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A bezoimidazole-based highly selective and low-background fluorescent sensor for Zn^{2+}

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ABSTRACT

In this article, a new benzoimidazole based Zn^{2+} fluorescence sensor DABI has been prepared. The sensor displays a rapid and a linear response to Zn^{2+} with a red-shifted 100-fold turn-on signal from the dark background. The presence of other metal ions especially Cd^{2+} does not interfere with its Zn^{2+} response. Molecular modeling study suggests that the Zn^{2+}-induced red shift of emission and fluorescence turn-on of DABI could be correlated to the coplanation of two aryl planes of 2-aryl substituted benzoimidazole.

Zinc is the second most abundant transition-metal ion in the human body, it plays an essential role in biological processes such as structural co-factors, catalytic centers, regulators of enzymes, regulators of gene expressions [1–3]. The spatiotemporal distribution of biological zinc ions in organs or intracellular organelles is tightly regulated by the homeostatic activity of zinc uptake/secretion and buffering systems. The up-regulated levels of zinc are causative in several neurodegenerative diseases, such as Alzheimer's, and Parkinson's diseases [4–6]. Moreover, the widely use of zinc in industrial, make of zinc contamination of natural waters are relatively frequent [7]. Therefore, it is meaningful to detect Zn^{2+} both in environmental and biological systems. Because Zn^{2+} is spectroscopically silent due to its d^{10} electron configuration, fluorescence techniques have become the gold standard for Zn^{2+} sensing because of their high sensitivity and spatiotemporal resolution [8–13].

A number of fluorescence sensors for detection of Zn^{2+} in living cells, tissues, and sample solutions have been reported to date [8–13]. Examples using fluoresceins (such as ZPs) [14], rhodamines (such as RhodZin-1) [15], naphthalimides (such as WZS) [16], NBDs (such as NBD-TPEA) [17] and 8-hydroxyquinoline (such as sensor 3) [18] have been documented. Such probes are among the current state of the art, yet limitations exist. For example, most documented fluorescence Zn^{2+} sensors cannot discriminate Zn^{2+} from Cd^{2+} owing to their closely related electronic and binding properties. Thus, the search for readily accessible fluorescence Zn^{2+} sensors with high selectivity is still a challenging task.

2-aryl substituted benzoimidazole derivatives (2-ABIs) are common fluorophore widely exploited in the construction of metal ion sensors [19]. The photo-induced energy transfer *via* the rotation of the biaryl plane in the excited state make 2-ABIs has very weak fluorescence. The metal ions coordination of 2-ABIs based metal ion sensors can induce coplanation of two aryl planes of 2-ABIs and result in the red shift and strong fluorescence enhancement of emission of 2-ABIs [19b]. The intrinsic characteristics such as dark-background and metal ions induced emission enhancement make 2-ABIs are suitable fluorophore for the construction of turn-on florescent sensors with low-background. In this work, we present the synthesis and properties of DABI, new 2-ABIs based "turn-on" fluorescent sensor for the selective detection of Zn^{2+}. DABI features high Zn^{2+} selectivity fluorescence response and a ca. 100-fold emission enhancement upon Zn^{2+} binding.

DABI combines a benzoimidazole dye reporter (2-(4-hydroxyphenyl)-benozimidazole (HPBI)) containing 2, 2′-bipicolylamine (BPA) as receptor to satisfy the Zn^{2+} detection. The synthetic route of DABI is depicted in Scheme 1. The reaction of 3-(chloromethyl)-4-hydroxybenzaldehyde (**1**) [20] with BPA in CH_3CN solution using K_2CO_3 as base afforded compound **2** in 48% yield. DABI was obtained in 54% yield via condensation of compound **2** with *o*-phenylenediamine in ethanol solution.

The photoresponsive properties of DABI were investigated by UV–vis and fluorescence spectroscopy in acetonitrile solution. As shown in Fig. 1, the UV–vis spectrum of DABI in acetonitrile exhibits an absorption maximum in 309 nm ($\varepsilon = 4.13 \times 10^4\ M^{-1}\ cm^{-1}$), which can be assigned into the π−π* transition band of benzoimidazole. When titrated by Zn^{2+} (0−2.0 equiv), this band is decreased gradually,

