Water Stability and Luminescence of Lanthanide Complexes of Tripodal Ligands Derived from 1,4,7-Triazacyclononane: Pyridinecarboxamide *versus* Pyridinecarboxylate Donors

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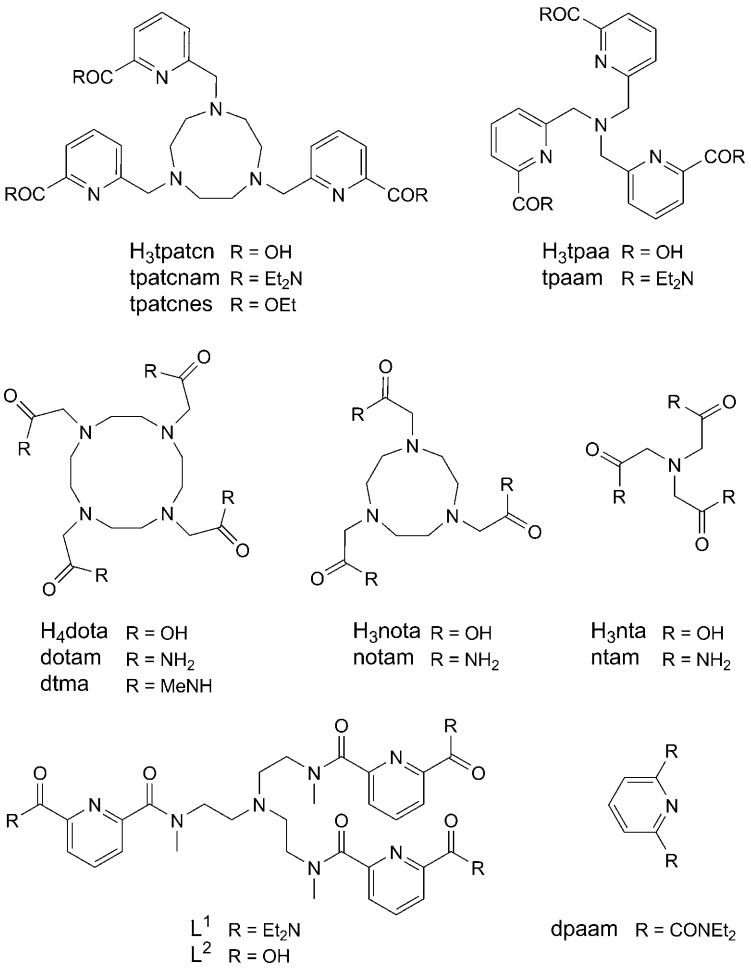
Dedicated to Professor *Jean-Claude Bünzli* on the occasion of his 65th birthday

A series of europium(III) and terbium(III) complexes of three 1,4,7-triazacyclononane-based pyridine containing ligands were synthesized. The three ligands differ from each other in the substitution of the pyridine pendant arm, namely they have a carboxylic acid, an ethylamide, or an ethyl ester substituent, *i.e.*, these ligands are 6,6′,6″-[1,4,7-triazacyclononane-1,4,7-triyltris(methylene)]tris[pyridine-2-carboxylic acid] (H_3tpatcn), -tris[pyridine-2-carboxamide] (tpatcnam), and -tris[pyridine-2-carboxylic acid] triethyl ester (tpatcnes) respectively. The quantum yields of both the europium(III) and terbium(III) emission, upon ligand excitation, were highly dependent upon ligand substitution, with a *ca.* 50-fold decrease for the carboxamide derivative in comparison to the picolinic acid (= pyridine-2-carboxylic acid) based ligand. Detailed analysis of the radiative rate constants and the energy of the triplet states for the three ligand systems revealed a less efficient energy transfer for the carboxamide-based systems. The stability of the three ligand systems in H_2O was investigated. Although hydrolysis of the ethyl ester occurred in H_2O for the [Ln(tpatcnes)]$(OTf)_3$ complexes, the tripositive [Ln(tpatcnam)]-$(OTf)_3$ complexes and the neutral [Ln(tpatcn)] complexes showed high stability in H_2O which makes them suitable for application in biological media. The [Tb(tpatcn)] complex formed easily in H_2O and was thermodynamically stable at physiological pH (pTb 14.9), whereas the [Ln(tpatcnam)]$(OTf)_3$ complexes showed a very high kinetic stability in H_2O, and once prepared in organic solvents, remained undissociated in H_2O.

Introduction. – The increasing number of biomedical applications of lanthanide complexes has resulted in a renewed interest for the coordination chemistry of trivalent lanthanide ions [1–3]. Current applications range from the use of gadolinium complexes as contrast agents in magnetic resonance imaging (MRI) [4] to the use of luminescent lanthanides emitting in the VIS (Eu^{III} or Tb^{III}) as sensors [5] or bio-probes in fluoro-immunoassays, or '*in cellulo*' imaging [2][6][7]. Moreover, positively charged lanthanide complexes promote or catalyze RNA cleavage and have been envisaged for the development of artificial nucleases [8][9]. Cationic lanthanide complexes have also been proposed as chemical-exchange saturation-transfer (CEST) agents for MRI [10–12]. One of the most important requirements, common to all these applications, is the thermodynamic and kinetic stability of the lanthanide complexes in biological media necessary to prevent the release of free lanthanide ions. Because lanthanide ions show high kinetic lability and form preferentially electrostatic bonds with negatively charged O- or N-donors, highly pre-organized polyaminocarboxylate ligands have been used to

synthetize stable complexes. Notably the high thermodynamic and kinetic stability of the lanthanide complexes of the poly-aminocarboxylate ligand dota^{4-} based on the cyclen (=1,4,7,10-tetraazacyclododecane) macrocycle has led to the commercialization and preferential utilization of [Gd(dota)]$^-$ as MRI contrast agent (dota^{4-} = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetato). However, the modification of the architecture of dota^{4-} to improve its efficiency as MRI contrast agent or to profit of its stability for different applications is not straightforward. For example the replacement of the carboxylato binding groups in dota^{4-} by neutral amide O-donors to obtain cationic lanthanide complexes for the application as catalysts in the hydrolysis of RNA results in a dramatic decrease of the thermodynamic stability, although lanthanide(III) complexes with macrocyclic tetraamide ligands such as dotam or dtma show an unusual kinetic stability and are remarkably resistant to metal dissociation in H_2O [13][14] (dotam = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide; dtma = N^1,N^4,N^7,N^{10}-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide). A particularly challenging task is the design of highly stable lanthanide complexes incorporating chromophores which can act as efficient sensitizers of lanthanide luminescence. Efficient chromophores are based on neutral aromatic N-donor ligands that do not form H_2O-stable lanthanides complexes. The incorporation of these chromophores in stable luminescent lanthanide architectures is a very difficult task which requires a careful ligand design. The group of *Bünzli* has played a key role in the development of this field [3][6][7][15][16]. One possible approach extensively studied by *Bünzli* and co-workers and *Parker* and co-workers uses macrocyclic cyclen derivatives to assemble chromophore groups in the close proximity of lanthanide ions [17–20]. The replacement of the macrocyclic platform with a single atom is particularly effective for assembling bidentate and tridentate aromatic N-donors into polydentate ligands partially pre-organized for the complexation of lanthanide ions [3]. Relatively high stability in H_2O was found for the gadolinium complex of the heptadentate tripodal tris-picolinato ligand tpaa^{3-} ($\mathrm{Log}K_{\mathrm{Gdtpaa}} = 10.2(2)$) [21][22] (tpaa^{3-} = 6,6′,6″-[nitrilotris(methylene)]tris[pyridine-2-carboxylato]) and for the lanthanide complexes of the nonadentate L^2 ($\mathrm{Log}K_{\mathrm{GdL}^2} = 6.5(2)$) [23]. The replacement of the carboxylato groups in these ligands with carboxamide groups to yield the tpaam and the L^1 ligands result in a strong decrease of the H_2O stability of the resulting lanthanide complexes (tpaam = 6,6′,6″-[nitrilotris(methylene)]tris[N^2,N^2-diethylpyridine-2-carboxamide]). Notably the lanthanide complexes of L^1 dissociate quantitatively in pure H_2O [23][24], while $\log K = 2.34(4)$ was found for the [Eu(tpaam)]Cl_3 complex in D_2O at 298 K.

