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PAPER

An 2-(2′-aminophenyl)benzoxazole-based OFF–ON fluorescent chemosensor for Zn^{2+} in aqueous solution†

Maliang Chen, Xin Lv, Yunlong Liu, Yun Zhao, Jing Liu, Pi Wang and Wei Guo*

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A water-soluble fluorescent sensor, **1**, based on the "receptor-spacer-fluorophore" [2-(2′-aminophenyl)benzoxazole-amide-2-picolylamine] sensor platform, demonstrates the high sensitivity for Zn^{2+} with a 25-fold fluorescence enhancement upon chelation to Zn^{2+} and also exhibits high selectivity to Zn^{2+} over other metal ions. X-ray crystal structure of Zn^{2+} complex reveals that the amide oxygen (O2) cooperates with 2-picolylamine unit (N3, N4) as a receptor bind Zn^{2+}.

Introduction

Detection and quantification of transition metal ions found in biological systems and in the environment remains an active area of research, as these ions are either quite beneficial or toxic to human health.[1] Among the various transition metal ions, Zn^{2+} is the second most abundant transition metal in human body, and plays crucial roles in many important biological processes in acting as the structural and catalytic cofactors, neural signal transmitters or modulators, and regulators of gene expression, and apoptosis.[2,3] Failure to maintain zinc homeostasis has been implicated in a number of severe neurological diseases such as Alzheimer's disease (AD), amyotrophic lateral sclerosis (ALS), Guam ALS-Parkinsonism-dementia Parkinson's disease, hypoxia ischemia, and epilepsy.[4–6] Therefore, highly selective and sensitive detection of Zn^{2+} in various samples is of toxicological and environmental concern.

Sensors based on the chemical species induced changes in fluorescence appear to be particularly attractive due to the highly sensitive, quick, simple and real time monitoring of the fluorescence.[7] Moreover, fluorescence-based chemosensors can be used to readily detect intracellular ion levels without the need for sophisticated instrumentation or time-consuming sample preparation. For sensitivity reasons, chemosensors exhibiting fluorescence enhancement (turn-on) are favored over those showing fluorescence quenching (turn-off). Therefore, a crucial issue is controlling the emission of a fluoroionophore so that it is nonfluorescent in the absence of metal ion, whereas highly fluorescent in its metal complex.

Numerous scientific endeavours have been engaged in the development of fluorescent chemosensors for the *in vitro* and *in vivo* detection of Zn^{2+}.[8–17] Quinoline-based fluorescent sensor molecules are the most widely used fluorescent Zn^{2+} chemosensors.[8] Recently, several fluorescent probes for Zn^{2+} have also been proposed based on different fluorophores such as boradizazindacene (bodipy),[9] rhodamine,[10] Bis(benzoxazole),[11] anthracene,[12] bipyridine,[13] spirobenzopyran,[14] naphthalimide,[15] tricarbocyanine,[16] and 4-amino-7-nitro-2,1,3-benzoxadiazole (ANBD).[17] However, some of them have poor water solubility, thus various solvent mixtures are used in characterization, which inevitably hinders their applications. In addition, many available Zn^{2+} sensors have difficulty in distinguishing Zn^{2+} and Cd^{2+}, since Cd^{2+} is in the same group of the periodic table and has similar properties with Zn^{2+} which results in similar fluorescence changes when Zn^{2+} and Cd^{2+} are coordinated with fluorescent sensors. Therefore, the exploration of new fluorescent turn-on probes for analyzing Zn^{2+} with appropriate selectivity, high sensitivity, rapid response, and good water solubility remains a challenge.

In this paper, we report the design and synthesis of a highly selective "off–on" fluorescent sensor **1** for Zn^{2+} in aqueous solution. Our approach is based on the "receptor-spacer-fluorophore" sensor platform to promote the fluorescence "off–on" changes. The choice of 2-(2′-aminophenyl)benzoxazole derivative as the fluorophore is based on the excellent photophysical properties of benzoxazole derivatives, which are extensively used as sensor molecules for a series of cations and anions.[18] The choice of 2-picolylamine as Zn^{2+}-chelator was based on the consideration that this unit and its derivatives are known to have an strong affinity for Zn^{2+}.[16,18b,19] In addition, a rigid amide group was introduced into the sensor not only to link two moieties of the 2-(2′-aminophenyl)benzoxazole fluorophore and 2-picolylamine chelator but also to provide another one metal-coordination site (amide carbonyl).

