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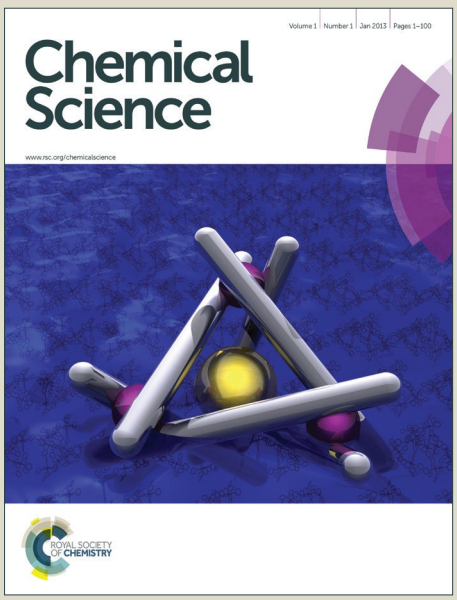

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ARTICLE

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

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Zhenhao Liang,[ab] Tik-Hung Tsoi,[b] Chi-Fai Chan,[c] Lixiong Dai,[c] 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]

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+} ion selectively (K_B = 1.2 x 10^5 M^{-1}) inducing a 17-fold of luminescence quenching and forming a 1:1 stoichiometric complex (**EuL1**-Cu^{2+}), which responses to H_2S selectively with restoration of the original Eu emission of **EuL1** followed by a further 40-fold luminescence enchantment, forming a 1:1 stoichiometric complex (**EuL1**-Na_2S, K_B = 1.5 x 10^4 M^{-1}). Without Cu^{2+} ion, **EuL1** showed a non-specific binding towards H_2S with only 5-fold luminescence enchantment.

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 cancers.[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 mode of actions.

One of the major approaches for developing luminescence H_2S detection[10] is based on sulphide-specific chemical reactions, such as reduction of azide[11] and nucleophilic addition of sulphide ion.[12] This type of luminescence probes 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 x 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 the biological autofluorescent noises and is suitable for time-gated detection. Recently, few studies have been found in the literature with irreversible H_2S lanthanide probe.[12a] Herein, we report the development of a novel responsive europium-based luminescence "off-on" gate for in-situ detection of H_2S in water.

As illustrated in Figure 1, **EuL1** contains a DO3A-Eu^{3+} complex and an aza-18-crown-6 moiety, which are linked to the 2- and 6- position of a pyridine-containing chromophore constituting a switch-like structure. In ground state, **EuL1** should be emissive due to the coordination of the pyridine chromophore to the Eu^{3+} ion, which favours the energy transfer from the organic chromophore to the Eu^{3+} ion. Upon binding of the aza-18-crown-6 moiety with Cu^{2+} ion, the pyridine is expected to coordinate with the Cu^{2+} ion and resulted in luminescence quenching. The europium emission should be recovered after displacement of the Cu^{2+} ion upon copper sulphide precipitation.

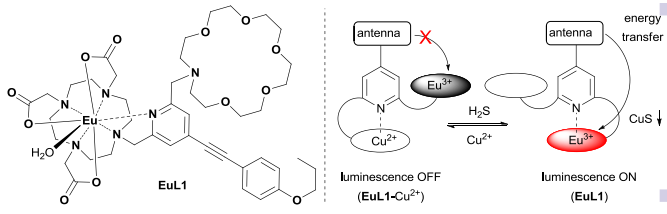
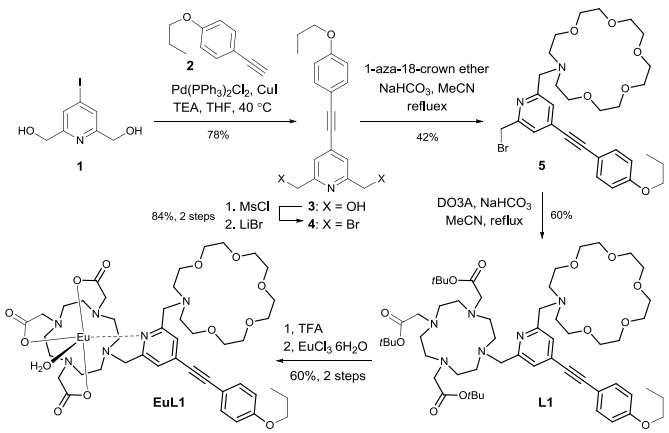


