



Ratiometric fluorescent and colorimetric sensors for Cu²⁺ based on 4,5-disubstituted-1,8-naphthalimide and sensing cyanide via Cu²⁺ displacement approach

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ABSTRACT

Two 4,5-disubstituted-1,8-naphthalimide derivatives **1** and **2** were synthesized as ratiometric fluorescent and colorimetric sensors for Cu²⁺, respectively. In 100% aqueous solutions of **1**, the presence of Cu²⁺ induces a strong and increasing fluorescent emission centered at 478 nm at the expense of the fluorescent emission of **1** centered at 534 nm. Compound **2** senses Cu²⁺ by means of a colorimetric (primrose yellow to pink) method with a thorough quench in emission attributed to the deprotonation of the secondary amine conjugated to the naphthalimide fluorophore. **1**-Cu²⁺ and **2**-Cu²⁺ sense cyanide in ratiometric way via colorimetric and fluorescent changes.

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1. Introduction

The development of fluorescent^{1–4} and colorimetric⁵ sensors for Cu²⁺ has received considerable attention as this metal ion is an essential trace element in biological systems and also a significant environmental pollutant.⁶ Fluorescent and colorimetric sensors combine the sensitivity of fluorescence with the convenience and esthetic appeal of a colorimetric assay.⁷ In particular, ratiometric fluorescent sensors are preferred because the ratio between the two emission intensities can be used to evaluate the analyte concentration and provide a built-in correction for environmental effects, such as photobleaching, sensor molecule concentration, the environment around the sensor molecule (pH, polarity, temperature, and so forth), and stability under illumination.⁸ Nevertheless, only a few ratiometric fluorescent sensors for Cu²⁺ have been reported due to the fluorescence quenching nature of paramagnetic Cu²⁺.^{7,9–12} However, these reported sensors were mostly only utilized in pure organic solvents or organic-aqueous solutions, and often showed poor selectivity with other metal ions such as Co²⁺, Ni²⁺, Ag⁺, Hg²⁺ and Pb²⁺. To date, there have been no reports of

ratiometric fluorescent and colorimetric sensors that are completely selective for Cu²⁺ that can be used in 100% aqueous solution. Here, we report the first examples.

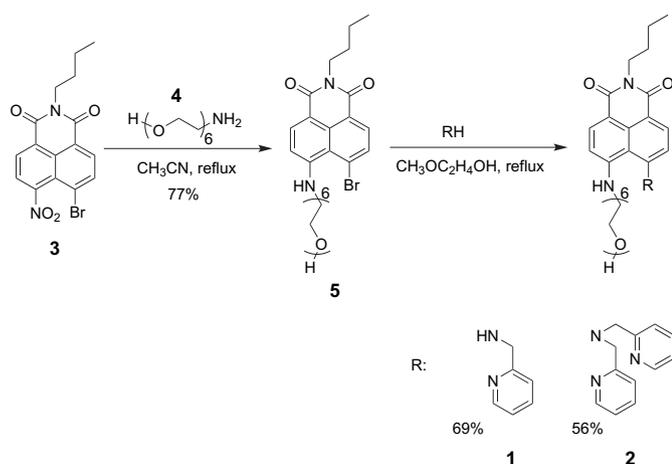
N-substituted-4-bromo-5-nitro-1,8-naphthalimide has been developed as a useful scaffold to construct various fluorescent sensors for Cu²⁺,^{4g,5i,9a} Zn²⁺,¹³ Cd²⁺,¹⁴ Pd²⁺,¹⁵ and F⁻.^{4f} Ion ligands can be effectively introduced to 4 and 5 positions of 1,8-naphthalimide through substitution reaction. More notably, 5-nitro group is much more active than 4-bromo group during substitution, which makes 5-nitro group be substituted at lower temperature (~80 °C) prior to 4-bromo group at relatively high temperature (>110 °C). With this feature, asymmetric 4,5-disubstituted-1,8-naphthalimide derivatives can be developed. For example, 2-(aminomethyl)pyridine and *N,N*-di-(2-picolyl)ethylenediamine (DPEN) were conjugated to 1,8-naphthalimide subsequently to construct a Cd²⁺ sensor.¹⁴ A recent case was to introduce thiophenemethylamine and phenylethyne as receptor for Pd²⁺.¹⁵

There are two basic requirements to construct a ratiometric fluorescent sensor for Cu²⁺. First, a signaling mechanism is required, which can turn the Cu²⁺ recognition event into a ratiometric fluorescence signal. The internal charge transfer (ICT) mechanism has been widely exploited for cation sensing.¹⁶ The interaction between receptor and cation would blue shift the fluorescence

