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ARTICLES

Molecular Dynamics and FEP Monte Carlo Studies of Calix[4]arene-Derived Complexes of Eu^{3+}: The Role of the Counterions Investigated

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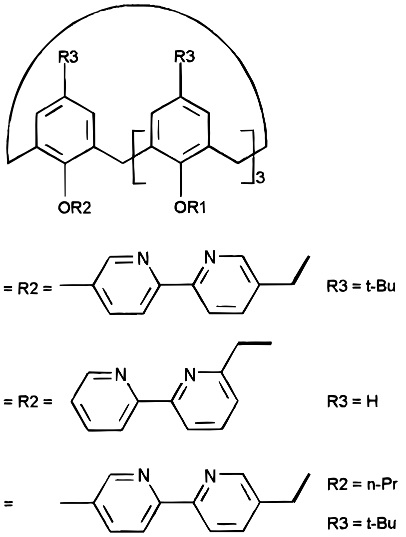
The structural properties of the Eu^{3+} complexes of three lower-rim functionalized calix[4]arenes have been investigated by means of molecular dynamics (MD) and free energy perturbation Monte Carlo (FEP-MC) simulations in OPLS acetonitrile. Ligand **1**, having four 2,2′-bipyridine-5-methyl groups on the lower rim, complexes Eu^{3+} tightly with all four bipy (2,2′-bipyridine) moieties as bidentate ligands. Additionally strong support is raised for the binding of one counterion (nitrate) in the first coordination shell of Eu^{3+}. Ligand **2**, having four 2,2′-bipyridine-6-methyl groups on the lower rim, shows less strong binding of Eu^{3+}. In fact, only three of the four bipy moieties are coordinated to the Eu^{3+}, which are likely to be in dynamic equilibrium. It is predicted that two nitrate ions are also coordinated and maybe one acetonitrile. These calculations support the explanation that this complex has a lower quantum yield of sensitized emission compared to system **1**·Eu^{3+} due to the fact that the bipy ligands interact less strongly with the Eu^{3+} and therefore will have a reduced "antenna" effect. The interaction between the bipy ligands and the Eu^{3+} determines, among others, the quantum yield of energy transfer. A factor also relevant to the quantum yield is the symmetry of the crystal field, which can be assessed by simulations but is not easily quantified. Calculations on the complex of **3,** having three 2,2′-bipyridine-5-methyl groups on the lower rim, with Eu^{3+} showed an artifact of the MD protocol, which was revealed by FEP-MC calculations and confirmed by some additional MD calculations. The structure of **3**·Eu^{3+} most likely has one monodentate and one bidentate nitrate coordinated to the Eu^{3+} besides the three tightly bound bipy moieties. This study shows that in general long MD simulations are needed.

Introduction

The luminescent properties of lanthanides, especially Eu^{3+} and Tb^{3+}, attract a lot of interest due to their potential applications as fluoroimmunoassays.[1] Cage-type multidentate ligands are intensively studied, for they are in principle able to form kinetically stable complexes, in addition to shielding the lanthanide from the environment (most often water or methanol). The shielding from OH-containing ligands is important because the OH oscillator is a very efficient quencher of the excited lanthanide ion.[2] Among others, cryptands,[3] bislariat crown ethers,[4] podands,[5] and calix[4]arenes-derived multidentate ligands[6] have been studied. One characteristic of the 4f transitions in trivalent lanthanide ions is their low extinction coefficient, which makes them intrinsically inefficient as luminescent probes. To overcome this disadvantage, "light harvesting" (organic) chromophores, with large extinction coefficients, can be attached to the complex, which should transfer energy to the lanthanide ion (the antenna effect).[7] Sometimes 2,2′-bipyridines (bipy) or phenanthrolines are used, which act both as bidentate and as light harvesters.

The calix[4]arene-based cages **1-3** (Chart 1) have been studied in a collaboration of the groups of Sabbatini, Ungaro, and Ziessel.[8] Although this is not the place to give an extensive exposé of their results, a few remarks are made that are relevant for the discussion. Contrary to **1** and **3**[9] no solid complexes of **2** could be isolated, indicating that the connection of the four bipy (2,2′-bipyridine) moities via the 6-position is less favorable. It was, however, shown that 1:1 complexes with Eu^{3+} and Tb^{3+} were formed in acetonitrile. Despite the fact that the complex **2**·Eu^{3+} has a large extinction coefficient (ϵ_{max} = 50 000 M^{-1} cm^{-1}), a very low quantum yield was obtained (<1%). This was explained by a smaller Eu^{3+}−bipy interaction compared to the other systems studied. Some comments will be made about this explanation. The best result were obtained for **1**·Eu^{3+},

CHART 1



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having a quantum yield of 15%. All complexes were studied as their nitrate salts in dry acetonitrile.

Although modern simulation techniques, like molecular mechanics (MM) and dynamics (MD) and Monte Carlo (MC), are mature[10] now, not many studies have appeared in which trivalent lanthanide complexes are dealt with.[11−13] Calix[4]-arene-derived cages for Ln^{3+} ions have been studied by Wipff and co-workers[12] and this author[13] and showed that information can be extracted from these simulations that make interpretation of the experimental results easier and that occasionally predictions can be made. A complication of the theoretical study in this article is the fact that the behavior of the counterions (nitrates) is not entirely known. The counterions are normally discarded in theoretical studies, but they have been studied to some extent by this author[13] and others.[12] They will be dealt with in detail and where possible a confrontation with experimental observations will be made. An issue that is beyond doubt the most difficult is how the electrostatic interactions should be treated. It is well documented that the way they are treated can have a large effect on the outcome of the simulations.[14] Unfortunately, polarization effects are not included in most current force fields.

In this paper a systematic study is presented on the role of the counterions, and the following points will be addressed. Firstly, the representation of the Eu^{3+} ion will be described. Secondly, the shielding of Eu^{3+} by the ligands **1**−**3** will be presented, without counterions and with bound counterions. Thirdly, simulations will be described in which the counterions are initially not bound but free to diffuse to the Eu^{3+} complex. These calculations showed that certainly one nitrate is coordinated to the Eu^{3+}. They also provide a possible explanation why ligand **2** behaves so poorly. Forthly, the effect of different cutoffs is discussed for ligand **1**. From the MD calculations, with explicit solvent, it also became apparent that the actual species might not be observed, even in quite lengthy simulations (400−500 ps). A critical assessment of this drawback is made via free energy perturbation MC calculations and some additional MD simulations of $Eu^{3+}(NO_3^-)_3$ in acetonitrile.

Experimental Section

Initial structures as well as visualizations were carried out with Quanta/CHARMm 3.3.[15] The MM and MD calculations were run with CHARMm 23.0.[16] Parameters were taken from Quanta 3.3, and point charges were calculated 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[15]) in combination with the +3 point charge have been applied (see Results and Discussion Section). The nitrate ion was charged to −1, resulting in $q_O = -0.598$ and $q_N = 0.794$.[17] The starting structures were minimized by ABNR (adopted basis set newton-raphson) until the rms (root mean square) on the energy gradient was ≤ 0.01 kcal·mol^{-1}·Å^{-1}. No cutoff on the nonbonded interactions was applied. A constant dielectric constant with an ϵ of 1 was used.

Details of the MD simulations were as follows. The minimized complexes, without counterions or with coordinated counterions, were placed in a cubic acetonitrile box of approximately 29 Å dimensions, filled with 267 OPLS CH_3CNs.[18] The simulation of Eu^{3+} in acetonitrile was treated accordingly. Simulations of minimized complexes without coordinated counterions but with "free" counterions were run in cubic acetonitrile boxes of approximately 45 Å dimensions, filled with 1028 OPLS CH_3CNs. In simulations with one nitrate it was placed at 10 Å from the Eu^{3+} along the long axis of the complex; if a second and a third nitrate were included, they were placed along an axis orthogonal to the long axis of the complex with the origin placed at the Eu^{3+}, also at 10 Å distance. The system of Eu^{3+} and three nitrates was treated accordingly. Solvent molecules that overlap with the complexes and nitrates were removed (based on heavy atom interatomic distances ≤ 2.3 Å). This in general resulted in removal of one acetonitrile per three non-hydrogen atoms of the systems under study. Full periodic boundary conditions were imposed. This was done by making 26 images in the $\pm x$, $\pm y$, and $\pm z$ directions. Before running the MD simulations the system was minimized by steepest descent, in order to remove the worst contacts, until the rms on the energy gradient was ≤ 1.0 kcal·mol^{-1}·Å^{-1} or a maximum of 1000 steps was reached. During the simulation the non-bonded list was updated every 20 time steps with a cutoff of 12 Å. Unless otherwise stated, the van der Waals interactions were treated with a switch function between 10 and 11 Å, whereas the shift function was applied to the electrostatic interactions (cutoff 11 Å). See the Results and Discussion section for different treatments of the nonbonded interactions. A constant dielectric constant and an ϵ of 1 were applied. The system was heated to 300 K in 5 ps, followed by 10 ps equilibration with scaling of the velocities within a temperature window of 10°. After equilibration no scaling of the velocities was applied. The production phase consisted of 50−500 ps, and coordinates were saved every 200 time steps (NVE ensemble; no systematic deviation from 300 K was observed). The verlet/leapfrog algorithm was used for the numerical intergration. The SHAKE algorithm[19] on bonds involving hydrogen was applied, allowing a time step of 1 fs.