Figure 1 The structure of **EuL1** and the illustration of the design of a reversible Eu based luminescence probe (**EuL1**-Cu^{2+}) for H_2S detection.

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

† Electronic Supplementary Information (ESI) available: Detail experimental procedures, characterization of compounds, figures of NMR analysis and supplementary fluormetric titration studies. See DOI: 10.1039/x0xx00000x



Scheme 1 Synthesis of **L1** and **EuL1**.

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

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 (Figure S2). The excitation spectrum of **EuL1** at 615 nm showed maxima at 240 and 340 nm (Figure S2), evidencing the antenna effect due to the energy transfer from the ligand to the Eu^{3+} ion. The $^{5}D_0 \rightarrow {}^{7}F_J$ transitions of **EuL1** (λ_{ex} = 325 nm) was 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 (Figure 2). The quantum yield of **EuL1** corresponding to the $^{5}D_0 \rightarrow {}^{7}F_2$ transitions of Eu^{3+} ion in water solution is 0.5% (Table S2).

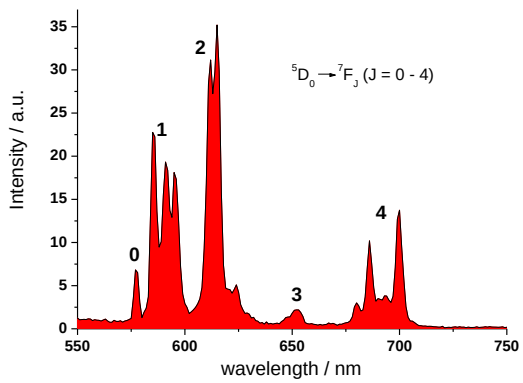


Figure 2 Emission spectrum of **EuL1** (H_2O, λ_{ex} = 325 nm, 10 μM)

Fluorimetric titration studies of EuL1

With **EuL1** in hand, its binding properties towards Cu^{2+} ion were investigated. Upon addition of 1 equiv of Cu^{2+} ion ($CuCl_2$ as the source of Cu^{2+} ions), the absorption maximum of **EuL1** has a slight red shift and the absorption ability slightly declined due to the effect of the copper metal. In a titration study, **EuL1** exhibited a 17-fold quenching of europium emission with an excess of Cu^{2+} ion and the Benesi-Hildebrand plot showed a 1:1 binding stoichiometry with K_B = 1.2 x 10^5 M^{-1} (insert of Figure 3a).[16] The job's plot also supported the formation of **EuL1**-Cu^{2+} complex in a 1:1 ratio (Figure S3). In a competitive study, addition of a large excesses 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 Figure 3b). Subsequent addition of excess Cu^{2+} ion caused significant luminescence quenching (blue columns in Figure 3b). These results indicate the high selectivity of **EuL1**

