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Cyclams Bearing Diametrically Disubstituted Pyrenes as Cu^{2+}- and Hg^{2+}-Selective Fluoroionophores

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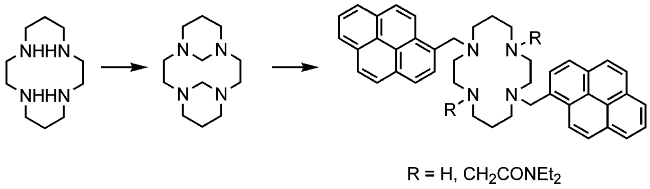

New cyclam derivatives having diametrically disubstituted pyrene fluorophores were prepared and their fluoroionophoric properties toward transition metal ions were investigated. The compounds exhibited significant selectivity toward Hg^{2+} and Cu^{2+} ions in switching-off type responses in aqueous methanol or acetonitrile solution. Dipyrene-diamide derivative **3**, having extra binding sites of the amide function, exhibited more pronounced chemosensing behavior toward Hg^{2+} and Cu^{2+} ions than its parent, dipyrene derivative **2**. Detection limits for the analysis of Hg^{2+} and Cu^{2+} ions of dipyrene-diamide derivative **3** were 1.45×10^{-6} and 1.30×10^{-6} M, respectively. The diametrically disubstituted dipyrene-cyclam **2** may be utilized as a new starting platform for the design of other supramolecular fluorescent signaling systems having switching or chemosensing behaviors toward transition metal ions.

The development of selective chemosensors for the signaling of chemically and biologically important metal ions is one of the most crucial research topics in the field of supramolecular chemistry.[1] For the preparation of transition metal ion selective chemosensors, cyclam and related structures are very attractive due to their high affinities toward some of the important transition metal ions.[2] To construct smart functional supramolecular systems, selective functionalizations of the cyclam are indispensable processes but are, in general, synthetically demanding.[3] Among many of the selectively functionalized derivatives, preparation of mono- or trisubstituted derivatives[4] seems to be more feasible than the preparation of disubstituted derivatives.[5] In fact, simple disubstituted derivatives can be easily obtained starting from the well-known 1,8-dimethyl derivative of cyclam.[6] However, the methyl groups on the cyclam cannot be further cleaved off, and macrocycles containing two tertiary amino groups result[5a] that are unfavorable for the construction of supramolecular systems having more advanced functions. In this regard, the preparation shown in Scheme 1of diametrically 1,8-disubstituted cyclam derivatives developed by Guilard[7] is very attractive for the design of multifunctional supramolecular systems based upon the cyclam scaffold.

The pyrene moiety is one of the most useful fluorophores for the construction of fluorogenic chemosensors for a variety of important chemical species.[8] Particularly, pyrene moiety having a nearby amino group has been widely employed for the selective signaling of specific metal ions by controlling the photoinduced electron transfer (PET) processes.[9] We have reported that a diametrically disubstituted dimethylcyclam derivative having two anthracene groups[6a] showed high Hg^{2+}- and Cd^{2+}-selective fluoroionophoric properties over other transition metal ions. However, as mentioned earlier, further modification of the compound is not possible due to the presence of inert methyl groups in the tertiary amine of the cyclam scaffold. In this paper, two cyclam derivatives having diametrically 1,8-disubstituted pyrenylmethyl subunits were prepared and their

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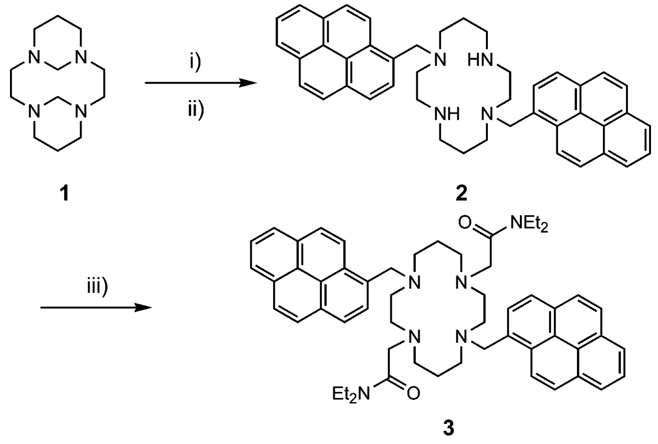
SCHEME 1. Synthesis of Chemosensors[a]



[a] Reagents and conditions: (i) 1-chloromethylpyrene, KI, CH_3CN, rt. (ii) NaOH, H_2O. (iii) *N*,*N*-diethyl bromoacetamide, K_2CO_3, KI, CH_3CN, reflux.

ionophoric properties toward Hg^{2+} and Cu^{2+} ions[10,11] were investigated.

