# Responsive lanthanide luminescent cyclen complexes: from switching/sensing to supramolecular architectures

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This article highlights some of the recent developments in the use of responsive cyclen based lanthanide luminescent devices, focusing on Eu(III), Tb(III), Nd(III) and Yb(III) complexes, where the photophysical properties, such as the excited state lifetimes, quantum yield/intensity and emission polarisation are modulated by the local chemical environment, *e.g.* ions and molecules, or through self-assembly of either f–f or mixed f–d cyclen complexes.

## Introduction

The coordination chemistry of lanthanide ions in aqueous solution is particularly exciting and of great current interest.[1,2] The lanthanide ions have found use in many areas of research, and over the last few decades these ions have been employed in synthesis,[3,4] coordination chemistry,[5,6] material chemistry and crystal engineering.[7] However, they have possibly found their greatest success in diagnostic medicine,[6] due to the development of magnetic resonance imaging (MRI) and the resulting exploitation of Gd(III) complexes, and more recently Yb(III) complexes, as paramagnetic MRI contrast agents.[1,6–8] Other applications include the use of Sm(III) and Yb(III) as catalysts for many chemical transformations[9,10] and La(III), Ce(III)/Ce(IV) and even Eu(III) as ribonuclease or ribozyme[11] mimics, that promote hydrolytic[12] or oxidative cleavage[13] of phosphodiester bonds (*e.g.* in RNA and DNA).[14] Moreover, polypeptides incorporating Tb(III) ion binding sites have recently been synthesised for both structural analysis[15] and as potential therapeutics,[16,17] whereas late lanthanide ions, such as Lu(III), have been used in cancer therapeutics.[18] These ions are therefore of great value as novel therapeutics and in biotechnology. The unique photophysical properties of ions such as Eu(III) and Tb(III), *etc.* have also been known for some time,[19] particularly in laser chemistry, but more recently these same ions have found their use in the development of novel biological probes,[20–22] as material for liquid crystals displays,[23] in light harvesting dendritic structures[24] and in photoactive polymers.[25] From this short account it is obvious that the lanthanide ions have not just an 'exciting',[1–2] but also a very 'bright' future!

The lanthanide ions have high coordination requirements, ranging from 9–12,[1,26] which for a long time was difficult to fulfil using single ligands.[27] However, with the birth of macrocyclic and supramolecular chemistry, more specifically targeted macrocyclic (as well as acyclic) ligands emerged that could, to a great extent, fulfil these high coordination requirements.[28] This coincided with the interest in exploring the photophysical[29] and the chemical properties of the lanthanide ions in greater detail for diagnostic purposes.[30] This work revealed many of the unique properties that lanthanide luminescence has to offer, such as long wavelength emissions (Fig. 1) and relatively long lived excited states in solution (see later).[1,2,19,22,31–34,45] However, as the emission occurs from symmetry forbidden excited states, it was also found that many lanthanide complexes were only weakly emissive and therefore of limited use. However, from this kind of work several luminescent assays like DELFIA,

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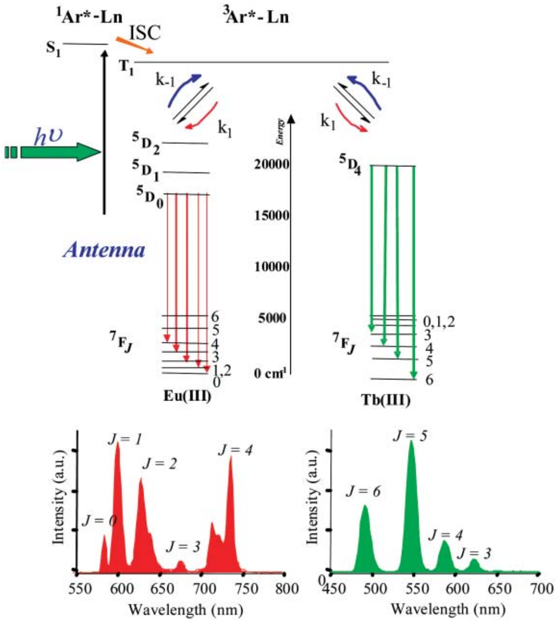


**Fig. 1** The deactivation of the $^5D_0 \rightarrow {}^4F_J$ and $^5D_4 \rightarrow {}^4F_J$ (left) transitions, after sensitized excitation from an antenna, gives rise to line-like emission bands occurring at long wavelengths; in the red for the Eu(III) and green for the Tb(III) emission.

CYBERFLUOR and DEFRET were eventually developed, clearing the way for future exploitations and developments of other new roles that these ions could take part in.[21]

Our own interest in the chemistry of the lanthanide ions has been mainly focused on developing ribonuclease mimics[36] and responsive luminescent devices. This article deals with the latter, and in particular with the development of kinetically and thermodynamically stable complexes based on the cyclen (1,4,7,10-tetraazacyclododecane) macrocyclic structure.[1,2] These complexes have been designed so that the aforementioned photophysical properties can be modulated by the local environment, or 'external' perturbation in the form of recognition of ions and molecules. This has yielded luminescent switches and sensors.[37,38] More recently, we have also become interested in using lanthanide ions to probe the generation of larger supramolecular structures and we will discuss some of the work carried out in this area.

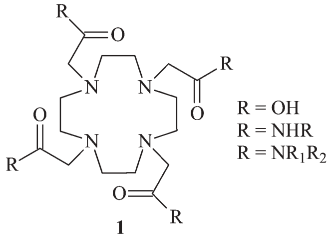
This article will begin with a brief introduction to some of the previously mentioned luminescence properties of the lanthanide ions, followed by the discussion of some of the design principles that we and others have employed in developing responsive lanthanide luminescent complexes, and finally selected examples of those developed to date. This article is not meant to be a comprehensive listing of all such devices, rather to give the reader some flavour of the field, and in particular the work carried out in our own laboratory in Dublin.

## Some properties/drawbacks of lanthanide luminescence

All the luminescent lanthanide ions have a partially filled 4f shell and the metal centred emission from the excited state, is $^5D_0$ ($E$ = 17 200 cm$^{-1}$), $^5D_4$ ($E$ = 20 500 cm$^{-1}$) and $^4F_{4/3}$ (10 200 cm$^{-1}$) for Eu(III), Tb(III) and Nd(III) respectively, is line-like due to the deactivation of the excited state to the ground states. These are the $^5D_0 \rightarrow {}^7F_J$ ($J$ = 0–6) and $^5D_4 \rightarrow {}^7F_J$ ($J$ = 6–3) transitions for Eu(III) and Tb(III) (Fig. 1), respectively.[1,2,7,29–35] These occur at relatively long wavelengths, in the red and the green region of the electromagnetic spectrum respectively, whereas ions such as Nd(III) and Yb(III) emit in the near IR. The latter is highly desirable for *in vivo* applications, even though most current assays have focused on the use of either Tb(III) or Eu(III). The lanthanide ions also have excited state lifetimes that occur in the micro or sub-micro second range for Yb(III) and Nd(III), whereas for ions such as Eu(III), Tb(III) and Sm(III) these occur in the millisecond or sub-millisecond range. These lifetimes are significantly longer than those which most organic chromophores display, which usually emit their singlet excited state ($S_1$) lifetimes within *ca.* 10 ns. The lanthanide emission is thus often termed as being 'delayed luminescence'. As a result of these characteristics, the lanthanide emission should be easily distinguishable from fluorescence emission by simple time-gating, a feature that most of today's fluorimeters offer. These characteristics are thus of great value for probing biological environments (*in vivo*) as background emission or autofluorescence, and light scattering from the biological environment can be excluded, greatly enhancing the signal-to-noise ratio and hence the reliability of such detection/monitoring.[20,21,30] A drawback to their use *in vivo* is that the f–f transitions are Laport-forbidden and subsequently weak, with extinction coefficients of less than 4 M$^{-1}$ cm$^{-1}$. Direct excitation of the ions is thus not often feasible, except at very high concentrations or by using high powered light sources. These shortcomings can be overcome by populating the lanthanide excited state indirectly *via* sensitisation, using chromophores, or antenna, which transfer their excited state energies to the lanthanide excited state, Fig. 1. This transpires by either a Dexter or Förster energy transfer mechanism, where the energy of the $S_1$ is transferred *via* the $T_1$ of the antenna.[2]

This sensitisation process is highly feasible if the chromophore has a high extinction coefficient and efficient $S_1 \rightarrow T_1$ intersystem crossing (ISC) rates, and is close to the metal centre. However, it is limited by the energy of the antenna, which necessarily has to be higher than that of the lanthanide exited states, for the sensitisation processes to be thermodynamically favourable ($k_1$ in Fig. 1). Accordingly, this confines the choice of chromophores that can be used for populating the Eu(III) and Tb(III) excited states. Moreover, the rule of thumb is that the $T_1$ of the antenna should be above 22 000 cm$^{-1}$ (*i.e.* $E \sim$ 22 500 cm$^{-1}$ for Tb(III)) to prevent thermally competitive back energy transfer from the lanthanide excited state to $T_1$ of the antenna, where it can be quenched ($k_{-1}$ in Fig. 1). This allows a window of excitation ($\lambda_{ex}$) from *ca.* 300 to 400 nm, even though population of Eu(III) has been achieved up to *ca.* 430 nm. Due to these limitations, the use of the IR-emitting ions has become more attractive as their low excited state energy allows the use of a greater range of visible light absorbing antennae.[39] This method is still relatively new, is limited by the detection of the IR luminescence, which currently requires advanced instrumentation.

Having formed the desired excited states by the above sensitisation process, this is by no means the end of the story. These excited states are vulnerable to quenching, particularly due to their long lifetimes, by non-radiative vibration energy transfer processes caused mainly by an O–H oscillator, but also by N–H and even C–H oscillators. This is an obvious drawback to the use of such ions particularly in aqueous media. Nevertheless, this quenching pathway can be minimised by the use of highly coordinative donating ligands that exclude such non desirable oscillators. Tetra-substituted cyclen ligands, such as **1**,[1,2] that have coordinated carboxylates (DOTA), phosphinates and amide pendant arms, indeed provide such an ideal environment; **1** provides eight coordination donors, four provided by the macrocyclic amines and four by the pendent arms. The remaining coordination sites are, however, usually occupied by a solvent molecule, in most instances water, which can be an active quencher.



**1**

The effectiveness of the above quenching pathway is a direct function of the metal to water distance, falling off as a function of $r^{-6}$. Parker *et al.* have recently determined the likelihood of this quenching, and where shown that an O–H oscillator that is separated by 2.9 Å from the metal centre gives rise to almost complete quenching of the metal centred luminescence, whereas at a distance of 3.6 Å, the efficiency is significantly reduced to 25%.[1] The number of such metal bound or closely diffusing water molecules, *i.e.*, the hydration state ($q$), can vary, depending on several factors, but mainly ligand design. The way of estimating $q$ was first determined by Horrocks *et al.*[32,40] by measuring the excited state lifetimes of Eu(III) and Tb(III) in $H_2O$ and $D_2O$ respectively. This method was reviewed by Parker *et al.*[41] for Eu(III) and now takes into account the effect of exchangeable amide N–H oscillators ($x$ in eqn (1)). Eqns (1) and (2) are now commonly used for Eu and Tb respectively:

$$q_{\mathrm{Eu}} = 1.2[(1/\tau_{\mathrm{H2O}} - 1/\tau_{\mathrm{D2O}}) - 0.25 - 0.075x] \qquad (1)$$

$$q_{\mathrm{Tb}} = 5[(1/\tau_{\mathrm{H2O}} - 1/\tau_{\mathrm{D2O}}) - 0.06] \qquad (2)$$

In a similar way, Parker *et al.* and Faulkner *et al.* have developed identical methods for determining $q$-values for the near IR emitting Nd(III) and Yb(III) ions.[42]

The geometry of such cyclen complexes has also been investigated in great detail, in both solution and solid state.[1–3,7] For Eu(III) and Tb(III) based cyclen ligands, which have eight donors *e.g.* **1**, $q$ is usually found to be *ca.* 1, and hence the overall geometry of such tetra-substituted, nine coordinated cyclen complexes (in either solution or solid state) is usually found to be either (twisted) square antiprism or (distorted) tricapped triagonal prism. For these, the 'quenching' metal bound water molecule is usually found to be in the axial position.[1–3,7]

This short summary gives an insight into some of the photophysical aspects and the geometry of typical cyclen based eight coordinated lanthanide complexes. The next section will discuss some of the ways these properties can be manipulated, by design, to yield responsive lanthanide luminescence complexes.

