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Lanthanide luminescence sensing of copper and mercury ions using an iminodiacetate-based Tb(III)-cyclen chemosensor

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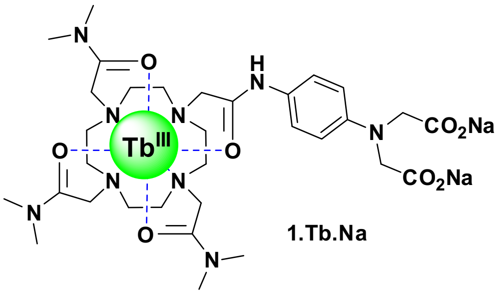
ABSTRACT

The design, synthesis and photophysical evaluation of **1.Tb.Na**, a Tb(III)-cyclen-based sensor, possessing a phenyl iminodiacetate-based receptor, for the selective detection of Cu(II) and Hg(II) ions in water is demonstrated. Sensitisation of the Tb(III) $^5D_4$ excited state was achieved by excitation of the phenyl receptor, which in water gave rise to a characteristic time-delayed and line-like Tb(III) emission. The Tb(III) emission was shown to be pH independent over the physiological pH window. The changes in the Tb(III) emission were monitored by carrying out metal titrations using various groups I, II and transition metal ions. Of these, only the titrations of Cu(II) and Hg(II) gave rise to modulations in the Tb(III) emission; resulting in quenching in the Tb(III) emission by ca. 65% and 40%, respectively.

One of the main research areas within the field of supramolecular chemistry is the development of sensors for use in competitive solution.[1–4] In particular, the detection and monitoring of biologically relevant ions in vitro and in vivo has become of critical importance using luminescent sensors.[3,4] Due to shorter-lived background emission (autofluorescence) and light scattering from such biological environments, the development of sensors possessing long-lived emission lifetimes has become an active area of research.[5–7] The unique photophysical properties of the lanthanides,[8–10] such as long wavelength emissions, sharp line-like bands and relatively long-lived excited state lifetimes [μs for Yb(III) and Nd(III) to ms for Eu(III) and Tb(III)], makes them very attractive candidates for such an application in in vivo sensing as well as for biological imaging, another topical area of research.[5,10–12] Careful functionalisation of the macrocyclic framework, 1,4,7,10-tetraazacyclododecane (cyclen) has allowed for the formation of many examples of thermodynamically stable and kinetically inert complexes with Ln^{III} ions, which have been employed in luminescent sensing of metal ions.[12–17] These possess a suitable antennae/receptor unit which can populate the lanthanide excited states via an energy sensitization process (e.g., the antenna effect); which are perturbed upon binding to ions, giving rise to changes in both the lanthanide emission intensities and lifetimes.[15,16] The design of sensors for detecting ions such as Cu(II) and Hg(II) in aqueous solution at low concentration levels is of current interest in both environmental and biomedical monitoring.[13,18–20] Bound Cu(II) plays a vital role in many enzymatic processes, whilst free Cu(II) can disrupt and damage various biological processes, and is the cause of several conditions such as Wilson and Menkes diseases.[21,22] Similarly, Hg(II) is toxic in humans and can accumulate in the blood–brain barrier which can result in severe neurological disorders.[19] Hence, the design and development of novel sensors which show a strong and selective response at low concentration values for these ions is both an important and a topical area of research.[23]

Herein, we describe the development of **1.Tb.Na**, a Tb(III)-cyclen-based chemosensor possessing an iminodiacetate antenna. The objective is to take advantage of the long-lived and long-wavelength emission properties of Tb(III) in conjunction with the use of a structurally simple and combined antenna/receptor moiety that could selectively recognize Cu(II) and Hg(II) ions in competitive media. Whilst many examples of luminescent lanthanide sensors of group I and II metal ions, as well as several transition metal ions such as Cu(II) and Zn(II) exist,[13–17] the sensing of Hg(II), has, to the best of our knowledge, not been achieved previously using lanthanide luminescence and hence sensor **1.Tb.Na** is the first example of a lanthanide sensor for targeting this ion.



