

N-Anthracenylmethyl Calix[4]azacrowns as New Fluorescent Ionophores

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Two novel calixarene-based fluoroionophores were synthesized. Their conformations were confirmed to 1,3-alternate by X-ray crystal structures. From CHEF by blocking the PET mechanism in fluorescence spectra, we observed In^{3+} and Pb^{2+} ion selectivity over other metal ions. For In^{3+} ion, calix[4]-*bis*-azacrown-5 showed about 20 times more sensitive than calix[4]-*mono*-azacrown-5 because the source of the binding selectivity comes from the calixarene framework and azacrown ligand by controlling the fluorescence and PET mechanisms associated with the amine moiety.

Key Words : Calixarenes, Complexation, Fluorescence, Conformation

Introduction

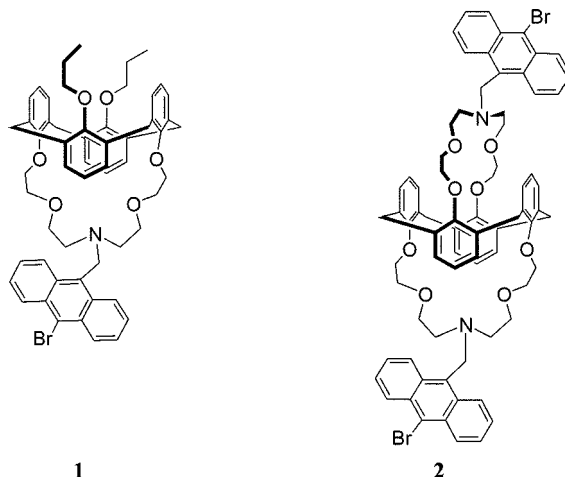
The exploitation of the development of fluorescence sensors and switches has been confined to the last two decades with much pioneering efforts. Fluorescent signaling via the PET (Photo-induced Electron Transfer) process is distinguished by its intrinsically supramolecular nature since distinct components perform each of the necessary functions.¹ For these PET process, Czarnik,² Fabbrizzi,³ Tsien,⁴ Kuhn,⁵ Desvergne,⁶ and Shinkai⁷ *et al.* have developed their own fluorescent materials selectively sensing a specific metal ion; those materials showed substantial fluorescence enhancements upon the guest entry.

Calix[4]arenes have been shown to be useful 3-D molecular building blocks for the synthesis of receptors with specific properties.^{8,9} They can exist in four different conformations: cone, partial cone, 1,2-alternate, and 1,3-alternate.¹⁰ Calixcrown ethers have also attracted intense interest as cesium-selective extractants. It has been reported that 1,3-dialkoxy-calix[4]arene crown-6 derivatives are exceptionally selective ionophores for cesium ion due to the complexation of cesium ion not only with the crown ether but also with the two aromatic rings (cation/ π -interaction) when fixed in the 1,3-alternate conformation.^{11,12} From this point of view, it is possible that the combination of *N*-fluorescent azacrown ether and calixcrown ether would result in an optimized structure for metal ion encapsulation due to (I) electrostatic interactions between the metal ion and both the oxygens and a nitrogen as electron donors and (II) π -metal interactions between the metal ion and two rotated aromatic nuclei of the 1,3-alternate calixarene.¹³ Dabestani reported that 9-cyanoanthracene armed-1,3-alternate conformer of calix[4]bis-*o*-benzocrown-6 showed a selective binding for Cs^+ ion. In the absence of cesium ions, fluorescence is partially quenched

