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An ATP-selective, lanthanide complex luminescent probe†

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A luminescent probe based on a europium complex is developed, which effectively distinguishes adenosine-5′-triphosphate (ATP) from adenosine diphosphate (ADP) and adenosine monophosphate (AMP) in pure water at pH 6.8. With a longer lifetime (in ms range), the probe is prospectively applied to biological systems to monitor ATP levels by completely removing the background fluorescence of other molecules.

Introduction

Phosphates play a very important role in biological systems and everyday life. Among these, adenosine-5′-triphosphate (ATP) is one of the most studied molecules in biological science due to its energy production and storage functions in living cells. ATP is involved in energy metabolism, DNA replication and transcription, and other fundamental activities of life.[1] Consequently, the real-time monitoring of ATP levels is essential for the study of multiple cellular mechanisms, enzyme activity, and other activities involving the production and consumption of ATP.[2] For the detection and quantification of ATP, a variety of colorimetric and fluorescent probes have been developed. The majority of these are based on acridone,[3] anthracene,[4] coumarin,[5] naphthalimide,[6] pyrene,[7] xanthenes,[8] other fluorescent dyes,[9] and transition metal-based complexes.[8b,10]

Compared with the probes based on organic molecules and transition metal-based complexes, lanthanide-based probes have many advantageous such as sharp line-like emission bands, large Stokes shifts, and long lifetimes.[11] The long luminescence lifetimes, typically in the ms range, make lanthanide-based complexes fascinating and useful candidates for time-gated probes in biological systems as they typically remove the background fluorescence of other organic substances.[12] For the past few years, D. Parker's group has developed some probes based on lanthanide complexes for anions and studied the mechanism of interactions between the probes and anions.[13–16] In 2000, they studied the selectivity of reversible oxy-anion binding in aqueous solution at a chiral europium and terbium center through synthesizing a series of lanthanide complexes.[13] In particular, the binding of carbonate to cationic Eu complexes was monitored by variation in the emission intensity, ratio of intensities (615/594 nm), and dissymmetry factors as a function of added total carbonate. Four years later, their group investigated the selectivity in the binding of phosphorylated tyrosine residues to the lanthanide complexes with heptadentate ligation by the changes in the luminescence emission spectra and ^{1}H NMR spectroscopy.[14] And then they researched into the chemoselective binding of *O*-phosphono-L-tyrosine residues to europium macrocyclic complexes by ratiometric changes in lanthanide-based emission and circularly polarized luminescence spectra.[15]

Until now, there are rare examples of ATP probes based on lanthanide complexes reported.[17–24] In 2004, R. F. Ziessel *et al.* designed a luminescent lanthanide complex with a marked selectivity for HPO_4^{2-} and ATP^{4-}, and investigated the interactions of these anions with the complex.[20] Two years later, Otto S. Wolfbeis *et al.* found that the europium tetracycline complex could be used as the probe of ATP, and studied the applicability of this fluorescent probe to the determination of kinase activity.[21] More recently, the group of Pierre has designed a molecular probe, Tb-DOTAm-Phen, for the direct time-gated detection of ATP based on the interactions including the stacking and electrostatic interactions between the probe and ATP.[22] The probe can be efficiently applied to the systems with millimolar concentrations of ATP which are relevant to intracellular conditions.

On the basis of the prior works, we here present a lanthanide-complex luminescent probe (probe **1**) which exhibits high selectivity for ATP, and can discriminate ATP from adenosine diphosphate (ADP) and adenosine monophosphate (AMP) in pure aqueous media of pH 6.8 (Scheme 1). This probe is a europium complex from a derivative of cyclen (1,4,7,10-tetraazacyclododecane) with three acetamide arms coordinated to europium and a fourth arm, a conjugated derivative of terpyridine, that serves as an antenna. The three acetamide arms