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spectra. Second, there is the requirement to protect fluorescence from being quenched by Cu^{2+} . In our previous study,^{9a} two 2-(aminomethyl)pyridine ligands had been introduced to 4 and 5 positions of 1,8-naphthalimide and formed a tetradentate receptor, which displayed a special cavity and had a strong binding with Cu^{2+} . The Cu^{2+} -fluorophore interaction might be then suppressed in a similar way with Bharadwaj's case,¹⁷ and as a result ratiometric fluorescence responses based on ICT mechanism were obtained. Soon afterward, it was observed that the amines conjugated to 1,8-naphthalimide can be deprotonated in the presence of Cu^{2+} , which resulted in the color change from primrose yellow to pink.^{5i,13} This deprotonation mechanism was used to design colorimetric sensors for Cu^{2+} and Zn^{2+} .^{5i,13} In the present report, we introduced hexa(ethylene glycol) as one ligand to increase the water solubility and synthesized compounds **1** and **2** (Scheme 1), which act as ratiometric fluorescent and colorimetric sensors, respectively, with complete selectivity for Cu^{2+} .



Scheme 1. Synthesis of sensor **1** and **2**.

On the other hand, due to the extreme toxicity of cyanide ion in physiological systems, as well as continuing concern in the environment from the widespread industrial uses of cyanide, considerable effort has been devoted for the determination of cyanide.¹⁸ Among the various sensing mechanisms, Cu^{2+} displacement method recently became one of the important approaches, which utilized high affinity between Cu^{2+} and cyanide.¹⁹ We successfully utilized **1**- Cu^{2+} and **2**- Cu^{2+} for the ratiometric detection of cyanide via fluorescent and colorimetric changes in 100% aqueous solution.

2. Results and discussion

2.1. Synthesis

The syntheses of **1** and **2** were shown in Scheme 1. The intermediate compound **3** was synthesized from acenaphthene following a literature procedure.¹³ Compound **5** was prepared by the condensation of **3** with hexa(ethylene glycol) and was subsequently converted into compound **1** and **2**, through reaction with 2-aminomethylpyridine and di-(2-picolyl)amine (DPA), respectively.

2.2. The effect of pH

The influence of pH on the fluorescence of **1** and **2** was first determined by fluorescence titration in water (Fig. 1). The fluorescence of **1** at 534 nm remains unaffected between pH 13 and 4.89 and then gradually decreases from pH 4.89 to 2.25; below pH 2.25,

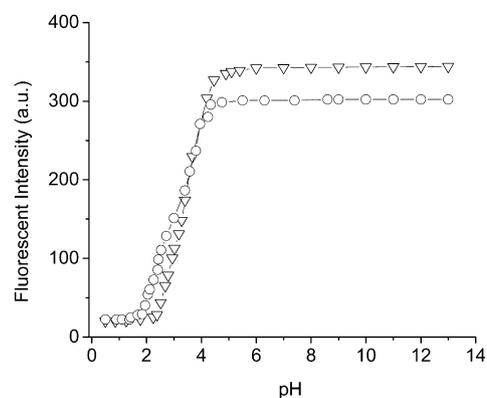


Figure 1. Influence of pH on the fluorescence of **1** and **2**. Excitation wavelength was 458 nm. [**1**]=10 μM , [**2**]=10 μM . The pH was modified by adding 75% HClO_4 or 10% $\text{N}^+(\text{CH}_3)_4\text{OH}^-$. (∇ , **1**), (\circ , **2**).

no change in fluorescence is obtained, leading to a sigmoid curve. Its pK_a value is 3.6. Sensor **2** displayed similar fluorescence responses toward pH. The fluorescence of **2** at 550 nm remains unaffected between pH 13 and 4.24 and then gradually decreases from pH 4.24 to 1.84; below pH 1.84, no change in fluorescence is obtained, leading to a sigmoid curve. Its pK_a value is 3.04. The fluorescence quenching was most likely caused by the photo-induced electron transfer (PET) from the fluorophore to protonated pyridine.²⁰ de Silva had found the similar phenomenon in the design of an 'off-on-off' fluorescent PET sensor.²¹ Therefore, further fluorescence studies were carried out at pH 7.4 maintained with HEPES buffer (50 mM).

