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Pyrene-Armed Calix[4]azacrowns as New Fluorescent Ionophores: "Molecular Taekowndo" Process via Fluorescence Change

Jong Seung Kim,*[,†] Ok Jae Shon,[†] Jeong Ah Rim,[†]
Sook Kyung Kim,[‡] and Juyoung Yoon*[,‡]

*Department of Chemistry, Konyang University,
Nonsan 320-711, Korea, and Department of New Materials
Chemistry, Silla University, Pusan 617-736, Korea*

jongskim@konyang.ac.kr

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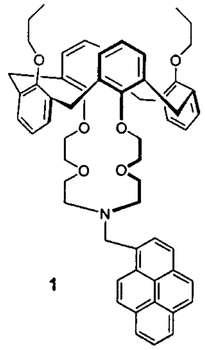
Abstract: A series of new calixarene-based fluoroionophores were synthesized. With our new calixarene derivative bearing a crown ether and an azacrown ether as two binding sites, the metal ion was found to selectively choose its better binding pocket between these two ligands. Interesting "molecular taekowndo" processes between Ag$^+$−K$^+$, Cu^{2+}−K$^+$, and Ag$^+$−Cs$^+$ pairs were easily monitored via fluorescence change.

As a consequence of the rapid development of supramolecular chemistry, supramolecular technology has allowed the development of fluorescent probes for metal cations.[1] Calixarenes with the appropriate appended groups are good candidates for probes because they have been shown to be highly specific ligands, and their potential applications as sensing agents have received increasing interest.[2,3] In fact, several calixarene-based fluorescent sensors have already been designed.[4−7]

Noteworthy is a paper reported by Dabestani and coworkers in which 9-cyanoanthracene is covalently attached to the parent molecule, a 1,3-alternate conformer of calix[4]bis-*o*-benzocrown-6, to prepare a fluorescent ionophore.[6a] Among Li$^+$, Na$^+$, K$^+$, and Cs$^+$ ions, this compound shows a selective binding for Cs$^+$ ion. In the absence of cesium ions, fluorescence is partially quenched by photoinduced electron transfer (PET) from the dialkoxybenzene moiety of the crown ring to the excited singlet state of 9-cyanoanthracene. Upon complexation, the oxygen lone pairs no longer participate in PET, causing the chelation-enhanced fluorescence (CHEF) effect.[6] However, studies indicate that this CHEF effect resulting from the elimination of PET can be maximized in a system that has a fairly reducing amine group.[1]

Table 1. CHEF Effects of 1 (6 μM) with Metal Ions (10 equiv, 60 μM) in Ethanol at 389 nm[a]



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Li(I)	2.5	Mg(II)	5.1	Zn(II)	15.2
Na(I)	9.8	Ca(II)	8.5	Cu(II)	655.5
K(I)	125.8	Sr(II)	9.5	Hg(II)	4.5
Rb(I)	160.0			Cd(II)	4.5
Cs(I)	21.9			Co(II)	53.9
				Mn(II)	31.2
Ag(I)	71.0			Pb(II)	650.1

[a] Numbers are calculated values ($I - I_o$) from three independent experiments.

Calixazacrown ethers as a fluorescent ionophore have not been investigated until now. In the present study, we report the first example of a calixarene-based azacrown fluoroionophore. In this system, the nitrogen moiety of the azacrown ring not only participates in the selective binding but also serves as a probe for the CHEF effect. Furthermore, we have observed an interesting *on*−*off* fluorescent effect, using our new calix[4]arene derivative bearing a crown ether and an azacrown ether as two different binding sites.

Our synthesis began with 25,27-bis(1-propyloxy)calix[4]azacrown-5[3a] for **1**, calix[4]crown-5-azacrown-5[3a] for **2**, and calix[4]crown-6-azacrown-5[3d] for **3**. Under a nitrogen atmosphere, treatment with 1-bromomethylpyrene and triethylamine in THF led to 1,3-alternate **1**−**3** in 21%, 20%, and 50% yield, respectively.