The replacement of the cyclen macrocycle with the 1,4,7-triazacyclononane (=octahydro-1*H*-1,4,7-triazonine) has received less attention [25][26]. We have reported the synthesis and crystal structure of lanthanide complexes (Nd, Eu, Gd, and Lu) of the 1,4,7-triazacyclononane-based tris-picolinato ligand tpatcn^{3-} (=6,6′,6″-[1,4,7-triazacyclononane-1,4,7-triyltris(methylene)]tris[pyridine-2-carboxylato]) [27]. The gadolinium complex of tpatcn^{3-} presents a fairly high relaxivity at low magnetic field in spite of the absence of coordinated H_2O molecules. An exceptionally slow electronic spin relaxation was suggested to be the origin of this high relaxivity (only 15% lower than monoaquo complexes) [27–29]. Moreover, very high luminescence efficiency ($\Phi_{\mathrm{Terbium}} = 43\%$) and good H_2O stability ($\log K_{\mathrm{GdL}} = 15.8(2)$) was obtained in our group for the terbium complex of the analogous ligand H_3bpatcn (=6,6′-{[7-



(carboxymethyl)-1,4,7-triazacyclononane-1,4-diyl]bis(methylene)}bis[pyridine-2-carboxylic acid]) in which two picolinic acid arms are connected to the 1,4,7-triazacyclononane ring, in spite of the presence of a H_2O molecule coordinated to the lanthanide ion. The [Ln(tpatcn)] complexes with their rigid coordination sphere should provide an efficient sensitization of lanthanide luminescence. However, the thermodynamic stability and the photophysical properties of the lanthanides complexes of $tpatcn^{3-}$ were never reported. Here, in celebration of the contribution of *J.-C. Bünzli* to the field of lanthanide chemistry, we report a new tris-carboxamide ligand based on the 1,4,7-triazacyclononane platform preorganized for lanthanide complexation, together with the H_2O stability and photophysical properties of three triazacyclononane-based nonadentate ligands.

Results and Discussion. – *Molecular Structure of [Tb(tpatcn)]*. The synthesis of the H_3tpatcn ligand and of its lanthanide complexes (Ln = Nd, Eu, Gd, and Lu) was

reported in a previous work [27]. The [Tb(tpatcn)] complex was prepared following the same synthetic procedure, and crystals suitable for X-ray diffraction analysis were obtained by slow evaporation of a H_2O solution of the complex at pH 5. The complex [Tb(tpatcn)] was found to be isostructural to the previously described [Ln(tpatcn)] complexes [27]. Selected bond distances are presented in *Table 1*. The Tb^{3+} ion is nine-coordinated by the three N-atoms of the 1,4,7-triazacyclononane core, the three pyridine N-atoms and the three carboxylato O-atoms of the pendant arms (*Fig. 1*). The coordination sphere can be described by a slightly distorted tricapped trigonal prism with a pseudo-C_3 axis passing through the centre of the 1,4,7-triazacyclononane core. The average distances of the M–O (2.36(2) Å), M–$N_{pyridine}$ (2.53(1) Å), and M–N_{tert} (2.66(2) Å) are intermediate between those reported for [Gd(tpatcn)] (2.38(2), 2.55(1), and 2.67(3) Å, resp.) and those reported for [Lu(tpatcn)] (2.31(1), 2.494(4), and 2.61(2) Å, resp.), in agreement with the regular decrease of the ionic radius along the lanthanide series [30].

Table 1. *Selected Bond Lengths* [Å] *in Complex [Tb(tpatcn)]·3 H_2O*

Bond lengths		Bond lengths		Bond lengths	
Tb(1)–O(1)	2.346(2)	Tb(1)–N(4)	2.523(3)	Tb(1)–N(2)	2.640(3)
Tb(1)–O(3)	2.361(2)	Tb(1)–N(5)	2.532(3)	Tb(1)–N(3)	2.666(3)
Tb(1)–O(5)	2.380(2)	Tb(1)–N(6)	2.533(3)	Tb(1)–N(1)	2.675(3)

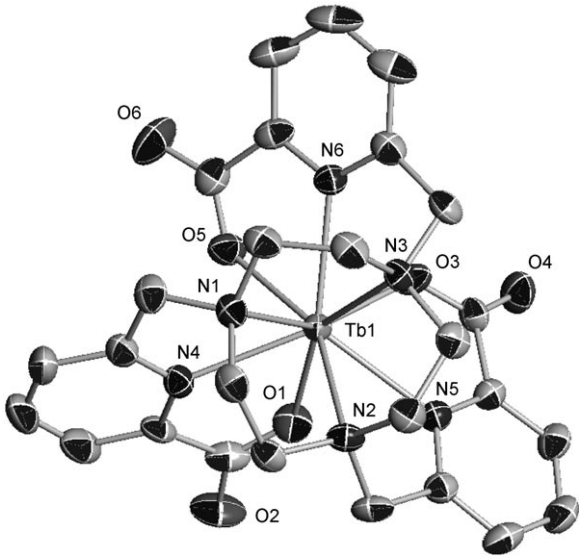
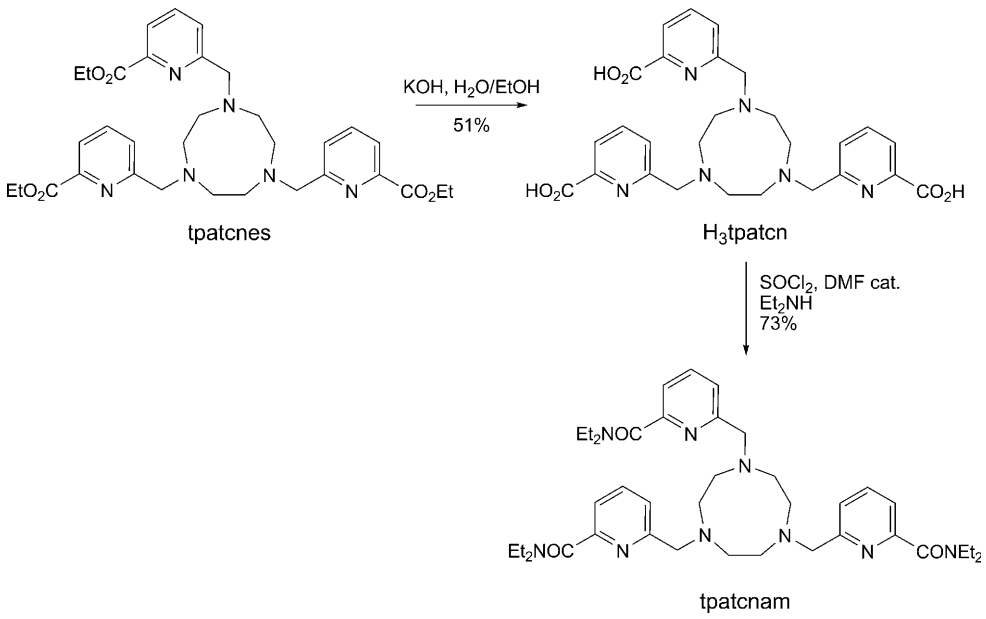


Fig. 1. *ORTEP View of the complex [Tb(tpatcn)] on up view.* H-Atoms and H_2O molecules are omitted for clarity; thermal ellipsoids are represented at the 30% probability level.

Synthesis of the Ligands and Their Lanthanide Complexes. The triethyl ester ligand tpatcnes of triacid H_3tpatcn was prepared as previously described [27]. The corresponding *N*,*N*-diethylamide ligand tpatcnam was synthesized in 73% yield by

means of a one-pot reaction from H_3tpatcn. The triacid H_3tpatcn was activated with thionyl chloride in the presence of DMF as catalyst to form the corresponding triacyl chloride which was then treated with 12 equiv. of diethylamine (*Scheme*).

