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Synthesis of Schiff base-Based 1,2,4-Oxadiazole Derivative as Fluorescence Turn-On Sensor for High Selectivity of Pb^{2+}

Wei Liu · Guangyu Wu · Xiaomin Gu · Xiaosheng Yuan · Jueyong Li · Haibo Wang

Abstract A new probe based on oxadiazole derivative (OXD) containing Schiff base moiety was synthesised as fluorescence turn-on sensor S1 . Furthermore, its fluorescents spectra (FS) result demonstrate that S1 selectively senses bivalent lead ion (Pb^{2+}) in HEPES buffer solution (10 mM, pH=7.0,DMF-H_2O, 9:1, v/v), so S1 was a viable candidate as fluorescent receptor for a new Pb^{2+} sensor. And the results of fluorescent spectral titration showed this sensor formed 1:1 complex with Pb^{2+}.

Keywords Fluorescent sensor · Lead ion · Oxadiazole

Introduction

Lead pollution is an ongoing danger to human health and the environment, as most of the 300 million tons of this heavy metal mined to date are still circulating in soil and groundwater [1]. Once introduced into the body, lead is a potent neurotoxin that can interfere with brain development, slow nerve conduction velocity, and trigger behavioral problems [2–4]. Interest in elucidating these, as well as public concerns over toxic lead exposure, provides a need for devising new ways to track Pb^{2+} in natural samples.

Recently, the development of fluorescent molecular sensors for metal ions, especially for cations with biological interest, has always been of particular importance and usually involves the design and synthesis of molecules containing binding sites and a signaling subunit able to display selective changes in fluorescence emission intensity upon guest binding [5–11]. And considerable efforts have been devoted to developing fluorescent chemosensors for various metal ions over the last few deca des [12], However, there have been relatively few reports on Pb^{2+}-selective fluorescent chemosensors. Czarnik reported a N-methyl-9-anthrylthio-hydroxamic acid as a new fluorescent chemosensor for Pb^{2+} [13]. Godwin et al. also reported a new ratiometric fluorescent sensor for Pb^{2+} based on the dansyl-tetrapeptide framework [14]. However, most of them still suffer from lowered selectivity and sensitivity. Moreover, most of fluorescent molecular sensors are limited by low water-solubility. Accordingly, it is expected to design an effective chemosensor for lead ion detection, which can be a new good candidate of Pb^{2+} sensor.

Recently, we are interested in oxadiazole derivative (OXD) fluorescent chemosensors used to identify Ag^{+}[15], especially, in an effort to develop highly chemosensor owned good sensitivity and selectivity. In addition, designing chemosensors based on oxadiazole derivative (OXD) has several advantages: There is not a strong color development against the colorless blank in HEPES buffer solution (10 mM, pH=7.0,DMF-H_2O, 9:1, v/v), but they display great absorbance and fluorescence intensity enhancement toward bivalent lead ion (Pb^{2+}). In this paper to synthesize a novel oxadiazole derivative containing Schiff base moiety (S1), which showed favourable recognition response to Pb^{2+} and could be applied as fluorescence Off-On sensor for high selectivity of Pb^{2+}. An oxadiazole derivative (OXD) connects a Schiff base which has a nitrogen atom and an oxygen atom, in which the above-mentioned oxygen atom and nitrogen atom were both the cation receptor and the quencher via Photoinduced electron transfer PET. Acceptance of metal ion increased the molecular conjugation and rebuilt rigid molecular system, which stopped the PET quenching and produced a fluorescent enhancement in the 1, 2,4-oxadiazole emission.

W. Liu
College of Science, Nanjing Tech University, Nanjing 211816, China

G. Wu · X. Gu · X. Yuan · J. Li · H. Wang (✉)
Institute of Food and Light-chemical Engineering, Nanjing Tech University, Nanjing 211816, China
e-mail: wanghaibo@njut.edu.cn

Experiment

Materials and General Methods

All the reagents and solvents were purchased from commercial sources and were of analytical grade. All reactions monitored by thin-layer chromatography (TLC) were visualized with UV. Melting points (M.p.) of prepared compounds were measured on an X4 micromelting point apparatus. A BRUKER DRX500 spectrometer recorded ^{1}HNMR spectra of objective products. Fluorescence spectra were taken on an Perkin Elmer LS −55 type fluorescence photometer.