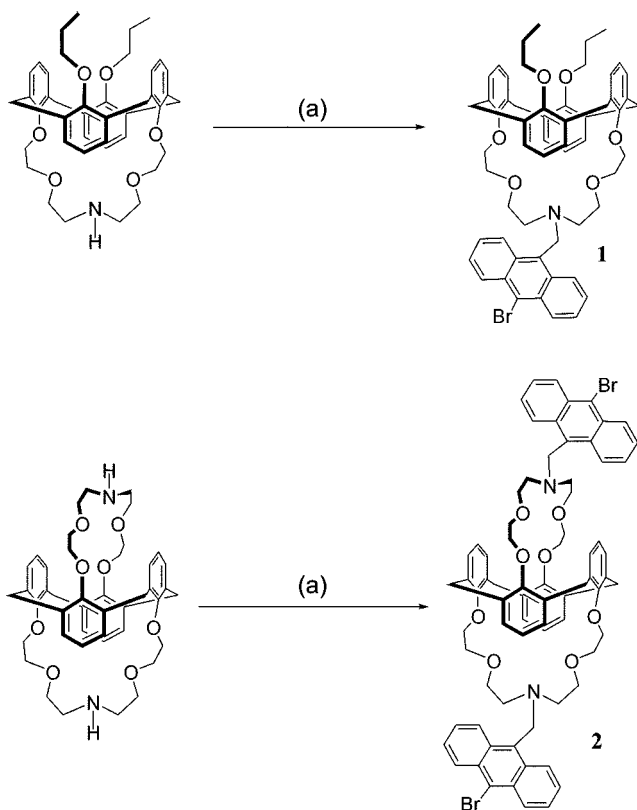
by photo-induced electron transfer (PET) from the dialkoxybenzene moiety of the crown ring to the excited singlet state of 9-cyanoanthracene.¹⁴ Upon complexation, the oxygen lone pairs no longer participate in PET, causing the chelation-enhanced fluorescence (CHEF) effect.

With those in mind, we have previously reported that calixazacrown ethers having pyrenylmethyl side arm on the nitrogen atom of the calixazacrown framework as a fluorescent ionophore showed an interesting metal ion exchange phenomena. "Molecular Taekwondo": *Coming-in and Kicking-out* process with respect to intensity of the corresponding fluorescence.¹⁵ As a continued project on the fluorescent ionophores, we here report the synthesis of *N*-anthracenylmethyl calixazacrown and corresponding calix-*bis*-azacrowns and their fluorescent changes upon the addition of various metal ions. 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.

Our synthesis began with 25,27-*bis*-(1-propyloxy)calix[4]azacrown-5^{11,16} and calix[4]-*bis*-azacrown-5¹¹ for 1 and 2.



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Scheme 1. Proposed synthetic route for anthracenyl calixazacrown series. (a) Et₃N, 9-bromo-10-bromomethylanthracene, THF, reflux, 48 hrs.

respectively. Under a nitrogen atmosphere, treatment with 9-bromo-10-bromomethylanthracene and triethylamine in THF for 48 h reflux led to 1,3-alternate **1** and **2** in 44% and 54% yield, respectively. According to the presence of a singlet peak at around 3.8 ppm in the ¹H NMR as well as the presence of a single peak at 38 ppm in the ¹³C NMR spectra, the compounds **1** and **2** were confirmed to maintain the 1,3-alternate conformations. Actually, bromination at 9-position of the anthracene was not intended to be carried out. Displacement of hydroxy group of the 9-hydroxymethylanthracene for Br group using HBr was expected to give the 9-bromomethylanthracene, but the major product was found to be 9-bromo-10-bromomethylanthracene. We decided to use the dibrominated reactant because it does not affect the fluorescence changes caused by CHEF.

Single crystals of **1** and **2** suitable for X-ray crystallography were prepared by slow evaporation of a methanol/CH₂CH₂ (1 : 4) solution. Compounds **1** and **2** were crystallized in the monoclinic space group *P*2₁/*c* and *C*2/*c*, respectively. In the crystal structure of **2**, a two-fold symmetry axis passes along the two methylene carbon atoms (C28 and C36) vector of the calix[4]arene skeleton of the molecule. The asymmetric unit, therefore, consists of a half of **2**. As shown in Figure 1, the crystal structures of both compounds are saddle-shaped 1,3-alternate conformations: the aromatic rings are tilted up (B and D) and down (A and C) alternately related to the α -C₄ core. The α -C₄ core forms a square plane, and the average displacements of the core

