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Photorelease of La^{3+} with turn-on fluorescent detection

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Keywords: photorelease, La^{3+}, fluorescent monitoring, photochemistry.

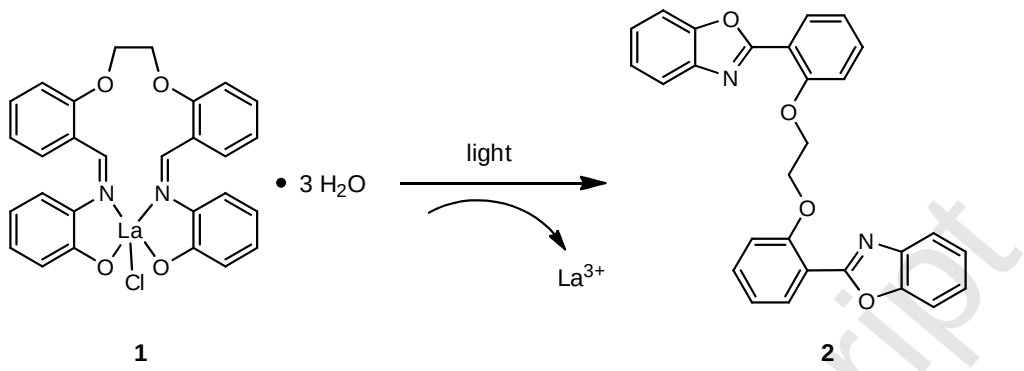
Abstract: Photorelease of La^{3+} with turn on fluorescent detection is described. Complex (**1**) is synthesized by treatment 2,2'-(((ethane-1,2-diylbis(oxy)bis(2,1-phenylene))bis(methanylylidene)) bis(azanylylidene))diphenol with $LaCl_3 \cdot 7H_2O$ in 1:1 molar ratio. Upon irradiation with UV light, **1** undergoes La^{3+} release and converts to 1,2-bis(2-(benzoxazol-2-yl)phenoxy)ethane (**2**). It is found that **2** exhibits strong fluorescence emission and the turn-on fluorescence is detected during the photo-conversion of **1** to **2**, which is beneficial for monitoring the photo-release of La^{3+}. Moreover, an excellent (R = 0.9963) linear correlation between the ratio of optical density (OD_1/OD_2) with irradiation time is obtained when **1** is photo-converted to **2**, which is beneficial for controlling or regulating the quantity of La^{3+}-released.

1. Introduction

The light-activated release provides a powerful tool for the rapid introduction of a variety of species to biological systems with spatial and temporal control, allowing the time-resolved study of the ensuing events [1-5]. Metal photo-release has currently attracted considerable attention

because of its potential since it will be a valuable tool for the delivery of biologically active metals, which are an essential cofactor in numerous enzymes [6-9], or of toxic metal ions to study the mechanisms of metal-ion trafficking and applications, such as chemotherapy, by means of inducing cell death by catalyzing DNA and RNA cleavage or by binding active sites of proteins competition with essential metals [10-13].

Lanthanum (La^{3+}) plays an important role in biological systems [14,15]. Lanthanum is a high-valence rare-earth metal used as a substitute for calcium as a blocker [16,17] of several nonselective ion channels in different systems based on the blocking activity of lanthanum including connexin hemichannels, murin frontal cortex networks, tobacco BY-2 cells, or the outward K^+ channel [18-21]. Although lanthanides have been known for their diversity in biological effects [22-24], and the application of lanthanides in medicine has high potential [25-28], the mechanism of the biological effects of lanthanides is not clearly known [29-31], specially at molecular and genetic level. Lanthanides (Ln^{3+}) including lanthanum (La^{3+}) are exogenous ions, the concentration of Ln^{3+} has great influenced on their biological effects [32,33]. Therefore, it is required that the development of a simple and efficient way to delivery exogenous lanthanides (Ln^{3+}) to biological systems. Photo-trigged release is a promising tool, and can fulfill to molecules/ions release with spatial, temporal and quantitative control. In this paper, we report a prototype for La^{3+} photo-release. Complex **1** is prepared by employing 2,2'-(((ethane-1,2-diylbis(oxy)bis(2,1-phenylene))bis(methanylylidene))bis(azanylylidene))diphenol as ligand (Scheme 1), it is found that upon irradiation the solution of **1** in DMSO, the bound La^{3+} can be released and the ligand is converted to 1,2-bis(2-(benzoxazol-2-yl)phenoxy)ethane **2**. It is also found that accompanying the process of photoconversion, turn on fluorescence is observed, which is beneficial to monitor the photorelease of La^{3+}.