School of Chemistry and Chemical Engineering, Shanxi University, Taiyuan, 030006, China. E-mail: guow@sxu.edu.cn; Tel: +86 351 7011600

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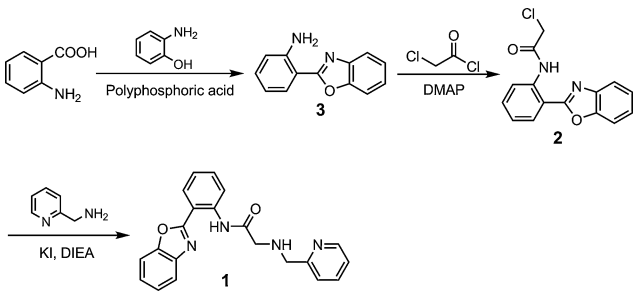
Results and discussion

The synthesis of **1** is shown in Scheme 1. The 2-(2′-aminophenyl)benzoxazole (**3**) was prepared in 65% yield according to a literature method,[20] then condensation of **3** with 2-chloroacetyl chloride to produce **2** in 70% yield. Reaction of **2** with 2-picolylamine under basic conditions gives **1** in 65% yield.



Scheme 1 Synthesis of fluorescent sensor **1**.

To obtain the clear insight on the **1**-Zn^{2+} interaction, we firstly performed the X-ray diffraction study of **1**-Zn^{2+} complex. The single crystal of **1**-Zn^{2+} complex was obtained by slow evaporation of the MeCN solution of **1** and equivalent $ZnCl_2$, and characterized using X-ray crystallography.[21] As shown in Fig. 1, X-ray structural analysis of **1**-Zn^{2+} complex reveals the formation of a 1 : 1 metal/ligand mononuclear complex. The amide oxygen (O2) cooperates with the 2-picolylamine unit (N3 and N4) and two chloride atoms as a receptor to bind Zn^{2+}. The bond lengths of Zn(1)–O(2), Zn(1)–N(3), and Zn(1)–N(4) are 2.522 Å, 2.113 Å, and 2.129 Å, respectively. Notably, the crystal structure of **1**-Zn^{2+} complex exhibits an intramolecular N–H···N hydrogen bond (N2…N1, 2.683 Å; H…N1, 1.905 Å) and a Zn^{2+}-ligand chelation interaction, both of which should provide added rigidity to the complex, thus resulting in a nearly planar molecule conformation. The rigid molecular structure appears to be favorable for fluorescence emission of the complex due to the decreased nonradiative decay through rotatory motion of the amide group or others.

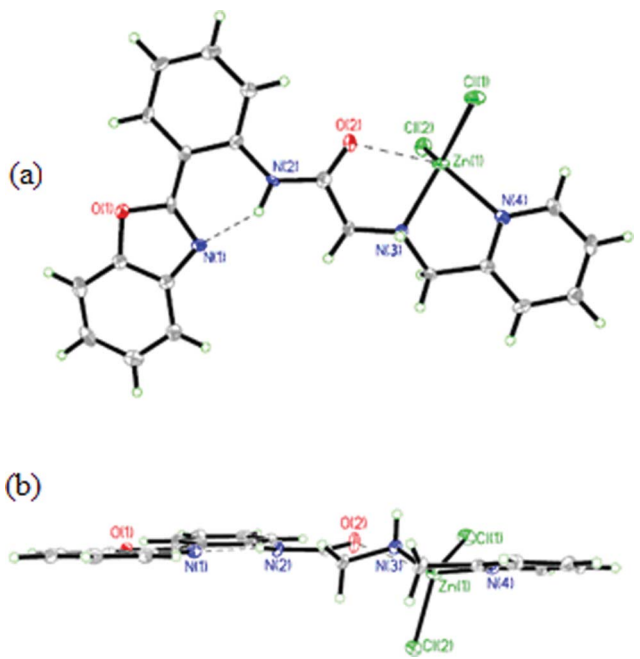


Fig. 1 (a) Crystal structure of **1**-Zn^{2+} complex, face-on view, with displacement atomic ellipsoids drawn at the 50% probability level. (b) Side view of the structure in (a) showing nearly planar molecular conformation.

