การนำสารประกอบโรดามีน 6G ที่มีหมู่ไทโอเซมิคาร์บาไซด์เป็นองค์ประกอบมาใช้เป็นเซ็นเซอร์ทางเคมีเชิงแสงสำหรับการตรวจวัดไอออนเหล็ก(III)

Rhodamine 6G Bearing Thiosemicarbazide as Optical Chemosensor for Determination of Iron(III) Ion

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บทคัดย่อ

ได้ทำการสังเคราะห์จากลิแกนด์ **L1** ซึ่งเป็นอนุพันธ์ของโรดามีน 6G เพื่อนำมาใช้เป็นเซ็นเซอร์ทางเคมีเชิงแสงสำหรับการตรวจวัดไอออนของ Fe^{3+} โดยใช้สารละลาย CH_3CN เป็นตัวทำละลาย จากการศึกษาพบว่าเมื่อมีไอออนของ Fe^{3+} อยู่ในระบบจะทำให้สารละลายเปลี่ยนสีจากใสไม่มีสีไปเป็นสีชมพูแดง เนื่องจากไอออนของ Fe^{3+} ไปเหนี่ยวนำให้เกิดการเปิดของวงสไปโรแลคแตมและจากการศึกษาด้วยเทคนิคฟลูออเรสเซนต์สเปคโตรโฟโตเมทรียังพบว่าไอออนของ Fe^{3+} สามารถทำให้ความเข้มของสัญญาณฟลูออเรสเซนต์ที่ความยาวคลื่น 556 นาโนเมตร มีค่าเพิ่มขึ้นด้วยกระบวนการถ่ายเทพลังงานแบบ FRET ในโมเลกุลของ **L1** จากการคำนวณหาค่าคงที่ความเสถียรของของการเกิดสารประกอบเชิงซ้อนมีค่าเท่ากับ 3.33×10^5 M^{-1} และการตรวจวัดไอออนของ Fe^{3+}ด้วยวิธีนี้มีค่าขีดจำกัดของการตรวจวัดเท่ากับ 0.004 ppm

คำสำคัญ : เฟรท, ไอออน (III), เคโมโดซิมิเตอร์, ไทโอเซมิคาร์บาไซด์, 1,3,4-ออกซาไดเอโซล

Abstract

A new rhodamine-based optical chemorsensor **L1** for the detection of Fe^{3+} ion in CH_3CN was synthesized. It was found that in the presence of Fe^{3+} the color solution of **L1** was changed from colorless to red-pink. This is due to the formation of spirolactam ring opening process which induced by Fe^{3+}. Moreover, Fe^{3+} can enhance the fluorescence intensity at 556 nm through the energy transfer respect to the FRET process. From fluorescence titration, complex formation constant was calculated to be 3.33×10^5 M^{-1}. The analytical detection limit of Iron(III) using this method is 0.004 ppm

Keywords : FRET, iron (III), chemodosimeter, thiosemicarbarzide , 1,3,4-oxadiazole

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Introduction

Fe^{3+}, the second most abundant metal element in the earth's crust, plays a significant role in biological processes such as oxygen transport, electron transport, and cofactors in oxidoreductase catalysis. (Andrew, 1999; Summer & Kopelman, 2005; Lee & Helmann, 2006). Iron deficiency and excess can both have severe effects on human health, including anemia, hemochromatosis, liver damage, diabetes, and Parkinson's disease. (Haas & Brownlie, 2001; Ajioka & Kushner, 2003; Theil & Goss, 2009) For the time being, a great deal of research have been devoted to develop colorimetric and fluorometric chemosensors for probing Fe^{3+} ions (McRae *et al*., 2009; Sahoo *et al*., 2012; Wang *et al*., 2015; Chen *et al*., 2017; Jun-jiea *et al*., 2017). Among them, chemodosimeters based chemical sensing through a specific chemical reaction between receptor molecules and target species are particularly attractive (Kaur *et al*., 2012; Du *et al.,* 2012; Gu *et al*., 2016). Rhodamine derivative dyes are popular employed as chemodosimeters for metal ions due to their excellent photophysical properties which gives rise a strong fluorescence emission with high quantum yield and a distinct color upon selective opening of rhodamine spirolactam ring (Kim *et al*., 2008; Chen *et al*., 2012). Several research groups have successfully detected Fe^{3+} ions using rhodamine derivatives in which Fe^{3+} can induce spirolactam ring opening (Zhang *et al*., 2008; *Yin et al*., 2011; Chereddy *et al*., 2012; Ge *et al*., 2013; Wu *et al*., 2014; Liu & Qian, 2017) and hydrolysis (Lee *et al*., 2010). Fluorescence resonance energy transfer (FRET) is also an interesting phenomenon toward chemical sensing of ions (Fan *et al*., 2013; Kumar *et al*., 2014). Few reports on Fe^{3+} chemodosimeters based on FRET mechanisms on rhodamine skeleton have been reviewed as selective and sensitive sensor for Fe^{3+} (Ding *et al*., 2013; Piao *et al*., 2014; Qin *et al*., 2015).

