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The Formation of Luminescent Supramolecular Ternary Complexes in Water: Delayed Luminescence Sensing of Aromatic Carboxylates Using Coordinated Unsaturated Cationic Heptadentate Lanthanide Ion Complexes

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The synthesis of four lanthanide ion complexes Eu·1, Eu·2, Tb·1 and Tb·2, from the heptadentate tri-arm cyclen (1,4,7,10-tetraazacyclododecane) ligands 1 and 2 that were made in one-pot syntheses is described. These coordinatively unsaturated complexes have two labile metal-bound water molecules, as demonstrated by X-ray crystallography. This was also confirmed by evaluating their hydration state ($q \sim 2$) by measuring their lifetimes in D_2O and H_2O, respectively. The above complexes were all designed as being "photophysically silent" prior to the recognition of the anion, since they do not possess antenna that can participate in sensitisation of the Eu(III) or the Tb(III) excited state. However, the two water molecules can be displaced upon anion binding by the appropriate aromatic carboxylates to give ternary complexes in water, through either four- or six-member ring chelates ($q \sim 0$), or possibly via a monodentate binding. In the case of Tb·1 and Tb·2, large luminescence enhancements were observed upon the formation of such ternary complexes with *N*,*N*-dimethylaminobenzoic acid at ambient pH. Such binding and luminescent enhancements were also observed for Tb·1 in

The Future of Supramolecular Chemistry

There is no doubt that Supramolecular Chemistry is a fast growing field of research. As the field grows, and more complex targets and applications are addressed, we must ensure that we do not neglect the fundamental science needed to achieve many of our principle aims. Recognition and signalling using chemosensors have become an ever more important part of supramolecular chemistry, particularly from a medical diagnostic point of view, since it enables the use of non-invasive, real-time monitoring of physiological species *in vivo*, something that we all will benefit from. In this paper, we try to address some of these fundamental aims such as recognition and signalling by developing "simple" self-assembly lanthanide-based sensors.

Thorfinnur (Thorri) Gunnlaugsson was born in Iceland in 1967. He obtained his PhD with Professor A. P. de Silva at Queen's University Belfast, working on luminescent switches and sensors. He then moved to Durham University, England, as a postdoctoral fellow with Professor David Parker, working on developing luminescent lanthanide sensors, an area which still features strongly in his work. In 1998. he was appointed as the Kinerton Lecture in Medicinal Chemistry at Trinity College Dublin, and in 2000 as a lecturer in Organic Chemistry. In 2002 he was elected as Fellow of Trinity College Dublin. His main research interests are in the areas of Supramolecular and Medicinal Chemistry, and particularly in the fields of recognition and targeting.

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the presence of salicylic acid. On all occasions, the anion recognition "switched" the emission "on" over two logarithmic units. At higher concentrations, the emission is reduced possibly due to quenching. In the case of aspirin, the binding was too weak to be measured, indicating that Tb·1 selectively detects salicylic acid, the active form of aspirin in water. In the case of Eu·1 and Eu·2, the affinity of these complexes towards such aromatic carboxylates was too weak for efficient ternary complex formation.

Keywords: Lanthanide luminescence; Lanthanide complexes; Sensing; Aspirin; Salicylic acid

INTRODUCTION

The use of luminescence detection for the sensing and monitoring of ions and molecules is of great current interest [1–13]. Whereas earlier work was mainly focused on the use of fluorescence as the mode of detection, which has excited state lifetimes in the nanosecond time range, the need for the development of luminescent chemical sensors that can be employed for online detection *in vivo* has led to the need to develop chemosensors that possess long-lived excited states [14–18]. The use of such delayed emission has great advantages over fluorescence, since it overcomes the poor signal-to-noise ratio that is caused by short-lived background emission (autofluorescence) and light scattering of the surrounding biological environment [19,20]. As in the case of fluorescence detection, the recognition event can be monitored by observing the changes in the various photophysical properties of the emitting moiety such as wavelength, intensity (or quantum yield of luminescence: Φ_L) or lifetime [21–25].

We have been interested in the sensing of cations and anions by employing fluorescence and/or colorimetric detection [26–32]. Recently, we have developed both luminescence switches [33,34] and chemosensors [35–37] which utilise lanthanide luminescence, by preparing well-defined and stable octadentate Eu(III) and Tb(III) cyclen (1,4,7,10-tetraazacyclododecane) macrocyclic complexes [38–40]. Such complexes possess long-lived excited states (approximately in the millisecond range) and emit at long wavelengths (500–750 nm) with large Stokes shifts and characteristic line-like emission bands (10–30 nm bandwidth) under ambient conditions [41–44]. These are all qualities necessary for online *in vivo* monitoring. However, normally the lanthanide ions are photophysically inert due to low molar absorptivities, which is related to Laporte forbidden f–f transitions making direct excitation difficult [33–46]. Nevertheless, this drawback can be overcome by incorporating one or more antennae covalently into the lanthanide complexes, ensuring that the lanthanide-excited states [which are $^5D_0$ and $^5D_4$ for Eu(III) and Tb(III), respectively] are efficiently populated through sensitisation [33–47]. This is a well-established process that occurs via an energy-transfer mechanism from the singlet-excited states of the antenna to the lanthanide excited states via the antenna triplet state [33–48]. Such lanthanide sensitisation has also been demonstrated by using non-covalently linked antennae by employing β-diketones [45–51] and other related organic ligands [52–63], and also by using β-cyclodextrins (CD)-based lanthanide complexes, as recently demonstrated by several researchers [64–69].

In designing our lanthanide chemosensors, we took advantage of the use of the sensitising antennae by simply incorporating the recognition site into the antennae themselves [33–37]. Hence, any perturbation at this site, i.e. recognition, subsequently led to the modulation in the sensitisation process with concomitant changes in the lanthanide luminescence. However, the drawback to such chemosensors is the elaborate synthetic pathways required for the desired sensors, which is both time-consuming and often results in a low overall yield. Because of this, we have recently turned our attention to the development of kinetically stable heptadentate coordinative unsaturated cyclen complexes that do not have the receptor-antenna moieties as an integrated part of their structures [70]. Examples are the triarm amide complexes **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** [70]. It has recently been reported by Parker *et al.* [71,72] that in water at pH 7.4, such related coordinatively unsaturated complexes have two water molecules associated with their structures, since the lanthanide ions fulfil their high coordination requirements (typically 9–10) by binding two solvent molecules. Furthermore, it has also been shown that these are labile water molecules, which can be removed upon binding of anions such as bicarbonates, acetate, phosphates and halides [71,72].

Inspired by this work, our aim was to develop novel chemosensors where the two labile metal-bonded water molecules could be displaced upon metal chelation yielding self-assembly ternary complexes between **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** and several aromatic carboxylates [70]. Here, the idea was that instead of having the antenna covalently bound to

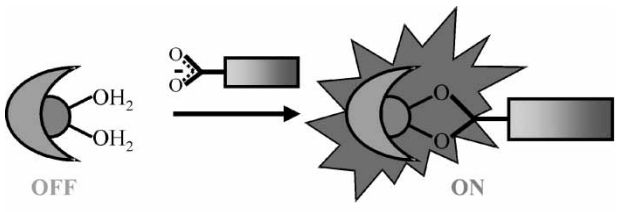
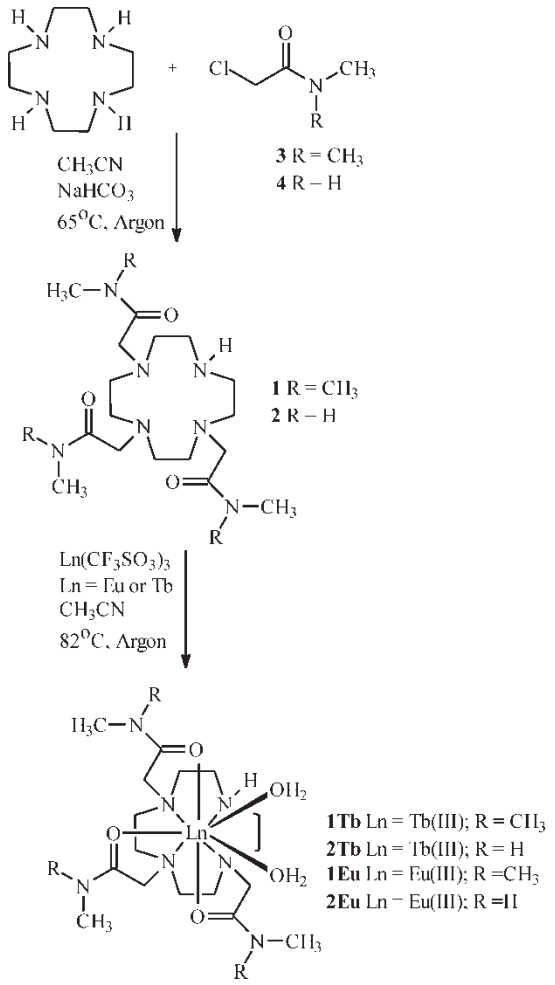