Scheme



The corresponding lanthanide complexes [Ln(tpatcnam)](OTf)$_3$ (Ln = La, Eu, Tb, and Lu) were prepared by reacting the ligand with the appropriate lanthanide salt at room temperature in anhydrous MeCN and were isolated in good yields and high purity by slow addition of Et_2O to the mixture. The formation of the complex in MeCN was monitored by ^{1}H-NMR spectroscopy. Complex formation occurs immediately after mixing the two starting materials in MeCN. Moreover, once isolated from MeCN, the complexes remain undissociated in H_2O solution for up to two months. The solution structure of the [Ln(tpatcnam)](OTf)$_3$ complexes was studied by ^{1}H-NMR (1D, 2D COSY, and NOESY experiments). The ^{1}H-NMR spectrum of [Eu(tpatcnam](OTf)$_3$ in D_2O at pD 6.4 at 400 MHz and 25° (*Fig. 2*) displays one set of 15 signals in agreement with the presence of rigid C_3 symmetric solution species with three signals assigned to the pyridine H-atoms, two *d* for the diastereotopic methylene H-atoms close to the pyridine, four broader peaks assigned to the ethylene moiety of the 1,4,7-triazacyclononane macrocycle, and two *t* for the *Me*CH_2N and four *m* for the MeCH_2N H-atoms of the amide moieties. The diastereotopic character of the CH_2 H-atoms close to the pyridine clearly indicates a long-lived coordination of the three equivalent ligand arms to the metal on the NMR timescale. Moreover, the nonequivalence of the two Et substituents of the amide moieties is in agreement with the absence of free rotation of the C(O)–N bond. This was further supported by the NOESY experiment which showed cross-peaks only between one of the two Et groups and the aromatic proton

(noted H_5, see *Fig. 2*) of the pyridine. A similar splitting pattern is observed for the tpatcnam complexes of the diamagnetic ions La^{3+} and Lu^{3+}, in agreement with a homogeneous behavior along the lanthanide series.

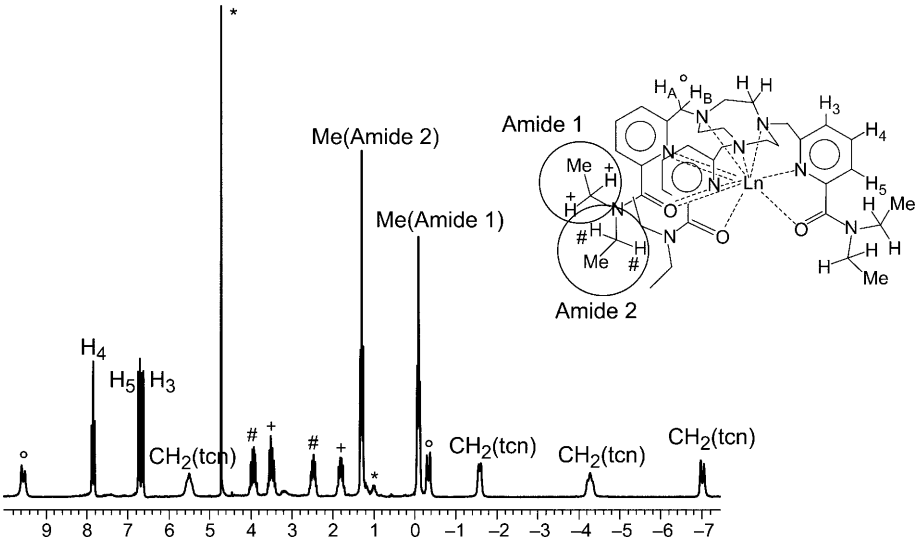


Fig. 2. *^{1}H-NMR Spectrum* (400 MHz, 298 K) *of [Eu(tpatcnam)](OTf)$_3$ in D_2O at pD 6.4*. Scale in ppm; * solvent and impurity, tcn = tetraazacyclononane.

The lanthanide complexes [Ln(tpatcnes)](OTf)$_3$ (Ln = Eu and Tb) were prepared by mixing the ligand tpatcnes with the appropriate lanthanide triflate salt at room temperature in anhydrous MeCN and were isolated in moderate yield by slow addition of Et_2O to the mixture. The ^{1}H-NMR spectrum of [Eu(tpatcnes)](OTf)$_3$ in MeCN solution displays twelve signals in agreement with the presence of rigid C_3-symmetric solution species. As observed for the complexes of [Eu(tpatcnam)](OTf)$_3$, the diastereotopic character of the CH_2 H-atoms close to the pyridine and those of the Et group of the ester clearly indicates a long-lived coordination of the three equivalent ligand arms to the metal on the NMR timescale.

Complex Stability. The deprotonation constants of H_3tpatcn defined as $K_{ai} = [H_{6-i}L]^{3-i}/[H_{5-i}L]^{1-i}[H]^+$ were determined to be $pK_{a1} = 2.5(2)$, $pK_{a2} = 3.0(1)$, $pK_{a3} = 3.8(2)$, $pK_{a4} = 5.7(2)$, and $pK_{a5} = 10.8(2)$ (0.1M KCl, 298 K) by potentiometric titration. The titration curves of H_3tpatcn and of its Tb^{III} complex are shown in *Fig. 3*. The protonation curve is in agreement with a simultaneous partial protonation of the three macrocyclic N-atoms as previously observed for the ligand H_3nota (=1,4,7-triazacyclononane-1,4-7-triacetic acid) [25], followed by the deprotonation of the carboxylate groups. The protonation of the third amine and of the pyridine N-atoms occurs at lower pH, and the associated pK_a could not be determined. H_3tpatcn shows a deprotonation scheme and pK_a values very similar to its parent ligand H_3nota and its disubstituted analogues H_3bpatcn [31]. The stability constant of the complex formed between the Tb^{3+} ion and H_3tpatcn were determined by direct titration of metal/H_3tpatcn

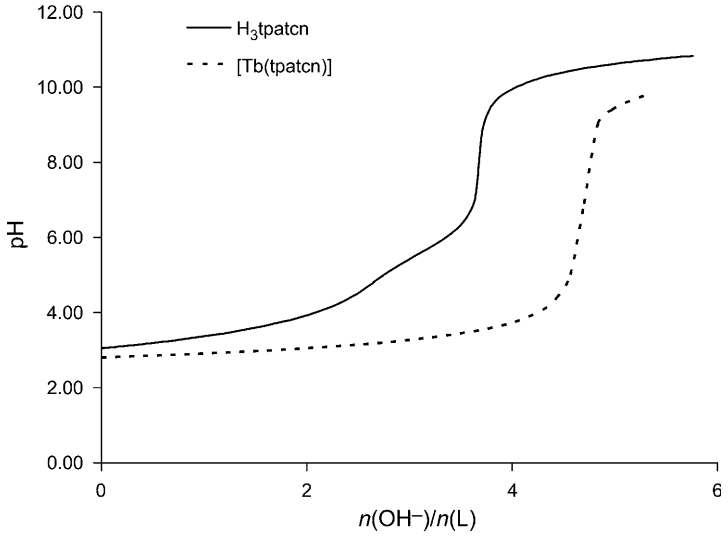


Fig. 3. *Normalized titration curves* (pH *vs.* $n(OH^-)/n(tpatcn^{3-})$) *for* H_3*tpatcn* (0.75 mM) *and [Tb(tpatcn)] solns.* (H_3tpatcn = 0.38 mM, Tb = 0.38 mM)

($5 \cdot 10^{-4}$ M) 1:1 mixtures in the pH range 2.5–8.5. Titration data could be fitted to the following equation:

$$Tb^{3+} + tpatcn^{3-} \leftrightarrows [Tb(tpatcn)] \qquad \log K_{TbL} = 17.4(4)$$

The pK_a values and the overall basicity of the three ligands H_3tpatcn, H_3nota, and H_3bpatcn are very similar, but the stability constant of the terbium complex of $tpatcn^{3-}$ is significantly higher than the one reported for the gadolinium complexes with the ligands $nota^{3-}$ and $bpatcn^{3-}$ ($\log K_{GdL} = 13.7$ and $\log K_{GdL} = 15.8(2)$ [31], resp.), in spite of the expected similar behavior of Tb^{3+} and Gd^{3+} ions. Along the series of the 1,4,7-triazacyclononane-based complexes [Ln(nota)], [Ln(bpatcn)], and [Ln(tpatcn)], the increase of the pyridinecarboxylato groups and subsequent N-donor atoms results in an increased stability of the complexes (3.7 log units from the $nota^{3-}$ complex to the $tpatcn^{3-}$ complex). As a result, the value of the stability at physiological pH, pTb 14.9 ($-\log[M]_{free}$ at pH 7.4, $[M]_{total} = 1$ μM, and $[tpatcn]_{total} = 10$ μM), is significantly higher than those calculated for [Gd(nota)] (pGd 10.7) and [Gd(bpatcn)] (pGd 13.6). This increase in stability can be related to a stronger chelate effect induced by the presence of additional N-donor atoms [32] with respect to the $nota^{3-}$ and $bpatcn^{3-}$ ligands.