## Design principles of responsive lanthanide luminescent complexes

From the above account, it becomes apparent that in designing luminescent lanthanide complexes several minimal requirements have to be fulfilled, such as: (i) the coordination environment should be $q \sim 0$ to ensure high quantum yields and (ii) the sensitising antenna(e) should be close to the lanthanide ion centre, *e.g.* covalently attached to the coordinating ligand, to ensure fast and efficient energy transfer (Fig. 2a). The choice of antenna should also fulfil the criteria discussed above, and the ligands should complex the ion tightly to yield kinetically and thermodynamically stable complexes. This final condition is important when considering *in vivo* applications to reduce toxicity as the ions can displace Ca(II) in proteins, as well as forming hydroxides that precipitate from water.[7]

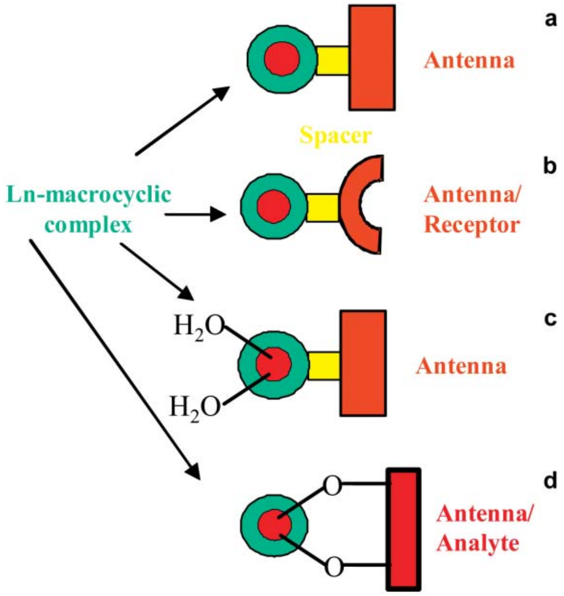


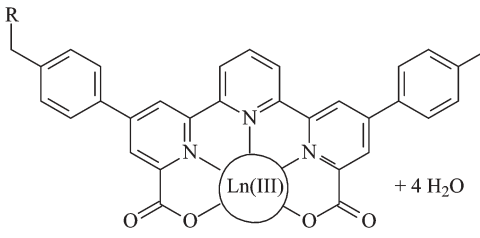
**Fig. 2** Cartoon description of: (a) Ln-complex-spacer-antenna model, showing the importance of having the antenna as close to the metal center (complex) to achieve maximum efficiency in sensitisation; (b) Ln-complex-spacer-antenna/receptor model, where the receptor is an integrated part of the antenna; (c) Ln-complex-spacer-antenna model, where metal bound water molecules can be displaced by stronger donors such as carboxylates, halides, phosphates, *etc.*; (d) Ln-complex-coordianted antenna, where the antenna is the coordinated ligand, such as aromatic carboxylates.

From the above description, it is apparent that there are several methods for modulating the emission properties by external sources, *e.g.* by ion and molecular *inputs*. Firstly, the sensitisation process can be tuned by simply incorporating a recognition unit into the antenna(e) yielding a *Ln-complex-spacer-antenna/receptor model* (Fig. 2b). Upon ion/molecular recognition, the physical properties of the antenna, such as the excited state energy, the redox properties, or even structural changes are modulated and, hence, the concomitant sensitisation process. This in turn affects the photophysical properties of the lanthanide ions themselves, such as their excited state lifetimes, quantum yields/emission intensity, and even chirality.

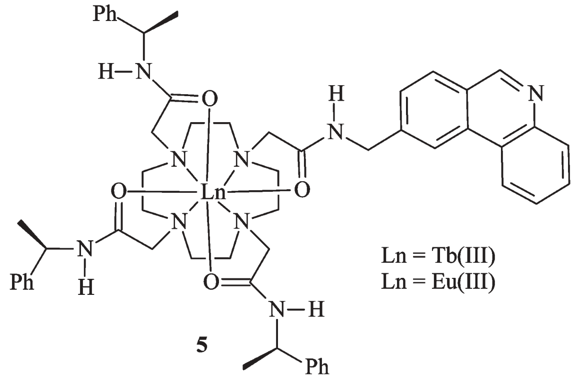
The recognition can also occur directly at the metal ion centre, provided that weakly bound ligands, such as solvents, or other ligands such as β-diketones,[22] can be replaced by the targeting analyte, forming ternary complexes (Fig. 2c). This has been achieved by several researchers,[20,22] where for instance the emission intensity or the chirality of the emission is modulated. This approach can be further elaborated on, by forming ternary complexes between the lanthanide complex and an analyte, which itself is an antenna and hence the sensitisation process can take place to the lanthanide ion from the ternary complexed anion (Fig. 2d). The following sections will deal with examples of these designs.

## Modulation of lanthanide luminescence by modified antenna/receptors

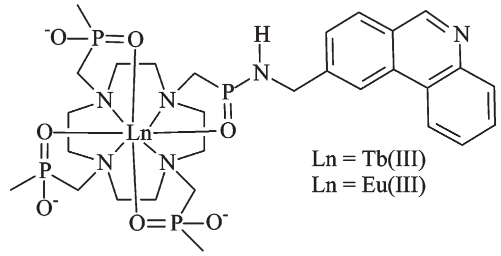
The modulation of Tb(III) and Eu(III) emission by using ions as external inputs, was first achieved by de Silva *et al.* who developed **2–3**, as pH sensors in water.[43] This system was based on a similar idea as the *Ln-complex-spacer-antenna/receptor model* discussed above, with minor modification, *i.e.* the $H^+$ receptor were not integrated components of the antenna. These compounds were based on the use of a terpyridyl functionalised dicarboxylate ligand as the combined antennae/chelates for the lanthanide ions. All the corresponding lanthanide complexes were formed *in situ* using 100-fold excess of the corresponding lanthanide ions. These compounds were flanked with two proton receptor sites in the form of the amino moieties that were separated from the antenna *via* a short spacer. In the unprotonated forms, the amines quench the singlet excited states of the antenna *via* a photoinduced electron transfer (PET) mechanism. Because of this quenching, the efficiency of the sensitisation process (Fig. 1) from the antenna to the lanthanide excited states was significantly reduced ('switched off'). However, upon protonation of the amine, the PET quenching was removed, causing the Tb(III) emission to be enhanced by *ca.* 10–16 fold as now the sensitising process was 'switched on'. The Eu(III) emission in contrast was only moderately enhanced, upon protonation of the amines. From the changes in the Tb(III) emission the binding constant (p$K_a$) was determined to be 8 and 5.5, respectively, for **2** and **3**. In **4**, which lacked the proton receptor, no changes were observed in the Eu(III) emission as a function of pH, proving that the emission enhancements were indeed due to the protonation of the tertiary amines. The main drawback to this design was that the terpyridyl ligands only provided five coordination sites, and as such were unable to fulfil the coordination requirements of nine for Tb(III). Hence, the remaining coordination sites were occupied by four metal bound water molecules, which themselves were able to quench the lanthanide excited state. This also reduced the stability of the complexes to metal dissociation. However, the focus of this was achieved.



**2**; R = $NEt_2$
**3**; R = $N[(CH_2)_2]O$
**4**; R = $CH_3$



**5**



**6**

As discussed above, cyclen macrocycles, when functionalised with pendent arms such as amides, carboxylates or phosphinate esters, providing eight coordination sites, are powerful ligands for the lanthanide ions. The cyclen based Eu(III) complexes **5** and **6** were developed by Parker *et al.* as novel pH sensors, furnished with a phenanthridine chromophore as a combined antenna/receptor moiety, fulfilling the criteria of Fig. 2b.[44,45] In **5** and **6** the protonation of the phenanthridine moiety gave rise to a large, 500 fold, enhancement in the Eu(III) emission, (*e.g.* as in Fig. 3, for **11**) demonstrating the sensitivity of the Eu(III) emission to the local environment of the antenna in a manner similar to that seen in **2–3**. Thus the modulation of the emission can be depicted as shown in Fig. 4, where the Eu(III) was only 'switched on' upon protonation, and that the reverse process was also possible. However, due to the low-lying triplet state energy of the antenna, the Tb(III) complexes were found to be non-emissive (see later).[46,47] The

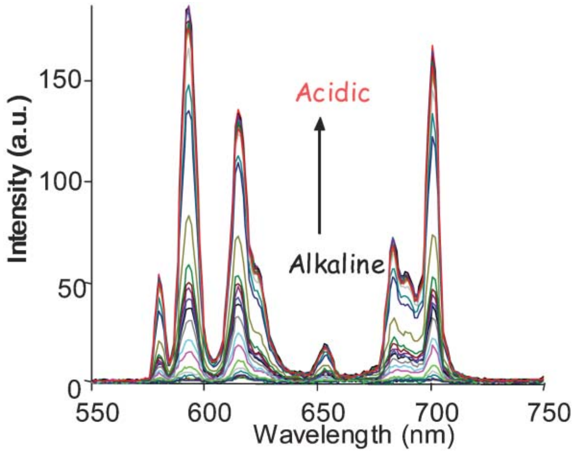
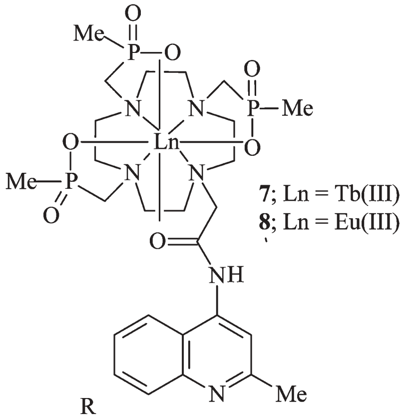
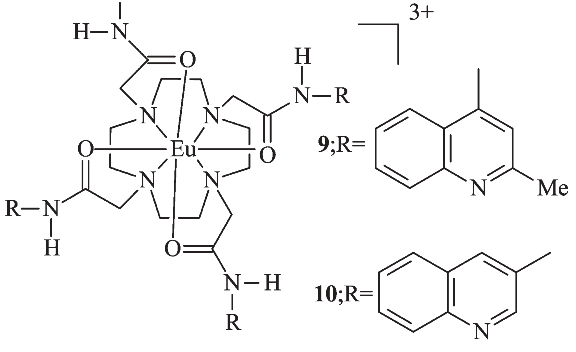


**Fig. 3** The deactivation of the $^5D_0 \rightarrow {}^4F_J$ transitions for **11** as a function of pH, where the emission is 'switched on' upon protonation.

advantage of these types of ligands in the design of lanthanide sensors as demonstrated with **5** and **6**, is that, unlike **1–3**, they are also kinetically and thermodynamically stable to metal dissociation, and could be made and stored as solids. Beeby *et al.* have also investigated the photophysical properties of such Yb(III) phenanthridine complexes as a function of pH and showed that the energy transfer and electron transfer in such complexes is highly pH dependent.[48]


**7**; Ln = Tb(III)
**8**; Ln = Eu(III)



Working with Parker, we developed the related systems **7–9** as pH sensors/switches, where the 2-methyl quinoline moieties were used as antennae/receptors.[49] Here the quinoline moiety was directly attached to one or more of the coordinated pendent arms without the methylene spacer, which gave rise to significant changes in the absorption spectra of these complexes in water as a function of pH. Of these, **8** and **9** also gave rise to large enhancements in the Eu(III) emission, in a similar way to that seen for **5** and **6**, with p$K_a$ of *ca.* 5.5 for **8**, where the emission changed over 2 pH units. For **9**, however, the stepwise protonation of the four quinolines moieties resulted in luminescent enhancements over the pH range 4–8. Interestingly, the concomitant changes in the fluorescence emission spectra, did not mirror those seen in either the ground state of the antenna or in the Eu(III) emission, when excited at 320 nm, but instead the changes occurred in the alkaline region and these were assigned to the deprotonation of the aryl amide. These combined effects led to the development of a luminescent 'pH-electrode' analogue, by which simple time gating techniques the pH of a solution could be monitored over a large pH range.

