Time-Resolved Luminescence in Aqueous Solution − New Europium Labels Derived from Macro(bi)cyclic Ligands with Aminocarboxylic Units

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Keywords: Cryptands / Lanthanides / Luminescence spectroscopy / Macrocyclic ligands

A new family of macro(bi)cyclic ligands has been designed and synthesized, with the goal of developing lanthanide labels suitable for time-resolved luminescence-based biological applications. They are constructed from diamide (**3**) or tetralactam (**4**) complexing moieties associated with an intracyclic 2,2′-bipyridine chromophore and two exocyclic carboxylic groups. The luminescence properties of their Eu^{3+} complexes were studied in aqueous solution. In this medium, noticeable enhancements in the lifetime and quantum yield were observed, in comparison with those of other bipyridine-based ligands considered interesting as luminescent labels. The effects of coordinated water molecules, LMCT states, and ligand triplet state energy on the nonradiative deactivation processes to the ground state were examined. According to these results and in view of the stability of these complexes in aqueous solutions, the $[Eu(\mathbf{3})]^+$ complex may be considered as a promising luminescent bioprobe.

Introduction

In time-resolved luminescence spectroscopy, the emission is recorded after an initial delay after excitation, thus allowing short-lived fluorescence background signals and scattered excitation radiation to dissipate to zero. A significant improvement in the signal-to-noise ratio, and thus the sensitivity, is obtained. Suitable organic fluorophores with long luminescence lifetimes ($\tau > 50$ ns) being very rare, most research work has focused on Eu^{III} and Tb^{III} labels, since these two ions display luminescence lifetimes greater than 0.1 ms in aqueous solution, under ambient conditions.[1] However, for practical bioanalytical purposes, organocomplexes of Eu^{3+} and Tb^{3+} ions are necessary for labelling the analyte and for overcoming the low luminescence efficiency of these aqueous ions, due to their weak molar absorptivities.[2] In order to populate the lanthanide excited state significantly, energy transfer from a sensitizer is required. In this phenomenon (termed the "antenna effect"), UV/Vis light energy is collected by allowed, chromophore-centered transitions ($\varepsilon > 10000$ $M^{-1}\cdot cm^{-1}$), followed by intramolecular energy transfer from ligand to Ln^{III}, resulting in metal-centered luminescence.[3]

Under these conditions, luminescent Eu^{3+} and Tb^{3+} complexes have many useful applications, especially in analytical and clinical chemistry: the biological analyte may be a nucleic acid fragment, an enzyme or an enzyme substrate or cofactor, or an antigen.[4−8] A detection limit of 5×10^{-14} M in aqueous solution has been reported with sensitized Eu^{III} ion, this lanthanide ion giving the highest sensitivity.[9] Luminescence resonance energy transfer (LRET), based on sensitized Eu^{3+} and Tb^{3+} ions as donors, has also been reported for homogeneous bioassays. This technique has been applied to various models representing molecular and cellular processes.[10−12]

In recent years, a considerable research effort has been directed towards two main classes of photoactive lanthanide receptors: macrocyclic ligands such as cryptands or branched macrocycles,[3,13−17] and aminopolycarboxylic chelates such as diethylenetriaminepentaacetic acid (DTPA)[18−20] or bis(imino-diacetic acid)[21,22] derivatives. Two structures, **1** and **2**, of bipyridine-based compounds used as luminescent labels for biological applications[23−25] and representative of these classes of ligands are shown in Scheme 1. Our interest in the properties of lanthanide complexes[26−29] prompted us to investigate the preparation of photoactive ligands presenting in the same structure these two features: a macrocyclic framework and aminocarboxylic groups. We found only a few reports about lanthanides bound by macrocyclic compounds incorporating both an intracyclic chromophoric unit and pendant carboxylic groups. Sherry has reported some luminescent properties of Eu^{3+} and Tb^{3+} complexes with polyazamacrocyclic ligands containing a pyridine moiety as part of the macrocyclic ring and pendant acetate groups.[30] Sasamoto's approach consisted of incorporating two phenanthroline [or 4,7-bis(chlorosulfonylphenyl)phenanthroline] moieties into an aza-crown framework containing two pendant carboxylate groups.[31] In his patent, he reported the use of the corresponding luminescent europium complexes for the immunoassay technology developed by Diamandis and coworkers.[7]

We report here our results concerning the synthesis and the luminescence properties of europium complexes derived from new macrocyclic and macrobicyclic ligands **3** and **4**, respectively (Scheme 1). These incorporate a diamide **3** or a tetralactam **4** complexing moiety in association with an intracyclic 2,2′-bipyridine (bpy) chromophore and two exocyclic carboxylic groups. As well as this, to furnish better

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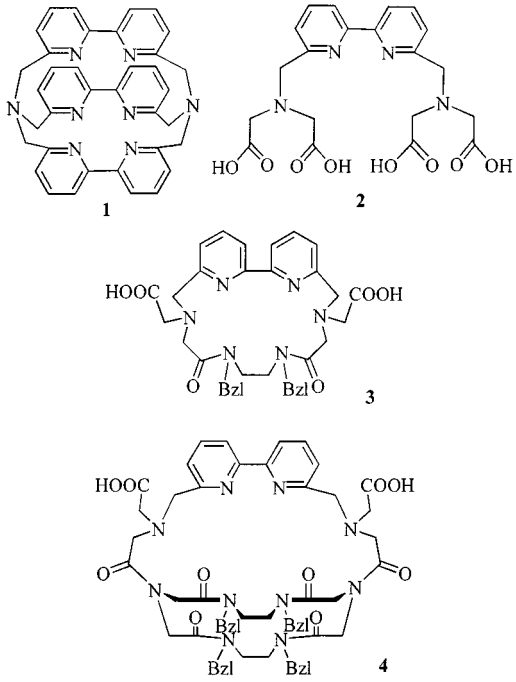
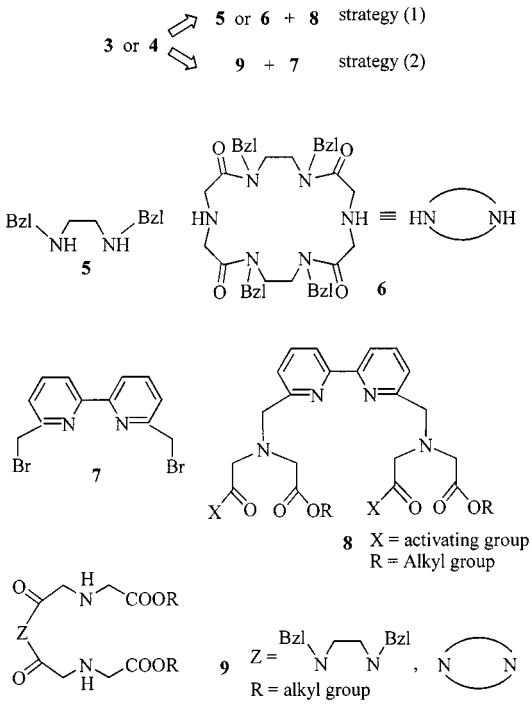


Scheme 1. Representative ligands from the literature (**1**, **2**) and new compounds (**3**, **4**)



Scheme 2. Synthetic strategies towards ligands **3** and **4**

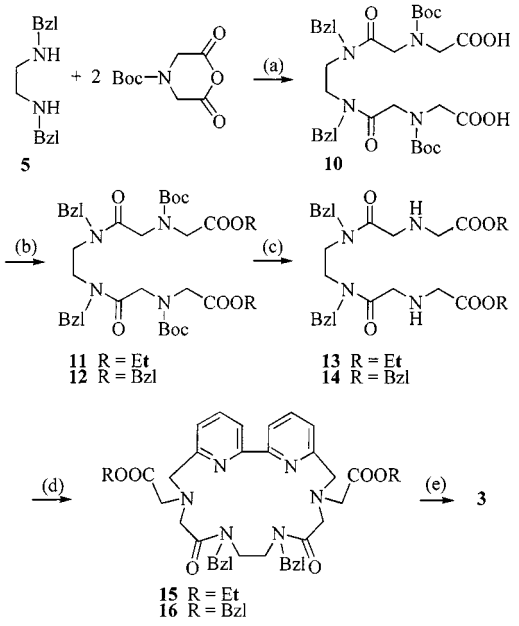
understanding of the role played by the various factors that determine the luminescence properties of this new lanthanide receptor family, we studied the Gd^{3+} and Tb^{3+} complexes of the macrocyclic ligand **3**. Preliminary results from this work have been published previously.[32]

Results and Discussion

Synthesis

The crucial step in the preparation of ligands **3** and **4** was the macro(bi)cyclization reaction. Two general strategies for these ring-closure reactions may be considered (Scheme 2): (1) acylation of diamine **5** or diazatetralactam **6** with activated diacid **8** and (2) alkylation of secondary diamine **9** with bis(bromomethyl)-2,2′-bipyridine (**7**). In process (1), production of the macrocyclic product generally requires the use of high-dilution conditions ([reactants] < 2 mmol·L^{-1}) to avoid predominant formation of oligomers. In the second process, generation of the cyclic product may be controlled by the presence of a metal "template" ion. Because of the presence, in the building blocks **9**, of coordinating functional groups that may interact with a metal ion, we preferred the second strategy.