FIGURE 1 Schematic diagram of the self-assembly process that leads to the formation of the luminescent ternary complex between the lanthanide complex and the carboxylate antenna.

the ligand, the aromatic carboxylate themselves would act as antennae. Hence, only upon coordination of the aromatic anion, through self-assembly, would the lanthanide ion emission be "switched on" (via excitation of the antennae). Such a recognition event is depicted in Fig. 1. Furthermore, because of the population of the lanthanide excited state by the coordinated anions, the above complexes could all be considered to be "photophysically silent" prior to the anion recognition. Moreover, as the binding of these antennae would be directly to the metal centre, the population of the lanthanide ions would be greatly improved due to the small distance between the antenna and the metal ion (assuming a Förster mechanism where efficiency is dependent on $\sim 1/r^6$) [73,74]. Furthermore, such binding would be expected to be in a 1:1 ratio. However, it would be expected that this binding would be highly dependent on the nature and the structure of the antenna, and their ability to chelate to the metal centre. Furthermore, the choise of aromatic carboxylates as sensitisers is somewhat limited by their triplet excited state energy, which needs to be greater than that of the excited states of Eu(III) and Tb(III) (20,400 and 17,200 cm^{-1} for $^5D_0$ and $^5D_4$, respectively). With this in mind, we decided to use neutral pendent amide arms, as they would ensure that the complexes were cationic, and as such would maximise the binding interactions.

In this paper, we give a full account of the synthesis of **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** from the heptadentate tri-arm functionalised cyclen ligands **1** and **2**, and the photophysical evaluations of these compounds in the presence of several aromatic carboxylic acid derivatives.



SCHEME 1 Synthesis of ligands **1** and **2** and their corresponding Eu(III) and Tb(III) complexes **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2**.

DESIGN AND SYNTHESIS OF 1 AND 2 AND THEIR Eu(III) AND Tb(III) COMPLEXES

We set out to develop simple lanthanide ion complexes that would allow for the monitoring of important aromatic carboxylic acids such as salicylic acid, the active form of the prodrug aspirin, at the same time of requiring only minimal synthetic efforts [75]. With this in mind, we set out to make the two ligands **1** and **2** in one-pot syntheses.

The synthesis of **1** and **2** was achieved by reacting the α-chloroamides of *N*-methylacetamide (**3**) and *N*,*N*-dimethylacetamide (**4**), respectively, with cyclen in dry CH_3CN (in 3:1 ratio of acetamide: cyclen) at 65°C for 3 days in the presence of $NaHCO_3$ (Scheme 1). For **1**, the macrocycle was purified by alumina column chromatography using CH_2Cl_2, followed by gradient elution using NH_3-saturated MeOH ($0 \rightarrow 3\%$). For **2**, the macrocycle was purified by tituration with diethyl ether. Both **1** and **2** were obtained in over 50% yield after purification. The ligands were characterised using standard methods. However, both were found to be hydroscopic, and elemental analyses were therefore not obtained. High-resolution accurate masses were obtained for both **1** and **2**. The ^1H NMR spectrum of both ligands showed the presence of C_2 symmetry that runs along an axis through the unalkylated amine in *position 1* and the tertiary amine in *position 7* of the cyclen ring. The ^1H NMR spectrum of **2** is shown in Fig. 2 and shows the presence of two N–H resonances at 7.60 and 7.30 ppm, in a ratio of 1:2, for the two amide protons. The two α-protons for the pendent arms appear as singlets at 3.06 and 2.97 ppm (in a ratio of 4:2), respectively, whereas the *N*–CH_3 protons appeared as two doublets in a ratio of 6:3 at 2.75 and 2.67 ppm, respectively. The cyclen methyl protons appear as four broad resonances in the region of 2.7–2.4 ppm. The ^1H NMR spectrum for **1** showed similar characteristics.

The Eu(III) and Tb(III) complexes of **1** and **2** were made by refluxing together an equivalent amount of **1** or **2** with either Eu(III) or Tb(III) triflate $(SO_3CF_3)_3$ in dry CH_3CN under an inert atmosphere for 24 h.

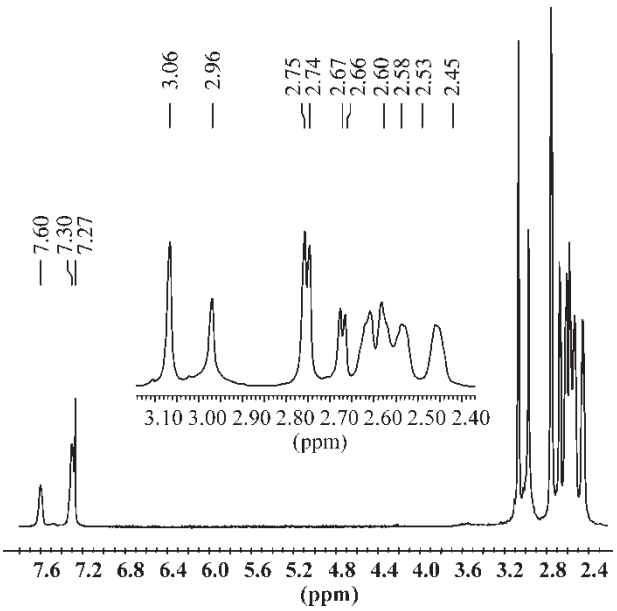


FIGURE 2 ^{1}H NMR spectrum of the ligand **2** in $CDCl_3$ (400 MHz) showing the presence of the C_2 symmetry in **2**.

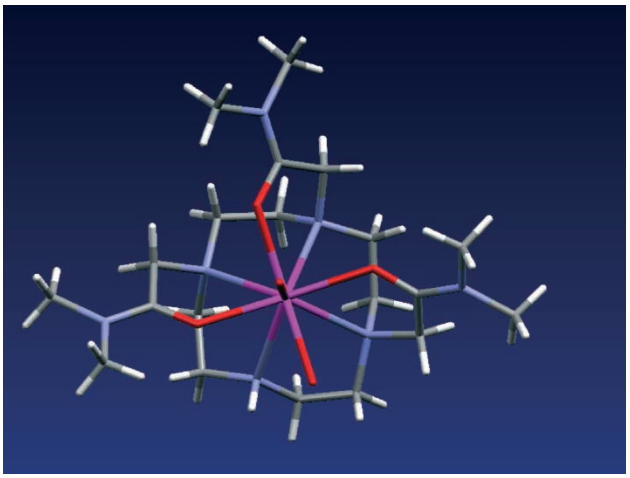


FIGURE 3 View from the top of **1·Tb** showing the binding of Tb(III) to **1** and the two water molecules. Anions and solvent molecules have been removed for clarity. (See colour plate 1 at the end of this issue.)

Upon cooling to room temperature the solution was poured into a stirring solution of dry diethyl ether, which resulted in oily residues that were collected by decanting the organic layers and rinsing the resulting residues with either CH_2Cl_2 or $CHCl_3$. These complexes were characterised by elemental analysis, electrospray MS (ESMS), IR and by NMR. The ^{1}H NMR spectrum of all the complexes showed the presence of the paramagnetic metal centres, as indicated by several broad resonances appearing over a large ppm range [76]. The ESMS for the four complexes showed the presence of two triflate counterions as the major peak with several other combinations of multiple charges, which had an identical isotopic pattern to the corresponding calculated spectrum. In the ESMS, the presence of the two expected metal-bonded water molecules was not observed. We were, however, able to obtain X-ray crystal structures of three of the four complexes, namely **Eu·1**, **Eu·2** and **Tb·1**.

