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Dimethylcyclam based fluoroionophore having Hg^{2+}- and Cd^{2+}-selective signaling behaviors

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Abstract—Diametrically disubstituted bis(anthrylmethyl) derivative of 1,8-dimethylcyclam exhibited pronounced Hg^{2+}- and Cd^{2+}-selective fluorogenic behaviors in aqueous acetonitrile solution. A distinctive OFF–ON type signaling was observed for Hg^{2+} and Cd^{2+} ions in aqueous acetonitrile (CH_3CN–H_2O = 90:10, v/v) solution, while a selective ON–OFF type switching behavior toward Hg^{2+} ions was observed in solution having higher water content (CH_3CN–H_2O = 50:50, v/v). The detection limit for the analysis of Hg^{2+} ions in 50% aqueous acetonitrile was found to be 3.8×10^{-6} M. The selective OR logic gate behavior of the prepared compound toward two toxic heavy metal ions of Hg^{2+} and Cd^{2+} ions in CH_3CN–H_2O (90:10, v/v) suggests the possibility as a new chemosensing device for the two important target metal ions.

Developments of chemosensors for the sensing of important ionic species are one of the most attractive research areas in supramolecular chemistry.[1] The underlying principle of the molecular design for the construction of selective chemosensors is generally the conjugation of the target-selective binding site with suitable signaling handles.[2] Crown ethers having anthrylmethyl groups[3] are classical examples of this principle and are well known for their characteristic PET (photoinduced electron transfer) type OFF–ON signaling toward many of the important ionic guests.[4] We are interested in the design of fluorogenic ionophores based upon cyclam (cyclam = 1,4,8,11-tetraazacyclotetradecane, **3**), a widely used molecular platform of nitrogen analogue of crown ethers, aiming for the selective and efficient sensing of transition metal ions.[5] In fact a variety of compounds derived from cyclams by appending suitable subunits having signaling functions have been devised to probe the important ionic guests and physical properties of the system.[6] For this purpose, chromogenic or fluorogenic signaling is much more attractive due to their sensitivity and easiness of signal detection.[7] Among the fluorophores, anthracene[8] and pyrene[9] functions are most widely employed due to their relatively well exploited photophysical behaviors. Particularly, 1,8-dianthryl derivative of the cyclam **4** has been prepared through the alkylation of tetraazatricyclohexadecane intermediate and the photophysical properties of Cr^{3+} complex[10] and intramolecular reductive nitrosylation by **4**-Cu^{2+} complex[11] were investigated. However, in spite of the potentially interesting structural characteristics of **4** as a fluorescence sensor, detailed sensing behavior toward transition metal ions has not been investigated. We report in this letter that the closely related 1,8-dimethylcyclam based dianthryl derivative **2** revealed a pronouncedly selective fluorescence enhancement or quenching behavior toward Hg^{2+} or Cd^{2+} ions in aqueous media. In fact, the developments of the detection[12] and treatment technique[13] for the heavy metal ions are very important in view of their extremely toxic impact on our environment.[14] The prepared compound can be used as a selective fluorescent molecular probe for the presence of the two toxic metal ions of Hg^{2+} or Cd^{2+} ions in environmental or biological samples.

Dianthryl derivative **2** was prepared by the alkylation of 1,8-dimethylcyclam **1** with 9-chloromethylanthracene (K_2CO_3, KI, CH_3CN) in good yield (89%) (Scheme 1).[15] The preparation of cyclam analogue **4** by direct alkylation of **3** was believed to be synthetically demanding due to the difficulties in the control of the degree of alkylation and regioselectivity. In fact, DeRosa et al.[10] have synthesized compound **4** by a three step reaction from **3** following the general procedure for the preparation

Keywords: Cyclam; Fluoroionophore; Anthracene; Hg^{2+}- and Cd^{2+}-selectivity; Chemosensor.