Our synthesis of the 18-membered ring dilactam **3** is outlined in Scheme 3. The approach involves the use of iminodiacetic acid, a core unit possessing three functionalization sites. As a cyclic anhydride, this starting material is self-activated for initial functionalization, liberating its second functionalization site (CO_2H) upon reaction. In situ closure of *N*-Boc-iminodiacetic acid to the corresponding cyclic anhydride (DCC, THF), followed by treatment with *N*,*N*′-dibenzylethylenediamine in a 2:1 molar ratio, gave the diamide diacid **10** in high yield.[33] Esterification of **10** with ethylchloroformate according to the procedure reported by S. Kim et al.,[34] followed by CF_3COOH cleavage of the Boc protecting group, gave the building block **13**, although only in 22% yield. The preparation of **13** was achieved more easily by using acetyl chloride-alcohol as reagent,[35] allowing carboxylic acid esterification and *N*-*t*Boc deprotection of **10** in a single-step procedure. Thus, treatment of **10** with an excess of acetyl chloride in ethanol solution at room temperature afforded **13** in 55% yield. Condensation of 6,6′-bis(bromomethyl)-2,2′-bipyridine with the secondary diamine **13** in refluxing CH_3CN and in the presence of Na_2CO_3 as a base gave the NaBr complex of the macrocycle **15**, which was purified by column chromatography. The high yield of the macrocycle formation (67% yield of $[Na(\mathbf{15})]^+$) obtained without the use of high-dilution techniques is certainly the result of a template effect of the sodium ion. In this macrocyclization reaction, it is interesting to note that replacement of ethyl ester groups by benzyl groups in the diamine compound (**14** vs. **13**) produced a better cyclization yield. As a matter of fact, treatment of dibromide **7** with the diamine **14**, carried out under conditions identical to those for the formation of $[Na(\mathbf{15})]^+$, gave $[Na(\mathbf{16})]^+$ in 93% isolated yield. This might be the result of restricted conformational freedom in **14,** caused by the bulkier benzyl groups, and consequently a smaller loss of internal entropy in the cyclization process. Similar effects were reported earlier, when the bulky *N*-tosyl groups were used in the formation of poly-*N*-tosylaza-crowns.[36] These results suggested that a combination of template and entropy effects was operative in this cyclization process.

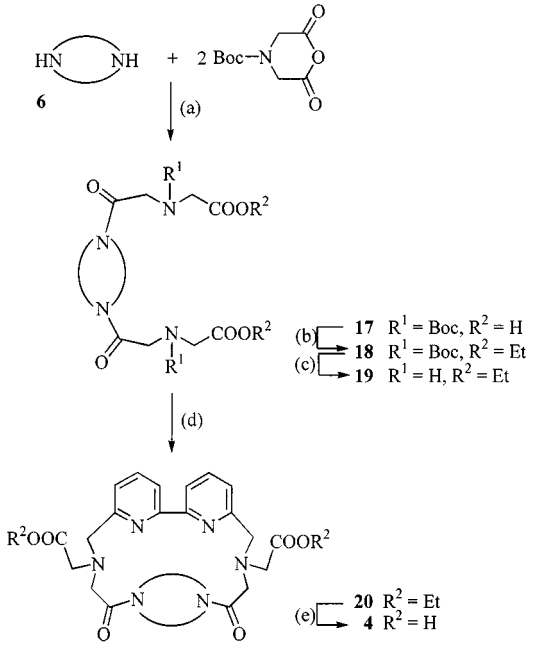


(a) THF, 50°C, 24 h, 87%; (b) ClCOOR, Et_3N, DMAP, CH_2Cl_2, 40% (R = Et), 69% (R = Bzl); (c) CF_3COOH/CH_2Cl_2, 55% (R = Et), 95% (R = Bzl); (d) 6,6'- bis (bromomethyl)-2,2'-bipyridine (**7**), Na_2CO_3,CH_3CN, 80°C, 24 h, reagent concentrations 0.002M, 67% (R = Et), 93% (R = Bzl); (e) K_2CO_3, $MeOH/H_2O$ (from R = Et) or KOH, EtOH (from R = Bzl) then HCl 1N, 66% (from R = Et), 78% (from R = Bzl).

Scheme 3. Synthesis of the doubly branched macrocycle **3**

The formulations $[Na(\mathbf{15})]^+$ and $[Na(\mathbf{16})]^+$ were consistent with the Elemental analyses and spectral properties. Ester and amide participation in sodium binding was established by IR spectroscopy, comparing the solid state spectra of the complexes and those of the open chain compounds **11** and **12**, in which no intramolecular H-bonding occurs. This comparison revealed a shift of the carbonyl stretching frequencies to lower wavenumbers: the amide stretch band dropped by ca. 20 cm^{-1} and the ester carbonyl band by 10 cm^{-1}. Similar shifts were observed in chloroform solution. This indicates simultaneous coordination of both types of carbonyl oxygen in the complex. Confirmation of cation complexation was provided by NMR techniques. In the ^1H decoupled ^{13}C NMR spectrum ($CDCl_3$) of these complexes, only one set of signals was observed, clearly pointing to the presence in solution of a single, symmetrical conformer. Several signals for the carbons on the bipyridine ring were shifted to lower fields ($\Delta\delta > 1$ ppm), compared to the open chain analogue (**7**), suggesting that the heterocyclic moiety was involved in the complexation process. On the other hand, the ^{13}C chemical shift of the benzylic CH_2 signals is of particular diagnostic value and was used to distinguish between the *cis* and the *trans* configurations (benzyl group vs. carbonyl group) of the amide linkages in macrocyclic polylactams ($\delta \approx 48$ and 51, respectively).[37] In $[Na(\mathbf{15})]^+$ and $[Na(\mathbf{16})]^+$ complexes, the observation of a low field signal ($\delta \geq 51$) for benzylic carbons indicated the presence of a conformer with both lactam groups assuming the *trans* configuration. This convergent arrangement of the lactam groups may be considered as the result of the interaction of the amide carbonyl groups and the sodium ion. In the ^1H NMR spectrum, the principal feature was the shift to higher field of the H-3 heteroatomic hydrogens, as compared to those in the open chain analogue **7** (δ = 8.05 vs. 8.38). As reported earlier by Newkome, for macrocycles containing 2,2′-bipyridine moieties,[38] this suggested that the bipyridyl unit, possessing an *anti* orientation in **7**, approached a *syn* conformation in these sodium complexes. This was consistent with the participation of the two heterocyclic nitrogen atoms in the complexation.

The cleavage of the ester functions in compounds **15** and **16** was achieved under alkaline conditions. Hydrolysis of ethyl and benzyl esters bonds using K_2CO_3 in refluxing $MeOH/H_2O$ (3:1) and KOH in EtOH (0.5 M) at room temperature, respectively, afforded the free diacid dilactam **3** in 65−80% yield. Attempted removal of the benzyl esters of **16** by catalytic hydrogenolysis (Pd/C in MeOH) was unsuccessful. Recovery of unchanged **16** indicated poisoning of the palladium on carbon catalyst by the heterocyclic nitrogens. The lack of reactivity of **16** provides additional support for recent observations concerning palladium catalyst poisoning by 2,2′-dipyridyl.[39] ^{13}C NMR spectroscopy gave clear evidence of conformational heterogeneity in **3** in $CDCl_3$. Several sets of signals were observed for each type of carbon atom. The presence of three sets of benzylic CH_2 signals suggested that at least two species exist in solution (most probably with the lactam groups assuming a *cis-trans* and a *trans-trans* configuration). In CD_3OD, only one set of



(a) THF, 50°C, 24 h, 80%; (b) ClCOOEt, Et_3N, DMAP, CH_2Cl_2, 66%; (c) CF_3COOH/CH_2Cl_2, 95%; (d) 6,6'-bis(bromomethyl)-2,2'-bipyridine (**7**), K_2CO_3, CH_3CN, 80°C, 24 h, reagent concentrations 0.002M, 33%; (e) K_2CO_3, $MeOH/H_2O$ then HCl 1N, 94%.

Scheme 4. Synthesis of the doubly branched cryptand **4**

signals was observed, indicating that the higher symmetry conformation predominates in this solvent.

The same strategy was applied to the synthesis of macrobicyclic ligand **4** (Scheme 4). Diamine **19** was obtained in three steps, in an overall yield of 50%, starting from the known diazatetralactam **6**.[33] Condensation of this building block **19** with dibromide **7** was carried out in the presence of various alkali metal carbonates M_2CO_3 (M = Li, Na, K, Cs). Analysis of the crude materials by size exclusion chromatography[29] showed that macrocyclization process was markedly conditioned by cation template effects. Potassium ion was found to be the best promoting ion for this macrocyclization reaction. Thus, with use of K_2CO_3 and after chromatographic purification on silica, macrobicycle **20** was isolated as its KBr complex in 33% yield. No formation of dimeric product (macrotricycle) was observed under these conditions. The lower cyclization yield seen for the formation of **20**, as compared to **15**, may be a function of the size of the ring to be formed (24-membered ring vs. 18-membered ring). Finally, base-catalyzed hydrolysis of **20** gave the target ligand **4** in almost quantitative yield.

