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An Eu_4L^4_4 tetrahedron with multiple recognition sites: a luminescent sensor for rapid and sensitive detection of biogenic amines†

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Biogenic amines are important bioactive substances in living organisms, and their abnormal metabolism can serve as biomarkers for certain diseases such as depression, Parkinson's disease and transient tic disorder. Therefore, developing a highly efficient and sensitive luminescent sensor for biogenic amines is essential. However, the biological system is a complex liquid environment containing multiple active substances, which can reduce effective collisions between the sensor and the target analyte, thereby diminishing the sensor's sensitivity. To address this issue, we introduced reaction sites that can undergo nucleophilic and hydrogen bonding interactions with amino groups into the structure of the sensor, and designed and synthesized a multi-site tetrahedral cage Eu_4L^4_4 to achieve specific capture of biogenic amines. By leveraging these dual interactions between Eu_4L^4_4 and amines, combined with the confined cavity effect of the cage, multiple spectroscopic analyses demonstrated that the detection limit for ethylenediamine (EDA) improved from 370 μM (Eu_4L^1_4) to 33 μM (Eu_4L^4_4), while the response time decreased from 1.1 seconds to 0.81 seconds. This design provides an effective strategy for enhancing sensor sensitivity and paves the way for its application in detecting biogenic amines within biological systems.

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1. Introduction

Biogenic amines (BAs) are a group of biologically active amine compounds widely present in living organisms.¹ Among them, diamines are the most common, including cadaverine, putrescine, histamine, tyramine, spermine, and spermidine.² Trace amounts of biogenic amines are normal active components in living organisms and play important physiological roles in biological cells. However, abnormal amounts of biogenic amines are associated with cell division and have been reported as biomarkers for human diseases, such as depression, Parkinson's disease and transient tic disorder.³ Therefore, it is essential to develop a biogenic amine sensor capable of detecting these compounds in biological systems.

Currently, various analytical methods for evaluating biogenic amines have been reported, including electrochemical

analysis (EC),⁴ capillary electrophoresis (CE),⁵ high-performance liquid chromatography (HPLC),⁶ and gas chromatography (GC) methods.⁷ However, these methods are often limited in practical applications due to their reliance on expensive instruments, complex sample pretreatment procedures, and cumbersome operations.⁸ In contrast, fluorescence sensors offer significant advantages, such as low cost, simple operation, rapid response time, high sensitivity and high selectivity.⁹ As a type of fluorescent sensor, lanthanide-based sensors have attracted increasing attention due to their high sensitivity, offering advantages such as high luminescence quantum yields, long luminescence lifetimes, and large Stokes shifts.¹⁰ Their long luminescence lifetimes enable lanthanide sensors to distinguish their signals from interfering background fluorescence in complex biological systems.¹¹ These sensors have been widely used for the detection of biogenic amines,¹² metal ions,¹³ anions,¹⁴ biomolecules,¹⁵ and amino acids¹⁶ in biological systems.

However, living organisms represent complex solution environments where numerous coexisting biomolecules with similar functional groups compete with the target analyte. This complexity significantly reduces the effective collisions between the sensor and the analyte, leading to poor selectivity and even erroneous signals. These drawbacks greatly compromise detection accuracy. In recent years, to improve selectivity

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Herein, a discrete tetrahedral cage, **Eu₄L⁴₄**, with multiple recognition sites is designed based on a tris-β-diketone ligand (**L¹**). In previous studies, we confirmed that weak intermolecular nucleophilic interactions between β-diketones and analytes containing amino groups can occur in **Eu₄L¹₄**, **Eu₄L²₄**, and **Yb₄L³₄** films at room temperature¹⁹ (the structures of ligands **L¹**, **L²**, and **L³** are shown in Fig. S1†). However, this weak nucleophilic effect is significantly diminished in the liquid state. To address this issue, **Eu₄L⁴₄** is designed with multiple pyridine sites on the cage's skeleton, which can interact with analytes *via* weak intermolecular nucleophilic interactions and hydrogen bonding. Additionally, the confined environment of the tetrahedral cavity may selectively accommodate target molecules of a specific size, further enhancing the sensor's selectivity. Based on a series of sensing performance tests, the detection limit of **Eu₄L⁴₄** for ethylenediamine (EDA) is reduced from 370 μM (**Eu₄L¹₄**) to 33 μM. This improvement demonstrates that introducing multiple reactive sites into the sensor significantly enhances its sensitivity. In summary, the design of a tetrahedral cage with multiple reactive sites provides a new strategy for improving the sensitivity and selectivity of sensors in complex biological systems (Chart 1).

