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A dual-model fluorescent Zn^{2+}/Cu^{2+} ions sensor with *in-situ* detection of $S^{2-}/(PO_4)^{-}$ and colorimetric detection of Fe^{2+} ion

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ABSTRACT

A simple (R)-(−)-2-phenylglycinol functionalized Schiff base exhibited a dual response to Zn^{2+}, Cu^{2+} and Fe^{2+} ions in water:methanol, (90:10 v/v). The compound displays an "off–on" fluorescent effect with Zn^{2+} ions. The emission response decreased with Cu^{2+} forming a Cu^{2+}/Zn^{2+} specie. The fluorescence signal is restored upon addition of sulfide anion (S^{2-}) using the Cu^{2+} *displacement approach*, forming again the Zinc complex. Additionally, the sensor exhibits a second channel (colorimetric) response with Fe^{2+} even in the presence of competing Fe^{3+} ions. The pH profiles allowed to determine the pK_a values and the pH-dependent change in the sensor recognition process. In addition, TD-DFT quantum chemical calculations were implemented to analyze the sensing mechanism by means of Natural Transition Orbital (NTO) analysis. Flow cytometry experiments demonstrated that the sensor successfully detects either exogenous or endogenous (natural) Zn^{2+} ions in Jurkat cells with high sensitivity.

1. Introduction

The selectivity and sensitivity for detecting trace metal ions is one of the challenges related to fluorimetric chemosensors [1–4]. Zn^{2+}, an essential trace ion, is the second most abundant metal ion in the human body [5], and is one of the most common in natural environments [6,7]. In humans, plants and animals Zinc is involved in many physiological processes for normal cell growth and reproduction; and is essential for the proper function of more than 300 enzymes [8–12]. On the other hand, the selective detection of Cu^{2+} ions is of special importance since copper (Cu^{2+}) is one of the essential trace heavy-metals in the human body [13,14]. It is worth mentioning that the safety concentration threshold in drinking water varies from 0.17 to 0.2 ppm according to the US Environmental Protection Agency [15]. In the environment, the release of Cu^{2+} ions induced by atmospheric corrosion, causes significant reduction in the growth rate of plants [16]. For this reason, the detection of environmental and chemically important anions has recently received more attention [17]. In this regard, sulfide is a relevant anion generated as a byproduct of the Kraft process for the production of wood pulp [18a]. Once hydrolyzed, H_2S plays important physiological functions such as blood pressure regulation and mediation of neurotransmission [18b, c]. Also, it is produced by anaerobic bacteria through microbial reduction of sulfate [18]. Phosphates are another important family of anions given their extreme facility to act as substrates or inhibitors by reversible coordination to Zn^{2+} ions [19–22].

Recently, the design of bi- and multi-functional fluorescent ion probes has become a field of intense research [21–30], as they eliminate the use of several probes and thus the possibility of having difficulties such as cross-talk and invasive effects [31]. Thus, one of the most challenging aspects in sensor design is to develop a probe that can selectively detect several analytes through a dual-model optical response. However, the design of relatively simple and low cost dual-sensors with high stability and sensitivity represents another important challenge. Moreover, metal-ion and anion detection in biological samples at low concentrations are highly pH and local-environment dependent [32], such that optical monitoring of these analytes is dramatically affected not only by pH but also by polarity, polarizability and local viscosity. To date, several Zn^{2+} ion sensors have been reported, however, only very few of them have been evaluated to detect natural (endogenous) Zn^{2+} ions in live cells as a result of the poor sensitivity for most of them [33].

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In this work we describe a highly fluorescent turn-on Schiff base sensor **L1** with high selectivity for Zn^{2+} ions as evidenced by competition experiments against other metal ions. Importantly, the selectivity of **L1** for Zn^{2+} in the presence of Cd^{2+} ions, a transition metal with very similar chemical properties, was detected. Thus, **L1** can discriminate Cd^{2+} from Zn^{2+} ions, which comprises a crucial characteristic for the Zn^{2+} ion fluorescent sensors [34,35]. Further experiments show that the formed complex **[Zn(L1)]** detects both, the presence of Cu^{2+} ions that quench the fluorescence by forming a new complex **[Cu(L1)] Zn** (copper complex surrounded by Zn^{2+} ions) and the specific solvent effects show a strong variation of the fluorescence quantum yield. In addition, the reversibility and cyclability properties of **L1** as sensor were demonstrated by testing a number of anions and measuring the fluorescence response. Interestingly, the signal response of **[Zn(L1)]** can be restored from the **[Cu(L1)] Zn** "off" complex upon addition of S^{2-} anions *via* the Cu^{2+} *displacement approach* [36–39]. Furthermore, **L1** can be restored from **[Zn(L1)]** upon interaction with phosphate anions ($H_2PO_4^-$/HPO_4^{2-} and ATP^{4-}), Fig. 1. Finally, since the obtained limit of detection for **L1** was of the order of 10^{-7} M and the Zn^{2+} ion typically found in cells is less than the 1 μM level, it was possible to detect Zn^{2+} in Jurkat cells cultured without Zn^{2+} ions enriched medium.

