

## Cyclam Based Hg(II)- and Cu(II)-selective Fluoroionophore Having Appended Pyrene Function

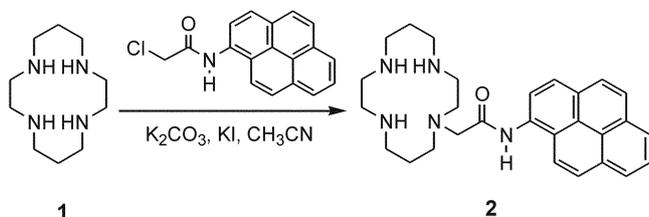
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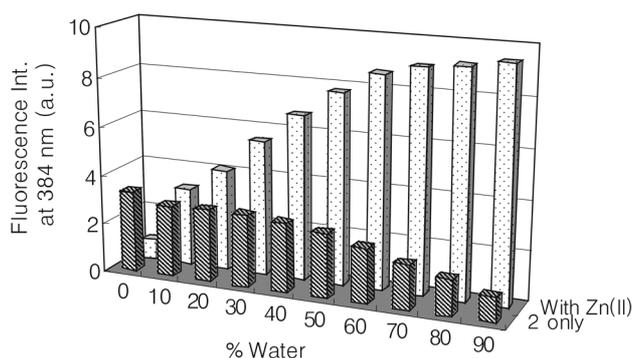
Received March 10, 2005

**Key Words :** Cyclam, Pyrene, Hg<sup>2+</sup>- and Cu<sup>2+</sup>-selectivity, Fluoroionophore, NOR logic gate

Developments of selective chemosensors for the signaling of environmentally and biologically important ionic species have been constantly attracted much attention in the field of supramolecular chemistry.<sup>1,2</sup> The compounds are generally designed by conjugating the selective binding site for the recognition of targeted guests with suitable signaling sub-units. Metal-ion selective chemosensors generally comprise a metal-ion recognition site and a signal transduction domain that is triggered upon metal-ion binding.<sup>3</sup> Cyclam and many of its derivatives are well-known for their unique ionophoric properties toward some representative transition metal ions.<sup>4</sup> We have tried to develop a new fluoroionophore by utilizing the excellent molecular recognition ability of cyclam by appending the efficient signaling fluorophore of anthracene or pyrene functions in 'fluorophore-spacer-receptor' mode.<sup>5</sup> The preliminary Zn<sup>2+</sup>-selective fluoroionophoric properties of monopyrene functionalized cyclam **2** in aqueous media have been reported.<sup>6</sup> During the search for the more optimized conditions for the enhanced Zn<sup>2+</sup>-selective ionophoric properties of **2**, we have found that the compound also exhibited a selective fluorescence quenching behavior toward two important transition metal ions of Hg<sup>2+</sup> and Cu<sup>2+</sup> ions in aqueous organic solutions having relatively lower water compositions. This paper reports that the pronouncedly selective ON-OFF type fluorescence quenching behavior of compound **2** toward environmentally important metal ions of Hg<sup>2+</sup> and Cu<sup>2+</sup>,<sup>7,8</sup> in addition to the previously reported OFF-ON type signaling toward Zn<sup>2+</sup> ions.



Reaction of 1,4,8,11-tetraazacyclotetradecane (cyclam) with 0.2 equiv of 2-chloro-*N*-pyren-1-yl-acetamide (K<sub>2</sub>CO<sub>3</sub>, KI, CH<sub>3</sub>CN) afforded desired mono-functionalized cyclam derivative **2** (yield based on **1** = 12%). Using higher ratio of alkylating agent resulted in the formation of complex mixture comprising other higher alkylated compounds. 2-Chloro-*N*-pyren-1-yl-acetamide was prepared by the reac-