2. Results and discussion

2.1 Synthesis and characterization

The ligand synthesis follows a four-step process outlined in Scheme 1 (details in the ESI†). The first step involves the copper-catalyzed Ullmann coupling of 3-methoxyaniline with 1-iodo-3-methoxybenzene to form 3,3',3''-trimethoxytriphenylamine (**TTA**). In the second step, Friedel-Crafts acylation is employed to synthesize 3,3',3''-trihydroxy-4,4',4''-triacyltriphenylamine (**TTTA**). The third step involves the Ullmann reaction of **TTTA** with trichloromethylpyridine hydrochloride, yielding tri

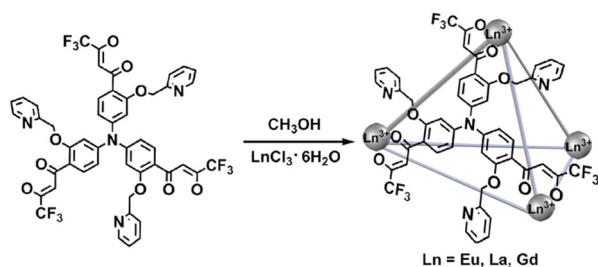
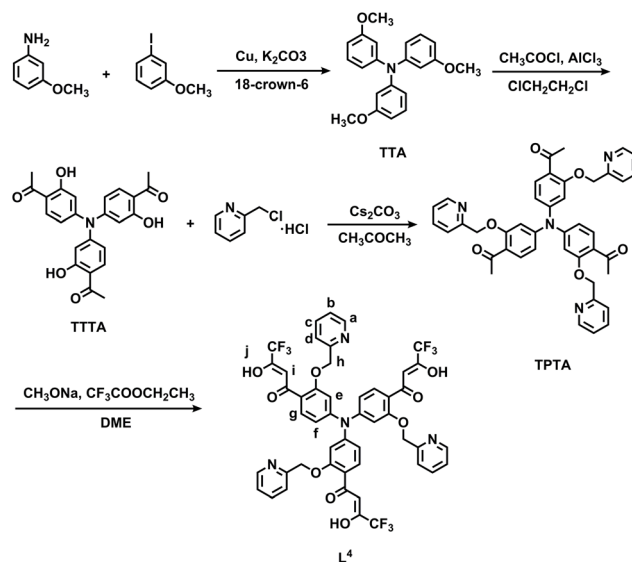


Chart 1 The synthetic method for preparing the lanthanide tetrahedron.



Scheme 1 The synthetic pathway for L⁴.

(3-(2-pyridyl methoxy)-tri(4-acetyl)triphenylamine (**TPTA**). Finally, a Claisen condensation between **TPTA** and ethyl trifluoroacetate produces the target ligand **L**⁴. The successful synthesis of the ligand and its intermediates was confirmed using ¹H NMR and ESI-TOF-MS (Fig. S2-S11†).

The ligand was then reacted with the corresponding Ln(III) salts in a methanol solution at a 1 : 1 stoichiometric ratio for 24 hours to form a lanthanide tetrahedron. ESI-TOF-MS analysis confirmed the formation of the tetrahedron. In Fig. 1a, the inset shows the isotopic pattern for the peak at $m/z = 4541.4255$, corresponding to $[\text{Eu}_4\text{L}^4_4 + \text{Na}]^+$, which aligns with the calculated values. The lanthanum complex La_4L^4_4 is shown in Fig. S9.† To further confirm that the tetrahedron exists as a single species in solution, ^1H NMR spectroscopy was employed. Given the low resolution of Eu(III) complexes in ^1H NMR, La(III) complexes were used for the NMR experiments. Compared to the free ligand, the result in Fig. 1b reveals that La_4L^4_4 exhibits only a single set of signals, indicating the formation of a single species in solution.