2. Experimental

2.1. Synthesis

Compound (*R*)-(−)-2-[3-(4-(diethylamino)salicylaldimine]-phenylglycinol (**L1**) was obtained from 4-(diethylamino) salicylaldehyde (0.50 g, 5.17 mmol) and (*R*)-(−)-2-phenylglycinol (0.35 g, 5.17 mmol) through a condensation reaction [40] (see Supplementary Material, Scheme S1). The reaction was carried out under reflux of ethanol using a Dean–Stark trap for 1 h. The product was obtained as an orange solid 0.77 g (4.93 mmol), Yield: 95%. M.p: 111–113 °C. IR ν_{max} (KBr): 3226, 2973, 2967, 2916, 1615 (C=N), 1558, 1523, 1423, 1378, 1351, 1300, 1242, 1132, 1067, 1040, 909, 855, 824, 788, 755, 695, 538, 457 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$, $(CH_3)_4Si$) [δ]: 1.17 (t, 6H, J = 7.0 Hz, CH_3-11), 3.35 (q, 4H, J = 7.0 Hz, CH_2-10), 3.83–3.93 (m, 2H, H-9), 4.40 (dd, 1H, J = 5.4 Hz, J = 7.5 Hz, H-8), 6.11 (d, 1H, J = 2.0 Hz H-3), 6.16 (dd, 1H, J = 2.0 Hz, J = 8.5 Hz, H-5), 6.94 (d, 1H, J = 8.5 Hz, H-6), 7.29–7.36 (m, 5H, H-ortho, H-meta, H-para), 8.14 (s, 1H, H-7). ^{13}C NMR (125.77 MHz, $CDCl_3$), [δ]: 12.9 (CH_3-11), 44.6 (CH_2-10), 67.7 (C-9), 73.1 (C-8), 98.4 (C-3), 103.5 (C-5), 108.3 (C-1), 127.1 (C-meta), 127.7 (C-para), 128.8 (C-ortho), 133.7 (C-6), 139.7 (C-ipso), 152.2 (C-4), 164.0 (C-7), 167.0 (C-2). *Anal.* Calc. for $C_{19}H_{24}N_2O_2$: C, 73.05; H, 7.74; N, 8.97. Found: C, 73.29; H, 7.71; N, 9.26%. HR-ESI-MS: m/z for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1905; found: 313.1911 (error 0.01367 ppm). The resultant Schiff base contains the 4-diethylamino-salicylaldehyde has been described as a potentially fluorescent fragment [41].

2.2. Materials and methods

All reagents and solvents were purchased from Sigma–Aldrich and used as received. The solvents were HPLC grade. The ^1H and ^{13}C NMR spectra were recorded on a JEOL ECA+500, using CD_3OD and $CDCl_3$ as solvent. Chemical shifts were reported in parts per million (ppm) relative to internal TMS. Mass spectra were recorded with an Agilent Technologies MS TOF using the ESI(+) technique. UV–Vis absorption spectra were recorded in a Perkin Elmer UV–Vis Spectrophotometer Lambda 12 and fluorescence spectra in a Varian Cary Eclipse Fluorescence Spectrometer. All fluorescence quantum yield measurements were obtained by using the experimental procedure reported in Ref. [42]. The fluorescence response of **L1** toward the acetate salts of Zn^{2+}, Cd^{2+}, Hg^{2+}, Co^{2+}, Mn^{2+}, Cu^{2+}, Ni^{2+}, Mg^{2+}, Pb^{2+}, Ca^{2+}, K^+, Li^+ and Na^+ ions is presented in the Supplementary Data. Stock solutions of metal acetates (1×10^{-4} mol L^{-1}) and **L1** (1×10^{-4} mol L^{-1}) were prepared in water:methanol (90:10, v/v).

3. Results and discussion

3.1. Environmental effect for *[Zn(L1)]* and pH effect for *L1*

With the aim to have information about the environmental and pH effects on the binding interactions, we carried out a solvatochromic and a pH analysis for **[Zn(L1)]**. The solvatochromic analysis was performed by means of the recently proposed multilinear regression analysis of Catalán [43] in order to establish the influence of local acidity, basicity, polarity and polarizability solvent parameters on the absorption ($\bar{\nu}_{abs}$), emission ($\bar{\nu}_{em}$), Stokes shift ($\Delta\bar{\nu}$) and quantum yield (Φ_{fl}) observables (see Table S1). The data showed a good multilinear correlation for $\bar{\nu}_{abs}$ (r = 0.91), $\bar{\nu}_{em}$ (r = 0.87) and $\Delta\bar{\nu}$ (r = 0.97) where the solvent polarizability parameter exerted the most important influence given its lower standard error and regression coefficient.

On the other hand, in the case of the fluorescent quantum yield we did not observe any linear trend (r = 0.59). This result highlights the strong specific behavior concerning Φ_{fl} for the complex in different solvents, Fig. 2 (inset). To the best of our knowledge, this strong specific polarizability dependence on Zn-complexes has not been described before. Our analysis showed that the

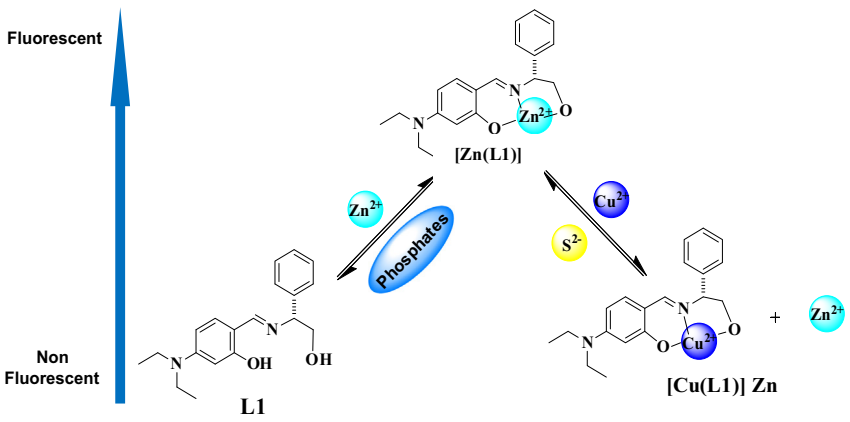

Fig. 1. Proposed sensing process for **L1**.