1.77660486	0.179082

Table 1. Parameters for the Eight Different Water Models^a.

wherein M represents a dummy atom. For the 4-point water models, the oxygen atom has a charge of zero, while the dummy atom has a negative charge.

Before the 12-6-4 LJ-type potential was developed, many systematic studies have pushed the parameterization of the LJ nonbonded model for charged ionic species to its cutting-edge. For example, Åqvist started parametrizing the alkali and alkaline-earth cations using the conventional LJ nonbonded parameter.⁸¹ Dang et al. similarly developed LJ parameters for numerous alkali cations and halide anions for both non-polarized and polarized water models.^{35, 38} Peng, Hagler, Jensen and Jorgensen parameterized the LJ potential or a similar 9-6 LJ-like potential for the halide ions in conjunction with the TIP4P water model.⁸²⁻⁸³ Lamoureux et al. conducted halide and alkali ion parametrization process in the polarized water model of SWM4-DP.⁸⁴⁻⁸⁵ As for M(II) ions in biological-related fields, Babu et al. re-optimized the LJ-potential-compatible parameters according to experimental HFE values using force switching function to truncate the calculation in an atom-based pattern.⁸⁶ As an increasing number of researchers started using TIP3P,⁷¹ SPC/E,⁷² and TIP4PEW⁷³ as their major water model for simulation in PME condition, Joung and Cheatham therefore developed a set of parameters for $M(\pm I)$ ions. Among these three water models, SPC/E stood out with a lot of parametrization works focused on it due to its high transferability and robustness.⁸⁷⁻⁹⁰ Having been developed following a variety of combining rules and simulation protocols. These parameter sets are aimed to reproduce a wide range of experimental/theoretical target values in various environments. For example, gas phase parameters are usually aimed to reproduce QM-calculated energies for a small ionic system with no solvent. In contrast, solventrelated properties such as HFE, IOD, CN and RDF of the solvation shell, diffusion coefficients, electric conductivity, osmotic coefficients, and lattice energies are usually aimed by condensed phase parameters during the parametrization process. It is a very challenging task to reproduce all the experimental results simultaneously because of the simple and high-speed nature of the 12-6 LJ nonbonded model.

Therefore, due to the limited transferability of the combination "conventional 12-6 LJ parameters in conjunction with the commonly used water models", new parameters and new water models are needed to match the rapidly developing community with novel simulation methods and more powerful computational resources. For example, the PME method, a new method that considers long-range electrostatic energy in periodic boundary simulation cells, has been widely used in many mainstream simulation software packages. By processing short-range interactions in real space while the long-range ones in Fourier-transformed space, PME can decrease the time complexity from O(N²) to O(NlogN).⁹¹⁻⁹⁴ More importantly, PMEMD is a method that can be parallelized using CUDA GPU acceleration.⁹⁵ Also, four new water models (OPC3,⁶⁷ OPC,⁶⁸ TIP3P-FB, and TIP4P-FB⁶⁹) have been developed to meet the need for these new simulation methods and computational hardware, as well as the users' demand for simulation complex systems such as membrane protein in a wide range of temperatures.

Other than the new water models, the augmented 12-6-4 LJ- type model can also be used to correct problems with the 12-6 model, as was previously seen, and the reason for adding the term of C_4 is displayed in **Figure 7**, where the r^{-4} is derived as an effect of the ion responding to the electrical potential generated by the induced dipole. Because the induced dipole generates an electrical field whose intensity is proportional to r^{-3} , while the dipole itself is proportional to r^{-2} . Multiplying these two values will yield a r^{-5} intensity of electrical field, and finally, integrating this electrical field intensity over the distance r will make the potential energy proportional to r^{-4} a physically meaningful term to apply onto the ionic charged system where induced dipole cannot be ignored. However, while the four new water models are in conjunction with the 12-6-4 LJ-type potential, no systematic parameterization was conducted on any charged ionic species using the PME method. The TI method allows the possibility to design a workflow with high efficiency of calculating HFE and IOD at the same time. By comparing the calculated HFE and IOD and match these values to the experimental references, the parameter tuning process can be completed as described in **Figure** *6* for 60 ions (4 M(-I), 8 M(I), 24M(II), 18 M(III) and 6 M(IV)) in four new water models (OPC3, ⁶⁷ OPC, ⁶⁸ TIP3P-FB and TIP4P-FB⁶⁹).



Figure 7. Derivation of C_4 interaction. Note here the θ angle is not considered in the equation of C_4 , because the induced dipole is assumed to have very little θ angle along the axis. Based on the parametrization results, it can be concluded that the previously used 12-6 LJ parameters are limited in their transferability of reproducing experimental HFE and IOD simultaneously. While the experimental HFE, IOD, and CN values are strongly correlated, an ion with more negative HFE usually has smaller IOD and CN because those trends are usually the results of strong binding free energy between the ionic specie and the water surrounding it. Other than the correlation between target values, the parametrization results also indicated that between different water models, the parameter needed to reproduce experimental values vary a lot. This is due to the fact that each water model has its unique geometry property and hence should be independently parametrized.

As for the input parameter of this parametrization process. Previous researchers have chosen to use fixed ε values for all the ions while only varying the $R_{min}/2$ as described in Equation 1.^{15, 82-83, 88-89}. In the present work, a correlation equation between Rmin/2 and ε is hence developed based on the fact that each ion has its electron configurations close to one of the noble gas atoms of the same period. Because such a correlation described by Equation 9 can be described by a curve in

the $R_{min}/2$ vs. ε plane, it is therefore also called Noble Gas Curve (NGC). The application of NGC will simplify the parametrization process of the 12-6-4 LJ-type model since the only two parameters feeding to the automatic workflow will be $R_{min}/2$ and C_4 values, as **Figure 8** indicates.



Figure 8. Illustration of the parametrization process.

To fulfill the need of different applications, four parameter sets were designed using the equation of NGC: HFE set which reproduces energetical properties (i.e., $\sim\pm1.0$ kcal/mol for the experimental HFEs), IOD set which reproduce geometrical properties (i.e., $\sim\pm0.01$ Å for the experimental IODs), Compromise (CM) set which is a 12-6 LJ parameter that controls both energetical and geometrical errors within a controllable range, and finally 12-6-4 set which introduces the C₄ term to reproduce both energetic and geometric behaviors simultaneously.

Error analysis-wise, the derived $R_{min}/2$ parameters showed strong similarity and agreement with the quantum scaling principle (OMSP) calculated VDW radii.⁹⁶ This is proved by the statistical fact that smaller unsigned average errors (UAEs) were yielded by the present parameter compared to other parameter sets while using the QMSP values as references. Further tests were also conducted on activity derivatives of monovalent and divalent ionic solution,⁹⁷⁻⁹⁸ QM calculation on the first solvation shell of divalent ions (MP4SDQ(FC)/HUZSP*//RHF/HUZSP* level theory),⁹⁹ and protein simulations on the trivalent ions (PDB ID: 4BV1). All these tests secured a better transferability of the 12-6-4 parameter as a result of two major reasons: First, the 12-6 part of this 12-6-4 LJ-type model has an enhanced balance between its $R_{min}/2$ and ε after correlating them using NGC described in Equation (9). Second, the C_4 term of this 12-6-4 LJ-type model successfully reproduced the ion-induced dipole effect according to the polarization effect of coordinating atoms, which narrows the gap between experimental fact and theoretical predictions. In conclusion, this parametrization process using a new forcefield in new water models completes a systematic investigation of parameters for a series of ions. These parameters can subsequently be employed in PME-based simulation methods which are compatible with FFs such as AMBER,⁴² CHARMM,⁴³ OPLS-AA,¹⁰⁰ and GROMOS¹⁰¹ when used with the PME model.

2.2 Target Values

Target HFEs, IODs, and CNs for investigated ions are given in Tables 1-3. Overall, we have parameterized the 12-6-4 LJ-type nonbonded model for 60 different ions (including 4 monovalent anions, 18 monovalent cations, 24 divalent cations, 18 trivalent cations, and 6 tetravalent cations) in four newly designed water models (OPC3, OPC, TIP3P-FB, TIP4P-FB) respectively.

Regarding the target HFE values, there exist two types of experimental HFE depends on the way of calculating proton-water interaction.¹⁰²⁻¹⁰³ In general, there are two different HFEs of ions that have been used in the literature: the real HFE and the intrinsic HFE (or called the "absolute" HFE).⁸⁵ The real HFE includes the contribution of the phase potential for ion crossing the air/water interface, while the intrinsic HFE is independent of the interfacial potential and only considers the interaction between ion and water molecules.⁸⁵ The real HFE and intrinsic HFE have the following relationship: $DG_{hydr}^{real} = DG_{hydr}^{intr} + zFf$ Where F is the Faraday constant, ϕ is the interfacial potential, which is negative and water model dependent. In the work of Lamoureux and Roux⁸⁵, the authors noted that Tissandier et al.¹⁰⁴ find DG_{hydr} of proton is -264 kcal/mol, if one interprets which as DG_{hydr}^{real} , which would provide a DG_{hydr}^{intr} of around -252 kcal/mol. And this value is highly consistent with the value obtained by Grossfield et al.¹⁰⁵ through the free energy simulations using the AMOEBA force field, which provides DG_{hydr}^{intr} -252.5 kcal/mol. Both values are very close to the value DG_{hydr}^0 of proton Marcus used in the Marcus data set (which is -252.4 kcal/mol)¹⁰². Based on which value and the conventional HFE of a certain cation, Marcus derived the HFE for this cation.¹⁰² This means the Marcus data set can be considered as the intrinsic HFE set for cations, which is directly comparable to the free energy simulations without considering the phase potential, as what has been processed in this work. However, the HFE of the proton has not been totally

determined, and this value may change if more experiments are performed or our understanding of ion solvation advances in the future.

As for the IODs, most of the values refer to the review by Marcus,¹⁰⁶. Some exceptions include Tl⁺, Cu⁺, NH₄⁺, and H⁺ ions. The Tl⁺ ion is isoelectronic to the Sn²⁺ ion, which has lone pair electrons in its valence shell. This will cause an observation of two IODs in the first solvation shell while being dissolved in water. Simulation-wise, it is hard to reproduce using conventional MD models because most of the models assume each ion to be isotropic, meaning the ion is treated as a sphere without any elliptical distortion. According to former research, the CN value of the Tl⁺ ion was reported to be in the range of 6~8. Nonetheless, it was also determined by Persson et al. that Tl⁺ has an aqueous CN of 4.¹⁰⁷. In this work, a 4-coordinated Tl⁺ was found with a distorted tetrahedral-shaped first solvation shell. This means that such a Tl⁺ ion will have two IOD values representing two sets of water molecules (each set with two counts). One IOD is 2.73 Å, and the other is at 3.18 Å. The average of these two IOD values (2.96 Å) was used as a target for the parametrization process for Tl⁺. Such a selection of IOD value can be further approved by the work of Shannon et al., where the effective ionic radii of highly coordinated (6~8) Tl⁺ ion was calculated to be in the range between 1.50 Å and 1.59 Å.¹⁰⁸ Then, summing up the Pauling effective ionic radius (1.40 Å) of O^{2-} , it can be estimated that the IOD values for Tl⁺ range from 2.90 Å to 2.99 Å respectively, which is consistent with the IOD value (2.96 Å) used in this parametrization process. Another piece of evidence is the QM/MM MD simulations performed on the aqueous Tl⁺ system by Vchirawongkwin et al. Such a simulation observed two different IODs (2.79 and 3.16 Å) with an average CN of 5.9 during the whole simulation period.¹⁰⁹ As for Cu⁺, it is challenging to experimentally obtain the IOD value because Cu⁺ can be easily oxidized by water. The target IOD value of Cu⁺ used for the parametrization process is also harvested from quantum calculations by

Burda *et al.*¹¹⁰ Similar situation applies to NH_4^+ as well, where no reliable experimental IOD value is accessible. The estimated IOD value was set to be 2.85 Å as a sum of 1.45 Å, which is the ionic radius of NH4⁺,¹¹¹, and 1.40 Å, which is the ionic radius of O²⁻. This value is validated by Car-Parrinello molecular dynamics (CPMD) results.¹¹²⁻¹¹³ Lastly, the H⁺ target IOD value is disagreement because it cannot exist as an independent ion in water. Instead, it was hydrolyzed as either Zundel ($H_5O_2^+$) model or Eigen ($H_9O_4^+$) model, or simply hydronium ion (H_3O^+), and an equilibrium exists between these three species. Meraj and Chaudhari used the QM method to obtain the IOD of Zundel H⁺.¹¹⁴, While Eigen H+ IOD was calculated using MP2 with a basis set of 6-31+G**.¹¹⁵ Other than these four exceptions, Ag⁺ ion is also commonly considered as a "structure-breaking" candidate.¹¹⁶ Using the quantum mechanical charge field (QMCF) method, Ag+ was found to have a CN of 6 for its first solvation shell. Compared to monovalent ions, divalent and highly charged ions have richer data sets for their HFE and IOD values due to their natural abundances in protein or material sciences. Some highly charged ions which readily hydrolyze water, such as As³⁺, Sn⁴⁺, and Pb⁴⁺ ions²⁶, were not considered in the present work. To keep the consistency with previous studies,⁸⁷ the target HFEs and IODs for all the 60 ions were hence selected and presented in Table 2, Table 3 and Table 4.
Ion	Mass (g/mol)	Electronic structure	HFE (kcal/mol) ^a	IOD (Å) ^b	CN^{c}
Li^+	6.94	[He]	-113.5	2.08 ± 0.06	4-6
Na^+	22.99	[Ne]	-87.2	2.35 ± 0.06	4-8
\mathbf{K}^+	39.10	[Ar]	-70.5	2.79 ± 0.08	6-8
\mathbf{Rb}^+	85.47	[Kr]	-65.7	2.89 ± 0.10	7–8
Cs^+	132.91	[Xe]	-59.8	3.13 ± 0.07	4-6
Tl^+	204.38	$[Xe] 4f^{14}5d^{10}6s^2$	-71.7	2.96^{c}	4 ^{<i>c</i>}
Cu^+	63.55	[Ar] 3d ¹⁰	-125.5	1.87^{d}	2^d
Ag^+	107.87	[Kr] 4d ¹⁰	-102.8	2.41 ± 0.02	2-4
\mathbf{F}^-	19.00	[Ne]	-119.7	2.63 ± 0.02	4.1-6.8
Cl^-	35.45	[Ar]	-89.1	3.18 ± 0.06	6-8.5
Br^-	79.90	[Kr]	-82.7	3.37 ± 0.05	6
I_	126.90	[Xe]	-74.3	3.64 ± 0.03	6-8.7

Table 2. Target Values of the HFE, IOD, and CN in the First Solvation Shell for Monovalent Ions.

The HFE values of positive ions come from Marcus¹⁰², while the HFE values of halide ions are from Schmid et al.¹⁰³

^bFrom Marcus¹⁰² unless specified otherwise.

^{*c*}Weighted average value of four bonds (two at 2.73 Å and two at 3.18 Å) from Persson et al.⁸⁶

 $d_{\rm From Burda \ et \ al.^{110}}$

Ions	Electronic Structures	HFE (kcal/mol)	IOD(Å)	CN
Be ²⁺	[He]	-572.4	1.67	4
Cu^{2+}	[Ar]3d ⁹	-480.4	2.11	6
Ni^{2+}	[Ar]3d ⁸	-473.2	2.06 ± 0.01	6
Pt^{2+}	$[Xe]4f^{14}5d^{8}$	-468.5	N/A	N/A
Zn^{2+}	$[Ar]3d^{10}$	-467.3	2.09 ± 0.06	6
Co^{2+}	[Ar]3d ⁷	-457.7	2.10 ± 0.02	6
Pd^{2+}	[Kr]4d ⁸	-456.5	N/A	N/A
Ag^{2+}	[Kr]4d ⁹	-445.7	N/A	N/A
Cr^{2+}	[Ar]3d ⁴	-442.2	2.08	6
Fe ²⁺	[Ar]3d ⁶	-439.8	2.11±0.01	6
Mg^{2+}	[Ne]	-437.4	2.09 ± 0.04	6
V^{2+}	[Ar]3d ³	-436.2	2.21	6
Mn^{2+}	[Ar]3d ⁵	-420.7	2.19 ± 0.01	6
Hg^{2+}	$[Xe]4f^{14}5d^{10}$	-420.7	2.41	6
Cd^{2+}	$[Kr]4d^{10}$	-419.5	2.30 ± 0.02	6
Yb^{2+}	$[Xe]4f^{14}$	-360.9	N/A	N/A
Ca^{2+}	[Ar]	-359.7	2.46	8
Sn^{2+}	$[Kr]4d^{10}5s^2$	-356.1	2.62	6
Pb^{2+}	$[Xe]4f^{14}5d^{10}6s^2$	-340.6	N/A	N/A
Eu^{2+}	$[Xe]4f^7$	-331.0	N/A	N/A
Sr^{2+}	[Kr]	-329.8	2.64 ± 0.04	8-15
Sm^{2+}	$[Xe]4f^6$	-328.6	N/A	N/A
Ba ²⁺	[Xe]	-298.8	2.83	9^g
Ra^{2+}	[Rn]	-298.8	N/A	N/A

Table 3. Experimental HFE, IOD, and CN of the first solvation shell for 24 divalent metal ions.

These HFE, IOD, and CN values are from reference³³, which publication cites the original work.

Ions	electronic configuration	HFE (kcal/mol)	IOD(Å) ^b	CN ^b	effective ion radii(Å)	first shell water radii(Å)
Al^{3+}	[Ne]	-1081.5	1.88	6	0.54	1.34
Fe ³⁺	[Ar]3d ⁵	-1019.4	2.03	6	0.65	1.38
Cr^{3+}	$[Ar]3d^3$	-958.4	1.96	6	0.62	1.34
In^{3+}	[Kr]4d ¹⁰	-951.2	2.15	6	0.80	1.35
Tl^{3+}	$[Xe]4f^{14}5d^{10}$	-948.9	2.23	4-6	0.89	1.34
Y^{3+}	[Kr]	-824.6	2.36	8	0.90	1.46
La ³⁺	[Xe]	-751.7	2.52	8.0-9.1	1.03	1.49
Ce ³⁺	[Xe]4f ¹	-764.8	2.55	7.5	1.01	1.54
Pr^{3+}	$[Xe]4f^2$	-775.6	2.54	9.2	0.99	1.55
Nd^{3+}	[Xe]4f ³	-783.9	2.47	8.0-8.9	0.98	1.49
Sm^{3+}	[Xe]4f ⁵	-794.7	2.44	8.0-9.9	0.96	1.48
Eu^{3+}	[Xe]4f ⁶	-803.1	2.45	8.3	0.95	1.50
Gd^{3+}	[Xe]4f ⁷	-806.6	2.39	8.0-9.9	0.94	1.45
Tb^{3+}	[Xe]4f ⁸	-812.6	2.40	8.0-8.2	0.92	1.48
Dy^{3+}	[Xe]4f ⁹	-818.6	2.37	7.4-7.9	0.91	1.46
Er^{3+}	[Xe]4f ¹¹	-835.3	2.36	6.3-8.2	0.89	1.47
Tm^{3+}	[Xe]4f ¹²	-840.1	2.36	8.1	0.88	1.48
Lu^{3+}	[Xe]4f ¹⁴	-840.1	2.34	8	0.86	1.48
Hf^{4+}	[Xe]4f ¹⁴	-1081.5	1.88	8 ^c	0.85	1.31
Zr^{4+}	[Kr]	-1019.4	2.03	8 ^c	0.86	1.33
Ce^{4+}	[Xe]	-958.4	1.96	9^{d}	0.87	1.55
U^{4+}	$[Rn]6d^15f^1$	-951.2	2.15	9-11 ^e	0.89	1.53
Pu^{4+}	$[Rn]5f^1$	-948.9	2.23	8^{f}	0.86	1.53
Th^{4+}	[Rn]	-824.6	2.36	9-11 ^e	0.84	1.51

Table 4. Experimental HFE, IOD, and CN of the first solvation shell for 18 trivalent and 6 tetravalent ions.

These HFE, IOD, and CN values are from reference⁴⁵, which cites the original work.

For the parameterization of a metal ion for a specific water model, since Rmin/2 and ε are already correlated by Equation (9), only two variables, $R_{min}/2$ and C_4 , need to be determined. In the present work, by treating HFE and IOD as the two target properties, which can be written in function format in Equation (10), "scanning" the parameter surface and then "determining" the optimal parameters are, therefore, a process that can be automatized.

$$\begin{cases} HFE = f(R_{min}, C_4) \\ IOD = g(R_{min}, C_4) \end{cases}$$
(10)

As illustrated in **Figure 8**, where the red dots are the scanned values of HFE and IOD as a result of varying the $R_{min}/2$ and C_4 inputs. The curved blue surfaces are the regression result of scanned data dots, and the flat brown planes are the target values for HFE and IOD. The resultant projection curves of the $R_{min}/2$ - C_4 surface (i.e., the green curves) crossover, where the cross point is marked by an orange circle, yielding the initial guesses for $R_{min}/2$ and C₄. Afterward, the parameters were fine-tuned to meet the desired accuracy.

To calculate the HFE, the thermodynamic cycle of **Figure 6** was used, in which the blue solid arrow represents the desired free energy value and the blue dashed arrow indicates the indirect pathway used to obtain the HFE. The bi-directional black arrows indicate that the free energies were calculated twice, both forward and backward, to better calculate the free energy values. The calculations of ΔG_{VDW} and $\Delta G_{Ele}+\Delta G_{Pol}$ were accomplished by using the thermodynamic integration (TI).¹¹⁷ In the TI method, the free energy change of an alchemical process is calculated in Equation (11).

$$\Delta F = \int_0^1 \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_{\lambda} d\lambda \tag{11}$$

Where $U(\lambda)$ is the potential function of λ that varies from 0 to 1. $\lambda = 0$ corresponds to the initial state, and $\lambda = 1$ corresponds to the final state. TI has recently been implemented into the CUDA platform of Amber 18^{95, 118}, and we have employed this implementation in the present study. In this work, four alchemical steps were simulated to obtain the HFE⁴⁴: (1) "turn on" the vdW interactions of a dummy atom in water to obtain ΔG_1 , (2) "turn on" the electrostatic interactions (and C₄ interactions, if applicable) of the neutral atom in water yielding ΔG_2 , (3) "turn off" the electrostatic interactions (and C₄ interactions, if applicable) of the neutral atom in water to get ΔG_4 . Steps (1) and (2) represent the hydration process of a metal ion, and steps (3) and (4) represent the dehydration

process of a metal ion. The final HFE value was calculated as $(\Delta G_1 + \Delta G_2 + \Delta G_3 + \Delta G_4)/2$. For the electrostatic scaling steps, i.e., steps (2) and (3), the linear mixing potential function was used as described in Equation (12):

$$U(\lambda) = (1 - \lambda)U_0 + \lambda U_1 \tag{12}$$

Where U_0 and U_1 represent the potential function of the initial and final states, respectively. For the vdW scaling steps, i.e., steps (1) and (4), the soft-core potential, described in Equation (13), was used to prevent "end-point catastrophes":

$$U(\lambda) = 4\varepsilon(1-\lambda) \left[\frac{1}{[\alpha\lambda + \left(\frac{r_{ij}}{\sigma}\right)^6]^2} - \frac{1}{\alpha\lambda + \left(\frac{r_{ij}}{\sigma}\right)^6} \right]$$
(13)

Where α is 0.5, and σ is the distance at which the LJ potential equals zero.

For each of the vdW scaling steps, three λ windows were used (0.1127, 0.5, and 0.88729). For each of the electrostatic scaling steps, seven λ windows were used (0.02544, 0.12923, 0.29707, 0.5, 0.70292, 0.87076. 0.97455). The free energy change for each step was calculated using Gaussian quadrature as presented in Equation (14):

$$\Delta F = \sum w_i \left\langle \frac{\partial U(\lambda)}{\partial \lambda} \right\rangle_i \tag{14}$$

Where w_i is the weighting factor for window *i*.

In order to obtain ΔG_1 and ΔG_4 , the simulation starts with making an equilibrated structure for a system which has a Zn²⁺ ion in a cuboid water box with a size of ~40 Å × 40 Å × 40 Å. Then the Zn²⁺ ion was treated as a dummy/neutral atom mixed state, and the system was prepared for the TI runs through the following procedure with λ equal to 0.11270. First, 5000 steps of minimization using the steepest descent algorithm were carried out, followed by 5000 steps of minimization using the conjugate gradient algorithm. Second, 360 ps of NVT was performed to heat the system

gradually from 0 to 300 K through following stages: (1) 30 ps simulation to heat the system from 0 to 50 K, followed by 30 ps of equilibration at 50 K; (2) 30 ps simulation was performed to heat the system from 50 to 100 K, followed by 30 ps of equilibration at 100 K; (3) 30 ps simulation was performed to heat the system from 100 to 150 K, followed by 30 ps of equilibration at 150 K; (4) 30 ps simulation was performed to heat the system from 150 to 200 K, followed by 30 ps of equilibration at 200 K; (5) 30 ps simulation was performed to heat the system from 200 to 250 K, followed by 30 ps of equilibration at 250 K; (6) 30 ps simulation was performed to heat the system from 250 to 300 K, followed by 30 ps of equilibration at 300 K. Third, a 2 ns NPT equilibration was performed at 300 K and 1 atm. The final structure was used for the initial structure for a set of three-window TI calculations to obtain ΔG_1 . TI calculations for the three windows were performed subsequently a λ values of 0.11270, 0.5, and 0.88729, respectively. Each of these windows covers 300 ps using NVT conditions, with the last 200 ps yielding the averaged $\partial U(\lambda)/\partial \lambda$ value. Afterwards, the vdW interactions of the neutral atom were turned off by another set of three-window TI simulations to obtain ΔG_4 . Each of these windows covered 300 ps using NVT conditions as well, with the last 200 ps yielding the averaged $\partial U(\lambda)/\partial \lambda$ value.

A similar protocol was used to obtain the ΔG_2 and ΔG_3 values. The same initial structure was used, and then Zn²⁺ ion was treated as a mixture of a neutral atom and a metal ion with a λ of 0.02544 for the following preparation steps: (1) 5000 steps of minimization using the steepest descent algorithm, (2) 5000 steps of minimization using the conjugate gradient algorithm, (3) 360 ps NVT heating, and (4) 2 ns NPT equilibration. Afterward, a set of seven-window TI calculations was performed to calculate ΔG_2 . The λ values of these windows are 0.02544, 0.12923, 0.29707, 0.5, 0.70292, 0.87076, 0.97455. Each window covered 300 ps using NVT conditions, with the last 200 ps yielding the averaged $\partial U(\lambda)/\partial \lambda$ value. Afterward, another set of seven-window TI calculations was performed to obtain ΔG_3 using the same protocol. To test the convergence of the current protocol, we performed benchmark calculations about the simulation length for the TI calculations; the results are shown in **Table 5** and **Table 6**. These benchmark calculations indicate that 300 ps simulations containing 200 ps production is enough for getting convergence results.

Table 5. Convergence for Calculations of the HFE of Zn^{2+} Using the 12-6-4 Parameter Set and the OPC Water Model.

Sampling in Each Window	VDW plus C ₄ appearing (kcal/mol)	Charge appearing (kcal/mol)	Charge disappearing (kcal/mol)	VDW plus C ₄ disappearing (kcal/mol)	Total HFE (kcal/mol)
100 ps w/ last 50 ps produce	-47.73	-419.76	421.37	48.15	-468.50
200 ps w/ last 150 ps produce	-47.96	-419.98	420.76	47.71	-468.21
300 ps w/ last 200 ps produce	-47.99	-420.22	420.01	47.75	-467.99

Table 6. Convergence for Calculations of the HFE of Zn^{2+} Using the CM Parameter Set and the OPC Water Model.

Sampling in Each Window	VDW appearing (kcal/mol)	Charge appearing (kcal/mol)	Charge disappearing (kcal/mol)	VDW disappearing (kcal/mol)	Total HFE (kcal/mol)
100 ps w/ last 50 ps produce	1.56	-444.71	444.99	-1.37	-443.38
200 ps w/ last 150 ps produce	1.21	-445.36	444.28	-1.42	-443.51
300 ps w/ last 200 ps produce	1.39	-443.98	444.93	-1.41	-443.06

To obtain the IOD and CN values, the same initial structure was used to simulate the metal ion in the aqueous phase. Similarly, 5000 steps of minimization using the steepest descent algorithm, 5000 steps of minimization using the conjugate gradient algorithm, 360 ps of NVT heating, and 2 ns NPT of equilibration were performed to equilibrate the system. Finally, 2 ns of NVT sampling at 300 K was performed with snapshots saved every 0.5 ps. The cpptraj program¹¹⁹ was used to generate the radial distribution function (RDF) between the metal ion and water oxygen atoms in the range of 0-10 Å with a resolution of 0.01 Å. Each RDF was generated based on the average

volume of that specific trajectory. Based on the RDF, we obtained the IOD and CN values with the method introduced in our previous study¹²⁰.

For all the MD simulations, the Langevin thermostat was used to maintain constant temperature with a collision frequency of 2 ps⁻¹. The time step was set to 1 fs, and the nonbonded cut-off was treated as 10 Å. The Berendsen barostat was used for pressure control in the NPT ensemble with a pressure relaxation time of 1 ps. The three-point SHAKE algorithm¹²¹⁻¹²² was used for the water molecules in all the simulations except the minimizations and vdW scaling steps. The simulations in the present work were assisted by the IPMach.py program in the AmberTools software package¹²³.

2.3 Parameter Space Scanning

Due to the uniqueness of each water model, as displayed in **Table 1**, it is challenging to design a one-for-all ion parameter set to fit all these models. Therefore, four sets of different combinations of the $R_{min}/2$ and ε parameters are parametrized individually for the four water models OPC3, OPC, TIP3P-FB and TIP4P-FB. Based on quadratic fitting, as mentioned in **Figure 8**. ~ **Figure 11** have indicated that similar trends exist in the fitting curves for ions in water. HFE increases as $R_{min}/2$ decreases, and small $R_{min}/2$ can be compensated by a large ε parameter to rescue the HFE value to a similar level, same as a large $R_{min}/2$ combined with a small ε value. The equation of the 12-6-4 LJ-type potential function mentioned in Equation (4) can explain this phenomenon. Small $R_{min}/2$ values with larger ε values and vice versa can both yield similar C_{12} and C_6 values.¹²⁴ Furthermore, ε is directly proportional to C_{12} and C_6 , but $R_{min}/2$ is raised to two significant powers (12th and 6th) each in the expression for C_{12} and C_6 . This explains why HFE is monotonically and almost linearly dependent on $R_{min}/2$ while the effect of ε on HFE is closer to logarithmic instead of being linear.



Figure 9. Fitting curves between the HFE and IOD values for the positive (left) and negative (right) monovalent ions in the four water models together with the target values of the ions investigated in the present work.



Figure 10. Fitting curves between the HFE and IOD values for the divalent ions in the four water models together with the target values of the ions investigated in the present work.

Generally, all of the fitting curves have a similar shape but different Y-intercepts for the all the four water models. The HFE values of LJ grids for different water models proved that even applying the same 12-6-4 LJ-type potential, the difference in each water model is still significant. Interestingly, the fitted curves converge when the ion has a large IOD but diverge when the ion has a small IOD. Moreover, all the target points are above the fitting curves in **Figure 10** and **Figure 11**. This indicates that all the water models underestimate the HFE values of positively charged ions when reproducing their experimental IOD values, which differs from **Figure 9**, where for monovalent ions, the experimental scatter points distribute on both sides of the fitted curves. This also agrees with the statement that it is challenging to reproduce both experimental HFE and IOD values using the 12-6 model when the cation has a charge of $\geq +2^{33}$. In general, the OPC3 water model yields the best performance as its curve is the closest to the scatter points of the experimental HFE and IOD values for divalent metal ions. Specifically, the performance of the

eight water models is as follows: OPC3 > TIP3P~SPC/E~TIP3P-FB > OPC~TIP4P-FB > TIP4P_{EW} > TIP4P.



Figure 11. Fitting curves between the HFE and IOD values for the positive (upper) and negative (lower) monovalent ions in the four water models together with the target values of the ions investigated in the present work.

These results are consistent with a previous study, which indicated the four-point water models tend to have larger errors when simulating cations⁴⁶. Moreover, the results also showed that the four new water models can provide improved or similar performance when compared to the previous water models in the same category. In the category of three-point water models, OPC3 provides better performance than the TIP3P-FB model, which showed similar performance to the widely used TIP3P and SPC/E water models. In the category of four-point water models, the two novel water models (OPC and TIP4P-FB) showed comparable performance to each other, and both are better than the TIP4P_{EW} and TIP4P water models.

In order to further compare the eight water models, curve fitting was performed between the HFE and $R_{min}/2$ values for each of the water models. These fitted curves are shown in **Figure 12** ~ **Figure 14**. Similar to the IOD vs. HFE fitting curves, the fitted curves also converge when $R_{min}/2$ is large but diverge when $R_{min}/2$ is small. The eight water models almost yield identical results when $R_{min}/2$ is ~2.3 Å. In contrast, these water models have significant differences when $R_{min}/2$ is ~0.9 Å. In general, the OPC3 water model tends to simulate a larger HFE value than the other water models when using the same Lennard-Jones parameters, especially when $R_{min}/2$ is smaller than 1.1 Å.

Similarly, to compare the performance of the eight water models for simulating IOD values, we performed quadratic fits for IOD vs. $R_{min}/2$ for each water model and illustrated the results in **Figure 15** ~ **Figure 17**. These IOD fitting curves of the eight water models are close to each other, which agrees with the previous study⁴⁶. By checking the figure carefully, it is found that the IOD fitting curves for these water models converge when $R_{min}/2$ is small but diverge when $R_{min}/2$ is larger, which is opposite to the trends of the HFE fitting curves. Specifically, when $R_{min}/2$ is larger than 2.1 Å, the OPC3 water model tends to simulate a smaller IOD value than other water models,

especially those of the four-point water models. However, this difference is relatively small, with a value of ~0.05 Å at most.



Figure 12. Fitting curves of HFE vs $R_{min}/2$ for the monovalent cations (top) and anions (bottom) for the four new water models.



Figure 13. Fitting curves of HFE vs $R_{min}/2$ for the divalent cations (top) and anions (bottom) for the four new water models.



Figure 14. 12-6 HFE fitting curves for the seven water models for trivalent (top) and tetravalent (bottom) ions. Fitting curves for the TIP3P-FB and SPC/E water models overlap with each other.



Figure 15. Fitting curves of IOD vs $R_{min}/2$ for the monovalent cations (top) and anions (bottom) for the four new water models.



Figure 16. Fitting curves of IOD vs $R_{min}/2$ for the divalent cations (top) and anions (bottom) for the four new water models.



Figure 17. 12-6 IOD fitting curves for the seven water models for trivalent (top) and tetravalent (bottom) ions.

Therefore, using merely 12-6 LJ parameter set for the ions cannot reproduce the true behavior of charged ionic species during the simulations, since none are able to reproduce the experimental HFE and IOD values simultaneously. Hence, it is concluded that introducing the C_4 term can close the gap. As displayed in **Figure 14** and **Figure 17**. the target experimental values are "sandwiched" by the two sets of curves representing the minimum and maximum of the C_4 value in the scan range. This indicates that through using a suitable C_4 parameter, the 12-6-4 model is able to reproduce both experimental HFE and IOD values of a highly charged metal ion simultaneously. Starting from the initial guesses obtained by the strategy described in **Figure 8**, the final parameter determination of the 12-6-4 model for all 24 metal ions can therefore be performed. And the detailed results are displayed from **Table 31** to **Table 40** (See APPENDIX A: TABLES).

2.4 Parameter Determination and Error Analysis

Based on the parameter space scanning results, the parameterization for the 12-6 model of all the 60 ions in conjunction with each of the four new water models is performed. Because the 12-6 model has intrinsic errors when modeling divalent metal ions, it is impossible to reproduce both the experimental HFE and IOD values at the same time. Hence, different parameter sets were parametrized to reproduce different target properties, as was done in previous works^{33, 45-46}. Specifically, the HFE parameter set was generated to reproduce the target HFE values, the IOD parameter set to reproduce the target IOD values, and for divalent ion only, the compromise (CM) parameter set to keep a balance of these two properties and reproduce the experimental relative HFE values. Because of all the 24 divalent ions, only 16 out of them have target IOD values; the IOD parameter set was, therefore, not designed for all the divalent metal ions. Herein we show the HFE, IOD, and (if divalent) CM parameter sets, as well as their simulated HFE, IOD, and CN values in **Table 41 ~ Table 52** (See APPENDIX A: TABLES) respectively. The HFE parameter set can reproduce the target HFE values within 1 kcal/mol, while the IOD parameter set can reproduce the target HFE values within 0.01 Å.

Because of divalent ions' uniquely moderate overestimation of HFE-set-produced IOD value and moderate underestimation (less negative) of IOD-set-produced HFE value, the CM set was parameterized by systematically shifting the target HFE values by a constant so the users can still use 12-6 LJ model to reproduce both HFE and IOD with a reasonably small error. In this way, the relative HFE values between different metal ions are still reproduced. By considering the differences in the four new water models, the constants of shifting were 20, 25, 25, and 30 kcal/mol for the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models, respectively. For a certain divalent ion, the CM parameter set usually has $R_{min,M}/2$ between its HFE and IOD parameter sets.

kcal/mol accuracy of reproducing experimental HFEs. The CM parameter set and its simulated

HFE, IOD, and CN values are listed in Table 7 and Table 8, respectively.

Table 7. The CM parameter set for 24 divalent metal ions in conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models.

	OPC3			OPC	TI	P3P-FB	TIP4P-FB		
	R _{min} /2 (Å)	ε (kcal/mol)							
Be ²⁺	0.971	0.00000621	0.921	0.00000128	0.963	0.00000489	0.924	0.00000142	
Cu^{2+}	1.228	0.00174080	1.178	0.0007549	1.223	0.00160860	1.181	0.00089969	
Ni ²⁺	1.251	0.00247282	1.197	0.00104974	1.257	0.00270120	1.213	0.00136949	
$\mathbf{P}t^{2+}$	1.272	0.00334975	1.219	0.00150903	1.274	0.00344520	1.229	0.00176831	
Zn^{2+}	1.280	0.00374505	1.219	0.00150903	1.276	0.00354287	1.234	0.00191142	
Co^{2+}	1.306	0.00530214	1.263	0.00294683	1.304	0.00516628	1.277	0.00359255	
Pd^{2+}	1.309	0.00551135	1.269	0.00321068	1.308	0.00544088	1.282	0.00384964	
Ag^{2+}	1.339	0.00799176	1.305	0.00523385	1.339	0.00799176	1.316	0.00602547	
Cr^{2+}	1.349	0.00899152	1.316	0.00602547	1.349	0.00899152	1.327	0.00691068	
Fe^{2+}	1.356	0.00974813	1.323	0.00657749	1.356	0.00974813	1.334	0.00752608	
Mg^2_+	1.363	0.01055378	1.330	0.0071693	1.363	0.01055378	1.342	0.00828195	
V^{2+}	1.366	0.01091456	1.334	0.00752608	1.366	0.01091456	1.345	0.00858042	
${\mathop{Mn^2}\limits_{\scriptscriptstyle +}}$	1.410	0.01738340	1.381	0.01286460	1.411	0.01755812	1.394	0.01476261	
Hg^{2+}	1.410	0.01738340	1.381	0.01286460	1.411	0.01755812	1.394	0.01476261	
Cd^{2+}	1.413	0.01791152	1.389	0.01400886	1.415	0.01827024	1.398	0.01538757	
Yb^{2+}	1.622	0.09072908	1.602	0.08034231	1.629	0.09454081	1.621	0.09019198	
Ca^{2+}	1.628	0.09399072	1.608	0.08337961	1.635	0.09788018	1.627	0.09344247	
\mathbf{Sn}^{2+}	1.641	0.10128575	1.625	0.09235154	1.652	0.1076997	1.645	0.10359269	
Pb^{2+}	1.723	0.15415012	1.707	0.14295367	1.730	0.15917293	1.728	0.15773029	
Eu^{2+}	1.772	0.19078645	1.753	0.17618319	1.782	0.19865859	1.782	0.19865859	
Sr^{2+}	1.778	0.1954949	1.766	0.18612361	1.789	0.20424131	1.789	0.20424131	
Sm^{2+}	1.784	0.2002477	1.766	0.18612361	1.795	0.20907204	1.796	0.20988115	
Ba ²⁺	1.966	0.35853865	1.960	0.35308749	1.983	0.37399087	1.992	0.38216886	
Ra^{2+}	1.966	0.35853865	1.960	0.35308749	1.983	0.37399087	1.992	0.38216886	

	OPC3 OPC				TIP3	P-FB	TIP4P-FB					
	HFE (kcal/mol)	IOD (Å)	CN	HFE (kcal/mol)	IOD	CN	HFE (kcal/mol)	IOD	CN	HFE (kcal/mol)	IOD (Å)	CN
Be ²⁺	-551.8	1.25	19	-547 7	1 18	2.0	-546.9	1.23	2.0	-542.5	1 18	2.0
Cu^{2+}	-459.6	1 91	6.0	-454 9	1 71	<u> </u>	-455.9	1.20	<u> </u>	-448.3	1 71	<u> </u>
Ni ²⁺	-454.0	1.93	6.0	-448.0	1.90	5.9	-448.7	1.93	6.0	-443.8	1.90	6.0
Pt ²⁺	-450.8	1.95	6.0	-444.8	1.93	6.0	-442.9	1.95	6.0	-438.1	1.99	6.0
Zn^{2+}	-446.9	1.96	6.0	-443.1	1.93	6.0	-442.8	1.95	6.0	-437.9	1.93	6.0
Co ²⁺	-437.8	1.98	6.0	-434.5	1.97	6.0	-432.8	1.98	6.0	-428.8	1.97	6.0
Pd^{2+}	-436.6	1.99	6.0	-431.7	1.98	6.0	-431.3	1.99	6.0	-425.9	1.97	6.0
Ag ²⁺	-426.3	2.02	6.0	-421.0	2.01	6.0	-421.6	2.02	6.0	-415.9	2.01	6.0
Cr^{2+}	-422.9	2.03	6.0	-417.1	2.03	6.0	-417.5	2.03	6.0	-412.1	2.02	6.0
Fe ²⁺	-420.1	2.04	6.0	-414.7	2.03	6.0	-414.9	2.04	6.0	-410.1	2.03	6.0
Mg^{2+}	-417.8	2.05	6.0	-412.4	2.04	6.0	-412.5	2.05	6.0	-407.6	2.04	6.0
V^{2+}	-416.1	2.05	6.0	-411.7	2.04	6.0	-411.3	2.05	6.0	-406.2	2.04	6.0
Mn^{2+}	-400.6	2.11	6.0	-396.1	2.10	6.0	-395.5	2.11	6.0	-390.5	2.10	6.0
Hg^{2+}	-400.0	2.11	6.0	-396.7	2.10	6.0	-395.4	2.11	6.0	-389.7	2.10	6.0
Cd^{2+}	-399.5	2.11	6.0	-393.5	2.11	6.0	-393.8	2.11	6.0	-388.8	2.11	6.0
Yb^{2+}	-340.7	2.47	7.9	-336.5	2.48	7.9	-335.4	2.48	7.9	-330.2	2.49	8.0
Ca^{2+}	-339.6	2.48	7.9	-334.8	2.49	7.9	-334.3	2.49	7.9	-330.2	2.49	8.0
\mathbf{Sn}^{2+}	-335.6	2.49	8.0	-331.3	2.51	8.0	-331.8	2.51	8.0	-326.2	2.51	8.0
Pb^{2+}	-320.1	2.59	8.1	-315.3	2.60	8.2	-316.0	2.60	8.1	-310.0	2.61	8.3
Eu^{2+}	-310.6	2.65	8.4	-306.6	2.67	8.6	-306.5	2.67	8.4	-301.1	2.69	8.7
Sr^{2+}	-309.5	2.66	8.4	-306.5	2.69	8.7	-304.7	2.68	8.5	-299.0	2.70	8.8
Sm^{2+}	-309.0	2.67	8.4	-304.1	2.69	8.7	-303.1	2.68	8.5	-297.9	2.71	8.8
Ba^{2+}	-278.3	2.88	9.1	-275.2	2.91	9.4	-274.2	2.90	9.2	-269.8	2.94	9.4
Ra^{2+}	-279.0	2.88	9.1	-274.5	2.91	9.3	-273.9	2.90	9.1	-269.5	2.93	9.4

Table 8. Calculated HFE, IOD, and CN values for the CM parameter set for the four water models.

