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Eu(III)–cyclen–*phen* conjugate as a luminescent copper sensor: the formation of mixed polymetallic macrocyclic complexes in water†

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The cationic cyclen based Eu(III)–*phen* conjugated 1·Eu was synthesised as a chemosensor for Cu(II), where the recognition in water at pH 7.4 gave rise to quenching of the Eu(III) luminescence and the formation of tetranuclear polymetallic Cu(II)–Eu(III) macrocyclic complexes in solution where Cu(II) was bound by three 1·Eu conjugates.

The development of photochemically based supramolecular devices is a dynamic area of research, where many excellent examples of luminescent sensors, switches, logic gates and wires have been reported.[1–5] To this end we have developed and studied several lanthanide luminescence Tb(III) and Eu(III) complexes as sensors, switches and logic gate mimics by employing ionic and molecular *inputs*.[6] The benefits of such lanthanide devices lie in their long lived excited states (~ ms) and their emission at long wavelengths (500–750 nm) with line-like emission bands which confer an advantage over most fluorescent systems.[6,7] Herein, we discuss the development of **1·Eu**, a kinetically stable cationic tri-amide cyclen (1,4,7,10-tetraazacyclododecane) based Eu(III) macrocycle conjugated to a 1,10-phenanthroline (*phen*) ligand. The role of the *phen* ligand is dual as it serves both as an antenna sensitizing chromophore[4,6,7] for the indirect population (*via* $S_1 \rightarrow T_1$) of the Eu(III) excited state ($^5D_0$), as well as a receptor for either H^+ or Cu(II). Both of these ionic *inputs* are expected to modulate the photophysical properties of the *phen* ligand upon ion recognition, and consequently the Eu(III) sensitisation process.[4,6,7] Furthermore, the interaction of the Cu(II) with **1·Eu** leads potentially to the formation of a mixed supramolecular macrocyclic complex in solution, containing three **1·Eu** complexes coordinating to the Cu(II) ion. Such mixed polymetallic transition–lanthanide ion arrays, using coordination macrocyclic systems, are rare.[8] **1·Eu** is also the first example of a kinetically stable lanthanide luminescent sensor that shows good selectivity and sensitivity for Cu(II) over other competitive cations in pH 7.4 water .

The synthesis of **1·Eu** was achieved in good yield by first reacting the α-chloroamide **2** with one equivalent of tri-substituted *N*,*N*-dimethylacetamide cyclen macrocycle[9] at 80 °C in DMF and Cs_2CO_3 giving the ligand **1**, followed by reaction with Eu-$(CF_3SO_3)_3$ in CH_3CN and precipitation from diethyl ether. ^1H NMR (400 MHz, D_2O) studies showed that **1·Eu** has a typical mono-capped square antiprism geometry in solution.

The pH dependence of the Eu(III) emission of **1·Eu** was investigated in water in the presence of 0.1 M tetramethylammonium chloride (I = 0.1 M TMACl) to maintain constant ionic strength. At neutral pH, **1·Eu** gave rise to typical Eu(III) emission bands[6] (λ_{ex} = 266 nm), at 581, 593, 615, 654, 686 and 702 nm due to the deactivation of the $^5D_0$ excited state to the ground states ^7F_J (J = 0, 1, 2, 3 and 4). A pH titration of **1·Eu** indeed showed that in the physiological pH range the Eu(III) emission was 'switched on' whereas at more acidic or alkaline pH the emission was 'switched off', giving rise to a bell-shaped emission-pH profile with pK_as of 3.8 (±0.1) and 8.1 (±0.1) respectively (ESI†). This process was fully reversible. Most importantly, the concomitant changes in the absorption and the fluorescence were only minor. The hydration state (q) of the sensor was found to be ~ 1 over the entire pH range, hence **1·Eu** has a single metal bound water molecule.