In order to determine the structure of the tetrahedral cage **Eu₄L⁴₄**, a molecular mechanical model was constructed using the MOPAC 2016 program integrated into the LUMPAC 3.0 software, employing the Sparkle/PM6 approach.²⁰ Considering the steric hindrance of the ligand, water was selected as the coordinating solvent to satisfy the coordination requirement (8–12) of the lanthanide ions. The optimization results showed that the tetrahedral cage **Eu₄L⁴₄** was synthesized by ligand and lanthanide ions at a stoichiometric ratio of 1 : 1. As shown in Fig. 1c and d, the optimized structure of **Eu₄L⁴₄** is similar to the single crystal structure of **Eu₄L¹₄**. They share similarities in that four Eu(III) ions are chelated with four ligands and located at four vertices of a tetrahedron. Each Eu(III) ion center is coordinated with three β-diketone units in three ligands and two solvent molecules. However, they differ in that the introduced

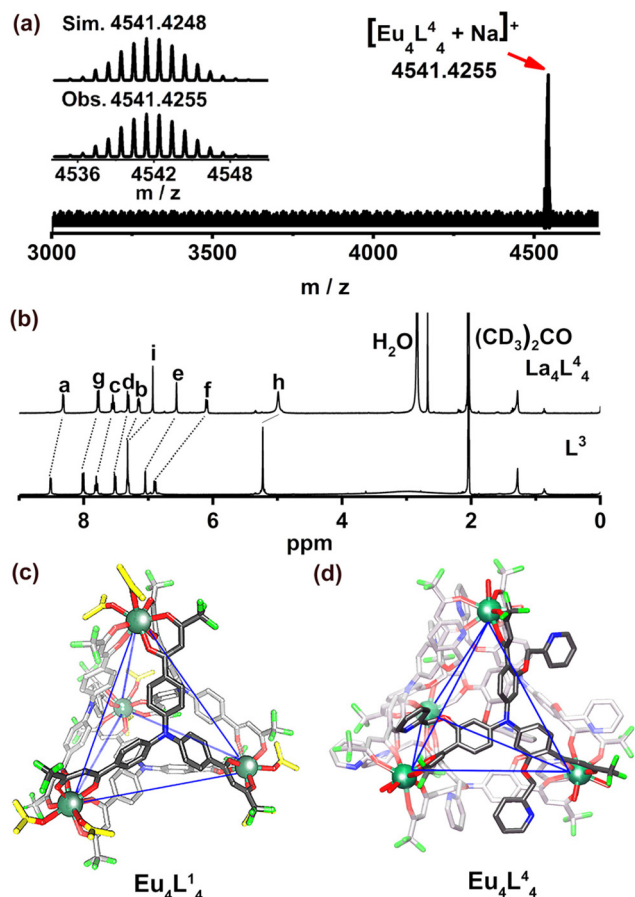


Fig. 1 (a) ESI-TOF-MS spectrum of Eu_4L_4 , with insets displaying the experimental (Obs.) and theoretical (Sim.) isotopic distribution; (b) ^1H NMR (400 MHz) spectra of the free ligand L^4 and La_4L_4 in $(\text{CD}_3)_2\text{CO}$; (c) crystallographic structures of Eu_4L_4 ; and (d) optimized ground-state geometry of Eu_4L_4 .

pyridine group in Eu_4L_4 is distributed along the three arms of the ligand like a propeller, which increases the interaction between the tetrahedron and the analytes. The cavity volume of the tetrahedral cage is calculated to be $301 \text{ \AA}^3$, and the specific cavity size imposes certain limitations on host-guest recognition.

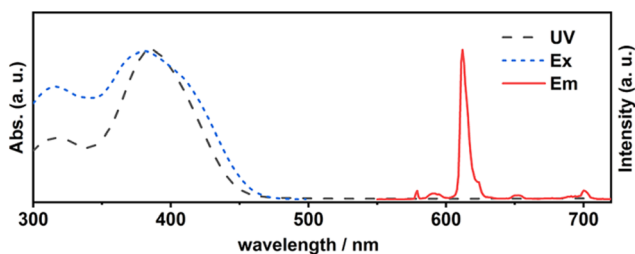


Fig. 2 The graph of emission, excitation and UV-vis absorption spectra of Eu_4L_4 in $\text{THF}/\text{CH}_3\text{CN}$ ($v\text{THF}/v\text{CH}_3\text{CN} = 1:9$, $c = 0.25 \times 10^{-5} \text{ M}$).

