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A Simple but Effective Ferrocene Derivative as a Redox, Colorimetric, and Fluorescent Receptor for Highly Selective Recognition of Zn^{2+} Ions

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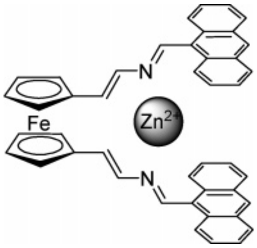
ABSTRACT



A new probe, based on a 1,1′-disubstituted ferrocene, senses Zn^{2+} selectively among heavy and transition-metal (HTM) ions through three different channels: anodic redox shift of the Fe(II)/Fe(III) redox couple, the orange to deep purple color change that is visible to the naked-eye, and a remarkable enhancement of the fluorescence.

Zinc(II) is the second most abundant transition metal following iron and a fundamental element in natural biological systems.[1] Zinc is an essential nutrient required for normal growth and development[2] and for key cellular processes such as DNA repair[3] and apoptosis.[4] Failure to maintain zinc homeostasis has been implicated in a number of severe neurological diseases.[5] It plays a key role in the synthesis of insulin and the pathological state of diabetes.[6] The demand for sensing Zn^{2+} cations, which is spectroscopically silent because of its $3d^{10}4s^0$ electronic configuration, in competitive media such as Ca^{2+} and Mg^{2+} is growing rapidly.[7] More importantly, it is still a challenge to develop chemosensors that can discriminate Zn^{2+} from Cd^{2+}. Because cadmium and zinc are in the same group of the periodic table and have similar properties, they usually cause similar spectral changes after interactions with chemosensors. In this sense, a number of fluorescent,[8] colorimetric,[8k,8r] and redox[9] selective Zn^{2+} chemosensors have been designed and synthesized.

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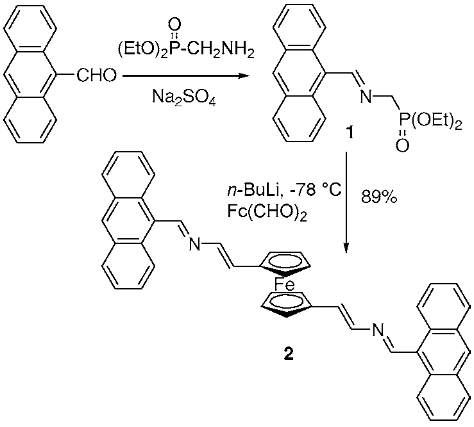
Despite the development of these classical single-signaling approximations, there is a paucity of use of multichannel receptors as potential guest reporters via multiple signaling patterns. Specifically, the development of triple chromogenic, fluorogenic, and electrochemical Zn^{2+} selective chemosensors is, as far as we know, an unexplored subject.

Previous studies on complexation of ferrocene with binding ligands have shown that not only the characteristic band between 400 and 500 nm, ascribed to the lowest energy metal−ligand transition, is perturbed by metal complexation but also a positive shift of the Fe(II)/Fe(III) redox couple is observed.[10] On the other hand, anthracene derivatives have found wide utilization in the recognition of various anions and cations.[11] On the basis of such precedents, suitable designed aza-substituted ferrocene and anthracene derivatives might be good candidates as multisignaling sensors. This can be realized by combining a 2-aza-1,3-butadiene bridge as a putative cation-binding site[12] with the redox activity of the ferrocene and the photoactivity of the anthracene.

As Scheme 1 shows, the synthesis of the receptor **2** starts from compound **1**, which was prepared according to the published procedure.[12a] Metalation of **1** with *n*-BuLi at −78 °C and subsequent reaction with 1,1′-diformylferrocene provided **2**, as a stable solid, in 89% yield.

