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A smart "off–on" gate for the *in situ* detection of hydrogen sulphide with Cu(II)-assisted europium emission†

Zhenhao Liang,[ab] Tik-Hung Tsoi,[b] Chi-Fai Chan,[c] Lixiong Dai,[bc] Yudan Wu,[a] Guangyan Du,[a] Lizhi Zhu,[ab] Chi-Sing Lee,*[a] Wing-Tak Wong,*[b] Ga-Lai Law*[b] and Ka-Leung Wong*[c]

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A water-soluble and emissive Eu-complex (**EuL1**) bearing a DO3A(Eu^{3+})–pyridine–aza-crown motif has been prepared and its Cu^{2+} complex has been demonstrated to be a smart luminescence "off–on" gate for H_2S detection in water with a nano-molar detection limit (60 nM). **EuL1** binds to Cu^{2+} ions selectively ($K_B = 1.2 \times 10^5$ M^{-1}) inducing 17-fold luminescence quenching and forming a 1 : 1 stoichiometric complex (**EuL1**–Cu^{2+}), which responds to H_2S selectively with restoration of the original Eu emission of **EuL1** followed by a further 40-fold luminescence enhancement, forming a 1 : 1 stoichiometric complex (**EuL1**–Na_2S, $K_B = 1.5 \times 10^4$ M^{-1}). Without Cu^{2+} ions, **EuL1** showed non-specific binding towards H_2S with only a 5-fold luminescence enhancement.

Introduction

Hydrogen sulphide (H_2S) is the smallest bioactive thiol that may act as a gaseous signalling agent,[1] and its production in different tissue types is associated with a wide range of physiological responses such as vascular smooth muscle relaxation,[2] mitochondrial ATP production,[3] insulin-signalling inhibition,[4] regulation of inflammation response[5] and mediation of neurotransmission.[6] Moreover, recent investigations show that abnormal levels of H_2S are associated with a variety of diseases, such as neurodegenerative diseases,[7] diabetes[8] and cancer.[9] However, the biological targets of H_2S and the mechanisms of these H_2S-related physiological phenomena remain unclear. Therefore the development of responsive and reversible luminescence probes for non-invasive real time monitoring of H_2S may be useful for understanding its biological modes of action.

One of the major approaches for developing luminescence H_2S detection[10] is based on sulphide-specific chemical reactions, such as reduction of an azide[11] and nucleophilic addition of a sulphide ion.[12] This type of luminescence probe is generally irreversible and usually requires a considerably long incubation time. An alternative approach is based on CuS precipitation[13] due to the low-solubility of CuS ($K_{sp} = 6.3 \times 10^{-36}$). These luminescence probes are generally reversible with low detection limits. We are particularly interested in developing H_2S luminescence sensors based on organo-lanthanide complexes due to their water-solubility and unique photophysical properties, including line-like emission spectra and long luminescence lifetimes (micro to milli second scale) that can effectively separate the observing signal from biological autofluorescence noise and are suitable for time-gated detection. Recently, a few studies have been found in the literature with irreversible H_2S lanthanide probes.[12a] Herein, we report the development of a novel responsive europium-based luminescence "off–on" gate for the *in situ* detection of H_2S in water.

As illustrated in Fig. 1, **EuL1** contains a DO3A–Eu^{3+} complex and an aza-18-crown-6 moiety, which are linked to the 2- and 6-positions of a pyridine-containing chromophore constituting a switch-like structure. In the ground state, **EuL1** should be emissive due to the coordination of the pyridine chromophore

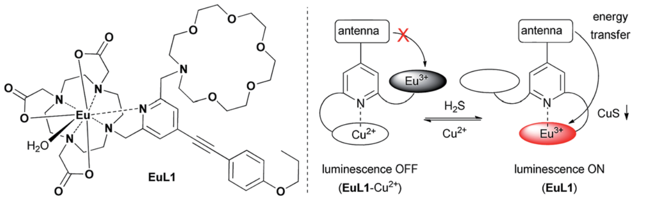

Fig. 1 The structure of **EuL1** and the illustration of the design of a reversible Eu-based luminescence probe (**EuL1**–Cu^{2+}) for H_2S detection.