Synthesis

Synthetic procedures of S1 were shown in Scheme 1.

N-Hydroxybenzimidamide (1) Benzonitrile (5.0 g, 48.5 mmol), hydroxylamine hydrochloride (5.02 g 72.7 mmol) and ethanol (50 mL) was added into a 100 mL four-neck flask and stirred at room temperature until TLC indicated the end of reaction. Then ethanol was removed under reduced pressure and the filtered solid was recrystallized to yield white product (5.7 g, 29.6 mmol, 87 %) M. p.,72–75 °C; Found 72–73 °C [16]. ^{1}HNMR (300 MHz, DMSO-d6, TMS) δ=7.65(d, *J*= 7.4Hz, 2H), 7.48–7.36 (m, 3H), 4.94 (s, 2H).

*5-(Chloromethyl)-3-phenyl-1,2,4-oxadiazole (2)* **1**(5.0 g, 36.7 mmol)) and toluene (25 mL) were put into a 100 mL four-neck flask firstly, following chloroacetyl chloride (4.2 g, 36.7 mmol) was added in the solution dropwise at 0 °C. The reaction mixture was stirred for 4 h at room temperature, then heated under reflux conditions overnight (18 h). The reaction mixture was concentrated and to diluted with ethyl acetate, washed with water, brine and dried over sodium sulfate. The solution was concentrated to dryness, then purified by column chromatography using ethyl acetate and petroleum ether (1:9) to get light yellow solid (4.8 g, 24.7 mmol, 67.5 %) . M. p.,36 °C; Found 33–34 °C [17]. ^{1}HNMR (300 MHz, DMSO-d6, TMS) δ=4.76 (s, 2H), 7.48–7.54 (m, 3H), 8.08–8.11 (m, 2H).

2- Hydroxy-1-Napthylaldehyde (3) ß- naphthol (7.23 g, 0.05 mol), (CH_2)_6N_4 (8.40 g, 0.06 mol), CH_3COOH (25 ml) and H_2SO_4 (9 ml) were added into a 100 mL four-neck flask. The reaction mixture was stirred for 3 h at 97 °C, then was cooled down. After diluting with water (85 ml), the precipitate was filtered and washed with water thus affording the target compound as a yellow solid M. p., 79–80 °C; Found, 80–81 °C [18]. ^{1}HNMR(300 MHz, DMSO-d6, TMS) δ= 10.25(s, 1H), 9.05(d, 1H), 7.04–7.92(m ,5H), 5.0(s, 1H).