X-RAY CRYSTALLOGRAPHIC INVESTIGATION OF Eu·1 AND Tb·1

We were able to grow crystals of **Eu·1**, **Eu·2** (not shown) and **Tb·1** that were suitable for X-ray crystallographic determination [77,78]. The Eu(III) crystals were obtained by slow evaporation from CH_3CN, whereas for **Tb·1**, this was achieved by slow evaporation from a mixture of CH_3CN and CH_2Cl_2 (in the ratio of 1:1). All the crystal structures showed the presence of the two metal-bonded water molecules. The structure of **Tb·1** is shown in Fig. 3, but we have previously published the structure of the Eu(III) analogue [70]. To the best of our knowledge, these are the first examples of such tri-amide lanthanide ion-based cyclen complexes [70,76,79]. From Fig. 3, it is evident that the Tb(III) centre is coordinating to the four nitrogen of the macrocyclic ring and to the three oxygens of the carboxylic amides on the pendent arms, with average Tb···N and Tb···O distances of 2.634(4) Å and 2.347(3) Å, respectively. In general, the lanthanide ions prefer a high-coordination environment, which is usually in the order of 9–10 [77,78]. For **Tb·1**, seven of these are provided by the ligand, with two further coordination sites being occupied by two metal-bound water molecules. The Tb···O1W and Tb···O2W distances are almost identical, being 2.429(3) Å and 2.441(3) Å, respectively. For the isostructural **Eu·1** complex, these distances were measured to be 2.418(5) and 2.421(5), respectively. Table I lists selected bond angles and distances for the two complexes. From these, it can be seen that there are only minimal differences observed for the two complexes. Similar results were observed for **Eu·2** (not shown here). From the crystal structure data of the complexes, it is apparent that they all adapt a general square antiprism geometry in the solid state. Such geometry is well known for the tetra-substituted octadentate lanthanide-based cyclen complexes.[†]

[†]For such square antiprism geometry, two elements of chirality can be observed, which are associated with the sign of the torsion angles of the NCCO chelate (Δ or Λ) and the NCCN chelate rings (δ or λ) helicity of the *N*-alkylated pendent arms [80,81]. For **Tb·1** (as shown in Fig. 3), these were determined to be an average of 19.2° and −58.5°, respectively. However, for **Tb·1**, the complex crystallised in a centrosymmetric space group containing both Δ and Λ conformations. Similar results were observed for **Eu·1**.

TABLE I Selected bond lengths and angles for **Eu·1** [70] and **Tb·1**

	Eu·1	**Tb·1**
Ln–O (Å)	2.342(5), 2.364(5), 2.378(5)	2.326(3), 2.348(3), 2.368(3)
Ln–O (water) (Å)	2.418(5), 2.421(5)	2.429(3), 2441(3)
Ln–N (Å)	2.605(6), 2.624(6), 2.625(6), 2.647(6)	2.600(4), 2.637(4), 2.642(4), 2.656(3)
N–C–C–N (°)	58.9(9), 59.4(9), 62.2(9), 57.0(9)	−57.7(6), −61.7(6), −58.0(6), −58.4(6)
N–C–C–O (°)	−2.5(11), −27.6(10), −25.4(10)	5.6(7), 25.6(6), 26.5(6)
OW1–Ln–OW2 (°)	72.20(18)	71.80(11)

For our design, it is essential that all the complexes possess two water-bonded molecules, as seen for **Tb·1** in Fig. 3. There are two main reasons for this. First, even though both ligands lack the covalently functionalised antennae, it is possible to generate an excited state in both Eu(III) and Tb(III) by direct excitation of the metal centres (see later). However, the water molecules can efficiently quench the excited state through OH vibrations (or by any other energy-matched oscillators), which further diminishes any lanthanide luminescence prior to the recognition event (the formation of the ternary complex). Secondly, the need for two "vacant" coordination sites at the metal centre would ensure that the binding of the carboxylate would be possible through a bidentate manner (for instance by both of the oxygens of the carboxylate). Subsequently, the water molecules would be expelled and no longer able to quench the lanthanide excited state. From the above crystal structures, it can be seen that this criterion is fulfilled. However, the angle at which these two water molecules bind to the ions is also of importance, since the nature of the binding mode would depend on the bite angle between the two water molecules. For **Tb·1**, the O1W–Tb–O2W bite angle was measured to be 71.80(11)° whereas for **Eu·1**, the O1W–Eu–O2W bite angle was measured to be 72.20(18)°, indicating that both complexes would be able to interact with the carboxylates via such a bidentate manner.

Recently, Parker *et al.* [71] and Dickins *et al.* [82] have shown that related three-arm cyclen complexes can form bidentate adducts with organic anions such as acetate, citrate, glycinate, and lactate through four- and five-member chelates. The bite angles for all of these complexes were between 54° and 69°. In the case of acetate, this binding occurred through both of the carboxylate oxygens. We thus proposed that the aromatic carboxylates would bind to **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** in a similar manner. However, to date, we have not been able to crystallise these complexes in the presence of any of the aromatic carboxylates to prove this theory.

LUMINESCENCE STUDIES

Determining the Hydration Numbers of Eu·1, Eu·2, Tb·1 and Tb·2 in the Absence and Presence of *N,N*-Dimethylaminobenzoic Acid (7) Antenna

As stated above, both the Eu(III) and the Tb(III) complexes were expected to possess two labile metal-bound water molecules. This was verified for three of these complexes by determining their solid-state structures. The number of metal-bound water molecules can also be evaluated by estimating the hydration state or number of the complexes using a luminescent method, where the rate constant for the radiative decay (k) of the $^5D_0$ excited state of Eu and the $^5D_4$ excited state of Tb are measured in H_2O (k_{H_2O}) and D_2O (k_{D_2O}), respectively [83]. These values can be obtained by direct excitation of the lanthanide ion complexes at high concentrations. The hydration number (q) can then be determined from Eqs. (1) and (2) for the Eu and Tb complexes, respectively.

$$q^{Eu(III)} = 1.2[(1/\tau_{H_2O} - 1/\tau_{D_2O}) - 0.25 - 0.075x] \quad (1)$$

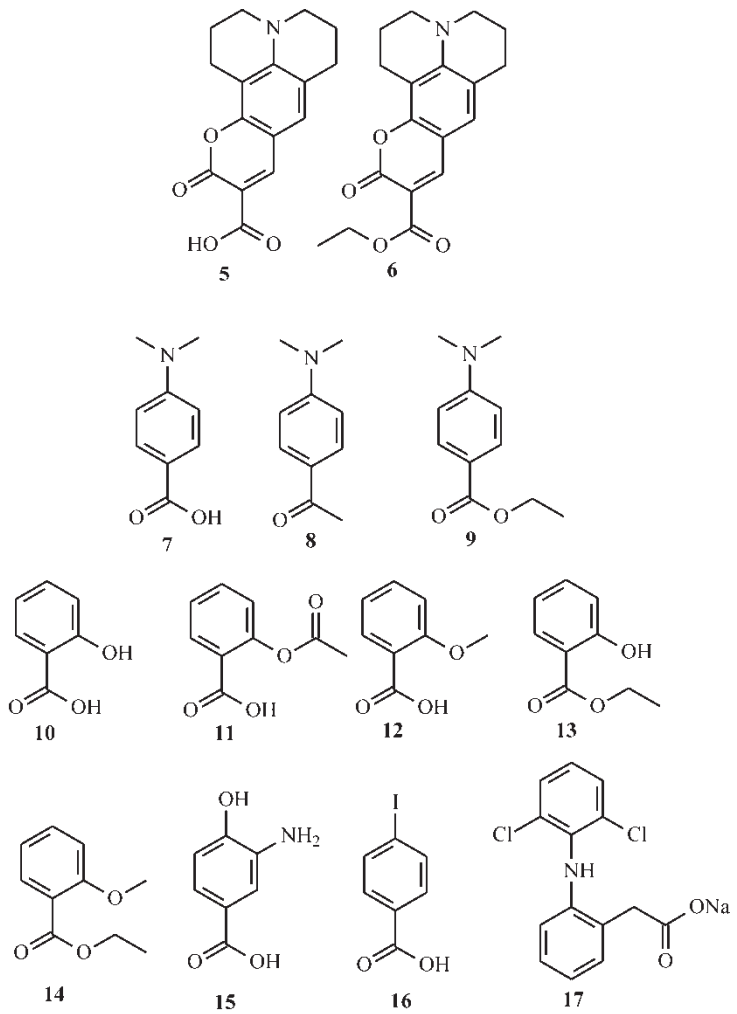
$$q^{Tb(III)} = 5[(1/\tau_{H_2O} - 1/\tau_{D_2O}) - 0.06] \quad (2)$$

Here, the prefixes 1.2 and 5 in Eqs. (1) and (2), respectively, are proportionality constants that mirror the sensitivity of the corresponding ions to quenching by metal-bound water molecules. The correction terms −0.25 and −0.66 represent quenching by second sphere water molecules, whereas $-0.075x$ in Eq. (1) represents the quenching by N–H oscillators, where x is the number of such oscillators within a given complex [83–85].