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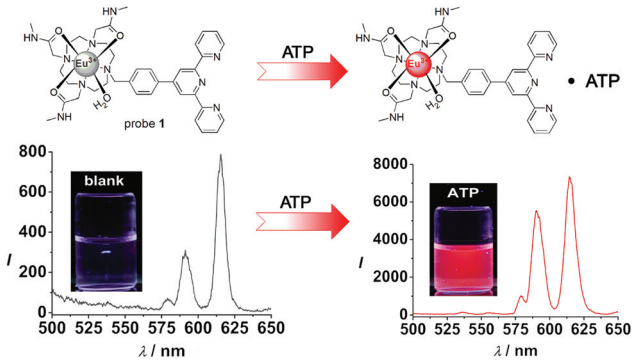
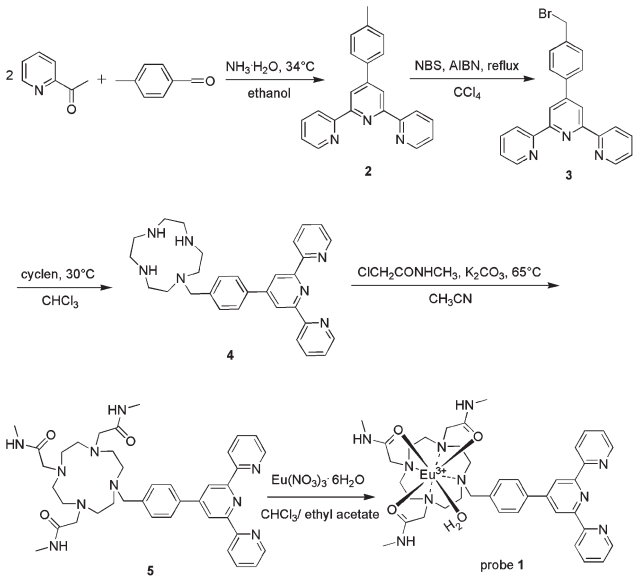


Scheme 1 Fluorescent sensing of ATP based on a europium complex probe (probe **1**).

stabilize the europium complex kinetically and thermodynamically, thereby limiting influence by the aqueous solution, while conferring a 3+ charge to the entire complex. The 3+ charged macrocyclic segments with the heptadentate ligation, which is likely to be bound one or two water molecules, can interact with the phosphates of ATP. The terpyridine arm bearing the large conjugation group acts both as an antenna and as a conjugate to the adenine base of ATP. In addition, the length of the terpyridine arm chain of the cyclen ligand is an important factor that influences the interactions of the complexes with ATP. The length of the probe molecule was a key principle considered in the process of designing the probe. It was expected that the combination of the interaction between the europium centre and the phospho group of ATP and the π–π stacking between the terpyridine derivative and the adenine base of ATP would present different luminescent phenomena compared with other anions.[22]

Synthesis of the ligand was initiated by first introducing the terpyridine group into the cyclen, followed by addition of the three acetamide arms. The lanthanide complex (probe **1**) was formed by adding the solution of $Eu(NO_3)_3{\cdot}6H_2O$ to the solution of the ligand (Scheme 2). The ^1H NMR of the ligand (see Fig. S1 in the ESI†) and the mass spectrum of probe **1** (see Fig. S2 in the ESI†) are reported in the ESI.†



Scheme 2 Synthesis of probe **1**.

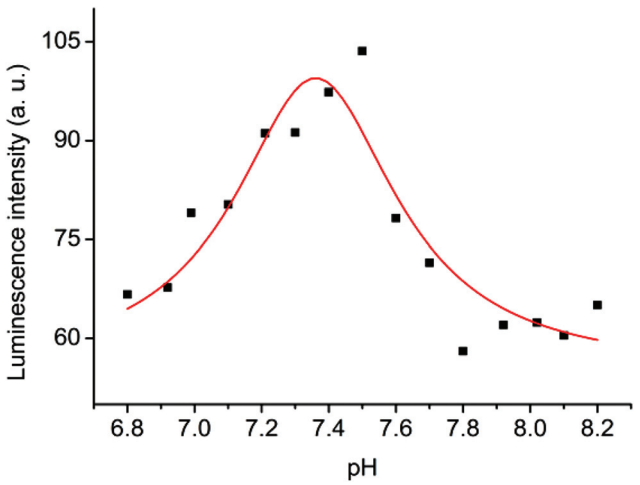


Fig. 1 The pH dependence of the emission spectra of probe **1**.

