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Naphthalimide-based fluorescent Zn^{2+} chemosensors showing PET effect according to their linker length in water

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ABSTRACT

We have developed naphthalimide-based fluorescent chemosensors that exhibit fluorescence enhancement upon binding Zn^{2+} ion in 10 mM HEPES buffer (pH 7.4) at 25 °C. The fluorescence enhancement was induced by a PET inhibition process in which electron transfer from the nitrogen lone pair electrons of the Dpa unit to naphthalimide was blocked upon the binding of the sensor to Zn^{2+}. The longer the linker length ($n = 1$–3) of the sensor, the less the PET efficiency becomes. Among the sensors (**1**, **2**, and **3**) examined, **1** shows the highest selectivity and sensitivity for Zn^{2+} over other transition metal ions and alkali metal ions in water.

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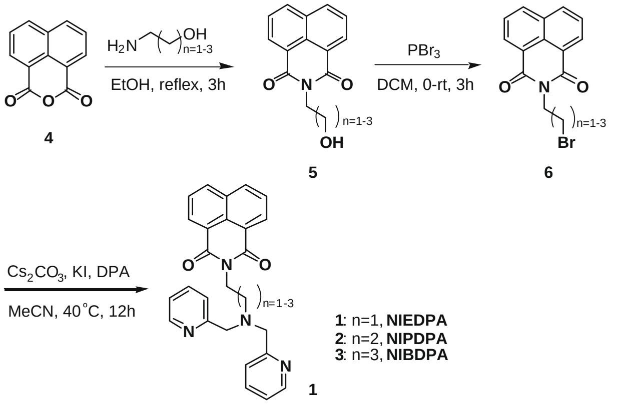
1,8-Naphthalimide has high photostability, a large Stokes shift, and strong fluorescence, and therefore has a range of applications in the fields of polymers,[1] optical storage,[2] photophysical dyads,[3] nucleic acids intercalators,[4] and DNA photocleavage.[5] Due to its favorable characteristics and numerous applications, naphthalimide-based fluorescent chemosensors have been developed by several research groups.[6–9] Most of these chemosensors, which were developed for the detection of transition metal ions, were constructed by introducing the binding site at 4-[*6a,c,d] or 4,5-positions[6b] of naphthalimide. In addition, most of them operate in an organic[6e,8] or organic/water environment.[6a,b,7,9]

A few fluorescent chemosensors based on naphthalimide have been reported concerning pH sensing[7] or the trend of PET efficiency according to the linker length between the fluorophore and the metal ion binding moiety.[8] However, there has been no report on naphthalimide-based fluorescent Zn^{2+} selective sensors that are able to control the PET effect in 100% aqueous solution according to the distance between the donor and acceptor.[9]

Zn^{2+} plays diverse roles in medicinal, chemical, and biological events. In the human body, protein scaffolds contain Zn^{2+} ions (e.g., carbonic anhydrase, zinc finger protein),[10] which play crucial roles in neurotransmission,[11] metalloenzymes, and gene transcription.[10b] Also, Zn^{2+} induces apoptosis,[12] and the formation of β-amyloid[13] which is important in the development of Alzheimer's disease. Due to the importance of Zn^{2+} ion in numerous biological systems, there is a great emphasis placed on the development of fluorogenic chemosensors for Zn^{2+} in water.[14]

Herein, we report fluorescent chemosensors (**1**–**3**) for Zn^{2+} which show different PET effects according to the length of the linker existing between the imide N and dipicolylamine (Dpa). The synthesis of **1**–**3** is described in Scheme 1. Compounds **5** and **6** ($n = 1$–3) were synthesized according to the reported methods.[15] Finally, **1**, **2**, and **3** were prepared by the S_N2 reaction of **6** with dipicolylamine in the presence of Cs_2CO_3 and KI in MeCN at 40 °C.[16]

First, the fluorescence emission changes ($\lambda_{ex} = 335$ nm, $\lambda_{em} = 394$ nm) of **NIEDPA** (**1**, 5 μM) according to the Zn^{2+} (perchlorate salt) concentration were measured in 10 mM HEPES buffer (pH 7.4) at 25 °C (Fig. 1). Upon the addition of Zn^{2+} ions, the fluorescence emission intensity of **1** gradually increased. When 1 equiv of Zn^{2+} ions was added to **1**, the emission intensity ratio (I/I_0) and FE value[17] of **1** showed 5.4- and 5.0-fold enhancements, respectively (SI). The association constant (K_a) between **1** and Zn^{2+} was estimated to be $1.22 \times 10^6\ M^{-1}$ by fluorescence titration curve fitting (SigmaPlot Program 2002 by Windows Version 8.0).[18] The job



Scheme 1. Synthesis of chemosensors **1–3**.