Table II summarises the observed lifetimes (τ_{Ln}), the corresponding k_{H_2O} and k_{D_2O} values and

TABLE II Measured lifetimes and rate constants for **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** and the corresponding hydration number ($q \pm 0.5$) in the *absence* of any carboxylate antennae

Complex	τ_{H_2O} (ms)	k_{H_2O} (1/ms)	τ_{D_2O} (ms)	k_{D_2O} (1/ms)	q
Eu·1	0.281	3.55	0.855	1.17	2.55
Eu·2	0.315	3.17	0.936	1.07	1.95
Tb·1	0.720	1.38	1.080	0.92	2.01
Tb·2	0.869	1.15	1.386	0.72	1.85



SCHEME 2 Various carboxylic-acid-based antennae tested.

the $q(\pm 0.5)$ values for the above complexes in the absence of any carboxylate antennae [hence, by direct excitation of the Ln(III) ions] [84,85]. From these data, it can be seen that all the complexes have two water molecules associated with their structure in solution. The above measurements were repeated by exciting the lanthanide ions at 300 nm, the same wavelength that most of the carboxylate antennae (Scheme 2) absorb at. However, in all cases, the emission was too weak for evaluating q accurately.

As stated above, it was hoped that the formation of a ternary complex between the lanthanide complexes and the antenna would lead to large enhancements in the lanthanide luminescence of these complexes. Such ternary complexes can be formed only if both or one of the water molecules are displaced. To evaluate this, the q values were measured in the presence of several antennae (Scheme 2). Here, the proof for the formation of such ternary complexes would be achieved if $q \approx 0$, with concomitant enhancements in the lanthanide luminescence.

Initially, the ability of the coumarin antennae **5** and **6** was investigated in water. However, neither of these gave rise to any enhancements in the Eu(III) or Tb(III) luminescence. This suggests that these antennae were unable to bind to the metal centre, because, according to their triplet state energies (T_1), the sensitisation by the Tb(III) excited state should be energetically favourable. Because of this, a series of structurally more simple carboxylates were tested, namely the benzoic acids and derivatives **7**–**16**. All of these have triplet state energies of ca. 22,000–26,000 cm^{-1}, which is close to that found for $^5D_0$ and $^5D_4$ for Eu(III) and Tb(III), respectively [86]. This suggested that an effective energy transfer form these antennae to the excited state of the lanthanide ions would be feasible, provided that the antennae were able to form stable ternary complexes with **Ln·1** and **Ln·2**. The first of these antennae to be investigated was the *N*,*N*-dimethylaminobenzoic acid **7**. Upon addition of **7** to either **Eu·1** or **Eu·2** (ca. 17 mM) in water, no Eu(III) emission was observed when excited at 300 nm, indicting that **7** was either not

TABLE III Measured lifetimes and rate constants for **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** and the corresponding hydration number ($q \pm 0.5$) in the presence of *N,N*-dimethylaminobenzoic acid

Complex	τ_{H_2O} (ms)	k_{H_2O} (1/ms)	τ_{D_2O} (ms)	k_{D_2O} (1/ms)	q
Eu·1	0.235	4.25	0.438	2.28	1.79
Eu·2	0.276	3.62	0.733	1.35	2.15
Tb·1	1.593	0.62	1.795	0.55	0.06
Tb·2	1.626	0.61	1.895	0.52	0.14

binding to the Eu(III) centre or not able to populate the Eu(III) excited state efficiently. Furthermore, it is also known that the Eu(III) excited state can be quenched by an electron-transfer mechanism using similar antennae [72].

When these measurements were repeated using **Tb·1** and **Tb·2**, a positive sensitisation occurred, with the Tb(III) emission being clearly visible. For instance, upon addition of 4 equivalents of **7**, the emission of **Tb·1** at 491, 548, 687 and 622 nm was "switched on" with luminescence enhancement factors of ca. 700 (the quantum yield was not determined). Here, the largest changes were seen in the $^5D_4 \rightarrow {}^7F_5$ transition at 548 nm, which is magnetic-dipole allowed. For **Tb·1**, these enhancements factors were somewhat smaller or ca. 220. These results indicate that for both **Tb·1** and **Tb·2**, the carboxylate was binding to the Tb(III) centres and successfully populating their excited states (upon excitation of the antenna at 300 nm).

Having established that **7** was able to sensitise the Tb(III) excited states, we measured the lifetimes of the excited states of **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2**, in the presence of **7** (0.68 mM, 4 equivalents) with the aim of determining the hydration numbers of the four complexes. These results are summarised in Table III. From these measurements it can be seen that for either **Eu·1** or **Eu·2** q was evaluated to be ca. 2, indicating that both have two water molecules associated with their structures and that neither are binding to **7**. However, for **Tb·1** and **Tb·2**, both give rise to similar excited state lifetimes in either H_2O or in D_2O, which indicates that no inner-sphere solvent molecules were present, so q was evaluated to be ca. 0 for both of these complexes. This signifies that for both **Tb·1** and **Tb·2**, a self-assembly process occurs between **7** and these complexes, giving rise to the formation of luminescent ternary complexes in solution. Furthermore, since both of the water molecules have been displaced upon coordination of the carboxylates to Tb(III), we conclude that such binding occurs through both of the oxygens of the carboxylate in a bidentate manner via a four-member ring chelates. This is depicted in Fig. 4, where the Tb(III) emission of **Tb·2** is only "switched on" upon sensitisation by **7** after the formation of the ternary complex.

Luminescent Sensing of Aromatic Amino Carboxylates and Related Derivatives

Having observed the self-assembly process between the Tb(III) complexes and **7**, which gives rise the formation of luminescent ternary complexes, we carried out a titration of all the complexes (typically in 17 μM solution) in the presence of **7–15** in H_2O and at pH 7.4 using either Tris or Hepes buffers containing 0.1 M of tetramethylammonium chloride to maintain a constant ionic strength. All measurements were carried out in aerated solutions. At such low concentrations, none of the complexes were particularly luminescent, and as such, the emission from these complexes is "switched off".

When **Tb·1** was titrated in water using 7, the Tb(III) emission was switched on as previously described. When these measurements were repeated in buffered solution at pH 7.4, the emission was also "switched on". However, the enhancement factors

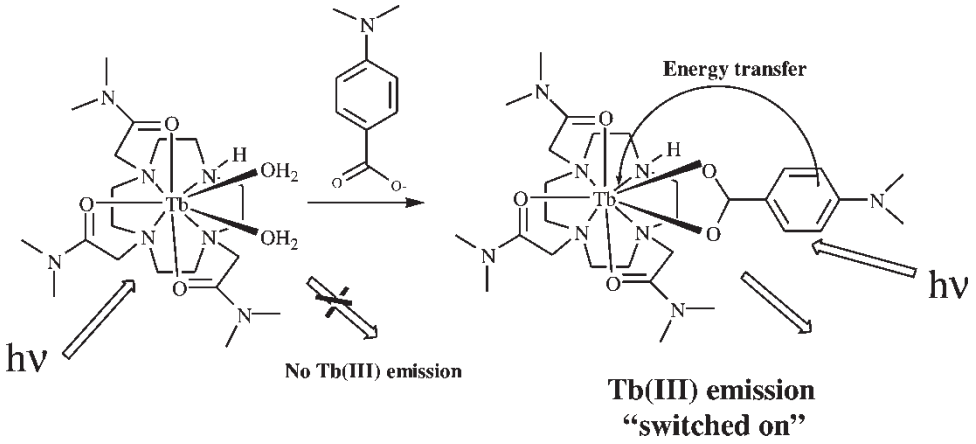


FIGURE 4 Formation of the ternary complex between 7 and **Tb·1** giving rise to large enhancements in the Tb(III) emission. The emission from **Tb·1** is said to be "switched on" upon excitation at 300 nm.

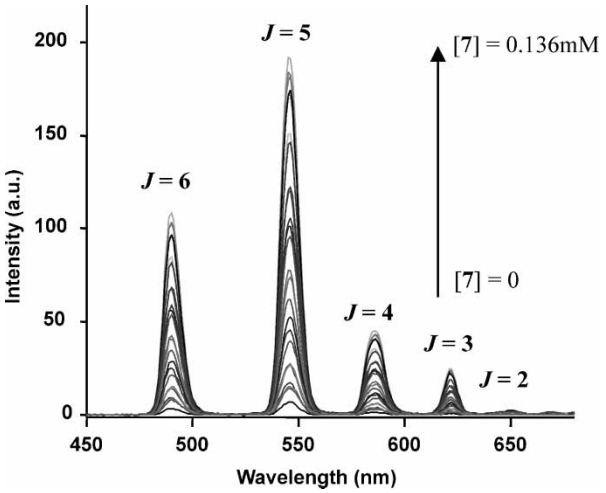


FIGURE 5 Changes in the Tb(III) emission of **Tb·1** upon addition of **7**. $J = 6$, 5, 4, 3 and 2 represent the bands corresponding to the deactivation of the $^5D_4 \rightarrow {}^7F_J$ transitions.

