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A naphthalimide–calixarene as a two-faced and highly selective fluorescent chemosensor for Cu^{2+} or F^-

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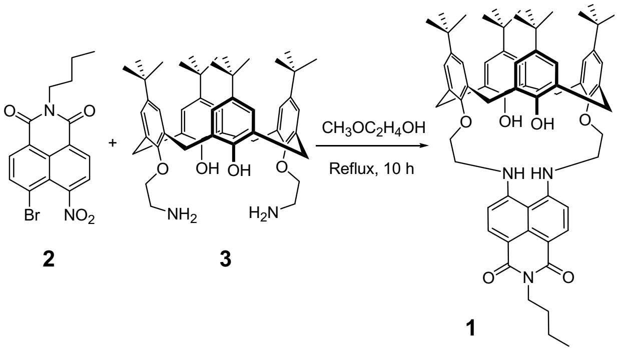
Abstract—A new naphthalimide–calix[4]arene was synthesized as a two-faced and highly selective fluorescent chemosensor for Cu^{2+} or F^-. This chemosensor displayed a selective fluorescence quenching effect only with Cu^{2+} among the various metal ions. On the other hand, among the various anions, the title chemosensor displayed a selective fluorescence quenching effect only with F^-. The binding mode with F^- was further investigated using fluorescence changes and ^1H NMR experiments.

Sensors based on the anion[1]- or metal ion[2]-induced changes in fluorescence appear to be particularly attractive due to the simplicity and high detection limit of the fluorescence. Especially, fluoride ions are biologically important anions because of their important role in dental care[3] and in the treatment of osteoporosis,[4] etc. On the other hand, Cu^{2+} is the third in abundance among the essential heavy metal ions in human body and plays an important role in various biological processes. In this regard, the fluorescent sensing of F^-[5–7] and Cu^{2+}[2,8,9d] has attracted growing attention.

Even though naphthalimide moiety has been recently utilized as an internal charge transfer (ICT) sensor for metal ions[9] and anions,[7] there has not been an example of calix[4] arene[10] derivative bearing a naphthalimide moiety. We report herein the synthesis and binding properties of the first naphthalimide–calix[4] arene (**1**), which displays an unusual two-faced and highly selective fluorescent change with F^- among the various anions or a highly selective fluorescent change with Cu^{2+} among the metal ions. This bifunctional and high selectivity can be attributed to a relatively rigid binding pocket of compound **1**, in which four hydrogens of NH and OH can make favorable hydrogen bonding interactions with F^-; on the other hand, two nitrogens in naphthalimide moiety and oxygens in calixarene moiety can provide a nice binding pocket for Cu^{2+}.

N-Butyl-4-bromo-5-nitro-1,8-naphthalimide **2**[9d] and 5,11,17,23-tetra-*tert*-25,27-bis(2-aminoethyloxy)-26,28-dihydroxycalix[4] arene **3** were prepared following the reported procedures.[11] Compounds **2** and **3** were then refluxed in methoxyethanol for 10 h to give **1**[12] in a yield of 74% after the column chromatography (Scheme 1). Compound **1** was fully characterized by ^1H NMR, ^{13}C



Scheme 1. Synthesis of compound **1**.

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NMR (see Supplementary data), and high resolution FAB mass spectroscopy.

The perchlorate salts of Ag^+, Ca^{2+}, Cd^{2+}, Co^{2+}, Cs^+, Cu^{2+}, Hg^{2+}, K^+, Li^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+}, Pb^{2+}, Rb^+, and Zn^{2+} ions were used to evaluate the metal ion binding properties of compound **1** in acetonitrile. The fluorescence spectra were obtained by excitation into the naphthalimide fluorophore at 435 nm. As shown in Figure 1, there was a large and highly selective fluorescent quenching effect in its emission spectrum only with Cu^{2+} among the metal ions examined. Overall emission change of 20-fold was observed for Cu^{2+} (Fig. 1). From the fluorescent titrations (S-Figure 1), the association constants of **1** with Cu^{2+} were calculated to be $6.1 \times 10^4\ M^{-1}$ (errors <10%).[13] Addition of Cu^{2+} also induced substantial decrease in the UV absorption spectra (see S-Figure 2). Selectivity for Cu^{2+} in the presence of water was then examined. Since the host was not quite soluble in aqueous system, 10% aqueous system (CH_3CN:water = 9:1, v/v) was adopted for the fluorescent study, and similar high selectivity for Cu^{2+} was also observed. From the fluorescent titrations (Fig. 2), the association constants of **1** with Cu^{2+} were calculated to be $2.9 \times 10^4\ M^{-1}$ (errors <10%).[13] The weak and red-shift emission was recorded for **1** with Cu^{2+}, this unique change can be attributed to the deprotonation of naphthalimide NH in the presence of Cu^{2+}, which was recently proposed.[9c]

