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Luminescent Eu(III) and Tb(III) Complexes: Developing Lanthanide Luminescent-Based Devices

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This mini review gives some highlights of the work recently carried out in our research group in Dublin on the developments of lanthanide luminescent devices, where the future goal is to produce devices that can operate as sensors. A few examples demonstrate our design principles for targeting both anion and cations that are of biological or pharmaceutical relevance, where the recognition occurs in aqueous competitive media. We also discuss the possibility of developing mixed f-d metal complexes and conjugates that can be employed as novel supramolecular architectures.

KEY WORDS: Lanthanide luminescence; Eu(III); Tb(III); sensing; recognition.

INTRODUCTION

The use of luminescent devices in the development of sensors has been a well-developed field of research [1,2]. Over the past 20 years there has been a myriad of examples in both cationic and anionic recognition systems, as well as examples for neutral molecules and biological entities such as DNA. To date some of the most successful systems have been those containing organic fluorophores. This has resulted in many commercial examples of medical diagnostic systems [3]. One example by He *et al*. is that of sodium and potassium sensors embedded upon a support structure and placed on a disposable cartridge for analysis of serum and blood samples [4]. Despite the success of such examples the use of these systems for *in vivo* applications is limited due to the inherent properties of fluorophores, i.e., their short emission lifetimes that must compete in biological media with naturally occurring fluorophore-containing entities. In recent times the long lifetime emissions possible from lanthanides has prompted a new emphasis on lanthanide-based emissions as part of optical sensing systems for *in vivo* applications [5]. Richardson [6] and Brittain [7] has shown this to be true using Tb(III) to probe the structure of proteins.

At first glance the use of lanthanides in solution for their photophysical properties may seem erroneous, as the f-f transitions are Laporte-forbidden and very weak, with extinction coefficients on the order of only 0.5–3 $dm^3\ mol^{-1}\ cm^{-1}$ [8]. This luminescence is only observed at high concentrations or when excited directly by lasers. This problem is nullified by using a process referred to as sensitisation which involves incorporating a sensitising chromophores, often termed as 'antenna' into the lanthanide-coordinating ligand, allowing indirect excitation of the lanthanide ion [9,10], usually through an intramolecular energy transfer process [11]. The process by which this photophysical emission is produced is illustrated in Figs. 1 and 2. This process is initiated by exciting the antenna chromophore (sensitiser, denoted Ar in Fig. 2) from the ground state, S_0, (Ar−Ln), to the singlet-excited state, S_1, (^{1}Ar−Ln). Formation of the triplet, T_1 state (^{3}Ar−Ln) by inter system crossing (ISC) allows for the potential excitation of the coordinated metal centre. This happens by way of an energy transfer from the excited T_1 state (^{3}Ar−Ln) of the antenna to the lanthanide excited state ($^5D_4$ and $^5D_0$ for Tb(III) and Eu(III), respectively) resulting in Ar−Ln* [12]. The process by which this energy transfer occurs has two proposed mechanisms (Dexter and Förster) [13,14].

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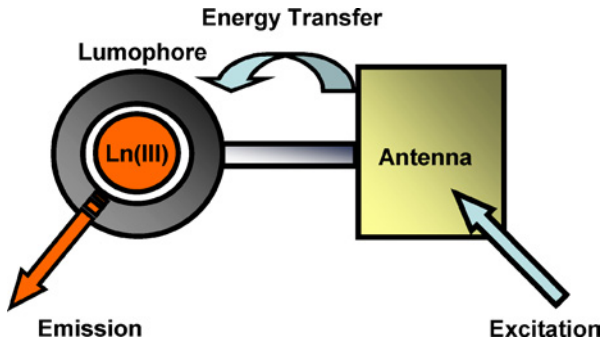


Fig. 1. Illustration of the sensitising process (antenna effect) in lanthanide complexes.

The formation of the lanthanide excited state (Ar—Ln*) is a reversible process that can result in the reformation of the antenna triplet excited state (^{3}Ar—Ln). It is also possible to quench this lanthanide excited state by vibrational quenching from energy-matched oscillators, ($k_{q'}$[XH]) such as OH, NH and CH [12]. In situations where the energy transfer is efficient in forming Ar—Ln*, a lanthanide emission can occur. Figure 2 shows that in the case of Tb(III) energy transfer occurs to the lowest excited state, $^5D_4$. The resulting emission involves transitions from this state. For Tb(III) these transitions are $^5D_4$–^7F_J, the most common of these transitions observed are those of $J = 6, 5, 4$ and 3. In Eu(III) where the transitions are $^5D_0$–^7F_J, and the most common of these transitions observed are those of $J = 0$, 1, 2, 3 and 4. Tb(III) and Eu(III) are the most commonly used lanthanides in sensor development as they emit in the visible spectrum.

There are a number of methods that can be used to produce lanthanide complexes that display photophysical changes in the presence of an analyte. Probably one of the most common methods is to develop lanthanide complexes with antenna into which a receptor has been synthetically engineered (Fig. 3).