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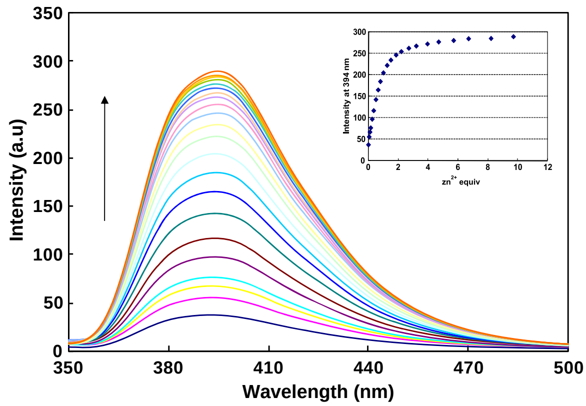


Figure 1. The fluorescence emission changes of **1** (5 μM) upon the addition of Zn^{2+} (perchlorate salt) in 10 mM HEPES buffer (pH 7.4) at 25 °C: $[Zn^{2+}] = 0$, 0.25, 0.50, 0.74, 1.22, 1.69, 2.38, 3.05, 3.70, 4.55, 5.56, 6.52, 7.81, 9.01, 10.6, 12.1, 14.2, 16.0, 18.2, 20.1, 22.5, 24.6 μM. (Inset: Changes in the fluorescence intensity of 1 at 394 nm with the addition of Zn^{2+}).

plot showed 1:1 stoichiometry between **1** and Zn^{2+} in 10 mM HEPES buffer at 25 °C (Fig. S3).

However, upon the addition of 1 equiv of Cd^{2+} into **1**, the fluorescence emission ($\lambda_{em} = 394$ nm) intensity ratio (I/I_0) and FE value of **1** showed 2.7- and 2.6-fold increases, respectively (Tables S1 and S2). The association constant (K_a) of **1** for Cd^{2+} was measured to be $7.21 \times 10^4\ M^{-1}$.[17] Other transition metal ions such as Fe^{2+}, Ag^+, Mn^{2+}, Hg^{2+}, Cu^{2+}, Co^{2+}, and Ni^{2+}, barely showed any emission increase after the addition of 1 equiv of each metal ion (Fig. 2).

Upon the addition of 1 equiv of each transition metal ion, the fluorescence emission changes of **NIPDPA** (**2**, 5 μM) were examined in 10 mM HEPES buffer solution (Fig. S1). After the addition of Zn^{2+} and Cd^{2+}, the fluorescence emission intensity of **2** increased less compared to that of **1**. When 1 equiv of Zn^{2+} ions was added to the solution of **2**, the fluorescence emission intensity ratio (I/I_0) and FE value of **2** showed 3.9- and 3.8-fold increases, respectively (Tables S1 and S2). Upon the addition of 1 equiv of Cd^{2+}, the fluorescence emission intensity ratio (I/I_0) and FE value of **2** exhibited 2.5- and 2.6-fold enhancements, respectively (Tables S1 and S2). As expected, the addition of 1 equiv of other transition metal ions rendered the fluorescence emission changes of **2** barely observable (Fig. S1).

A sensing mechanism for the fluorescence OFF–ON of chemosensors is shown in Scheme 2. When Zn^{2+} ions were absent in the host solution, the fluorescence emission of chemosensors was quenched by a PET (Photo-induced Electron Transfer) process, which takes place through electron transfer from the nitrogen lone pair (donor) of the Dpa moiety to the naphthalimide (acceptor).

By the strong coordination of Zn^{2+} to the Dpa unit,[6c,9,14,19] the PET effect is blocked, and as a result, fluorescence revives (fluorescence-ON). The critical factor of the PET efficiency is the distance between the donor and acceptor. Therefore, the longer the linker length ($n = 1$–3), the less effective the PET becomes. As a result, the fluorescence emission efficiency due to PET is largest in **1** among the chemosensors **1**–**3** (Fig. 3).

