Computational Study of a Terphenyl-Based Eu^{3+} Complex: Effect of Small Amounts of Water

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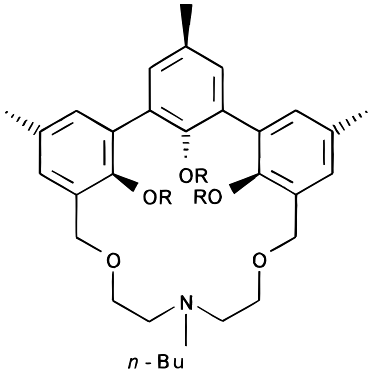
The shielding properties of the terphenyl-based complex $L{\cdot}Eu^{3+}$ in methanol solution have been studied by computer simulations with an emphasis on the influence of small amounts of water on the shielding properties. The theoretical studies were carried out in explicit solvent models by molecular mechanics and dynamics simulations (up to 2000 ps), Monte Carlo free energy perturbations, and a potential of mean force calculation. In dry methanol solutions, complex $L{\cdot}Eu^{3+}$ is predicted to have one methanol coordinated to the Eu^{3+}. The presence of 1.0 ± 0.5 OH groups (from methanol) is in agreement with fluorescence measurements. Millimolar concentrations of water lead to a monohydrated complex and possibly to a dihydrated complex. At these concentrations of water in the methanol solutions of $L{\cdot}Eu^{3+}$, the luminescence intensities decrease, which supports the conclusion that one and possibly two waters are preferentially coordinated to the Eu^{3+} ion. This study also shows that molecular dynamics runs of 1 ns or more are needed to allow major transitions in the first coordination sphere of Eu^{3+} to occur, but even simulations up to 2 ns do not guarantee that the global energy minimum is calculated.

Introduction

There are several reasons why the luminescence properties of trivalent lanthanide ions are important. The Tb^{3+} and Eu^{3+} and to a lesser extent the Sm^{3+} and Dy^{3+} luminescence in the visible region of the electromagnetic spectrum has been thoroughly investigated for application as diagnostic tools, such as fluoroimmuno assays.[1] The luminescence properties of lanthanide ions emitting in the near-infrared, such as Pr^{3+}, Nd^{3+}, Er^{3+}, and Yb^{3+}, may find application in polymer-based waveguide optical amplifiers.[2] It is well documented that the excited state of lanthanide ions is efficiently quenched by high-vibrating oscillators such as OH, NH, and CH.[3] Because of the quenching by OH groups from, for example, water or methanol, polydentate ligands have been synthesized that can strongly complex the lanthanide ion and shield it from the surroundings. However, if no or small amounts of OH groups are present, the ligand becomes the dominant quencher because of the abundantly present CH groups. We[4] and others[5] have demonstrated that this quenching by CH oscillators can be reduced by substitution for CD groups. There are two reasons why Eu^{3+} is often used as a good model for other lanthanides. The first is that the number of coordinated water or methanol molecules can be estimated by the “Horrocks equation”, although this relation is not very accurate when a small number of OH groups is present in the first coordination sphere.[6] The second reason why Eu^{3+} complexes are very informative is the fact that both levels of the $^5D_0-^7F_0$ transition of Eu^{3+} are nondegenerate, giving only one emission line around 580 nm if only one species is present.[7]

CHART 1



Encapsulating ligand L : R = CH_2COO^-

Recently, we have described[4] the synthesis and luminescence properties of shielded Eu^{3+} complexes of the preorganized hemispherand-based ligand L (Chart 1). From lifetime measurements in dry methanol and methanol-d_1 using the “Horrocks equation”,[6] it was derived that 1.0 ± 0.5 OH groups are still present in the first coordination sphere. An initial molecular dynamics run of 50 ps showed that one methanol can be accommodated in the first coordination sphere.[8] This molecular dynamics simulation has now been extended to 1000 ps. The luminescence studies on $L{\cdot}Eu^{3+}$ showed that small amounts of water had a large effect on the optical properties. This stimulated us to perform a systematic theoretical investigation. The results are compared with the available experimental data.

The theoretical studies used in this paper are based on molecular mechanics (MM) and dynamics (MD) calculations and Monte Carlo free energy perturbations (MC FEP) simulations. The MD and MC FEP simulations have been carried out in an explicit solvent. These simulation techniques are now mature and give reliable information on the shielding properties of (trivalent) cations.[9,10] The following issues will be dealt with. First, what does experiment tell us with respect to the shielding of $L{\cdot}Eu^{3+}$? Then the following questions will be raised and

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addressed by simulations. Is a water or a methanol coordinated to the Eu^{3+}, and are they in equilibrium? Can more than one water be coordinated in the first coordination shell of Eu^{3+}? What is the influence of increasing amounts of water on the relative ratios of the various Eu^{3+} complexes?