The complex [Eu(tpatcnes)]$(OTf)_3$ is soluble in H_2O but decomposes rapidly. The ^{1}H-NMR recorded immediately after dissolution in H_2O shows the presence of several species. Mass-spectrometric analysis allowed the identification of the mono-, bis- and tris-hydrolyzed complexes. The degradation process was further monitored (for a week) by NMR. In the final spectrum, it was possible to clearly identify the presence of the lanthanide complexes of $tpatcn^{3-}$ as the main decomposition product. This result indicates that the ester moiety undergoes hydrolysis in H_2O in the presence of the

lanthanide metal as a result of the high *Lewis* acidity of the lanthanide ion encapsulated in a cationic complex. This interesting unexpected reactivity prevents further study of the luminescence properties of the [Eu(tpatcnes)][$(OTf)_3$] complex in H_2O. However this reaction could eventually be exploited in the preparation of new lanthanide-based sensors.

The H_2O stability of the [Eu(tpatcnam)]$(OTf)_3$ complex was qualitatively studied by NMR spectroscopy. The ^{1}H-NMR spectrum in D_2O at pD 6.0 and 298 K of the 1:1 mixture of the ligand tpatcnam and Eu^{3+} did not show any signals of the complex. The ^{1}H-NMR recorded after maintaining the mixture for 10 d under stirring at 60° showed only the partial formation of the complex (70% formed). Because of the observed slow kinetics, no attempts were made to further pursue the determination of the stability constant of the tpatcnam complex in H_2O. Very slow formation in H_2O has already been observed for the lanthanide complexes of the tetraamide derivative dotam of $dota^{4-}$ which are for this reason usually prepared in organic solvents [13][33]. Also similarly to the dotam complexes, the [Ln(tpatcnam)]$(OTf)_3$ complexes, once isolated from MeCN, can be dissolved in H_2O where they remain undissociated for up to two months. The observed H_2O stability of the cationic complex $[Eu(tpatcnam)]^{3+}$ and its rigid solution structure suggests a high kinetic inertness. This was confirmed by adding good competitors such as $ZnCl_2$ or $dota^{4-}$ to a 2 mM solution of the Eu^{III} complex. No dissociation was observed over a period of several months. In the literature, there are only few examples of cationic complexes which are kinetically stable in H_2O. One of the few reported examples of kinetically stable cationic lanthanide complexes has been obtained with the octadentate macrocyclic ligand dotam [13]. Although an important loss in complex stability has been observed for the tripositive Gd^{III} complex of the tetraamide dtma ($\log K = 12.8(1)$) [34] with respect to the Gd^{III} complex of $dota^{3-}$ ($\log K = 24.67(7)$) [35], the high kinetic stability of these complexes has attracted many studies, and their uses in various biomedical applications have been envisaged [9][20]. Although less effective than macrocycle-based podates, the organization of tridentate binding groups into the tripodal ligand L^1 results in an increase of the kinetic inertness of its nonacoordinated lanthanide complexes [24] compared to the related non-clipped triple helical complexes $[Ln(dpaam)_3]^{3+}$ [36] (dpaam = N^2,N^2,N^6,N^6-tetraethylpyridine-2,6-dicarboxamide). However, in spite of the important chelate effect, the lanthanide complexes of L^1 dissociate in H_2O. Most often, the replacement of carboxylato binding groups with amide O-donors reduces dramatically the thermodynamic stability of their lanthanide complexes [23][24]. Notably, while the $nota^{3-}$ and the nta^{3-} (= 2,2′,2″-nitrilotris[acetato]) ligands form H_2O-stable lanthanide complexes ($\log\beta_{Gdnota} = 13.7$ [25] and $\log\beta_{Gdnta} = 11.4$ [37]), the cationic lanthanide complexes of the amide analogues notam [38] and ntam [39], dissociate completely in H_2O solution. The presence in the tripodal ligand tpaam of three additional pyridine N-donor atoms results in an increased thermodynamic stability of the [Eu(tpaam)Cl_3] complex in D_2O at 298 K ($\log\beta_{110} = 2.34(4)$), with respect to the ntam complex. However, the presence of the amide groups in the heptadentate ligand tpaam do not result in high kinetic stability of its lanthanide complexes which form and dissociate rapidly in H_2O solution [40]. In contrast, the additional presence of three pyridine N-donors in the ligand tpatcnam with respect to the notam ligand leads to a dramatic increase in the kinetic stability of the respective lanthanide complexes. Quite remarkable is the increase in

kinetic stability observed with respect to the complexes of L^1 in spite of the presence of the similar pyridinecarboxamide groups and of the same number of donor atoms. The kinetic stability of the tpatcnam complexes is probably the result of the association of the pyridinecarboxamide chelating unit to the 1,4,7-triazacyclononane macrocycle in a nonadentate ligand perfectly tuned for lanthanide complexation.

Photophysical Properties. In H_2O, the ligands H_3tpatcn, tpatcnam, and tpatcnes display one absorption band at 274, 281, and 280 nm, respectively, which were assigned to $\pi \rightarrow \pi^*$ transitions.

The photophysical properties of the ligands and of some of their 1:1 Ln^{III} complexes (Ln = Eu and Tb) in H_2O for H_3tpatcn and tpatcnam (pH 7.4, *Tris* buffer), and in anhydrous MeCN for tpatcnam and tpatcnes are summarized in *Table 2* (see also *Fig. 4*). At room temperature and upon band excitation between 274 and 281 nm for the three ligands, the luminescence spectra are identical and display the bands corresponding to the metal-centered $^5D_0 \rightarrow {}^7F_J$ ($J = 0-4$) and $^5D_4 \rightarrow {}^7F_J$ ($J = 6-0$) for the Eu^{3+} and Tb^{3+} ions, respectively. The Eu^{III} complexes of the ligands $tpatcn^{3-}$ and tpatcnam are characterized by five bands in the 570–730 nm range with the main band attributed to the $^5D_0 \rightarrow {}^7F_2$ transition appearing in the 600–630 nm range with a maximum at 615 nm. The Tb^{III} complexes of the ligands $tpatcn^{3-}$ and tpatcnam are