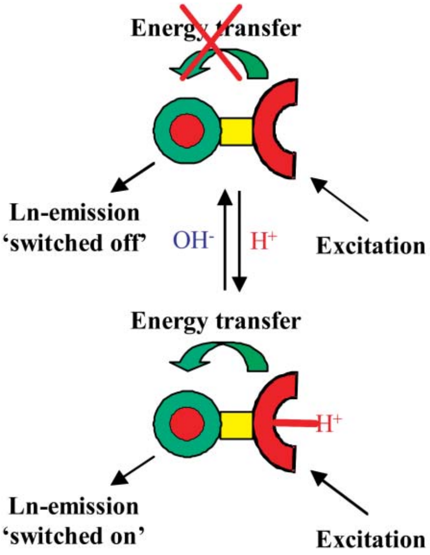


**Fig. 4** Modulation of the lanthanide emission by external input, *e.g.* $H^+$ as observed for examples **5–10**. In the 'free form' (unprotonated) the energy transfer to the lanthanide excited state upon excitation of the combined antenna/receptor moiety is inefficient. The emission can be said to be 'switched on' in acidic media. This process should (and is in the case of **5–10**) be fully reversible.

As in the case of the Tb(III) complexes of **5** and **6**, the Tb(III) complex of **7**, did not demonstrate any changes in the Tb(III) emission as a function of pH under ambient conditions. As before, we determined this to be due to the presence of a low-lying triplet state energy in the antenna.[49] By measuring the $T_1$ in acidic media, this was indeed found to be the case, with the $T_1$ energy $E = 21\,980\ \mathrm{cm}^{-1}$, suggesting an efficient back energy transfer from the Tb(III) $^5D_4$ excited state to the $T_1$ of the antenna, where quenching by $O_2$, was possible. Hence, under ambient conditions, the Tb(III) emission was weak in alkaline solution with only a small *ca.* 20% enhancement being observed upon acidification. Consequently, we foresaw that degassing the solution would overcome this quenching and that the Tb(III) emission should be re-established. When this was tested, some interesting results emerged; firstly, in alkaline solution, no significant enhancements were recorded in the absence of $O_2$ in comparison with the gassed solution (Fig. 5 right). However, when the emission was recorded in degassed acidic solution, large order emission enhancements were observed (Fig. 5 left).[50,51]

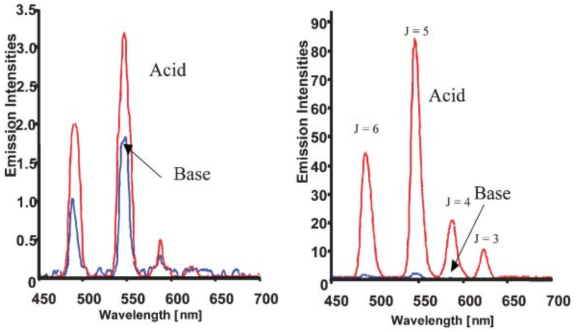
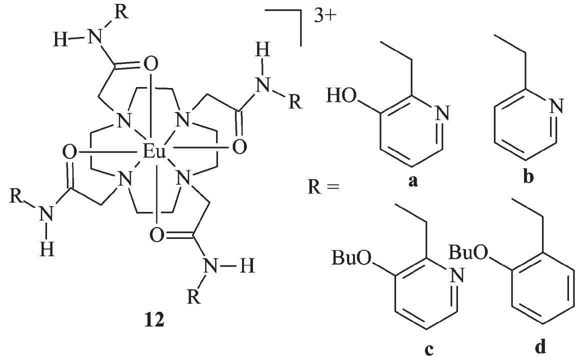


**Fig. 5** The changes in the Tb(III) emission in acid (red) and alkaline media (blue) due to the deactivation of the ${}^5D_4 \rightarrow {}^7F_J$ excited states for **7** in: aerated solution (left) and degassed solution (right). Please note the difference in the intensity scale 3.5 (left) *vs.* 90 (right).

The above changes clearly demonstrate the efficiency of the $O_2$ quenching of the $T_1$. However, because of this, the results for **7** can also be determined in a different fashion. That is to say, in **8** and **9**, the Eu(III) emission (*output*) was modulated by a single ionic *input*, namely $H^+$. Conversely, in **7**, this is not the case as both $H^+$ and molecular $O_2$ determine the magnitude of the Tb(III) emission, hence two *inputs* are necessary to achieve maximum *output*. For this reason, the changes in the Tb(III) emission can be viewed as mimicking the function of the inhibit two bit logic-gate operation[52,53] ($A \wedge B'$), based on the inputs $A$ and $B$ and the output $C$, where $A = H^+$ and $B = O_2$, Fig. 6. Subsequently, only when $A$ is active, giving the binary notation '1' and $B$ is inactive, given the binary notation '0' is the output active, '1'. Such molecular logic gate mimics where the inputs are ionic, were first discussed by de Silva *et al.*, since then several other examples of molecular logic mimics have been presented.[52,53] Of these, **7** was the first one to only require two inputs for the demonstration of the INH logic gate, but recently Pischel *et al.*[54] have demonstrated the same function using Eu(III) emission as the output. Parker *et al.* have also demonstrated that the Tb(III) complex of **6** can operate as a NAND logic gate mimic, where the emission was "switched off" when $H^+$ and $O_2$ were simultaneously present.[46]

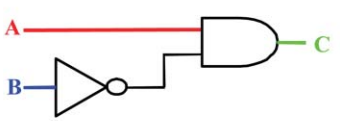
As stated earlier, **7–9** were designed as luminescent sensors or switches for pH. With the aim of broadening the pH target range of such lanthanide sensors, we developed **10**.[55] Whereas **9** gave a p$K_a$ reading between 4–7, the simple modification employed in **10** had a dramatic effect on the pH sensitivity, as the Eu(III) emission was only 'switched on' in acidic media below pH 3, allowing the potential determination of highly acidic media. Furthermore, analysing the changes in the 616 nm transition showed that between pH 1 and 2, the emission was beginning to 'switch off' again, giving rise to a semi 'off–on–off' pH emission profile. In a similar manner Parker *et al.* have modified **5** by incorporating a butyl chain onto the phenanthridine antenna, with the aim of tuning the pH target range.[56]

The above pH sensors have all been analysed in solutions. However, for practical purposes such sensors should ideally be incorporated into a matrix such as polymers, sol–gels or onto glass surfaces. Whereas Parker *et al.* demonstrated the incorporation of some of these pH sensors into sol–gels,[56] we have recently developed **11**, a tetraamide analogue of **8**, for the incorporation into soft material such as hydrogels in a non-covalent manner.[57] As for **8**, the Eu(III) emission of **11** was found to be highly dependent on the pH in solution being reversibly switched 'off–on' (the changes are shown in Fig. 7). In the hydrogel matrix, made from methylmethacrylate (MMA) and 2-(hydroxyethyl-methacrylate) (HEMA) in three different ratios: 1 : 1 (MMA : HEMA, w/w), 1 : 3 (MMA: HEMA, w/w) and 100% HEMA the emission was also 'switched on' (Fig. 7). However, in acidic media the response time was much slower than in solution. Also the luminescence switching was not fully reversible. In spite of this the changes in Fig. 7 demonstrate the viability of such sensing in soft materials and we are currently working on overcoming these shortcomings.



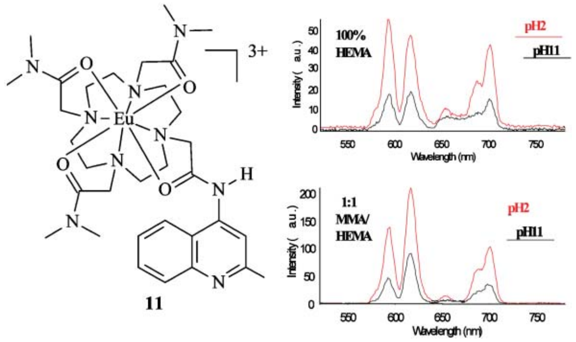
**12**

Recently other researchers such as Pina *et al.*[58] and Sherry *et al.*,[59] who made the cyclen derivatives of **12**, have shown that the lanthanide emission can be modulated by pH in a



| A | B | C |
|---|---|---|
| 0 | 0 | 0 |
| 0 | 1 | 0 |
| 1 | 0 | 1 |
| 1 | 1 | 0 |

**Fig. 6** Logic gate representation of the changes in **7** (left) with the truth table (right) for the INH logic function, when active output signal (1) is obtained only when the input $A$ is active ($A = 1$) and $B$ is inactive ($B = 0$).

