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Divergent Approach to a Large Variety of Versatile Luminescent Lanthanide Complexes

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Using a regioselective strategy for nucleophilic aromatic substitution on polyfluoropyridines, a nonacoordinating precursor was designed that is adequately suited for complexation of lanthanide cations. Further functionalizations afforded numerous applications for near-IR emission, two-photon absorption spectroscopy, or the formation of luminescent gels.

Luminescent lanthanide complexes and labels offer numerous advantages over fluorescent organic compounds or other luminescent coordination complexes.[1] They display linelike emission bands, large Stokes shifts, and generally very long luminescence lifetimes and emit over the visible and near-IR (NIR) domains, depending on the lanthanide used. While still in their infancy in luminescence microscopy with one-[2] or two-photon excitation,[3] they have undoubtedly reached the level of standards in fluoroimmunoassays, easily reaching subpicomolar detection limits.[4]

For this class of complexes, a bright luminescence can only be achieved by taking advantage of the antenna effect,[5] allowing for indirect population of the lanthanide-centered excited states through ligand excitation. The choice of the ligand acting as an antenna must be guided by the matching of the intermediate ligand-centered excited states with that of the targeted emitting lanthanide cation. This generally requires synthesis of the proper ligand for each specific lanthanide. Furthermore, efficient luminescence can only be obtained by optimal protection of the cation from solvent molecules including water. Coordination of the latter in the first sphere of the lanthanide leads to detrimental nonradiative processes[6] that drastically quench the luminescence, in particular for NIR emitters. Finally, a targeted use of luminescent lanthanide complexes will also require the synthetic input of a specific function to integrate the complex into a functional molecular device, e.g., a grafting function, for labeling applications,[4,7] or a recognition site, for sensing and detection.[8] Up to now, fulfillment of all of these requirements is achieved by a specific synthetic design of the ligand fitted to the selected lanthanide cation.

We here propose an alternative synthetic approach in which the ligand design offers diverging pathways providing first an efficient complexation site, which can then be functionalized at will to tune the required electronic properties and/or to introduce specific functions. Using this new methodology, a broad scope of highly luminescent lanthanide complexes with visible and NIR emission can be obtained for various applications.

The synthesis of the complexation pocket relies on the largely underexploited nucleophilic aromatic substitution reaction of polyfluoropyridine derivatives (Scheme 1).

Following the pioneering work of Schlosser an co-workers,[9] it was possible to take advantage of the higher reactivity of the para-fluorinated position in 2,4,6-trifluoropyridine to introduce a hydrazine function, which is further transformed into **1** using dibromide in chloroform.[10] This key intermediate allows one to direct the nucleophilic substitution reactions toward the 2 and 6 positions, with the bromine function being

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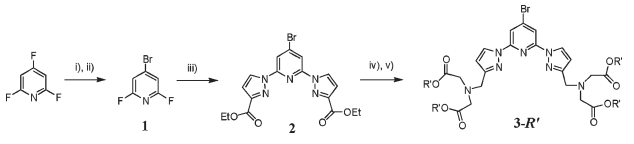
Table 1. Photophysical Properties of the Complexes

	absorption[a]	emission			
	λ/nm (ε/M^{-1} cm^{-1})	λ_{max}/nm	τ_{H_2O}/ms (τ_{D_2O}/ms)	Φ_{H_2O}/%[e]	q[f]
$Na_2[EuL_1]$	328 (8670), 278 (21 200), 271 (21 100)	616[b]	1.3 (2.4)	8	0.1
$Na_2[TbL_1]$	325 (9950), 278 (23 700), 271 (23 300)	545[c]	2.5 (3.1)	quantitative[e]	0.0
$Na_2[YbL_1]$	272 (18 500), 279 (18 700), 327 (7860)	976[d]	1.95 μs		
$Na_2[EuL_2]$	334 (22 800), 277 (20 600), 267 (22 800)	621	1.1 (2.3)	15	0
$Na_2[TbL_2]$	330 (23 700), 271 (23 400)	545[c]	1.15 (2.70)	2.6	
$(NH_4)[EuL_3]$	320 (30 200), 280 (51 800)	621[b]	1.68 (91%); 0.54 (9%)	4	