Free energy perturbation Monte Carlo (FEP-MC) simulations were performed with the BOSS program.[20] Details are as follows. The appropiate **z**-matrices were constructed from the minimized structure of **3**·Eu^{3+}·$2NO_3^-$, having the two nitrates as monodentate, and from a snapshot from the MD simulation of **3**·Eu^{3+}·$2NO_3^-$, having one nitrate as monodentate along the long axis of the complex and the other nitrate as bidentate. The nitrate coordinated from the side was perturbed into an acetonitrile. A bond shrinkage to 0.5 Å between the initial nitrogen and the "disappearing" oxygen atom was applied in order to avoid a singularity.[21] A linear coupling parameter is used without decoupling of the van der Waals and electrostatic forces.[22] 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 along the long axis of a rectangular box of 28.9 × 28.9 × 43.3 Å, initially filled with 400 OPLS CH_3CNs. Based on the worst interaction energies 40 molecules of acetonitrile 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 −0.5 Å. The ligand **3**, the Eu^{3+}, and the two nitrate ions were sampled independently. Translational and rotational sampling was not applied to the ligand, but 12 dihedrals were sampled ($C{=}C{-}O{-}CH_2$, $C{-}O{-}CH_2{-}C{=}$, and $O{-}CH_2{-}C{=}C$ for the three bipy bearing phenyl rings and $C{=}C{-}O{-}CH_2$, $C{-}O{-}CH_2{-}CH_2$, and $O{-}CH_2{-}CH_2{-}CH_3$ for the remaining phenyl ring of the calix[4]arene; all with a sampling range of 1.5°, resulting in an acceptance ratio of about 15%). The translational sampling range of Eu^{3+} was only 0.03

Å, which gave an acceptance ratio of about 15%. The translational and rotational ranges for the two nitrates were automatically adjusted to give an acceptance range of about 40−50%. The perturbations were carried out in five double-wide windows or in 10 double-wide windows. All calculation were equilibrated for 1 million configurations, followed by averaging over 2 million configurations in the NPT ensemble at 1 atm and 298 K. Full periodic boundary conditions were imposed. This was done by making 26 images in the $\pm x$, $\pm y$, and $\pm z$ directions. The perturbation of nitrate into acetonitrile was done similarly, in a cubic box of OPLS CH_3CN of 28.9 Å dimensions. As a lower bound estimation of the error, the deviation from the average of 2 times 1 million is taken.

Results and Discussion

This section is divided into the following subjects. Firstly, the parameters for the Eu^{3+} ion are described. Secondly, the behavior of the complexes without nitrates and initially coordinated nitrates is presented. Thirdly, the effect of initially unbound nitrate(s) is discussed. The large influence of the way the nonbonded interactions are treated is also included. The results given in this section raise the question for complex **3** whether one or two counterions are bound to the Eu^{3+}. To address this point, free energy perturbation monte Carlo (FEP-MC) simulations have been performed, which indicated different structures. Some additional calculations have been carried out to confirm the predictions based on the FEP-MC results.

The Parameters of Eu^{3+}. The interactions of trivalent lanthanide ions with ligands are essentially non-directional electrostatic bonds.[23] The Lennard-Jones parameters ($R_{\min} =$ 3.488 Å and $\epsilon = -0.060$ kcal/mol) in combination with a +3 point charge give a correct solvation shell of Eu^{3+} in OPLS methanol.[13] The calculated radial distribution function ($Eu^{3+}\cdots$MeOH(O)) from a 50 ps MD simulation shows the first coordination peak at approximately 2.3 Å. This peak integrates to 7.5 oxygen atoms, which corresponds well with the experimental value of 7.1 ± 0.5 determined by Horrocks and co-workers.[24] More details can be found in ref 13.

Complexes without Counterions and with Initially Bound Counterions. *Tetrakis(bipy)-calix[4]arene **1**.* The minimized structure of the Eu^{3+} complex of the tetrakis(bipy)-calix[4]arene **1** is shown in Figure 1a and shows the four bipy moieties to be coordinated in the expected bidentate fashion ($Eu^{3+}\cdots N_{py} =$ 2.39−2.48 Å). The interaction energy between the ligand and the Eu^{3+} is very favorable (−864.3 kcal/mol) and is clearly dominated by the electrostatics (Table 1).

Visual inspection of the van der Waals representation indicates that the europium ion is well shielded from the environment, but it has recently been shown that this may be very misleading due to the fact that no competition with solvent molecules is present.[13] Therefore, the complex was dissolved in a cubic box of OPLS acetonitrile,[18] and an MD simulation of 50 ps was calculated. A snapshot from this simulation is shown in Figure 1b. One molecule of acetonitrile is approaching the ion with the cyano group first at a relatively long distance ($Eu^{3+}\cdots NCCH_3 = 4-5$ Å). Apparently the interaction between the europium ion and the acetonitrile is too weak to induce a conformational change such that it can enter the first coordination shell. This simulation suggests that a counter ion (i.e. nitrate) might induce a conformational change because the (electrostatic) interaction with the europium ion is much stronger. Therefore, a nitrate was placed at the position of the acetonitrile molecule, followed by minimization *in vacuo*. Besides the bidentate coordination of the four bipy moieties ($Eu^{3+}\cdots N_{py} = 2.42-2.78$), the nitrate is coordinated as a monodentate in the first coordination shell ($Eu^{3+}\cdots NO_3^- = 2.23$ Å). This slightly different coordination environment is also reflected in the interaction energy between the ligand and the Eu^{3+} (−821.8 vs −864.3 kcal/mol in **1**·Eu^{3+}, Table 2). This small loss is, however, more than compensated by the interaction between the Eu^{3+} and the nitrate (−315.4 kcal/mol). The MD simulation (50 ps) of this complex in acetonitrile did not show any major conformational changes due to interactions with the solvent (Figure 2). Although this simulation indicates that one nitrate is likely to be coordinated to the Eu^{3+}, it might however be purely coincidental. The release of the bound nitrate might be not observed due to a too high barrier or due to the small length of the calculation. This point will be addressed further below. The observed nine coordination of Eu^{3+} is generally observed for ligands offering eight or nine donors.[1]

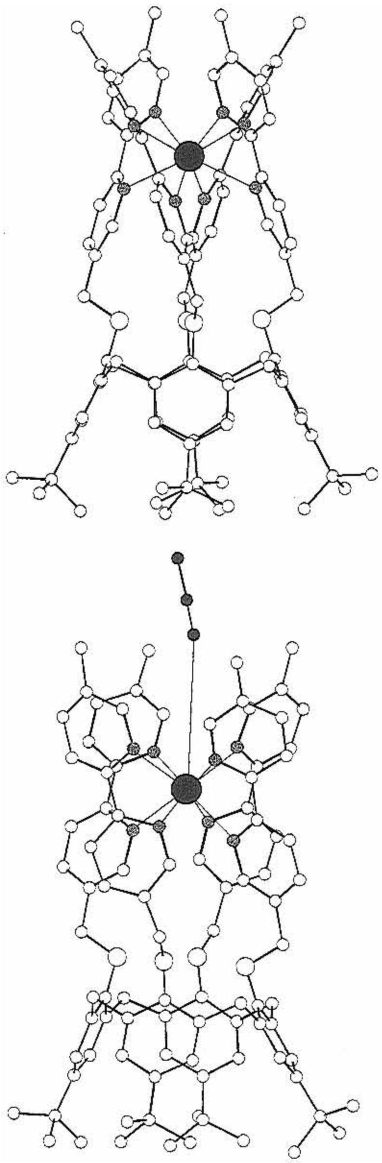

Figure 1. (a, top) Minimized structure of **1**·Eu^{3+}. The Eu^{3+} is represented as a black circle, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity. (b, bottom) Snapshot from the MD of **1**·Eu^{3+} in acetonitrile. The Eu^{3+} and the weakly coordinated CH_3CN are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

