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On/off fluorescence switch of a calix[4]arene by metal ion exchange

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Abstract—A new calix[4]arene-based fluorescence chemosensor displaying a strong excimer emission was prepared. When a Pb^{2+} ion is bound to the two amide oxygen atoms linked to the fluorophores, the ligand exhibits a marked quenched excimer emission due to its geometrical change during the complexation. By the addition of Ca^{2+} ion into the **1**·Pb^{2+}, the excimer emission band was revived, by which an interesting on/off switch process is proposed.

Since calixarenes with appropriate sensing units have been good candidates as specific ligands, their potential applications as sensing probes have thus received an increasing interest.[1,2] The fluorescent chemosensors capable of selectively recognizing cations have a wide variety of analytical applications in various fields, including chemistry, biology, and medicine.[3–6]

Reported calixarene-based fluorescence sensors utilize photo-physical changes produced by a cation binding: photo-induced electron transfer (PET),[3,5–7] excimer/exciplex formation and extinction,[4,8] or energy transfer.[9] For the PET type, we have previously reported a series of 'Molecular Taekwondo I–II' based on the intramolecular metal ion exchange. In these systems, the metal ion exchange processes are ascribed not only to an electrostatic repulsion between metal ions, but also to an allosteric effect.[10]

In a continuation on the research with fluorescent pyrene-monomer and excimer changes upon the metal cation or anion complexations, we newly synthesized 1,3-alternate calix[4]arene (**1**) having bispyrenylamide on the two lower rims and two carboxylic acids on the other two lower rims, as shown in Figure 1.

Compound **1** was prepared as shown in Scheme 1.[11] Reaction of calix[4]arene with 2.1 equiv of *N*-(1-pyrenylmethyl)chloroacetamide[12] in the presence of a catalytic amount of NaI and 1.0 equiv of K_2CO_3 as a base in

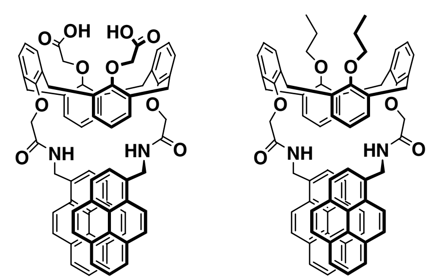

Figure 1. Fluorescence chemosensors **1** and **2**.

CH_3CN afforded 25,27-bis[(*N*-(1-pyrenylmethyl)aminocarbonyl)methoxy]calix[4]arene (**3**) in quantitative yield. Compound **3** was subsequently treated with ethyl bromoacetate in the presence of Cs_2CO_3 in CH_3CN to produce **4** in 75% yield.[11] Compound **4** was hydrolyzed to give a corresponding calix[4]arene dicarboxylic acid **1** in 96% yield. Compound **2** was also prepared by following the literature procedures.[10c,13] The presence of a singlet peak at 3.8 ppm in the ^1H NMR spectra as well as the presence of a single peak at 38 ppm in the ^{13}C NMR spectra confirmed that both **1** and **2** retain 1,3-alternate conformation.

As a fluorogenic unit, pyrene is known to be one of the most useful sensing moieties because of its efficient monomer and excimer formation.[14] The intensity ratio of the excimer to the monomer emission ($I_{excimer}/I_{monomer}$) is sensitive to conformational change of the pyrene-appended receptors, thus I_e/I_m changes upon