[a] In Tris/HCl, 0.01 M, pH 7.0, except for $(NH_4)[EuL_3]$ in CH_2Cl_2. [b] $^5D_0 \rightarrow {}^7F_2$ transition of Eu. [c] $^5D_4 \rightarrow {}^7F_5$ transition of Tb. [d] $^2F_{5/2} \rightarrow {}^2F_{7/2}$ transition of Yb. [e] Estimated relative uncertainty ±10%. [f] Number of first-sphere coordinated water molecules according to ref 6a (Eu) and 6b (Tb).

Scheme 1. Synthesis of the Complexation Pocket[a]



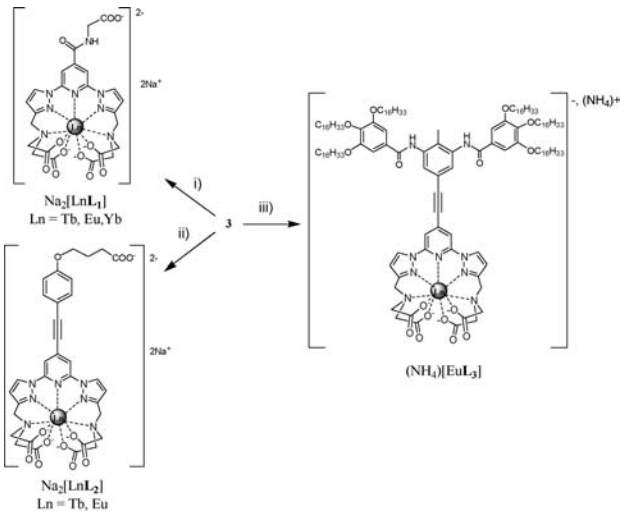
[a] (i) $H_2NNH_2 \cdot H_2O$, THF, 50 °C, 2 h, 85%.[9] (ii) Br_2, $CHCl_3$, reflux, 6 h, 38%.[10] (iii) ethylpyrazolate, NaH, DMF, 0 °C, 2 h, 47%. (iv) $LiAlH_4$, THF, −5 °C, 1 h, and then PBr_3, DMF, rt, 14 h, 43% for the two steps. (v) $HN(CH_2COOR')_2$, THF/Et_3N, 50 °C, 14 h, R′ = Et, 87%; R′ = t-Bu, 85%.

far less reactive than the fluorine one.[11] Hence, a nucleophilic substitution with 2 equiv of 3-ethylpyrazolate afforded the intermediate **2**. Reduction of the ester functions, followed by reaction with PBr_3 and reaction with the dialkyl ester of iminodiacetic acid, readily produced the synthon **3-R′**, possessing a *p*-bromo function for further derivatization and an nonacoordinated complexation site for lanthanide after hydrolysis of the ester functions.[12] The ester functions of **3-R′** allow for an easy purification of the intermediates and can be deprotected orthogonally in either basic (R′ = Et) or acidic (R′ = *t*-Bu) conditions.

Scheme 2 summarizes different illustrations of the large scope of applications of the approach.[13] As a first example, **3-Et** was reacted in a carboamidation reaction using the ethyl ester of glycine, allowing for the formation of an amide function at the para position of the central pyridine ring. Saponification of the ester functions, followed by complexation with chloride salts of lanthanides, afforded the $Na_2[LnL_1]$ complexes (Ln = Eu, Tb, Yb), the photophysical properties of which are summarized in Table 1.