Complexation and Luminescence Properties

The europium complexes derived from **3** and **4** were readily prepared by mixing equimolar amounts of ligands and $EuCl_3 \cdot 6H_2O$ in methanol/water solutions and were isolated by precipitation with diethyl ether (77 and 82% yield, respectively). The same experimental procedure was used to prepare the terbium and gadolinium complexes derived from **3**. All of these complexes were easily soluble in protic solvents. They were characterized by electrospray mass spectrometry (ES^+-MS), which showed that 1:1 complexes had been obtained. In the ES^+-MS mass spectra, the most abundant ion corresponded to $[(L\text{-}2\ H)Ln]^+$ species (L = ligand **3**, **4**); the assignment was confirmed by the agreement with the observed and calculated isotope patterns, and the m/z = 1 a.m.u. separation between adjacent peaks, indicating a singly charged cation. No peak ascribable to the free ligands was observed in these mass spectra and no loss of metal ion was detected when Vc (extraction cone voltage) was increased. This suggests a high affinity of ligands **3** and **4** for lanthanide ions.

All the photophysical properties of solutions of the complexes in aerated methanol or water remained unchanged after several days at room temperature, indicating that they are kinetically inert in these solvents. Absorption, emission lifetime, and quantum yield data for $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ are reported in Table 1, with the data for the previously reported complexes with ligands **1** and **2** included for comparison.[21,23,25] The absorption spectra of $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ are dominated by the typical feature of the $\pi-\pi^*$ transition of the bpy chromophore. This absorption band is located at $\lambda_{max} \approx 306$ nm and its intensity is similar to that of $[Eu(\mathbf{2})]^-$ (one bpy unit) and about three times lower than that of $[Eu(\mathbf{1})]^{3+}$(three bpy units). Excitation at this wavelength gives entirely typical and intense europium(III) emission spectra, containing the expected sequence of $^5D_0 \rightarrow {}^7F_j$ transitions, j = 0 to 4 (Figure 1). Luminescence excitation spectra monitored at the metal emission closely matched the absorption bands of the bpy moiety. These results are indicative of the occurrence of an energy transfer process from the sensitizing heterocyclic chromophore to the metal ion.

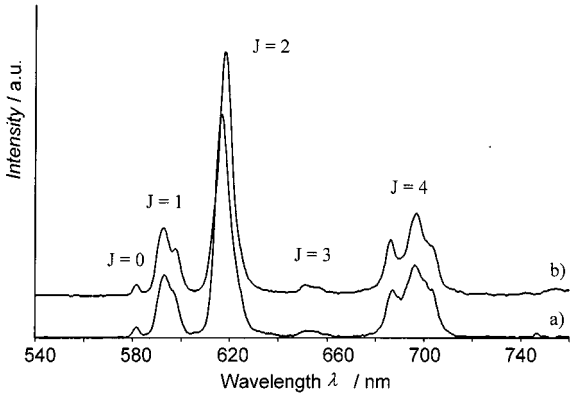


Figure 1. Emission spectra of: a) $[Eu(\mathbf{3})]^+$, and b) $[Eu(\mathbf{4})]^+$ in water ($5 \cdot 10^{-6}$ M). The bands arise from $^5D_o \rightarrow {}^7F_j$ transitions; the J values are shown on the spectra

The emission spectra of $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ are similar (Figure 1). In both cases, a $^5D_0 \rightarrow {}^7F_0$ transition (at 581 nm), although relatively weak, is observed and ≈50% of the total emission is centered on the 617−618 nm peak

Table 1. Absorption and luminescence properties of the Eu^{3+} complexes

[a]	Absorption[b]		Luminescence Lifetimes[c]					Quantum yields[d]	
	λ_{max} [nm]	ε_{max} [$M^{-1} \cdot cm^{-1}$]	τ (CH_3CN) [ms]	τ (CH_3OH) [ms]	τ (H_2O) [ms]	τ (D_2O) [ms]	τ (D_2O, 77 K) [ms]	Φ (H_2O) [$\times 10^2$]	Φ (D_2O) [$\times 10^2$]
$[Eu(\mathbf{3})]^+$	306	10700	1.62	1.14	0.42	2.20	2.39	7.3	36
$[Eu(\mathbf{4})]^+$	307	10200	1.67	0.96	0.42	2.25	2.36	7.7	39
$[Eu(\mathbf{1})]^{3+}$ [e]	303	28000	–	–	0.34	1.70	1.70	2	10
$[Eu(\mathbf{2})]^-$ [f]	310	9500	–	–	0.59	–	–	5	12

[a] In aerated solution at 300 K, unless otherwise noted. – [b] In water solution. – [c] Measured by excitation of the lowest-energy ligand-centered absorption band and recording the emitted light intensity of the most intense metal emission band ($^5D_0 \rightarrow {}^7F_2$, 617−618 nm); experimental error <10%. – [d] Excitation in ligand-centered bands; experimental error <30%. – [e] Data from ref.[23] – [f] Data from ref.[21]

($^5D_0 \rightarrow {}^7F_2$ transition). Moreover, the ratios between the intensity of the $^5D_0 \rightarrow {}^7F_1$ transition and the intensity of the $^5D_0 \rightarrow {}^7F_2$ or $^5D_0 \rightarrow {}^7F_4$ transitions are equal for these two complexes. The $^5D_0 \rightarrow {}^7F_1$ transition is magnetic dipolar in character and its radiative transition probability is relatively unaffected by the ligand environment.[1] In contrast, the $^5D_0 \rightarrow {}^7F_2$ and $^5D_0 \rightarrow {}^7F_4$ transitions are predominantly electric dipolar in character and their emission intensities are sensitive to the immediate coordination environment of the Eu^{III}. This implies similar symmetries induced by the ligands **3**, **4**, and the solvent around the Eu^{3+} ion.

The lifetimes of $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ in 5×10^{-6} M solutions were determined by excitation at 306−307 nm and recording the intensity of the emitted light of the $^5D_0 \rightarrow {}^7F_2$ transition. In these two cases, the data could be fitted to monoexponential decay curves, indicating the presence of only a single type of Eu^{3+} environment per complex, or more than one Eu^{3+} environment in "fast exchange" on the $^5D_0$ excited state timescale. From the results in Table 1, we may consider that the $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ lifetime values in each solvent studied are equal within experimental error. Interestingly, these values are rather high in CH_3CN and are similar to or even greater than those reported for other Eu^{3+} complexes with encapsulating ligands containing the bipyridine chromophore, studied in the same solvent.[13,17,40−42] On the other hand, the excited state lifetimes increase from H_2O to MeOH to CH_3CN. In aqueous solution, and upon solvent deuteration, the lifetimes are also increased by a factor of 5.3, due to the greater efficiency of energy transfer to the vibration of O−H bonds of coordinated water molecules in comparison with that to O−D bonds.[43,44] In $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$, the ion is not entirely protected and is thus accessible and coordinated to external species (CH_3OH, H_2O), as well as to the binding sites provided by the ligands. The inner-sphere water coordination number (q) of the lanthanide ion can be calculated by using the conventional equation of Horrocks or the more recent Parker equation, which takes into account the contribution of unbound closely diffusing water molecules.[45,46] The q values calculated with these empirical correlations reveal that both $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ complexes have two inner-sphere coordinated water molecules. No unbound molecule should be present in the second coordination sphere of the metal ion. Although **4** provides additional donor atoms (four amide carbonyls) and is potentially a better encapsulating structure, as compared to **3**, the lanthanide ion is not shielded more effectively from the water molecules when complexed by this cryptand ligand. We may also note that the luminescence quantum yield of $[Eu(\mathbf{4})]^+$ (in H_2O and D_2O) is analogous to that of $[Eu(\mathbf{3})]^+$. This indicates a similar efficiency of ligand-to-metal energy transfer, and suggests a similar metal-bipyridine interaction. This is in agreement with the complexation characteristics of **3** and **4** as deduced from their ultraviolet spectroscopic data. Both $[Eu(\mathbf{3})]^+$ and $[Eu(\mathbf{4})]^+$ display an absorption band with a maximum at 306−307 nm. This band, attributed to the $\pi-\pi^*$ transition of the coordinated bpy unit, is a diagnostic feature for the degree of ligand-metal interaction in lanthanide complexes. The observed absorption maximum is close to that previously reported for other complexes of Eu^{3+} ion with macrocyclic ligands containing bpy units.[3] Further information pertaining to the cation binding behavior of ligands **3** and **4** was obtained with the aid of solid state (KBr disc) infrared spectroscopic data. In the two complexes, we observed shifts of the carboxyl stretching modes to lower frequency ($\Delta\tilde{\nu} = 120\ cm^{-1}$), revealing that all carboxyl groups were deprotonated and involved in the binding of the lanthanide ion. On the other hand, unlike with $[Eu(\mathbf{3})]^+$, two amide carbonyl stretching frequencies were observed in $[Eu(\mathbf{4})]^+$: $\nu_{C=O} = 1652, 1603\ cm^{-1}$, for free and bound carbonyl groups, respectively. This suggests that some amide carbonyl groups are unbound in $[Eu(\mathbf{4})]^+$ and is consistent with the inefficiency of **4**, with respect to **3**, in terms of improving the shielding of the lanthanide ion from the solvent molecules. In these complexes the metal ion is very probably in closer proximity to the bipyridine group.