*Tetrakis(bipy)-calix[4]arene **2**.* The Eu^{3+} complex of the tetrakis(bipy)-calix[4]arene **2** was minimized *in vacuo* and shows (see Figure 3) the four bipy moieties coordinated to the Eu^{3+} ion ($Eu^{3+}\cdots N_{py} = 2.36-2.60$ Å (4×), 3.09 Å, and 3.15 Å), in a propellar-shaped arrangement. These distances are certainly longer than for **1**·Eu^{3+} and indicate that the connection of the bipy moities via the 6-positions is less optimal for a tight

TABLE 1: (Interaction) Energies of the Gas-Phase Minimized Structures (kcal/mol)

		E_{sum}	E_{el}	E_{vdW}
1·Eu^{3+}	E_{total}	−733.66	−850.06	48.42
	E_{host}	130.65	63.06	−0.40
	$E_{\mathrm{interaction}}{}^{a}$	−864.31	−913.12	48.82
1·Eu^{3+}·NO_3^-	E_{total}	−930.26	−1047.80	43.84
	E_{host}	108.95	45.17	−2.25
	$E_{\mathrm{interaction}}{}^{a}$	−821.84	−855.62	33.79
	$E_{\mathrm{interaction}}{}^{b}$	−315.40	−323.97	8.58
2·Eu^{3+}	E_{total}	−537.30	−696.98	49.17
	E_{host}	59.85	−28.04	13.40
	$E_{\mathrm{interaction}}{}^{a}$	−633.15	−668.94	35.77
3·Eu^{3+}	E_{total}	−645.32	−756.12	50.38
	E_{host}	47.30	9.63	−22.76
	$E_{\mathrm{interaction}}$	−692.62	−765.75	73.14
3·Eu^{3+}·NO_3^-	E_{total}	−706.52	−948.01	48.96
	E_{host}	186.66	0.05	1.24
	$E_{\mathrm{interaction}}{}^{a}$	−665.85	−703.89	38.04
	$E_{\mathrm{interaction}}{}^{b}$	−338.25	−340.95	2.69
3·Eu^{3+}·$2NO_3^-$	E_{total}	−760.92	−1023.39	100.99
	E_{host}	287.10	110.51	29.45
	$E_{\mathrm{interaction}}{}^{a}$	−553.26	−623.26	70.0
	$E_{\mathrm{interaction}}{}^{b}$	−570.45	−572.28	1.83

[a] Between the ligand and the Eu^{3+}. [b] Between the Eu^{3+} and the nitrate(s).

TABLE 2: Coordination Distances of Gas-Phase Minimized Structures (Å)

	$Eu^{3+}\cdots N_{\mathrm{py}}$	$Eu^{3+}\cdots NO_3^-(O)$	$Eu^{3+}\cdots NO_3^-(O)$
1·Eu^{3+}	2.39−2.48		
1·Eu^{3+}·NO_3^-	2.40−2.76	2.23	
2·Eu^{3+}	2.36−3.15[a]		
3·Eu^{3+}	2.31−2.32		
3·Eu^{3+}·NO_3^-	2.35−2.51	2.55/2.55	
3·Eu^{3+}·$2NO_3^-$	2.35−2.51	2.61	2.54
2.61			

[a] 2.36−2.60 (6×), 3.09, 3.15.

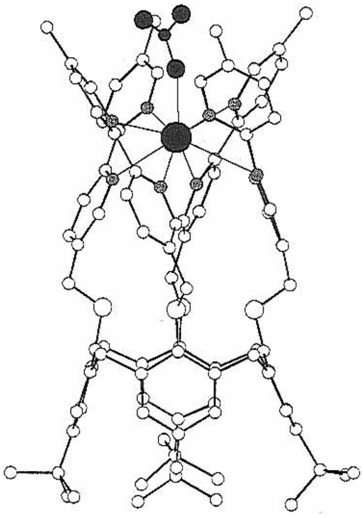

Figure 2. Snapshot from the MD of **1**·Eu^{3+}·NO_3^- in acetonitrile. The Eu^{3+} and the coordinated NO_3^- are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

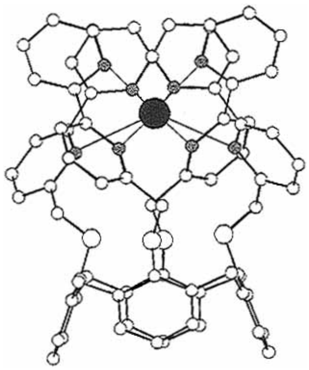

Figure 3. Minimized structure of **2**·Eu^{3+}. The Eu^{3+} is represented as a black circle, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

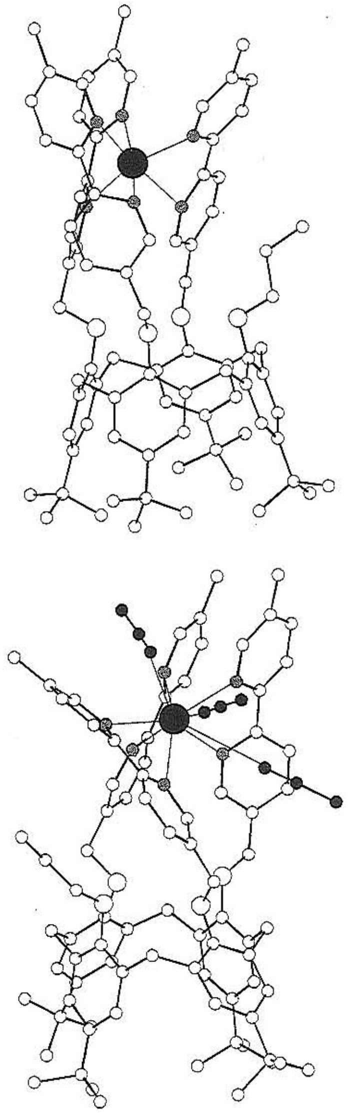

Figure 4. (a, top) Minimized structure of **3**·Eu^{3+}. The Eu^{3+} is represented as a black circle, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity. (b, bottom) Snapshot from the MD of **3**·Eu^{3+} in acetonitrile. The Eu^{3+} and the coordinated CH_3CNs are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

binding. This is also indicated by a much smaller interaction energy between the ligand and the Eu^{3+} (−633.2 vs −864.3 kcal/mol in **1**·Eu^{3+}). This complex has only be subjected to a simulation with three, initially free nitrates and is discussed below.

*Tris(bipy)-calix[4]arene **3***. The minimized structure of the europium complex of tris(bipy)-calix[4]arene **3** is shown in Figure 4a, showing the three bipy moieties in the expected bidentate fashion ($Eu^{3+}\cdots N_{\mathrm{py}}$ = 2.30−2.32 Å). The MD simulation (50 ps) in acetonitrile shows that the europium ion can accommodate three molecules of acetonitrile in the first coordination shell; two strongly bound acetonitriles at 2.58 ± 0.12 and 2.63 ± 0.14 Å, respectively, and one weakly bound acetonitrile at 4.51 ± 1.14 Å. The three bipy moieties stayed as bidentate ligands (Table 3; see Figure 4b for a snapshot).

This coordination shell raises the question whether one or

TABLE 3: Averaged Coordination Distances and Standard Deviation (in Parentheses) (in Å) in the MD Simulations

run[f]	$\mathrm{Eu}^{3+}\cdots\mathrm{N}_{\mathrm{py}}$	$\mathrm{Eu}^{3+}\cdots\mathrm{NO}_3^-(\mathrm{O})$	$\mathrm{Eu}^{3+}\cdots\mathrm{NO}_3^-(\mathrm{O})$	$\mathrm{Eu}^{3+}\cdots\mathrm{NCCH}_3(\mathrm{N})$
1 $\mathbf{1}\cdot\mathrm{Eu}^{3+}$	2.38−2.55 (0.05−0.09)			4.98 (0.03)
2 $\mathbf{1}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$	2.43−2.82 (0.05−0.17)	2.24 (0.06)		
3 $\mathbf{1}\cdot\mathrm{Eu}^{3+} + \mathrm{NO}_3^-$ [a]	2.42−2.82 (0.05−0.19)	2.24 (0.06)		
4 $\mathbf{1}\cdot\mathrm{Eu}^{3+} + \mathrm{NO}_3^-$ [b]	2.41−2.85 (0.05−0.14)	2.22 (0.04)		
5 $\mathbf{1}\cdot\mathrm{Eu}^{3+} + \mathrm{NO}_3^-$ [c]	2.40−2.74 (0.05−0.21)	2.24 (0.05)		
6 $\mathbf{1}\cdot\mathrm{Eu}^{3+}+\mathrm{NO}_3^-$ [d]	2.42−2.85 (0.06−0.17)	2.24 (0.06)		
7 $\mathbf{1}\cdot\mathrm{Eu}^{3+}+\mathrm{NO}_3^-$ [e]	2.44−2.76 (0.06−0.20)	2.28 (0.05)		
8 $\mathbf{1}\cdot\mathrm{Eu}^{3+}+2\mathrm{NO}_3^-$	2.43−2.85 (0.05−0.16)	2.23 (0.05)	≥5.0	
9 $\mathbf{2}\cdot\mathrm{Eu}^{3+}+3\mathrm{NO}_3^-$	2.39−2.76 (0.05−0.19)[g]	2.29 (0.07), 2.31 (0.09)	≥6.7	3.11 (0.57)
10 $\mathbf{3}\cdot\mathrm{Eu}^{3+}$	2.40−2.43 (0.05−0.08)			2.71 (0.12), 2.63 (0.14), 4.51 (1.14)
11 $\mathbf{3}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$	2.41−2.51 (0.05−0.08)	2.31 (0.07), 2.31 (0.07)		2.71 (0.16)
12 $\mathbf{3}\cdot\mathrm{Eu}^{3+}\cdot2\mathrm{NO}_3^-$	2.42−2.54 (0.06−0.08)	2.32 (0.06), 2.45 (0.15)	2.21 (0.05)	
13 $\mathbf{3}\cdot\mathrm{Eu}^{3+}+3\mathrm{NO}_3^-$	2.41−2.49 (0.06−0.08)	2.22 (0.05)	≥4.6	2.56 (0.11), 3.39 (0.39)
14 $\mathbf{3}\cdot\mathrm{Eu}^{3+}+3\mathrm{NO}_3^-$ [h]	2.45−2.55 (0.07−0.09)	2.31 (0.08), 2.46 (0.22)	2.23 (0.05)	