Scheme 1. Preparation of 2-Aza-1,3-butadiene Derivatives



The metal-recognition properties of receptor **2** were evaluated by electrochemical and optical analysis. The reversibility and relative oxidation potential of the redox process was determined by cyclic voltammetry (CV) and Osteryoung square wave voltammetry (OSWV) in CH_2Cl_2 solutions containing 0.1 M $[(n\text{-Bu})_4N]ClO_4$ as supporting electrolyte. Compound **2** is expected to show electroactivity due both to the Fe(II)/Fe(III) redox couple and the oxidation of the 2-aza-1,3-butadiene bridge. Indeed, receptor **2** displays two oxidation waves in the range 0−1.0 V versus SCE. The first oxidation wave is reversible and occurs at $\Delta E_{1/2} = 0.51$ V versus decamethylferrocene (DMFc), and the second wave, $E_p = 0.99$ V, is clearly irreversible and may be assigned to the oxidation of the bridge.[13] Whereas negligible changes in the OSWV voltammogram of **2** were observed upon addition of Ca^{2+}, Mg^{2+}, Cu^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Hg^{2+}, and Cd^{2+} metal cations a significant modification was observed upon the addition of Zn^{2+} ions: the first oxidation peak was shifted anodically by 140 mV ($\Delta E_{1/2} = 0.65$ V versus DMFc) and the second oxidation peak disappeared. One of the current challenges in cation recognition chemistry involves the preparation of receptors that show high Zn^{2+}/Cd^{2+} selectivity. Therefore, the ability to recognize electrochemically Zn^{2+} in the presence of Cd^{2+} is one attractive feature of this new ferrocene derivative.

The UV/vis spectrum of **2** in CH_2Cl_2 was also substantially affected by the Zn^{2+} recognition. Thus, after the addition of 1 equiv of Zn^{2+} (as trifluoromethanesulfonate salt), the low-energy (LE) absorption band at 417 nm ($\epsilon = 2830$ M^{-1} cm^{-1}), produced by a metal-to-ligand charge transfer (MLCT) process, was red-shifted to 487 nm ($\Delta\delta = 70$ nm) ($\epsilon = 3170$ M^{-1} cm^{-1}). In addition, a new and weak lower-energy band appeared at 628 nm ($\epsilon = 786$ M^{-1} cm^{-1}). These facts are responsible for the change of color from orange to deep-

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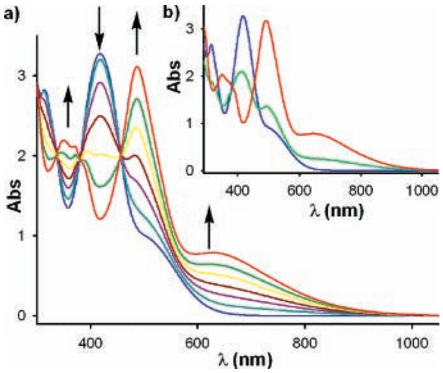

Figure 1. (a) Changes in the absorption spectra of **2** (0.1 mM) in CH_2Cl_2 upon addition of increasing amounts of Zn^{2+}; (b) comparison between absorption spectra of **2** (0.1 mM) in CH_2Cl_2 (blue) with addition of 1 equiv of Zn^{2+} (red) and 1 equiv of Cd^{2+} (green).

purple, which is perceptible to the naked-eye. The well-defined isosbestic points at 337, 380, and 456 nm clearly indicate the presence of an unique complex in equilibrium with the free receptor (Figure 1). A Job plot for the binding between **2** and Zn^{2+} shows a 1:1 stoichiometry. From the resulting titration data[14] the association constant was calculated: $K_a = 1.0 \times 10^5$ M^{-1}. This result has also been confirmed by ESI-MS, where a peak at m/z 709 corresponding to the 1:1 complex is observed. The relative abundance of the isotopic cluster was in good agreement with the simulated spectrum of the [**2**·Zn^{2+}] complex. In addition, a less intense peak at m/z 1007 corresponding to the [**2**·Zn-$(CF_3{-}SO_3)_2$] complex also appeared (see the Supporting Information). On the other hand, upon the addition of 1 equiv of Cu^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Hg^{2+}, or Cd^{2+} metal ions, the absorption maxima did not shift, although the intensity of the absorption band at 417 nm weakens and the shoulder at 510 nm exhibits a slight increase, with isosbestic points appearing at 345, 376, and 470 nm. No perturbation was observed upon addition of Ca^{2+} and Mg^{2+} metal ions (see the Supporting Information).