Ligands **1**, **2**, and **3** have eight possible coordinating atoms and the same chromophoric bpy unit, but their europium(III) complexes exhibit significantly different photophysical properties. The luminescence lifetime value of $[Eu(\mathbf{3})]^+$ is intermediate between those reported for $[Eu(\mathbf{1})]^{3+}$ and $[Eu(\mathbf{2})]^-$, owing to the different hydration state of the Eu^{3+} ion in these complexes. The solvation parameter for $[Eu(\mathbf{3})]^+$ ($q = 2$) is smaller than that reported for the cryptate $[Eu(\mathbf{1})]^{3+}$ ($q = 2.5$), but higher than that of the chelate $[Eu(\mathbf{2})]^-$ ($q = 1$). The difference in luminescence quantum yields between $[Eu(\mathbf{1})]^{3+}$ and $[Eu(\mathbf{3})]^+$ in H_2O at 300 K cannot be interpreted only on the basis of a better shielding offered in **3** towards interaction of the excited state of the metal ion with O−H oscillators. As a matter of fact, the quantum yield of $[Eu(\mathbf{3})]^+$ is higher in D_2O, in which the shielding effect does not play any role. We may also note that $[Eu(\mathbf{3})]^+$ exhibits a quantum yield in D_2O three times higher than that of $[Eu(\mathbf{2})]^-$. These results suggest that the efficiency of the bipyridine collector for energy transfer to the metal is larger in $[Eu(\mathbf{3})]^+$. An estimation of this efficiency may be obtained with the aid of the quantity $\eta_{en.tr.}$, which represents the energy conversion efficiency from the absorbing singlet state of the ligand to the emitting state of the metal ion.[3] Usually, and with the assumption that the decay process at 77 K in deuterated water is purely radiative, $\eta_{en.tr.}$ can be calculated by Equation (1).

$$\eta_{en.tr.} = \Phi \cdot \tau_{D_2O}^{77K} / \tau_{H_2O}^{300K} \quad (1)$$

The estimated $\eta_{en.tr.}$ value is 0.42 for $[Eu(\mathbf{3})]^+$ (Table 2) and is among the highest obtained, in aqueous solution, for Eu^{3+} complexes with bipyridine-based ligands.[3,42,47] In particular, we note a marked increase in this value, by a factor of four, in $[Eu(\mathbf{3})]^+$, as compared to $[Eu(\mathbf{1})]^{3+}$. With regard to $[Eu(\mathbf{2})]^-$, direct comparison is not possible since all the reported measurements for this complex were carried out at 300 K.[21,25]

The efficiency of ligand-to-Ln^{III} energy transfer and the Ln^{III} luminescence quantum yield are greatly dependent on

Table 2. Energy transfer ($\eta_{en.tr.}$), decay characteristics, and number of coordinated water molecules (q)

[a]	$\eta_{en.tr.}$ [b]	k_r [c] [s^{-1}]	k_{nr} (T)[d] [s^{-1}]	k_{nr} (OH)[e] [s^{-1}]	q[f]
$[Eu(\mathbf{3})]^{+}$	0.42	420	< 50	1930	2.0
$[Eu(\mathbf{1})]^{3+}$ [g]	0.10	590	< 50	2400	2.5
$[Tb(\mathbf{3})]^{+}$ [h]	0.53[i]	370	115	480	2.0
$[Tb(\mathbf{1})]^{3+}$ [g]	≈ 1	260	1300	630	2.7

[a] In water solution. – [b] Obtained from Equation (1). – [c] From the lifetimes in D_2O solution at 77 K, assumed to be purely radiative; $k_r = 1/\tau_D^{77K}$. – [d] From the lifetimes in D_2O (τ_D) solution at 300 and 77 K; $k_{nr}(T) = 1/\tau_D^{300K} - 1/\tau_D^{77K}$. – [e] From the lifetimes in H_2O (τ_H) and D_2O (τ_D) solutions at 300 K; $k_{nr}(OH) = 1/\tau_H^{300K} - 1/\tau_D^{300K}$. – [f] Number of coordinated water molecules at 300 K, as obtained from Horrocks' empirical Equation in water:[45] $q = A(1/\tau_H - 1/\tau_D)$, τ_H and τ_D in ms, $A = 1.05$ and 4.2 for the Eu^{3+} and Tb^{3+} compounds, respectively. – [g] Data from ref.[3]. – [h] Values of the experimental excited state lifetimes under various conditions are given in the Exp. Section. – [i] Calculated with the assumption that the equilibrium between the emitting state of the Tb^{3+} ion and the triplet excited state of the ligand does not play an important role.

the distance between the chromophore and the complexed Ln^{III} ion. However, the quenching mechanisms involving inner-sphere coordinated water molecules or ligand-to-Ln^{III} charge transfer (LMCT) and the energy level of the lowest triplet state of the ligand are also important factors contributing to the luminescence properties of a lanthanide complex. In order to analyze the factors that determine the luminescence intensity of Ln^{III} complexes derived from the promising ligand **3**, we evaluated the contributions of the different paths to the decay of the luminescent excited states of $[Eu(\mathbf{3})]^{+}$ and $[Tb(\mathbf{3})]^{+}$ complexes. For $[Ln(\mathbf{3})]^{+}$ complexes in aqueous solution, the overall decay rate constant k_{obs} (i.e., $1/\tau_{obs}$) of the luminescent level may be represented by Equation (2).

$$k_{obs} = k_r + k_{nr}(OH) + k_{nr}(CH)_{lig} + k_{nr}(T) \quad (2)$$

The term k_r is the natural rate constant for emission of photons, while the terms k_{nr} represent the rate constants for radiationless deexcitation processes involving coupling with high-energy vibrations (O–H, C–H oscillators in the first coordination sphere). The term $k_{nr}(T)$ accounts for temperature-dependent, radiationless processes, which can play an important role when short-lived, upper lying excited states are thermally accessible. Population of ligand excited states (by back transfer) or population of LMCT excited states from the Ln^{3+} emitting state are representative of such deactivating processes.

With the usual assumption that the quenching by X–D vibrations can be neglected, the contributions of the various terms expressed in Equation (2) can be evaluated by comparing the results obtained in non-deuterated and deuterated solvents and at low (77 K) and higher (300 K) temperature.[3] The values of decay rate constants obtained in H_2O solution for $[Eu(\mathbf{3})]^{+}$ and $[Tb(\mathbf{3})]^{+}$ are collected in Table 2; the decay characteristics of $[Eu(\mathbf{4})]^{+}$ are similar to those of $[Eu(\mathbf{3})]^{+}$.

As far as k_{nr} is concerned, it appears that high frequency vibrational C–H modes of the ligand **3** have a modest quenching effect, as suggested by the long luminescent lifetime of $[Eu(\mathbf{3})]^{+}$ in D_2O (2.2 ms), compared to 2.3–2.6 ms for free ions in this solvent [$k_{nr}(CH)_{lig} = (1/\tau_{[Eu(\mathbf{3})]^{+}} - 1/\tau_{EuCl_3})_{D_2O} < 100\ s^{-1}$].[48] Quenching by O–H vibrations is dominant; the calculated rate constant $k_{nr}(OH)$ is 1930 s^{-1} for $[Eu(\mathbf{3})]^{+}$, and thus a contribution of ca 1000 s^{-1} per coordinated water molecule or 500 s^{-1} per O–H oscillator. This value is in good agreement with the literature data.[44] We also note that the hydration state values obtained for $[Tb(\mathbf{3})]^{+}$ and $[Eu(\mathbf{3})]^{+}$ are in good agreement with one another, at 2.0 in each case. The less efficient quenching by O–H vibrations in $[Tb(\mathbf{3})]^{+}$ [$k_{nr}(OH) = 480\ s^{-1}$] is the result of the larger energy gap between the lowest luminescent excited state and the highest ground state for the Tb^{3+} ions ($^5D_4 \rightarrow {}^7F_0$ gap at about 14200 cm^{-1} for Tb^{3+} compared to $^5D_0 \rightarrow {}^7F_6$ gap at about 12300 cm^{-1} for Eu^{3+}).[49]

