New, Accurate Lennard-Jones Parameters for Trivalent Lanthanide Ions, Tested on [18]Crown-6

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Abstract: Lennard-Jones parameters for La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+} have been derived by Monte Carlo free-energy perturbation simulations that correctly reproduce the experimental free energy of hydration in water, modeled as TIP3P, to within 1% both absolutely and relatively. The radial distribution functions are in good agreement with available experimental data. The relative binding free energies of these lanthanide ions with [18]crown-6 could correctly be reproduced in methanol, with charges of -0.430 e on the oxygen and 0.215 e altogether on the CH_2 atoms. Based on the Lennard-Jones parameters of La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+} a fast method is presented for the derivation of Lennard-Jones parameters for other trivalent lanthanide and actinide ions. All calculations were performed with the BOSS program.

Keywords: crown compounds · lanthanides · molecular modeling · Monte Carlo · thermodynamics

Introduction

Molecular mechanics and dynamics (MM and MD, respectively) and Monte Carlo (MC) simulations, with well-known force fields like AMBER,[1] CHARMM,[2] BOSS-OPLS,[3] UFF,[4] Dreiding,[5] Merck,[6] and MM4,[7] are mature,[8] but the number of studies on complexes of trivalent lanthanides is still limited. These are important to obtain a good understanding of the complexes at the molecular level in order to improve such complexes for application in fluoroimmunoassays, optical amplification, extraction from (nuclear) waste streams, etc. The majority of studies have focused on a good description of the coordination distances with mostly an emphasis on the shielding of the trivalent lanthanide ion by the ligand.[9] We have also studied the shielding by polydentate ligands using a Eu^{3+} model (Lennard-Jones parameters: $\sigma = 3.107$ Å and $\varepsilon = 0.060$ kcal mol^{-1}) that gave a correct solvation number in OPLS methanol.[10] However, this model had not yet been tested for the free energy of hydration or solvation. With the protocol described here, the hydration free energy (ΔG_{hydr}) was estimated (vide infra) to be -831.2 kcal mol^{-1} when scaled to Gd^{3+} and -835.5 kcal mol^{-1} when scaled to Yb^{3+}, making it actually a better model for Ho^{3+} ($\Delta G_{\text{hydr}} = -832.5$ kcal mol^{-1}).[11] Merbach and co-workers have derived a set of nonbonded potentials for a number of trivalent lanthanide ions based on the enthalpy of hydration.[12] They used a cutoff of 8 Å and approximated the cutoff corrections with the Born model.[13] They emphasized the number of waters in the first coordination shell and the exchange rate of bound waters. Modern computers allow a much larger cutoff, which is necessary for accurate ΔGs. As has been stipulated by Åqvist,[14] the agreement with experiment should not only be in a relative sense, that is the $\Delta\Delta G$ of hydration/solvation between two cations, but also in an absolute sense. Another reason to apply a much larger cutoff is that the radial distribution function (RDF) of trivalent cations has structure up to approximately 9 Å. This makes the Born correction, a continuum approximation, probably a poor model for the electrostatic interactions from 8 Å until infinity. In this paper, we present new Lennard-Jones parameters for trivalent lanthanide ions that give a correct ΔG of hydration (i.e. within 1% of the experimental value), and these have been tested on the binding of these ions by [18]crown-6. A cutoff of 15 Å and a cutoff with the Born model were applied. The van der Waals interactions were calculated with the Lennard-Jones potential because this is computationally efficient. This approach makes these Lennard-Jones potentials useful for application in other frequently used force fields like those mentioned above. Polarization effects have not been included for the same reason.[12a, 15] Another reason is that solvent and solute models that include polarization are not routinely available; this also limits a wider application. It would require a complete reparametrization of the solvent and solute(s). The incorporation of polarization would also certainly increase the already heavy demands on computational resources (vide infra). In principle both molecular dynamics and Monte Carlo simulations can be used for the present study. We have used Monte Carlo simulations,

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because it has recently been shown by Jorgensen and coworkers[16] that the sampling of the Boltzmann distribution with MC is more efficient than with MD. The most difficult part in these empirical force fields is the description of the electrostatic interactions. The most simple approach employs point charges on the atoms, which can be derived empirically or, for example, by fitting the electrostatic potential. We followed the first approach for the fine-tuning of the point charges on [18]crown-6. A number of different sets of point charges for [18]crown-6 have been used.[17]