The perchlorate salts of Ca^{2+}, Cd^{2+}, Co^{2+}, Cs$^+$, Cu^{2+}, Hg^{2+}, Ag$^+$, K$^+$, Li$^+$, Mg^{2+}, Mn^{2+}, Na$^+$, Pb^{2+}, Rb$^+$, Sr^{2+}, and Zn^{2+} have been used to evaluate metal ion binding. Using these metal ions (60 μM, 10 equiv), we found that **1** (6 μM) displayed large chelation-enhanced fluorescence (CHEF) effects with Cu^{2+}, K$^+$, Pb^{2+}, and Rb$^+$ (Table 1). Compound **1** also showed relatively small CHEF effects with Ag$^+$ and Co^{2+}. The CHEF effect of the Na$^+$ ion was negligible compared with that of the K$^+$ ion under these conditions. The association constants were estimated from the change in fluorescence as the concentration of metal ion changed, yielding with Cu^{2+} = 7.5×10^4, K$^+$ = 1.0×10^5, Pb^{2+} = 3.3×10^4, Ag$^+$ = 5.1×10^5, and Rb$^+$ = 5.0×10^4 M^{-1} in ethanol.[8] The overall emission changes were dramatic: 50-fold for Cu^{2+} and Pb^{2+}, 12-fold for Rb$^+$, and 10-fold for the K$^+$ ion. We believe we were simply observing fluorescence quenching via a PET process. Fluorescence quenching by inter- and intramolecular amines is, of course, a well-known phenomenon.[9] CHEF

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* To whom correspondence should be addressed. E-mail: (J.Y.) jyoon@silla.ac.kr.

[†] Konyang University.

[‡] Silla University.

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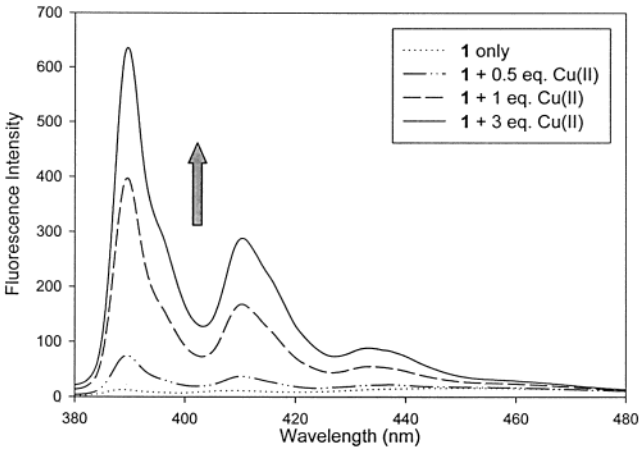

Figure 1. Fluorescence emission spectra of **1** (6 μM) upon the addition of various amounts of Cu^{2+} in ethanol.

on metal ion addition thus results when metal ion complexation of the amine lone pairs decreases amine oxidizability such that the amine cannot reduce the pyrene S_1 excited state. Fluorescence emission spectra of **1** upon the addition of Cu^{2+} are shown in Figure 1.

On the other hand, **2** displayed similar CHEF effects only with Ag^+, Co^{2+}, Cu^{2+}, and Pb^{2+}. Unlike **1**, this compound did not show any CHEF effect with K^+ and Rb^+. As shown in Figure 2, when the metal ion is bound to **2**, the metal ion itself can choose its better binding partner between the two different binding sites, such as crown ether and azacrown bearing a pyrene group. Obviously, the azacrown ligand is participating in the binding with Cu^{2+} and Pb^{2+}, which results in the large CHEF effects. On the contrary, K^+ shows a better binding affinity with the crown ether moiety of **2**, and therefore, no CHEF effect was observed. Furthermore, the complexation of the second metal ion is not happening in this system, which is probably due not only to electrostatic repulsion between the two metal ions but also to an induced conformation change that does not favor binding of the second metal.[10]