1.Tb.Na

The synthesis of ligand **1** began with the formation of **2**, Scheme 1. This involved the initial di-alkylation of aniline with ethyl bromoacetate using Na_2HPO_4 and KI in refluxing CH_3CN for 24 h, which upon purification by flash silica gel column chromatography

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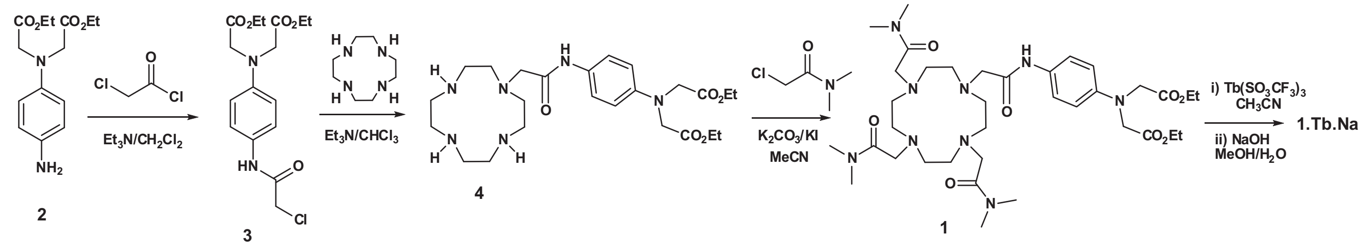
(gradient elution of 100 to 90:10 CH_2Cl_2/CH_3OH), resulted in the isolation of the desired intermediate in 56% yield. Nitration at the *para* position was achieved in acetic acid, at 0 °C, using 70% nitric acid. The desired product was obtained in 93% yield after recrystallisation from EtOH.[24] The product was then subjected to catalytic hydrogenation using 10% Pd/C, in DMF, giving **2** in 90% yield. The formation of the α-chloroamide of **2**, was achieved using chloroacetyl chloride, in the presence of Et_3N, at −10 °C in CH_2Cl_2, which after washing the organic layer with water, 0.1 M HCl and brine, gave **3**, in 86% yield. With the receptor/antenna unit successfully synthesised, the next step involved the introduction to the cyclen framework using the mono alkylation procedure recently published by our group.[25] involving refluxing 4 equiv of cyclen with 1 equiv of **3**, in dry $CHCl_3$, in the presence of Et_3N for 12 h. Isolation of **4** was achieved in 90% yield after the successful removal of the unreacted cyclen by extraction using 1 M NaOH. The final step involved refluxing **4** with 3 equiv of dimethyl acetamide using K_2CO_3 and KI in freshly distiled CH_3CN for five days. Purification of the crude mixture by alumina column chromatography (elution gradient 100 to 80:20 CH_2Cl_2/CH_3OH) was required to give the desired ligand, in 63% yield. The formation of the Tb(III) complex of ligand **1** was achieved by refluxing overnight with an equivalent amount of Tb(III) triflate [$Tb(CF_3SO_3)_3$] in freshly distiled CH_3CN, under an inert atmosphere. Upon completion, the solvent was removed under reduced pressure and the resulting residue re-dissolved in MeOH and added slowly into a large volume of dry diethyl ether, resulting in precipitation of **1.Tb** in 80% yield, as a pale orange solid. The final step involved alkaline hydrolysis of the diethyl diester moiety of **1.Tb** in $MeOH/H_2O$, which gave **1.Tb.Na** in 81% yield.[26]

The design of **1.Tb.Na** envisaged sensitization of the Tb(III) metal ion via excitation of the covalently attached phenyl chromophore, that is, the antenna (possessing both π–π^* and n–π^* transitions). This would enable sensititization of the Tb(III) $^5D_4$ excited state, with concomitant characteristic line-like Tb(III) emission; which would then be expected to be modulated upon binding of d-metal ions at the iminodiacetate moiety, possibly involving electron transfer quenching. Indeed, excitation of **1.Tb.Na** in H_2O at 285 nm (λ_{max} for the antenna) gave rise to Tb-centred emissions at 490, 545, 586 and 622 nm, respectively, verifying successful energy transfer from the antennae to the $^5D_4$ excited state, and deactivation to the ^7F_J (J = 6, 5, 4, 3) ground state. The excited state lifetimes were also measured in both H_2O and D_2O, upon excitation at 285 nm. This gave τ_{H2O} = 1.469 ms and τ_{D2O} = 1.984 ms, demonstrating the long excited state lifetime, from which the hydration state q was determined as ~1 indicating that **1.Tb.Na** possesses one metal bound water molecule, and therefore the Tb(III) ion being overall nine-coordinates within the complex.