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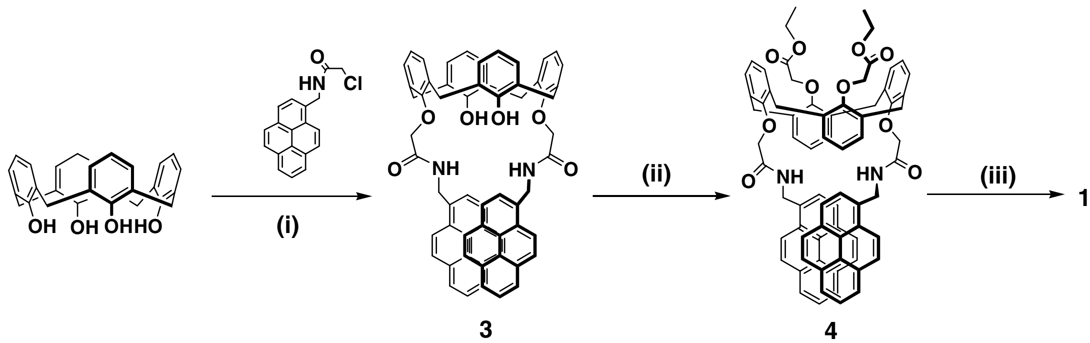

Scheme 1. Synthetic route of fluorescent chemosensor **1**. Reagents: (i) K_2CO_3, NaI, CH_3CN; (ii) ethyl bromoacetate, Cs_2CO_3, CH_3CN; (iii) NaOH, H_2O/EtOH.

metal ion complexation can be an informative parameter in various sensing system.[15,16] It was reported that a calixarene containing pyrenyl esters shows a marked excimer emission by a strong π–π interaction between two pyrenes.[17] In this study, we also observed that free **1** and **2** exhibit a strong monomer ($\lambda_{em} = 370$ nm) and an excimer ($\lambda_{em} = 470$ nm) band, suggesting that the two pyrene units be in the face-to-face π-stack so as to form a dynamic excimer.[10c] The relative ratios of excimer to monomer (I_e/I_m) bands for **1** and **2** are 3.23 and 1.34, respectively, as shown in Figure 2. The larger value (I_e/I_m) of **1** than that of **2** is presumably due to its greater conformational rigidity, mainly by an intramolecular H-bonding interaction between two carboxylic acids, which is not seen in the case of **2**.

The perchlorate salts of Ag^+, Cs^+, K^+, Li^+, Na^+, Rb^+, Ca^{2+}, Pb^{2+}, and Zn^{2+} were used to investigate the cation binding ability of **1** and **2** with respect to the fluorescence response.[18] The results are presented in Figure 3. On the basis of fluorescence changes upon metal cation complexation, we found that **1** exhibits Pb^{2+} (quenching) and Ca^{2+} (enhancing) selectivity over other metal cations tested.

Figure 4 shows the fluorescence changes of **1** and **2** with Pb^{2+} ion concentration. The fluorescence intensity

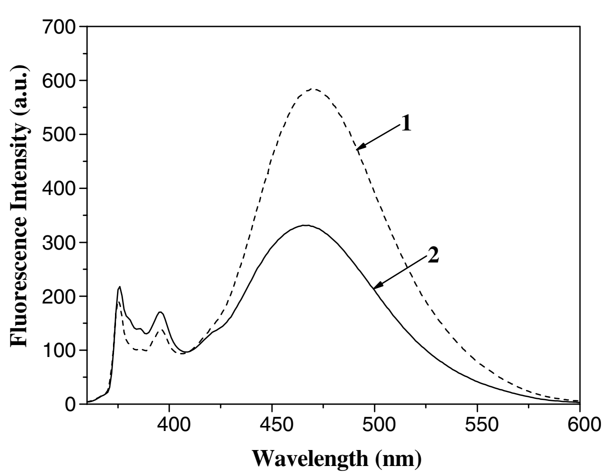

Figure 2. Fluorescence spectra of free **1** and **2** (6.0 μM) in CH_3CN. The excitation wavelength is 343 nm.