Estimation of the hydration number using Horrocks' method based on the luminescence lifetimes in water and D_2O[6] showed the lanthanide cations to be perfectly protected from water molecules, with hydration numbers close to zero for both europium and terbium (Table 1). A striking result arose from the luminescence quantum yield of the terbium complex, which was found to be quantitative within experimental error, as previously observed for other *p*-carbonyl-substituted pyridine derivatives.[12] Also noticeable, spectrophotometric titration with ytterbium revealed the formation of a YbL_1 complex, which, upon excitation in the UV region, led to the observation of a NIR emission in aqueous solution (Tris/HCl 0.01 M, pH 7.0) with a maximum at 976 nm (Figure 1) and a long lifetime of 1.95 μs, only observed in aqueous solution with a very good shielding of the metal and

Scheme 2. Synthetic Methodology for the Formation of Lanthanide Complexes[a]



[a] (i) (a) ethylglycinate hydrochloride, $[Pd(PPh_3)_2Cl_2]$, CO (1 atm), Et_3N/PhMe, 100 °C, 14 h, 81%. (b) NaOH, MeOH/H_2O, 60 °C, 3 h, 89%. (c) $LnCl_3 \cdot 6H_2O$, H_2O, 50 °C, 2 h, Ln = Eu, 92%; Ln = Tb, 74%. (ii and iii) See the Supporting Information for full synthetic details.

no water molecules in the first coordination sphere.[6,14] Finally, the presence of the pending carboxylate function of the glycine residue offers large opportunities for grafting of the complex on amine residues through conventional peptide coupling reactions,[15] representing a rare (if not unique) example of a NIR-emitting lanthanide label.

As a second illustration of this versatile synthetic approach, we used a palladium-assisted coupling reaction to extend the electronic delocalization on the ligand, allowing for a tuning of the absorption properties. A Sonogashira reaction of **3-Et** with 4-[(4-ethynylphenyl)oxy]butyrate ethyl ester, followed by saponification of the ester functions, afforded ligand L_2 and the europium and terbium complexes after reaction with equimolar amounts of the corresponding hydrated $LnCl_3$ salts. The extension of electronic delocalization on the ligand was translated into a 6 nm bathochromic shift of the low-energy absorption band with an important increase of the absorption coefficient (Table 1).

Upon laser excitation at 705 nm, the europium complex displayed the typical $^5D_0 \rightarrow {}^7F_J$ (J = 0−2) emission bands of europium (Figure 2). Representing the emitted intensity as a

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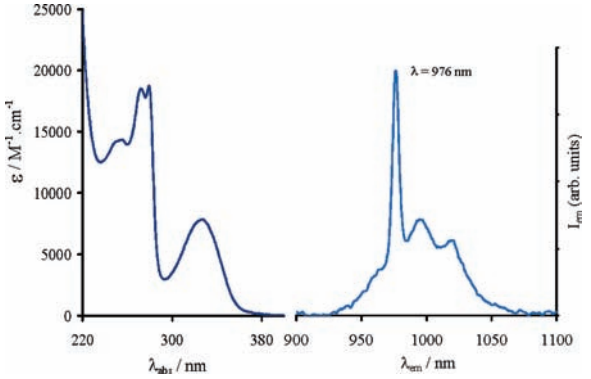

Figure 1. UV−vis absorption (left) and NIR emission (right, high-pass filter at 590 nm, λ_{exc} = 320 nm) spectra of Na_2[Yb**L**$_1$] in water ($c = 4.9 \times 10^{-5}$ M, Tris/HCl 0.01 M, pH 7.0).

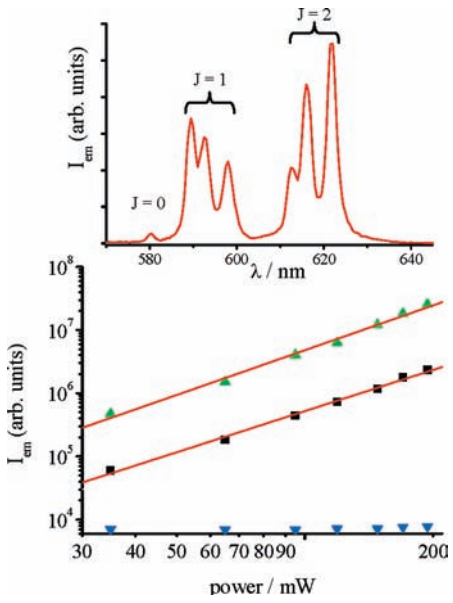

Figure 2. Emission spectrum of Na_2[Eu**L**$_2$] in water ($c = 5.0 \times 10^{-5}$ M in Tris/HCl, 0.01 M, pH 7.0) upon excitation at 705 nm (top, high-pass filter at 630 nm) and europium-centered emitted intensity vs laser power (bottom, in log units for both axes: ▲, fluoresceine; ■, Na_2[Eu**L**$_2$]; ▼, water).