It was clear from the structure of **1.Tb.Na** that possible protonation of the aniline moiety as well as potential deprotonation of the secondary amide (as well as the metal bound water) could perturb the photophysical properties of the Tb(III) complex.[27] In order to quantify the pH dependence of the Tb(III) emission from **1.Tb.Na**, we carried out a pH titration, the result of which is shown in Figure 1. Here, the Tb(III) emission corresponding to the $^5D_4 \rightarrow {}^7F_J$ (J = 6, 5, 4, 3) transition occurring at 490 nm, 545 nm, 586 nm and 622 nm, respectively, showed some change with respect to the pH environment, Figure 1. Analysis of the Tb(III) emission for the ΔJ = 5 transition (see inset in Fig. 1) clearly demonstrates that the Tb(III) emission is 'switched on' within the physiological pH range, with any major modulations in emission intensity only occurring below pH 5.5, or above pH 11.5. Hence, there exists a large pH window in which no change in the Tb(III) emission of **1.Tb.Na** is observed, and that this window overlaps with the physiological pH range. Hence, we would anticipate that any modulation in the emission intensity observed within this pH range upon titration with various transition metal ions is solely due to some form of interaction with the



Scheme 1. Synthesis of **1.Tb.Na**.

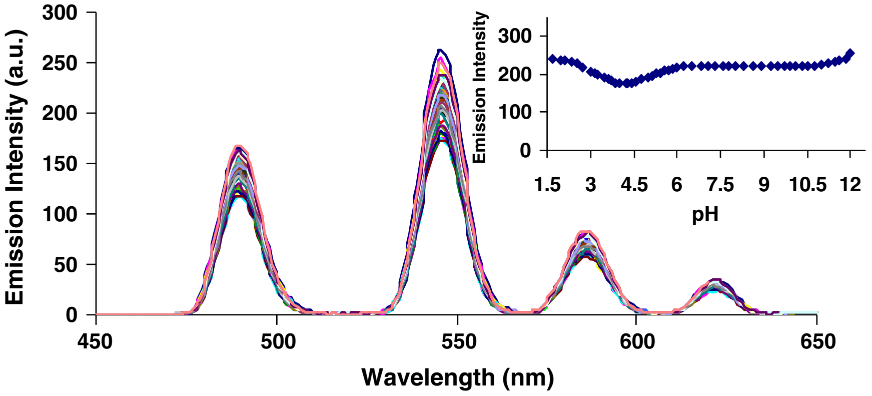


Figure 1. The overall changes in the Tb(III) luminescence of **1.Tb.Na** (10 μM) upon excitation of the phenyl antenna (λ_{ex} = 285 nm) as a function of pH (I = 0.1 M NEt_4HClO_4 (TEAP)). Inset: The changes at 545 nm versus pH.

complex, and not as a result of a change in the pH of the solution.[8,15]

Having established the pH behaviour of **1.Tb.Na**, the next step was to investigate its ability to recognise various group I, group II and transition metal ions in solution. Screening a large library of these in water at pH 7, demonstrated that the Tb(III) emission was only affected by the presence of Cu(II) and Hg(II), using either the Cl^- or $HClO_4^-$ salts of these ions. However, ions such as Co(II) and Ni(II) also gave rise to changes in the Tb(III) emission, but these were due to the appearance of an absorption band corresponding to these ions, and hence, an inner filter effect, and not the direct binding of these ions to the receptor of **1.Tb.Na**.[28] Moreover, it was observed that in the presence of either HEPES or TRIS buffers alone, both the Cu(II) and Hg(II) ions showed some form of complexation with the buffers resulting in the formation of a strong absorption band which overlapped with the absorption of the antenna in **1.Tb.Na**. Given the fact that the Tb(III) emission can be considered as pH independent within the physiological pH range, for example, as demonstrated as an inset in Figure 1, all the titrations discussed herein were carried out in the absence of any buffer in deionised H_2O. Nevertheless, to ensure that there was no pH effect, the pHs of all the samples were recorded before and after carrying out these titrations; the pH was not found to change by more than 0.2 pH units.

