

Ratiometrically Fluorescent Sensing of Zn(II) Based on Dual-Emission of 2-Pyridylthiazole Derivatives

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Received: 16 July 2015 / Accepted: 28 September 2015 / Published online: 8 October 2015
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Abstract A new fluorophore, 4-methyl-2-(2-pyridyl)-5-(2-thiophenyl)thiazole (2-PTT), was reported as a ratiometrically fluorescent sensor of zinc(II) based on dual-emission with selectivity and sensitivity. Two emission bands at 440 and 497 nm were observed before and after addition of zinc(II), respectively. Job's plot disclosed the 1:1 stoichiometry between 2-PTT and zinc(II). The binding constant was evaluated as $2.09 \times 10^5 \text{ M}^{-1}$ based on fluorescence titration experiment.

Keywords Fluorescence · Zinc ion · Ratiometric sensor · 2-Pyridylthiazole

Introduction

Being the second abundant transition metal ions in human body, zinc(II) is widely spread in the brain, intestine, pancreas, retina, and other tissues [1]. It plays various roles in diverse biological processes, such as gene transcription, neurotransmission, and enzymatic catalysis [2–4]. Imbalance of zinc ion is believed to be closely related to various pathological symptoms including Alzheimer's diseases, Parkinson's diseases, ischemia, and epilepsy [5–7]. Detection of zinc ion is thus pursued for a long term. Because zinc(II) is spectroscopically silent due to its $3d^{10}4s^0$ electronic configuration, it is thus difficult to be monitored. Consequently, the fluorescent sensors of zinc(II) is widely applied due to the high sensitivity and good selectivity [8]. However, for the “turn-on” or “turn-off”

fluorescent sensors, it is difficult to relate fluorescence intensity to analyte concentrations. A proposed solution is to develop ratiometric probes, where the ratio of intensities at two different wavelengths could be related to the analyte concentrations [9]. Further, ratiometric sensing based on dual-emission could significantly eliminate most of the interferences such as photo-bleaching, probe concentration, and instrument efficiency in the measurement, which is thus regarded as the most effective method in fluorescent sensing [10, 11].

Most of the reported fluorescent sensors of zinc(II) are generally based on various fluorophores including quinoline, fluorescein, coumarine, BIDOPY, and so on [12]. In previous, we have demonstrated (2-PT) unit as a robust fluorophore, which could be applied in the development of pH, Cu(II), and Ag(I) fluorescent probes [13–17]. In the presented paper, we develop a new 2-PT derivative, 4-methyl-2-(2-pyridyl)-5-(2-thiophenyl)thiazole (2-PTT), as a new ratiometric fluorescent sensor of zinc (II).

Experimental

Materials and Methods

All chemicals were purchased from Acros and used as received without further purification. All reactions were performed under argon atmosphere using purified solvents by standard methods. For all spectrometric measurements, HPLC grade solvents were used. Flash chromatography was performed with 100–200 mesh silica gel (Qingdao, China) and thin-layer chromatography (TLC) was carried out on silica coated glass sheets (Qingdao silica gel 60 F-254).

UV–Vis absorption spectra were measured with a Hitachi UV-3010 spectrophotometer and the fluorescence spectra

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were recorded on a Hitachi F-4500 fluorescence spectrophotometer. All spectra measurements were recorded at 20 °C. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and uncorrected. ^1H nuclear magnetic resonance (NMR) and ^{13}C NMR spectra were recorded with a Burkert AV300 (300 MHz) instrument using tetramethylsilane as the internal standard. IR spectra were recorded on a Perkin-Elmer 1200 FT-IR spectrometer. High-resolution mass spectra were taken on a Shimadzu GC-MS-QP2010. Elemental analysis were performed at Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun, China.

Synthesis

Synthesis of 4-methyl-2-(2-pyridyl)thiazole (2-PTM) [18]

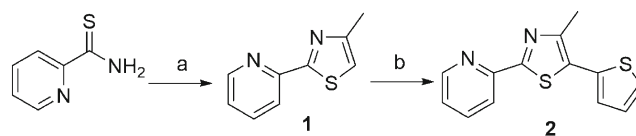
To 10 mL absolute EtOH containing α -bromo acetone (0.2 mL, 2.3 mmol), 2-pyridinecarbothioamide (290 mg, 2.1 mmol) was added. After refluxed for 10 h, the solvent was evaporated under reduced pressure. The residue was redissolved with 20 mL EtOAc and then washed by saturated NaHCO_3 solution and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. Separation through flash column chromatography using *n*-hexane and EtOAc as eluent provided the product.

