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# 2-Pyridylthiazole derivative as ICT-based ratiometric fluorescent sensor for Fe(III)

Yue Wang [a,b], Ming-Yang Yang [a], Ming-Hua Zheng [a,*], Xiao-Long Zhao [a], Yu-Zhong Xie [a,c], Jing-Yi Jin [a,b,*]

[a] Research Centre of Chemical Biology, Yanbian University, Yanji 133002, China
[b] Key Labaratory of Natural Resources of Changbai Mountains & Functional Molecules, Ministry of Education, Yanbian University, Yanji 133002, China
[c] College of Chemistry, Northeast Normal University, Changchun 130024, China

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## ABSTRACT

2-Pyridylthiazole (2-PT) as a robust fluorophore has been applied in various fluorescent sensors. Based on the intramolecular charge transfer (ICT) process of 2-PT unit, we develop its new derivatives, 4-phenyl-5-phenylethynyl-2-(2-pyridyl)thiazole (4-PPT), as a ratiometric fluorescent sensor of Fe(III). 4-PPT exhibits fluorescence emission at 431 nm. Addition of Fe(III) can result in a red-shifted emission at 517 nm. The stoichiometry, binding constant, and detection limit are also investigated. Effects of Fe(III) on the fluorescence of 4-PPT could be removed by introduction of a strong chelator, and thus the reversibility is checked.

## Introduction

Iron is the most abundant transition metal species in human body, which plays important roles in various enzyme catalysis, cellular metabolism, and DNA, RNA synthesis.[1–3] Iron homeostasis is also tightly related to the oxygen homeostasis, which has been ascribed to the versatile oxidative states of the metal.[4] The redox activities are regulated in subtle way found in the mitochondria-related functions.[5,6] Imbalance of iron could lead to cell damage and death.[6,7] Furthermore, overloading of iron may result in various pathological processes related to neurodegeneration including Alzheimer's disease, Parkinson's disease, and Friedreich's ataxia.[8–13] Detection of Fe(III) is thus of great importance. Because of the high sensitivity, noninvasiveness and easy operation, fluorescence-based measurement is deeply appreciated among various detection methods,[14] which has been thus intensively pursed based on the chemosensors with high selectivity.[15–17] It has been also well exemplified in recent development of rhodamine-based fluorescent indicators for Fe(III).[18–25]

On the other hand, ratiometric fluorescent probes based on dual-emission, where the ratio of intensities at two different wavelengths could be related to the analyte concentrations,[26] could significantly eliminate most of the interferences such as photo-bleaching, probe concentration, and instrument efficiency in the measurement and have been thus most appreciated.[27] Therefore, some ratiometric sensors for Fe(III) were then developed using rhodamine as the report unit based on fluorescence resonance energy transfer (FRET) mechanism as reported.[23–25] However, most of them processed the relatively complicated structures demanded by the FRET design rationale, which needed the multi-step synthesis in general. On the other hand, we noted that intramolecular charge transfer (ICT), the alternative approach to ratiometric fluorescent sensing, has been rarely applied in detection of Fe(III). In our opinion, the ICT-based sensor could also fulfill the ratiometric fluorescent sensing of the metal ion without loss of structural simplicity.

2-Pyridylthiazole units (2-PT) have been reported as the ICT-induced fluorophores, which exhibited good fluorescence emission with acceptable water solubility as well as relatively simple structures.[28] Based on the ICT process of 2-PT, we have developed a series of fluorescent switches and sensors.[29–34] In the presented Letter, we hope to report a new 2-PT derivative, 4-phenyl-5-phenylethynyl-2-(2-pyridyl)thiazole (4-PPT), as a ratiometric fluorescent sensor for Fe(III). 4-PPT exhibits a fluorescent emission at 413 nm resulted from the ICT process, which is supported by both experimental investigation and theoretical calculation. We then check the effects of various metal ions on both absorption and fluorescence of the ligand. It is found that only addition of Fe(III) could result in the red-shifted emission at 517 nm with enhanced

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* Corresponding authors. Tel.: +86 433 2732449; fax: +86 433 2732242 (M.-H.Z.); tel./fax: +86 433 2733405 (J.-Y.J.).