The stoichiometry of the complex was confirmed by a Job plot utilizing the fluorescent titrations of **2** with silver perchlorate in ethanol/acetone (3:1, v/v).[8b] The Job plot indicating a 1:1 complex ratio is shown in the Supporting Information (Figure S1). The ratio of **2** to silver ion was also assessed by high-resolution mass spectrometry. A mixture of **2** (20 mg) dissolved in $CHCl_3$ (10 mL) and excess $AgClO_4$ (at least 5 equiv) was stirred for 1 h. After filtration of the precipitated excess $AgClO_4$, the filtrate was evaporized in vacuo to give a white solid complex **2**·Ag^+. A FAB-MS molecular ion peak of *m*/*z* 1061.1

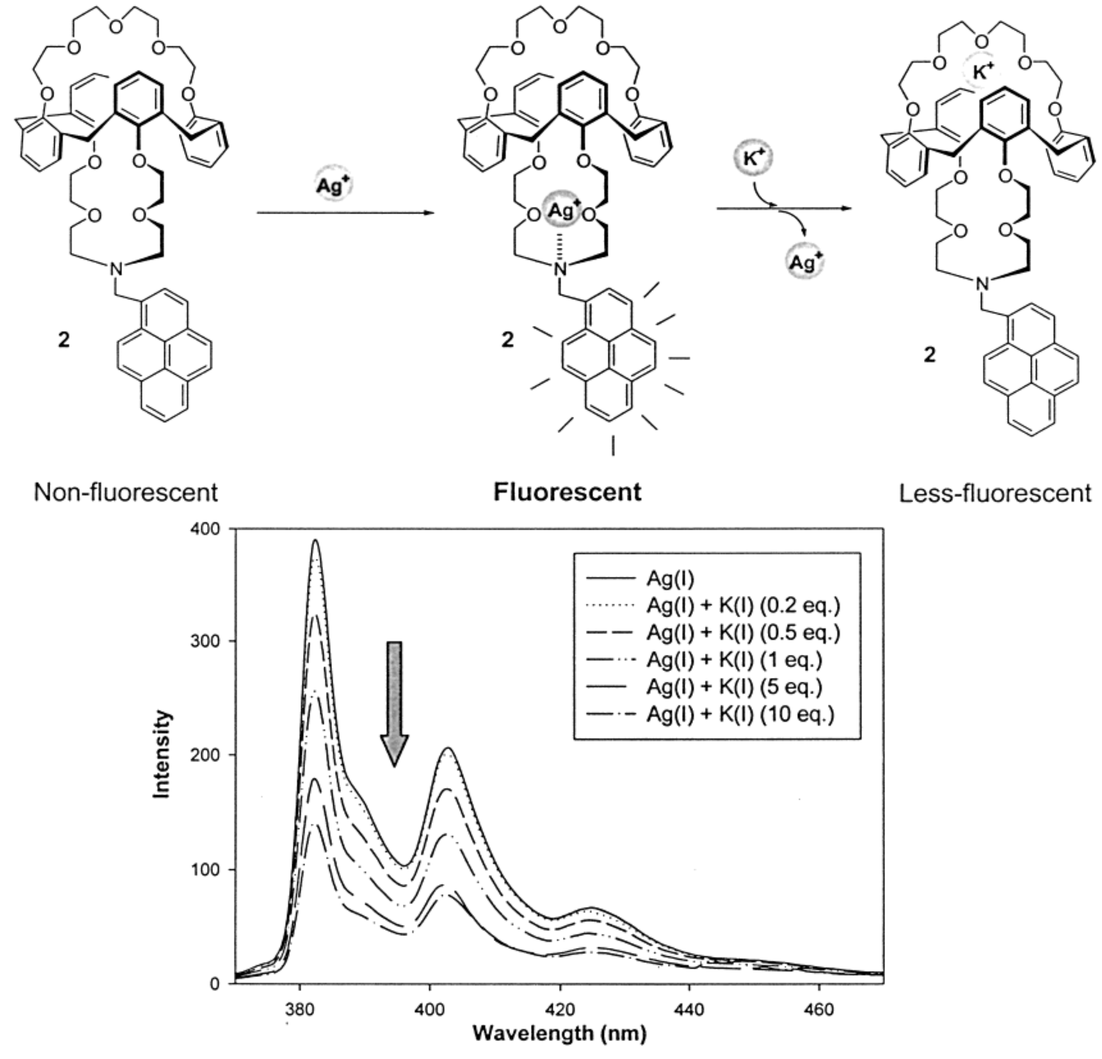

Figure 2. Fluorescence emission spectra of **2** (6 μM)·Ag^+ (10 equiv) upon the addition of various amount of K^+ in ethanol.

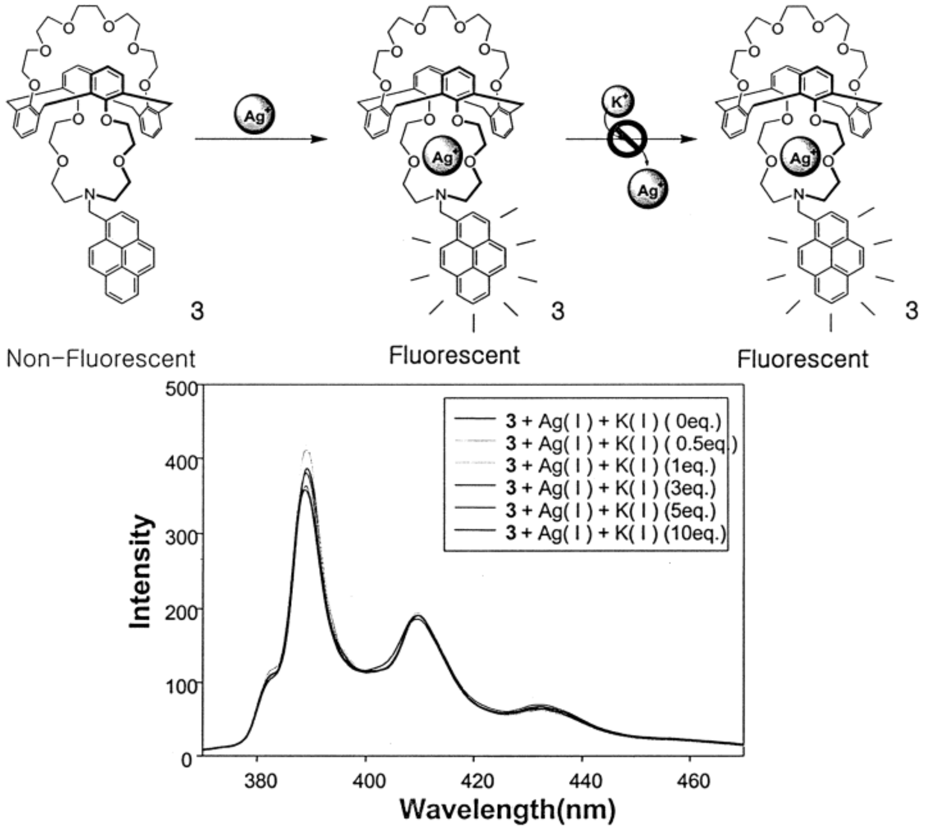

Figure 3. Fluorescence emission spectra of **3** (6 μM)·Ag^+ (10 equiv) upon the addition of various amount of K^+ in ethanol.

indicates a 1:1 complex of **2**·Ag^+. No other mass fragmentation (e.g., 1:2 or 2:1) complexes were observed. Therefore, from the results of the Job plot experiment, mass analysis and the fluorescence spectrum (vide infra), one can conclude that the silver ion favors the azacrown part rather than the crown-5 loop by a 1:1 ligand−metal ion ratio.