Unlike positively charged ions, the localized charges on halide ions in an aqueous environment lead to differences in the preferred orientations of water molecules towards ions. Rajamani *et al.* describe the charge hydration asymmetry (CHA) effect,⁹² where for the cations the water molecules interact with the ion through the negatively charged oxygen atoms. The anion interacts with the positively charged hydrogen atoms of the water molecules following Coulomb's law. In accord with earlier studies with TIP3P, TIP4P_{EW}, and SPC/E,⁴⁴, the performance of the 12-6

parameter sets was evaluated for simulating the CHA effect in conjunction with the four new water models. Again, K⁺ and F⁻ ions were used as examples because they have similar effective radii (1.38 and 1.33 Å) but different HFEs (with the HFE of F⁻ is more negative than that of K⁺ by ~41 or ~49 kcal/mol according to the Schmid and Marcus *et al.* data set, respectively). In the IOD parameter set, they have similar $R_{min}/2$ parameters, irrespective of the water model used. However, the computed HFE differences between K⁺ and F⁻ are ~60, ~66, ~61, and ~64 kcal/mol for the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models, respectively, indicating that the four-point water models showed a stronger CHA effect, which is consistent with our previous studies.⁴⁶ This may arise from the fact that the four-point water models usually have larger positive charges on the hydrogen atoms that coordinate to the anions.

Therefore, the CHA effects were further characterized for different water models based on the scanning results, and the results are shown in **Figure 18**. In agreement with the previous study,⁴⁴ it was found that anions have shorter IODs and more negative HFEs in comparison to that of cations with the same LJ parameters, and this effect decreases to some extent for the HFE values but has no apparent trend for the IOD values as $R_{min}/2$ increases. Interested readers are encouraged to be directed to a more detailed discussion on the CHA effect on the features of hydrated monovalent ions in our previous work.⁴⁴



Figure 18. The (a) HFE fitting curves and (b) IOD fitting curves for monovalent cations and anions for each of the four new water models.

To better understand the errors in the 12-6 model other than the CHA effect, an error analysis was performed for the 12-6 model while running simulations using the HFE and IOD values. By treating the OPC3 water model as an example, the corresponding HFE and IOD errors (as a percentage) was shown for monovalent ions are displayed in **Figure 19**. Similarly, for other ions, The corresponding results for all four water models are shown in **Figure 20** and **Figure 21**, respectively, for divalent and highly-charge ions. The HFE percent errors were calculated for the IOD parameter set, indicating the percent error of the 12-6 model when simulating the HFE values while reproducing the IOD values. Similarly, the IOD percent errors were calculated for the HFE

parameter set, indicating the percent error of the 12-6 model when simulating the IOD values while reproducing the HFE values. Based on these results, it appears that there is a reverse correlation between the size of the divalent metal ion and the percentage of error, which aligns with our previous research.¹²⁵. For example, the biggest divalent ion Ba²⁺ has both the HFE percent error and IOD percent error of less than 5% when using the 12-6 model in conjunction with the OPC3 water model. By comparison, the smallest divalent ion Be²⁺ has the biggest percent errors: the HFE percent error and IOD percent error for Be²⁺ are 16% and 29%, respectively. These errors for Be²⁺ are even larger when using the other three water models. Moreover, it can be seen that except for the Be²⁺ ion, the alkaline earth metal ions generally have smaller percent errors than the transition metal ions. This is consistent with the fact that the C_6 term in the 12-6 model considers the induced dipole-induced dipole interaction that is isotropic in nature. The alkaline earth metal ions have electronic structures identical to the noble gas atoms, making the point charge representation in the 12-6 model better able to represent these ions relative to the transition metal ions.



Figure 19. Absolute errors in (a) calculated HFE (in kcal/mol) and (b) calculated IOD (Å).



Figure 20. HFE and IOD percent errors for the 12-6 nonbonded model of metal ions in conjunction with the OPC3, OPC, TIP3P-FB and TIP4P-FB water model (from top to bottom). The HFE percentage errors were for the 12-6 IOD parameter set that can reproduce the target IOD values. The IOD percentage errors were for the 12-6 HFE parameter set that can reproduce the target HFE values.



Figure 21. HFE and IOD percent errors for the 12-6 nonbonded model of highly charged metal ions in conjugation with OPC3, OPC, TIP3P-FB and TIP4P-FB water models (indicated at each figure's legend and Y-axis). The HFE percent errors were for the 12-6 IOD parameter set which can reproduce the experimental IOD values. The IOD percent errors were for the 12-6 HFE parameter set which can reproduce the experimental HFE values.

For trivalent and tetravalent metal ions, especially the transition metals, comparing differences in percent errors leads to a conclusion that tetravalent ions have generally larger errors than trivalent ions for both the HFE and the IOD. This, apart from the fact that the absolute HFE and IOD values are larger for tetravalent ions, can also be explained by Equation (4). According to Equation (4), the induced-dipole-related energies have a 9:16 ratio between trivalent and tetravalent metal ions. Since neither of the 9:16 energies were taken into account in the 12-6 model, they will respectively contribute a 9:16 ratio on average for the errors seen in Figure 3. As anticipated, this error was overall much larger than for the divalent⁴⁷ and monovalent⁴⁶ ions due to the stronger effect of the ion-induced dipole for the highly charged metal ions.

In summary, our results indicate that the 12-6 model has significant errors in simulating charged ionic species in conjunction with the four new water models, as we found for previous water models⁴⁴. We have attributed this error to the absence of ion-induced dipole interactions in the 12-6 model and proposed the addition of a C_4 term into the 12-6 model to take this interaction into account. The new model was named the 12-6-4 model, and it can reproduce experimental HFE and IOD values simultaneously for various ions¹²⁶.

After the new model was established, the first thing was to conduct parameter space scanning for the 12-6-4 model. The results are altogether shown from **Table 31** to **Table 40**. Based on the parameter scanning results, a full round of parameterizations was conducted for the 12-6-4 model in conjunction with the four new water models. In these parameterizations, it was aimed to reproduce both the experimental HFE and IOD values. Again, since only 16 out of 24 divalent ions have both experimental HFE and IOD values, the 12-6-4 parameterization was only performed on these 16 divalent ions. The final parameters and the simulated HFE, IOD, and CN values obtained by these parameters are shown from **Table 9** to **Table 57** (Only **Table 9** is shown here, please see

APPENDIX A: TABLES for others). These parameters can simultaneously reproduce the experimental HFE and IOD values with excellent accuracy, *i.e.*, the experimental HFE is within 1 kcal/mol and the experimental IOD values within 0.01 Å.

According to the results displayed from **Table 9** to **Table 57** it is common to find that the threepoint water models generally have bigger C₄ terms than the four-point water models. This is consistent with the previous 12-6-4 parameterization work for the TIP3P, SPC/E, TIP4P/EW water models¹²⁷. metal ions with similar $R_{min}/2$ values but very different C₄ values. For example, La³⁺ and Ce³⁺ have $R_{min}/2$ values differing by only ~0.03 Å, but Ce³⁺ ion has a C₄ value which is more than 1.5 times that of the La³⁺ ion. According to Equation (4), the C₄ value can, in turn, yield information about the relative permittivity between the metal ion and water molecules, as described by Equation (14).

$$\varepsilon = \frac{ze}{4\pi\varepsilon_0} \sqrt{\frac{\alpha}{2C_4}}$$
(14)

Using the C_4 value from the TIP3P-FB water model, the relative permittivity was calculated to be 16.03 for La³⁺ and 12.41 for Ce³⁺, which physically makes sense since the effective ion radius of La³⁺ is slightly larger than Ce³⁺ due to its noble gas electron configuration. Therefore, the electron cloud of Ce³⁺ will be "harder" and more contracted compared to La³⁺, leading to more space between the metal ion and its surrounding water molecules, which then brings down the relative permittivity value.

		OPC3		OPC			
	$\frac{R_{\min}/2}{(\text{\AA})}$	ε (kcal/mol)	C ₄ (kcal/mol· Å ⁴)	$\frac{R_{\min}/2}{(\text{\AA})}$	£ (kcal/mol)	C_4 (kcal/mol·Å ⁴)
Li ⁺	1.329	0.00708225	29	1.304	0.0	00516628	29
Na ⁺	1.475	0.03171494	2	1.448	0.0)2499549	1
\mathbf{K}^+	1.760	0.18150763	16	1.746	0.	17092614	20
\mathbf{Rb}^+	1.833	0.24055479	8	1.802	0.2	21475916	6
Cs^+	2.002	0.39124724	6	1.993	0.3	38307717	13
Tl^+	1.893	0.29273756	63	1.876	0.2	27770866	60
Cu^+	1.229	0.00176831	12	1.221	0.0	0155814	16
Ag^+	1.519	0.04525501	83	1.504	0.0	04026281	83
F^-	1.739	0.16573832	-40	1.725	0.	15557763	-67
Cl^{-}	2.165	0.53403341	-47	2.143	0.5	51564233	-69
Br^{-}	2.327	0.65680855	-43	2.313	0.0	64716164	-60
I_	2.586	0.80119052	-39	2.572	0.7	79496382	-60
		TIP3P-FE	3	TIP4P-FB			
	$R_{\rm min}/2$ (Å)	ε (kcal/mol)	C_4 (kcal/mol·Å ⁴)	$R_{\min}/2$	(Å)	ε (kcal/mol)	C_4 (kcal/mol·Å ⁴)
Li ⁺	1.321	0.00641580	30	1.30	8	0.00544088	33
Na^+	1.470	0.03038310	2	1.46	1	0.02808726	8
\mathbf{K}^+	1.750	0.17392181	15	1.75	4	0.17693975	25
Rb^+	1.815	0.22546047	7	1.81	1	0.22214904	9
Cs^+	2.004	0.39306142	17	1.99	8	0.38761725	13
Tl^+	1.892	0.29184918	65	1.88	4	0.28476102	68
Cu^+	1.232	0.00185305	17	1.22	8	0.00174080	25
Ag^+	1.519	0.04525501	85	1.51	7	0.04456630	90
F^{-}	1.745	0.17018074	-45	1.74	1	0.16721338	-57
Cl^{-}	2.158	0.52822042	-49	2.16	9	0.53733840	-55
Br^{-}	2.325	0.65544212	-40	2.33	1	0.65952968	-51
Ι-	2.589	0.80250319	-52	2.59	1	0.80337410	-53

Table 9. Final Optimized 12-6-4 Parameter Set for the Four Water Models.

Noticeably, for the three main group trivalent elements Al, In, and Tl, their C4 values follow the trend of "Tl > Al > In". A reasonable explanation is that Tl⁺ can have a monovalent oxidation state due to its 6s inert pair effect.¹²⁸ Therefore, the HFE of Tl⁺ is similar to that of K⁺ in the Marcus HFE set.¹⁰² Because it can be partially reduced, Tl³⁺ is the only one among these three trivalent ions which has a positive reduced electric potential.¹²⁹ Comparatively, the Al³⁺ ion is a "harder" acid compared to In^{3+} , which leads to more covalent-like interactions with the coordinated water molecules. For the Lanthanide ions, their C₄ terms are generally within the range of 131-326 kcal/mol·Å⁴, while for main-group and d-orbital transition metals the range is 209-531 kcal/mol·Å⁴. For a specific metal ion, the larger the HFE and IOD error it has, the larger its C₄ value will be to compensate for that error. In comparison, among the Actinide series tetravalent ions, U^{4+} is the only ion that has a C₄ about or above 1000 kcal/mol·Å⁴. U⁴⁺ ion seems to be the metal ion with the strongest dipole-inducing ability among all the 24 metal ions investigated. Compared to the experimental CNs, we found that the 12-6-4 model tends to over-coordinate the Pu⁴⁺ and Ce⁴⁺ ions, with Pu⁴⁺ being slightly worse than Ce⁴⁺. This is probably a combined effect of inaccurate water interactions within the first solvation shell and the non-noble gas configuration of Pu⁴⁺. TIP3P usually has the highest CN values compared to other water models, which is likely due to its small Lennard-Jones C_{12} term (6.6 × 10⁵ kcal/mol·Å¹²) that describes repulsions between metal ions and water oxygens.⁶⁹

As a conclusion, all of the three parameters in the present study ($R_{min}/2$, ε , and C_4) have physical meanings. On the other hand, all these three parameters are correlated with each other such that unphysical assignment of one can cause over-fitting of the others. Balancing these parameters relative to each other is important to ensure their transferability to other systems, such as materials and biomolecules. In our present study, we compared our parameters to the vdW radii calculated

by the quantum mechanics scaling principle (QMSP) method and showed that our parameters, which are obtained based on the NGC, show better agreement with the QMSP results than other parameter sets⁹⁶. Again, to analyze the balance of the obtained parameters in the present work, we compared the $R_{min}/2$ parameters to the QMSP calculated vdW radii. The QMSP calculated vdW radii of some of the ions in the gas phase are shown in **Table 10** and **Table 11**. By treating these four values as a reference, the average unsigned error (AUE) for each parameter set obtained herein was calculated, and results are shown in **Table 12**, **Figure 22**, and **Figure 23**.

In comparison, the AUEs for the parameter sets obtained previously were also calcualted⁴⁴ altogether with the parameter sets developed by Lim *et al.*⁸⁶ and Åqvist *et al.*¹⁰

Table 10. VDW Radii Calculated from the QMSP Method for the Ions with the same Electronic Structure with Noble Gas Atoms.

Ions	VDW radii (Å)
Na ⁺	1.352
\mathbf{K}^+	1.671
Rb ⁺	1.801
Cs ⁺	1.997
F^-	1.909
Cl [_]	2.252
Br^-	2.298
I	2.548

Table 11. VDW Radii Calculated Using the QMSP Method for Divalent Ions Which Have the Same Electronic Structures as the Noble Gas Atoms⁹⁶.

Ions	vdW radii (Å)
Mg^{2+}	1.180
Ca^{2+}	1.480
Sr^{2+}	1.625
Ba^{2+}	1.802

Previous OPC3 OPC Lim Lim 12-6-12-6-Åqvist^a HFE IOD HFE IOD Set 1^b 4 Set 2^c 4 Mg^{2+} 1.433 0.787 1.183 1.364 1.306 1.400 1.239 1.373 1.405 Ca^{2+} 1.831 1.541 1.632 1.590 1.602 1.326 1.936 1.617 1.493 Sr^{2+} 1.742 1.968 2.092 1.677 1.762 1.777 1.631 1.731 1.738 Ba^{2+} 2.124 2.062 2.245 1.840 1.918 1.936 1.797 1.883 1.898 Average Error (Å) -0.027 0.239 0.388 0.069 0.152 0.173 0.018 0.122 0.139 Std. Dev. (Å) 0.270 0.141 0.118 0.034 0.040 0.047 0.024 0.042 0.050 AUE (Å) 0.246 0.239 0.388 0.069 0.152 0.173 0.021 0.122 0.139

Table 12. vdW Radii (R_{min}/2 values) of Different Parameter Sets and Their Statistical Analysis against Quantum Scaling Principle Calculated Values.

]	FIP3P-FB]	TIP4P-FB			
	HFE	IOD	12-6- 4	HFE	IOD	12-6- 4		
Mg^{2+}	1.288	1.400	1.433	1.238	1.383	1.409		
Ca ²⁺	1.525	1.617	1.636	1.488	1.600	1.625		
Sr^{2+}	1.659	1.762	1.769	1.626	1.746	1.755		
Ba ²⁺	1.824	1.918	1.922	1.795	1.900	1.917		
Average Error (Å)	0.052	0.152	0.168	0.015	0.136	0.155		
Std Dev. (Å)	0.033	0.040	0.051	0.025	0.040	0.044		
AUE (Å)	0.052	0.152	0.168	0.018	0.136	0.155		

^aFrom Ref.¹⁰.

^{*b*}From Ref.⁸⁶ by reproducing the relative HFEs towards Zn²⁺. ^{*c*}From Ref.⁸⁶ by reproducing the relative HFEs towards Cd²⁺.



Figure 22. AUEs of the calculated VDW radii using selected different parameter sets. The parameter sets developed herein are shown in the five blue columns on the right side of the figure.



Figure 23. AUEs of the $R_{min}/2$ parameters in different parameter sets when using the QMSP result as reference.

2.5 Assessment and Validation

To validate the transferability of these developed parameters. Four individual tests were carried out to systematically investigate these parameters' performances while being applied to the ions in a variety of circumstances, ranging from testing methods of QM test on ion-water complex to RMSD robustness test on a metalloprotein, and also ranging from testing cases of ionic solutions' activity coefficients to aqueous diffusion coefficient.

For monovalent ions, the parameters have been proven capable of reproducing structural and thermodynamic features of solvated ions, so the applicability of these parameters to simulate ion pairs is subsequently evaluated. Activity derivatives of six salt solutions (NaCl, KCl, NaBr, KF, NaI and CsI) were calculated for the 12-6 HFE, 12-6 IOD and 12-6-4 parameter sets in conjunction with the OPC and OPC3 water model with some changes in the protocol in our previous study.⁴⁴ The details of the simulation methods are below, and the results are presented in **Table 13**.

Table 13. Simulated activity derivatives for six ion solutions using the different parameter sets in conjunction with the SPC/E, OPC3, and OPC water models.

		SPC/E			OPC3			OPC		Expt ^c
	12-6	12-6	1264	12-6	12-6	1264	12-6	12-6	1264	
	HFE	IOD	12-0-4	HFE	IOD	12-0-4	HFE	IOD	12-0-4	
N ₂ C1	0.90	0.88	0.87	0.93	0.91	0.88	0.97	0.87	0.86	0.02
NaCI	±0.12	±0.06	± 0.05	±0.03	±0.06	± 0.08	±0.02	± 0.06	± 0.05	0.95
VC 1	0.88	0.88	0.87	0.87	0.88	0.86	0.83	0.92	0.93	0.00
KU	±0.03	±0.10	± 0.02	±0.02	±0.03	± 0.08	±0.04	± 0.05	±0.04	0.90
N _o D _n	0.94	0.94	0.91	0.98	0.93	0.94	0.96	0.95	1.00	0.04
INADI	±0.06	±0.03	± 0.05	± 0.07	± 0.08	±0.02	±0.09	± 0.05	± 0.08	0.94
VE	0.78	0.81	0.75	0.76	0.80	0.82	0.84	0.77	0.84	0.02
ΝГ	±0.11	±0.05	± 0.06	±0.10	±0.02	± 0.08	±0.10	± 0.05	±0.03	0.92
Nat	1.03	0.97	0.97	1.00	0.98	0.99	1.12	0.99	0.96	0.07
INAL	± 0.02	± 0.04	± 0.04	±0.03	± 0.04	±0.12	±0.01	± 0.07	±0.04	0.97
C-I	0.87	0.91	0.86	0.86±0.	0.84	0.88	0.93	0.91	0.90	0.96
CSI	± 0.05	± 0.05	± 0.01	01	± 0.07	±0.04	± 0.05	± 0.08	± 0.07	0.80
Avg	0.02	0.02	0.05	0.02	0.02	0.02	0.02	0.02	0.01	
Error	0.02	0.02	0.05	0.05	0.02	0.02	0.02	-0.02	0.01	
Std	0.00	0.07	0.00	0.04	0.07	0.04	0.07	0.00	0.00	
Dev.	0.06	0.07	0.00	0.04	0.07	0.04	0.07	0.09	0.00	
UAE	0.04	0.04	0.05	0.05	0.03	0.04	0.07	0.05	0.05	

To compute the activity derivatives, the Kirkwood-Buff integral was calculated from the RDF via eq 1, where $g_{ij}(r)$ is the RDF between species *i* and *j*, *dr* was set as 0.01 Å, and the cutoff was set as 12 Å for the RDF.

$$G_{ij} = \int_0^\infty 4\pi r^2 [g_{ij}(r) - 1] dr$$
 (15)

Subsequently, eq 2 was applied to calculate the activity derivative (a_{cc}) for each salt solution.

$$a_{cc} = \frac{1}{1 + \rho_c (G_{cc} - G_{cw})} = \frac{1}{1 + N_{cc} - \frac{\rho_c N_{cw}}{\rho_w}}$$
(16)

Herein ρ_c stands for the number density of the ions, with cations and anions treated indistinguishably. Similarly, ρ_w represents the number density of water molecules. G_{cc} and G_{cw} are the Kirkwood-Buff integral for ion-ion and ion-water pairs, respectively, and N_{cc} and N_{cw} are the corresponding excess coordination numbers.

Result-wise, it was observed that the three water models showed similar performance for simulating the activity derivatives. All of the combinations of parameter sets and water models provide unsigned average error (AUE) equal or smaller than 0.07, indicating an excellent performance of the parameters we developed. Note that the current simulations showed slight deviation from the previous results for the different parameter sets in conjunction with the SPC/E water model,⁴⁴, which is due to the variations in the computational protocols employed.

For divalent ions, in order to further evaluate the parameter performances, a series of additional tests and analyses was performed on ion-dimer dimers or even clusters. First, to test the transferability, ion-water dimers of Mg^{2+} and Ca^{2+} ions. The optimized IOD and ion-water interaction energy for each combination of parameter set and water model were harvested. The obtained results are shown in **Table 14** and **Table 15**, along with the results based on the Drude Oscillator Model⁴⁰ as well as the density functional theory (DFT) and the AMOEBA polarizable

force field⁵⁸. It can be seen that although the current parameter sets were designed for liquid phase properties, they still provide a reasonable description of ion-water dimers. Encouragingly, the 12-6 HFE parameter set in conjugation with the OPC3/TIP3P-FB water model provides excellent performance for simulating each of the Mg^{2+} -water and Ca^{2+} -water dimers, which can reproduce the QM calculated ion-water interaction energy and optimized IOD within 1 kcal/mol and 0.1 Å, respectively. However, one certain combination of parameter set and water model, which provides excellent performance (when compared to the QM results) for modeling a certain ion-water dimer, may not necessarily provide comparable performance for simulating another ion-water dimer. For example, the 12-6 HFE parameter in conjugation with the TIP4P-FB water model performs reasonably well for modeling the Ca^{2+} -water dimer, but it considerably underestimates the IOD value and overestimates the interaction strength for modeling the Mg^{2+} -water dimer.

			Interaction			
Ion	Model	Water Model	Energy	IOD (Å)		
			(kcal/mol)			
Mg ²⁺ -H ₂ O dimer						
Mg^{2+}	12-6 HFE	OPC3	-84.23	1.84		
Mg^{2+}	12-6 IOD	OPC3	-71.80	2.00		
Mg^{2+}	12-6 CM	OPC3	-76.25	1.94		
Mg^{2+}	12-6-4	OPC3	-75.15	2.02		
Mg^{2+}	Drude Oscillator Model ^a	SWM4-NDP ^a	-89.4	1.86		
Mg^{2+}	$AMOEBA^b$	$AMOEBA^b$	-79.56	1.88		
Mg^{2+}	ω B97X-V/def2-QZVPPD ^b	N/A	-83.12	1.91		
$Ca^{2+}-H_2O$ dimer						
Ca^{2+}	12-6 HFE	OPC3	-58.76	2.23		
Ca^{2+}	12-6 IOD	OPC3	-53.57	2.34		
Ca^{2+}	12-6 CM	OPC3	-52.89	2.36		
Ca^{2+}	12-6-4	OPC3	-55.18	2.34		
Ca^{2+}	Drude Oscillator Model ^a	SWM4-NDP ^a	-55.6	2.18		
Ca^{2+}	$AMOEBA^b$	$AMOEBA^b$	-54.65	2.22		
Ca^{2+}	ω B97X-V/def2-QZVPPD ^b	N/A	-57.97	2.22		
$a = \frac{10}{b}$	D 0.58					

Table 14. Benchmark Calculations Using the OPC3 Water Model for the Ion-Water Dimer Systems Containing Mg^{2+} or Ca^{2+} .

^{*a*}From Ref.⁴⁰; ^{*b*}From Ref.⁵⁸.

Ion	Model	Water Model	Interaction	IOD			
			Energy	(Å)			
			(kcal/mol)				
	Mg ²⁺ -H ₂ O dimer						
Mg^{2+}	12-6 HFE	OPC	-102.92	1.72			
Mg^{2+}	12-6 IOD	OPC	-80.43	1.97			
Mg^{2+}	12-6 CM	OPC	-86.58	1.89			
Mg^{2+}	12-6-4	OPC	-84.50	1.99			
Mg^{2+}	12-6 HFE	TIP3P-FB	-84.05	1.81			
Mg^{2+}	12-6 IOD	TIP3P-FB	-69.44	2.00			
Mg^{2+}	12-6 CM	TIP3P-FB	-73.69	1.94			
Mg^{2+}	12-6-4	TIP3P-FB	-73.55	2.02			
Mg^{2+}	12-6 HFE	TIP4P-FB	-92.69	1.72			
Mg^{2+}	12-6 IOD	TIP4P-FB	-71.55	1.99			
Mg^{2+}	12-6 CM	TIP4P-FB	-76.54	1.91			
Mg^{2+}	12-6-4	TIP4P-FB	-77.05	1.99			
Mg^{2+}	Drude Oscillator Model ^a	SWM4-NDP ^{a}	-89.4	1.86			
Mg^{2+}	\mathbf{AMOEBA}^{b}	$AMOEBA^b$	-79.56	1.88			
Mg^{2+}	ω B97X-V/def2-QZVPPD ^b	N/A	-83.12	1.91			
Ca ²⁺ -H ₂ O dimer							
Ca^{2+}	12-6 HFE	OPC	-67.03	2.17			
Ca^{2+}	12-6 IOD	OPC	-59.09	2.32			
Ca^{2+}	12-6 CM	OPC	-57.82	2.34			
Ca^{2+}	12-6-4	OPC	-61.29	2.31			
Ca^{2+}	12-6 HFE	TIP3P-FB	-58.13	2.21			
Ca^{2+}	12-6 IOD	TIP3P-FB	-51.97	2.34			
Ca^{2+}	12-6 CM	TIP3P-FB	-50.93	2.37			
Ca^{2+}	12-6-4	TIP3P-FB	-53.89	2.35			
Ca^{2+}	12-6 HFE	TIP4P-FB	-61.30	2.16			
Ca^{2+}	12-6 IOD	TIP4P-FB	-53.24	2.33			
Ca^{2+}	12-6 CM	TIP4P-FB	-51.61	2.37			
Ca^{2+}	12-6-4	TIP4P-FB	-55.37	2.34			
Ca^{2+}	Drude Oscillator Model ^a	SWM4-NDP ^a	-55.6	2.18			
Ca^{2+}	\mathbf{AMOEBA}^{b}	$AMOEBA^b$	-54.65	2.22			
Ca^{2+}	ω B97X-V/def2-QZVPPD ^b	N/A	-57.97	2.22			

Table 15. Benchmark Calculations for the Ion-Water Dimer Systems Containing Mg²⁺ or Ca²⁺ Using the OPC, TIP3P-FB, and TIP4P-FB Water Models.

^{*a*}From Ref.⁴⁰; ^{*b*}From Ref.⁵⁸.
For simulating ion-water clusters, which are more complex than ion-water dimers, the energy change of the $[Zn(H_2O)_n]^{2+} + H_2O \rightarrow [Zn(H_2O)_{n+1}]^{2+}$ reaction as a function of *n* where calculated. The computational details are described below, and the computed numbers are shown in **Table 16**. **Table 16.** Reaction Energies for the $[Zn(H_2O)_n]^{2+} + H_2O \rightarrow [Zn(H_2O)_{n+1}]^{2+}$ Reaction^s.

Set	Water Model	<i>n</i> = 0	<i>n</i> = 1	<i>n</i> = 2	<i>n</i> = 3	<i>n</i> = 4	<i>n</i> = 5	AUE
12-6 HFE	OPC3	-104.04	-98.08	-82.95	-64.69	-29.28	-14.90	12.63
12-6 IOD	OPC3	-71.80	-68.53	-62.07	-55.25	-40.14	-37.12	11.00
12-6 CM	OPC3	-88.42	-83.88	-74.05	-62.73	-32.21	-33.36	6.97
12-6-4	OPC3	-79.12	-75.92	-69.59	-62.90	-47.90	-44.45	13.59
12-6 HFE	OPC	-124.70	-115.03	-88.21	-59.66	-31.88	-31.39	16.79
12-6 IOD	OPC	-80.43	-75.82	-66.84	-57.58	-37.30	-34.67	8.65
12-6 CM	OPC	-107.27	-99.91	-82.90	-63.74	-31.03	-10.95	13.68
12-6-4	OPC	-88.14	-83.74	-75.15	-66.27	-46.66	-43.17	11.86
12-6 HFE	TIP3P-FB	-104.93	-98.98	-82.76	-63.08	-29.06	-9.74	13.53
12-6 IOD	TIP3P-FB	-69.44	-66.42	-60.43	-54.05	-39.83	-36.91	11.20
12-6 CM	TIP3P-FB	-85.97	-81.73	-72.48	-61.68	-31.98	-33.27	7.25
12-6-4	TIP3P-FB	-77.29	-74.34	-68.50	-62.27	-48.21	-44.88	14.00
12-6 HFE	TIP4P-FB	-113.99	-106.50	-83.89	-58.64	-29.94	-28.25	12.51
12-6 IOD	TIP4P-FB	-71.55	-68.17	-61.48	-54.40	-38.42	-35.77	10.35
12-6 CM	TIP4P-FB	-93.44	-88.23	-76.19	-61.97	-24.15	-28.76	6.74
12-6-4	TIP4P-FB	-80.08	-76.80	-70.37	-63.54	-47.97	-44.70	13.58
$\mathbf{Q}\mathbf{M}^b$	N/A	-95.10	-85.86	-60.48	-48.53	-31.18	-29.01	0.00

^{*a*}Unit is kcal/mol. Depending on the parameters and water model, the optimized structure may not have all the water molecules in the first coordination shell.

^bThe QM calculations were performed at the MP4SDQ(FC)/HUZSP*//RHF/HUZSP* level of theory⁹⁹.

The interaction energies of Mg²⁺- H₂O and Ca²⁺- H₂O in the gas phase were evaluated for different ion parameter sets (*i.e.*, the 12-6 HFE, 12-6 IOD, 12-6 CM, and 12-6-4 parameter sets) along with different water models (*i.e.* the OPC3, OPC, TIP3P-FB, TIP4P-FB water models). The LEaP and ParmEd modules in the AmberTools19 software package¹³⁰ were used to generate the topologies. For each system, geometry optimization was performed through 2500 steps of minimization using the steepest descent algorithm, followed by 2500 steps of minimization using the conjugate gradient algorithm. Afterward, the optimized structure was used to calculate the ion-water interaction energy and ion-oxygen distance in the gas phase. No periodic boundary condition (PBC) was employed, and the cut-off value was set to 9999 Å. All these simulations were performed using the sander program in the Amber19 software package¹³⁰. The vdW and electrostatic energies were extracted from the output file, and the sum of these two terms is the total interaction energy. We compared our results to the values obtained based on the Drude oscillator model, AMOEBA polarizable model, DFT (ω B97X-V/def2-QZVPPD) calculations reported in previous studies^{40, 58}, as shown in Table 7 and Table S10.

The reaction energies of $[Zn(H_2O)_n]^{2+} + H_2O$ à $[Zn(H_2O)_{n+1}]^{2+}$, with *n*=0-5, were also calculated for different ion parameter sets (*i.e.* the 12-6 HFE, 12-6 IOD, 12-6 CM and 12-6-4 parameter sets) along with different water models (*i.e.* the OPC3, OPC, TIP3P-FB, TIP4P-FB water models). For each of the $[Zn(H_2O)_n]^{2+}$ complexes or H₂O molecule, its energy was computed based on the optimized geometry after 50000 steps of minimization (25000 steps using the steepest descent algorithm followed by 25000 steps using the conjugate gradient algorithm). Afterwards, the reaction energies were calculated along with the results from quantum mechanical (QM) calculations based on the MP4SDQ(FC)/HUZSP*//RHF/HUZSP* level of theory⁹⁹ for comparison.

Here these values were depicted in **Figure 24** by comparing to the results based on the MP4SDQ(FC)/HUZSP*//RHF/HUZSP* level of theory⁹⁹. In general, it is challenging to quantitively reproduce the trends illustrated by the QM results; that said, our results showed qualitative agreement with the QM results. Among the different combinations, the 12-6 CM parameter set showed the best performance for reproducing the QM calculated values when used in conjugation with the OPC3/TIP3P-FB/TIP4P-FB water models, providing an AUE value of ~7 kcal/mol for these reaction energies.



Figure 24. Reaction energies of the $[Zn(H_2O)_n]^{2+} + H_2O \rightarrow [Zn(H_2O)_{n+1}]^{2+}$ reaction along with *n* for different parameter sets in conjugation with different water models. The QM results are shown in black.

In addition, to further evaluate the performance of the parameters to simulate the structural properties of the liquid phase, the RDFs were shown together with the cumulative coordination numbers between Zn^{2+} and water oxygen atoms calculated by different combinations of parameter sets and water models in **Figure 25**. In comparison to a previous study based on ab initio molecular dynamics (AIMD) and AIMD/MM simulations¹³¹, which showed a height of ~12 and a half-width of ~0.2 Å for the first peak in the RDF between Zn^{2+} and water oxygen atoms, our results show sharper peaks (higher peak heights with smaller half-widths) for the first peak using all the parameter combinations. This is likely because the C_{12} term generates a more repulsive potential than the ab initio calculations. Moreover, it was found that certain parameter sets showed different peak heights in conjugation with different water models when using the 12-6 HFE or 12-6 CM parameter set. For example, in terms of the 12-6 HFE parameter set, the OPC3 water model reproduces the same HFE with a significantly larger IOD value than other water models. In

comparison, each of the 12-6 IOD and 12-6-4 parameter sets showed similar peak heights when used with different water models.



Figure 25. Radial distribution function (RDF) and cumulative coordination number between the Zn^{2+} ion and oxygen atoms of the water molecules, simulated by using different parameter sets along with different water models.

Finally, to assess the performance of the parameters to simulate the ion transport process, the diffusivity constant of Mg^{2+} was calculated using the new parameter sets in conjugation with the OPC water model. These values were calculated using a protocol adapted from previous studies^{68, 132} and are shown in **Table 17** along with the experimental value. From the table, it can be derived that all of these parameter sets can reproduce the experimental diffusivity coefficient of Mg^{2+} , showing agreement with a previous benchmark study for several other water models¹³² and illustrating the transferability of the parameters developed in the present study.

Table 17. Performance of the Parameters Sets Developed in the Present Study in Simulating the Diffusivity Coefficient of Mg^{2+} When Used in Conjugation with the OPC Water Model.

Parameter Set	Diffusion coefficient $(10^{-5} \text{ cm}^2/\text{s})$
12-6 HFE	0.742 ± 0.074
12-6 CM	0.771 ± 0.068
12-6 IOD	0.824 ± 0.081
12-6-4	0.810 ± 0.076
Experiment	0.706

Method-wise, the diffusion coefficient of Mg²⁺ was calculated for the 12-6 HFE, 12-6 IOD, 12-6 CM, and 12-6-4 parameter sets with the OPC water model, using a protocol adapted from Pantera et al.¹³² and Izadi et al.⁶⁸. To simulate systems with different concentrations, an Mg²⁺ ion was solvated by four quasi cubic boxes with box lengths of 40, 50, 58, and 62 Å, respectively. For each system, 10 individual simulations were performed as described below: (1) 5000 steps of minimization using the steepest descent algorithm followed by 5000 steps of minimization using the conjugate gradient algorithm; (2) 360 ps simulation using the NVT ensemble to gradually heat the system from 0 K to 300 K with a series of stages as described in the main text; (3) 2 ns equilibration using the NPT ensemble at 300 K and 1 atm; (4) 1 ns NVT simulation at 300 K to further equilibrate the system; (5) 2 ns simulations were performed which consisted of 80 successive cycles, with each cycle consisting of 5 ps of NPT equilibration followed by 20 ps NVE production with snapshots were saved every 0.2 ps. The cut-off was set to 10.0 Å for all these simulations. The cpptraj program¹¹⁹ in the AmberTools software package¹³³⁻¹³⁴ was used to calculate the diffusion coefficient D of the Mg²⁺ ion for each of the 20 ps NVE production runs. Then the D values of the 80 NVT production runs were averaged to obtain the diffusion coefficient of the Mg²⁺ ion for the individual run. Afterward, the diffusion coefficients of all 10 individual runs were averaged to get the size-dependent diffusion coefficient for a specific water box. To account for the intrinsic errors of different water models and make a more reasonable comparison with the experimental data, each of the size-dependent diffusion coefficients was then scaled by a factor of $2.3/D_w$, where 2.3 (unit is 10^{-5} cm²/s) is the experimentally determined diffusion constant for water molecules while D_w is the averaged diffusion coefficient for water molecules inside that same water box. Finally, the diffusion coefficient of Mg^{2+} at infinite dilution D_o^{sim} was obtained

using the equation below through extrapolation based on the four scaled size-dependent diffusion coefficients D_L :

$$D_o^{sim} = D_L + k \frac{1}{L} \tag{17}$$

Herein k is a constant that is related to viscosity, and L is the length of the side of the water box. The error was calculated by multiplying the final result with the averaged percentage error of the four size-dependent diffusion coefficients, where the error of each was obtained as the standard deviation of the values obtained from the 10 individual runs.

For all of these minimizations and MD simulations, the periodic boundary conditions (PBCs) were used. The particle mesh Ewald (PME) method⁹³ was used to deal with the long-range electrostatic interactions. The nonbonded cut-off was set as 10 Å in these simulations. The "three-point" SHAKE algorithm¹²² was used to constrain the geometries of the water molecules. The Langevin thermostat with a collision frequency of 2.0 ps⁻¹ was used to control the temperature in all the MD simulations. The Berendsen barostat with a relaxation time of 1.0 ps was used to control the pressure in the NPT ensembles.

Similarly, the diffusion coefficient of Fe^{3+} was calculated by using the OPC water model and based on the three-parameter sets developed in the present study. Using linear extrapolation, the diffusion coefficient at infinite dilution (which corresponds to intercepts of the extrapolations) can therefore be obtained. The results are displayed in **Figure 26**. For comparison, the experimental diffusion coefficient for Fe^{3+} is $6.04x10^{-5}$ cm²/s.¹³⁵



Figure 26. Diffusion coefficient of Fe^{3+} under different ion concentrations. Error bars are the standard deviation over multiple simulations, while the dashed lines are linear extrapolations for each parameter set, with their Y-intercepts are the final diffusion coefficients.

In general, all three parameter sets gave reasonable diffusion coefficients. Among the three parameter sets, we find that the 12-6 HFE parameter set yields the closest value to the experiment, while 12-6-4 was higher and IOD was even higher. By considering the performance of different parameters in reproducing experimental HFE and IOD values, we can say that the 12-6-4 model can reasonably reproduce HFE, IOD, and the diffusion coefficient simultaneously.

Strengthened by the previous tests, MD simulations on large protein systems were therefore performed. The test object is superoxide reductase, which is an iron-containing metalloprotein system. The crystal structure of superoxide reductase from *Nanoarchaeum equitans* was obtained from the protein data bank (PDB ID: 4BV1, resolution: 1.90 Å). Superoxide reductase is a Homotetramer, and each monomer has a Fe³⁺ ion binding site at the surface; its activity center structure is depicted in **Figure 27**. Each of the binding sites of chains A, B, and D consists of a Fe³⁺ ion, four His residues, and one Cys residue, while the binding site of chain C has an additional water

coordinating with the Fe³⁺ ion. In total, we performed nine independent MD simulations on this protein using different ion parameters combined with different water models, *i.e.* the 12-6 HFE, 12-6 IOD, and 12-6-4 parameter sets for each of the OPC3, OPC, and TIP3P water models. Each simulation consists of 100 ns sampling, and details of the simulation procedure can be found in the SI. RMSD analyses on the protein backbone heavy atoms yielded a result described in Figure 28, and the results on the binding site residues (excluding the coordinating water) were displayed from Figure 46 to Figure 48(See APPENDIX B: FIGURES). These RMSD tests successfully assessed the performance of the metal ion parameters in a complex environment. From the RSMD plots, it can be seen that except for the HFE parameter set of the OPC and OPC3 water models and the IOD parameter set of the TIP3P water model, the RMSDs of the protein backbone heavy atoms are fluctuating by ~0.8 Å, and the RMSDs of the binding site residues are fluctuating by ~0.6 Å. The small RMSDs suggest that the protein and the binding sites are stable during the course of the simulation. It is interesting to note that for TIP3P, it was the IOD parameter set that did not retain the binding site, while for the new water models (OPC and OPC3), it was the HFE set. This suggests that for metal ion binding in proteins, the thermodynamics are complicated and are delicately balanced amongst metal-water, metal-protein, protein-water, protein-protein, and waterwater interactions.⁶⁶ In comparison, the 12-6-4 parameters perform consistently well across the different water models in terms of retaining the active site structure, which could be a better choice for simulating the metalloprotein systems than the 12-6 model.



Figure 27. a) The overall structure of superoxide reductase and b) the metal ion binding site in chain A, with the metal ion and coordinating residues are labelled. This figure was created based on the crystal structure by using Chimera.



Figure 28. RMSDs of the protein backbone heavy atoms for the nine independent simulations which used different ion parameters and water models. The RMSDs were calculated against the initial coordinates generated based on the crystal structure.

2.6 Conclusions

In the present study, 60 ions were parametrized in conjunction with four new water models (OPC3,⁶⁷ OPC,⁶⁸ TIP3P-FB,⁶⁹ and TIP4P-FB⁶⁹). To meet different needs, the parameterization process was conducted separately to generate three sets: 12-6 HFE, 12-6 IOD, and 12-6-4 parameter sets, which were aimed to reproduce the experimental HFE, IOD, and both of them, respectively. The performance of the 12-6 nonbonded models was also evaluated to simulate charged ionic species in conjugation with the four new water models as well as three previous and commonly used water models (TIP3P, SPC/E and TIP4P-Ew). The results indicated that these four new water models provide comparable or significantly better performance than the previous water models.⁷⁴ In general, the three-point water models yield better results than the four-point water models when using the 12-6 model, with the OPC3 water model providing the best performance for simulating trivalent and tetravalent ions in aqueous solution. Compared to the 12-6 HFE and 12-6 IOD parameter sets, the 12-6-4 model showed significant improvement which can reproduce the target HFE within 1 kcal/mol and the target IOD within 0.01 Å simultaneously. Moreover, multiple aqueous environment-related examinations were carried out to evaluate the activity coefficient of ionic solutions and the diffusion coefficient of Mg²⁺ and Fe³⁺. All of the 12-6 HFE, IOD, and 12-6-4 parameter sets gave a reasonable agreement with the experimental value, indicating that our parameters are well-designed and transferable. Finally, MD simulation was performed on the superoxide reductase from Nanoarchaeum equitans based on different water models and parameter sets. Overall, most of the simulations were able to well represent the metal sites. These results further supported the outperformance of the 12-6-4 model over the 12-6 model. These new parameters can well serve the molecular modeling community for simulating systems containing charged metal ionic species.