2.3. Optical behavior of **1** and **2** with Cu^{2+}

The emission spectra of **1** and **2**, and their fluorescence titration with Cu^{2+} were recorded in HEPES buffer solutions (0.5 M, pH 7.4) (Fig. 2). As shown in Figure 2a, the emission spectrum of free **1** displays a broad band with a maximum at 534 nm. When Cu^{2+} was added to the solution of **1**, a decrease in the 534 nm emission and a blue-shifted emission band centered at 478 nm, which was attributed to the formation of a **1**/ Cu^{2+} complex and increased in intensity, were observed. The inset in Figure 2a exhibits the dependence of the intensity ratios of emission at 478 nm to that at 534 nm (I_{478}/I_{534}) on Cu^{2+} . The Job's plot indicates the formation of a **1**/ Cu^{2+} adduct of 1:1 stoichiometry (Fig. S1). The association constant (K) of **1** with Cu^{2+} is $2.7 \times 10^{-5} \text{ M}^{-1}$ (error <10%).²² Furthermore, Cu^{2+} could be detected by **1** at least down to $1.0 \times 10^{-8} \text{ M}$. The Φ_F values of free **1** and **1**/ Cu^{2+} adduct (1:1) are 0.1 and 0.16, respectively.²³ Figure 2b displayed the fluorescence responses of **2** to Cu^{2+} . With the addition of Cu^{2+} , the fluorescence emission of **2** ($\Phi_F=0.21$) centered at 550 nm decreased drastically due to the quenching nature of Cu^{2+} . The dissociation constant (K) of **2** with Cu^{2+} is $2.2 \times 10^{-6} \text{ M}^{-1}$. Cu^{2+} could be detected by **2** down to $1.0 \times 10^{-9} \text{ M}$.

It is noticeable that the resonance of the conjugated NH proton of **2** shows a large downfield shift to 10.56 ppm compared to that of **1** at 6.36 and 7.32 ppm. Then the NH proton of **2** was much more active because of the strengthened intramolecular hydrogen bonding, and could be easily deprotonated with the interaction of Cu^{2+} . The changes in absorption spectra of **2** during the Cu^{2+} titration are shown in Figure 3. On addition of Cu^{2+} to the solution of **2**, the absorption band at 459 nm decreased, and the other two bands at 306 and 504 nm occurred and increased prominently to their limiting values with isosbestic points at 390 and 492 nm, respectively. However, in the absorption spectra of **1**

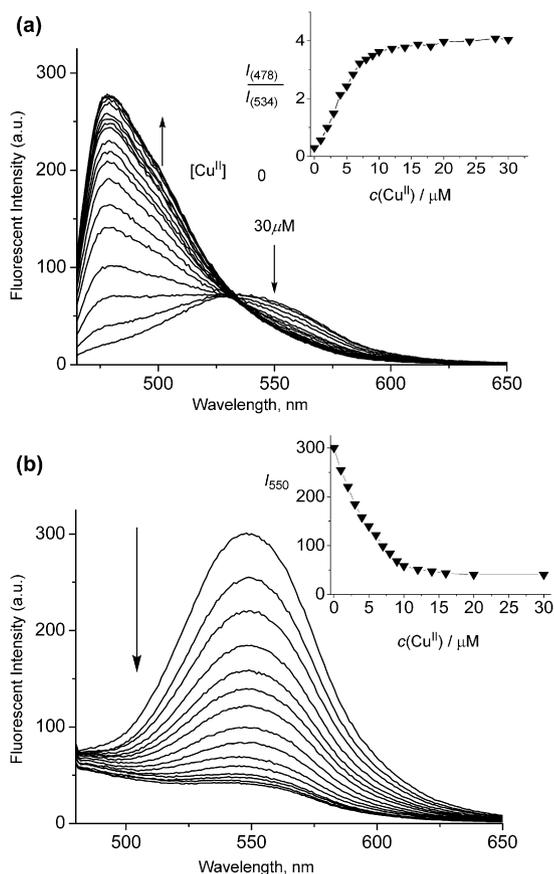


Figure 2. Fluorescent emission spectra of (a) 10 μM **1** and (b) 10 μM **2** in the presence of different concentrations of Cu²⁺ in HEPES buffer solutions (0.5 M, pH 7.4). Excitation wavelength was 458 nm. Inset: (a) Ratiometric calibration curve I_{478}/I_{534} as a function of Cu²⁺ concentration; (b) I_{550} as a function of Cu²⁺ concentration.