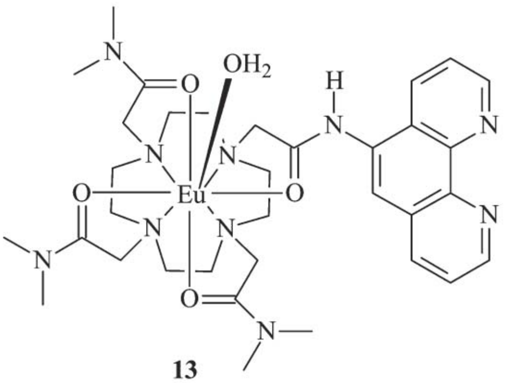


**11**

**Fig. 7** The cationic Eu(III) complexes **11**, and the changes in the Eu(III) emission in two hydrogel matrixes aqueous acidic and base solutions. The changes in the solution are shown in comparison (Fig. 3).

similar manner to that shown above. Recently, Sherry *et al.* have extended this kind of research by incorporating a *p*-nitrophenolic pendant arm into a coordinatively unsaturated triamide cyclen complex, where the phenolate can coordinate to the central Eu(III) ion.[60]

We have recently designed new Eu(III) cyclen complexes with the aim of forming large supramolecular structures by combining ligands for lanthanide ions with those of transition metal ions such as Cu(II), Ru(II) and Os(II). Our first target was the 1,10-phenanthradine (*phen*) Eu(III) complex **13**.[61,62] In alkaline solution between pH 12–8.5 the Eu(III) emission was found to be weak upon excitation at 266 nm, signifying the rather inefficient population of the $^5D_0$ by the *phen* ligand in this pH range. However, upon further acidification the emission was gradually 'switched on', reaching a maximum in the physiological pH range as shown in blue, in Fig. 8. Upon further additions of acid, the Eu(III) emission decreased to *ca.* pH 3, being pH independent between pH 1 and 2.5. Analysis of these changes gave the bell-shaped pH profile shown in Fig. 8, where the emission can be described as switched 'off–on–off' as a function of pH. Importantly, this bell-shape pH dependence was fully reversible as shown in Fig. 8, in red. From these changes two p$K_a$ of 3.8 and 8.1 were determined. These were assigned to the protonation of the *phen* nitrogen moiety and the deprotonation of the aryl amide. Similar p$K_a$ were determined from potentiometric titrations carried out on a *phen*-acetamide analogue of **13**. As the hydration state ($q$) of the complex did not change over the entire pH range, being *ca.* 1, we attributed the changes in the alkaline region to be due to the reduction of Eu(III) to Eu(II), which is non-emissive, by the deprotonated *phen* ligand.[61] This theory has not yet been fully proven and we are currently carrying out experiments in our laboratory to evaluate the changes in the coordination environment of Eu(III) and Tb(III) complexes as a function of pH. However, from the design principle point of view, the most important result, from the pH titration was that in the physiological pH range the emission was 'almost' pH independent and 'switched on'. Complex **13** was designed to give rise to larger supramolecular architectures (as depicted in Fig. 9) for instance by using Cu(II) to bridge two or more units of **13**. It was also important that the emission was 'switched on' as it was foreseen that Cu(II) would be able to quench the Eu(III) emission. Consequently, we would be able to use the changes in the Eu(III) luminescence to predict the coordination environment of the Cu(II) and hence the resulting supramolecular structures. The latter will be discussed in detail further on in this article, but for the former, the effect of adding ions such as Zn(II), Cu(II), Co(II) and Fe(II) to **13** in pH 7.4 solution, was the aforementioned quenching for all the above, with the exception of Zn(II).[22] These changes are shown in Fig. 10, where the Eu(III) luminescence at 615 nm was


**13**

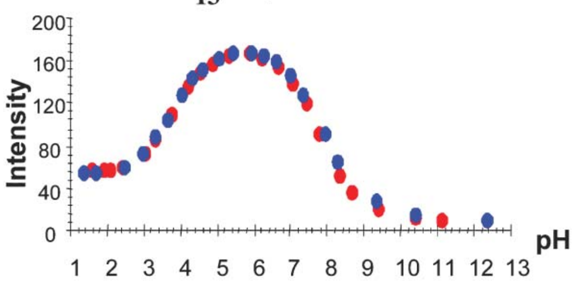


**Fig. 8** The Eu(III) complex **13** and the resulting changes in the 592 nm transition as a function of pH: *red* the titration from pH 12 → 1.5; *blue* the back titration.

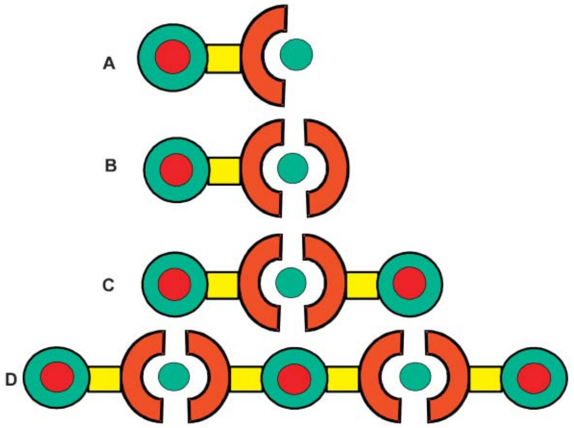


**Fig. 9** The various structural motifs possible by using mixed d–f metal ions. All the above give liner arrays. A: compounds of analogous structures to **13**, where the red ball is the lanthanide ion and the green ball is the transition metal ion, like Cu(II). B: Capped f–d metal assembly. C: By using a 'bridging transition metal ion' two, or more lanthanide ion complexes can form a linear or three dimensional array. D: The design from C can be further elaborated on and larger supramolecular mixed f–d metal ion assemblies can be formed.

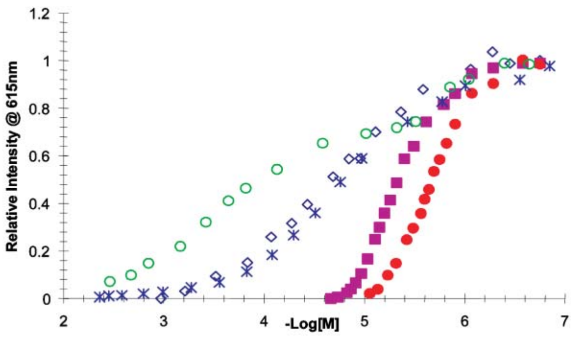
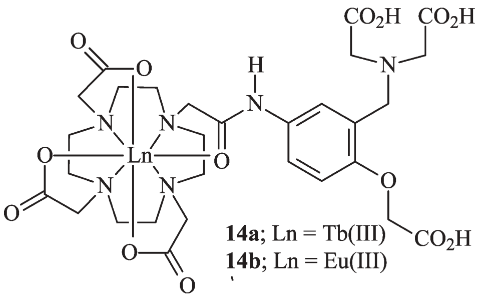
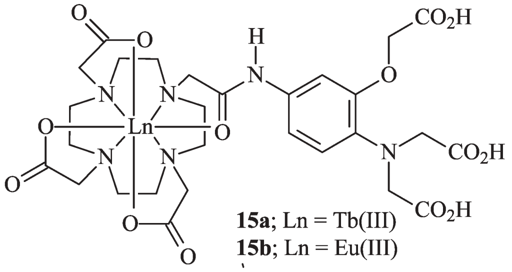


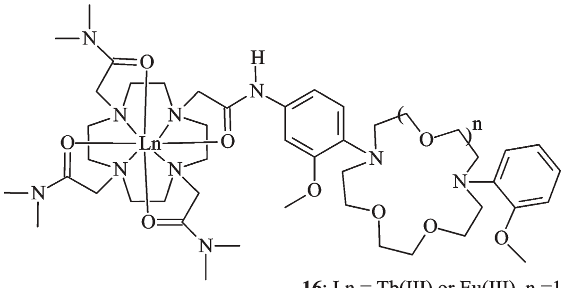
**Fig. 10** The changes (normalised) in the Eu(III) emission at 615 nm, at pH 7.4, as a function of increasing concentration of: Fe(III) (green circles); Fe(II) (blue diamonds); Co(II) (blue stars); Cu(II) (pink squares). The changes for Cu(II) in mimicked biological ionic strength are shown in red.

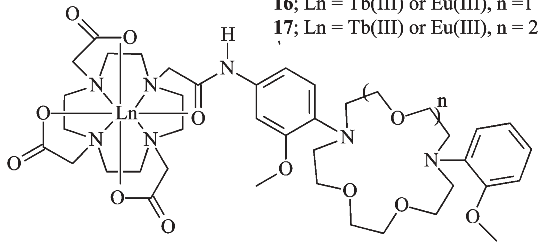
'switched off' as a function of increasing metal ion concentration ($-\log[\mathrm{M(II)}]$, M = Fe, Co and Cu). These changes clearly demonstrated that Cu(II) was detected selectively over either Co(II) or Fe(II)/Fe(III). However, the disadvantage of this design was the use of the short excitation wavelength of 278 nm, which render the use of this system for *in vivo* detection difficult. As for the INHB logic gate mimic **7** discussed above, the changes in the Eu(III) emission of **13** can also be envisaged in a form of a truth-table where the inputs are $H^+$ and Cu(II), yielding again an INHB logic gate mimic with two ionic inputs.[62]


**14a**; Ln = Tb(III)
**14b**; Ln = Eu(III)


**15a**; Ln = Tb(III)
**15b**; Ln = Eu(III)

The simple design of the *Ln-complex-spacer-antenna/receptor model* in Fig. 2b, has been used to develop a series of lanthanide complexes where the emission is modulated by Group I, II and other transition metal ions. Compounds **14** and **15** were developed as luminescence sensors for ions such as Zn(II) and Ca(II) or Mg(II).[63,64] In both cases the receptors are structurally similar, based on the so called 'London type' receptor, with one being synthesised from benzyl amine and the other from aniline. Both the Eu(II) and Tb(III) complexes were made of these ligands, yielding the charge neutral complexes **14a** and **14b**, and **15a** and **15b** for Tb(III) and Eu(III), respectively. For all the complexes a single water molecule was found to be coordinated to the Tb(III) or the Eu(III) centres. On addition of Zn(II) to a solution of either **14a** or **14b**, under simulated physiological conditions at pH 7.4, the lanthanide luminescent emission was enhanced by 26% and 42% respectively.[64] These were much lower than those observed in most of the examples previously discussed above for examples **7–10** where the enhancement was an order of magnitude or larger. In the case of **15a** and **15b** we found that the binding of Zn(II) resulted in deconjugation of the aniline nitrogen lone pair of **15a**, which results in a suppression of PET, from or to the intermediate aryl singlet excited state of the aniline moiety, which leads to a luminescent enhancement. Whereas, for **15b** the emission was weak, independent of either pH or Zn(II). The important observation was the high selectivity of these complexes for Zn(II) over other physiological competitive ions, particularly Mg(II) and Ca(II), which also gave rise to some luminescent enhancement but at much higher concentrations than Zn(II), which gave an apparent dissociation constant of *ca.* 0.6 μM for **15a**. These were the first examples of such sensors for Zn(II). The drawback to these complexes was the relatively minor luminescence enhancements observed in the presence of Zn(II). Recently, two other examples of lanthanide based luminescence sensors for Zn(II) have been developed by Hanaoka *et al.*[65,66] with the aim of improving the emission response. However, both have been developed using acyclic ligands. We are also focusing our efforts on improving the Ca(II) detection by incorporating BAPTA based ligands designed by Tsien *et al.*[67] for intracellular Ca(II) detection, into the cyclen system.[68] This work is ongoing, but similar structures, where two Gd(III) cyclen complexes were incorporated into the BAPTA ligand have been reported as MRI contrast agents.[69] The corresponding Eu(III) or Tb(III) complexes have, to the best of our knowledge, not been reported.


**16**; Ln = Tb(III) or Eu(III), n =1
**17**; Ln = Tb(III) or Eu(III), n = 2


**18**; Ln = Tb(III) or Eu(III), n =1
**19**; Ln = Tb(III) or Eu(III), n = 2

Recently, we have developed other lanthanide complexes based on the above design with the aim of modulating the lanthanide emission using Group I ions.[70] This was achieved by simply conjugating aromatic crown ether moieties onto one of the pendent arms of the cyclen structure, forming bis-macrocyclic structures. Compounds **16** and **17** are examples of this design, giving overall cationic complexes, whereas **18** and **19** gave the corresponding charge neutral complexes. Of the eight Eu(III) and Tb(III) complexes formed from **16–19**, only the Tb(III) complexes showed the lanthanide emission modulated upon detection of either $Na^+$ or $K^+$. The inability to modulate the Eu(III) emission was most likely due to the inefficient sensitisation of the Eu(III) excited state, or more likely by a competitive electron transfer or LMCT quenching of the Eu(III) state, yielding Eu(II), which is not emissive. When designing these complexes, we foresaw that unlike that seen for **13**, where the Eu(III) emission was 'switched on' prior to the Cu(II) detection at physiological pH, the ideal scenario here would be that the emission would be 'switched off' and hence pH independent in the physiological pH range.