Methodology

We have followed the methodology used by Åqvist[14] to derive a set of Lennard-Jones parameters for the alkali and alkaline earth metal ions. A similar approach has been used by Straatsma and Berendsen.[18] This approximation is also justified for Ln^{3+} because there is little metal-imposed directionality.[19] The free energy of solvation, ΔG_{hydr} (I^{n+}), can be computed as described in Equation (1), where ΔG_{FEP} ($I^0 \rightarrow I^{n+}$) is the free energy change as a consequence of charging the ion, obtained by Monte Carlo free-energy perturbation calculations. ΔG_{Born} is the correction for the applied finite cutoff and is given by Equation (2). This gives the Born

$$\Delta G_{\mathrm{hydr}}\ (\mathrm{I}^{n+}) = \Delta G_{\mathrm{FEP}}\ (\mathrm{I}^0 \rightarrow \mathrm{I}^{n+}) + \Delta G_{\mathrm{Born}} + \Delta G_{\mathrm{cav}} \tag{1}$$

$$\Delta G_{\mathrm{Born}} = -322\,(1-\varepsilon^{-1})q^2/2r_{\mathrm{Born}} \tag{2}$$

correction in kcal mol^{-1} with ε the dielectric constant, q the charge, and r_{Born} the radius of the cavity in the macroscopic medium. The Born model gives an estimation of the free energy change when a cation is brought from vacuum into a solvent. In $\Delta\Delta G$ calculations by thermodynamic cycles this correction will cancel. The term ΔG_{cav} gives the free energy change for the formation of a cavity in water.[20] The electrostatic and van der Waals interactions have been computed with atom-based point charges and Lennard-Jones potentials, respectively. The initial parameters were from previous work.[10] They were used in a grid search in which both Lennard-Jones parameters (σ and ε) were systematically varied to give estimates for La^{3+}, Eu^{3+}/Gd^{3+}, and Yb^{3+}. Subsequently, these parameters were fine-tuned to give the correct ΔG_{hydr} (and coordination number).

The calculations of the relative binding affinities of La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+} by [18]crown-6 in methanol have been obtained from a thermodynamic cycle (Figure 1). In the ideal case one would like to calculate the complexation of a guest (here the trivalent cation) by the host (i.e. [18]crown-6), but this is technically still a very difficult and CPU intensive task. It is easier to calculate the vertical, unphysical processes and use the fact that the Gibbs free energy is a state function to calculate the relative binding free energies. Being a state function implies that the closed path integral is zero.

$$\begin{tikzcd}
\mathrm{Ln}_1^{3+} + \text{18-crown-6} \arrow[r, "\Delta G_1^{\mathrm{exp}}"] \arrow[d, "\Delta G_3^{\mathrm{calcd}}"] & \text{18-crown-6}\cdot\mathrm{Ln}_1^{3+} \arrow[d, "\Delta G_4^{\mathrm{calcd}}"] \\
\mathrm{Ln}_2^{3+} + \text{18-crown-6} \arrow[r, "\Delta G_2^{\mathrm{exp}}"] & \text{18-crown-6}\cdot\mathrm{Ln}_2^{3+}
\end{tikzcd}$$

$$\Delta G_1^{\mathrm{exp}} - \Delta G_2^{\mathrm{exp}} = \Delta G_3^{\mathrm{calcd}} - \Delta G_4^{\mathrm{calcd}}$$

Figure 1. Thermodynamic cycle for calculation of relative binding affinities.

Experimental Section

Monte Carlo free-energy perturbation (MC-FEP) simulations were performed with the BOSS program.[21] The trivalent ion was placed in the center of a box of TIP3P water molecules[22] of approximately 31.2 × 32.1 × 35.6 Å^3 dimensions. Solvent molecules at distances smaller than 2.5 Å from the solute were removed, leaving 1182 water molecules. The charge was perturbed in forward and backward directions in 10 or 20 equally spaced windows, allowing an estimation of the hysteresis. A linear coupling parameter λ was applied.[23] A cutoff of 12 or 15 Å was used for the nonbonded interactions, which were quadratically smoothed to zero between the cutoff and the cutoff – 0.5 Å. If an atom of a solvent molecule is within the cutoff distance the interactions with the whole molecule are taken into account.[24] The ranges of attempts of translational and rotational moves of the waters was 0.20 Å and 20°, respectively, giving an acceptance ratio of approximately 40%. Preferential sampling was applied.[25] The range of translational attempts of the solute was set such that an acceptance ratio of roughly 40% resulted. This means that in a run from +3 to +0 the range in the first window was set to 0.05 Å and in the last window to 0.55 Å. The system was equilibrated first in the NVT ensemble for 1 million configurations, followed by 2 million in the NPT ensemble at 1 atm and 298 K. The averaging was done for 2 million configurations in the NPT ensemble. Full periodic boundary conditions were imposed. This was done by making 26 images in the $\pm x$, $\pm y$, and $\pm z$ directions. The average of the forward and backward runs was taken as the value with the standard deviation as a lower bound estimate of the error.