The presence of the antenna/receptor allows for an analyte to be bound. Typically the binding event causes changes to the photophysical properties of the antenna/receptor. The changes in the photophysical properties of the antenna/receptor can be manifested in a number of ways. In some cases the binding event alters the T_1 state thus affecting the energy transfer rate and therefore the luminescence emission [15]. Other changes that can occur upon binding which result in the modulation of the lanthanide luminescence emission are the lifetimes of the emission and in some cases the chiral emission [16]. Other systems rely on the disturbance of inbuilt photo-induced electron transfer (PET) processes. In many examples such as that of cation sensing devices the binding of the cation results in the suppression of the inherent PET process resulting in the increase in the emission from the lanthanide. Any of these changes can be used to measure the presence of an analyte [17].

Our research group is interested in the use of lanthanides within supramolecular architectures as both potential sensing devices [18] and RNA cleavage agents [19]. In our exploits into the design of sensing systems we have concentrated on both designing anion [20] as well as cation [21,22] responsive devices. Both type of systems rely on the previously mentioned 'antenna effect' to modulate the emissions produced in a sensing event. However, to date both types of sensing have relied on different strategies to produce this desired effect. Herein we describe the developments and contributions of our

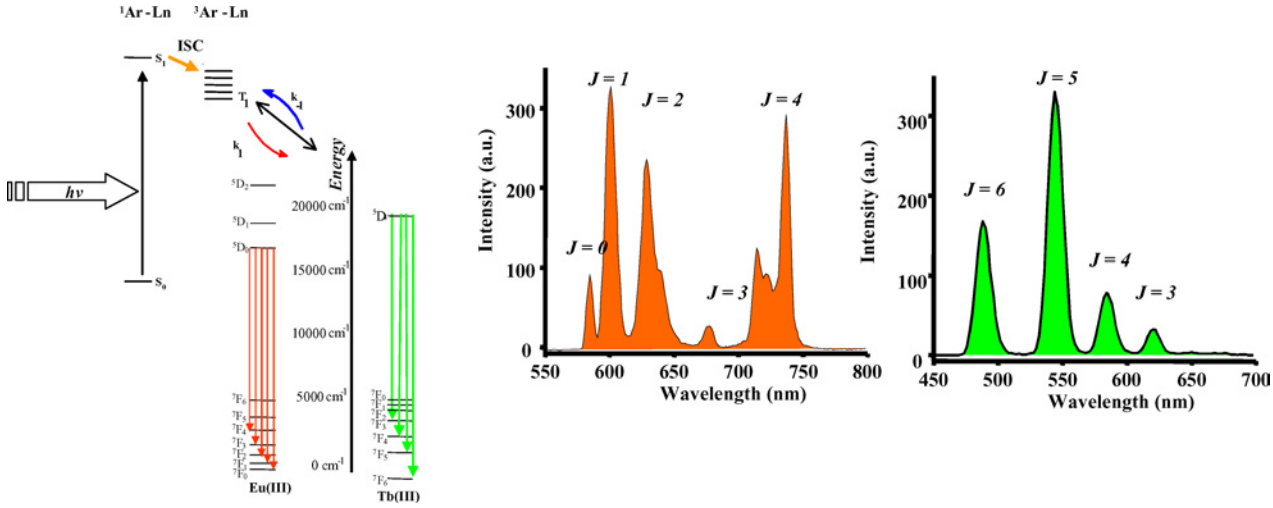


Fig. 2. Illustration of how a lanthanide luminescence emission is produced.

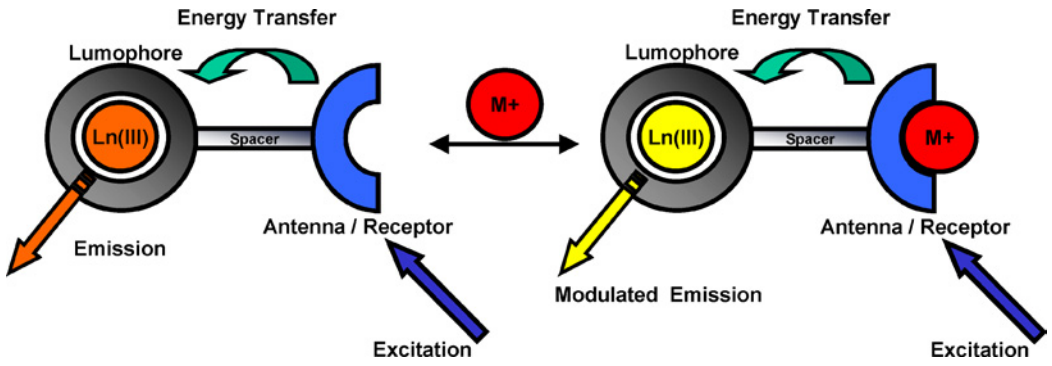


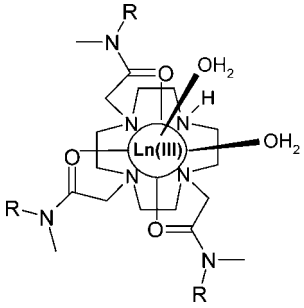
Fig. 3. Illustration of how to design a sensor based on 'antenna effect.'

research group to this field over the last few years. In all cases the design and operation of the examples presented will be discussed and when possible contrast and comparison to the contributions from other research groups to this exciting field will be mentioned.