Results and discussion

Luminescence ATP-sensing with probe 1

To investigate the influence of pH, the changes in the luminescence intensity of probe **1** at 615 nm between pH 6.8–8.2 are shown in Fig. 1. As the pH mounted up, the luminescence intensity of probe **1** increased firstly and then decreased, with maximum intensity being reached at pH *ca.* 7.3–7.4. The enhanced luminescence between pH 6.8–7.4 could be attributed to the protonation of the terpyridine moiety, which could impact the energy-transfer from the antenna to europium ions.[25] And then OH^- might coordinate to Eu^{3+} between pH 7.4–8.2, which could quench the luminescence. In view of the fact that the probes with enhanced luminescence may have higher sensitivity than the ones with quenched luminescence, all of the experiments on probe **1** were carried out at pH 6.8.

The luminescence emission changes of probe **1**, by itself or following addition of F^-, Cl^-, Br^-, I^-, SO_4^{2-}, S^{2-}, HS^-, HSO_3^-, SO_3^{2-}, $S_2O_3^{2-}$, $S_2O_8^{2-}$, CO_3^{2-}, NO_2^-, NO_3^-, $H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}, $P_2O_7^{4-}$, AMP, ADP, or ATP, are plotted in Fig. 2. The luminescence intensity of probe **1** (the quantum yield, Φ = 1.75%) is enhanced by approximately 8.3-fold with the addition of ATP, while the other anions produced negligible responses. The probe not only distinguishes ATP from other inorganic anions including $H_2PO_4^-$, HPO_4^{2-}, PO_4^{3-}, and $P_2O_7^{4-}$, but also discriminates ATP from ADP and AMP remarkably well, which can be observed by the naked eye under an ultraviolet lamp.

The luminescence changes of probe **1** following the continuous addition of ATP are seen in Fig. 3 and Fig. S3† (see

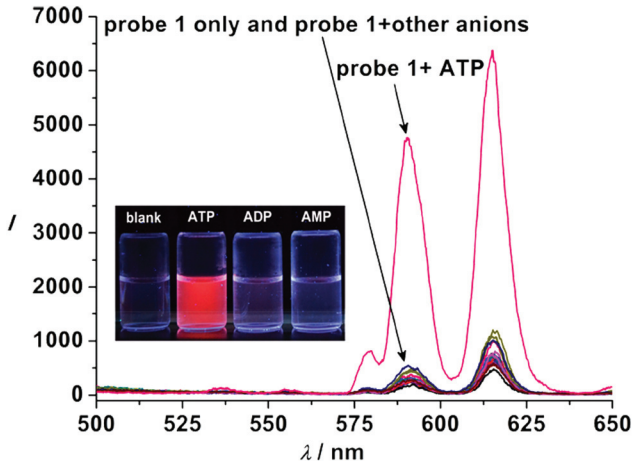


Fig. 2 Luminescence responses of probe **1** (50 μM) in the presence of various anions (25 μM ATP, 25 μM ADP, 25 μM AMP and others 50 μM) in the pure aqueous media at pH 6.8 (30 mM HEPES) with an excitation at 335 nm (excitation slit width = 10 nm and emission slit width = 5 nm) (inset: probe **1** only, and probe **1** with the addition of ATP, ADP, or AMP, observed under an ultraviolet lamp at 365 nm).