The relative free energies of hydration ($\Delta\Delta G_{\mathrm{hydr}}$) have been obtained by perturbation of the Lennard-Jones parameters in 8 equally spaced windows in both forward and reverse direction. Other details as above. All calculations were run in forward and backward directions, but the results are always presented from the earlier to the later lanthanide ion.

The appropriate z matrix was constructed from the [18]crown-6 · K^+ structure with D_{3d} symmetry, with the lanthanide ion at the center of the ring. The z matrix of the [18]crown-6 was constructed as follows. Starting at an oxygen atom, one half of the ring was defined counterclockwise and the other clockwise. With one additional bond the cycle was closed. In this way the swing at the end of a string when a torsion is sampled in the beginning of that string was kept to a minimum, allowing a more efficient sampling. The methylene groups were treated as united atoms. The complexes were placed along the long axis of a rectangular box of OPLS MeOHs of approximately 36.7 × 36.0 × 40.5 Å dimensions. Solvent molecules with heavy atom distances smaller than 2.5 Å to the solutes were removed, leaving 764 molecules of MeOH. A cutoff of 15 Å was used for the nonbonded interactions, which were quadratically smoothed to zero between the cutoff and the cutoff – 0.5 Å. The solvent molecules were sampled with a translational range of 0.20 Å and a rotational range of 20°. The crown ether and the Ln^{3+} were sampled independently. The Lennard-Jones parameters of one lanthanide ion were perturbed into those of the other in 8 equally spaced windows, in both forward and backward direction. Translational and rotational sampling was applied to the ligand, in addition to all bonds, angles, and dihedrals. The crown ether was sampled with a translational range of 0.01 Å and a rotational range of 1°. The sampling of the bonds and angles was done automatically. The sampling range of the dihedrals was set to 0.50°, giving an acceptance ratio of 40%. Dihedrals changed up to 40–50° in merely 2 million configurations. The translational sampling range of Ln^{3+} ion was set to 0.03 Å, giving an acceptance ratio of about 45–50%. All calculations were equilibrated for 1 million configurations in the NVT ensemble, followed by 16 million configurations in the NPT ensemble at 1 atm and 298 K. Averaging was done over 8 million configurations in the NPT ensemble. Full periodic boundary conditions were imposed. The average of the forward and backward runs was calculated with the standard deviation as a lower bound estimate of the error. In order to close the thermodynamic cycle, the calculations of the trivalent lanthanide ions in methanol solutions were treated accordingly. The translational sampling range was 0.05 Å, giving an acceptance ratio of 45–50%. Equilibration was done in the NVT ensemble for 1 million configurations, followed by 1 million in the NPT ensemble. The averaging was done over 2 million configurations.

The calculations in which the sampling of the coordinated solvent molecules was investigated were performed by taking the appropriate solvated complexes from a simulation described in the previous paragraph and defining the z matrix accordingly. This allowed the rotational and translational sampling of the coordinated methanols to be optimized automatically by the program to give an acceptance ratio of roughly 50%. Other details are as above. Calculations were run on Pentium-based PCs.[26]

