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Halide, Ammonium, and Alkali Metal Ion Parameters for Modeling Aqueous Solutions

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Abstract: A complete set of Lennard Jones parameters for the halide ions, F^-, Cl^-, Br^-, and I^-, ammonium ion, and the alkali metal ions is reported. The parameters have been optimized using Monte Carlo simulations and free energy perturbation theory with the TIP4P water model to reproduce experimental free energies of hydration and locations of the first maxima of the ion-oxygen radial distribution functions, to provide water coordination numbers consistent with experimental ranges, and to exhibit gas-phase monohydrate energies in reasonable agreement with ab initio values. Average errors for absolute and relative free energies of hydration for the ions are ca. 1 kcal/mol. For the halides, this is the first self-consistent set of parameters that has been optimized for aqueous-phase performance. The good results for relative free energies of hydration are particularly auspicious for use of the new parameters in a wide variety of liquid-phase simulations where halide and alkali cations are systematically varied.

Introduction

The study of the hydration of ions is of major importance in chemistry and biochemistry. When ions are part of a system to be studied by classical simulations, a set of parameters describing the interactions of the ions with other atoms is necessary. These parameters are usually those of a Lennard-Jones (LJ) potential, which is an empirical, effective two-atom potential. Electrostatic interactions are described by Coulomb's law and fixed atomic charges. The LJ parameters of the ions can be fitted to reproduce thermodynamic and structural data, whereas the atomic charges are assigned a priori as the formal charges of the ions. The properties are derived from statistical-mechanical simulations of model systems, which are intended to resemble an infinitely dilute solution.

A main problem with simulating hydration of ions is the electrostatic interactions. Because of their range, it is necessary to correct for the use of a finite model system. Doing this can strongly affect both structure and free energy of hydrated ions.[1-3] For an ion in an aqueous model system, both the ion−water (IW) and water−water (WW) interactions contribute to the hydration free energy:[2] WW interactions disfavor ion hydration, whereas IW interactions favor

hydration. The problem of long-range electrostatics in general remains unsolved, although progress is taking place.[4-6]

When the simulation system is truncated, corrections for the absent bulk are needed. Born theory can be applied to correct to the asymptotic limit of cavity sizes, as this limit is determined by the long-range behavior of Coulomb's law. For normal ions with small cavities given by ionic or covalent radii, the hydration enthalpies are inversely proportional to the radii as implied by Born theory.[7] However, the contributions to the free energy of solvation from the region closest to even a spherical ion are not well modeled by Born theory, since deviations from continuum theory are largest at short range.[3,8] Notably, the hydration of anions and cations with the same cavity sizes should differ, owing to the different structure of the water molecules around an anion and a cation, but Born theory only depends on the squared ion charge. However, a Born correction is justified at longer distances and can be used to correct for hydration energies outside a cavity radius defined by the cutoff procedure.

There are two main approaches to modeling ion hydration: One is to use space-filling replicas of the simulation cell with periodic boundary conditions (PBC), typically boxes of water with a central ion in each cell. Another is to simulate only one cell without replicas and include nonperiodic boundary conditions (NPBD). Examples of the latter include

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a pure vacuum calculation, a truncated physical system without periodicity, or possibly a truncated system with constraints to the surface region, as in a droplet with spherical boundary conditions (SBC). There are advantages and disadvantages to both approaches.[9]

For PBC, the use of lattice techniques such as Ewald summation provides an opportunity to calculate the electrostatics of the system, as a periodic solution to the Poisson equation. However, Ewald summation does not describe the asymptotically decaying electrostatic field, because of the periodicity, i.e., the finite concentration. A self-energy correction can be used to remove the artificial self-interaction, but the model system is still made up of replicas of finite systems. In charged systems, the use of a neutralizing background charge density, usually chosen to be uniform, is deemed necessary, even though this does not model a real counterion density.[10] Another issue is the boundary conditions: It has been found that tin foil boundary conditions give substantial errors.[11] However, this artifact can be remedied by using vacuum boundary conditions instead.[11,12]

Even with these approximations, calculations with PBC on small clusters give reasonable and size independent hydration energies when using Ewald summation with a self-energy correction.[13] A cancellation of self-energies and water polarization contributes to this success, but this effect is not yet well understood.[9] As an alternative, a Born correction may be applied in PBC with a cavity radius equal to the IW cutoff radius, but the resulting free energies will depend critically, even arbitrarily, on the value of the WW cutoff.[3]

The alternative to PBC is typically to use a droplet of water with the ion situated in the center. To remove finite-size effects, several suggestions for SBC are available. Constraints on the density of the droplet and on the polarization of surface water molecules to fit bulk properties are common.[14] The surface potential, the work required to move a unit charge through the surface, was suggested to make up for the difference between PBC and SBC.[15,16] It varies less than 0.5 kcal/mol with increasing system size beyond a cavity radius of 10 Å,[15] though estimates of its magnitude vary, e.g., 2.3 kcal/mol,[17,18] 4 kcal/mol,[19] and 12 kcal/mol,[15] depending on the model.[20] A value of 3 kcal/mol was calculated specifically for the TIP4P water model used in the present work.[21] Interestingly, experiments face very similar problems, with pros and cons on the sides of cluster-ion experiments and bulk solutions.[19]

With PBC, a decision on truncation of the IW and WW interactions is necessary. There is still no consensus on the best way to truncate interactions. While people often use exactly half the box length as the IW cutoff,[22,23] it is also advised to use IW cutoffs "significantly shorter than half the box length".[24] Cutoff corrections from continuum theory have been made for both IW and WW interactions, rendering the earlier problematic calculations[3] size independent to within ±0.7 kcal/mol.[25] A comparison was done between PBC and SBC, in the form of the surface constrained all-atom solvent model by Warshel and co-workers (SCAAS).[26] It was pointed out that when applying the corrections, the discrepancy between the methods was 5 kcal/mol for the Ne → Na$^+$ mutation. This suggests that at least one method is

Table 1. Experimental Ionic Radii, First Maxima of Radial Distribution Functions, and Free Energies and Entropies of Hydration

ion	r_i (Å)^a	R_1 (Å)^b	$-\Delta G_{hyd}{}^c$ Marcus^d	Noyes^e	Tissandier^f	$-T\Delta S_{Hyd}{}^c$ Marcus^d
Li$^+$	0.69	2.08	113.5	122.1	126.4	13.1
Na$^+$	1.02	2.36	87.2	98.4	101.3	12.0
K$^+$	1.38	2.80	70.5	80.6	84.1	8.4
Rb$^+$	1.49	2.89	65.7	75.5	78.6	7.2
Cs$^+$	1.70	3.14	59.8	67.8	73.1	7.2
NH$_4{}^+$	1.48		68.1			9.6
F$^-$	1.33	2.63	111.1	89.5	102.5	10.8
Cl$^-$	1.81	3.19	81.3	76.1	72.7	6.0
Br$^-$	1.96	3.37	75.3	69.2	66.2	4.8
I$^-$	2.20	3.65	65.7	60.3	57.4	3.6