Diametrically disubstituted bis(pyrenylmethyl) derivative **2** was prepared following the procedure for the preparation of the bis(anthrylmethyl) derivative of cyclam.[12] Reaction of the bisaldolaminal tricyclic cyclam derivative **1**[7] with 1-chloromethylpyrene in acetonitrile followed by the hydrolysis with NaOH resulted in the formation of the diametrically disubstituted bis(pyrenylmethyl) derivative **2** in good yield (71%). Further functionalization of the pyrene derivative **2** with *N*,*N*-diethyl bromoacetamide (K_2CO_3, KI, CH_3CN) afforded the tetrasubstituted dipyrene-diamide derivative **3** (65%). The structure was designed by combining the two well-known molecular motifs of the cyclam binding unit and the frequently employed signaling handle of the pyrene subunit, hoping that the complexed metal ion would induce suppression of the PET processes. Further modification of the parent dipyrene-cyclam derivative with amide functions may allow more selective or possibly more enhanced ion sensing properties of the resulting cyclam-based derivatives by utilizing efficient ligating amide carbonyl functions for the complexation of targeted metal ions.

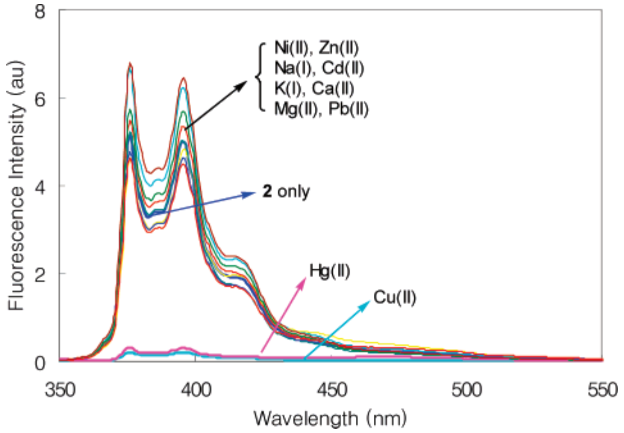


FIGURE 1. Fluorescence spectra of **2** in the presence of various metal ions. [**2**] = 5.0×10^{-6} M, [M^{n+}] = 5.0×10^{-4} M, [acetate buffer] = 1.0×10^{-2} M (pH 4.9) in MeOH−H_2O (30:70, v/v). $\lambda_{ex} = 340$ nm.

The chemosensing behaviors of the parent cyclam-dipyrene derivative **2** were investigated by fluorescence measurements. In 30% aqueous methanol, compound **2** exhibited strong monomer emissions of pyrene at 376, 396, and 418 nm with very weak excimer emission around 480 nm. Upon interaction with metal ions, the monomer emissions were efficiently quenched, particularly by Hg^{2+} and Cu^{2+} ions (Figure 1). The quenching efficiencies (I/I_o) observed at 395 nm were about 0.04 and 0.06 for Hg^{2+} and Cu^{2+} ions, respectively. On the other hand, the excimer region was affected less and no discrete selectivity toward any metal ions was observed.

The K_{assoc} values for the two most responding metal ions were obtained by a nonlinear curve fitting[13] of the fluorescence titration results and were 1.21×10^6 M^{-1} for **2**-Cu^{2+} and 2.25×10^4 M^{-1} for **2**-Hg^{2+} systems. Competition experiments also confirmed the selective signaling of **2** toward Hg^{2+} and Cu^{2+} ions in the presence of other common interfering alkali, alkaline earth, and transition metal ions (Figures S6 and S7 in the Supporting Information).