CHAPTER 3: PREDICTING ION DIFFUSION USING THE 12-6-4 MODEL

3.1 History of Diffusion Coefficient Research

Diffusion has been both theoretically and experimentally studied for more than a century, from first being described by Fick's Laws in 1855,¹³⁶ to a steady-state model in 1935,¹³⁷ and then to the more advanced frame-of-reference model in 1960⁹⁸. In 1969, the first ion diffusion coefficient was experimentally measured for Th⁺ and Th³⁺ using isotopic exchange radiochemical techniques.¹³⁸ Later, in 1989, microfluidic devices and direct compositional analysis were employed to obtain higher accuracy for both water and ion diffusion coefficient measurements under different solute concentrations.¹³⁹⁻¹⁴⁰ NMR is also a powerful tool to experimentally measure diffusion coefficients of open-shell systems, including molecules containing isotopes with non-zero spin quantum numbers.¹⁴¹ However, in contrast to the continuous development of experimental methods for measuring diffusion coefficients, computational evaluation of diffusion coefficients is challenging, especially for proteins and other macromolecules, which require long simulation timescales largely due to sampling issues and the lack of well-defined algorithms.⁶⁶ Dufrêche et al. developed a selfconsistent microscopic theory to compute the self-diffusion coefficient of LiCl, NaCl, and KCl as a continuous function of concentration up to 1M.¹⁴² Wang et al. designed a molecular dynamics workflow for simulating and calculating diffusion coefficients of many solvents using Green's functions.¹⁴³ Ohba et al. used the QM/MM method to simulate Li⁺ diffusion in graphite,¹⁴⁴, and a similar quantum-classical hybrid model was later used by Tomanek et al. for simulating water desalination by an all-carbon membrane.¹⁴⁵ However, a pure molecular mechanics model that represents all the physics of ions in solution (e.g., polarization, charge transfer, ion-induced dipole interactions) has not been fully developed for simulating single ions, especially divalent and trivalent ion diffusion in bulk water systems, due to the nature of these highly charged ions.

The strong polarizability of highly charged ions will generate charge-induced dipoles on interacting ligand molecules. Many molecular mechanical models have been developed to take polarization and related effects into account.¹²⁵ For example, Åqvist and Warshel⁸¹ and Peng¹⁴⁶ derived a cation dummy-atom model to better represent the coordination sphere of an ion. Li *et al.* developed a 12-6-4 Lennard-Jones model to incorporate ion-induced dipole interactions with ligand molecules.⁴⁴ Considering the simplicity, accuracy, and accessibility of the latter model for many ions of interest, we have explored in detail the ability of the 12-6-4 LJ model (relative to the 12-6 model) to predict the diffusion coefficients of 15 ions with charges varying from -1 to +3. Mathematically, the 12-6-4 LJ model can be described by Equation (18)

$$U_{ij}(r_{ij}) = \frac{e^2 Q_i Q_j}{r_{ij}} + \frac{C_{12}^{ij}}{r_{ij}^{12}} - \frac{C_6^{ij}}{r_{ij}^6} - \frac{C_4^{ij}}{r_{ij}^4} = \frac{e^2 Q_i Q_j}{r_{ij}} + \varepsilon_{ij} \left[\left(\frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{min,ij}}{r_{ij}} \right)^6 \right] - \frac{C_4^{ij}}{r_4^{ij}}$$
(18)

Overall, the 12-6-4 LJ model has two advantages. First, it is physically meaningful and can be mathematically derived.⁶⁴ Second, by using the noble gas curve (NGC) ³³ to couple $R_{min,ij}$, and ε_{ij} , only $R_{min,ij}$, and C_4^{ij} are the only variables involved in the parametrization process.⁴⁸ In previous work,⁴⁷⁻⁴⁹ we successfully parametrized the $R_{min,ij}$ and C_4^{ij} terms for various ions with charges ranging from -1 to +4 in four new water models: OPC3,⁷⁴ OPC,⁶⁸ TIP3P-FB (TIP3P-FB) and TIP4P-FB (TIP4P-FB).^{69, 147} These new water models were developed as ideal candidates for predicting diffusion coefficients of ions in aqueous environments. Moreover, because diffusion is an effect involving both geometric changes in the ion coordination sphere and the concomitant energy changes, our reported parameter sets are useful starting points to estimate diffusion coefficients using ISAIAH (Ion Simulation using AMBER for dIffusion Action when Hydrated). Details of our approach are provided below. 3.2 Theoretical Equations of Diffusion Coefficient and Simulation Methods

The ISAIAH workflow functionality takes the ion mass, ion charge, water model, and parameter set (*i.e.*, HFE, IOD, or 12-6-4) as inputs and outputs their diffusion coefficients at infinite dilution. Each parameter set is named after the targeted physical property. For example, the HFE set is aimed to reproduce the experimental HFE value. The method used by the ISAIAH workflow was adapted from Pantera *et al.*,¹³² modified as suggested by Bullerjahn *et al.*¹⁴⁸ to reduce the standard deviation by changing the sampling step from 1 fs to 0.2 ps. In the AMBER package,⁷⁰ the diffusion coefficient was calculated using Equation (19a) and (19b) in the CPPTRAJ program:¹¹⁹

$$MSD = \frac{\sum_{i=0}^{N} |x_{i+1} - x_i|^2}{(N-1)}$$
(19a)

$$D = \lim_{t \to \infty} \frac{MSD}{6t} \tag{19b}$$

Where *MSD* stands for the mean square displacement of a single particle. In Equation (19), *N* is the total number of frames taken from the production phases of the simulations, which is equal to the total simulation time divided by the sampling window. x_i is the coordinates of the particle at the *i*-th step, and $|x_{i+1} - x_i|^2$ is the squared distance that the particle has traveled between step *i* and *i*+1. Equation (19b) was then used to calculate the final diffusion coefficient *D* using the *MSD* value.

Because the diffusion coefficient is a concentration-dependent property, the diffusion coefficient of an ion in an infinitely dilute solution was calculated using the workflow in ISAIAH and then compared to experimental values.¹³⁵ First, four identical ions were solvated individually in four boxes with box lengths of 40, 50, 58, and 62 Å, which refers to concentrations of 26.0mM, 13.2mM, 8.5mM and 7.0mM respectively. For each system, 20 independent simulations were performed as described below: (1) 5000 steps of minimization using the steepest descent algorithm followed by

5000 steps of minimization using the conjugate gradient algorithm; (2) 360 ps simulation in the NVT ensemble to gradually heat the system from 0 K to 298.15 K; (3) 2 ns of equilibration in the NPT ensemble at 298.15 K and 1 atm; (4) 1 ns NVT simulation at 298.15 K to further equilibrate the system; (5) 2 ns of simulation was performed in 80 successive cycles in order to guarantee MSD vs. time linearity. Each cycle consists of 5 ps of NPT equilibration followed by 20 ps of NVE production, whose snapshots were saved every 0.2 ps. Over the 80 cycles, the water box sizes changed slightly during the NPT step but by less than $\pm 1\%$, so we used the box size of the last NPT cycle for linear extrapolation. For all these minimizations and MD simulations, periodic boundary conditions (PBCs) were used. The particle mesh Ewald (PME) method was applied to handle the long-range electrostatic interactions.⁹² The nonbonded cutoff was set to 10 Å in these simulations. The "three-point" SHAKE algorithm was used to constrain the geometries of the water molecules.¹²² The Langevin thermostat with a collision frequency of 2.0 ps⁻¹ was used to control the temperature in all MD simulations that required temperature control.¹⁴⁹ The Berendsen barostat with a relaxation time of 1.0 ps was used to control the pressure in the NPT ensembles.¹⁵⁰ To validate the workflow further, a benchmark on the number of NPT-NVE cycles was conducted on Al^{3+} with a 12-6-4 parameter set in OPC water, and the result is shown in **Figure 29** left panel. The MSD vs. time plot for one of the 8000-water simulations is also presented in Figure 29 right panel, which demonstrates that 20ps is long enough for the system to converge.



Figure 29. (Left). Linear extrapolation plots of diffusion coefficient calculation for Al^{3+} and Pu^{4+} with 1264 parameter in OPC water using different NVE simulation window durations of 10ps, 20ps and 40ps. (Right). MSD vs. time plot in a 8000-water box to show that 20ps is long enough to conduct diffusion calculations using the NPT-NVE iteration method. Note here the approximate six-time difference between S1A diffusion coefficient and S1B MSD vs. t slope also validates equation 3.

Using Eq. (19a) and Eq. (19b), the intrinsic diffusion coefficients D_I of the ions for each of the 20 ps NVE production runs was calculated. Then the D_I values of the 80 NVE production runs were averaged to obtain the real diffusion coefficient D_R of the ion for the individual run over the 1.6 ns of production simulation following Equation (20).

$$D_R = \frac{\sum_{i=1}^{80} D_I^i}{80} \tag{20}$$

Afterwards, D_R values of all 20 independent runs were averaged to get the concentration-dependent diffusion coefficient D_C for each water box respectively using Equation (21). The standard deviations *s.d.*_C of these 20 independent runs were calculated in this step as well using Equation (22).

$$D_C = \frac{\sum_{j=1}^{20} D_R^j}{20}$$
(21)

s.
$$d_{C} = \sqrt{\frac{\sum_{j=1}^{20} (D_{R}^{j} - D_{C})^{2}}{19}}$$
 (22)

Finally, to achieve a more reasonable comparison with the experimental data, each of the D_C values, as well as *s.d.* values, were then scaled by a factor of $(2.3 \times 10^{-5} \text{ cm}^2/\text{s}) / D_W$ to get D_L and *s.d.*, using Equation (23) and (24),

$$D_L = D_C \times \frac{2.3 \times 10^5 \, cm^2/_s}{D_W} \tag{23}$$

$$s. d._L = s. d._C \times \frac{2.3 \times 10^5 \ cm^2/_S}{D_W}$$
 (24)

where 2.3×10^{-5} cm²/s is the experimentally determined diffusion constant for water molecules, and D_W is the averaged diffusion coefficient for water molecules inside that same water box. Note here that the *L*s are the lengths of simulation boxes (40, 50, 58, and 62 Å), so D_L and *s.d.* are both functions of the box sizes. Lastly, the ion diffusion coefficient at infinite dilution D_0^{sim} was obtained using Equation (25) through extrapolation based on the four scaled size-dependent diffusion coefficients D_L , while the standard deviation *s.d.*^{sim} were obtained by averaging the error ratio and multiplying that by the final D_0^{sim} value, as elaborated in Equation (26).

$$D_0^{sim} = (D_L)_{L \to +\infty} = \left(\hat{a} \times \frac{1}{L} + \hat{b}\right)_{L \to +\infty}$$
(25)

$$s. d._{0}^{sim} = \frac{\sum_{k=1}^{4} \frac{s. d._{L}^{k}}{s. d._{L}^{k}}}{4} \times D_{0}^{sim}$$
(26)

Herein \hat{a} and \hat{b} values are the slope and intercept from the linear regression. \hat{a} is related to viscosity, and \hat{b} is related to the water molecule size, while *L* is the length of the side of the water box. The whole process has been automated in the ISAIAH workflow. The open-source code is available at <u>https://github.com/lizhen62017/ISAIAH</u>, along with a tutorial on how to run this workflow.

After establishing the calculation protocol, it has been noticed that the differences between water models and parameter sets will result in variations in the computed diffusion constants, so we computed the average diffusion coefficient and average standard deviation over all water models and parameter sets and compared them with experimental values. This was done to get a sense of trends within a water model to make ion diffusion predictions. The relative differences and their standard deviations are given by Equation (27) and Equation (28).

$$P.E.\% = \frac{\langle D_0^{sim} \rangle}{D_0^{exp}} \times 100\%$$
(27)

$$S.D.\% = \langle s.d._0^{sim} \rangle \times \frac{\langle D_0^{sim} \rangle}{D_0^{exp}} \times 100\%$$
(28)

Where $\langle D_0^{sim} \rangle$ and $\langle s. d._0^{sim} \rangle$ are the expected diffusion coefficient and standard deviation of that infinitely diluted ion, averaged over all water models and parameter sets. D_0^{exp} is the experimental diffusion coefficient of that ion under infinite dilution conditions as well. These quantities are discussed below.

To further investigate the molecular-level factors affecting diffusion, the ligand-exchange rate was calculated for five representative ions, Ca²⁺, Li⁺, Na⁺, K⁺, and Mg²⁺ in 40 Å OPC water boxes using the 12-6-4 LJ parameter sets. The reason for selecting these five ions is because they are ubiquitous in materials and biological sciences while having a wide range of exchange rates. The method is derived from Grotz *et al.*¹⁵¹ To start, the 80 simulations previously described were concatenated to form a 1.6 ns (80*20ps) trajectory containing 8000 frames. Then, using the "bond" function in CPPTRAJ,¹¹⁹ a screening was conducted overall water oxygens to only select ions that approached the metal ion below a defined cutoff distance, where this cutoff was defined as the average value between the first and second peak of the RDF displayed by **Figure 30**, *i.e.*, the boundary of the first solvation shell. Next, the "distance" function in CPPTRAJ was used to build

the distance *vs.* frame relationship for all the selected water oxygens. Lastly, a Python script was used to count the total number of water insertions/deletions (denoted as N). An insertion was defined as a water molecule entering from beyond the cutoff distance (first local minimum in the RDF) to less than 90% of it and then staying within that threshold for at least 4ps (20 frames), while deletion was defined as a water molecule leaving from below the cutoff distance to more than 110% of it and staying beyond that threshold for at least 4ps (20 frames).

After obtaining the total ligand insertion/deletion count N, this number was then inserted into Equation (29) to calculate the ligand exchange rate in the unit of M/s.



Figure 30. Definition of the cutoff distance for the water exchange rate calculation on Ca²⁺, Li⁺, Na⁺, K⁺ and Mg²⁺. 90% of r_{cutoff} is the threshold for defining insertion, while 110% of r_{cutoff} is the threshold for defining deletion.

$$rate = \frac{CN \times \left[M(H_2O)_{CN}^{n+1}\right] \times N}{2 \times t_B \times N_{H_2O}}$$
(29)

Where N_{H_2O} is the total number of water (herein it is 1477, 1501, 1549, 1607, 1466 respectively for Ca²⁺, Li⁺, Na⁺, K⁺ and Mg²⁺), while t_B is described by Equation (30):

$$t_B = \frac{CN \times N_M \times t_{sim}}{N_{H_2O} - CN} \tag{30}$$

In Eq. (14), t_{sim} is the time of simulation, which is 1.6ns. N_M is the number of metal ions, *i.e.*, one in all our simulations, and *CN* is the coordination number of the metal ion. By inserting our computed values into these two equations, the ligand exchange rate can be determined and compared with experimental values.

This method is a compromise between the protocols provided by Pantera et al.¹³² and Grotz et al.¹⁵¹ in order to find a reasonable balance between simulating the Mg²⁺ diffusion coefficient (which requires a single ion with no counter ions) and water exchange rate (which requires a long simulation time). First, a single Mg²⁺ with no counter ion was dissolved in a 40Å water box, giving a concentration of 26.0mM. The simulation was set up as described below and carried on a single V100 GPU that took about 50 hours: (1) 5000 steps of minimization using the steepest descent algorithm followed by 5000 steps of minimization using the conjugate gradient algorithm; (2) 360 ps simulation in the NVT ensemble to gradually heat the system from 0 K to 298.15 K; (3) 2 ns of equilibration in the NPT ensemble at 298.15 K and 1 atm; (4) 1 ns NVT simulation at 298.15 K to further equilibrate the system; (5) 1µs NVE production whose snapshots were saved every 0.2 ps. Both periodic boundary conditions (PBCs) and particle mesh Ewald (PME) methods were applied to handle the long-range electrostatic interactions.⁹² The nonbonded cutoff was set to 10 Å in these simulations. Other than minimization, the "three-point" SHAKE algorithm was used to constrain the hydrogen geometries of the water molecules.¹²² The Langevin thermostat with a collision frequency of 2.0 ps⁻¹ was used to control the temperature,¹⁴⁹ while the Berendsen barostat with a relaxation time of 1.0 ps was used to control the pressure in the NPT ensembles.¹⁵⁰

3.3 Simulation Results and Discussion Comparing to Experimental Values

The experimental diffusion coefficients of all 15 ions are given in **Table 18**¹³⁵ together with their coordination numbers (CNs),¹²⁵ which has been hypothesized to be a key factor affecting the diffusion rate. From **Table 18**, the previous theory can be confirmed that the diffusion coefficients strongly correlate with the charge and size of specific ions.¹⁵² Many computational works on halides and monovalent cations also validate this theory.¹⁵³⁻¹⁵⁵ Similarly, the ISAIAH workflow also calculates the diffusion coefficients as outputs controlled by variables like Q_i , Q_j , and C_4^{ij} (charge related), as well as $R_{min,ij}$, and ε_{ij} (radius-related), allowing us to thoroughly consider as many factors as possible. To visualize and illustrate the details of the diffusion coefficient calculation, the original linear extrapolation plots for Mg²⁺ and Ca²⁺ in all four water models are shown in **Figure 31**. Similar linear extrapolation plots for the other 13 ions can be found.

Ion	Electronic structure	Diffusion coefficient $(10^{-5} \text{ cm}^2/\text{s})^{135}$	CN ¹²⁵
F^-	[Ne]	14.8	4.1-6.8
Cl^{-}	[Ar]	20.3	6-8.5
Br^{-}	[Kr]	20.8	6
Li ⁺	[He]	10.29	4-6
Na^+	[Ne]	13.34	4-8
\mathbf{K}^+	[Ar]	19.57	6-8
Ag^+	[Kr] 4d ¹⁰	16.48	2-4
Be ²⁺	[He]	5.99	4
Mg^{2+}	[Ne]	7.06	6
Ca^{2+}	[Ar]	7.92	8
Cu^{2+}	[Ar]3d ⁹	7.14	6
Zn^{2+}	[Ar]3d ¹⁰	7.03	6
Al^{3+}	[Ne]	5.41	6
Cr^{3+}	$[Ar]3d^3$	5.95	6
Fe ³⁺	$[Ar]3d^5$	6.04	6

 Table 18. Experimental diffusion coefficients and CNs for all 15 ions.

Herein the hydration-free energy (HFE) set means the parameters $R_{min,ij}$, and ε_{ij} can successfully reproduce the HFE of that ion, but not the ion-oxygen distance (IOD); the IOD set means $R_{min,ij}$, and ε_{ij} can successfully reproduce the IOD but not the HFE. CM means the compromise set, where $R_{min,ij}$, and ε_{ij} underestimate the IOD and overestimate HFE but within an acceptable error range; only divalent ions had their CM sets determined in our previous work.⁴⁷ The12-6-4 set means using the augmented LJ model, where $R_{min,ij}$, ε_{ij} , and C_4^{ij} can successfully reproduce both the HFE and IOD at the same time.



Figure 31. Linear extrapolation of Mg^{2+} (top) and Ca^{2+} (bottom) diffusion in different sizes of water boxes, with different water models and different parameter sets. Vertical bars indicate standard deviations among 20 replicate simulations for each ion-water combination. Final intercepts of each extrapolation are the final diffusion coefficients (10^{-5} cm²/s). Experimental values are $0.706*10^{-5}$ cm²/s for Mg²⁺ and $0.792*10^{-5}$ cm²/s for Ca²⁺.





Overall, the linearity of each extrapolation is acceptable. Similar extrapolation plots are available from **Figure 49** to **Figure 61** (See APPENDIX B: FIGURES). The overall results for the diffusion coefficients, as well as their standard deviations, are listed in **Table 19** which also displays the percentage differences between simulations and experiments as a heat plot, where red indicates an overestimation and blue indicates an underestimation, respectively. A detailed color scale is provided below the table. The comparison results showed a very systematic trend of relative differences.

Table 19. Simulated diffusion coefficients and standard deviations as well as percent error relative to the experiment of 15 ions in four water models. The numbers below each element name are their experimental diffusion coefficients. All units are in 10^{-5} cm²/s.

lon	Water	HFE	10	D	12	64	lon	Water	HFE		IOD	1264
F-	OPC3	1.11±0.04(75%)	0.99±0.0)5(67%)	0.93±0.0	04(63%)	Li+	OPC3	1.07±0.05(1	104%)	1.16±0.05(113%)	1.27±0.05(124%)
1.48	OPC	1.20±0.07(81%)	0.98±0.0	04(66%)	0.93±0.0	04(63%)	1.03	OPC	1.22±0.05(1	19%)	1.26±0.06(122%)	1.15±0.06(112%)
	FB3	1.11±0.05(75%)	0.99±0.0)5(67%)	1.17±0.0	05(79%)		FB3	1.07±0.04(1	104%)	1.31±0.05(127%)	1.20±0.04(117%)
	FB4	1.14±0.05(77%)	0.93±0.0	04(63%)	0.99±0.0	04(67%)		FB4	1.07±0.05(1	103%)	1.21±0.06(117%)	1.11±0.05(107%)
CI-	OPC3	1.65±0.07(81%)	1.53±0.0)7(75%)	1.56±0.0	08(77%)	Na ⁺	OPC3	1.18±0.05(89%)	1.10±0.05(82%)	1.20±0.05(90%)
2.03	OPC	1.74±0.09(86%)	1.62±0.0	07(80%)	1.73±0.0	06(85%)	1.33	OPC	1.08±0.05(81%)	0.97±0.04(73%)	1.01±0.04()76%
	FB3	1.73±0.08(85%)	1.54±0.0	07(76%)	1.68±0.0	07(83%)		FB3	1.18±0.05(88%)	1.17±0.05(88%)	1.19±0.04(89%)
	FB4	1.87±0.07(92%)	1.63±0.0	07(80%)	1.66±0.0	06(82%)		FB4	1.12±0.04(84%)	1.00±0.04(75%)	1.18±0.05(89%)
Br	OPC3	1.70±0.08(81%)	1.57±0.0	08(75%)	1.65±0.0)9(79%)	K+	OPC3	1.67±0.08(85%)	1.79±0.08(91%)	1.82±0.09(93%)
2.08	OPC	1.86±0.07(89%)	1.66±0.0	07(79%)	1.69±0.0	09(81%)	1.96	OPC	1.76±0.08(90%)	1.63±0.08(83%)	1.63±0.07(83%)
	FB3	1.78±0.08(85%)	1.62±0.0	08(77%)	1.63±0.0	07(78%)		FB3	1.74±0.07(89%)	1.89±0.09(97%)	1.91±0.07(97%)
	FB4	1.73±0.08(83%)	1.78±0.0	08(85%)	1.86±0.0	08(89%)		FB4	1.70±0.08(87%)	1.73±0.07(88%)	1.80±0.08(92%)
Ag ⁺	OPC3	1.18±0.05(72%)	1.12±0.0	06(68%)	1.07±0.0	04(65%)	Cr ³⁺	OPC3	0.65±0.02(1	(09%)	0.73±0.03(122%)	0.71±0.03(119%)
1.65	OPC	1.18±0.04(72%)	1.01±0.0	05(61%)	1.11±0.1	L1(67%)	0.59	OPC	0.62±0.03(1	104%)	0.79±0.03(133%)	0.73±0.03(123%)
	FB3	1.28±0.05(77%)	1.20±0.0	05(73%)	1.07±0.0	07(65%)		FB3	0.59±0.02(98%)	0.65±0.03(109%)	0.60±0.02(101%)
	FB4	1.26±0.06(77%)	1.20±0.0	06(73%)	0.96±0.0	05(58%)		FB4	0.65±0.03(1	09%)	0.75±0.03(126%)	0.73±0.02(123%)
Al ³⁺	OPC3	0.71±0.03(132%)	0.62±0.0	2(114%)	0.60±0.0	2(111%)	Fe ³⁺	OPC3	0.71±0.02(1	18%)	0.70±0.03(116%)	0.66±0.04(109%)
0.54	OPC	0.59±0.03(109%)	0.74±0.0	3(137%)	0.72±0.0	3(132%)	0.60	OPC	0.60±0.03(1	100%)	0.76±0.03(127%)	0.71±0.03(117%)
	FB3	0.64±0.02(118%)	0.58±0.0	2(108%)		3(116%)		FB3	0.65±0.03(1	108%)	0.74±0.03(122%)	0.67±0.04(111%)
	FB4	0.66±0.02(122%)	0.69±0.0	3(128%)	0.67±0.0	3(124%)		FB4	0.76±0.03(1	(25%)	0.82±0.03(136%)	0.67±0.03(112%)
		lon	Water	н	IFE	10	DD		CM		1264	
		D = 2+	0.002	0.77+0	02/1200/1	0.00+0	05/1400/	1 0.004	0.04/1619/1	0.024	0.04/1269/1	

						0			
Be ²⁺	OP	C3 0.	77±0.03(129%) 0.89±0.0	05(148%)	0.96±0.04(1	61%) 0.8	2±0.04(136	%)
0.60	OP	PC 0.	77±0.03(129%) 0.77±0.0	04(128%)	0.72±0.03(1	21%) 0.8	6±0.04(143	%)
	FB	3 0.	70±0.03(116%	0.92±0.0	04(153%)	0.83±0.03(1	39%) 0.8	3±0.03(139	%)
	FB	4 0.	82±0.03(137%	0.92±0.0	04(153%)	0.76±0.03(1	27%) 0.8	2±0.04(137	%)
Mg ²⁺	OP	C3 0.	76±0.03(107%) 0.75±0.0	03(106%)	0.72±0.03(1	02%) 0.7	2±0.02(102	%)
0.71	OP	PC 0.	74±0.02(105%) 0.82±0.0	03(117%)	0.77±0.03(1	09%) 0.8	1±0.04(115	%)
	FB	3 0.	74±0.02(105%) 0.77±0.0	03(109%)	0.73±0.03(1	04%) 0.7	3±0.02(104	%)
	FB	4 0.	71±0.02(101%) 0.84±0.0	02(119%)	0.71±0.03(1	01%) 0.7	8±0.02(111	%)
Ca ²⁺	OP	C3 0	.75±0.04(94%)	0.75±0.	.04(94%)	0.74±0.03(93%) 0.7	74±0.04(949	6)
0.79	OP	PC 0.	80±0.03(101%) 0.82±0.0	03(103%)	0.78±0.03(98%) 0.7	72±0.03(91%	%)
	FB	3 0	.78±0.03(99%)	0.74±0.	.02(93%)	0.78±0.03(99%) 0.8	0±0.03(110	%)
	FB	4 0	.77±0.03(97%)	0.77±0.	.03(97%)	0.79±0.03(9	99%) 0.8	3±0.03(104	%)
Zn ²⁺	OP	C3 0.	75±0.03(123%) 0.78±0.0	03(104%)	0.74±0.03(1	01%) 0.7	3±0.03(116	
0.70	OP	PC 0.	90±0.03(146%	0.78±0.0	03(112%)	0.73±0.04(1	29%) 0.7	8±0.03(109	%)
	FB	3 0.	86±0.04(124%	0.72±0.	.02(98%)	0.77±0.03(99%) 0.7	9±0.03(110	
	FB	4 0	.92±0.03(136)	0.72±0.0	03(108%)	0.74±0.03(1	13%) 0.7	8±0.03(117	%)
Cu ²⁺	OP	C3 0.	88±0.04(107%) 0.74±0.0	03(109%)	0.72±0.04(1	06%) 0.8	3±0.03(103	%)
0.71	OP	PC 1.	05±0.05(128%) 0.80±0.0	04(111%)	0.93±0.04(1	04%) 0.7	8±0.03(111	
	FB	3 0.	89±0.04(122%	0.70±0.0	03(103%)	0.71±0.03(1	10%) 0.7	9±0.03(112	
	FB	4 0.	97±0.05(131%) 0.77±0.0	03(103%)	0.80±0.03(1	05%) 0.8	4±0.03(111	%)
60~70	%	70~80%	80~90%	90~100%	100~110%	110~120%	120~130%	130~140%	140

An AUE (average of unsigned error) analysis was conducted over all ions for each combination of water model and parameter set. The result is presented in **Table 20** According to **Table 19** and **Table 20**, between different parameter sets, HFE sets are generally robust but deviate from the average values significantly for Cu^{2+} and Zn^{2+} , while the IOD sets are usually outliers for the other

13 ions. In comparison, CM (if applicable) and 12-6-4 sets are closer to the average value. As discussed above, the better behavior of the CM and 12-6-4 parameter sets can still be explained by the interaction energy. In previous work,⁴⁷ interaction energies played a significant role between different water models and parameter sets in conjunction with the same ion. Taking Mg²⁺ in the OPC water model as the example again, the interaction energy for HFE, IOD, CM and 12-6-4 sets are -102.92, -80.43, -86.58 and -84.50 kcal/mol respectively, showing a trend in the diffusion coefficients of IOD > 1264 > CM > HFE, which matches what is shown in Table 2. In contrast, the variations between different water models are not that significant when compared to those between parameter sets for the same ion, except that most four-point water models (OPC and TIP4P-FB) generally have higher diffusion coefficients than three-point water models (OPC3 and TIP3P-FB). This cannot be explained solely by the ion-water interaction energy since the interaction energy for four-point water models is generally more negative than three-point water models.⁷⁴ A possible explanation lies in the water-water interaction,¹⁵⁶ which was given as an explanation for the overestimation of Be²⁺ and Al³⁺. In general, three-point water models have a larger volume per molecule when compared to four-point water models.¹⁵⁷ This makes the water exchange favor a S_N1-like reaction to undergo a dissociative exchange mechanism, where the water being replaced will leave first, then the new water will fill in the cavity in the first hydration shell. In comparison, four-point water models tend to undergo S_N2-like or associative mechanisms while exchanging water molecules.⁵⁵ This is demonstrated by the fact that three-point water models usually have lower coordination numbers compared to four-point water models, indicating the transition state for three-point water exchange is under-coordinated while over-coordinated for four-point water exchange transitions.

Table 20. AUE of each combination of water model and parameter set. Value in each cell is calculated by averaging differences between 100% and the calculated percentage of all 15 (5 if the parameter set is CM) ions.

Water Models	HFE	IOD	CM (divalent only)	12-6-4
OPC3	16.85%	18.69%	15.41%	17.46%
OPC	16.24%	23.08%	13.16%	21.08%
TIP3P-FB	13.36%	17.50%	11.00%	14.58%
TIP4P-FB	17.92%	21.94%	9.35%	17.98%

According to **Table 19**, the overall simulated diffusion coefficients are highly correlated with the charges and radii of each ion tested. This can be analyzed individually using two factors: energy and geometry. For example, the diffusion coefficient is highly dependent on the interaction energy according to previous research.⁴⁷⁻⁴⁸ Using the comparison between Mg²⁺ and Ca²⁺ as an example, the interaction between Mg²⁺ and water has been shown to be stronger than the interaction between Ca²⁺ and water by multiple methods.^{40, 58} Therefore, the ion-water interaction will be stronger for Mg^{2+} relative to Ca^{2+} . As expected, the results of both simulation and experiment showed a lower diffusion coefficient for Mg^{2+} compared to Ca^{2+} . The only exception, according to **Table 19**, is the OPC3 water model in conjunction with the HFE parameter set, which gives a higher diffusion coefficient for Mg^{2+} than Ca^{2+} ; this may be due to the observed standard deviation of the infinitely diluted diffusion coefficient in this instance. From the method section, the standard deviations of each infinitely diluted diffusion coefficient are highly dependent on each water box's standard deviation before the extrapolation. Meanwhile, each water box's standard deviation is dependent on the uniformity between 20 individual runs. The first factor that may affect the simulation outcome is intrinsic, where the ion box size does not have an exact linear relationship because the experimental water diffusion coefficient will not always be 2.3×10^{-5} cm²/s. Most of the

simulations yield water diffusion coefficients slightly lower than what has been reported by previous research listed in **Table 21**, likely due to the presence of the ion.

Water Models	Average diffusion coefficients in this research	Diffusion coefficients without ions
OPC3	2.28	2.3067
OPC	2.34	2.3568
TIP3P-FB	2.27	2.2869
TIP4P-FB	2.19	2.2169

Table 21. The water model diffusion coefficient averaged over all ions and box sizes $(10^{-5} \text{ cm}^2/\text{s})$; all values are collected at 298.15K.

Other previous research also suggests that the existence of ions will further decrease the water diffusion coefficient when the ion concentration increases.¹⁵⁸ The second factor affecting the standard deviation is variations in the water-water interaction in either the 12-6 model or the augmented 12-6-4 model. This uncertainty may affect the diffusion coefficient, especially when the water box sizes are changing during the linear extrapolation.¹⁵⁹ For example, in a previous study,¹⁶⁰⁻¹⁶¹ it was shown for a long water wire, increasing the wire length will significantly enlarge the standard deviation and percent error of H⁺ and OH⁻ diffusion coefficients. A similar situation might be occurring here, where the ions are in 3D water boxes of various sizes.

Nonetheless, energetic factors alone cannot explain a significant error in the simulation result, where Be^{2+} diffuses faster than both Ca^{2+} and Mg^{2+} . In fact, the simulation of Be^{2+} also gives the highest overestimation percentage of the overall diffusion coefficient compared to the experiment. This can likely be explained by the second factor, *i.e.*, the geometric influences on diffusion cannot be correctly simulated due to the fact that for some ions, their parameters do not reproduce the CN value well.⁴⁷ Specifically, the geometric factor caused by different CN values on diffusion can be further dissected into two parts: The diffusion pattern and the ligand exchange pattern.¹⁴⁸ Different diffusion patterns may lead to different errors between simulation and experiment. It has been proposed by previous research that there are three types of diffusion patterns:¹⁶²⁻¹⁶³ independent diffusion with a very short residence time scale for the first solvation shell, codiffusion with a clear separation between the solvation shell and bulk water, as illustrated by Figure 32 left panel, and intermediate diffusion, with an unstable first shell of solvation that keeps exchanging waters with the solvent, as illustrated by Figure 32 right panel. For the intermediate diffusion case, two exchange mechanisms have been described^{55, 164}, where the associative mechanism resembles a S_N 2-like exchange between water molecules, while the dissociative case resembles a S_N1-like exchange. In the present research, these three diffusion patterns and two exchange mechanisms were also observed. Be²⁺ undergoes co-diffusion with one stable hydration shell layer, but the second hydration layer undergoes dissociative exchange between water molecules. This, however, does not reflect the real situation, as Be²⁺ and water may form a stable two-layer $[Be(OH_2)_{6+12}]^{2+}$ cluster complex to slow down the diffusion speed even more.¹⁶⁵ Hence, we can hypothesize that Be^{2+} is diffusing too fast since it is not pulling along two solvation shells in our case. A similar explanation is also applicable to Al^{3+} , where the diffusion coefficient is overestimated by about 20% compared to the experiment since Al³⁺ is known for forming large ion-water clusters or even a cross-linking gel structure.²⁵ The simulation indicates a stable first solvation shell for Al³⁺ but a second solvation shell following an associative exchange mechanism. This may not reflect the real situation, where both the first and second solvation shells of Al^{3+} are stable.¹⁶⁶ To successfully simulate this effect, we hypothesize that the forcefield may need to include a more realistic description of water-water interaction.



Figure 32. Illustration of diffusion models: the co-diffusing model (left) and exchange model (right). Green arrows and circles depict the first solvation shell diffusion, while blue arrows and circles depict the water exchange of first solvation shell. The process indicated by the blue arrow can be further classified as an associative or dissociative mechanism.

Systematically, various diffusion patterns can be the result of different levels of the relationship between ion-water interaction energies and diffusion coefficients. Based on **Table 19**, it is reasonable to propose that as the charge of an ion increases, the interaction energy between the ion and water gets stronger, which makes the ion more likely to undergo a co-diffusion pattern or intermediate diffusion with an associative mechanism, *i.e.*, surrounding water molecules are strongly attracted to the ion during the entire simulation. This was observed for all the trivalent ions during our simulations, as well as most of the divalent ions. However, for all the halides and some monovalent ions, they are more favored to undergo an independent diffusion pattern or intermediate diffusion with a dissociative mechanism, with the first solvation shell water weakly attracted by the ion during the simulation. Hence, we observe that if an ion undergoes co-diffusion or intermediate diffusion with an associative mechanism, the simulation usually overestimates the diffusion coefficients, while if an ion undergoes independent diffusion or intermediate diffusion with a dissociative pattern, the simulation usually underestimates the diffusion coefficients. For the overestimation of the divalent/trivalent ion diffusion coefficients (except Ca^{2+}), a possible molecular level explanation is the overestimated ligand-exchange rate we observed in our simulations,¹⁶⁷ because the exchange of water is believed to increase the diffusion speed (see Table 5, experimental values of Mg^{2+} and Ca^{2+}). However, the underestimation of the halide/monovalent ion diffusion coefficients, except Li^+ , is likely a complex outcome of ligand exchange and steric hindrance. Since the ligand exchange rate itself has little effect on the diffusion rate if water molecules are weakly attracted by ions (see Table 5, experimental values of Li^+ and Na^+). Under this circumstance, more exchange might block the diffusion transit pathway of the ion rather than increase the diffusion rate.

In order to further explore the theory proposed in **Figure 32**, Equations (29) and (30) given in the method section were applied to calculate the ligand exchange rate for Ca²⁺, Li⁺, Na⁺, K⁺ and Mg²⁺ in 40 Å OPC water boxes using the 12-6-4 LJ parameter sets. The results are organized in **Table 22**. Note here due to the extremely low ligand exchange rate of Mg²⁺, the simulation duration was adjusted to 1µs accordingly.

The results in **Table 22** show that Ca^{2+} and Mg^{2+} undergo a co-diffusion pattern while their first solvation shell seldom exchanges with other water molecules. The relative differences between the five representative ions also agree with the theory described in Figure 3. Also, from the last column of **Table 22**, it can be concluded that a larger charge over radius ratio will lead to less rapid water exchange in the first solvation shell and, finally, lower diffusion coefficients. However, when comparing with the results from Marcus,¹⁶⁷, it is clear that all five *k* values are overestimated, especially for the monovalent ions. The overestimation could be due to the chosen distance cutoff. In the work of Grotz *et al.*, two cutoffs were selected according to the energy profile and were shown to have little effect while varying both cutoffs slightly for one ion. In light of this, we chose

to use the RDF to avoid doing PMF profiles for multiple ions with the expectation it would only

play a minor role, as seen in the work.¹⁵¹

Ion Name	Total insertion/	Exchange frequency (k)	Exchange rate $k \times CN \times$	Charge over radius ratio	Diffusion Coefficients
	deletion in $1.6n_{\odot}(N)$	(1/ns)	$[M(H_2O)_{CN}^{n+}]$	(e*A)	$10^{-5} \text{cm}^2/\text{s}$
	$(1 \mu s \text{ for})$	$(1/\mu s \text{ for } Mg^{2+})$	(M/ns) (Experiment) ¹⁶⁷	(Calculated from	(Experimental)
	Mg ²⁺)		$(M/\mu s \text{ for } Mg^{2+})$	Couture and Laidler) ¹⁶⁸	
Ca ²⁺	15	0.58 (0.32)	0.12 (0.07)	1.89	0.77 (0.79)
Li^+	100	6.22 (1.25)	0.81 (0.16)	1.28	1.15 (1.03)
Na^+	114	5.91 (1.25)	0.92 (0.19)	1.02	1.09 (1.33)
\mathbf{K}^+	199	8.84 (1.99)	1.61 (0.36)	0.75	1.68 (1.96)
Mg^{2+}	22	1.82 (0.51)	0.28 (0.08)	2.56	0.76 (0.71)

Table 22. Ligand exchange rate results for Ca^{2+} , Li^+ , Na^+ , K^+ , and Mg^{2+} in 40 Å OPC water boxes in conjunction with 12-6-4 LJ parameter sets.

Debate exists on whether 90%~110% of the average between the first and second peak of the RDF is too arbitrary when defining "insertion" and "deletion", as shown in Figure 1. In previous research on the convergence behavior of solvation shells in condensed phases, the cutoffs were also selected arbitrarily and scaled up as the solvent molecule radii increased.¹⁶⁹ Indeed, there is sensitivity to the choice of insertion and deletion, but we feel our choice is reasonable and reproducible given that RDFs can be easily generated. Overall, this strategy of defining water insertion/deletion cutoffs has been shown to control the error in a reasonable range for multiple ions. Other than the kinetic analysis of the ligand exchange rate, the exchange effect can also be analyzed in a thermodynamic way, with the free energy ΔG_{ex} being estimated by Equation (31).¹⁷⁰

$$\frac{dln\mu_{ion}}{dT} + \frac{1}{T} - \frac{dlnD_{wat}}{dT} = \frac{\frac{\Delta G_{ex}}{RT^2}}{1 + 0.0655e^{\frac{\Delta G_{ex}}{RT}}}$$
(31)

. .

$$D_{ion} = \mu_{ion} \times k_B T \tag{32}$$

Where μ_{ion} is the ion mobility that can be converted to a diffusion coefficient using Equation (32), *i.e.* the Einstein relation.¹⁷¹ ΔG_{ex} will be the free energy of ligand exchange (in this case, water exchange). By analyzing Equation (31) qualitatively, it is reasonable to derive that if the diffusion of an ion is less temperature sensitive, the ion will tend to have a higher exchange free energy, meaning the exchange ratio will be slower. According to Wang *et al.*, the AMBER forcefield tends to underestimate the temperature sensitivity of the diffusion coefficient for both solvents and small solutes,¹⁴³ which explains why Ca²⁺, Li⁺, Na⁺, and K⁺ mostly underestimate diffusion coefficients compared to experimental values according to Table 2. 3.4 Prediction of the ²³⁹Pu⁴⁺ and Conclusive Marks

With the understanding that we can predict diffusion coefficients with an overall relative difference of no more than $\pm 30\%$, the prediction of the diffusion coefficient for ²³⁹Pu⁴⁺ was undertaken. ²³⁹Pu⁴⁺ is highly radioactive and is difficult to extract using PUREX,¹⁷² which has diffusion-related steps in its process. Due to the lack of reliable experimental data for ²³⁹Pu⁴⁺ diffusion in pure water, we decided to computationally estimate this value. In this computational experiment, only OPC water was used, and the results are displayed in **Figure 33**. Simulations conducted in the OPC water model are believed to have a strong transferability between bulky water environments and water-gel mixture conditions, making it a good choice.⁷⁴



Figure 33. Prediction of the ²³⁹Pu⁴⁺ diffusion coefficient. Only the OPC water model was used and parameter sets are from previous work.⁴⁸

According to Cusnir *et al.*, the diffusion coefficient of 239 Pu⁴⁺ in 10mM MOPS buffer inside a polyacrylamide (PAM) gel (pH=6.50) at room temperature is $0.229\pm0.015\times10^{-5}$ cm²/s.¹⁷³ According to a previous study, it was shown that the PAM gel could slow down the diffusion of a large ion (like SeCN⁻) by a factor of about two.¹⁷⁴ Hence, the final simulation result of

 $0.5579\pm0.04\times10^{-5}$ cm²/s using the 12-6-4 parameter set in OPC water is a reasonable prediction for the experimental diffusion rate of ²³⁹Pu⁴⁺ in a pure aqueous solution. This claim can be further validated by a strong agreement with metadynamic simulations.¹⁷⁵

In this project, the ISAIAH workflow was created to automate the workflow for the determination of diffusion coefficients, and it was then applied to the study of the diffusion coefficient of 15 ions in conjunction with a variety of water box and parameter set conditions. The overall results suggest that the maximum deviation between theory and experiment was <30%, but with most ions/water model combinations having lower uncertainties. A prediction for the diffusion coefficient of a highly charged, radioactive 239 Pu⁴⁺ was also conducted, and the results provide qualitative guidance on experiments regarding 239 Pu⁴⁺ diffusion in water or even in PUREX extractions.