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[a] *Laboratory of Chemical Genomics, School of Chemical Biology and Biotechnology, Peking University Shenzhen Graduate School, Shenzhen University Town, Xili, Shenzhen 518055, China. E-mail: lizc@pkusz.edu.cn*

[b] *State Key Laboratory for Chiral Sciences, Department of Applied Biological and Chemical Technology, Hong Kong Polytechnic University Shenzhen Research Institute, Shenzhen, China*

[c] *Department of Chemistry, Hong Kong Baptist University, Kowloon Tong, Hong Kong*

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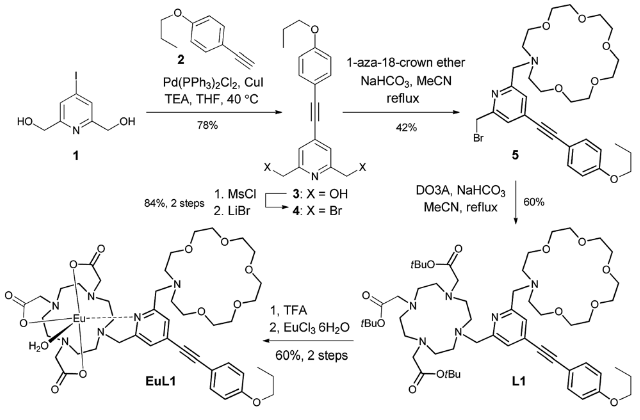
to a Eu^{3+} ion, which favours energy transfer from the organic chromophore to the Eu^{3+} ion. Upon binding of the aza-18-crown-6 moiety with a Cu^{2+} ion, pyridine is expected to coordinate with the Cu^{2+} ion, resulting in luminescence quenching. The europium emission should be recovered after the displacement of the Cu^{2+} ion upon copper sulphide precipitation.

Results and discussion

Synthesis and photophysical properties of L1 and EuL1

Ligand **L1** was readily prepared from (4-iodopyridine-2,6-diyl) dimethanol (**1**)[14] *via* a desymmetrization synthetic strategy. As shown in Scheme 1, a pyridine-containing chromophore (based on a D–π–A motif) was established *via* a Sonogashira cross-coupling reaction between **1** and 1-ethynyl-4-propoxybenzene (**2**).[15] After converting both hydroxyl groups of **3** into the corresponding bromide, the aza-18-crown-6 and DO3A moieties were incorporated into **4** sequentially under basic conditions and afforded **L1** in good yields. **L1** was fully characterized using ^1H and ^{13}C NMR spectroscopy and HRMS. Finally, acid hydrolysis of the *t*-butyl esters followed by Eu complex formation provided **EuL1**, which was characterized unambiguously using HRMS and HPLC (Table S1 and Fig. S1†).



Scheme 1 Synthesis of L1 and EuL1.

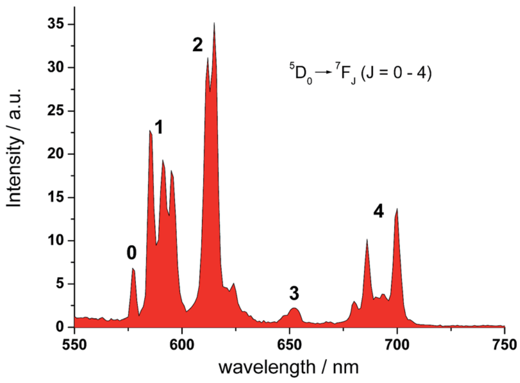


Fig. 2 Emission spectrum of **EuL1** (H_2O, $\lambda_{ex} = 325$ nm, 10 μM).

In the UV-vis absorption spectrum, **L1** showed strong absorption bands at 235 and 310 nm in methanol which are attributed to the π to π* transitions. The absorption bands were broadened and red-shifted in **EuL1** (245 and 333 nm, $\varepsilon_{333\ nm} = 7560\ M^{-1}\ cm^{-1}$) in water (Fig. S2†). The excitation spectrum of **EuL1** at 615 nm showed maxima at 240 and 340 nm (Fig. S2†), evidencing an antenna effect due to energy transfer from the ligand to the Eu^{3+} ion. The $^5D_0 \rightarrow {}^7F_J$ transitions of **EuL1** ($\lambda_{ex} = 325$ nm) were found at 578 ($J = 0$), 585–603 ($J = 1$), 604–637 ($J = 2$), 646–658 ($J = 3$), and 673–712 nm ($J = 4$) in the emission spectrum (Fig. 2). The quantum yield of **EuL1** corresponding to the $^5D_0 \rightarrow {}^7F_2$ transitions of Eu^{3+} ions in water is 0.5% (Table S2†).