1 2

Scheme 1. Outline of photorelease of La^{3+} form complex **1.**

2. Experimental

2.1. General

^{1}H NMR spectra were recorded at 400 MHz with TMS as an internal reference and DMSO-d_6 as solvent. HRMS spectra were recorded with Q-Exactive MS spectrometer (Thermo Fisher). UV absorption spectra and fluorescence spectra were measured on an absorption spectrophotometer (Hitachi U-3010) and a fluorescence spectrophotometer (F-2500), respectively. IR spectra (KBr) were recorded on spectrophotometers Excalibur 3100 (Varian). All chemicals for synthesis were purchased from commercial suppliers, and solvents were purified according to standard procedures. Reactions were monitored by TLC silica gel plate (60F-254). Column chromatography was performed on silica gel (70-230 mesh). A UV lamp (36 watt) was used as light sources for photo-release (irradiation energy: 4.3 mW/cm^2).

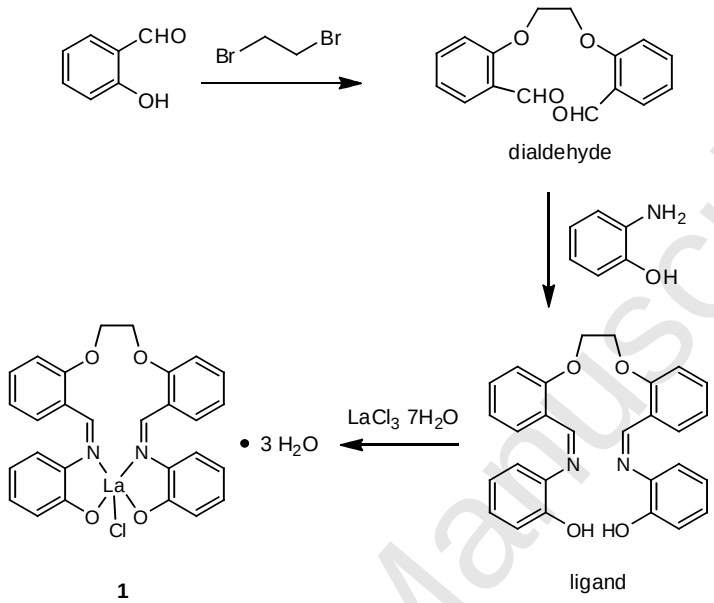
2.2. Materials.

2.2.1. *Synthesis of complex **1**.*

The complex **1** was synthesized by reaction of lanthanum (III) salt and the ligand in amount equal to metal: ligand molar ratio of 1:1. The synthetic route for **1** was presented in Scheme 2, and the detailed procedures were as follows. (a) To the solution of salicylaldehyde (6.1 g, 50

mmol) and 1,2-dibromoethane (4.7 g, 25 mmol) in acetonitrile (150 ml) was added potassium carbonate (6.9 g, 50 mmol) and potassium iodide (0.4 g, 2.5 mmol). The solution mixture was refluxed. When no starting material (salicylaldehyde) was detectable by TLC plate, the solution was concentrated and the crude product was added to water (100 ml) and the solution mixture was extracted with dichloromethane (50 ml × 3). The combined organic solution was dried over Na_2SO_4, the resulting solution was concentrated and the crude product was purified by flash column chromatography (petroleum ether / ethyl acetate, 2:1) to afford intermed product dialdehyde in 80% yield. (b) A solution of dialdehyde (0.54 g, 2 mmol) in absolute ethanol (20 ml) was heated to dissolved completely, to the solution was added a solution of 2-aminophenol (436 mg, 4 mmol) in absolute ethanol (10 ml), the solution mixture was reflexed till the dialdehyde was disappeared. The crude product was purified by recrystallization from ethanol to afford ligand in 80% yiled. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 7.47 (d, J = 7.7 Hz, 2H), 7.29 (t, J = 7.5 Hz, 2H), 7.10 (d, J = 7.9 Hz, 2H), 6.97 (t, J = 7.5 Hz, 2H), 6.95-6.82 (m, 4H), 6.80 (s, 2H), 6.78-6.68 (m, 2H), 6.62-6.51 (m, 4H), 4.51 (d, J = 3.2 Hz, 4H). HRMS (EI) Calcd for $C_{28}H_{24}N_2O_4$, (M^+): 452.1736. Found: 452.1741. (c) To the boiling solution of ligand (452 mg, 1.0 mmol) in ethanol (100 ml) was added dropwise a solution of lanthanum (III) chloride heptahydrate (371 mg, 1.0 mmol) in ethanol (10 ml). The mixture solution was refluxed for 1 hr and then cooled down to ambient temperature. The yellow crystalline was filtered off, washed with ethanol (10 ml × 3), and pure complex **1** was obtained after vacuum-dried without further purification. Yield: 96%. M.p. > 300 °C. IR (v, cm^{-1})**:** 3570.14, 3556.87, 3410.64 (br), 1645.21, 1601.90, 1573.20, 1286.23, 1182.07. ^{1}H NMR (400 MHz, DMSO-d_6, ppm): 8.74 (s, 2H), 7.90-7.78 (m, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.8 Hz, 4H), 7.21 (dd, J = 7.5, 1.8 Hz, 2H),