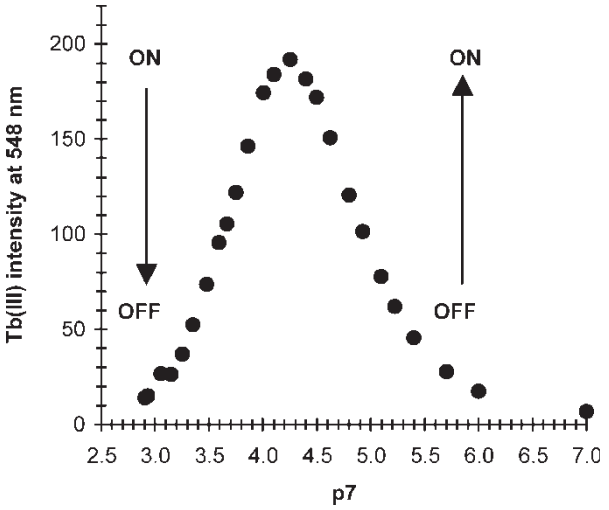


FIGURE 6 Changes in the $J = 5$ transition of **Tb·1** as a function of p7.

were somewhat smaller or 480 for **Tb·1**. The changes in the Tb(III) emission as a function of increased concentration of **7**, between pN 0–4.2 (where pN = $-\log[N]$, and N is the number of the compound in Scheme 2), can be seen in Fig. 5, where J represents the emission bands corresponding to the deactivation of the $^5D_4 \rightarrow {}^7F_J$ transitions. Here, the largest changes occurred in the $J = 5$ and 6. However, to our surprise, upon increasing the concentration of the antenna, the emission was "switched off" again. This became apparent when plotting the changes in the intensity of the 548 nm transition as a function of p7 (Fig. 6). From these changes, a sigmoidal curve was observed between p7 = ca. 6.5 and 4.5, where the emission was "switched on". Since this occurs over ca. two pN units, it can be concluded that this represents a 1:1 binding and a simple equilibrium between the Tb(III) centre of **Tb·1** and **7** [26–32,48]. From these changes, a binding constant, log β, of 4.9 ($\pm$0.2) was determined [48]. However, between p7 = 4.2–2.9, the emission was "switched off", giving rise to the formation of a sigmoidal "Off–On–Off" switch.

To investigate this, we looked at the changes in the 548-nm transition as a function of (equivalents of) **7**. These changes can be seen in Fig. 7, where the emission is highly dependent on the concentration of **7**. From 0 to ca. 3 equivalents of **7**, the Tb(III) is dramatically "switched on", with large order of magnitude enhancements (with ca. 80% of the emission being switched on after 1 equivalent). However, beyond these equivalents, the emission is quenched (see insert in Fig. 7 for 0 → 80 equivalents). Furthermore, the pH of the solution upon addition of **7** did not change during these measurements (in buffered solution), indicating that this quenching was not due to the protonation of **7** with concomitant dissociation of the ternary complex, but rather was directly due to the increased concentration of the antenna. Consequently, we investigated the effect of increasing the concentration of the complexes in the presence of high concentration of the carboxylate (in ca. 20-fold excess prior to increasing the concentration of **Tb·1**). As expected, this gave rise to large enhancements in the Tb(III) emission, suggesting that the luminescent ternary complex was formed.‡ Degassing the solution only led to minor additional increase in the luminescence, indicating that quenching of T_1 by oxygen was only minor.

Similar results were observed when **Tb·2** was titrated using **7**, but the enhancement factors were somewhat smaller. This is possibly due to additional quenching of the Tb(III) excited state by N–H oscillators in **Tb·2** which are absent in **Tb·1**. As before, the emission was highly dependent on the concentration of the antenna. Between p7 = 6.2 and 4.4, the emission was "switched on", with log $\beta = 5.0$ ($\pm$0.2), whereas between 3.5 and 4.5, the emission was "switched off".

The above measurements were repeated using other related derivatives of *N*,*N*-dimethylaminobenzoic acid, namely the ketone **8** and the ester **9**. No changes were seen in the emission spectra of **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2** upon titration with either **8** or **9**, suggesting that it was necessary to have

‡There is also a possibility that at a very high concentration of **7** (OD ~ 0.6 at its max.), some inner filter effects are observed. However, **8** and **9** (see below), which absorb at similar wavelengths, did not give rise to any sensitisation when interacting with **Tb·1**. Furthermore, using **10**, this quenching was much less pronounced (see Fig. 11) for the same concentration range (see later).

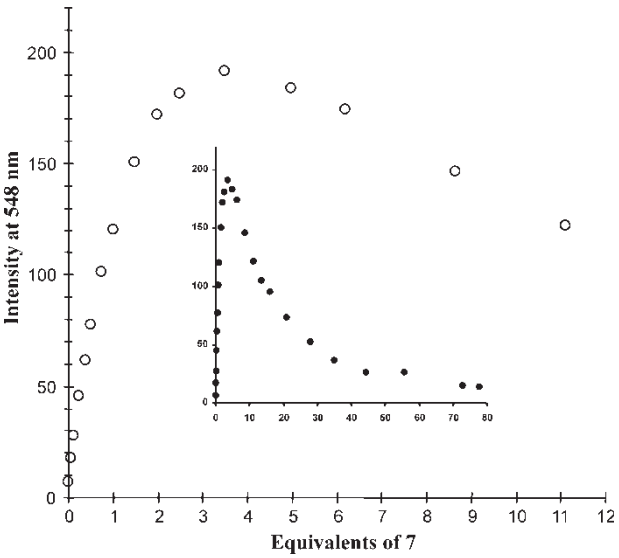


FIGURE 7 Changes in the intensity of the $J = 5$ transition of **Tb·1** as a function of added equivalents of **7**. Inserted are the changes up to 80 equivalents of **7**.

the carboxylate present as the part of the antenna for efficient binding to the metal ion and for sensitisation to occur. Hence, such binding would have to take place through the formation of at least a four-member ring chelate, involving the two oxygens of the carboxylate binding to the metal centre in a bidented manner. This is depicted in Fig. 8A. Furthermore, addition of **7** to a solution of **Tb·1** and **8** or **9** gave rise to large enhancements in the Tb(III) emission, indicating that these potential antennae were not able to bind to the metal ion centre. We thus conclude that **7** can be selectively recognised in the presence of these potential antennae.

Over the last few months, two other research groups have reported the use of similar complexes to bind aromatic carboxylates. Faulkner *et al.* [87] have shown that using tetrathiafulvalene carboxylic acid, the sensitisation of neutral Yb(III)-based triarm carboxylate derived cyclen complexes is possible in the near IR, whereas Li and Wong [88] have shown that Tb(III)-based cyclam complexes functionalised with pendent crown ethers can be used to determining Na^+ and K^+ in the presence of *p*-chlorobenzoate. On both occasions, the q values were found to be reduced from ca. 2 to ~ 0 after binding to these carboxylates antennae to the metal centre for these complexes.

Luminescent Sensing of Salicylic Acid and Related Derivatives

The above luminescence studies were also repeated using salicylic acid (which has a biological concentration of ca. 0.4 mM), and several of its derivatives. Salicylic acid is the active form of aspirin, a well-known non-steroidal anti-inflammatory drug. Salicylic acid is also a good painkiller but causes gastric bleeding due to the free phenolic group [89]. Because of this, it is necessary to mask the phenolic group as an ester (aspirin), which is hydrolysed by esterases to yield the free active drug in circulating blood. Furthermore, aspirin has many other pharmacological actions, some of which have the salicylic acid as the active form. For instance, it has anti-thrombotic action *via* the suppression of plated COX-1 (cyclooxygenase) activity and is thought to have potential anti-tumour actions [90]. However, the cause of gastric bleeding is of major concern, since it can lead to fatal conditions, but currently it is estimated that up to 17,000 people die from this condition every year in USA. The fatal dose of salicylic acid is estimated to be 0.2–0.5 g/kg [91]. Toxic effects appear at varying plasma levels, depending on the duration of poisoning, but are uncommon below 30 mg/dL [91]. However, ingestion of 4 g of salicylic acid has been fatal to infants. It is thus valuable to be able to monitor salicylic acid levels in blood or in serum. With this in mind, we investigated the effect on the Eu(III) and Tb(III) emission of our complexes upon binding to **10** and **11**.