The metal-binding behavior of **1** has been determined by fluorescence spectroscopic studies. Sensor **1** showed a very weak fluorescence in Tri-HCl buffer (10 mM, pH 7.2) solution. Upon addition of Zn^{2+}, the fluorescence intensity increased remarkably and a fluorescence enhancement factor at 445 nm of approximately 25-fold was estimated (Fig. 2a). These changes in the fluorescence spectrum stopped and the emission intensities became constant when the amount of Zn^{2+} added reached 3 equiv, and a clear blue fluorescence could be observed. The association constant for Zn^{2+} was estimated to be 4.3×10^5 M^{-1} ($R^2 = 0.9969$) on the basis of nonlinear fitting of the titration curve assuming 1 : 1 stoichiometry (Fig. 2b). Job plot analysis of the fluorescence titrations revealed a maximum at about 0.5 mole fraction (Fig. 2b, inset), in accord with the proposed 1 : 1 binding stoichiometry. The solid evidence of the 1 : 1 binding mode comes from the ESI-MS spectra of the complex of **1** with Zn^{2+}, in which the peaks at m/z 421.0635 (calcd = 421.0643) corresponding to [**1**+Zn^{2+}–H^+]$^+$ was clearly observed (Fig. S1, ESI†).

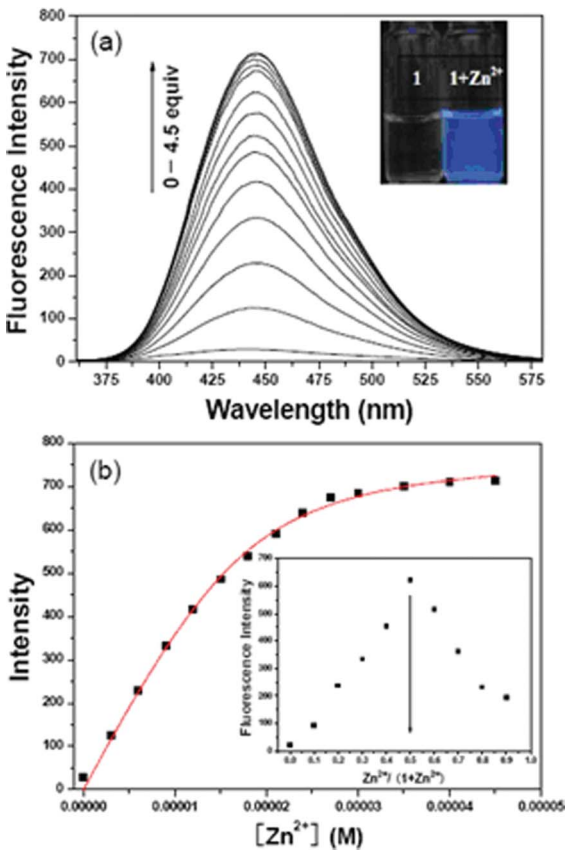


Fig. 2 (a) Fluorescence sprctra of **1** (10 μM) in Tris-HCl buffer (10 mM, pH = 7.2) in the presence of different amounts of Zn^{2+}. Inset: fluorescence changes of **1** (10 μM) upon addition of 3 equiv of Zn^{2+}. (b) Fluorescence titration profile *vs.* concentration of Zn^{2+} in Tris-HCl buffer (10 mM, pH = 7.2) for **1**. Inset: Job's plot for determining the stoichiometry of **1** and Zn^{2+}. Slit: 5 nm/5 nm.

When **1** was employed at 5 μM and the slit was adjusted to 10 nm/10 nm, the linear dynamic response concentration range for Zn^{2+} covers from 1.0×10^{-7} to 1.0×10^{-6} M (Fig. 3). The detection limit (LOD) and quantification limit (LOQ) were measured to be 3.66×10^{-8} M (3σ/slope) and 1.22×10^{-7} M (10σ/slope), respectively. In addition, the interaction of **1** with Zn^{2+} was completed in a few seconds (Fig. S2, ESI†), therefore **1** could be used for the real-time and real-space analysis of Zn^{2+} ions in cells and organisms.

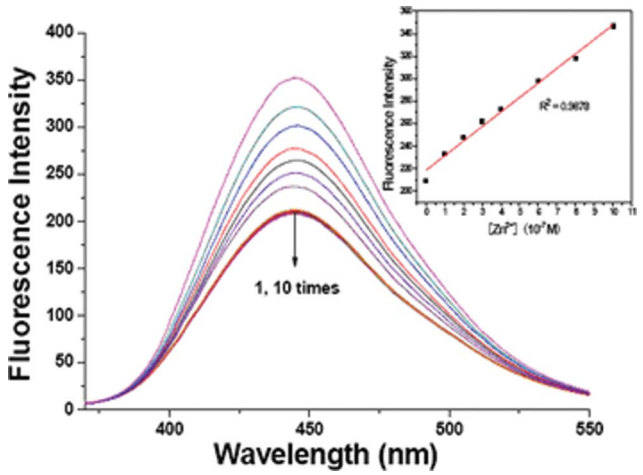


Fig. 3 Fluorescence response of **1** (5 μM) to Zn^{2+} in Tris-HCl buffer (10 mM, pH = 7.2). $\lambda_{ex}/\lambda_{em}$ = 350/445 nm. Slit: 10 nm/10 nm.