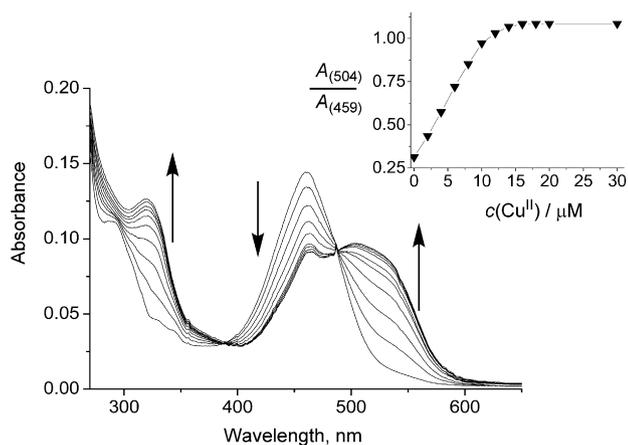


Figure 3. UV-vis absorption spectra of 10 μM **2** in the presence of different concentrations of Cu²⁺ in HEPES buffer solutions (0.5 M, pH 7.4). Inset: Ratiometric calibration curve A_{504}/A_{459} as a function of Cu²⁺ concentration.

(Fig. S2, Supplementary data), an increasing band around 430 nm was found with the addition of Cu²⁺. This would indicate that the blue shift of fluorescence spectra was caused by a change of the charge-transfer character of the emissive species. When a fluorophore contains an electron-donating group (often an amino group) conjugated to an electron-withdrawing group, it undergoes ICT from the donor to the acceptor upon excitation by

light. If the electron-rich terminal of the fluorophore (e.g., an amino group) interacts with a cation (Cu²⁺ in our case), a partial positive charge is photogenerated adjacent to the cation, and that affects the fluorescence and absorption spectral wavelength of the fluorophore with an ICT excited state. Therefore, a cation-induced blue shift is expected in the fluorescence and absorption spectra.

The solutions of Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Mn²⁺, Al³⁺, Cu²⁺, Co²⁺, Ni²⁺, Zn²⁺, Cd²⁺, Fe²⁺, Fe³⁺, Cr³⁺, Ag⁺, Hg²⁺, and Pb²⁺ were then used to evaluate the metal ion selectivity of **1** and **2**. The fluorescence emission changes of **1** and **2** upon the addition of various metal ions (3 equiv) are illustrated in Figure 4a and b, respectively. Only the addition of Cu²⁺ can induce selective changes both in fluorescence emissions of **1** and **2**. Correspondingly, as shown in Figure 5, the addition of Cu²⁺ induced a selective red-shift in absorption. The addition of other metal ions produced a negligible change in the absorption spectra of **2**. The competition experiments were conducted in the presence of 3 equiv of Li⁺, Na⁺, K⁺, Mg²⁺, or Ca²⁺, Co²⁺, Ni²⁺, Zn²⁺, Cd²⁺, Fe²⁺, Fe³⁺, Cr³⁺, Ag⁺, Hg²⁺ or Pb²⁺, with the subsequent addition of 1 equiv of Cu²⁺. As shown in Figure 6a and b, the emission profiles of the **1**/Cu²⁺ and **2**/Cu²⁺ complexes are unperturbed in the presence of these metal ions. These results suggest that **1** is a highly selective and ratiometric fluorescent sensor for Cu²⁺, while **2** is a colorimetric sensor for Cu²⁺ with excellent selectivity. Additionally, to explore the effects of anionic counterions on the sensing behavior of **1** and **2** to metal ions, fluorescence responses of **1** and **2** to perchlorate, chloride, and nitrate salts with differing cations were examined at pH 7.4 maintained with HEPES buffer (50 mM). The results were similar to that shown in Figure 4. There were no obvious changes in the fluorescence responses of **1** and **2** to Cu(ClO₄)₂, CuCl₂, and Cu(NO₃)₂.

