

## pH Responsive Eu(III)–Phenanthroline Supramolecular Conjugate: Novel “Off–On–Off” Luminescent Signaling in the Physiological pH Range

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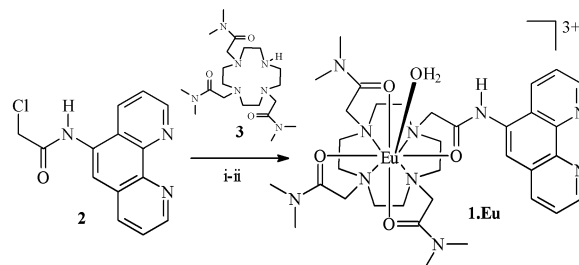
The development of luminescent signaling devices is an active area of supramolecular chemistry.<sup>1</sup> Those where the emission is modulated by single or several external sources (*inputs*) such as light, ions, and molecules are of particular interest.<sup>2</sup> In this regard luminescent switches, sensors, and logic gate mimics have recently been reported.<sup>2,3</sup> Many life processes, such as enzymes, operate within a very narrow pH window, where their function or activity can be described as being “switched on” or “switched off” as a function of pH.<sup>4</sup> Attempts to mimic such “off–on–off” or “on–off–on” behavior by constructing luminescence devices that are modulated by a single *input*, e.g., pH, have recently been achieved by employing organic fluorophores.<sup>5</sup> Lately, Pallavicini et. al. have extended this kind of work and reported “on–off–on” fluorescent indicators for H<sup>+</sup> using a tetraaza ligand, Cu(II) and Coumarin 343 as a fluorescent “chemosensing ensemble”.<sup>6</sup>

We have been particularly interested in designing robust multifunctional lanthanide complexes from cyclen (1,4,7,10-tetraazacyclododecane) as kinetically and thermodynamically stable luminescent chemosensors, switches, and logic gate mimics, as well as ribonuclease mimics.<sup>7–9</sup> Herein we present the synthesis and the photophysical evaluation of the cationic tetraamide 1,10-phenanthroline (*phen*)-based Eu(III) complex **1.Eu**, which is the first example of a fully reversible pH controlled “off–on–off” signaling system that employs lanthanide luminescence rather than fluorescence, where the “off–on–off” process is due to pH modulation of the *phen* ligand.<sup>10</sup> In addition to being purely metal-based emission, the Eu(III) emission changes occur in the physiological pH range, in a pH window between ca. 4–8. Moreover, the emission of **1.Eu** is long-lived (ms range), emitting at long wavelengths (between 500 and 750 nm) with line-like emission bands under ambient conditions. As such, **1.Eu** holds greater advantages over fluorescence systems that can be seriously affected by autofluorescence and light scattering, for instance from the physiological environment.

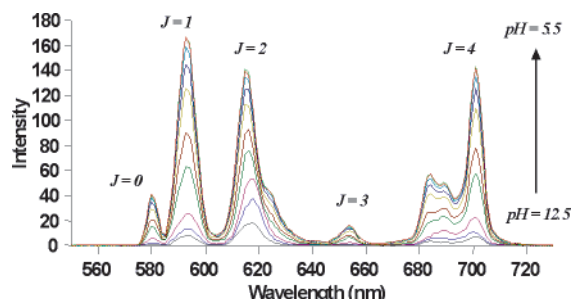
The synthesis of **1.Eu** (ESI) was achieved as shown in Scheme 1. **1.Eu** was purified by multiple precipitation; first from ether and then from CH<sub>2</sub>Cl<sub>2</sub>, giving the desired complex in 80% yield from **1**. **1.Eu** was characterized by conventional methods (calculated for **1.Eu**: C<sub>35</sub>H<sub>51</sub>N<sub>10</sub>O<sub>7</sub>F<sub>3</sub>SEu: 965.2876. Found: 965.2827). The ESMS showed peaks at 406.9 and 481.9 (*m/z*) for the M<sup>2+</sup> and (M + triflate)/2 respectively, whereas the <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O) indicated a typical mono-capped square antiprism geometry<sup>11</sup> as a major isomer (ca. 95%) in solution, with resonances at 28.4, 0.28, –3.3, –8.8, –12.1, and –15.7 ppm for the equatorial and axial ring, and the methylene protons of the pendent arms.