1-[(phenylimino)methyl]-2-naphthol (4) **3**(1.7 g, 10 mmol), methanol (30 mL) were put into a 100 mL four-neck flask firstly, then aniline (1.0 g, 11 mmol) was added over a 5 min time at reflux conditions in the presence of a trace amount of 4-toluenesulfonic acid as a catalyst. The reaction was monitored by TLC and after the disappearance of the initial
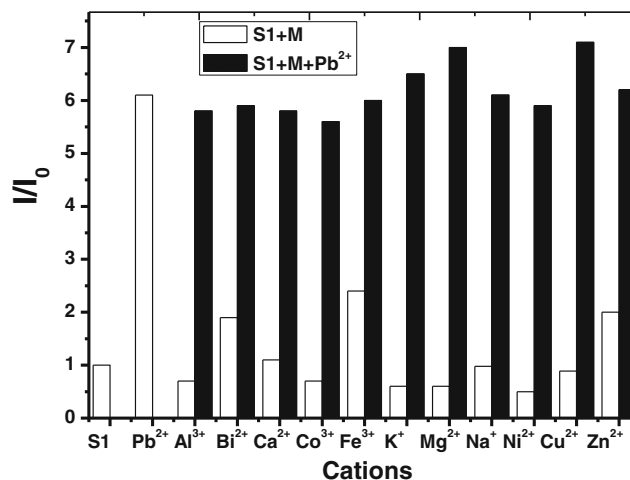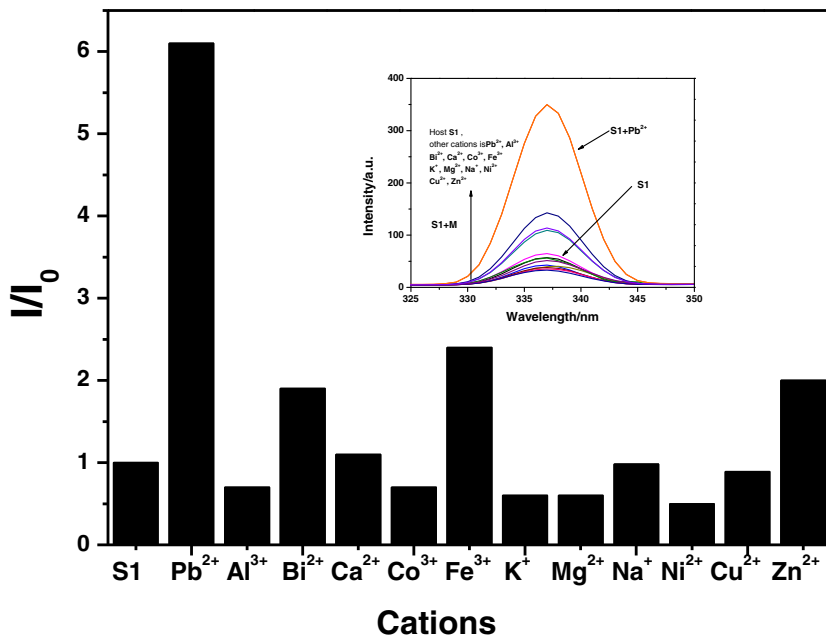
Scheme 1 Synthetic procedures of S1
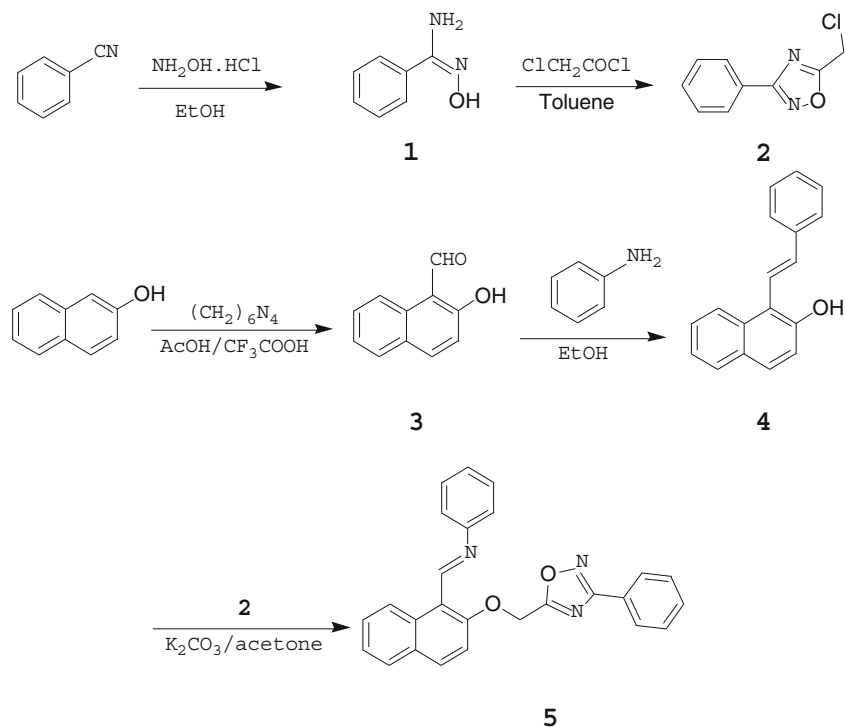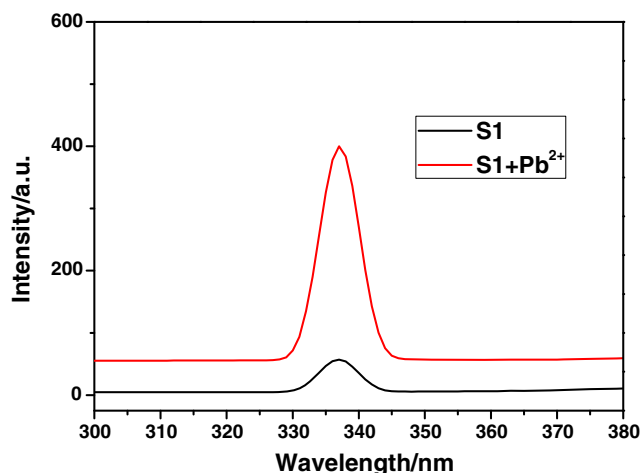
Fig. 1 Fluorescence emission spectra of S1 in the presence of Pb^{2+} in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v), λ_{ex}=337 nm
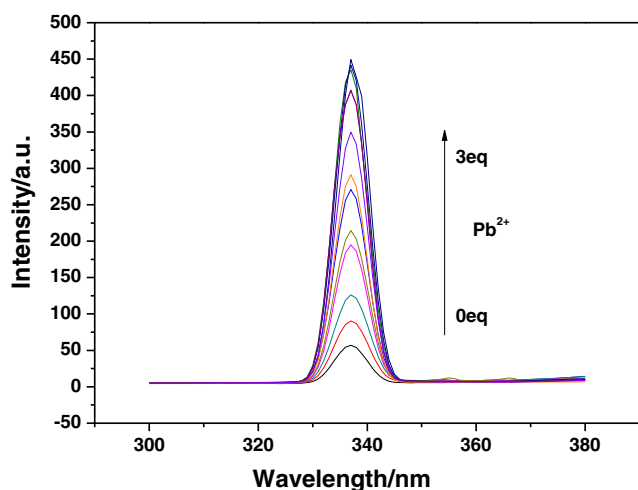