The changes in the ground-state properties of **1.Tb.Na** upon titration with Cu(II) ions (using the $HClO_4^-$ salt) were first investigated, the results of which are shown in Figure 2. The changes observed in the spectra clearly indicate an interaction between the Cu(II) ions in solution and the iminodiacetate moiety of **1.Tb.Na**, where the absorption band centred at 285 nm was blue-shifted to 260 nm, with the formation of an isobestic point at ca. 266 nm. The titration profile of the absorbance changes at 285 nm versus the number of equivalents of Cu(II) added is shown as an inset in Figure 2, and suggests that the most significant interaction occurs between 0 and 1 equiv of Cu(II), with minor changes occurring between 1 and 2 equiv (0–20 μM). A similar response was observed on analysis of the singlet excited state of **1.Tb.Na**, where, in the absence of Cu(II), a broad emission band was observed, centred at 350 nm with a slight shoulder at ca. 300 nm. Upon binding to Cu(II), a moderate emission intensity increase of ca. 15% was observed (with a slight hypsochromic shift to 345 nm) being most significant within the addition of 0–2 equiv of Cu(II), as seen above in the absorption spectra.

We next monitored changes in the Tb(III) emission upon Cu(II) binding to the receptor which was expected to effect the energy transfer process from the antenna to the lanthanide, and hence, the Tb(III) emission. The luminescence spectrum of **1.Tb.Na**, upon titration with Cu(II) is shown in Figure 3, and clearly demonstrates a gradual decrease in the Tb(III) emission as a function of increased Cu(II) concentration with ca. 65% quenching being observed at 545 nm, with a similar magnitude of quenching being seen for the other transitions. The Tb(III) excited state lifetime was also shortened upon binding to Cu(II), with $\tau_{H2O} = 1.180$ ms. A plot of the Tb(III) intensity at 545 nm versus Cu(II) equivalents is shown

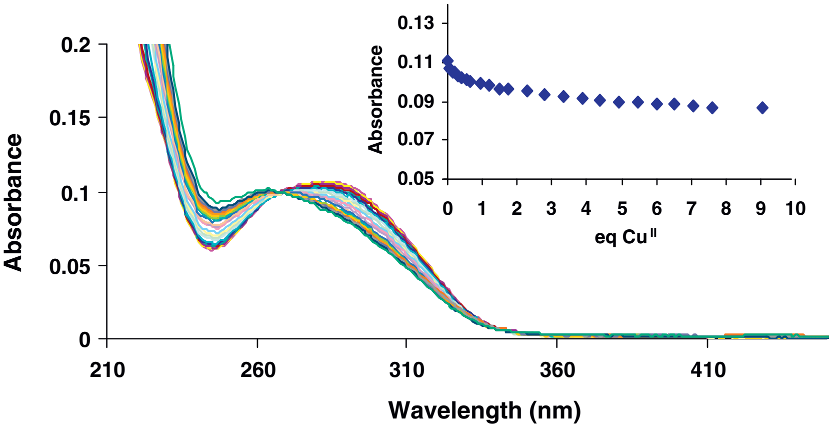


Figure 2. The overall changes in the absorption spectra (uncorrected) of **1.Tb.Na** (10 μM) upon titration with $Cu(HClO_4)_2$ in deionised H_2O. Inset: Changes observed at 285 nm as a function of equivalents of Cu(II) added.