ANION SENSING USING LANTHANIDE LUMINESCENCE

The concept of using lanthanide complexes as luminescent sensing devices has been an area of active development over the last few years. In the development of complexes as anion sensors the strategy has been to create complexes, which are coordinately unsaturated within the coordinating ligand [23]. The uncoordinated sites are usually taken up by labile ligands such as solvent molecules. The fact that they are labile allows for their displacement in the presence of competing anions. In situations were a complex is luminescent due to the incorporation of an antenna, the displacement of the deactivating solvent ligands usually results in a modulation of the emission. This modulation quite commonly results in an increase in the luminescent emission intensity due to the displacement of the deactivating ligands, e.g., OH oscillators of water ligands, (and/or an increase in the lifetime emission). Examples of such devices have been reported where selectivity to anions such as Cl^- [24], NO_3^- [24,25] and HCO_3^- [26] are possible. Using this concept we have designed complexes, which are unsaturated and contain no antenna. (Fig. 4) It is well known that complexes such as these bind carboxylate anions as previously demonstrated by Parker *et al*. [26] Our contribution to this area was to produce ternary complexes with a resulting luminescent emission as an indicator of the event.

As these complexes were purposely designed without an incorporated antenna, any sensitisation would have to be caused by the binding analyte. The use of carboxylates containing aromatic residues can result in luminescence due to the sensitisation process brought about by exciting this close proximity coordinated anion/antenna, provided of course that the antenna has a sufficiently high T_1 state to allow sensitisation. Fortunately there are many examples of such ligands with sufficiently high T_1 states [27].



Eu.1: R = CH_3, Ln(III) = Eu(III)
Tb.1: R = CH_3, Ln(III) = Tb(III)
Eu.2: R = H, Ln(III) = Eu(III)
Tb.2: R = H, Ln(III) = Tb(III)

The formation of these complexes began with the development of an efficient synthetic method for **1** and **2** [28]. Both of these ligands comprise of a cyclen framework to which three of the four nitrogens are functionalised with alkyl amide substituents. This afforded ligands that have heptadentate coordination potential. In both cases, after much experimentation it was found that a one step reaction followed by precipitation in the case of **2** or alumina column chromatography in the case of **1** resulted in yields of *ca*. 55% on scales as large as 10 g. Quantitative yields of the subsequent Eu(III) and Tb(III) complexes resulted from refluxing **1** or **2** with the appropriate lanthanide salt in acetonitrile. In all of these complexes the presence of the two metal bound water molecules for the Tb(III) and Eu(III) complexes were confirmed by lifetime measurements of the $^5D_4$ and $^5D_0$ excited states, respectively, as well as by X-ray crystallography. Determination of the metal bound water molecules was determined from *q*-value analysis using the equations of Horrocks *et al*.

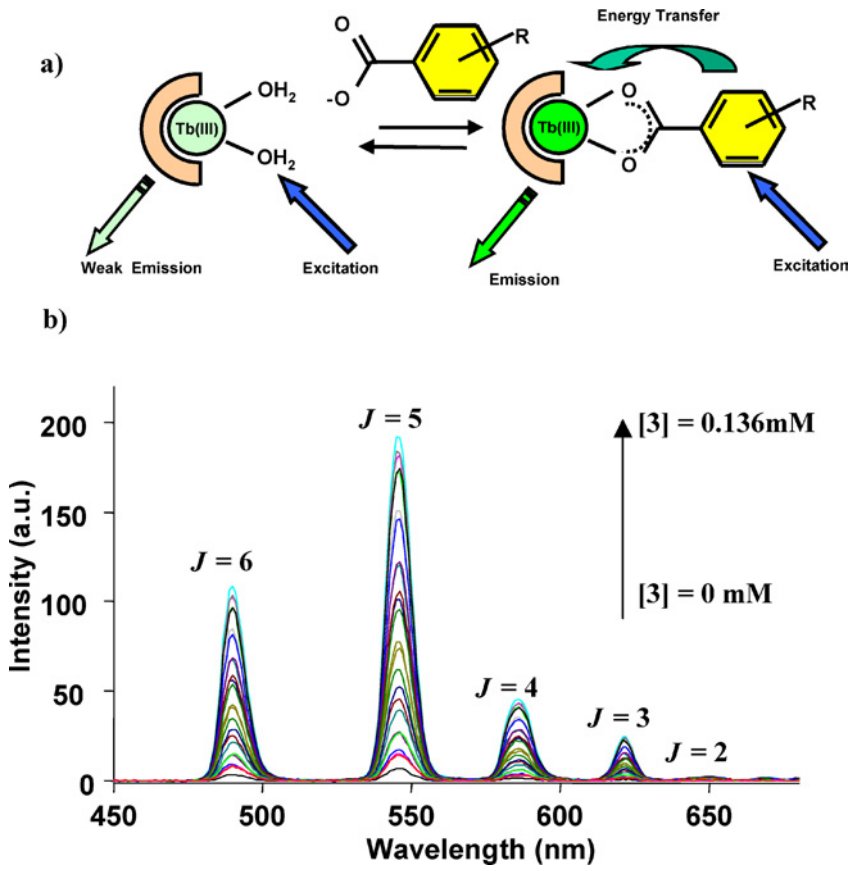


Fig. 4. (a) Illustration of how to sense for aromatic carboxylates based on 'antenna effect.' (b) The changes in the Tb(III) emission upon addition of 3.