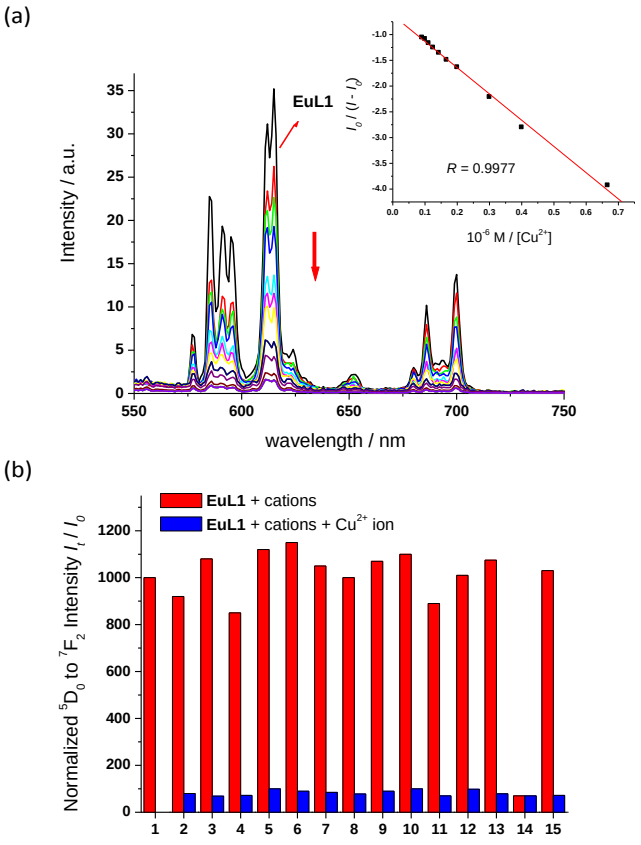


Figure 3 Fluorimetric titration of **EuL1** (10 μM) towards Cu^{2+}. The Inset shows the plot of I_0 / (I - I_0) vs. [Cu^{2+}] (0 - 20 μM). I and I_0 stand for intensity of europium emission $^{5}D_0 \rightarrow {}^{7}F_2$. (b) Effects of various metal ions on the luminescence intensity of **EuL1** (10 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 the spectra were acquired in water solution with excitation at 325 nm.

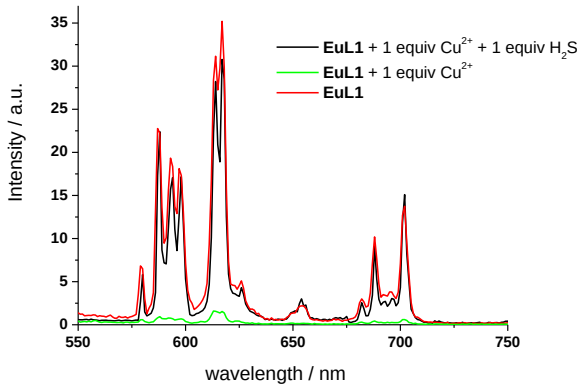
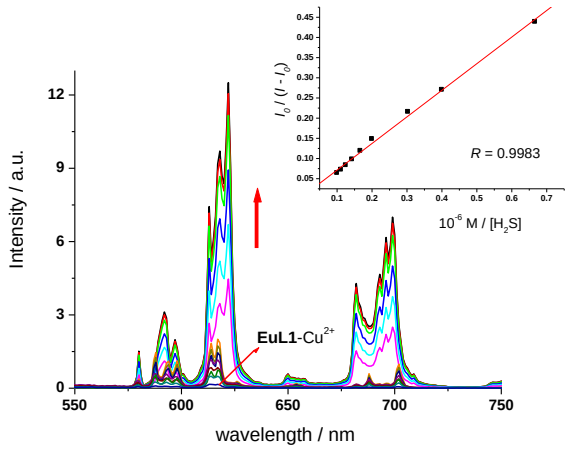


Figure 4 The emission spectra of **EuL1** (10 μM) (red), with 1 equiv of Cu^{2+} ion (green), and with 1 equiv of Cu^{2+} ion and 1 equiv of H_2S (black). All spectra were acquired in water with λ_{ex} at 325 nm.

towards Cu^{2+} ion and the binding between **EuL1** and Cu^{2+} ion is not interfered by other metal ions. In a pH study, **EuL1** remains highly emissive and was quenched by Cu^{2+} ion in the pH range 6 to 8 (Figure S4), indicating **EuL1** is stable and can bind to Cu^{2+} ion under the physiological conditions.