Consequently, if the emission was modulated by either $Na^+$ or $K^+$ ($n = 1$ for **16** and **18**, and $n = 2$ for **17** and **19**, respectively), it could only be 'switched on'. This would be possible, provided that the acidity of the nitrogen moieties of the *o*-anisidine derived 18-crown-6 and 15-crown-6 ether antenna/receptors would be low. Fortunately, this was indeed found to be the case, as the Tb(III) emission was 'switched off' in the physiological pH range, and 'switched on' with large order of magnitude enhancements below *ca.* pH 3.2 for all the complexes. From the changes in the Tb(III) emission as a function of pH, we determined a p$K_a$ of *ca.* 2.4 for these complexes, which is particularly low, and demonstrated a significant inductive effect enforced by the Tb(III) ion and the subsequent delocalisation of the aniline moiety, adjacent to the Tb(III)–cyclen complex. In the case of **16** and **17**, the emission was also significantly affected in alkaline pH. This gave rise to an overall 'on–off–on' pH profile, as demonstrated in Fig. 11. However, this inverted-bell shape was absent in the charge neutral complexes **18** and **19**. We thus investigated the effect on the coordination environment of the Tb(III) ion by evaluating the hydration state of the complex over the entire pH range. For the cationic complexes, $q$ remained on average constant ($q$ *ca.* 1). For **18** and **19**, the $q$ value was *ca.* 1 from *ca.* pH 2 → 9. Beyond this region we were unable to determine the $q$ value accurately. This indicated the possibility that the coordination environment was indeed affected for these carboxylate based complexes in highly alkaline media. As stated above, the Tb(III) emission was 'switched on' at pH 7.4, upon addition of either $Na^+$ or $K^+$. However, in both cases this only occurred at high concentration of the ions >0.1 mM. For both **17** and **19**, selective $K^+$ recognition was observed, with large order of *ca.* 30–40 fold enhancements in the Tb(III) emission, whereas, for **16** and **18**, selective $Na^+$ recognition was observed. These emission enhancements were more moderate; *ca.* 7–9 fold. The most important, and most unexpected, results from this investigation was the implication that pH has on the coordination environment of the lanthanide ion and the concomitant changes in the excited states properties of the lanthanide ions.

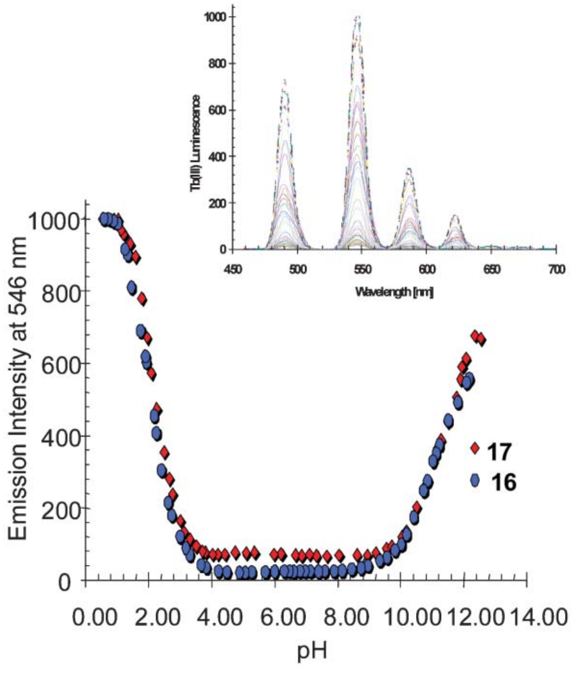
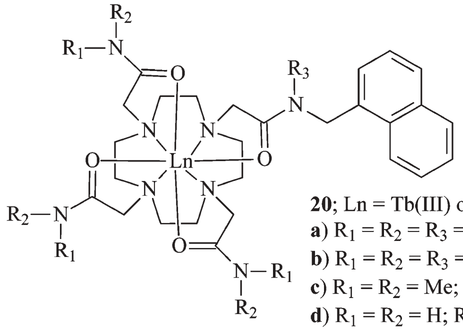
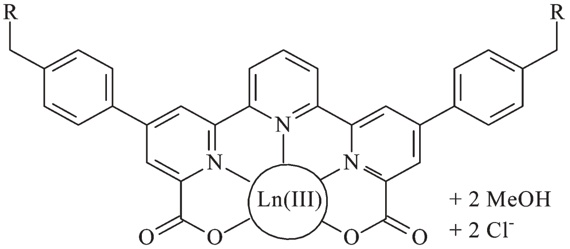


**Fig. 11** The changes in the Tb(III) emission of **17** and **16** as a function of pH, showing the 'off–on–off' pH dependence of the Tb(III) emission. *Insert*: the overall changes $^5D_4 \rightarrow {}^7F_J$ observed for **17** between pH 2 → 14.



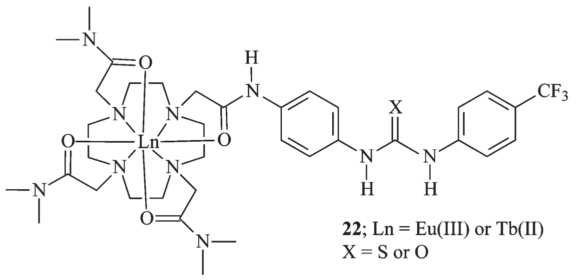
**20**; Ln = Tb(III) or Eu(III)
**a**) $R_1 = R_2 = R_3 = H$
**b**) $R_1 = R_2 = R_3 = Me$
**c**) $R_1 = R_2 = Me; R_3 = H$
**d**) $R_1 = R_2 = H; R_3 = Me$
**e**) $R_1 = Me; R_2 = R_3 = H$
**f**) $R_1 = Me; R_2 = H; R_3 = Me$

To gain some further insight into these possible effects, we are currently evaluating the changes in the lanthanide luminescence intensities and lifetimes of two families of cationic and neutral Tb(III) and Eu(III) cyclen model compounds based on **20**, and the DOTA analogue with $R_3$ = H or Me, and for the Eu(III) complexes of **1** ($R = R_1 = R_2 = Me$), with the aim of relating these to the changes in the coordination environment of these lanthanide ions.[71,72]



**21 a)** R = monoaza-18-crown-6
**b)** R = monoaza-15-crown-5

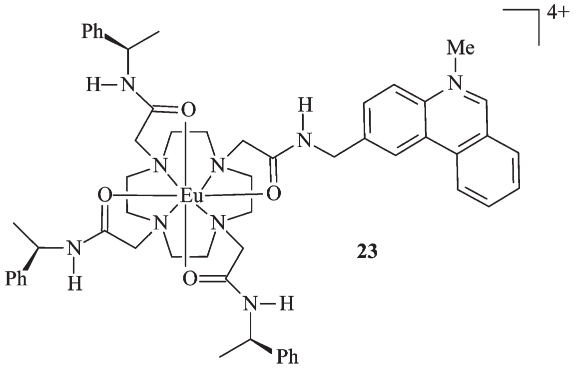
The modulation of lanthanide luminescence by Group I ions has also been demonstrated by de Silva *et al.*,[73] who made crown ether analogues of **2–4**, by using 18-crown-6 and 15-crown-5 mono aza crown ethers, giving **21a** and **21b**, respectively. In both of these cases over an order of magnitude enhancements in luminescence were seen for Eu(III) in MeOH, with $\phi = 0.47$ for **21a**. The 'switching on' of luminescence was attributed to the alkali cation—induced suppression of PET from the azacrown to the antenna. Similar results were obtained for Tb(III) complexes of **21a** and **21b**, but the quantum yields, $\phi$, were measured to be less than 0.0016 in both cases due to a low lying triplet state in the antenna, which caused quenching by oxygen molecules in a similar manner to that shown for **8**. Recently, Wong *et al.*[74,75] have also shown that the introduction of a crown ether moiety conjugated to a Tb(III)–cyclen complex, and the subsequent recognition of either $Na^+$ or $K^+$ can give rise to enhancements in the Tb(III) emission. However, these systems lack the covalently connected antennae, and will be discussed later in this article.



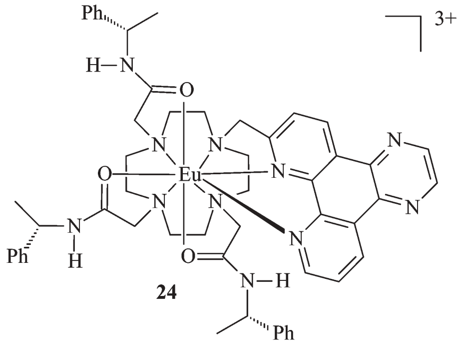
**22**; Ln = Eu(III) or Tb(II)
X = S or O

The lanthanide luminescence emission can also be modulated by anions. Parker *et al.* showed that by simply methylating the nitrogen moiety of the antenna in the Tb(III) complexes of **5** and **6**, these could be converted to $O_2$ sensitive sensors. However, it was also discovered that the Eu(III) analogues were not sensitive to $O_2$, but instead, these were highly sensitive to chloride.[46,47] Here, the excited state of the antenna was quenched by electron transfer, which inhibits the population of the lanthanide excited state. This is a very attractive chloride sensor as it operated in aqueous solution, which is often difficult to achieve for anion recognition.[76]

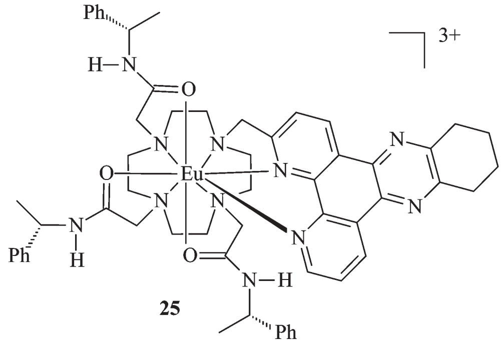
In work currently being undertaken in our laboratory, we have developed **22**, a thiourea or a urea based diaryl antenna/receptor for anions such as acetate, phosphate and fluoride.[77] Here the formation of hydrogen bonds between the thiourea protons and the anions in 1 : 1 binding, in DMSO, gave rise to an increase in both the fluorescence and the lanthanide luminescence of **22**. No binding was observed for $Cl^-$ or $Br^-$. The recognition of acetate, or phosphate was achieved and was unaffected by the presence of high concentrations of either $Cl^-$ or $Br^-$. Unfortunately, no such recognition and luminescence changes were seen in more competitive solvents, such as water or ethanol. Anion recognition in such media has, however, been achieved by the direct coordination of the anion at the metal ion centre by several research groups. This will be discussed in detail later in this article.