In ethanol, the fluorescence of **2** was almost completely quenched via the PET process. Upon the addition of Ag^+, the CHEF effect was observed due to the inhibition of the PET mechanism. This CHEF effect also confirms that Ag^+ ($K_a = 6.0 \times 10^3$ M^{-1}) is in the azacrown site. When K^+ ion was added to a solution containing **2** (6 μM) and Ag^+ (10 equiv), we observed fluorescence quenching effects with K^+ ion. Complexation of K^+ into the crown ether site induced the decomplexation of Ag^+ from the azacrown site. In the present study, this “molecular taekwondo: coming-in and kicking-out” process was easily monitored via fluorescence change (Figure 2). The above observation was repeated using a Cu^{2+}−K^+ pair. Since Cu^{2+} ($K_a = 1.5 \times 10^5$ M^{-1}) binds more tightly than Ag^+, the fluorescence of **2** in the presence of 10 equiv of Cu^{2+} showed no decrease upon the addition of K^+ (up to 10 equiv). However, a gradual decrease in fluorescent emission was observed when K^+ was added to an ethanol solution of **2** containing 1 equiv of Cu^{2+}.

More interestingly, for **3** in which crown-6 suitable for cesium ion is attached on the calix[4]azacrown-5, the fluorescence intensity was scarcely changed when the K^+ ion was added (0−10 equiv) to the fluorescent solution of **3**·Ag^+ as shown Figure 3, meaning that the metal ion exchange process did not take place. This is obviously because the cavity size of the crown-6 loop is too large to capture the K^+ ion. On the contrary, the fluorescence intensity is found to gradually decrease when the cesium ion (0−10 equiv) was triturated to the fluorescent **3**·Ag^+ solution as shown in Figure 4. This is also because the cesium ion does fit with the crown-6 cavity very well, and then the silver ion is extracted from the azacrown-5 loop by metal−metal ion repulsion as previously mentioned. This can be an additional proof for the “coming-in and kicking-out” process through the fluorescence change.

In conclusion, we reported a synthesis and binding study of new calixarene-based fluoroionophores. By blocking the PET mechanism, we observed up to a 50-fold emission enhancement in ethanol. Among the metal ions examined, **1** displayed large CHEF effects with Cu^{2+}, K^+, Pb^{2+}, and Rb^+. Furthermore, with our new calixarene derivative bearing a crown ether and an azacrown ether as two binding sites, the metal ion can selectively choose its better binding pocket between these two ligands. Also, interesting “molecular taekowndo” processes between Ag^+−K^+, Cu^{2+}−K^+, and Ag^+−Cs^+ pairs were easily monitored via fluorescence change. These results suggest that the source of the binding selectivity comes from the calixarene and azacrown ligand and the sensitivity comes from controlling the fluorescence and PET mechanisms associated with the amine moiety, which may be employed successfully in the creation of selective and practical chemosensors.