The fluorescence emission changes of **1** (6 μM) upon the addition of $H_2PO_4^-$, HSO^{4-}, $CH_3CO_2^-$, I^-, Br^-, Cl^-, and F^- (100 equiv, tetrabutylammonium salts) in acetonitrile are illustrated in Figure 3. As shown in Figure 3, there was a selective fluorescent quenching effect in its emission spectrum only with F^- even though relatively smaller quenching effect was observed with $CH_3CO_2^-$. Job plot for the binding between **1** with F^- shows a 1:1 stoichiometry. Figure 4 explains the fluorescent titration data for **1** with F^-. From the fluorescence titration, the association constant of complex **1** with F^- was observed to be $1.1 \times 10^4\ M^{-1}$ (errors <10%).[13]

Recently, colorimetric changes due to the deprotonation of NH, which is directly attached to the fluorophore, have been utilized as sensors for F^-.[5,7,14] It is reported that F^- is sufficiently basic to deprotonate NH, which can cause usually long wavelength color change. We observed a similar process, which was confirmed by the color change to yellow upon addition of F^- (see S-Figure 3) as well as UV titration with F^- (see S-Figure

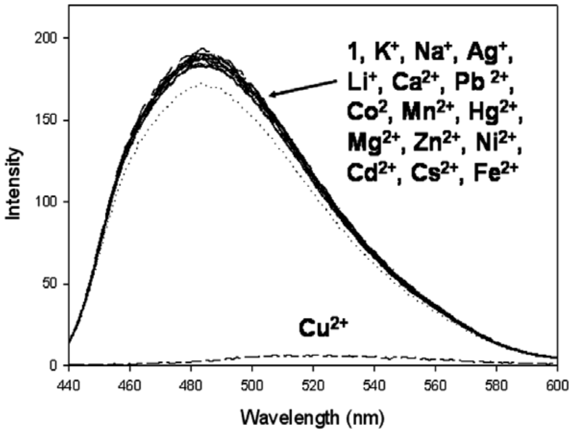

Figure 1. Fluorescent changes of **1** (6 μM) with various metal ions (100 equiv) in CH_3CN (excitation at 435 nm).

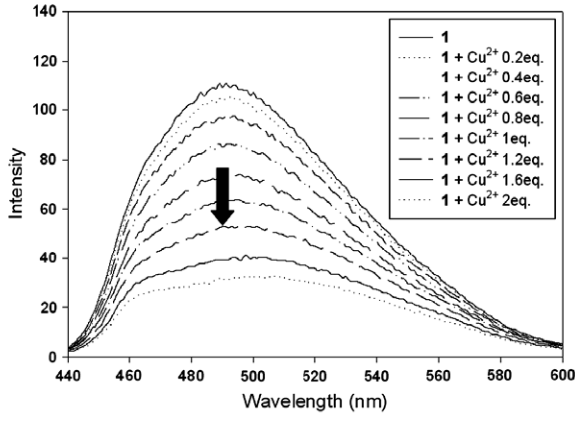

Figure 2. Fluorescent titrations of **1** (6 μM) with Cu^{2+} in CH_3CN–water (9:1, v/v) (excitation at 435 nm).

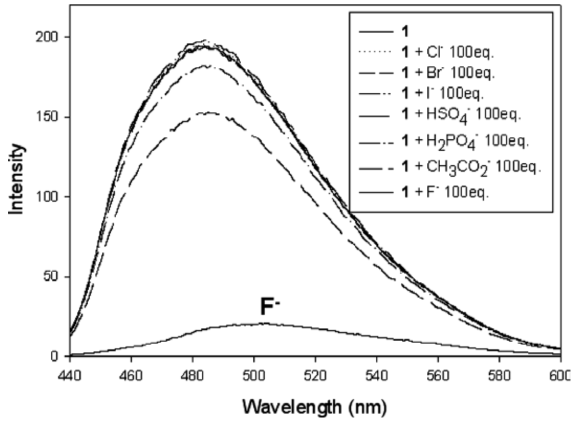

Figure 3. Fluorescent emission changes of **1** (6 μM) upon addition of tetrabutyl ammonium salts of $H_2PO_4^-$, HSO^{4-}, $CH_3CO_2^-$, F^-, Cl^-, Br^- and I^- (100 equiv) in CH_3CN (excitation at 435 nm).

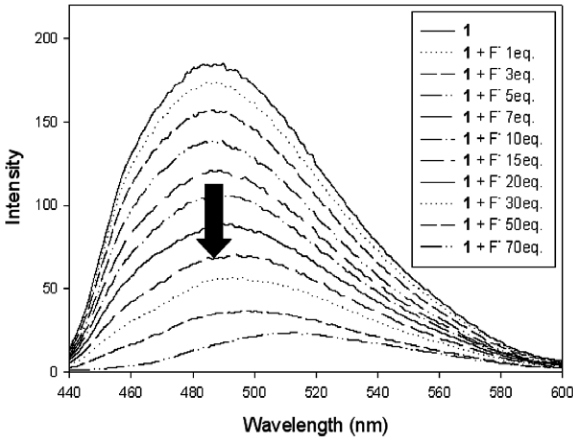

Figure 4. Fluorescent titrations of **1** (6 μM) with F^- in CH_3CN (excitation at 435 nm).