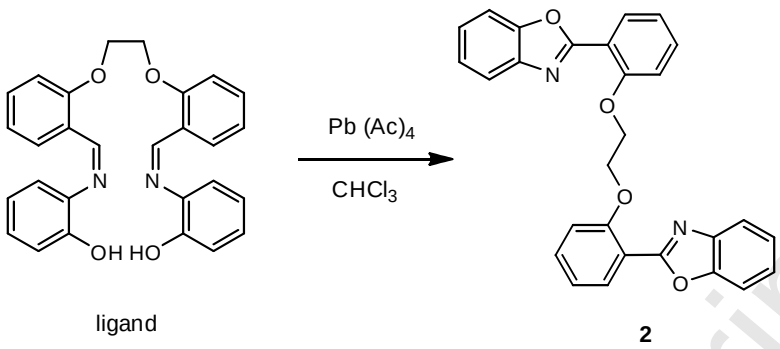
6.95 (t, J = 7.5 Hz, 2H), 6.85-6.78 (m, 4H), 4.61 (s, 4H). HRMS (EI) calcd for $C_{28}H_{22}ClLaN_2O_4$ $3H_2O$ (M^++Na): 701.0547. Found: 701.4920.



Scheme 2. Synthetic route for complex **1**.

*2.2.2 Synthesis of photo-product **2***

The synthetic route for **2** was presented in Scheme 3, and the detailed procedure was as follows. A mixture of **1** (226 mg, 0.5 mmol) and lead acetate, $Pb(OAc)_4$ (244 mg, 0.55 mmol), dissolved in 20 ml of $CHCl_3$ was refluxed till no starting material was detected by TLC plate. The solution was filtered and the filtrate was extracted with CH_2Cl_2-H_2O (v/v = 1:1, 10 ml × 3). The conbined organic solution was dried over Na_2SO_4. The resulting solution was concentrated and the crude product was purified by flash column chromatography (petroleum ether/CH_2Cl_2, 1:1) to afford **2**. Yield: 15%. ^{1}H NMR (400 MHz, DMSO-d_6): 8.55 (dt, J = 8.0, 1.6 Hz, 2H), 7.72-7.70 (m, 2H), 7.50-7.31 (m, 10H), 7.11 (t, J_1 = 7.6 Hz, J_2 = 7.2 Hz, 2H), 4.62 (s, 4H). TOF-MS (EI) calcd for $C_{28}H_{20}N_2O_2S_2$ (M^+): 480.0966. Found: 480.0991.



Scheme 3. Synthesis of **2**.

3. Results and discussion

3.1. Photorelease of La^{3+}

Photorelease of La^{3+} from complex **1** was performed in DMSO solution. Upon irradiation with 254 nm light, the absorption of complex **1** at λ_{max} = 352 nm ($\varepsilon = 1.5 \times 10^4$ L mol^{-1} cm^{-1}, in DMSO) decreased with the increase of irradiation time, accompanying this process, a new band at λ_{max} = 320 nm appeared (Fig. 1). The absorption of 320 nm attributed to the photo-product **2**, whose structure is suggested in Scheme 1. Further study found that the photorelease of La^{3+} from complex **1** could also be performed in other organic solvents such as ethanol (EtOH) and N,N-dimethylformamide (DMF), the obtained results were similar to that in DMSO. It was worth noting that the photorelease of La^{3+} could not performed in aqueous solution since **1** was insoluble in water. The investigation of **1** in mixture solution of H_2O-DMSO found that the photorelease of La^{3+} could be conducted in H_2O-DMSO (v/v = 5/95) mixture solution with H_2O not more than 5%.