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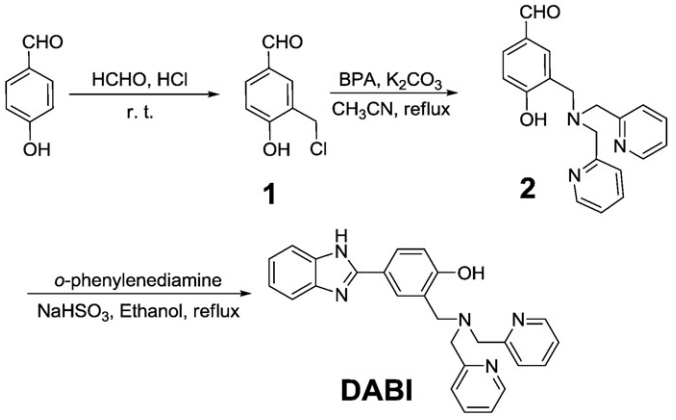

Scheme 1. Synthesis of DABI.

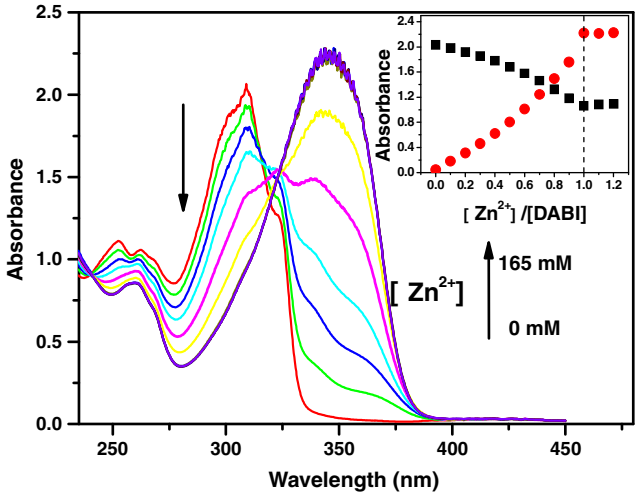

Fig. 1. Absorption spectra of DABI (50 μM) in acetonitrile solution in the presence of different concentrations of Zn^{2+} (0–2 equiv). Inset: The calibration curves $A_{309\ nm}$ and $A_{345\ nm}$ as a function of Zn^{2+} concentration.

accompanied by the red-shift to 345 nm ($\varepsilon = 3.8 \times 10^4\ M^{-1}\ cm^{-1}$). The linear decrease of absorbance at 309 nm and increase of absorbance at 345 nm with $[Zn^{2+}]_{total}$ up to a molar ratio ($[Zn^{2+}]_{total}/[DABI]$) of 1:1 and the unchangeable spectrum at even higher $[Zn^{2+}]_{total}$ imply the 1:1 binding stoichiometry. Following a Benesi–Hildebrand-type analysis, the binding constant of DABI was determined to be $7.4 \times 10^3\ mol^{-1}\ dm^3$.

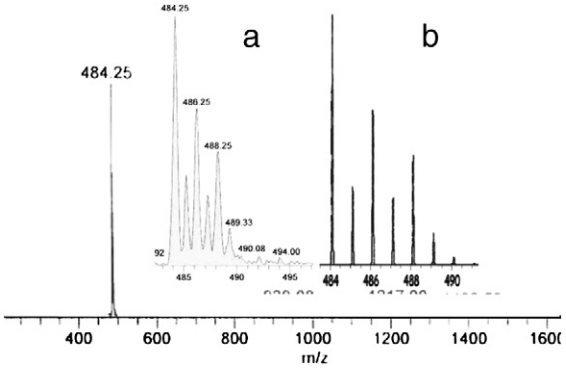

Fig. 2. The MS spectrum of Zn^{2+}/DABI complex. The determined isotopic distribution patterns of the peak with m/z of 484.25 are shown as inset (a). $[M+Zn-H]^+$ is shown as inset (b).

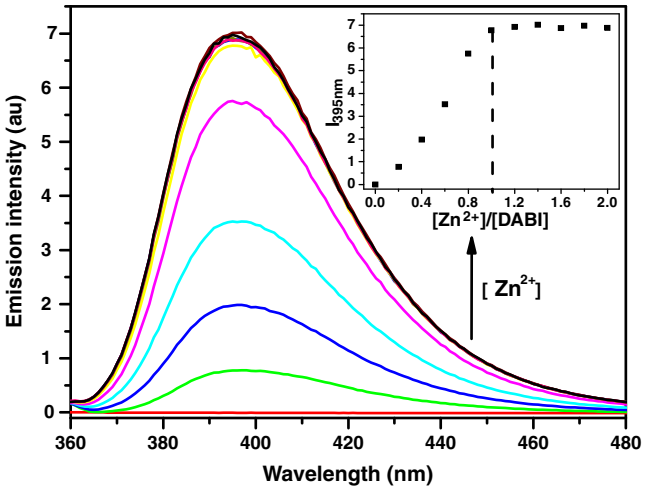

Fig. 3. Fluorescence spectra of DABI (50 μM) in acetonitrile solution in the presence of different concentrations of Zn^{2+} (0–2 equiv). (Inset:) The calibration curve $I_{395\ nm}$ as a function of Zn^{2+} concentration.