To study the reversibility of the binding between **EuL1** and

(a)



(b)

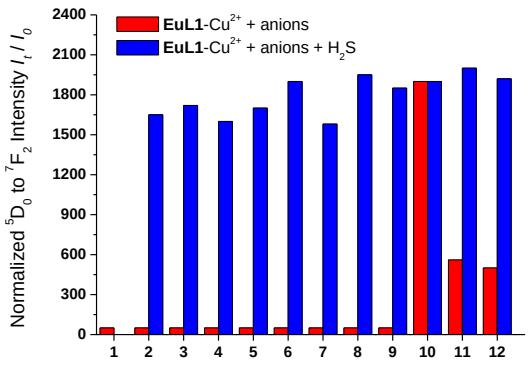


Figure 5 Fluorimetric titration of **EuL1**-Cu^{2+} (10 μM, generated *in situ* with 2 equiv of Cu^{2+}) towards H_2S (0 – 100 μM). The insert shows the plot of $I_0/(I-I_0)$ vs. [Na_2S] (0 – 100 μM). I and I_0 stand for intensity of europium emission $^5D_0 \rightarrow {}^7F_2$. (b) Effects of various 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 solution with excitation at 325 nm.

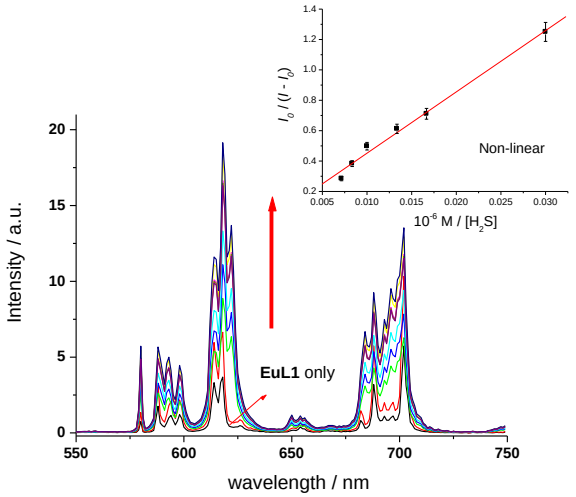


Figure 6 Fluorimetric titration of **EuL1** (10 μM) towards H_2S (0 – 300 μM). The inset shows the plot of $I_0/(I-I_0)$ vs. [H_2S] (0 - 300 μM). I and I_0 stand for intensity of europium emission $^5D_0 \rightarrow {}^7F_2$. All spectra were acquired in water with λ_{ex} at 325 nm.

Cu^{2+} ion, a small amount of H_2S (Na_2S as the source of H_2S) was added. **EuL1**-Cu^{2+} complex responded instantaneously (required only 40 s for reaching saturation without stirring or shaking) (Figure S5), and the Eu emission resumed with a similar profile of the emission spectrum to that of **EuL1** (Figure 4). This result indicated that the DO3A-Eu^{3+} complex was not displaced by Cu^{2+} ion, and forming the **EuL1**-Cu^{2+} in the previous step. More interestingly, the Eu emission was further enhanced (40-fold) with an excess of H_2S and the Eu^{3+} emission profile showed significant changes, suggesting the binding between **EuL1** and H_2S (Figure 5a). The Benesi-Hildebrand plot showed a 1:1 binding stoichiometry with K_B = 1.5 x 10^4 M^{-1} (insert of Figure 5a).[16] The detection limit of the **EuL1** towards H_2S was calculated according to the $3^{\cdot}S_D$/slope as low as 60 nM. Surprisingly, direct titration of **EuL1** against H_2S resulted in only about 5-fold of luminescence enhancement with non-linear relationship in the 1:1 Benesi-Hildebrand plot (Figure 6). These results indicated that the Cu^{2+} ion facilitates the specific 1:1 binding of **EuL1** towards H_2S, presumably via pre-organizing the conformation of **EuL1**. On the other hand, a non-specific binding (possibly a mixture of 1:1 and 2:1 binding) between **EuL1** and H_2S was resulted without the favourable conformation that induced by the pre-complexation of Cu^{2+} ion. This proposal was further supported by the dramatic luminescence drop of the **EuL1**-Na_2S complex upon heating (>70 °C) (Figure S6). This type of Cu^{2+}-assisted luminescence enhancement of Eu emission is unprecedented. In a competitive study, **EuL1**-Cu^{2+} showed insignificant changes of luminescence with a large excess of anions, including Cl^-, SO_4^{2-}, HSO_4^-, I^-, CO_3^{2-}, HPO_4^{2-}, Br^-, HCO_3^- and only small changes for GSH and cysteine (red columns in Figure 5b). Upon 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+} ion and **EuL1**-Cu^{2+} complex towards H_2S were studied by a comparative