[a] No NOE constraints. [b] NOE constraints. [c] Cutoff of 16 Å (elec. int. with shift function). [d] Cutoff of 20 Å (elec. int. with shift function). [e] Cutoff of 16 Å (elec. int. with switch between 6−16Å). [f] $\cdot\mathrm{NO}_3^-$ means a coordinated NO_3^- in the initial structures; $+\mathrm{NO}_3^-$ means a dissolved NO_3^- at 10 Å from the Eu^{3+}. [g] The noncoordinating $\mathrm{Eu}^{3+}-\mathrm{N}_{\mathrm{py}}$ distances (2+) are: 6.33 (0.28) and 6.67 (0.40). [h] See text.

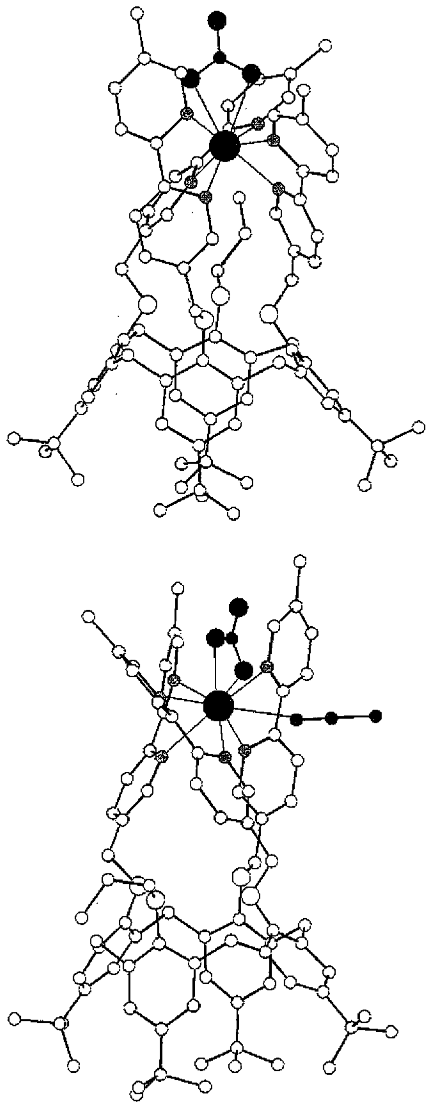

Figure 5. (a, top) Minimized structure of $\mathbf{3}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$. The Eu^{3+} and the coordinated NO_3^- are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity. (b, bottom) Snapshot from the MD of $\mathbf{3}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$ in acetonitrile. The Eu^{3+} and the coordinated NO_3^- and $\mathrm{CH}_3\mathrm{CN}$ are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

more nitrates are coordinated. The minimized structure of tris(bipy-calix[4]arene)$\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$ (Figure 5a) shows the nitrate coordinated as a bidentate ($\mathrm{Eu}^{3+}\cdots\mathrm{O} = 2.55$ and 2.55 Å), with the three bipy moieties as bidentate ligands ($\mathrm{Eu}^{3+}\cdots\mathrm{N}_{\mathrm{py}} = 2.35-2.52$ Å). The MD simulation (50 ps) shows that besides the three bipy moieties and the nitrate ion as bidentate there is space for one molecule of acetonitrile at 2.71 ± 0.16 Å (see Figure 5b for a snapshot).

The fact that one solvent molecule can enter the first coordination sphere indicates that in principle another anion might be coordinated. To test this, two nitrate ions were placed, as monodentates, at coordination distances, followed by minimization *in vacuo* (see Figure 6a). The three bipy moieties are as expected ($\mathrm{Eu}^{3+}\cdots\mathrm{N}_{\mathrm{py}} = 2.35-2.51$ Å), and the nitrate coordination distances are 2.54 and 2.61 Å, respectively. The MD simulation (50 ps) in acetonitrile shows a rearrangement of one of the nitrate ions into a bidentate ligand (Table 3; see Figure 6b for a snapshot), leaving apparently no space for solvent molecules to enter the first coordination sphere.

The averaged interaction energy between the Eu^{3+} and the bidentate nitrate is more favorable than for the monodentate nitrate (−312.5 ± 7.6 and −268.1 ± 5.0 kcal/mol, respectively). The presence of one or two nitrates in the first coordination shell of Eu^{3+} induces no significant changes in the ligation by the ligand; the coordination distances as well as the interaction energy between Eu^{3+} and the ligand are comparable (Tables 3 and 4, entries 10−12). Based on the fact that acetonitrile is less polar compared to water and methanol, it is not unlikely that the actual species in acetonitrile solution is the complex with two nitrate ions coordinated to the europium, in combination with the three bipy moieties. I will come back to this point.

Complexes with Initially Free Counterions. *Tetrakis(bipy)-calix[4]arene **1**.* The effect of the cutoff distance and the way the electrostatic interactions are dealt with will be discussed in some detail for $\mathbf{1}\cdot\mathrm{Eu}^{3+}$. One nitrate was placed at a distance of 10 Å from the Eu^{3+} along the long axis of the complex. This species was dissolved in a cubic box of OPLS $\mathrm{CH}_3\mathrm{CN}$ of approximately 45 Å dimensions. The unconstrained MD simulation shows that the nitrate enters the first coordination sphere at about 20 ps in the production phase (see Figure 7) and it remains there during the rest of the simulation. *All four bipy moieties remain coordinated.* Two of the $\mathrm{N}_{\mathrm{py}}\cdots\mathrm{Eu}^{3+}$ distances, involving the first aromatic ring with respect to the calixarene of two opposite bipy mioties, are significantly longer when compared to the minimized structure (see Tables 2 and 3).

The overall picture of the structure of $\mathbf{1}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$ is more or less the same as that starting from the minimized $\mathbf{1}\cdot\mathrm{Eu}^{3+}\cdot\mathrm{NO}_3^-$ (see Figure 8). The coordination of the nitrate may be fortuitous due to a solvation shell around the complex that has not completely relaxed. To test this, a distance constraint was placed between the nitrate and the Eu^{3+} ion, which was released at the beginning of the production phase. Also during this

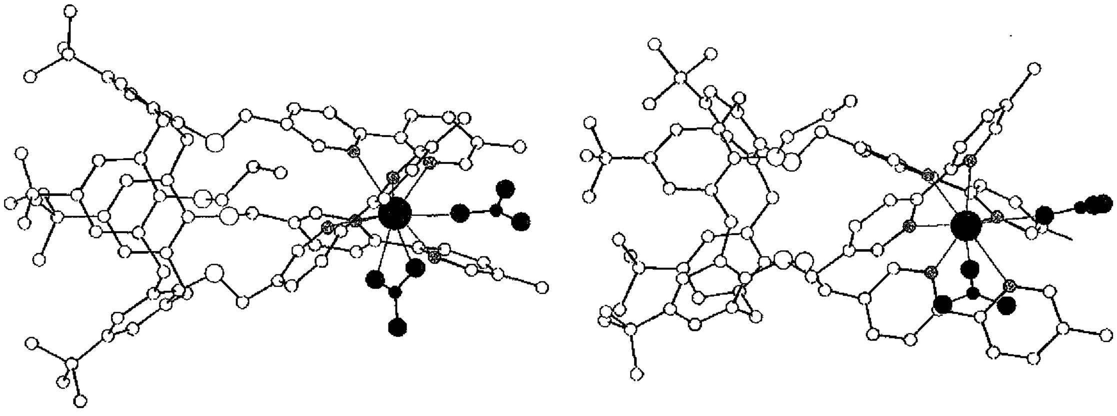

Figure 6. (a, top) Minimized structure of **3**·Eu^{3+}·2NO$_3^-$. The Eu^{3+} and the two coordinated NO$_3^-$ are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity. (b, bottom) Snapshot from the MD of **3**·Eu^{3+}·2NO$_3^-$ in acetonitrile. The Eu^{3+} and the two coordinated NO$_3^-$ are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

simulation the nitrate was able to penetrate into the first coordination shell of the Eu^{3+}, but the event took place after a longer time (after approximately 90 ps). In this simulation the nitrate had to substitute the weakly coordinated acetonitrile (*vide supra*). The mechanism resembles an interchange process, with synchronous bond making and bond breaking. Such a mechanism has been observed by Merbach et al.[25] in simulations of trivalent lanthanide ions in water.