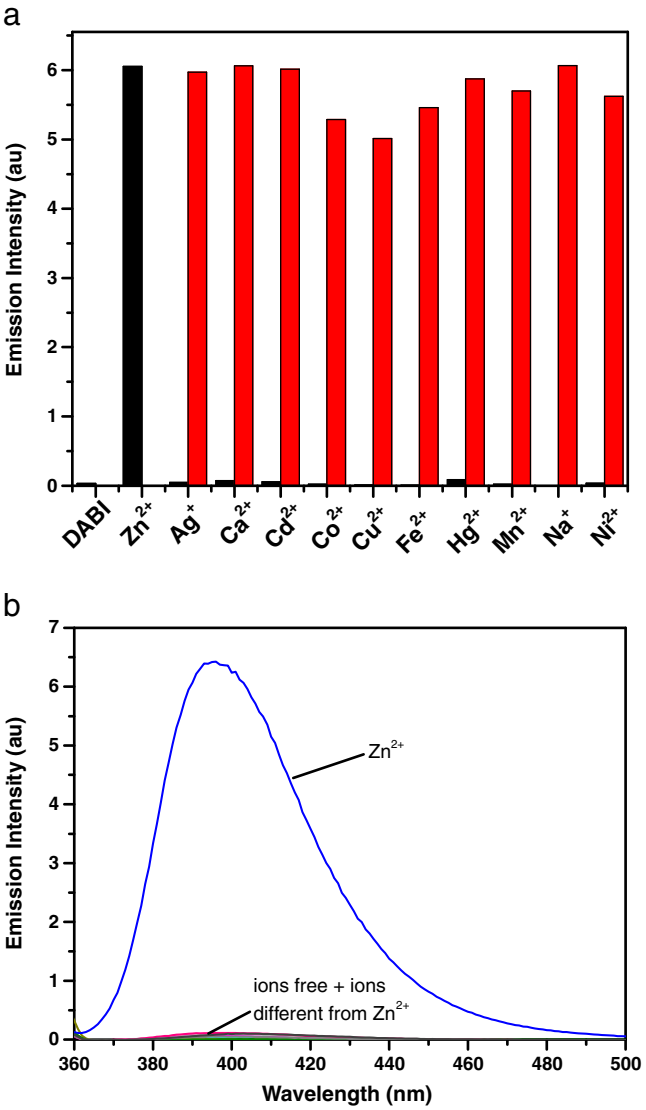

Fig. 4. (a) F_{396} of DABI (50 μM) in CH_3CN induced by different metal cations. Black bars represent the F_{396} of free sensor or in the presence of 1 equiv of Ag^+, Cd^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mn^{2+}, Ni^{2+}, Na^+ and Ca^{2+}. Black bars, F_{396} in the presence of the indicated metal ions, followed by addition of 1 equiv of Zn^{2+}; (b) The emission spectra of DABI in the presence of different metal ions in acetonitrile solution.

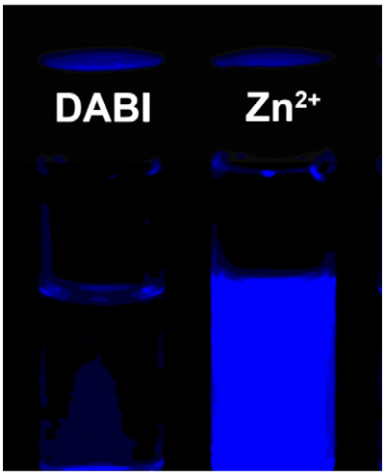

Fig. 5. Photograph showing the fluorescence changes of DABI before (left) and after (right) the addition of 1 equiv of Zn^{2+} in acetonitrile solution upon UV irradiation.

The stoichiometry of the Zn^{2+}/DABI complex has also been confirmed by mass spectroscopic determination. As shown in Fig. 2, the electrospray ionization mass spectrum of this complex displays one signal of *m/z* 484.25, which can be assigned as the signal for $[M+Zn-H]^+$.