In the future, we will optimize the ISAIAH workflow to further speed the workflow, increase its accuracy and storage costs. The determination of ion diffusion constants provides an interesting probe to understand the effect of parameter choices on molecular hydration. Hence, future work will also focus on exploring the molecular-level details of why some ions/water model combinations have large errors and how these can be reduced in future model development. For example, the water-water interaction is something to look at further to improve computed diffusion constants. Finally, developing a better understanding of the ion diffusion mechanism and its variation among ions may better help understand the functional role of biologically relevant ions.¹⁵¹

CHAPTER 4: IMPLEMENTING PAIRWISE 12-6-4 INTERACTION

4.1 Background of Atom-Specific Pairwise C4 interactions

As **Figure 4** indicates, in many simulation scenarios, only C_4 interactions between certain ions are needed; this has been raised to awareness after the parametrization work was completed. Even though the parameters have been guaranteed to work in pure aqueous situations, it still needs to be reproducible in complex protein systems. The protein simulation from **Figure 27** to **Figure 46** revealed a relatively stable protein structure while implementing the 12-6-4 nonbonded model. However, some RMSDs are still unstable for the 12-6-4 parameter set, and the binding free energy of the four Fe³⁺ ions into their binding pockets is not guaranteed to be the same as the experimental value.

To fill this gap between simulation and experiment, we start implementing the atom-specific pairwise C_4 code and testing that on a one-ion-multiple imidazole system since only the chelating nitrogen of imidazole is needed to have C_4 to accomplish accurate simulations. To achieve this goal, two major steps are needed: (1). Implementing the command of adding atom-specific pairwise code to LEaP, the program that builds PRMTOP and INPCRD files from the original PDB file in the AMBER package. (2). Implementing the calculation algorithm into the MD simulation engine. In step (1), the original code of adding C_4 interactions between two whole atom types was also migrated from ParmEd to LEaP to provide the user with a one-stop-solution feeling of using AMBER while constructing the initial files for AMBER. In step (2), both the CPU and GPU algorithms need to have the new features to read the atom-specific pairwise C4 interaction information from the initial PRMTOP file, then feed to the algorithm to iteratively calculate the energy, force, and motion of each MD simulation step.

4.2 Implementing addC4pairwise and addC4type Command into LEaP

To achieve the goal of allowing the user to customize the C4 interaction between individual atoms, three questions need to be resolved: (1) What input information does the user need to feed to the program? (2) How does LEaP parse the command input by the user, and how to save the parsed information? (3) Where shall LEaP output the parsed information into the PRMTOP file? To answer the first question by following the traditional LEaP command format, the input format should have the four parts as displayed in Figure 34: (1): Command declaration, which is addC4pairwise. (2) The first atom of that pairwise interaction. (3) The second atom of that pairwise interaction. (4) The C_4 value between those two atoms, with a unit of kcal/mol/(Å⁴). Among all these four entries of this input command, (2) and (3) have their own specific format, which is <unitID>.<residueID>.<atomID>. This is because LEaP has a built-in function to parse such a format of text. This built-in function can extract the molecule unit information, map the specific residue address, and then locate the specific atom as an output. Later, other functions can take the output from the built-in parsing function, which is an atom object, to retrieve the atom object's properties accordingly, such as bonded neighbors, bond order, charge, nonbonded parameters, and C_4 values, etc.


Figure 34. Example of the LEaP code implementing atom-specific pairwise C4 interactions. Red frame denotes the key command.

The second question is a continuation of the first one. Since the built-in parsing function can process part of the input information, the leftover technical difficulty is to parse the C_4 value and save that in a proper format. This was resolved by introducing a new dynamic array with a maximal length of 8 in the atom object. If an atom-specific pairwise C_4 interaction is invoked by the user command, the atom object will allocate space for this array, where each item of this array will record and ID of the other atom in the atom pair, together with the C_4 value of such an atomspecific pairwise interaction.

The last question is to print out the whole molecule's atom-specific pairwise C_4 interaction in a time and space-efficient way. While looping over all the atoms to collect the atom-specific pairwise C_4 interaction, double counting was avoided by applying a criterion stating that "the first atom's ID must be smaller than the second atom's ID". Therefore, no matter how the user swaps the first and second atoms in the input command, the output PRMTOP file will always show the same entry with the fixed ascending ID sequence, as shown in Figure 35.

As the figure indicates, the output was also split into two entries, named DCOEF and VALUE. This will be helpful for the subsequent file reading done by the MD engine because these two entries will co-work in a pattern similar to a dictionary's "key-value" pair to enhance the computational speed.



Figure 35. Example of the LEaP code output that displays how the atom-specific pairwise C4 interactions was saved in the PRMTOP file.

In the meantime, another command called addC4type was also implemented into LEaP. This command was added by introducing four new keywords: bC4Type, sA, sB, daC4Type, where the first variable is a binary switch to turn on/off the function of printing atom-type-specific C_4 , the second and the third variables are strings to indicate the two atom types that need to have C_4 interactions in between, the last variable is a double accuracy number to save the C_4 value. With the help of these four new keywords, the program can successfully apply the daC4Type value between all atom pairs, which fulfills such a rule: one atom of the pair belongs to atom type sA, while the other belongs to atom type sB. The function call stack passing these four keywords is illustrated by following the pattern displayed in **Figure 36**. As an outcome, the function call stack would print an n(n-1)/2 size array to store all atom-type-specific pairwise C_4 values, where n is the

total number of atom types. Details of such an output are displayed in **Figure 37**. Basically, the output flattens an $n \times n$ matrix and only takes half of the matrix plus its diagonal terms.



Figure 36. Illustration of the modification of function call stack in LEaP to introduce a new command: Adding atom-type-specific pairwise C_4 interaction which was originally from ParmEd.



Figure 37. Illustrations of how the addC4Type command is executed and instructed to print out the C_4 matrix.

PMEMD Version	VDW	EEL
Old without Type C4	<mark>3.9884</mark>	<mark>-113.1163</mark>
Old with Type C4	<mark>3.9791</mark>	<mark>-112.9535</mark>
New without either Pairwise/Type C4	<mark>3.9884</mark>	- <mark>113.1163</mark>
New with atom Type C4	<mark>3.9791</mark>	- <mark>112.9535</mark>
New with Pairwise C4	<mark>-1.7242</mark>	- <mark>112.9535</mark>
New with both Type/Pairwise C4	- <mark>1.7336</mark>	- <mark>112.9535</mark>



Figure 38. Result comparison of traditional atom-type-specific C_4 and new atom-specific pairwise C_4 .

4.3 Implementing the plj1264=1 Keyword into Sander and PMEMD

Up to this point, the LEaP code can successfully implement both the atom-type-specific and atomspecific C_4 interactions into the PRMTOP file before simulation, and the simulation engine can already calculate the atom-type-specific C_4 interaction thanks to previous works.¹³⁴ Therefore, the next step's goal is to implement the algorithm for calculating atom-specific pairwise C_4 interactions in an efficient way. To achieve this, according to **Figure 5**, a highly selective code is written to process the rare occurrence of C_4 interactions between a small number of atom pairs. the introduction of such a fast code will significantly increase the accuracy of the overall free energy and geometry calculation. Because it still considers the charge-induced dipole effect, which is usually considered as a short-range, local effect.

The detailed execution of such an algorithm is presented in the FORTRAN code below: And the related file is <code>\$AMBERHOME/src/pmemd/src/pairs_calc_lj1264plj1264.i</code>.

r6 = delr2inv * delr2inv * delr2inv
f6 = cn2(ic) * r6
f12 = cn1(ic) * (r6 * r6)
mr4 = delr2inv * delr2inv
f4 = mr4 * cn6(ic) ! Calculated C4 between atom types
do im_c4 = 1, C4Pairwise
 if(MIN(img i,img j)==(MIN(cn7(im c4*3-2), cn7(im c4*3-1))+3)/3 &

.and. MAX(img_i,img_j) == (MAX(cn7(im_c4*3-2), cn7(im_c4*3-1))+3)/3 & then

```
f4 = f4 + cn8(im_c4)*mr4 ! Calculate C4 between atom pairs
end if
end do
```

Here the array cn6(ic) stores all the information of C_4 values between all atom types, as illustrated by Figure 37. In comparison, $cn7(im_c4*3-2)$ and $cn7(im_c4*3-1)$ are rather shorter arrays, storing only the index of the atom pairs that need C_4 in between, and $cn8(im_c4)$ stores the related value of C_4 , as illustrated by LENNARD_JONES_DCOEF and LENNARD_JONES_DVALUE in Figure 35. Because such an algorithm only loops over a number of atom pairs that need C_4 interaction, its effect on the time complexity is negligible.

The results of this code are displayed in **Figure 38**, where the energy comparison between old and new versions of AMBER are presented in yellow and green colors, respectively. Comparing rows #1 and #3, as well as rows #2 and #4, respectively, it can be proved that the new atom-type-specific C_4 output by LEaP can still be recognized and calculated by Sander and PMEMD, just like the same value output by ParmEd. Moreover, the values in rows #5 and #6 have the same energy difference (0.095kcal/mol) as the values in rows #3 and #4, indicating that the new atom-specific pairwise code is still compatible with conventional atom-type-specific pairwise code. Such a compatibility will allow the application of this code in much more complex circumstances, like multi-imidazole ion-water-ligand systems with TI calculation.

4.4 A Multi-Imidazole TI Examples and Conclusions

Because the atom-specific pairwise C_4 code in both Sander and PMEMD are proven to be compatible with the current version of forcefield calculation, an application was conducted to test the transferability from a simple "one ion, one water, one ethylenediamine" case in **Figure 38** to a more complex case where an ion with a variety number of imidazole molecules were dissolved in a 40Å water box. During the simulation time, the ion is also slowly transitioning from Ni(II) to Cu(II) in a seven-window TI pattern. The TI results are subsequently compared to experimental relative free energies, which are all calculated from previous works.¹⁷⁶⁻¹⁷⁸

Detailed TI cycles are displayed by the top panel of Figure 39 while the bottom left panel of Figure 39 illustrates the ion's first solvation shell of the ion-imidazole-dissolved system, with green sphere indicating Ni(II) and yellow sphere indicating Cu(II). From the result at the bottom right panel of Figure 39 (only the PMEMD result is shown here since it is more popular than Sander), two discoveries can be concluded: First, by comparing the first and second columns, it is obvious to find that the atom-specific pairwise C_4 code can successfully reproduce what the conventional atom-type-specific code did, but in a more time and storage efficient way. As a comparison, for each single atom that needs atom-specific C_4 , the conventional atom-type-specific code has to assign a new atom type one by one and enlarge the C_4 matrix exponentially after adding these new atom types. The new atom-specific pairwise C_4 code, however, works by index, so the new storage occupied by this code is also negligible. Second, by comparing the first/second columns with the third column, it is confident to conclude that for up to 4 imidazole molecules in the ion's first solvation shell, the relative free energy between Ni(II)- and Cu(II)-imidazole affinity can be successfully reproduced against the experimental values. This matches the previous discovery that in common proteins, the Histidine coordination numbers for ions like Zn(II), Ni(II),

and Cu(II) are usually four instead of six, which is these ions' common coordination number is water.⁶⁶ To resolve this conflict, further investigation on metal-imidazole interaction is needed, and some correction terms on imidazole-imidazole repulsion are possibly needed to correct this disagreement between computer-simulated and experimental-derived values.



Figure 39. (Top) TI illustration of a one-ion-one-imidazole system where the thermodynamic cycle was represented by the figure at bottom. (Bottom) Table of TI results on similar system.

CHAPTER 5: IMIDAZOLE METAL INTERACTION

5.1 Significance of Parametrizing the Ion-Ligand Interaction

Metal ions are essential elements for the maintenance of plants, animals, and humans^{2-3, 179}. The absence of specific metal ions can result in growth disorders, carcinogenesis, severe malnutrition, or death. Over 25% of proteins contain metal ions which function in either a structural or catalytic role.^{6, 180-181} Computational chemistry has become an effective tool to investigate metal ioncoordinating systems present in various biological systems (such as proteins, nucleic acids, carbohydrates, and lipids).¹⁸²⁻¹⁸⁶ When compared to quantum mechanics-based models, force field models have significant advantages in computational cost. However, reproducing the structural features (e.g., ion-oxygen distance) and thermodynamics (e.g., hydration-free energy) of metal ions in water or protein systems is a challenging task.¹⁸⁷ Depending on the system and the research question, various force field models are available; for instance, the bonded¹⁸⁸, nonbonded¹⁸⁹, Drude oscillator¹⁹⁰⁻¹⁹¹, cationic dummy atom (CDA)¹⁹², CDA_{pol}¹⁹³ and the ReaxFF model¹⁹⁴. The 12-6 Lennard-Jones (LJ) nonbonded model is used extensively because it has a simple form, is easy to parametrize, and has excellent transferability.^{16, 192, 195} Nevertheless, the 12-6 LJ nonbonded fails to reproduce the experimental ion-oxygen distance (IOD) and hydration free energy (HFE) of the first solvation shell at the same time for many ions due to an underestimation of the ionwater interaction energy.¹⁸⁷ This can be compensated for by scaling the LJ parameters in unphysical ways,^{52, 196}, which, in our work, we have studiously avoided by working with a physically reasonable parameter range.¹²⁵ The deficiency of the 12-6 model is primarily because it does not include ion-induced dipole interactions, which should not be neglected in highly polarized systems.¹⁹⁷

In the bonded model, the metal ion is covalently bound to the coordinated residues, in which the bond angle, dihedral, van der Waals, and electrostatic interactions are defined by classical terms. Several schemes have been devised to parametrize these terms. Despite the success of the bonded model in replicating the experimentally determined structures, it cannot simulate the coordination number or ligand changes, which is crucial to model catalytic metal centers and metal transport. The nonbonded model is another popular model for metal ions, where the metal ion is represented by a soft sphere that interacts with the surroundings through vdW and electrostatic interactions. The vdW interactions are defined by the 12-6 LJ¹⁹⁸ or Born-Mayer potential¹⁹⁹. In the 12-6 LJ model, the C_4 term was introduced by Li, Merz and co-workers to account for the ion-induced dipole interaction. The ion-induced dipole interaction is proportional to r^{-4} , where r is the distance between the two particles.¹⁹⁷ Therefore, the new model is called the "12-6-4 nonbonded model," which can successfully reproduce the experimental HFE and IOD simultaneously for various metal ions.¹⁹⁷

Since the 12-6-4 model is easy to apply, is computationally efficient, and accurately describes the interactions between the metal ion and its coordinating ligands, it serves as an excellent model for simulating metal ions in molecular dynamics (MD) simulations. In earlier research,⁶⁶ we only studied Co²⁺ and Ni²⁺ interactions with HID-charged (delta nitrogen protonated) histidine in TIP3P water. In the present study, we have been more systematic, including 11 ions (Ag²⁺, Ca²⁺, Cd²⁺, Co²⁺ Cu¹⁺, Cu²⁺, Fe²⁺, Mg²⁺, Mn²⁺, Ni²⁺, and Zn²⁺) with both HID- and HIE- (epsilon nitrogen protonated) charged histidine and in three water models: TIP3P, SPC/E, and OPC.²⁰⁰ By tuning the *C*₄ term in the 12-6-4 model, were able to successful match related experimental interaction energies for each of the "ion-imidazole charge-water model" combinations. This work will benefit

metalloprotein research significantly since these 11 ions are reported to have up to 2992 occurrences of interacting with Histidine(s) in the PDB databank, as listed in **Table 23**.

Ion	Count if at least one histidine coordinates
Ag(I)	17
Ca(II)	246
Cd(II)	552
Co(II)	282
Cu(I)	229
Cu(II)	314
Fe(II)	654
Mg(II)	583
Mn(II)	386
Ni(II)	625
Zn(II)	2992

Table 23. The count of occurrence where each ion has at least one histidine in its binding sphere of any protein in PDB.

The present work provides a validated set of His-metal ion interactions that can be used to study, with a higher degree of confidence than before, metal ions coordinated by His in proteins. This will facilitate metalloprotein design, understanding the mechanism of transition metal ion transport and metal ion selectivity in protein systems. The provided models are compatible with the AMBER class of force fields as well as several water models, allowing a range of applications.

5.2 Optimization of Polarizabilities Based on the Current 12-6-4 Potential

In this work we have used a 12-6-4 nonbonded model along with the AMBER force field, described by Equation (33):

$$U_{ij}(r_{ij}) = \frac{C_{12}^{ij}}{r_{ij}^{12}} - \frac{C_6^{ij}}{r_6^6} - \frac{C_4^{ij}}{r_{ij}^4} + \frac{e^2 Q_i Q_j}{r_{ij}}$$
$$= \varepsilon_{ij} \left[\left(\frac{R_{min,ij}}{r_{ij}} \right)^{12} - 2 \left(\frac{R_{min,ij}}{r_{ij}} \right)^6 \right] - \frac{C_4^{ij}}{r_{ij}^4} + \frac{e^2 Q_i Q_j}{r_{ij}}$$
$$= 4\varepsilon_{ij} \left[\left(\frac{\sigma_{ij}}{r_{ij}} \right)^{12} - \left(\frac{\sigma_{ij}}{r_{ij}} \right)^6 \right] - \frac{C_4^{ij}}{r_{ij}^4} + \frac{e^2 Q_i Q_j}{r_{ij}}$$
(33)

where *e* depicts the proton charge while Q_i and Q_j represent the partial charge of atoms *i* and *j*. The Coulomb pair potential was utilized to represent the electrostatic interaction between atoms *i* and *j*, while the classic 12-6 LJ potential plus an extra r^{-4} term represented the van der Waals interactions. The C_4 terms between water and ions were taken from our previous studies.^{189, 197, 201} The C_4 terms between histidine and metal ions were optimized based on Equation (34):

$$U_{q-\alpha_0} = -\frac{1}{2}\alpha_0 \left(\frac{q}{4\pi\varepsilon_0\varepsilon_r r^2}\right)^2 \cos\theta = -\frac{C_4^U}{r^4} \tag{34}$$

where α_0 is an atom type-dependent polarizability. The metal binds to water molecules and imidazole (which mimics the sidechain of His). PMF (Potential of Mean Force) calculations were used to optimize the pairwise parameters to reproduce the experimental free energies of each metal bound to imidazole. The HID-charge and HIE-charges used on imidazole molecules are described in **Figure 40**, which is the same as what ff19sb uses in AMBER 20²⁰². The major difference between HID- and HIE-charged histidine are the nitrogen charge values and the protonation locations. In order to remove uncertain interactions from amine and carboxyl groups from histidine, the connecting carbon (termed CC in **Figure 40**) is not connected to the α -carbon of histidine but rather hydrogen in the present work. This has been shown to be a reasonable approximation²⁸ since, in real protein simulation, the backbone of histidine is usually rigidly connected to the protein and will not interfere with the metal-ligand interaction as a free amino acid does.



Figure 40. Illustration and comparison of the charge distribution for both HID and HIE imidazole molecules. Heavy atom type names in AMBER are also marked.

A PMF simulation protocol was prepared according to the standard MD procedure. The parametrization was conducted in an iterative manner. For each iteration, a PMF with a short umbrella sampling (termed us1) of 1ns for each window was conducted first to calculate approximate interaction energies. When the PMF-calculated interaction energy was ± 0.25 kcal/mol within the experimental binding free energy, a final round of PMFs was conducted with longer umbrella sampling (termed us2) of 3ns for each window to get a precise estimate of calculated interaction free energy. If us1 or us2 does not give a binding free energy within the range of ± 0.25 kcal/mol of the experimental value (generally rare since us2 is based on a successful us1), a new round of us1 is initiated with a newly assigned polarizability value to continue the iteration until an accurate binding free energy was obtained.

The CUDA version of PMEMD from the AMBER 20²⁰² package was utilized to perform all the molecular dynamics (MD) simulations. The minimization of the system was performed in three steps; (a) minimization of water molecules, with the imidazole group and ions restrained; (b)

minimization of side chain hydrogens (which are imidazole hydrogens) on the non-water molecules; (c) minimization of the whole system. Steps (a) and (b) consist of 10000 cycles of minimization using the steepest descent method followed by 10000 cycles using the conjugate gradient method. Meanwhile, step (c) yields three "steepest descent then conjugate gradient" cycles, as mentioned in steps (a) and (b). In the next step, the system was heated to 300 K gradually during a 1 ns NVT simulation. For system equilibration, a 550000-step run was done at 300 K employing the NPT ensemble. Finally, a production run for 500000 steps at 300 K under constant NPT conditions was performed. The Langevin thermostat with a collision frequency of 1 ps⁻¹ was applied to control the temperature, and the Berendsen barostat¹⁵⁰, with a pressure relaxation time of 5 ps, was employed for the pressure control. The time step was 2 fs, and the nonbonded cutoff was 10 Å. The SHAKE²⁰³ algorithm was used to constrain bonds involving hydrogen atoms, and the time step was set to 2fs. Cluster analysis was utilized to obtain the most representative structure from the MD simulations. The UCSF Chimera²⁰⁴ and VMD programs were used for the visualization and preparation of the figures shown in this study.

The 12-6-4 parameter set was used to reproduce the experimental metal-imidazole binding free energies compared against experimental results. The target binding free energies computed from experimental log K values are shown in **Table 24**¹⁷⁶. Amongst all the experimental values, Ag(I), Cu(II), Fe(II), Mn(II), Ni(II), and Zn(II) were obtained from thermometric titration²⁰⁵⁻²⁰⁷, Ca(II) and Mg(II) were obtained from indicator titrations²⁰⁸, Co(II) and Cd(II) were obtained from potentiometric titration with perchloric acid²⁰⁹, while Cu(I) was obtained from electron absorption spectrum during ligand exchange²¹⁰. The experimental free energies of the interaction of each ion show a high dependence on both the ionic radius and the electronic configuration. Overall, the larger effective ionic radius ions have the lower binding free energy with imidazole molecules,

with a couple of exceptions in the transition metal series. For these exceptions, when the *d*-orbitals of the ions are full or half full, they tend to have higher, meaning less negative binding free energies with imidazole molecules, indicating a connection between *d*-orbital symmetry and imidazole binding free energies.¹⁷⁶

After investigating the correlation between ion properties and their interaction-free energies with imidazole molecules, the parametrization process was conducted following the protocol summarized in the method section. The results agree well with previous studies²¹¹ as well as what **Table 25** shows, where the current 12-6-4 LJ model globally underestimates the interaction. Therefore, higher polarizability values for nitrogen are needed. However, according to the parametrized polarizability data displayed in Table 26, it is interesting to observe that a higher experimental interaction energy does not always correspond to higher polarizability on nitrogen. This inconsistency between binding free energies and polarizabilities indicates that the interaction between a metal ion and imidazole is a result of both the dipole-inducing ability of the metal ion and the capability of the imidazole nitrogen to respond to that induced dipole. The first dipoleinducing ability is solely a feature of the metal ion itself, while the second response depends on both the imidazole nitrogen and the aqueous environment. Hence, we parametrized the polarizability of nitrogen based on the dependences of both water models and imidazole charges, as displayed in Table 26. Here, three common water models (TIP3P, SPC/E, OPC) and two common AMBER imidazole charges (HID and HIE) are applied to form six combinations for parametrization.

Ions	Electronic	Effective Ionic	Energy ³⁵
	Configuration	Radius ⁴² (Å)	(kcal/mol)
Ag(I)	[Kr]4d10	1.15	-3.98
Ca(II)	[Ar]	1.00	0.16
Cd(II)	[Kr]4d10	0.95	-3.63
Co(II)	[Ar]3d7	0.75	-3.36
Cu(I)	[Ar]3d10	1.40	-7.89
Cu(II)	[Ar]3d9	0.73	-5.70
Fe(II)	[Ar]3d6	0.78	-2.46
Mg(II)	[Ne]	0.72	-0.10
Mn(II)	[Ar]3d5	0.83	-1.64
Ni(II)	[Ar]3d7	0.69	-4.12
Zn(II)	[Ar]3d10	0.74	-3.48

Table 24. The experimental interaction energy of each ion.

Table 25. Default energy (kcal/mol) using the default polarizability (1.09 Å^3) of nitrogen for each ion to reproduce binding free energy using PMF studies.

Ions	TIF	P3P	SPO	C/E	O	PC
	HID	HIE	HID	HIE	HID	HIE
Ag(I)	1.78	2.10	1.62	1.78	1.55	1.83
Ca(II)	4.05	4.58	4.03	4.12	3.08	3.78
Cd(II)	7.03	7.34	7.28	7.45	6.49	7.09
Co(II)	9.95	10.56	9.95	10.25	8.68	9.2
Cu(I)	2.87	3.62	2.93	3.02	3.05	3.49
Cu(II)	11.44	12.68	11.61	12.52	10.10	10.53
Fe(II)	8.53	9.37	8.91	9.36	7.41	8.12
Mg(II)	8.17	9.00	8.11	8.93	7.15	8.01
Mn(II)	7.50	8.15	7.70	8.21	7.02	8.03
Ni(ÌI)	9.99	11.44	10.62	11.54	9.40	9.44
Zn(II)	10.25	11.69	10.65	11.72	8.97	9.03

Further analysis of the parameterized polarizabilities from **Table 26** suggests that imidazole with the HIE charge (**Figure 40**, protonated epsilon nitrogen) of -0.5432 needs a higher polarizability value than imidazole ring with the HID charge (Figure 1; protonated delta nitrogen) of -0.5727, meaning a stronger C_4 interaction is required for the HIE-charged imidazole than HID-charged imidazole. Therefore, to reproduce the experimental value with less electron density, the HIE-charged imidazole needs to have a higher polarizability value on the chelating nitrogen to match the same experimental value.

Ions		TIP3P			SPC/E				0	PC		
	H	D	H	ΙE	HI	D	H	ΙE	HI	D	H	ΙE
	Pol	C4	Pol	C4	Pol	C4	Pol	C4	Pol	C4	Pol	C4
Ag(I)	4.65	267	5.05	290	4.52	288	4.55	290	4.23	243	4.63	266
Ca(II)	3.75	226	4.40	265	3.71	229	3.77	232	3.68	219	3.69	220
Cd(II)	3.75	483	3.95	509	3.50	482	3.72	512	3.20	485	3.25	499
Co(II)	3.10	451	3.18	462	3.00	434	3.15	456	2.90	410	3.03	428
Cu(I)	29.31	142	30.01	145	22.33	139	24.61	153	13.29	147	13.49	149
Cu(II)	2.93	590	3.05	615	2.89	608	2.99	629	2.75	554	2.79	562
Fe(II)	3.25	367	3.55	401	3.41	366	3.75	403	3.11	332	3.35	357
Mg(II)	3.25	299	3.48	320	3.39	286	3.47	293	2.90	255	3.05	268
Mn(II)	3.41	345	3.68	372	3.46	371	3.50	376	3.00	364	3.03	367
Ni(II)	3.00	442	3.11	459	3.10	440	3.30	468	2.75	403	2.95	433
Zn(II)	2.94	472	3.05	490	2.95	472	3.09	494	2.71	422	2.87	447

Table 26. Parametrized polarizability (Å³) of nitrogen and final C4 value (kcal·mol⁻¹·Å⁻⁴) between metal ion and nitrogen to reproduce the binding free energy using PMF studies.

Amongst the different water models, the polarizability showed a trend where the polarizability of the TIP3P and SPC/E water models are similar, while the polarizability of the OPC water model is lower than the TIP3P and SPC/E water models ("TIP3P \approx SPC/E > OPC"). This is an interesting ranking because it shows a strong correlation between the intrinsic properties of three/four-point water models and the parametrized polarizabilities of the imidazole nitrogen. As shown in **Figure 41** and **Table 27**, both the TIP3P and SPC/E models are three-point water models, and they also have larger H-O-H angles and longer O-H bond lengths in comparison to the four-point OPC water model. The unique geometry of OPC allows the metal ion to experience less steric hindrance when one water molecule in the first hydration shell is replaced by a larger imidazole molecule. Therefore, the binding of imidazole in a water shell formed by OPC is thermodynamically more favored than in water shells formed by TIP3P or SPC/E, meaning the interaction between the metal ion and imidazole is by nature stronger in OPC water. In short, the OPC water model does not require a higher polarizability value on the imidazole nitrogen to reproduce the same experimental interaction energy relative to TIP3P and SPC/E.

Water	OH	OD	HOH	Oxygen/Dummy	Hydrogen	VDW	VDW
Model	Bond	Bond	Bond	Charge	Charge	σ	3
	Length	Length	Angle				
$TIP3P^{71}$,	0.9572	N/A	104.72	-0.8340	0.4170	3.1506	0.6364
SPC/E^{72}	1.0000	N/A	109.47	-0.8476	0.4238	3.166	0.650
OPC ⁶⁸	0.8724	0.1594	103.6	-1.3582	0.6791	3.1666	0.8903

Table 27. Properties of all the three water models parametrized in this research.



Figure 41. Images of the structure of TIP3P⁷¹, SPC/E⁷² and OPC⁶⁸ water models.

Among all the ten ions parametrized in this work, their C_4 -dependent polarizabilities showed strong dependence on both the ion charges and electron configurations. First, it can be concluded that if the ions are monovalent, like Ag(I) and Cu(I), the chelating nitrogen needs higher polarizabilities, meaning higher C_4 values to reproduce the experimental values. This indicates a larger underestimation of the dipole-inducing ability of monovalent ions on ligands compared to the smaller underestimation of divalent ions. The phenomenon can be explained theoretically using crystal field theory. Being different from water, imidazole nitrogen is considered a strong-field ligand that will enlarge the energy gap between the e_8 , and t_{28} orbitals and push more electrons to the lower-energy t_{2g} -orbital. This will break the *d*-orbital symmetry and the electrostatic screening effect, thereby enhancing the dipole-inducing abilities of the metal ions. However, this enhancement is not obvious on the only two monovalent ions Ag(I) and Cu(I) because both have filled d-orbitals, *i.e.*, both the e_g and t_{2g} orbital groups are fully occupied. As a result, Ag(I) and Cu(I) still have strong d-orbital screening (meaning the metal ion charge cannot "reach" and "induce" the nitrogen atom as effectively), so the parametrized polarizability of nitrogen needs to be larger, in this way the nitrogen atoms can be more "responsive" to the weak inducing power from the metal ion. This hypothesis also matches the fact that both Ag(I) and Cu(I) are soft acids, which can have a strong induced dipole effect.²¹² Further comparison of the equilibrium distances between Ag(I)-N (2.35Å) and Cu(I)-N (1.86Å) reveals that they tend to have closer metal-nitrogen distances compared to other ions.

For the other nine divalent ions, the rule mentioned above: "a symmetric d-orbital group leads to a higher nitrogen polarizability" is not as obvious as for the monovalent ions, likely due to the high charge and small radii of the divalent ions, especially on Zn(II). However, for a large divalent ion like Fe(II) and Cd(II), they still yield slightly higher polarizabilities on the nitrogen compared to other ions because for Fe(II), its t_{2g} orbital group is symmetric with 6 electrons filling three orbitals, while Cd(II) has filled d-orbitals.

Lastly, by comparing ions of the same family, *e.g.* Mg(II) and Ca(II), Zn(II) and Cd(II), Cu(I) and Ag(I), it is interesting to draw the conclusion that for monovalent ions, a larger radius will lead to a lower nitrogen polarizability, while for divalent ions, a larger radius will lead to a higher nitrogen polarizability. This is because the induced dipole decays faster for divalent ions than monovalent ions.²⁵ When the ion is divalent, a larger ion radius will significantly reduce the distortion of the nitrogen atom on the imidazole, so it needs higher polarizability to counter this decay. However, when the ion is monovalent, a larger radius will not significantly reduce the dipole-inducing ability, while a smaller radius would, in turn, overestimate the electron-electron repulsion between metal ions and nitrogen. To balance the overestimation of the repulsion, Cu(I) needs to have its chelating nitrogen be very polarizable to reproduce the experimental interaction energy.

5.3 Effect of Introducing the 12-6-4 Model and Final Conclusion

As Figure 42 and Table 28 indicate, the modified parameters generated energy values (green bars) that agree well with the experimental values (red bars). However, we have discovered that the default 12-6-4 LJ parameter set (orange bars) underperformed compared to the 12-6 compromise (CM) set (blue bars) except for Ca(II) and Cu(I). This indicates an underestimation of the aqueous C_4 parameter while being applied in the protein systems, so according to Equation (33), the C_4 contribution is less negative, making the total binding free energy more positive. To explain this phenomenon, Equation (34) can be used in support because in the ion-water-imidazole system, the dielectric constant ε_r (≈ 27)²¹³ is smaller than that of the aqueous system (≈ 80) due to the existence of the point charge of the metal ion and the electron cloud of nitrogen. Therefore, if the polarizability is kept small (1.09 Å^3) at the numerator, but the denominator has been reduced, the whole C_4 term will have a significant underestimation. Then according to Equation. (33), the contribution of the C_4 term will be less negative, leading to a more positive final interaction energy as the orange bars show in Figure 3. This can be fixed by increasing the polarizability of the chelating nitrogen via parametrization to fit the environment of the metal binding site. Previous work²¹⁴ suggested a de-correlation between two 12-6-LJ parameters, Rmin/2 and ε , is able to reproduce the hydration-free energy of metal ions in aqueous systems, but this 12-6 model was not adopted herein because of our desire to keep the parameters physically meaningful.



Figure 42. Comparison between experimental binding free energies and calculated binding free energies generated by the 12-6 CM parameter set, default 12-6-4 set and modified 12-6-4 set for 11 metal ions.

Table 28. The first three data columns are calculated binding free energies generated by 12-6 CM parameter set, default 12-6-4 set and modified 12-6-4 set, while the last column lists the experimental binding free energies for all 11 metals.

	12-6	12-6-4 Default	12-6-4 Modified	Experimental
Ag(I)	2.11	1.55	-4.16	-3.98
Ca(II)	10.03	3.08	0.10	0.16
Cd(II)	5.46	6.49	-3.74	-3.63
Co(II)	6.14	8.68	-3.26	-3.36
Cu(I)	3.94	3.05	-8.14	-7.89
Cu(II)	7.54	10.10	-5.93	-5.70
Fe(II)	4.94	7.41	-2.64	-2.46
Mg(II)	5.83	7.15	-0.11	-0.10
Mn(II)	5.17	7.02	-1.57	-1.64
Ni(II)	5.93	9.40	-4.28	-4.12
Zn(II)	6.40	8.97	-3.41	-3.48

In the present work, the parametrization was done based on the 12-6-4 Lennard-Jones (LJ) nonbonded model for 11 metal ions for HID (delta nitrogen protonated)- and HIE (epsilon nitrogen protonated)-charged histidine for three water models (*i.e.*, TIP3P, SPC/E, and OPC). The final parametrized polarizabilities can successfully reproduce experimental interaction-free energy. Moreover, the results showed a strong correlation with the polarizability of the imidazole nitrogen, the geometry of the water model, and the electronic configuration of the metal. This means that by merely tuning how polarizable the chelating nitrogen is, the model can rationally reproduce the three-component interaction between imidazole, water, and metal. Since this work has successfully extended the reliability of the 12-6-4 LJ nonbonded model from an aqueous system to a metal-ligand system, we are in a position to tackle related problems in biology and chemistry. Overall, the developed metal-imidazole parameter sets will provide the basis for the research community to conduct accurate MD simulations of metalloproteins at a higher level of accuracy than heretofore possible.

CHAPTER 6: APPLICATION CASES OF TriCyt3 AND hZIP8 SYSTEMS

6.1 Test of the m12-6-4 model on an artificial protein 6WZ3

According to the pairwise code results for the "one-ion-multiple-imidazole dissolved" system, as well as the PMF results from the "one-ion, one-imidazole dissolved" system, it can be confidently concluded that the m12-6-4 nonbonded model is ready to be tested in a complex protein system. The first protein system to be tested is an artificially constructed protein which is specially designed to bind several metal ions with high affinity.²¹⁵ The binding site of this artificial protein is all made of imidazole residues. This fact makes the energy calculation very scalable for testing the m12-6-4 LJ model, since the interactions with various numbers of imidazole molecules have been thoroughly tested by both atom-type specific C_4 code in GPU and atom-specific pairwise C_4 code in CPU. Shifting the simulation system from six free imidazole molecules to a protein with a six-imidazole binding site will be a meaningful challenge for the newly developed forcefield model.

The methods used in this research contain mainly two aspects: TI and PMF. Where TI showed high agreement to the experimental values,¹⁷⁶, while PMF tends to underestimate the interaction between ions and the ligands compared to previous results on one-imidazole systems.⁸⁰ To compromise the difference between TI and PMF, an optimized set of C_4 values is applied on the TI run to reproduce the energy while considering the unknown fact of PMF underestimating most of the \geq 4 imidazole binding free energies. The new C_4 parameters and benchmark results of both methods' calculating the binding free energy of five ions (Co²⁺, Cu²⁺, Mn²⁺, Ni²⁺, Zn²⁺) with a gradient of imidazole molecules (1~6) are listed in **Table 29**. According to the benchmark results, TI was finally selected for the final protein simulation.

Method	Imidazole #	Co ²⁺ (371)	Cu ²⁺ (530)	Mn ²⁺ (333)	Ni ²⁺ (404)	Zn ²⁺ (401)
	1	-5.68	-8.64	-4.50	-6.67	-6.20
	2	-6.99	-12.96	-5.39	-9.36	-7.83
TI	3	-8.83	-17.81	-6.98	-12.46	-10.96
11	4	-9.18	-21.13	-7.19	-13.98	-10.59
	5	-9.29	-24.21	-7.38	-15.13	-10.96
	6	-9.31	-27.16	-7.59	-16.07	-11.20
	1	-3.36	-5.70	-1.64	-4.12	-3.48
	2	-3.62	-12.32	-5.97	-2.76	-4.29
DME	3	-4.49	-17.58	-5.99	-2.67	-5.53
PNIF	4	-5.60	-22.05	-7.49	-2.33	-10.11
	5	-6.49	-24.76	-8.22	-3.46	-10.31
	6	-7.00	-28.11	-9.38.	-8.20	-11.96
	1	-3.36	-5.70	-1.64	-4.12	-3.48
	2	-5.61	-11.86	-3.16	-8.16	-7.21
EVD	3	-6.86	-16.39	-4.43	-11.12	-10.27
EAF	4	-8.25	-20.04	N/A	-13.38	-13.01
	5	-9.21	-21.42	N/A	-14.92	-15.10
	6	-9.99	-21.97	N/A	-15.63	N/A

Table 29. Preliminary benchmark results of ion-imidazole-water system energy calculation using two different methods. The last column indicates the experimental value. First row C_4 values are in units of kcal/mol/Å⁴, and all other data are in units of kcal/mol.

In detail, the TI was conducted in a workflow similar to what **Figure 6** and **Figure 39** show,⁴⁷ where the ion was disappearing from its surrounding in a two-step pattern: first disappearing charge, then VDW, soft-core was applied on the step disappearing charge to avoid endpoint catastrophe. The only difference is that for the imidazole-water system, each imidazole will have a weak distance-angle-dihedral restraint applied to both the ion and the dummy atom. This extra restraint was added onto the system in order not to let the imidazole diffuse away from the first solvation shell during simulation, especially at the end of disappearing VDW interactions where the water molecules can easily replace any imidazole from the vicinity of the ion. These restraints are also moderate (200kcal/mol/Å or 200kcal/mol/degree), so the complex can still maintain its

preferred equilibrium distance. After the TI workflow provided convincing binding free energy of each ion in an imidazole-water-only system, protein simulation was introduced to compare absolute energy between simulations and experiments.²¹⁵ The results are presented in **Table 30** and the experimental setup is elaborated in **Figure 43**. All simulations are conducted in OPC water models to be consistent with previous benchmark tests on ion-imidazole-water systems.

Table 30. TI calculated absolute (top) and relative (bottom) energy of each ion's binding to the protein (PDB: 6WZ3). For the relative energy, each row indicates the starting ion, and each column indicates the ending ion for TI mutation. *i.e.*, the starting ion is being mutated to the ending ion using multiple window TI techniques.

	Ion TI absolute results (kcal/mol)		ults (kcal/mol)	Experimental results (kcal/mol)	
	Co ²⁺	-11	.57	-11	.28
	Cu^{2+}	-13	.74	-16	6.68
	Mn^{2+}	-9.	.60	-10	0.02
	Ni ²⁺	-9.	.54	-11	.19
	Zn^{2+}	-11	.29	-12.90	
TI	Co ²⁺	Cu^{2+}	Mn^{2+}	Ni ²⁺	Zn^{2+}
Co^{2+}		-3.00	1.18	1.61	0.28
Cu^{2+}			4.12	6.82	2.45
Mn^{2+}				1.49	-1.69
Ni ²⁺					-1.75
Zn^{2+}					
EXP	Co ²⁺	Cu ²⁺	Mn ²⁺	Ni ²⁺	Zn ²⁺
Co^{2+}		-5.40	1.26	0.09	-1.62
Cu^{2+}			6.66	5.49	4.78
Mn^{2+}				-1.17	-2.88
Ni ²⁺					-1.71



Figure 43. Illustration of the experimental setup on simulating 6WZ3 (left), the upper right panel indicates the metal binding center that was treated using TI to calculate absolute and relative energy. While the lower right panel is a HEME "staple" to stabilize the trimer. MCPB.py was used on the HEME center to guarantee a proper charge distribution of the "staple" areas.

According to the results, it is safe to conclude that all the transition ions which do not have a Jahn-Teller effect can reproduce the experimental value to a \pm 2kcal/mol tolerance range. However, ions with a Jahn-Teller effect, especially Cu²⁺, show a larger deviation from the experimental value in the simulation. Indicating that the m12-6-4 model needs further optimization toward the anisotropic structure of some metal-binding centers.

6.2 Test of the m12-6-4 model on a modified hZIP8 membrane protein

Engineering of transporters to alter substrate specificity as desired holds great potential for applications, including metabolic engineering. However, the lack of knowledge on molecular mechanisms of substrate specificity hinders designing effective strategies for transporter engineering. Here, an integrated approach was applied to rationally alter the substrate preference of ZIP8, a Zrt-/Irt-like protein (ZIP) metal transporter with multiple natural substrates, which uncovered the determinants of substrate specificity. By systematically replacing the differentially conserved residues with the counterparts in zinc-preferring ZIP4, a zinc-specific quadruple variant was created, and such a variant exhibited largely reduced transport activities towards Cd^{2+} , Fe^{2+} , and Mn^{2+} whereas increased activity toward Zn^{2+} . Combined mutagenesis, modeling, covariance analysis, and computational studies revealed a conditional selective filter which functions only when the transporter adopts the outward-facing conformation. The demonstrated approach for transporter engineering and the gained knowledge about substrate specificity will facilitate engineering and mechanistic studies of other transporters.

In this work, a systematic approach was applied to rationally alter the substrate specificity of a multi-metal transporter, ZIP8, from humans, initially aiming to increase the preference toward Zn^{2+} over Cd^{2+} (described Zn/Cd selectivity hereafter). The quadruple variant of ZIP8 created in this study exhibited a drastically increased preference for Zn^{2+} over not only Cd^{2+} but also Fe^{2+} and Mn^{2+} , which are the other two physiological substrates of ZIP8 besides $Zn^{2+}.^{134}$ Structural modeling, evolutionary covariance analysis, and computational studies revealed a residue pair that forms a selective filter at the entrance of the transport pathway only when ZIP8, an elevator-type transporter, adopts the outward-facing conformation, providing the structural and biochemical basis of the strong epistasis among the mutations introduced in the quadruple variant.