On the basis of the fluoroionophoric behavior of **2**, the chemosensing properties of compound **3** having two extra binding sites of amide functions were investigated. The optimization for the selective signaling of targeting metal ions was also performed in common organic solvents including their aqueous solutions. The fluorescence behavior of compound **3** in the presence and in the absence of metal ions was investigated as a function of water content in common water-miscible organic solvent systems (Figure S8 in the Supporting Information). Aqueous acetonitrile was found to be the most selective, and as the water content increased in aqueous acetonitrile, the fluorescence of the ionophore **3** increased up to 50% composition and then decreased (Figure 2). On the other hand, the fluorescence of the **3**-Hg^{2+} and **3**-Cu^{2+} systems was not as significantly affected by the changes in water composition. This observation suggests that a significant ON−OFF type signaling toward Hg^{2+} and Cu^{2+} ions could be realized in 50% aqueous acetonitrile solution.

Upon interaction with 100 equiv of various metal ions, the cyclam **3** exhibited pronouncedly selective ON−OFF type

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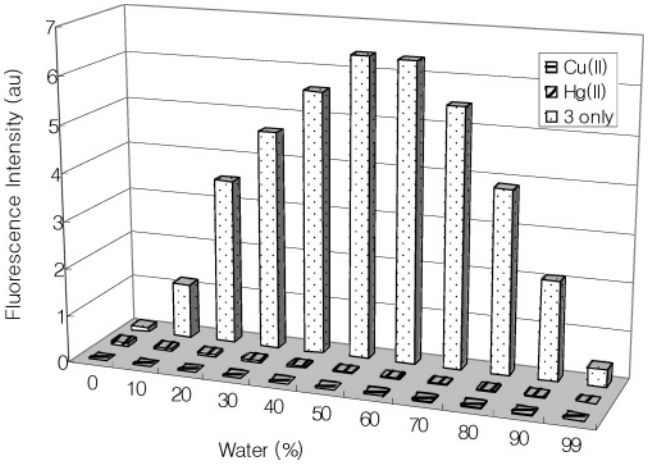

FIGURE 2. Fluorescence intensity changes of **3** as a function of water content in aqueous acetonitrile solution at 397 nm. [**3**] = 5.0 × 10^{-6} M, [M^{2+}] = 5.0 × 10^{-4} M, [acetate buffer] = 1.0 × 10^{-2} M (pH 4.9). λ_{ex} = 340 nm.

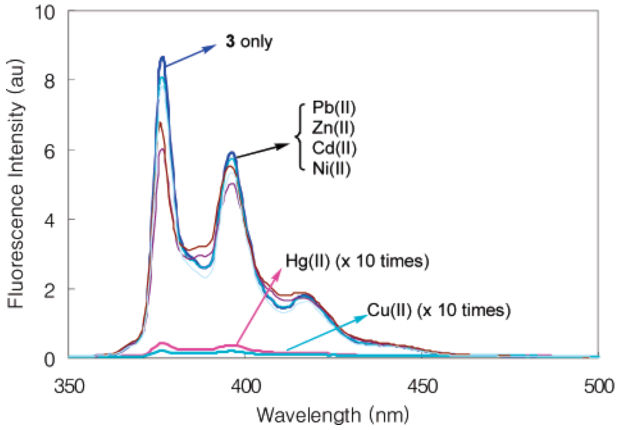

FIGURE 3. Fluorescence spectra of **3** in the presence of various metal ions in aqueous acetonitrile solution. [**3**] = 5.0 × 10^{-6} M, [M^{2+}] = 5.0 × 10^{-4} M, [acetate buffer] = 1.0 × 10^{-2} M (pH 4.9), CH_3CN:H_2O = 50:50, v/v. λ_{ex} = 340 nm.

fluorescence responses toward Hg^{2+} and Cu^{2+} ions in the 50% aqueous acetonitrile solution (Figure 3). Other representative metal ions of Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}, as well as alkali and alkaline earth metal ions, showed less significant changes in fluorescence intensity at 397 nm. With Hg^{2+} and Cu^{2+} ions, the fluorescence quenching was quite effective: the pyrene monomer emissions were efficiently quenched down to the baseline. The effective fluorescence quenching of **3** might be due to the inherent quenching nature[14] of the two metal ions of Hg^{2+} and Cu^{2+}. The possible fluorescence enhancing effects of the complex formation, attributable to the suppression of the PET process between the amine and pyrene functions, have been overwhelmed by the quenching effects of the complexed metal ions. In fact, the fluorescence quantum yields of the compounds **2** and **3** were 0.049 (in MeOH−H_2O, 30:70, v/v) and 0.15 (in CH_3CN−H_2O, 50:50, v/v), which are significantly lower than that of pyrene (0.66 in cyclohexane).[15] The lower quantum yield of the compounds indicates that the fluorescence of pyrene moieties was significantly suppressed by the PET processes operating from nearby nitrogen atoms of the amine to the pyrene fluorophores. The complex formation of **3** with Cu^{2+} and Hg^{2+} ions was also evidenced by the FAB-MS and IR measurements. In the FAB-MS spectra (*m*-NBA matrix), an intense peak for [**3**-Cu]$^+$ at *m*/*z* 917.4 was observed while that of the free **3** itself was not observed. Upon treatment with 3 equiv of metal perchlorates, the carbonyl stretching band of **3** was shifted from 1653 cm^{-1} to 1614 and 1610 cm^{-1} for Hg^{2+} and Cu^{2+} ions, respectively.