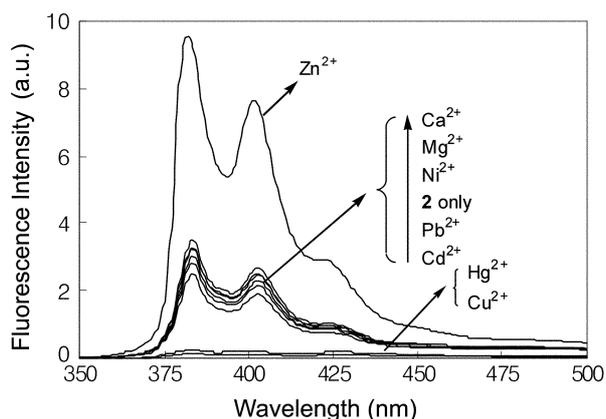


**Figure 1.** Fluorescence intensity of **2** in the presence and absence of Zn<sup>2+</sup> ions as a function of water composition in aqueous MeOH solution. Buffered with 10 mM HEPES at pH 7.0. [2] = 1.0 × 10<sup>-5</sup> M. [Zn<sup>2+</sup>] = 1.0 × 10<sup>-3</sup> M. λ<sub>ex</sub> = 340 nm. Fluorescence intensity was observed at 384 nm.

tion of 1-aminopyrene with chloroacetyl chloride (NEt<sub>3</sub>/CH<sub>2</sub>Cl<sub>2</sub>).<sup>9</sup>

The cyclam and various related derivatives are known to have strong affinity toward some of important transition metal ions.<sup>10</sup> We have tried to find more enhanced structure and optimized conditions for the previously reported OFF-ON type Zn<sup>2+</sup>-selectivity of **2** by surveying the conditions of varying pH and various solvent systems. Aqueous MeOH system was found to be relatively well optimized for the realization of Zn<sup>2+</sup> selectivity, among the tested three representative water miscible organic solvents of dioxane, acetonitrile, and MeOH. In aqueous MeOH solution, the fluorescence intensity of compound **2** observed at 384 nm decreased as the water content increased, while that of **2** in the presence of 100 equiv of Zn<sup>2+</sup> increased significantly (Figure 1). From this observation we could reconfirm that the selective fluorescence sensing of Zn<sup>2+</sup> with **2** became more favorable with increasing water contents in aqueous MeOH solution.

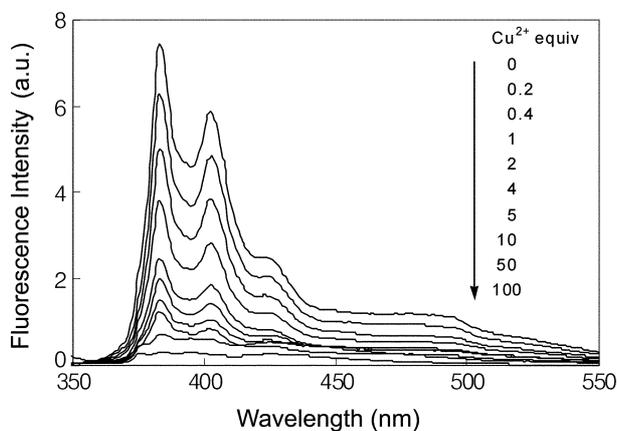
As discussed above, during the search for the optimized condition for the Zn<sup>2+</sup>-selectivity of **2**, we have found that in aqueous solutions of lower water contents the Zn<sup>2+</sup>-selectivity of **2** was significantly decreased. Interesting observation is that the compound **2** showed a selective and efficient quenching effect toward Hg<sup>2+</sup> and Cu<sup>2+</sup> ions in aqueous solution as the water composition lowered. For example, treatment of the ionophore solution with 100 equiv of Cu<sup>2+</sup> ions resulted in almost complete quenching of the



**Figure 2.** Fluorescence spectra of **2** in the presence of varying metal ions. In MeOH : H<sub>2</sub>O (50 : 50, v/v) buffered with 10 mM HEPES at pH 7.0. [2] = 1.0 × 10<sup>-5</sup> M. [M<sup>2+</sup>] = 1.0 × 10<sup>-3</sup> M. λ<sub>ex</sub> = 340 nm.