2.2 Photophysical properties of Eu_4L_4

The photophysical properties of a tetrahydrofuran solution of Eu_4L_4 ($0.25 \times 10^{-5} \text{ mol L}^{-1}$) are shown in Fig. 2. The UV-Vis spectrum exhibits two prominent absorption bands, one between 300 and 330 nm and another between 350 and 450 nm. The lower-energy absorption band is attributed to the $\pi-\pi^*$ charge transfer from the triphenylamine skeleton to the β -diketone unit, while the higher-energy absorption band (300–330 nm) arises from contributions of both the triphenylamine and β -diketone units. When the characteristic emission of the $\text{Eu}(\text{III})$ ion at 612 nm is used as the emission wavelength, the excitation spectrum of the complex largely overlaps with the UV absorption spectrum, confirming efficient energy transfer from the ligand to the $\text{Eu}(\text{III})$ ions. Upon excitation at 380 nm, the emission spectrum of the Eu_4L_4 complex in solution reveals a series of sharp transitions corresponding to $^5\text{D}_0 \rightarrow ^7\text{D}_J$ ($J = 0-4$) emissions from the $\text{Eu}(\text{III})$ ion, with observed wavelengths at 579, 593, 612, 650, and 702 nm.

2.3 Responses of Eu_4L_4 to biogenic amine

As shown in Fig. 3a, to explore the sensitivity of the lanthanide tetrahedron Eu_4L_4 to biogenic amines with different steric hindrance in the solution state, ethylenediamine (EDA),

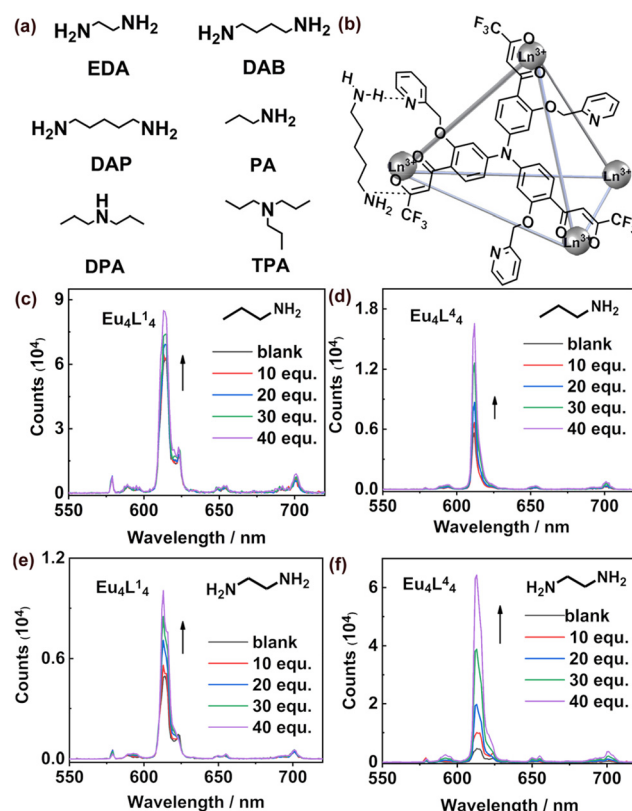


Fig. 3 (a) Biogenic amines studied in this paper; (b) the structure produced by the reaction of Ln_4L_4 with diamine; (c) emission spectra of Eu_4L_4 after adding PA; (d) emission spectra of Eu_4L_4 after adding EDA; (e) emission spectra of Eu_4L_4 after adding EDA; and (f) emission spectra of Eu_4L_4 after adding EDA ($c = 0.25 \times 10^{-5} \text{ M}$ in THF).

putrescine (DAB), cadaverine (DAP), propylamine (PA), di-propylamine (DPA), and tripropylamine (TPA) were gradually added to a tetrahydrofuran (THF) solution of the Eu(III) complex (concentration: 0.25×10^{-5} mol L⁻¹). The concentration-dependent curve of the luminescence intensity at 612 nm was then recorded. In the solution state, the sensing performance of **Eu₄L⁴₄** and **Eu₄L¹₄** toward monoamines are shown in Fig. 3c and d. It can be observed that as the concentration of various monoamines increases, the luminescence intensity of both complex solutions gradually increases. However, at the same concentration of **Eu₄L¹₄** and **Eu₄L⁴₄** in THF solution, the change in luminescence intensity of **Eu₄L⁴₄** is significantly more pronounced than that of **Eu₄L¹₄** upon the addition of the same concentration of monoamine.