^{a} Ionic radii from ref 27. ^{b} First maximum of ion−water oxygen radial distribution functions from ref 29. ^{c} ΔG and $T\Delta S$ for ion(gas) → ion(aq) in kcal/mol. ^{d} Reference 27. ^{e} Reference 28. ^{f} Reference 19.

less accurate, or both have uncertainties of that magnitude.[25] However, similar numbers (−109 and −108 kcal/mol) were obtained for PBC and SCAAS using 10 Å cutoffs, suggesting that the methods yield similar results when the cutoffs are identical.[25] Instead, the infinite cutoffs that can be applied in the SCAAS models seem to be responsible for the difference. Since this effect mainly applies to WW interactions, these calculations are more repulsive than the solvent−solvent cutoff correction would imply, thereby giving less favorable hydration energies by up to 5 kcal/mol. Other corrections for WW cutoffs have been studied, but the results were only reasonably independent of system size when differences in IW and WW cutoffs were 2 Å or less.[24]

Some compilations of experimental data on ion hydration are shown in Table 1. Since experimental hydration free energies range over at least 10 kcal/mol,[19,27,28] reproducing absolute free energies of hydration is not as important as obtaining *size independent* models of ion hydration, i.e., models that give similar answers for various cell sizes, and therefore can be corrected with a simple constant independent of system size.

Importantly, relative free energies of hydration within a series remain in quantitative agreement, except for the value for F$^-$ computed by Noyes, which is off by 15 kcal/mol. Another problem is the relative free energies between the alkali metal ion and halide series. In the Marcus compilation,[27] Li$^+$ ≈ F$^-$, whereas in the Tissandier compilation,[19] Li$^+$ is better hydrated by 24 kcal/mol. In particular, the Tissandier values are similar for Cs$^+$ and Cl$^-$, which have similar ionic radii (r_I) and first maxima of their radial density distributions (R_1) (these two properties are linearly correlated). However, it is well-known that anions have more negative ΔG_{hyd} for similar radii,[30] so Tissandier's cluster-pair approximation seems less adequate for separating hydration contributions for anions and cations. Because of these considerations, the Marcus compilation has been used as the target data for the present work.

A number of additional computational studies of ions in solution should be noted. For the particular case of halide and alkali metal ions, early Monte Carlo simulations of Li$^+$,

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Na^+, K^+, F^-, and Cl^- in water were carried out by Mezei and Beveridge,[31] and simulations of Na^+ in water, methanol, and tetrahydrofuran were performed by Chandrasekhar and Jorgensen.[32] Another detailed study described the volumes, coordination numbers, hydration energies, and energy components for Li^+, Na^+, F^-, and Cl^- based on a parameter set fitted to HF/3-21G* or HF/3-21+G geometries and interaction energies.[33] For obtaining hydration free energies, Brooks studied Cl^- and Br^- ions by thermodynamic perturbation and temperature derivatives.[23] Free energy perturbations (FEPs) have been applied by Lybrand et al. to compute the difference in ΔG_{hyd} for Cl^- and Br^-,[34] by Jorgensen et al. to compute the absolute ΔG_{hyd} of Cl^-,[35] and by Åqvist to obtain absolute free energies for alkaline and alkaline earth metal ions.[36] These studies showed that relative free energies of hydration can be obtained with good accuracy. The study by Åqvist demonstrated that it is also meaningful to aim for *absolute* free energies of hydration, and from there, relative free energies follow. Another study by Migliore et al.[37] used a similar perturbation approach to calculate the relative hydration free energies of Li^+, Na^+, and K^+ as well as F^- and Cl^-.

Ion parameters used in standard software packages differ substantially and give rise to different structures and energetics for ions in water.[38] The present focus is on development of parameters optimized to reproduce liquid-phase properties, as in the philosophy of the OPLS force fields and the approach by Åqvist.[36] In addition to Åqvist's widely used parameters, other LJ parameters were developed for Li^+, Na^+, F^-, and Cl^- by Chandrasekhar et al.,[33] for these ions and K^+ by Pettitt et al.,[39] and for Na^+ and K^+ by Marrone and Merz.[40] All alkali metal ions and halide ions were parametrized by Peng et al. based on experimental crystal data.[41] They also included a compilation and discussion of other alkali metal and halide ion parameters. Some negative conclusions[40] regarding transferability of ion models were found to be invalid.[42,43] The treatment of long-range interactions remains a major reason for discrepancies between ion hydration studies.

Despite these efforts, no consistent OPLS-style (based on fitting to liquid-phase data) set of parameters has so far been developed for the halide ion series. By consistent, it is meant that relative free energies and structures between the ions should be well reproduced. The purpose of the present work is to develop such a consistent set of force field parameters for the halide ions. In addition, it would be highly desirable to have one set of force field parameters giving free energies and structures consistent for *both* cations and anions, since an important goal is to obtain reliable energies and structures also in situations containing multiple ions, such as for a protein with counterions and added salt. Therefore, parameters have also been obtained for the alkali metal ions and united-atom NH_4^+, using the same set of experimental target data.

It has been argued that the effective, additive LJ potential is suitable for simulations as long as parameters are obtained in a consistent manner;[42] the limited adoption of polarizable force fields indicates that effective pair potentials will continue to play an important role in molecular simulations.

Methods

Computational Details. Monte Carlo (MC) statistical mechanics simulations were performed to obtain averaged thermodynamic and structural results. All calculations were carried out with the BOSS software, version 4.6, following standard protocols including use of the TIP4P water model[44] and preferential sampling for water molecules near the ion.[45] As described below, most simulations were carried out for a single ion in water droplets with 10- or 15-Å radii containing 137 or 472 water molecules. Free energy perturbations (FEPs) were carried out to obtain ensemble-averaged free energies of hydration by annihilating the ions. In one set of FEPs, charges were neutralized, and subsequently the Lennard-Jones parameters were perturbed to zero. Absolute free energies were obtained in this way for all ions. Generally, 10 windows with double-wide sampling were used for an FEP. Each MC simulation was run for 5−10M configurations of equilibration and 10−20M configurations of averaging, depending on system size. The typical statistical uncertainty for the computed free-energy changes was ca. 0.1 kcal/mol. The temperature for all simulations was 298 K and the pressure was 1 atm when periodic boundary conditions were used. In the cutoff procedure, the nonbonded energy between the entire water molecule and the ion was evaluated if any of the three water atoms was closer than the cutoff distance to the ion. The simulations with PBC and TIP4P boxes were subject to a variety of both WW and IW cutoff distances, whereas in the droplet simulations all interactions were evaluated within the droplets using cutoffs of 100 Å. The Lennard-Jones parameters for the ions were developed to simultaneously yield good agreement with the experimental free energies of hydration and locations of the first peaks in ion−water radial distribution functions. Consistent with the practice for the OPLS-AA force field, geometric combining rules are used here for the Lennard-Jones parameters, i.e., $\epsilon_{ij} = (\epsilon_{ii}\epsilon_{jj})^{1/2}$, $\sigma_{ij} = (\sigma_{ii}\sigma_{jj})^{1/2}$. As noted previously,[43] lack of attention to this detail can lead to significant discrepancies.