To apply **1** in more complicated systems, like in an organism and the environment, the influence of pH on the fluorescence of **1** was examined by fluorescence titration in water (Fig. 4). The fluorescence spectrum of **1** exhibits a weak emission band with a maximum at 445 nm, and remained unaffected with increasing acidity from pH 13.7 to 2.0. Upon addition of Zn^{2+}, **1** responds stably to Zn^{2+} between pH 5.2 and 12.1 without any interference by protons, indicating that **1** successfully reacts with Zn^{2+} and allows Zn^{2+} detection in a wide pH range.

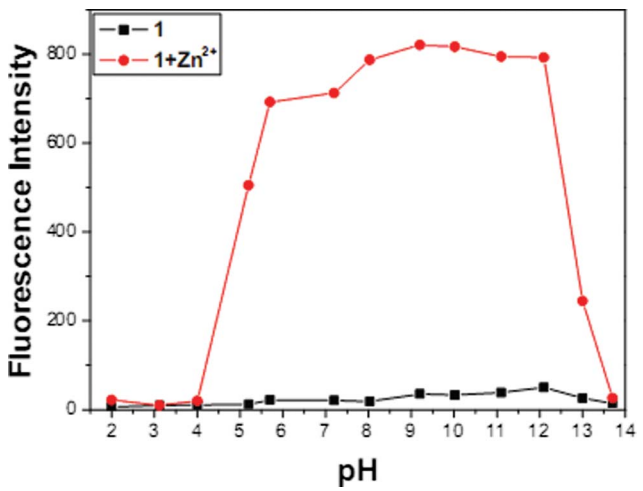


Fig. 4 Changes in fluorescence intensity ($\lambda_{ex}/\lambda_{em}$ = 350 nm/445 nm) of **1** (10 μM) in water measured with and without Zn^{2+} (3.0 equiv) as a function of pH.

An important feature of **1** is its high selectivity toward the Zn^{2+} over the other competitive species. Changes of fluorescence spectra of **1** (10 μM) caused by Zn^{2+} (3 equiv) and miscellaneous cations including Na^+, K^+, Mg^{2+}, Ca^{2+} (30 equiv); Cd^{2+}, Cr^{3+}, Mn^{2+}, Hg^{2+}, Ag^+, Pb^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}, Cu^{2+} (3 equiv), in Tris-HCl buffer (10 mM, pH = 7.2) are recorded in Fig. 5. Most of tested metal cations including Cd^{2+} did not induce any distinct emission shift and enhancement. Moreover, the presence of these competitive cations, Zn^{2+} ion still resulted in the similar fluorescence changes (Fig. 6). However, some paramagnetic metal ions, such as Cu^{2+}, Co^{2+}, and Ni^{2+}, obviously quench the fluorescence, which is always encountered in the other metal ion sensors.

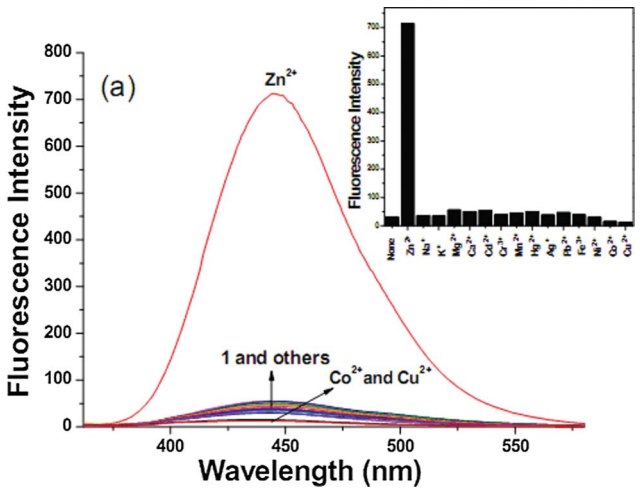


Fig. 5 The fluorescence spectra of **1** (10 μM) upon addition of 3 equiv of Zn^{2+} and various other metal ions, including of Na^+, K^+, Mg^{2+}, Ca^{2+} (30 equiv); Cd^{2+}, Cr^{3+}, Mn^{2+}, Hg^{2+}, Ag^+, Pb^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}, Cu^{2+} (3 equiv), in Tris-HCl buffer (10 mM, pH = 7.2). Inset: Fluorescence responses of **1** towards Zn^{2+} to various cations. Intensity was recorded at 445 nm, excitation at 350 nm.