The calculated $k_{nr}(T)$ value is small ($< 50\ s^{-1}$) for $[Eu(\mathbf{3})]^{+}$, showing that nonradiative deactivation of the europium emitting states by ligand-to-metal charge transfer states (LMCT states) is negligible. However, the decay of the $[Tb(\mathbf{3})]^{+}$ complex is more dependent on the temperature. This suggests that back transfer from the MC level to triplet LC level excited state may take place in $[Tb(\mathbf{3})]^{+}$, as observed for the Tb^{3+} complexes of bpy-based ligands.[3,41,42,47] However, the $k_{nr}(T)$ value estimated for $[Tb(\mathbf{3})]^{+}$ is lower than that obtained for $[Tb(\mathbf{1})]^{3+}$ by one order of magnitude (Table 2). In order to gain better insight into the nature of the temperature-dependent quenching processes, we examined energy matching between the triplet state level of the ligand **3** and the resonance level of the metal ion. The $[Gd(\mathbf{3})]^{+}$ complex was used to determine the triplet state energy of the ligand in a structure analogous to that of the Tb^{3+} and Eu^{3+} complexes. In a rigid matrix at 77 K, $[Gd(\mathbf{3})]^{+}$ showed ligand phosphorescence emission (Figure 2) with a maximum at 481 nm and a lifetime of 3 ms. From the highest energy phosphorescence feature of this spectrum, the value of the zero-zero energy for the $^3\pi\pi^*$ ligand level in $[Ln(\mathbf{3})]^{+}$ complexes is estimated to be 22200 cm^{-1}. Such a value is about 5000 and 1800 cm^{-1} higher than the $^5D_0$ europium(III) and the $^5D_4$ terbium(III) excited states, respectively. From their study on the luminescent properties of 41 different Tb^{III} chelates, Latva et al. concluded that deactivation of the emitting level through back energy transfer to the ligand ($Tb^* \rightarrow {}^3\pi\pi^*$) occurs when the energy difference between the ligand $^3\pi\pi^*$ and the metal $^5D_4$ excited states is less than about 1850 cm^{-1}.[21] The energy gap measured for $[Gd(\mathbf{3})]^{+}$ is close to that minimum difference, offering the possibility of thermally activated population of the low-lying ligand triplet state in $[Tb(\mathbf{3})]^{+}$. In comparison with $[Tb(\mathbf{1})]^{3+}$, in which the lowest bpy triplet excited state lies at lower energy (21600 cm^{-1}),[23] this radiationless deexcitation process is one order of magnitude less efficient in $[Tb(\mathbf{3})]^{+}$.

In conclusion, the main quenching pathway for the Eu^{3+} and Tb^{3+} luminescence in $[Ln(\mathbf{3})]^{+}$ complexes is the product of the high-energy vibrational modes of two coordin-

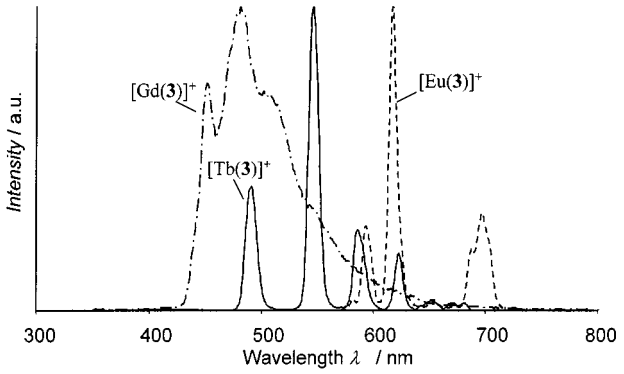


Figure 2. Emission spectra of $[Gd(\mathbf{3})]^+$ (–·–·–) in a ethanol/methanol 4:1 rigid matrix at 77 K, $[Tb(\mathbf{3})]^+$ (——) and $[Eu(\mathbf{3})]^+$ (- - -) in H_2O at 300 K

ated water molecules. On the other hand, the higher luminescence lifetime value [τ (H_2O) = 1.04 ms] and quantum yield [Φ (H_2O) = 0.20] of $[Tb(\mathbf{3})]^+$, as compared to those of the corresponding Eu^{3+} complex, may be explained by less efficient quenching of the Tb^{3+} ion by coordinated water molecules (vide supra).

Finally, a luminescent lanthanide complex suitable for biomedical applications should be characterized by good kinetic stability with respect to metal ion dissociation. Indeed, any biological sample is a highly complex mixture containing a wide variety of molecules and ions that might potentially quench the luminescent label. As reported (vide supra), the $[Ln(\mathbf{3})]^+$ complexes (Ln = Eu, Tb) were found to be stable in coordinating solvents and water. The kinetic inertness of these complexes in the presence of other competing metal ions that might be involved in a cation-promoted dissociation pathway was also studied. No dissociation was observed after several days when the $[Ln(\mathbf{3})]^+$ complexes (0.01 mM) were incubated at 37 °C and physiological pH, in the presence of an excess of calcium (126 mM, which is the concentration of Ca^{2+} in human serum), another ion presenting features similar to those of europium. Luminescence intensities and lifetimes of these complexes also remained unchanged in the presence of other abundant human serum cations (Mg^{2+}, 0.8 mM; Zn^{2+}, 0.01 mM; Na^+, 140 mM; K^+, 5 mM).

Conclusion

The results described in this paper represent an efficient means of access to a novel class of macro(bi)cyclic ligand-based lanthanide complexes. The introduction of two carboxylic units as pendant arms in these ligands gives rise to solubility and stability in the complexes in aqueous solutions. The corresponding Eu^{3+} complexes show luminescence typical of the metal and display equivalent luminescent properties. They have relatively high luminescence quantum yields (Φ = 0.36 in D_2O) in comparison with complexes of other representative cryptands or polyaminocarboxylic ligands containing the bipyridine chromophore. The simplest ligand **3**, obtained in four high-yielding steps, represents a very readily available prototype for luminescent applications. The photophysical behavior of the studied complexes is related to an efficient ligand to Ln^{III} energy transfer in conjunction with a close proximity of the bipyridine chromophore and the metal ion. A detailed analysis of the photophysical properties showed that the main quenching pathway for Eu^{3+} and Tb^{3+} luminescence in these complexes is a function of the high-energy vibrational modes of two coordinated water molecules. Our synthetic approach permits substantial variation of the heterocyclic moiety of the prototype ligand **1**, and we are currently investigating the introduction of more intensely absorbing chromophoric units in this series of macrocycles with the aim of obtaining more intense luminescence.

Experimental Section

General: Melting points were determined on a Kofler apparatus. – ^1H magnetic resonance spectra were recorded on Bruker AC 200 or 250 spectrometers. Data are reported in the following order: chemical shift δ in ppm, spin multiplicity, integration and assignment. – ^{13}C magnetic resonance spectra were recorded on Bruker AC 200 or 250 spectrometers. The multiplicity of signals (*n*) is given under the interval. – Infrared spectra were recorded on a Perkin–Elmer spectrometer [$\tilde{\nu}$ cm^{-1}] in potassium bromide. – Positive ESI-MS spectra [mass range 400–2000, *m/z* (relative intensity%)] were recorded with a Perkin–Elmer SCIEX API 100 apparatus, in methanol solution. Positive FAB-MS spectra were recorded with a Nermag R10–10C mass spectrometer in a 3-nitrobenzyl alcohol (NBA) matrix. – Elemental analyses were carried out by the "Service Commun de Microanalyse élémentaire UPS-INP" in Toulouse. – UV spectra [λ nm (ε $M^{-1}\cdot cm^{-1}$)] were measured on a Perkin–Elmer Lambda 17 spectrophotometer. The luminescence spectra [λ nm (relative intensity%)] were obtained with a LS-50B Perkin–Elmer spectrofluorimeter equipped with a Hamamatsu-R928 photomultiplier tube and with the low-temperature accessory no. *L2250136*. The decay of the metal emitting state was recorded using the same instrument and analyzed with a least-squares fitting program. The luminescence quantum yields were obtained by the method described by Haas and Stein[50] with the standards $[Ru(bipy)_3]^{2+}$ (Φ = 0.028 in aerated water[51]) for the Eu^{3+} complex and quinine sulfate (Φ = 0.546 in H_2SO_4 1 N[52]) for the Tb^{3+} complex. The measured values were corrected for the refractive indices.

Starting Materials: *N-tert*-Butoxycarbonyliminodiacetic acid, diazatetralactam **6**, and diamide diacid **10** were prepared as described in the literature.[33]

6,6′-Bis(bromomethyl)-2,2′-bipyridine was prepared in five steps, starting from 6-bromo-2-methylpyridine. 6-Bromo-2-methylpyridine was reductively coupled using the reactive reagent $Ni[P(C_6H_5)_3]_4$,[53] generated in situ, to give 6,6′-dimethyl-2,2′-bipyridine in 84% yield. The two methyl groups were then converted into bismethanol groups (62% overall yield) by the procedure described by Newkome.[54] 6,6′-Bis(hydroxymethyl)-2,2′-bipyridine was further transformed into 6,6′-bis(bromomethyl)-2,2′-bipyridine with PBr_3, using the standard method (51% yield). White solid, m.p. 180–182 °C (ref.[55] 180–181 °C).