Mp: 84–85 °C. ^1H NMR (CDCl_3 , 300 MHz, ppm), δ =2.53 (s, 3H), 7.00 (s, 1H), 7.30 (ddd, 1H, J =1.8, 7.5, 7.8 Hz), 7.79 (ddd, 1H, J =1.8, 7.5, 7.8 Hz), 8.15 (dd, 1H, J =1.2, 7.8 Hz), 8.61 (dd, 1H, J =1.2, 7.5 Hz). ^{13}C NMR (CDCl_3 , 75 MHz, ppm) δ =17.3, 116.1, 119.6, 124.3, 136.9, 149.5, 151.5, 154.2, 168.3.

Synthesis of 4-methyl-2-(2-pyridyl)-5-(2-thiophenyl)thiazole (2-PTT)

To 5 mL *N,N*-dimethylacetamide (DMAc) containing 2-PTM (30 mg, 0.17 mmol), tetrabutylamine hydrochloride (55.6 mg, 0.2 mmol), NaHCO_3 (16.8 mg, 0.2 mmol) and $\text{Pd}(\text{OAc})_2$ (4.5 mg, 0.02 mmol), 2-bromo thiophene (33 mg, 0.2 mmol) was added under argon atmosphere. The reaction mixture were kept at 140 °C for 24 h and then quenched by addition of 20 mL water. After extraction with EtOAc (15 mL \times 3), the combined organic layer was washed by saturated NaHCO_3 solution and brine. After dried over anhydrous Na_2SO_4 and evaporated under reduced pressure, the obtained residue was separated through flash column chromatography using *n*-hexane and EtOAc as eluent. Recrystallization provided a pale yellow solid as the product (5 mg, yield: 11.4 %).

Mp: 91–93 °C. IR (film, cm^{-1}): 3016, 2399, 1518, 1475, 1421, 1217, 771. ^1H NMR (CDCl_3 , 300 MHz, ppm), δ =2.68 (s, 3H), 7.13 (dd, 1H, J =3.9, 5.1 Hz), 7.23 (dd, 1H, J =1.2, 3.9), 7.32 (dd, 1H, J =5.1, 7.8 Hz), 7.37 (dd, 1H, J =1.2, 5.1 Hz), 7.80 (dd, 1H, J =7.8, 7.8 Hz), 8.20 (d, 1H, J =



- a. $\text{BrCH}_2\text{COCH}_3$, EtOH, reflux;
b. 2-bromo thiophene, $\text{Pd}(\text{OAc})_2$, NaHCO_3 , $(\text{Bu})_4\text{NCl}$, DMAc, 140 °C.

Scheme 1 Synthesis of 4-methyl-2-(2-pyridyl)-5-(2-thiophenyl)thiazole

7.8 Hz), 8.61 (d, 1H, J =5.1 Hz). ^{13}C NMR (CDCl_3 , 75 MHz, ppm) δ =17.0, 119.5, 124.4, 126.2, 127.0, 127.8, 137.0, 149.5, 177.8. Calcd for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{S}_2$: C 60.44, H 3.90, N 10.84. Found: C 60.02, H 3.96, N 9.97. Calcd for : 258.0285, HRMS (m/z): 258.0286.

Results and Discussion

Synthesis of 2-PTT is shown as in Scheme 1. Both 2-PTM and 2-PTT are fluorescent with emission at 370 and 440 nm excited at 318 and 362 nm, respectively (Fig. 1). Compared with 2-PTM, a red-shift of the emission of 2-PTT about 70 nm could be ascribed to the introduction of thiophenyl group at the 5-position of thiazole ring, which should expand the delocalization of the π -electrons in theory. We further examined the effects of various metal ions (Ag(I) , Ca(II) , Mg(II) , Cd(II) , Co(II) , Cu(II) , Fe(III) , Ni(II) , Hg(II) , Pb(II) and Zn(II)) on the fluorescence of both ligands. For 2-PTM, only zinc ion could enhance its fluorescence whereas the other screened metal ions could quench the emission at 370 nm to some extent (Figs. 1 and 2a). In the other hand, only addition of zinc(II) could red-shift the emission of 2-PTT at 440 nm to 497 nm accompanied by the enhancement of the intensity (Figs. 1 and 2b). According to the observed selectivity and the change of fluorescence, 2-PPT should be suggested as a ratiometrically fluorescent probe for Zn(II) .