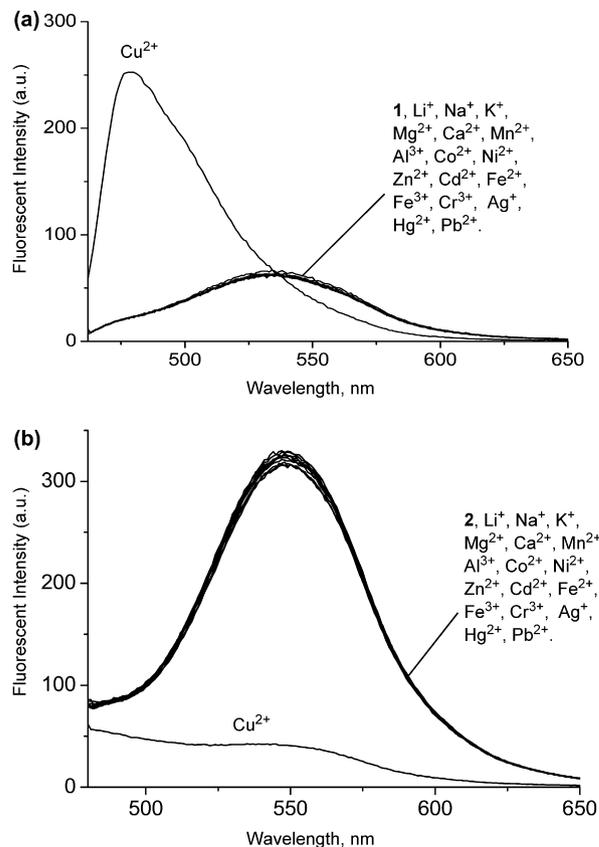


Figure 4. Fluorescence spectra of (a) 10 μM **1** and (b) 10 μM **2** in the presence of different metal ions (30 μM) in HEPES buffer solutions (0.5 M, pH 7.4).

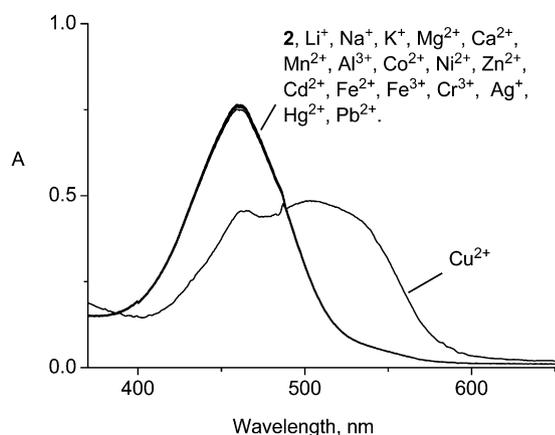


Figure 5. UV-vis absorption spectra of 10 μM **2** in the presence of different metal ions (30 μM) in HEPES buffer solutions (0.5 M, pH 7.4).

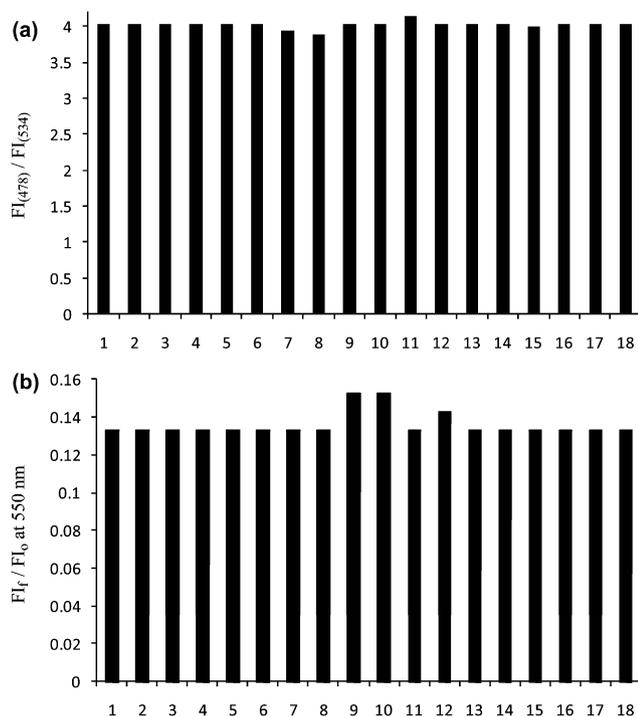


Figure 6. (a) Fluorescence responses of 10 μM **1**- Cu^{2+} complex (1:1) to various metal ions (30 μM) in HEPES buffer solutions (0.5 M, pH 7.4). (b) Fluorescence responses of 10 μM **2**- Cu^{2+} complex (1:1) to various metal ions (30 μM) in HEPES buffer solutions (0.5 M, pH 7.4). (1) Cu^{2+} ; (2) Li^{+} ; (3) Na^{+} ; (4) K^{+} ; (5) Mg^{2+} ; (6) Ca^{2+} ; (7) Mn^{2+} ; (8) Al^{3+} ; (9) Co^{2+} ; (10) Ni^{2+} ; (11) Zn^{2+} ; (12) Cd^{2+} ; (13) Fe^{2+} ; (14) Fe^{3+} ; (15) Cr^{3+} ; (16) Ag^{+} ; (17) Hg^{2+} ; (18) Pb^{2+} . Binding competition measurements were acquired after equilibration for 5 min.