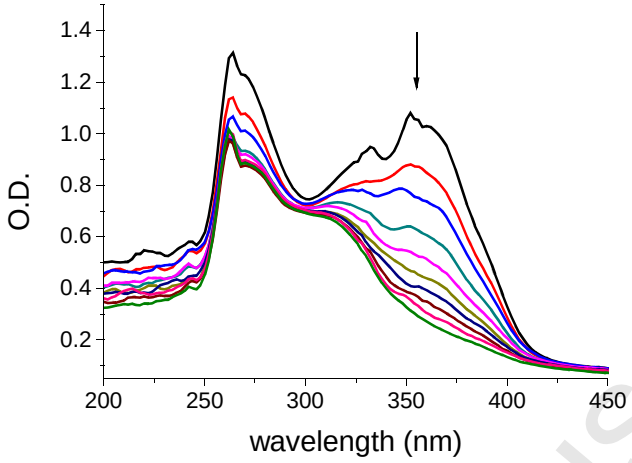


Fig. 1. Absorption changes of **1** (50μM, in DMSO) with UV light irradiation (irradiation wavelength: λ = 254 nm, irradiation periods: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min).

The kinetics of photorelease of La^{3+} was investigated by determination the optical density (OD) changes of **1** with different irradiation time according to Fig. 1. The ratio of $OD_{352\ nm}$ (maximum absorption of complex **1**) to $OD_{320\ nm}$ (maximum absorption of photo-product **2**) as function of irradiation time was presented in Fig. 2. The linear correlation between the OD_{320nm} / OD_{352nm} with irradiation time is excellent (R = 0.9963) in the process of La^{3+}-photorelease till it was completed. Photorelease with ratiometric detection suggested that the amount of La^{3+} release could be manipulated via controlling irradiation time, which is beneficial for the regulation of La^{3+} release in terms of quantity, location and time.

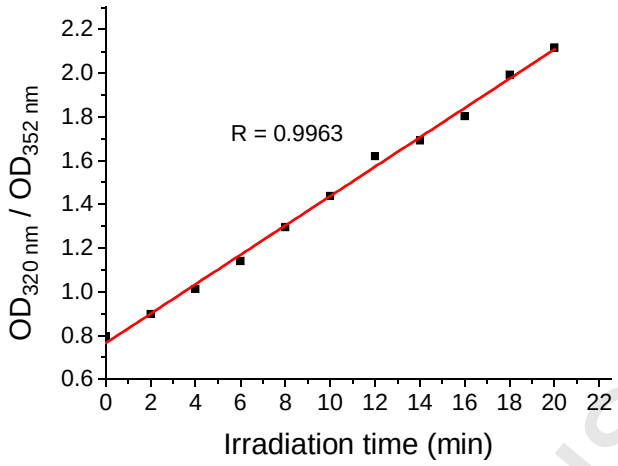


Fig. 2. The plot of optical density changes of **1** (50μM, in DMSO) with different irradiation time (irradiation wavelength: λ = 254 nm, irradiation periods: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20 min). $OD_{320\ nm}$: optical density at 320 nm, OD_{352nm}: optical density at 352 nm.

3.2. Fluorescence monitoring of photorelease of La^{3+}

In term of our previously study [34,35], phenolic Schiff bases are photo-converted to benzoxazole derivatives accompanying metal-ion photo-release, and a strong fluorescence is detected at the same time. Complex **1** showed no fluorescence in DMSO solution using 352 nm or 320 nm as excitation wavelength. Upon irradiating the solution of **1** in DMSO, the turn on fluorescence (λ_{em} = 364 nm), which attributed to the emission of photo-product **2**, was observed. As presented in Fig. 3, the fluorescence was increased with increase of irradiation time till the photorelease of La^{3+} was completed, which provides a convenient method to monitor the process of photorelease of La^{3+}.