Experimental Section

Initial structures as well as visualizations were carried out with Quanta/CHARMm 3.3.[11] The MM and MD calculations were run with CHARMM 22.0 and 23.0.[12] Parameters were taken from Quanta 3.3, and point charges were assigned with the charge-template option in Quanta/CHARMm. The ligands were charged to 0, with a small "excess" charge smoothed to nonpolar carbons and hydrogens. The europium cation was represented as a calcium ion with a point charge of +3. The Lennard-Jones parameters of Ca^{2+} ($R_{\min} = 3.488$ Å and $\epsilon = 0.060$ kcal/mol, as implemented in Quanta/CHARMm 3.3[11]) in combination with the +3 point charge have been used (see Results and Discussion). The starting structures were minimized by ABNR (adopted basis set Newton−Raphson) until the root-mean-square (rms) of the energy gradient was ≤ 0.01 kcal mol^{-1} $Å^{-1}$. No cutoff on the nonbonded interactions was applied in the gas-phase minimizations of the complexes. A dielectric constant ϵ of 1 was used. The structure of the complex $L \cdot Eu^{3+} \cdot H_2O$ was manually created by adjusting the outer pendant arm slightly and placing the water molecule in the first coordination shell followed by minimization. The dihydrated complex $L \cdot Eu^{3+} \cdot 2H_2O$ was made by rotating away one outer pendant arm and placing the two waters in the first coordination shell followed by minimization. The trihydrate $L \cdot Eu^{3+} \cdot 3H_2O$ was formed by rotating both outer pendant arms away and placing the three waters at coordination distances followed by minimization.

Details of the MD simulations were as follows. The minimized complexes were placed in a cubic box of approximately 30.7 Å dimensions, initially filled with 429 OPLS MeOHs.[13] Solvent molecules that overlap with the complexes were removed (on the basis of heavy-atom interatomic distances of ≤ 2.3 Å). This in general resulted in removal of one MeOH per two non-hydrogen atoms of the systems under study. Full periodic boundary conditions were imposed. Before the MD simulations were run, the system was minimized by steepest descent, to remove the worst contacts, until the rms of the energy gradient was ≤ 0.5 kcal mol^{-1} $Å^{-1}$ or a maximum of 100 steps was reached, followed by ABNR until the rms of the energy gradient was ≤ 0.01 kcal mol^{-1} $Å^{-1}$ or a maximum of 1000 steps was reached. The water was modeled as the TIP3P model,[14] as implemented in CHARMM. The system $L \cdot Eu^{3+} \cdot MeOH$ was minimized by steepest decent until the rms of the energy gradient was ≤ 1.0 kcal mol^{-1} $Å^{-1}$ or a maximum of 1000 steps was reached. During the simulation the nonbonded list was updated every 20 time steps with a cutoff of 14 Å. The van der Waals interactions were treated with a switch function between 10 and 13 Å, whereas the shift function was applied to the electrostatic interactions (cutoff of 13 Å). A dielectric constant ϵ of 1 was applied. The system was heated to 300 K in 5 ps followed by a 10 ps equilibration with scaling of the velocities within a temperature window of 10 °C. After equilibration no scaling of the velocities was applied. The production phase consisted of 500−2000 ps, and coordinates were saved regularly for subsequent analysis (NVE ensemble; no systematic deviation from 300 K was observed). The verlet/leapfrog algorithm was used for the numerical intergration. The SHAKE algorithm[15] on bonds involving hydrogen was applied, allowing a time step of 1 fs. The MD in water was performed by placing the minimized complex $L \cdot Eu^{3+}$ in a cubic box of TIP3P waters, as implemented in CHARMM, of approximately 31.0 Å dimensions, initially filled with 1000 waters. Other details are as above.

Monte Carlo free energy perturbation (MC FEP), or importance sampling, simulations were performed with the BOSS program, using the OPLS water and solvent models.[16] Details are as follows. The appropriate **z** matrix for $L \cdot Eu^{3+} \cdot MeOH$ was constructed from a typical structure from the MD run of $L \cdot Eu^{3+}$ in MeOH having the coordinated MeOH as shown in Figure 2b. The coordinated MeOH was perturbed into a water and vice versa. A linear coupling parameter was used without decoupling of the van der Waals and electrostatic forces.[17] All methyl and methylene groups were treated as united atoms. The point charges were the same as in the MD simulations, but the charges on the hydrogens of the methyl and methylene groups were added to the parent carbon atom. The Lennard-Jones parameters were taken from the BOSS parameters file in order to be consistent with the combining rules. The Lennard-Jones parameters for Eu^{3+} were the same as above. The complexes were placed in a cubic box of 22.7 Å length initially filled with 267 MeOHs. On the basis of the worst interaction energies, 16 molecules of MeOH were removed at the start of the simulations. A cutoff of 11 Å was used for the nonbonded interactions, which were quadratically smoothed to zero between the cutoff and the cutoff minus 0.5 Å. The ligand L, the Eu^{3+}, and coordinated solvent/water were sampled independently. Translational and rotational sampling was not applied to the ligand, but the three pendant arms were sampled through their dihedrals ($C{=}C{-}O{-}CH_2$, $C{-}O{-}CH_2{-}C{=}$, and $O{-}CH_2{-}C{=}O$) in addition to the *n*-butyl substituent on the nitrogen atom of the hemispherand. With a sampling range of 2° the acceptance ratio was approximately 40%. The translational sampling range of Eu^{3+} was 0.03 Å, giving an acceptance ratio of roughly 40%. The translational and rotational ranges for the coordinated solvent/water was automatically adjusted to give an acceptance range of about 40−50%. A solute move was attempted every 25 solvent moves. Preferential sampling was used.[18] The perturbations were carried out in five double-wide windows. All calculations were equilibrated for 1 million configurations followed by averaging over two million configurations in the NPT ensemble at 1 atm and 298 K. Full periodic boundary conditions were imposed. As a lower-bound estimation of the error, a deviation from the average of 2 million is taken. The perturbation of methanol into water and the reverse was carried out similarly (1 million equilibration and 3 million averaging).