Fig. 3 Relative fluorescence intensity changes of S1 in the presence of various metal ions (20 eq.) and Pb^{2+} (20 eq.) in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).λ_{ex}=337 nm

compounds and the solvent was removed. The solid product was purified by recrystalization from methanol to yield a yellow solid (2.2 g, 9.3 mmol, 93 %). M. p., 99 °C; Found, 97–99 °C [19] .^{1}HNMR (300 MHz, DMSO-d6,TMS) δ=7.02 (d, 1H), 7.10 (d, 1H), 7.12 (d, 2H), 7.14 (d, 2H), 7.60 (d, 1H), 7.70 (d, 2H), 7.95 (d, 1H), 8.05 (d, 1H), 8.90 (s, 1H), 5.0(s , 1H).

S1(5) **2**(1.60 g,8.2 mmol), **4**(2.03 g,8.2 mmol), K_2CO_3(1.70 g,12.3 mmol) and acetone (20 mL) and were added into a 100 mL four-neck flask, heated to reflux for 10 h. Then acetone was removed under reduced pressure and the solid purified by column chromatography using ethyl acetate and petroleum ether (1:9) as eluent to get a off-white prower(1.68 g,3.81 mmol, 47.5 %.). M.p.,210–

212 °C.^{1}HNMR(300 MHz, DMSO-d6) δ=8.90(s,1H), 7.92(d,1H),7.21–7,63(m,15H),5.30(s,2H).

Fluorescence Sensing of S1 for Metal Ions

Deionized water was used throughout all experiments. Solutions of Pb^{2+}, Fe^{3+}, Cu^{2+}, Ag^+, Zn^{2+}, Hg^{2+}, Ba^{2+}, Fe^{2+}, Cr^{3+}, Cd^{2+}, Mg^{2+}, Mn^{2+}, Co^{3+}, Ni^{2+}, K^+, Na^+, and Bi^{3+} were prepared from their nitrate salts. All measurements of fluorescence spectra(FS) were obtained with a Perkin Elmer LS-55 fluorescence spectrophotometer linked to a Pentium PC running SpectraCalc software package. All measurements were carried out in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).