Results and Discussion

Free energies of hydration: The Lennard-Jones parameters derived in this study are summarized in Table 1, showing a few aspects which will be further discussed. These sets of Lennard-Jones potentials reproduce the free energy of hydration to within 1 % of the experimental value.[11] The parameter set of $\sigma = 3.30$ Å and $\varepsilon = 0.050$ kcal mol^{-1} gives a calculated free energy of hydration which is equally good for Eu^{3+} and Gd^{3+}. In a relative sense this set of parameters is better for Gd^{3+} (vide infra). From now on we will refer to this set as the Gd^{3+} parameters. The calculations are dependent on the number of applied windows, not in an absolute sense but in a relative sense; the estimated error is roughly three times as large when 10 windows are applied as when 20 are applied. The calculations are, in an absolute sense, dependent on the cutoff. The same set of Lennard-Jones potentials for Gd^{3+} gave a calculated free energy of -819.6 and -811.1 kcal mol^{-1} for a cutoff of 12 and 15 Å, respectively. A value for σ of 3.35 Å and a cutoff of 12 Å gave a value of -810.9 kcal mol^{-1}. The Lennard-Jones parameters for Nd^{3+} were obtained by linear interpolation between the parameters of La^{3+} and Gd^{3+}, with the experimental free energy of hydration as the scale. In this way it proved possible to get a fair estimate of ΔG_{calcd} with a new set of parameters by calculation of only a few windows and scaling the result on a full calculation. In general the estimate was within 1–2 % of the full run, making it a convenient and quick way to fine-tune the parameters.

Radial distribution functions and coordination numbers: The radial distribution functions (RDF) in TIP3P (O) are presented in Figure 2 and show a distinct first coordination peak at 2.65, 2.55, 2.45, and 2.35 Å for La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+}, respectively. These peak positions are in good agreement with available experimental data of 2.58 Å for La^{3+}, 2.50–2.51 Å for Nd^{3+}, 2.41 Å for Gd^{3+}, and 2.32 Å for Yb^{3+}.[27] These peaks integrate to 10, 10, 9, and 9 oxygens, respectively. This is possibly a slight overestimation of the number of water molecules in the first coordination shell compared to experimental data, but these data are not entirely consistent. These slight overestimations are not necessarily an artifact of the simulations. The experimental data by X-ray diffraction, EXAFS, or neutron diffraction are often obtained from quite concentrated solutions (up to 3 M) and under these conditions ion pairing is likely to occur, even in water.[28] In contrast to these data, the free energies of hydration are extrapolated from infinite dilution. This makes the protocol we followed, where no interactions between the ions exist, probably more applicable to the free energies of hydration. A distinct second coordination peak is present around 4.8 Å, and a third, broader peak is present around 7.5 Å. The RDFs are essentially featureless after 10 Å, providing justification for the applied cutoff of 15 Å. The small feature around 14.5 Å is an artifact due to the cutoff. Possible artifacts introduced by the way the cutoff is treated have been the subject of numerous studies and are not discussed here.[29] The RDFs in methanol are given in Figure 3. The observed features are quite similar to those in water. The first coordination peaks are found at similar values, with coordination numbers of 9, 9, 9, and 8 for La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+}, respectively. Unfortunately no experimental data are available.

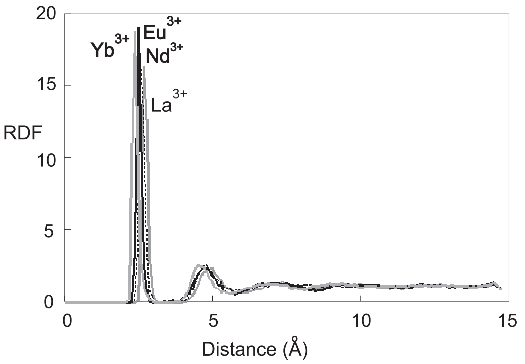

Figure 2. Radial distribution function of La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+} (peak positions from right to left) in TIP3P water.

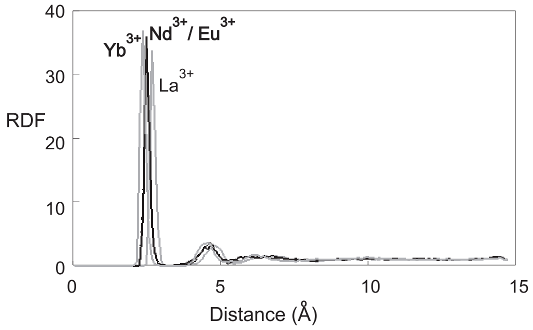

Figure 3. Radial distribution function of La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+} (peak positions from right to left) in OPLS methanol. The RDFs of Nd^{3+} and Eu^{3+} almost completely coincide.

Table 1. Absolute free energies of hydration; standard deviation in parentheses.