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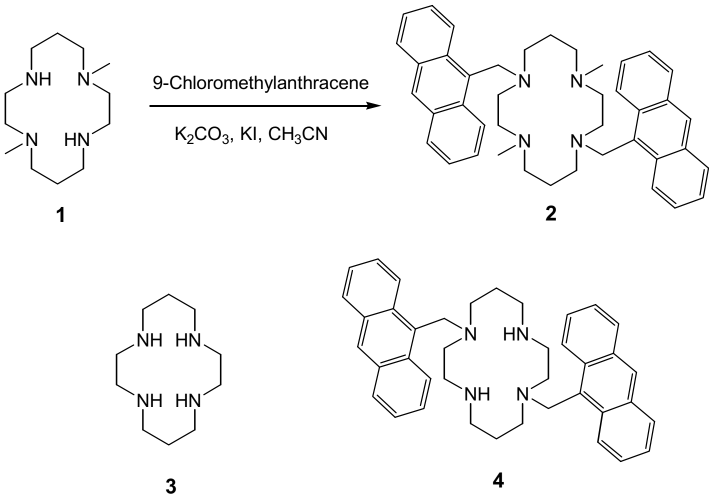

1 **2** **3** **4**

Scheme 1.

of 1,8-R$_2$cyclam by Guilard and co-workers[16] with 9-chloromethylanthracene. The synthesis of **2** instead of **4** seems to be reasonable and straightforward because the two distal tertiary amino groups are in a sense protected against the required alkylation reaction. Therefore, we prepared compound **2** having similar structural characteristics compared with **4** except for the two methyl groups on 1,8-positions and investigated the chemosensor behavior toward transition metal ions in aqueous media.

The fluorescence behavior of the prepared compound was strongly dependent on the pH of the medium due to the presence of basic amino groups adjacent to the PET type signaling anthrylmethyl fluorophores as expected.[3,4] Therefore, we first measured the fluorescence intensity changes of **2** at 417 nm as a function of the solution pH in CH$_3$CN–H$_2$O (50:50, v/v) (Fig. 1). In this case, the indicated pH values are pertinent to the apparent ones because the mixed aqueous acetonitrile solution was employed. In basic region of pH 11 the fluorescence of **2** was weak and starts to increase considerably around pH 6.5. Then the changes in intensity became plateau down to pH 5 with almost 10-fold increase in fluorescence intensity compared with that of pH 8. From pH 5 the intensity increased further 4.5-fold again down to pH 4 then no significant changes were observed until very acidic region of pH 2. This fluorescence enhancement behavior in the acidic solution is due to the inhibition of the PET processes between amine and anthracene fluorophore by the protonation of the amine groups of cyclam, which is responsible for the quenching of the fluorescence of **2**. Based on this preliminary observation, we carried out all the fluorescence experiments in acetate buffered solution at pH 5.0 where relatively optimized selectivity toward targeted metal ions was observed.

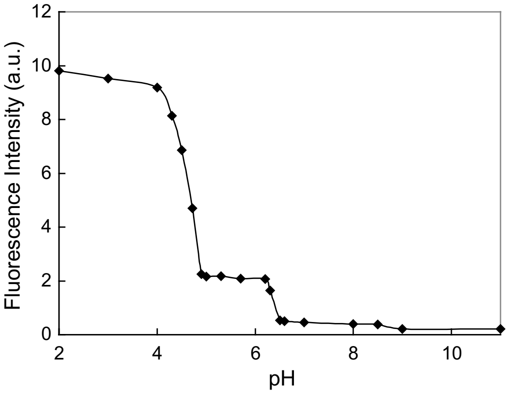

Figure 1. The fluorescence intensity of **2** at 417 nm as a function of apparent pH values in CH$_3$CN–H$_2$O (50:50, v/v). [**2**] = 5.0×10^{-6} M, λ_{ex} = 340 nm.

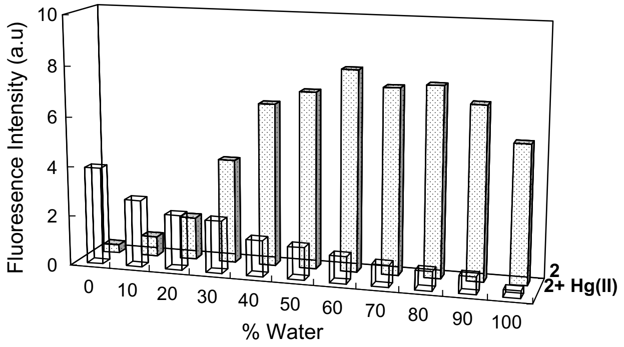

Figure 2. Fluorescence intensity of **2** at 417 nm in aqueous acetonitrile. [**2**] = 5.0×10^{-6} M, [Hg^{2+}] = 5.0×10^{-4} M, [acetate buffer] = 1.0×10^{-2} M at pH 5, λ_{ex} = 340 nm.