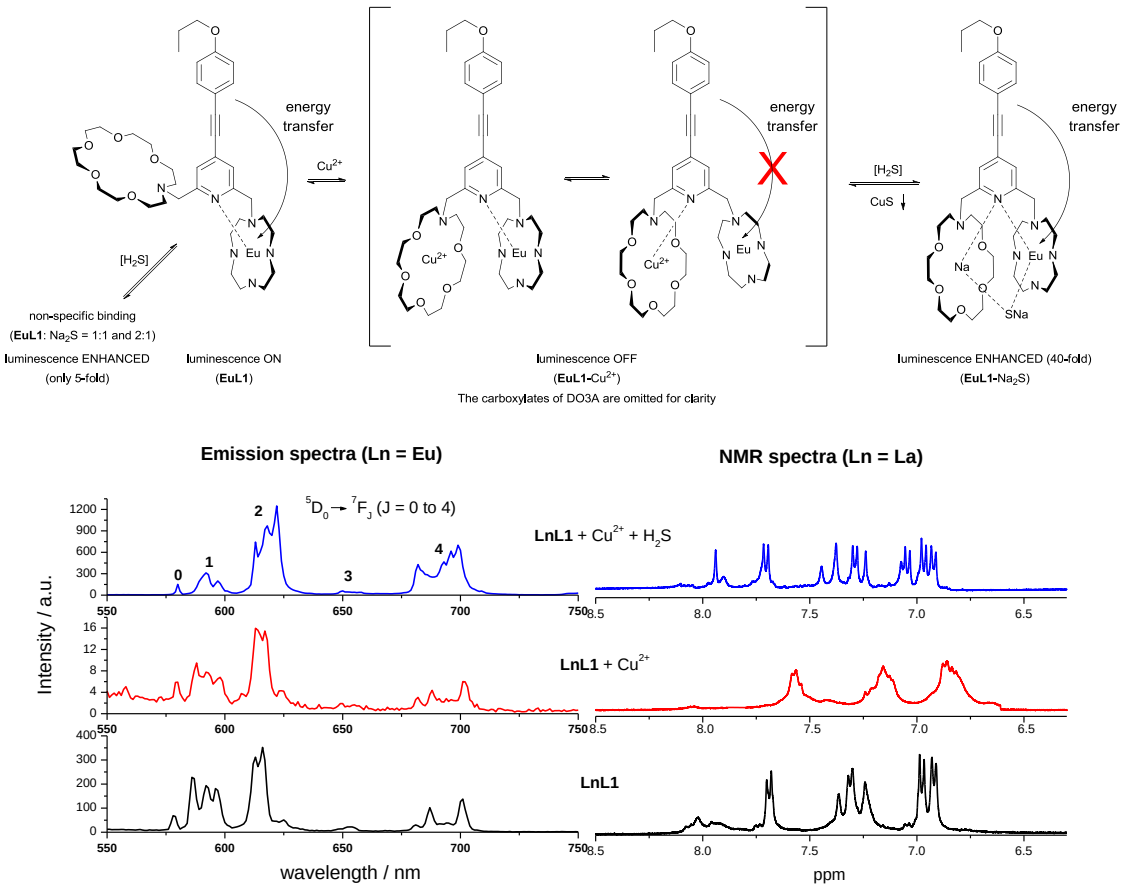


Figure 7 Top: proposed binding mechanism of **EuL1** towards Cu^{2+} and H_2S (Na_2S as the source of H_2S). Bottom left: emission spectral analysis of the Eu complexes (λ_{ex} = 325 nm). Bottom right: ^1H NMR spectral analysis of the La complexes (6.5 – 8.5 ppm).

analysis of the emission spectra of the Eu complexes and the ^1H NMR spectra of the La complexes.[17] As shown in Figure 7,the profile of the emission spectrum of **EuL1** did not change significantly upon addition of Cu^{2+} ion. Comparing [**EuL1**], [**EuL1** + Cu^{2+}] and [**EuL1** + Cu^{2+} + H_2S], measured under the same solution conditions, similar spectra were observed [**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 shown the Cu^{2+} ion is coordinated in the aza-crown. However, signal broadening was observed in the ^1H NMR of **LaL1**, indicating a rapid metal-ligand exchange. These results suggested that the pyridine moiety of the organic chromophore is rapidly switching between the DO3A-Eu^{3+} and aza-18-crown-6-Cu^{2+} complexes, causing