Diamide Diester 11: Ethyl chloroformate (860 µL, 9 mmol) was added at 0 °C to a solution of diamide diacid **10** (2 g, 3 mmol) and

triethylamine (1.25 mL, 9 mmol) in dichloromethane (20 mL). After 10 min. of stirring at 0 °C, DMAP (0.18 g, 1.47 mmol) was added and the resulting solution was stirred for 20 h at room temperature. The reaction mixture was washed with 1 N NaOH (10 mL), 1 N HCl (10 mL), and water (10 mL). The dichloromethane solution was dried over Na_2SO_4, evaporated to dryness, and chromatographed (silica gel, CH_2Cl_2/CH_3OH, 98:2) to afford **11** (0.88 g, 40%) as a pale yellow oil. − ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 1.14−1.22 (m, 6 H, CH_3), 1.23−1.34 (m, 18 H, CH_3), 3.31−3.37 (m, 4 H, NCH_2CH_2N), 3.90−4.20 (m, 12 H, NCH_2), 4.40−4.53 (m, 4 H, OCH_2), 7.10−7.34 (m, 10 H, C*H* Ar). − ^{13}C NMR (63 MHz, [D$_6$]DMSO, 25 °C): δ = 14.0 (*C*H$_3$), 27.7 (*C*H$_3$ Boc), 43.1−43.8 (m, NCH_2CH_2N), 48.4−50.2 (m, NCH_2), 60.3 (OCH_2), 79.3, 79.4 (*C*q Boc), 126.5−128.6 (m, *C*H Ar), 136.9−137.8 (*n* ≥ 4, *C*q Ar), 154.5−154.9 (*n* ≥ 3, *C*O Boc), 168.3−168.6 (*n* ≥ 2, *C*O amide), 169.6 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 1745 (CO ester), 1698 (CO Boc), 1662 (CO amide) cm^{-1}. − MS (ES$^+$, CH_3OH): *m*/*z* (%) = 727.3 (100) [M + H]$^+$. − $C_{38}H_{54}O_{10}N_4$ (726.9): calcd. C 62.79, H 7.49, N 7.71; found C 62.66, H 7.45, N 7.29.

Diamide Diester 12: This compound was prepared in similar manner to compound **11**, starting from the diamide diacid **10** (1 g, 1.50 mmol), triethylamine (540 μL, 3.90 mmol), benzyl chloroformate (560 μL, 3.90 mmol), and DMAP (0.09 g, 0.74 mmol). HPLC (silica gel, CH_2Cl_2/CH_3OH, 100:0 → 98:2) gave **12** (0.88 g, 69%) as a colorless oil. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.32−1.39 (m, 18 H, CH_3), 3.00−3.55 (m, 4 H, NCH_2CH_2N), 4.00−4.24 (m, 8 H, NCH_2CO), 4.24−4.60 (m, 4 H, NCH_2Ar), 5.10−5.15 (m, 4 H, OCH_2), 7.17−7.35 (m, 20 H, C*H* Ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ = 28.1, 28.3 (*C*H$_3$), 42.4−43.5 (m, NCH_2CH_2N), 48.5−50.1 (m, NCH_2), 66.6 (OCH_2), 80.7−80.9 (*n* ≥ 3, *C*q Boc), 126.3−129.1 (m, *C*H Ar), 135.6−136.3 (*n* ≥ 4, *C*q Ar), 155.3 (*C*O Boc), 169.4−169.7 (*n* ≥ 2, *C*O amide), 170.1 (*n* ≥ 2, *C*O ester). − IR (KBr): $\tilde{\nu}$ = 1749 (CO ester), 1704 (CO Boc), 1660 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 851 (7) [M + H]$^+$, 751 (25) [(M − Boc) + 2H]$^+$, 651 (100) [(M − 2Boc) + 3H]$^+$. − $C_{48}H_{58}O_{10}N_4$ (851.0): calcd. C 67.75, H 6.87, N 6.58; found C 67.41, H 6.80, N 6.40.

Diamine 13: Diamide diester **11** (1.20 g, 1.65 mmol) was dissolved in 40 mL of CH_2Cl_2/CF_3COOH (1:1). The solution was stirred for 24 h at room temperature. The solvent and the excess of acid were then removed under vacuum. The residue was dissolved in 80 mL of ethyl acetate and the solution was washed with a 2 N NaOH aqueous solution and brine. The organic layer was dried over Na_2SO_4 and the solvent was removed to afford the pure product **13** (0.48 g, 55%) as a pale yellow oil. − ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 1.14, 1.19 (t, ^3J = 7.1 Hz, 6 H, CH_3), 2.33 (s, 2 H, N*H*), 3.30−3.40 (m, 12 H, NCH_2),4.02, 4.09 (q, ^3J = 7.1 Hz, 4 H, OCH_2), 4.47−4.50 (m, 4 H, NCH_2Ar), 7.10−7.36 (m, 10 H, C*H* Ar). − ^{13}C NMR (63 MHz, [D$_6$]DMSO, 25 °C): δ = 14.0 (*C*H$_3$), 42.8−44.3 (m, NCH_2CH_2N), 47.8−50.2 (m, NCH_2), 59.8 (OCH_2), 126.4−128.6 (m, *C*H Ar), 137.1−137.8 (*n* ≥ 3, *C*q Ar), 170.4−171.0 (*n* = 4, *C*O amide), 171.7 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 3297 (NH), 1733 (CO ester), 1651 (CO amide) cm^{-1}. − MS (ES$^+$, CH_3OH): *m*/*z* (%) = 527.2 (100) [M + H]$^+$, 549.2 (48) [M + Na]$^+$, 565.1 (14) [M + K]$^+$. − $C_{28}H_{38}O_6N_4$ (526.6): calcd. C 63.86, H 7.27, N 10.64; found C 63.69, H 7.21, N 10.37.

Procedure for the Direct Conversion of the Diamide Diacid 10 to Diamine 13: Acetyl chloride (250 μL, 3.52 mmol) was added at 0 °C to a solution of diamide diacid **10** (0.50 g, 0.75 mmol) in ethanol (10 mL). The solution was allowed to warm to room temperature and stirred for 4 h. Acetyl chloride (125 μL, 1.26 mmol) was then added every 15 h, three times in all. After removal of the solvent, the residue was dissolved in ethyl acetate (40 mL) and washed with satd. aqueous $NaHCO_3$ solution (2 × 20 mL) and water (2 × 20 mL). The organic layer was dried over Na_2SO_4 and the solvent was removed to afford the pure product **13** (0.22 g, 55%) as a pale yellow oil.

Diamine 14: The same procedure as described for **13** was followed, using diamide diester compound **12** to yield **14** in 95% yield. White solid, m.p. 130−132 °C. − ^{1}H NMR (250 MHz, [D$_6$]DMSO, 25 °C): δ = 3.00−3.43 (m, 14 H, N*H*, NCH_2), 4.45−4.55 (m, 4 H, NCH_2Ar), 5.08, 5.13 (s, 4 H, OCH_2), 7.18−7.36 (m, 20 H, C*H* Ar). − ^{13}C NMR (63 MHz, [D$_6$]DMSO, 25 °C): δ = 43.1−44.3 (m, NCH_2CH_2N), 47.8−50.2 (m, NCH_2), 65.39, 65.41 (OCH_2), 126.5−128.6 (m, *C*H Ar), 135.9 (*C*q Ar), 137.1−137.8 (*n* = 4, *C*q Ar), 170.4−171.0 (*n* = 4, *C*O amide), 171.6 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 3286 (NH), 1731 (CO ester), 1648 (CO amide) cm^{-1}. − $C_{38}H_{42}O_6N_4$ (650.8): calcd. C 70.13, H 6.51, N 8.61; found C 70.03, H 6.46, N 8.20.

Doubly Branched Dilactam 15: A mixture of **13** (0.40 g, 0.76 mmol) and Na_2CO_3 (0.81 g, 7.64 mmol) in anhydrous acetonitrile (380 mL) under argon was heated to reflux for 1.5 h. 6,6′-Bis(bromomethyl)-2,2′-bipyridine (0.26 g, 0.76 mmol) was then added in one portion. The resulting suspension was refluxed, with efficient magnetic stirring, for a further 24 h. After cooling to room temperature, the insoluble solid was filtered off and the filtrate evaporated. HPLC (silica gel, CH_2Cl_2, then $CH_2Cl_2/CH_3OH/Et_3N$: 90:10:1) afforded the NaBr complex of **15** (0.43 g, 67%) as a pale yellow solid, m.p. 140−142 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.30 (t, ^3J = 7.1 Hz, 6 H, CH_3), 3.43−4.50 (m, 20 H, NCH_2), 4.10 (q, ^3J = 7.1 Hz, 4 H, OCH_2), 6.73−6.75 (m, 4 H, C*H* Ar), 7.17−7.21 (m, 6 H, C*H* Ar), 7.35 (d, ^3J = 7.8 Hz, 2 H, C*H* bpy 5,5′), 7.86 (t, ^3J = 7.8 Hz, 2 H, C*H* bpy 4,4′), 8.05 (d, ^3J = 7.8 Hz, 2 H, C*H* bpy 3,3′). − ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ = 14.1 (*C*H$_3$), 45.6 (NCH_2CH_2N), 51.0 (NCH_2Ar), 54.7 (NCH_2CO), 56.1 (NCH_2COOEt), 60.7 (NCH_2bpy), 61.4 (OCH_2), 120.8 (*C*H bpy 3,3′), 124.9 (*C*H bpy 5,5′), 125.6−128.8 (*C*H Ar), 135.5 (*C*q Ar), 139.1 (*C*H bpy 4,4′), 154.4 (*C*q bpy 2,2′), 157.7 (*C*q bpy 6,6′), 170.9 (*C*O amide), 172.8 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 1735 (CO ester), 1642 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 707 (10) [M + H]$^+$, 729 (100) [M + Na]$^+$. − $C_{40}H_{46}O_6N_6$·NaBr·2H$_2$O (706.8 + 102.9 + 36.0): calcd. C 56.81, H 5.96, N 9.94; found C 56.99, H 5.59, N 9.61.