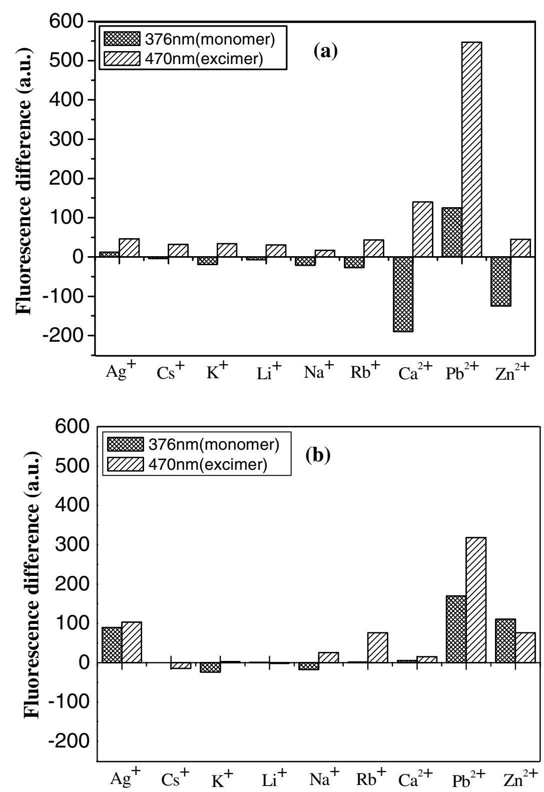

Figure 3. Bar profiles of fluorescence changes ($I_0 - I$) of (a) **1** and (b) **2** upon the addition of various metal cations. Compounds **1** and **2**: 6.0 μM in CH_3CN; excitation at 343 nm; metal ions, 500 equiv in CH_3CN. I_0: fluorescence emission intensity of free **1** and **2**; I: fluorescence emission intensity of metal ion-complexed **1** and **2**.

was gradually decreased by the addition of Pb^{2+} ion and the changes became a plateau with ca. 500 equiv lead ion addition. From the data, association constants of **1** and **2** for complexation of the Pb^{2+} in CH_3CN were calculated to be 2.1×10^5 and 7.8×10^5 M^{-1}, respectively.[18] The rather small association constant of **1** for Pb^{2+} ion than that of **2** is probably due to a strong intramolecular H-bonding between two carboxylic acid units, which executes a reverse-allosteric effect on the two amide units. The remarkable fluorescence quenching induced by Pb^{2+} is ascribed not only to reverse PET from the pyrene units to the carbonyl oxygen atoms of which

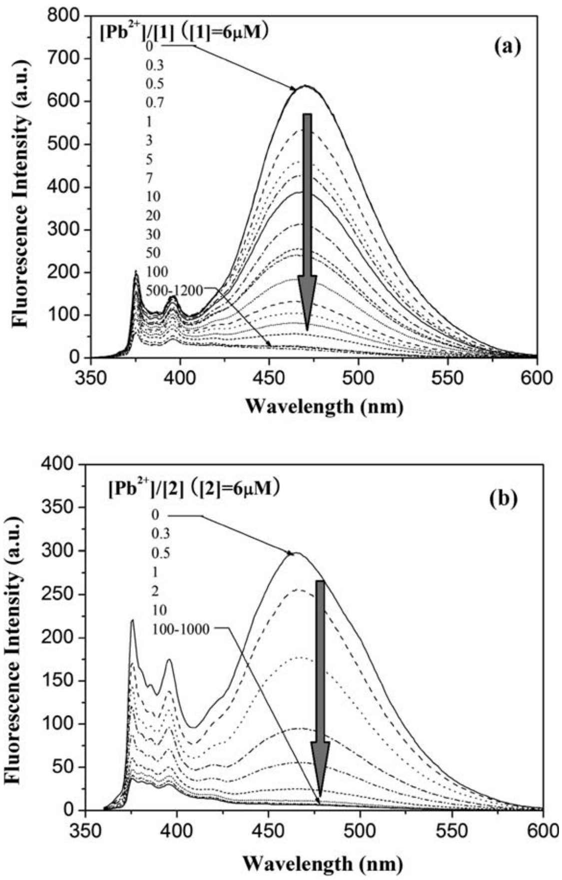

Figure 4. Fluorescence spectra of (a) **1** and (b) **2** (6.0 μM) upon the addition with Pb^{2+} in CH_3CN. The excitation wavelength is 343 nm.