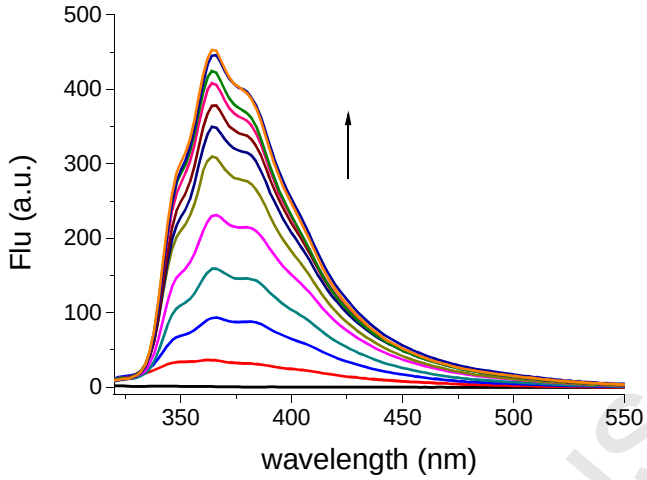


Fig. 3. Fluorescence changes of **1** (50μM, in DMSO) with UV light irradiation (irradiation wavelength: λ = 254 nm, irradiation periods: 0, 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22 min, excitation wavelength: λ_{ex} = 290 nm).

To check the chemical structure of photo-product **2** and elucidate the fluorescence properties of photo-product **2**, pure **2** was prepared by treatment of the ligand with $Pb(OAc)_4$ in $CHCl_3$ (Scheme 3) (detailed procedure see experimental section). The TLC (thin layer chromatography) test showed that both photo-product **2** and pure **2** has the same value of R_f (R_f = 0.26, elute: ethyl acetate/petroleum = 1 : 2, v/v) at the TLC plate. Moreover, it was found that both absorption and emission profiles of **2** were similar to those of pure **2**, and absorption (λ_{max} = 320 nm) and emission (λ_{em} = 364 nm) maxima were at the same position (Fig.s 1 and 3 vs. Fig. 4). Obtained results confirmed that photo-product **2** has the same chemical structure as that of pure **2**. Further study found that **2** exhibited strong fluorescence in DMSO, and a large fluorescence quantum yield (ϕ_f = 0.76) was obtained using quinine sulphate as a standard.

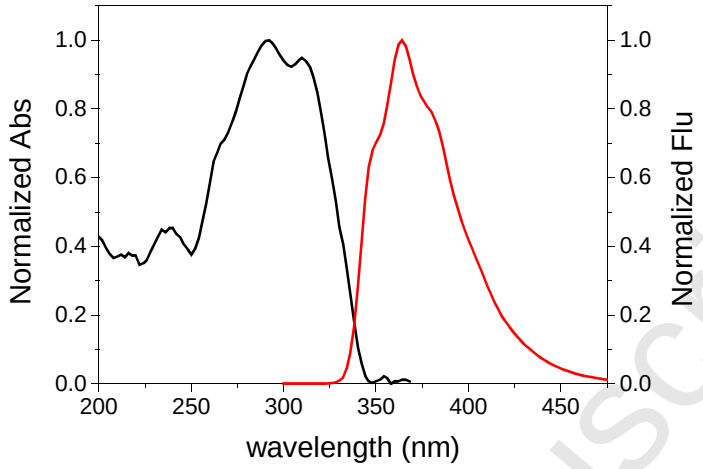
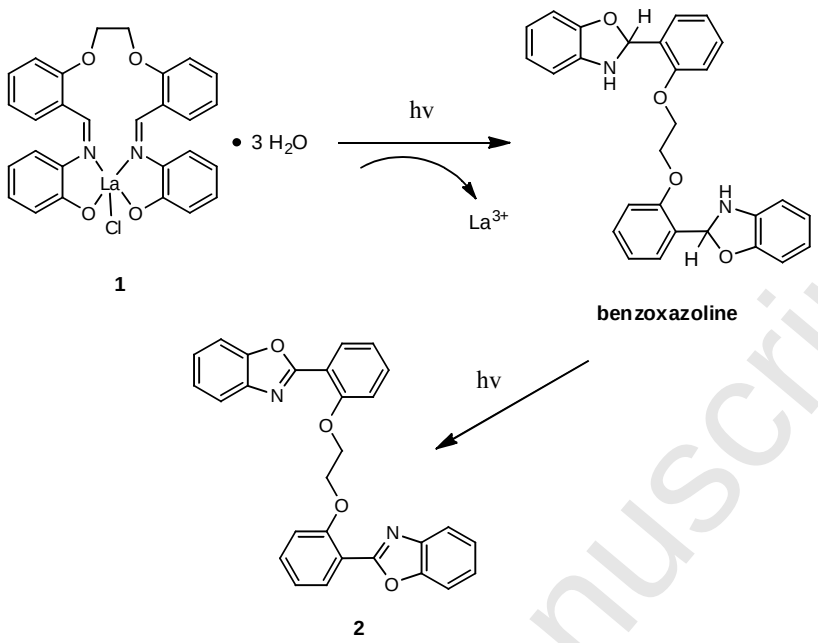


Fig. 4. Absorption and fluorescence of **2** in DMSO solution (50 μM, irradiation wavelength: λ_{ex} = 290 nm).