The appropriate **z** matrix for $L \cdot Eu^{3+} \cdot 2H_2O$ was constructed from a typical structure from the MD run of $L \cdot Eu^{3+} \cdot 3H_2O$ in MeOH **after** one water had left the first coordination shell having the coordinated waters as shown in Figure 7b. The coordinated water between the two pendant outer substituents was perturbed into a dummy atom having no interactions with its surroundings. The point charges were first perturbed to zero followed by perturbation of the van der Waals interactions. A harmonic constraint of 10 or 25 kcal mol^{-1} $Å^{-2}$ with a $Eu^{3+} \cdots OH_2$ distance of 2.45 Å was applied on the "disappearing" water. Other details are as above. The H_2O-to-dummy perturbation in methanol was treated accordingly.

The potential of mean force (PMF)[19] was calculated as follows. The **z** matrix of the $L \cdot Eu^{3+} \cdot 2H_2O$ systems was used, and the water coordinated between the two outer pendant arms was displaced along a reaction coordinate defined by the angle

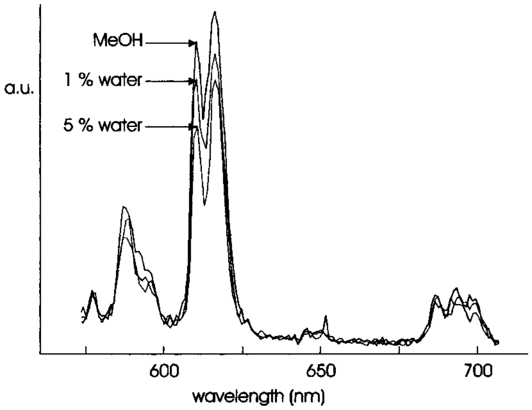

Figure 1. Luminescence spectra of L·Eu^{3+} in MeOH and with 1 and 5% (v/v) water. Excitation is at 393 nm. See also ref 4.

$PhO_{inner}-Eu^{3+}-OH_2$ of approximately 80°. To close the created gap after displacement of the water, i.e., to prevent solvent coordination, the solute sampling in the equilibration phase was done every five solvent attempts. Gap closure was checked on regularly saved plot files. During the averaging phase the solute sampling frequency was every 25 solvent moves. The PMF was calculated from 2.1 to 10.3 Å in steps of 0.2 Å double wide. Equilibration was done over 3 million configurations, and the averaging was done over 3 million configurations. Other details are as above. To get an estimation of the error in this calculation, the following procedure was used. After equilibration, the PMF of each times 1 million configurations was evaluated with eq 3. These three association constants were averaged, and the standard deviation was calculated.

Results and Discussion

Luminescence of Excited L·Eu^{3+}. The luminescence of the L·Eu^{3+} complex in dry methanol is shown in Figure 1. Upon excitation at 393 nm the typical emission lines of Eu^{3+} are observed. Only one peak is observed at 580 nm, which is due to the $^5D_0-^7F_0$ transition, showing that only one (time-averaged) species is present. The influence of small amounts of water on the luminescence intensities of L·Eu^{3+} is also shown in Figure 1. The luminescence intensities clearly drop if a few percent of water are added to the methanol solution. This indicates that water is preferentially coordinated to the Eu^{3+} ion. There is still only one peak at 580 nm; thus, only one (time-averaged) species is present.

Molecular Mechanics and Dynamics. *Eu^{3+} Model.* The model of Eu^{3+} has been the same as used in previous studies.[9] The Lennard-Jones parameters $R_{min} = 3.488$ Å and $\epsilon = 0.060$ kcal/mol with a point charge of +3 gave the correct number of methanol molecules in the first coordination shell of Eu^{3+}. For more details see the cited references.[9]

L·Eu^{3+}. The minimized structure of L·Eu^{3+} is shown in Figure 2a. All donor atoms are in the first coordination sphere of Eu^{3+} ($Eu^{3+}\cdots$O/N, 2.24−2.49 Å), with a significantly longer distance between Eu^{3+} and PhO_{inner} of 3.00 Å, and the Eu^{3+} *seems* very well shielded. However, an MD run in OPLS methanol[13] showed that one methanol can coordinate to the Eu^{3+} ion. The methanol entered the first coordination sphere of Eu^{3+} after approximately 6 ps in the production phase, and it remained there throughout the rest of the 1000 ps run (Figure 3). No significant changes occurred between 6 and 1000 ps. A typical structure is shown in Figure 2b, showing that one of the pendant outer arms had adjusted to allow the additional coordination of one methanol.

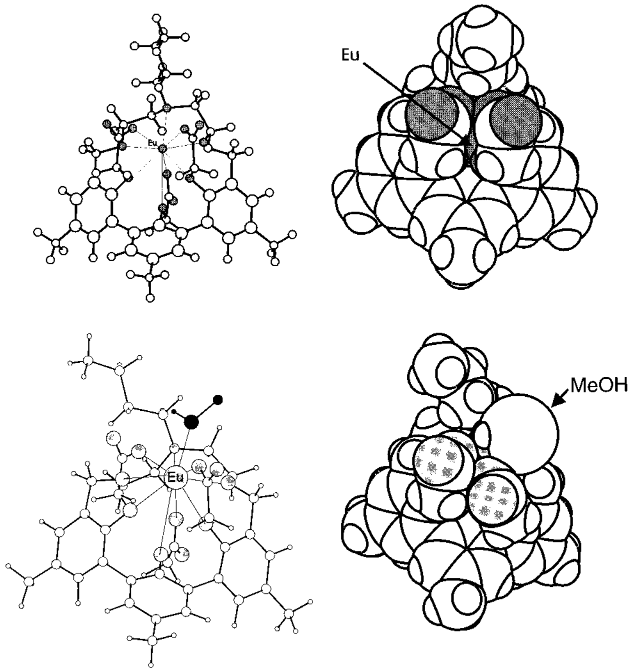

Figure 2. Minimized structure of L·Eu^{3+} (a, top) and snapshot from the MD run (b, bottom). Stick and ball (left) and space-filling (right) representation. Heteroatoms are in gray and the coordinated solvent molecule(s) in black.