The pH dependence of the Eu(III) emission was evaluated in H<sub>2</sub>O in the presence of 0.1 M tetramethylammonium perchlorate to maintain constant ionic strength (*I*).<sup>8</sup> Due to the low molar

**Scheme 1.** Synthesis of the Eu(III)-Based Cyclen Derivative **1<sup>a</sup>**



<sup>a</sup> Reaction conditions: (i) Cs<sub>2</sub>CO<sub>3</sub>, **2** and **3**,<sup>7</sup> DMF reflux; (ii) Eu(SO<sub>3</sub>CF<sub>3</sub>)<sub>3</sub>, CH<sub>3</sub>CN, reflux.

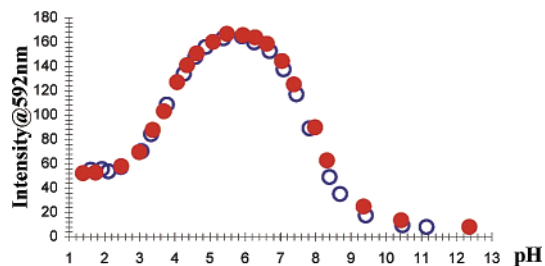


**Figure 1.** Changes in the Eu(III) emission as a function of pH between 12.5 (bottom spectrum) and 5.5 (top spectrum) upon excitation at 266 nm.

absorptivities of Eu(III) the population of the Eu(III) excited state (<sup>5</sup>D<sub>0</sub>) is achieved indirectly by the *phen* antenna via sensitization.<sup>8,9,11</sup> We predicted that the ability of the *phen* ligand to engage in such sensitization would be pH dependent since both the amide and the nitrogens of the *phen* ligand are sensitive to protonation. Indeed, this was found to be the case. In alkaline solution between pH 12–8.5 only a weak Eu(III) emission was observed at 581, 593, 615, 624, 654, 686, and 702 nm for the deactivation of the <sup>5</sup>D<sub>0</sub> to the ground states <sup>7</sup>F<sub>J</sub> (*J* = 0, 1, 2, 3, and 4) after excitation at 266 nm. This signifies the rather inefficient population of the <sup>5</sup>D<sub>0</sub> by the *phen* ligand in this pH range. The hydration number (*q*) for **1.Eu** was determined by measuring the Eu(III) luminescent lifetimes [τ<sub>Eu(III)</sub>] in H<sub>2</sub>O and D<sub>2</sub>O. This gave τ<sub>Eu(III)</sub> = 0.271 ms and 0.371 ms for H<sub>2</sub>O and D<sub>2</sub>O, respectively (at pH 11), giving *q* ≈ 1, and as such an overall nine-coordinated complex.<sup>11</sup> Upon further acidification, this sensitization process was greatly enhanced, and the Eu(III) emission was “switched on” between pH 8.5–5.5, with sharp luminescence enhancements as demonstrated in Figure 1; e.g. LE ≈ 20 for <sup>5</sup>D<sub>0</sub> → <sup>7</sup>F<sub>1</sub>, with τ<sub>Eu(III)</sub> = 0.395 and 0.952 ms in H<sub>2</sub>O and D<sub>2</sub>O respectively, which gives *q* ≈ 1.3, again indicating that the complex was monohydrated. Further acidification gave rise to two effects; notably between pH 5–6.5 the Eu(III) emission was almost constant, whereas between pH 5–3 the emission was gradually “switched off”, being ca. 70% quenched at pH 2.5 vs that at pH 6 (Supporting Information). Similarly, using *I* = 0.1 M

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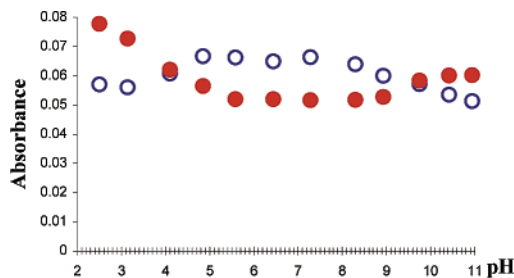
**Figure 2.** pH-dependence in the luminescent profile for **1.Eu**, showing the “off–on–off” pH-dependent changes in the Eu(III) emission at 592 nm. This pH dependence was fully reversible: in blue the changes from pH 12  $\rightarrow$  1.5, and in red the back-titration of the same sample.