Calibration of the Model. The following describes the choice of simulation model used here. Due to problems mentioned already with Ewald summation (boundary conditions, finite ion concentration, and the use of uniform background charges), such an approach was deemed impractical for the present purpose. As an alternative, using a Born correction in PBC without Ewald summation makes little sense insofar as the problem of WW interactions is not well accounted for. Ideally, all WW interactions within the "cavity" formed by the IW cutoff should be included, so that the remaining hydration free energy outside the cavity is effectively that predicted by continuum theory. But with the use of PBC, IW cutoffs have to be smaller than or equal to half the box length. As described earlier, the magnitude of the hydration free energy then depends critically on the choice of WW cutoff.[3] To get a clearer picture of these effects, FEP annihilations were performed for Åqvist's Na^+ ion in boxes of TIP4P water with PBC and various WW and IW cutoffs. The results are shown in Figure 1. When the IW and WW cutoffs are equal, ΔG_{hyd} varies little beyond a cutoff of 9 Å, implying cancellation of errors. However,
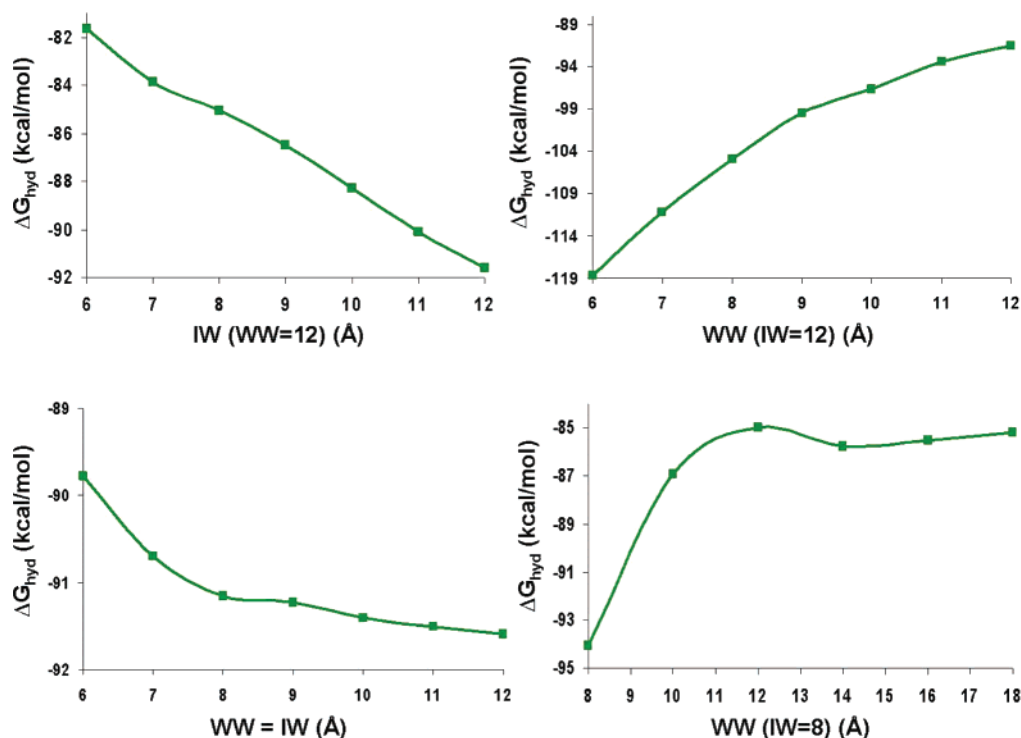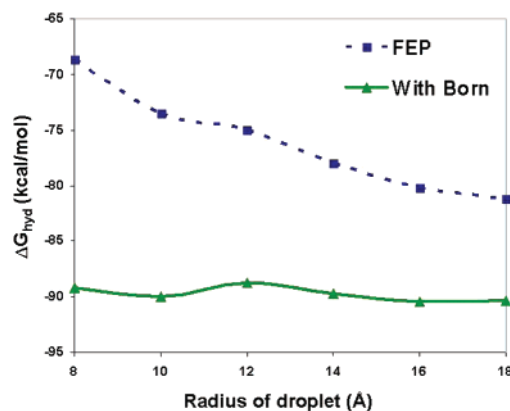
Figure 1. Simulations of Åqvist's Na$^+$ in TIP4P boxes with PBC. Effect of IW and WW cutoffs.

the additional results are not consistent with continuum theory, implying that this model is unbalanced. Interestingly, size consistency is obtained as the WW cutoff increases to twice the IW cutoff. The box used to study the dependence on WW cutoff from 8 to 18 Å contained 2500 water molecules, using 10 M configurations for equilibration and 20 M for averaging. However, these calculations are very time-consuming, in particular for parametrization work, where large numbers of FEP calculations are required.

As an alternative, use of a droplet with a Born correction should give size-independent results within the error of the surface potential and the SBC.[15] These errors amount to 3−4 kcal/mol for pure water[19] independent of system size and 1 kcal/mol for the surface polarization (as calculated with SCAAS),[25] i.e., less than the errors in estimates of absolute hydration free energies for ions from experiment. This was tested in FEP annihilations of Na$^+$ in TIP4P water droplets of varying size. A half-harmonic restoring force of 1 kcal/mol-Å^2 was used to inhibit potential evaporation of water molecules from the surface of the droplet, though this is a very rare event in the absence of the restoring potential. The results are shown in Figure 2. When the hydration free energy is given as the simulated free energy plus the Born correction, with the Born radius equal to the droplet radius, the free energies of hydration become size independent and give a free energy of hydration of −90 kcal/mol. Åqvist's result with the same ion parameters, SCAAS model, and SPC water was −98 kcal/mol.[36]

Because of these considerations, the present work has been carried out on water droplets using infinite IW and WW cutoffs. Use of a droplet with a 10-Å radius for parametrization was justified by the preliminary results. However, all optimized parameter sets were also validated in droplets with 15-Å radii. Larger droplets do not affect the free energy of
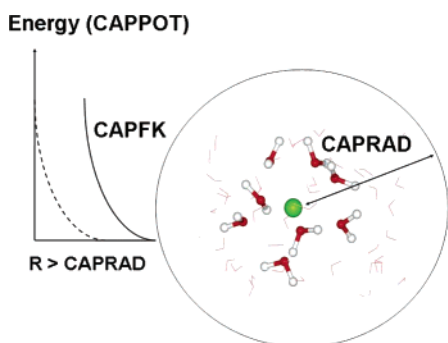