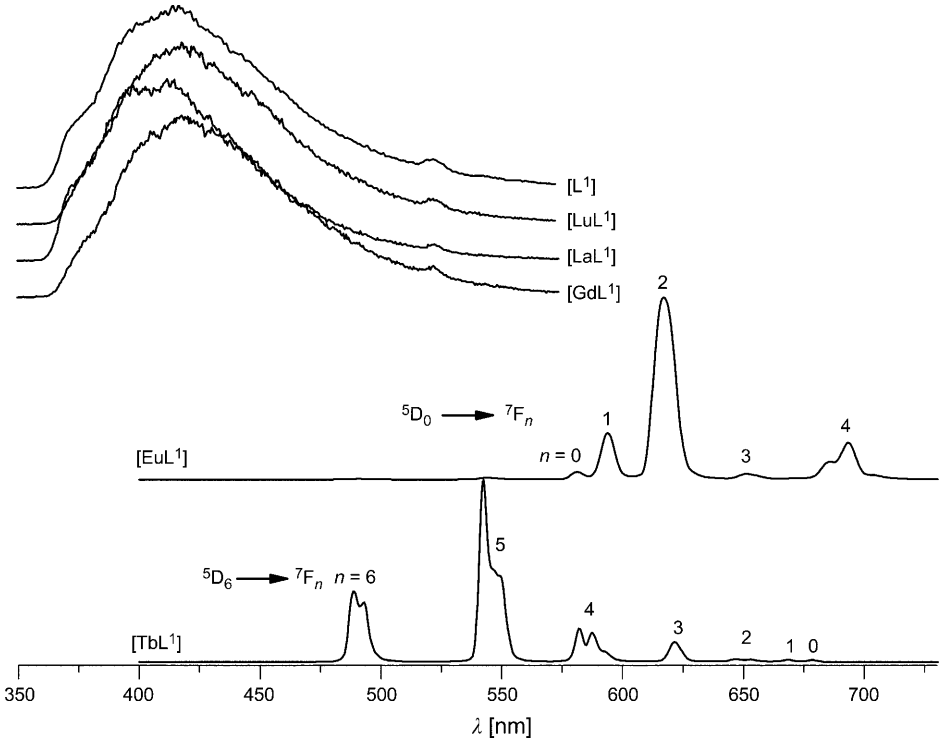


Fig. 4. *Emission spectra of the* $tpatcn^{3-}$ *complexes* (Ln = La, Eu, Gd, Tb, and Lu) *in buffered* H_2O (pH 7.4). Top: phosphorescence spectra at 77 K (delay 0.05 ms, 10% of glycerol). Bottom: fluorescence spectra at 295 K.

characterized by seven bands in the 450–700 nm range. The main band displays a maximum at 545 nm and was attributed to the $^5D_4 \rightarrow {}^7F_5$ transition. No big changes in the shape of the spectra were observed between the complexes of the ligands tpatcn^{3-} and tpatcnam. The luminescence decays obtained upon excitation through the ligands electronics levels are mono-exponential functions of time, both in H_2O and in D_2O, and the corresponding lifetimes τ_{H_2O} and τ_{D_2O} of the Eu($^5D_0$) and Tb($^5D_4$) excited states are reported in *Table 2*. Lifetime data allow the determination of the number of H_2O molecules, q, bonded to the metal center by the use of *Eqn. 1* proposed by *Parker* and co-workers [41]. For solutions of polyaminocarboxylato complexes with $q \leq 1$ (including cyclen derivatives with $q^N = 2$), *Eqn. 1* holds, where $A_{Eu} = 1.2$ ms, $A_{Tb} = 5.0$ ms, $k_{Eu} = 0.25$ ms, and $k_{Tb} = 0.06$ ms. τ_{H_2O} and τ_{D_2O} are the lifetimes in ms of the complexes measured in H_2O and in D_2O respectively. In this way, the number of H_2O molecules was determined to be zero for the Ln^{III} complexes (Ln = Eu and Tb) with both ligands H_3tpatcn and tpatcnam. These values indicate that there is no H_2O molecule coordinated in the first coordination sphere of the metal in solutions of these complexes and are in agreement with the determined solid-state crystal structure of [Tb(tpatcn)]. We can, therefore, conclude that in H_2O solution, the coordination sphere of the Ln^{3+} ion is fully saturated with the three N-atoms of the triazacyclononane, the three N-atoms of the pyridine and the three O-atoms either of the acetato function in the case of the complexes formed with H_3tpatcn, or of the carbonyl of the carboxamide function in the case of the complexes formed with tpatcnam. The lifetimes of the [Tb(tpatcn)] and [Eu(tpatcn)] complexes in H_2O are longer than those previously observed for the analogous monoaquo complexes of the bis-picolinato ligand bpatcn^{3-} ($\tau_{H_2O} = 1.49(2)$ ms for Tb and $\tau_{H_2O} = 0.542(4)$ ms for Eu) [31] due to the absence of H_2O O–H oscillators in their coordination spheres.

$$q = A_{Ln}\left(\frac{1}{\tau_{H_2O}} - \frac{1}{\tau_{D_2O}} - k_{Ln}\right) \quad (1)$$

Table 2. *Lifetime and Absolute Quantum Yields in* Tris *Buffer* (pH 7.4; 298 K)

	λ_{exc} [nm]	ε [M^{-1} cm^{-1}]	τ_{H_2O} [ms]	τ_{MeCN} [ms]	τ_{D_2O} [ms]	Φ_{H_2O}	Φ_{MeCN}	q
tpatcn^{3-}	274	15000						
[Eu(tpatcn)]	274	14400	1.08(2)		1.47(2)	0.09		0.0(2)
[Tb(tpatcn)]	274	15800	2.00(2)		2.14(2)	0.60		0.0(2)
tpatcnam	281	21300						
[Eu(tpatcnam)]$^{3+}$	281	20500	1.01(5)	1.19(2)	1.20(2)	0.002	0.001	−0.1(1)
[Tb(tpatcnam)]$^{3+}$	281	23400	1.77(5)	1.83(2)	1.91(2)	0.012	0.012	−0.1(1)
tpatcnes	280	20400						
[Eu(tpatcnes)]$^{3+}$	280	19200	–	0.85(5)	–	–	0.013	–
[Tb(tpatcnes)]$^{3+}$	280	21050	–	1.78(5)	–	–	0.225	–

To quantify the ability of the chromophoric subunits of the ligands to sensitize the lanthanides emitting in the VIS range, the absolute quantum yields of their Ln^{III} complexes (Ln = Eu and Tb) were determined in MeCN solution (tpatcnes and tpatcnam) and in buffered H_2O (H_3tpatcn and tpatcnam) for which we established that the major species present are the fully complexed ligands. The value of the quantum

yields measured relative to $[Tb(dpa)_3]^{3-}$ (H_2dpa = dipicolinic acid = pyridine-2,6-dicarboxylic acid) in aerated 0.1M *Tris* buffer with an experimental error of 15% are 9.0 and 60% for the Eu^{III} and Tb^{III} complexes of H_3tpatcn, respectively, while they are 0.2 and 1.2% for the Eu^{III} and Tb^{III} complexes of tpatcnam, respectively (*Table 2*). The value of the quantum yield for the terbium complex of $tpatcn^{3-}$ is one of the highest reported to date in the literature [26][31][42–44]. The solid-state luminescence quantum yield has also been measured to be 58.6% for [Tb(tpatcn)] which is very close to the quantum yield measured in the solid state for the Tb^{III} complex of a nonadentate 1,4,7-triazacyclononane-based ligand containing tetrazolylpyridine binding units [45]. The value of the solid-state quantum yield is in perfect agreement with the value measured in solution suggesting that the complex is well protected in solution from the quenching effects of the solvent molecules in the second coordination sphere. These results confirm that the 1,4,7-triazacyclononane anchor is well suited for the pre-organization of chelating chromophores around lanthanide ions for the design of highly luminescent probes [46]. However, a dramatic decrease of the luminescence quantum yield is observed in the complexes of the tpacnam and tpacnes ligands although they do not present any coordinated H_2O molecule in the first coordination sphere. To verify that this is not the result of partial de-coordination of the [Ln(tpatcnam)] complexes in H_2O at the low concentrations used for the luminescence measurements (10^{-6} M), the quantum yields of the Ln^{III} complexes were also measured in anhydrous MeCN. The values of the quantum yields, 0.1% for the Eu^{III} and and 1.2% for the Tb^{III} complex, remain unchanged with respect to those measured in H_2O. This rules out the possibility of an eventual partial dissociation of the $[Ln(tpatcnam)]^{3+}$ complexes in H_2O solution, even at this low concentration, confirming the high kinetic stability of these complexes. A similar decrease of the quantum-yield value is observed for the complexes of the L^1 ligand ($\Phi_{MeCN/H_2O\ 4:1} = 0.29\%$) with respect to the carboxylate analogue L^2 ($\Phi_{H_2O} = 0.89\%$) [23][24], although here the decrease is more evident because of the high value of the quantum yield found for the [Tb(tpatcn)] complex. The quantum yield of the complexes of tpatcnes were also measured in MeCN (1.3% for the Eu^{III} and 22.5% for the Tb^{III} complex, respectively), and the observed values were found intermediate between those of the $tpatcn^{3-}$ complexes and those of the tpatcnam ones.