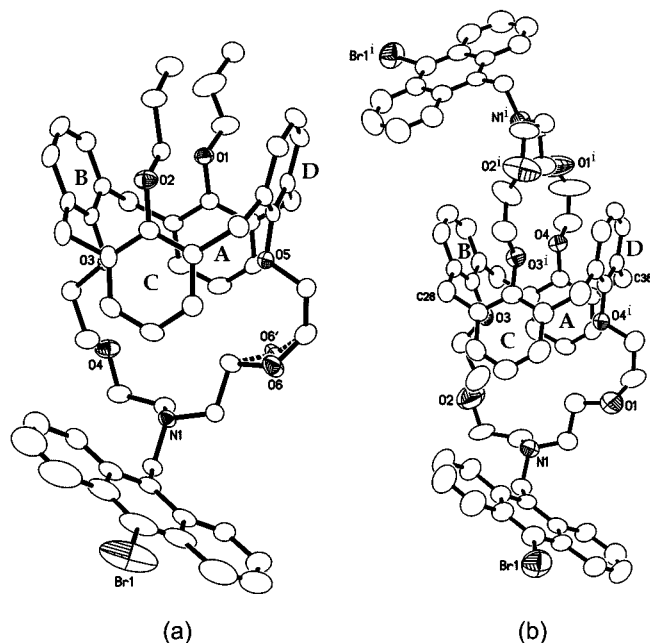


Figure 1. X-ray crystal structures of (a) **1** and (b) **2**. Hydrogen atoms are omitted for clarity. [symmetry code: (i) $x + 2, y, -z + 1/2$].

atoms from the mean plane are 0.05 Å for **1** and 0.00 Å for **2**. The dihedral angles between the mean planes of anthracenyl group and the α -C₄ core are 36.80(9)° for **1** and 34.0(1)° for **2**. In crystal structures of **1** and **2**, the nitrogen atoms (N1) of azacrown moiety are *ca.* 5.932(3) Å and 6.097(5) Å apart from the α -C₄ core plane, respectively. Crystallographic data and structure refinement parameters for **1** and **2** are listed in Table 1. The torsion angles associated with donor atoms and the distances between donor atoms in the azacrown moieties are compiled in Table 2, together with the dihedral angles between the α -C₄ core plane and xylyl ring planes, and those between each xylyl ring planes. Considering the distance between nitrogen atom and calix[4]arene as well as the flexibility of the long azacrown moiety, both two structures have potential azacrown cavities for encapsulating the specific metal ion.

For investigation of CHEF using compound **1** and **2**, the perchlorate salts of Li⁺, Na⁺, K⁺, Rb⁺, Cs⁺, Mg²⁺, Ca²⁺, Sr²⁺, Ag⁺, Zn²⁺, In³⁺, and Pb²⁺ have been used to evaluate metal ion binding. Fluorescence quenching by inter- and intramolecular amines is a well-known phenomenon.¹⁴ CHEF 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 anthracene S₁ excited state. Using these metal ions (50.0 μ M, 10 eq.), we found that **1** (5.0 μ M) displayed large chelation-enhanced fluorescence (CHEF) effects with Zn²⁺, In³⁺, and Pb²⁺ ions as shown in Figure 2. For alkali metal ions, fluorescence intensity of **1** scarcely changed. Among alkaline-earth metal ions, Mg²⁺ ion revealed rather selectivity. Compound **2** having two binding sites for the guest ions as well as two fluorogenic sites with symmetrical array were also investigated. Previously we reported that the parent calix[4]-*bis*-azacrown-5 of **2** showed 1 : 1 complexation which was proven by Job

Table 1. Crystallographic Data and Structure Refinement Parameters for **1** and **2**

	1	2
empirical formula	C ₃₇ H ₄₆ O ₃ N ₄	C ₄₁ H ₅₂ N ₄ O ₈
fw	934.97	1277.16
temperature (K)	298(2)	293(2)
crystal size (mm)	0.3 × 0.3 × 0.5	0.2 × 0.2 × 0.35
crystal system	Monoclinic	Monoclinic
space group	<i>P</i> 2 ₁ <i>c</i>	<i>C</i> 2 <i>c</i>
<i>a</i> (Å)	21.5160(15)	10.4611(8)
<i>b</i> (Å)	10.3525(7)	16.649(2)
<i>c</i> (Å)	21.8913(14)	35.282(2)
β (°)	102.5260(10)	96.179(6)
<i>V</i> (Å ³)	4760.1(6)	6109.4(10)
<i>Z</i>	4	4
<i>F</i> (000)	1968	2656
radiation (Å) (Mo K α)	0.71073	0.71069
calculated density (g cm ⁻³)	1.305	1.389
μ (mm ⁻¹)	0.917	1.388
2 θ range (°)	0.97 to 28.35	1.16 to 24.97
reflections collected	30000	5474
independent reflections	11474 [<i>R</i> _{int} = 0.0867]	5379 [<i>R</i> _{int} = 0.0369]
goodness-of-fit on <i>F</i> ²	0.959	1.013
<i>R</i> ₁ [<i>I</i> > 2 σ (<i>I</i>)]	0.0701	0.0649
<i>wR</i> ₂ (all)	0.2361	0.2041
Largest diff peak and hole (e Å ⁻³)	0.998 and -1.160	1.083 and -0.471
Diffractometer	Siemens Smart CCD	Enraf-Nonius CAD-4