The detection performance of tetrahedral **Eu₄L⁴₄** and **Eu₄L¹₄** for diamines is shown in Fig. 3e and f. Notably, the luminescence intensity of **Eu₄L⁴₄** increases up to 16 times its initial value when 40 equiv. of EDA are added to the THF solution, whereas the luminescence intensity of **Eu₄L¹₄** increases only 3-fold. This demonstrates that **Eu₄L⁴₄** exhibits significantly better diamine detection performance in solution compared to **Eu₄L¹₄**. The emission spectral changes for other biogenic amines are shown in Fig. S12.† Additionally, the luminescence lifetimes of **Eu₄L⁴₄** before and after the addition of DAB were measured. As shown in Fig. S13,† when 12 equiv. of DAB were added, the luminescence lifetime of **Eu₄L⁴₄** increased to twice its original value. This change in lifetime is consistent with the observed increase in luminescence intensity upon amine addition.

Sensitivity is one of the most essential properties of high-quality sensors; therefore, the lower detection limit has always been a challenge in this field. The limit of detection (LOD) was estimated at a signal-to-noise ratio of 3. The linear relationship between the luminescence intensity of the two cages and the concentration of various amines are shown in Fig. 4 and

Fig. S14,† as well as Tables S1 and S2.† The detection limits of the two tetrahedral cages for various amines range from micromolar to millimolar levels. The low detection limit provides a necessary prerequisite for the detection of biogenic amines by the tetrahedral cage **Eu₄L⁴₄**. As seen in Fig. 4a and b, the detection limit of **Eu₄L⁴₄** for PA is 0.22 mM, whereas that of **Eu₄L¹₄** for propylamine is 1.12 mM. Additionally, **Eu₄L⁴₄** exhibits slightly lower detection limits for other monoamines compared to **Eu₄L¹₄** in tetrahydrofuran solution.

The detection limits of **Eu₄L⁴₄** and **Eu₄L¹₄** for various diamines are shown in Fig. 4c and d. **Eu₄L⁴₄** (33 μM) has a much lower detection limit for diamines than **Eu₄L¹₄** (370 μM). This is due to the fact that **Eu₄L⁴₄** has two sites, trifluoroacetyl and pyridine, which can both interact with amines, and is more likely to form a ring-like stable structure with diamines than **Eu₄L¹₄** with only one site of trifluoroacetyl²¹ (as shown in Fig. 3b). Therefore, **Eu₄L⁴₄** has stronger interaction with diamines than monoamines. This stronger intermolecular interaction results in a lower detection limit for diamines.

To further validate that **Eu₄L⁴₄** exhibits higher sensitivity towards biogenic amines than **Eu₄L¹₄**, we employed the following Hill equation (luminescence turn on) to calculate the binding constants.²²

$$\log \frac{F - F_0}{F_{\max} - F} = n \log [c] - \log K_d$$

$$K_a = 1/K_d$$

where F_0 and F are luminescence intensities in the absence and presence of biogenic amines, $F_{\max}$ is the luminescence intensity at saturation binding, and $[c]$ is the biogenic amine concentration. K_d is the intercept of the linear regressions, which corresponds to the dissociation constant, and K_a is the binding constant.

Luminescence intensities of **Eu₄L⁴₄** and **Eu₄L¹₄** with biogenic amines at the concentration range of 2.5 mM–10 mM were recorded. The dissociation constants (K_d) were determined by plotting $\log F - F_0/F_{\max} - F$ versus $\log [c]$. As shown in Fig. 5, the linear fitting results show that the binding constants of **Eu₄L⁴₄** for PA and EDA are 0.2820×10^3 M⁻¹ and 0.4229×10^3 M⁻¹, respectively, while the binding constants of **Eu₄L¹₄** for these two amines are 0.04968×10^3 M⁻¹ and 0.07447×10^3 M⁻¹, respectively. **Eu₄L⁴₄** exhibits significantly higher binding constants for monoamines and diamines compared to **Eu₄L¹₄**, which is consistent with the calculated detection limits. This indicates that **Eu₄L⁴₄** has stronger interactions with biogenic amines, demonstrating higher sensitivity than **Eu₄L¹₄**. The other spectra and binding constants for these amines are shown in the ESI (Fig. S15, S16 and Tables S3, S4†).

Compared with chromatographic detection, the fast response time is a prominent advantage of luminescent sensors. In order to investigate the response time of **Eu₄L⁴₄** to various amines, the time-dependent luminescence intensity curves were obtained after adding PA and EDA, as shown in Fig. 6a and b. When 40 equiv. of PA and EDA were added, the luminescence intensity of **Eu₄L⁴₄** increased instantaneously.



Fig. 4 (a) The variation in luminescence emission of **Eu₄L¹₄** upon the addition of PA; (b) the variation in luminescence emission of **Eu₄L⁴₄** upon the addition of PA; (c) the luminescence emission change of **Eu₄L¹₄** with the addition of EDA; (d) the luminescence emission change of **Eu₄L⁴₄** with the addition of EDA (0 → 10 mM).