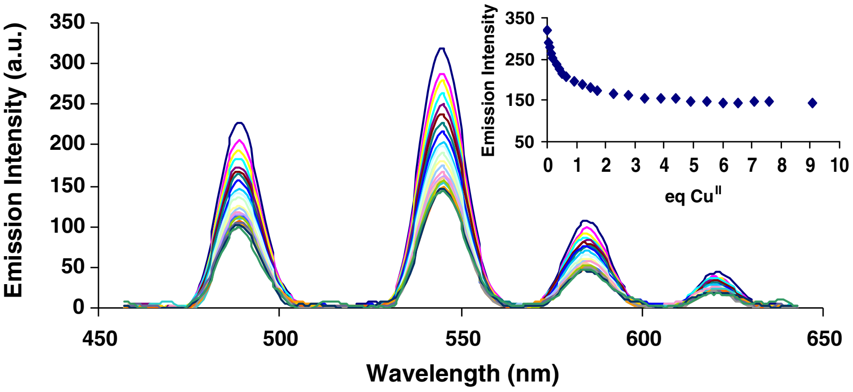


Figure 3. Changes in the Tb(III) luminescence spectra of **1.Tb.Na** (10 μM) upon titration with $Cu(HClO_4)_2$ (being quenched) in deionised H_2O (0–100 μM). Inset: Changes observed at 454 nm as a function of equivalents of Cu(II) added.

as an inset in Figure 3, and demonstrates the ability of **1.Tb.Na** to bind Cu(II), with concomitant changes in the emission properties. Analysis of the changes in Figure 3 also showed that the sensor bound the ion in a 1:1 stoichiometry, Figure 4, which demonstrates that the binding occurs over two log units, with an estimated binding constant[29] of log $K = 5.5$ (±0.2). Figure 4, also shows the response observed for ions such as Zn(II) and Cd(II) as well as the group II ions Mg(II) and Ca(II), which did not give rise to any significant changes in the Tb(III) emission. This also demonstrates the importance of our receptor design, as structurally related sensors have been developed by Parker and co-wokers.[16] for the selective sensing of Zn(II); which is not detected by **1.Tb.Na**. With the free Cu(II) concentrations in serum being in the range of 12.5–21 μM,[30] it is clear from the titration profile in Figure 4, that **1.Tb.Na** can detect Cu(II) within this concentration window. Figure 4 also shows the changes observed in the Tb(III) emission of **1.Tb.Na**, upon titration with Hg(II), the overall spectral changes being shown in Figure 5. A similar response to that seen with Cu(II) was observed, that is, only the intensity and lifetime were affected, where upon the addition of 10 equiv (100 μM) of Hg(II) gave rise to ca. 40% luminescence quenching in the Tb(III) emission, with $\tau_{H2O} = 1.302$ ms. From these changes, we estimated the Hg(II) binding affinity of **1.Tb.Na** as log $K = 4.6$ (±0.2). These studies suggest that **1.Tb.Na** shows both high sensitivity and selectivity for both Cu(II) and Hg(II) ions; which was achieved through binding at the iminodiacetate receptor moiety in solution. These results also demonstrate that the sensor is more sensitive to Cu(II) over Hg(II) (cf. Fig. 4). To confirm this, we also carried out a test where first, an excess amount of Hg(II) was added to a solution of the sensor. This again, gave rise to quenching in the Tb(III) emission to the same degree as seen for the Hg(II) titrations. However, subsequent addition of Cu(II) lead to further quenching in the Tb(III) emission, clearly demonstrating this selectivity. We also investigated the response of **1.Tb.Na** toward Cu(II) and Hg(II) in a simulated biological environment with 150 mM NaCl, 10 mM KCl, 10 mM $CaCl_2$, 10 mM $MgCl_2$, 10 mM $CdCl_2$ and 10 mM $ZnCl_2$, at pH 7. As expected, no significant modulation in the singlet excited state properties of the Tb(III) metal was observed in the presence of this mimicked biological background, but addition of both Cu(II) and Hg(II) to the solution resulted in quenching of the Tb(III) metal luminescence, to the same extent as seen in the above titrations.