Ion	Windows	σ [Å]	ε [kcal mol^{-1}]	n_{coord}	r_{cut} [Å]	$-\Delta G_{pert}$ [kcal mol^{-1}]	$-\Delta G_{calcd}$ [kcal mol^{-1}]	$-\Delta G_{exp}$[a] [kcal mol^{-1}]
La^{3+}	20	3.75	0.060	10	15	656.7 (6.1)	755.0	754.8
Nd^{3+}	20	3.473	0.054	10	15	689.3 (5.5)	787.5	786.4
Eu^{3+}/Gd^{3+}	10	3.30	0.050	9	12	696.7 (16.5)	819.6	806.2/809.8
	20	3.30	0.050	9	12	695.4 (5.5)	818.3	806.2/809.8
	10	3.30	0.050	9	15	712.8 (20.3)	811.1	806.2/809.8
	10	3.35	0.050	9	12	688.0 (18.9)	810.9	806.2/809.8
Yb^{3+}	20	2.95	0.040	9	15	757.7 (7.6)	856.0	856.2

[a] Taken from ref. [11].

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Relative free energies of hydration: The relative free energies of hydration are presented in Table 2, from which it can be seen that these Lennard-Jones parameters accurately reproduce the experimental values. It is also evident that the Lennard-Jones parameters ($\sigma = 3.30$ Å and $\varepsilon = 0.050$ kcal mol^{-1}) give a better description for Gd^{3+} than for Eu^{3+}. Being a state function dictates that the path along which the calculation is performed from one point to the other is irrelevant, so it should not matter, for example, whether one calculates the $\Delta\Delta G$ from La^{3+} to Yb^{3+} in one simulation or one takes the sum of the $\Delta\Delta G$ from La^{3+} to Gd^{3+} and the $\Delta\Delta G$ from Gd^{3+} to Yb^{3+}. This is reflected in the data of Table 2. This comparison has been advocated as a more reliable discriminator of the reliability of the simulations than the quoted statistical errors.[30] Table 2 also shows that the perturbation from La^{3+} to Yb^{3+} is not very sensitive to the applied number of windows. The computed $\Delta\Delta G$s are -99.87 and -100.37 kcal mol^{-1} for 8 and 16 windows, respectively. The estimated error is, however, somewhat smaller with 16 windows.

Table 2. Relative free energies of hydration; standard deviation in parentheses.

	$\Delta\Delta G_{calcd}$ [kcal mol^{-1}]	$\Delta\Delta G_{exp}$ [kcal mol^{-1}][a]
La^{3+}–Eu^{3+}/Gd^{3+}	-55.61 (0.56)	-51.4 (Eu^{3+})/-55.0 (Gd^{3+})
La^{3+}–Nd^{3+}	-32.33 (0.15)	-31.6
La^{3+}–Yb^{3+}	-99.87 (1.45)/-100.37 (0.58)[b]	-101.4
Nd^{3+}–Eu^{3+}/Gd^{3+}	-22.09 (0.24)	-20.0 (Eu^{3+})/-23.4 (Gd^{3+})
Nd^{3+}–Yb^{3+}	-67.83 (0.97)	-69.8
Eu^{3+}/Gd^{3+}–Yb^{3+}	-46.45 (0.16)	-50.0 (Eu^{3+})/-46.4 (Gd^{3+})

[a] Taken from ref. [11]. [b] 16 equally spaced windows.