Hg^{2+} promote the cyclization of thiosemicarbazide to form 1,3,4-oxadiazole on some rhodamine based chemodosimeters have been reported (Yu *et al*., 2008; Zhang *et al*., 2008; Bera *et al*., 2014). However, there has been no reports that Fe^{3+} could catalyzed the cyclization of thiosemicarbazide to 1,3,4-oxadiazoles. Therefore, we report herein chemosensor **L1** (Figure 1a) which is demonstrated to be a chemodosimeter for Fe^{3+} under a PET-FRET sensing strategy. The skeleton of **L1** consists of a rhodamine 6G dye and naphtyl group, which displayed a significant spectral overlap between the emission spectra of the naphtyl donor and the absorption spectra of the rhodamine 6G (in the form of ring-opening spirolactam structure) energy acceptor in the presence of Fe^{3+}. The spectral overlap between naphthyl emission and ring-opened rhodamine 6G absorption in CH_3CN are presented in Figure 1b. Moreover, we also found that Fe^{3+} could promote the desulfurization reaction of **L1** following the cyclization to yield 1,3,4-oxadiazoles. Finally, the cyclization product was characterized by ^{1}H-NMR, ^{13}C-NMR and HRMS.

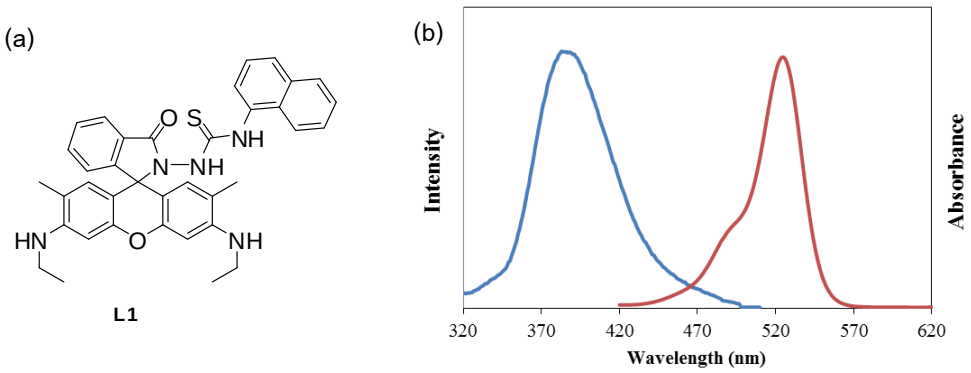


Figure 1 (a) Structure of ligand **L1** (b) Spectral overlap between naphthyl emission (blue line) and ring-opened rhodamine 6G absorption (red line) in CH_3CN.

Methods

Chemicals and instruments

All chemicals were of analytical grade and used without further purification. ^{1}H- and ^{13}C-NMR were recorded using the Bruker AVANCE 400 MHz Ultra Shield spectrometer. UV absorption spectra were obtained on Agilent 8453 UV/Vis Spectrophotometer. Fluorescence emission spectra were obtained using an Agilent Cary Eclipse spectrophotometer.

Synthesis of ligand L1

1-Naphthylisothiocyanate (0.47 g, 2.5 mmol) was added to the solution of rhodamine 6G hydrazide (Yang *et al*., 2002) (0.85 g, 2 mmol) in CH_3CN (40 mL). The reaction mixture was refluxed for 15 h. After the solvent was evaporated under reduced pressure, the crude product was obtained and was purified by column chromatography on silica gel (elution with 1% ethanol in CH_2Cl_2) to give **L1** (0.46 g, 38%). ^{1}H-NMR (400 MHz, $CDCl_3$, ppm) : δ 8.10 (d, 1H, *J* =7.6 Hz, Ar*H*), 7.81 (d, 1H, *J* = 7.2 Hz, Ar*H*), 7.75 (d, 2H, *J* =7.2 Hz, Ar*H*), 7.65 (m, 2H, Ar*H*), 7.40 (m, 4H, Ar*H*), 7.28 (s, 1H, -N*H*), 7.08 (m, 2H, Ar*H*), 6.48 (s, 2H, Ar*H* + -NH-CH_2-), 6.29 (s, 2H, Ar*H*), 3.56 (s, 2H, -N*H*-), 3.28 (s, 4H, -CH_2-), 1.60 (s, 6H, -CH_3), 1.36 (m,6H, -CH_3). ^{13}C-NMR (100 MHz, $CDCl_3$, ppm) : δ 183.97, 167.01, 152.71, 150.76, 148.11, 134.41, 133.67, 132.60, 129.90, 129.06, 128.79, 128.15, 128.02, 127.82, 127.69, 127.42, 127.11, 126.58, 126.09, 125.36, 125.08, 124.77, 123.87, 123.04, 122.62, 118.79, 118.03, 104.27, 97.21, 96.89, 67.17, 38.38, 38.32, 16.72, 16.65, 14.76. HRMS (positive mode); 614.2681 [**L1** + H^+].