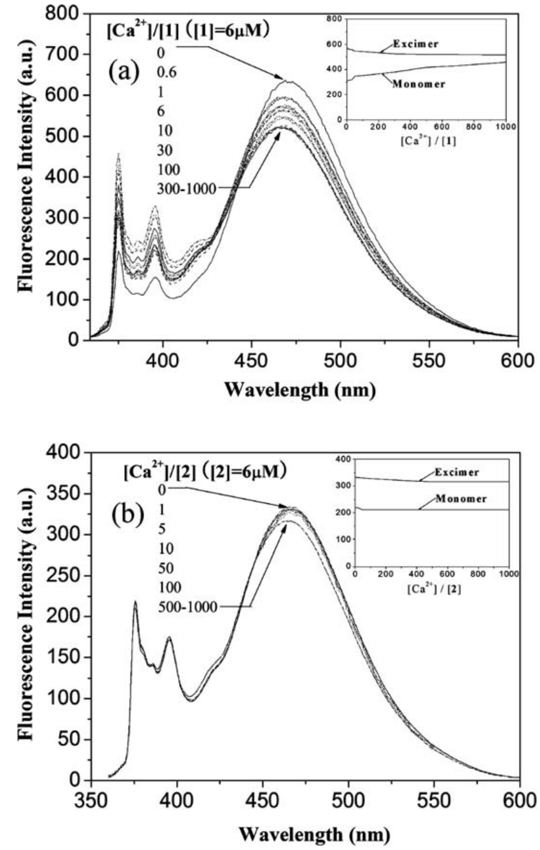

Figure 5. Fluorescence spectra of (a) **1** and (b) **2** (6.0 μM) upon the addition with Ca^{2+} in CH_3CN. (The excitation wavelength is 343 nm.)

the electron density is diminished by the metal ion complexation, but also to the heavy metal ion effect.[10c]

Figure 5a shows that titration of Ca^{2+} into a solution of **1** displays a decreased excimer emission with an increased monomer emission at the same time. Figure 5b, however, exhibits no change in the fluorescence intensity of **2** by the addition of Ca^{2+}. These two facts strongly suggest that the Ca^{2+} ion prefer to bind to carboxylic acid rather than to the amide group. A blue-shifted excimer emission of **1** with Ca^{2+} may result from less overlapping pyrenes dimer to provide the less effective HOMO–LUMO interaction in the excited state.[15]

When the Pb^{2+} ion was added to a solution of **1**, we observed a quenched excimer emission which is in good agreement with the previously reported fact that the Pb^{2+} ion is encapsulated in the cage of the two pyrene amide groups giving a $C{=}O\cdots Pb^{2+}$ coordination followed by a conformational change.[10c,19] Concomitantly decreasing monomer emission is mainly due to a reverse-PET and a heavy metal ion effect.[10c,19–21] On the other hand, in the case of $\mathbf{1}\cdot Ca^{2+}$, the monomer and excimer emissions declined and enhanced, respectively, indicating that those of reverse-PET and heavy metal ion effects are excluded.

With regard to cation exchanges based upon the selectivity between Ca^{2+} and Pb^{2+}, we observed an interesting on/off switching process. When the Ca^{2+} was titrated with a solution of the $\mathbf{1}\cdot Pb^{2+}$ complex, both excimer and monomer bands gradually reformed and then became saturated upon addition of about 3000 equiv of Ca^{2+} (Fig. 6). This is due not only to an electrostatic repulsion between the two metal ions, but also to a