Relative binding free energies of [18]crown-6: In order to obtain the relative binding free energies of the various Ln^{3+} ions in methanol, both the relative free energies of the ions bound to the [18]crown-6 and the solvated ions have been calculated (Table 3). The application of these parameters implies that they are transferable from TIP3P to the OPLS methanol. This is probably a valid argument because both models have been derived with a similar methodology, that is, rigid solvent models with empirically derived point charges on the atoms to reproduce the heats of vaporization and densities to within 1% of experiment at 298 K and 1 atm. A second reason is that systematic errors are likely to cancel in relative binding free energy calculations. The La^{3+}, Nd^{3+}, and Gd^{3+} ions were displaced from the center of the [18]crown-6 within the first few million configurations. The estimated error in the calculations (see experimental section) is on the order of 1%, similar to the calculations in Tables 1 and 2. As stated above, the point charges are to a certain extent arbitrary and for [18]crown-6 a number of different sets have been used.[17] Initially we applied the point charges ($q_{O} = -0.40$ e and $q_{CH_2} = 0.20$ e) similar to those used by Kollman and coworkers in simulations of the complexes with alkali cations in methanol, but this gave an overestimation of the binding selectivity of La^{3+} over Gd^{3+} ($\Delta\Delta G_{calcd} = -3.65$ kcal mol^{-1} vs. $\Delta\Delta G_{exp} = -2.69$ kcal mol^{-1}).[31] Therefore, it was decided to fine-tune (i.e. to balance) the point charges on the [18]crown-6 with respect to the Ln^{3+} ions and the solvent by means of the $\Delta\Delta G_{exp}$ of La^{3+}–Gd^{3+}. With point charges of $q_{O} = -0.430$ e and $q_{CH_2} = 0.215$ e the experimental $\Delta\Delta G$ could be well reproduced (Table 4). These increased charges might reflect some polarization.[32] With these point charges a consistent set of $\Delta\Delta G$ values has been calculated (Table 4). Also here it is satisfying to note that the data without a host comply with the rule that the Gibbs free energy is a state function (Table 3). This agreement is somewhat less for the calculations in the presence of [18]crown-6. The agreement with experiment is excellent, the binding of one lanthanide ion over the other by [18]crown-6 is correctly reproduced for all calculations, except for the perturbation from La^{3+} to Yb^{3+}. The error in this calculation is considerably larger than for the other calculations due to the fact that two transitions (vide infra) occurred, both introducing a hysteresis. Here the sampling is obviously inadequate. However, adding the calculations from the runs La^{3+}–Gd^{3+}/Gd^{3+}–Yb^{3+} and the runs La^{3+}–Nd^{3+}/Nd^{3+}–Yb^{3+} gives a relative binding free energy of -4.95 and -6.05 kcal mol^{-1}, respectively, consistent with the experimental data ($\Delta\Delta G_{exp} < -4.49$ kcal mol^{-1}). In order to reduce the hysteresis, a run was performed with 16 equally spaced windows, giving a $\Delta\Delta G_{calcd} = -4.13$ kcal mol^{-1}, nicely reproducing the experimentally observed selectivity. It also implies that the Lennard-Jones parameters for the lanthanide ions are in balance with respect to each other and with respect to the OPLS MeOH. It is obvious from these results that the sampling of complexes remains an inherently difficult problem.

Table 3. Relative free energies of solvation in methanol; standard deviation in parentheses.

	Host	$\Delta\Delta G_{calcd}$ [kcal mol^{-1}]
La^{3+}–Nd^{3+}	none	-26.55 (0.18)
La^{3+}–Gd^{3+}	none	-43.01 (0.15)
La^{3+}–Yb^{3+}	none	-78.96 (0.48)/-80.06 (0.46)[a]
Nd^{3+}–Gd^{3+}	none	-16.58 (0.16)
Nd^{3+}–Yb^{3+}	none	-53.37 (0.58)
Gd^{3+}–Yb^{3+}	none	-36.45 (0.29)
La^{3+}–Nd^{3+}	18C6	-24.54 (0.47)
La^{3+}–Gd^{3+}	18C6	-40.50 (0.59)
La^{3+}–Yb^{3+}	18C6	-80.32 (2.61)/-75.93 (1.46)[a]
Nd^{3+}–Gd^{3+}	18C6	-16.28 (0.03)
Nd^{3+}–Yb^{3+}	18C6	-48.61 (1.03)
Gd^{3+}–Yb^{3+}	18C6	-34.01 (0.66)

[a] 16 equally spaced windows.

Table 4. Relative binding free energies in methanol of Ln^{3+} by [18]crown-6. Data from Table 3.

	$\Delta\Delta G_{calcd}$ (kcal mol^{-1})	$\Delta\Delta G_{exp}$ (kcal mol^{-1})[a]
La^{3+}–Nd^{3+}	-1.29	-1.16
La^{3+}–Gd^{3+}	-2.51[b]	-2.69
La^{3+}–Yb^{3+}	1.36/-4.13[c]	≤ -4.49
Nd^{3+}–Gd^{3+}	-0.30	-0.82
Nd^{3+}–Yb^{3+}	-4.76	≤ -3.33
Gd^{3+}–Yb^{3+}	-2.44	≤ -1.80

[a] Taken from ref. [31]. [b] Used for scaling the point charges on [18]crown-6 (see text). [c] 16 equally spaced windows.