[29] (q = number of bound water molecules). These complexes were all shown to be stable in solution over long periods of time.

Initial studies on all of these complexes with *p*-Dimethyl Amino Benzoic Acid (DMABA) (**3**) an antenna capable of sensitising both Eu(III) and Tb(III) showed that the formation of luminescent lanthanide complexes was only possible with the Tb(III) complexes. Luminescent enhancements of up to 680 fold were observed for **Tb.1** with **3**. The formation of this ternary luminescent lanthanide complex was confirmed by analysis of the lifetimes of all these complexes in the presence of **3**, which showed that the water molecules were displaced, as shown by the q value changing from 2 to 0. Binding was observed to be strong with Log K_a values of *ca.* 5.0. The emission of the Eu(III) complexes was not modulated in either water or buffered solutions at pH 7.4. Lifetime analysis of these complexes showed that the metal bound water molecules had not been displaced, therefore the formation of the ternary complex and the concomitant modulation of the lanthanide emission was not possible. This inability to form ternary complexes with Eu(III) complexes and **3** was unexpected and in the last year the ability to form ternary complexes between aromatic carboxylates and azacrown based Eu(III) complexes has been demonstrated by Magennis *et al.* [30] The difference in these type of complexes compared to that of **Eu.1–2** was the overall charge of the complexes.

The most important result from this investigation was that both **Tb.1** and **Tb.2** could selectively detect salicylic acid (**4**) while Aspirin (**5**) was not detected at pH 7.4 in the presence of a high ionic strength of tetra methyl ammonium chloride (TMACl). [28(b-c)] In both cases the formation of these ternary complexes were reported to have bound strongly with Log K_a values of 4.5. Coincidentally at the same time Li and Wong [31] showed similar results were possible using (overall neutral charged) Eu(III) and Tb(III) complexes of a cyclam derived ligand that contained monoaza-15-crown-5 ether or 15-crown-5 ether moieties conjugated *via* a short alkyl or ether spacer. The rational for these aza crown and crown appendages was to aid binding of carboxylic acids, in this particular case benzoic acid. Further reports on cyclen derivatives with salicylic acid, **4** [32] confirmed that these appendages

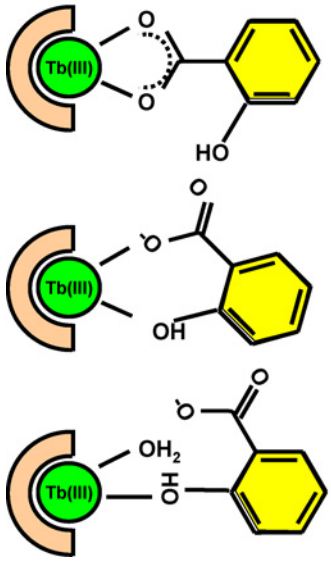
did actually improve binding (Log $K_a = 3.9$) when compared to test model complexes. In a direct comparison with our examples under the same experimental conditions it is interesting to note that the complexes **Tb.1** and **Tb.2** showed higher binding with salicylic acid (Log $K_a = 4.5$) than the complex above suggesting that the effect of using a charged complex has more effect on binding than the use of cooperating appendages.

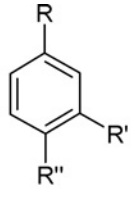
As part of this work we looked at many possible antennae and found that a number of aromatic carboxylates and some esters could produce the same effect, with different degrees of luminescent enhancement. However, none of these test antennae are found naturally *in vivo* or are administered in any know pharmaceutical products therefore the potential for selective sensing of salicylic acid over all of these aromatic carboxylates on biological samples is still valid. Of more interest to us is that of all the test ligands used some were unable to coordinate through the carboxyl functionality as they had been blocked and yet the formation of luminescent ternary complexes was still possible. In all cases 1:1 binding was shown. The results for **6**, **7** and **8** indicate that this binding process can be achieved through other modes as postulated in Fig. 5 for Tb(III) with salicylic acid. Experiments to determine the exact mode of binding were attempted but to date have been unsuccessful.

In our example above and the work of other groups referred to within it is obvious that the design of lanthanide-based sensors which can operate in aqueous solution is achievable, a feat that is not very common to organic fluorophore systems, which usually operate, in non aqueous media. We have also highlighted briefly how changing the charge on these type of complexes can alter binding ability as well as by the addition of appendages such as aza crowns. However, these type of systems are still limited in terms of how selectivity can be tuned into them to make them specific to one analyte anion. It is possible that such systems can be modified in terms of the open faced cleft to be made more complimentary to a specific analyte. A more likely development route for anion sensing with lanthanide complexes would probably be the use of covalently attached antennae/receptor appendages with more conventionally synthesised receptor modules. At present within our group the development of such systems is underway. In our first unpublished example we use a cyclen-based complex to which an aromatic urea functionalised receptor acts as an antenna/receptor. We have been able to show selectivity towards acetate with such systems in DMSO with large orders of magnitude enhancement [33].