An interesting observation is that the fluorescence profiles for the compound **2** were somewhat different in the presence and absence of two most responding metal ions of Hg^{2+} and Cd^{2+} in varying water compositions of aqueous organic solvents. Figure 2 shows the effects of water composition on the fluorescence behavior of **2**-Hg^{2+} system in aqueous acetonitrile solution ([**2**] = 5.0×10^{-6} M and [Hg^{2+}] = 5.0×10^{-4} M). As the water composition increased, the fluorescence intensity at 417 nm for the ionophore itself gradually increased in lower water content region then decreased steadily, while that of **2** in the presence of 100 equiv of Hg^{2+} ions decreased monotonously. This profile suggests that the 90:10

$CH_3CN–H_2O$ and 50:50 $CH_3CN–H_2O$ solutions are relatively optimized conditions for the sensing of Hg^{2+} ions in OFF–ON and ON–OFF type modes, respectively, in terms of selectivity and the necessity for the employment of aqueous solution in the analysis of real samples.[17] We also tried to realize the enhanced selectivity toward Hg^{2+} ions by employing various solvent systems, and the selectivity was found to be decreased in sequence of acetonitrile > MeOH > dioxane among the surveyed aqueous organic solvents. Therefore, the fluorescence chemosensing behavior of compound **2** was investigated in two aqueous acetonitrile solutions having 10% and 50% water compositions.

We first investigated the ON–OFF type signaling behavior of **2** toward the metal ions in 50:50 $CH_3CN–H_2O$ solution. As can be seen from Figure 3, the compound **2** exhibited a pronouncedly selective quenching behavior toward Hg^{2+} ions among the representative alkali, alkaline earth, and transition metal ions. The quenching efficiency expressed by the ratio of the fluorescence intensity of **2** in the presence (I) and absence (I_o) of 100 equiv metal ions at 417 nm was 97% for Hg^{2+} ions. Other metal ions exhibited not so pronounced effects and the ratio was less than 15% even for the most interfering metal ions of Cu^{2+}.

The association constant (K_{assoc}) for the **2**-Hg^{2+} system was determined by fluorescence titration of **2** with Hg^{2+} ions in $CH_3CN–H_2O$ (50:50, v/v) solution. Upon interaction with Hg^{2+} ions, the fluorescence intensity was progressively decreased and the binding stoichiometry of **2**-Hg^{2+} complex was found to be 1:1 (Fig. 4). The fluorescence quenching was quite effective, such that with 10 equiv of Hg^{2+} ions more than two-thirds of the total quenching was observed. The nonlinear regression analysis of the titration results performed by the software Dynafit[18] afforded K_{assoc} value of $8.7 \times 10^4 M^{-1}$ for **2**-Hg^{2+} system. The K_{assoc} values of other metal ions could not be estimated due to the small changes in fluorescence intensities. From the titration results the detection limit[19] for the analysis of Hg^{2+} ions in $CH_3CN–H_2O$ (50:50, v/v) solution could also be determined and was found to be 3.8×10^{-6} M. The selective complexation of Hg^{2+} ions was also evidenced by the competition experiments. The fluorescence intensity of **2** in the presence of 10 equiv of Hg^{2+} ions was almost unaffected by the addition of 10 equiv of competing metal ions (Na^+, K^+, Mg^{2+}, Ca^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}).