To determine the number of zinc(II) bound to 2-PTT, the Job's plot for the absorbance was performed by keeping the

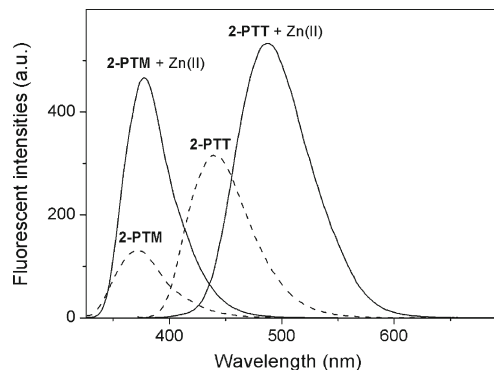


Fig. 1 Fluorescence spectra of 1 μM free ligands (dashed line) and after addition of 10 eq. Zn(II) (solid line) in MeCN at 25 °C. (Excitation at 318 nm and 362 nm for 2-PTM and 2-PTT, respectively)

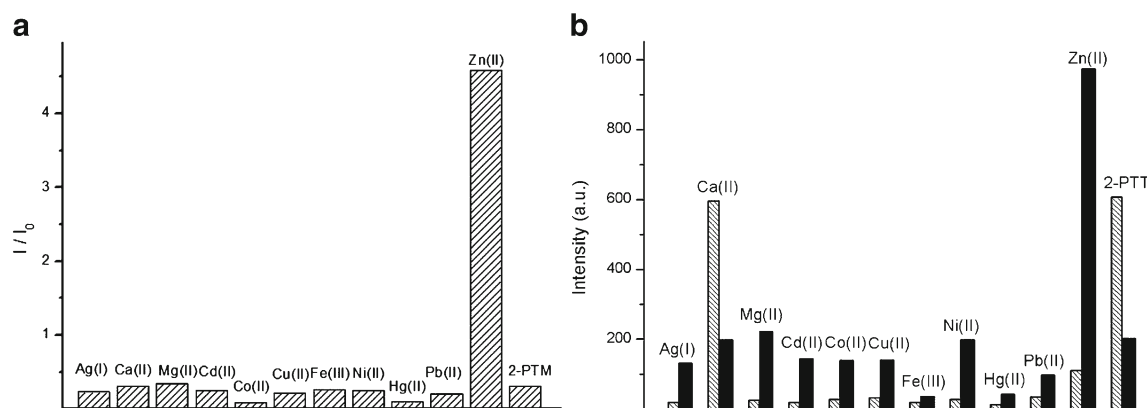


Fig. 2 Fluorescence response of 1 μ M free ligands to various screened metal ions (10 eq.) in MeCN at 25 $^{\circ}$ C. **a**) Fluorescent intensity of 2-PTM at 370 nm; and **b**) Fluorescent intensity of 2-PTT at 440 nm (meshed bar) and 497 nm (solid bar)

sum of initial concentrations of zinc(II) and 2-PTT constant at 50 μ M and changing the molar ratio of zinc(II) ($[\text{zinc(II)}]/([\text{zinc(II)}] + [\text{2-PTT}])$) from 0 to 1. As depicted in Fig. 3, the absorbance value at 362 nm ($A_{362\text{nm}}$) is highest at a molar fraction of ca. 0.5, which indicates that a 1:1 stoichiometry should be existed between zinc(II) and 2-PTT.

In the fluorescence titration experiment of 2-PTT (Fig. 4), it could be found that emission at 440 nm decreased accompanied with a gradual increase of a new emission at 497 nm with addition of zinc(II) from 0 to 15.0 eq. An iso-emission point at 455 nm could be observed, which should be ascribed to the 1:1 coordination equilibrium between zinc(II) and 2-PTT. To determine the binding constant K_{as} , $\log[(I - I_{\infty})/(I_0 - I_{\infty})]$ was plotted against $[\text{zinc(II)}]$ (Fig. 5) [19], where I_0 and I_{∞} are the fluorescence intensity at 440 nm in absence of zinc(II) and in presence of the saturated concentration of zinc(II) (15.0 eq.), respectively. Here the fraction, $(I - I_{\infty})/(I_0 - I_{\infty})$, is named after α , which could be regarded as the representative

of the free 2-PTT in the system. The binding constant K_{as} could be rewritten as below (Eq. 1).

$$K_{\text{as}} = [\text{2-PTT} - \text{Zn(II)}] / [\text{2-PTT}][\text{Zn(II)}] = (1 - \alpha) / \alpha [\text{Zn(II)}] \quad (1)$$

According to the 1:1 stoichiometry and Eq. 1, K_{as} was fitted as $(2.09 \pm 0.07) \times 10^5$ L/mol with $R^2 = 0.991$, which is comparable to the reported ratiometric fluorescent sensor of zinc (II) based on 8-aminoquinoline [20]. Accordingly, the detection limit was calculated as 1.4×10^{-6} M [21].