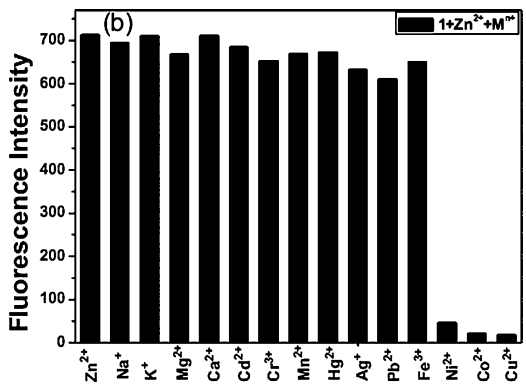


Fig. 6 Fluorescence responses of **1** (10 μM) to Zn^{2+} (3 equiv) containing various metal ions including of Na^+, K^+, Mg^{2+}, Ca^{2+} (30 equiv); Cd^{2+}, Cr^{3+}, Mn^{2+}, Hg^{2+}, Ag^+, Pb^{2+}, Fe^{3+}, Ni^{2+}, Co^{2+}, Cu^{2+} (3 equiv), in Tris-HCl buffer (10 mM, pH = 7.2). Intensity was recorded at 445 nm, excitation at 350 nm.

Several factors can be listed for rationalizing the observed emission enhancement. The weak fluorescence of **1** in the absence of Zn^{2+} might be attributed to radiationless channels from the nπ* state.[22] In the presence of Zn^{2+} that coordinates with the lone pair of the carbonyl oxygen (O2), the energy of the nπ* state would

be raised so that the ππ* state becomes the lowest excited state, leading a substantial increase in the fluorescence intensity.[23] In addition, Zn^{2+} binding to **1** could not only induce a conformation restriction[24] but also block PET quenching of the singlet excited state of the 2-(2′-aminophenyl)benzoxazole moiety, thus, a big fluorescence enhancement could be observed (Fig. 7).

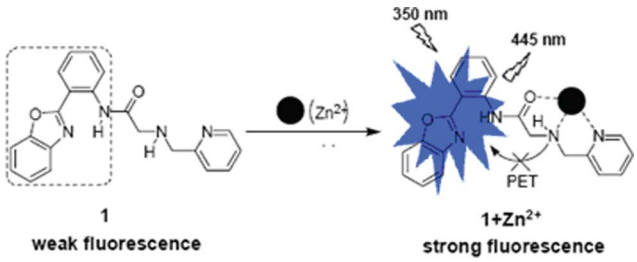


Fig. 7 The proposed sensing mechanisms of **1** for Zn^{2+}.

Conclusions

In summary, we have successfully prepared a water-soluble and small molecular fluorescent sensor for Zn^{2+}. The sensor displays an obvious fluorescence enhancement up to 25-fold with Zn^{2+} in aqueous solution. Moreover, the sensor shows good selectivity for Zn^{2+} over other metal ions. The binding mode of the sensor with Zn^{2+} was probed by X-ray diffraction study. We expect that the method will serve as practical tool for environmental samples analysis and biological studies. Further investigations on its applications in life science are underway in our lab.

Experimental section

Materials and general methods

2-(2′-Aminophenyl)benzoxazole (**3**) were prepared by literature procedures.[20] All other reagents and solvents were purchased from commercial sources and were of the highest grade. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC). Flash chromatography (FC) was performed using silica gel 60 (230–400 mesh). Absorption spectra were taken on an Agilent 8453 spectrophotometer. Fluorescence spectra were taken on HITACHI F-2500 fluorescence spectrometer. The ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. High resolution mass spectra were obtained on a Varian QFT-ESI mass spectrometer.

Synthesis of compound 2

A solution of 0.34 g (3 mmol) of 2-chloroacetyl chloride in 5 mL of dry CH_2Cl_2 was added dropwise to a solution of 0.42 g (2 mmol) 2-(2′-aminophenyl)benzoxazole (**3**) and 0.5 g (4.1 mmol) 4-dimethylaminopyridine (DMAP) in 10 mL of dry CH_2Cl_2 stirred in an ice bath. After stirred 2 h at room temperature, the mixture was evaporated under reduced pressure, and the residues were purified by silica gel column chromatography using PE/CH_2Cl_2 (2 : 1) as eluent to afford compound **2**. Yield: 0.4 g (70%). Mp: 135–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 12.78 (b, 1H), 8.86 (d, J = 8.4, 1H), 8.28 (d, J = 7.8, 1H), 7.34–7.81 (m, 6H), 4.36 (s, 2H).