Figure 2. Calculated free energy of hydration for Åqvist's Na$^+$ in TIP4P water droplets with infinite (100 Å) cutoffs for both water−water and ion−water interactions.

hydration beyond the uncertainty of the simulations (∼ 1 kcal/mol), as long as infinite cutoffs and a Born correction are applied. The Born model was shown to be consistent with the scaling of size corrections in large water clusters containing an ion.[46]

The present model is depicted in Figure 3. The ion is positioned at the CAP origin; it is not moved so it remains at the center of the droplet throughout the simulation. Otherwise, as the ion is discharged and becomes more hydrophobic it would tend to migrate to the surface. Three setups were tried to test the stability of the model using different boundary treatments: (i) droplets without any constraints (a restoring force constant CAPFK = 0); (ii) droplets with a potential CAPPOT starting at the droplet radius CAPRAD, with CAPFK = 1 kcal/mol-Å^2; and (iii) droplets with CAPFK = 1 kcal/mol-Å^2, but starting at CAPRAD + 5 Å. The small values of CAPFK reflect a

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Figure 3. The spherical model used in the present work. CAPRAD is the radius of the droplet in Å, CAPPOT is the half-harmonic restraint potential beyond CAPRAD (full line) or CAPRAD + 5 Å (dashed line), and CAPFK is the force constant for the half-harmonic potential.

Table 2. Optimized Lennard-Jones Parameters for Ions

ion	σ	ϵ
F⁻	3.05	0.71
Cl⁻	4.02	0.71
Br⁻	4.28	0.71
I⁻	4.81	0.71
Li⁺	2.87	0.0005
Na⁺	4.07	0.0005
K⁺	5.17	0.0005
Rb⁺	5.60	0.0005
Cs⁺	6.20	0.0005
NH₄⁺	5.34	0.0005

compromise to minimize artificial constraints on the density of the droplets, while still preventing significant evaporation of water molecules, which could compromise the validity of the Born correction. As shown below, all three setups give very similar results. The free energies of hydration are insensitive to these mild boundary constraints, mainly due to the larger radial force that the ion and neighboring water molecules already exert on the water molecules near the surface.

Results and Discussion

Halide Parameters. The optimized Lennard-Jones parameters are shown in Table 2. There exists a positive correlation between both σ and ϵ and R_1 and a negative correlation between both σ and ϵ and the magnitude of ΔG_{hyd}. Because of this, freedom is limited during parametrization when fitting to R_1 and ΔG_{hyd}. Even then, it was possible to find one value of ϵ, which could be used to fit all halide ions and all cations, respectively. It is not obvious that there should be a particular trend in ϵ parameters for ions when going down a period. The trends in existing force field parameter sets[41] are mainly due to predefined end points of the free energy curves used during fitting. In fact, for the noble gases, the trend in ϵ parameters is opposite of that in most ion sets, i.e., ϵ increases going down the period.[47] This is reasonable, as dispersion interactions are expected to scale with the size of the neutral atoms. However, for ions, the LJ potential must include polarization effects indirectly through fitting of parameters and not with an explicit physical term, so no particular trend

Table 3. Results for Halide Ions in Aqueous Solution

ion	$-\Delta G_{hyd}$ (10)[a]	$-\Delta G_{hyd}$ (15)	R_1(15)[b]	$-\Delta G_{hyd}$ (exp)	R_1 (exp)
	CAPFK = 0 kcal/mol-Å²				
F⁻	111.8	110.3	2.75	111.1	2.63
Cl⁻	81.0	80.3	3.25	81.3	3.19
Br⁻	75.3	77.5	3.35	75.3	3.37
I⁻	66.0	67.2	3.55	65.7	3.65
RMS	0.4	1.5	0.08		
	CAPFK = 1 kcal/mol-Å², R_0 = CAPRAD + 5 Å				
F⁻	110.5	109.5	2.75	111.1	2.63
Cl⁻	81.5	81.2	3.25	81.3	3.19
Br⁻	76.5	76.2	3.35	75.3	3.37
I⁻	67.6	65.0	3.55	65.7	3.65
RMS	1.2	1.0	0.08		
	CAPFK = 1 kcal/mol-Å²				
F⁻	111.6	110.4	2.75	111.1	2.63
Cl⁻	81.4	79.6	3.25	81.3	3.19
Br⁻	75.9	76.3	3.35	75.3	3.37
I⁻	66.1	66.9	3.60	65.7	3.65
RMS	0.4	1.2	0.07		

[a] Free energies of hydration ΔG_{hyd} in kcal/mol ± 0.5 kcal/mol. [b] First maxima of radial distribution functions, R_1 in Å ± 0.025 Å. Parentheses refer to the radius of the water droplet, CAPRAD.

is trivially anticipated. Thus, the minimal model of identical ϵ parameters for all halides has been adopted here. A value of $\epsilon = 0.71$ kcal/mol gave the best fit to both structure and energies for all halide ions. On the other hand, the σ parameters follow the clear trend of increasing ion sizes, which is consistent with the physical picture of increasing ionic radii.

Table 3 shows the obtained free energies of hydration with the three different models: no restraint force, a force constant CAPFK of 1 kcal/mol Å² turned on at CAPRAD, and shifted to CAPRAD + 5 Å. All three models were applied with a CAPRAD of both 10 and 15 Å to test for size effects. Thus, for each final set of halide parameters, six values of ΔG_{hyd} are presented. While optimization of the parameters was done with the smaller droplets, it is seen from Table 2 that all six models provide good absolute free energies, with a RMS deviation of 0.4−1.5 kcal/mol. This is the limiting accuracy given the approximations in the setup. Notably, the system size independence for all three CAP models is excellent.

Furthermore, the first maxima of the ion-oxygen radial distribution functions (RDFs), R_1, display a RMS deviation from experiment of 0.07−0.08 Å. The structure of the first solvation shell is very insensitive to the choice of model, again confirming the validity of the approach. Only the maxima for the models with a 15-Å radius are listed since the results are essentially identical for the smaller droplets. The largest discrepancy is for F⁻; the peak position could not be fit to better than 0.12 Å without losing accuracy for the free energy result. This conclusion was drawn from an extensive search that involved simultaneously varying both ϵ and σ, with ϵ varying from 0.0001 to 1.0 kcal/mol and σ from 2 to 4 Å. Larger values of ϵ worked well for the halide ions, whereas smaller values were optimal for the cations. The difference again arises from the variations in the hydration of anions and cations for a given ionic radius.