A more detailed analysis may be performed by evaluating the parameters in *Eqn. 2*, where η_{sens} is the efficiency of the sensitization and Φ_{Ln}^{Ln} the intrinsic quantum yield of the lanthanide. An estimation of the radiative rate constant k_r is obtained from the ratio of the integrated emission intensity $I(0,1)$ of the $^5D_0 \rightarrow {}^7F_1$ transition of the Eu^{III} complex (which is a purely magnetic-dipolar interaction) to the total emission intensity I_{tot}, according to *Eqn. 3*.

$$\Phi_{Tot}^{Eu} = \eta_{ISC}\eta_{ET}\Phi_{Eu}^{Eu} = \eta_{sens}\Phi_{Eu}^{Eu} \tag{2}$$

$$k_r = \frac{14.65 \cdot n^3}{\left(I(0,1)/I_{tot}\right)} \tag{3}$$

From this analysis (*Table 3*), it is clear that, whereas the intrinsic quantum yield Φ_{Eu}^{Eu} of the Eu^{III} is the same for the two complexes (32 and 30%) with a calculated $\eta_{sens} = 0.29$

and 0.007 for the [Eu(tpatcn)] and [Eu(tpatcnam)]$^{3+}$ complexes, respectively, the emission intensity of [Eu(tpatcnam)]$^{3+}$ is limited by the product $\eta_{ISC}\eta_{ET}$, which is probably due to a decrease of the η_{ET} (efficiency of the energy transfer). This was further supported by the values obtained for the triplet-states energies in the two complexes.

Table 3. *Calculated Photophysical Parameters for [Eu(tpatcn)] and [Eu(tpatcnam)]$^{3+}$ in H_2O*

	[Eu(tpatcn)]	[Eu(tpatcnam)]$^{3+}$
$I(0,1)]/I_{tot}$ [a])	0.12	0.12
k_r [s^{-1}] [b])	295	296
k_{obs} [s^{-1}]	926	990
Φ_{Eu}^{Eu}	0.32	0.30
Φ_{lum} [c])	0.090	0.002
$\Phi_T\ \eta_{ET}$	0.282	0.007

[a]) Estimated error ±5%. [b]) Estimated error ±10%. [c]) Estimated error ±20%.

The determined value of the triplet-state energies for the ligands and selected complexes are reported in *Table 4*. The observed increase of the triplet-state energy from the tpatcnam to the tpatcn complexes renders the sensitization more efficient with the tpatcn^{3-} as compared to the tpatcnam analogue, resulting in higher quantum yields. This is in agreement with previous literature reports describing a progressively more efficient sensitization of the lanthanide luminescence when moving from carboxamide to ester and to carboxylato ligands [23][24].

Table 4. *Ligand-Centered Absorption at 298 K and Emission Properties at 77 K for the Ligands tpatcn^{3-}and tpatcnam and the Selected Complexes [Ln(tpatcn)]* (Ln = La, Gd, and Lu) *and [Ln(tpatcnam)]$^{3+}$* (Ln = Gd and Lu)

	$E(^3\pi\pi^*)$ [cm^{-1}] (0 – phonon)	$E(^3\pi\pi^*)$ [cm^{-1}] (max)	$\tau(^3\pi\pi^*)$ [ms]
tpatcn^{3-}	26700	24000	807(9)
[La(tpatcn)]	27030	24000	718(1)
[Gd(tpatcn)]	26590	23900	920(27)
[Lu(tpatcn)]	26670	24100	223(1)
tpatcnam	25550	22200	348(2)
[Gd(tpatcnam)]$^{3+}$	25650	22300	776(10)
[Lu(tpatcnam)]$^{3+}$	25680	22300	277(4)

Conclusions. – In this work, we have synthesized and characterized the new neutral tripodal ligand tpacnam which presents three bidentate pyridinecarboxamide arms connected to a 1,4,7-triazacyclononane anchor. This ligand forms tripositive lanthanide complexes that display in MeCN and H_2O solution a rigid structure in which all the nine donor atoms of the ligand remain bound to the lanthanide ion preventing the coordination of solvent molecules. The H_2O stability and the photophysical properties of these complexes were studied and compared with those of the lanthanide complexes of the two corresponding triazacyclononane-based tripodal ligands containing three

pyridinecarboxylic acid ester (tpatcnes) or three pyridinecarboxylato binding groups (tpatcn). All these triazacyclononane-based ligands show a good H_2O stability confirming that the triazacyclononane anchor is particularly fitted to build polydentate ligands for lanthanide complexation. The Tb^{III} complex of tpatcn shows a high thermodynamic stability (log*K*) and one of the highest luminescence quantum yields reported (60%). The value of the luminescence quantum yield is dramatically reduced in the Tb^{III} and Eu^{III} complexes of the amide and ester derivatives. This is due to the lower triplet state of these ligands which render the sensitization less effective. However, the tripositive complexes of the tris-carboxamide ligand show a remarkably high kinetic stability in H_2O rendering this ligand particularly attractive for biomedical applications. Preliminary work shows that the denticity of the ligand can be easily reduced to obtain analogous mono-aquo complexes which maintain significant kinetic inertness. Such complexes could be very relevant for the development of PARACEST (paramagnetic chemical-exchange saturation transfer) contrast agents or new catalysts for the hydrolytic cleavage of DNA. Work in this direction is in progress.

Supplementary Material. – Supporting information (^{1}H-NMR and emission spectra) is available upon request from *M. M.*

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Experimental Part

1. *Abbreviations.* H_3nta = 2,2′,2″-nitrilotris[acetic acid], ntam = 2,2′,2″-nitrilotris[acetamide], H_3tpaa = 6,6′,6″-[nitrilotris(methylene)]tris[pyridine-2-carboxylic acid], H_3tpatcn = 6,6′,6″-[1,4,7-triazacylononane-1,4,7-triyltris(methylene)]tris[pyridine-2-carboxylic acid], tpatcnam = 6,6′,6″-[1,4,7-triazacyclononane-1,4,7-triyltris(methylene)]tris[*N*,*N*-diethylpyridine-2-carboxamide], tpatcnes = 1,4,7-triazacyclononane-1,4,7-triyltris(methylene)]tris[pyridine-2-carboxylic acid] triethyl ester, H_4dota = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid, dotam = 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide, dpaam = N^2,N^2,N^6,N^6-tetraethylpyridine-2,6-dicarboxamide, dtma = N^1,N^4,N^7,N^{10}-tetramethyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetamide, tpaam = 6,6′,6″-[nitrilotris(methylene)]tris[N^2,N^2-diethylpyridine-2-carboxamide], H_3nota = 1,4,7-triazacyclononane-1,4,7-triacetic acid, and notam = 1,4,7-triazacyclononane-1,4,7-triacetamide.

2. *General.* Solvents and starting materials were obtained from commercial suppliers and were used as received. The ligands H_3tpatcn and H_3tpatcnes were synthesized following the procedure previously described [27]. ^{1}H-NMR Spectra: *Varian Unity-400-MHz* and *Bruker-200-MHz* spectrometers; chemical shifts δ in ppm with solvent as internal reference. MS: *LCQ* ion trap equipped with an electrospray source. Microanalyses were performed by the Service Central d'Analyses (Vernaison).

3. *{6,6′,6″-[(1,4,7-Triazacyclononane-*κN^1,κN^4,κN^7*)tris(methylene)]tris[pyridin-2-carboxylato-*κN^1,κO*](3−)}terbium Hydrate (1:3)* ([Tb(tpatcn)] · 3 H_2O). A soln. of $TbCl_3 \cdot 6\ H_2O$ (0.142 mmol) in H_2O (3 ml) was added to a soln. of H_3tpatcn (108 mg, 0.150 mmol) in H_2O (8 ml). The resulting soln. was stirred at r.t. for 2 h, and then the pH was adjusted to 5 by adding 0.5M aq. KOH. After concentration to *ca.* half volume, slow evaporation of the remaining solvent yielded, after several days, [Tb(tpatcn)] · 3 H_2O (61%) as white crystals suitable for X-ray diffraction. Anal. calc. for [Tb(tpatcn)] · 3 H_2O · 0.6 KCl ($C_{27}H_{33}Cl_{0.6}K_{0.6}N_6O_9Tb$; 789.25): C 41.09, H 4.21, N 10.65; found: C 41.13, H 4.34, N 10.48.