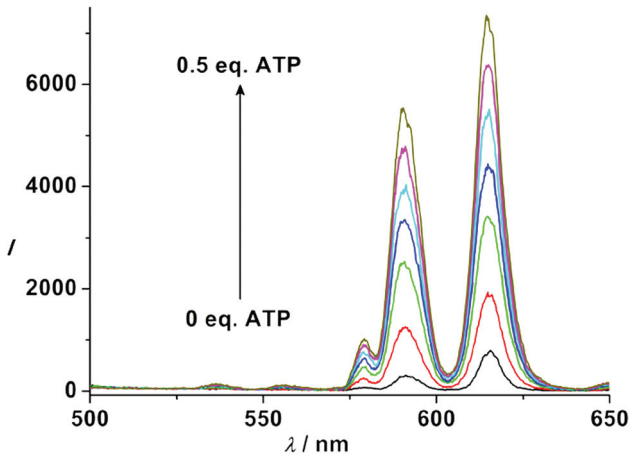


Fig. 3 Enhanced luminescence titrations of probe **1** with ATP in the pure aqueous media at pH 6.8 (30 mM HEPES) with an excitation at 335 nm (excitation slit width = 10 nm and emission slit width = 5 nm).

Fig. S3 in the ESI†). The fluorescence titration shows that the luminescence intensity of probe **1** increased progressively with continuous addition of ATP, and the binding stoichiometry between probe **1** and ATP was calculated at 2 : 1 at peak luminescence intensity (the quantum yield, Φ = 4.69%). The structure suggested by these data likely involves a single ATP molecule bound between two probe **1** molecules, resulting in the observed luminescence. As shown in Fig. 3, the intensity ratio of the bands at 615 nm to 591 nm in the emission spectra changed gradually with the continuous addition of ATP. The value of the intensity ratio of the bands at 615/591 nm changed from 2.5 at the beginning to 1.3 in the end, which indicated that the coordination environment of europium ions of probe **1** has been changed with the addition of ATP.[13,26] It is inferred that the phospho group of ATP has coordinated to the europium centre.

Table 1 The lifetime data of probe **1** and probe **1** + ATP in water and deuterated water

	τ_{H_2O} (ms)	τ_{D_2O} (ms)	q_{H_2O} [a]
Probe **1**	0.55	1.64	0.88
Probe **1** + ATP	0.52	2.29	1.21

[a] Values for q were calculated based on the method from D. Parker *et al.*[27]

The luminescence lifetime data of probe **1** with and without the addition of ATP were measured to determine the hydration number (q) of the water molecules coordinated to Eu^{3+} in aqueous solution. The data of the luminescence time (τ) determined in H_2O and D_2O were listed in Table 1. Hydration numbers, q, were calculated using the following eqn:

$$q = 1.2[\tau_{H_2O}{}^{-1} - \tau_{D_2O}{}^{-1} - 0.25 - 0.075n_{O=CNH}] \quad (1)$$

where $n_{O=CNH}$ is the number of amide N–H oscillators in which the amide carbonyl oxygen is coordinated to Eu^{3+}.[27]

These data suggest that the europium centre of probe **1** binds one water molecule, and the bound water molecule won't be displaced when the probe **1** associated with ATP. The europium centre still binds the phospho group of ATP whilst retaining a bound water molecule.[13,26]

The conditional association constant[20] for the formation of the species with a 2 : 1 stoichiometry between probe **1** and ATP during the enhanced luminescence titrations was calculated to be 7.85 × 10^3 M^{-2}, and the detection limit for ATP was 8.87 × 10^{-6} M (see Fig. S4 in the ESI†). As shown in Fig. 4, the luminescence intensity of probe **1** with the addition of ATP decreased continuously as the enhanced pH, with a rapid decline between 7.4–7.8. It suggests that it has a potential application for pH determination in the range between 7.4–7.8.

In order to investigate the possibility of applying the probe to the bio-fluids and biological systems, competition experiments were carried out (Fig. 5). The experiments with 20 mM CO_3^{2-} or HCO_3^- were performed at pH 7.4, and the experiments with 0.13 mM citrate or 0.1 mM other anions were all achieved at pH 6.8. Other phosphate anions appeared to have some influence on the selectivity of probe **1** for ATP, possibly by competing with the ATP phosphate. Also, citrate^{3-} impacted the selectivity of probe **1** for ATP because the 3+ charged complex with heptadentate ligation had high affinity to the highly charged anions, especially if they were sterically demanding.[16] In addition, the selectivity was also influenced by CO_3^{2-} and HCO_3^- at pH 7.4, and the influence of CO_3^{2-} was more serious than HCO_3^-. The sandwich-like structure is likely formed due to the coordinated interactions between Eu^{3+} and the phosphate component of ATP, as well as π–π stacking interactions between the antenna terpyridine group and the adenine base of ATP.