Method-wise, MD simulations were performed using AMBER20.¹³⁴ The system was prepared using CHARMMGUI,²¹⁶ in which the box dimension was 101×101×126 Å containing one ZIP8 protein, 262 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC) molecules, and 25973 OPC water molecules. Minimization was done in five stages with a gradient of restriction from protein backbone to side chain, each step yield 10, 000 steps of steepest descendent and 10 000 steps of conjugate gradient methods; then 36 ns of NVT heating was performed with the temperature increasing gradually from 0 to 300 K. Then another 3 µs of simulation was performed to equilibrate the system in the NPT ensemble. Finally, a seven-window thermodynamic integration was conducted on the equilibrated system; each window yielded 300 ns. For every 50 ps, the snapshot was saved to the trajectory file, yielding 420 000 snapshots for the Gaussian Quadrature analysis. A 10 Å cutoff was used for the non-bonded interaction. The PME method and PBC were used for the simulations, and the Langevin algorithm with a 2.0 ps^{-1} friction coefficient was used for maintaining the temperature.¹⁴⁹ Berendsen barostat was used for pressure control with a relaxation time of 1.0 ps.¹⁵⁰ The time step was 1.0 fs, with SHAKE used to constrain the bonds containing hydrogen atoms.¹²² To compare free energy changes upon metal ions binding to the selective filter involving the side chains of H180, H343, D318, and E184 in the 4M variant, a modified 12-6-4 Lennard-Jones (m12-6-4 LJ) non-bonded model was introduced to consider the induced dipole effect between the metal ion and coordinating atoms during simulation.²¹¹ Since the induced dipole effect is highly dependent on the polarizability of coordinating atoms, all parametrized polarizabilities used in this research were provided by the table in Figure 44. Because the m12-6-4 LJ model mainly yields strongly localized interactions, only the residues at the metal binding sites were applied with modified polarizabilities and m12-6-4 LJ potentials.

A

Metal ion	Metal Imidazole (His)			Acetate (Asp and Glu)			
	logK	Energy (kcal/mol)	Polarizability on coordinating nitrogen	logK	Energy (kcal/mol)	Polarizability on coordinating oxygen	
Zn ²⁺	2.55	-3.48	2.71	1.58	-2.16	0.77	
Fe ²⁺	1.80	-2.46	N/A	1.40	-1.91	N/A	
Mn ²⁺	1.20	-1.64	N/A	1.40	-1.91	N/A	
Cd ²⁺	2.66	-3.63	3.20	1.93	-2.63	1.17	

B



Figure 44. Computational characterization of metal binding at the selective filter. (A) Free energy changes of metal ion binding with small molecule ligands filter (left) moved to the transport site in the ending model (right) where it is coordinated with the residues from M1 (H314, H343), M2 (E344), and a bridging residue involved in both M1 and M2 (D318).

The free energy calculation result of metal binding to the selective filter indicates that the substitution of Q180 and E343 by histidine residues introduced two imidazole groups in the selective filter, as illustrated in Figure 44, generating a metal binding site preferring Zn^{2+} over Fe^{2+} and Mn^{2+} according to the previously determined free energies of metal binding with small molecule ligands as mentioned in Figure 45. However, this estimation cannot satisfactorily explain why histidine replacement also improved the Zn/Cd selectivity since the free energy reduction upon ligand replacement with imidazole is similar for Zn^{2+} and Cd^{2+} . To address this issue, we conducted molecular dynamics (MD) simulations on the 4M variant in the OFC with a bound metal ion at the selective filter to obtain an energy-minimized structural model, which will be subsequently used for free energy calculation of metal binding using thermodynamic integration.²¹⁷⁻²²³ In the first trial, only after 10 ns of MD simulation, the Zn^{2+} initially located at the selective filter moved to a deeper place within the transport pathway where the metal ion was coordinated by the residues from both M1 and M2 sites described in Figure 45. To prevent metal ion translocation to the transport site, a second metal ion was added in the starting model at the position which would otherwise be occupied by the metal ion at the selective filter. As expected, the metal ion bound at the selective filter was stabilized throughout a 3 µs MD simulation only with a small displacement as recorded in Figure 44. Notably, E184, which was not included in metal chelation in the starting model, was found to join the metal binding site with H180, H343, and D318 during the MD simulations, likely improving metal binding at the selective filter. Meanwhile, due to the repulsion between the two metal ions in the starting model, the second metal ion added to the transport site moved further down the transport pathway and then stabilized by three carboxylic acid residues (E344, D311, 242, and D351). Using this energy-minimized and structure-stabilized ending model, we calculated and compared the free energy changes of Zn^{2+}

and Cd^{2+} binding at the selective filter. As shown in Figure 6C, the selective filter (with E184 being included) of the 4M variant prefers binding Zn^{2+} over Cd^{2+} by 3.8 ± 0.3 kcal/mol (n=3), while the experimental result indicated a seven-time increase in the Zn^{2+} -protein binding affinity over Cd^{2+} -protein affinity. This seven-time increase can then be converted to a difference in binding free energy of 1.16 kcal/mol according to the Boltzmann distribution. Overall, the results of free energy calculation supported that the amino acid composition of the identified selective filter critically determines the substrate preference and that metal screening at the selective filter is a crucial step in distinguishing metal substrates.



Figure 45. Computational characterization of the interactions of the 4M variant with metal substrates at the selective filter. (A) Structural model of the 4M variant with a zinc ion bound (grey sphere) at the selective filter. The structural model was generated by homology modeling. The metal ion is coordinated with H180, D318, and H343 with the metal-ligand distances labeled in angstrom. (B) MD simulations of the 4M variant with two bound zinc ions. Left: the starting model. One zinc ion was placed at the selective filter and the other at the transport site to prevent the former from entering the channel. Right: the ending model. The metal ion initially placed at the selective filter was stabilized by four residues, including E184, whereas the second one in the transport site moved down the transport pathway to a deeper position where two highly conservative aspartate residues (D311 and D351) joined E344 to form a new metal binding site. (C) Free energy calculation of Zn²⁺ and Cd²⁺ binding to the selective filter (with E184 included) of the 4M variant. M²⁺(aq) and M²⁺(pro) indicate Zn²⁺ (or Cd²⁺) in aqueous solution or bound at the selective filter, respectively. The free energy change resulting from the mutation of Zn²⁺ to Cd²⁺ in aqueous solution ($\Delta G_{Zn-Cd, aq}$) or at the selective filter ($\Delta G_{Zn-Cd, pro}$) was calculated using thermodynamic integration and the results are expressed in kcal/mol.

In conclusion, the engineering of metal transporters with altered substrate specificity can be

strategized for potential applications in agriculture and environmental protection. In this work, we

developed and applied an approach to rationally alter the substrate specificity of a multi-metal ZIP transporter, human ZIP8. We created zinc-preferring ZIP8 variant by combining four designed mutations on selected residues at the entrance or along the transport pathway, demonstrating that these mutations increased the Zn^{2+} transport activity while largely suppressing the activities toward Cd^{2+} , Fe^{2+} , and Mn^{2+} . To apply this approach to a transporter of interest, it is crucial to identify a close homolog (referred to as the reference) with a distinct substrate spectrum. ZIP4 was chosen as the reference of ZIP8 because it strongly prefers Zn^{2+} over Cd^{2+} .²²⁴⁻²²⁶ Subsequent MD simulations also approved this selection of the homology model since the protein and added metal ions showed great stability during free simulation and provided free energy data that resembles the experimental phenomenon. If both MD geometry trajectory and energy data agree well with experimental value, it can be confidently concluded that m12-6-4 LJ model is a solid tool to reproduce the behavior of such a membrane protein in a complex simulation box.

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APPENDIX A: TABLES

Table 31. Calculated HFE values (in kcal/mol) of monovalent cations with values from Parameter Space Scans for (A) OPC3 (B) OPC (C) TIP3P-FB (D) TIP4P-FB.

$R_{min}/2$	a(lxaa1/mc1)			C4 (kcal	/mol*Å ⁴)		
(Å)	E (KCal/IIIOI)	0	20	40	60	80	100
1.0	0.00001423	-159.2	-174.0	-189.7	-206.0	-222.9	-239.3
1.1	0.00016377	-144.2	-155.0	-166.4	-178.3	-191.1	-204.5
1.2	0.00110429	-126.1	-135.0	-144.0	-153.4	-163.1	-172.9
1.3	0.00490301	-108.1	-114.9	-121.8	-129.1	-136.4	-144.0
1.4	0.01570749	-94.5	-100.7	-106.6	-112.9	-119.2	-125.4
1.5	0.03899838	-84.2	-89.3	-94.1	-99.1	-104.5	-110.0
1.6	0.07934493	-76.3	-80.8	-84.7	-88.7	-93.2	-98.0
1.7	0.13818331	-70.7	-74.0	-77.8	-81.6	-85.1	-89.4
1.8	0.21312875	-66.0	-68.5	-72.2	-75.7	-79.5	-82.7
1.9	0.29896986	-61.8	-65.1	-68.3	-71.5	-74.3	-78.0
2.0	0.38943250	-58.9	-61.9	-64.6	-67.3	-70.5	-73.3
2.1	0.47874242	-55.8	-58.5	-61.3	-64.1	-67.2	-70.1
2.2	0.56252208	-53.8	-56.2	-59.1	-61.9	-64.4	-66.9
2.3	0.63803333	-52.0	-54.2	-56.7	-59.2	-61.5	-64.2

A. OPC3 water model.

B. OPC water model.

$R_{min}/2$	a(1rac1/mc1)			C4 (kcal/i	mol*Å ⁴)		
(Å)	ε (kcal/mol)	0	20	40	60	80	100
1.0	0.00001423	-150.8	-164.2	-179.5	-195.7	-211.8	-228.1
1.1	0.00016377	-137.6	-147.9	-158.6	-170.1	-181.7	-193.9
1.2	0.00110429	-121.3	-129.5	-138.5	-147.5	-156.3	-165.4
1.3	0.00490301	-104.9	-111.5	-118.3	-125.0	-132.5	-139.6
1.4	0.01570749	-93.4	-98.6	-104.6	-110.8	-116.7	-123
1.5	0.03899838	-83.6	-88.4	-92.90	-97.8	-102.8	-108.3
1.6	0.07934493	-75.7	-79.4	-83.90	-88.0	-92.1	-96.1
1.7	0.13818331	-70.2	-73.6	-77.2	-80.9	-84.7	-88.5
1.8	0.21312875	-65.2	-66.0	-71.5	-75.2	-78.0	-82.2
1.9	0.29896986	-61.2	-64.5	-68.5	-70.1	-73.4	-77.5
2.0	0.38943250	-57.5	-61.2	-61.8	-65.4	-69.0	-72.9
2.1	0.47874242	-54.6	-56.1	-59.1	-61.3	-65.6	-68.5
2.2	0.56252208	-51.2	-54.0	-58.0	-62.3	-62.5	-65.5
2.3	0.63803333	-48.7	-53.3	-55.1	-59.0	-58.5	-62.0

Table 31. (cont'd)

$R_{min}/2$	a(1rac1/ma1)	$C_4 (kcal/mol*Å^4)$					
(Å)	e (kcal/mol)	0	20	40	60	80	100
1.0	0.00001423	-156.3	-170.9	-187.4	-203.5	-220.0	-236.0
1.1	0.00016377	-141.8	-152.7	-163.7	-176.0	-188.8	-202.3
1.2	0.00110429	-124.4	-133.1	-142.2	-151.3	-161.2	-170.6
1.3	0.00490301	-106.5	-113.5	-120.6	-127.6	-134.8	-142.3
1.4	0.01570749	-93.6	-99.6	-105.5	-111.5	-117.7	-124.2
1.5	0.03899838	-83.7	-87.9	-93.4	-98.3	-103.6	-109.4
1.6	0.07934493	-75.9	-79.9	-83.9	-87.9	-92.5	-96.8
1.7	0.13818331	-69.8	-73.6	-77.2	-80.9	-84.9	-88.5
1.8	0.21312875	-65.3	-68.8	-71.6	-75.2	-78.6	-82.5
1.9	0.29896986	-61.1	-64.3	-67.7	-70.6	-74.2	-77.2
2.0	0.38943250	-58.4	-61.5	-64.4	-67.1	-70.0	-73.3
2.1	0.47874242	-55.8	-58.7	-61.6	-63.9	-66.8	-69.8
2.2	0.56252208	-54.0	-56.5	-58.5	-61.2	-64.3	-66.4
2.3	0.63803333	-52.0	-54.0	-56.4	-58.8	-61.5	-64.0

C. TIP3P-FB water model.

D. TIP4P-FB water model.

R _{min} /2	a(1raa1/maa1)	$C_4 (kcal/mol*Å^4)$					
(Å)	e (kcal/mol)	0	20	40	60	80	100
1.0	0.00001423	-150.0	-163.4	-179.2	-195.2	-211.8	-227.7
1.1	0.00016377	-136.6	-147.3	-158.8	-170.4	-182.8	-195.8
1.2	0.00110429	-120.2	-128.9	-137.7	-146.8	-156.3	-165.6
1.3	0.00490301	-103.8	-110.5	-117.6	-124.8	-132.2	-139.3
1.4	0.01570749	-92.0	-97.9	-104.0	-110.0	-116.2	-122.4
1.5	0.03899838	-82.6	-87.2	-92.3	-97.3	-102.6	-107.6
1.6	0.07934493	-75.5	-79.2	-83.5	-87.4	-91.8	-96.2
1.7	0.13818331	-69.2	-72.8	-76.6	-80.8	-84.4	-87.9
1.8	0.21312875	-64.3	-68.2	-71.8	-74.9	-78.6	-81.6
1.9	0.29896986	-61.1	-64.3	-67.3	-70.5	-73.4	-76.7
2.0	0.38943250	-58.2	-61.4	-63.9	-67.0	-69.4	-72.6
2.1	0.47874242	-55.7	-57.6	-60.4	-64.0	-66.3	-69.0
2.2	0.56252208	-52.9	-56.0	-58.5	-61.0	-63.0	-65.9
2.3	0.63803333	-51.1	-53.9	-56.1	-58.6	-60.8	-63.4

Table 32. Calculated IOD values (in Å) and CN of monovalent cations with values from Parameter Space Scans for (A) OPC3 (B) OPC (C) TIP3P-FB (D) TIP4P-FB.

$R_{min}/2$	c (kaal/mal)			C ₄ (kcal	/mol*Å ⁴)		
(Å)	E (KCal/IIIOI)	0	20	40	60	80	100
1.0	0.00001423	1.47/3.0	1.44/3.0	1.39/3.0	1.33/3.3	1.30/2.0	1.27/2.0
1.1	0.00016377	1.70/4.0	1.62/3.2	1.67/4.0	1.65/4.0	1.63/4.0	1.62/4.0
1.2	0.00110429	1.85/4.0	1.83/4.0	1.81/4.0	1.80/4.0	1.78/4.0	1.77/4.0
1.3	0.00490301	2.02/4.3	2.01/4.4	2.00/4.4	1.99/4.5	1.99/4.6	1.98/4.7
1.4	0.01570749	2.24/5.4	2.23/5.5	2.22/5.6	2.22/5.7	2.21/5.8	2.20/5.8
1.5	0.03899838	2.40/5.7	2.40/5.7	2.39/5.8	2.38/5.9	2.37/5.9	2.36/6.0
1.6	0.07934493	2.56/6.2	2.55/6.3	2.54/6.3	2.54/6.3	2.53/6.3	2.52/6.4
1.7	0.13818331	2.71/7.2	2.71/6.7	2.70/6.8	2.69/6.9	2.69/7.0	2.68/7.2
1.8	0.21312875	2.87/7.2	2.85/7.9	2.85/7.7	2.84/7.8	2.84/8.2	2.83/8.0
1.9	0.29896986	3.00/8.5	2.99/3.5	3.00/8.7	2.98/8.8	2.97/8.8	2.98/9.5
2.0	0.38943250	3.14/9.6	3.13/9.7	3.13/9.9	3.11/10.3	3.11/10.8	3.10/9.8
2.1	0.47874242	3.27/10.8	3.28/3.2	3.26/10.2	3.24/12.2	3.25/10.7	3.24/12.2
2.2	0.56252208	3.41/13.2	3.38/14.2	3.39/13.8	3.37/13.9	3.37/14.8	3.36/14.9
2.3	0.63803333	3.52/12.8	3.52/14.2	3.51/16.2	3.49/14.5	3.49/14.6	3.48/17.8

A. OPC3 water model.

B. OPC water model.

R _{min} /2	a(lraal/mal)	$C_4 (kcal/mol*Å^4)$						
(Å)	ε (kcal/mol)	0	20	40	60	80	100	
1.0	0.00001423	1.49/3.0	1.44/2.9	1.38/3.0	1.34/2.1	1.32/2.0	1.30/2.0	
1.1	0.00016377	1.73/4.0	1.71/4.0	1.69/4.0	1.68/4.0	1.66/4.0	1.65/4.0	
1.2	0.00110429	1.87/4.0	1.85/4.0	1.84/4.0	1.82/4.0	1.81/4.0	1.80/4.0	
1.3	0.00490301	2.08/4.9	2.07/5.0	2.07/5.1	2.06/5.2	2.06/5.4	2.05/5.5	
1.4	0.01570749	2.28/5.8	2.27/5.8	2.26/5.8	2.26/5.9	2.24/6.0	2.23/6.0	
1.5	0.03899838	2.44/6.0	2.43/6.0	2.42/6.0	2.41/6.0	2.40/6.0	2.39/6.0	
1.6	0.07934493	2.59/6.2	2.59/6.4	2.58/6.3	2.56/6.4	2.56/6.3	2.55/6.5	
1.7	0.13818331	2.75/6.9	2.74/6.9	2.73/6.8	2.72/7.1	2.72/7.2	2.71/7.2	
1.8	0.21312875	2.90/7.4	2.88/7.6	2.88/7.9	2.87/7.7	2.86/7.8	2.86/8.3	
1.9	0.29896986	3.03/8.1	3.02/7.8	3.01/8.2	3.00/8.4	3.00/8.9	3.00/8.8	
2.0	0.38943250	3.15/9.8	3.15/8.5	3.15/9.9	3.14/9.2	3.13/9.3	3.12/9.3	
2.1	0.47874242	3.29/9.7	3.27/10.3	3.28/10.8	3.26/10.2	3.26/9.7	3.25/11.7	
2.2	0.56252208	3.40/11.2	3.40/12.0	3.40/12.5	3.40/11.1	3.39/12.3	3.38/12.4	
2.3	0.63803333	3.52/14.6	3.53/14.9	3.51/12.8	3.50/17.0	3.51/16.5	3.50/14.4	

Table 32. (cont'd)

С.	TIP3P-FB	water	model.
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$R_{min}/2$	a (kaal/mal)			C ₄ (kcal	∣/mol*Å⁴)		
(Å)	E (KCal/IIIOI)	0	20	40	60	80	100
1.0	0.00001423	1.48/3.0	1.44/3.0	1.40/3.0	1.34/3.0	1.30/2.1	1.28/2.0
1.1	0.00016377	1.70/4.0	1.68/4.0	1.66/4.0	1.62/3.6	1.63/4.0	1.62/4.0
1.2	0.00110429	1.85/4.0	1.83/ 4.0	1.81/4.0	1.80/4.0	1.78/4.0	1.77/4.0
1.3	0.00490301	2.03/4.4	2.01/4.4	2.00/4.4	1.98/3.8	1.99/4.7	1.98/4.8
1.4	0.01570749	2.24/5.3	2.23/5.5	2.22/5.5	2.22/5.7	2.21/5.8	2.08/3.9
1.5	0.03899838	2.41/5.7	2.40/5.8	2.39/5.9	2.38/5.9	2.37/6.0	2.36/6.0
1.6	0.07934493	2.56/6.2	2.56/6.4	2.54/6.3	2.53/6.4	2.53/6.4	2.52/6.3
1.7	0.13818331	2.72/6.7	2.71/6.9	2.70/7.0	2.70/7.1	2.69/7.4	2.68/7.3
1.8	0.21312875	2.86/7.4	2.86/7.4	2.85/7.5	2.84/8.1	2.84/8.5	2.83/7.9
1.9	0.29896986	3.00/8.6	3.00/8.3	2.99/8.4	2.98/8.1	2.98/8.9	2.97/9.3
2.0	0.38943250	3.14/9.6	3.13/9.6	3.12/11.5	3.12/10.1	3.11/10.3	3.10/10.2
2.1	0.47874242	3.27/10.2	3.27/11.3	3.24/11.0	3.24/10.3	3.24/12.7	3.24/10.6
2.2	0.56252208	3.40/13.7	3.39/11.6	3.38/12.7	3.37/11.7	3.35/6.0	3.36/14.4
2.3	0.63803333	3.52/15.0	3.50/19.2	3.50/16.6	3.50/18.7	3.49/14.8	3.47/12.4

D. TIP4P-FB water model.

$R_{min}/2$	a(lraal/mal)	$C_4 (kcal/mol*Å^4)$					
(Å)	e (kcal/mol)	0	20	40	60	80	100
1.0	0.00001423	1.49/3.0	1.45/3.0	1.40/2.9	1.35/3.4	1.31/2.0	1.29/2.0
1.1	0.00016377	1.71/4.0	1.69/4.0	1.68/4.0	1.66/4.0	1.65/4.0	1.63/4.0
1.2	0.00110429	1.86/4.0	1.84/4.0	1.83/4.0	1.81/4.0	1.80/4.0	1.78/4.0
1.3	0.00490301	2.06/4.7	2.05/4.8	2.05/5.0	2.05/5.2	2.04/5.2	2.04/5.4
1.4	0.01570749	2.27/5.8	2.25/5.8	2.25/5.8	2.24/5.9	2.23/5.9	2.22/6.0
1.5	0.03899838	2.43/5.9	2.42/5.9	2.40/6.0	2.39/6.0	2.38/6.0	2.37/6.0
1.6	0.07934493	2.58/6.2	2.57/6.4	2.56/6.4	2.56/5.2	2.54/6.4	2.53/6.4
1.7	0.13818331	2.73/6.8	2.73/7.0	2.72/6.8	2.71/7.3	2.71/7.1	2.69/7.3
1.8	0.21312875	2.88/7.8	2.86/7.5	2.86/7.3	2.86/7.8	2.85/8.0	2.84/7.7
1.9	0.29896986	3.02/8.2	3.00/8.5	3.00/8.2	2.99/8.3	2.99/8.9	2.98/8.4
2.0	0.3894325	3.14/9.0	3.14/8.8	3.13/9.7	3.13/9.1	3.12/ 9.7	3.12/9.3
2.1	0.47874242	3.28/10.3	3.27/10.4	3.27/10.3	3.26/10.8	3.25/11.0	3.24/10.9
2.2	0.56252208	3.40/11.6	3.39/11.4	3.37/13.7	3.37/11.3	3.38/13.3	3.37/15.5
2.3	0.63803333	3.52/12.9	3.51/12.8	3.50/16.9	3.50/12.6	3.49/13.8	3.49/15.0

Table 33. Calculated HFE values (in kcal/mol) of halide ions with values from Parameter Space Scans for (A) OPC3 (B) OPC (C) TIP3P-FB (D) TIP4P-FB.

$R_{\rm min}/2$	a (kaal/mal)	$C_4 (kcal/mol*Å^4)$					
(Å)	е (ксаі/шоі)	0	-20	-40	-60	-80	-100
1.7	0.13818331	-132.9	-128.4	-124.3	-120.1	-115.9	-112.7
1.8	0.21312875	-121.1	-117.7	-113.5	-110.4	-106.6	-103.0
1.9	0.29896986	-111.7	-108.4	-105.4	-102.6	-98.9	-95.4
2.0	0.38943250	-104.7	-101.8	-98.6	-95.6	-92.2	-89.7
2.1	0.47874242	-98.9	-95.5	-93.2	-90.0	-87.4	-84.4
2.2	0.56252208	-93.7	-90.7	-88.0	-85.2	-83.0	-80.2
2.3	0.63803333	-89.2	-86.5	-84.5	-81.7	-79.0	-76.7
2.4	0.70399643	-85.2	-83.1	-80.4	-78.1	-75.8	-74.0
2.5	0.76022647	-81.5	-79.4	-77.3	-75.4	-73.3	-70.7
2.6	0.80725180	-78.6	-76.3	-74.6	-71.9	-70.7	-68.7
2.7	0.84599584	-75.8	-74.2	-72.2	-70.3	-67.6	-66.3
2.8	0.87754630	-73.7	-72.2	-69.8	-67.5	-65.9	-64.4
2.9	0.90300541	-71.3	-68.9	-67.8	-65.8	-64.3	-62.4
3.0	0.92340323	-69.0	-67.7	-65.9	-63.9	-62.1	-61.6
3.1	0.93965518	-66.9	-66.1	-64.0	-62.4	-61.1	-59.0
3.2	0.95254766	-65.7	-64.0	-61.9	-60.8	-58.6	-57.8

A. OPC3 water model.

B. OPC water model.

$R_{\rm min}/2$	a (kaal/mal)	$C_4 (kcal/mol*Å^4)$					
(Å)	E (KCal/11101)	0	-20	-40	-60	-80	-100
1.7	0.13818331	-135.1	-131.8	-126.6	-122.9	-118.8	-115.6
1.8	0.21312875	-124.8	-119.6	-116.3	-113.7	-109.1	-106.6
1.9	0.29896986	-114.1	-110.2	-109.0	-103.7	-102.3	-97.5
2.0	0.38943250	-104.6	-104.9	-101.0	-95.9	-94.8	-91.2
2.1	0.47874242	-101.1	-98.3	-95.2	-92.9	-89.6	-87.8
2.2	0.56252208	-95.7	-92.5	-88.2	-88.8	-84.0	-83.3
2.3	0.63803333	-92.9	-88.5	-86.0	-84.8	-78.6	-79.3
2.4	0.70399643	-86.5	-84.6	-82.1	-79.1	-76.0	-74.2
2.5	0.76022647	-83.5	-79.1	-79.4	-77.8	-72.2	-72.3
2.6	0.80725180	-80.2	-79.2	-75.8	-72.8	-69.9	-70.1
2.7	0.84599584	-77.5	-72.9	-72.5	-71.1	-69.7	-67.1
2.8	0.87754630	-75.4	-69.6	-72.8	-70.5	-69.5	-66.3
2.9	0.90300541	-73.7	-69.8	-69.4	-66.2	-64.6	-64.7
3.0	0.92340323	-70.3	-67.7	-66.7	-66.1	-63.7	-58.2
3.1	0.93965518	-66.9	-63.9	-65.2	-64.1	-62.1	-58.3
3.2	0.95254766	-68.3	-64.9	-64.9	-61.0	-59.7	-58.6

Table 33. (cont'd)

C. TIP3P-FB	water	model.
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$R_{\rm min}/2$	o (kool/mol)			C4 (kcal	/mol*Å ⁴)		
(Å)	ε (kcal/mol)	0	-20	-40	-60	-80	-100
1.7	0.13818331	-134.6	-130.5	-126.4	-122.1	-117.7	-114.5
1.8	0.21312875	-122.3	-118.8	-115.1	-111.3	-108.0	-104.0
1.9	0.29896986	-113.1	-109.5	-106.2	-103.3	-100.1	-96.4
2.0	0.38943250	-105.5	-102.5	-99.5	-97.0	-93.0	-90.4
2.1	0.47874242	-99.4	-96.3	-93.5	-91.3	-87.7	-85.0
2.2	0.56252208	-93.7	-91.1	-89.0	-85.8	-83.8	-80.9
2.3	0.63803333	-89.0	-87.0	-84.5	-82.2	-79.4	-77.3
2.4	0.70399643	-85.1	-83.2	-81.3	-78.0	-76.5	-73.9
2.5	0.76022647	-81.9	-79.6	-77.1	-75.3	-73.2	-70.5
2.6	0.80725180	-78.8	-76.9	-74.6	-72.5	-70.3	-68.4
2.7	0.84599584	-75.4	-73.7	-72.2	-70.1	-68.3	-65.9
2.8	0.87754630	-73.2	-71.5	-69.9	-68.0	-66.1	-63.8
2.9	0.90300541	-70.9	-69.1	-67.9	-65.4	-64.8	-62.8
3.0	0.92340323	-69.0	-67.4	-66.0	-63.9	-62.3	-60.5
3.1	0.93965518	-67.2	-65.8	-64.5	-61.4	-60.5	-58.1
3.2	0.95254766	-64.5	-63.4	-62.3	-60.1	-59.3	-56.6

D. TIP4P-FB water model.

$R_{\rm min}/2$	a(1,a,a,1/m,a,1)	$C_4 (kcal/mol*Å^4)$						
(Å)	ε (kcal/mol)	0	-20	-40	-60	-80	-100	
1.7	0.13818331	-136.8	-132.3	-128.6	-123.4	-119.3	-115.8	
1.8	0.21312875	-124.5	-119.9	-117.2	-112.9	-109.5	-105.6	
1.9	0.29896986	-114.2	-111.8	-107.9	-104.8	-101.0	-98.9	
2.0	0.38943250	-106.9	-103.6	-100.3	-97.8	-95.9	-91.8	
2.1	0.47874242	-100.8	-98.2	-95.3	-91.9	-90.0	-86.7	
2.2	0.56252208	-95.5	-92.5	-90.0	-87.2	-84.5	-82.5	
2.3	0.63803333	-90.5	-88.3	-85.9	-83.5	-81.3	-78.3	
2.4	0.70399643	-86.0	-84.4	-81.7	-79.1	-76.6	-75.3	
2.5	0.76022647	-82.7	-80.6	-79.5	-76.0	-74.8	-72.8	
2.6	0.80725180	-80.1	-77.8	-75.5	-74.3	-71.8	-69.9	
2.7	0.84599584	-76.4	-74.1	-73.5	-70.5	-68.7	-66.7	
2.8	0.87754630	-74.5	-73.0	-71.3	-68.8	-67.7	-65.8	
2.9	0.90300541	-72.9	-70.4	-68.2	-66.9	-65.0	-63.0	
3.0	0.92340323	-69.8	-68.4	-66.5	-64.6	-63.8	-62.1	
3.1	0.93965518	-67.5	-67.0	-65.3	-63.7	-61.7	-59.5	
3.2	0.95254766	-66.7	-64.4	-63.7	-61.4	-60.5	-58.9	

Table 34. Calculated IOD values (in Å) and CN of halide ions with values from Parameter Space Scans for (A) OPC3 (B) OPC (C) TIP3P-FB (D) TIP4P-FB

$R_{\rm min}/2$	a (kaal/mal)	$C_4 (kcal/mol*Å^4)$							
(Å)	E (Kcal/III0I)	0	-20	-40	-60	-80	-100		
1.7	0.13818331	2.58/6.1	2.58/6.1	2.58/6.1	2.58/6.1	2.58/6.1	2.58/6.1		
1.8	0.21312875	2.73/6.5	2.73/6.6	2.73/6.3	2.73/6.4	2.72/6.5	2.73/6.5		
1.9	0.29896986	2.86/6.8	2.86/6.6	2.87/6.7	2.86/6.7	2.86/6.6	2.86/6.7		
2.0	0.38943250	2.99/7.0	2.99/7.0	2.99/6.9	2.99/6.8	2.99/6.9	2.99/6.8		
2.1	0.47874242	3.11/7.2	3.11/7.1	3.11/7.1	3.11/7.0	3.11/7.3	3.11/7.1		
2.2	0.56252208	3.23/7.4	3.23/7.1	3.23/7.2	3.23/7.4	3.23/7.2	3.23/7.1		
2.3	0.63803333	3.34/7.4	3.34/7.1	3.35/7.1	3.33/7.9	3.33/7.6	3.34/7.6		
2.4	0.70399643	3.45/7.2	3.45/7.6	3.44/7.5	3.45/7.8	3.45/7.8	3.45/7.9		
2.5	0.76022647	3.55/7.6	3.55/7.4	3.56/7.4	3.55/7.4	3.55/8.3	3.55/7.8		
2.6	0.80725180	3.65/7.8	3.67/6.3	3.66/7.1	3.66/8.4	3.65/7.4	3.65/7.7		
2.7	0.84599584	3.76/7.7	3.75/6.7	3.77/7.4	3.76/7.4	3.76/7.4	3.76/7.9		
2.8	0.87754630	3.86/8.4	3.86/5.4	3.86/5.7	3.87/8.3	3.87/7.6	3.86/7.2		
2.9	0.90300541	3.96/4.7	3.96/6.7	3.96/6.0	3.97/6.2	3.97/6.7	3.96/7.2		
3.0	0.92340323	4.06/3.2	4.06/4.8	4.07/8.4	4.07/5.3	4.07/5.6	4.08/4.0		
3.1	0.93965518	4.17/6.6	4.17/6.1	4.16/7.4	4.16/4.2	4.18/7.6	4.16/5.2		
3.2	0.95254766	4.27/7.3	4.28/4.5	4.26/3.3	4.29/6.8	4.25/6.3	4.28/6.8		

A. OPC3 water model.

B. OPC water model.

$R_{\rm min}/2$	a(lraal/mal)		$C_4 (kcal/mol*Å^4)$						
(Å)	E (Kcal/III0I)	0	-20	-40	-60	-80	-100		
1.7	0.13818331	2.60/6.1	2.60/6.0	2.60/6.0	2.60/6.0	2.60/6.0	2.60/6.0		
1.8	0.21312875	2.74/6.3	2.74/6.3	2.74/6.3	2.74/6.2	2.74/6.3	2.74/6.2		
1.9	0.29896986	2.88/6.6	2.88/6.4	2.88/6.6	2.88/6.6	2.88/6.5	2.88/6.5		
2.0	0.38943250	3.00/6.8	3.01/6.6	3.01/7.0	3.01/6.9	3.00/6.7	3.00/6.8		
2.1	0.47874242	3.13/6.7	3.13/6.9	3.12/6.9	3.12/7.0	3.12/6.7	3.13/7.2		
2.2	0.56252208	3.24/6.7	3.25/7.0	3.24/7.4	3.24/6.4	3.24/7.0	3.24/6.6		
2.3	0.63803333	3.35/7.4	3.35/7.0	3.36/7.3	3.36/6.6	3.35/7.0	3.35/6.8		
2.4	0.70399643	3.46/6.9	3.46/6.5	3.47/6.7	3.46/7.5	3.46/7.4	3.46/7.5		
2.5	0.76022647	3.56/5.8	3.56/6.8	3.56/7.1	3.57/7.1	3.56/7.4	3.57/7.1		
2.6	0.80725180	3.67/6.7	3.66/7.2	3.68/7.6	3.67/7.0	3.67/4.5	3.67/4.9		
2.7	0.84599584	3.77/7.2	3.78/4.8	3.78/7.1	3.78/4.7	3.76/6.9	3.78/5.6		
2.8	0.87754630	3.88/4.5	3.88/4.6	3.88/4.1	3.87/4.9	3.87/3.5	3.89/5.8		
2.9	0.90300541	3.98/4.0	3.99/3.3	3.97/3.4	3.98/4.4	3.98/3.3	3.97/4.6		
3.0	0.92340323	4.10/3.3	4.08/3.4	4.09/3.4	4.08/3.4	4.11/4.3	4.09/5.0		
3.1	0.93965518	4.19/4.2	4.18/4.3	4.21/3.9	4.21/4.3	4.22/3.6	4.19/3.8		
3.2	0.95254766	4.34/4.2	4.32/3.6	4.33/3.9	4.21/3.8	4.31/4.2	4.30/3.3		

Table 34. (cont'd)

C. TIP3P-FB	water	model.
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$R_{\rm min}/2$				C4 (kcal	l/mol*Å ⁴)		
(Å)	ε (kcal/mol)	0	-20	-40	-60	-80	-100
1.7	0.13818331	2.57/6.1	2.57/6.1	2.57/6.1	2.57/6.1	2.57/6.1	2.57/6.1
1.8	0.21312875	2.72/6.4	2.71/6.3	2.72/6.4	2.72/6.3	2.72/6.3	2.71/6.4
1.9	0.29896986	2.85/6.7	2.86/6.7	2.86/6.7	2.85/6.7	2.85/6.7	2.85/6.7
2.0	0.38943250	2.98/7.0	2.98/7.0	2.98/6.9	2.98/6.8	2.98/6.9	2.98/6.7
2.1	0.47874242	3.10/7.1	3.10/6.8	3.10/7.1	3.11/7.0	3.10/7.0	3.10/7.1
2.2	0.56252208	3.22/7.1	3.22/6.9	3.22/7.1	3.22/7.3	3.22/7.0	3.22/7.4
2.3	0.63803333	3.33/7.3	3.33/7.2	3.32/7.5	3.33/6.9	3.33/6.9	3.33/6.8
2.4	0.70399643	3.43/7.4	3.44/7.2	3.44/6.8	3.44/7.3	3.44/7.5	3.44/7.8
2.5	0.76022647	3.54/7.9	3.54/7.2	3.55/8.0	3.55/7.2	3.55/7.0	3.55/7.0
2.6	0.80725180	3.64/6.5	3.65/8.6	3.65/7.0	3.65/7.3	3.65/7.3	3.64/8.6
2.7	0.84599584	3.75/6.5	3.74/6.8	3.75/7.1	3.75/7.1	3.75/5.9	3.75/6.3
2.8	0.87754630	3.86/5.1	3.85/6.7	3.86/8.8	3.84/6.6	3.85/6.4	3.85/7.7
2.9	0.90300541	3.95/4.1	3.95/5.4	3.95/4.6	3.96/5.7	3.96/5.2	3.94/6.5
3.0	0.92340323	4.05/4.2	4.06/5.7	4.06/5.3	4.05/4.7	4.06/4.3	4.04/5.1
3.1	0.93965518	4.15/3.7	4.14/5.9	4.15/4.0	4.16/4.8	4.16/4.8	4.15/4.0
3.2	0.95254766	4.25/8.0	4.26/3.4	4.26/4.3	4.26/3.7	4.24/4.0	4.25/3.5

D. TIP4P-FB v	water model.
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$R_{\rm min}/2$	a (Iraal/mal)			C4 (kcal	/mol*Å ⁴)		
(Å)	E (Kcal/III0I)	0	-20	-40	-60	-80	-100
1.7	0.13818331	2.57/6.0	2.57/6.0	2.57/6.0	2.57/6.0	2.57/6.1	2.57/6.0
1.8	0.21312875	2.72/6.3	2.72/6.2	2.72/6.3	2.72/6.3	2.72/6.2	2.72/6.3
1.9	0.29896986	2.85/6.4	2.86/6.5	2.86/6.5	2.86/6.5	2.86/6.5	2.86/6.5
2.0	0.38943250	2.98/6.8	2.98/6.6	2.98/6.8	2.99/6.7	2.99/6.8	2.98/6.6
2.1	0.47874242	3.11/7.0	3.10/6.8	3.10/6.9	3.10/6.8	3.11/6.4	3.10/6.8
2.2	0.56252208	3.22/6.9	3.22/7.0	3.22/6.9	3.22/6.8	3.22/7.0	3.22/6.9
2.3	0.63803333	3.33/7.1	3.33/6.7	3.33/6.9	3.33/6.9	3.33/7.2	3.33/6.6
2.4	0.70399643	3.44/6.1	3.44/6.7	3.44/7.3	3.44/6.7	3.43/6.4	3.44/7.1
2.5	0.76022647	3.54/6.7	3.54/6.8	3.55/6.3	3.54/6.4	3.54/6.5	3.54/7.5
2.6	0.80725180	3.66/6.1	3.65/6.6	3.65/6.6	3.64/6.4	3.65/7.7	3.65/6.0
2.7	0.84599584	3.75/6.4	3.76/6.7	3.75/5.0	3.76/5.9	3.75/5.2	3.75/6.5
2.8	0.87754630	3.86/3.9	3.86/5.9	3.86/4.2	3.86/5.3	3.85/5.7	3.86/4.2
2.9	0.90300541	3.96/6.8	3.95/4.2	3.96/4.0	3.95/5.3	3.95/4.3	3.95/4.1
3.0	0.92340323	4.07/6.2	4.07/5.4	4.05/3.6	4.07/5.6	4.06/6.0	4.05/6.0
3.1	0.93965518	4.17/3.2	4.18/3.4	4.17/5.4	4.18/3.4	4.16/3.7	4.16/5.0
3.2	0.95254766	4.27/3.6	4.27/4.3	4.28/3.5	4.28/4.3	4.29/4.2	4.27/4.2

Table 35. Calculated HFE values from the divalent ions' parameter space scans for the OPC3(A), OPC(B), TIP3P-FB(C), TIP4P-FB(D) water model^{*a*}.

А

D /2	6	$C_4=0$	$C_4 = 100$	$C_4 = 200$	$C_4 = 300$	$C_4 = 400$
$\mathbf{K}_{\min,M}/2$	$\epsilon_{\rm M}$	kcal/mol*Å ⁴				
(A)	(Kcal/mor)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)
0.9	0.0000062	-588.3	N/A	-834.8	-937.7	-1039.0
1.0	0.00001422	-542.5	-642.3	-737.8	-833.4	-930.4
1.1	0.00016377	-510.6	-588.8	-673.9	-760.0	-847.7
1.2	0.00110429	-466.5	-524.5	-590.8	-664.4	-743.0
1.3	0.00490301	-439.7	-488.2	-541.0	-596.3	-656.0
1.4	0.01570749	-404.1	-445.3	-488.9	-533.4	-581.4
1.5	0.03899838	-369.8	-403.6	-438.1	-475.6	-513.3
1.6	0.07934493	-345.4	-375.0	-405.1	-436.9	-470.2
1.7	0.13818331	-325.2	-350.6	-376.7	-404.4	-433.4
1.8	0.21312875	-305.5	-328.5	-351.8	-377.4	-402.0
1.9	0.29896986	-288.9	-309.7	-331.0	-352.6	-375.4
2.0	0.38943250	-273.7	-292.7	-311.7	-331.7	-352.7
2.1	0.47874242	-260.4	-277.7	-295.5	-313.7	-332.5
2.2	0.56252208	-248.6	-264.9	-281.7	-298.0	-315.9
2.3	0.63803333	-237.3	-253.0	-268.6	-284.4	-300.2

В

R _{min,M} / 2 (Å)	ε _M (kcal/mol)	C ₄ =0 kcal/mol* Å ⁴ (kcal/mol)	C ₄ =100 kcal/mol*Å ⁴ (kcal/mol)	C4=200 kcal/mol*Å ⁴ (kcal/mol)	C ₄ =300 kcal/mol*Å ⁴ (kcal/mol)	C ₄ =400 kcal/mol*Å ⁴ (kcal/mol)
0.9	0.00000062	-556.0	-680.0	-786.5	N/A	N/A
1.0	0.00001422	-514.6	-609.1	-703.1	-795.5	-887.9
1.1	0.00016377	-485.7	-557.8	-639.0	-720.4	-803.5
1.2	0.00110429	-446.9	-501.6	-564.6	-632.7	-708.2
1.3	0.00490301	-422.4	-468.4	-518.7	-569.0	-623.5
1.4	0.01570749	-389.4	-429.0	-469.5	-511.9	-557.4
1.5	0.03899838	-357.4	-389.4	-422.7	-458.1	-494.8
1.6	0.07934493	-336.3	-364.1	-393.5	-423.5	-455.2
1.7	0.13818331	-315.4	-340.4	-366.3	-393.1	-421.7
1.8	0.21312875	-297.6	-322.0	-344.2	-367.8	-392.4
1.9	0.29896986	-282.8	-302.9	-324.4	-345.8	-365.2
2.0	0.38943250	-267.7	-288.5	-306.8	-325.7	-346.2
2.1	0.47874242	-255.0	-269.7	-291.4	-309.4	-325.6
2.2	0.56252208	-243.3	-261.8	-277.5	-294.0	-309.7
2.3	0.63803333	-233.0	-249.3	-265.4	-280.8	-297.3

"Herein "N/A" means the job failed along the simulation process. These points were not used in the curve fittings.