Fig. 2 Relative fluorescence intensity changes of S1 in the presence of various metal ions (10 eq.) in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v), λ_{ex}=337 nm

Fig. 4 Fluorescence spectra of S1 with addition of various equiv of Pb^{2+} in HEPES buffered (10 mM, pH=7.0, DMF-H_2O, 9:1, v/v).λ_{ex}=337 nm
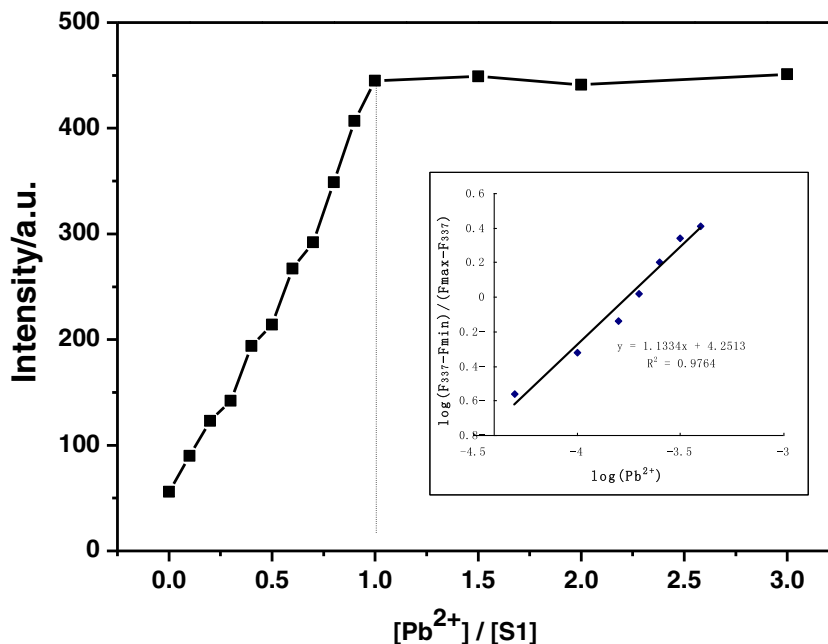
Chemical Complexion Stoichiometric Ratio of S1 and Pb^{2+}

In the titration experiments, a 2.5 mL solution of S1 (10 mM and 1 mM) was poured into a quartz optical cell of 1 cm optical path length each time, and Pb^{2+} solution was added into the quartz optical cell gradually with a micro-pipette. FS data were recorded in an indicated time after the addition.

Titration experiments were carried out and Job's analyses [20] was applied to calculate the stoichiometric ratio of S1- Pb^{2+} complex according to the following equation.

$$\log\frac{F\text{-}F_{min}}{F_{max}\text{-}F} = n\log\left[Pb^{2+}\right] + B$$

In above equation, F_{min}, F_{max} and F were the fluorescent intensity of metal-free S1, S1 with excessive Pb^{2+} and S1 with Pb^{2+} at any concentration between the former two, respectively. n meant the stoichiometry of S1 - Pb^{2+}complex.

Results and Discussion

Spectroscopic Properties of Molecular Sensor S1

Fluorescence and UV–vis studies were performed using a solution of S1 in HEPES buffer (DMF-H_2O, 9:1, v/v) at an excitation wavelength of 337 nm. Figure 1 shows a change in the fluorescence spectra of S1. It is easy to find in Fig. 1, when no metal ion was added to the solution, almost no fluorescence signal could be observed, whereas a significant increasing of the characteristic fluorescence could be found soon after Pb^{2+} was injected into the solution.