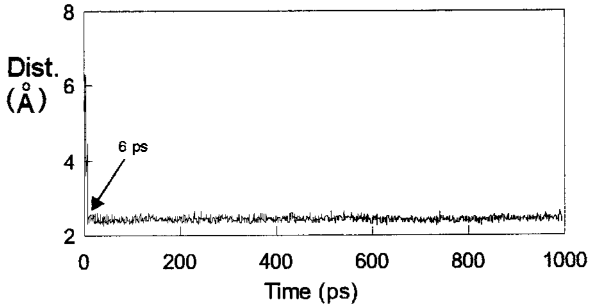

Figure 3. Distance between MeOH (O) and Eu^{3+} as a function of time in the MD run of the minimized structure of L·Eu^{3+} in MeOH.

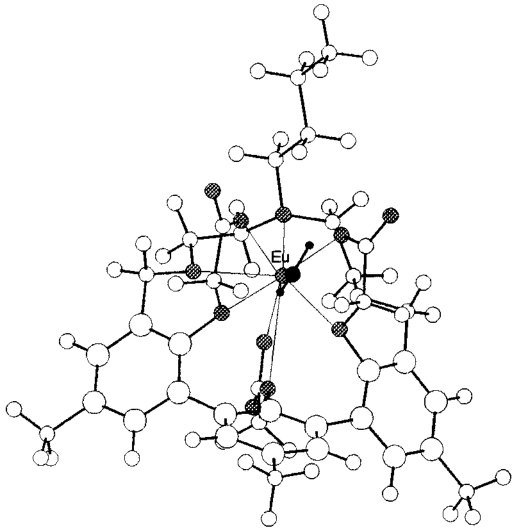

Figure 4. Minimized structure of L·Eu^{3+}·H_2O. See also caption to Figure 2.

L·Eu^{3+}·H_2O. The minimized structure of L·Eu^{3+}·H_2O is shown in Figure 4. It shows that the pendant outer arms can easily adjust to make room for one water and still be coordinated

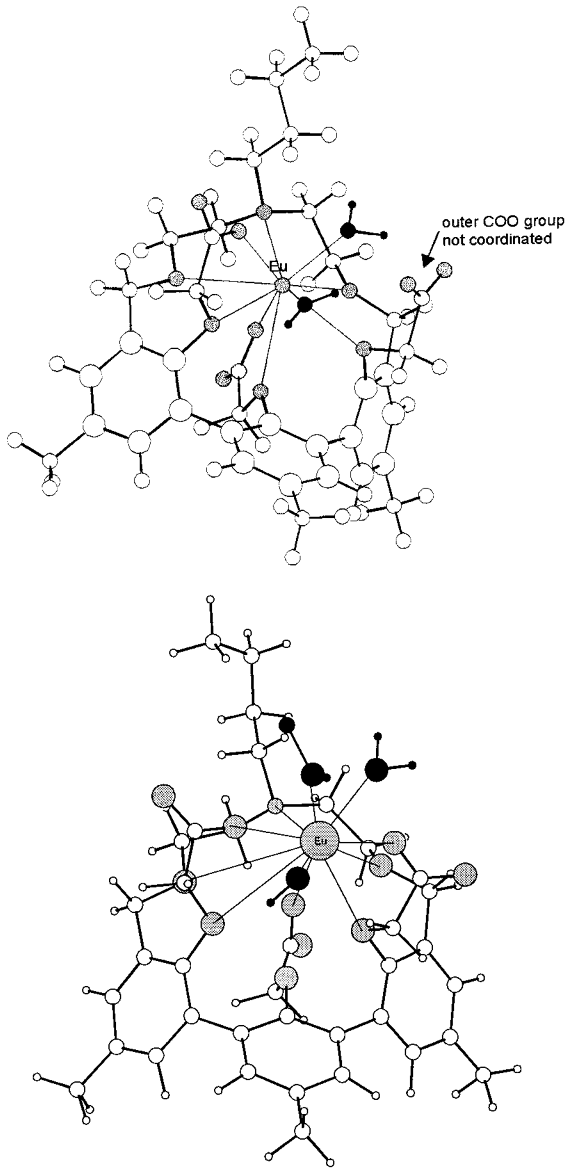

Figure 5. Minimized structure of L·Eu^{3+}·2H$_2$O (a, top) and snapshot from the MD run (b, bottom). See also caption to Figure 2.