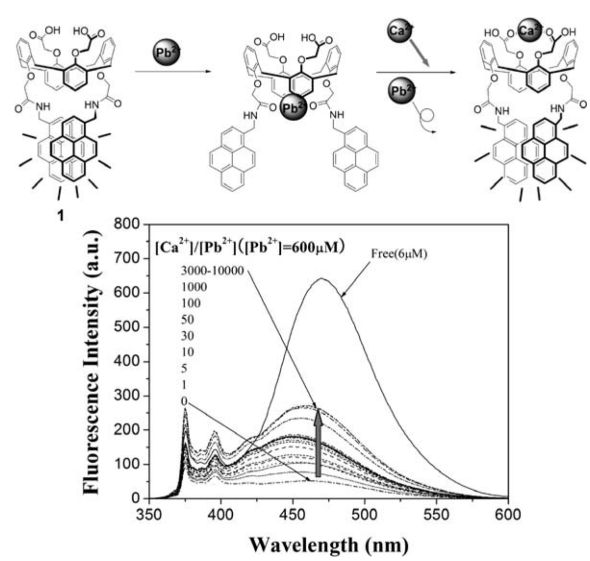

Figure 6. Fluorescence emission change for the $\mathbf{1}\cdot Pb^{2+}$ complex in CH_3CN upon the addition of Ca^{2+}. (The excitation wavelength is 343 nm.)

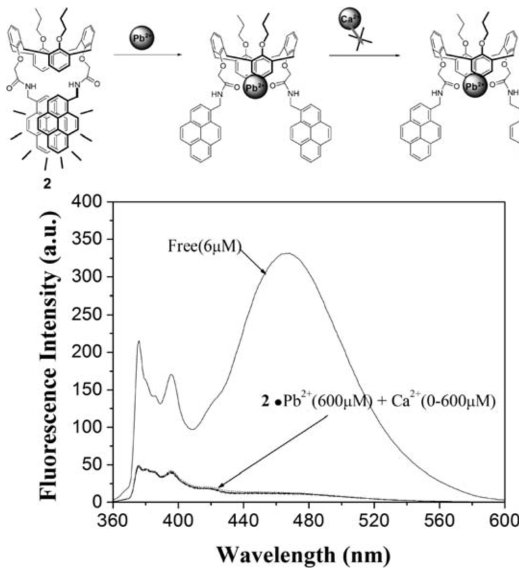

Figure 7. Fluorescence emission change for the $\mathbf{2}\cdot Pb^{2+}$ complex in CH_3CN upon the addition of Ca^{2+}. (The excitation wavelength is 343 nm.)

reverse allosteric effect-induced conformation change that does not favor the binding of the approaching second metal.[22]

In order to prove the metal ion exchange behavior, we chose **2** not having carboxylic acid groups but having propyl units on the lower rim of the calixarene. When Ca^{2+} was added to a solution of $\mathbf{2}\cdot Pb^{2+}$ complex, the fluorescence intensity scarcely changed, as shown in Figure 7, implying that no cation exchange occurred in **2** obviously because the two propyloxy groups were unable to function as a Ca^{2+} recognition site. This supports that Ca^{2+} binds to the carboxylic acid and not to the amide groups, where the metal–ion binding would induce a conformational change of the ligand.

In conclusion, fluorogenic calix[4]arenes **1** and **2** with two facing amide groups linked to pyrene units were synthesized. Upon addition of Pb^{2+} ion to a solution of **1** or **2** in CH_3CN, both monomer and excimer bands were strongly quenched because of the reverse-PET from the pyrene unit to the electron-deficient amide groups and because of a conformational change of the two pyrene amide groups, respectively. On the other hand, upon addition of Ca^{2+} ion into the $\mathbf{1}\cdot Pb^{2+}$, the excimer band is revived, by which the interesting on/off switch process like a 'Molecular Taekwondo' is proposed.