Fluorescence Sensing of S1 for Pb^{2+}

The Fig. 2 is fluorescence spectra of S1 in HEPES buffer and tested metal ions. The mixed solutions should be shaken for 30 min in order to make the metal ions chelate with the sensors sufficiently. As can be seen through the experiment, other than Pb^{2+} no obvious response could be observed including Fe^{3+}, Cu^{2+}, Ag^+, Zn^{2+}, Hg^{2+}, Ba^{2+}, Cr^{3+}, Cd^{2+}, Mg^{2+}, Mn^{2+}, Co^{3+}, Ni^{2+}, K^+, Na^+ . It demonstrate that S1 selectively senses bivalent lead ion(Pb^{2+}) in HEPES buffer solution ,so S1 was a viable candidate as fluorescent receptor for a new Pb^{2+} sensor . It probably result from the suitable coordination geometry conformation of the receptor and the radius of the

Fig. 5 A Job of S1 and Pb2+ at 337 nm which indicated that the stoichiometry of S1-Pb2+ complex was 1:1

Pb^{2+} ion . Compared with other ions, appropriate radius of the Pb^{2+} ion more easily connected to S1.

With gradual addition of Pb^{2+} ion to the solution of S1, the fluorescence intensity was increased obviously. Due to the formation of chelate Pb^{2+} with cavity of N and O in molecular structure of S1, it caused the increase of coplanarity and molecular rigidity of S1 result in the fluorescence increasing. Figure 2b shows that emission peak increase gradually with the addition of Pb^{2+}, but the peak patterns do not shift. When the titration achieves a balance, the fluorescence tensity increases about 7 times .

S1 also exhibits a selective turn-on fluorescence response to Pb^{2+} in aqueous solution. In order to investigate the Pb^{2+} recognition abilities of S1, we carried out interference experiments in the same HEPES buffer solution to discuss the competition effects from above selected metal ions. Responses of 10 uM S1 to the presence of various environmentally relevant metal ions are collected in Fig. 3. The fluorescence profiles of Pb^{2+}-bound S1 are unchanged in the presence of 50 mM Fe^{3+}, Cu^{2+}, Ag$^+$, Zn^{2+}, Hg^{2+}, Ba^{2+}, Cr^{3+}, Cd^{2+}, Mg^{2+}, Mn^{2+}, Co^{3+}, Ni^{2+}, K$^+$, Na$^+$, indicating excellent selectivities for Pb^{2+} over these metal cations. These results indicated that the selectivity of S1 for Pb^{2+} was hardly affected by the coexisted metal ions as shown in Fig. 3.

Inset: Linear fitting curve of the changes in fluorescence intensity at 337 nm of S1 versus increasing Pb2+ concentration.

The binding properties of sensor S1 with Pb^{2+} were studied by fluorescence spectral titration experiments (Fig. 4) and the method of continuous variations (Job 's analyses) was further used to gain an insight into the stoichiometry of S1- Pb^{2+} complex (Fig. 5). Fig. 4 showed the typical fluorescence response spectra of sensor S1 in HEPES buffer solution (10 mM, pH=7.0, DMF-H$_2$O, 9:1, v/v) with increasing Pb^{2+} concentrations and the background signal of HEPES alone was deducted to evaluate the fluorescent response of proposed assay. The sensing system exhibited a significant change in fluorescence in the presence of different concent rations of Pb^{2+}

The bottom curve was measured in the absence of Pb^{2+}, where the sensing system had a very weak emission. When different concent rations of Pb^{2+} were added into the solution of S1, a drastic increase in the fluorescence emission was observed. In the Fig. 5, Once the concentration of Pb^{2+} was over 5.0 μM, the fluorescence intensity reached a plateau

which suggesting the Saturated recognition sites of Pb^{2+} binding. According to Job 's analyses, the linear fitting curve in the inset further elucidated the binding mode between sensor S1 and Pb^{2+} that a stable 1:1 S1-Pb^{2+} complex was obtained.

Conclusion

In conclusion, We designed a new type of synthetic fluorescent sensor based on oxadiazole derivative (OXD) for probing Pb^{2+}. The ion binding properties of this receptor with a large number of metal ions have been investigated and the ion recognition events have been monitored by fluorescence spectral changes. Our study revealed that the fluorescence selective of **S1** to Pb^{2+} is high selectivity and anti-disturbance. The calculation confirmed that a stable 1:1 **S1**-Pb^{2+} complex formed.

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