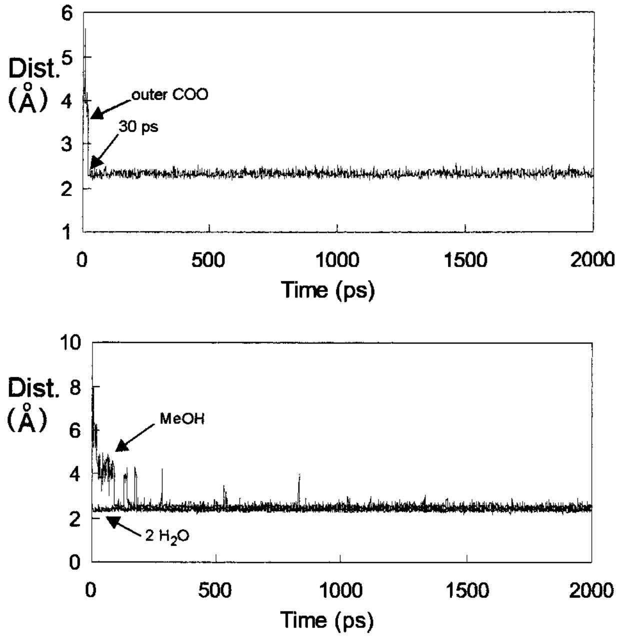

Figure 6. Distance between COO$^-$ (O$_{coord}$) and Eu^{3+} (a, top) and MeOH (O) and Eu^{3+} (b, bottom) as a function of time in the MD run of the minimized structure of L·Eu^{3+}·2H$_2$O in MeOH.

to the Eu^{3+} ion (COO$_{outer}^{-}$···Eu^{3+} distances are 2.07 and 2.00 Å; H$_2$O···Eu^{3+} = 2.53 Å[20]). A 1000 ps MD run showed no major changes of the coordination environment of Eu^{3+}. The water, the three carboxylates, the two outer PhO, the two PhCH$_2$O, and the nitrogen remained coordinated to the Eu^{3+}. The inner PhO donor atom was at a relatively long distance from the Eu^{3+} (Eu^{3+}···PhO$_{inner}$ = 3.00 Å).

L·Eu^{3+}·2H$_2$O. The structure of L·Eu^{3+}·2H$_2$O was obtained by rotating away one of the outer pendant arms and placing two waters at the coordination distance of Eu^{3+} followed by minimization (Figure 5a). This complex was subjected to a 2000 ps MD run and had two major events. The initially noncoordinated outer carboxylate returned to the coordination shell of Eu^{3+} after ~30 ps and remained there with the other two carboxylates throughout the rest of the run (Figure 6a). The two waters remained coordinated and an additional methanol entered the first coordination shell at ~100 ps (Figure 6b). None of the three solvent molecules left the coordination sphere of Eu^{3+} during the entire run.

L·Eu^{3+}·3H$_2$O. The trihydrated complex L·Eu^{3+}·3H$_2$O was formed similarly to L·Eu^{3+}·2H$_2$O (Figure 7a) and subjected to a 1500 ps MD simulation in methanol. As observed for L·Eu^{3+}·2H$_2$O, the initially noncoordinated outer carboxylates returned to the first coordination shell, one in the equilibration phase and the other early in the simulation, respectively (Figure 8a), and remained there during the rest of the simulation. The first, significant transition occurred only after 750 ps. One of the three coordinated waters is pushed out of the first coordination shell of Eu^{3+} into the second coordination sphere at a Eu^{3+}···O distance of 4.7–5.0 Å (Figure 8b). This situation remained until an attempt to leave the complex occurred at ~1210 ps. This water, however, returned to the second coordination shell to leave definitely after 1400 ps.

L·Eu^{3+} in Water. To expose the minimized complex L·Eu^{3+} to a maximum amount of water, a 500 ps MD run was calculated in pure water. During the MD two water molecules entered the first coordination sphere of Eu^{3+} at ~30 and ~65 ps, respectively (Figure 9a). The coordination behavior of the donor atoms of the ligand L was similar to those described above. A typical structure of the dihydrated complex is shown in Figure 9b and shows different positions for the two water molecules compared with the simulation of L·Eu^{3+}·3H$_2$O in methanol *after* the departure of one water. If the coordination environment depicted in Figure 9 also exists in methanol, it is most likely in fast equilibrium[21] on a luminescence time scale as that shown in Figure 7b.

The MD simulations in methanol on L·Eu^{3+} suggest that one methanol or one water is coordinated to Eu^{3+} and that with increasing amounts of water, possibly two waters are coordinated to Eu^{3+}. This is consistent with the experimental data (vide supra). We believe that the structure of L·Eu^{3+}·2H$_2$O·MeOH in the run of L·Eu^{3+}·2H$_2$O in MeOH is *kinetically* trapped. Despite some attempts of the MeOH to leave the complex (see the "spikes" in Figure 6b), the 2000 ps was apparently still too short to observe the definite removal of one water or the methanol from the first coordination shell. Therefore, we assume that three species are likely to be present, L·Eu^{3+}·MeOH, L·Eu^{3+}·H$_2$O, and L·Eu^{3+}·2H$_2$O, and that these species will be in equilibrium because of a fast exchange of the solvent molecules on the luminescence time scale.[21] These equilibria