Synthesis of L1'

A solution of **L1** (0.25 g, 0.4 mmol) in CH_3CN (60 mL) was stirred, and $FeCl_3 \cdot 6H_2O$ (10.8 g, 40 mmol) was added. The reaction mixture was stirred for 3 hours. After the solvent was evaporated under reduced pressure, the crude product was dissolved in CH_2Cl_2 and washed with water and purified by column chromatography on silica gel (CH_2Cl_2/MeOH = 96:4) to give **L1'** (110 mg, 47%). ^{1}H-NMR (400 MHz, DMSO-d_6, ppm) : δ 10.49 (s, 1H, -N*H*-), 8.13 (2, 2H, Ar*H*), 7.87 (m, 5H, Ar*H*), 7.59 (m, 5H, Ar*H*), 7.35 (broad s, 1H, -N*H*), 6.81 (broad s, 3H, Ar*H*), 3.44 (s, 4H + 1H, -C*H*$_2$-CH_3 and -N*H*-CH_2- + H_2O in DMSO), 2.06 (broad s, 6H, -C*H*$_3$), 1.24 (broad s, 6H, -C*H*$_3$). ^{13}C-NMR (100 MHz, DMSO-d_6, ppm) : δ 161.91, 157.25, 157.07, 156.25, 155.54, 134.24, 133.99, 131.40, 131.06, 130.83, 128.74, 128.63, 128.43, 127.03, 126.62, 126.31, 125.94, 124.98, 123.40, 122.53, 118.33, 113.47, 94.18, 38.46, 29.40, 29.08, 17.88, 17.50, 14.06. HRMS (positive mode); 580.2722 [**L1'**+H^+].

Screening test for selective sensing of metal ions

A solution of various metal ions (10 equivalents) in acetonitrile solution was added into a solution of **L1** (10 μM) in the same solvent system. The mixtures were allowed to stand still for 1 min and then were subjected to UV-vis spectroscopy measurements. Photographs were taken using a digital camera (Canon EOS 7D with Tamron 17-50 mm lens).

UV-visible studies

All UV-vis experiments were performed in acetonitrile solutions in quartz cuvettes. The binding constants were determined by adding aliquots of 400 μM of Fe^{3+} solution (10 μL) to 10 μM of **L1** solution (2 mL) using a syringe. After each addition, the absorption spectra of the solution were recorded. All measurements were conducted at least in triplicate.

Fluorescence studies

All fluorescence experiments were performed in acetonitrile solutions in quartz cuvettes. Upon excitation at 350 nm, the emission spectra of **L1** and the mixture of **L1** with various metal ions were integrated over the range 400 nm to 650 nm. All measurements were conducted at least in triplicate.

Results and discussion

Synthesis and characterization of L1

The rhodamine derivative **L1** was prepared in high yield from rhodamine 6G using a two-step procedure. The structure of **L1** was confirmed by ^{1}H-NMR, ^{13}C-NMR (Figure S1 and S2) and HRMS (Figure 2b). The characteristic peak of two N*H* thiourea protons of **L1** in DMSO-d_6 appeared as the two singlet peaks at δ 9.36 and 9.22 ppm in the ^{1}H-NMR spectrum (Figure 2a). Moreover, the peak at δ 67.17 ppm (Figure S2) in the ^{13}C NMR spectrum of **L1** confirmed the characteristic of spirolactam in the closed form (He *et al*., 2010).