Fluorimetric titration studies of EuL1

With **EuL1** in hand, its binding properties towards Cu^{2+} ions were investigated. Upon the addition of 1 equiv. of Cu^{2+} ions ($CuCl_2$ as the source of Cu^{2+} ions), the absorption maximum of **EuL1** showed a slight red shift and the absorption ability slightly decreased due to the effect of the copper metal. In a titration study, **EuL1** exhibited a 17-fold quenching of the

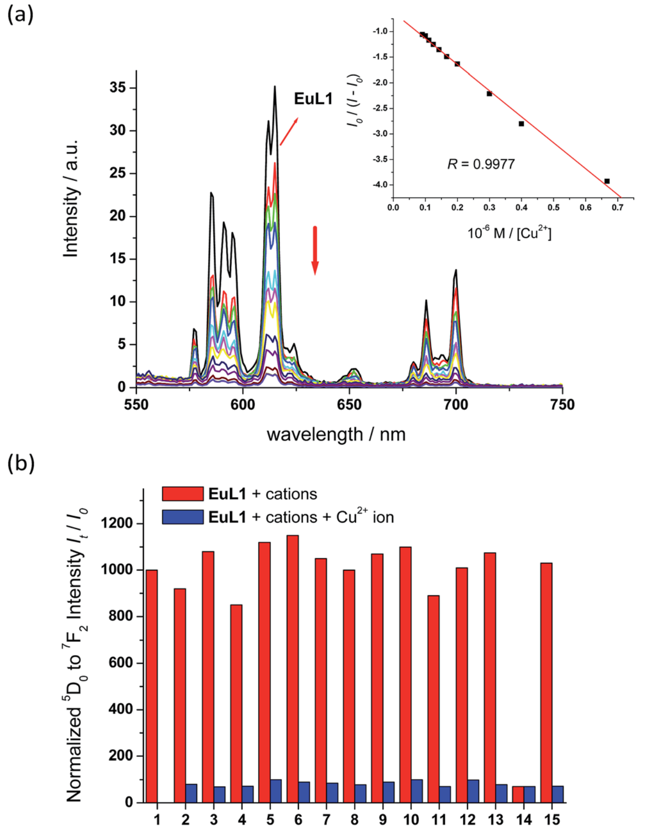


Fig. 3 (a) Fluorimetric titration of **EuL1** (10 μM) towards Cu^{2+}. The inset shows the plot of $I_0/(I - I_0)$ *vs.* [Cu^{2+}] (0–20 μM). I and I_0 stand for intensity of europium emission $^5D_0 \rightarrow {}^7F_2$. (b) Effects of various metal ions on the luminescence intensity of **EuL1** (10 μM). 1: **EuL1** only; 2: Na^+; 3: K^+; 4: Ca^{2+}; 5: Mg^{2+}; 6: Ba^{2+}; 7: Co^{2+}; 8: Zn^{2+}; 9: Ni^{2+}; 10: Fe^{2+}; 11: Mn^{2+}; 12: Cu^+; 13: Li^+; 14: Cu^{2+}; 15: all of the above metal ions except Cu^{2+}. All spectra were acquired in water with excitation at 325 nm.

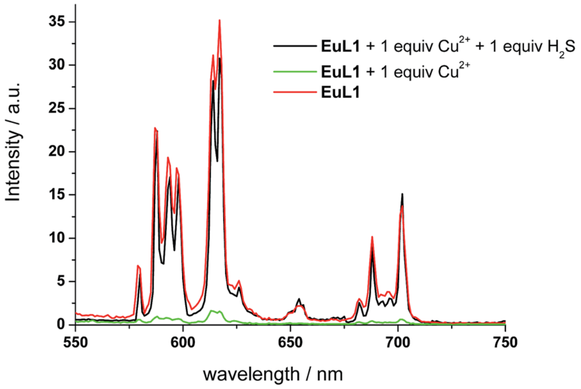


Fig. 4 The emission spectra of **EuL1** (10 μM) (red), with 1 equiv. of Cu^{2+} ions (green), and with 1 equiv. of Cu^{2+} ions and 1 equiv. of H_2S (black). All spectra were acquired in water with λ_{ex} at 325 nm.