Assessments of the cation affinities also came from observing the extent to which the fluorescence intensity of receptor **2** was affected in the presence of cations. Receptor **2** exhibits a very weak fluorescence in CH_3CN ($c = 2.5 \times 10^{-5}$ M). The emission spectrum displays typical emission bands at 394, 416, and 439 nm, which are attributed to the anthracene monomeric emission ($\lambda_{exc} = 250$ nm), with a low quantum yield ($\Phi = 0.001$). The addition of 1 equiv of Zn^{2+} to a solution of receptor **2** in CH_3CN ($c = 2.5 \times 10^{-5}$M) increases the integrated fluorescence intensity 16-fold and the quantum yield ($\Phi = 0.015$) resulted in a 15-fold increase. This chelation-enhanced fluorescence (CHEF) effect increase compares favorably to those of the most known zinc-specific chemosensors. The stoichiometry of the complex system was also determined by the changes in the fluorogenic response of **2** in the presence of varying concentrations of Zn^{2+}, and the results obtained indicate the formation of a 1:1 complex (Figure 2) giving an association constant of 1.6×10^4 M^{-1} and a detection limit[15] of 6.9×10^{-6} M. (see the Supporting Information).

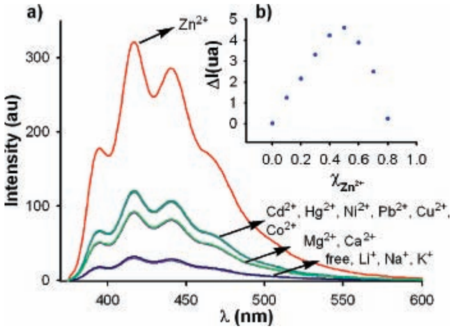

Figure 2. (a) Changes in the fluorescence spectra of **2** (2.5×10^{-5} M) in CH_3CN upon addition of the several cations tested; (b) Job's plot for **2** and Zn^{2+} indicating the formation of 1:1 complexes. The total $[Zn^{2+}] = 2.5 \times 10^{-5}$ M ($\lambda_{exc} = 250$ nm).

The fluorescence titration of receptor **2** with various metal ions was conducted to examine its selectivity. The receptor was exempt from the influence of a high concentration of Li^+, Na^+, and K^+. The responses toward Cu^{2+}, Ni^{2+}, Co^{2+}, Pb^{2+}, Hg^{2+}, or Cd^{2+} metal ions were negligible and mirrored the Zn^{2+} response, with an overall 6-fold increase in fluorescence, while Ca^{2+} and Mg^{2+} metal ions gave even smaller enhancements (Figure 2). These results clearly demonstrate that the receptor has excellent affinity for Zn^{2+} over these ions which is a very important fact because most of the previous Zn^{2+} sensors do not exhibit good selectivity to this metal cation, bringing troubles to certain applications (e.g., in environmental science) where those metal cations are interfering. The values of the association constants corresponding to the other metal ions are included in the Supporting Information.

To further evaluate the practical applicability of **2** as a Zn^{2+} selective fluorescence probe, competition experiments were carried out. Thus, a solution of **2** ($c = 2.5 \times 10^{-5}$ M) was treated with 0.5 equiv of Zn^{2+} in the presence of 0.5 equiv of each of the metal ions tested. From the resulting titrations (see the Supporting Information) small or no obvious interference with the detection of Zn^{2+} could be observed. These results clearly demonstrate the selectivity for Zn^{2+} over the other metal ions.

For the reported constants to be taken with confidence, we have proved the reversibility of the complexation process by carrying out the following experiment: a stepwise addition of a solution of the receptor **2** in CH_2Cl_2 to a solution

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of the complex [**2**·Zn^{2+}] in the same solvent. This addition induced an increase of the absorption band in the optical spectrum of the receptor which is proportional to the amount of free ligand added. This fact can be taken as a clear evidence for reversibility. Moreover, extraction experiments also confirmed the high degree of reversibility of the complexation/decomplexation process (see the Supporting Information).