2.4. Optical behavior of **1**- Cu^{2+} and **2**- Cu^{2+} with cyanide ion

Finally, **1**- Cu^{2+} and **2**- Cu^{2+} were used to sense cyanide ion. Optical sensing for cyanide ion has also been actively investigated, owing to its poisoning in biology and the environment.¹⁸ Among the various approaches to sense cyanide, sensors utilizing copper–cyanide affinity draw our special attention.¹⁹ Cyanide is known to react with copper ions to form very stable $\text{Cu}(\text{CN})_2$ species.

As shown in Figure S3–S5, with the addition of various anions, including F^{-} , Cl^{-} , Br^{-} , I^{-} , NO_3^{-} , SO_4^{2-} , $\text{H}_2\text{PO}_4^{-}$, and CN^{-} , to the solutions of **1**- Cu^{2+} (1:1) and **2**- Cu^{2+} (1:1), only CN^{-} (100 equiv) can induce the revival of fluorescence of **1** and **2** (with the detection

limits of 2.48 ppm and 0.52 ppm, respectively). In other words, the addition of CN^{-} to the solution of **1**- Cu^{2+} resulted in the enhancement of fluorescent emission centered at 534 nm at the expense of the fluorescent emission centered at 478 nm (Fig. 7). With the addition of CN^{-} , the fluorescence of **2**- Cu^{2+} increased and the color changed from pink to primrose yellow (Fig. 8). These visible emissions and color changes can be readily distinguished by naked eye (Fig. 9). The association constants (K) of **1**- Cu^{2+} and **2**- Cu^{2+} with CN^{-} are $6.3 \times 10^{-3} \text{ M}^{-1}$ and $1.4 \times 10^{-5} \text{ M}^{-1}$, respectively. The proposed mechanism of sensing cyanide ion by **2**- Cu^{2+} was illustrated in Scheme 2.

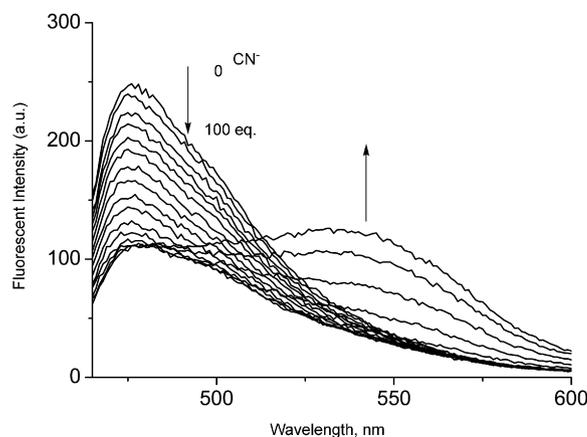


Figure 7. Fluorescence spectra of 10 μM **1**- Cu^{2+} in the presence of cyanide ion in HEPES buffer solutions (0.5 M, pH 7.4).

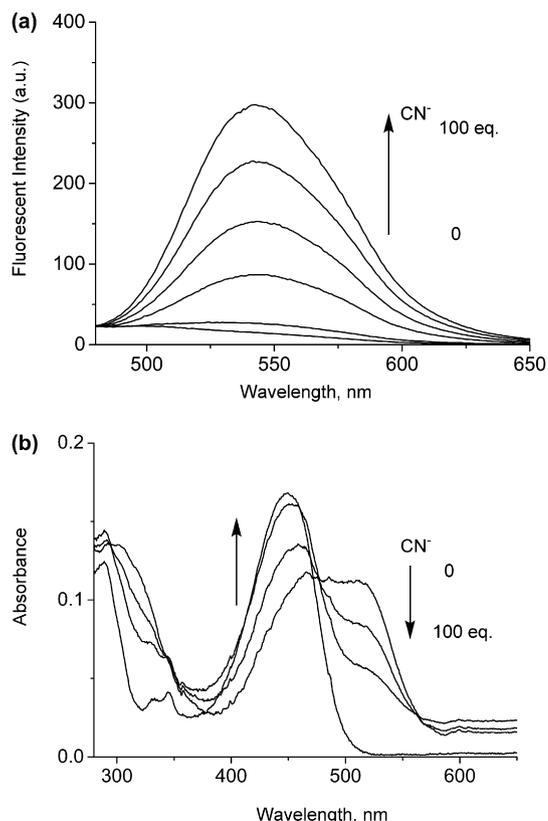


Figure 8. (a) Fluorescence spectra of 10 μM **2**- Cu^{2+} in the presence of cyanide ion in HEPES buffer solutions (0.5 M, pH 7.4); (b) UV-vis absorption spectra of 10 μM **2**- Cu^{2+} in the presence of cyanide ion in HEPES buffer solutions (0.5 M, pH 7.4).