Doubly Branched Dilactam 16: This compound was prepared similarly to compound **15**, starting from **14** (0.17 g, 0.26 mmol), Na_2CO_3 (0.28 g, 2.64 mmol) and 6,6′-bis(bromomethyl)-2,2′-bipyridine (0.09 g, 0.26 mmol). After filtration off of the insoluble products and evaporation of the filtrate, the product was dissolved in dichloromethane (2 mL), then filtered again and evaporated to give the NaBr complex of **16** (0.235 g, 93%) as a pale yellow solid, m.p. 93−95 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 3.00−4.60 (m, 20 H, NCH_2), 5.17 (s, 4 H, OCH_2), 6.75 (m, 4 H, C*H* Ar), 7.15−7.22 (m, 16 H, C*H* Ar), 7.34 (d, ^3J = 7.8 Hz, 2 H, C*H* bpy 5,5′), 7.86 (t, ^3J = 7.8 Hz, 2 H, C*H* bpy 4,4′), 8.05 (d, ^3J = 7.8 Hz, 2 H, C*H* bpy 3,3′). − ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 45.7 (NCH_2CH_2N), 51.1 (NCH_2Ar), 55.0 (NCH_2CO), 56.3 (NCH_2COOBn), 60.8 (NCH_2bpy), 67.1 (OCH_2), 120.9 (*C*H bpy 3,3′), 125.1 (*C*H bpy 5,5′), 127.6−128.9 (*C*H Ar), 134.9, 135.7 (*C*q Ar), 139.3 (*C*H bpy 4,4′), 154.3 (*C*q bpy 2,2′), 157.5 (*C*q bpy 6,6′), 170.9 (*C*O amide), 172.7 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 1736 (CO ester), 1642 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 831 (23) [M + H]$^+$, 853 (100) [M + Na]$^+$. −

$C_{50}H_{50}O_6N_6$·NaBr·2H_2O (830.9 + 102.9 + 36.0): calcd. C 62.25, H 5.22, N 8.71; found C 61.92, H 5.61, N 8.66.

Doubly Branched Dilactam 3. − Preparation from 15: A mixture of **15** (0.35 g, 0.41 mmol) and K_2CO_3 (0.07 g, 0.51 mmol) in methanol (30 mL) and water (10 mL) was heated to reflux for 24 h. After evaporation to dryness, the residue was dissolved in water (5 mL) and treated with 1 N HCl to reach pH = 4. The diacid was extracted with dichloromethane (3 × 10 mL). The combined extracts were dried over Na_2SO_4, the solvent was evaporated, and the residue was tritured with ethyl acetate to give the pure product **3** (0.20 g, 66%) as a pale yellow solid.

Preparation from 16: A mixture of **16** (0.20 g, 0.21 mmol) and 0.5 N KOH (5 mL) in ethanol was heated to reflux for 5 h, followed by workup analogous to the procedure described above for the hydrolysis of **15**. The diacid **3** was obtained as a white solid (0.12 g, 78%), m.p. 123−124 °C. − ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 2.90 (m, 2 H, NCH_2CH_2N), 3.15, 3.29 (s, 2 H, NCH_2CH_2N), 3.60−3.74 (m, 8 H, NCH_2CO), 3.93−4.09 (m, 4 H, NCH_2bpy), 4.21−4.37 (m, 4 H, NCH_2Ar), 6.75−7.37 (m, 10 H, C*H* Ar), 7.60 (d, ^3J = 7.8 Hz, 1 H, C*H* bpy 5′), 7.63 (d, ^3J = 7.8 Hz, 1 H, C*H* bpy 5), 7.8 (t, ^3J = 7.8 Hz, 1 H, C*H* bpy 4′), 7.85 (d, ^3J = 7.8 Hz, 1 H, C*H* bpy 3′), 7.92 (t, ^3J = 7.8 Hz, 1 H, C*H* bpy 4), 8.13 (d, ^3J = 7.8 Hz, 1 H, C*H* bpy 3). − ^{13}C NMR (50 MHz, CD_3OD, 25 °C): δ = 46.5 (N*C*H$_2$*C*H$_2$N), 51.7 (N*C*H$_2$Ar), 55.8 (N*C*H$_2$CO), 57.3 (N*C*H$_2$COOH), 61.4 (N*C*H$_2$bpy), 122.2 (*C*H bpy 3,3′), 125.8 (*C*H bpy 5,5′), 126.8−130.1 (*C*H Ar), 137.4 (*C*q Ar), 140.4 (*C*H bpy 4,4′), 155.7 (*C*q bpy 2,2′), 159.4 (*C*q bpy 6,6′), 172.5 (*C*O amide), 175.4 (*C*O acid). − IR (KBr): $\tilde{\nu}$ = 3431 (OH acid), 1729, 1706 (CO acid), 1645 (CO amide) cm^{-1}. − UV (H_2O, pH = 6.2): λ_{max} (ε) = 290 nm (13000 M^{-1}·cm^{-1}). − MS (FAB$^+$, NBA): *m*/*z* (%) = 651 (10) [M + H]$^+$, 673 (100) [M + Na]$^+$. − $C_{36}H_{38}O_6N_6$·AcOEt (650.7 + 88.1): calcd. C 65.03, H 6.28, N 11.37; found C 65.10, H 6.14, N 11.75.

Doubly Branched Tetralactam 17: Dicyclohexylcarbodiimide (0.61 g, 2.96 mmol) was added under argon atmosphere to a solution of *N*-*tert*-butoxycarbonyliminodiacetic acid (0.69 g, 2.96 mmol) in 30 mL of THF (freshly distilled from sodium). The solution was stirred for 24 h. Diazatetralactam **6** (1 g, 1.48 mmol) was then added, and the reaction mixture was maintained at 50 °C for 24 h. After removal of the dicyclohexylurea by filtration, the solvent was removed under vacuum, and the crude product was dissolved in satd. aqueous $NaHCO_3$ solution (100 mL). The aqueous solution was treated with ethyl acetate (2 × 50 mL), acidified with 1 N HCl (pH = 2−3), and extracted with ethyl acetate (3 × 50 mL), and the organic layer was dried over Na_2SO_4. After removal of the solvent, the crude product was subjected to HPLC purification (silica gel, $CHCl_3$/$(CH_3)_2CHOH$/CH_3COOH, 95:5:1 → 90:10:1) to give **17** (1.33 g, 80%) as a white solid, m.p. 174−175 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.37−1.45 (m, 18 H, CH_3), 2.30−3.00 (m, 4 H, NCH_2CH_2N), 3.00−5.00 (m, 26 H, CH_2), 5.00−5.30 (m, 2 H, NCH_2), 7.26−7.41 (m, 20 H, C*H* Ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ = 28.1 (*C*H$_3$), 40.7−43.1 (*n* ≥ 4, N*C*H$_2$*C*H$_2$N), 48.8−50.7 (m, N*C*H$_2$Ar, N*C*H$_2$CO), 52.8, 53.4 (N*C*H$_2$COOH), 82.0, 82.6 (*C*q Boc), 125.9−129.6 (m, *C*H Ar), 134.5−136.2 (*n* ≥ 5, *C*q Ar), 154.15, 154.24 (*C*O Boc), 167.9, 168.1, 168.8, 169.0 (*C*O amide), 170.8, 171.0 (*C*O amide), 172.3 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 3442 (OH acid), 1740 (CO acid), 1706 (CO Boc), 1664 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 1105 (4) [M + H]$^+$, 1005 (100) [(M − Boc) + 2H]$^+$, 905 (10) [(M − 2Boc) + 3H]$^+$. − $C_{58}H_{72}O_{14}N_8$·H_2O (1105.2 + 18.0): calcd. C 62.02, H 6.64, N 9.98; found C 61.82, H 6.57, N 9.77.

Doubly Branched Tetralactam 18: This compound was prepared similarly to compound **11**, starting from the diamide diacid **17** (1 g, 0.89 mmol), triethylamine (400 μL, 2.71 mmol), ethyl chloroformate (260 μL, 2.71 mmol), and DMAP (0.06 g, 0.49 mmol). HPLC (silica gel, CH_2Cl_2/CH_3OH, 98:2) afforded **18** (0.68 g, 66%) as a white solid, m.p. 123−124 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.21, 1.22 (t, ^3J = 7.1 Hz, 6 H, CH_3), 1.33−1.44 (m, 18 H, CH_3), 2.30−2.90 (m, 4 H, NCH_2CH_2N), 3.40−4.90 (m, 26 H, NCH_2), 4.11 (q, ^3J = 7.1 Hz, 4 H, OCH_2), 5.20−5.40 (m, 2 H, NCH_2), 7.10−7.50 (m, 20 H, C*H* Ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ = 14.2, 14.3 (*C*H$_3$), 28.1, 28.2 (*C*H$_3$), 39.7−42.0 (m, N*C*H$_2$*C*H$_2$N), 47.9−49.4 (m, N*C*H$_2$), 60.7 (O*C*H$_2$), 80.6, 80.7 (*C*q Boc), 125.7−129.5 (*n* ≥ 9, *C*H Ar), 135.2−135.6 (*n* ≥ 3, *C*q Ar), 155.0, 155.2 (*C*O Boc), 168.7−169.4 (*n* ≥ 5, *C*O amide), 170.0 (*C*O ester). − IR (KBr): $\tilde{\nu}$ = 1745 (CO ester), 1700 (CO Boc), 1666 (CO amide) cm^{-1}. − $C_{62}H_{80}O_{14}N_8$ (1161.4): calcd. C 64.12, H 6.94, N 9.65; found C 63.88, H 7.05, N 9.65.