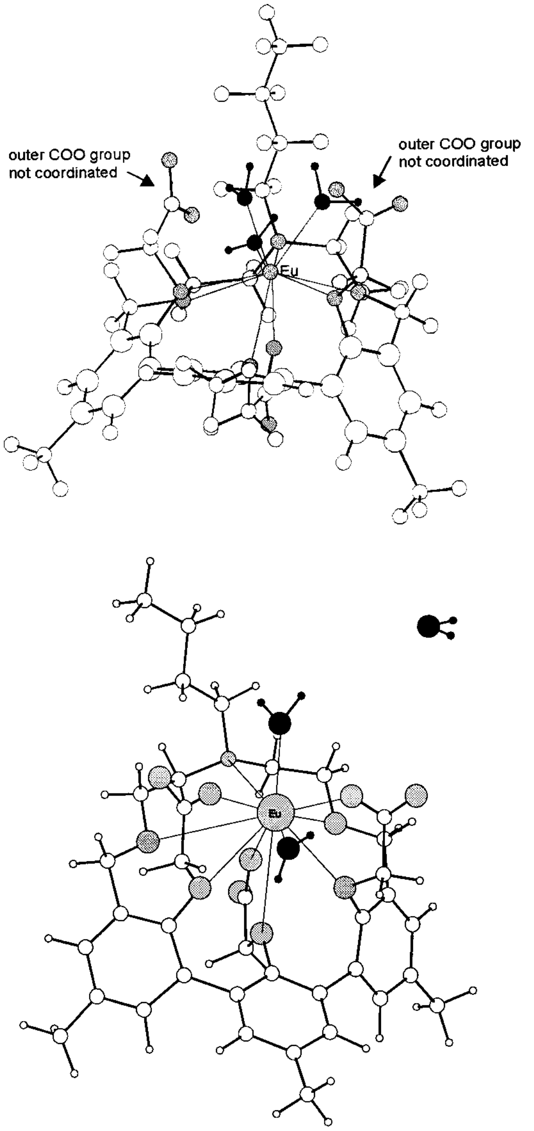

Figure 7. Minimized structure of L•Eu^{3+}•3H$_2$O (a, top) and snapshot from the MD run (b, bottom). See also caption to Figure 2.

have been calculated by means of MC FEP simulations and PMF calculations (vide infra).

Free Energy Perturbations and Potential of Mean Force Simulations. From the MD runs on L•Eu^{3+}•xH$_2$O/MeOH in methanol and water, we postulate that two equilibria exist. The first is the exchange of a coordinated methanol for a coordinated water (eq 1), and the second is the change from a monohydrated to a dihydrated L•Eu^{3+} complex (eq 2).

$$\mathrm{L{\cdot}Eu^{3+}{\cdot}MeOH} + \mathrm{H_2O} \overset{K_1}{=} \mathrm{L{\cdot}Eu^{3+}{\cdot}H_2O} + \mathrm{MeOH} \qquad (1)$$

$$\mathrm{L{\cdot}Eu^{3+}{\cdot}H_2O} + \mathrm{H_2O} \overset{K_2}{=} \mathrm{L{\cdot}Eu^{3+}{\cdot}2H_2O} \qquad (2)$$

The equilibrium constant of eq 1 can be calculated by means of MC FEP simulations. This is done by perturbing the bound methanol in L•Eu^{3+}•MeOH into a bound water, in methanol solution. To close the thermodynamic cycle, the perturbation of water into methanol in methanol solution also has to be calculated. Both reverse calculations have also been done and should theoretically give exactly the same result. In practice, however, this is seldom the case because only a limited number of configurations are used to describe the Boltzmann distribution. Nevertheless, calculations on modern computers can be sufficiently long to give a fair agreement between the two calculations, i.e., between forward and backward runs.

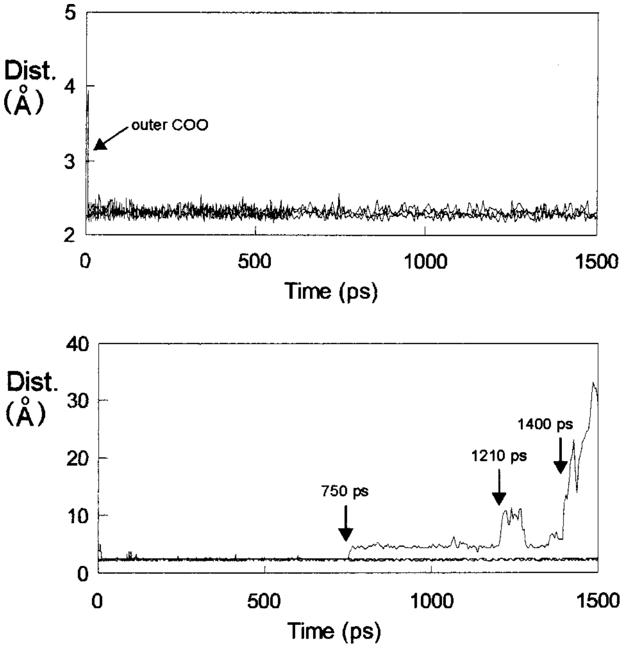

Figure 8. Distance between COO$^-$ (O$_{\mathrm{coord}}$) and Eu^{3+} (a, top) and three waters (O) and Eu^{3+} (b, bottom) as a function of time in the MD run of the minimized structure of L•Eu^{3+}•3H$_2$O in MeOH.