europium emission with an excess of Cu^{2+} ions and the Benesi–Hildebrand plot showed a 1 : 1 binding stoichiometry with $K_B = 1.2 \times 10^5\ M^{-1}$ (inset of Fig. 3a).[16] The Job's plot also supported the formation of a **EuL1**–Cu^{2+} complex in a 1 : 1 ratio (Fig. S3†).

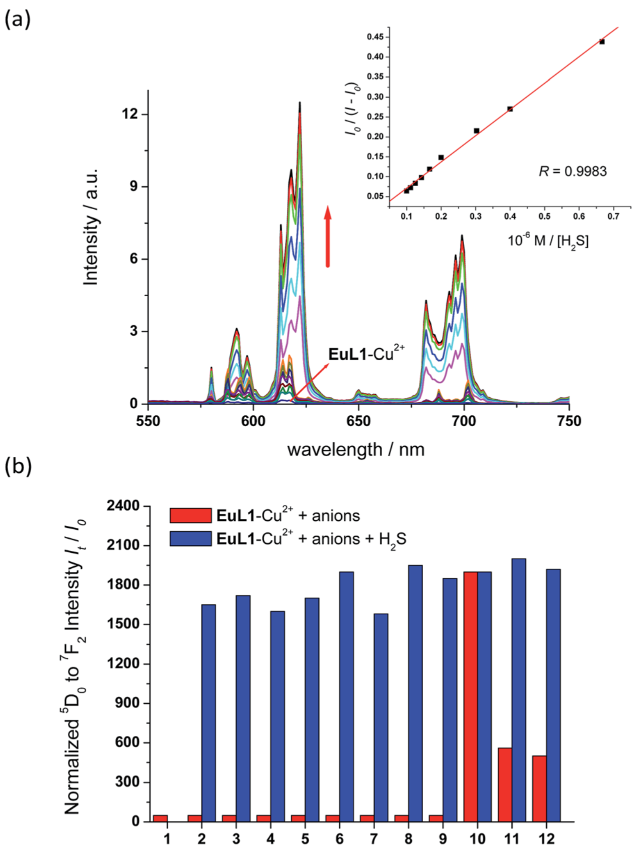


Fig. 5 (a) Fluorimetric titration of **EuL1**–Cu^{2+} (10 μM, generated *in situ* with 2 equiv. of Cu^{2+}) towards H_2S (0–100 μM). The inset shows the plot of $I_0/(I - I_0)$ *vs.* [Na_2S] (0–100 μM). I and I_0 stand for intensity of europium emission $^5D_0 \rightarrow {}^7F_2$. (b) Effects of various anions on the luminescence intensity of **EuL1** (10 μM). 1: **EuL1** only; 2: Cl^-; 3: SO_4^{2-}; 4: HSO_4^-; 5: I^-; 6: CO_3^{2-}; 7: HPO_4^{2-}; 8: Br^-; 9: HCO_3^-; 10: S^{2-}; 11: GSH; 12: cysteine. All spectra were acquired in water with excitation at 325 nm.

In a competitive study, the addition of a large excess of various metal ions, such as Na^+, K^+, Ca^{2+}, Mg^{2+}, Ba^{2+}, Co^{2+}, Zn^{2+}, Ni^{2+}, Fe^{2+}, Mn^{2+}, Cu^+ and Li^+ ions, to **EuL1** resulted in only slight luminescence changes (red columns in Fig. 3b). The subsequent addition of excess Cu^{2+} ions caused significant luminescence quenching (blue columns in Fig. 3b). These results indicate the high selectivity of **EuL1** towards Cu^{2+} ions and that the binding between **EuL1** and Cu^{2+} ions is not interfered by other metal ions. In a pH study, **EuL1** remains highly emissive and was quenched by Cu^{2+} ions in the pH range 6 to 8 (Fig. S4†), indicating that **EuL1** is stable and can bind to Cu^{2+} ions under physiological conditions.