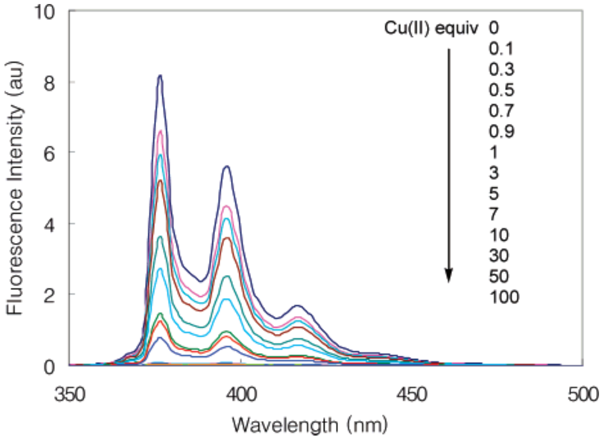

FIGURE 4. Fluorescence titration of **3** with Cu^{2+} ions in aqueous acetonitrile solution. [**3**] = 5.0 × 10^{-6} M, [acetate buffer] = 1.0 × 10^{-2} M (pH 4.9), CH_3CN:H_2O = 50:50, v/v. λ_{ex} = 340 nm.

To clarify the quantitative binding affinity of compound **3**, fluorescence titrations with Cu^{2+} and Hg^{2+} ions were carried out (Figure 4 and Figure S9 in the Supporting Information). The association constants, K_{assoc}, were determined by nonlinear curve fitting of the changes in fluorescence intensity of **3** at 377 nm and were found to be 3.25 × 10^7 and 6.88 × 10^6 M^{-1} for Cu^{2+} and Hg^{2+} ions, respectively. As can be seen from the K_{assoc} values, the compound exhibits similar binding strengths toward the two metal ions of Cu^{2+} and Hg^{2+}. From the titration results, the detection limits for the sensing of Cu^{2+} and Hg^{2+} ions were estimated to be 1.30 × 10^{-6} and 1.45 × 10^{-6} M, respectively.[16]

Finally, the selective recognition behavior of **3** toward Cu^{2+} or Hg^{2+} ions was confirmed by the competition experiments in the presence of other possibly interfering metal ions. The fluorescence changes of **3** were measured by the treatment of 10 equiv each of Cu^{2+} or Hg^{2+} ions in the presence of 100 equiv of other common interfering metal ions. As can be seen in Figure 5, the fluorescence of free **3** was quenched effectively by Cu^{2+} ions even in the presence of 100 equiv of other interfering metal ions, which means that the ionophore can signal the presence of Cu^{2+} ions in common analytes having various metal ions as a background. Similar experiments were also carried out with Hg^{2+} ions and the general tendency was similar to the results of Cu^{2+} ions, except for somewhat larger effects of Cu^{2+} ions on the responses of the **3**-Hg^{2+} system (Figure S10 in the Supporting Information).

In conclusion, the diametrically disubstituted pyrene derivative of cyclam showed a selective fluorescence quenching behavior toward Hg^{2+} and Cu^{2+} ions in aqueous acetonitrile solution. Introduction of amide functions into the pyrene-cyclam

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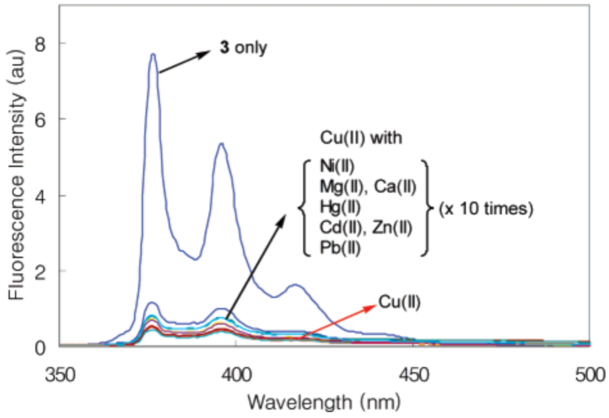