The ability of **1·Eu** to detect several group I, II and transition metal ions such as Fe(II), Fe(III), Co(II), Cu(II) and Zn(II) was investigated under three different sets of conditions: at pH 7.4 using 0.1M HEPES buffer; at pH 7.4 and with I = 0.1 M TMACl and finally at pH 7.4 in the presence of 'mimicked' biological ionic strength. For all of these conditions, Zn(II) and group I and II ions did not modulate the excited state properties of the *phen* ligand or the Eu(III) emission. However, the rest of the transition metal ions did. The absorption spectra of the free *phen* ligand of **1·Eu** was centred at 266 nm. Upon Cu(II) titration, it was slightly red shifted with the formation of an isosbestic point at 280 nm (ESI), signifying the coordination of Cu(II) by the *phen* moiety. Similar results were seen for the other transition metal ions. The concurrent changes in the fluorescence emission spectra of **1·Eu**, which had a $\lambda_{F\max} \approx$ 430 nm, showed *ca.* 80% quenching with a shift to the red, due to complexation, and consequent electron transfer quenching of the *phen* S_1 excited state by Cu(II). From these results it is clear that the delayed lanthanide luminescence of **1·Eu** would also be expected to be strongly effected by Cu(II) recognition, as the population of the $^5D_0$ excited state would be substantially reduced or removed. Indeed this was found to be the case, as seen in Fig. 1, where the well defined and line-like emission bands of the Eu(III) emission were gradually 'switched off' (~ 100%) upon recognition of Cu(II) by the *phen* ligand at pH 7.4.‡ By plotting the changes of any of these transitions, as a function of Cu(II) concentration it was possible to evaluate the binding affinity of **1·Eu** for Cu(II). These changes are shown in Fig. 2 for the J = 2 transition, as a function of −log [M], where M = Cu(II). From these changes it is evident that the binding of Cu(II) occurs over a narrow concentration range (−log [Cu] ≈ 6–5, which overlaps with that of the physiological concentration of Cu(II)). This is not surprising, given the high coordination requirement of the Cu(II) and its affinity for *phen* type ligands.[10] Importantly, the addition of EDTA (using the same concentration that gave rise to fully 'switched off' state by Cu(II)) to this fully quenched solution, switched the emission back 'on'. This signifies that the Cu(II) detection by **1·Eu** is reversible. Similar titrations were carried out using other transition metal ions. From Fig. 2, it is evident that in water at pH 7.4 the Cu(II) is selectively detected over both Co(II) and Fe(II) (M = Co(II) and Fe(II)). For both the Eu(III) emission is quenched upon recognition but at significantly higher concentration than for Cu(II). We also evaluated the recognition of Cu(II) at high ionic strength, I = 0.1

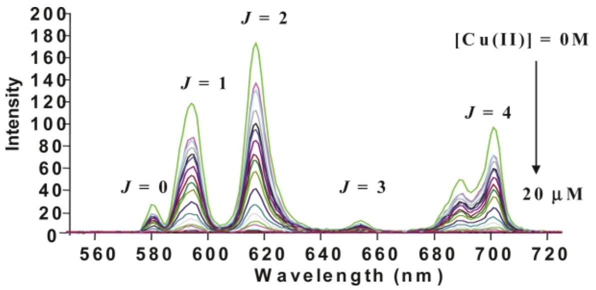

Fig. 1 The quenching of the Eu(III) emission of **1·Eu** upon titration with Cu(II) at pH 7.4. Excitation 266 nm.

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† Electronic supplementary information (ESI) available: experimental and spectroscopic data. See http://www.rsc.org/suppdata/cc/b3/b316176e/

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TMACl as well as in a simulated biological cationic background of 150 mM NaCl, 10 mM KCl, 5 mM $MgCl_2$, and 5 mM $CaCl_2$ at pH 7.4 (Fig. 2). As previously demonstrated the Eu(III) emission was always 'switched off' upon titration with Cu(II) in both media, and upon addition of EDTA it was switched back on. However, under these conditions the Cu(II) sensitivity was marginally increased. Similar results were observed for Co(II), but in high ionic strength the Co(II) sensitivity was substantially modulated and become similar to that of Cu(II) (ESI†).