3.3. Possible mechanism for the photoreaction

A possible mechanism for the photoreaction consists of a two-step sequence involving the formation of benzoxazoline followed by oxidation and dehydration (Scheme 4) [36]. Preliminary investigation found that benzoxazoline formation is a prerequisite to convert a Schiff base into benzoxazoline by photon induction. Control experiments showed that oxygen in the air played a minor role in the conversion reaction. A similar conversion was obtained (detection by absorption spectroscopy) when the irradiation of **1** was carried out in an air saturated solution or in degassed solution, although the mechanism for the photoreaction in the absence of oxygen is not known. It is worth noting that complex **1** is stable at ambient temperature and no significant change (detection by absorption spectral) was detected when a solution of **1** was kept in the dark, which indicates that the conversion of **1** into **2** did not occur in the absence of light.



Scheme 4. A possible pathway for the photo-conversion of **1** into **2**.

3.4. Control experiments

The binding of **2** with La^{3+} was investigated. No significant absorption changes were detected upon addition of $LaCl_3$ $7H_2O$ to a solution of **2** in DMSO, which indicated that no (or only weak) binding between **2** and La^{3+}. To confirm this suggestion, ^1H NMR studies of **2** with and without addition of La^{3+} were performed. It was found that ^1H NMR spectrum of **2** with addition of La^{3+} agreed quite well with that of **2** without addition of La^{3+}, except for the signal at δ = 3.3 ppm, which is attributed to the proton of H_2O resulting from the addition of $LaCl_3$ $7H_2O$. As presented in Fig. 5, the signals of **2** with addition of La^{3+} (above), assigned to the aromatic protons in the range of 7.93 – 7.05 ppm, are exactly as same as those of **2** without addition of La^{3+} (below), no significant chemical shifts were detected. These results confirmed that there was no (or only a very weak) binding between **2** and La^{3+}.

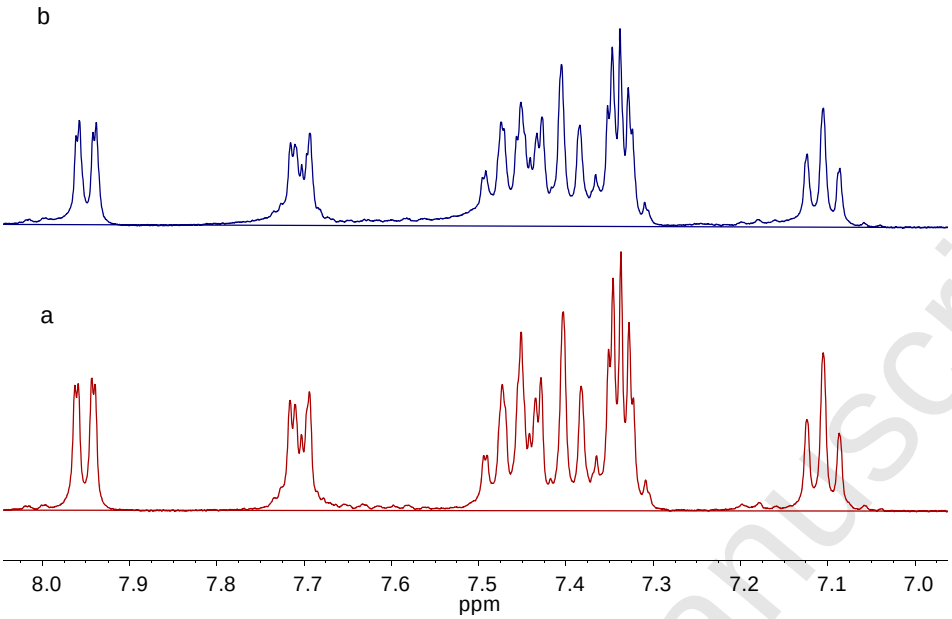


Fig. 5. Partial ^{1}H NMR spectra of **2** with (a) and without (b) addition of $LaCl_3$ $7H_2O$ (solvent: DMSO-d_6).