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11. Preparation of **1**. A solution of **4** (0.50 g, 0.43 mmol) and NaOH (0.18 g, 4.4 mmol) in THF (5 mL), ethanol (10 mL), and water (5 mL) were refluxed for 12 h and evaporated in vacuo. The residue was dissolved in EtOAc, and the solution was washed twice with 20% HCl and then three times with water. The organic layer was dried over $MgSO_4$ and evaporated in vacuo to yield 0.45 g (96%) of **1** as a white solid. Mp: 265–270 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.16–7.86 (m, 18H, Ar*H*, pyrene), 7.10–7.06 (m, 4H, ArH_m; 2H, ArH_p), 6.80–6.76 (m, 2H, ArH_p; 4H, ArH_m), 6.27–6.20 (m, 2H, CON*H*CH_2), 5.02–4.99 (m, 4H, ArCH_2NH), 4.14–4.06 (m, 8H, AroCH_2CO), 3.82–3.76 (m, 8H, ArCH_2Ar). ^{13}C NMR (75 MHz, $CDCl_3$): 178.7, 169.0, 155.3, 135.0, 134.5, 132.3, 131.3, 131.0, 129.0, 128.7, 128.1, 127.4, 126.7, 126.0, 125.4, 125.2, 123.6, 79.3, 41.7, 41.3, 40.9, 40.5, 38.1, 30.5, 29.6, 25.9 ppm. FAB MS *m/z* (m^+) calcd 1083.19, found 1083.0. Anal. Calcd for $C_{70}H_{54}N_2O_{10}$: C, 77.62; H, 5.02. Found: C, 77.61; H, 5.03.
Preparation of **4**. A mixture of **3** (1.00 g, 1.03 mmol), Cs_2CO_3 (1.01 g, 3.09 mmol), and CH_3CN (60 mL) was stirred magnetically for 20 min, and then ethyl bromoacetate (0.69 g, 4.13 mmol) was added. The reaction mixture was refluxed for 2 days and evaporated in vacuo. The residue was extracted with CH_2Cl_2, and the organic solution was washed with water, dried over $MgSO_4$, and evaporated in vacuo to afford a colored residue. Recrystallization from CH_2Cl_2–hexane produced 0.87 g (75%) of **4** as crystalline solid. Mp: 250–256 °C. ^1H NMR (200 MHz, $CDCl_3$): δ 8.34–7.88 (m, 18H, Ar*H*, pyrene), 7.35–7.08 (m, 4H, ArH_m; 2H, ArH_p), 6.75–6.64 (m, 2H, ArH_p; 4H, ArH_m), 5.90–5.87 (t, 2H, CON*H*CH_2, $J = 7.59$), 5.22–5.19 (d, 4H, ArCH_2NH, $J = 5.79$), 4.22–4.11 (m, 8H, ArOCH_2CO), 3.86–3.79 (d, 4H, ArCH_2Ar; $J = 13.99$), 3.48–3.41 (d, 4H, ArCH_2Ar; $J = 14.79$) 3.22–3.10 (m, 4H, COC$H_2$$CH_3$), 1.29–1.21 (t, 6H, $COCH_2$CH_3, $J = 7.39$). ^{13}C NMR (75 MHz, $CDCl_3$): 178.8, 170.1, 169.6, 157.6, 154.8, 135.1, 134.1, 132.6, 132.4, 132.1, 131.9, 131.6, 131.2, 129.8, 128.9, 128.3, 128.2, 127.9, 126.8, 126.2, 125.9, 125.6, 125.4, 124.0, 123.8, 123.8, 71.4, 70.3, 61.8, 42.0, 37.5, 15.1 ppm. FAB MS *m/z* (m^+) calcd 1139.29, found 1139.0. Anal. Calcd for $C_{74}H_{62}N_2O_{10}$: C,78.01; H, 5.49. Found: C, 78.02; H, 5.47.
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18. General: Fluorescence spectra were recorded with a RF-5301PC spectrofluorophotometer. Stock solutions (1.00 mM) of the metal perchlorate salts were prepared in CH_3CN. Stock solutions of **1** and **2** (0.06 mM) were prepared in CH_3CN. For all measurements, excitation was at 343 nm with excitation and emission slit widths at 3.0 nm. Fluorescence titration experiments were performed using 6.0 μM solutions of **1** and **2** in CH_3CN, and various concentrations of metal perchlorate in CH_3CN. After calculating the concentrations of the free ligands and complexed forms of **1** and **2** from the fluorescence titration experiments, the association constants were obtained using the computer program ENZFITTER.[23]
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23. Association constants were obtained using the computer program ENZFITTER, available from Elsevier-BIOSOFT, 68 Hills Road, Cambridge CB2 1LA, United Kingdom.