pH Dependent self-assembly of dimetallic lanthanide complexes†

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pH dependent self-association has been observed in a series of DO3A-derived lanthanide complexes bearing a carboxylate group that can act as a bridging ligand at high pH, switching on the luminescence from the lanthanide.

Luminescent lanthanide complexes have been widely applied in bioassay and imaging applications.[1,2] The luminescence from lanthanide ions is long-lived, allowing lanthanide-centred signals to be separated from fluorescent backgrounds. This is particularly important in biological applications. The study of lanthanide luminescence has tended to centre on the properties of europium and terbium complexes, though more recently, the properties of near-IR luminescent complexes have been exploited to broaden the range of potential sensitizers.[3–6]

There has also been considerable interest in the synthesis of polynuclear lanthanide complexes.[7–9] We recently reported the synthesis of a hetero-trinuclear lanthanide complex, and demonstrated that one lanthanide can be used to sensitise the luminescence of another in such a system.[10] This complex contains a series of covalently linked binding sites, and relatively complicated synthetic strategies are required to achieve differentiation between these sites. Our interest in the photophysical interactions between lanthanide ions led us to conclude that a coordination chemistry approach would provide the ideal tool to investigate such heteronuclear assemblies in solution: the flexibility of such an approach more than outweighs the fact that the kinetic stability of such systems is likely to be relatively low.

Heptadentate ligands derived from azamacrocycles exhibit interesting anion binding properties, with a range of ions of biological importance.[11–14] Such systems have also been shown to interact with aryl carboxylic acids. We now report the synthesis of the carboxybenzyl DO3A derivative (**1**). This is a ligand in which seven of the donor groups can chelate to a single metal centre, while the benzyl group bears a carboxylic acid which can act as a bridging group to a second metal centre. These molecules represent an important development in that they allow self-assembly processes to be used to study the properties of polynuclear lanthanide complexes. Furthermore, these systems show pH dependent self-association and thus have potential as pH sensors in which the spectrum, quantum yield and luminescence lifetime change as a result of self-assembly.

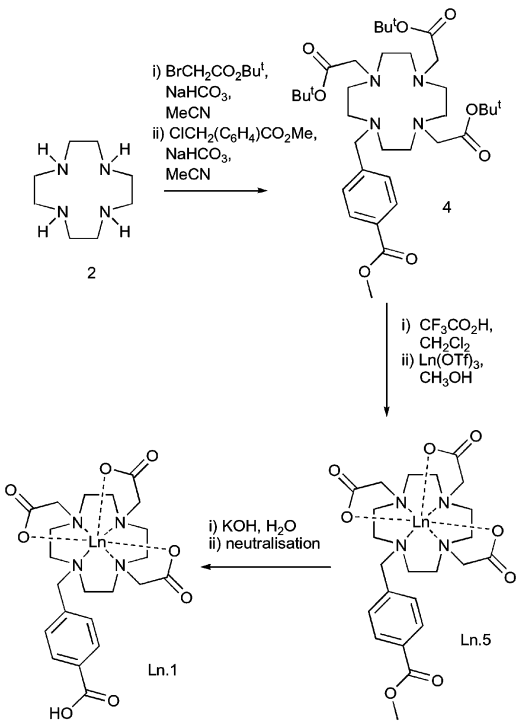
Ln.1 was synthesised using the procedures outlined in Scheme 1.‡ 1,4,7,10-tetraazacyclododecane (**2**) was treated with *tert*-butylbromoacetate, yielding the well-known *tert*-butyl ester of DO3A (**3**).[15] Reaction of this product with methyl 4-chloromethylbenzoate gave access to compound **4**. Cleavage of the *tert*-butyl esters was accomplished by treatment with trifluoroacetic acid in dichloromethane, yielding the monoester **5**. The terbium and europium complexes were prepared by reaction of **5** with the appropriate lanthanide trifluoromethanesulfonate. Hydrolysis in aqueous base and subsequent neutralisation unmasked carboxylate bearing complex, **Ln.1**.

Having prepared the complexes **Ln.1** and **Ln.5**, we then investigated their photophysical properties in isolation. All complexes gave line-like emission spectra characteristic of the lanthanide ions under study, while the benzoate group proved an effective sensitizer for lanthanide-centred emission. Luminescence lifetimes of the complexes in H_2O and D_2O are shown in Table 1. These can be used to calculate the numbers of bound solvent molecules around the metal centre using the equation

$$q = A_{Ln}(k_{H_2O} - k_{D_2O} - B)$$

where A_{Ln} and B are constants for a given lanthanide (1.2 ms and 0.25 ms^{-1} for Eu^{3+}, 5 ms and 0.06 ms^{-1} for Tb^{3+}), k_{H_2O} and k_{D_2O} are the observed rate constants for luminescence.[16]

Calculated values for q are also shown in Table 1. It may be seen that the values of q for **Ln.1** are significantly lower than those



Scheme 1 Synthesis of ligands and complexes.