FIGURE 5. Changes in fluorescence spectra of the **3**-Cu^{2+} system in the presence of other common interfering metal ions. [**3**] = 5.0 × 10^{-6} M. [Cu^{2+}] = 5.0 × 10^{-5} M, [M^{2+}] = 5.0 × 10^{-4} M, [acetate buffer] = 1.0 × 10^{-2} M (pH 4.9) in CH_3CN-H_2O (50:50, v/v). λ_{ex} = 340 nm.

molecular framework enhanced the binding behavior of the compound. The selective ON−OFF type signaling responses toward Hg^{2+} and Cu^{2+} ions may be used as a new molecular switch or chemosensor for the analysis of these metal ions in aqueous environments. The pyrene-cyclam molecular motif can also be used as a starting platform for the construction of more sophisticated functional supramolecular systems.

Experimental Section

Cyclam and 1-chloromethylpyrene were purchased and used without further purification. ^{1}H NMR and ^{13}C NMR spectra were obtained with 300 and 75 MHz NMR spectrometers, respectively. Fluorescence spectra were measured with use of spectroscopic grade solvents.

Preparation of Dipyrene-cyclam 2. To a solution of tricyclic-cyclam **1**[7] (100 mg, 0.45 mmol) in acetonitrile was added 1-chloromethylpyrene (220 mg, 0.9 mmol) and KI (150 mg, 0.9 mmol), and the mixture was stirred under N_2 at room temperature. After 48 h, the precipitate formed was filtered and washed with a small amount of acetonitrile. The yellowish green powder was dissolved in a mixture of aqueous NaOH solution (3 M, 50 mL) and dioxane (15 mL). After the solution was stirred for 8 h at room temperature, the precipitated product was filtered and successively washed with cold water and a small amount of dioxane. The product was purified by the crystallization from DMF (yield 71%). ^{1}H NMR ($CDCl_3$) δ 8.65 (2H, d, J = 9 Hz), 7.86−8.15 (16H, m), 4.28 (4H, s), 2.56−2.82 (16H, m), 1.83 (4H, m). ^{13}C NMR ($CDCl_3$) δ 132.6, 131.5, 131.0, 130.7, 129.8, 128.0, 127.5, 127.4, 127.1, 126.0, 125.3, 125.1, 125.0, 124.9, 124.6, 123.8, 57.1, 53.9, 53.0, 48.8, 48.0, 26.4. HRMS (FAB, PEG-600) m/z calcd for $C_{44}H_{45}N_4$ 629.3644, found 629.3685.

Preparation of Dipyrene-diamide-cyclam 3. To a solution of compound **2** (50 mg, 0.08 mmol), K_2CO_3 (44 mg, 0.32 mmol), and KI (13 mg, 0.08 mmol) in acetonitrile was added *N*,*N*-diethyl bromoacetamide (80 mg, 0.4 mmol) and the mixture was refluxed under N_2 for 72 h. After the solution was cooled to room temperature, the solvent was removed and the residue formed was washed with acetonitrile and cold water to obtain an amber colored powder. The product was purified by the crystallization from DMF (yield 65%). ^{1}H NMR ($CDCl_3$) δ 8.87 (2H, d, J = 9.3 Hz), 7.96−8.19 (16H, m), 4.18 (4H, s), 3.04 (4H, q, J = 6.9 Hz), 2.95 (4H, s), 2.74−2.85 (12H, m), 2.53 (8H, m), 1.85 (4H, m), 0.73 (12H, q, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 170.0, 133.7, 131.5, 131.2, 130.9, 130.2, 128.9, 127.7, 127.2, 126.7, 126.1, 125.6, 125.3, 125.1, 125.0, 124.6, 58.1, 57.2, 51.6, 51.1, 50.6, 41.0, 39.4, 24.6, 14.0, 12.7. HRMS (FAB, PEG-600) m/z calcd for $C_{56}H_{67}N_6O_2$ 855.5325, found 855.5171.

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Supporting Information Available: NMR spectra and fluorescence behavior in the presence of various metal ions of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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