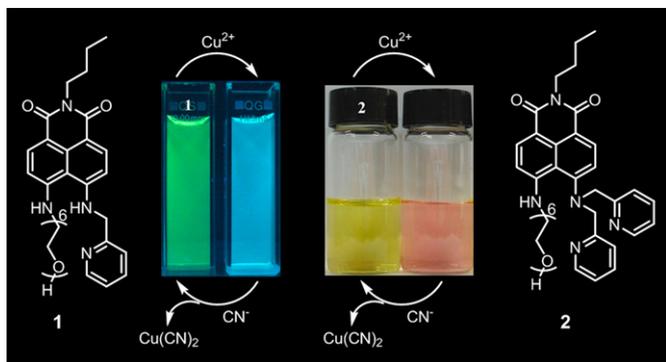
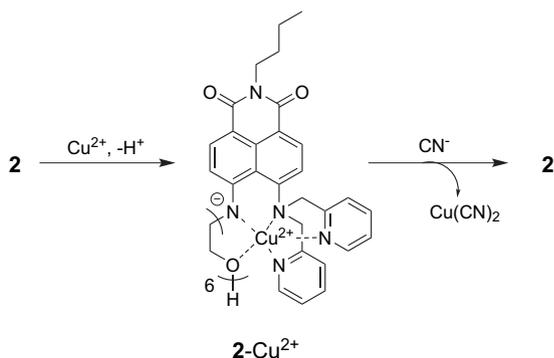


Figure 9. Visible emissions and color changes observed from samples of **1** and **2** with the addition of Cu^{2+} and CN^- .



Scheme 2. Proposed mechanism of sensing cyanide of **2**.

3. Conclusions

We have developed two new fluorescent sensors for Cu^{2+} on the basis of ICT and deprotonation mechanisms with complete selectivity. Moreover, sensor **1** makes it possible to detect Cu^{2+} ratiometrically, and **2** can sense Cu^{2+} colorimetrically. These two copper complexes can be used as ratiometric fluorescent and colorimetric sensors for cyanide ion in 100% aqueous solution.

4. Experimental section

4.1. Materials and methods

Unless otherwise noted, materials were obtained from commercial suppliers and were used without further purification. Flash chromatography was carried out on silica gel 60 (230–400 mesh ASTM; Merck). ^1H NMR and ^{13}C NMR spectra were recorded using Bruker 250 MHz or Varian 500 MHz. Chemical shifts were given in ppm and coupling constants (J) in Hertz. Fluorescence emission spectra were obtained using RF-5301/PC Spectrofluorophotometer (Shimadzu).

4.2. Preparation of fluorometric metal ion titration solutions

Stock solutions (1 mM) of the perchlorate salts of Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Mn^{2+} , Al^{3+} , Cu^{2+} , Co^{2+} , Ni^{2+} , Zn^{2+} , Cd^{2+} , Fe^{2+} , Fe^{3+} , Cr^{3+} , Ag^+ , Hg^{2+} , Pb^{2+} ions in distilled water were prepared. Stock solutions of host (0.01 mM) in distilled water were also prepared. Test solutions were prepared by placing 4–40 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with 0.5 M HEPES (pH 7.2). For all measurements, excitation was at 458 nm. Both excitation and emission slit widths were 3 nm or 5 nm.

4.3. Synthesis of compound 5

Compound **3**^{9a} (400 mg, 1.1 mmol) and **4**²⁴ (320 mg, 1.1 mmol) were added to 15 mL CH_3CN and then heated under reflux for 24 h. The reaction was monitored by TLC. After the reaction was completed, the solvent was evaporated under reduced pressure. The product was then purified by column chromatography (SiO_2 , $\text{CHCl}_3/\text{MeOH}$, 100:1, v/v) to give **5** as a red semisolid in 77% yield (500 mg). ^1H NMR (CDCl_3 , 250 MHz) δ 0.90 (t, $J=7.2$ Hz, 3H), 1.37 (m, $J=7.2$ Hz, 2H), 1.60 (m, $J=7.2$ Hz, 2H), 3.35–3.67 (m, 22H), 3.83 (t, $J=4.5$ Hz, 2H), 4.04 (t, $J=7.2$ Hz, 2H), 6.55 (d, $J=8.7$ Hz, 1H), 7.67 (d, $J=8.0$ Hz, 1H), 7.88 (s, 1H, NH), 8.15 (d, $J=8.7$ Hz, 1H), 8.42 (d, $J=8.6$ Hz, 1H). ^{13}C NMR (CDCl_3 , 62.5 MHz) δ 13.88, 20.39, 30.10, 40.01, 43.41, 61.61, 68.31, 70.23, 70.43, 70.47, 70.53, 70.59, 72.49, 105.74, 109.68, 117.49, 122.25, 124.81, 130.94, 131.68, 132.17, 134.69, 150.29, 163.48, 163.93. HRMS (FAB) calcd for $\text{C}_{28}\text{H}_{40}\text{BrN}_2\text{O}_8$ [MH^+] 611.1968, found 611.1972.