The treatment of the nonbonded interactions, in particular the electrostatic, is among the most difficult ones, and therefore it was decided to vary systematically the effect of the cutoff distance and the way the truncation is carried out. The CHARMM force field allows the use of the switch or shift function. The switch function truncates the interaction at the end of the cutoff between two given values, whereas the shift function applies a gradual truncation from the beginning to the end of the cutoff.[16] In addition to the simulation discussed above with a shift function applied to the electrostatic interaction and a cutoff distance of 11 Å, similar simulations with shift functions and cutoff distances of 16 and 20 Å, respectively, have been calculated. Although these calculations are feasible on modern workstations, they become very CPU expensive. A

TABLE 4: Averaged (Interaction) Energies and Standard Deviation (in Parentheses) (in kcal/mol) in the MD Simulations[a]

	E_{ligand}	$E_{\text{complex}}{}^{b}$	E_{int} Eu^{3+}−ligand	$E_{\text{int}}{}^{c}$ Eu^{3+}−xNO$_3^-$	$E_{\text{int}}{}^{d}$ Eu^{3+}−xCH$_3$CN	$E_{\text{int}}{}^{d}$ ligand−xCH$_3$CN	$E_{\text{int}}{}^{e}$ ligand−solvent	$E_{\text{int}}{}^{c}$ ligand-xNO$_3^-$	$E_{\text{int}}{}^{b,c}$ complex−xNO$_3^-$	$E_{\text{int}}{}^{b,d}$ complex−xCH$_3$CN
1 **1**·Eu^{3+}	329.4 (9.9)	−601.4 (7.2)	−930.8 (9.0)		−13.5 (2.5)	6.5 (2.5)	−116.3 (12.2)			−20.0 (1.5)
2 **1**·Eu^{3+}·NO$_3^-$	306.5 (10.8)	−573.7 (8.6)	−879.8 (12.1)	−295.4 (5.0)			−131.5 (12.8)	86.7 (5.2)	−172.6 (5.2)	
3 **1**·Eu^{3+}+NO$_3^-$	309.6 (15.3)	−581.0 (11.4)	−880.0 (12.6)	−260.3 (3.9)			−157.8 (9.2)	89.1 (5.1)	−171.2 (5.6)	
4 **1**·Eu^{3+} + NO$_3^-$	293.7 (11.4)	−584.7 (11.8)	−880.5 (11.7)	−260.8 (4.2)			−143.6 (10.7)	88.3 (4.9)	−172.5 (4.4)	
5 **1**·Eu^{3+} + NO$_3^-$	281.8 (9.7)	−575.3 (8.6)	−856.9 (11.4)	−283.3 (4.3)			−140.5 (13.1)	93.2 (4.9)	−190.0 (5.6)	
6 **1**·Eu^{3+} + NO$_3^-$	263.9 (11.6)	−567.1 (8.8)	−830.9 (11.1)	−295.0 (4.4)			−145.2 (11.1)	92.9 (4.7)	−202.1 (4.3)	
7 **1**·Eu^{3+} + NO$_3^-$	254.7 (11.8)	−568.7 (8.9)	−801.9 (10.7)	−311.2 (3.8)			−110.9 (14.5)	94.4 (4.5)	−216.7 (4.9)	
8 **1**·Eu^{3+}+2NO$_3^-$	303.9 (12.0)	−575.5 (10.1)	−879.4 (10.6)	−260.4 (4.2)			−154.5 (11.5)	87.9 (5.0)	−172.4 (4.4)	
9 **2**·Eu^{3+}+3NO$_3^-$	153.0 (10.5)	−427.0 (12.8)	−585.3 (14.3)	−321.5 (5.5)	−54.3 (12.8)	18.0 (5.3)	−61.8 (9.6)	85.6 (5.0)	−234.9 (6.2)	−36.3 (8.2)
10 **3**·Eu^{3+}	226.5 (10.0)	−485.8 (7.9)	−712.3 (8.4)		−67.2 (3.9), −68.7 (3.5), −32.8 (12.0)	26.1 (2.9), 26.7 (3.0), 14.0 (5.9)	20.0 (14.0)			−41.2 (2.9), −42.0 (3.2), −18.8 (6.3)
11 **3**·Eu^{3+}·NO$_3^-$	220.0 (8.5)	−478.5 (9.6)	−698.5 (8.8)	−320.3 (4.9)	−64.8 (5.3)		−81.7 (10.0)	98.2 (4.3)	−222.1 (4.4)	−39.3 (3.6)
12 **3**·Eu^{3+}·2NO$_3^-$	215.1 (8.4)	−469.9 (9.1)	−685.0 (10.5)	−312.5 (7.6), −261.8 (5.0)			−140.6 (9.7)	110.5 (4.5), 66.1 (4.9)	−202.0 (6.6), −195.7 (4.9)	
13 **3**·Eu^{3+}+3NO$_3^-$	214.4 (9.0)	−491.6 (9.5)	−700.8 (10.3)	−261.8 (4.2)	−68.5 (4.1), −42.6 (8.8)	22.9 (2.9), 16.8 (4.6)	−92.8 (12.7)	70.2 (4.3)	−191.5 (4.6)	−45.6 (3.8), −25.7 (4.8)
14 **3**·Eu^{3+}+3NO$_3^-$	215.5 (10.2)	−469.8 (13.5)	−685.3 (11.0)	−312.1 (9.3), −260.4 (4.8)			−173.8 (10.1)	106.1 (4.0), 67.9 (5.4)	−207.3 (6.6), −192.7 (4.8)	

[a] See footnotes to Table 3. [b] Defined as L·Eu^{3+}, with L compound **1**−**3**. [c] With x the number of coordinated NO$_3^-$. [d] With x the number of coordinated CH$_3$CNs. [e] Including the coordinated CH$_3$CN(s), if applicable.

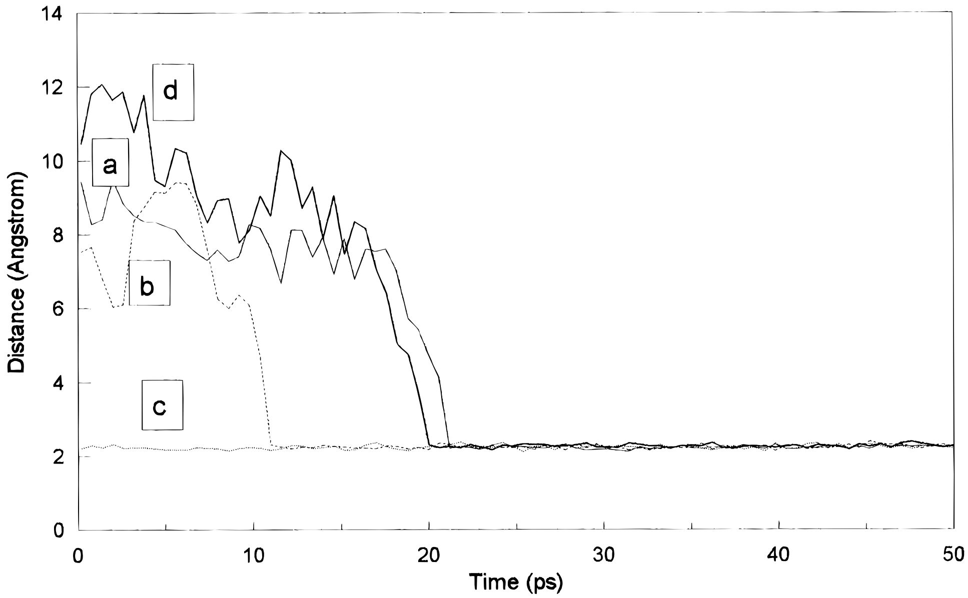

Figure 7. Effect of the cutoff on the diffusion of the nitrate ion into the first coordination shell of **1**·Eu^{3+}: (a) cutoff 12 Å (shift), (b) cutoff 16 Å (shift), (c) cutoff 20 Å (shift), and (d) switch 6−16 Å.