4. *6,6′,6″-[1,4,7-Triazacyclononane-1,4,7-triyltris(methylene)]tris[*N,N-*diethylpyridine-2-carboxamide]* (tpatcnam). A suspension of H_3tpatcn · 1 H_2O · 2 CF_3COOH (100 mg, 0.128 mmol), thionyl chloride (1 ml), and 1 drop of DMF (as catalyst) was stirred under Ar at r.t. for 4 h until complete dissolution of H_3tpatcn. Excess of thionyl chloride was then evaporated and co-distilled with toluene under reduced pression. The resulting crude acid chloride was dissolved in dry CH_2Cl_2 (2 ml), and Et_2NH (0.16 ml, 1.537 mmol) was added under Ar. The mixture was stirred overnight at r.t. Then the mixture was diluted in CH_2Cl_2 (20 ml), the org. layer washed with H_2O (2 × 10 ml) and brine (10 ml), dried (Na_2SO_4), and concentrated, and the resulting crude product (94 mg) purified by flash chromatography (alumina act. III (10 ml), CH_2Cl_2 (25 ml), then CH_2Cl_2/EtOH 98 : 2 (25 ml) and 95 : 5 (25 ml)): tpatcnam (147 mg, 73%). Yellow oil. ^{1}H-NMR ($CDCl_3$, 200 MHz, 298 K): 7.73 (*t*, *J* = 7.8, 3 H); 7.53 (*d*, *J* = 7.0, 3 H); 7.42 (*d*, *J* = 7.4, 3 H); 3.83 (*s*, 6 H); 3.55 (*q*, *J* = 7.2, 6 H); 3.32 (*q*, *J* = 7.0, 6 H); 2.86 (*s*, 12 H); 1.26 (*t*, *J* = 7.0, 9 H); 1.15 (*t*, *J* = 7.0, 9 H).

5. *Lanthanide Complexes [Ln(tpatcnam)](OTf)$_3$* (Ln = La, Eu, Tb, and Lu). A soln. of the ligand tpatcnam (0.10 mmol) in anh. MeCN (1 ml) was added under Ar to a suspension of the corresponding $Ln(OTf)_3$ (Ln = La, Eu, Tb, or Lu; 0.11 mmol) in anh. MeCN (1 ml). The mixture was stirred for 1 h at r.t. The complexes [Ln(tpatcnam)]$(OTf)_3$ (Ln = La, Eu, Tb, and Lu) were obtained in 56 – 70% yield as white solids by slow diffusion of Et_2O into the resulting soln. at r.t.

[La(tpatcnam)](OTf)$_3$. ^{1}H-NMR (D_2O, pD 8.0, 400 MHz, 298 K): 8.21 (*t*, *J* = 8, 3 H); 8.00 (*d*, *J* = 7.6, 3 H); 7.78 (*d*, *J* = 8, 3 H); 4.14, 4.47 (*AB*, *J* = 15.6, 6 H); 3.75 – 3.90 (*m*, 6 H); 3.55 – 3.70 (*m*, 3 H); 3.30 – 3.40 (*m*, 3 H); 3.00 – 3.12 (*m*, 3 H); 2.88 (*d*, *J* = 16.8, 3 H); 2.61 – 2.69 (*m*, 6 H); 1.40 (*t*, *J* = 7.2, 9 H); 0.83 (*t*, *J* = 6.8, 9 H). ESI-MS (pos.): 1136 ([ML – OTf]$^+$). Anal. calc. for [La(tpatcnam)]$(OTf)_3$ ($C_{42}H_{57}F_9LaN_9O_{12}S_3$; 1286.055): C 39.23, H 4.47, N 9.80; found: C 39.42, H 4.50, N 9.78.

[Eu(tpatcnam)](OTf)$_3$. ^{1}H-NMR (D_2O, pD 6.4, 400 MHz, 298 K): 9.48 (br. *s*, 3 H); 7.79 (*t*, *J* = 8, 3 H); 6.67 (*d*, *J* = 7.8, 3 H);. 6.58 (*d*, *J* = 7.8, 3 H); 6.58 (*d*, *J* = 7.8, 3 H); 5.44 (br. *s*, 3 H); 3.88 (br. *s*, 3 H); 3.44 (br. *s*, 3 H); 2.42 (br. *s*, 3 H); 1.76 (br. *s*, 3 H); 1.25 (br. *s*, 9 H); – 0.14 (br. *s*, 9 H); – 0.37 (br. *s*, 3 H); – 1.61 (br. *s*, 3 H); – 4.27 (br. *s*, 3 H); – 7.01 (*d*, *J* = 16, 3 H). ESI-MS (pos.): 1150 ([ML_2 – OTf]$^+$). Anal. calc. for {[Eu(tpatcnam)]$(OTf)_3$} · MeCN ($C_{44}H_{60}EuF_9N_{10}O_{12}S_3$; 1340.14): C 37.64, H 4.29, N 9.41; found: C 37.74, H 4.30, N 9.17.

[Tb(tpatcnam)](OTf)$_3$. ESI-MS (pos.): 1156 ([ML – OTf]$^+$). Anal. calc. for [Tb(tpatcnam)]$(OTf)_3$ ($C_{42}H_{57}F_9N_9O_{12}S_3Tb$; 1306.06): C 38.62, H 4.40, N 9.65; found: C 38.36, H 4.36, N 9.42.

[Lu(tpatcnam)](OTf)$_3$. ^{1}H-NMR (D_2O, pD 8.0, 400 MHz, 298 K): 8.29 (*t*, *J* = 8.0, 3 H); 8.11 (*d*, *J* = 8.0, 3 H); 7.87 (*d*, *J* = 7.6, 3 H); 4.15, 4.40 (*AB*, *J* = 15.6, 6 H); 3.90 – 4.00 (*m*, 3 H); 3.68 – 3.76 (*m*, 6 H); 3.14 (*dd*, *J* = 15.6, 4.8, 3 H); 2.90 – 2.98 (*m*, 3 H); 2.84 (*dd*, *J* = 15.6, 4.8, 3 H); 2.62 – 2.76 (*m*, 6 H); 1.41 (*t*, *J* = 7.2, 9 H); 0.68 (*t*, *J* = 7.2, 9 H). ES-MS (pos.): 1172 ([ML – OTf]$^+$). Anal. calc. for {[Lu(tpatcnam)]$(OTf)_3$} · MeCN ($C_{44}H_{60}F_9N_{10}O_{12}S_3Tb$; 1363.169): C 37.01, H 4.21, N 9.25; found: C 37.00, H 4.26, N 9.13.

6. *Lanthanide Complexes [Ln(tpatcnes)](OTf)$_3$* (Ln = Eu and Tb). A soln. of the ligand tpatcnes (0.10 mmol) in anh. MeCN (1 ml) was added under Ar to a suspension of the corresponding $Ln(OTf)_3$ (Ln = Eu or Tb; 0.11 mmol) in anh. MeCN (1 ml). The mixture was stirred for 1 h at r.t. The complexes [Ln(tpatcnes)]$(OTf)_3$ (Ln = Eu and Tb) were obtained in 46 – 55% yield as white solids by slow diffusion of Et_2O into the resulting soln. at r.t.

[Eu(tpatcnes)](OTf)$_3$. ^{1}H-NMR (D_2O, pD 6.0, 400 MHz, 298 K): – 6.82 (*d*, *J* = 16.8, 3 H); – 5.12 (*d*, *J* = 15.2, 3 H); – 4.13 (br. *s*, 3 H); – 3.30 (br. *s*, 3 H); 0.95 (*t*, *J* = 7.0, 9 H); 3.50 – 3.62 (*m*, 3 H); 3.80 – 3.90 (*m*, 3 H); 5.02 (br. *s*, 3 H); 6.10 (*d*, *J* = 7.6, 3 H); 6.47 (*d*, *J* = 7.6, 3 H); 7.88 (*t*, *J* = 7.6, 3 H); 7.96 (*d*, *J* = 15.2, 3 H). ESI-MS (pos.): 1069 ([ML – OTf]$^+$). Anal. calc. for {[Eu(tpatcnes)]$(OTf)_3$]} · 0.25 MeCN ($C_{42.5}H_{57.75}F_9GdN_{9.25}O_{12}S_3$; 1228.162): C 35.21, H 3.45, N 6.84; found: C 35.00, H 3.54, N 7.09.