pyrene fluorescence in MeOH-H<sub>2</sub>O (5 : 5, v/v) solution (Figure 2). Hg<sup>2+</sup> ions also exhibited a strong quenching of the fluorescence which was comparable with the case of Cu<sup>2+</sup> ions. That might be due to the efficient quenching effects of intrinsically quenching nature of selectively complexed Cu<sup>2+</sup> and Hg<sup>2+</sup> ions.<sup>11</sup> Other metal ions of Cd<sup>2+</sup>, Pb<sup>2+</sup> and Ni<sup>2+</sup> showed much minor quenching of the fluorescence and alkali and alkaline earth metal ions revealed almost no changes in fluorescence behavior of the ionophore **2**. Another interesting observation is the fluorescence enhancement with the Zn<sup>2+</sup> ions in aqueous MeOH solution of higher water composition is somewhat retained in this experimental condition. Under this relatively optimized condition for the selective sensing of Cu<sup>2+</sup> and Hg<sup>2+</sup> ions, Zn<sup>2+</sup> solely enhanced the fluorescence intensity of **2** around 2.8-fold of the free ionophore among the tested metal ions, although which is much smaller than the value obtained with 90% aqueous methanol solution.

From the fluorescence titration results of **2** with Hg<sup>2+</sup> and Cu<sup>2+</sup> ions the association constants ( $K_{\text{assoc}}$ ) were estimated



**Figure 3.** Fluorescence titration of **2** with Cu<sup>2+</sup> ions. In MeOH : H<sub>2</sub>O (50 : 50, v/v) buffered with 10 mM HEPES at pH 7.0. [2] = 1.0 × 10<sup>-5</sup> M. λ<sub>ex</sub> = 340 nm.

**Table 1.** Selective NOR logic gate behavior of **2** toward chemical inputs of Hg<sup>2+</sup> and Cu<sup>2+</sup> ions

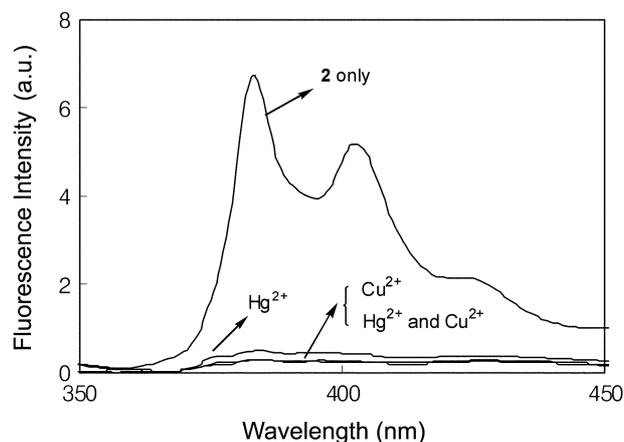
Input A Hg <sup>2+</sup>	Input B Cu <sup>2+</sup>	Fluorescence Intensity (a.u.) <sup>a</sup>	Output
X	X	High (6.63)	ON
O	X	Low (0.50)	OFF
X	O	Low (0.28)	OFF
O	O	Low (0.29)	OFF

<sup>a</sup>Fluorescence intensities were measured at 384 nm. 'O' and 'X' denote the presence and absence of the specified chemical inputs, respectively. [2] = 1.0 × 10<sup>-5</sup> M. [M<sup>2+</sup>] = 1.0 × 10<sup>-3</sup> M. In MeOH : H<sub>2</sub>O (50 : 50, v/v).

by non-linear curve fitting procedure by using the software Dynafit.<sup>12</sup> The concentration dependent fluorescence changes toward Cu<sup>2+</sup> ions were prominent and the fluorescence intensity was almost completely quenched with 10 equiv of added metal ions showing clear break around one equiv of metal ions (Figure 3). The association constants were found to be 9.8 × 10<sup>4</sup> M<sup>-1</sup> and 7.9 × 10<sup>5</sup> M<sup>-1</sup> for Hg<sup>2+</sup> and Cu<sup>2+</sup>, respectively. The  $K_{\text{assoc}}$  values for other metal ions could not be estimated due to the marginal changes in fluorescence intensity.