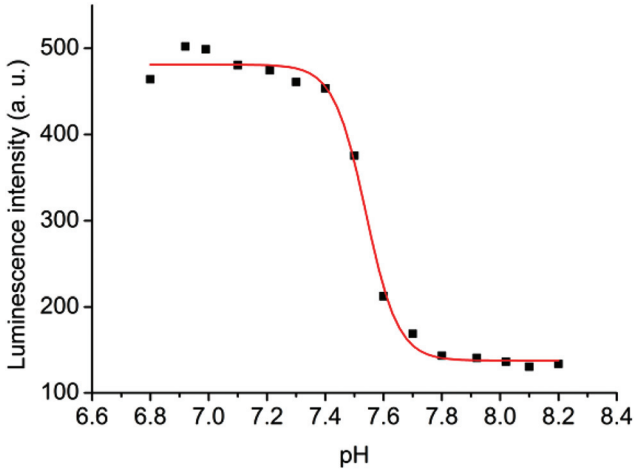


Fig. 4 The pH dependence of the emission spectra of probe **1** with the addition of ATP.

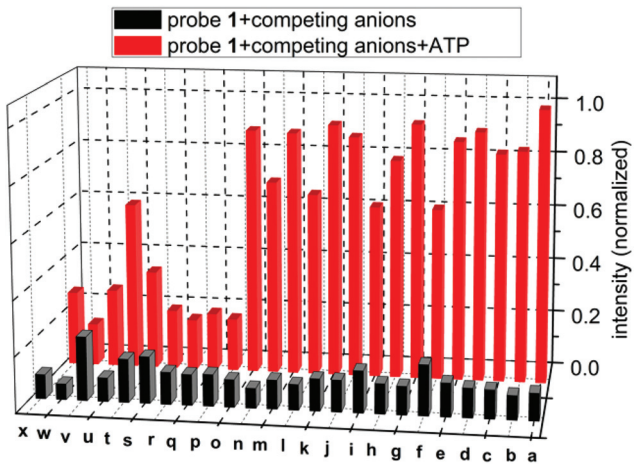


Fig. 5 Competition experiments. The black bars represent the solutions of probe **1** (0.05 mM) with the addition of an excess of anions, and the red bars represent the solution mentioned above with the sequential addition of 0.025 mM ATP. a, blank; b, F^-; c, Cl^-; d, Br^-; e, I^-; f, CO_3^{2-}; g, HS^-; h, S^{2-}; i, HSO_3^-; j, SO_3^{2-}; k, SO_4^{2-}; l, $S_2O_3^{2-}$; m, $S_2O_8^{2-}$; n, NO_2^-; o, NO_3^-; p, $H_2PO_4^-$; q, HPO_4^{2-}; r, PO_4^{3-}; s, $P_2O_7^{4-}$; t, ADP; u, AMP; v, citrate^{3-}; w, CO_3^{2-}; x, HCO_3^-. The concentrations of these anions represented by the letters from a to u were all 0.1 mM, and the competition experiments were carried out at pH 6.8. The concentration of citrate^{3-} was 0.13 mM, and the competition experiments were carried out at pH 6.8. The concentrations of CO_3^{2-} and HCO_3^- were all 20 mM, and the competition experiments were carried out at pH 7.4.