To study the reversibility of the binding between **EuL1** and Cu^{2+} ions, a small amount of H_2S (Na_2S as the source of H_2S) was added. The **EuL1**–Cu^{2+} complex responded instantaneously (requiring only 40 s to reach saturation without stirring or shaking) (Fig. S5†), and Eu emission resumed with a similar profile for the emission spectrum to that of **EuL1** (Fig. 4). This result indicated that the DO3A–Eu^{3+} complex was not displaced by a Cu^{2+} ion, forming the **EuL1**–Cu^{2+} complex in the previous step. More interestingly, Eu emission was further enhanced (40-fold) with an excess of H_2S and the Eu^{3+} emission profile showed significant changes, suggesting binding between **EuL1** and H_2S (Fig. 5a). The Benesi–Hildebrand plot showed a 1 : 1 binding stoichiometry with $K_B = 1.5 \times 10^4\ M^{-1}$ (inset of Fig. 5a).[16] The detection limit of **EuL1** towards H_2S was calculated according to the $3S_D$/slope as low as 60 nM. Surprisingly, direct titration of **EuL1** against H_2S resulted in only about a 5-fold luminescence enhancement with a non-linear relationship in the 1 : 1 Benesi–Hildebrand plot (Fig. 6). These results indicated that the Cu^{2+} ion facilitates the specific 1 : 1 binding of **EuL1** and H_2S, presumably *via* pre-organizing the conformation of **EuL1**. On the other hand, non-specific binding (possibly a mixture of 1 : 1 and 2 : 1 binding) between **EuL1** and H_2S resulted without the favourable conformation that is induced by

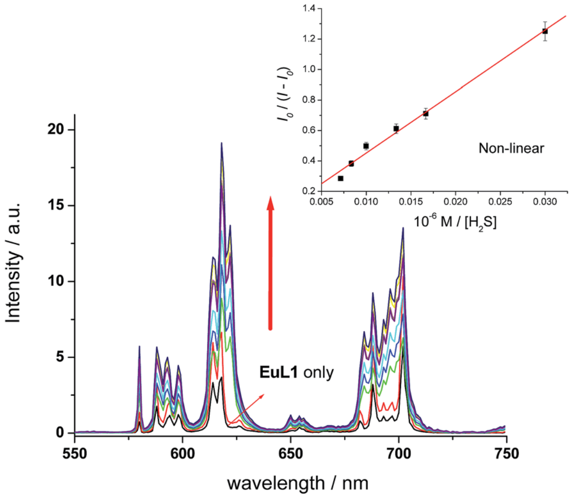


Fig. 6 Fluorimetric titration of **EuL1** (10 μM) towards H_2S (0–300 μM). The inset shows the plot of $I_0/(I - I_0)$ *vs.* [H_2S] (0–300 μM). I and I_0 stand for intensity of europium emission $^5D_0 \rightarrow {}^7F_2$. All spectra were acquired in water with λ_{ex} at 325 nm.