**23**



**24**



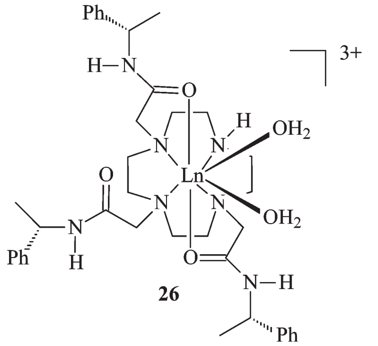
**25**

The above examples have demonstrated the use of the ***Ln-complex-spacer-antenna/receptor*** model in Fig. 2b, to explore the local environment of the complex by cations, anions and small molecules, *e.g.* $O_2$. Recently these types of systems have been used to probe the local environment of large biologically relevant molecules, such as DNA. In work carried out by Parker *et al.*,[78] using the enantiomers Δ(*SSS*) **23** and Λ(*RRR*) (*e.g.* the methylated version of **5**), it was shown that these highly cationic complexes interacted with calf-thymus DNA and the oligonucleotides $[(CG)_6]_2$ and $[(AT)_6]_2$, by monitoring the absorption spectra and the fluorescence emission spectra of the *N*-mehyl-phenanthridinium antenna and in the intensity, lifetimes and the polarisation of the Eu(III) emission. It was observed that the Eu(III) emission was quenched upon interaction with DNA or $[(CG)_6]_2$ and $[(AT)_6]_2$, but the lifetimes of the delayed emission were not affected, suggesting that direct PET quenching of the $^5D_4$ excited state was not occurring. From the changes in the emission spectra, the authors evaluated the intrinsic binding constants *K* for the interactions of both complexes with $[(CG)_6]_2$ and $[(AT)_6]_2$ and reported that both showed preferences for $[(CG)_6]_2$ over $[(AT)_6]_2$, and that Δ(*SSS*) **23** bound stronger to $[(CG)_6]_2$ of the two enantiomers. These were the first examples of the use of enantiomerially pure lanthanide complexes as DNA binders.

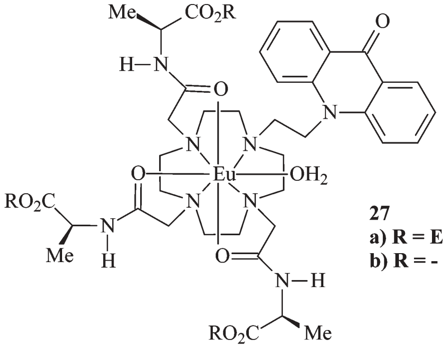
This area of research has been further developed by the Parker group,[79] who have, for instance, developed palladium–porphyrin based cyclen–Yb(III) conjugates, which allowed for the monitoring of the DNA interactions in the near-IR region, by monitoring the changes in either the Yb(III) luminescence or the circular polarised luminescence (CPL) spectroscopy from Yb(III) centre,[80] and more recently, by the synthesis of the tetraazatriphenylene based Δ and Λ lanthanide complexes of **24** and **25**.[79,81] Unlike that seen for **23**, and similar tetraamide complexes, the *q*-value was determined to be zero in **24** and **25**. This was due to the combined effects of the coordinatively unsaturated cyclen ligands (*e.g.* three pendent amide arms), and the covalently bound tetraazaphenylene antennae, which coordinated to the metal ion *via* the two nitrogen moieties, yielding nine coordinate complexes. The exclusion of any metal bound water molecules was particularly evident from the relatively high absolute quantum yields, when measured in water, which were found to be 0.21 and 0.16 respectively for the **24** and **25**, which is significantly higher than for any cyclen complexes with $q \geqslant 1$ as discussed above. The corresponding Tb(III) complexes were also formed and these showed similar trends, with quantum yields of 0.36 and 0.40 respectively. It was evident from the changes in the ground state, the singlet excited states and the delayed lanthanide luminescence of the Tb(III) and the Eu(III) complexes of **24** and **25**, that in the presence of DNA as well as poly(dAdT) and poly(dGdC), binding was occurring, in a similar way as was demonstrated for **23**. Further analysis of these binding interactions showed that these were due to the intercalation of the tetraazaphenylene antennae between the base pairs. It was also evident from these investigations that the coordination environment of the metal ion (Δ *vs.* Λ) also influenced the strength and the selectivity of this binding. For all the complexes the metal centered emission was quenched upon binding to DNA, which was determined to be due to charge transfer interactions with the DNA base pairs. Furthermore, these interactions resulted in enhanced resolution of the $\Delta J = 1$ band as well as a greater decrease in the 681 nm *vs.* the 687 nm bands within the $\Delta J = 4$ manifold, clearly demonstrating the sensitivity of the lanthanide luminescence towards probing by the local chemical environment. Recently the Parker group has elegantly shown that **24** and **25** can be used for cellular imaging, showing the potential use of such complexes as real-life probes for biological imaging.[82]

In a similar way to the sensors described above, *e.g.* **5–19**, and depicted in Fig. 2b, compounds **23–25** can also be said to belong to this family of design principles, as here the antennae selectively interacts with DNA, giving rise to changes in the physical properties of the antenna and hence its ability to populate the lanthanide excited states of Eu(III) and Tb(III). Recently Barigelletti *et al.*[83] have also developed cyclen based complexes bearing an appended phenanthroline chromophore, which is structurally similar to **24** and **25**. They showed that the addition of Eu(III) to an aqueous solution of this ligand gave rise to enhancements in the Eu(III) emission upon excitation of the phenanthroline ligand. However, the authors have not yet reported the use of these for luminescence sensing.

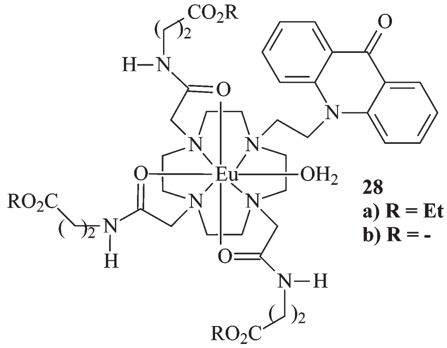
The above examples give some account of the versatility of the use of combined antenna/receptor design, which has been used for the detection of simple ions to larger biomolecules. It also allows for the construction of larger supramolecular structures as suggested in the case of **13** in the presence of 'bridging' transition metal ions, but this will be the topic of discussion later herein. Before that, we will discuss examples of ion and molecular recognition involving the binding of the targeted species directly at the lanthanide ion centre itself.



**26**



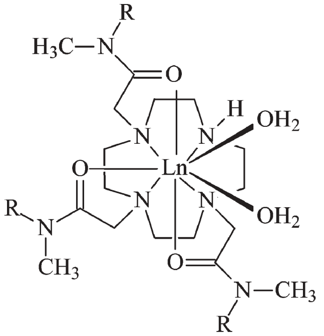
**27**
**a) R = Et**
**b) R = -**



**28**
**a) R = Et**
**b) R = -**

## Modulation of lanthanide luminescence by coordination of analytes at the metal centre

It has been known for some time that counter ions can coordinate to lanthanide ions in coordiantively unsaturated ligands to fulfil the coordination requirements of the lanthanides. Furthermore, it is also known that weakly coordinated ligands can be displaced by stronger ones as discussed in the introduction. As ligands such as water, quench the excited states of many lanthanide ions, it was foreseen that by displacing these from the complexes such as those depicted in Fig. 2c, would lead to changes in the luminescence properties of the lanthanide ions, *i.e.* the local environment would be probed by the coordination of an analyte at the metal ion centre itself. The Tb(III) and the Eu(III) complexes of **26** are examples of such a design, where the phenyl antennae populate the excited state *via* sensitisation, which subsequently was quenched by the two metal bound water molecules (determined by lifetime measurements) giving rise to only weakly emissive complexes. The addition of several anions such as $CH_3CO_2^-$, $F^-$, $H_2PO_4^-$, $HCO_3^-$, $CO_3^{2-}$ in a buffered solution of **26**, gave rise to enhancements in the excited state lifetimes of both the Tb(III) and the Eu(III) complexes, whereas for ions such as $Br^-$ and $Cl^-$ the lifetimes were unchanged.[84,85] From analysis of the *q* values for these changes, it became apparent that for $Cl^-$ and $Br^-$ the value remained *ca.* 2, whereas in the case of $CH_3CO_2^-$, $F^-$ or $H_2PO_4^-$, *q* was determined to be *ca.* 1; signifying the coordination of these ions to the lanthanide ions, with the loss of a single water molecule, and the formation of a ternary complex. However, in the case of $HCO_3^-$, $CO_3^{2-}$, *q* was determined to be ~0, suggesting that both water molecules had been displaced. This not only effected the lifetimes of the emission but also the intensity of the emission, which was 'switched on', as well as the CPL of lanthanide ions in these enantiomerically pure complexes. It also became apparent that the binding of these anions was generally much stronger for the Tb(III) complexes than for the corresponding Eu(III) complexes.



**29**
**a)** Ln = Tb(III); R = CH3
**b)** Ln = Tb(III); R = H
**c)** Ln = Eu(III); R =CH3
**d)** Ln = Eu(III); R =H

Parker *et al.*[86] have developed several other such cyclen systems, particularly for the detection of bicarbonate in intra- or extracellular environments.[87] Compounds **27** and **28** are examples of these kinds of cationic or charge neutral Eu(III) complexes, developed by the Parker group, where an acridone chromophore was incorporated into enantiomerically pure tri-amide complexes as an antenna, however, Faulkner *et al.*[88] had previously shown the advantages of the use of such antenna as a sensitizer. Unlike that seen for **26**, both **27** and **28** were determined to have a single metal bound water molecule. These showed that upon recognition of bicarbonate, at pH 7.4, the luminescence lifetimes and the Eu(III) intensities were affected, where *q* changed from 1 → 0, demonstrating the displacement of the inner sphere water. To probe these changes the ratio of the 618 nm and 588 nm transition was used as a measure of the affinity of these complexes for the anion. Of the complexes tested, the cationic species **27a** and **27b**, showed stronger affinity for the anion than the corresponding charge neutral complexes. By further modifying these structures, by adding additional anionic moieties onto the pendent arms, giving overall anionic complexes, gave the poorest binding. These types of complexes have recently been used as luminescent probes to monitor the concentration and the location of bicarbonate in cells, taking this simple design towards real-life applications.[87]

Parker *et al.* have recently extended the use of such Eu(III) acridone complexes such as **27**, by showing that they can bind to phosphate, and that phosphorylated amino acids and peptides could be detected by the binding/coordination of the phosphate anion at the metal centre (see later).[89] This gave rise, as in the above cases, to changes in the lifetimes and, in particular, the appearance of the Eu(III) emission transitions.

We have also demonstrated the binding of carboxylates at the lanthanide metal ion.[90,91] Unlike the designs discussed above, which are based on Fig. 2c, our approach was to synthesise lanthanide complexes that lacked antennae, and, hence, would display poor or no emission upon excitation. However, these could interact or bind to antennae, which would have groups that could displace any metal bound water molecules, *e.g.* aromatic carboxylates. This would thus give rise to ternary complexes as depicted in Fig. 2d, where the excitation of the antenna would sensitise the lanthanide excited state. The Tb(III) complexes **29** are examples of our design. The presence of the two metal bound water molecules was confirmed by lifetime measurements of the $^5D_4$ and $^5D_0$ excited states, and also by X-ray crystallography. As is evident from the crystal structure of **29a** (Fig. 12) the Tb(III) ion is coordinated to the four nitrogens of the ring and the three oxygens of the pendent amides, with the remaining two coordination sites being occupied by water molecules. Analysis of these structures showed that the Tb…O1W and the Tb…O2W bond distances were almost identical being 2.429(3)Å and 2.441(3)Å, respectively. Whereas for the isostructural Eu(III) complex **29c** these distances were measured to be 2.418(5) and 2.421(5), respectively. For **29a** the O1W–Tb–O2W bite angle was measured to be 71.80(11)°, whereas for **29c** the O1W–Eu–O2W bite angle was measured to be 72.20(18)°. These angles indicated that both complexes should be able to interact with ligands/antenna, such as aromatic carboxylates, displacing both the water molecules. Analysis of the luminescence lifetimes of the Eu(III) and Tb(III) complexes of **29** using several different families of antennae, such as **30–32**, resulted in some interesting findings. All the antennae were chosen so that sensitisation would be possible from the antenna to the lanthanide excited state, provided that binding between the two and the formation of ternary complexes occurred. For **30** this was not found to be the case, and no emission was observed upon exciting the antenna and observing the lanthanide luminescence. However, the Tb(III) emission was gradually switched on, upon titrating **29a** and **29b**, respectively, with a solution of **31a**, in water at pH 7.4.