The selectivity for Zn^{2+} versus alkali metal ions was also investigated. After the addition of 0–40 equiv of each Na^+, K^+, Mg^{2+}, and Ca^{2+} (perchlorate salts), the fluorescence emission intensity of **1**

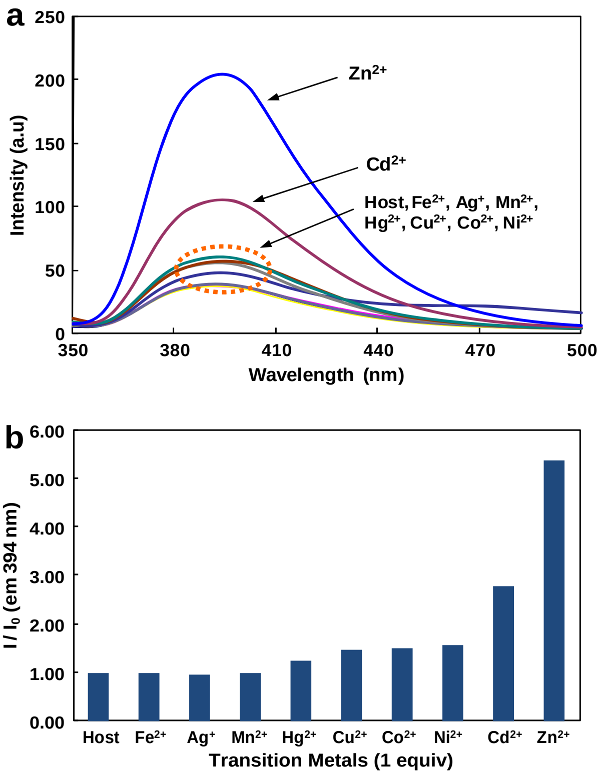
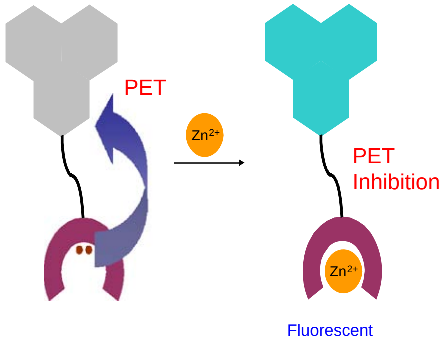


Figure 2. (a) The fluorescence emission spectra of **1** (5 μM) after the addition of 1 equiv of each transition metal ion (perchlorate salt) in 10 mM HEPES buffer (pH 7.4) at 25 °C. (b) The comparison of the fluorescence emission intensity (I) at 394 nm of **1** after the addition of 1 equiv of each transition metal ion with the emission intensity (I_0) at 394 nm of **1** (5 μM) before the addition of each metal ion.



Scheme 2. Sensing mechanism.

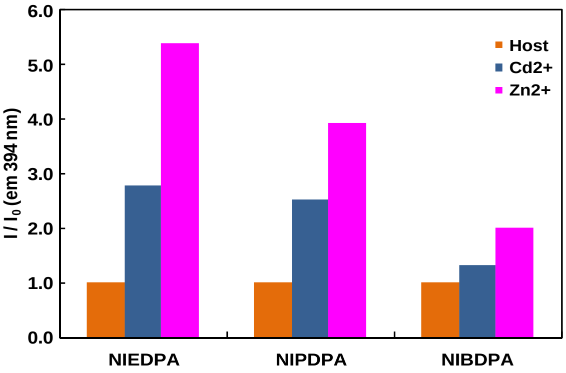


Figure 3. The comparison of the emission intensity (I) at 394 nm of **1** after the addition of 1 equiv of each Zn^{2+} and Cd^{2+} ion with the emission intensity (I_0) at 394 nm of **1**–**3** (5 μM) before the addition of each metal ion in 10 mM HEPES buffer (pH 7.4) at 25 °C.

did not change. However, the fluorescence emission intensities of **1** displayed about twofold increase after the addition of 2 equiv of Zn^{2+} (perchlorate salt) and 40 equiv of each cation (Fig. S4). Therefore, **1** can selectively detect Zn^{2+} ion in the presence of excess alkali metal ions under physiological conditions. The selectivity for Zn^{2+} is due to the high affinity of Zn^{2+} for three nitrogen atoms of the Dpa unit.

In conclusion, we have developed naphthalimide-based fluorescent chemosensors **1–3** which exhibit fluorescence enhancement upon binding with Zn^{2+} ions in 10 mM HEPES buffer (pH 7.4) at 25 °C. Chemosensors **1–3** exhibited a different fluorescence emission response according to the length of the spacer between the donor (nitrogen lone pair electrons of the Dpa moiety) and acceptor (naphthalimide); the longer the linker length of chemosensors is, the less efficient the PET process becomes. As a result, **1** ($n = 1$) shows the highest PET efficiency, high selectivity, and sensitivity for Zn^{2+} over other transition metal ions and alkali metal ions in water.