Some snapshots of the complexes are shown in Figure 4. They show that going from La^{3+} to Yb^{3+} there is a gradual encapsulation of the ion by the [18]crown-6, leaving less space for solvent molecules. The binding of one molecule of methanol through the cavity of the [18]crown-6 is a general phenomenon. The binding of the lanthanide ion is abbreviated as $MeOH \cdot 18C6 \cdot Ln^{3+} \cdot n\,MeOH$. Although there are no data available on the actual solvation of these complexes in methanol, they make chemical sense. The larger La^{3+} ion is complexed in a sandwich-type structure, with the [18]crown-6 and one methanol forming one face of the sandwich and four methanols the other. Similar coordination is observed for Nd^{3+} and Gd^{3+}, with three instead of four methanols on one face of the sandwich. The much smaller Yb^{3+} is encapsulated by the [18]crown-6, leaving only space for three methanols. This is very similar to the binding modes of various crown ethers with alkali and alkaline earth metal ions.[33] The observed structures also resemble those obtained by X-ray analyses.[33, 34] The stability of the solvation of [18]crown-6 $\cdot$ La^{3+} and [18]crown-6 $\cdot$ Nd^{3+} in methanol has been checked by a run of an additional 30 million configurations. Regular checks of saved configurations gave stable coordinations as $MeOH \cdot 18C6 \cdot La^{3+} \cdot 4\,MeOH$ and $MeOH \cdot 18C6 \cdot Nd^{3+} \cdot 3\,MeOH$, respectively.

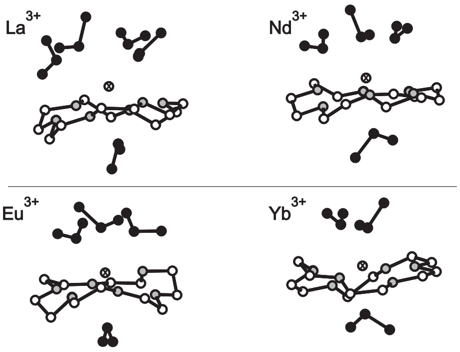

Figure 4. Snapshots of the Ln^{3+} complexes of [18]crown-6 in OPLS methanol.

The decreased solvation number going from La^{3+} to Yb^{3+} is also observed along the perturbation. At a certain value of the coupling parameter λ a change in the solvation number by one molecule of methanol is observed. One such transition occurred in most perturbations, but two occurred in the perturbation from La^{3+} to Yb^{3+}. In the forward and backward run this is clearly reflected in the calculated free energy changes and it is the main contribution to the estimated errors. More windows around the transition will most likely decrease the hysteresis (not performed).

The sampling of the solvent investigated: In the MC-FEP calculations of solvated [18]crown-6 $\cdot$ Ln^{3+} in methanol discussed above, the coordinated methanols were treated as the bulk methanols with respect to the sampling ranges of rotation and translation. Analyzing the acceptance ratios of the methanols in a particular run showed that the acceptance ratio of the coordinated methanols is only roughly 10%. In order to investigate the influence of this fact, the appropriate z matrices were constructed from saved configurations with the coordinated methanols explicitly in the z matrix, allowing the independent sampling of these coordinated methanols to be optimized easily. This gave a ΔG_{pert} for [18]crown-6 $\cdot$ $La^{3+} \Rightarrow Gd^{3+}$ of $-41.68\ \text{kcal}\,\text{mol}^{-1}$, giving a $\Delta\Delta G_{\text{calcd}} = -1.33$ vs $\Delta\Delta G_{\text{exp}} = -2.69\ \text{kcal}\,\text{mol}^{-1}$. Relatively this is still correct, but absolutely it underestimates the binding selectivity. It clearly shows that the way the coordinated solvent molecules are sampled has a significant effect on the calculations. Probably this observation also applies to other calculations.

Conclusions

We have obtained accurate Lennard-Jones parameters that correctly reproduce the hydration free energies for La^{3+}, Nd^{3+}, Gd^{3+}, and Yb^{3+}, using a cutoff of 15 Å and TIP3P as water model. The Born correction was applied to correct for the finite cutoff. From these parameters it is easy to derive parameters for other trivalent lanthanide ions and also trivalent actinide ions.[35] We have also shown that the calculations are quite sensitive to changing the cutoff length, making them in this sense probably not transferable.[36] However, small adjustments to the Lennard-Jones parameters are easily made. With a slight increase of the point charges on [18]crown-6 with respect to similar charges used by Kollman and co-workers,[17f,g] the relative binding free energies in methanol could be reproduced. This implies that these parameters can be used in the design of selective receptors for trivalent lanthanide ions.

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