CATION SENSING USING LANTHANIDE LUMINESCENCE

The above examples describe the simplest method by which lanthanide luminescent sensing of analyte species can be achieved. In most of these type systems synthesis was achieved with ease. The development of lanthanide complexes that can be used for cation sensing has typically been shown to be more complicated, often requiring elaborate synthesis especially in the case





3: R = NMe_2, R' = H, R = COOH

4: R = H, R' = OH, R = COOH

5: R = H, R' = OAc, R = COOH

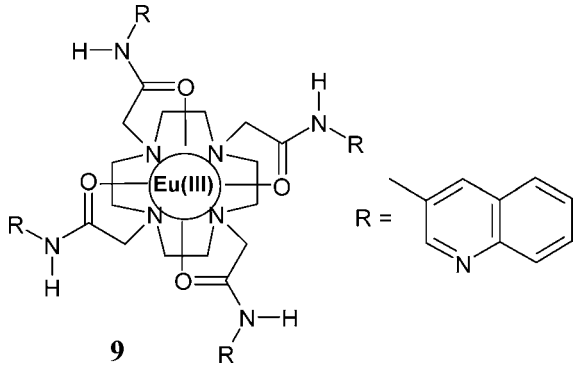
6: R = H, R' = OH, R = COOEt

7: R = H, R' = OMe, R = COOEt

8: R = H, R' = OMe, R = COOH

Fig. 5. Illustration of possible binding modes for salicylic acid with Tb(III) metal centre.

of metal cation sensing. The typical ideology for cation sensing is to develop lanthanide complexes that contain antenna/receptors as part of the overall complex as mentioned previously and illustrated in Fig. 3. Modulation of the luminescent properties of the complex can occur upon the binding/recognition event. For this category of sensor we begin with the simplest (with respect to synthesis) form possible; a proton sensor **9** [34] is an example of a tetra substituted cyclen ligand with four quinoline receptor moieties, capable of sensing protons.



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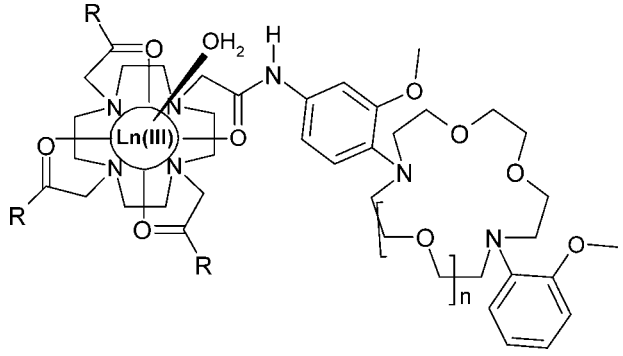
The cyclen ligand is once again used as the basic scaffold for the coordinating ligand. The ability to further functionalise this macrocycle with additional coordinating groups as well as antenna make it a very useful system for such designs. Due to the synthetic simplicity involved in this design it should be no surprise that this is just one of many examples of such complexes that have been reported as pH sensing devices [35]. The major differences in all these examples is the use of different antenna/receptor appendages. Differences in the pK_a of the antenna/receptor proton-binding site have resulted in complexes with different pH response ranges.

In **Eu.9** the lanthanide emission was found to be 'switched on' in highly acidic conditions, with a luminescent enhancement of over 300 fold. A bell shaped pH profile was found to exist from pH 1.8 to pH 3.5. Luminescent enhancement was attributed to an enhancement in the population of the S_1 and subsequent T_1 excited state of the quinoline chromophore when in acidic media. Of most interest are the response at very low pH and its subsequent stability in such environments. This was the first example of such pH sensor type complexes reported with these properties.

The Tb(III) and Eu(III) complexes of **10–13** represent the first examples of lanthanide complexes that show a luminescence emission modulation in the presence of group I cations in buffered aqueous solutions [36]. Our initial goal was the development of complexes that could sense cellular levels of Na^+ and K^+ under physiological type conditions. This goal is driven by the need to be able to determine the levels of such ions in many biological processes in which Na^+ and K^+ are involved such as nutrient uptake, regulation of intracellular ions and the transmission of electrical impulses [37]. Previously, in collaboration with David Parker in Durham University, England, we reported similar systems for sensing Zn(II) using London type antenna/receptors, however, the degree of modulation was rather small [38]. In our present examples we again opted for a cyclen-based ligand. As before the cyclen was used as the basic scaffold to which three coordinating arms were attached to allow for coordination of a lanthanide ion. The fourth position had a diaza crown (18-crown-6 or 15-crown-5) attached that functioned as an antenna/receptor. The covalent attachment to the cyclen scaffold was through an alkyl amide appendage that allows for an eight coordinate complex. The synthesis of these ligands was long requiring up to 15 steps to produce the final products. The antenna/receptor contains two aromatic systems as part of the design but only the aromatic moiety closest to the coordinating lanthanide was expected to be near enough to allow sensitisation to occur. The inclusion of this second aromatic system into this design was to allow for later synthetic modification that could result in covalent attachment to a solid support, a future goal of our research group. In all cases the complexes were shown to be kinetically stable in solution over long periods of time.