Synthesis of compound 1

Compound **2** (0.143 g, 0.5 mmol), 2-picolylamine (0.065 g, 0.6 mmol), *N*, *N*-diisopropylethylamine (DIEA, 0.8 mL), and potassium iodide (30 mg) were added to acetonitrile (50 mL). After stirring and refluxing for 10 h under nitrogen atmosphere, the mixture was cooled to room temperature, and was evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography using $CHCl_3$–MeOH (200 : 1) as eluent to afford compound **1**. Yield: 0.12 g (65%). Mp: 85–86 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.82 (d, J = 8.7, 1H), 8.52 (d, J = 4.5, 1H), 8.20 (d, J = 7.8, 1H), 7.79 (d, J = 8.1, 1H), 7.58–7.66 (m, 2H), 7.51 (d, J = 7.8, 1H), 7.45 (m, 1H), 7.24–7.35 (m, 4H), 3.98 (s, 1H), 3.46 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): 171.8, 161.9, 159.1, 149.6, 141.3, 138.8, 136.7, 132.8, 128.7, 125.6, 124.7, 123.3, 122.7, 122.4, 120.9, 119.8, 113.8, 110.7, 55.2, 53.8. IR (KBr) cm^{-1}: 3434, 3178, 2931, 1676, 1618, 1589, 1548, 1531, 1438. HRMS (ESI) calcd. for (M–H)– 357.1351, found 357.1354.

Crystallography

Intensity data of **1**-Zn^{2+} complex were collected on a Siemens SMART-CCD diffractometer with graphite-monochromated Mo-Kα (λ = 0.71073 Å) using the SMART and SAINT programs. Crystal data for **1**-Zn^{2+}, $C_{21}H_{18}C_{l2}N_4O_2Zn$, M = 494.66, Triclinic, space group $P\bar{1}$, a = 8.6993(17) Å, b = 10.744(2) Å, c = 11.593(2) Å, α = 75.65(3)°, β = 74.28(3)°, γ = 86.28(3)°, V = 1010.6(3) Å^3, μ = 1.506 mm^{-1}, Z = 2, T = 113(2) K, cyrstal dimensions 0.20 × 0.18 × 0.10 mm^3, θ range 1.88–25.01°. 9125 reflections were collected of which 3541 reflections were unique (R_{int} = 0.0382). Final R indices [$I \geq 2\sigma(I)$]: R_1 = 0.0319, wR_2 = 0.0946, R indices (all data): R_1 = 0.0380, wR_2 = 0.1052, goodness of fit on F^2 = 1.022. CCDC: 799368.

Procedures of ions sensing

Deionized water was used throughout all experiments. Solutions of Ca^{2+} were prepared from their chloride salts; solutions of Na^+, K^+, Ag^+, Mg^{2+}, Cu^{2+}, Cd^{2+}, Co^{2+}, Mn^{2+}, Ni^{2+}, Zn^{2+}, Hg^{2+}, Pb^{2+}, Cr^{3+}, and Fe^{3+} were prepared from their nitrate salts. A stock solution of **1** (25 mM) was prepared in MeCN. The stock solution of **1** was then diluted to the corresponding concentration (10 μM and 5 μM) with the buffer solution (10 mM Tris-HCl, pH 7.2]. The Zn^{2+} stock solution of 1.0×10^{-1} M was diluted to 1.0×10^{-2} M, 1.0×10^{-3} M and 1.0×10^{-4} M with deionized water for spectra titration studies. In the titration experiments, a 2.0 mL solution of **1** (10 μM and 5 μM) was poured into a quartz optical cell of 1 cm optical path length each time, and Zn^{2+} solution was added into the quartz optical cell gradually by using a micro-pipette. Spectral data were recorded in an indicated time after the addition.

Acknowledgements

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21 We also prepared the single crystal of **1**-Zn^{2+} complex in 1 : 1 of MeCN–H_2O instead of in pure MeCN, and reexamined it by X-ray structural analysis. The result reveals that the single structure of **1**-Zn^{2+} obtained in aqueous solution is fully the same to that obtained in pure MeCN.

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