Cation Parameters. The optimized Lennard-Jones parameters for the alkali metal ions and a united-atom model

Table 4. Optimized Parameters and Results for Cations in Aqueous Solution[c]

ion	$-\Delta G_{hyd}$ (10)[a]	$-\Delta G_{hyd}$(15)	R_1(15)[b]	$-\Delta G_{hyd}$ (exp)	R_1 (exp)
		CAPFK = 0 kcal/mol-Å²			
Li⁺	114.4	111.9	2.05	113.5	2.08
Na⁺	87.6	87.4	2.45	87.2	2.36
K⁺	69.4	72.9	2.85	70.5	2.80
Rb⁺	65.7	65.4	2.95	65.7	2.89
Cs⁺	59.1	60.5	3.20	59.8	3.14
NH₄⁺	68.8	68.4	2.90	68.1	2.85
RMS	0.7	1.2	0.06		
		CAPFK = 1 kcal/mol-Å², R_0 = CAPRAD + 5 Å			
Li⁺	113.8	112.8	2.05	113.5	2.08
Na⁺	88.8	87.4	2.50	87.2	2.36
K⁺	70.8	71.6	2.85	70.5	2.80
Rb⁺	66.6	66.5	3.00	65.7	2.89
Cs⁺	59.3	60.0	3.20	59.8	3.14
NH₄⁺	70.3	68.4	2.90	68.1	2.85
RMS	1.2	0.7	0.08		
		CAPFK = 1 kcal/mol-Å²			
Li⁺	114.5	113.3	2.05	113.5	2.08
Na⁺	87.9	86.4	2.50	87.2	2.36
K⁺	71.1	69.7	2.85	70.5	2.80
Rb⁺	66.1	64.4	3.00	65.7	2.89
Cs⁺	59.7	58.9	3.20	59.8	3.14
NH₄⁺	68.8	68.3	2.90	68.1	2.85
RMS	0.7	0.8	0.08		

[a] Free energies of hydration ΔG_{hyd} in kcal/mol. [b] First maxima of radial distribution functions, R_1 in Å. [c] Parentheses refer to the radius of the water droplet, CAPRAD.

of ammonium ion are displayed in Table 2. The alkali metal parameters have been reparametrized from Åqvist's original parameters and fitted to the ΔG_{hyd} and R_1 of Marcus' compilation, with the aim of providing parameters that reproduce experimental data from the same data set. Again, a minimal model with a single choice for ϵ was successfully applied. The value of 0.0005 kcal/mol for ϵ was best-suited to reproduce both structure and free energies simultaneously. The σ parameters again followed the trend of increasing ion size.

The results obtained with the new cation parameters are displayed in Table 4. As before, all six models provide good absolute free energies of hydration, this time with a RMS deviation of 0.7–1.2 kcal/mol, a similar range as for the halide ions. As seen, system-size independence of the results is obtained with both anions and cations.

The values for R_1 are reproduced with a similar accuracy as before, i.e., with a RMS deviation from experiment of 0.06–0.08 Å. These deviations are similar to the experimental uncertainty, which is estimated at 0.06–0.08 Å.[29] Except for Li⁺, all peak positions are slightly larger than from experiment, but other choices of ϵ did not provide as good overall results. As a rough conclusion, it can be said that the new parameters reproduce absolute free energies of hydration to about 1 kcal/mol and absolute and relative first maxima of ion-oxygen RDFs to within 0.1 Å.

Comparison with Results using Prior Parameters. To evaluate the quality of the new parameter set in more detail, its performance is compared to that using previous param-

Table 5. (a) Free Energies of Hydration ΔG_{hyd} (kcal/mol) with Old Halide Parameters and (b) Comparison of Relative Free Energies of Hydration $\Delta\Delta G_{hyd}$ (kcal/mol) Obtained with Old and New Halide Parameters

a

ion	σ	ϵ	$-\Delta G_{hyd}$ (10)[a]	$-\Delta G_{hyd}$ (15)[a]	$-\Delta G_{hyd}$ (exp)
F⁻ [b]	2.73295	0.72	126.8	126.5	111.1
Cl⁻ [b]	4.41724	0.11779	77.7	79.6	81.3
Br⁻ [c]	4.62376	0.09	73.8	76.1	75.3
I⁻ [d]	5.40	0.07	61.3	62.9	65.7
RMS			8.4	7.9	

b

ion	$\Delta\Delta G_{hyd}$ old[e]	$\Delta\Delta G_{hyd}$ new[e]	$\Delta\Delta G_{hyd}$ (exp)
F⁻ − Cl⁻	48.0	30.4	29.8
Cl⁻ − Br⁻	3.7	4.3	6.0
Br⁻ − I⁻	14.1	9.8	9.6
RMS	10.9	1.1	

[a] Parentheses refer to the radius of the water droplet. CAPFK = 0 kcal/mol Å². [b] Reference 33. [c] Reference 34. [d] Reference 48. [e] Average of models with CAPRAD = 10 and 15. CAPFK = 0 kcal/mol Å².

Table 6. (a) Free Energies of Hydration ΔG_{hyd} (kcal/mol) with Old Cation Parameters and (b) Comparison of Relative Free Energies of Hydration ΔG_{hyd} (kcal/mol) Obtained with Old and New Cation Parameters

a

ion	σ	ϵ	$-\Delta G_{hyd}$ (10)[a]	$-\Delta G_{hyd}$ (15)[a]	$-\Delta G_{hyd}$ (exp)[a]
Li⁺ [b]	2.12645	0.01828	116.5	115.0	113.5
Na⁺ [b]	3.33045	0.00277	88.9	91.9	87.2
K⁺ [b]	4.93463	0.00033	73.9	75.5	70.5
Rb⁺ [b]	5.62177	0.00017	69.2	71.2	65.7
Cs⁺ [b]	6.71700	0.00008	66.5	64.1	59.8
NH₄⁺ [c]	3.25	0.17	76.6	78.2	68.1
RMS			5.1	5.8	
RMS[d]			4.0	4.4	

b

ions	$\Delta\Delta G_{hyd}$ old[e]	$\Delta\Delta G_{hyd}$ new[e]	$\Delta\Delta G_{hyd}$ (exp)
Li⁺ − Na⁺	25.4	25.7	26.3
Na⁺ − K⁺	15.7	16.4	16.7
K⁺ − Rb⁺	4.5	5.6	4.8
Rb⁺ − Cs⁺	4.9	5.8	5.9
K⁺ − NH₄⁺	−2.7	2.6	2.4
RMS	2.4	0.5	- - -
RMS[f]	0.9	0.6	- - -

[a] Parentheses refer to the radius of the water droplet. CAPFK = 0 kcal/mol Å². [b] Reference 36. [c] Reference 49. Charges: −0.40 (N), +0.35 (H). [d] Excluding NH₄⁺. [e] Average of models with CAPRAD 10 and 15. CAPFK = 0 kcal/mol Å². [f] Excluding NH₄⁺.

eters in Tables 5 and 6. Table 5a shows the absolute free energies of hydration for the halide ions obtained with the small and large droplets with CAPFK = 0 kcal/mol-Å² and using the old parameters for F⁻,[33] Cl⁻,[33] Br⁻,[34] and I⁻.[48] These parameters also yield good system-size independence, confirming the general quality of the droplet model. However, the old halide parameters yield greater deviations from the absolute free energies of hydration, which is expected

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since their derivation was different. The absolute free energies for Cl⁻, Br⁻, and I⁻ are not far from experiment; the main error is due to a large overestimation of the magnitude of the free energy of hydration for F⁻. For the halide ions taken together, the RMS deviation from the Marcus free energies is 8.4 kcal/mol for the smaller droplet and 7.9 kcal/mol for the larger droplet.