plotting experiment.¹⁵ This is because there is an electrostatic repulsion between the two metal ions in solution and is an induced conformation change that does not favor binding of the second metal ion.¹⁷ From the results of fluorescence changes indicated in Figure 2, one can conclude that **2** is somewhat less sensitive for metal ion binding than **1** in alkali and alkaline-earth metal ion series. But the selectivity of **2** towards the In³⁺ and Pb²⁺ ions over other tested metal ions was found to be more remarkable than **1**. In order to obtain the association constants (*K*_a) of the complex,¹⁸ various amount of metal perchlorate were added stepwise to **1** and **2**, respectively. The titration profiles for **1** and **2** are depicted in Figure 3. When the metal salt was gradually added from 0 to 10 equivalents, the fluorescence changes (ΔI) of the **1** increased by CHEF. For Pb²⁺, In³⁺, and Mg²⁺ ions, complexation upon the addition of 1 equivalent of metal ions reached to saturation. In the case of **2**, the saturation reached before the addition of 1.5-2.0 equiv of Pb²⁺ and In³⁺ ions. Those saturation points from which the association constant can be calculated were dependent on the metal ion species. Using the computer program ENZFITTER,¹⁸ association constants (*K*_a) and free energy changes for each metal ion were obtained and listed in Table 3. For **1** with selected metal ions, complex with Mg²⁺ gave the largest association constant. Interestingly, for In³⁺ ion, **2** was about 20 times more sensitive than **1** and revealed the best selectivity over other metal ions.

Table 2. Dihedral and torsion angles [°], and inter-atomic distances [Å] for **1** and **2**^a

	1	2
dihedral angles		
α -C ₁ core plane and A	78.57(8)	80.3(1)
α -C ₁ core plane and B	107.81(8)	110.2(2)
α -C ₁ core plane and C	78.85(9)	69.8(2)
α -C ₁ core plane and D	105.5(1)	99.7(1)
A and B	86.2(1)	89.2(1)
A and C	22.6(1)	29.9(2)
A and D	83.6(1)	84.9(1)
B and C	86.0(1)	81.4(1)
B and D	33.6(1)	29.9(2)
C and D	88.6(1)	89.2(1)
torsion angles		
O3-C-C-O4	-89.0(4)	
O6-C-C-O5	-62.0(7)	
N1-C-C-O4	58.3(4)	
N1-C-C-O6	161.6(4)	
O1-C-C-O4 ⁱ		-33(2)
O2-C-C-O3		-138.6(6)
N1-C-C-O1		168.0(6)
N1-C-C-O2		94.9(8)
Inter-atomic distances		
O3...O5	4.847(3)	
O3...O6	5.838(4)	
O3...N1	4.910(4)	
O5...O4	6.258(4)	
O5...N1	5.586(3)	
O6...O4	5.810(5)	
O3...O4 ⁱ		4.522(5)
O3...O1		5.811(7)
O3...N1		5.207(6)
O4 ⁱ ...O2		6.308(7)
O4 ⁱ ...N1		5.528(6)
O1...O2 ^j		9.431(9)
N1...N1 ⁱ		12.195(9)

^aA, B, C, and D define each xylyl ring planes of the calix[4]arene in Figure 1.