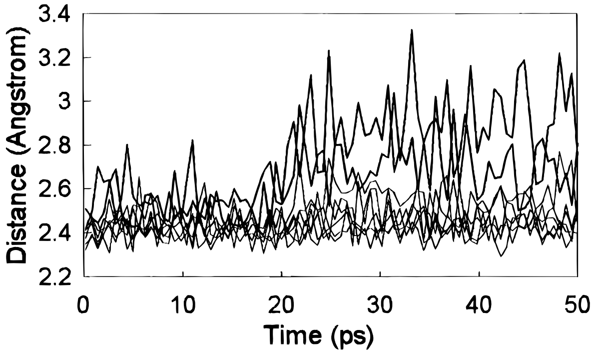

Figure 8. Coordination distances $Eu^{3+}\cdots N_{py}$ in **1**·Eu^{3+} + NO_3^- as a function of time. The nitrate entered the first coordination sphere at approximately 20 ps.

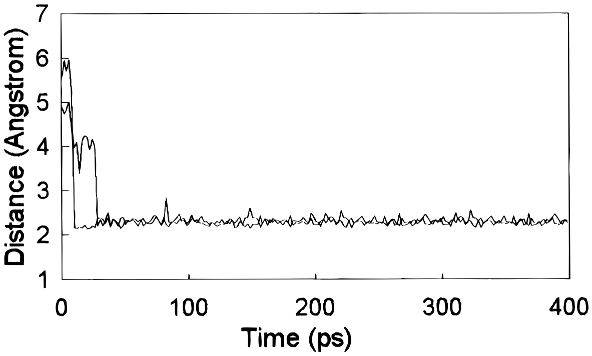

Figure 9. Coordination distance $Eu^{3+}\cdots NO_3^-(O)$ in **2**·Eu^{3+} + $3NO_3^-$ as a function of time. The nitrate was initially bound as monodentate, but it changed into a bidentate binding.

simulation in the NVE ensemble with a switch function for the electrostatic interactions proved stable when the truncation was done between 6 and 16 Å.[26] The results are summarized in Figure 7 and show that in all cases the nitrate enters the first coordination shell of the Eu^{3+}, albeit at very different times. In the case with the shift function with a cutoff at 20 Å the nitrate was already coordinated to the Eu^{3+} in the equilibration phase. It is quite obvious that the treatment of the electrostatic interactions has a prominent influence on the binding kinetics of the counter ion to Eu^{3+}. Nevertheless, all calculations suggest that one nitrate will be coordinated to the Eu^{3+}, but the question arises if a second nitrate can induce a change such that it also can coordinate to the Eu^{3+}, maybe at the expense of one bipy moiety. Therefore, an MD simulation of 400 ps was done with a second nitrate in solution. Also in this case one nitrate enters the coordination sphere of the Eu^{3+} as a monodentate at about 50 ps and remains there throughout the rest of the simulation. The second nitrate "tried" to enter (shortest $Eu^{3+}\cdots NO_3^-$ distance ≈5 Å) in the period 250−300 ps, but diffused away afterward. Apparently, it could not substitute any of the four bipy moieties. These calculations strongly suggest that the actual species in acetonitrile solution is a complex with four bipy moities as bidentate ligands and one nitrate as monodentate coordinated along the long axis of the molecule. All calculations presented in this paragraph gave **1**·Eu^{3+}·NO_3^- structures that are overall the same, despite the clear differences in (interaction) energies (Tables 3 and 4, entries 2−7). The concentration in this simulation is approximately 18 mM, which is higher than used by the experimenters. Although the experimental concentration was not stated in the articles, it is probably in the millimolar range.[8] This may have an effect on the observed ion pairing.

Tetrakis(bipy)-calix[4]arene **2.** The minimized Eu^{3+} complex of ligand **2** was dissolved in a 45 Å cubic box of OPLS CH_3CN with three nitrates placed at 10 Å from the Eu^{3+} along the three Cartesian axes. The simulation was run for 400 ps, during which various significant transitions occurred. The first was the penetration of one acetonitrile, at a relatively large averaged distance of 3.11 ± 0.57 Å, into the first coordination sphere of Eu^{3+}, which had occurred in the equilibration phase. This penetration already indicates that the binding of the Eu^{3+} by the ligand is less tight with respect to that of ligand **1**. The second occurred at approximately 10 ps and involved one bipy moiety leaving the first coordination sphere of the Eu^{3+}; $Eu^{3+}\cdots N_{py} \geq 6$ Å between 10 and 400 ps. This change was accompanied (or perhaps induced) by the coordination of one nitrate to the Eu^{3+}, initially as a monodentate, but after about 28 ps this turned into a bidentate coordination (see Figures 9 and 10).

The interaction energy between Eu^{3+} and the ligand is much less favorable than in **1**·Eu^{3+}·NO_3^- and **3**·Eu^{3+}·NO_3^- (−585.3, −880.0, and −698.5 kcal/mol, respectively; Table 4). The smaller Eu^{3+}−ligand interaction in **2**·Eu^{3+}·NO_3^- may be the reason for the observed low quantum yield compared to **1**·Eu^{3+}·NO_3^- and **3**·Eu^{3+}·NO_3^-, as has been suggested by Sabbatini et al.[8] In addition, also only three of the four bipy

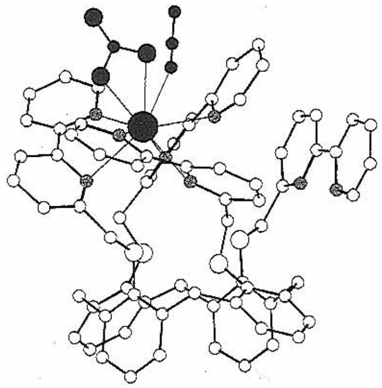

Figure 10. Snapshot from the MD of **2**·Eu^{3+} + $3NO_3^-$ in acetonitrile. The Eu^{3+} and the coordinated NO_3^- and CH_3CN are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

moieties are effectively used in the "light harvesting". However, I feel that caution is needed in these kind of reasonings. It is well-known that the Laporte-forbidden 4f transitions, in particular the electrical dipole transitions, of trivalent lanthanide ions are affected by the symmetry of the crystal field. The more asymmetric the crystal field is, the larger the radiative rate constant (k_{rad}) is.[28] Quantifying this relation is, however, very difficult. A larger radiative rate constant consequently decreases the lifetime of the excited lanthanide. The lifetime (τ) is the reciprocal of $k_{rad} + k_{nonrad}$ (k_{nonrad} is the sum of all processes that contribute to the nonradiative decay). Both the radiative rate constant and the life time also determine the sensitized quantum yield, defined as $\Phi_{lum} = \Phi_{isc}\Phi_{et}k_{rad}\tau$; lum = luminescence, isc = intersystem crossing, and et = energy transfer.[7] The presented calculations clearly show that (very) different crystal fields will be present in the various complexes, and hence the smaller Eu^{3+}–ligand interaction may not be the only reason for different quantum yields. Although no exchange of one coordinated bipy moiety by the uncoordinated has been observed, due to the small length of the calculation, it is likely that a dynamic equilibrium exists. Unfortunately, the available information in ref 8 is too limited to elaborate upon.

The three bidentate bipy moieties, the bidentate nitrate, and the acetonitrile make a coordination number of 9, which is usual for Eu^{3+}. The other two present nitrates are never very close to the complex ($Eu^{3+}\cdots N_{py}$ distances are ≥6.7 Å throughout the simulation). The space-filling representation of various snapshots (not shown) in conjunction with the relatively weakly bound acetonitrile seems to indicate that there is no space for a second nitrate around the Eu^{3+}. But this is, however, no guarantee, as will be shown for **3**·Eu^{3+}·xNO_3^-.