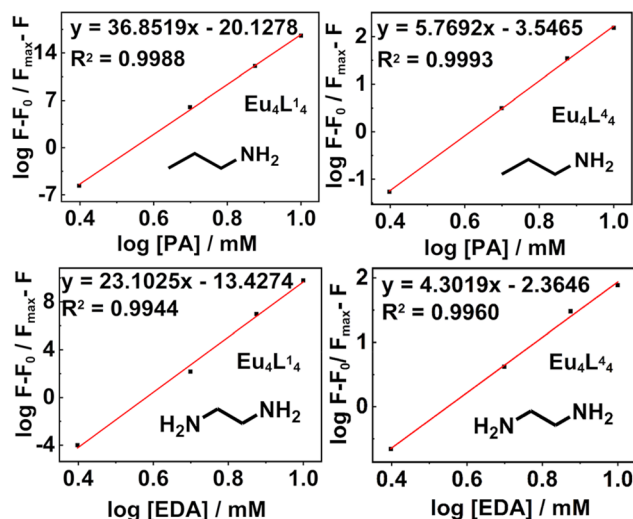


Fig. 5 Linear range of $\log F - F_0/F_{\max} - F$ for Eu_4L_4 and Eu_4L_{44} towards $\log[\text{amine}]$. The reciprocal of the intercept of the linear regressions is the binding constant of Eu_4L_4 and Eu_4L_{44} .



Fig. 6 (a) Response time and time-resolved emission of Eu_4L_{44} before and after the addition of PA; (b) response time and time-resolved emission of Eu_4L_{44} before and after the introduction of EDA; and (c) emission changes of Eu_4L_{44} upon adding various biogenic amines and O-containing compounds.

By fitting the enhancement part of the luminescence intensity enhancement curve, the response times of Eu_4L_{44} were determined to be 1.1 seconds and 0.81 seconds, respectively. As shown in Fig. S17,† it can be observed that the response times of Eu_4L_{44} to all biogenic amines are all in the second range, which is far faster than that of any previously reported amine luminescence sensor (Table S5†). Such a fast response time makes Eu_4L_{44} suitable for real-time monitoring of biogenic amines.

In order to investigate the selectivity of Eu_4L_{44} to biogenic amines, we selected a series of nucleophilic substances containing oxygen atoms for comparative testing. As shown in Fig. 6c, when 40 equiv. of these nucleophiles were added to

the tetrahydrofuran solution of Eu_4L_4 , the luminescence intensity enhancement ratio $(I/I_0 - 1)$ of Eu_4L_4 showed no significant change, with all values remaining below 2%. This result indicates that Eu_4L_4 exhibits high specificity for biogenic amines over these nucleophiles.

2.4 Sensing mechanism and luminescence turn on analysis

The interaction mechanism between Eu_4L_4 and biogenic amines primarily originates from two aspects: the coordination between biogenic amines and lanthanide ions, or the interaction between amines and ligands in the tetrahedral cage. First, we investigated the intensity ratio of the $^5\text{D}_0 \rightarrow ^7\text{F}_2$ to $^5\text{D}_0 \rightarrow ^7\text{F}_1$ transitions (I_{F_2}/I_{F_1}), which reflects the symmetry and nature of the Eu(III) ion coordination environment. As shown in Table S6,† the addition of EDA did not induce a significant change in I_{F_2}/I_{F_1} ; all the values are around 20, indicating that the introduction of amines did not alter the symmetry around Eu(III). Meanwhile, if amine molecules coordinate to Eu(III), the luminescence intensity of the sensor will decrease due to non-radiative decay. Thus, the possibility of amine coordination to the lanthanide ions can be ruled out.

In order to further explore the interaction mechanism of the lanthanide tetrahedron Eu_4L_4 with biogenic amines, the ^1H NMR of Eu_4L_4 was measured before and after the addition of DAB. The testing procedure is detailed in ESI 1.3.† Due to the paramagnetism of the Eu(III) complex, the resolution of its ^1H NMR spectrum is low; La_4L_4 was selected as substitution for testing. As shown in Fig. 7, when 12, 24 and 48 equivalents of DAB were titrated into THF- d_8 containing 1 equiv. of La_4L_4 , all the hydrogen protons in the complex remained observable. Upon the addition of DAB, the signal intensities of all hydrogen protons gradually decreased. The hydrogen proton i on the diketone moiety and the hydrogen protons e, f, and g on the phenyl rings of the triphenylamine shifted slightly upfield. These changes are consistent with the trend observed when