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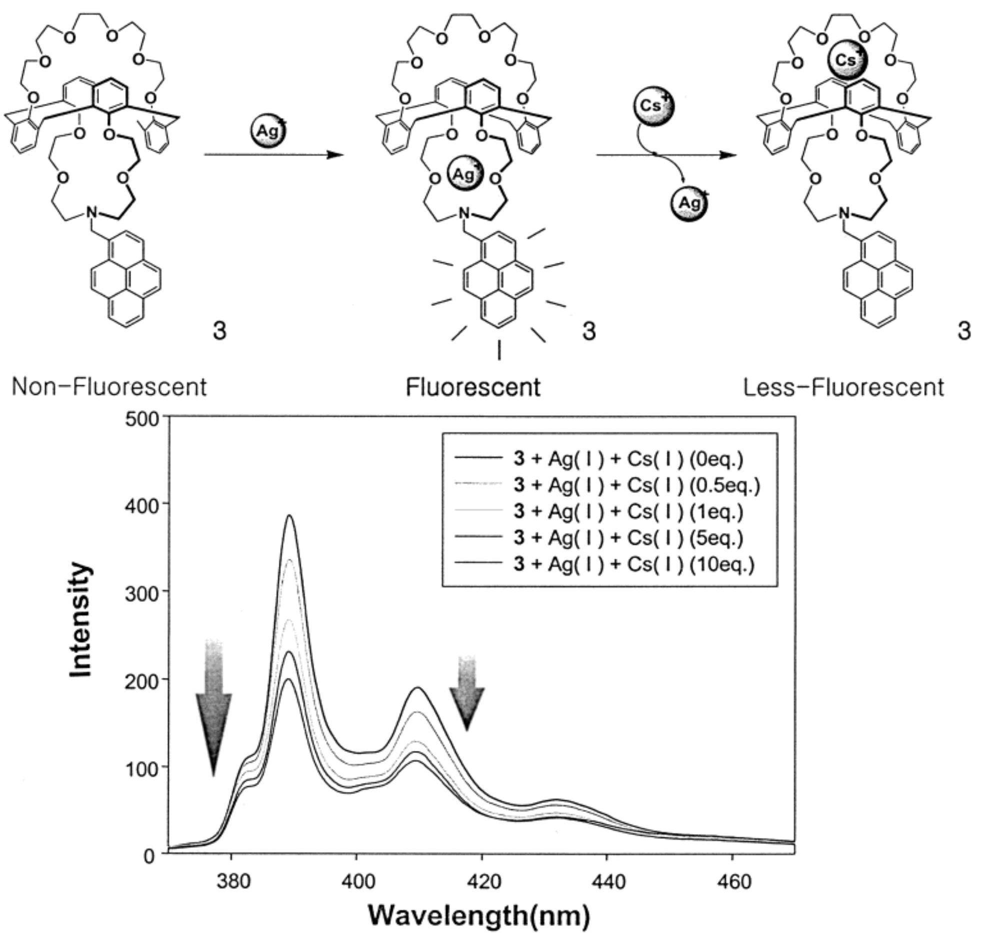

Figure 4. Fluorescence emission spectra of **3** (6 μM)·Ag$^+$ (10 equiv) upon the addition of various amount of Cs$^+$ in ethanol.

Experimental Section

1,3-Alternate *N*-(1-Pyrenemethyl)-25,27-bis(1-propyloxy)-calix[4]arene Azacrown-5 (1). Under nitrogen, to a solution of 0.5 g (0.75 mmol) of 25,27-bis(1-propyloxy)calix[4]azacrown-5[3a] and 0.31 mL (2.24 mmol) of triethylamine in 50 mL of THF was added dropwise 0.24 g (0.83 mmol) of 1-bromomethylpyrene over 30 min at 0 °C. Upon complete addition, the reaction solution was stirred for 24 h at 65 °C. Removal of THF in vacuo gave a yellow oil. The crude product was extracted several times with CH_2Cl_2 (100 mL) and with water (100 mL). Column chromatography using ethyl acetate/hexane (1:5) as eluents on silica gel gave **1** as a pale yellowish solid in 21% yield: mp 211 °C dec, 113−115 °C (melting); IR (KBr, cm^{-1}) 2888, 1457, 1135, 1212, 1096, 1003, 818; ^{1}H NMR (600 Hz, $CDCl_3$) δ 8.69−8.25 (m, 9 H, C*H*-pyrene), 7.12−7.09 (d, *J* = 7.4 Hz, 8 H, ArH_m), 7.04−7.02 (d, *J* = 7.5 Hz, 4 H, ArH_m), 6.86−6.75 (m, 4 H, ArH_p), 4.28 (s, 2 H, NCH_2-pyrene), 3.82 (s, 8 H, ArCH_2Ar), 3.57−3.54 (s, 4 H, ArO$CH_2$$CH_2$O), 3.41−3.31 (m, 12 H, O$CH_2$$CH_2$$CH_3$, $CH_2$$CH_2$-O$CH_2$$CH_2$), 2.76−2.72 (t, *J* = 2.6 Hz, 4 H, $CH_2$$CH_2NCH_2$$CH_2$), 1.22−1.14 (m, *J* = 7.4 Hz, 4 H, O$CH_2$$CH_2$$CH_3$), 0.72−0.67 (t, *J* = 7.4 Hz, 6 H, O$CH_2$$CH_2$$CH_3$); FAB MS *m*/*z* (M$^+$) calcd 879.06, found 879.11. Anal. Calcd for $C_{59}H_{61}NO_6$: C, 80.54; H, 6.94. Found: C, 80.59; H, 6.91.