To have more insight into the cation binding properties of the receptor **2**, ^1H NMR experiments were carried out in the presence of Zn^{2+} metal cations in CD_2Cl_2 at room temperature. When 1 equiv of $Zn(CF_3-SO_3)_2$ was added to a solution of **2**, its ^1H NMR spectrum displayed the following dramatic changes (Figure 3): (i) the iminic protons (δ = 9.23 ppm) move to downfield ($\Delta\delta = +2.26$ ppm); (ii) the -N-*CH*=CH- move from $\delta = 6.89$ (doublet) to the multiplet arising at 7.54−7.70 ppm, which also includes the H_b and H_c protons of the anthracene ring; (iii) whereas the signals corresponding to the 9-anthryl unit are appreciably downfield shifted ($\Delta\delta = 0.6-0.3$ ppm, the highest value being due to the H_e protons), the signal corresponding to the α-protons ($\Delta\delta = 0.2$ ppm) and β-protons ($\Delta\delta = 0.1$ ppm) of the cyclopentadienyl rings are slightly shifted. From the magnitude of these observed shifts, it can be surmised that complexation exerts a more powerful effect both on the aza-unsaturated bridge and anthracene ring than in the ferrocene moiety. This statement is further supported by the calculated structure for the **2**·$Zn(OTf)_2$ complex (Figure 4), at the DFT level (see the Supporting Information), that shows the loss of coplanarity between the azadiene and anthracene moieties upon complexation, as well as a large separation between anthracene end-groups (minimum distance 6.08 Å) that prevents excimer formation in the fluorescence spectrum.

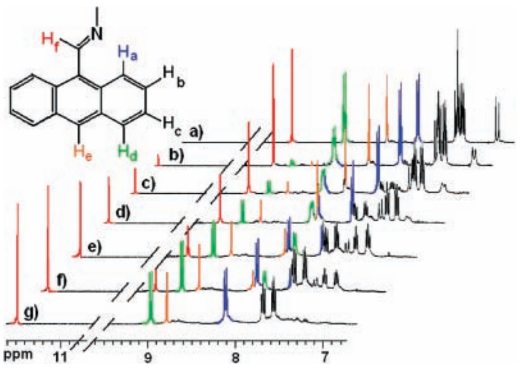

Figure 3. Evolution of the ^1H NMR spectra of **2** in CD_2Cl_2 upon addition of (a) 0, (b) 0.16, (c) 0.33, (d) 0.5, (e) 0.66, (f) 0.83, and (g) 1 equiv of Zn^{2+}.

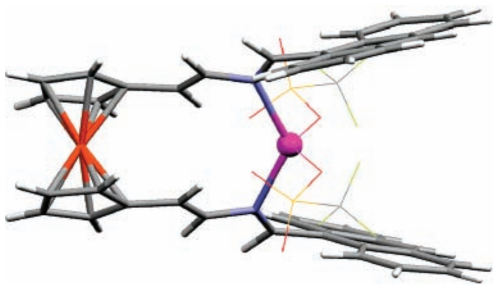

Figure 4. Calculated (B3LYP/6-31G*/Lanl2DZ-ecp) structure of **2**·$Zn(OTf)_2$ (triflate ligands displayed in wireframe for clarity).

In conclusion, we have succeeded in preparing a simple and easy-to-make new class Zn^{2+} cation chemosensor that displays not only the capability for the electrochemical and fluorescent detection, but which is also amenable to the facile colorimetric sensing of Zn^{2+} metal cation, thus allowing the potential for "naked-eye" highly selective detection over some other cations, including the strong competitor Cd^{2+}. Thus the receptor **2** represents the first example of a Zn^{2+} chemosensor molecule, which combines the simplicity of the electrochemical detection and the sensitivity of fluorescence with the convenience and aesthetic appeal of a colorimetric assay.

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Supporting Information Available: Synthesis and characterization data of **2**; electrochemical data; UV−vis and fluorescence spectra upon titration with metal ions; titration profiles; semilogarithmic plot for determining the detection limits; experiments showing the selectivity in the detection of Zn^{2+}; EM-ES spectrum of [**2**·Zn^{2+}]; figure with the calculated structure for the **2**·$Zn(OTf)_2$ 1:1 complex and Cartesian coordinates. This material is available free of charge via the Internet at http://pubs.acs.org.

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