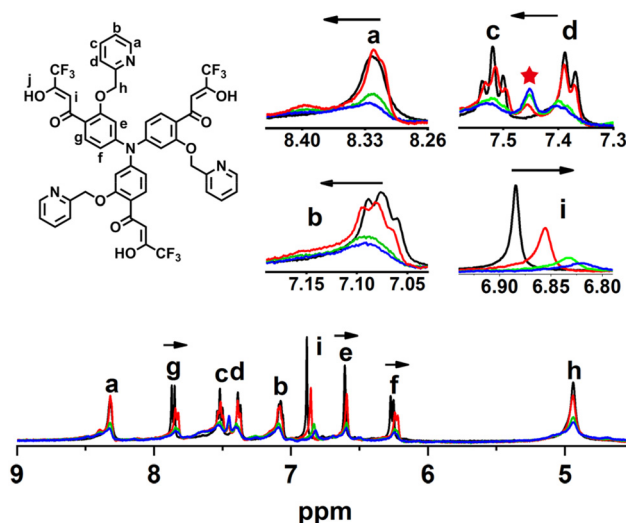


Fig. 7 ^1H NMR studies of La_4L_{44} with the addition of DAB.

La_4L^4_4 was treated with amines,^{19a} indicating that La_4L^4_4 , similar to La_4L^1_4 , can undergo weak intermolecular nucleophilic interactions with biogenic amines. However, the difference is that the hydrogen protons a, b, c, and d on the pyridine ring shifted downfield; generally, hydrogen bonding causes the hydrogen proton to shift downfield. Meanwhile, a new signal peak at 7.45 ppm is obtained, which indicates that there is a stronger intermolecular interaction between La_4L^4_4 and DAB compared to nucleophilic interaction. This additional interaction can only be attributed to intermolecular hydrogen bonding between the nitrogen atom on the pyridine ring and the hydrogen atom on the amine.

To further investigate the interaction mechanism between La_4L^4_4 and biogenic amines, the NOESY spectrum of La_4L^4_4 was tested after adding DAB. The NOE effect requires the distance of adjacent protons to be shorter than 4.5 Å.²³ However, as shown in Fig. S18,[†] no correlation signals were observed between La_4L^4_4 and DAB. Therefore, we can further confirm that no chemical bond was formed between the tetrahedral cage La_4L^4_4 and DAB, and the interaction is more likely to involve weak intermolecular nucleophilic interactions and hydrogen bonding. In addition, the 2D-1H-DOSY NMR spectra of La_4L^4_4 were examined before and after the addition of DAB. As shown in Fig. S19,[†] no new diffusion rates were generated; the diffusion rates of both La_4L^4_4 and DAB decreased, which may be attributed to their intermolecular nucleophilic interactions and hydrogen bonding interaction leading to a reduction in mobility.

The luminescence quantum yield of Eu(III) complexes mainly depends on the sensitization efficiency of ligands. The alignment between the excited-state energy level and the $^5\text{D}_0$ energy level of Eu(III) plays a crucial role in influencing the luminescence intensity of the complex. To explore the reason for the enhanced luminescence intensity of Eu_4L^4_4 after the addition of amines, we need to determine the energy levels before and after the addition of amines. The singlet (S_1 , $^1\pi\pi^*$) and triplet (T_1 , $^3\pi\pi^*$) energy levels of the ligand were calculated using Gd_4L^4_4 ; the UV absorption spectra and phosphorescence spectra of Gd_4L^4_4 were examined before and after adding various amines in THF and CH_3CN solution (Fig. S20 and S21[†]). As shown in Fig. 8a, when 12 equiv. of DAB were added to the acetonitrile solution of Gd_4L^4_4 , the UV absorption spectrum and phosphorescence emission spectrum exhibited a blue shift, indicating that the singlet and triplet energy levels of the ligand increased after the addition of DAB.