***N*-(1-Pyrenemethyl) Calix[4]crown-5-azacrown-5 (2).** Procedures are the same as for the synthesis of **1**: 47% yield; mp 115−117 °C; IR (KBr pellet, cm^{-1}) 2903, 1451, 1243, 1204, 1127, 1042, 1127, 1042, 988, 834, 764; ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.75−7.96 (m, 9 H, pyrene unit), 7.12−7.09 (m, 8 H, ArH_m), 6.91−6.84 (m, 4 H, ArH_p), 4.28 (s, 2 H, NCH_2-pyrene), 3.86 (s, 8 H, ArCH_2Ar), 3.63−3.09 (m, 28 H, O$CH_2$$CH_2N, OCH_2$$CH_2$O), 2.71 (s, 4 H, $CH_2$$CH_2NCH_2$$CH_2$); ^{13}C NMR ($CDCl_3$) 157.60, 156.98, 134.78, 134.55, 129.74, 129.43, 128.46, 123.52, 123.32, 73.68, 71.50, 71.34, 71.00, 70.40, 70.35, 70.29, 68.63, 61.07, 59.77, 59.76, 54.76, 38.84 ppm; FAB MS *m*/*z* (M$^+$) calcd 953.14, found 953.49. Anal. Calcd for $C_{61}H_{63}NO_9$: C, 76.81; H, 6.61. Found: C, 76.84; H, 6.60.

***N*-(1-Pyrenemethyl) Calix[4]crown-6-azacrown-5 (3).** Procedures are the same as for the synthesis of **1**: mp 105−110 °C; IR (KBr pellet, cm^{-1}) 2903, 1451, 1351, 1204, 1127, 1088, 1034, 926, 764; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.63−7.99 (m, 9 H, pyrene unit), 7.12−7.10 (m, 8 H, ArH_m), 6.89−6.84 (m, 4 H, ArH_p), 4.27 (s, 2 H, NCH_2-pyrene), 3.84 (s, 8 H, ArCH_2Ar), 3.71−3.23 (m, 32 H, O$CH_2$$CH_2N, OCH_2$$CH_2$O), 2.76 (s, 4 H, $CH_2$$CH_2$-N$CH_2$$CH_2$); ^{13}C NMR ($CDCl_3$) 157.68, 157.40, 134.55, 131.32, 130.47, 130.39, 128.94, 126.14, 123.40, 123.20, 71.79, 71.53, 71.01, 70.48, 70.11, 69.87, 54.60, 54.09, 51.53, 38.83 ppm; FAB MS *m*/*z* (M$^+$) calcd 997.25, found 997.44. Anal. Calcd for $C_{63}H_{67}NO_{10}$: C, 75.82; H, 6.72. Found: C, 75.81; H: 6.74.

Preparation of Fluorometric Metal Ion Titration Solutions. Stock solutions (1 or 0.1 mM) of the metal perchlorate salts (for Cd(II), chloride salt was used) were prepared using ethanol. Stock solutions of **1**−**3** were prepared in ethanol (0.06 mM). The solutions were used on the day of preparation. Test solutions were prepared by placing 400 μL of the probe stock solution into a test tube, adding an appropriate aliquot of each metal stock, and diluting the solution to 4 mL with ethanol. For all measurements, excitation was at 360 nm. Excitation and emission slit widths were 5 and 3 nm, respectively.

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Supporting Information Available: Fluorescence Job plot of the titration of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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