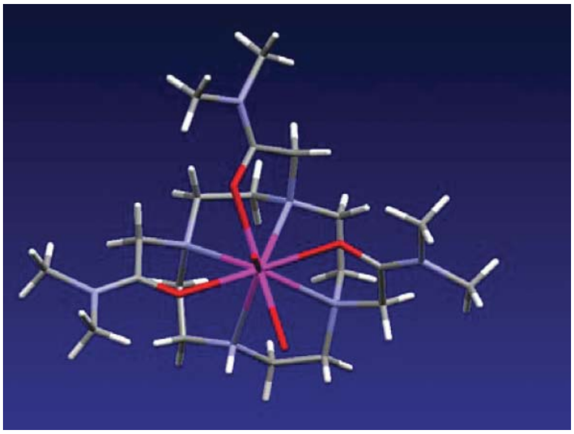


**Fig. 12** The X-ray crystal structure of **29a**.

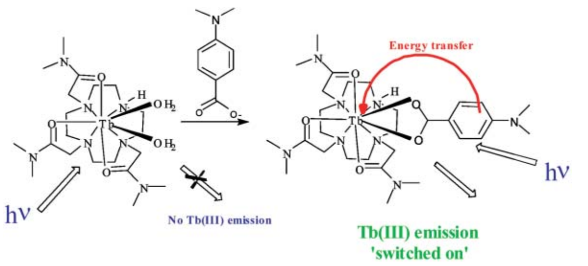
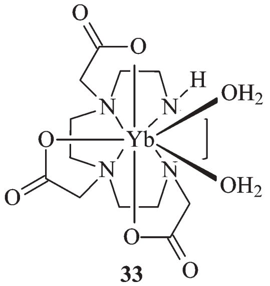
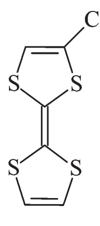


**Fig. 13** The recognition of **31a** by **29a** and the concomitant formation of a luminescent ternary complex.

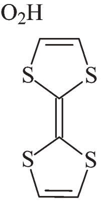
This signified the formation of the aforementioned ternary complexes and the displacement of the labile metal bound water molecules, Fig. 13. This was also evident from the determination of the *q*-value which for **29a** and **29b**, was ∼0 after the formation of the ternary complexes. However, no such luminescence enhancements were observed for **29c** and **29d**, and the *q* value remained the same in the presence or the absence of **31a**. Furthermore, the luminescence enhancement was greater for **29a** than **29b**. Analysis of this binding was undertaken by titrating these complexes with **31b** and **31c**. If the binding was bidentate, as shown in Fig. 12, it would be expected that neither **31b** nor **31c** would be able to bind to the lanthanide ions and hence, no luminescence enhancements would be observed. This was indeed found to be the case. The most important result from this investigation was that both **29a** and **29b** could selectively detect salicylic acid, **32a**, while Aspirin, **32b**, was not detected at pH 7.4 in the presence of high ionic strength of tetramethylammonium chloride. The design principle of **29** has also been used in our laboratory to develop bridged lanthanide complexes, using aromatic antennae that have two carboxylic binding sites.[92] Pikramenou *et al.*[93] have recently shown the detection of aromatic carboxylic acids *via* the formation of ternary complexes, by using lanthanide ion complexes of functionalised diaza-crown ethers.



**33**



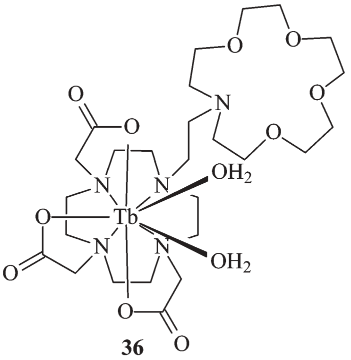
**34**



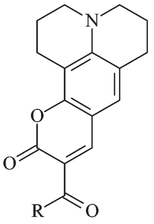
**35**

Similar design principles were adopted by Faulkner *et al.*[94] who have synthesised the IR-emitting Yb(III) complex **33**. In a similar manner to that shown above, the Yb(III) emission was 'switched on' upon the formation of a ternary complex between the charge neutral **33** and tetrathiafulvalene carboxylic acid **34** in methanolic solution, while no such luminescence enhancements were observed when tetrathiafulvalene **35** was used. The authors also evaluated the binding of **34** directly to Yb(III) and determined the *q*-value as 3.25 in methanol, *i.e.* Yb(III) was bounded to three ligands of **34**. This complex was also emissive. When the same measurements were carried out on **33** in the presence of **34**, a *q*-value of 0.21 was observed, when excited at 337 nm suggesting the formation of a ternary complex, caused by the displacement of two water molecules from **33**. The binding of the carboxylic acid was also visible in the Yb(III) emission centered at *ca.* 980 nm, where the luminescence was significantly enhanced in comparison to that seen for the 1 : 3 Yb(III) complex of **34**. Recently Ziessel *et al.*[95] and Tsukubo *et al.*[96] have also shown that anions can modulate lanthanide luminescence by direct coordination to the metal ion centre. In both cases, acyclic ligands were used to demonstrate this sensing.

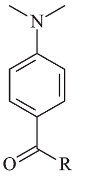
Recently, Faulkner *et al.* have also used **33**,[97] as well as its Nd(III) analogue, to study the efficiency of the near-IR sensitisation process in ternary complexes, using pyrene carboxylate as an antenna. On both occasions the Yb(III) and the Nd(III) emissions, the latter occurring with characteristically intense emission bands at 1055 and 1350 nm, was observed in water. For the former, a *q*-value of 0.9 was determined, whereas for the latter, a *q*-value of 0.3 was observed. These results are of significant importance for the future development of lanthanide based sensors and probes for biological application. The main advantages of using Yb(III) and Nd(III) as probes/reporters is that antennae which absorb at longer wavelengths, exceeding 400 nm, can be used as sensitizers. Whereas for the sensitisation of either Tb(III) or Eu(III), *e.g.* **30–32**, exceeding 330 nm is not so easy. Furthermore, the emission occurs in the near IR and it is not masked by general auto-fluorescence, and light scattering from any biological environments, making detection easier.



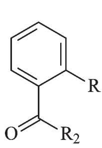
**36**



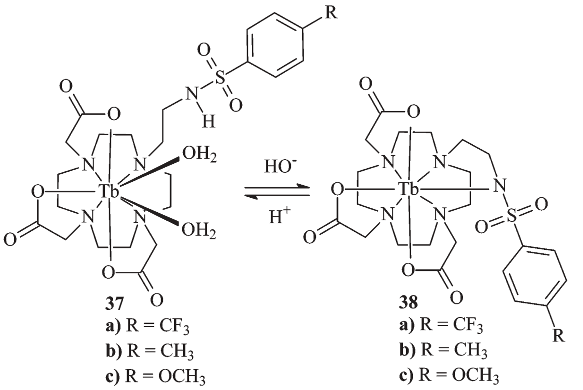
**30**
**a)** R = OH
**b)** R = OEt



**31**
**a)** R = OH
**b)** R = $CH_3$
**c)** R = OEt



**32**
**a)** $R_1$ = OH; $R_2$ = OH
**b)** $R_1$ = OAc; $R_2$ = OH
**c)** $R_1$ = OMe; $R_2$ = OH
**d)** $R_1$ = OH; $R_2$ = OEt
**e)** $R_1$ = OEt; $R_2$ = OMe



**37**
**a)** R = $CF_3$
**b)** R = $CH_3$
**c)** R = $OCH_3$

**38**
**a)** R = $CF_3$
**b)** R = $CH_3$
**c)** R = $OCH_3$

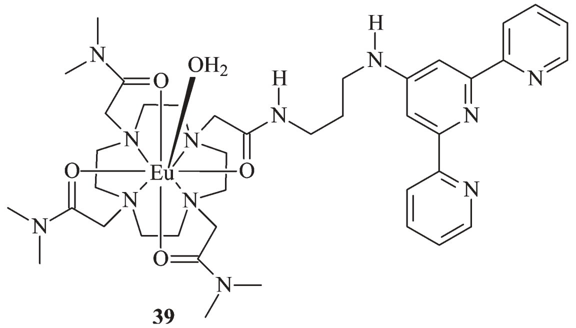
Li and Wong,[74] have recently developed cyclam based Tb(III) complexes where a monoaza-15-crown-5 ether and 15-crown-5 ether moieties were conjugated *via* a short alkyl or ether spacer to the cyclam complex. These complexes lack the antenna, and as such were not found to be emissive. However, upon addition of *p*-chlorobenzoate, and excitation at 246 nm in pH 7.4 buffer solution, the Tb(III) emission was found to be switched on. Furthermore, upon addition of perchlorate salts of $Li^+$, $Na^+$ and $K^+$, the emission was further 'switched on'. This design has recently been further developed by Li and Wong in the development of cyclen analogues, such as **36**.[75] Here the *q* value was determined to be *ca.* 2 and upon addition of either salicylate (as in the case of **29**) or benzoate the emission was greatly enhanced, and *q* was reduced to *ca.* 0. By titration experiments the authors showed that the salicylate was bound in a 1 : 1 ratio to **36**, and proposed similar binding motif of the bidentate antenna as we had in the case of **29**, and Parker *et al.*[98] and Dickins *et al.*[99] in the binding of caroboxylates and other anions.

In the above examples the water molecules have been displaced by intermolecular changes *e.g.* by external analytes. However, there are a few examples of the use of cyclen complexes where intramolecular motion, caused by external stimuli, can displace such metal bound water molecules, in a reversible way. Lowe and Parker[100,101] developed **37** as a pH sensitive Eu(III) luminescent switch. The complexes were shown to have *ca.* 2 water molecules ($q \sim 1.7$) in acidic media. However, in more alkaline solutions, deprotonation of the sulfamide occurred, and the resulting anions were shown to coordinate to the Eu(III) ion by displacing the water molecules, yielding **38**, and $q \sim 0$. By simply changing the nature of the substituent (R) in **37**, the pH sensitivity of this motion could be tuned, *e.g.* for the change in **37a** → **38a** (R = $CF_3$) a p$K_a$ of 5.7 was determined, whereas for **37c** → **38c** (R = $OCH_3$) a p$K_a$ of 6.7 was determined. The authors further modified their design by synthesising polyanionic analogues of **37** with the aim of using these in more competitive 'biological' background. For all the complexes the 'on–off' motion was found to be fully reversible.

Structurally similar cyclen complexes have been developed by Kimura *et al.* using tri amide based cyclen ligands conjugated to a dansyl fluorophore, as sensors for lanthanide ions.[102] Even though the authors made the La(III) and the Eu(III) complexes of this molecule and evaluated the changes in the fluorescence of the dansyl group as a function of the added ions they did not, to the best of our knowledge, evaluate the changes in the lanthanide luminescence.