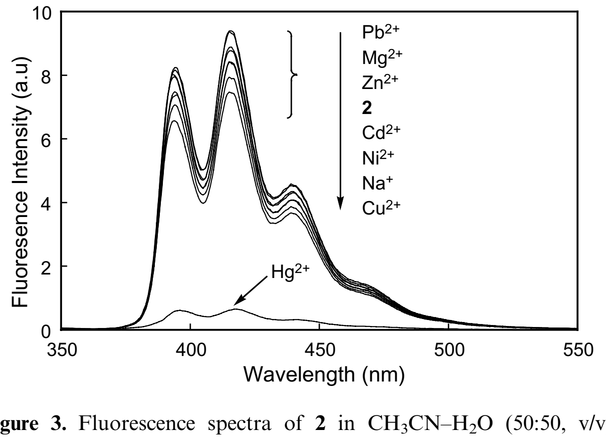

Figure 3. Fluorescence spectra of **2** in $CH_3CN–H_2O$ (50:50, v/v). $[\mathbf{2}] = 5.0 \times 10^{-6}$ M, $[M^{n+}] = 5.0 \times 10^{-4}$ M, [acetate buffer] $= 1.0 \times 10^{-2}$ M at pH 5, $\lambda_{ex} = 340$ nm.

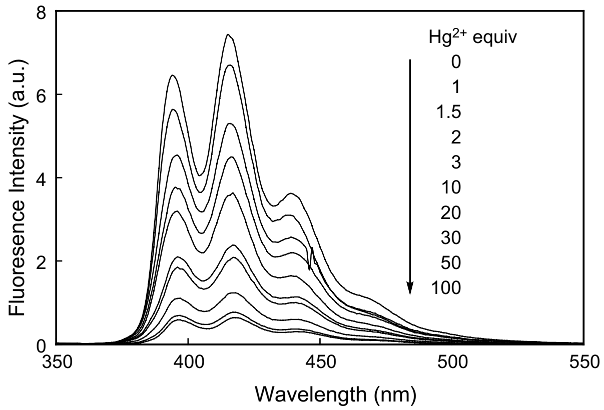

Figure 4. Fluorescence spectra of **2** as a function of Hg^{2+} ions in $CH_3CN–H_2O$ (50:50, v/v). $[\mathbf{2}] = 5.0 \times 10^{-6}$ M, [acetate buffer] $= 1.0 \times 10^{-2}$ M at pH 5, $\lambda_{ex} = 340$ nm.

On the other hand, the fluorescence enhancements of **2** were observed upon interaction with Hg^{2+} and Cd^{2+} ions in a media of lower water composition of 90:10 $CH_3CN–H_2O$ (Fig. 5). Here, relatively weak fluorescence of the ionophore and relatively intense fluorescence of the **2**-Hg^{2+} and **2**-Cd^{2+} systems resulted in OFF–ON type fluorescence signaling. In this case, the Hg^{2+} and Cd^{2+} ions revealed quite large enhancements of the fluorescence intensity and the relative fluorescence enhancement factors as expressed by the fluorescence intensity ratio of I/I_o observed at 417 nm were 5.8 and 4.9 for 100 equiv of Hg^{2+} and Cd^{2+} ions, respectively. The enhancement might be due to the participation of the cyclam amine groups in metal ion complexation that resulted in the inhibition of the PET process between the amine and the anthryl fluorophore. Such fluorescence enhancements in the presence of the intrinsically quenching ions are possible when the binding-induced

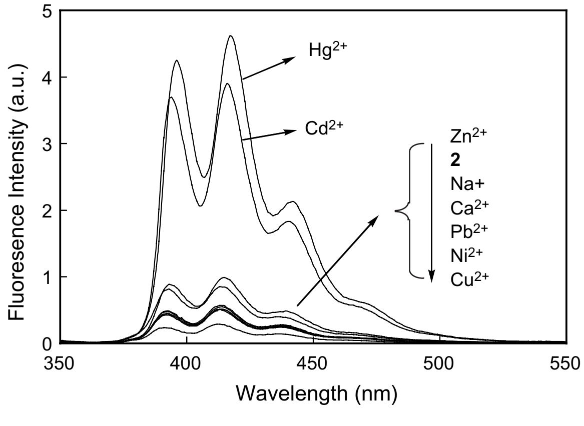

Figure 5. Fluorescence spectra of **2** in $CH_3CN–H_2O$ (90:10, v/v). $[\mathbf{2}] = 5.0 \times 10^{-6}$ M, $[M^{n+}] = 5.0 \times 10^{-4}$ M, [acetate buffer] $= 1.0 \times 10^{-2}$ M at pH 5, $\lambda_{ex} = 340$ nm.