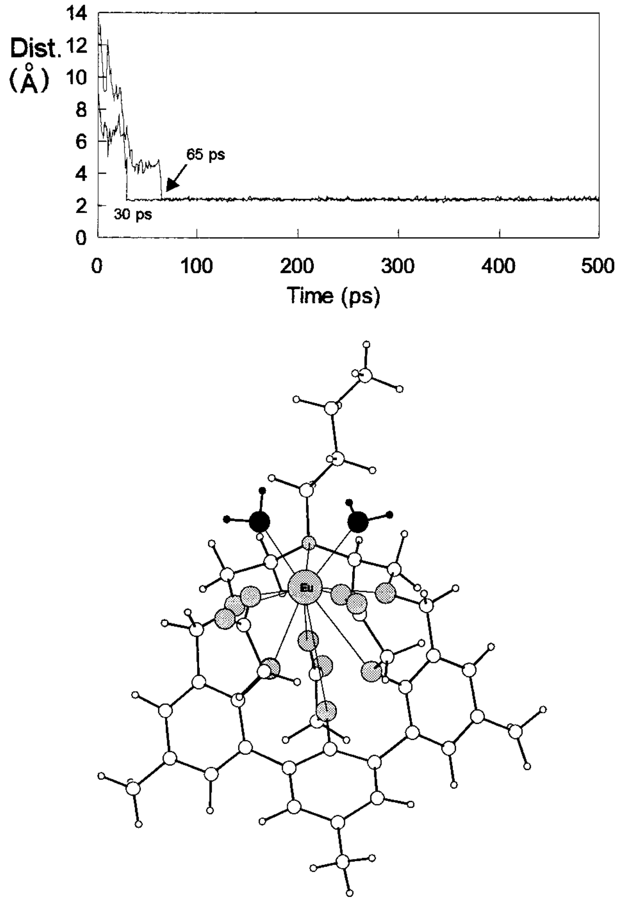

Figure 9. Distance between two waters (O) and Eu^{3+} as a function of time (a, top) and snapshot (b, bottom) in the MD run of the minimized structure of L•Eu^{3+} in water.

Equilibrium 2 can be calculated by two methods. The first method uses MC FEP simulations in which one bound water is

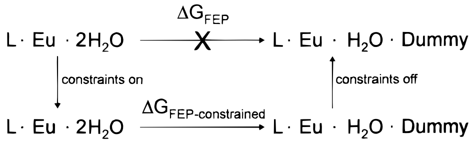

Figure 10. Thermodynamic cycle with a harmonic constraint.

perturbed into a species having no interactions with its environment (a dummy species). This should be done by decoupling of the electrostatic and van der Waals parts of the nonbonded interactions.[22] First, the electrostatic interactions are turned off by perturbing the point charges to zero followed by perturbation of the Lennard-Jones parameters to zero. Similarly, the "disappearing" of a molecule of water dissolved in methanol has to be calculated to close the thermodynamic cycle. The second method uses the potential of mean force (PMF) to estimate the binding affinity. In a PMF calculation the change of the Gibbs free energy is calculated when a water is approaching the Eu^{3+} complex from infinity and finally enters the first coordination shell of the Eu^{3+}. Calculations from infinity are impossible, but the approach should come from "far away".

The perturbation of a bound methanol into a bound water and the reverse resulted in a ΔG (forward) of -6.70 ± 1.2 kcal/mol and a ΔG (backward) of $+5.51 \pm 0.58$ kcal/mol, respectively. These numbers are in absolute sense the same, although longer calculations are expected to give better convergence. The perturbation of a methanol into water and the reverse gave a ΔG (forward) of -0.58 ± 0.46 kcal/mol and a ΔG (backward) of $+0.58 \pm 0.13$ kcal/mol, respectively. This results in binding constants K_1 of $30.4 \pm 2.6\ 10^3$ [−] and $10.9 \pm 0.4\ 10^3$ [−] for the forward and backward runs, respectively.

From preliminary perturbations of a water to a dummy species in $L\cdot Eu^{3+}\cdot 2H_2O$, it became clear that the disappearing species had to be constrained to the vicinity of the Eu^{3+}. Without a constraint, the species drifted away from the complex at the end of the perturbation of the point charges. This problem could be easily solved by applying a harmonic constraint between the Eu^{3+} and the oxygen atom of water. The thermodynamic cycle involving the constraints is shown in Figure 10.

At the start of the calculations the change in ΔG by applying the harmonic constraint is calculated followed by perturbing the water to a dummy, and finally the harmonic constraint is relieved.[23] This resulted in $\Delta G_{\text{constraint on}} = 0.047 \pm 0.005$ kcal/mol, $\Delta G_{\text{FEPconstrained}} = 12.54 \pm 1.77$ kcal/mol (electrostatic part $= 38.74 \pm 1.33$ and Lennard-Jones part $= -26.20 \pm 0.43$ kcal/mol), and $\Delta G_{\text{constraint off}} = -0.789 \pm 0.042$ kcal/mol, leading to $\Delta G_{\text{FEP}} = 11.8 \pm 1.8$ kcal/mol. It is satisfying to note that the ΔGs in placing and removing the harmonic constraint are small, indicating that the sampling is probably not biased too much. The thermodynamic cycle is closed by the perturbation of water into a dummy in methanol solution, giving $\Delta G_{\text{FEP}} = 5.82 \pm 0.82$ kcal/mol (electrostatic part $= 6.79 \pm 0.64$ and the Lennard-Jones part $= -0.97 \pm 0.18$ kcal/mol). This gives the binding constant $K_2 = 980 \pm 150$ L/mol. The position of the species at the end of the perturbation of the Lennard-Jones parameters is rather ill-defined, which has been observed by others in similar calculations.[24] This introduces an error in the calculations, but this does not seriously hamper the calculations because the involved ΔG's are very small in these final windows (<0.1 kcal/mol). However, an attempt to solve this problem by increasing the harmonic constraint from 10 to 25 kcal mol^{-1} $Å^{-2}$ was not successful. It gave a $K_2 = 475 \pm 80$ L/mol. The PMF of $L\cdot Eu^{3+}\cdot H_2O$ and the approaching water are shown in Figure 11. The PMF is scaled to zero at 10.3 Å, which introduces a small error due to the fact that the electrostatic interactions are long-ranged. The distinct barrier at 4.0 Å is due to the enforced adjustments of the outer pendant arms. The minimum is found at 2.4−2.5 Å, which is the coordination distance of a bound water to Eu^{3+}. This distinct minimum supports the possible binding of a second water to $L\cdot Eu^{3+}\cdot H_2O$. With eq 3[25] the binding constant can be estimated, which gives $K_2 = 1353 \pm 1384$ L/mol.