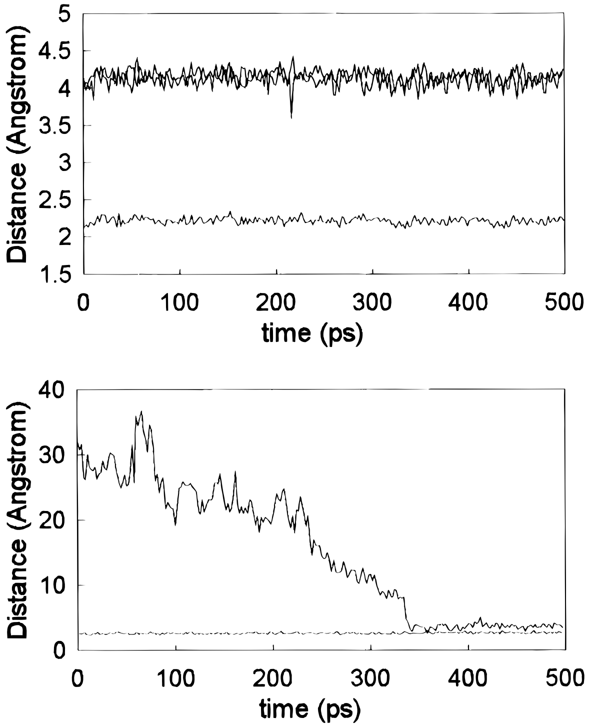

Figure 11. (a, top) Coordination distance $Eu^{3+}\cdots NO_3^-(O)$ in **3**·Eu^{3+} + $3NO_3^-$ as a function of time. (b, bottom). Coordination distance $Eu^{3+}\cdots CH_3CN$ (N) in **3**·Eu^{3+} + $3NO_3^-$ as a function of time.

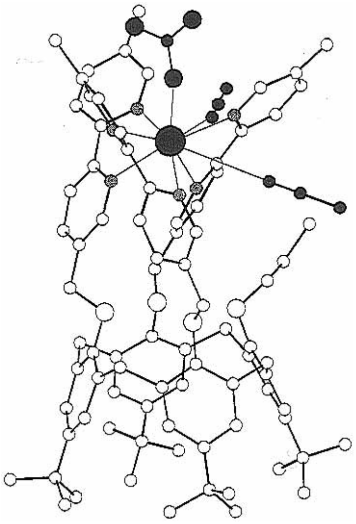

Figure 12. Snapshot from the MD of **3**·Eu^{3+} + $3NO_3^-$ in acetonitrile. The Eu^{3+}, the coordinated NO_3^-, and the two CH_3CNs are in black, and the pyridine nitrogens are in gray. Hydrogens are omitted for clarity.

Tris(bipy)-calix[4]arene **3.** The observation that both **3**·Eu^{3+}·NO_3^- and **3**·Eu^{3+}·$2NO_3^-$ seem to be stable species in acetonitrile solution (*vide supra*) raises the question, what would the actual species be in acetonitrile solution, i.e. a Eu^{3+} with one bidentate nitrate and one acetonitrile, in addition to the three bidentate bipy moieties, or a Eu^{3+} complex with one bidentate and one monodentate nitrate with the three bipy moieties as bidentate? An answer to this might be obtained from the simulation with the complex **3**·Eu^{3+} and three, initially free nitrate ions placed 10 Å away from the Eu^{3+} along the three Cartesian axes. The MD simulation was carried out in a 45 Å cubic box of OPLS acetonitrile for 500 ps. Throughout the simulation the three bipy moieties remained coordinated as bidentate ligands (see Table 3). One nitrate had entered the coordination sphere of Eu^{3+} as a monodentate during the equilibration phase and remained as such during the production phase (see Figure 11a and Table 3). In addition one acetonitrile had settled around the Eu^{3+} during the equilibration phase. The resulting eight coordination lasted for about 350 ps, after which a second acetonitrile coordinated to the Eu^{3+} at a slightly larger distance (see Figure 11b). This complex showed no changes during the next 150 ps. See Figure 12 for a snapshot and note that this structure is different from that starting from the minimized structure of **3**·Eu^{3+}·NO_3^-, which has the nitrate as bidentate and one additional acetonitrile. The other two nitrates did not make any "real" attempt to come into the first coordination shell of the complex ($Eu^{3+}\cdots O(NO_3^-)$ ≥ 6 Å).

This simulation shows that it is most likely that at least one nitrate will be coordinated to the Eu^{3+} in acetonitrile solution, but about the second no conclusion can be drawn. The fact that the second nitrate did not become coordinated to the Eu^{3+} might be for thermodynamical reasons or for kinetic reasons. The barrier for entering the coordination shell might be too large or the length of the simulation was simply too short for the event to occur. One also has to realize that only calculations on one species were carried out. The quantum yield of **3**·Eu^{3+}

is higher than of **2**·Eu^{3+}, 3 and <1% respectively, which may find its origin in the larger interaction between the bipy moieties and the Eu^{3+}. The calculations support this; the interaction energies are −585 for **2** and −685 to −712 kcal/mol for **3** (Table 4, entries 9−13). The possible effect of the symmetry of the crystal field has been discussed above.

So, the question remains whether one or two nitrates are coordinated to the Eu^{3+} in **3**·Eu^{3+}; one as monodentate along the long axis of the complex and one possibly as bidentate from aside. It is not *a priori* possible to conclude that the species with two coordinated nitrates will be the actual species in acetonitrile solution. Acetonitrile is a relatively polar solvent (relative dielectric constant is 37.5). To address this point, FEP-MC calculations have been performed (see next section). Experimental proof for the raised question can in principle be obtained by conductometric measurements.

Free Energy Perturbation Monte Carlo Studies on 3. To answer the question raised in the paragraph, three FEP-MC calculations have been performed. It basically comes down to the equilibrium given in eq 1. Species A has the nitrate as monodentate along the long axis of the complex and two coordinated acetonitrile molecules to make a coordination number of 9. Species B has one nitrate as monodentate and the other as bidentate.

$$\underset{(A)}{\mathbf{3}\cdot Eu^{3+}\cdot NO_3^{-}\cdot 2CH_3CN} + NO_3^{-} \overset{\Delta G_{eq}}{=} \underset{(B)}{\mathbf{3}\cdot Eu^{3+}\cdot 2NO_3^{-}} + 2CH_3CN \quad (1)$$

The appropiate **z**-matrices of the minimized structure of **3**·Eu^{3+}·$2NO_3^-$ (having both nitrates as monodentate, *vide supra*) and a snapshot from the MD simulation of this compound (having a monodentate and bidentate nitrate, *vide supra*) have been constructed, which allow the independent sampling of the ligand, the Eu^{3+}, and both coordinated nitrates. The calix[4]arene skeleton has not been sampled. The efficient sampling of large ring systems is an intrinsically difficult matter in MC and MD calculations. It is not likely that this simplification will really influence the calculations, i.e. change the order of magnitude, due to the fact that the complexation of Eu^{3+} is relatively remote from the calix[4]arene.

In the FEP-MC runs the nitrate coordinated from aside was perturbed into an acetonitrile.[29−31] The perturbation of nitrate into acetonitrile was carried out in 10, equally spaced windows. The runs starting from the minimized structure and the snapshot gave a ΔG of 134 (±1) and 140 (±5) kcal/mol, respectively. To close the thermodynamic cycle, also a dissolved nitrate was perturbed into an acetonitrile, giving a ΔG of 45 (±1) kcal/mol, which allows the calculation of the ΔG_{eq} of eq 1. These numbers should in principle be corrected for the neglect of long-range (electrostatic) interactions, as has been discussed by Åqvist[29] and Straatsma and Berendsen.[32] However, it is likely that the corrections will cancel, as has been argued by Miyamoto and Kollman.[29] This results in a calculated ΔG_{eq} of −89 (±2) and −95 (±6) kcal/mol, respectively. Hence, the equilibrium in eq 1 is completely to the right; that is, only species B is predicted to be present in acetonitrile solution. Regular checks of saved (unphysically) configurations showed that also here in almost all cases a 9-fold coordination of the Eu^{3+} was obtained. Although the structural perturbation of a nitrate into an acetonitrile is not large, the ΔG's in the individual windows are. Therefore, the FEP-MC starting from the snapshot and from a dissolved nitrate have been repeated with 20 equally spaced windows. The former gave a ΔG of 132 (±1) and the latter a ΔG of 46 (±1), leading to a ΔG_{eq} of −86 (±2) kcal/mol, which is only slightly less negative. This shows that the calculations are not very sensitive to the number of applied windows. Increasing the number of windows will certainly change the calculations, but it is unlikely that the order of magnitude will change. Due to the limited way the sampling has been performed, these FEP-MC calculations only give a crude estimation of the binding affinity. Even if they are off by 10−20 kcal/mol the conclusion that the equilibrium is entirely to the right still holds. These FEP-MC calculations may point at a drawback of MD simulations, even quite lengthy ones. Events are sometimes simply not observed, although the thermodynamics are in favor. This may be due to too high kinetic barriers. Another reason may be the choice of the protocol. This point will be discussed in the next paragraph.