The selective Hg<sup>2+</sup>- and Cu<sup>2+</sup>-induced ON-OFF type signaling pattern of the compound **2** could be utilized for the construction of a molecular logic gate.<sup>13</sup> The fluorescence intensity changes observed at 384 nm were a typical pattern of a NOR logic gate behavior (Table 1).<sup>14</sup> Relatively strong fluorescence of **2** was selectively quenched in the presence of each or both of the chemical inputs of Hg<sup>2+</sup> and Cu<sup>2+</sup> (Figure 4). That might be useful for the design of selective molecular switching system utilizing the selective ON-OFF type responses of two important chemical inputs of Hg<sup>2+</sup> and Cu<sup>2+</sup> ions without affected by the presence of other metal ions.

In summary, a simple derivative of cyclam having one monopyrene subunit as signaling fluorophore exhibited a highly selective ON-OFF type fluoroionophoric behavior toward Hg<sup>2+</sup> and Cu<sup>2+</sup> ions in aqueous solution. The



**Figure 4.** Fluorescence spectral changes of **2** toward chemical inputs of Hg<sup>2+</sup> or Cu<sup>2+</sup> ions. [2] = 1.0 × 10<sup>-5</sup> M. [M<sup>2+</sup>] = 1.0 × 10<sup>-3</sup> M. In MeOH : H<sub>2</sub>O (50 : 50, v/v).

fluorescence quenching pattern is typical of a NOR logic gate behavior in response to the two important chemical inputs of Hg<sup>2+</sup> and Cu<sup>2+</sup> ions. The observed fluoroionophoric behavior can be used as a new chemosensor for the analysis of Hg<sup>2+</sup> and Cu<sup>2+</sup> ions and molecular switching device in designing new functional supramolecular devices.

### Experimental Section

**General.** <sup>1</sup>H NMR spectra were recorded at 300 MHz on a Varian Gemini-2000 spectrometer. Mass spectra were obtained with a Micromass Autospec Mass Spectrometer. UV-vis absorption spectra were acquired on a JASCO V-550 spectrophotometer. Fluorescence measurements were carried out using an Aminco-Bowman Series 2 Spectrometer. Flash column chromatography was performed with Biotage Flash 40 system using prepacked silica gel cartridge. Spectroscopic grade solvents were used for the fluorescence measurements. Cyclam and 1-aminopyrene were purchased from Aldrich Chemical Co. and used without further purifications. 2-Chloro-*N*-pyren-1-yl-acetamide was prepared following the reported procedure.<sup>9</sup>

***N*-Pyren-1-yl-2-(1,4,8,11-tetraazacyclotetradec-1-yl)-acetamide (2).** A mixture of cyclam **1** (1 mmol, 200 mg), 2-chloro-*N*-pyren-1-yl-acetamide (0.2 mmol, 59 mg), K<sub>2</sub>CO<sub>3</sub> (1 mmol, 138 mg), and KI (0.1 mmol, 17 mg) in CH<sub>3</sub>CN (40 mL) was heated reflux under N<sub>2</sub>. After 24 h the solvent was evaporated under reduced pressure and the residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> and washed with water. The organic layer was separated and the solvent was removed. The crude product was purified by column chromatography (silica gel, CH<sub>2</sub>Cl<sub>2</sub>-MeOH) to yield desired product **2**. Yield: 12% based on **1**. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 8.27 (d, *J* = 9.3 Hz, 1H), 8.19-7.96 (m, 8H), 3.45 (s, 2H), 2.90 (t, *J* = 5.4 Hz, 2H), 2.80 (m, 8H), 2.41 (t, *J* = 5.1 Hz, 2H), 2.28 (t, *J* = 5.1 Hz, 2H), 2.10 (m, 2H), 1.93 (m, 2H), 1.49 (m, 2H). HRFAB-MS (*m*-NBA): calcd *m/z* for C<sub>28</sub>H<sub>36</sub>N<sub>5</sub>O 458.292, Found, 458.297 (100%).

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