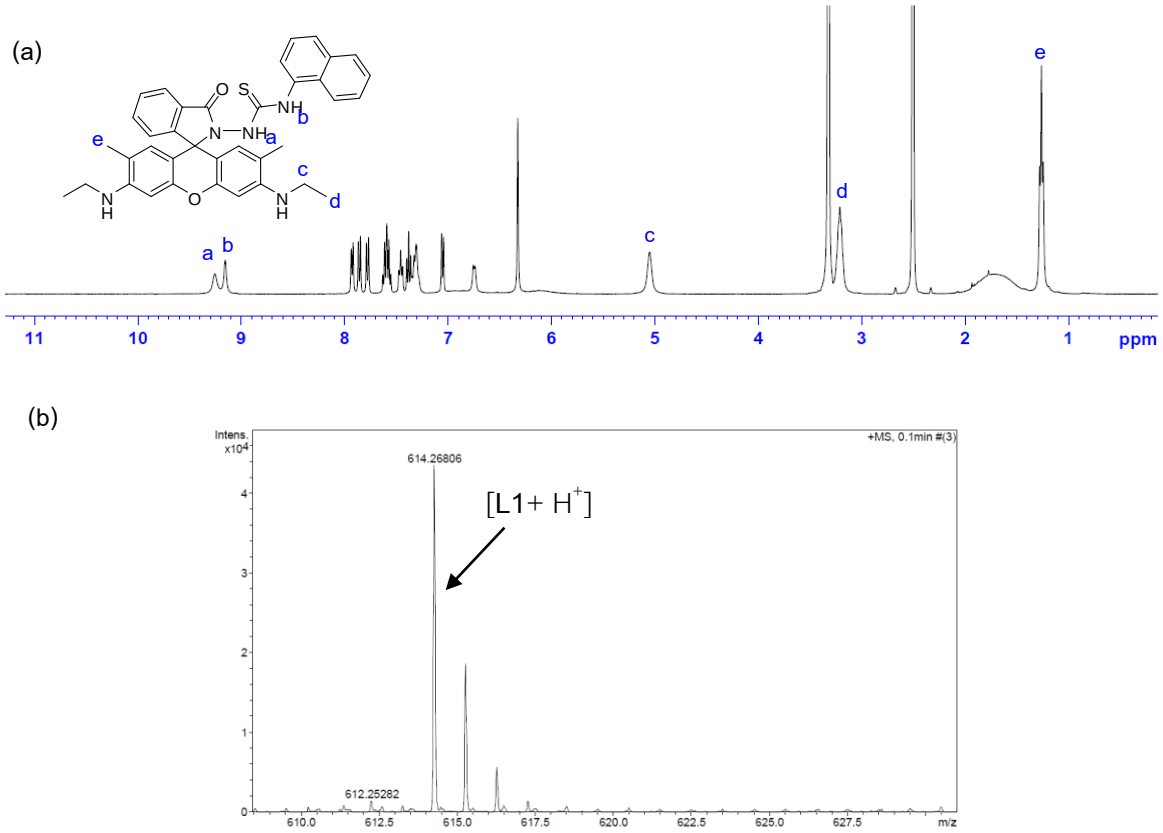


Figure 2 (a) ^{1}H NMR spectrum of **L1** in DMSO-d_6 and (b) HRMS spectrum of **L1**.

Screening test for metal ions

We first tested the metal ions sensing abilities of the sensor **L1** by the addition of various metal ions (10 equiv.) to the solution of **L1** (10 μM) in CH_3CN solution. We found that only Fe^{3+} could change the colorless solution of free **L1** to red-pink color, Figure 3. This result indicated that Fe^{3+} could induce the ring-opening spirolactam in **L1** structure. More interestingly, **L1** showed noteworthy high selectivity to detect Fe^{3+} over Fe^{2+} with respect to its "naked-eye" sensing. Then, the sensing properties of **L1** with Fe^{3+} and also various metal ions have been studied by UV-vis and fluorescence experiments.

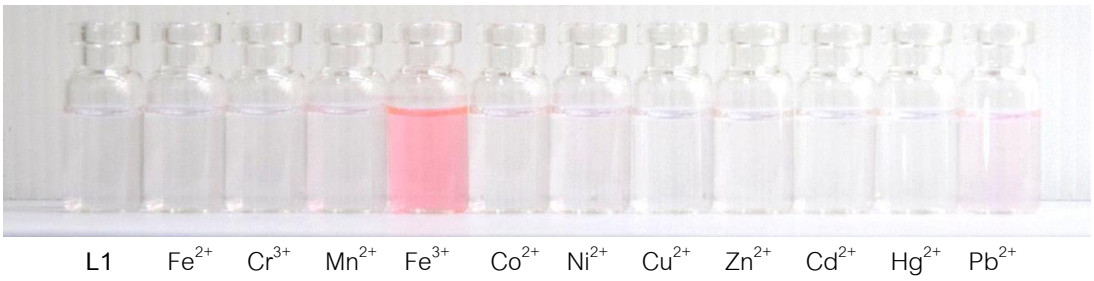


Figure 3 Color changes of **L1** (10 μM) in the presence of various metal ions (10 equivalents) in CH_3CN.