Doubly Branched Tetralactam 19: The same procedure as described for **13** was followed, using compound **18**, to yield **19** in 95% yield. White solid, m.p. 118−120 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.26 (t, ^3J = 7.1 Hz, 6 H, CH_3), 2.29 (s, 2 H, N*H*), 2.30−2.80 (m, 4 H, NCH_2CH_2N), 3.02, 3.04, 3.26, 3.28 (s, 8 H, NHCH_2), 3.49, 3.55 (d, ^3J = 3.1 Hz, 2 H, NCH_2Ar), 3.95, 4.03 (d, ^3J = 5.6 Hz, 2 H, NCH_2Ar), 4.15 (q, ^3J = 7.1 Hz, 4 H, OCH_2), 4.40−4.80 (m, 14 H, NCH_2), 5.27, 5.32 (d, ^3J = 5.7 Hz, 2 H, NCH_2Ar), 7.23−7.43 (m, 20 H, C*H* Ar). − ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ = 14.2 (*C*H$_3$), 39.9, 40.4, 42.3, 42.5 (N*C*H$_2$*C*H$_2$N), 48.1−49.7 (*n* ≥ 4, N*C*H$_2$), 61.0 (O*C*H$_2$), 126.0−129.4 (*n* ≥ 10, *C*H Ar), 135.2, 135.4, 135.9, 136.1 (*C*q Ar), 168.9, 169.1, 169.3, 169.5 (*C*O amide), 170.2, 170.3, 170.8, 170.9 (*C*O ester). − IR ($CHCl_3$): $\tilde{\nu}$ = 1736 (CO ester), 1663 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 983 (25) [M + Na]$^+$, 961 (100) [M + H]$^+$. − $C_{52}H_{64}O_{10}N_8$·NaCl (961.1 + 58.4): calcd. C 61.26, H 6.33, N 10.99; found C 61.31, H 6.40, N 10.76.

Doubly Branched Cryptand 20: This compound was prepared in a similar way to compound **15**, starting from **19** (0.29 g, 0.29 mmol), K_2CO_3 (0.42 g, 3.04 mmol), and 6,6′-bis(bromomethyl)-2,2′-bipyridine (0.11 g, 0.32 mmol). HPLC (silica gel, CH_2Cl_2/CH_3OH, 98:2 → 85:15) afforded the KBr complex of **20** (0.135 g, 33%) as a white solid, m.p. > 250 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 1.05−1.23 (m, 6 H, CH_3), 2.20−5.80 (m, 40 H, CH_2), 6.90−7.44 (m, 22 H, C*H* Ar, C*H* bpy), 7.92−8.10 (m, 4 H, C*H* bpy). − IR (KBr): $\tilde{\nu}$ = 1730 (CO ester), 1641 (CO amide) cm^{-1}. − MS (FAB$^+$, NBA): *m*/*z* (%) = 1141.5 (100) [M + H]$^+$. − $C_{64}H_{72}O_{10}N_{10}$·2KBr·2H_2O (1141.3 + 238.0 + 36.0): calcd. C 54.31, H 5.41, N 9.90; found C 54.29, H 5.34, N 9.84.

Doubly Branched Cryptand 4: This compound was prepared in a similar way to compound **3**, starting from **20** (0.107 g, 0.076 mmol), K_2CO_3 (0.02 g, 0.15 mmol) in methanol (5 mL), and water (2 mL). White solid (0.085 g, 94%), m.p. > 250 °C. − ^{1}H NMR (250 MHz, $CDCl_3$, 25 °C): δ = 2.20−5.80 (m, 36 H, CH_2), 6.90−7.50 (m, 22 H, C*H* Ar, C*H* bpy), 7.90−8.10 (m, 4 H, C*H* bpy). − IR (KBr): $\tilde{\nu}$ = 3435 (OH acid), 1722 (CO acid), 1664, 1641 (CO amide) cm^{-1}. − UV (H_2O, pH = 6.5): λ_{max} (ε) = 298 nm (12500 M^{-1}·cm^{-1}). − MS (ES$^+$, CH_3OH): *m*/*z* (%) = 1123.5 (24) [M + K]$^+$, 1145.5 (100) [[M − H)]Na + K]$^+$, 1161.4 (38) [[M − H]K + K]$^+$. − $C_{60}H_{64}O_{10}N_{10}$·KCl·1.5H_2O (1085.2 + 74.5 + 27.0): calcd. C 60.72, H 5.69, N 11.80; found C 60.88, H 5.69, N 11.30.

General Procedure for the Synthesis of Lanthanide Complexes: The lanthanide chloride salt (1 equiv.) was added to a solution of the appropriate ligand (0.020 g, 1 equiv.) in methanol (5 mL) and water

(5 mL). The mixture was stirred at room temperature overnight. The solution was concentrated and the pH was raised to 7.5 using 1 N NaOH or KOH solution. After evaporation, the residue was dissolved in methanol (5 mL) and diethyl ether was added, resulting in the formation of a precipitate, which was isolated after centrifugation.

[Eu(3−2H)]Cl: Yield 77%. − IR (KBr): $\tilde{\nu}$ = 1602 (CO acid, CO amide) cm^{-1}. − UV (H_2O, pH = 6.7): λ_{max} (ε) = 306 nm (10700 $M^{-1}\cdot cm^{-1}$). − Luminescence (H_2O, λ_{ex} = 306 nm): λ_{em} = 581 (4), 593 (27), 617 (100), 652 (3), 687 (20), 696 (32), 703 *sh* (24) nm. − MS (ES^+, CH_3OH): *m/z* (%) = 859.2 (20) $[M + Na]^+$, 801.2 (100) $[M - Cl]^+$. − $C_{36}H_{36}O_6N_6EuCl\cdot NaCl\cdot 6H_2O$ (836.1 + 58.4 + 108.1): calcd. C 43.12, H 4.83, N 8.38; found C 43.51, H 4.94, N 7.95.

[Tb(3−2H)]Cl: Yield 70%. − IR (KBr): $\tilde{\nu}$ = 1603 (CO acid, CO amide) cm^{-1}. − UV (H_2O): λ_{max} = 307 nm. − Luminescence (H_2O, λ_{ex} = 307 nm): λ_{em} = 490 (42), 545 (100), 584 (30), 588 *sh* (23), 622 (20) nm; τ (H_2O, 300 K) = 1.04 ms; τ (D_2O, 300 K) = 2.08 ms; τ (D_2O, 77 K) = 2.73 ms. − MS (ES^+, CH_3OH): *m/z* (%) = 865.3 (8) $[M + Na]^+$, 829.3 (12) $[M - HCl + Na]^+$, 807.4 (100) $[M - Cl]^+$. − $C_{36}H_{36}O_6N_6TbCl\cdot NaCl\cdot 5H_2O$ (843.1 + 58.4 + 90.1): calcd. C 43.61, H 4.68, N 8.48; found C 43.89, H 4.43, N 8.62.

[Gd(3−2H)]Cl: Yield 63%. − IR (KBr): $\tilde{\nu}$ = 1603 (CO acid, CO amide) cm^{-1}. − UV (H_2O): λ_{max} = 306 nm. − Phosphorescence (EtOH/MeOH, 4:1, λ_{ex} = 306 nm): λ_{em} = 451 (75), 481 (100), 508 *sh* (71) nm. − MS (ES^+, CH_3OH): *m/z* (%) = 828.3 (20) $[M - HCl + Na]^+$, 806.2 (100) $[M - Cl]^+$, 414.7 (33) $[M - Cl + Na]^{2+}$. − $C_{36}H_{36}O_6N_6GdCl\cdot NaCl\cdot 6H_2O$ (841.4 + 58.4 + 108.1): calcd. C 42.90, H 4.80, N 8.34; found C 42.42, H 4.45, N 8.06.

[Eu(4−2H)]Cl: Yield 82%. − IR (KBr): $\tilde{\nu}$ = 1652 (CO amide), 1603 (CO acid, CO amide) cm^{-1}. − UV (H_2O): λ_{max} (ε) = 307 nm (10200 $M^{-1}\cdot cm^{-1}$). − Luminescence (H_2O, λ_{ex} = 307 nm): λ_{em} = 581 (3), 592 (28), 618 (100), 652 (4), 687 (22), 697 (35), 703 *sh* (22) nm. − MS (ES^+, CH_3OH): *m/z* (%) = 1235.6 (100) $[M - Cl]^+$, 425.0 (50) $[M - Cl + H + K]^{3+}$. − $C_{60}H_{62}O_{10}N_{10}EuCl\cdot KCl\cdot 12H_2O$ (1270.6 + 74.5 + 216): calcd. C 46.16, H 5.55, N 8.97; found C 45.99, H 5.15, N 8.75.

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Received November 27, 2000
[O00610]