As in the case of **7**, no enhancements were observed in the Eu(III) emission using **Eu·1** and **Eu·2** in the presence of **10** or **11** when measured in either H_2O or in buffer solution at pH 7.4. However, for both **Tb·1** and **Tb·2**, significant enhancements were seen in the Tb(III) emission upon addition of **10**. For instance, upon addition of 10 equivalents of **10**, the Tb(III) emission of **Tb·1** was enhanced by a factor of ca. 40 and 30 in H_2O and in buffer at pH 7.4, respectively. The changes in the Tb(III) emission of

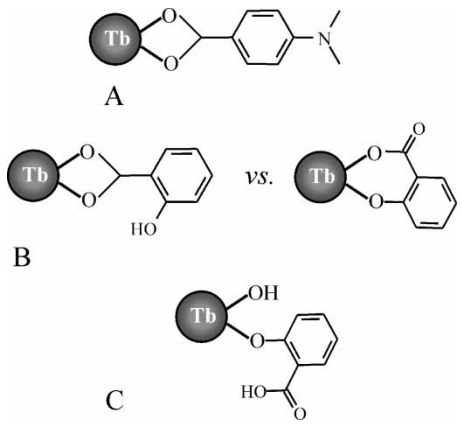


FIGURE 8 (A) Binding of **7** via four-member ring chelate to the Tb(III) centre. (B) Two possible binding modes for salicylic acid: (i) through the four member bidentated carboxylate (left) and (ii) through the six-member chelate involving one of the carboxylate oxygen and the phenolic oxygen. (C) Monocoordinating.

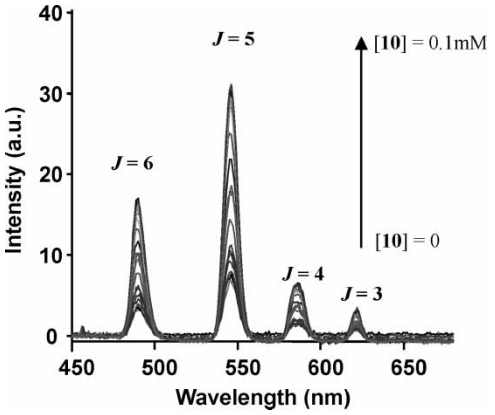


FIGURE 9 Changes in the Tb(III) emission of **Tb·1** upon addition of **10**.

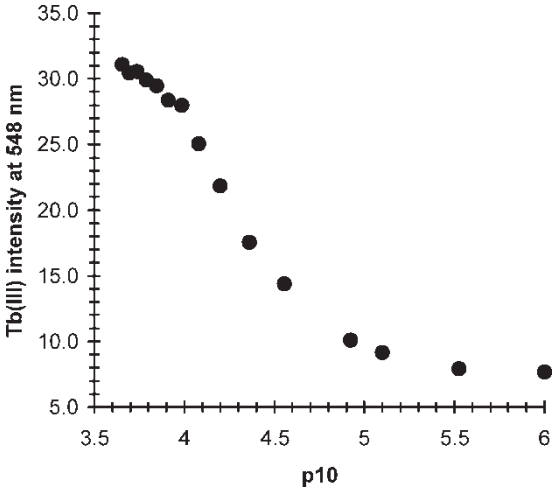


FIGURE 10 Changes in the Tb(III) emission of **Tb·1** at 548 nm as a function of p10.

Tb·1 can be seen in Fig. 9 when recorded in 0.1 M Tris buffer and in the presence of 0.1 M TMACl. However, these are substantially smaller changes than that seen previously for **7**, with the $J = 5$ transition showing the largest changes. For **Tb·2**, the relative enhancement was large, but the relative intensities were much smaller than that seen for **Tb·1**, and it was thus not investigated any further.

As before, the changes in the Tb(III) emission were highly concentration-dependent, though not to the same extent as that seen for **7**. This is clear from Fig. 10, where the intensity at 548 nm is plotted vs. p10. Here, the luminescence is switched on over ca. 2 log units from 5.5 to 3.5, an indication of 1:1 binding and simple equilibrium. From these changes, a binding constant $\log \beta = 4.5$ (± 0.2) was determined. The self-quenching by the anion was also less pronounced, as can be seen in Fig. 11. Here, the Tb(III) emission gradually increases until ca. 6 equivalents have been added. However, between 6 and ca. 15 equivalents of **10**, the emission was not dependent on the concentration of **10**. At higher concentrations, ca. 17 equivalents and above, the emission was however "switched off" (not shown).[§]

When these titrations were repeated using **11**, no luminescent enhancements were observed in the Tb(III) emission for either **Tb·1** or **Tb·2**. This indicates that aspirin was not able to bind to the metal centre strongly enough. It is possible that this is due to the size of the compounds (the presence of the ester), which hinders the access to the metal centre. This was confirmed by measuring the $q \sim 2$ for **Tb·1** in the presence of **11**. Hence, even though **11** has a free carboxylate, no binding was observed.

To investigate the discrimination of **10** over **11** by **Tb·1**, we carried out a series of tritrations using other derivatives of salicylic acid, namely **12**–**14**. As expected, no luminescence enhancements were observed when the mixed ether–ester derivative **14** was used, since both of its possible binding sites are protected. However, when either **12** or **13** was used, large enhancements were seen in the Tb(III) emission. For **12**, these enhancements were in the order of ca. 80, whereas for **13**, a factor of several hundred was observed. These are very interesting results, since they suggest that two possible binding modes can exist for the binding of these salicylic acid derivatives, as depicted in Fig. 8B and C, respectively. In the former, the binding to the Tb(III) centre occurs through a bidentate manner, where the binding occurs via either a four-member ring chelate which involves both of the oxygens of the carboxylates, whereas in the latter, or only one of these oxygens can participate in the binding, and the second coordination site is occupied by the phenolic oxygen, giving rise to a six-member chelate. Nevertheless, since **13** was also found to be a good sensitiser, this suggests that the binding can occur through the phenolic oxygen alone as depicted in Fig. 8 C.

With the aim of shedding some light on this puzzle, we evaluated the q values for **Tb·1** in the presence of **10**, **12** and **13** (0.68 mM). The results of this investigation indicated that $q \sim 0$–1, so it is obvious that the removal of the two metal-bound water molecules is not as pronounced as in the case

[§]In our earlier communication [70], we reported that we were unable to observe more than two emission bands (at 491 and 548 nm corresponding to $J = 6$ and 5, respectively) when measuring these antennae. Though we did not conclude why this was the case, we have since then recorded all the above measurements on a new fluorimeter. As can be seen from Fig. 9, only the $J = 2$ transition is not observed. Hence, our original measurements were carried out on a machine that was not sensitive to these long-wavelength emission bands.

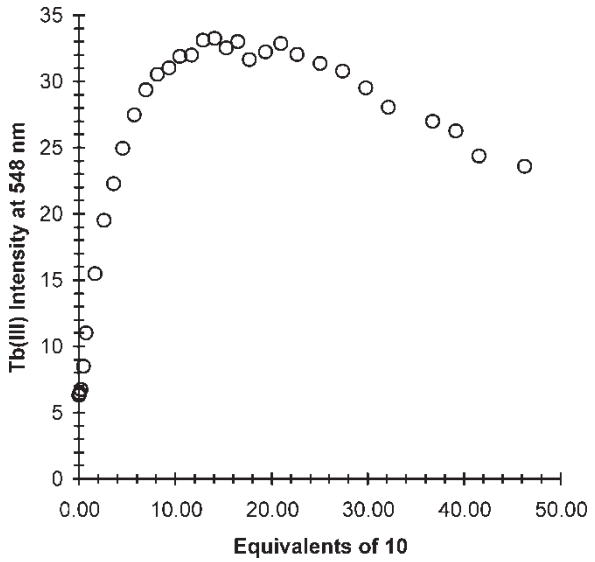


FIGURE 11 Changes in the Tb(III) emission of **Tb·1** at 548 nm as a function of equivalents of **10**.

of **7**. An estimated error of ± 0.5 is generally acceptable for determining q by this method. It is thus quite likely that only one of the metal-bound water molecules is replaced upon the binding of these compounds. This is most likely the case for **13**, which also might explain the relatively smaller luminescent enhancement factors observed for **13** in comparison with **12**. However, we have not been able to fully determine to date whether one or both of these metal-bound water molecules are removed either concurrently or in a stepwise manner. It is also possible that a mixture of these binding modes is operating in the case of **10**, **12** and **13**. Nevertheless, from the above results, we can conclude that **Tb·1** can selectively bind salicylic acid **10** over aspirin **11**. We are currently studying these interactions in greater detail. The above measurements were also carried out in the presence of several other carboxylates, namely **15**, **16** and **17**. Of these, **17** (Diclofenac®) is another well-known non-steroidal anti-inflammatory drug like aspirin. However, for all of these compounds, no enhancements were observed in the Tb(III) emission of either **Tb·1** or **Tb·2**.