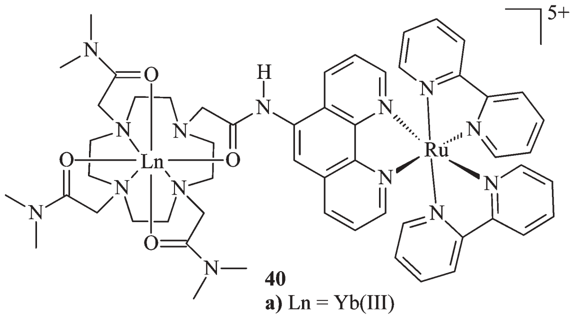
## Modulation of lanthanide luminescence; from recognition to molecular assemblies

The above discussion has focused on the development of single molecular components as luminescent sensors or switches. However, the choice of antenna can also be used to build larger supramolecular complexes. This was briefly discussed for **13** earlier, where the lanthanide emission and lifetimes were modulated upon coordination of the *phen* ligand to Cu(II), Co(II) *etc.* These structures can be described as being self-assembly mixed f–d metal ion complexes, and can be looked at as being examples of structures depicted in Fig. 9c. We have carried out investigation into the stoichiometry of such interactions between **13** and Cu(II).[62] Our earlier results showed that both 2 : 1 and 3 : 1 complexes were possible, depending on the counter ion used, the former yielding Fig. 9c, whereas the latter would give disordered octahedral geometry around the Cu(II) bridge. We now believe that in solution the self assembly complexes are most likely in the 2 : 1 stoichiometry. As a result of this we have also developed **39**, using the terpyridine ligand as an antenna.[103] As can be seen from this design, the antenna and hence the bridging ligand are separated by a propyl spacer, as we were unable to incorporate the antenna directly at the amide moiety. The pH titration of **39** showed that as for **13**, the emission was switched on at pH 7.4. The addition of Fe(II) gave rise to the formation of a new band in the absorption spectra centred at 570 nm corresponding to the MLCT band of the newly formed Fe(II) complex. The fluorescence emission spectra was also significantly affected, being quenched and shifted to the red upon the recognition of Fe(II). Furthermore, the Eu(III) emission was 'switched off', signifying the formation of the new supramolecular species in solution. From these changes we have determined that the stoichiometry is 2 : 1 and that we have formed mixed f–d metal complexes with overall charge of +VIII. We are currently investigating these kinds of structures in greater detail.[103]



**39**

The development of novel supramolecular architectures using such mixed metal ion complexes (f–f or mixed f–d) has been extensively explored by Bünzli and Piguet.[5] Their research effort has led to the development of many exciting supramolecular structures, many of which are helical in nature and chiral.[5,104] However, as these are not based on the cyclen framework this work falls outside the scope of this article. However, we direct interested readers to explore several excellent reviews and papers that these authors have published on their work. The self assembly principle can be further elaborated on, as demonstrated by both Faulkner *et al.*[105] and Pikramenou *et al.*[106] who have individually developed f–f or mixed f–d luminescent systems capable of recognizing biological molecules, using either cyclic or acyclic ligands, or the combination of both.



**40**
**a)** Ln = Yb(III)
**b)** Ln = Nd(III)

The use of designs such as **13** and **39** to build other mixed f–d supramolecular complexes that fulfil the structure depicted in Fig. 8b, has also been undertaken in our laboratory.[107] Fig. 9b, can be described as a capped f–d supramolecular system. These systems are of potential use for diagnostic purposes such as for binding to biological systems, *e.g.* DNA, *etc*. With this in mind we synthesised **40**, which is based on the use of *phen*-cyclen ligand used in **13**. However, as our interest lay in developing new systems where we combined the use of near-IR emitting probes and mixed f–d metal ion hybrids, we chose to use Yb(III) and Nd(III) as the emitting lanthanide reporters and ruthenium bipyridine [Ru(byp)$_2$] as the stopper. The formation of **40a** and **40b** was evident from the absorption spectra of these complexes and the formation of a MLCT band centred at 450 nm. In collaboration with the Faulkner group in the University of Manchester, we have also investigated the near-IR emission from these complexes. By excitation of the MLCT band, or at the *phen* moiety at 285 nm, the sensitised emission from the lanthanide ions occurred at long wavelengths as is clearly evident from Fig. 14, for the Nd(III) emission of **40b**. Here both the Nd(III) emission and the Ru(II) emission were in fact observed, where the lifetime of the Nd(III) emission was determined to be 192 and 30 ns in $D_2O$ and $H_2O$ respectively, signifying the substantial quenching of the excited state in water. At the same time the Ru(II) excited state lifetimes were found to be 202 ns in both $D_2O$ and $H_2O$. In the case of **40a**, the Yb(III) emission overlapped with that of Ru(II), with Yb(III) excited state lifetimes of 6.37 μs and *ca.* 2 μs being determined in $D_2O$ and $H_2O$, respectively. The preliminary investigation of the interactions of these complexes with calf-thymus DNA showed that the complexes only bound weakly to DNA. We are thus currently improving on this design with the aim of being able to probe such binding in a stronger and more selective manner.

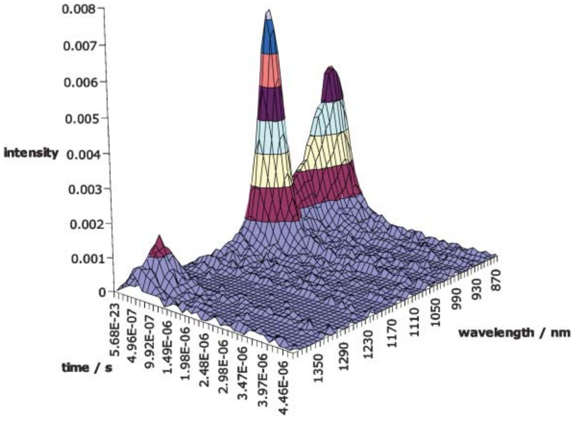
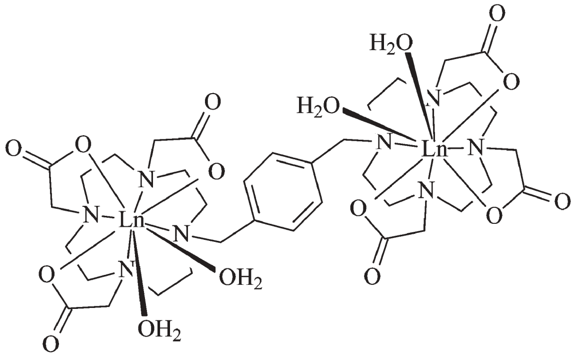
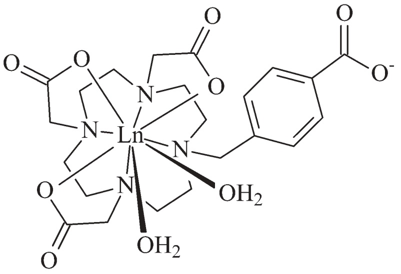


**Fig. 14** The TRES spectra of the Nd(III) emission of **40b** (and the Ru(II) at shorter wavelengths) upon excitation of the MLCT band in water.



**41**
**a)** Ln =Tb(III).



**42**
**a)** Ln =Tb(III).
**b)** Ln =Eu(III)

Faulkner *et al.*[108] have elegantly extended the use of long wavelength and near-IR emitting complexes, by developing other mixed f–f and f–d based cyclen complexes. The bis-cyclen lanthanide complex **41** is an example of such a design where two lanthanide ions were used. Excitation of the bridging antenna gave on all occasions the characteristic metal luminescence from the lanthanide ions. In a similar way, we have developed in our laboratory the cationic analogue (with overall +VI charge), using the same coordination environment as employed for **29**.[109] As in the case of **29**, we have demonstrated that the Tb(III) ions of these dinuclear complexes are 'switched on' upon excitation of the *p*-xylene-bridge, and that anions that have two binding sites, which can be used to displace the metal bound water molecules, can indeed do so. This gave rise to even higher emission intensities. However, in the case of anions such as pyrophosphate the full 'switching on' was not achieved immediately, indicating that equilibrium between the bound and the free sensor was in favour of the free/uncomplexed form.

Recently Faulkner *et al.*[110] have also developed **42**, with the aim of constructing new self-assembly dimetallic supramolecular architectures. Based on the work similar to **29** and **33**, the authors have elegantly incorporated an anion binding site into neutral Eu(III) or Tb(III) complexes and shown that as a function of pH these complexes can associate or dissociate. For instance, at pH 8, where **42** exists as the anion, a linear array is formed upon self-recognition, with *q ca.* 1. However, in acidic media the protonated form of **42** is obtained and the dimetallic complexes dissociate, giving rise to *q ca.* 1.5–2. This 'on–off' self assembly was also evident from the lanthanide luminescence, which was greatly enhanced in the dimer, signifying the displacement of the water molecules. Recently the authors have also developed hetero-metallic analogues of **42**.[111] This design principle has also been used in the development of mixed f–d complexes, as in the case of the Ru(II)–Ln(II) complexes. Here, the excitation of the Ru(II) moiety gives rise to energy transfer sensitisation, with concomitant emission of the near IR emitting lanthanide complex, in a similar manner to that discussed for **40a** and **40b**.

## Future scope and developments of lanthanide luminescence

The above discussion has focused on the development of simple functional lanthanide luminescence complexes based almost entirely on the cyclen structure. We have shown that in a relatively short time ($\sim$6 years) such complexes have been developed from simple luminescent switches and sensors, where the lanthanide luminescence was modulated by the local ionic and/or the molecular environment, to larger mixed f–f and f–d metal based supramolecular architectures. The latter are often formed through weak coordination interactions, through the use of non-coordinatively saturated cyclen complexes, in competitive media. We have shown that for the former, the emission of Eu(III) or Tb(III) was usually the choice of reporter, whereas more recently, the use of near IR Yb(III) and Nd(III) emission has become even more attractive.

So what lies ahead? How is this field going to develop in the near future? From the above account it is obvious that the advantages of long wavelength and long excited state lifetimes have enormous advantages over conventional fluorescence probes, used today in ion and molecular sensing. However, one of the main drawbacks is that often the lanthanide complexes have low quantum yields and due to potential toxicity they have to be formed as kinetically and thermodynamically stable complexes. This can call upon the use of tedious and multi-step synthesis. Despite this, many of the examples discussed towards the end of this article are usually achieved in a few and high yielding steps, are stable to metal dissociation and at the same time provide an avenue for the development of more challenging architectures. The use of such complexes are also finding there way into material chemistry and nanotechnology; particularly as new alternative imagining agents come on-stream. It will thus be 'exciting' to watch the rapid developments of such new materials in the years to come.

## Acknowledgements

We have been fortunate to have hosted many strong, determined and skilled researchers in our laboratory over the last six years. Their work has been featured in this article and our sincere gratitude goes to Claire, Katell, Andrew, Ann-Marie, Floriana, Cidália, Niamh and Naomi. The work has been supported by Kinerton Ltd. (now IPSEN), Enterprise Ireland, Biomedical Research Ireland, The Health Research Board, IRCSET, CSCB, The Wellcome Trust and Trinity College. We have had the privilege of collaborating on many of these projects with good friends and colleagues, and our many thanks goes to David Parker, A. P. de Silva, John M. Kelly, Robert Peacock, Stephen Faulkner, Mark Nieuwenhuyzen, Colin P. McCoy and in particular to Paul E. Kruger, all of which have made this work, extremely exciting! We also thank Lisa Jane Gillespie and Dr. Sally Plush for their help during the writing of this article.

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