The corresponding relative free energies obtained with the old parameters are compared to the results from the new ones in Table 5b; the averages of the results obtained with the small and large droplets are used. Whereas the differential hydration free energy of F⁻ and Cl⁻ is overestimated by 18 kcal/mol with the old parameter set, the error is reduced to 0.6 kcal/mol with the new set. Because the parameters for the last three halide ions are reasonable, they also yield better relative free energies. However, the overall RMS deviation from the experimental relative free energies remains high, 10.9 kcal/mol, for the old halide parameters. This was one of the main problems to be corrected in the present work. With the new parameters, the RMS deviation from experimental relative free energies is 1.1 kcal/mol.

Table 6a,b provides similar comparisons with results using the earlier parameters for cations, i.e., the alkali metal ion parameters of Åqvist[36] and the all-atom OPLS parameters for ammonium ion.[49] The old alkali cation parameters provide free energies that are uniformly larger in magnitude by just a few kcal/mol than the experimental numbers, even though they were parametrized toward slightly different target data. This shows that the models used by Åqvist and here in fact provide similar results. Nevertheless, the reparametrization was carried for both the halide ions and cations for consistency and to achieve lower overall errors in comparison to the Marcus data.

The largest deviation is for the old ammonium ion, which was parametrized independently.[49] The Åqvist set alone has a RMS deviation from our target data of only 4.0 and 4.4 kcal/mol for the small and large droplets, respectively. As shown in Table 6b, the Åqvist parameters perform very well for relative free energies with a RMS deviation of 0.9 kcal/mol. Thus, it appears that relative free energies can be well reproduced with a variety of models if the parameter set is well parametrized to fit absolute free energies.[36] The new cation set performs similarly for the alkali metal ions with a RMS deviation of 0.6 kcal/mol. Therefore, the only effect of reparametrizing the alkali metal ion parameters has been to put anions and cations on a common scale and make the parameters simpler. Larger errors are seen for ammonium, for which the old OPLS all-atom model actually gives the wrong relative free energy of hydration compared to K⁺. With the new united-atom parameters, this artifact is removed, and the complete cation set including NH₄⁺ has a RMS deviation of 0.5 kcal/mol from the experimental relative free energies.

Gas-Phase Ion−Water Interactions. To test the reasonability of the developed force-field parameters, it is common to calculate the interaction energies for monohydrates (complexes of the ions with a single water molecule) and compare them to ab initio or experimental data. Indeed, many force fields have been parametrized to fit such energies.

Table 7. Ion−Oxygen Distances and Interaction Energies for Ion−Water Complexes in the Gas Phase

ion	R_O (Å) OPLS TIP4P	R_O (Å) OPLS TIP3P	R_O (Å) ab initio	ΔE OPLS TIP4P	ΔE OPLS TIP3P	ΔE_0 ab initio	$\Delta H_{hyd,1}$ exp[d]
F⁻	2.71	2.73	2.44[a]	−19.5	−19.3	−25.1[a]	−23.3
Cl⁻	3.24	3.26	3.11[a]	−13.0	−13.5	−13.1[a]	−13.1
Br⁻	3.38	3.38	3.32[a]	−11.9	−12.5	−11.5[a]	−12.6
I⁻	3.62	3.63	3.63[a]	−10.3	−11.0	−9.6[a]	−10.2
Li⁺	1.99	1.96	1.85[b]	−28.1	−31.6	−33.5[b]	−34.0
Na⁺	2.43	2.41	2.28[b]	−19.4	−21.6	−22.4[b]	−24.0
K⁺	2.80	2.77	2.59	−15.0	−16.6	−17.9[b]	−16.9
Rb⁺	2.93	2.90	2.86	−13.7	−15.2	−15.1[c]	−16.0
Cs⁺	3.11	3.08	3.07	−12.3	−13.6	−13.8[c]	−14.0
NH₄⁺	2.85	2.82		−14.5	−16.0		−17.2

[a] MP2/6-311++G** from ref 50. [b] MP2/cc-pVQZ values from ref 51. [c] MP2/cc-pVTZ values from ref 52. [d] Reference 52.

However, in the case of force-field parameters fit to liquid-state data, it is not expected that a perfect fit is also obtained for the interaction energies. Deviations are expected owing to polarization effects, as effective two-body potentials are biased toward the *average* many-body situation in the liquid. Nevertheless, reasonable results for complexes are expected in view of the dominant Coulombic component of the interaction energy.

Table 7 provides a comparison of the interaction energies for monohydrates obtained with ab initio methods as well as with the new force field parameters and both a TIP4P and TIP3P water molecule. The force-field results are from energy minimizations, while the ab initio values are the electronic energy difference plus a correction for the change in zero-point energy, which is quite steady near +1 kcal/mol.[49,50] As can be seen, the interaction energies obtained with the liquid-phase force field are mostly a little less negative than the ab initio values. Concomitantly, the force field yields slightly larger ion-oxygen distances than the ab initio calculations. The differences are greatest for the smallest ions, F⁻ and Li⁺, which are the most bound and most polarizing. Overall, the results appear reasonable and follow the expected trends with increasing ion size. Furthermore, the differences for the ion-oxygen distances between the TIP3P and TIP4P water models are negligible, while the interaction energies are generally more favorable with TIP3P by 1−2 kcal/mol. However, the optimal water−water interaction is also stronger for the TIP3P water dimer (−6.50 kcal/mol) than the TIP4P dimer (−6.24 kcal/mol),[44] so the free energies of hydration for the ions with either water model should be similar.

Structure for Ions in TIP4P Water. Structural information for the ions in aqueous solution is reflected in the ion−water radial distribution functions and coordination numbers. For the first solvent shell, the coordination number is estimated by integrating the computed RDF to the first minimum. The results described here come from the MC simulations with the 15-Å droplets and with the restoring potential turned on 5 Å beyond CAPRAD.