3.3 UV-visible studies

The UV-vis absorption spectrum of **L1** (10 mM) in CH_3CN exhibited a very weak band around 500 nm, which are attributed to the trace ring-opened form of molecules of **L1**. Interestingly, significant enhancement of the absorption band at 528 nm of **L1** was observed on the addition of Fe^{3+} and the color of the solution changed from colorless to red-pink color, Figure 4a. To get an insight into the sensing properties of **L1** to Fe^{3+}, UV-vis titration experiments were then performed. As shown in Figure 4b, upon incremental addition of Fe^{3+} to **L1** solution, the absorption band at 528 nm was gradually increased and reached the saturation state when 10.0 equivalents of Fe^{3+} ions were added. This indicated that the opened-ring form of **L1** became the main species in the examined solution. Moreover, the Job's plot analysis revealed a maximum at about 0.5 mol fraction, indicating 1:1 binding stoichiometry between **L1** and Fe^{3+} (Figure S3).

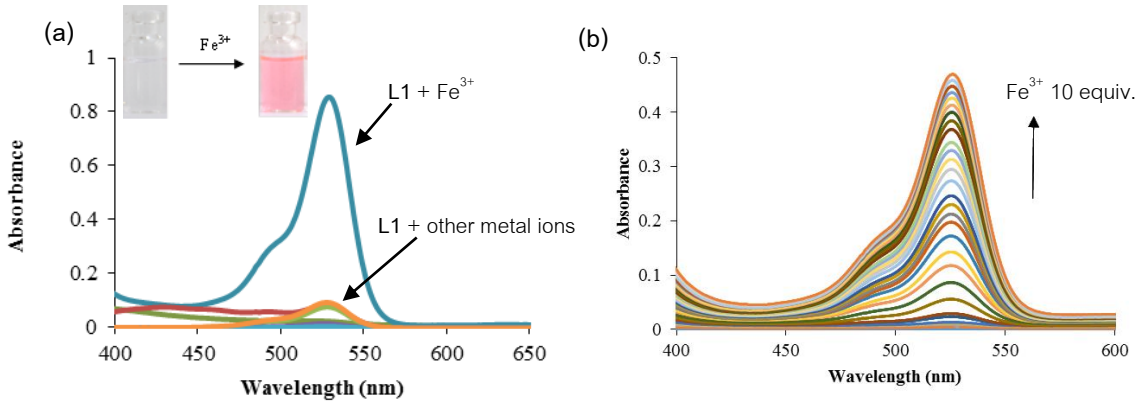


Figure 4 **(a)** UV-vis spectra obtained by addition of various metal ions (10 equivalents) and **(b)** UV-vis titration spectra obtained by addition of Fe^{3+} (0-10 equivalents) to the solution of **L1** (10 μM) in CH_3CN.

Fluorescence studies

Fluorescence studies of **L1** in the presence of metal ions were carried out. Upon exciting **L1** at 350 nm (excitation of naphthyl group), the emission of naphthyl around 400 nm was not observed probably due to photoinduced electron transfer (PET) from the lone pair electron of the N donor of the spirolactam ring and thiosemicarbazide group to the naphthyl moiety (Xu *et al*., 2012; Farrugia *et al*., 2016). However, the addition of Fe^{3+} gave a new emission band centered at 555 nm, Figure 5a. This emission peak became saturation upon addition of 10 equivalents of Fe^{3+}, Figure 5b. This phenomenon suggests that the "FRET" process has occurred in the presence of Fe^{3+} since the excitation of naphthyl group at 350 nm results in emission of the rhodamine unit at 555 nm. The fluorescence quantum yield of the adduct between **L1** and Fe^{3+} was calculated to be $\varnothing_F$ = 0.60 in

CH_3CN using quinine sulfate ($\varnothing_F$ = 0.546 in 0.1 M H_2SO_4) as a standard (Goswami *et al*., 2014). The apparent binding constant (*K*) between **L1** and Fe^{3+} was calculated to be 3.33 × 10^5 M^{-1} using the Benesi-Hildebrand equation (Figure S4) (Lohar *et al*., 2013). Then subjected the solution of **L1** + Fe^{3+} from fluorescence experiments to MALDI-TOF MS, the *m/z* at 580.20 belong to the cyclization product of oxadiazole derivative [**L1'** + H^+] was also observed, Figure 5c.