Table 1. OR logic gate behavior of **2** toward two toxic chemical inputs of Hg^{2+} and Cd^{2+} ions

Input A (Hg^{2+})	Input B (Cd^{2+})	Fluorescence intensity at 417 nm	Output
X	X	0.79	OFF, 0
X	O	3.85	ON, 1
O	X	4.61	ON, 1
O	O	4.73	ON, 1

In $CH_3CN–H_2O$ (90:10, v/v) buffered at pH 5 ([acetate buffer] = 1.0×10^{-2} M), [**2**] = 5.0×10^{-6} M, $[M^{2+}] = 5.0 \times 10^{-4}$ M, λ_{ex} = 340 nm.

recovery of fluorescence is greater than the quenching-induced reduction in fluorescence intensity.[20] Other metal ions including representative transition metal ions revealed relatively insignificant responses or some fluorescence quenching. The association constants for the 90:10 $CH_3CN–H_2O$ solution were also estimated by the fluorescence titrations of **2** with the two most responding metal ions. The K_{assoc} values for Hg^{2+} and Cd^{2+} ions were 4.4×10^5 and $1.7 \times 10^4\,M^{-1}$, respectively. The detection limits of **2** for the analysis of Hg^{2+} and Cd^{2+} ions in 10% aqueous acetonitrile solution were calculated to be 2.1×10^{-6} and 1.1×10^{-5} M, respectively.

The selective fluorescence enhancements of **2** in response to the Hg^{2+} and Cd^{2+} ions in 10% aqueous acetonitrile solution suggest the possibility of the present compound as a molecular OR logic gate toward the two important chemical inputs.[21] The fluorescence intensity observed at 417 nm was significantly enhanced in the presence of each or both of the two chemical inputs of Hg^{2+} and Cd^{2+} ions, that is, a typical of OR logic gates (Table 1). The fluorescence enhancements observed at 417 nm were at least larger than 4.8-fold compared with the free ionophore **2**. This type of response can be utilized as a selective signaling probe for the presence of either of the two toxic heavy metal ions in a variety of environmental or biological samples.

In summary, a simple bis(anthrylmethyl) derivative of 1,8-dimethylcyclam exhibited pronounced Hg^{2+}- and Cd^{2+}-selective fluorogenic behaviors in aqueous acetonitrile solutions. A distinctive OFF–ON type signaling was observed for Hg^{2+} and Cd^{2+} ions in lower water content solutions, while a selective ON–OFF type switching behavior toward Hg^{2+} ions was observed in media of higher water contents. The ionophore showed a selective OR logic gate behavior toward two toxic chemical inputs of Hg^{2+} and Cd^{2+} ions. The compound could be utilized as a new switching or sensing device for the presence and analysis of these two toxic metal ions in chemical and biological systems.

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15. 1,8-Dimethylcyclam and 9-chloromethylanthracene were purchased from Aldrich. Synthesis of **2**: A mixture of 1,8-dimethylcyclam (102 mg, 0.45 mmol), 9-chloromethylanthracene (210 mg, 0.95 mmol), K_2CO_3 (131 mg, 0.95 mmol), and KI (75 mg, 0.45 mmol) in CH_3CN (30 mL) was refluxed under N_2 for 24 h. After cooling, the solution was filtered and the filtrate was evaporated. The residue was partitioned between H_2O and CH_2Cl_2 and the organic layer was washed with water. The separated organic layer was evaporated and the product was purified by the crystallization from DMF to yield white solids. Yield, 89%. ^1H NMR (300 MHz, $CDCl_3$) δ 8.90 (d, $J = 8.4$ Hz, 4H, ArH), 8.40 (s, 2H, ArH), 8.00 (d, $J = 9.9$ Hz, 4H, ArH), 7.48 (m, 8H, ArH), 4.42 (s, 4H, $ArCH_2$), 2.68 (br t, 4H, NCH_2), 2.47 (br t, 4H, NCH_2), 2.37 (br t, 4H, NCH_2), 2.02 (s, 6H, NCH_3), 1.90 (m, 4H, NCH_2), 1.70 (m, 4H, $NCH_2C\mathit{H}_2CH_2N$). HR-MS (FAB, *m*-NBA) Calcd for $C_{42}H_{49}N_4$ $[M+H]^+$ 609.3957. Found 609.3956.
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