Mechanism of response

The proposed mechanism of luminescence enhancement is described as follows: (1) the length of the terpyridine arm chain of the ligand fits for ATP to realize the coordinated interactions and the π–π stacking interactions with the probe; (2) the π–π stacking interactions between the terpyridine group of the ligand and ATP could strengthen the rigidity of the conjugate planes of the antenna groups and restrict the rotations of C–C bonds between the aromatic rings. Thus the ligands improve the Eu^{3+} sensitization with the energy absorbed by

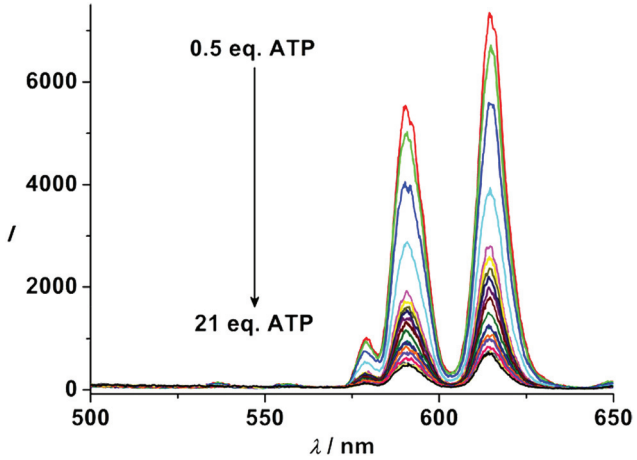
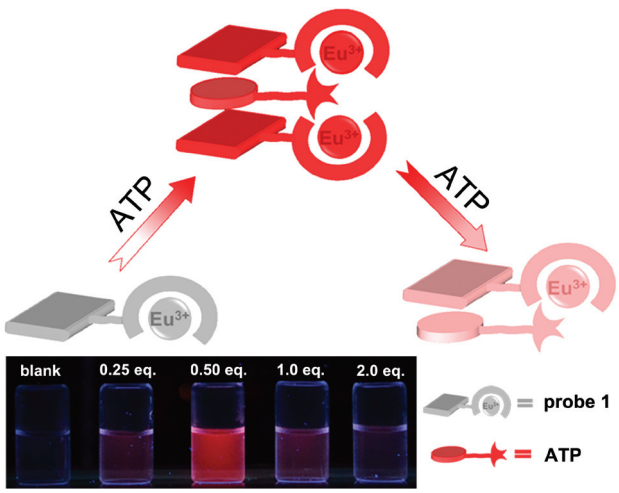


Fig. 6 Quenched luminescence titrations of probe **1** with ATP in the pure aqueous media at pH 6.8 (30 mM HEPES) with an excitation at 335 nm (excitation slit width = 10 nm and emission slit width = 5 nm).

ATP and transferred from ATP molecules and with the obviously nonradiative transitions weakened.[28] The adaptive length of the arm chain of the ligand and the combination of interactions between probe **1** and ATP are believed to be sufficient to differentiate ATP from ADP and AMP.[22]

During luminescence titrations, the luminescence intensity reached a maximum when the ATP concentration was half that of probe **1**, following which a steady decline in luminescence was observed with continued addition of ATP (Fig. 6). These data suggest that the sandwich-like structure formed by probe **1** and ATP at a 2 : 1 ratio is gradually modified with the continuous addition of ATP, forming a new structure with a 1 : 1 stoichiometry between probe **1** and ATP (Scheme 3). This latter structure (the quantum yield, Φ = 4.89%) would include fewer conjugated planes and weaker rigidity than the original structure, thereby producing less luminescence intensity. In spite of



Scheme 3 The proposed mechanism for ATP sensing based on probe **1** (inset: probe **1** only, and probe **1** with the addition of 0.25 eq., 0.50 eq., 1.0 eq., 2.0 eq. of ATP, respectively, observed under an ultraviolet lamp at 365 nm).

coordinating with one adenosine nucleotide, the complex would remain positively-charged and would thus exhibit some affinity for the negatively-charged adenosine nucleotide, while the conjugated group would still align to produce π–π stacking even at the 1 : 1 stoichiometry. The luminescence intensity at 1 : 2 stoichiometry between probe **1** and ATP (the quantum yield, Φ = 2.82%) decreases very slowly with the continuous addition of ATP. During the quenched luminescence titrations of probe **1** with ATP, the values of the intensity ratio of the bands at 615/591 nm stay at 1.4 ± 0.1. It indicates that the coordination environment of europium ions has not been changed. At the same time, it suggests that the following π–π stacking from the excess of ATP does not change the coordination environment of europium ions.