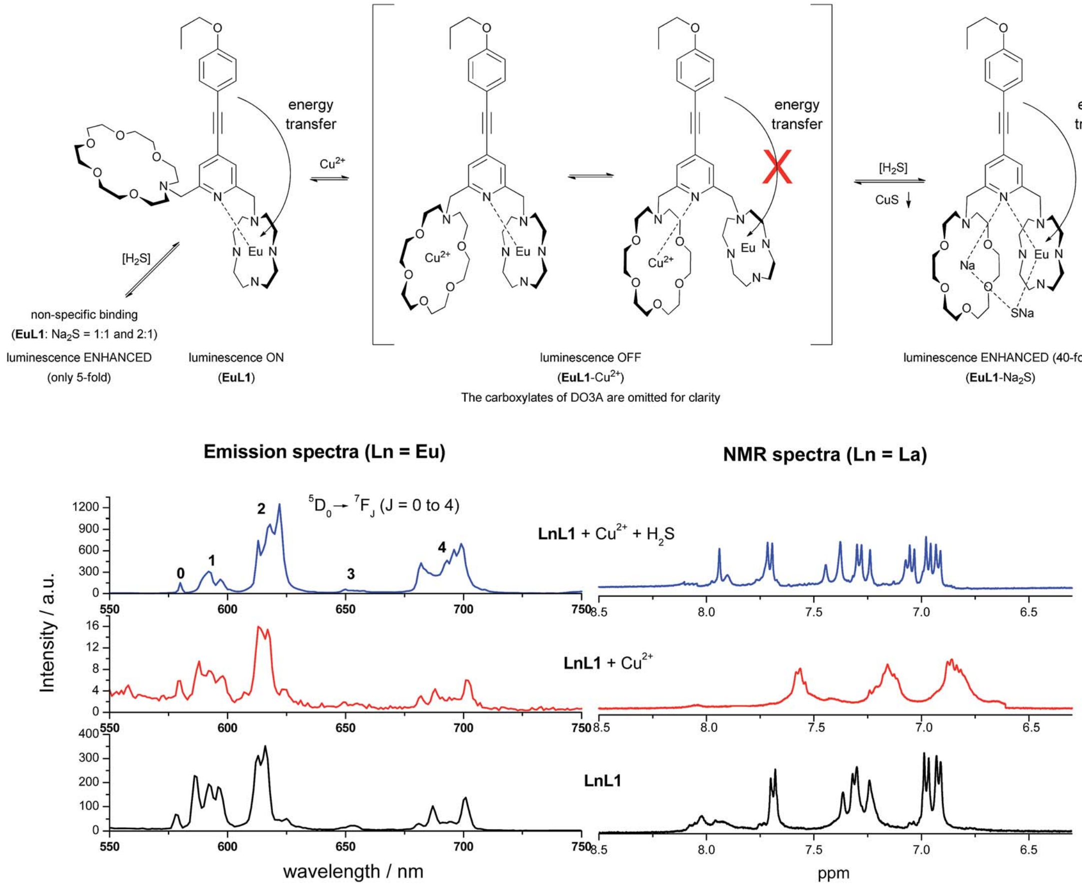


Fig. 7 Top: proposed binding mechanism of **EuL1** towards Cu^{2+} and H_2S (Na_2S as the source of H_2S). Bottom left: emission spectra of the Eu complexes ($\lambda_{ex} = 325$ nm). Bottom right: ^1H NMR spectra of the La complexes (6.5–8.5 ppm).

the pre-complexation of a Cu^{2+} ion. This proposal was further supported by the dramatic luminescence drop of the **EuL1**–Na_2S complex upon heating (>70 °C) (Fig. S6†). This type of Cu^{2+}-assisted luminescence enhancement of Eu emission is unprecedented. In a competitive study, **EuL1**–Cu^{2+} showed insignificant changes in luminescence with a large excess of anions, including Cl^-, SO_4^{2-}, HSO_4^-, I^-, CO_3^{2-}, HPO_4^{2-}, Br^- and HCO_3^-, and only small changes for GSH and cysteine (red columns in Fig. 5b). Upon the addition of H_2S, the Eu emissions were recovered in all the above cases, indicating a high selectivity of **EuL1**–Cu^{2+} towards H_2S.

Mechanistic studies

The binding mechanisms of **EuL1** towards Cu^{2+} ions and the **EuL1**–Cu^{2+} complex towards H_2S were studied using a comparative analysis of the emission spectra of the Eu complexes and the ^1H NMR spectra of La complexes.[17] As shown in Fig. 7, the profile of the emission spectrum of **EuL1** did not change significantly upon the addition of Cu^{2+} ions. Comparing [**EuL1**], [**EuL1** + Cu^{2+}] and [**EuL1** + Cu^{2+} + H_2S], measured under the same solution conditions, similar spectra were observed for [**EuL1**] and [**EuL1** + Cu^{2+}] ($^5D_0 \rightarrow {}^7F_1 : {}^7F_2 : {}^7F_4$ of [**EuL1**] = 1 : 1.122 : 0.55 and $^5D_0 \rightarrow {}^7F_1 : {}^7F_2 : {}^7F_4$ [**EuL1** + Cu^{2+}] = 1 : 1.186 : 0.91, Table 1). This is correlated with the NMR data and shows that the Cu^{2+} ion is coordinated in the aza-crown. However, signal broadening was observed in the ^1H NMR spectrum of **LaL1**, indicating rapid metal–ligand exchange. These results suggested that the pyridine moiety of the organic chromophore is rapidly switching between the DO3A–Eu^{3+} and