† Electronic supplementary information (ESI) available: Fig. S1: Change of form and increase in intensity of the europium centred emission between pH 2 and 8. See http://www.rsc.org/suppdata/cc/b4/b412329h/

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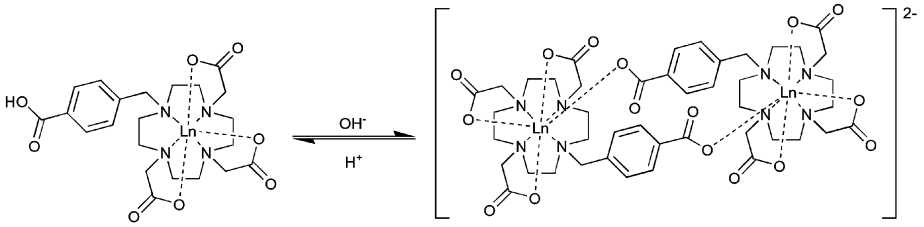

Scheme 2 pH Dependent self-association of **Ln.1**.

Table 1 Luminescence lifetimes and calculated inner sphere hydration numbers (q) for the complexes under study

Complex	λ_{ex}/nm	λ_{em}/nm	τ_{H_2O}/ms	τ_{D_2O}/ms	q	$\Phi_{H_2O}{}^{b}$ (%)
Eu.1 (pH 8)	274	616	0.53	1.26	1.0	7
Eu.1 (pH 2)	274	616	0.37	1.29	2.0	0.2
Tb.1 (pH 8)	274	545	1.73	2.73	0.8	64
Tb.1 (pH 2)	274	545	1.24	2.73	1.8	30
Eu.5 (pH 8)[a]	274	616	0.39	1.62	2.1	0.9
Tb.5 (pH 8)[a]	274	545	1.23	2.58	1.8	29

[a] Luminescence lifetimes and q values were constant across the pH range of these experiments. [b] Quantum yields were calculated relative to quinine sulfate. Errors are $\pm 10\%$.

observed for **Ln.5**. This may be rationalized on the basis that **Ln.5** has two water molecules bound at the metal centre; indeed, the q values obtained are consistent with those observed for other DO3A derivatives.

In the case of **Ln.1** the observed values of q are considerably lower at neutral and high pH, and are also pH dependent (Scheme 2). This can be explained by invoking self-association of the complex in solution. At neutral pH, the carboxylate group is deprotonated, and able to act as a ligand, displacing water from another lanthanide complex. By contrast, under acid conditions, the carboxylate is protonated, and the carboxylate group is unable to displace water from the metal centre. Such association is unlikely to occur in **Ln.5**, as the carboxymethyl group is a very poor ligand for lanthanide ions.

Fig. 1 shows time-gated luminescence spectra for the europium complex at low and high pH, and associated time resolved decays are shown in Fig. S1, ESI†. The differences are clear and dramatic. The emission at low pH is much less intense than that at high pH. This is probably a result of displacement of water from the metal centre, but there may also be a contribution from the coordination of a sensitising chromophore. Furthermore, it can be seen that the relative intensities of the peaks at 595 and 616 nm change with changing pH, indicating a change in local environment at the lanthanide centre (Fig. 1). Similar changes in the relative intensities of these peaks have been used by others as the basis of ratiometric probes for pH and p[HCO_3^-]:[17] such probes have the advantage that they can be used to determine pH without their concentration being known. This is also true in the case of **Ln.1**, and provides an additional check on the validity of such measurements.

Further evidence for our hypothesis is provided by the mass spectrum, which shows clear evidence for the existence of a peak corresponding to the dimer. ^{1}H NMR spectroscopy on the europium complex is also supportive of this hypothesis. In this case, a single species is observed at low pH. However, as the pH is raised, the spectrum becomes more complex, indicating the formation of a second species, likely to be the result of self-association.

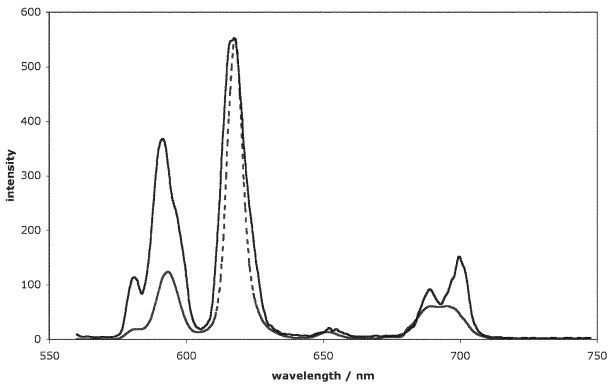

Fig. 1 Emission spectra at pH 2 (solid line) and pH 8 (dotted line), normalised at 616 nm to show the variation in the relative intensities of the emission lines at 595 and 616 nm.

Such self-association, and the concomitant change in luminescence lifetime (see Fig. S1, ESI†), potentially provides a means for monitoring pH. The luminescence at high pH is much more intense than at low pH, as well as being much longer lived, the variation in lifetime and intensity can potentially be used as a probe of pH. Further studies are ongoing to explore the possibilities of related gadolinium containing species as pH dependent contrast agents.

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Notes and references

‡ All compounds gave satisfactory analytical data: Selected data for **Eu.1**; m/z (MALDI) 669 (MK^+), 896 (MK_2(alpha)$^+$), 1259 ($2M^+$), 1297 ($2MK^+$), 1527 ($2MK_2$(alpha)$^+$): δ_H (pH 2) 16.83, 13.91, 10.52, 9.84, 9.49, 8.81, 7.61, 7.21, 3.88, 3.33, 3.10, 2.78, 2.16, 1.08, 0.95, −0.25, −5.78, −11.84, δ_H (pH 10) 8.01, 7.64, 6.91, 3.90, 3.3, 2.75, 0.9, −6.0, −10, −16, −20.

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