The stoichiometry of the above interactions between Cu(II) and **1·Eu** was investigated using various methods. By plotting the emission changes as a function of equivalents of Cu(II), it became apparent that the emission was fully quenched after *ca.* 0.35 equivalents of Cu(II) (ESI) suggesting that Cu(II) was indeed coordinating to three **1·Eu** complexes. Cu(II) is known to be able to coordinate to *phen* in either 1 : 2 or 1 : 3 ratio, the latter being achieved by distorted octahedral geometry.[10] However, the most reliable proof for the stoichiometric ratio between Cu(II) and **1·Eu** was obtained from Job method analysis.[11] By plotting the changes in the Eu(III) emission (Fig. 3) against mole fraction, and analysing these changes using the equation: Ratio = $f_{extr}/(1 - f_{extr})$ (where f_{extr} is ([Cu]/[Cu]+[**1·Eu**]) when the Eu(III) emission is fully quenched (extreme)) we determined that the Ratio = 3. This suggests the formation of mixed 1 : 3 Cu(II) : Eu(III) supramolecular complexes in solution, as many isomeric 1 : 3 complexes are possible due to the asymmetry of **1·Eu** ligand. To the best of our knowledge, such mixed multinuclear macrocyclic transition–lanthanide ion complexes are not common, and have not previously been shown for cyclen based Cu(II)–Eu(III) macrocyclic *phen* ligands.[8] Furthermore, this supramolecular complex is reversibly formed as the addition of EDTA switches the Eu(III) emission back on, signifying its dissociation. In comparison, when the fluorescence emission spectra of *Acm-phen*[12] was monitored upon addition of Cu(II), the emission was *ca.* 90% quenched after *ca.* 0.5 equivalents of Cu(II), suggesting 1 : 2 complex formation.

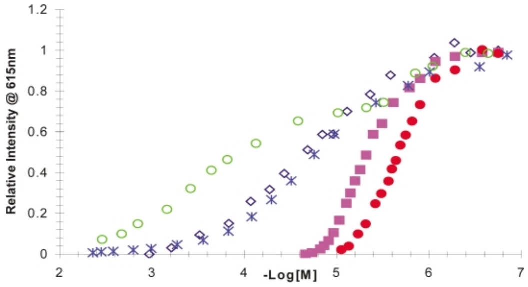

Fig. 2 The relative changes in the Eu(III) emission of **1·Eu** as function of various transition metal ions at J = 2 at 615 nm. All measured at pH 7.4 : pink ■ = Cu(II); blue * = Co(II); black ◇ = Fe(II); green ○ = Fe(III); red ● = Cu(II) in the presence of 150 mM NaCl, 10 mM KCl, 5 mM $MgCl_2$, and 5 mM $CaCl_2$.

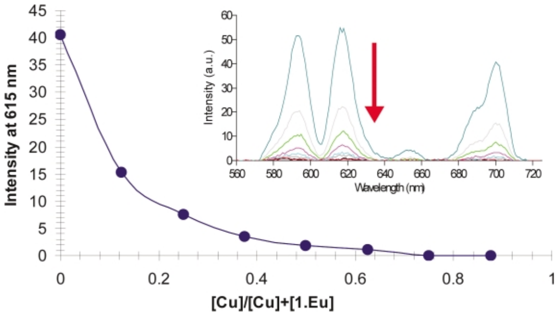

Fig. 3 Job plot analysis (intensity changes *vs.* molar fraction) for the changes in the Eu(III) emission at 700 nm at pH 7.4. $[\mathbf{1{\cdot}Eu}]_{initial}$ = 7.16 µM; $[\mathbf{1{\cdot}Eu}]_{final}$ 0.89 µM; $[Cu(II)]_{initial}$ = 0 M, $[Cu(II)]_{final}$ = 6.26 µM. Insert are the changes in the Eu(III) emission when recorded at this low concentration.

In summary we have developed a delayed lanthanide luminescent sensor for Cu(II), which shows good selectivity for Cu(II) over other ions such as Co(II), Fe(II) and Fe(III) at pH 7.4. Job method analysis of the Cu(II) recognition indicated the formation of a cationic (11+) tetranuclear mixed polymetallic macrocyclic supramolecular complexes in solution where the Cu(II) ion is coordinating to three **1·Eu** complexes. For all the cases, these supramolecular complexes were reversibly formed as the Eu(III) emission was reversibly 'switched on' upon addition of EDTA. We are currently investigating these systems in greater detail, as well as using other lanthanide ions.

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Notes and references

‡ The Eu(III) emission quenching can also been envisaged in the form of a truth-table where the Eu(III) emission change is the *output* and the *input* (A or B) are either H^+ (or OH^-) and Cu(II). This gives rise to the two ionic based logic-gate mimics A·B′ or A′·B (depending on the *input* order). This is the *inhibit* logic gate function, which is an extension of our mixed Tb(III) based *molecular-ionic* logic gate mimic described in reference 6 (*e*) and (*f*).

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