of tetramethylammonium chloride showed identical luminescence behavior, i.e. these changes were not anion dependent.<sup>7</sup>

By plotting the changes in the intensity of the  $^5D_0 \rightarrow ^7F_1$  transitions as a function of pH gave, for all of these emission bands, a bell shaped curve, consisting of two sigmoidal slopes, between pH ca. 3–5 and 6.5–8.5, with maximum intensity being reached at pH 5.8–6.0. Figure 2 shows these changes for the  $^5D_0 \rightarrow ^7F_1$  in blue for the titration of the alkaline solution with HCl, and the back-titration of this same solution in red, indicating that this pH dependence is fully reversible. It also clearly shows that the changes of these “off–on–off” pH-dependent emissions clearly transpire over the physiological pH range, and, as such, mimic the pH dependences of many enzymatic processes.<sup>4,9</sup> From these luminescence changes two  $pK_a$ s were determined as 3.8 ( $\pm 0.1$ ) and 8.1 ( $\pm 0.1$ ), the latter being assigned to the deprotonation of the aryl amide proton in alkaline solution, whereas the former was assigned to the protonation of one of the *phen* nitrogen moieties. In comparison, potentiometric titrations of **1.Eu** gave  $pK_a$ s of 3.6 ( $\pm 0.1$ ) and 7.6 ( $\pm 0.1$ ), respectively, which is similar to those observed spectroscopically. Furthermore, **1.Eu** was found to be stable to Eu(III) dissociation in this solution over a period of months, without any loss of its luminescence properties. To the best of our knowledge **1.Eu** is the first example of a lanthanide luminescent system capable of successfully mimicking such pH dependence by modulating the sensitization process from the antenna. Furthermore, these changes cannot be attributed to changes in  $q$  as it was pH independent, with  $q = 1$ .<sup>7</sup>

The concomitant changes in the fluorescence emission spectra between 300 and 550 nm ( $\lambda_{ex} = 266$  nm) were less drastic, being ca. 40% quenched upon acidification from pH 11 to 1.5 with an associated shift in  $\lambda_{em}$  max from ca. 420 nm to 440 nm (Supporting Information). In tandem, the absorption spectrum of **1.Eu** showed hypochromic effects and evidence of some bell-shaped pH dependence, but these were much less drastic in comparison to the Eu(III) emission, as is evident from Figure 3.

From these combined spectroscopic changes, it is obvious that only the lanthanide luminescence is substantially affected by pH. However, what determines the large observed bell-shaped pH dependence for the Eu(III) emission? We predict that in an established manner, the excitation of the antenna sensitizes the Eu(III)  $^5D_0$  excited state via an energy-transfer mechanism,<sup>7,8,10</sup> and that, in relatively alkaline solution, the Eu(III) ion can be reduced by an electron transfer<sup>11</sup> to Eu(II) which is not emissive. Secondly, the deprotonation of the amide proton increases the reduction potential of the antenna which is reflected in its reduced ability to populate the excited state of the Eu(III) ion.<sup>8</sup> Within a narrow pH window of ca. pH 5–6.5 and within experimental error, the emission is fully pH independent. In acidic solution upon proto-



**Figure 3.** pH dependence in the absorption spectra of **1.Eu**, at 266 nm blue circles, and at 278 nm in red.

nation of the *phen* nitrogen moiety, the oxidation potential is increased in conjunction with modification of the ICT excited state of the *phen*–amide ligand,<sup>9</sup> which reduces the ability of the ligand to populate the  $^5D_0$  state efficiently. We are currently investigating these features in greater detail.

In summary we have developed a novel lanthanide luminescence device that displays a clear and complete bell-shaped luminescent “off–on–off” switching as a function of pH in water. This dual switching takes place over 4–5 pH units, being centered at pH  $\approx$  6, as well as being fully reversible.

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**Supporting Information Available:** Synthesis and experimental details for **1.Eu**, UV–vis, fluorescence, lanthanide luminescence spectra and  $q$  as a function of pH. Potentiometric titration of **1.Eu** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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