The singlet energy of the ligand is determined by the maximum absorption edge of the UV spectrum of the complex Gd_4L^4_4 , as shown in Fig. 8b. Upon adding DAB to the solution of Gd_4L^4_4 , the singlet energy level of the ligand increases from 21 459 cm^{-1} (466 nm) to 22 124 cm^{-1} (451 nm). The triplet energy level of the ligand is calculated based on the lower emission peak wavelength in the phosphorescence spectrum. With the addition of DAB to the Gd_4L^4_4 solution, the triplet energy level rises from 19 417 cm^{-1} (515 nm) to 19 881 cm^{-1} (503 nm). Consequently, the energy difference ΔE ($3\pi\pi^* - ^5\text{D}_0$) between the ligand's triplet state and the excited state of

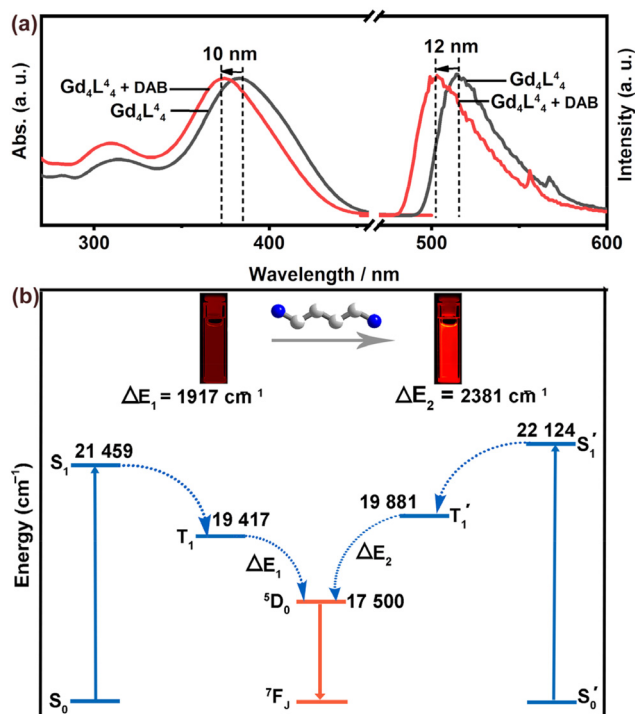


Fig. 8 (a) Phosphorescence and UV/vis absorption spectra of Gd_4L^4_4 in THF/ CH_3CN before and after DAB addition ($V_{\text{THF}}/V_{\text{CH}_3\text{CN}} = 1:9$, $c = 0.25 \times 10^{-5}$ M). (b) Schematic illustration of the energy transfer mechanism for Gd_4L^4_4 upon DAB addition.

Eu_4L^4_4 increases from 1917 cm^{-1} to 2381 cm^{-1} . For Eu(III) complexes, an optimal energy level difference ΔE is typically between 5000 cm^{-1} and 2500 cm^{-1} . After adding DAB, the energy difference of $\Delta E = 2381 \text{ cm}^{-1}$ is closer to the optimal value of 2500 cm^{-1} . This results in a significant inhibition of energy transfer from the excited state of Eu(III) to the ligand, leading to a noticeable enhancement in the luminescence intensity of Eu_4L^4_4 .

3. Conclusion

In conclusion, L^4 with multiple reaction sites was synthesized by introducing pyridine groups into the structure of ligand L^1 ; the tetrahedral cage Eu_4L^4_4 was synthesized by coordination-directed self-assembly with lanthanide for the detection of biogenic amines. Combining the comprehensive spectral analyses, an intermolecular weak nucleophilic interaction and a hydrogen-bonding interaction are proposed for this response mechanism. The fitting electrophilic capability of the β -diketonate units to amine nitrogen and hydrogen-bonding interaction endows Eu_4L^4_4 with high sensitivity toward biogenic amines. In addition, the confined effect of the tetrahedral cavity could further improve the selectivity of the sensor. Compared with Eu_4L^1_4 , a series of sensing tests showed that the detection limit of Eu_4L^4_4 for DAB was reduced from 370 μM (Eu_4L^1_4) to 33 μM , and the response time was reduced

from 1.1 seconds (Eu_4L^1_4) to 0.8 seconds. These results illustrate the effectiveness of increasing the reaction site to improve the sensitivity and selectivity of the sensor, and provide a new strategy for the application of lanthanide sensors in complex organisms.

Author contributions

Yuan Yao: investigation, writing – original draft, data curation, and software. Li Li and Tongxi Zhou: software, formal analysis, and validation. Su Wang and Ying Qin: supervision, data curation, and resources. Chao Fan and Yuying Fu: supervision and writing – review & editing. Guoliang Liu and Hongfeng Li: design, supervision, resources, and writing – review & editing.

Conflicts of interest

The authors declare no competing financial interest.

Data availability

The data that support the findings of this study are available in the ESI† of this article.

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