С

D

D /2		$C_4 = 0$	C ₄ =100	$C_4 = 200$	C ₄ =300	$C_4 = 400$
$\mathbf{K}_{\min,M/2}$	٤ _M	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴
(A)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)
0.9	0.00000062	-578.8	-708.3	-823.1	-924.8	N/A
1.0	0.00001422	-533.9	-632.5	-729.2	-824.3	-920.8
1.1	0.00016377	-503.0	-580.8	-665.8	-752.3	-840.1
1.2	0.00110429	-460.0	-518.6	-584.4	-659.0	-736.5
1.3	0.00490301	-434.2	-483.4	-535.5	-591.5	-651.3
1.4	0.01570749	-399.6	-439.9	-483.4	-528.4	-575.6
1.5	0.03899838	-365.6	-399.4	-434.5	-470.6	-509.0
1.6	0.07934493	-342.0	-371.1	-402.0	-433.6	-467.5
1.7	0.13818331	-321.2	-346.9	-373.0	-401.2	-430.2
1.8	0.21312875	-302.7	-325.9	-348.6	-373.6	-399.7
1.9	0.29896986	-286.2	-307.4	-328.1	-350.4	-372.9
2.0	0.38943250	-271.2	-290.4	-309.4	-329.1	-349.9
2.1	0.47874242	-258.7	-275.5	-293.8	-311.9	-330.4
2.2	0.56252208	-246.5	-263.3	-279.3	-296.4	-313.7
2.3	0.63803333	-236.1	-251.1	-266.8	-282.0	-298.7
D /2		$C_4 = 0$	C ₄ =100	C ₄ =200	C ₄ =300	$C_4 = 400$
$\mathbf{K}_{\min,M/2}$	$\epsilon_{\rm M}$	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴
(A)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)
0.9	0.00000062	-552.2	-678.5	N/A	N/A	N/A
1.0	0.00001422	-512.0	-607.8	-703.1	-794.5	-890.7
1.1	0.00016377	-482.9	-558.9	-641.9	-726.3	-812.6
1.2	0.00110429	-445.8	-501.2	-564.8	-636.2	-713.5
1.3	0.00490301	-420.8	-469.4	-519.7	-573.3	-630.3
1.4	0.01570749	-388.7	-428.1	-470.1	-514.4	-560.5
1.5	0.03899838	-357.0	-388.1	-422.9	-459.1	-495.2
1.6	0.07934493	-334.9	-363.3	-392.6	-424.5	-457.6
1.7	0.13818331	-315.5	-340.3	-366.2	-394.0	-421.4
1.8	0.21312875	-297.9	-320.6	-344.0	-367.7	-392.7
1.9	0.29896986	-282.1	-302.6	-323.1	-345.7	-367.5
2.0			2010	206.2	225.2	3156
	0.38943250	-267.7	-286.9	-306.2	-323.2	-345.0
2.1	$\begin{array}{c} 0.38943250 \\ 0.47874242 \end{array}$	-267.7 -255.2	-286.9 -272.6	-306.2 -290.1	-323.2 -308.7	-327.4
2.1 2.2	0.38943250 0.47874242 0.56252208	-267.7 -255.2 -243.8	-286.9 -272.6 -260.1	-306.2 -290.1 -276.2	-323.2 -308.7 -293.7	-327.4 -311.1

*a*Herein "N/A" means the job failed along the simulation process. These points were not used in the curve fittings.

		TIP3P	SPC/E	TIP4P	TIP4P-Ew
$R_{min,M}/2$	ε _M	$C_4=0$	$C_4 = 0$	$C_4=0$	$C_4 = 0$
(Å)	(kcal/mol)	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴	kcal/mol*Å ⁴
		(kcal/mol)	(kcal/mol)	(kcal/mol)	(kcal/mol)
0.9	0.0000062	-575.7	-578.4	-520.5	-539.5
1.0	0.00001422	-530.2	-533.4	-485.0	-500.9
1.1	0.00016377	-499.8	-502.6	-458.4	-472.8
1.2	0.00110429	-460.8	-460.7	-425.9	-439.3
1.3	0.00490301	-432.5	-433.8	-401.2	-413.1
1.4	0.01570749	-397.9	-398.6	-370.2	-380.8
1.5	0.03899838	-366.4	-364.6	-343.1	-351.7
1.6	0.07934493	-344.2	-342.8	-324.1	-330.7
1.7	0.13818331	-324.2	-321.9	-305.2	-311.0
1.8	0.21312875	-306.1	-303.4	-289.9	-294.7
1.9	0.29896986	-290.3	-286.6	-275.2	-279.2
2.0	0.38943250	-275.9	-271.9	-261.9	-265.1
2.1	0.47874242	-263.1	-259.3	-249.9	-253.6
2.2	0.56252208	-251.2	-247.6	-239.2	-243.0
2.3	0.63803333	-241.0	-237.0	-230.8	-233.1

Table 36. Calculated HFE values from the divalent ions' parameter scans for the TIP3P, SPC/E, TIP4P, and TIP4P-Ew water models.

Table 37. Calculated HFE values from the divalent ions' parameter space scans for the OPC3(A), OPC(B), TIP3P-FB(C), TIP4P-FB(D) water model.

А

R _{min,M} /2	ε _M	C4=0 kcal/mol*Å ⁴		C4=100 kcal/mol*Å ⁴		C4=200 kcal/mol*Å ⁴		C4=300 kcal/mol*Å ⁴		C4=400 kcal/mol*Å ⁴	
(A)	(kcal/mol)	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	=400 nol*Å ⁴ CN 2.0 2.0 4.0 4.0 6.0 6.1 8.0 8.2 9.0 9.2 9.8 10.2 11.0
0.9	0.0000062	1.14	2.0	N/A	N/A	1.03	2.0	0.99	2.0	0.97	2.0
1.0	0.00001422	1.40	3.0	1.30	2.0	1.19	2.0	1.14	2.0	1.11	2.0
1.1	0.00016377	1.59	4.0	1.54	4.0	1.51	4.0	1.48	4.0	1.45	4.0
1.2	0.00110429	1.87	6.0	1.68	4.4	1.64	4.0	1.61	4.0	1.58	4.0
1.3	0.00490301	1.98	6.0	1.94	6.0	1.91	6.0	1.88	6.0	1.86	6.0
1.4	0.01570749	2.09	6.0	2.06	6.0	2.03	6.0	2.01	6.0	1.98	6.0
1.5	0.03899838	2.25	6.4	2.21	6.3	2.19	6.5	2.15	6.1	2.12	6.1
1.6	0.07934493	2.44	7.8	2.42	7.9	2.39	8.0	2.37	8.0	2.35	8.0
1.7	0.13818331	2.56	8.0	2.54	8.0	2.51	8.1	2.49	8.2	2.47	8.2
1.8	0.21312875	2.69	8.5	2.67	8.7	2.65	8.9	2.63	9.0	2.62	9.0
1.9	0.29896986	2.81	8.9	2.79	9.0	2.77	9.1	2.75	9.1	2.73	9.2
2.0	0.38943250	2.92	9.2	2.91	9.4	2.89	9.5	2.87	9.7	2.86	9.8
2.1	0.47874242	3.04	9.6	3.02	9.8	3.00	10.0	2.99	10.1	2.97	10.2
2.2	0.56252208	3.14	10.0	3.13	10.3	3.11	10.6	3.10	10.7	3.09	11.0
2.3	0.63803333	3.25	10.6	3.23	10.7	3.22	10.9	3.21	11.3	3.19	11.3

В

$R_{min,}$ ϵ_{M} M/2 (kcal/mol)	C4 kcal/m	=0 nol*Å ⁴	C4= kcal/m	100 ol*Å ⁴	C4= kcal/m	200 101*Å ⁴	C4= kcal/m	300 101*Å ⁴	C4= kcal/m	C4=400 kcal/mol*Å ⁴	
(Å)	(kcal/mol)	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN
0.9	0.0000062	1.16	2.0	1.10	2.0	1.05	2.0	N/A	N/A	N/A	N/A
1.0	0.00001422	1.43	2.0	1.27	2.0	1.20	2.0	1.16	2.0	1.13	2.0
1.1	0.00016377	1.62	4.0	1.58	4.0	1.54	4.0	1.51	4.0	1.48	4.0
1.2	0.00110429	1.90	6.0	1.70	4.1	1.67	4.0	1.64	4.0	1.61	4.0
1.3	0.00490301	2.01	6.0	1.98	6.0	1.94	6.0	1.92	6.0	1.89	6.0
1.4	0.01570749	2.12	6.0	2.09	6.0	2.06	6.0	2.04	6.0	2.01	6.0
1.5	0.03899838	2.28	6.5	2.25	6.5	2.22	6.4	2.19	6.7	2.16	6.7
1.6	0.07934493	2.48	7.9	2.45	6.5	2.43	8.0	2.41	8.0	2.38	8.0
1.7	0.13818331	2.60	8.2	2.57	8.3	2.55	8.3	2.53	8.4	2.52	8.6
1.8	0.21312875	2.73	8.9	2.71	6.5	2.69	9.0	2.67	9.0	2.65	9.0
1.9	0.29896986	2.85	9.1	2.82	9.2	2.81	9.2	2.79	9.3	2.77	9.6
2.0	0.38943250	2.96	9.5	2.95	9.7	2.93	9.9	2.91	10.0	2.90	10.0
2.1	0.47874242	3.08	10.0	3.06	10.2	3.05	10.3	3.03	10.6	3.02	11.0
2.2	0.56252208	3.19	10.5	3.17	10.7	3.16	11.0	3.15	11.3	3.14	11.5
2.3	0.63803333	3.30	11.0	3.28	11.1	3.27	11.5	3.25	11.8	3.24	11.8

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$R_{\min,M}/2$	$\epsilon_{\rm M}$	C4=0 kcal/mol*Å ⁴		C4=100 kcal/mol*Å ⁴		C4=200 kcal/mol* $Å^4$		C4=300 kcal/mol* $Å^4$		C4=400 kcal/mol* $Å^4$	
(A)	(kcal/mol) -	IOD	CN	IOD	CN	IOD	CN	IOD	CN	IOD	CN
		(A)		(A)		(A)		(A)		(A)	
0.9	0.00000062	1.14	2.0	1.07	2.0	1.02	2.0	0.99	2.0	N/A	N/A
1.0	0.00001422	1.41	3.0	1.32	3.0	1.18	2.0	1.14	2.0	1.11	2.0
1.1	0.00016377	1.59	4.0	1.54	4.0	1.51	4.0	1.48	4.0	1.45	4.0
1.2	0.00110429	1.87	6.0	1.68	4.9	1.64	4.0	1.61	4.0	1.58	4.0
1.3	0.00490301	1.98	6.0	1.94	6.0	1.91	6.0	1.88	6.0	1.86	6.0
1.4	0.01570749	2.09	6.0	2.06	6.0	2.03	6.0	2.00	6.0	1.98	6.0
1.5	0.03899838	2.25	6.4	2.22	6.4	2.20	6.5	2.16	6.3	2.14	6.4
1.6	0.07934493	2.44	7.8	2.42	7.9	2.39	8.0	2.37	8.0	2.35	8.0
1.7	0.13818331	2.56	8.0	2.53	8.1	2.51	8.1	2.49	8.2	2.47	8.3
1.8	0.21312875	2.69	8.6	2.67	8.7	2.65	8.9	2.63	9.0	2.61	9.0
1.9	0.29896986	2.81	8.9	2.79	9.0	2.77	9.1	2.75	9.1	2.73	9.2
2.0	0.38943250	2.92	9.2	2.91	9.3	2.89	9.5	2.87	9.7	2.86	9.9
2.1	0.47874242	3.03	9.6	3.02	9.8	3.00	10.0	2.99	10.1	2.97	10.3
2.2	0.56252208	3.14	10.0	3.13	10.2	3.12	10.4	3.10	9.4	3.09	11.1
2.3	0.63803333	3.25	10.6	3.24	10.9	3.22	11.0	3.21	11.3	3.20	11.5

D

$R_{\min,M}/2$	$\epsilon_{\rm M}$	C4=0 kcal/mol*Å ⁴		C4=100 kcal/mol*Å ⁴		C4=200 kcal/mol*Å ⁴		C4=300 kcal/mol*Å ⁴		C4=400 kcal/mol*Å ⁴	
(A)	(kcal/mol)	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN	IOD (Å)	CN
0.9	0.00000062	1.15	2.0	1.08	2.0	N/A	N/A	N/A	N/A	N/A	N/A
1.0	0.00001422	1.42	3.0	1.29	3.0	1.19	2.0	1.15	2.0	1.12	2.0
1.1	0.00016377	1.60	4.0	1.56	4.0	1.52	4.0	1.49	4.0	1.47	4.0
1.2	0.00110429	1.89	6.0	1.70	4.8	1.65	4.0	1.62	4.0	1.59	4.0
1.3	0.00490301	1.99	6.0	1.96	6.0	1.93	6.0	1.90	6.0	1.87	6.0
1.4	0.01570749	2.11	6.0	2.08	6.0	2.04	6.0	2.02	6.0	1.99	6.0
1.5	0.03899838	2.28	6.8	2.25	6.7	2.23	6.8	2.19	6.7	2.17	6.7
1.6	0.07934493	2.46	7.9	2.43	8.0	2.41	8.0	2.39	8.0	2.36	8.0
1.7	0.13818331	2.58	8.1	2.55	8.2	2.53	8.3	2.52	8.5	2.50	8.7
1.8	0.21312875	2.71	8.9	2.69	8.9	2.67	9.0	2.65	9.0	2.63	9.0
1.9	0.29896986	2.83	9.0	2.81	9.2	2.79	9.2	2.77	9.3	2.75	9.5
2.0	0.38943250	2.95	9.5	2.93	9.7	2.91	9.8	2.89	9.9	2.88	10.0
2.1	0.47874242	3.06	9.9	3.04	10.1	3.02	10.2	3.01	10.4	3.00	10.7
2.2	0.56252208	3.17	10.4	3.15	10.6	3.14	10.9	3.13	11.2	3.12	11.4
2.3	0.63803333	3.28	11.0	3.26	11.1	3.25	11.4	3.24	11.5	3.22	11.6

		TI	P3P	SPO	C/E	TIF	P4P	TIP4	P-Ew	
D /2	6	C4	=0	C4	=0	C4	=0	C4	$\begin{array}{c c} TIP4P-Ew \\ C4=0 \\ kcal/mol*Å^4 \\ \hline IOD \\ (Å) \\ \hline 1.15 & 2.0 \\ 1.42 & 3.0 \\ 1.60 & 4.0 \\ 1.89 & 6.0 \\ 1.99 & 6.0 \\ 2.10 & 6.0 \\ 2.30 & 7.0 \\ \hline \end{array}$	
$\mathbf{K}_{\min,M/2}$	$\epsilon_{\rm M}$	kcal/n	nol*Å ⁴	kcal/n	10l*Å4	kcal/m	10l*Å4	kcal/n	10l*Å4	
(A)	(Kcal/mor)	IOD	CN	IOD	CN	IOD	CN	IOD	CN	
		(Å)	CN	(Å)	CN	(Å)	CN	(Å)	CN	
0.9	0.0000062	1.13	2.0	1.13	2.0	1.15	2.0	1.15	2.0	
1.0	0.00001422	1.40	3.0	1.40	3.0	1.42	3.0	1.42	3.0	
1.1	0.00016377	1.58	4.0	1.58	4.0	1.60	4.0	1.60	4.0	
1.2	0.00110429	1.86	6.0	1.87	6.0	1.88	6.0	1.89	6.0	
1.3	0.00490301	1.96	6.0	1.97	6.0	1.98	6.0	1.99	6.0	
1.4	0.01570749	2.08	6.0	2.09	6.0	2.10	6.0	2.10	6.0	
1.5	0.03899838	2.28	7.1	2.26	6.7	2.31	7.4	2.30	7.0	
1.6	0.07934493	2.44	8.0	2.44	7.9	2.46	8.0	2.46	8.0	
1.7	0.13818331	2.56	8.3	2.56	8.0	2.59	8.7	2.58	8.3	
1.8	0.21312875	2.69	8.9	2.69	8.7	2.71	9.0	2.71	8.9	
1.9	0.29896986	2.80	9.1	2.80	9.0	2.83	9.3	2.82	9.1	
2.0	0.38943250	2.92	9.6	2.92	9.3	2.95	9.9	2.94	9.6	
2.1	0.47874242	3.03	10.0	3.03	9.8	3.06	10.2	3.06	10.0	
2.2	0.56252208	3.14	10.4	3.14	10.0	3.17	10.9	3.16	10.5	
2.3	0.63803333	3.24	10.9	3.25	10.6	3.28	11.4	3.27	11.0	

Table 38. Calculated IOD/CN values from the divalent ions' parameter scans for the TIP3P, SPC/E, TIP4P, and TIP4P-Ew water models.

 $C_4 = 125$ $R_{min,M}/2$ ε_M $C_4 = 0$ C₄=250 C₄=375 $C_4 = 500$ (kcal/mol) $(kcal/mol^* Å^4)$ $(kcal/mol^* Å^4)$ $(kcal/mol*Å^4)$ (kcal/mol*Å⁴) (kcal/mol*Å⁴) (Å) 0.9 0.0000062 -1163.4 -1356.2 -1514.3 -1656.3 N/A 1.0 0.00001422 -1084.6 -1228.1 N/A -1636.5 -1365.8 1.1 0.00016377 -1033.5 -1396.6 -1150.6 -1273.1 -1521.3 1.2 0.00110429 -968.6 -1052.9 -1147.9 -1253.9 -1365.0 1.3 0.00490301 -921.0 -992.2 -1070.3 -1153.8 -1239.8 -980.9 1.4 0.01570749 -855.5 -916.7 -1047.7 -1116.7 1.5 -856.9 -912.6 -965.7 -1023.1 0.03899838 -808.5 0.07934493 1.6 -768.7 -812.9 -857.7 -904.6 -953.7 1.7 0.13818331 -731.4 -770.4 -811.0 -852.8 -895.2 -697.8 -767.4 -803.9 1.8 0.21312875 -731.7 -841.3 1.9 0.29896986 -667.0 -698.2 -729.4 -762.1 -797.6 2.0 0.38943250 -640.8 -668.1 -698.9 -728.8 -759.0 2.1 0.47874242 -670.2 -697.2 -725.9 -614.5 -641.6 2.2 0.56252208 -591.9 -615.9 -640.8 -692.8 -665.7 2.3 0.63803333 -567.1 -590.6 -614.1 -637.4 -660.1 $R_{min,M}/2$ $C_4 = 0$ $C_4 = 250$ $C_4 = 500$ C₄=750 $C_4 = 1000$ ϵ_{M} (kcal/mol*Å⁴) (kcal/mol*Å4) (kcal/mol*Å⁴) (Å) (kcal/mol) (kcal/mol*Å⁴) (kcal/mol*Å⁴) 0.9 0.0000062-1874.1 N/A N/A N/A N/A N/A 1.0 0.00001422 -1765.6 -2075.6 -2372.7 N/A 1.1 0.00016377 -1695.7 -1959.1 -2230.1 -2499.6 -2781.4 1.2 0.00110429 -1605.3 -1800.2 -2037.8 -2284.5 -2538.5 1.3 0.00490301 -1525 -1701 -1885.6 -2086.6 -2295.6 1.4 0.01570749 -1435.7 -1575.3 -1725.6 -1892.4 -2066.9 -1880.1 1.5 0.03899838 -1374.6 -1492.7 -1619.2 -1746.2 1.6 0.07934493 -1317.4 -1419.1 -1526.1 -1638.9 -1755.5 1.7 0.13818331 -1260.2 -1349.6 -1443.9 -1542.6 -1647.8 1.8 0.21312875 -1211.8 -1291.5 -1374.7 -1460.6 -1548.8 1.9 -1404.8 0.29896986 -1173.2 -1243.8 -1323 -1481.7 2.0 0.38943250 -1133 -1205 -1345 -1419.6 -1275.5 2.10.47874242-1097.4-1158 -1220.7 -1284.3 -1353.3 2.2 0.56252208 -1055.2 -1111.1 -1168.2 -1228.5 -1289.7 -1068.1 -1229.5 2.3 0.63803333 -1017.5 -1121 -1175.4

Table 39. Calculated HFE values from the trivalent (left) and tetravalent (right) ions' parameter space scans for the OPC3(A), OPC(B), TIP3P-FB(C), TIP4P-FB(D) water model^a. A

Tab	le 39	. (cont	'd)
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$\frac{D}{R_{\min,M}/2}$	ε _M (kcal/mol)	$C_4=0$ (kcal/mol*Å ⁴)	$C_4=125$ (kcal/mol*Å ⁴)	$C_4=250$ (kcal/mol*Å ⁴)	$C_4=375$ (kcal/mol*Å ⁴)	$C_4=500$ (kcal/mol*Å ⁴)
0.9	0.00000062	-1098.2	-1279.0	N/A	N/A	N/A
1.0	0.00001422	-1029.2	-1165.8	-1298.3	-1426.3	N/A
1.1	0.00016377	-985.8	-1093.4	-1205.9	-1323.2	-1439.6
1.2	0.00110429	-925.4	-1002.8	-1095.3	-1196.1	-1300.1
1.3	0.00490301	-880.9	-949.4	-1022.7	-1099.5	-1181.6
1.4	0.01570749	-824.0	-882.6	-942.1	-1004.5	-1070.4
1.5	0.03899838	-778.8	-827.5	-877.8	-927.5	-981.5
1.6	0.07934493	-743.8	-785.6	-828.5	-872.0	-919.3
1.7	0.13818331	-708.7	-747.1	-785.9	-824.0	-864.4
1.8	0.21312875	-678.4	-711.0	-745.1	-778.8	-814.1
1.9	0.29896986	-647.6	-679.9	-709.3	-740.9	-772.1
2.0	0.38943250	-623.2	-650.7	-681.6	-710.5	-740.7
2.1	0.47874242	-600.1	-627.1	-651.6	-679.6	-708.6
2.2	0.56252208	-576.4	-602.1	-627.5	-650.0	-676.2
2.3	0.63803333	-554.9	-576.9	-600.1	-621.5	-646.0
R _{min,M} /2 (Å)	ε _M (kcal/mol)	C ₄ =0 (kcal/mol*Å ⁴)	C ₄ =250 (kcal/mol*Å ⁴)	C ₄ =500 (kcal/mol*Å ⁴)	C ₄ =750 (kcal/mol*Å ⁴)	C ₄ =1000 (kcal/mol*Å ⁴)
0.9	0.0000062	-1771.3	-2144.3	N/A	N/A	N/A
1.0	0.00001422	-1677.1	N/A	N/A	N/A	N/A
1.1	0.00016377	-1616	-1860.6	-2111.2	-2369.3	N/A
1.2	0.00110429	-1534.3	-1722.6	-1943.8	-2176.9	-2415.5
1.3	0.00490301	-1468.1	-1628.2	-1799.1	-1984.5	-2182.4
1.4	0.01570749	-1384.3	-1515.1	-1656.9	-1811.7	-1977.1
1.5	0.03899838	-1325.9	-1433.7	-1548	-1665	-1799.5
1.6	0.07934493	-1273	-1367.9	-1467	-1580.7	-1685.6
1.7	0.13818331	-1220.2	-1304.8	-1393.8	-1488.8	-1587.2
1.8	0.21312875	-1174.2	-1250.2	-1327.1	-1410.5	-1493.6
1.9	0.29896986	-1141.8	-1209.3	-1285.9	-1358.2	-1434.7
2.0	0.38943250	-1104	-1171.2	-1234.9	-1299.8	-1374.9
2.1	0.47874242	-1068	-1126.2	-1186.6	-1249.1	-1310.7
2.2	0.56252208	-1028.5	-1081.6	-1137.3	-1195.1	-1255.8
23	0.63803333	-991.6	-1041	-1091 3	-1141 1	-11967

Table	39.	(cont'	d)
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$\frac{C}{R_{\min} M/2}$	£.,	C ₄ -0	C ₄ =125	C ₄ =250	C ₄ =375	C ₄ =500
(Å)	(kcal/mol)	$(\text{kcal/mol}^*\text{\AA}^4)$	$(\text{kcal/mol}^*\text{Å}^4)$	$(\text{kcal/mol}^*\text{Å}^4)$	$(\text{kcal/mol}^*\text{Å}^4)$	$(\text{kcal/mol}^*\text{Å}^4)$
0.9	0.0000062	N/A	-1335.5	-1492.6	N/A	N/A
1.0	0.00001422	-1069.4	-1210.8	-1350.0	-1484.2	N/A
1.1	0.00016377	-1019.6	-1135.2	-1257.9	-1382.8	-1509.0
1.2	0.00110429	-956.4	-1042.6	-1134.4	-1242.4	-1353.6
1.3	0.00490301	-908.7	-980.6	-1058.7	-1141.9	-1228.6
1.4	0.01570749	-845.9	-906.9	-970.8	-1037.2	-1107.8
1.5	0.03899838	-799.5	-850.8	-904.0	-957.6	-1014.6
1.6	0.07934493	-760.4	-805.5	-849.0	-896.8	-946.3
1.7	0.13818331	-724.8	-763.6	-803.0	-846.3	-889.0
1.8	0.21312875	-690.4	-726.4	-760.5	-797.3	-834.7
1.9	0.29896986	-660.9	-692.7	-724.4	-756.5	-790.0
2.0	0.38943250	-632.3	-662.4	-692.6	-722.6	-756.1
2.1	0.47874242	-610.2	-637.7	-664.7	-692.5	-719.4
2.2	0.56252208	-586.3	-611.6	-635.8	-661.7	-687.1
2.3	0.63803333	-563.8	-587.4	-609.4	-633.1	-656.9
R _{min,M} /2 (Å)	ε _M (kcal/mol)	C ₄ =0 (kcal/mol*Å ⁴)	C ₄ =250 (kcal/mol*Å ⁴)	C ₄ =500 (kcal/mol*Å ⁴)	C ₄ =750 (kcal/mol*Å ⁴)	C ₄ =1000 (kcal/mol*Å ⁴)
0.9	0.0000062	-1844.5	N/A	N/A	N/A	N/A
1.0	0.00001422	-1740.5	-2049.4	N/A	N/A	-2948.5
1.1	0.00016377	-1672.4	-1937.4	-2207.2	-2480.1	-2757.6
1.2	0.00110429	-1586.1	-1780.2	-2018.7	-2265	-2518.4
1.3	0.00490301	-1508.4	-1682.4	-1867.6	-2068.8	-2277.7
1.4	0.01570749	-1420.9	-1559.9	-1708.3	-1875.1	-2052.3
1.5	0.03899838	-1363.1	-1476.6	-1600.2	-1730.9	-1867.1
1.6	0.07934493	-1304.5	-1406.5	-1513.8	-1625.7	-1742.5
1.7	0.13818331	-1249.8	-1336.7	-1432.9	-1531.5	-1635.4
1.8	0.21312875	-1200.4	-1280.1	-1364.1	-1451.2	-1541.7
1.9	0.29896986	-1168.4	-1237.7	-1317.3	-1390.6	-1472.3
2.0	0.38943250	-1122.9	-1191.9	-1261.2	-1335.7	-1411.4
2.1	0.47874242	-1088.5	-1148.5	-1211.1	-1276.8	-1343.5
2.2	0.56252208	-1048.5	-1103.3	-1160.1	-1220.7	-1280.1
2.3	0.63803333	-1010	-1061	-1113.9	-1168 5	-1222.1

Table	39 .	(cont'	'd)
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$R_{\min,M}/2$	۶ _M (keal/mol)	$C_4=0$	$C_4=125$	$C_4=250$	$C_4=375$	$C_4=500$
0.9	0.00000062	-1092.1	N/A	-1429.2	N/A	N/A
1.0	0.00001422	-1025.4	-1163.3	-1297.8	N/A	-1559.5
1.1	0.00016377	-983.1	-1093.3	-1211.8	-1331.8	-1452.6
1.2	0.00110429	-922.0	-1008.2	-1098.2	-1201.8	-1309.6
1.3	0.00490301	-878.0	-949.1	-1025.1	-1105.8	-1190.1
1.4	0.01570749	-819.2	-880.0	-941.9	-1006.5	-1075.0
1.5	0.03899838	-777.6	-827.5	-879.1	-931.4	-987.8
1.6	0.07934493	-742.8	-784.9	-828.1	-874.9	-922.8
1.7	0.13818331	-708.0	-745.6	-785.3	-826.5	-868.1
1.8	0.21312875	-676.9	-710.3	-744.0	-779.9	-816.4
1.9	0.29896986	-648.2	-678.0	-709.9	-742.9	-774.6
2.0	0.38943250	-623.0	-651.2	-681.2	-708.6	-741.3
2.1	0.47874242	-599.1	-626.3	-653.0	-680.0	-708.6
2.2	0.56252208	-576.7	-601.1	-625.5	-651.5	-676.5
2.3	0.63803333	-555.7	-577.0	-600.5	-623.4	-645.9
R _{min,M} /2 (Å)	ε _M (kcal/mol)	C4=0 (kcal/mol*Å ⁴)	C ₄ =250 (kcal/mol*Å ⁴)	$C_4=500$ (kcal/mol*Å ⁴)	$C_4=750$ (kcal/mol*Å ⁴)	C ₄ =1000 (kcal/mol*Å ⁴)
0.9	0.0000062	-1762.9	N/A	-2451.3	N/A	N/A
1.0	0.00001422	-1673.1	-1971.6	-2256.9	-2548.1	N/A
1.1	0.00016377	-1611.2	-1865.4	-2125.3	-2391.9	-2666.5
1.2	0.00110429	-1529.8	-1720.5	-1951.2	-2190.9	-2439.7
1.3	0.00490301	-1463.3	-1627.2	-1807.4	-2001.6	-2204.1
1.4	0.01570749	-1380.1	-1512.3	-1661	-1820	-1992.4
1.5	0.03899838	-1324.7	-1437.2	-1557.4	-1681	-1816.8
1.6	0.07934493	-1270.8	-1369.5	-1473.7	-1584.9	-1697.7
1.7	0.13818331	-1218.8	-1305	-1397.6	-1494.3	-1595
1.8	0.21312875	-1174	-1250.5	-1331.5	-1417.2	-1506.1
1.9	0.29896986	-1140.4	-1209.9	-1288.5	-1363.9	-1443.9
2.0	0.38943250	-1103.9	-1171.1	-1237.4	-1306.2	-1381.2
2.1	0.47874242	-1065.8	-1124.5	-1187	-1249.3	-1315.9
2.2	0.56252208	-1026.3	-1081.6	-1135.7	-1197.2	-1256.5
2.3	0.63803333	-990.6	-1040.9	-1092	-1147.2	-1201.1

 $\overline{{}^{a}$ Here "N/A" means the simulation job failed. These points were not used in the curve fittings.

Table 40. Calculated IOD/CN values from the trivalent (top) and tetravalent (bottom) ions' parameter space scans for the OPC3(A), OPC(B), TIP3P-FB(C), TIP4P-FB(D) water model^a. A

D /		C4	=0	C4=	=125	C4=	250	C4=	375	C4=	500
K _{min,M} /	٤ _M	kcal/m	nol*Å4	kcal/n	nol*Å4	kcal/m	ol*Å4	kcal/n	nol*Å4	kcal/m	nol*Å4
2 (Å)	(kcal/mol)	IOD	CN	IOD	CN	IOD	CN	IOD	CN	IOD	CN
(A)		(Å)	CN	(Å)	ĊŇ	(Å)	CN	(Å)	CN	(Å)	CN
0.9	0.0000062	1.09	2.0	1.03	2.0	0.99	2.0	0.96	2.0	N/A	N/A
1.0	0.00001422	1.35	3.0	1.23	2.3	1.14	2.0	N/A	N/A	1.08	2.0
1.1	0.00016377	1.53	4.0	1.49	4.0	1.46	4.0	1.43	4.0	1.41	4.0
1.2	0.00110429	1.81	6.0	1.77	6.0	1.74	6.0	1.55	4.0	1.53	4.0
1.3	0.00490301	1.89	6.0	1.86	6.0	1.83	6.0	1.81	6.0	1.79	6.0
1.4	0.01570749	2.00	6.0	1.97	6.0	1.95	6.0	1.92	6.0	1.90	6.0
1.5	0.03899838	2.24	8.0	2.22	8.0	2.19	8.0	2.17	8.0	2.16	8.0
1.6	0.07934493	2.36	8.7	2.33	8.5	2.30	8.3	2.28	8.2	2.26	8.1
1.7	0.13818331	2.48	9.0	2.46	9.0	2.44	9.0	2.42	5.0	2.40	9.0
1.8	0.21312875	2.60	9.6	2.59	9.7	2.57	9.7	2.55	9.7	2.54	9.7
1.9	0.29896986	2.72	10.0	2.70	10.0	2.68	10.0	2.66	10.0	2.65	10.0
2.0	0.38943250	2.88	12.0	2.86	12.0	2.84	12.0	2.82	12.0	2.81	12.0
2.1	0.47874242	2.96	12.0	2.95	12.0	2.93	12.0	2.91	12.0	2.89	12.0
2.2	0.56252208	3.05	12.0	3.03	12.0	3.02	12.0	3.00	12.0	2.98	12.0
2.3	0.63803333	3.14	12.0	3.12	12.0	3.11	12.0	3.09	12.0	3.08	12.0
		<u>C1-0</u>									
D /		C4	=0	C4=	=250	C4=	500	C4=	750	C4=	1000
R _{min,M} /	ε _M	C4 kcal/m	=0 nol*Å ⁴	C4= kcal/m	=250 nol*Å ⁴	C4= kcal/m	500 101*Å ⁴	C4= kcal/m	:750 nol*Å ⁴	C4= kcal/m	1000 101*Å ⁴
$\frac{R_{\min,M}}{2}$	ε _M (kcal/mol)	C4 kcal/m IOD	=0 nol*Å ⁴	C4= kcal/m IOD	=250 nol*Å ⁴	C4= kcal/m IOD	500 101*Å ⁴	C4= kcal/m IOD	750 nol*Å ⁴	C4= kcal/m IOD	1000 nol*Å ⁴
R _{min,M} / 2 (Å)	ε _M (kcal/mol)	C4 kcal/m IOD (Å)	=0 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	=250 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	500 iol*Å ⁴ CN	C4= kcal/m IOD (Å)	750 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	1000 nol*Å ⁴ CN
R _{min,M} / 2 (Å) 0.9	ε _M (kcal/mol) 0.00000062	C4 kcal/m IOD (Å) 1.06	=0 nol*Å ⁴ CN 2.0	C4= kcal/m IOD (Å) N/A	=250 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) N/A	500 ool*Å ⁴ CN N.A	C4= kcal/m IOD (Å) N/A	750 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) N/A	1000 nol*Å ⁴ CN N/A
R _{min,M} / 2 (Å) 0.9 1.0	ε _M (kcal/mol) 0.00000062 0.00001422	C4 kcal/m IOD (Å) 1.06 1.32		C4= kcal/m IOD (Å) N/A 1.13	=250 nol*Å ⁴ CN N/A 1.8	C4= kcal/m IOD (Å) N/A 1.07	500 101*Å ⁴ CN N.A 2.0	C4= kcal/m IOD (Å) N/A N/A	750 nol*Å ⁴ CN N/A N/A	C4= kcal/m IOD (Å) N/A N/A	1000 nol*Å ⁴ CN N/A N/A
R _{min,M} / 2 (Å) 0.9 1.0 1.1	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377	C4 kcal/m IOD (Å) 1.06 1.32 1.48	$ \frac{=0}{\text{nol*}Å^{4}} $ CN 2.0 3.0 4.0	C4= kcal/m IOD (Å) N/A 1.13 1.43	-250 nol*Å ⁴ CN N/A 1.8 4.0	C4= kcal/m IOD (Å) N/A 1.07 1.38	500 nol*Å ⁴ CN N.A 2.0 4.0	C4= kcal/m IOD (Å) N/A N/A 1.35	750 nol*Å ⁴ CN N/A N/A 4.0	C4= kcal/m IOD (Å) N/A N/A 1.32	1000 nol*Å ⁴ CN N/A N/A 4.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377 0.00110429	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50	500 101*Å ⁴ CN N.A 2.0 4.0 4.0	C4= kcal/m IOD (Å) N/A N/A 1.35 1.47	750 nol*Å ⁴ CN N/A N/A 4.0 4.0	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75	500 101*Å ⁴ CN N.A 2.0 4.0 4.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86		C4= kcal/n IOD (Å) N/A N/A 1.35 1.47 1.72 1.82	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.1	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5	$\begin{array}{c} \epsilon_{M} \\ (kcal/mol) \end{array}$	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18	$ =0 \\ =0 \\ = 0 \\ =$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0 8.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08	750 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.1 8.0	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06	1000 nol*Å ⁴ CN N/A 4.0 4.0 6.0 6.0 8.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6	$\begin{array}{c} \epsilon_{M} \\ (kcal/mol) \end{array}$	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30	$ =0 \\ =0 \\ = 0 \\ =$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25	-250 hol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0 6.0 8.0 7.1	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18	$ \frac{1750}{\text{nol}*\text{Å}^4} \\ \hline $	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 8.0
$\begin{array}{c} R_{\rm min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ \end{array}$	$\begin{array}{c} \epsilon_{M} \\ (kcal/mol) \end{array}$	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41	$=0 \\ nol*Å^{4} \\ \hline CN \\ 2.0 \\ 3.0 \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.9 \\ 9.1 \\ \hline$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0 6.0 8.0 7.1 9.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.1 8.0 8.0 9.0	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0 8.0 9.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	$\begin{array}{c} \epsilon_{M} \\ (kcal/mol) \end{array}$	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41 2.54	$=0 \\ nol*Å^{4} \\ \hline CN \\ 2.0 \\ 3.0 \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.9 \\ 9.1 \\ 10.0 \\ \hline$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51	-250 hol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0 6.0 8.0 7.1 9.0 10.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34 2.48		C4= <u>kcal/n</u> IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32 2.46	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.1 8.0 8.0 9.0 10.0	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29 2.44	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0 9.0 10.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41 2.54 2.71	$=0 \\ nol*Å^{4} \\ \hline CN \\ \hline 2.0 \\ 3.0 \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.9 \\ 9.1 \\ 10.0 \\ 12.0 \\ \hline$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68	-250 nol*Å ⁴ CN N/A 1.8 4.0 6.0 6.0 6.0 6.0 6.0 8.0 7.1 9.0 10.0 12.0	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34 2.48 2.65		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32 2.46 2.63	$\begin{array}{c} 750 \\ \hline nol*Å^4 \\ \hline CN \\ \hline N/A \\ N/A \\ 4.0 \\ 4.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.0 \\ 9.0 \\ 10.0 \\ 12.0 \\ \end{array}$	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29 2.44 2.60	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ \end{array}$	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41 2.54 2.71 2.78	=0 nol*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 10.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75	$\begin{array}{c} -250 \\ nol^* {\rm \AA}^4 \\ \hline {\rm CN} \\ \hline {\rm N/A} \\ 1.8 \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.0 \\ 6.0 \\ 6.0 \\ 8.0 \\ 7.1 \\ 9.0 \\ 10.0 \\ 12.0 \\ 12.0 \\ 12.0 \end{array}$	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32 2.46 2.63 2.70	$\begin{array}{c} 750 \\ \hline nol*Å^4 \\ \hline CN \\ \hline N/A \\ N/A \\ 4.0 \\ 4.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.0 \\ 9.0 \\ 10.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ \end{array}$	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29 2.44 2.60 2.68	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ \end{array}$	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41 2.54 2.71 2.78 2.86	=0 nol*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 10.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75 2.84	$\begin{array}{r} -250 \\ nol^* \mathring{A}^4 \\ \hline \\ $	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73 2.81		C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32 2.46 2.63 2.70 2.79	$\begin{array}{c} 750 \\ \hline nol*Å^4 \\ \hline CN \\ \hline N/A \\ N/A \\ 4.0 \\ 4.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.0 \\ 9.0 \\ 10.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \end{array}$	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29 2.44 2.60 2.68 2.77	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0
$\begin{array}{c} R_{\rm min,M} / \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ \end{array}$	ϵ_{M} (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 1.99 2.18 2.30 2.41 2.54 2.71 2.78 2.86 2.95	=0 nol*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75 2.84 2.92	$\begin{array}{c} -250 \\ nol^* \mathring{A}^4 \\ \hline \\ $	C4= kcal/m IOD (Å) N/A 1.07 1.38 1.50 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73 2.81 2.90		C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.82 2.08 2.18 2.32 2.46 2.63 2.70 2.79 2.87	$\begin{array}{c} 750 \\ \hline nol*Å^4 \\ \hline CN \\ \hline N/A \\ N/A \\ 4.0 \\ 4.0 \\ 4.0 \\ 6.0 \\ 6.1 \\ 8.0 \\ 8.0 \\ 9.0 \\ 10.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ 12.0 \end{array}$	C4= kcal/m IOD (Å) N/A N/A 1.32 1.44 1.69 1.81 2.06 2.16 2.29 2.44 2.60 2.68 2.77 2.85	1000 nol*Å ⁴ CN N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0