DABI exhibits very weak fluorescence in its apo form ($\Phi<0.1\%$) with one emission band centered at 345 nm in acetonitrile solution (Fig. 3). Upon addition of Zn^{2+} into DABI solution, a new emission band centered at 396 nm appears from dark background, and a remarkable fluorescence enhancement of over 100-fold is observed. The emission enhancement of DABI shows a linear enhancement with the increase of $[Zn^{2+}]_{total}$ when the ratio of $[Zn^{2+}]_{total}$/[DABI] is below or equal to 1:1. When the ratio reached to 1:1, however, higher $[Zn^{2+}]_{total}$ does lead to any further emission enhancement. The quantum yield for the DABI/Zn^{2+} complex is about 0.5.

The Zn^{2+}-specific turn-on response of DABI was further confirmed by screening other metal ions. As shown in Fig. 4, all tested metal ions such as Ag^+, Ca^{2+}, Co^{2+}, Cu^{2+}, Fe^{2+}, Hg^{2+}, Mn^{2+}, Na^+, Pb^{2+}, and Ni^{2+} did not induce any emission enhancement. It should be noted that Cd^{2+} addition did not induce any emission enhancement; this result suggests that DABI is a potential sensor for the discrimination of Zn^{2+} from Cd^{2+}. Moreover, as depicted in Fig. 5, an obvious fluorescence change from dark to blue can be observed after the addition of Zn^{2+} to the DABI solution.

The turn-on sensing behavior of DABI was further investigated by molecular modeling. The stable conformations of free DABI and DABI/Zn^{2+} complex optimized by density functional theory (DFT) calculations at the B3LYP/6-31G(d,p) level (Gaussian 03) are shown in Fig. 6 [21]. The dihedral angle between 2-aryl plane and benzoimidazole plane of free DABI is about 30.63°. The photo-induced energy transfer *via* the rotation of the biaryl plane and the photo-induced electron transfer from 3°N atom of BPA group to the fluorophore in the excited state should be response to the weak fluorescence of DABI in acetonitrile. On the other hand, the structure of the Zn^{2+}/DABI complex (b) was also optimized with an initial structure constructed with direct Zn^{2+} coordination by three N atoms of BPA, and one oxygen atom of HPBI. The optimized structure of the Zn^{2+}/DABI complex displays a dihedral angle of 19.63° between two aryl planes. Based on these data, the Zn^{2+} coordination induced coplanation of two aryl planes of fluorophore results the red shift of both absorption and emission band of DABI. The blockage of the photoinduced electron transfer (PET) process from a BPA amine to a HPBI fluorophore induced by Zn^{2+} coordination to a BPA amine should provide for Zn^{2+}-induced emission enhancement.

In conclusion, we have developed a new benzoimidazole based Zn^{2+} fluorescent sensor, DABI, which displays a rapid and a linear response to Zn^{2+} with a red-shifted 100-fold turn-on signal from the dark background. Excellent selectivity was observed against other metal ions, especially Cd^{2+} that interferes with the existing Zn^{2+} sensors. Molecular modeling study results suggest that the Zn^{2+}-induced red shift of emission and fluorescence turn-on of DABI could be correlated to the coplanation of two aryl planes of 2-HPBI.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.inoche.2011.10.018.

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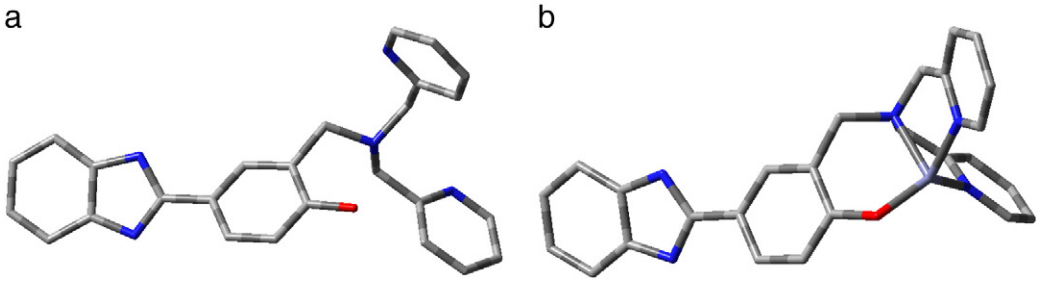

Fig. 6. Conformations of DABI optimized by density functional theory calculations: free DABI (a) and DABI/Zn^{2+} complex (b). All of the protons are omitted for clarity.

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