10: R= NMe_2, n=1, Ln(III) = Eu(III) or Tb(III)
11: R= NMe_2, n=2, Ln(III) = Eu(III) or Tb(III)
12: R= OH, n=1, Ln(III) = Tb(III)
13: R= OH, n=2, Ln(III) = Tb(III)

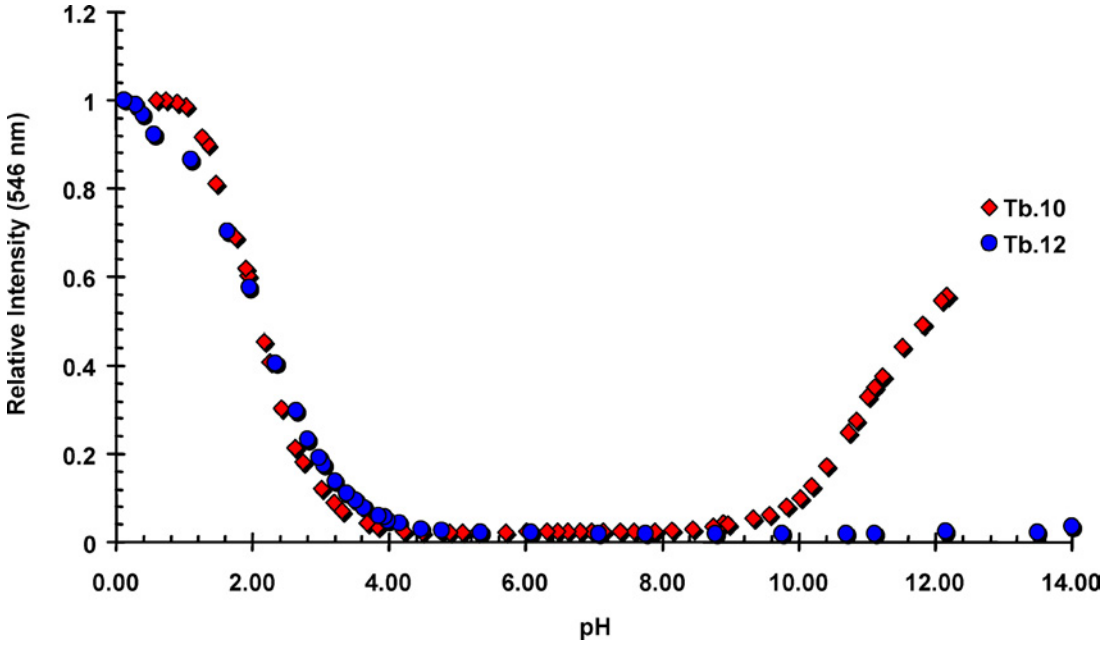


Fig. 6. Comparison of pH response of **Tb.10** and **Tb.12**.

Initial studies on these complexes involved monitoring their behaviour in solution with respect to pH, which resulted in unexpected behaviour in terms of the lanthanide luminescence emission. A number of observations were made from the studies on these complexes. Firstly, the Eu(III) complexes were found to be non-emissive irrespective of pH conditions which was attributed to an inherent deactivation process in the complex. Secondly, the luminescent emission of the Tb(III) complexes were found to be modulated by changes in pH resulting in changes of large orders of magnitude. For all the Tb(III) complexes at low pH when the aza crown nitrogen closest to the lanthanide centre was protonated the luminescence was 'switched on' in some cases with up to 20 fold enhancement. From lifetime studies it was shown that upon protonation on the antenna/receptor the emission lifetimes increased by up to 716% (from 0.18 to 1.29 ms in the case of **Tb.10**) indicating that the protonation event results in a more efficient sensitisation process, perhaps by the elimination of PET quenching from the antenna/receptor nitrogen lone pairs. The pK_a of these complexes were all similar at *ca.* 1.8, which was extremely low, as the free aza crown receptors have been shown to have pK_a of *ca.* 5. [18(d)] This low pK_a was attributed to an inductive effect from the close proximity of the antenna/receptor to the 3^+ charged lanthanide centre. Above pH 4 these complexes were all 'switched off' (Fig. 6) and were independent of changes in luminescence with respect to pH at higher pH values. A further unexpected observation (Fig. 6) in these preliminary studies was that in the case of the neutral complexes this pH independence remained at pH 10–12, however, in the case of the charged complexes the emission was again 'switched on.' This 'switching on' at high pH was attributed to the deprotonation of the amide of the antenna with pK_a of *ca.* 10.8 being determined. Similarly, increases in the Tb(III) emission lifetimes were observed (from 0.16 to 1.06 ms in the case of **Tb.10**). As the neutral complexes also contained the same antenna/receptor modules covalently attached through the same alkyl amide it was expected that the pH response at high pH would be the same. Analysis of the *q*-values and as such the coordination environment of the complexes gave rise to the notion that there maybe some dramatic changes in the coordination environment of these complexes. This phenomenon is not clearly understood and is being studied in greater detail within our group using control model complexes.

The most significant fact to be taken from these pH studies is that all these complexes showed no luminescence at neutral pH, therefore in the presence of metal cations in neutral pH solutions any modulation of the emission could be associated with metal binding and not protonation.