Table 40. (cont'd)
В

		C4	=0	C4=	125	C4=	=250	C4=	375	C4=	=500
$R_{min,M}$	٤ _M	kcal/m	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/n	nol*Å4
2	(kcal/mol)	IOD	CN	IOD	CN	IOD	CN	IOD	CN	IOD	CN
(A)		(Å)	CN	(Å)	ĊŇ	(Å)	ĊŇ	(Å)	ĊŇ	(Å)	CN
0.9	0.0000062	1.12	2.0	1.06	2.0	N/A	N/A	N/A	N/A	N/A	N/A
1.0	0.00001422	1.38	3.0	1.21	1.9	1.16	2.0	1.12	2.0	N/A	N/A
1.1	0.00016377	1.56	4.0	1.52	4.0	1.49	4.0	1.46	4.0	1.44	4.0
1.2	0.00110429	1.84	6.0	1.81	6.0	1.61	4.0	1.58	4.0	1.55	4.0
1.3	0.00490301	1.92	6.0	1.89	6.0	1.87	6.0	1.85	6.0	1.82	6.0
1.4	0.01570749	2.03	6.0	2.00	6.0	1.98	6.0	1.96	6.0	1.94	6.0
1.5	0.03899838	2.27	8.0	2.25	8.0	2.22	7.9	2.20	7.9	2.18	7.8
1.6	0.07934493	2.39	8.6	2.36	8.4	2.34	8.1	2.32	8.1	2.30	8.0
1.7	0.13818331	2.52	9.0	2.49	9.0	2.47	9.0	2.46	9.0	2.44	5.4
1.8	0.21312875	2.64	9.7	2.62	9.7	2.61	9.8	2.59	9.8	2.57	9.8
1.9	0.29896986	2.75	10.0	2.73	10.1	2.72	10.1	2.72	10.7	2.74	11.4
2.0	0.38943250	2.91	12.0	2.89	12.0	2.88	12.0	2.86	12.0	2.84	12.0
2.1	0.47874242	3.00	12.0	2.98	12.0	2.96	12.0	2.95	12.0	2.93	12.0
2.2	0.56252208	3.08	12.0	3.07	12.0	3.05	12.0	3.03	12.0	3.02	12.0
2.3	0.63803333	3.17	12.0	3.15	12.0	3.14	12.0	3.12	12.0	3.11	12.0
D /		C4	=0	C4=	250	C4=	=500	C4=	:750	C4=	1000
$\frac{R_{\min,M}}{2}$	ε _M	C4 kcal/m	=0 nol*Å ⁴	C4= kcal/m	250 101*Å ⁴	C4= kcal/m	=500 101*Å ⁴	C4= kcal/m	:750 101*Å4	C4= kcal/n	1000 101*Å ⁴
$\frac{R_{\min,M}}{2}$	ε _M (kcal/mol)	C4 kcal/m IOD	=0 no1*Å ⁴	C4= kcal/m IOD	250 101*Å ⁴	C4= kcal/m IOD	=500 nol*Å ⁴	C4= kcal/m IOD	750 101*Å ⁴	C4= kcal/m IOD	1000 101*Å ⁴
R _{min,M} / 2 (Å)	ε _M (kcal/mol)	C4 kcal/m IOD (Å)	=0 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	250 101*Å ⁴ CN	C4= kcal/m IOD (Å)	=500 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	750 101*Å ⁴ CN	C4= kcal/m IOD (Å)	1000 101*Å ⁴ CN
R _{min,M} / 2 (Å) 0.9	ε _M (kcal/mol)	C4 kcal/m IOD (Å) 1.09	$ =0 \\ =0^{-1} \dot{A}^{4} \\ CN \\ =2.0^{-1} $	C4= kcal/m IOD (Å) 1.01	$\frac{250}{\text{cN}}$	C4= kcal/m IOD (Å) N/A	=500 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) N/A	750 nol*Å ⁴ CN N/A	C4= kcal/n IOD (Å) N/A	1000 nol*Å ⁴ CN N/A
$\begin{array}{c} R_{min,M} \\ 2 \\ (\mathring{A}) \\ \hline 0.9 \\ 1.0 \end{array}$	ε _M (kcal/mol) 0.00000062 0.00001422	C4 kcal/m IOD (Å) 1.09 1.35	=0 =0 =0 = CN 2.0 3.0 = =	C4= kcal/m IOD (Å) 1.01 N/A	250 nol*Å ⁴ CN 2.0 N/A	C4= kcal/m IOD (Å) N/A N/A	=500 nol*Å ⁴ CN N/A N/A	C4= kcal/m IOD (Å) N/A N/A	750 nol*Å ⁴ CN N/A N/A	C4= kcal/n IOD (Å) N/A N/A	1000 nol*Å ⁴ CN N/A N/A
$\frac{\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377	C4 kcal/m IOD (Å) 1.09 1.35 1.52	$ =0 \\ =0 \\ = 0 \\ =$	C4= kcal/m IOD (Å) 1.01 N/A 1.46	$ \frac{250}{\text{nol*}Å^4} \\ $	C4= kcal/m IOD (Å) N/A N/A 1.42	500 nol*Å ⁴ CN N/A N/A 4.0	C4= kcal/m IOD (Å) N/A N/A 1.38	750 nol*Å ⁴ CN N/A N/A 4.0	C4= kcal/m IOD (Å) N/A N/A N/A	1000 nol*Å ⁴ CN N/A N/A N/A
$\frac{\begin{array}{c} R_{min,M} \\ 2 \\ (\mathring{A}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377 0.00110429	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79	$ =0 \\ =0 \\ = 10^{-10} \\ $	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74	250 nol*Å ⁴ CN 2.0 N/A 4.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53	500 nol*Å ⁴ CN N/A N/A 4.0 4.0	C4= kcal/m IOD (Å) N/A N/A 1.38 1.49	750 nol*Å ⁴ CN N/A N/A 4.0 4.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47	1000 nol*Å ⁴ CN N/A N/A N/A 4.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87	$ =0 \\ =0 \\ = \frac{100 + \text{Å}^4}{\text{CN}} \\ = \frac{100 + \text{Å}^4}{2.0} \\ = \frac{100 + \text{Å}^4}{3.0} \\ = \frac{100 + \text{Å}^4}{4.0} \\ = \frac{100 + \text{Å}^4}{6.0} \\ = \frac{100 + \text{Å}^4}{6.0} \\ = \frac{100 + \text{Å}^4}$	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82	250 nol*Å ⁴ CN 2.0 N/A 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ \end{array}$	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301 0.01570749	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97	$ =0 \\ =0 \\ = 10^{-10^{-10^{-10^{-10^{-10^{-10^{-10^{-$	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93	$ \frac{1250}{\text{nol}*\text{Å}^4} \\ \hline CN \\ 2.0 \\ N/A \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.0 \\ 6.0 $	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22	$ =0 \\ $	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18	$ \frac{1250}{\text{nol}*\text{Å}^4} \\ \hline $	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90 2.15	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0	C4= kcal/m IOD (Å) N/A N/A 1.38 1.49 1.76 1.86 2.12	750 nol*Å ⁴ <u>CN</u> <u>N/A</u> 4.0 4.0 6.0 6.0 8.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0 8.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32	$ =0 \\ $	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28	$ \frac{1250}{\text{nol}*\text{Å}^4} \\ \hline $	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90 2.15 2.25	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 8.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22	750 nol*Å ⁴ CN N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0 6.0 8.0 8.0 8.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44	$ =0 \\ $	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41	$ \frac{1250}{\text{nol}*\text{Å}^4} \frac{\text{CN}}{2.0} \text{N/A} 4.0 6.0 6.0 6.0 8.0 8.1 9.0 $	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0 9.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0 9.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0 8.0 8.0 8.0 9.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ \end{array}$	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67	$ =0 \\ =0 \\ = 10^{-10} \\ $	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55	$ \frac{1250}{\text{nol}*\text{Å}^4} \frac{\text{CN}}{2.0} \text{N/A} 4.0 6.0 6.0 6.0 8.0 8.1 9.0 10.0 $	C4= kcal/m IOD (Å) N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 8.0 8.0 9.0 10.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50		C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0 6.0 8.0 8.0 9.0 10.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67 2.74	$ =0 \\ =0 \\ =0 \\ = 10^{-10} \\ = 10^{$	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55 2.72	$ \frac{1250}{\text{nol}*\text{Å}^4} \frac{\text{CN}}{2.0} \frac{1}{\text{N/A}} 4.0 6.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 $	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52 2.69	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50 2.67	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47 2.64	1000 nol*Å ⁴ CN N/A N/A N/A 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67 2.74 2.82	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.5 9.0 12.	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55 2.72 2.79	$\begin{array}{r} 250 \\ \hline \text{nol}*\text{Å}^4 \\ \hline \text{CN} \\ \hline 2.0 \\ \hline \text{N/A} \\ 4.0 \\ 6.0 \\ 6.0 \\ 6.0 \\ 8.0 \\ 8.1 \\ 9.0 \\ 10.0 \\ 12.0 \\ 12.0 \\ 12.0 \\ \end{array}$	C4= kcal/m IOD (Å) N/A N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52 2.69 2.77	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50 2.67 2.74	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 8.0 9.0 10.0 12.0 12.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47 2.64 2.72	1000 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 8.0 8.0 8.0 9.0 10.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67 2.74 2.82 2.90	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.5 9.0 12.	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55 2.72 2.79 2.87	250 nol*Å ⁴ CN 2.0 N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52 2.69 2.77 2.85	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50 2.67 2.74 2.82	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47 2.64 2.72 2.80	1000 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67 2.74 2.82 2.90 2.98	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.5 9.0 12.	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55 2.72 2.79 2.87 2.96	250 nol*Å ⁴ CN 2.0 N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52 2.69 2.77 2.85 2.93	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50 2.67 2.74 2.82 2.91	750 nol*Å ⁴ CN N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47 2.64 2.72 2.80 2.89	1000 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ 2.3 \\ \end{array}$	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208 0.63803333	C4 kcal/m IOD (Å) 1.09 1.35 1.52 1.79 1.87 1.97 2.22 2.32 2.44 2.67 2.74 2.67 2.74 2.82 2.90 2.98 3.07	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 6.0 8.0 8.5 9.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12	C4= kcal/m IOD (Å) 1.01 N/A 1.46 1.74 1.82 1.93 2.18 2.28 2.41 2.55 2.72 2.79 2.87 2.96 3.05	250 nol*Å ⁴ CN 2.0 N/A 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 12.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.42 1.53 1.79 1.90 2.15 2.25 2.38 2.52 2.69 2.77 2.85 2.93 3.03	500 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.2	C4= kcal/m IOD (Å) N/A 1.38 1.49 1.76 1.86 2.12 2.22 2.35 2.50 2.67 2.74 2.82 2.91 3.01	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.3	C4= kcal/n IOD (Å) N/A N/A N/A 1.47 1.73 1.84 2.10 2.19 2.33 2.47 2.64 2.72 2.80 2.89 3.02	1000 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 8.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0 12.0 13.1

Table 40.	(cont'd)
С	

		C4	=0	C4=	=125	C4=	250	C4=	375	C4=	500
R _{min,M} /	ε _M	kcal/m	nol*Å ⁴	kcal/n	nol*Å ⁴	kcal/n	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/n	nol*Å ⁴
$\begin{pmatrix} 2\\ \end{pmatrix}$	(kcal/mol)	IOD	CN	IOD	CN	IOD	CN	IOD	CN	IOD	CN
(A)		(Å)	CN	(Å)	CN	(Å)	CN	(Å)	CN	(Å)	CN
0.9	0.00000062	N/A	N/A	1.03	2.0	0.99	2.0	N/A	N/A	N/A	N/A
1.0	0.00001422	1.36	3.0	1.24	0.9	1.14	2.0	1.10	2.0	N/A	N/A
1.1	0.00016377	1.53	4.0	1.49	4.0	1.46	4.0	1.43	4.0	1.40	4.0
1.2	0.00110429	1.81	6.0	1.77	6.0	1.74	6.0	1.55	4.0	1.53	4.0
1.3	0.00490301	1.89	6.0	1.86	6.0	1.83	6.0	1.81	6.0	1.79	6.0
1.4	0.01570749	2.00	6.0	1.97	6.0	1.95	6.0	1.92	6.0	1.90	6.0
1.5	0.03899838	2.24	8.0	2.22	8.0	2.19	8.0	2.17	8.0	2.15	8.0
1.6	0.07934493	2.36	8.8	2.33	8.7	2.31	8.5	2.28	8.3	2.26	8.2
1.7	0.13818331	2.48	9.0	2.46	9.0	2.44	9.0	2.42	9.0	2.40	9.0
1.8	0.21312875	2.61	9.7	2.59	9.8	2.57	9.8	2.56	9.8	2.54	9.9
1.9	0.29896986	2.72	10.0	2.70	10.0	2.68	10.0	2.66	10.0	2.65	10.0
2.0	0.38943250	2.88	11.9	2.86	12.0	2.84	12.0	2.82	12.0	2.80	12.0
2.1	0.47874242	2.96	12.0	2.94	12.0	2.93	12.0	2.91	12.0	2.89	12.0
2.2	0.56252208	3.05	12.0	3.03	12.0	3.02	12.0	3.00	12.0	2.98	12.0
2.3	0.63803333	3.14	12.0	3.12	12.0	3.11	12.0	3.09	12.0	3.07	12.0
						~ .	=	C 1	750	C 4	1000
Rmin M/		C4	=0	C4=	250	C4=	:500	C4=	:/50	C4=	1000
$\frac{R_{\min,M}}{2}$	ε _M	C4 kcal/m	=0 101*Å ⁴	C4= kcal/m	=250 nol*Å ⁴	C4= kcal/m	=500 101*Å ⁴	C4= kcal/m	⊧/50 nol*Å⁴	C4= kcal/m	1000 101*Å ⁴
$\frac{R_{\min,M}}{2}$ (Å)	ε _M (kcal/mol)	C4 kcal/m IOD	=0 nol*Å ⁴ CN	C4= kcal/m IOD	=250 nol*Å ⁴ CN	C4= kcal/m IOD	-500 nol*Å ⁴ CN	Kcal/m IOD	i / 50 nol*Å ⁴ CN	$\frac{c4=}{c4}$ $\frac{c4=}{c4}$ $\frac{c4=}{c4}$	1000 101*Å ⁴ CN
R _{min,M} / 2 (Å)	ε _M (kcal/mol)	C4 kcal/m IOD (Å)	=0 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	250 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	500 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	r/50 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	1000 nol*Å ⁴ CN
R _{min,M} / 2 (Å) 0.9	ε _M (kcal/mol)	C4 kcal/m IOD (Å) 1.06	$ \begin{array}{r} =0 \\ nol * Å^4 \\ \hline \\ CN \\ \hline \\ 2.0 \\ \hline \\ 2.0 \\ \hline \end{array} $	C4= kcal/m IOD (Å) N/A	250 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) N/A	500 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) N/A	$\frac{1}{100} \frac{1}{100} \frac{1}$	$C4= \frac{\text{kcal/m}}{\text{IOD}}$ (Å) N/A	1000 nol*Å ⁴ CN N/A
R _{min,M} / 2 (Å) 0.9 1.0	ε _M (kcal/mol)	C4 kcal/m IOD (Å) 1.06 1.32	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13	250 nol*Å ⁴ CN N/A 2.0	C4= kcal/m IOD (Å) N/A N/A	500 nol*Å ⁴ CN N/A N/A	C4= kcal/m IOD (Å) N/A N/A	r/S0 nol*Å ⁴ CN N/A N/A	$C4= \frac{\text{kcal/m}}{\text{IOD}}$ (Å) N/A 1.00	1000 nol*Å ⁴ CN N/A 2.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377	C4 kcal/m IOD (Å) 1.06 1.32 1.48	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43	250 nol*Å ⁴ CN N/A 2.0 4.0	C4= kcal/m IOD (Å) N/A N/A 1.38	500 nol*Å ⁴ CN N/A N/A 4.0	C4= kcal/m IOD (Å) N/A N/A 1.35	750 nol*Å ⁴ CN N/A N/A 4.0	C4= kcal/m IOD (Å) N/A 1.00 1.32	1000 nol*Å ⁴ CN N/A 2.0 4.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75	$ =0 \\ =0 \\ = \frac{100 + \text{Å}^4}{\text{CN}} \\ = \frac{100 + \text{Å}^4}{2.0} \\ = \frac{100 + \text{Å}^4}{3.0} \\ = \frac{100 + \text{Å}^4}{4.0} \\ = \frac{100 + \text{Å}^4}{6.0} \\ = \frac{100 + \text{Å}^4}{100 + \text{Å}^4} \\ = 100 + \text{$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71	$ \frac{1250}{\text{nol}*\text{Å}^{4}} \\ \frac{\text{CN}}{\text{N/A}} \\ 2.0 \\ 4.0 \\ 6.0 \\ 10^{2} $	C4= kcal/m IOD (Å) N/A N/A 1.38 1.66	500 nol*Å ⁴ CN N/A N/A 4.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.35 1.47	 750 nol*Å⁴ CN N/A N/A 4.0 4.0 4.0 	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44	1000 nol*Å ⁴ CN N/A 2.0 4.0 4.0
Rmin,M/ 2 (Å) 0.9 1.0 1.1 1.2 1.3	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.38 1.66 1.75	500 nol*Å ⁴ <u>CN</u> <u>N/A</u> 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72	750 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69	1000 nol*Å ⁴ CN N/A 2.0 4.0 4.0 6.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301 0.01570749	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00	$ =0 \\ =0 \\ = 10^{-10} \\ $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.38 1.66 1.75 1.86	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0	C4= kcal/m IOD (Å) N/A N/A 1.35 1.47 1.72 1.83	 750 nol*Å⁴ CN N/A N/A 4.0 4.0 6.0 6.0 6.0 	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80	N/A 2.0 4.0 4.0 6.0 6.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18	$ =0 \\ $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14	$ \frac{1250}{\text{nol}*\text{Å}^4} \frac{\text{CN}}{\text{N/A}} \frac{1}{2.0} 4.0 6.0 6.0 6.0 8.0 8.0 7 7 $	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11	500 nol*Å ⁴ <u>CN</u> <u>N/A</u> 4.0 6.0 6.0 6.0 8.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08	Implexity Implexity <t< td=""><td>C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06</td><td></td></t<>	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06	
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25	$ \frac{1250}{\text{nol}*\text{Å}^4} \frac{\text{CN}}{\text{N/A}} \frac{1}{2.0} 4.0 6.0 6.0 6.0 6.0 8.0 8.6 8.6 6.0 6$	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21	500 nol*Å ⁴ CN N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.2	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18	F/50 nol*Å ⁴ CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.1 6.0	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15	N/A N/A 4.0 4.0 6.0 8.0 8.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41	$ =0 \\ =0 \\ = 10 \\ $	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 8.0 8.6 9.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 8.0 8.2 9.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32	Image: 750 nol*Å4 CN N/A N/A 4.0 6.0 6.0 8.0 8.1 9.0	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15 2.29	Iooo nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 8.0 9.0
Rmin,M/ 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63	$ =0 \\ =0 \\ =0 \\ = 10^{-10} \\ = 10^{$	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.6 9.0 10.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.2 9.0 10.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46	Image: 750 mol*Å4 CN N/A N/A 4.0 4.0 6.0 6.0 8.0 8.1 9.0 10.0	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15 2.29 2.43	Iouo nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0
Rmin,M/ 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63 2.70	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 12.0 12.	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.6 9.0 10.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48 2.65	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.2 9.0 10.0 12.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46 2.62	Image: 750 nol*Å4 CN N/A N/A 4.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15 2.29 2.43 2.60	N/A N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0
R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6 1.7 1.8 1.9 2.0	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63 2.70 2.78	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 12.0 12.	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.6 9.0 10.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.2 9.0 10.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46 2.62 2.70	Image: 750 nol*Å4 CN N/A N/A 4.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 12.3	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15 2.29 2.43 2.60 2.68	N/A N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63 2.70 2.78 2.86	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 12.0 12.	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75 2.84	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.6 9.0 10.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73 2.81	500 nol*Å ⁴ CN N/A N/A 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.2 9.0 10.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46 2.62 2.70 2.79	K K <thk< th=""> K K K</thk<>	C4= kcal/m IOD (Å) N/A 1.00 1.32 1.44 1.69 1.80 2.06 2.15 2.29 2.43 2.60 2.68 2.76	N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63 2.70 2.78 2.86 2.95	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.1 8.0 8.9 9.1 12.0 12.	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75 2.84 2.92	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.6 9.0 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73 2.81 2.90	500 nol*Å ⁴ CN N/A 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.2 9.0 10.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46 2.62 2.70 2.79 2.87	K K <thk< th=""> K K K</thk<>	$\begin{array}{c} \text{C4}=\\ \text{kcal/m}\\ \text{IOD}\\ \text{(Å)}\\ \text{N/A}\\ 1.00\\ 1.32\\ 1.44\\ 1.69\\ 1.80\\ 2.06\\ 2.15\\ 2.29\\ 2.43\\ 2.60\\ 2.68\\ 2.76\\ 2.85\\ \end{array}$	I000 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0
$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ 2.3 \\ \hline \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208 0.63803333	C4 kcal/m IOD (Å) 1.06 1.32 1.48 1.75 1.83 2.00 2.18 2.30 2.41 2.63 2.70 2.78 2.86 2.95 3.04	$=0$ $to 1*Å^4$ CN 2.0 3.0 4.0 6.0 6.1 8.0 8.9 9.1 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.0 12.1	C4= kcal/m IOD (Å) N/A 1.13 1.43 1.71 1.79 1.90 2.14 2.25 2.37 2.51 2.68 2.75 2.84 2.92 3.01	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.0 8.6 9.0 10.0 12.0 12.0 12.0 12.0 12.1	C4= kcal/m IOD (Å) N/A 1.38 1.66 1.75 1.86 2.11 2.21 2.34 2.48 2.65 2.73 2.81 2.90 3.00	500 nol*Å ⁴ CN N/A 4.0 6.0 6.0 6.0 6.0 8.0 8.0 8.2 9.0 10.0 12.0 12.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.35 1.47 1.72 1.83 2.08 2.18 2.32 2.46 2.62 2.70 2.79 2.87 2.97	Image: 750 nol*Å4 CN N/A N/A 4.0 6.0 6.0 8.0 8.1 9.0 10.0 12.0 12.0 12.0 12.0 12.3	$\begin{array}{c} \text{C4}=\\ \text{kcal/m}\\ \text{IOD}\\ \text{(Å)}\\ \text{N/A}\\ 1.00\\ 1.32\\ 1.44\\ 1.69\\ 1.80\\ 2.06\\ 2.15\\ 2.29\\ 2.43\\ 2.60\\ 2.68\\ 2.76\\ 2.85\\ 2.98\\ \end{array}$	N/A 2.0 4.0 4.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0 12.0 13.1

Table 40.	(cont'd)
D	

$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$			C4	=0	C4=	=125	C4=	250	C4=	375	C4=	=500
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	R _{min,M} /	ε _M	kcal/m	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/m	nol*Å ⁴	kcal/n	nol*Å ⁴	kcal/n	nol*Å ⁴
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	$\begin{pmatrix} 2\\ (\dot{\lambda}) \end{pmatrix}$	(kcal/mol)	IOD	CN	IOD	CN	IOD	CN	IOD	CN	IOD	CN
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	(A)		(Å)	CN	(Å)	CN	(Å)	CN	(Å)	CN	(Å)	CN
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	0.9	0.00000062	1.11	2.0	N/A	N/A	1.00	2.0	N/A	N/A	N/A	N/A
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.0	0.00001422	1.37	3.0	1.22	1.5	1.15	2.0	N/A	N/A	1.09	2.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.1	0.00016377	1.54	4.0	1.50	4.0	1.47	4.0	1.44	4.0	1.42	4.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.2	0.00110429	1.82	6.0	1.79	6.0	1.76	6.0	1.56	4.0	1.54	4.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.3	0.00490301	1.91	6.0	1.88	6.0	1.85	6.0	1.82	6.0	1.80	6.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.4	0.01570749	2.02	6.0	1.99	6.0	1.96	6.0	1.94	6.0	1.92	6.0
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.5	0.03899838	2.26	8.0	2.23	8.0	2.21	8.0	2.19	8.0	2.17	8.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.6	0.07934493	2.38	8.9	2.35	8.9	2.33	8.6	2.30	8.5	2.28	8.2
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.7	0.13818331	2.50	9.0	2.48	9.0	2.46	9.0	2.44	9.0	2.42	9.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.8	0.21312875	2.63	9.8	2.61	9.9	2.59	9.9	2.58	9.9	2.56	9.9
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1.9	0.29896986	2.76	10.8	2.74	10.9	2.72	10.9	2.69	10.3	2.66	10.1
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	2.0	0.38943250	2.89	12.0	2.88	12.0	2.86	12.0	2.84	12.0	2.82	12.0
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	2.1	0.47874242	2.98	12.0	2.96	12.0	2.94	12.0	2.93	12.0	2.91	12.0
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	2.2	0.56252208	3.07	12.0	3.05	12.0	3.03	12.0	3.01	12.0	3.00	12.0
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	2.3	0.63803333	3.15	12.0	3.14	12.0	3.12	12.0	3.11	12.0	3.09	12.0
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$			~ .	~	~ .	250	C 4	E 00	01	750	C 1	1000
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\mathbf{R} \cdot \mathbf{v}$		C4	=0	C4=	:250	C4=	500	C4=	=/50	C4=	1000
$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	$\frac{R_{\min,M}}{2}$	ε _M	C4 kcal/m	=0 101*Å ⁴	C4= kcal/m	=250 nol*Å ⁴	C4= kcal/m	500 101*Å⁴	kcal/n	=750 nol*Å⁴	C4= kcal/n	1000 101*Å ⁴
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$\frac{R_{\min,M}}{2}$	ε _M (kcal/mol)	C4 <u>kcal/m</u> IOD	=0 nol*Å ⁴ CN	C4= kcal/m IOD	250 nol*Å ⁴	C4= kcal/m IOD	-500 nol*Å ⁴ CN	kcal/m IOD	=750 nol*Å ⁴	$\frac{\text{c4}=}{\text{kcal/m}}$	1000 nol*Å ⁴
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å)	ε _M (kcal/mol)	C4 kcal/m IOD (Å)	=0 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	250 nol*Å ⁴ CN	C4= kcal/m IOD (Å)	500 nol*Å ⁴ CN	L4= kcal/m IOD (Å)	nol*Å ⁴	C4= kcal/n IOD (Å)	nol*Å ⁴
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9	ε _M (kcal/mol)	C4 kcal/m IOD (Å) 1.08	=0 no1*Å ⁴ CN 2.0	C4= kcal/m IOD (Å) N/A	250 nol*Å ⁴ CN N/A	C4= kcal/m IOD (Å) 0.94	$\frac{500}{\text{nol*}Å^4}$ CN 2.0	IOD (Å) N/A	$\frac{1}{100} \frac{1}{100} \frac{1}$	$\begin{array}{c} C4=\\ kcal/n\\ IOD\\ (Å)\\ N/A\\ \end{array}$	1000 nol*Å ⁴ CN N/A
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0	ε _M (kcal/mol) 0.00000062 0.00001422	C4 kcal/m IOD (Å) 1.08 1.34	$ =0 \\ =0 \\ =0 \\ = 0 \\ = CN \\ = 2.0 \\ = 3.0 \\ = 0 \\ $	C4= kcal/m IOD (Å) N/A 1.14	250 nol*Å ⁴ CN N/A 2.0	C4= kcal/m IOD (Å) 0.94 1.08	$\frac{100^{+}\text{Å}^{4}}{\text{CN}}$	C4= kcal/m IOD (Å) N/A 1.04	r/S0 nol*Å ⁴ CN N/A 2.0	C4= kcal/n IOD (Å) N/A N/A	I000 nol*Å ⁴ CN N/A N/A
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0 1.1	ε _M (kcal/mol) 0.00000062 0.00001422 0.00016377	C4 kcal/m IOD (Å) 1.08 1.34 1.50	=0 =0 =0 = 2.0 = 3.0 = 4.0	C4= kcal/m IOD (Å) N/A 1.14 1.44	2250 nol*Å ⁴ CN N/A 2.0 4.0	C4= kcal/m IOD (Å) 0.94 1.08 1.40	1000000000000000000000000000000000000	C4= kcal/m IOD (Å) N/A 1.04 1.36	-/50 nol*Å ⁴ CN N/A 2.0 4.0	C4= kcal/n IOD (Å) N/A N/A 1.33	1000 nol*Å ⁴ CN N/A N/A 4.0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429	C4 kcal/m IOD (Å) 1.08 1.34 1.50 1.77	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51	1000000000000000000000000000000000000	kcal/n IOD (Å) N/A 1.04 1.36 1.48	 750 nol*Å⁴ CN N/A 2.0 4.0 4.0 	C4= kcal/n IOD (Å) N/A N/A 1.33 1.45	1000 nol*Å ⁴ CN N/A N/A 4.0 4.0
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Rmin,M/ 2 (Å) 0.9 1.0 1.1 1.2 1.3	$\frac{\epsilon_{M}}{(kcal/mol)}$ 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301	C4 kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73	Image: 750 nol*Å ⁴ CN N/A 2.0 4.0 6.0	C4= kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71	N/A N/A N/A 4.0 6.0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749	C4 kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01	$ =0 \\ =0 \\ =0 \\ = $	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91	$ \frac{1250}{\text{nol}*\text{Å}^4} \\ \hline $	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85	Image: 750 nol*Å4 CN N/A 2.0 4.0 6.0 6.0	C4= kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82	N/A N/A N/A 4.0 4.0 6.0 6.0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838	C4 kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20	$ =0 \\ =0 \\ =0 \\ = 1 \\ = 2.0 \\ = 3.0 \\ = 4.0 \\ = 6.0 \\ $	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 8.0	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88 2.13		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10	N/A 2.0 4.0 4.0 6.0 8.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07	N/A N/A N/A 4.0 6.0 6.0 8.0
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	R _{min,M} / 2 (Å) 0.9 1.0 1.1 1.2 1.3 1.4 1.5 1.6	ε _M (kcal/mol) 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493	Kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31	$ =0 \\ =0 \\ = 10^{-10^{-10^{-10^{-10^{-10^{-10^{-10^{-$	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.4	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88 2.13 2.23		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20	Image: 750 nol*Å4 CN N/A 2.0 4.0 6.0 6.0 8.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17	N/A N/A N/A 4.0 6.0 6.0 8.0
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	$\begin{array}{c} R_{min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43	$ =0 \\ =0 \\ =0 \\ = 1 \\ = 1 \\ = 2.0 \\ = 3.0 \\ = 4.0 \\ = 4.0 \\ = 6.0 \\ = 6.0 \\ = 6.0 \\ = 6.0 \\ = 8.0 \\ = 8.0 \\ = 8.8 \\ = 9.2 $	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 8.0 8.4 9.0	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88 2.13 2.23 2.36		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33	Image: 750 nol*Å4 CN N/A 2.0 4.0 6.0 6.0 8.0 9.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31	N/A N/A N/A 4.0 6.0 6.0 8.0 9.0
2.0 0.38943250 2.80 12.0 2.77 12.0 2.74 12.0 2.72 12.0 2.70 12 2.1 0.47874242 2.88 12.0 2.85 12.0 2.83 12.0 2.80 12.0 2.78 12 2.2 0.56252208 2.96 12.0 2.94 12.0 2.91 12.0 2.89 12.0 2.87 12 2.3 0.63803333 3.07 12.6 3.05 9.2 3.02 12.6 3.00 12.7 2.98 12	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ $\frac{0.00000062}{0.0001422}$ 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88 2.13 2.23 2.36 2.58		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48	Image: 750 nol*Å4 CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0	kcal/n IOD (Å) N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45	N/A N/A N/A 4.0 4.0 6.0 6.0 8.0 9.0 10.0
2.1 0.47874242 2.88 12.0 2.85 12.0 2.83 12.0 2.80 12.0 2.78 12 2.2 0.56252208 2.96 12.0 2.94 12.0 2.91 12.0 2.89 12.0 2.87 12 2.3 0.63803333 3.07 12.6 3.05 9.2 3.02 12.6 3.00 12.7 2.98 12	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ $\frac{0.00000062}{0.00001422}$ 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65 2.72	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61 2.69	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6 12.0	$\begin{array}{c} \text{Kcal/m} \\ \hline \text{IOD} \\ (\text{Å}) \\ \hline 0.94 \\ 1.08 \\ 1.40 \\ 1.51 \\ 1.77 \\ 1.88 \\ 2.13 \\ 2.23 \\ 2.36 \\ 2.58 \\ 2.67 \end{array}$		kcal/m IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48 2.64	Image: 750 nol*Å4 CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45 2.62	N/A N/A N/A 4.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0
2.2 0.56252208 2.96 12.0 2.94 12.0 2.91 12.0 2.89 12.0 2.87 12 2.3 0.63803333 3.07 12.6 3.05 9.2 3.02 12.6 3.00 12.7 2.98 12	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ $\frac{0.00000062}{0.00001422}$ 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65 2.72 2.80	$=0$ $to 1 + A^4$ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61 2.69 2.77	250 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6 12.0 12.0	$\begin{array}{c} \text{Kcal/m} \\ \hline \text{IOD} \\ (\text{Å}) \\ \hline 0.94 \\ 1.08 \\ 1.40 \\ 1.51 \\ 1.77 \\ 1.88 \\ 2.13 \\ 2.23 \\ 2.36 \\ 2.58 \\ 2.67 \\ 2.74 \end{array}$	$\begin{array}{c} 500\\ nol^* {\rm \AA}^4\\ \hline \\ \hline \\ \hline \\ 2.0\\ 2.0\\ 4.0\\ 4.0\\ 6.0\\ 6.0\\ 6.0\\ 6.9\\ 8.1\\ 9.0\\ 11.5\\ 12.0\\ 12.0\\ 12.0\\ \end{array}$	kcal/m IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48 2.64 2.72	N/A N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45 2.62 2.70	N/A N/A N/A 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0
2.3 0.63803333 3.07 12.6 3.05 9.2 3.02 12.6 3.00 12.7 2.98 12	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65 2.72 2.80 2.88	$=0$ $to 1 + A^4$ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0 12.0 12.0 12.0 12.0	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61 2.69 2.77 2.85	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6 12.0 12.0 12.0	$\begin{array}{c} \text{Kcal/m} \\ \hline \text{IOD} \\ (\text{Å}) \\ \hline 0.94 \\ 1.08 \\ 1.40 \\ 1.51 \\ 1.77 \\ 1.88 \\ 2.13 \\ 2.23 \\ 2.36 \\ 2.58 \\ 2.67 \\ 2.74 \\ 2.83 \end{array}$	$\begin{array}{c} 500\\ nol^* {\rm \AA}^4\\ \hline \\ \hline \\ \hline \\ 2.0\\ 2.0\\ 4.0\\ 4.0\\ 6.0\\ 6.0\\ 6.0\\ 6.9\\ 8.1\\ 9.0\\ 11.5\\ 12.0\\ 12.0\\ 12.0\\ 12.0\\ \end{array}$	kcal/m IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48 2.64 2.72 2.80	N/A CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0	kcal/n IOD (Å) N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45 2.62 2.70 2.78	N/A N/A N/A 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0
	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ 1.9 \\ 2.0 \\ 2.1 \\ 2.2 \\ \end{array}$	$\frac{\epsilon_{M}}{(\text{kcal/mol})}$ 0.00000062 0.0001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875 0.29896986 0.38943250 0.47874242 0.56252208	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65 2.72 2.80 2.88 2.96	$=0$ $=0$ $101*Å^{4}$ CN 2.0 3.0 4.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0 $12.$	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61 2.69 2.77 2.85 2.94	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6 12.0 12.0 12.0 12.0	$\begin{array}{c} \text{Kcal/m} \\ \hline \text{IOD} \\ (\text{Å}) \\ \hline 0.94 \\ 1.08 \\ 1.40 \\ 1.51 \\ 1.77 \\ 1.88 \\ 2.13 \\ 2.23 \\ 2.36 \\ 2.58 \\ 2.67 \\ 2.74 \\ 2.83 \\ 2.91 \end{array}$	$\begin{array}{c} 500\\ \hline nol^* {\rm \AA}^4\\ \hline \\ \hline \\ \hline \\ \hline \\ 2.0\\ 2.0\\ 4.0\\ 4.0\\ 6.0\\ 6.0\\ 6.0\\ 6.0\\ 6.9\\ 8.1\\ 9.0\\ 11.5\\ 12.0\\ 12.0\\ 12.0\\ 12.0\\ 12.0\\ 12.0\\ \end{array}$	kcal/m IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48 2.64 2.72 2.80 2.89	Image: 750 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0 12.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45 2.62 2.70 2.78 2.87	N/A N/A N/A 4.0 4.0 6.0 6.0 8.0 9.0 10.0 12.0 12.0 12.0 12.0
	$\begin{array}{c} R_{\min,M} \\ 2 \\ ({\rm \AA}) \\ \hline \\ \hline 0.9 \\ 1.0 \\ 1.1 \\ 1.2 \\ 1.3 \\ 1.4 \\ 1.5 \\ 1.6 \\ 1.7 \\ 1.8 \\ \end{array}$	ϵ_{M} (kcal/mol) 0.00000062 0.00001422 0.00016377 0.00110429 0.00490301 0.01570749 0.03899838 0.07934493 0.13818331 0.21312875	kcal/m IOD (Å) 1.08 1.34 1.50 1.77 1.85 2.01 2.20 2.31 2.43 2.65	=0 no1*Å ⁴ CN 2.0 3.0 4.0 6.0 6.0 6.0 6.0 8.0 8.8 9.2 12.0	C4= kcal/m IOD (Å) N/A 1.14 1.44 1.72 1.80 1.91 2.16 2.27 2.39 2.61	250 nol*Å ⁴ CN 2.0 4.0 6.0 6.0 6.0 6.0 8.0 8.4 9.0 11.6	C4= kcal/m IOD (Å) 0.94 1.08 1.40 1.51 1.77 1.88 2.13 2.23 2.36 2.58		kcal/n IOD (Å) N/A 1.04 1.36 1.48 1.73 1.85 2.10 2.20 2.33 2.48	Image: 750 nol*Å ⁴ CN N/A 2.0 4.0 6.0 6.0 8.0 9.0 10.0	kcal/n IOD (Å) N/A N/A 1.33 1.45 1.71 1.82 2.07 2.17 2.31 2.45	N/A N/A N/A 4.0 6.0 6.0 8.0 9.0 10.0

				:					
		OPC3		OPC	TI	P3P-FB	TI	P4P-FB	
	$R_{\rm min}/2$	s (kcal/mol)	$R_{\min}/2$	s (kcal/mol)	$R_{\min}/2$	З	$R_{\min}/2$	3	
	(Å)	c (Keal/III01)	(Å)		(Å)	(kcal/mol)	(Å)	(kcal/mol)	
Li ⁺	1.270	0.00325650	1.242	0.00216058	1.260	0.00282180	1.240	0.00209587	
Na^+	1.469	0.03012160	1.467	0.02960343	1.459	0.02759452	1.448	0.02499549	
K^+	1.703	0.14021803	1.702	0.13953816	1.705	0.14158262	1.685	0.12823270	
\mathbf{Rb}^+	1.800	0.21312875	1.818	0.22795460	1.802	0.21475916	1.795	0.20907204	
Cs^+	1.965	0.35762995	1.960	0.35308749	1.970	0.36217399	1.950	0.34401021	
Tl^+	1.682	0.12628793	1.696	0.13549328	1.676	0.12244452	1.666	0.11617738	
Cu^+	1.201	0.00112300	1.180	0.00078213	1.192	0.00096394	1.172	0.00067804	
Ag^+	1.335	0.00761745	1.316	0.00602547	1.328	0.00699604	1.313	0.00580060	
F^-	1.818	0.22795460	1.840	0.24650465	1.834	0.24140216	1.845	0.25078000	
Cl^{-}	2.306	0.64226672	2.360	0.67878870	2.300	0.63803333	2.313	0.64716164	
Br^{-}	2.501	0.76074098	2.499	0.75971103	2.481	0.75027433	2.454	0.73554824	
Ι-	2.780	0.87175814	2.900	0.90300541	2.742	0.86005879	2.804	0.87867445	

Table 41. Final Optimized 12-6 HFE Parameter Set for the Four Water Models.

Table 42. Calculated HFE, IOD, and CN values for the HFE parameter set for the four water models.

	OPC3			OPC			TIP3P-FB			TIP4P-FB		
	HFE (kcal/mol)	IOD (Å)	CN									
Li ⁺	-113.2	1.96	4.0	-113.9	1.94	4.0	-113.0	1.95	4.0	-113.0	1.93	4.0
Na^+	-87.1	2.35	5.7	-86.6	2.39	5.9	-87.2	2.34	5.6	-87.5	2.35	5.8
\mathbf{K}^+	-70.5	2.72	7.2	-69.7	2.75	6.7	-70.0	2.72	6.9	-70.5	2.71	7.0
Rb^+	-65.3	2.87	7.2	-65.0	2.91	7.6	-65.3	2.87	7.5	-65.4	2.87	7.6
Cs^+	-59.8	3.09	8.4	-59.8	3.10	8.1	-59.6	3.11	8.9	-59.7	3.08	8.8
Tl^+	-71.2	2.69	6.5	-70.5	2.74	7.0	-71.1	2.68	6.3	-71.3	2.68	6.4
Cu^+	-125.8	1.85	4.0	-124.9	1.84	4.0	-125.6	1.83	4.0	-125.5	1.82	4.0
Ag^+	-102.8	2.11	4.8	-102.7	2.13	5.2	-102.2	2.10	4.8	-101.8	2.10	5.0
F^{-}	-119.1	2.75	6.6	-120.2	2.80	6.4	-119.0	2.77	6.5	-119.9	2.78	6.4
Cl ⁻	-89.0	3.35	7.2	-89.2	3.42	5.0	-89.1	3.32	7.5	-89.4	3.34	6.9
Br-	-81.7	3.55	6.9	-83.5	3.56	7.3	-82.7	3.53	7.6	-83.6	3.49	6.6
I-	-73.9	3.85	6.6	-73.8	3.98	4.6	-74.2	3.80	7.4	-74.2	3.86	4.2
	C	OPC3	(OPC	TIF	P3P-FB	TIF	P4P-FB				
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	R _{min,M} /2 (Å)	ε _M (kcal/mol)										
Be ²⁺	0.935	0.00000204	0.852	0.00000010	0.914	0.00000101	0.840	0.00000006				
Cu^{2+}	1.166	0.00060803	1.114	0.00022027	1.153	0.00047746	1.107	0.00019018				
Ni ²⁺	1.179	0.00076841	1.132	0.00031773	1.169	0.00064221	1.127	0.00028746				
Pt^{2+}	1.195	0.00101467	1.144	0.00040203	1.176	0.00072849	1.139	0.00036479				
Zn^{2+}	1.200	0.00110429	1.151	0.00045971	1.179	0.00076841	1.142	0.00038675				
Co^{2+}	1.233	0.00188205	1.172	0.00067804	1.220	0.00153342	1.164	0.00058613				
Pd^{2+}	1.237	0.00200187	1.175	0.00071558	1.220	0.00153342	1.168	0.00063064				
Ag^{2+}	1.284	0.00395662	1.205	0.00120058	1.269	0.00321068	1.200	0.00110429				
Cr^{2+}	1.291	0.00435036	1.219	0.00150903	1.278	0.00364281	1.218	0.00148497				
Fe^{2+}	1.300	0.00490301	1.229	0.00176831	1.284	0.00395662	1.224	0.00163434				
Mg^{2+}	1.306	0.00530214	1.239	0.00206414	1.288	0.00417787	1.238	0.00203280				
V^{2+}	1.310	0.00558254	1.244	0.00222695	1.292	0.00440914	1.255	0.00262320				
Mn^{2+}	1.353	0.00941798	1.305	0.00523385	1.339	0.00799176	1.300	0.00490301				
Hg^{2+}	1.353	0.00941798	1.305	0.00523385	1.339	0.00799176	1.300	0.00490301				
Cd^{2+}	1.357	0.00986018	1.309	0.00551135	1.342	0.00828195	1.302	0.00503325				
Yb^{2+}	1.534	0.05065033	1.489	0.03566355	1.520	0.04560206	1.485	0.03450196				
Ca^{2+}	1.541	0.05330850	1.493	0.03685224	1.525	0.04736426	1.488	0.03537062				
Sn^{2+}	1.556	0.05930945	1.506	0.04090549	1.540	0.05292325	1.500	0.03899838				
Pb^{2+}	1.624	0.09180886	1.577	0.06841702	1.607	0.0828687	1.574	0.06706518				
Eu^{2+}	1.671	0.11928915	1.625	0.09235154	1.653	0.10829364	1.620	0.08965674				
\mathbf{Sr}^{2+}	1.677	0.12308079	1.631	0.09564656	1.659	0.11189491	1.626	0.09289608				
Sm^{2+}	1.683	0.12693448	1.637	0.09900804	1.664	0.11494497	1.632	0.0962022				
Ba^{2+}	1.840	0.24650465	1.797	0.21069138	1.824	0.23296929	1.795	0.20907204				
Ra^{2+}	1.840	0.24650465	1.797	0.21069138	1.824	0.23296929	1.795	0.20907204				

Table 43. The HFE Parameter Set for 24 Divalent Metal Ions in Conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB Water Model.