a 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 addition of H_2S, the emission profile of **EuL1** changed significantly, $\Delta J = 2/\Delta J = 1$ of [**EuL1** + Cu^{2+} + H_2S],[18] intensity ratio was about >200% higher for [**EuL1**] and [**EuL1** + Cu^{2+}]. This increase can be attributed to the lower the symmetry of the complexes with the addition of sulphide ion (Figure 7) and the signals ^1H NMR of motif **LaL1** became 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 of the **EuL1**-Na_2S complex (Figure S7) and the change o 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 by a series of negative control compounds (Figure 8).[19] **EuL2** showed no luminescence quenching upon addition of Cu^{2+} ion

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]

$^5D_0$ →	$^7F_0$	$^7F_1$	$^7F_2$	$^7F_3$	$^7F_4$
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 solution with excitation at 325 nm.

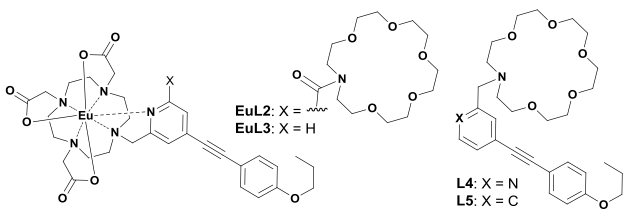


Figure 8 The structures of the negative control compounds **EuL2**, **EuL3**, **L4** and **L5**.