We are also interested in the potential application of these complexes in highly competitive environments. For instant, using the sodium salts of AMP, ADP or ATP, which can potentially bind to the Tb(III) complexes via their phosphate ester terminus, no luminescence enhancements were observed when measured at neutral pH. Concurrently, Parker *et al.* have shown that coordinately unsaturated Eu(III) and Tb(III) complexes with covalently bonded chiral antennae can be employed as lanthanide luminescent sensors for simple aliphatic carboxylates such as bicarbonate, carbonate and amino acids [71]. In these complexes, the acetate and carbonates were found to have a stronger affinity for Tb(III) complexes over that of Eu(III). Because of this, we were interested in investigating the effect of competitive binding of carbonate and other biologically active acids to our complexes in the presence of **7** or **10**. We thus monitored the changes in the Tb(III) emission upon addition of a solution containing 30 mM of $NaHCO_3$, 2.3 mM lactate (Na^+ salt), 0.13 mM citric acid and 0.9 mM of $Na_2H_2PO_4$. However, these additions led to a reduction in the Tb(III) emission, most likely indicting that HCO_3^- or the acids were binding to the Tb(III) centre in a competitive manner and causing the dissociation of the ternary luminescent complex within their physiological concentration ranges. We thus conclude that for the monitoring of **10** in serum, it would be necessary to at least degas the sample prior to its use, but we are currently developing new systems for overcoming these drawbacks.

CONCLUSION

We have shown that it is possible to develop simple sensory systems for aromatic carboxylates by employing self-assembly ternary complexes, where the analyte can function as an antenna, and give rise to the population of the lanthanide excited state in water or in buffered aqueous solution at pH 7.4. We have shown using X-ray crystallography that these complexes have two metal-bound water molecules that can be displaced upon binding to aromatic carboxylates such as **7** and **10**. The presence of these water molecules was also confirmed by measuring the luminescent lifetimes of the lanthanide-excited states of these commplexes in H_2O and D_2O. Of the four complexes **Eu·1**, **Eu·2**, **Tb·1** and **Tb·2**, the Eu(III) complexes did not give rise to the formation of such self-assembly complexes. We conclude that this is due to a lower affinity of these complexes towards the carboxylates antennas. Similar observations have been made by other researchers [71,72]. We propose that the binding of **7** to either **Tb·1** or **Tb·2** is *via* the formation of four-member bidented ring chelate, whereas for the binding of **10** to **Tb·1**, this can be through either a mono- or bidentate manner. Such binding was confirmed using **12** and **13**. In retrospect, salicylic acid **10**, the active form of **11**, was found to bind to **Tb·1** (and **Tb·2**) with concomitant enhancements in the Tb(III) luminescence. Related structures such as **17**, another well-known non-steroidal anti-inflammatory drug like aspirin, was not detected. These complexes all gave bell-shaped dependent p*N* profiles, which were determined to be due to self-quenching of the anions. Proof for such quenching was obtained by gradually increasing the amount of the Tb(III) complexes in the presence

of excess amount of **7** or **10**. On both occasions, large enhancements were seen in the Tb(III) emission, indicating the formation of luminescent ternary complexes.

In summary, we have developed new types of chemosensors for anions such as aromatic carboxylates. We are currently working towards enhancing the selectivity and sensitivity of these complexes towards important drugs such as salicylic acid the active form of aspirin for use in blood or serum analysis.

EXPERIMENTAL

General Procedures

Infrared spectra were recorded on a Mattson Genesis II FTIR spectrophotometer equipped with a Gateway 2000 4DX2-66 workstation. Oils were analysed using NaCl plates, and solid samples were dispersed in KBr and recorded as clear pressed discs. ^{1}H NMR spectra were recorded at 400 MHz using a Bruker Spectrospin DPX-400 instrument. Tetramethylsilane (TMS) was used as an internal reference standard, with chemical shifts expressed in parts per million (ppm or δ) downfield from the standard. ^{13}C NMR spectra were recorded at 100 MHz, and ^{19}F NMR spectra were recorded at 376 MHz using a Bruker Spectrospin DPX-400 instrument. Mass spectroscopy was carried out using HPLC-grade solvents. Mass spectra were determined by detection using Electrospray on a Micromass LCT spectrometer, Waters 9360 to pump solvent. The whole system was controlled by MassLynx 3.5 on a Compaq Deskpro workstation. Starting materials were obtained from Sigma Aldrich, Strem Chemicals and Fluka. Columns were run using aluminium oxide (activated, Neutral, Brockmann I STD grade 150 mesh). Solvents were used at GPR grade unless otherwise stated.

X-ray Crystallography

Crystal data for $C_{23}H_{49}F_9N_7O_{16}S_3Tb$ (**Tb·1**): $M = 1105.79$, triclinic, space group $P\bar{1}$, $a = 8.930$ (2) Å, $b = 13.321$ (3) Å, $c = 18.691$ (4) Å, $\alpha = 95.615$ (4), $\beta = 97.542$ (4), $\gamma = 104.149$ (4), $U = 2117.6$ (9) Å^{-3}, $Z = 2$, $\mu = 1.928\,\mathrm{mm}^{-1}$, $R_{\mathrm{int}} = 0.0275$, transmission ratio(max, min) = 0.738. A total of 18,996 reflections were measured for the angle range $2 < 2\theta < 57$, and 9140 independent reflections were used in the refinement. The final parameters were $wR2 = 0.1069$ and $R1 = 0.0406$ [$I > 2\sigma$I].

Diffraction data were collected on a Bruker SMART diffractometer using the SAINT-NT [77,78] software with graphite monochromated Mo-K_α radiation. A crystal was mounted on the diffractometer at room temperature (ca. 298 K) for **Tb·1**. Lorentz and polarisation corrections were applied. Empirical absorption correction was applied using SADABS. The structure was solved using direct methods and refined with the program package [77,78], and the non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen-atom positions were added at idealised positions, and a riding model with fixed thermal parameters [$U_{ij} = 1.2U_{eq}$ for the atom to which they are bonded (1.5 for CH_3)] was used for subsequent refinements. Hydrogen atoms could not be located for the water molecules. The function minimised was $\Sigma[w(|F_o|^2 - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2|F_o|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max|F_o|^2 + 2|F_c|^2]/3$. Additional material available from the Cambridge Crystallographic Data Centre comprises relevant tables of atomic coordinates, bond lengths and angles, and thermal parameters (CCDC number 198706).

Luminescence Studies

All luminescence studies were carried out in aqueous solution or in aqueous solution with a buffer and high ionic strength at pH 7.4. Buffered solutions were made up in aqueous phase with 0.1 M TMACl, 0.1 M HEPES and or 0.1 M Tris buffer, at pH 7.4. Solution concentrations were ~16.7 μM. Test solutions were 5 mL or 10 mL Sensitising chromophore solutions were made up in water 2.0×10^{-3} M and 5.0×10^{-4} M. Luminescence measurements were made on a Perkin Elmer LS 50B and repeated on a Varian Cary Eclipse.

2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethylacetamide (1)

1,4,7,10-Tetraazacyclododecane (98%), (0.375 g, 2.13 mmol) was placed in a 50-mL single-necked RBF. To this were added $NaHCO_3$ (0.537 g, 6.39 mmol) and 15 mL of dried acetonitrile. 2-Chloro-*N*,*N*-dimethylacetamide (0.804 g, 6.6 mmol) was added, and the mixture was stirred at 65°C for a further 72 h. The resulting solution was then cooled and passed through a celite filter. The pale yellow solution was reduced to a yellow residue and dried under vacuum for 1 h to produce (0.829 g, 90.89% yield) a mixture of products, as shown by TLC, that were purified by alumina column using 100% DCM, with a gradient elution to 97:3 DCM:MeOH(NH_3) mobile phase. 0.470 g (1.1 mmol), 52% yield, of 2-(4,10-bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethylacetamide was collected as a white foam after drying under vacuum, which returned to a residue state over time. Calculated for $C_{20}H_{42}N_7O_3$: [M + H peak] $m/z = 428.3344$, found: 428.3349; δ_H ($CDCl_3$, 400 MHz) 10.00 (broad s, 1H, N–H), 3.61(s, 2H, CH_2– acetamide), 3.58(s, 4H, CH_2– acetamide),

3.09(s, 8H), 3.04(s, 3H), 2.96(s, 6H), 2.90(s, 10H), 2.84 (s, 7H); δ_C($CDCl_3$, 100 MHz) 170.25, 170.15, 55.51, 53.80, 51.70, 50.57, 49.72, 46.70, 36.39, 35.27; Mass Spec (MeOH, ES +) m/z. Expected: 427.59. Found: 428.33 (M + H), 450.30 (M + Na), 472.30 (M + K); IR ν_{max} (cm^{-1}) 3434, 2927, 2852, 1637, 1508, 1475, 1402, 1338, 1261, 1103, 1064, 1022, 881, 806, 769, 667, 649, 574, 484.