The MD Protocol Criticized. As a test for the protocol, additional MD runs have been performed. The first was on $Eu^{3+}(NO_3^-)_3$ in acetonitrile with the three nitrates initially placed 10 Å away from the Eu^{3+}. The MD run (200 ps) showed that two nitrates were able to coordinate to the Eu^{3+}, one as monodentate and the other as bidentate. The coordination shell is completed by seven acetonitrile molecules. Although the exact coordination shell of $Eu^{3+}(NO_3^-)_3$ in acetonitrile is not known, data are available for $La^{3+}(NO_3^-)_3$ in acetonitrile.[33] The reaction of $La^{3+}(NO_3^-)_3\cdot 6H_2O$ with 2,2′-bipyridine in acetonitrile gave five species, among which $La^{3+}(NO_3^-)_3(CH_3CN)_4$ is present. The La^{3+} has a coordination number of 10; hence, the three nitrates all behave as bidentate. The other four species also have three nitrates coordinated to the La^{3+}. These data are not in agreement with the calculation, which may be a result of the protocol. Therefore, a 200 ps MD trajectory with the three nitrates placed at 7.5 Å from the Eu^{3+} was calculated, which showed a different behavior. At 22 ps all three nitrates had found their way to the Eu^{3+}, two as monodentate and one as bidentate, in addition to six acetonitrile molecules. At 43 ps one of the monodentate nitrates changed into a bidentate, which gave place to five acetonitrile molecules. During the rest of the simulation no changes occurred. These results are in good agreement with the available data for $La^{3+}(NO_3^-)_3$ in acetonitrile. The fact that five instead of four acetonitrile are present in the first coordination sphere of Eu^{3+} and the concurrence of two bidentate nitrates and one monodentate nitrate may be due to the different steric demands of the Eu^{3+} ion. These results provide further evidence that the model for Eu^{3+} suffices. The ion pairing of nitrates and Eu^{3+} ions in acetonitrile has been reported before[34] and is even present in water.[35]

This considerable effect of the protocol on the outcome of an MD simulation may be the reason for the discrepancy between the MD and FEP-MC calculations, but also the different treatment of the electrostatic interactions may be the source. The results below show that the latter possibility is not likely to be the case. A simulation of **3**·$Eu^{3+}(NO_3^-)_3$ was performed with the three nitrates initially not coordinated to the Eu^{3+} at a distance of 7.5 Å. Early in the 300 ps simulation *two nitrates* became coordinated as monodentates, in addition to one acetonitrile (Figure 13). The three bipy moieties remained coordinated to the Eu^{3+}. Only after approximately 200 ps did one nitrate change into a bidentate ligand and the coordinated acetonitrile was expelled from the first coordination sphere.[36] The resulting coordination sphere lasted throughout the rest of the simulation, which resembles that shown in Figure 6b (compare also Tables 3 and 4, entries 12 and 14). This structure is fully consistent with the FEP-MC predictions. The fact that the acetonitrile is expelled from the Eu^{3+} can be understood on thermodynamic grounds. The interaction energy of a bidentate nitrate is more favorable by approximately 50−60 kcal/mol compared to a monodentate nitrate (Table 4, entries 11−13),

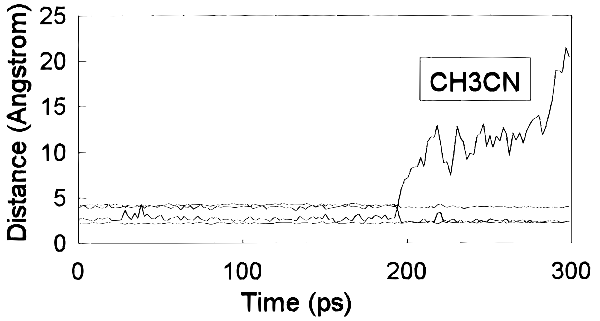

Figure 13. Coordination distance $Eu^{3+}\cdots CH_3CN(N)$ and $Eu^{3+}\cdots NO_3^-(O)$ in **3**$\cdot Eu^{3+} + 3NO_3^-$ as a function of time (for difference in MD protocol see text).

and this can compensate the loss by removal of one acetonitrile from the first coordination sphere (E_{int} between Eu^{3+} and CH_3CN is 33−69 kcal/mol). The release of one acetonitrile will most likely increase the entropy, so there will be a net decrease in the Gibbs free energy. The absence of acetonitrile in the first coordination sphere of Eu^{3+} can in principle be experimentally tested by measuring the lifetimes of the excited Eu^{3+} in CH_3CN and CD_3CN. Namely, it is well-known that CH groups are more efficient quenchers of the excited state than CD groups.[34]

Conclusions

All MD simulations show that there is a strong tendency to form a nine coordination around the Eu^{3+} ion, which is consistent with literature.[1−7] This also implies that the Lennard-Jones parameters for Eu^{3+} are realistic. A general conclusion is that the role of the counterions cannot be neglected in acetonitrile; that is, ion pairing also occurs in well-shielded Eu^{3+} complexes. It is therefore advised to always include all counterions at relatively close distance. It is concluded that the Eu^{3+} complex of ligand **1** has the four bipy moieties tightly coordinated as bidentate ligands and that the ninth coordinated site is occupied by a nitrate. The complex of ligand **2** and $Eu^{3+}(NO_3^-)_3$ in acetonitrile is predicted to have three bipy moieties, out of four, as bidentate, two nitrates, and possibly one acetonitrile. It is reasonable to assume that the bipy moieties will interchange. Evidence is provided that supports the explanation given in ref 8 why this complex has a much lower quantum yield than system **1**. The bipy moieties have a smaller interaction with the Eu^{3+}, which is reflected in a lower quantum yield of the energy transfer. It is, however, argued that other factors, like the symmetry of the crystal field, might be important as well. The calculations of the complex of ligand **3** and $Eu^{3+}(NO_3^-)_3$ showed that the MD protocol may not result in the actual species. This artifact was predicted on the basis of FEP-MC calculations and subsequently supported by some additional MD simulations. On the basis of all these calculations the structure of the complex of ligand **3** and $Eu^{3+}(NO_3^-)_3$ is predicted to have the three bipy moieties as bidentate and two nitrate ions in the first coordination sphere of Eu^{3+}. An experiment has been suggested to verify the absence of acetonitrile in the first coordination shell of Eu^{3+}. This report shows that modern simulation techniques give relevant structural information about the shielding properties of trivalent lanthanide complexes by cage compounds and the influence of counterions in polar, nonprotic solvents. In other words, theoretical results can steer the explanation if experimental results are not conclusive.[37]

Supporting Information Available: Parameters, atom types, and point charges (4 pages). Ordering information is given on any current masthead page.

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(30) Before running the CPU expensive FEP-MC calculations the efficiency of the sampling was tested by running four simulations. Both the minimized and the snapshot structure with two unperturbed nitrates and with one nitrate and one acetonitrile have been subjected to an MC simulation. From all simulations 20 configurations (every 100 000 steps) were saved and inspected visually. The simulation starting from the minimized **3**$\cdot Eu^{3+} \cdot 2NO_3^-$ showed a nine coordination; beside the three bipy moieties and the two monodentate nitrates, one acetonitrile was coordinated at 3.5−4.5 Å. The sampling starting from the minimized **3**$\cdot Eu^{3+} \cdot CH_3CN \cdot NO_3^-$ also shows a nine coordination, albeit with the second acetonitrile at somewhat longer distances (∼4.5 Å). The simulation starting from the snapshot of **3**$\cdot Eu^{3+} \cdot 2NO_3^-$ did not show any major conformational change, i.e. one nitrate as monodentate and the other as bidentate in addition to the three bidentate bipy moieties. The calculation of the typical **3**$\cdot Eu^{3+} \cdot CH_3CN \cdot NO_3^-$ structure showed that an additional acetonitrile entered the first coordination shell at a distance of 3.6−4.0 Å. All four tests showed that the sampling protocol seemed adequate. In general a coordination number of 9 is obtained, which is a common number for Eu^{3+}. The fact that occasionally one acetonitrile is bound at a longer distance than the other eight donors is consistent with observations from the MD calculations (see Table 3, entries 10−13). The MC sampling efficiency seems, therefore, adequate. For a comparison between MD and MC see: Mordasini Denti, T. Z.; Beutler, T. C.; van Gunsteren, W. F.; Diederich, F. *J. Phys. Chem.* **1996**, *100*, 4256. Jorgensen, W. L.; Tirado-Rives, J. *J. Phys. Chem.* **1996**, *100*, 14508.

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(37) The referee suggested to make some remarks on how to improve the reliability of the presented findings. As for all simulations, the reliability is in the parameters. The parameters for Eu^{3+} are probably the most approximate. Currently, I am deriving parameters for the trivalent lanthanide ions that reproduce accurately the hydration free energy, i.e. within a standard deviation of 1%.