E-mail addresses: zhengmh@ybu.edu.cn (M.-H. Zheng), jyjin-chem@ybu.edu.cn (J.-Y. Jin).

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intensity at the expense of the original fluorescence of the free ligand in aqueous system. The other metal ions in screening have no similar changes. The change induced by Fe(III) could be eliminated by addition of excess of *N*,*N*,*N*′,*N*′-tetrakis(2-pyridylmethyl) ethylenediamine (TPEN) as a strong chelator, and thus 4-PPT is suggested as a ICT-based ratiometric fluorescent sensor for Fe(III) with structural simplicity.

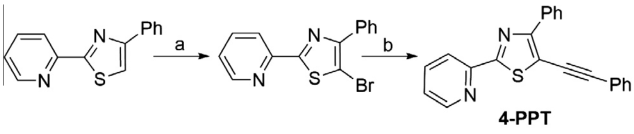
## Results and discussion

Synthesis of 4-PPT is shown as in Scheme 1. Bromination of 4-phenyl-2-(2-pyridyl)thiazole[35] with *N*-bromo succinimide followed by the Sonogashira reaction[36–38] with phenylacetylene provided the desired ligand with high yields (S1).

Absorption and fluorescence maxima of 4-PPT in different solvents are collected in Table 1. It could be found that polarities of solvents have little effects on the maxima of absorption but promote a increasing Stokes shift, which should be ascribed to the photo-induced charge transfer for the typical push–pull conjugated molecules.[41] We further performed density functional calculations at the B3LYP/6-31G(d,p) level using Gaussian 03.[42–46] The predicated electron densities of both HOMO and LUMO are shown as in Figure 1, where it should be expected that the ICT process upon excitation occur from the electron donating 5-phenylethynyl group to the 2-pyridyl group.

Effects of various metal ions (Na(I), K(I), Ag(I), Mg(II), Ca(II), Cr(III), Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II), Hg(II), Pb(II), and Fe(III)) on UV–Vis absorbance of 4-PPT were then investigated in aqueous system (MeCN/Tris buffer = 9:1, v/v).

The free ligand exhibited an absorption peak at 359 nm (Fig. S1). Firstly, any addition of 10.0 equiv of Fe(III), Cd(II), Co(II), or Mn(II) resulted in a significant red-shift of the absorption maximum to 400–405 nm. Secondly, any of Ni(II), Cu(II), and Hg(II) brought about a slighter bathochromic shift of absorption to 370, 379, and 385 nm, respectively. The other metal ions in screening had little effects except an additional weak peak emerging at 420 nm for Ag(I). To explore the distinct missing of the isosbestic point upon the addition of 10 equiv of Fe(III), we further carried out a UV–Vis titration experiment. It was found that the absorption intensity at 359 nm decreased gradually accompanied by the increasing absorption band at 403 nm upon the addition of 0–1.0 equiv of Fe(III), where a clear and fixed isosbestic point at 380 nm could be observed (Fig. 2). The absorption spectra were identical in the presence of 1.0 equiv and 2.0 of Fe(III). Further introduction of Fe(III) only enhanced the absorption band at ~350 nm, which may be ascribed to the existence of the excess of Fe(III) in the system (Fig. S2).



a. NBS; b. $Pd(PPh_3)_2Cl_2$, CuI, $Et_3N$, phenylacetylene, 80 °C.