At pH 7.4 in buffered solutions of high ionic strength it was shown that this modulation could again be produced in the presence of group I cations such as Na^+ and K^+. Again substantial enhancements in the emission intensity were observed as well as large increases in lifetime

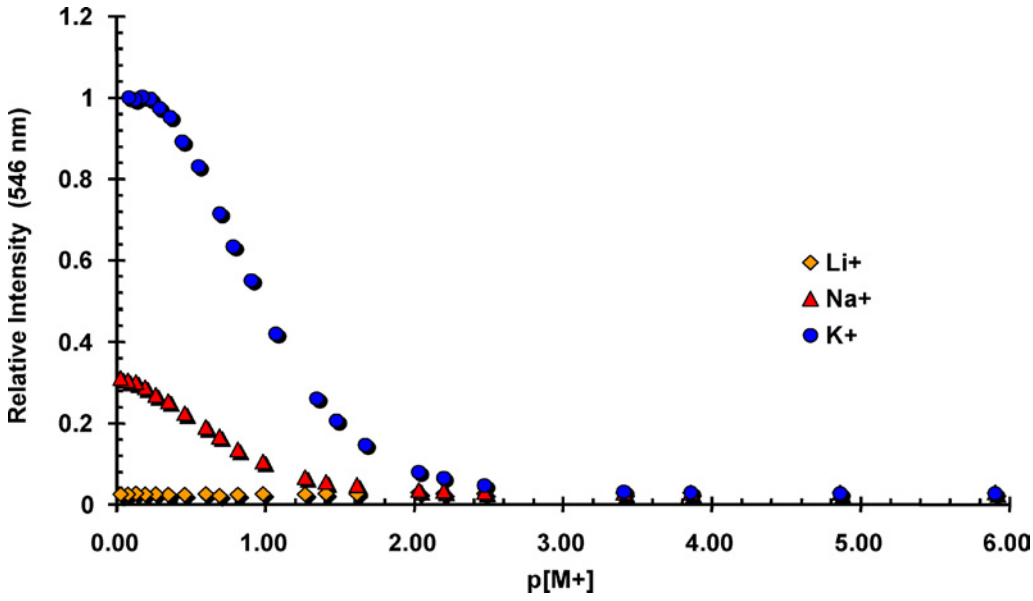


Fig. 7. Comparison of response of **Tb.13** to Group I cations showing selectivity for K^+.

emissions suggesting that the binding of group I cations induces the same physical changes on the properties of the antenna/receptor as that caused by protonation. In all cases the expected selectivity of the 15-crown-5 for Na^+ and 18-crown-6 for K^+ was demonstrated (Fig. 7). A major drawback to this design was that the concentration range in which this luminescence enhancement was observed was too high for particle biological application. The receptors contained in these designs have been seen in different forms previously reported and have been shown to bind group I cations in the mM concentration range. A similar result was expected here, however, this weaker binding was as a consequence of the previously observed inductive effect from the Tb(III) centre.

Nevertheless these examples serve to show **10–13** as examples of ligands that can be used to produce stable water soluble lanthanide complexes that can work under near physiological conditions and selectively sense either Na^+ or K^+ with large orders of enhancement in the luminescence emission intensity. We are currently reengineering these type of systems to respond to group I cations at concentration levels in the millimolar concentration range that can be attached to solid supports as our contribution to the next generation of lanthanide luminescent sensing devices.

In our final example we present the Eu(III) complex of **14** [39,40], which was designed to function as a sensor for Cu(II) under simulated physiological conditions. Furthermore, by incorporating a second metal ion binding site into our structures we opened up the avenue of making mixed f-d metal conjugates and hence novel supramolecular structures. This work is currently being undertaken in our laboratory.

The importance of Cu(II) in physiological processes is well known with respect to such conditions as Menkes disease (an often fatal condition in young boys resulting from the irregular metabolism of copper.). The structure of **14** is related closely to the design used in **10–13** except of course in this example the antenna/receptor has been replaced with a phenanthroline derivative. Phenanthroline is well documented as a ligand capable of coordinating Cu(II) and it also has a triplet energy sufficient to sensitise Eu(III) [27]. In this particular ligand the advantage of a commercially available receptor resulted in a short efficient synthesis. As with all the previous examples this Eu(III) complex was found to be stable in aqueous solution. The pH dependence with respect to the Eu(III) emission intensity was found to be the inverse of our previous examples. In this case (Fig. 8) it was found that the luminescence was 'switched on' between pH 4–7 and 'switched off' above and below this range. 'Switching off' below pH 4.5 was due to protonation of the phenanthroline moiety, while 'switching off' above pH 7 was attributed to deprotonation of the amide functionality. *pKa*'s of 3.8 and 8.1 were determined, respectively. In both situations, deprotonation and protonation resulted in a reduction of the ligand fluorescence which therefore reduces the possibility of forming the T_1 state necessary to sensitise the Eu(III) metal centre.