In summary, we have developed a Tb(III) cyclen-based chemosensor, with the incorporation of an iminodiacetate receptor/antenna unit, for Cu(II) and Hg(II) ions in water at pH 7. Whilst only minor changes were observed in both the absorption and fluorescence spectra of **1.Tb.Na**, upon recognition of these ions, a substantial quenching was observed in the Tb(III) emission. These studies showed that the sensor has a high affinity for both of these ions, where Cu(II) is selectively bound. It was also shown that in the presence of other biologically relevant ions, the emission

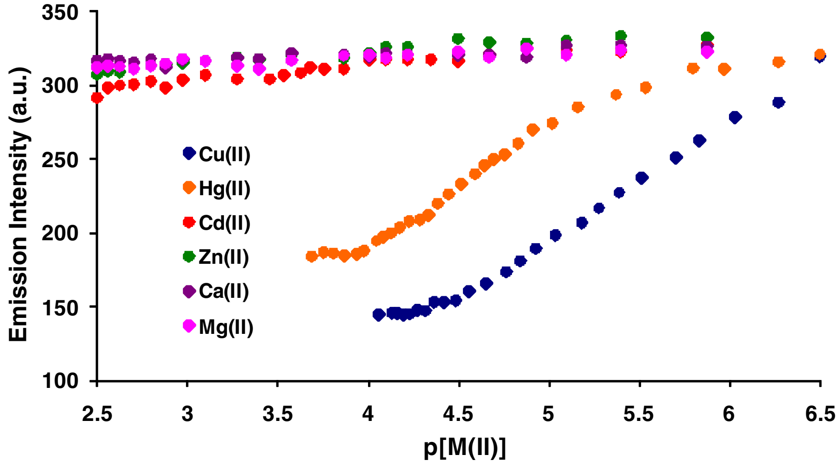


Figure 4. Plot of the changes in the Tb(III) luminescence of **1.Tb.Na** (10 μM) at 545 nm upon titration with $M(HClO_4)_2$ or MCl_2 (expressed as pM = −log [M]) in deionised H_2O.

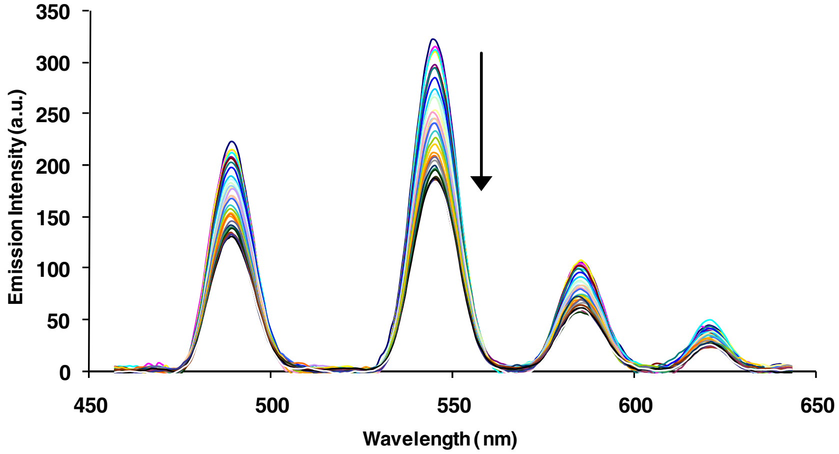


Figure 5. Changes in the Tb(III) luminescence spectra of **1.Tb.Na** (10 μM) upon titration with $Hg(HClO_4)_2$ (being quenched) in deionised H_2O (0–100 μM).

properties of the Tb(III) metal were not modulated, confirming the **1.Tb.Na** selectivity for Cu(II) and Hg(II). We are in the process of developing analogues of **1.Tb.Na**, using other antennae, which will enable us to achieve sensitisation of Tb(III) at longer wavelengths and at the same time preserve the binding ability of the receptor unit, already used for **1.Tb.Na**.