**Scheme 1.** Synthesis of the reported 2-PT derivative.

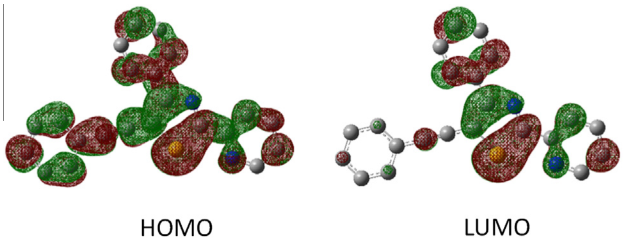


**Figure 1.** HOMO and LUMO of 4-PPT at the B3LYP/6-31G(d,p) level of theory predicated by Gaussian 03. Gray: carbon atom; blue: nitrogen atom; yellow: sulfur atom; to clarify the representation, hydrogen atoms are omitted.

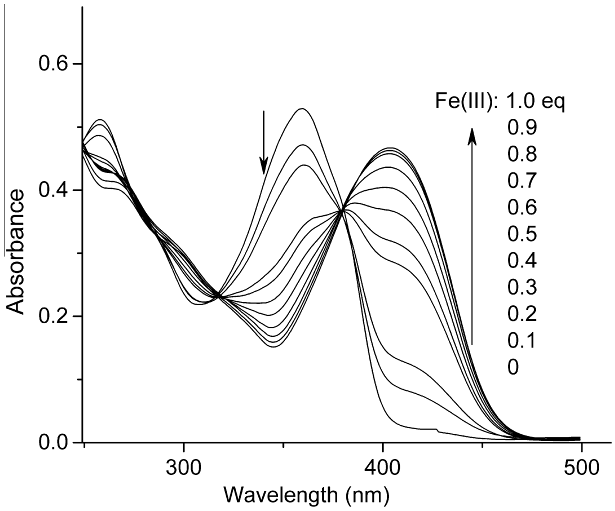


**Figure 2.** UV–Vis spectral changes of 4-PPT (20.0 μM) in aqueous system (MeCN/Tris buffer = 9:1, v/v, Tris buffer: 50 mM, pH = 7.4) in the presence of 0–1.0 equiv of Fe(III) at 20 °C.

Different to the finding that various effects of different metal species on the absorption of 4-PPT, preliminary tests disclosed that Fe(III) could induce a specific change of the emission of the free ligand (Fig. S3). The free ligand displayed fluorescence at 431 nm, whereas a new bathochromic emission appeared at 517 nm with intensity enhancement after 10.0 equiv of Fe(III) was introduced

**Table 1**

Photophysical properties of 4-PPT. Maxima[a] of absorption $\lambda_{abs}$ and of fluorescence emission[b] $\lambda_{em}$, molar absorption coefficients $\varepsilon_{max}$ ± 5%, fluorescence quantum yields[c] $\phi$ ± 5%, the Stokes shifts in different solvents

| Solvent ($\Delta f$)[d] | Chloroform<br>0.149 | Tetrahydrofuran<br>0.210 | Dichloromethane<br>0.219 | Acetonitrile<br>0.306 | Methanol<br>0.309 | Water<br>0.320 |
|---|---|---|---|---|---|---|
| $\lambda_{abs}$/nm | 362 | 363 | 362 | 359 | 361 | 359 |
| Log($\varepsilon_{max}$/M$^{-1}$ cm$^{-1}$) | 4.31 | 4.32 | 4.23 | 4.34 | 4.36 | 4.09 |
| $\lambda_{em}$/nm | 425 | 428 | 427 | 429 | 432 | 443 |
| $\phi$ | 0.63 | 0.61 | 0.67 | 0.78 | 0.65 | 0.58 |
| $\Delta S$/cm$^{-1}$ | 4095 | 4184 | 4205 | 4545 | 4553 | 5282 |

[a] All spectra were recorded at 20 °C. Concentrations of the ligand were 20 and 1.0 μM, respectively, for measurement of absorption and fluorescence.

[b] Excited at 360 nm.

[c] Relative quantum yields were evaluated using quinine sulfate ($\phi = 0.54 \pm 0.2$ in 0.5 M $H_2SO_4$ excited at 365 nm) as the standard compound.[39]

[d] $\Delta f$ was Lippert's solvent polarity parameter,[11,40] which was used to correlate the Stokes shifts and the polarities of solvents.