Conclusions

In conclusion, we have developed a new europium-based probe with high selectivity to ATP over ADP and AMP in pure aqueous solution at pH 6.8. With the advantages cited for lanthanides, this probe is a promising candidate for the detection of ATP and for monitoring activities involving the production or consumption of ATP in biological systems. This work provides a method for developing lanthanide probes with high specificity and sensitivity for biological molecules.

Experiment section

Instrumentation

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 300 MHz and a Bruker 400 MHz spectrometer respectively. Chemical shifts (δ) are given in parts per million (ppm). Mass spectra were obtained on a Bruker esquire 6000 and a Bruker maxis 4G respectively. Steady state luminescence spectra were measured on a Hitachi F-4500 fluorescence spectrophotometer, and the luminescence emission spectra on the pH dependence were measured on a Shimadzu RF-5301 PC spectrofluorophotometer. The luminescence lifetime data were determined by an absolute method on an Edinburgh Instrument FLS920 fluorescence spectrophotometer. Quantum yields were determined by an absolute method using an integrating sphere on Edinburgh Instrument FLS920. The overall quantum yields Φ measured were determined by an absolute method using an integrating sphere (150 mm diameter, $BaSO_4$ coating) with three measurements carried out for each sample. The pH measurements were performed with a METTLER TOLEDO EL20 pH-meter.

Chemicals

2-Chloroacetyl chloride, 2-acetylpyridine, 4-methylbenzaldehyde, and cyclen (1,4,7,10-tetraazacyclododecane) were purchased from J&K Scientific Ltd. Adenosine-5′-triphosphate disodium salt (ATP) and adenosine-5′-diphosphate disodium salt (ADP) were purchased from Alfa Aesar. Adenosine-5′-monophosphate sodium was purchased from Acros Organics Company. Europium nitrate ($Eu(NO_3)_3{\cdot}6H_2O$) was obtained by dissolving Eu_2O_3 (99.99%, Shanghai Yuelong) in nitric acid followed by successive fuming to remove excess acid. The other chemicals were all commercially available. All of the chemicals were used as received. Deionized water was used to prepare all aqueous solutions. The anions used in the fluorescence experiments were all sodium salts. All measurements were repeated three times, and the general average was obtained.

Syntheses

Synthesis of 2-chloro-*N*-methylacetamide.[29] 2-Chloroacetyl chloride (9.0 g, 80 mmol) was added dropwise to aqueous methylamine (40%, 6.2 g, 80 mmol) in 60 mL of water at −20 °C with stirring magnetically. The temperature rose to 0 °C slowly, and was controlled at 0 °C with stirring until the reaction didn't release heat any more. The hydrochloric acid (36%–38%, 0.5 mL) was added to the solution, and then the resulting solution was extracted with dichloromethane (4 × 50 mL). The organic layer was washed with water (3 × 50 mL), dried with anhydrous sodium sulfate, filtrated, and then spin-evaporated *in vacuo* to give a clear liquid residue. The residue was diluted with pentane (60 mL) and spin-evaporated *in vacuo* to give a white solid (2.3 g, 26.7% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.90 (d, 3 H), 4.07 (s, 2 H), 6.61 (s, 1 H). MS: m/z = 108.2, 110.2 $[M + H]^+$, m/z = 130.2, 132.2 $[M + Na]^+$.