Acknowledgments

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Supplementary data

Supplementary data (synthesis, ^1H NMR, ^{13}C NMR and HRMS data for chemosensors **1**–**3**, fluorescence emission spectra of **2**, **3** for various transition metal ions, I/I_0 ratios and FE values of **1**–**3**, competition experiments for excess alkali metal ions, Job's plot) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.179.

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16. *NIEDPA* **(1)** To a solution of compound **6** (300 mg, 0.99 mmol) in MeCN were added successively Cs_2CO_3 (355 mg, 1.09 mmol), KI (181 mg, 1.09 mmol), and di-2-picolylamine (217 mg, 1.09 mmol). The reaction mixture was stirred at 40 °C overnight, and then all the volatile components were evaporated. The residue was partitioned between CH_2Cl_2 and brine (×2). The combined organic phase was washed with water, and then dried in anhydrous Na_2SO_4. Flash chromatographic purification (CH_2Cl_2 to CH_2Cl_2/MeOH = 20:1) yielded **1** (220 mg, 53% yield). ^1H NMR (300 MHz, acetone-d_6): δ 2.89 (t, J = 6 Hz, 2H), 3.84 (s, 4H), 4.37 (t, J = 6 Hz, 2H), 7.02 (t, J = 5.4 Hz, 2H), 7.27 (t, J = 7.3 Hz, 2H), 7.35 (d, J = 7.7 Hz, 2H), 7.87 (t, J = 7.7 Hz, 2H), 8.33 (d, J = 4.3 Hz, 2H), 8.42–8.49 (m, 4H). ^{13}C NMR (75 MHz, acetone-d_6): δ 37.48, 51.53, 60.07, 121.61, 122.51, 122.90, 127.04, 128.01, 130.66, 131.84, 133.95, 135.70, 148.61, 159.86, 163.54. HRMS (FAB): *m/e* calcd for $C_{26}H_{22}N_4O_2$ $[M+H]^+$: 423.1821, found: 423.1821. **NIPDPA (2) 2** was similarly prepared using the same procedure as used in the synthesis of **1** (56% yield). ^1H NMR (300 MHz, acetone-d_6): δ 1.98 (t, J = 7.0 Hz, 2H), 2.67 (t, J = 6.9 Hz, 2H), 3.83 (s, 4H), 4.18 (t, J = 7.6 Hz, 2H), 7.13 (t, J = 11.7 Hz, 2H), 7.62–7.70 (m, 4H), 7.80 (t, J = 7.8 Hz, 2H), 8.34 (d, J = 8.2 Hz, 2H), 8.41 (d, J = 4.7 Hz, 2H), 8.46 (d, J = 7.3 Hz, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 25.50, 38.32, 51.46, 59.87, 121.76, 122.72, 122.84, 126.95, 127.87, 130.56, 131.73, 133.89, 136.07, 148.89, 159.97, 163.51. HRMS (FAB): *m/e* calcd for $C_{26}H_{22}N_4O_2$ $[M+H]^+$: 423.1821, found: 423.1821. **NIBDPA (3) 3** was similarly prepared using the same procedure as used in the synthesis of **1** (53% yield). ^1H NMR (300 MHz, acetone-d_6): δ 1.67–1.79 (m, 4H), 2.06 (t, J = 4.3 Hz, 2H), 3.83 (s, 4H), 4.12 (t, J = 7.1 Hz, 2H), 7.17 (t, J = 5.7 Hz, 2H), 7.62–7.73 (m, 4H), 7.86 (t, J = 7.8 Hz, 2H), 8.39–8.45 (m, 4H), 8.53 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, acetone-d_6): δ 24.76, 25.71, 39.77, 53.92, 60.24, 121.79, 122.63, 122.69, 126.93, 127.79, 130.56, 131.65, 133.87, 136.19, 148.70, 160.11, 163.48. HRMS (FAB): *m/e* calcd for $C_{27}H_{24}N_4O_2$ $[M+H]^+$: 437.1978, found: 437.1972.
17. Quantitatively, FE value is the factor of the final integrated fluorescence emission intensity over the initial integrated fluorescence emission intensity upon the addition of 1 equiv of transition metal ions.
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