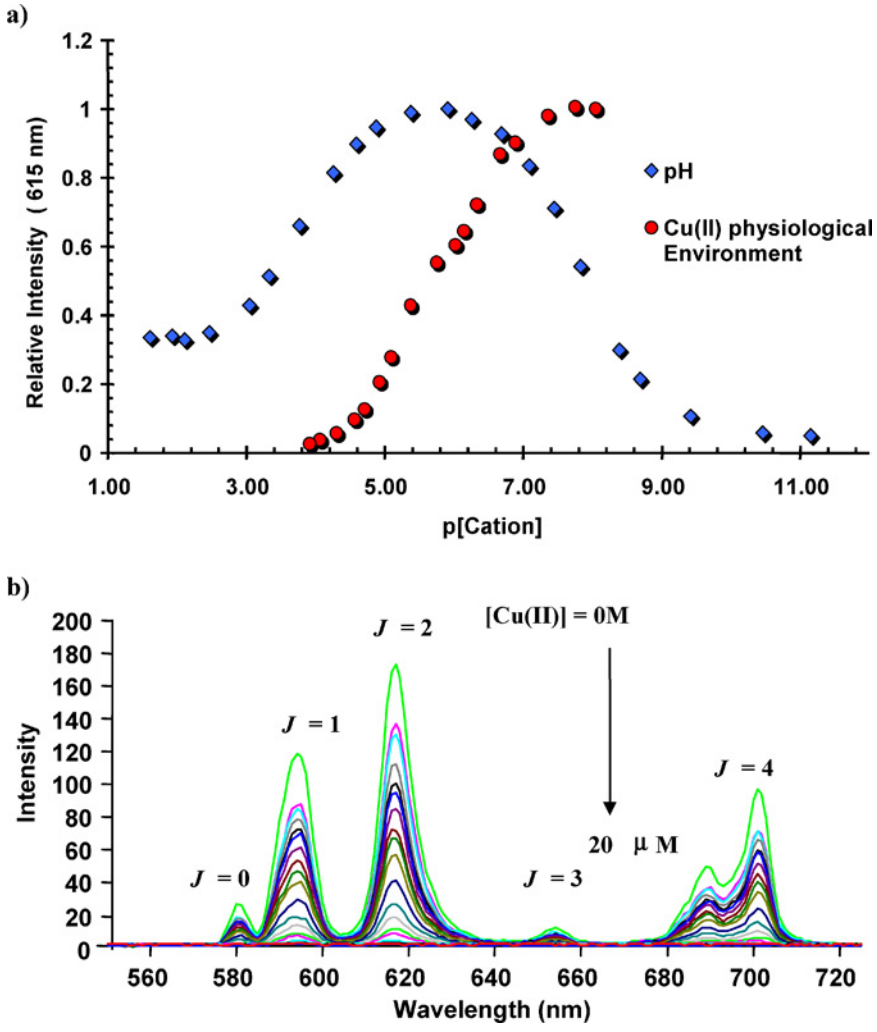
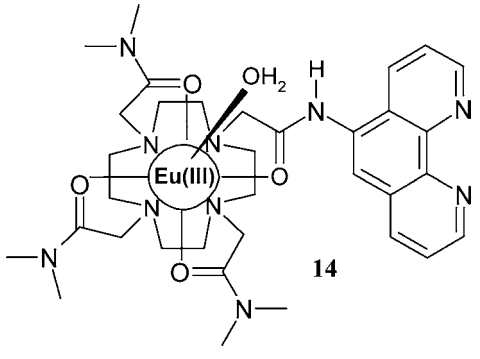


Fig. 8. (a) Comparison of response of **Eu.14** to H^+ and Cu(II). (b) The changes in the Eu(III) emission upon titration with Cu(II).



In further studies at pH 7.4 it was found that this Eu(III) complex could have its luminescent emission fully quenched in the presence of Cu(II), Fe(II), Fe(III) and Co(II). However, the sensing event for Cu(II) occurs in the concentration range 0–20 μM, (Fig. 8a), where the Eu(III) emission was 'switched off' (Fig. 8b) whereas for all the other cations the operating concentration range is higher in the mM range. This ability to preferentially sense Cu(II) over other transition cations is highly desirable for use as a diagnostic device for *in vivo* applications as biological Cu(II) levels coincidently lie in this range.

This system is still of great interest to us as we have not yet fully ascertained the mode of binding. Our most recent Job plot analysis suggests a 2:1 binding event occurs. The fact that this system can determine Cu(II) at physiological levels gives potential to develop this complex for *in vivo* applications. However, the implementation of this exact system for *in vivo* applications is not foreseen as the excitation wavelength of 278 nm is too short for practical applications. Instead we are currently developing a

new generation of complex that can operate in the same concentration range with the same specificity but with an excitation wavelength $\geq$300 nm.

Analysis of the above systems have shown that we can now make mixed f-d complexes and that we can employ the changes in the lanthanide luminescence to determine structural feature of the resulting architectures. This is now one of our fast growing areas of research.

CONCLUSIONS: THE FUTURE

The few examples we have described herein represent merely the tip of the iceberg in terms of the research carried out in this field with more and more examples being reported. The results as we see them suggest that the use of lanthanide luminescence in future sensing devices has a bright future. We envisage that the future developments in this field will be the development of sensing devices that can operate *in vivo* as well as systems that can be attached to solid supports for use in other diagnostic systems such as lab on a chip technology. Both of these developments are current goals within our research group. We have also demonstrated that the lanthanide complexes can be modified to allow for their use as 'structural' diagnostic tools, where the changes in the lanthanide emission can be used as indicator for determining larger supramolecular architectures in solution.

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