Table 1 The ratio of $^5D_0 \rightarrow {}^7F_J$ ($J = 0$ to 4) emission bands of **EuL1**, **EuL1** + Cu^{2+} and **EuL1** + Cu^{2+} + H_2S^a

$^5D_0 \rightarrow$	$^7F_0$	$^7F_1$	$^7F_2$	$^7F_3$	$^7F_4$
EuL1	0.01	1	1.22	0.08	0.55
EuL1 + Cu^{2+}	0.08	1	1.86	0.15	0.91
EuL1 + Cu^{2+} + H_2S	0.48	1	3.98	0.15	1.95

[a] All spectra were acquired in water with excitation at 325 nm.

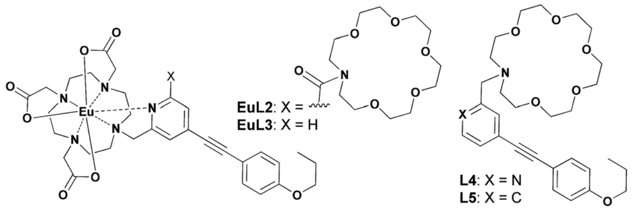


Fig. 8 The structures of the negative control compounds **EuL2**, **EuL3**, **L4** and **L5**.

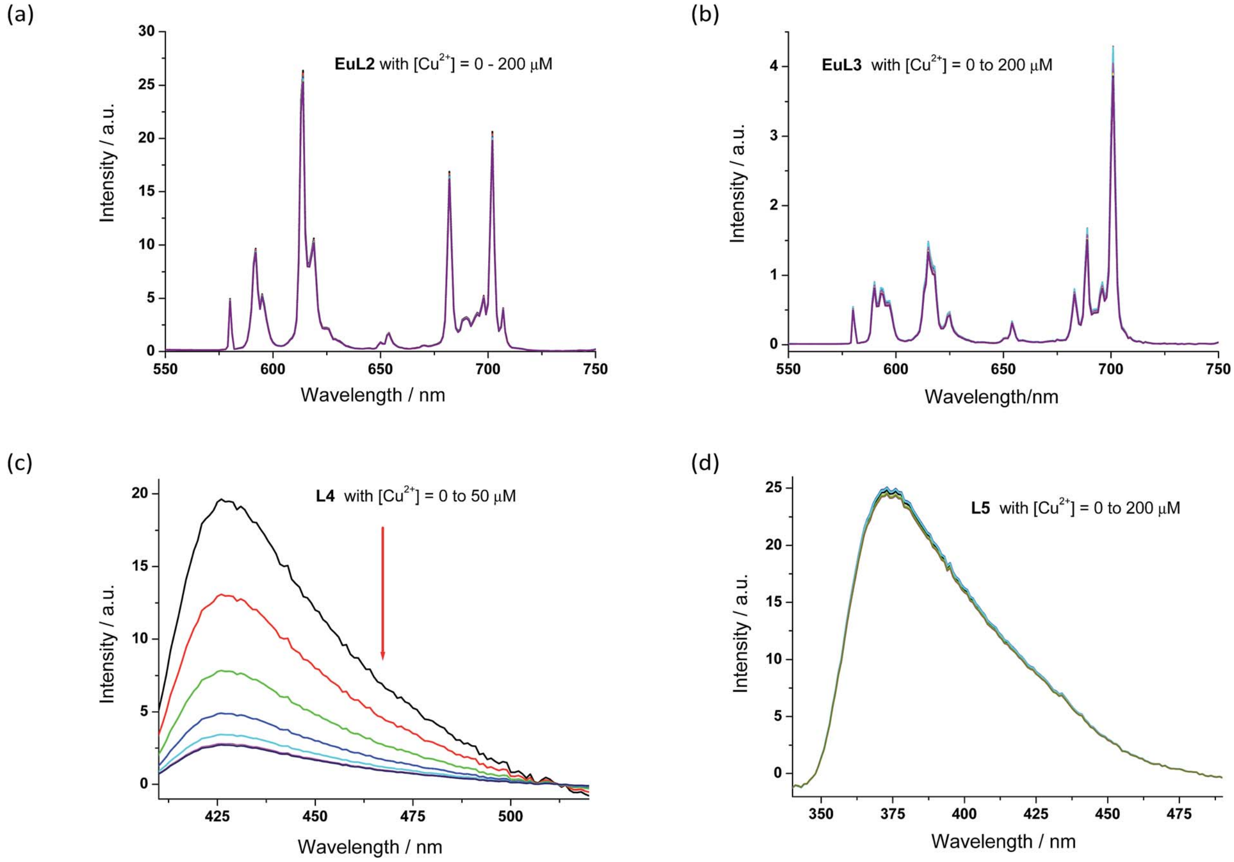


Fig. 9 The emission spectra of negative control compounds (10 μM) with various concentration of Cu^{2+} ions. (a): **EuL2**; (b): **EuL3**; (c): **L4**; (d): **L5**. All spectra were acquired in water with λ_{ex} at 325 nm.

aza-18-crown-6–Cu^{2+} complexes, causing significant luminescence quenching. Moreover, the binding of Cu^{2+} would also provide a favourable conformation for forming a new 1 : 1 complex with H_2S. Upon the addition of H_2S, the emission profile of **EuL1** changed significantly, $\Delta J = 2/\Delta J = 1$ for [**EuL1** + Cu^{2+} + H_2S],[18] and the intensity ratio was about >200% higher for [**EuL1**] and [**EuL1** + Cu^{2+}]. This increase can be attributed to the lower symmetry of the complexes with the addition of sulphide ions (Fig. 7) and the ^{1}H NMR signals of **LaL1** were sharpened. These results suggested new complex formation after the displacement of the Cu^{2+} ion *via* CuS precipitation. This proposal is further supported by the HRMS spectrum of the **EuL1**–Na_2S complex (Fig. S7†) and the change in the quantum yields (Table S2†). The **EuL1**–Na_2S complex is highly emissive probably due to its rigid structure.

The proposed binding mechanism was also examined using a series of negative control compounds (Fig. 8).