Synthesis of 2.[30] Under magnetic stirring, 2-acetylpyridine (4.84 g, 40 mmol) and 4-methylbenzaldehyde (2.40 g, 20 mmol) were added into ethanol (100 mL), and then NaOH (1.60 g, 40 mmol) and ammonia water (25%–28%, 65 mL) were added into the solution. The solution was stirred at 34 °C for 24 h. The mixture was cooled to the room temperature. The off-white solid was obtained by filtration, washed with cold ethanol (10 mL), and then dried at 55 °C under vacuum. The white crystalline solid was obtained by crystallization from ethanol, and then dried at 55 °C under vacuum (4.0 g, 62% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 2.42 (s, 3 H), 7.29–7.35 (m, 4 H), 7.80–7.89 (m, 4 H), 8.66 (d, 2 H), 8.71–8.73 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 156.3, 155.8, 150.1, 149.1, 139.0, 136.8, 135.5, 129.6, 127.1, 123.7, 121.3, 118.6, 21.25. MS: m/z = 324.3 $[M + H]^+$.

Synthesis of 3.[30] **2** (3.23 g, 10 mmol) was dissolved in CCl_4 (40 mL), and then *N*-bromosuccinimide (NBS, 1.96 g, 12 mmol) and α,α-azoisobutyronitrile (AIBN, 0.130 g, 0.80 mmol) were added into the solution in order. The mixture was stirred magnetically and refluxed for 2 h. Then the mixture was cooled to room temperature. The succinimide was removed by filtration and the solvent was evaporated under vacuum. The crude product was crystallized from ethanol to afford the pure light-yellow solid. The pure solid was dried at 60 °C under vacuum (2.06 g, 51% yield). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 4.55 (s, 2 H), 7.33 (dd, 2 H), 7.53 (d, 2 H), 7.88 (m, 4 H), 8.65 (d, 2 H), 8.71 (m, 4 H). MS: m/z = 402.4, 404.4 $[M + H]^+$.

Synthesis of 4.[31] The solution of **3** (0.402 g, 1.0 mmol) in $CHCl_3$ (10 mL) was added dropwise to a solution of cyclen

(0.688 g, 4.0 mmol) in $CHCl_3$ (100 mL) in 20 minutes. The mixture was stirred at 30 °C for 10 hours, and then filtrated. The organic layer was washed with saturated brine for five times (5 × 100 mL), dried with anhydrous sodium sulfate, filtrated, and then spin-evaporated under vacuum to yield a light yellow solid without purification. The product was used in the next reaction directly.

Synthesis of 5.[32] **4** (0.2296 g, 0.460 mmol), 2-chloro-*N*-methylacetamide (0.165 g, 1.54 mmol), and K_2CO_3 (0.212 g, 1.54 mmol) were added to 16 mL of anhydrous acetonitrile. The mixture was stirred at 65 °C for 3 days under argon. The resulting mixture was filtrated to remove the undissolved substance, and the solvent was removed under reduced pressure. Purification was achieved by alumina column chromatography using a gradient elution 100% CH_2Cl_2 to 95% CH_2Cl_2–5% CH_3OH. The product was obtained as a pale yellow solid (0.0318 g, 9.8% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.56–2.84 (m, 24 H), 3.08–3.10 (m, 5 H), 3.72 (s, 2 H), 7.35–7.38 (m, 4 H), 7.85–7.91 (m, 4 H), 8.67–8.73 (m, 6 H). MS: m/z = 707.6 $[M + H]^+$.

Synthesis of probe 1. **5** (35.3 mg, 50 mmol) and $Eu(NO_3)_3{\cdot}6H_2O$ (22.3 mg, 50 mmol) were dissolved in the same solution of $CHCl_3$ (3 mL) and ethyl acetate (3 mL) respectively. With stirring magnetically, the former solution and the latter solution were filtrated into one round bottom flask successively. Then the mixture was stirred for 4 hours and centrifuged. The solid was washed with the solution of $CHCl_3$ and ethyl acetate (v/v = 1 : 1) for three times (3 × 10 mL). After drying at 55 °C, probe **1** was obtained (25.5 mg, 48.2% yield). MS: m/z = 460.66 $[Eu{\cdot}\mathbf{5} + NO_3^-]^{2+}$, m/z = 982.32 $[Eu{\cdot}\mathbf{5} + 2NO_3^-]^+$.

Acknowledgements

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