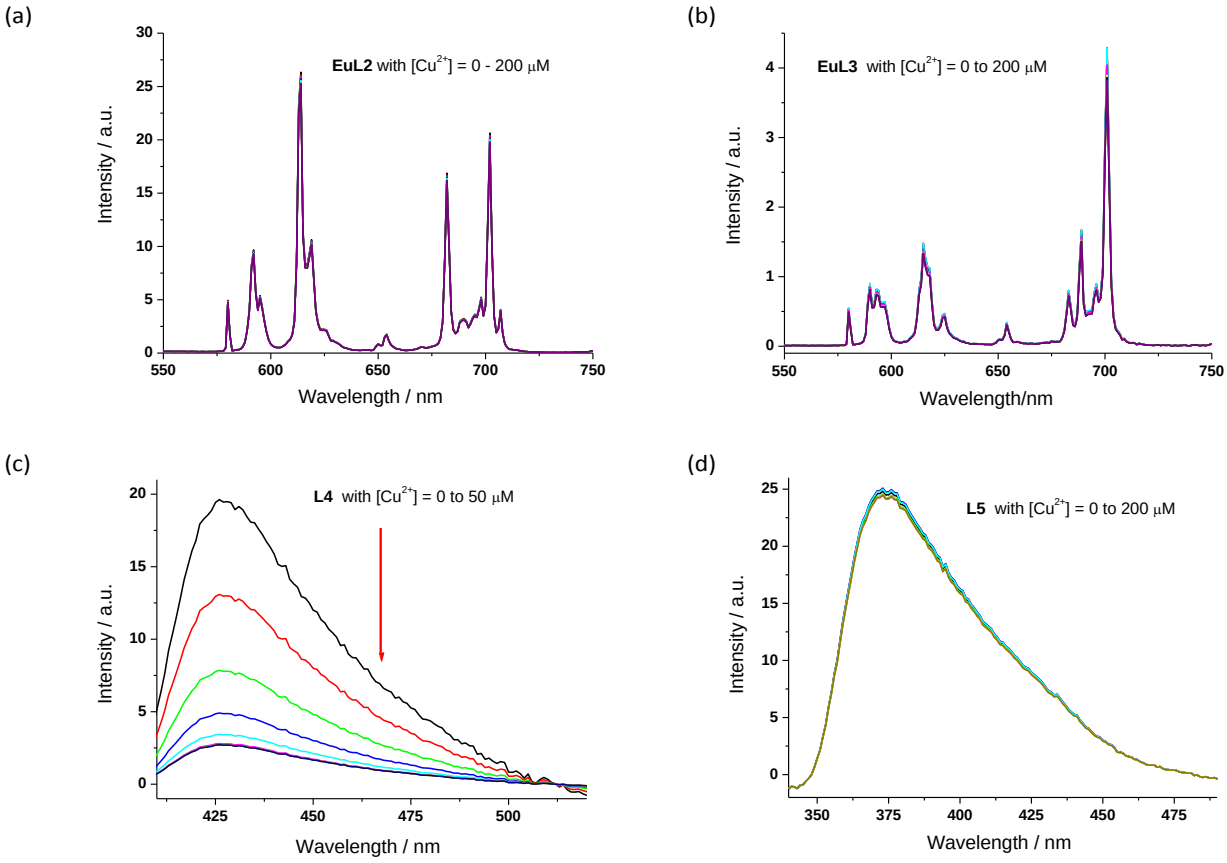


Figure 9 The emission spectra of negative control compounds (10 μM) with various concentration of Cu^{2+} ion. (a): **EuL2**; (b): **EuL3**; (c): **L4**; (d): **L5**. All spectra were acquired in water with λ_{ex} at 325 nm.

(Figure 9a). This result indicated that the carbonyl linker of the aza-18-crown-6 may be too rigid for the coordination between the Cu^{2+} and the pyridine, which could be essential for the Eu emission quenching. Without the aza-crown moiety, **EuL3** also showed no luminescence quenching towards Cu^{2+} (Figure 9b), suggesting the 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 the phenyl analogue (**L5**) showed no significant change of luminescence upon addition of Cu^{2+} ion (Figure 9c-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 Figure 7.

Conclusions

In summary, we have prepared a water-soluble and emissive Eu-complex (**EuL1**) based on the 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+} ion selectively (K_B = 1.2 x 10^5 M^{-1}) inducing a 17-fold of luminescence quenching and forming a 1:1 stoichiometric complex (**EuL1**-Cu^{2+}), which responses 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 x 10^4 M^{-1}. Without Cu^{2+} ion, **EuL1** shows a non-specific binding towards H_2S with only 5-fold luminescence enchantment. These results indicate that the Cu^{2+} ion may pre-organize the conformation of **EuL1** and facilitates 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 the long-lived Eu emission reversible binding property, 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.

Acknowledgements

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