4.4. Synthesis of compound 1

Compound **5** (187 mg, 0.3 mmol) and 2-(aminomethyl)pyridine (400 μL , 425 mg, 3.9 mmol) were added to 10 mL 2-methoxyethanol. The solution was heated under reflux for 10 h and monitored by TLC. After the reaction was completed, the solvent was evaporated under reduced pressure. The product was then purified by column chromatography (SiO_2 , $\text{CHCl}_3/\text{MeOH}$, 100:2, v/v) to give **1** as a red semisolid in 69% yield (134 mg). ^1H NMR (CDCl_3 , 250 MHz) δ 0.87 (t, $J=7.2$ Hz, 3H), 1.36 (m, $J=7.2$ Hz, 2H), 1.61 (m, $J=7.2$ Hz, 2H), 3.13 (s, 1H, O–H), 3.36–3.60 (m, 22H), 3.78 (t, $J=4.3$ Hz, 2H), 4.04 (t, $J=7.2$ Hz, 2H), 4.49 (s, 2H), 6.36 (s, 1H, N–H), 6.59–6.69 (m, 2H), 7.20 (t, $J=8.2$ Hz, 1H), 7.27 (d, $J=7.8$ Hz, 1H), 7.62–7.68 (m, 2H, 1N–H), 8.27–8.32 (m, 2H), 8.55 (d, $J=8.2$ Hz, 1H). ^{13}C NMR (CDCl_3 , 62.5 MHz) δ 13.93, 20.45, 30.32, 39.70, 44.30, 48.79, 61.57, 68.72, 70.14, 70.20, 70.32, 70.38, 70.47, 72.54, 106.58, 107.28, 111.45, 111.51, 112.12, 121.96, 122.65, 132.18, 133.49, 133.65, 136.93, 148.94, 151.75, 152.51, 155.89, 164.57. HRMS (FAB) calcd for $\text{C}_{34}\text{H}_{47}\text{N}_4\text{O}_8$ [MH^+] 639.3394, found 639.3391.

4.5. Synthesis of compound 2

Compound **5** (310 mg, 0.5 mmol) and DPA (220 mg, 1.1 mmol) were added to 10 mL 2-methoxyethanol. The solution was heated under reflux for 10 h and monitored by TLC. After the reaction was completed, the solvent was evaporated under reduced pressure. The product was then purified by alumina column chromatography ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 125:1, v/v) to give **2** as a red oil in 56% yield (207 mg). ^1H NMR (CDCl_3 , 250 MHz) δ 0.87 (t, $J=7.2$ Hz, 3H), 1.36 (m, $J=7.2$ Hz, 2H), 1.61 (m, $J=7.2$ Hz, 2H), 2.74 (s, 1H, O–H), 3.45–3.67 (m, 22H), 3.78 (t, $J=4.3$ Hz, 2H), 4.05 (t, $J=7.2$ Hz, 2H), 4.38 (s, 4H), 6.65 (d, $J=8.8$ Hz, 1H), 6.87–6.92 (m, 3H), 7.07–7.12 (m, 2H), 7.45–7.51 (m, 2H), 8.23 (d, $J=8.1$ Hz, 1H), 8.33 (d, $J=8.6$ Hz, 1H), 8.49 (m, 2H), 10.65 (s, 1H, N–H). ^{13}C NMR (CDCl_3 , 62.5 MHz) δ 13.91, 20.44, 30.28, 39.80, 43.01, 59.16, 61.57, 69.07, 70.12, 70.37, 70.42, 70.51, 72.71, 104.15, 108.30, 114.95, 118.73, 119.03, 122.59, 123.72, 131.23, 132.71, 134.60, 136.52, 149.40, 152.78, 154.09, 156.04, 164.32, 164.58. HRMS (ESI) calcd for $\text{C}_{40}\text{H}_{52}\text{N}_5\text{O}_8$ [MH^+] 730.3816, found 730.3819.

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Supplementary data

Job's plot and absorption spectra of **1** in the presence of Cu²⁺. NMR spectra of **1**, **2** and **5**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2010.01.008.

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