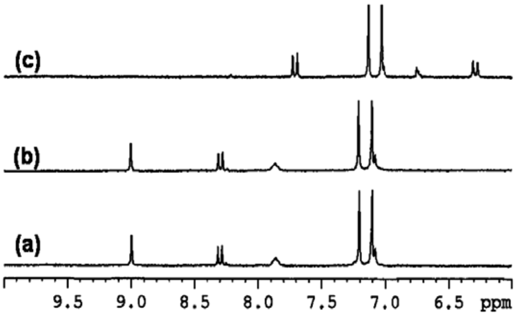

Figure 5. Partial ^{1}H NMR spectra (250 MHz) of **1** (3 mM) with Cl^- and F^- in DMSO-d_6: (a) **1** only, (b) **1**+2 equiv of Cl^- and (c) **1**+2 equiv of F^-.

4). The ^{1}H NMR experiments also support the deprotonation process. In our case, in addition to the two NH hydrogens, there are two phenolic OH hydrogens which can also participate in binding with F^-. As expected, severe broadness of both NH (δ 8.99 ppm) and OH (δ 7.86 ppm) hydrogens was observed upon the addition of F^- (Fig. 5 and see S-Figure 5). Furthermore, a new triplet, which corresponds to the formation of FHF,[7] was also observed at around 16 ppm (S-Figure 6). On the other hand, the addition of excess Cl^- did not induce any change in ^{1}H NMR spectra (Fig. 5 and S-Figure 7). Since the main interaction between host and F^- is hydrogen bonding, host **1** did not show any significant fluorescent change upon the addition of F^- in CH_3CN–water (9:1, v/v).

In conclusion, a new naphthalimide–calix[4] arene derivative **1** was synthesized as a two-faced and highly selective fluorescent chemosensor for Cu^{2+} or F^-, which displays a highly selective fluorescent change with F^- among the various anions and a highly selective fluorescent change with Cu^{2+} among the metal ions. Especially, the selectivity for Cu^{2+} was further confirmed in aqueous solution. This high selectivity can be attributed to a relatively rigid binding pocket of compound **1**, in which four hydrogens of NH and OH can make favorable hydrogen bonding interactions with F^-, on the other hand, two nitrogens in naphthalimide moiety and oxygens in calixarene moiety may provide a nice binding pocket for Cu^{2+}.

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Supplementary data

The NMR spectra, fluorescence spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.10.109.

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12. *Compound* **1**: 40 mg (0.054 mmol) of 5,11,17,23-Tetra-*tert*-25,27-bis(2-aminoethyloxy)-26,28-dihydroxycalix^4 arene **3** was added slowly to a solution of 20 mg (0.053 mmol) *N*-butyl-4-bromo-5-nitro-1,8-naphthalimide **2** in 150 mL of 2-methoxyethanol, and then the mixture was heated to reflux for 10 h and monitored by TLC. After the reaction was completed, the solvents were removed under reduced pressure. The product was then purified by column chromatography (SiO_2, CH_2Cl_2/EtOAc, 98:1, v/v) to give **1** as a yellow powder in 74% yield (40 mg). Mp: 200–202 °C. ^{1}H NMR ($CDCl_3$, 250 MHz) δ 0.95 (t, $J = 7.6$ Hz, 3H), 1.19 (m, 36 H), 1.42 (m, $J = 7.6$ Hz, 2H), 1.70 (m, $J = 7.6$ Hz, 2H), 3.40 (d, $J = 12.8$ Hz, 4H), 3.94 (s, 4H), 4.17 (m, 6H), 4.57 (s, 4H), 6.89 (d, $J = 8.4$ Hz, 2H), 6.98 (s, 4H), 7.09 (s, 4H), 7.97 (s, 2H, NH), 8.48 (d, $J = 8.4$ Hz, 2H), 9.11 (s, 2H, OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.95, 14.17, 20.43, 21.07, 29.71, 30.31, 30.90, 31.21, 31.49, 33.01, 33.84, 34.30, 39.77, 44.21, 60.42, 72.88, 106.30, 112.72, 112.81, 125.49, 126.21, 127.85, 132.69, 133.63, 142.61, 148.20, 149.76, 150.38, 152.94, 164.67, 171.20. HRMS (FAB) calcd for $C_{64}H_{78}N_3\ O_6$ $[M+H]^+$ 984.5891, found 984.5897.
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