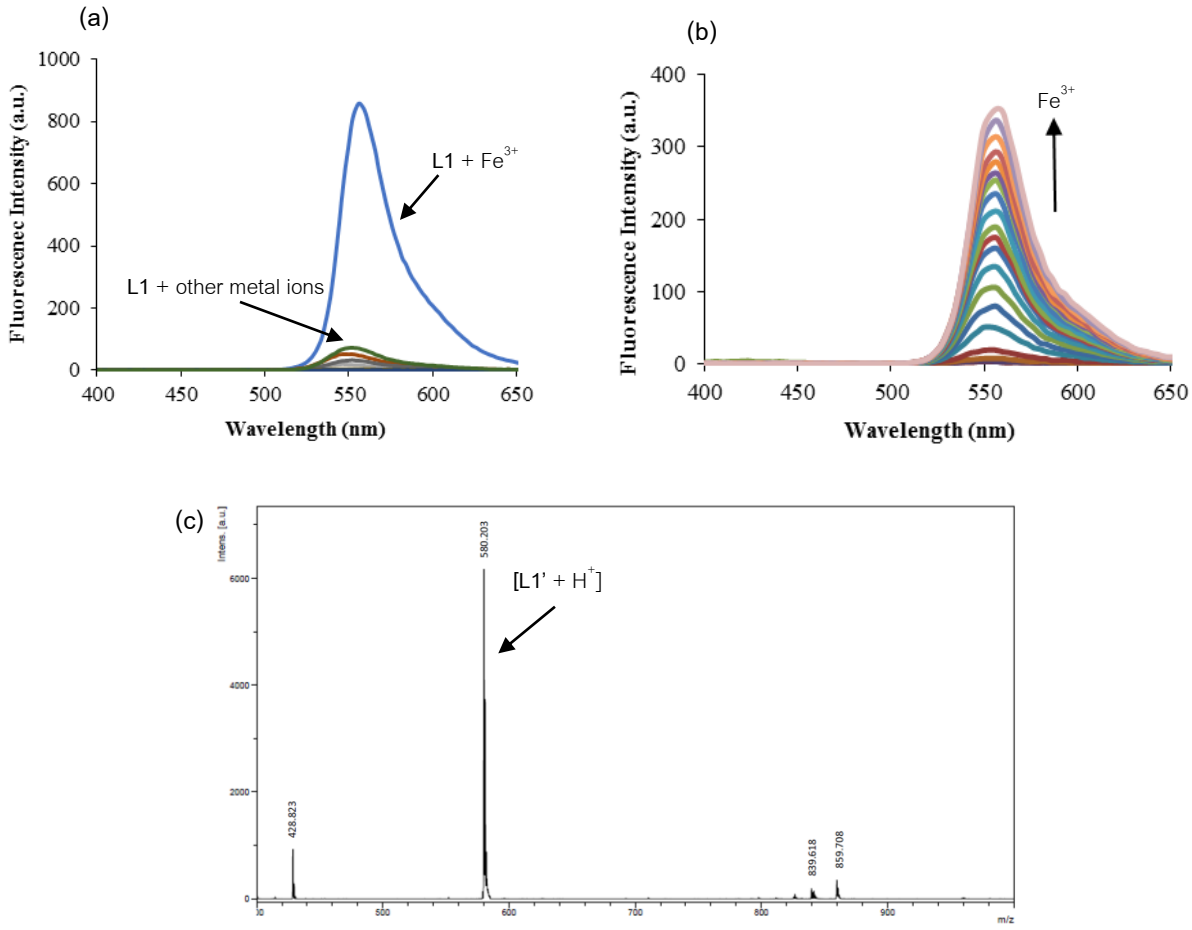


Figure 5 **(a)** Fluorescence spectra obtained by addition of various metal ions (10 equivalents), **(b)** fluorescence titration spectra obtained by addition of Fe^{3+} (10 equivalents) to the solution of **L1** (10 μM) in CH_3CN. (λ_{ex} = 350 nm) and **(c)** MALDI-TOF mass spectrum of the solution of **L1** + Fe^{3+} from fluorescence experiments.

We then investigated the sensing mechanism by performing the reaction between **L1** and $FeCl_3$ in CH_3CN. The crude product of the reaction of **L1**-Fe^{3+} was subjected to MALDI-TOF MS, and interestingly the *m/z* at 580.203, presumably belonging to the 1,3,4-oxadiazole derivative of [**L1'** + H^+] species, was presented, Figure 6a. Moreover, Figure 6a also showed the fine structure of peak at the *m/z* 821.050 assigned to the [**L1** + Fe^{3+} + $2CH_3CN$ + $2Cl^-$] + complex ions. This result suggested the existence of a 1:1 coordination mode between **L1** and Fe^{3+} corroborated well with Job's plot analysis results (Figure S3). Therefore, it might be expected that the addition of the Fe^{3+} to **L1** in CH_3CN solution could induced the cyclization to form product **L1'**, Scheme 1.