function of the laser power revealed a typical behavior of two-photon absorption (Figure 2; bottom, slope of 2.17 for Na_2[Eu**L**$_2$]), and calculation of the two-photon absorption cross section (see the Supporting Information),[16] using fluorescein as the reference (H_2O, pH 11.0, σ_{2PA}(705 nm) = 32.5 GM),[17] yielded a value of 28.6 GM for Na_2[Eu**L**$_2$] in water, comparable with values reported on a functionalized tris-dipicolinate europium complex.[3]

Finally, functionalization of the para position on the central pyridine ring can be used to modulate the physicochemical properties of the luminescent complexes. Palladium-assisted introduction of a trimethylsilyl-protected acetylene function on **3-tBu** followed by deprotection with fluoride allows isolation of the platform with a terminal alkyne, which can then be further coupled to iodo aromatic derivatives in Sonogashira-type cross-coupling reactions.

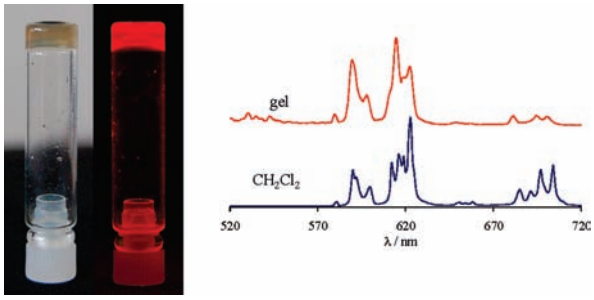

Figure 3. Photograph of the gel formed by (NH_4)[Eu**L**$_3$] in dodecane upon white-light (left) and UV irradiation (right) and its corresponding emission spectrum (red, λ_{exc} = 350 nm, high-pass filter at 395 nm) compared to the emission spectrum in a CH_2Cl_2 solution (blue, same conditions).

Using such an approach, a lypophilic platform was introduced on the ligand backbone, and, after hydrolysis of the ester functions and complexation with 1 equiv of europium, the luminescent europium complex (NH_4)[Eu**L**$_3$] was isolated. This type of platform is known to introduce multiple weak interactions such as aromatic stacking and hydrogen bonds within the amide functions, potentially resulting in rich mesomorphic behavior such as gelation or liquid-crystalline properties. Unfortunately, examination of the sample by polarized optical microscopy, differential scanning calorimetry, and small-angle X-ray diffraction did not reveal any liquid-crystalline behavior. Nevertheless, upon dissolution of the complex into hot dodecane, slow cooling of the sample resulted in the formation of a luminescent gel (Figure 3). The emission spectra observed for a solution of the complex in dichloromethane and for the gel are different, probably as a result of the supramolecular interactions within the luminescent gel.[18] Current efforts are directed toward an understanding of the structure/activity relationship in the gel.

In conclusion, we have developed a new synthetic strategy to synthesize visible and NIR luminescent lanthanide complexes. The methodology opens perspectives for a broad scope of functionalizations, allowing for the extension of electronic delocalization, for the introduction of targeted functions for labeling applications, or for the grafting of promesomorphic functions. Current efforts are directed toward the introduction of recognition sites for sensing applications and into the labeling of biological compounds for highly sensitive time-resolved fluoroimmunoassays.

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Supporting Information Available: Synthetic details for the preparation and characterization of compounds **2** and **3** and characterization of **L**$_1$, **L**$_2$, and **L**$_3$, materials and methods for spectroscopic measurements, emission spectra of Na_2[Eu**L**$_1$], Na_2[Tb**L**$_1$], and Na_2[Tb**L**$_2$], and SEM pictures of the Na[Eu**L**$_3$] gel. This material is available free of charge via the Internet at http://pubs.acs.org.

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