Further investigation found that the fluorescence of **2** was not affected by La^{3+}. As presented in Fig. 6, the emission spectral of **2** (both profile and strength) with addition of La^{3+} was exactly as same as that of **2** without addition of La^{3+}, no significant fluorescence changes were detected, which indicated that La^{3+} did not quench the fluorescence of **2**. In addition, control experiments showed that **2** is photostable, and no distinct changes in absorption or fluorescence was detected after the solution of **2** was irradiated for 60 min with 320 nm light. No significant binding between **2** and La^{3+} and no distinct fluorescence quench/decrease are beneficial for application of photorelease of La^{3+} with fluorescent monitoring.

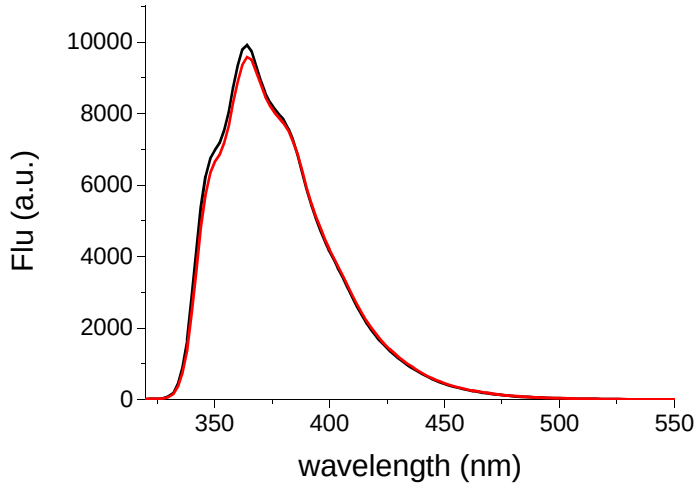


Fig. 6. Fluorescence of **2** (50μM, in DMSO) with (red) and without (black) addition of $LaCl_3$ $7H_2O$ (100μM). Irradiation wavelength: λ_{ex} = 290 nm.

4. Conclusions

A platform for La^{3+}-photorelease with fluorescence monitoring has been developed. Although the system presented herein has some shortcomings including unable to be performed in aqueous solution, irradiation, excitation and detection in short wavelength region, the system has some advantages such as controlled photo-release and turn on fluorescence monitor. Controlled photo-release system is great beneficial for the drug delivery in terms of quantity, location and time as improved control maximizes therapeutic effect while minimizing side effects. From a practical viewpoint, it is desirable for the system to be used in buffer solution and with visible light irradiation, excitation and detection. Modifying molecular structure to meet the requirements, and exploring the applications in biological processing will be the subject of future studies.

Acknowledgments

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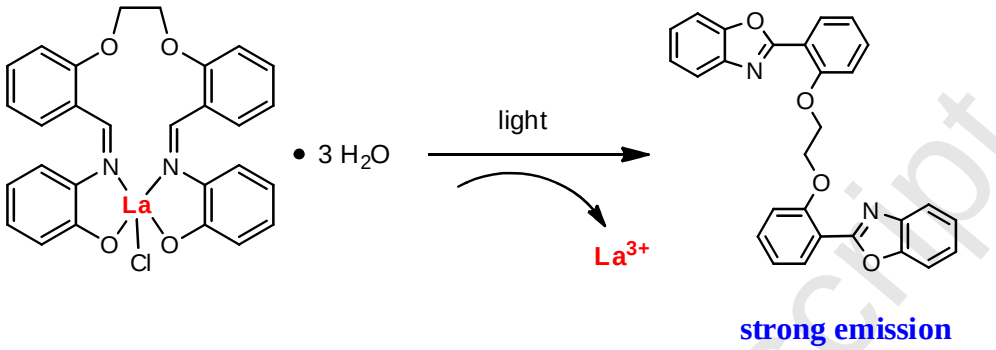
Graphical Abstract



strong emission

Highlights

(1) A platform for La^{3+}-photorelease with turn on fluorescence monitoring has been developed.

(2) La-complex is synthesized by employing a Schiff base derivative as ligand.

(3) La-complex undergoes photorelease of La^{3+} and photo-converts to fluorescent benzoxazole derivative.