We then attempted to isolate the reaction product of the probe **L1** and Fe^{3+} by column chromatography on silica-gel and only **L1'** could be obtained according the MS spectrum, as shown in Figure 6b. The HRMS spectrum showed the peak at *m/z* = 580.2744 which strongly confirmed the formation of **L1'**. The cyclization product **L1'** was furthered characterized by ^{1}H-NMR, ^{13}C-NMR and HMQC (Figure S5 – S7). It should be mentioned that the disappearance of C=O from ^{13}C-NMR spectrum of **L1'** could also confirmed the formation of 1,3,4-oxadiazole derivative.

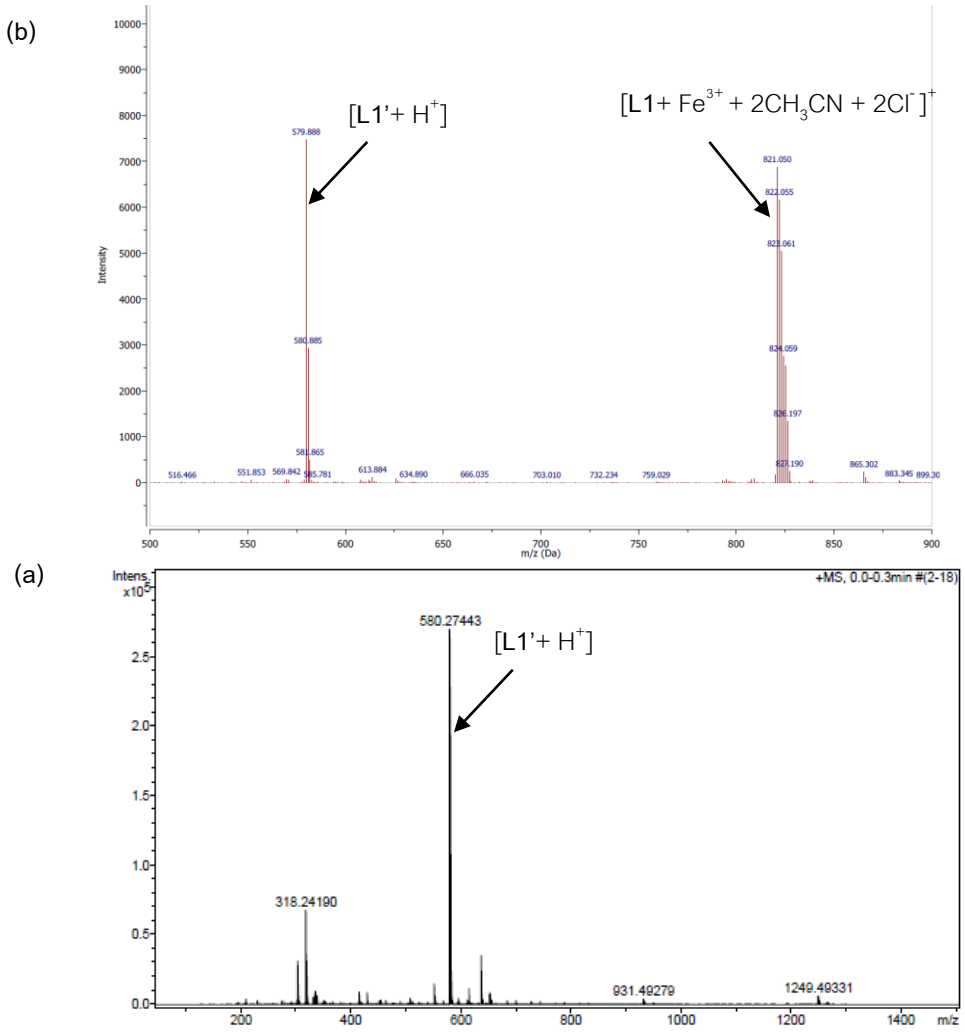
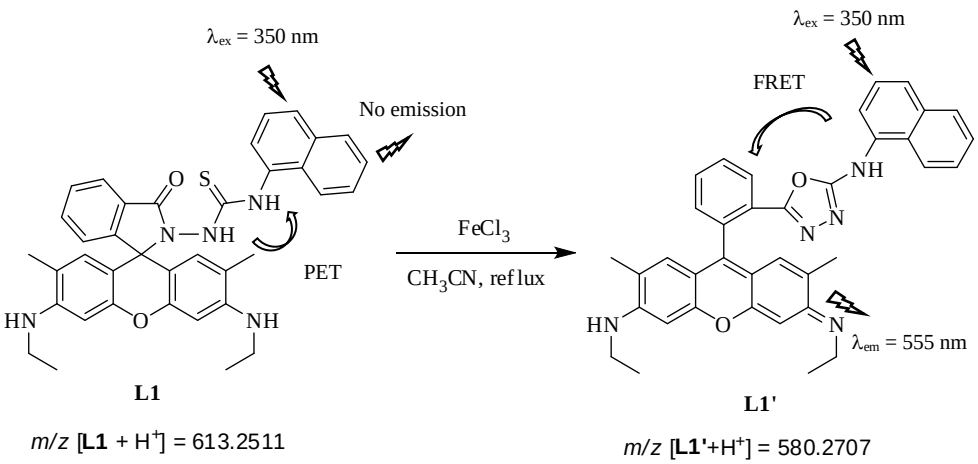