Table 8 compares the performance of the new and old parameters for the first-shell coordination numbers. First of all, experimental estimates of coordination numbers vary widely,[29] indicating that different techniques and counterions

Table 8. First-Shell Coordination Numbers for Ions in Water

ion	CN (new)	CN (old)	CN (lit.)
F^-	6.6	6.2	$4.0-6.8^a$
Cl^-	7.6	7.3	$5.9-8.5^a$
Br^-	7.7	7.4	$4.2-8.9^a$
I^-	7.9	7.7	$6.0-8.9^a$
Li^+	4.8	5.0	$4.0-6.1^a$
Na^+	6.2	5.9	$4.0-8.0^a$
K^+	7.0	7.6	$5.0-8.0^a$
Rb^+	7.2	7.7	$5,^b 7.1,^c 7.9^d$
Cs^+	7.9	7.5	$6.0-8.0^a$
NH_4^+	7.3	6.6	$8.1-10.0^a$

a Literature values from ref 29. *b* Reference 53. *c* From QM/MM simulations, ref 54. *d* Reference 55.

give different results. In addition, the computational estimate has an uncertainty of ca. 0.5 owing to the flatness of the RDFs near the first minima. Thus, differences in the coordination numbers should not be overinterpreted.

Looking first at the halide ions, both old and new parameters give similar results, which all fall comfortably within the experimental ranges. In addition, the expected increase in coordination number going down the periods is observed, with values of 6.6, 7.6, 7.7, and 7.9 for F^-, Cl^-, Br^-, and I^-. Qualitatively, the results confirm that the structures of the hydrated ions are consistent with experiment, in terms of how many water molecules on average are located within the first hydration sphere.

For the cations, a similar pattern is seen, with coordination numbers well within the experimental ranges and the expected trend of increasing coordination numbers with size, 4.8 for Li^+, 6.2 for Na^+, 7.0 for K^+, 7.2 for Rb^+, and 7.9 for Cs^+. The coordination number of 7.3 for NH_4^+ falls below the experimental range of $8.1-10.0$, even though the value is what could be expected from the trends in size. With the new parameters, NH_4^+ is between K^+ and Rb^+ in size, and all three have a coordination number of about 7. It is unclear how a model with the hydrogens of NH_4^+ explicit would lead to a higher coordination number. In fact, the old model for NH_4^+ is an all-atom one and yields a coordination number of 6.6. Also, again both the free energy of hydration and position of the first maximum in the N−O RDF can be well reproduced with the present united-atom model for ammonium ion.

The computed RDFs are shown in Figure 4 for the halide ions, and the computed positions of the first maxima for all ion-oxygen RDFs are listed in Table 9 using both the old and new parameters. For the halide ions, substantial improvement is made with the new parameters in the first-peak positions with a better trend and a lower RMS deviation from experiment, 0.08 Å vs 0.16 Å for the old halide parameter set. The experimental uncertainty is reported as $0.03-0.07$ Å for halide ions.[29] A better fit that was also accurate for the free energies of hydration could not be obtained with any other choice of ϵ, nor with freely varying ϵ-values, which was initially attempted.

The second part of Table 9 compares the coordination data for the cations. The Åqvist parameter set[36] displays a RMS deviation from experiment of 0.08 Å, similar to that from
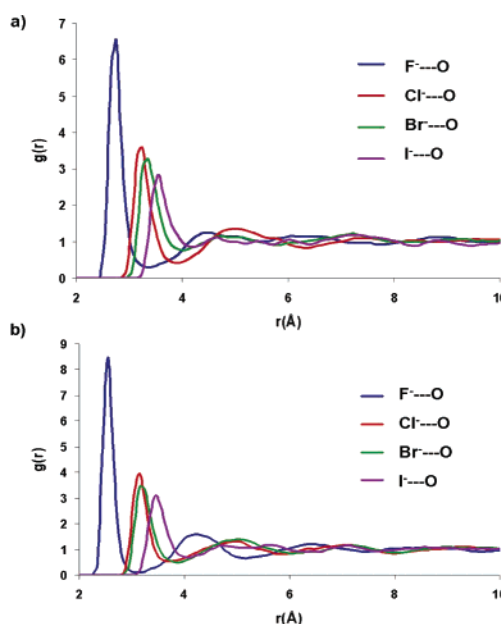
Figure 4. Radial distribution functions for halide ions with the (a) new and (b) old parameters in TIP4P water droplets with 15-Å radii at 298 K.

Table 9. Calculated and Experimental Positions for the First Maxima of Ion−Water Oxygen Radial Distribution Functions

ion	R_1 (new)	R_1 (old)	R_1 (lit.)^a
F^-	2.75	2.55	2.63
Cl^-	3.25	3.15	3.19
Br^-	3.35	3.15	3.37
I^-	3.55	3.45	3.65
RMS	0.08	0.16	
Li^+	2.05	2.05	2.08
Na^+	2.50	2.35	2.36
K^+	2.85	2.65	2.80
Rb^+	2.95	2.85	2.89
Cs^+	3.20	3.05	3.14
NH_4^+	2.90	2.75	2.85
RMS	0.07	0.08	
RMS^b	0.08	0.08	

a Reference 29. *b* Excluding NH_4^+.

both the new alkali metal and halide parameters. The experimental uncertainty is reported as $0.06-0.08$ Å for alkali metal ions.[29] Thus, structural accuracy similar to the Åqvist set was obtained now for both the cations and halide ions.

Transferability to a PBC Setup. Fluid simulations are often carried out in periodic cells. Therefore, it is important to test the validity of the relative hydration free energies and structures under such conditions. Tables 10−13 show the results calculated with a typical setup of 749 TIP4P water molecules in a periodic box with the ion in the center. Importantly, a choice of cutoff has to be made, as discussed in the Introduction. Commonly, cutoffs of 10 Å for both WW and IW interactions are chosen. As illustrated in Figure 1, the resultant absolute free energies are somewhat arbitrary. However, reasonably accurate relative free energies should be obtained since they should be dominated by the differ-

Table 10. Absolute and Relative Free Energies of Hydration (kcal/mol) Obtained with New Halide Parameters under Periodic Boundary Conditions

ion	$-\Delta G_{hyd}$ (calc)	$-\Delta G_{hyd}$ (exp)	diff
F^-	107.0	111.1	4.1
Cl^-	75.2	81.3	6.1
Br^-	72.8	75.3	2.5
I^-	61.9	65.7	3.8

ion	$\Delta\Delta G_{hyd}$	$\Delta\Delta G_{hyd}$	diff
$F^- - Cl^-$	31.8	29.8	2.0
$Cl^- - Br^-$	2.4	6.0	−3.6
$Br^- - I^-$	10.9	9.6	1.3
RMS			2.5