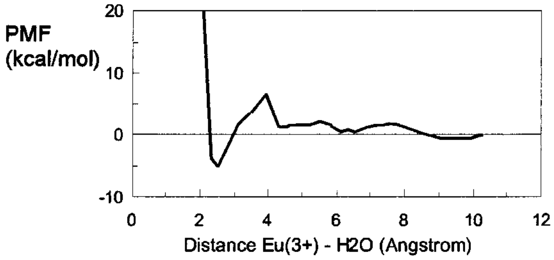

Figure 11. Potential of mean force of $L\cdot Eu^{3+}\cdot H_2O$ and an additional water in MeOH.

TABLE 1: Calculated Distribution (%) of $L\cdot Eu^{3+}\cdot MeOH$, $L\cdot Eu^{3+}\cdot H_2O$, and $L\cdot Eu^{3+}\cdot 2H_2O$[a]

water[b] (mM)	$L\cdot Eu^{3+}\cdot MeOH$	$L\cdot Eu^{3+}\cdot H_2O$	$L\cdot Eu^{3+}\cdot 2H_2O$
0	90	10	0
10^{-3}	38	47	15
2.5×10^{-3}	15	48	37

[a] In MeOH, with $K_1 = 30.5 \times 10^3$ [−], $K_2 = 475$ L/mol, and complex dissolved as $L\cdot Eu^{3+}\cdot H_2O$ (10^{-4} M). [b] Added additionally to the amount of water from the Eu^{3+} complex.

$$K = 4\pi N_A \int_0^r r^2\, e^{-\Delta G/(RT)}\, dr \tag{3}$$

This number is of the same order of magnitude as that calculated by the MC FEP method, but the (estimated) error is much larger. It would require a much longer equilibration and averaging to get better results.

Two Equilibria. The estimates of the binding constants of equilibria 1 and 2 allow a qualitative check on how sensitive the distribution is of $L\cdot Eu^{3+}\cdot MeOH$, $L\cdot Eu^{3+}\cdot H_2O$, and $L\cdot Eu^{3+}\cdot 2H_2O$ in methanol upon addition of small amounts of water. It should be stressed here that this distribution can only be made in a qualitative sense, since experimental binding free energies of water(s) and methanol are not available. Taking a value of $K_1 = 30.4 \times 10^3$ [−] and a value of $K_2 = 475$ L/mol and assuming that the complex is added as $L\cdot Eu^{3+}\cdot H_2O$[4] at 10^{-4} M concentration gave the results in Table 1.[26]

It shows that in dry methanol the dominant species is $L\cdot Eu^{3+}\cdot MeOH$ (90%) and that also $L\cdot Eu^{3+}\cdot H_2O$ is present (10%). The fact that the solvated complex is the dominant species despite a binding constant K_1 of 30.4×10^3 [−] is due to its large excess of methanol compared with that of water (24.68 vs 10^{-4} M). When the methanol contains 10^{-3} M water, all three species are present. When water is present at 2.5×10^{-3} M concentration, the dominant species are $L\cdot Eu^{3+}\cdot H_2O$ and $L\cdot Eu^{3+}\cdot 2H_2O$ (48 and 37%, respectively). It is also clear that when water is present at millimolar concentrations the monohydrate $L\cdot Eu^{3+}\cdot H_2O$ acts as a buffer. This is no surprise, since the monohydrate is a *product* in equilibrium 1 and a *reactant* in equilibrium 2. These calculations are in agreement with the MD simulations in the sense that it also supports the presence of a hydrated and probably a dihydrated species when "wet" methanol is being used. These predictions are in qualitative agreement with results from experiments. It also implies that for other Ln^{3+} complexes a distribution of solvated and hydrated species will be present if water is not scrupulously eliminated.

Experimentally, this is, however, almost impossible because the complexes and solutions are hygroscopic.

Conclusions

The experimental observation that small amounts of water in methanol solutions of L·Eu^{3+} lead to a decrease of the luminescence intensities, which is attributed to the coordination of one or two water molecules to Eu^{3+}, has been supported by molecular dynamics simulations and free energy calculations in an explicit solvent. It also shows that modern computational techniques give valuable structural information and that these tools can be used in a predictive sense. Furthermore, it shows that long MD runs, up to 2000 ps, are necessary to observe major transitions in the coordination sphere of (trivalent) cations, but even they are no guarantee.

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Supporting Information Available: Listing of parameters, point charges, atom types, and force constants (5 pages). Ordering information is given on any current masthead page.

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