Conclusions

In summary, we successfully developed 2-PTT as a new ratiometric fluorescent sensor of zinc(II). We also noted the different sensing performances between 2-PTM and 2-PTT, where a simple adjustment of substituent at the 5-position of the thiazole ring of 2-PT unit could result in the interesting finding.

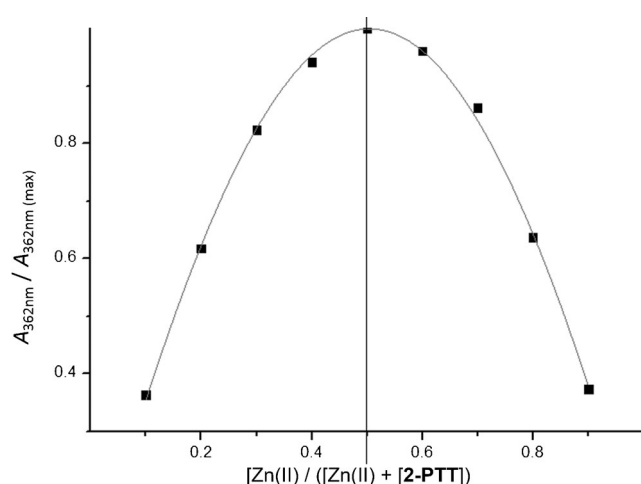


Fig. 3 Job's plot for the determination of the binding stoichiometry of 2-PTT with zinc(II) obtained from variations in absorbance at 362 nm

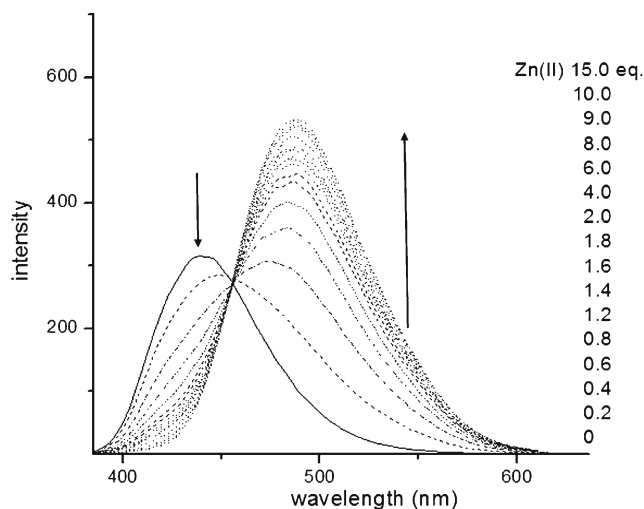


Fig. 4 Fluorescence emission spectra of 2-PTT (1 μ M) in the presence of different concentrations of zinc(II) in MeCN at 25 $^{\circ}$ C

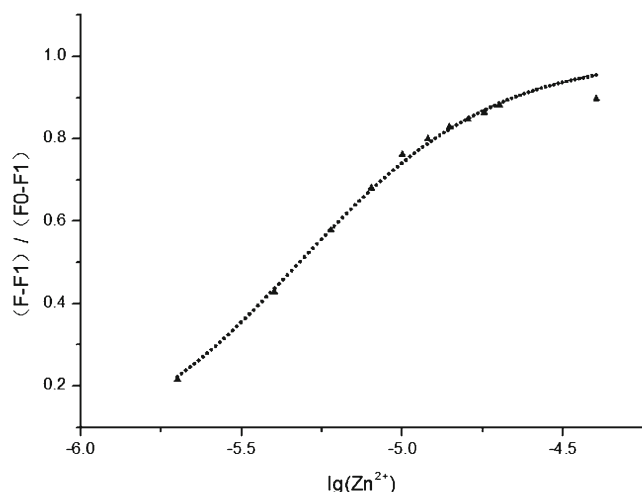


Fig. 5 Relative fluorescence ratio, α , as a function of $\log[\text{Zn(II)}]$ (M) in MeCN. The curve fitting for experimental data was calculated as mentioned in text (\blacktriangle , experimentally observed data points)

Origin of the problem should be further investigated based on both more experimental design and theoretical studies.

Acknowledgments We thanks the financial supports from the National Natural Science Foundation of China (NSFC 21062023).

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