2-(4,7-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methylacetamide (2)

1,4,7,10-Tetraazacyclododecane (98%) (0.375 g, 2.13 mmol) was placed in a 50-mL single-necked RBF. To this were added $NaHCO_3$ (0.537 g, 6.39 mmol) and 15 mL of dried acetonitrile. 2-Chloro-*N*-methylacetamide, (0.706 g, 6.6 mmol) was added, and the mixture was stirred at 65°C for a further 72 h. The resulting inorganic precipitate was filtered and the filtrate reduced to dryness and triturated from a solution of ethanol by dropping on to ether, giving the desired compound in 59% yield. Calculated for $C_{17}H_{36}N_7O_3$: [M + H peak] $m/z = 386.2880$. Found: 386.2874; δ_H($CDCl_3$, 400 MHz) 7.60 (s, 1H, N–H), 7.30 (s,2H, N–H), 3.06 (s, 4H, CH_2 acetamide), 2.96 (s, 2H, CH_2 acetamide), 2.75 (d, 6H, $J = 4.52$ N–CH_3), 2.67 (d, 3H, $J = 4.52$ N–CH_3), 2.60 (s, 4H, CH_2), 2.58 (s, 4H, CH_2), 2.53 (s, 4H, CH_2), 2.49 (s, 4H, CH_2); δ_C($CDCl_3$, 100 MHz) 171.51, 171.41, 59.54, 57.53, 53.31, 52.63, 51.18, 46.15, 25.89, 25.72. Mass Spec. (MeOH, ES+) m/z. Expected: 385.51. Found: 386.3(M + H), 408.4 (M + Na), 424.4 (M + K); IR ν_{max}(cm − 1) 3430, 2846, 2103, 1643, 1567, 1456, 1415, 1367, 1311, 1257, 1164, 1110, 989, 482.

General Synthesis of 2-(4,10-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methylacetamide Ln(III) (1Ln), and 2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethylacetamide Ln(III) (2Ln)

88.2 mg (0.23 mmol) of **1** or 94.7 mg (0.22 mmol) of **2** and 0.26 mmol of Ln (III) Trifluoromethane sulphonate [$Ln(SO_3CF_3)_3$] was added to a 25-mL single-necked RBF which contained 10 mL of freshly dried acetonitrile. The solution was freeze–thawed three times, placed under an argon atmosphere and left stirring at 82°C for 24 h. The resulting solution was cooled to room temperature and then dropped slowly on to 100 mL of dry diethyl ether. The diethyl ether was poured off to leave **1Ln or 2Ln** as oil that was washed with CH_2Cl_2 or $CHCl_3$ and dried under high vacuum. Yields were ca. 95% in all cases.

2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethylacetamide Tb(III) (Tb·1)

Calculated for $C_{23}H_{41}N_7O_{12}F_9S_3Tb\cdot(H_2O)_2(CHCl_3)_2$: C, 22.95; H, 3.62; N, 7.49. Found: C, 22.23; H, 3.71; N, 7.36. Calculated for $C_{22}H_{42}N_7O_6F_3STb$: [M + H peak] $m/z = 736.2123$. Found: 736.2148; δ_H(CD_3OCD_3, 400 MHz); 39.92, 32.70, 9.00, 3.95, 3.02, 1.02 δ_F (CD_3OCD_3, 376 MHz) − 78.74. Mass spec. (MeCN, ES +) m/z. Expected: 586.5. Found: 884.15 (M[Triflate]$_2$ + H), 736.21 (M[Triflate] + H); IR ν_{max} (cm^{-1}) 3434, 2957, 2927, 2856, 1625, 1508, 1465, 1438, 1412, 1279, 1256, 1171, 1084, 1171, 1084, 1030, 960, 824, 761, 640, 574, 518.

2-(4,10-Bis-dimethylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*,*N*-dimethylacetamide Eu(III) (Eu·1)

Calculated for $C_{23}H_{41}N_7O_{12}F_9S_3Eu\cdot(H_2O)_2(CHCl_3)_2$: C, 23.07; H, 3.64; N, 7.53. Found: C, 22.67; H, 3.74; N, 7.55. Calculated for $C_{21}H_{42}N_7O_6F_3SEu$: [M + H peak] $m/z = 730.2082$. Found: 730.2045; δ_H (CD_3OCD_3, 400 MHz) 13.91, 3.24, 2.60, 2.06, 1.30, 0.89, 0.01, −1.32, −4.95, −8.95, −12.87, −17.65; δ_F (CD_3OCD_3, 376 MHz) − 78.74. Mass spec. (MeCN, ES +) m/z. Expected: 579.56. Found: 878.15 (M[Triflate]$_2$ + H), 730.20 (M[Triflate] + H); IR ν_{max} (cm^{-1}) 3434, 2982, 2927, 2884, 1625, 1508, 1459, 1438, 1413, 1280, 1258, 1173, 1084, 1031, 960, 824, 762, 641, 573, 518.

2-(4,10-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methylacetamide Tb (III) (Tb·2)

Calculated for $C_{20}H_{35}N_7O_{12}F_9S_3Tb\cdot(H_2O)_2(CH_2Cl_2)_2$: C, 22.07; H, 3.62; N, 8.19, Found: C, 21.61; H, 3.59; N, 7.85. Calculated for $C_{19}H_{36}N_7O_9F_6S_2Tb$: [M + H peak] $m/z = 843.1174$. Found: 843.1171. Calculated for $C_{18}H_{36}N_7O_6F_3STb$: [M + H peak] $m/z = 694.1653$. Found: 694.1674; δ_H(MeOD, 400 MHz) 121.87, 107.11, 78.35, 71.89, 68.58, 39.94, 14.52, 7.75, 6.28, 4.26, 1.96, 1.78, 1.49, 1.07, − 7.21; δ_F (MeOD, 376 MHz) − 85.54. Mass spec. (MeCN, ES+) m/z. Expected: 544.4. Found: 272.3 (M + H/2), 843.1(M[Triflate]$_2$ + H), 694.16 (M[Triflate] + H); IR ν_{max}(cm^{-1}) 3435, 3137, 2960, 2924, 1637, 1420, 1259, 1169, 1087, 1030, 994, 974, 798, 639, 574, 519.

2-(4,10-Bis-methylcarbamoylmethyl-1,4,7,10-tetraaza-cyclododec-1-yl)-*N*-methylacetamide Eu (III) (Eu·2)

Calculated for $C_{20}H_{35}N_7O_{12}F_9S_3Eu\cdot(H_2O)_2(CH_2Cl_2)_2$: C, 22.19; H, 3.64; N, 8.24, Found: C, 22.29; H, 3.74; N, 8.38. Calculated for $C_{17}H_{36}N_7O_3Eu$: [M+H peak]

$m/z = 539.2092$, found: 539.2087. Calculated for $C_{18}H_{36}N_7O_6F_3SEu$: [M + H peak] $m/z = 688.1612$, found: 688.1548. Calculated for $C_{19}H_{36}N_7O_9F_6S_2Eu$: [$MH^+$ peak] $m/z = 837.1133$, found: 837.1181; δ_H(MeOD, 400 MHz) 27.04, 14.96, 11.44, 5.20, 3.68, 2.76, 2.41, 1.55, −0.09, −1.84, −4.93, −7.35, −10.77, −12.31, −16.66; δ_F(MeOD, 376 MHz) − 80.45. Mass spec. (MeCN, ES+) m/z. Expected: 538.2. Found: 539.2(M+H), 668.1 (M[Triflate] + H), 837.1 (M[Triflate]$_2$ + H); IR ν_{max} (cm^{-1}) 3455, 3386, 3297, 3143, 3000, 2933, 2885, 1639, 1587, 1465, 1419, 1288, 1245, 1160, 1091, 1027, 725, 638, 576, 516.

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