[Tb(tpatcnes)](OTf)$_3$. ESI-MS (pos.): 1075 ([ML – OTf]$^+$).

7. *Photophysical Measurements.* UV/VIS Spectra: *Cary-50-Probe* UV/VIS spectrometer; *Perkin-Elmer* luminescence cells with a path length of 1 cm. Soln. luminescence lifetime measurements: *Perkin-Elmer-LS-50B* spectrometer at 293 K (without external temp. regulation). The phosphorescence lifetime (τ) was measured by recording the decay at the maximum of the emission spectra. The signals were analyzed as mono-exponential decays. The instrument settings were as follows: gate time 10 ms, integration time 1 s, flash count 5, excitation and emission slit widths 2.5 nm, and a varied delay time.

Lifetimes are the average of three independent experiments. Phosphorescence excitation and emission spectra were recorded on the same instrument with a delay of 0.05 ms, a gate time of 10 ms, a cycle time of 200 ms, and a flash count of 5. Solns. ($1 \cdot 10^{-6}$ M) of [Tb(tpatcn)], [Eu(tpatcn)], [Eu(tpatcnam)]-$(OTf)_3$, [Tb tpatcnam)]$(OTf)_3$, [Eu(tpatcnes)]$(OTf)_3$, and [Tb(tpatcnes)]$(OTf)_3$ for quantum-yield measurements were prepared by dissolution of the isolated complexes in *Tris* buffer (0.1M) or in MeCN, or *in situ* by mixing of the appropriate volumes of $Ln(OTf)_3$ and H_3tpatcn. Quantum yields Φ were calculated with *Eqns. 4* and *5*, where x refers to the sample and, ref to the reference, A is the absorbance at the excitation wavelength, n is the refractive index, and S is the integrated emitted intensity. Φ^{abs} is the absolute quantum yield and Φ^{rel} is the relative quantum yield.

$$\Phi^{rel}(x) = \frac{A_{ref}}{A_x} * \left(\frac{n_x}{n_{ref}}\right)^2 * \frac{S_x}{S_{ref}} \tag{4}$$

$$\Phi^{abs}(x) = \Phi^{rel}(x) * \Phi^{abs}(ref) \tag{5}$$

The tris(dipicolinato) complex $[Eu(dpa)_3]^{3-}$ (H_2dpa = dipicolinic acid = pyridine-2,6-dicarboxylic acid; Φ 24%, 0.1M in *Tris* buffer) [47] and $[Eu(tpaen)]^-$ (H_4tpaen = 6,6′,6″,6‴-{ethane-1,2-diylbis[nitrilobis(methylene)]}tetrakis[pyridine-2-carboxylic acid]; Φ 7%, $2.31 \cdot 10^{-6}$ M in 0.1M *Tris* buffer) [48] were used as references for the determination of quantum yields.

Low-resolution luminescence measurements in the solid state were recorded on a *Fluorolog-FL-3-22* spectrometer from *Spex-Jobin-Yvon-Horiba* with double-grating emission and excitation monochromators, and a *R928P* photomultiplier. Quantum yields of the complexes in solid state were determined with a home-modified integrating sphere from *Oriel* and the previously described procedure [49]. Spectra were corrected for the instrumental function.

8. *Potentiometric Titrations.* The ligand protonation constants of H_3tpatcn and the metal-ion stability constant of Tb^{III} with H_3tpatcn were determined by potentiometric titrations. Tb^{III} solns. were prepared by dissolving the appropriate amounts of $TbCl_3 \cdot 6\,H_2O$ (*Aldrich*) in H_2O. The exact Tb^{3+}-ion concentration was determined by colorimetric titration in acetate buffer (pH 4.5) with standardized H_2Na_2edta solns. (*Aldrich*) and xylenol orange as the indicator. Solns. of H_3tpatcn (20 ml, $0.75 \cdot 10^{-3}$ M) alone and acidified (pH *ca.* 2.6) 1:1 Tb/ligand mixtures ($[L] = 0.38.10^{-3}$ M) were titrated in a thermostated cell ($25.0° \pm 0.1°$) under a stream of Ar with a 0.1M KOH soln. added by means of a 5 ml piston burette (*Metrohm*). The ionic strength was fixed with KCl ($\mu = 0.1$M). Titrations were carried out with a *Metrohm-751-GPD-Titrino* potentiometer equipped with a combined pH glass electrode (*Metrohm*). Calibration of the electrode system was performed prior to each measurement. The electromotive force is given by $E = E° + s\mathrm{p}[H^+]$ and both $E°$ and s were determined by titrating a known amount of HCl by 0.1M KOH at $\mu = 0.1$M (KCl), by using the acid range of the titration. The value used for the ion product of H_2O is $\log K_w = 13.77$. More than 70 data points were collected for each experiment. The data were mathematically treated by the program HYPERQUAD2000. All values and errors represent the average of at least three independent experiments.

9. *NMR Studies.* The stability of the complex [Eu(tpatcnam)]$(OTf)_3$ in H_2O was studied by NMR. A 2 mM soln. of [Eu(tpatcnam)]$(OTf)_3$ in D_2O was monitored by ^{1}H-NMR over a period of two months. The influence of $dota^{4-}$ and $ZnCl_2$ on the kinetic stability of the complex was also studied by monitoring [Eu(tpatcnam)][$(OTf)_3$]/$dota^{4-}$ (5 mM) 1:1 and [Eu(tpatcnam)][$(OTf)_3$]/Zn^{2+} 1:2 D_2O solutions, at pD *ca.* 7.4, over a period of two months.

10. *X-Ray Crystallography.* The diffraction data were recorded with a *Bruker-SMART CCD* area detector three-circle diffractometer (ω scans, MoK_α radiation, graphite monochromator, λ 0.71073 Å). To prevent evaporation of co-crystallized H_2O molecules, the crystals were coated with light hydrocarbon oil, and the data were collected at $-50°$. The cell parameters were obtained at $-50°$ with intensities detected on three batches of 15 frames with a 10 s exposure. The crystal-detector distance was 5 cm. For three settings of Φ, 4661 narrow data frames were collected for 0.3° increments in ω with an exposure time of 30 s. At the end of the data collection, the first 50 frames were recollected to establish that crystal decay had not taken place during the collection. Unique intensities with $I > 10\sigma(I)$ detected on all frames with the *Bruker* Saint program [50] were used to refine the values of the cell parameters. The substantial

redundancy in the data allows empirical absorption corrections to be applied by means of multiple measurements of equivalent reflections with the SADABS *Bruker* program [50]. Space groups were determined from systematic absences, and they were confirmed by the successful solution of the structure (*Table 5*). The structures were solved by direct methods with the SHELXTL 6.10 package [51]. CCDC-729999 contains the supplementary crystallographic data for the structure of [Tb(tpatcn)]. These data can be obtained free of charge *via* http://www.ccdc.cam.ac.uk/data_request.cif.

Table 5. *Crystallographic Data for the Structure of the [Tb(tpatcn)]·3 H_2O Complex*

	[Tb(tpatcn)]·3 H_2O		[Tb(tpatcn)]·3 H_2O
Formula	$C_{27}H_{33}N_6O_9Tb$	V [Å^3]/Z	1439(4)/2
M_r	744.51	Λ	0.71073
Crystal system	monoclinic	D_{calc} [g cm^{-3}]	1.771
Space group	*Pn*	μ(MoK_α) [mm^{-1}]	2.584
a [Å]	8.0253(12)	Temp. [K]	298
b [Å]	11.9313(19)	R_1, wR_2	0.0216, 0.0505
c [Å]	14.885(2)		

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