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26. Ligand **1** was obtained as an orange crystalline solid. (0.5 g, 63% yield). Mp 189–192 °C; HRMS (m/z, ES$^+$) calcd for $C_{36}H_{61}N_9O_8Na$ $m/z = 770.4541$ [M+Na]. Found $m/z = 770.4549$; ^{1}H NMR (400 MHz, $CDCl_3$, δ_H): 10.40 (s, 1H, N–*H*), 7.70 (d, 2 H, $J = 9$ Hz, Ar–*H*), 6.47 (d, 2 H, $J = 9$ Hz, Ar-*H*), 4.17 (q, 4 H, $J = 7$ Hz, $NCH_2CO_2CH_2CH_3$) 4.08 (s, 4H, $NCH_2CO_2CH_2CH_3$), 3.30–1.98 (br m, 42H, cyclen-CH_2 + 4,7,10-$CH_2CON(CH_3)_2$ + 1-$CH_2CONH)_1$ 1.26 (t, 6 H, $J = 7$ Hz, $NCH_2CO_2CH_2CH_3$); ^{13}C NMR (100 MHz, $CDCl_3$, δ_c): 170.58 (q), 170.52 (q), 170.24 (q), 169.58 (q), 143.48 (CH), 130.65 (CH), 120.72 (CH_2), 112.06 (CH_2), 60.59 (CH_2), 57.44 (CH_2), 54.42 (CH_2), 53.36 (CH_2), 53.03 (CH_2), 50.13 (CH_2), 35.96 (CH_3), 35.71 (CH_3), 35.22 (CH_3), 35.12 (CH_3), 13.80 (CH_3); IR ν_{max} (cm^{-1}): 2818, 1740, 1646, 1518, 1450, 1400, 1370, 1346, 1297, 1262, 1179, 1102, 1062, 1005, 974, 902, 818, 772, 730, 631.

    Complex **1.Tb** was obtained as a pale orange solid (0.06 g, 80% yield). Mp decomposed above 200 °C; calcd for $C_{42}H_{84}Cl_9F_9N_9O_{17}S_3Tb$: C, 29.17; H, 3.85; N, 7.29. Found C, 29.19; H, 3.85; N, 7.47; HRMS (m/z) calcd for $C_{38}H_{61}F_6N_9O_{14}S_2Tb$ $m/z = 1204.2937$ [M+2(CF_3SO_3)]. Found $m/z = 1204.2952$; ^{1}H NMR (400 MHz, $CDCl_3$, δ_H) 72.47, 61.18, 50.78, 49.44, 46.20, 42.74, 36,48, 35,48, 34.58, 23.40, 19.48, 17.81, 13.79, 7.64, 6.75, 4.25, 3.79, 3.06, 2.76, 2.43, 1.43, 1.34, 0.93. IR ν_{max} (cm^{-1}): 3458, 2941, 1735, 1618, 1560, 1520, 1459, 1411, 1246, 1224, 1158, 1081, 1028, 958, 910, 823, 759, 635.

    Complex **1.Tb.Na** was obtained as a pale yellow solid (0.080 g, 81% yield). Mp decomposed above 250 °C; HRMS (m/z, ES$^+$) calcd for $C_{34}H_{53}N_9O_{14}S_2F_6Tb$ $m/z = 1148.2311$ [M−CF_3SO_3−2Na+2H]$^+$. Found $m/z = 1148.2357$; ^{1}H NMR (400 MHz, D_2O, δ_H): 85.92, 79.51, 69.02, 67.04, 61.52, 58.42, 54.56, 53.79, 52.79, 49.04, 44.07, 44.38, 22.96, 21.53, 20.53, 16.67, 15.77, 14.20, 11.41, 10.37, 8.35, 7.84, 7.19, 6.72, 6.59, 6.43, 6.34, 3.52, 1.30, 1.17, −0.06, −82.05, −85.69, −88.45, −97.73, −101.59, −103.47; IR ν_{max} (cm^{-1}): 2972, 1603, 1438, 1251, 1229, 1168, 1088, 1035, 945, 906, 878, 864, 765, 687, 638.
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28. This was verified by carrying out titrations using these ions in the absence of the sensor, which on both occasions, gave rise to large absorptions with a λ_{max} of 400 and 505, which partially overlapped with the emission wavelengths of Tb(III).
29. We were unable to fit the changes in the Tb(III) accurately using non-linear regression analysis.
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