	OPC3			O	PC		TIP3P-FB			TIP4P-FB		
	HFE	IOD	CN									
	(kcal/mol)	(A)		(kcal/mol)	(A)		(kcal/mol)	(A)		(kcal/mol)	(A)	
Be ²⁺	-572.3	1.18	2.0	-571.7	0.98	1.0	-573.1	1.15	2.0	-572.2	0.95	1.0
Cu ²⁺	-480.2	1.66	4.0	-481.1	1.63	4.0	-479.8	1.65	4.0	-480.4	1.61	4.0
Ni ²⁺	-473.9	1.68	4.0	-473.8	1.65	4.0	-472.2	1.67	4.0	-473.3	1.63	4.0
Pt^{2+}	-468.9	1.86	5.9	-469.5	1.67	4.0	-468.8	1.68	4.0	-468.6	1.65	4.0
Zn^{2+}	-466.6	1.87	6.0	-466.8	1.67	4.0	-467.0	1.68	4.1	-466.7	1.65	4.0
Co^{2+}	-457.3	1.91	6.0	-457.7	1.70	4.0	-456.7	1.90	6.0	457.6	1.68	4.0
Pd^{2+}	-456.5	1.92	6.0	-456.5	1.71	4.0	-456.7	1.90	6.0	-456.0	1.68	4.0
Ag^{2+}	-445.1	1.96	6.0	-444.9	1.91	6.0	-445.9	1.94	6.0	-445.8	1.89	6.0
Cr^{2+}	-442.4	1.97	6.0	-443.1	1.93	6.0	-441.2	1.95	6.0	442.2	1.91	6.0
Fe^{2+}	-439.7	1.98	6.0	-440.2	1.94	6.0	-439.7	1.96	6.0	-439.7	1.92	6.0
Mg^{2+}	-437.8	1.98	6.0	-436.9	1.95	6.0	-437.9	1.96	6.0	-437.7	1.93	6.0
V^{2+}	-435.9	1.99	6.0	-437.1	1.95	6.0	-437.2	1.97	6.0	-436.2	1.95	6.0
Mn^{2+}	-421.4	2.04	6.0	-420.4	2.01	6.0	-420.6	2.02	6.0	-420.8	1.99	6.0
Hg^{2+}	-420.7	2.04	6.0	-420.4	2.01	6.0	-420.6	2.02	6.0	-420.8	1.99	6.0
Cd^{2+}	-419.5	2.04	6.0	-419.0	2.02	6.0	-420.1	2.02	6.0	419.8	1.99	6.0
Yb^{2+}	-361.2	2.33	7.0	-360.9	2.25	6.3	-360.7	2.31	6.9	-360.5	2.23	6.2
Ca^{2+}	-358.9	2.34	7.1	-359.4	2.26	6.4	-359.4	2.31	6.9	-359.8	2.24	6.4
Sn^{2+}	-355.2	2.36	7.2	-356.5	2.31	6.8	-355.4	2.34	7.1	-357.0	2.28	6.7
Pb^{2+}	-340.3	2.47	7.9	-339.8	2.44	7.8	-340.1	2.45	7.8	-340.1	2.42	7.8
Eu^{2+}	-331.0	2.53	8.0	-331.2	2.51	8.0	-331.3	2.51	8.0	-330.4	2.49	8.0
Sr^{2+}	-329.4	2.54	8.0	-329.6	2.51	8.0	-330.3	2.52	8.0	-329.9	2.49	8.0
Sm^{2+}	-327.8	2.54	8.0	-328.9	2.52	8.0	-328.9	2.52	8.0	-328.8	2.50	8.0
Ba^{2+}	-298.9	2.74	8.8	-298.4	2.73	8.9	-299.3	2.72	8.7	-298.4	2.71	8.8
Ra^{2+}	-298.5	2.74	8.8	-298.4	2.73	8.8	-299.3	2.72	8.7	-298.3	2.70	8.8

Table 44. Calculated HFE, IOD, and CN values for the HFE parameter set for the four water models.

	C	OPC3	(OPC	TIF	P3P-FB	TIF	P4P-FB
	$R_{\min,M}/2$	Е <u>М</u>	$R_{\min,M}/2$	ε _M	$R_{\min,M}/2$	ε _M	$R_{\min,M}/2$	ε _M
	(A)	(kcal/mol)	(A)	(kcal/mol)	(A)	(kcal/mol)	(A)	(kcal/mol)
Al ³⁺	1.005	0.00001631	0.924	0.00000142	0.972	0.00000639	0.916	0.00000108
Fe ³⁺	1.121	0.00025449	1.023	0.00002635	1.099	0.00016028	1.013	0.00002024
Cr^{3+}	1.217	0.00146124	1.145	0.00040986	1.197	0.00104974	1.140	0.00037198
In ³⁺	1.241	0.00212802	1.157	0.00051476	1.211	0.00132548	1.148	0.00043416
$T1^{3+}$	1.253	0.00254709	1.157	0.00051476	1.211	0.00132548	1.152	0.00046851
Y^{3+}	1.458	0.02735051	1.399	0.01554690	1.431	0.02133669	1.391	0.01430674
La ³⁺	1.646	0.10417397	1.577	0.06841702	1.624	0.09180886	1.574	0.06706518
Ce^{3+}	1.610	0.08440707	1.540	0.05292325	1.589	0.07399405	1.537	0.05177853
Pr^{3+}	1.583	0.07117158	1.509	0.04188268	1.561	0.06140287	1.506	0.04090549
Nd^{3+}	1.562	0.06182717	1.489	0.03566355	1.540	0.05292325	1.485	0.03450196
Sm^{3+}	1.531	0.04953859	1.458	0.02735051	1.512	0.04287573	1.459	0.02759452
Eu^{3+}	1.514	0.04354662	1.438	0.02279185	1.492	0.03655251	1.439	0.02300555
Gd^{3+}	1.505	0.04058327	1.431	0.02133669	1.485	0.03450196	1.421	0.01937874
Tb^{3+}	1.479	0.03280986	1.420	0.01919059	1.459	0.02759452	1.409	0.01721000
Dy^{3+}	1.467	0.02960343	1.409	0.01721000	1.446	0.02454281	1.401	0.01586934
Er^{3+}	1.433	0.02174524	1.380	0.01272679	1.415	0.01827024	1.373	0.01179373
Tm^{3+}	1.423	0.01975917	1.372	0.01166488	1.412	0.01773416	1.364	0.01067299
Lu^{3+}	1.423	0.01975917	1.372	0.01166488	1.412	0.01773416	1.364	0.01067299
Hf^{4+}	1.134	0.00033060	1.023	0.00002635	1.109	0.00019838	1.014	0.00002079
Zr^{4+}	1.169	0.00064221	1.092	0.00013761	1.150	0.00045105	1.087	0.00012321
Ce^{4+}	1.370	0.01141046	1.306	0.00530214	1.352	0.00930991	1.301	0.00496778
U^{4+}	1.247	0.00232970	1.155	0.00049581	1.223	0.00160860	1.148	0.00043416
Pu^{4+}	1.308	0.00544088	1.221	0.00155814	1.285	0.00401101	1.215	0.00141473
Th^{4+}	1.475	0.03171494	1.393	0.01460944	1.454	0.02639002	1.388	0.01386171

Table 45. The HFE parameter set for 18 trivalent and 6 tetravalent metal ions in conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models.

	OPC3			OPC			TIP3P-FB			TIP4P-FB		
	HFE (kcal/mol)	IOD (Å)	CN									
Al^{3+}	-1082.8	1.36	3.0	-1082.8	1.14	2.0	-1083.4	1.19	2.0	-1082.2	1.13	2.0
Fe^{3+}	-1019.6	1.55	4.0	-1019.2	1.41	3.0	-1019.9	1.53	4.0	-1020.1	1.39	3.0
Cr^{3+}	-958.6	1.82	6.0	-958.3	1.60	4.0	-958.4	1.80	6.0	-956.9	1.58	4.0
In^{3+}	-952.5	1.84	6.0	-949.8	1.62	4.0	-949.7	1.82	6.0	-951.8	1.59	4.0
$T1^{3+}$	-949.0	1.85	6.0	-949.8	1.62	4.0	-949.7	1.81	6.0	-948.4	1.60	4.0
Y^{3+}	-821.6	2.16	7.7	-824.3	2.03	6.0	-825.1	2.09	6.9	-825.3	2.00	6.0
La ³⁺	-752.1	2.43	9.0	-751.6	2.35	8.1	-752.8	2.40	9.0	-751.9	2.34	8.2
Ce^{3+}	-764.2	2.37	8.8	-766.7	2.32	8.0	-764.8	2.34	8.7	-763.7	2.30	8.0
Pr^{3+}	-773.8	2.33	8.2	-777.4	2.28	8.0	-774.7	2.30	8.0	-775.3	2.26	8.0
Nd^{3+}	-783.8	2.30	8.0	-782.3	2.25	7.9	-784.3	2.28	8.0	-782.6	2.24	8.0
Sm^{3+}	-794.0	2.27	8.0	-794.4	2.18	8.3	-795.4	2.25	8.0	-793.4	2.19	8.2
Eu^{3+}	-802.0	2.26	8.0	-803.0	2.14	8.1	-801.4	2.23	8.0	-799.6	2.11	7.0
Gd^{3+}	-805.4	2.25	8.0	-805.5	2.09	6.2	-805.3	2.22	8.0	-807.5	2.05	6.2
Tb^{3+}	-814.5	2.21	8.0	-811.6	2.06	6.0	-814.3	2.18	8.0	-814.4	2.03	6.0
Dy^{3+}	-820.0	2.19	8.0	-819.0	2.04	6.0	-818.8	2.14	7.4	-820.0	2.02	6.0
Er^{3+}	-835.0	2.06	6.5	-835.1	2.01	6.0	-834.8	2.02	6.0	-835.8	1.98	6.0
Tm^{3+}	-839.8	2.03	6.0	-839.9	2.00	6.0	-838.4	2.01	6.0	-841.7	1.97	6.0
Lu^{3+}	-839.8	2.03	6.0	-840.5	2.00	6.0	-838.4	2.01	6.0	-841.7	1.97	6.0
Hf^{4+}	-1662.1	1.51	4.0	-1664.0	1.37	3.0	-1664.9	1.49	4.0	-1665.1	1.35	3.0
Zr^{4+}	-1623.0	1.55	4.0	-1623.1	1.51	4.0	-1622.6	1.53	4.0	-1621.0	1.49	4.0
Ce^{4+}	-1463.2	1.90	6.0	-1463.7	1.87	6.0	-1463.8	1.88	6.0	-1462.6	1.85	6.0
U^{4+}	-1567.1	1.79	6.0	-1568.9	1.57	4.0	-1567.3	1.77	6.0	-1568.9	1.55	4.0
Pu^{4+}	-1520.2	1.84	6.0	-1520.5	1.81	6.0	-1520.4	1.82	6.0	-1520.0	1.78	6.0
Th^{4+}	-1389.2	2.15	8.0	-1390.0	1.96	6.0	-1389.6	2.11	8.3	-1388.2	1.94	6.0

Table 46. Calculated HFE, IOD, and CN values for the HFE parameter set for the four water models.

		OPC3		OPC	TI	P3P-FB	TIP4P-FB		
	$\frac{R_{\min}/2}{(\text{\AA})}$	ε (kcal/mol)	$\frac{R_{\min}/2}{(\text{\AA})} \varepsilon \text{ (kcal/mol)}$		$\frac{R_{\min}/2}{(\text{\AA})}$	ε (kcal/mol)	$\frac{R_{\min}/2}{(\text{\AA})}$	ε (kcal/mol)	
Li ⁺	1.321	0.00641580	1.305	0.00523385	1.320	0.00633615	1.306	0.00530214	
Na^+	1.470	0.03038310	1.440	0.02322071	1.460	0.02784010	1.450	0.02545423	
\mathbf{K}^+	1.743	0.16869420	1.738	0.16500296	1.741	0.16721338	1.737	0.16426906	
Rb^+	1.810	0.22132374	1.802	0.21475916	1.810	0.22132374	1.810	0.22132374	
Cs^+	1.990	0.38035199	1.990	0.38035199	1.988	0.37853483	2.000	0.38943250	
Tl^+	1.866	0.26894857	1.845	0.25078000	1.865	0.26807617	1.860	0.26372453	
Cu^+	1.213	0.00136949	1.201	0.00112300	1.214	0.00139196	1.208	0.00126172	
Ag^+	1.502	0.03962711	1.489	0.03566355	1.505	0.04058327	1.481	0.03336723	
F^{-}	1.737	0.16426906	1.720	0.15202035	1.743	0.16869420	1.740	0.16647513	
Cl^{-}	2.160	0.52988504	2.150	0.52153239	2.166	0.53486081	2.166	0.53486081	
Br^{-}	2.315	0.64855145	2.312	0.64646527	2.330	0.65885086	2.340	0.66559495	
I^-	2.590	0.80293907	2.573	0.79541413	2.597	0.80596674	2.588	0.80206648	

 Table 47. Final Optimized 12-6 IOD Parameter Set for the Four Water Models

Table 48. Calculated HFE, IOD, and CN values for the IOD parameter set for the four water models.

	OPC3			(OPC		TI	P3P-FB		TIP4P-FB			
	HFE (kcal/ mol)	IOD (Å)	CN	HFE (kcal/ mol)	IOD (Å)	CN	HFE (kcal/ mol)	IOD (Å)	CN	HFE (kcal/ mol)	IOD (Å)	C N	
Li ⁺	-104.9	2.08	4.6	-103.8	2.09	4.9	-103.4	2.08	4.7	-103.0	2.08	4.9	
Na	-87.4	2.36	5.6	-88.9	2.35	5.9	-87.5	2.35	5.6	-86.9	2.35	5.8	
\mathbf{K}^+	-68.5	2.78	6.8	-67.8	2.80	6.9	-67.9	2.78	6.9	-67.3	2.79	7.1	
Rb	-65.5	2.88	7.6	-65.8	2.89	7.1	-64.8	2.88	7.9	-64.2	2.89	7.4	
Cs	-59.0	3.13	9.1	-58.5	3.14	8.3	-58.6	3.14	9.2	-57.9	3.14	9.4	
Tl^+	-63.1	2.95	7.8	-62.4	2.95	8.2	-62.8	2.96	8.0	-62.7	2.96	8.1	
Cu	-123.9	1.87	4.0	-121.1	1.87	4.0	-121.5	1.87	4.0	-118.9	1.87	4.0	
Ag	-84.1	2.41	5.8	-84.2	2.42	5.9	-83.0	2.41	5.7	-84.3	2.40	5.8	
F^{-}	-128.2	2.63	6.2	-133.5	2.63	6.1	-129.1	2.63	6.1	-131.2	2.63	6.1	
Cl^{-}	-95.3	3.18	7.3	-98.3	3.18	7.0	-95.2	3.18	7.2	-97.1	3.18	6.6	
Br^{-}	-88.5	3.36	7.3	-91.6	3.36	7.2	-88.2	3.37	7.2	-89.0	3.38	6.6	
I ⁻	-78.7	3.64	7.2	-81.0	3.64	6.2	-78.4	3.65	7.8	-79.8	3.63	6.5	

	(OPC3		OPC	TI	P3P-FB	TIP4P-FB		
	R _{min} /2 (Å)	ε (kcal/mol)							
Be ²⁺	1.162	0.00056491	1.136	0.00034392	1.163	0.00057544	1.150	0.00045105	
Cu^{2+}	1.413	0.01791152	1.391	0.01430674	1.413	0.01791152	1.400	0.01570749	
Ni ²⁺	1.373	0.01179373	1.345	0.00858042	1.373	0.01179373	1.358	0.00997323	
Zn^{2+}	1.400	0.01570749	1.373	0.01179373	1.400	0.01570749	1.383	0.01314367	
Co^{2+}	1.406	0.01669760	1.382	0.01300356	1.406	0.01669760	1.392	0.01445748	
Cr^{2+}	1.391	0.01430674	1.364	0.01067299	1.391	0.01430674	1.375	0.01205473	
Fe^{2+}	1.413	0.01430674	1.391	0.01430674	1.413	0.01791152	1.400	0.01570749	
Mg^{2+}	1.400	0.01570749	1.373	0.01179373	1.400	0.01570749	1.383	0.01314367	
V^{2+}	1.480	0.03308772	1.456	0.02686716	1.480	0.03308772	1.465	0.02909167	
Mn^{2+}	1.462	0.02833599	1.444	0.02409615	1.462	0.02833599	1.459	0.02759452	
Hg^{2+}	1.584	0.07163727	1.565	0.06311131	1.584	0.07163727	1.572	0.06617338	
Cd^{2+}	1.526	0.04772212	1.506	0.04090549	1.520	0.04560206	1.511	0.04254294	
Ca^{2+}	1.617	0.08806221	1.590	0.07447106	1.617	0.08806221	1.600	0.07934493	
Sn^{2+}	1.746	0.17092614	1.715	0.14850170	1.746	0.17092614	1.731	0.15989650	
Sr^{2+}	1.762	0.18304100	1.731	0.15989650	1.762	0.18304100	1.746	0.17092614	
Ba^{2+}	1.918	0.31509345	1.883	0.28387745	1.918	0.31509345	1.900	0.29896986	

Table 49. The IOD parameter set for 16 divalent metal ions in conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models.

Table 50. Calculated HFE, IOD, and CN values for the IOD parameter set for the four water	r
models.	

	OPC3			Ol	PC		TIP3P-FB			TIP4P-FB			
	HFE (kcal/mol)	IOD (Å)	CN										
Be^{2+}	-482.1	1.66	4.0	-472.2	1.66	4.0	-474.4	1.66	4.0	-463.8	1.66	4.0	
Cu^{2+}	-400.1	2.11	6.0	-392.7	2.11	6.0	-395.0	2.11	6.0	-388.3	2.11	6.0	
Ni ²⁺	-413.6	2.06	6.0	-407.6	2.06	6.0	-409.0	2.06	6.0	-401.9	2.06	6.0	
Zn^{2+}	-404.0	2.09	6.0	-399.6	2.09	6.0	-398.8	2.09	6.0	-393.9	2.09	6.0	
Co^{2+}	-401.6	2.10	6.0	-395.9	2.10	6.0	-397.2	2.10	6.0	-391.1	2.10	6.0	
Cr^{2+}	-407.4	2.08	6.0	-401.8	2.08	6.0	-402.4	2.08	6.0	-396.3	2.08	6.0	
Fe^{2+}	-399.5	2.11	6.0	-392.9	2.11	6.0	-394.3	2.11	6.0	-388.0	2.11	6.0	
Mg^{2+}	-404.2	2.09	6.0	-398.2	2.09	6.0	-399.3	2.09	6.0	-393.5	2.09	6.0	
V^{2+}	-376.4	2.20	6.0	-371.3	2.20	6.0	-371.3	2.20	6.0	-366.2	2.20	6.0	
Mn^{2+}	-382.1	2.18	6.0	-375.0	2.18	6.0	-377.6	2.18	6.0	-367.9	2.19	6.0	
Hg^{2+}	-349.6	2.41	7.6	-342.9	2.42	7.7	-345.1	2.41	7.6	-339.8	2.42	7.8	
Cd^{2+}	-363.0	2.31	6.9	-355.9	2.31	6.8	-360.9	2.31	6.9	-353.9	2.31	7.0	
Ca^{2+}	-341.2	2.46	7.9	-337.9	2.46	7.9	-338.4	2.46	7.9	-335.4	2.46	7.9	
Sn^{2+}	-315.6	2.62	8.1	-313.0	2.62	8.3	-312.8	2.62	8.2	-309.7	2.62	8.4	
\mathbf{Sr}^{2+}	-313.2	2.64	8.2	-310.2	2.64	8.4	-309.4	2.64	8.3	-306.6	2.64	8.4	
Ba^{2+}	-285.8	2.83	9.0	-284.8	2.83	9.1	-284.1	2.83	9.0	-282.6	2.83	9.1	

	C	OPC3	(OPC	TIF	'3P-FB	TII	P4P-FB
	$R_{min,M}/2$	E _M	$R_{min,M}/2$	E _M	$R_{min,M}/2$	ε _M	$R_{\min,M}/2$	EM
	(A)	(kcal/mol)	(A)	(kcal/mol)	(A)	(kcal/mol)	(A)	(kcal/mol)
Al ³⁺	1.287	0.00412163	1.250	0.00243637	1.287	1.287 0.00412163		0.00312065
Fe ³⁺	1.419	0.01900380	1.400	0.01570749	1.419	0.01900380	1.404	0.01636246
Cr^{3+}	1.364	0.01067299	1.336	0.00770969	1.364	0.01067299	1.345	0.00858042
In ³⁺	1.453	0.02615377	1.440	0.02322071	1.445	0.02431873	1.443	0.02387506
$T1^{3+}$	1.496	0.03776169	1.483	0.03393126	1.496	0.03776169	1.488	0.03537062
Y^{3+}	1.600	0.07934493	1.575	0.06751391	1.600	0.07934493	1.583	0.07117158
La ³⁺	1.733	0.16134811	1.700	0.13818331	1.731	0.15989650	1.715	0.14850170
Ce^{3+}	1.758	0.1799796	1.725	0.15557763	1.754	0.17693975	1.738	0.16500296
Pr^{3+}	1.750	0.17392181	1.717	0.14990448	1.746	0.17092614	1.731	0.15989650
Nd^{3+}	1.692	0.13282966	1.662	0.11371963	1.692	0.13282966	1.675	0.12180998
Sm^{3+}	1.667	0.11679623	1.638	0.09957472	1.667	0.11679623	1.650	0.10651723
Eu^{3+}	1.675	0.12180998	1.646	0.10417397	1.675	0.12180998	1.658	0.11129023
Gd^{3+}	1.625	0.09235154	1.600	0.07934493	1.625	0.09235154	1.608	0.08337961
Tb^{3+}	1.633	0.09675968	1.608	0.08337961	1.633	0.09675968	1.617	0.08806221
Dy^{3+}	1.608	0.08337961	1.583	0.07117158	1.608	0.08337961	1.592	0.07543075
Er^{3+}	1.600	0.07934493	1.575	0.06751391	1.600	0.07934493	1.583	0.07117158
Tm^{3+}	1.600	0.07934493	1.575	0.06751391	1.600	0.07934493	1.583	0.07117158
Lu^{3+}	1.583	0.07117158	1.558	0.06014121	1.583	0.07117158	1.567	0.06397679
Hf^{4+}	1.489	0.03566355	1.461	0.02808726	1.489	0.03566355	1.467	0.02960343
Zr^{4+}	1.508	0.04155519	1.488	0.03537062	1.508	0.04155519	1.495	0.03745682
Ce^{4+}	1.708	0.14364160	1.683	0.12693448	1.705	0.14158262	1.692	0.13282966
U^{4+}	1.708	0.14364160	1.683	0.12693448	1.705	0.14158262	1.692	0.13282966
Pu^{4+}	1.682	0.12628793	1.658	0.11129023	1.682	0.12628793	1.667	0.11679623
Th ⁴⁺	1.721	0.15272873	1.704	0.14089951	1.718	0.15060822	1.709	0.14433113

Table 51. The IOD parameter set for 18 trivalent and 6 tetravalent metal ions in conjunction with the OPC, OPC3, TIP3P-FB, and TIP4P-FB water models.

	OPC3			OPC			TIP3P-FB			TIP4P-FB		
	HFE (kcal/mol)	IOD (Å)	CN									
Al^{3+}	-929.6	1.88	6.0	-907.9	1.88	6.0	-917.3	1.88	6.0	-896.5	1.88	6.0
Fe ³⁺	-842.8	2.02	6.0	-823.5	2.03	6.0	-832.5	2.02	6.0	-817.3	2.02	6.0
Cr^{3+}	-879.0	1.96	6.0	-861.2	1.96	6.0	-868.5	1.96	6.0	-852.6	1.95	6.0
In^{3+}	-825.0	2.15	8.1	-801.3	2.14	6.9	-820.4	2.14	8.0	-798.6	2.15	8.3
Tl^{3+}	-810.4	2.24	8.0	-785.1	2.24	8.0	-802.5	2.24	8.0	-782.5	2.24	8.0
Y^{3+}	-767.3	2.36	8.7	-752.7	2.35	8.2	-760.4	2.36	8.8	-747.9	2.35	8.7
La ³⁺	-719.9	2.52	9.0	-710.0	2.52	9.0	-714.6	2.51	9.0	-703.1	2.51	9.0
Ce^{3+}	-710.3	2.54	9.0	-702.2	2.54	9.0	-705.5	2.54	9.0	-696.7	2.54	9.0
Pr^{3+}	-714.3	2.53	9.0	-704.7	2.53	9.0	-707.8	2.53	9.0	-698.5	2.53	9.0
Nd^{3+}	-735.1	2.48	9.0	-722.9	2.48	9.0	-727.9	2.48	9.0	-716.3	2.47	9.0
Sm^{3+}	-744.5	2.45	9.0	-730.6	2.45	9.0	-736.6	2.45	9.0	-724.8	2.45	9.0
Eu^{3+}	-741.6	2.46	9.0	-727.9	2.46	9.0	-733.7	2.46	9.0	-722.4	2.46	9.0
Gd^{3+}	-759.3	2.40	9.0	-744.1	2.39	8.6	-751.4	2.40	9.0	-739.3	2.39	9.0
Tb^{3+}	-756.6	2.41	9.0	-741.8	2.40	9.0	-748.5	2.41	9.0	-735.7	2.41	9.0
Dy^{3+}	-765.4	2.37	8.9	-750.4	2.36	8.2	-758.6	2.38	8.9	-744.4	2.37	8.8
Er^{3+}	-768.5	2.36	8.7	-752.5	2.35	8.1	-760.8	2.36	8.8	-748.1	2.35	8.5
Tm^{3+}	-768.3	2.36	8.7	-752.9	2.35	8.1	-760.7	2.36	8.7	-748.0	2.35	8.6
Lu^{3+}	-775.2	2.33	8.2	-758.7	2.33	8.0	-767.1	2.33	8.4	-753.5	2.33	8.1
Hf^{4+}	-1380.3	2.17	8.0	-1349.9	2.16	7.9	-1367.0	2.17	8.0	-1341.4	2.16	7.9
Zr^{4+}	-1367.8	2.19	8.0	-1331.3	2.20	8.0	-1357.6	2.19	8.0	-1327.9	2.19	8.0
Ce^{4+}	-1255.7	2.42	9.2	-1229.8	2.42	9.0	-1247.6	2.41	9.2	-1222.4	2.42	9.0
U^{4+}	-1256.0	2.42	9.2	-1229.7	2.42	9.0	-1246.8	2.42	9.2	-1222.4	2.42	9.1
Pu^{4+}	-1272.8	2.39	9.0	-1244.2	2.40	9.0	-1259.7	2.39	9.0	-1235.8	2.39	9.0
Th^{4+}	-1249.3	2.44	9.7	-1219.2	2.44	9.1	-1239.5	2.44	9.7	-1213.3	2.44	9.6

Table 52. Calculated HFE, IOD, and CN values for the IOD parameter set for the four water models.

	OPC3			OI	PC		TIP3P-FB			TIP4P-FB			
	HFE	ΙΟ	С	HFE	IO	С	HFE	ΙΟ	С	HFE	IO	С	
	(kcal/mo	D	N										
	1)	(Å)	11										
Li ⁺	-113.4	2.0	4.	-113.9	2.0	5.	-113.4	2.0	4.	-113.8	2.0	5.	
Na	-87.3	2.3	5.	-88.3	2.3	5.	-86.8	2.3	5.	-88.0	2.3	5.	
\mathbf{K}^+	-70.4	2.8	7.	-71.0	2.8	7.	-70.0	2.7	6.	-71.1	2.8	7.	
Rb	-65.5	2.9	7.	-65.4	2.8	7.	-65.7	2.8	7.	-65.7	2.8	7.	
Cs	-59.4	3.1	8.	-59.9	3.1	9.	-60.7	3.1	9.	-60.1	3.1	8.	
Tl^+	-72.2	2.9	8.	-71.8	2.9	8.	-71.7	2.9	8.	-72.1	2.9	8.	
Cu	-125.6	1.8	4.	-125.9	1.8	4.	-125.1	1.8	4.	-125.4	1.8	4.	
Ag	-102.9	2.4	6.	-103.3	2.4	6.	-102.6	2.4	6.	-102.7	2.4	6.	
F^{-}	-120.2	2.6	6.	-118.9	2.6	6.	-120.0	2.6	6.	-118.8	2.6	6.	
Cl^{-}	-89.0	3.1	7.	-89.5	3.1	6.	-89.2	3.1	7.	-89.0	3.1	6.	
Br^{-}	-83.0	3.3	7.	-82.0	3.3	7.	-83.6	3.3	7.	-83.7	3.3	7.	
Ι-	-75.4	3.6	7.	-73.8	3.6	6.	-73.8	3.6	6.	-74.6	3.6	7.	

Table 53. Calculated HFE, IOD, and CN values for the 12-6-4 parameter set for the four water models.

		OPC3			OPC	
	$R_{min}/2$	c (keal/mol)	C_4	$R_{min}/2$	c (keal/mol)	C_4
	(Å)	ε (Kcal/1101)	(kcal/mol·Å ⁴)	(Å)	ε (Kcal/1101)	(kcal/mol·Å ⁴)
Be ²⁺	1.211	0.00132548	186	1.201	0.00112300	214
Cu^{2+}	1.467	0.02960343	269	1.448	0.02499549	291
Ni ²⁺	1.435	0.02215953	207	1.402	0.01603244	212
Zn^{2+}	1.441	0.02343735	199	1.423	0.01975917	225
Co^{2+}	1.443	0.02387506	182	1.426	0.02034021	204
Cr^{2+}	1.416	0.01845160	109	1.400	0.01570749	132
Fe ²⁺	1.441	0.02343735	131	1.423	0.01975917	154
Mg^{2+}	1.433	0.02174524	117	1.405	0.01652939	127
V^{2+}	1.505	0.04058327	201	1.501	0.03931188	239
Mn^{2+}	1.495	0.03745682	137	1.485	0.03450196	175
Hg^{2+}	1.625	0.09235154	276	1.599	0.07884906	289
Cd^{2+}	1.551	0.05726270	200	1.526	0.05292325	219
Ca ²⁺	1.632	0.09620220	76	1.602	0.08034231	86
Sn^{2+}	1.770	0.18922704	188	1.743	0.16869420	199
Sr^{2+}	1.777	0.19470705	85	1.738	0.16500296	87
Ba ²⁺	1.936	0.33132862	77	1.898	0.29718682	78
		TIP3P-FB			TIP4P-FB	
	$R_{\min}/2$	ε (kcal/mol)	C4	$R_{\min}/2$	ε (kcal/mol)	C4
	(Å)	e (Real/mol)	(kcal/mol·Å ⁴)	(Å)	e (keul/mor)	(kcal/mol·Å ⁴)
Be ²⁺	1.209	0.00128267	193	1.213	0.00136949	227
Cu^{2+}	1.467	0.02960343	279	1.469	0.03012160	313
Ni ²⁺	1.437	0.02257962	223	1.409	0.01721000	218
Zn^{2+}	1.446	0.02454281	217	1.436	0.02236885	239
Co^{2+}	1.445	0.02431873	192	1.433	0.02174524	206
Cr^{2+}	1.433	0.02174524	138	1.424	0.01995146	159
Fe ²⁺	1.454	0.02639002	157	1.451	0.02568588	187
Mg^{2+}	1.433	0.02174524	128	1.409	0.01721000	133
V^{2+}	1.506	0.04090549	212	1.497	0.03806827	234
Mn^{2+}	1.491	0.03625449	149	1.489	0.03566355	181
Hg^{2+}	1.627	0.09344247	289	1.637	0.09900804	331
Cd^{2+}	1 545	0.05486796	201	1.539	0.05253984	227
C_{2}^{2+}	1.0 10					
Ca	1.636	0.09844319	92	1.625	0.09235154	109
Ca Sn ²⁺	1.636 1.774	0.09844319 0.19235093	92 205	1.625 1.760	0.09235154 0.18150763	109 215
Sn^{2+} Sr^{2+}	1.636 1.774 1.769	0.09844319 0.19235093 0.18844925	92 205 91	1.625 1.760 1.755	0.09235154 0.18150763 0.17769767	109 215 103

Table 54. The 12-6-4 parameter set for 16 divalent metal ions in conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models.

	OPC3		O	PC		TIP3P-FB TIP			TIP4	P-FB		
	HFE (kcal/mol)	IOD (Å)	CN	HFE (kcal/mol)	IOD (Å)	CN	HFE (kcal/mol)	IOD (Å)	CN	HFE (kcal/mol)	IOD (Å)	CN
Be ²⁺	-571.7	1.66	4.5	-572.8	1.66	4.0	-572.4	1.66	4.5	-572.8	1.67	4.9
Cu^{2+}	-480.7	2.11	6.0	-480.6	2.10	6.0	-480.3	2.10	6.0	-479.6	2.11	6.0
Ni ²⁺	-473.6	2.07	6.0	-473.8	2.06	6.0	-473.8	2.07	5.8	-473.1	2.05	6.0
Zn^{2+}	-467.3	2.09	6.0	-468.0	2.09	6.0	-466.9	2.09	6.0	-468.1	2.08	6.0
Co^{2+}	-458.7	2.09	6.0	-458.1	2.10	6.0	-457.3	2.09	6.0	-456.6	2.09	6.0
Cr^{2+}	-442.7	2.08	6.0	-441.7	2.08	6.0	-442.0	2.09	6.0	-441.8	2.09	6.0
Fe^{2+}	-439.6	2.11	6.0	-439.8	2.11	6.0	-439.2	2.12	6.0	-440.1	2.12	6.0
Mg^{2+}	-438.0	2.10	6.0	-437.6	2.09	6.0	-437.3	2.10	6.0	-438.0	2.08	6.0
V^{2+}	-437.1	2.20	6.5	-436.1	2.22	6.5	-437.2	2.22	6.8	-436.5	2.20	6.0
Mn^{2+}	-420.5	2.19	6.2	-420.3	2.19	6.0	-420.0	2.18	6.1	-420.4	2.18	6.2
Hg^{2+}	-421.1	2.41	8.0	-419.7	2.41	8.0	-420.9	2.41	8.0	-421.7	2.42	8.0
Cd^{2+}	-420.4	2.31	7.4	-420.0	2.30	7.3	-419.2	2.30	7.4	-419.0	2.31	7.6
Ca^{2+}	-359.5	2.46	8.0	-360.1	2.46	8.0	-359.4	2.47	8.0	-360.2	2.46	3.4
Sn^{2+}	-355.6	2.62	8.7	-356.1	2.62	8.8	-356.6	2.62	8.8	-355.9	2.62	8.9
\mathbf{Sr}^{2+}	-329.8	2.64	8.5	-330.2	2.63	8.6	-329.6	2.63	8.5	-329.7	2.64	8.8
Ba ²⁺	-298.9	2.84	9.1	-299.4	2.83	9.1	-298.6	2.82	9.1	-298.3	2.83	9.2

Table 55. Calculated HFE, IOD, and CN values for the 12-6-4 parameter set for the four water models.

		OPC3		OPC				
	R _{min,M} /2 (Å)	ε _M (kcal/mol)	C ₄ (kcal/mol·Å ⁴)	R _{min,M} /2 (Å)	$\epsilon_{\rm M}$ (kcal/mol)	C ₄ (kcal/mol·Å ⁴)		
Al ³⁺	1.361	0.01031847	363	1.335	0.00761745	399		
Fe ³⁺	1.455	0.02662782	429	1.461	0.02808726	531		
Cr ³⁺	1.402	0.01603244	209	1.379	0.01259012	243		
In ³⁺	1.487	0.03507938	330	1.485	0.03450196	413		
Tl^{3+}	1.567	0.06397679	437	1.537	0.05177853	479		
Y^{3+}	1.626	0.09289608	192	1.615	0.08700853	260		
La ³⁺	1.751	0.17467422	131	1.719	0.15131351	165		
Ce ³⁺	1.781	0.19786584	215	1.775	0.19313505	289		
Pr^{3+}	1.785	0.20104406	255	1.765	0.18535099	311		
Nd^{3+}	1.712	0.14640930	184	1.699	0.13750834	243		
Sm ³⁺	1.690	0.13150785	188	1.666	0.11617738	236		
Eu^{3+}	1.704	0.14089951	233	1.680	0.12499993	279		
Gd^{3+}	1.644	0.10301322	164	1.627	0.09344247	222		
Tb^{3+}	1.657	0.11068733	199	1.639	0.10014323	256		
Dy ³⁺	1.632	0.09620220	183	1.616	0.08753443	243		
Er^{3+}	1.630	0.09509276	228	1.620	0.08965674	298		
Tm ³⁺	1.633	0.09675968	246	1.622	0.09072908	314		
Lu ³⁺	1.616	0.08753443	222	1.605	0.08185250	289		
Hf^{4+}	1.563	0.06225334	718	1.556	0.05930945	847		
Zr^{4+}	1.597	0.07786298	707	1.576	0.06796452	804		
Ce^{4+}	1.752	0.17542802	653	1.747	0.17167295	789		
U^{4+}	1.770	0.18922704	980	1.767	0.18689752	1123		
Pu^{4+}	1.755	0.17769767	817	1.745	0.17018074	941		
Th^{4+}	1.755	0.17769767	452	1.755	0.17769767	598		

Table 56. The 12-6-4 parameter set for the 18 trivalent and 6 tetravalent metal ions in conjunction with the OPC3, OPC, TIP3P-FB, and TIP4P-FB water models.

		TIP3P-FB		TIP4P-FB				
	R _{min,M} /2 (Å)	ε _M (kcal/mol)	C ₄ (kcal/mol·Å ⁴)	R _{min,M} /2 (Å)	ε _M (kcal/mol)	C ₄ (kcal/mol·Å ⁴)		
Al ³⁺	1.366	0.01091456	387	1.357	0.00986018	427		
Fe ³⁺	1.452	0.02591906	446	1.451	0.02568588	502		
Cr^{3+}	1.404	0.01636246	232	1.403	0.01619682	286		
In^{3+}	1.488	0.03537062	343	1.484	0.03421577	403		
Tl^{3+}	1.572	0.06617338	464	1.565	0.06311131	514		
Y^{3+}	1.629	0.09454081	218	1.622	0.09072908	268		
La ³⁺	1.757	0.17921760	155	1.751	0.17467422	211		
Ce^{3+}	1.791	0.20584696	251	1.781	0.19786584	294		
Pr^{3+}	1.791	0.20584696	291	1.777	0.19470705	326		
Nd^{3+}	1.716	0.14920231	211	1.707	0.14295367	256		
Sm^{3+}	1.695	0.13482489	218	1.683	0.12693448	257		
Eu^{3+}	1.708	0.14364160	261	1.699	0.13750834	302		
Gd^{3+}	1.648	0.10534198	191	1.639	0.10014323	238		
Tb^{3+}	1.661	0.11310961	226	1.651	0.10710756	270		
Dy ³⁺	1.643	0.10243558	219	1.627	0.09344247	253		
Er^{3+}	1.634	0.09731901	256	1.626	0.09289608	304		
Tm^{3+}	1.645	0.10359269	285	1.628	0.09399072	320		
Lu^{3+}	1.619	0.08912336	250	1.615	0.08700853	303		
Hf^{4+}	1.580	0.06978581	787	1.561	0.06140287	837		
Zr^{4+}	1.611	0.08492362	769	1.603	0.08084383	845		
Ce^{4+}	1.760	0.18150763	701	1.750	0.17392181	771		
U^{4+}	1.788	0.20344023	1044	1.787	0.20264033	1140		
Pu^{4+}	1.744	0.16943676	817	1.744	0.16943676	919		
Th^{4+}	1.763	0.18380968	507	1.761	0.18227365	601		

Table 56. (cont'd).

	OPC3				OPC		TIF	P3P-FB		TIP4P-FB		
	HFE (kcal/m ol)	IOD (Å)	CN	HFE (kcal/m ol)	IOD (Å)	CN	HFE (kcal/mo l)	IOD (Å)	CN	HFE (kcal/m ol)	IOD (Å)	CN
Al^{3+}	-1081.3	1.88	6.0	-1081.0	1.88	6.0	-1081.1	1.88	6.0	-1080.4	1.88	6.0
Fe^{3+}	-1019.0	2.03	6.7	-1018.8	2.03	6.4	-1020.1	2.03	6.7	-1020.2	2.02	6.5
Cr^{3+}	-958.7	1.96	6.0	-956.4	1.95	6.0	-957.6	1.95	6.0	-958.1	1.96	6.0
In^{3+}	-951.4	2.16	8.0	-952.9	2.15	7.4	-950.2	2.16	8.0	-951.9	2.15	7.8
Tl^{3+}	-950.1	2.23	8.0	-949.1	2.23	8.0	-949.7	2.24	8.0	-950.3	2.24	8.0
Y^{3+}	-822.9	2.37	9.0	-823.9	2.37	8.9	-825.0	2.37	9.0	-825.7	2.36	9.0
La ³⁺	-753.0	2.51	9.0	-752.6	2.51	9.0	-750.8	2.51	9.1	-752.4	2.52	9.1
Ce^{3+}	-765.4	2.54	9.3	-765.3	2.55	9.2	-764.6	2.55	9.6	-764.2	2.55	9.5
Pr^{3+}	-775.6	2.54	9.4	-775.5	2.53	9.1	-776.0	2.55	9.7	-755.5	2.54	9.5
Nd^{3+}	-784.0	2.46	9.0	-782.2	2.47	9.0	-784.2	2.46	9.0	-785.7	2.46	9.0
Sm^{3+}	-794.8	2.44	9.0	-794.9	2.44	9.0	-795.0	2.44	9.0	-794.5	2.44	9.0
Eu^{3+}	-803.9	2.45	9.0	-802.4	2.45	9.0	-804.2	2.45	9.0	-803.3	2.45	9.0
Gd^{3+}	-807.4	2.40	9.0	-807.1	2.39	8.9	-807.4	2.39	9.0	-808.0	2.39	9.0
Tb^{3+}	-812.5	2.40	9.0	-814.2	2.4	9.0	-813.6	2.40	9.0	-813.8	2.40	9.0
Dy^{3+}	-818.1	2.38	9.0	-817.9	2.37	8.9	-818.8	2.38	9.0	-817.8	2.37	9.0
Er^{3+}	-835.0	2.37	9.0	-835.6	2.36	8.9	-835.5	2.37	9.0	-836.3	2.36	9.0
Tm^{3+}	-839.2	2.37	9.0	-841.2	2.36	9.0	-841.9	2.35	9.0	-842.0	2.36	9.0
Lu^{3+}	-839.8	2.34	8.8	-840.3	2.34	8.2	-841.5	2.35	9.0	-841.2	2.34	9.0
Hf^{4+}	-1663.2	2.15	8.0	-1664.0	2.16	8.0	-1663.7	2.15	8.0	-1664.1	2.15	8.0
Zr^{4+}	-1621.6	2.18	8.1	-1622.0	2.19	8.0	-1624.0	2.20	8.3	-1622.0	2.19	8.2
Ce^{4+}	-1462.5	2.42	10.0	-1462.8	2.41	9.9	-1463.3	2.42	10.0	-1461.2	2.42	10.0
U^{4+}	-1568.7	2.41	10.0	-1569.8	2.42	9.9	-1567.9	2.42	10.0	-1566.4	2.43	10.0
Pu^{4+}	-1521.9	2.40	9.9	-1521.3	2.38	9.0	-1519.8	2.39	9.9	-1521.4	2.39	10.0
Th^{4+}	-1388.2	2.44	10.0	-1389.8	2.45	10.0	-1390.1	2.45	10.0	-1391.2	2.45	10.0

Table 57. Calculated HFE, IOD, and CN values for the 12-6-4 parameter set for the four water models.

APPENDIX B: FIGURES



Figure 46. RMSDs of the binding site residues from the simulations using the 12-6 HFE, 12-6 IOD, and 12-6-4 parameter sets for Fe^{3+} in conjugation with the OPC water model. The RMSDs were calculated against the initial coordinates generated based on the crystal structure.



Figure 47. RMSDs of the binding site residues from the simulations using the 12-6 HFE, 12-6 IOD, and 12-6-4 parameter sets for Fe^{3+} in conjugation with the OPC3 water model. The RMSDs were calculated against the initial coordinates generated based on the crystal structure.



Figure 48. RMSDs of the binding site residues from the simulations using the 12-6 HFE, 12-6 IOD, and 12-6-4 parameter sets for Fe^{3+} in conjugation with the TIP3P water model. The RMSDs were calculated against the initial coordinates generated based on the crystal structure.



Figure 49. Linear extrapolation plots to calculate the diffusion coefficient of F



Figure 50. Linear extrapolation plots to calculate the diffusion coefficient of Cl⁻



Figure 51. Linear extrapolation plots to calculate the diffusion coefficient of Br⁻



Figure 52. Linear extrapolation plots to calculate the diffusion coefficient of Li⁺



Figure 53. Linear extrapolation plots to calculate the diffusion coefficient of Na⁺



Figure 54. Linear extrapolation plots to calculate the diffusion coefficient of K⁺



Figure 55. Linear extrapolation plots to calculate the diffusion coefficient of Ag⁺



Figure 56. Linear extrapolation plots to calculate the diffusion coefficient of Be^{2+}



Figure 57. Linear extrapolation plots to calculate the diffusion coefficient of Cu²⁺



Figure 58. Linear extrapolation plots to calculate the diffusion coefficient of Zn^{2+}



Figure 59. Linear extrapolation plots to calculate the diffusion coefficient of Al³⁺



Figure 60. Linear extrapolation plots to calculate the diffusion coefficient of Cr³⁺



Figure 61. Linear extrapolation plots to calculate the diffusion coefficient of Fe^{3+}

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