[19] **EuL2** showed no luminescence quenching upon the addition of Cu^{2+} ions (Fig. 9a). This result indicated that the carbonyl linker of aza-18-crown-6 may be too rigid for coordination between Cu^{2+} and pyridine, which could be essential for Eu emission quenching. Without the aza-crown moiety, **EuL3** also showed no luminescence quenching towards Cu^{2+} (Fig. 9b), suggesting DO3A–Eu^{3+} is stable with Cu^{2+} and the aza-crown motif is important for the Cu^{2+} binding. **L4** bearing the pyridine-chromophore showed profound luminescence quenching, but its phenyl analogue (**L5**) showed no significant change in luminescence upon the addition of Cu^{2+} ions (Fig. 9c and d). These results indicated that the pyridine moiety of the chromophore is essential for the binding of Cu^{2+} to the aza-crown moiety. The results of this series of negative control compounds are in full agreement with the proposed mechanism in Fig. 7.

Conclusions

In summary, we have prepared a water-soluble and emissive Eu-complex (**EuL1**) based on a DO3A(Eu^{3+})–pyridine–aza-crown motif, and studied its consecutive binding properties towards Cu^{2+} and H_2S extensively. **EuL1** binds to Cu^{2+} ions selectively ($K_B = 1.2 \times 10^5$ M^{-1}) inducing 17-fold luminescence quenching and forming a 1 : 1 stoichiometric complex (**EuL1**–Cu^{2+}), which responds to H_2S selectively with restoration of the original **EuL1** emission followed by a further 40-fold luminescence enhancement and a nano-molar detection limit (60 nM). Mass spectroscopic analysis showed the formation of a 1 : 1 stoichiometric complex (**EuL1**–Na_2S) with $K_B = 1.5 \times 10^4$ M^{-1}. Without Cu^{2+} ions, **EuL1** shows non-specific binding towards H_2S with only a 5-fold luminescence enhancement. These results indicate that the Cu^{2+} ion may pre-organize the conformation of **EuL1** and facilitate the formation of the **EuL1**–Na_2S complex. The studies on this unprecedented Cu^{2+}-assisted luminescence enhancement of Eu emission are still ongoing. With long-lived Eu emission, reversible binding properties, an instantaneous response and high selectivity towards H_2S, this Eu-based luminescence "off–on" gate could find suitable applications for H_2S imaging in biological systems.

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