Table 11. Location of First Maxima of Radial Distribution Functions (Å) Obtained with New Halide Parameters under Periodic Boundary Conditions

ion	R_1 (calc)	R_1 (exp)	diff
F^-	2.75	2.63	0.12
Cl^-	3.25	3.19	0.06
Br^-	3.35	3.37	0.02
I^-	3.55	3.65	0.10

Table 12. Absolute and Relative Free Energies of Hydration (kcal/mol) Obtained with New Cation Parameters under Periodic Boundary Conditions

ion	$-\Delta G_{hyd}$ (calc)	$-\Delta G_{hyd}$ (exp)	diff
Li^+	127.8	113.5	14.3
Na^+	102.5	87.2	15.3
K^+	86.6	70.5	16.1
Rb^+	80.5	65.7	14.8
Cs^+	76.2	59.8	16.4
NH_4^+	85.0	68.1	16.9

ion	$\Delta\Delta G_{hyd}$	$\Delta\Delta G_{hyd}$	diff
$Li^+ - Na^+$	25.3	26.3	−1.0
$Na^+ - K^+$	15.9	16.7	−0.8
$K^+ - Rb^+$	6.1	4.8	1.3
$Rb^+ - Cs^+$	4.3	5.9	−1.6
$K^+ - NH_4^+$	1.6	2.4	−0.8
RMS			1.1

Table 13. Location of First Maxima of Radial Distribution Functions (Å) for Cations under Periodic Boundary Conditions

ion	R_1 (calc)	R_1 (exp)	diff
Li^+	2.05	2.08	0.03
Na^+	2.50	2.36	0.14
K^+	2.85	2.80	0.05
Rb^+	3.05	2.89	0.16
Cs^+	3.20	3.14	0.06
NH_4^+	2.90	2.85	0.05

ences in the electrostatic interactions with the water molecules nearest to the ions.

Table 10 lists the free energy results obtained with the new halide parameters and the PBC setup. The absolute free energies are systematically less negative than experiment by 2.5−6.1 kcal/mol. The relative free energies computed with the PBC setup have a RMS deviation from experiment of 2.5 kcal/mol. This is 1.5 kcal/mol less accurate than for the spherical setups used to parametrize the force field (Table 3), but a substantial improvement over the results with the old parameters in Table 5b.

Table 11 shows the computed locations of the first maxima for the halide ion-oxygen RDFs with the new parameters under PBC. This property is insensitive to the choice of system geometry, since it is controlled by the sampling of water molecules close to the ions. The RMS deviation from experiment is again 0.08 Å, as in Table 9.

Table 12 shows the corresponding absolute and relative free energies of hydration obtained with the new cation parameters under PBC. The absolute free energies of hydration are systematically 14.3−16.9 kcal/mol too negative. However, the relative free energies have a RMS deviation from experiment of only 1.1 kcal/mol, an accuracy similar to that obtained with the droplet models. Table 13 gives the positions of the first maxima of the RDFs; the RMS deviation from experiment is 0.1 Å. Thus, for computing structures and relative free energies of hydration, the current parameter sets also work well for periodic boundary conditions.

As a last test of the transferability of the developed parameters, the absolute and relative free energies for all ions were computed with the TIP3P water model instead of TIP4P,[44] using a CAPRAD of 15 Å and the modified CAPPOT. Interestingly, the TIP3P water model hydrates the cations (Table 14a) more strongly, whereas it hydrates the anions (Table 14b) less than with TIP4P, in both cases by approximately 5 kcal/mol. This means that the consistency between the cation and anion series only applies when using the TIP4P water model. However, the *relative* free energies within each series are well reproduced in both TIP3P and TIP4P water. The RMS deviations from experiment using TIP3P are 1.2 and 1.7 kcal/mol for the cations and anions, respectively.

Conclusions

Free energy perturbation calculations in the context of Monte Carlo simulations have been used to obtain a mutually consistent set of Lennard-Jones parameters for the halide ions, F^-, Cl^-, Br^-, and I^-, and for the alkali metal ions, Li^+, Na^+, K^+, Rb^+, Cs^+, as well as united-atom ammonium ion. The system setup for the calculations featured droplet models with different boundary restraints and radii. The alternatives gave very similar and system-size independent results when Born corrections were applied to correct for the contribution to the free energy of hydration from outside the droplet. The parameters were optimized for use with TIP4P water and yield absolute and relative free energies of hydration for the ions within about 1 kcal/mol of experiment. Structural characteristics are also well reproduced with average errors for ion−water oxygen distances of 0.1 Å or less, and the first-shell water coordination numbers fall within experimental ranges. Interaction energies and ion-oxygen distances for complexes of the ions with a single water molecule in

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Table 14. Absolute and Relative Free Energies of Hydration for (a) Cations and (b) Anions in TIP3P Water

a. Cations

ion	$-\Delta G_{hyd}$ (calc)	$-\Delta G_{hyd}$ (exp)	diff
Li^+	120.8	113.5	7.3
Na^+	92.3	87.2	5.1
K^+	75.5	70.5	5.0
Rb^+	70.1	65.7	4.4
Cs^+	63.0	59.8	3.2
NH_4^+	73.1	68.1	5.0

ion	$\Delta\Delta G_{hyd}$	$\Delta\Delta G_{hyd}$	diff
$Li^+ - Na^+$	28.5	26.3	2.2
$Na^+ - K^+$	16.8	16.7	0.1
$K^+ - Rb^+$	5.4	4.8	0.6
$Rb^+ - Cs^+$	7.1	5.9	1.2
$K^+ - NH_4^+$	2.4	2.4	0.0
RMS			1.2

b. Anions

ion	$-\Delta G_{hyd}$ (calc)	$-\Delta G_{hyd}$ (exp)	diff
F^-	104.8	111.1	6.3
Cl^-	77.6	81.3	3.7
Br^-	72.5	75.3	2.8
I^-	64.1	65.7	1.6

ion	$\Delta\Delta G_{hyd}$	$\Delta\Delta G_{hyd}$	diff
$F^- - Cl^-$	27.2	29.8	2.6
$Cl^- - Br^-$	5.1	6.0	0.9
$Br^- - I^-$	8.4	9.6	1.2
RMS			1.7

the gas phase were also found to be in good accord with ab initio results with the expected differences for the most polarizing ions, Li^+ and F^-. Additional investigations included simulations under periodic boundary conditions and in TIP3P water; the high accuracy for relative free energies of hydration is maintained.

The new ion parameters are notable for their performance in these tests and for their simplicity with just a single value of the Lennard-Jones ϵ for the anions and one for the cations. The good results for relative free energies of hydration are particularly auspicious for use of the new parameters in a wide variety of liquid-phase simulations, especially when halide and alkali cations are systematically varied.

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