Figure 6 **(a)** MALDI-TOF mass spectrum of mixture of [**L1'** + H^+] and [**L1**+ Fe^{3+} + $2CH_3CN$ + $2Cl^-$]$^+$ from the reaction between **L1** and Fe^{3+} and **(b)** HRMS spectrum of product [**L1'** + H^+] from column chromatography.

According to the NMR and mass spectra results, this is the first time to find that Fe^{3+} could catalyze the cyclization of thiosemicarbazide to 1,3,4-oxadiazole on rhodamine 6G chemodosimeter. Based on our observations, a plausible mechanism for the selective sensing performance of Fe^{3+} by **L1** is shown in Scheme 1.



Scheme 1 Schemetic representation of Fe^{3+} induced the spirolactam ring opening followed by the cyclization of **L1**.

To check further the practical applicability of chemodosimeter **L1** as a Fe^{3+}-selective sensor, we carried out competition experiments. For the competition tests, sensor **L1** was treated with 10 equivalents of Fe^{3+} and 10 equivalents of other coexistent metal ions such as Fe^{2+}, Ni^{2+}, Mn^{2+}, Cu^{2+}, Hg^{2+}, Zn^{2+}, Co^{2+}, Cr^{3+}, Cd^{2+} and Pb^{2+} and the resulting individual test solution was analyzed by fluorescence experiments. As displayed in Figure 7, there was no significant spectral change for the **L1**-Fe^{3+} complex with and without other metal ions, which confirmed that **L1** can be used as a selective probe for Fe^{3+} in the presence of other metal ions using fluorescence spectroscopy.

Finally, calibration curves and the detection limit were obtained for Fe^{3+} ions with different concentrations. The linear range of the method was found to be at least 17 – 47 μM of Fe^{3+} with a correlation coefficient R^2 = 0.9988 (Figure S8) and the limit of detection (LOD) was calculated to be 0.07 μM according to formula LOD = $3\sigma/k$ where σ is the standard deviation and k is the slope of calibration plot (Zhu *et al*., 2008). The analytical performance for detection of Fe^{3+} by **L1** is compared with other rhodamine base sensors as shown in Table S1.

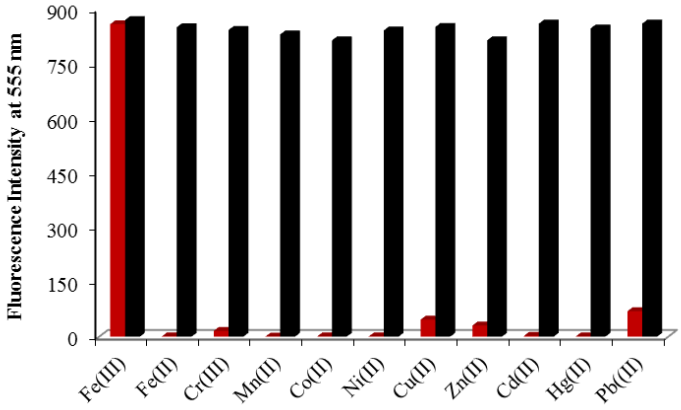


Figure 7 Fluorescence intensity of **L1** (10 μM) upon addition of various metal ions (10 equiv.) in CH_3CN (red bars). Black bars represent the **L1**-Fe^{3+} system in the presence of other metal ions, respectively (λ_{ex} = 350 nm).

Conclusions

In summary, a new fluorescent probe containing a rhodamine 6G energy acceptor and a naphthyl moiety energy donor was simply synthesized and applied for selective detection of Fe^{3+} based on "PET-FRET" sensing mechanism. The relatively high selectivity and sensitivity for Fe^{3+} over other metal ions showed the possibility for potential use in complex samples containing various competitive metal ions. To the best of our knowledge, this is also the first report of Fe^{3+} catalyzed the cyclization of thiosemicarbazide to 1,3,4-oxadiazole and its employment as effective chemodosimeter for Fe^{3+}.

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