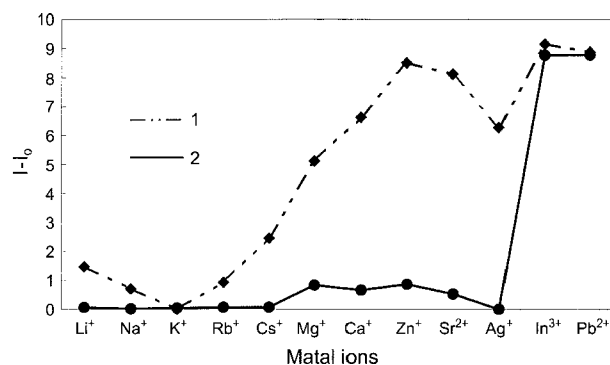


Figure 2. Fluorescence changes of **1** and **2** upon the addition of various metal ions. ^a*I* (Fluorescence intensity of complex I), *I*₀ (Fluorescence intensity of free **1** and **2**). Ligand: 5.0 × 10⁻⁶ M; metal ion: 5.0 × 10⁻⁴ M. Calculated fluorescence intensity changes at 408 nm.

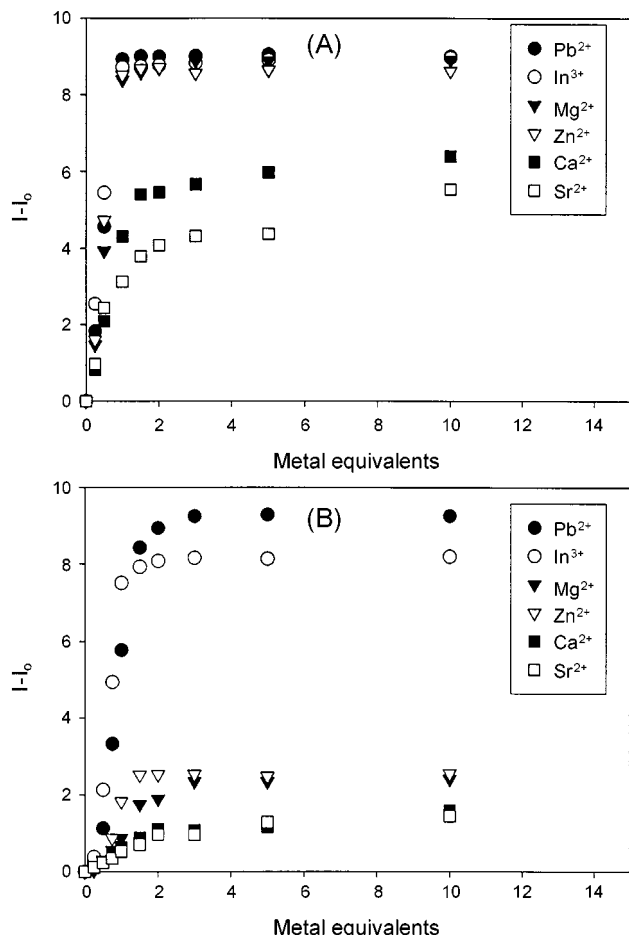


Figure 3. Fluorescence changes of calixazacrown **1** and **2** upon the addition of metal ions at 408 nm. A: compound **1**; B: compound **2**.

Table 3. Association constants^a and free energy changes^b of the ligands for metal ion complexes

Compound		Selected metal ions					
		In ³⁺	Pb ²⁺	Zn ²⁺	Mg ²⁺	Ca ²⁺	Sr ²⁺
1	$K_a (\cdot 10^5)$	11.27	7.47	24.79	38.9	4.45	24.79
	$-\Delta G (\cdot 10^5)$	0.34	0.33	0.36	0.37	0.32	0.36
2	$K_a (\cdot 10^5)$	228.7	56.7	19.7	1.96	0.71	0.90
	$-\Delta G (\cdot 10^5)$	0.42	0.38	0.36	0.30	0.28	0.28

^aThe K_a (M⁻¹) values were obtained from ENZFITTER program.
^bJ·mol⁻¹·K.

In conclusion, new calixarene-based fluoroionophores **1** and **2** were synthesized and their conformations were confirmed to 1,3-alternate by X-ray crystal structures, respectively. Concerning CHEF by blocking the PET mechanism, we observed In³⁺ and Pb²⁺ ion selectivity over other metal ions. For In³⁺ ion, calix[4]-bis-azacrown-5 (**2**) showed about 20 times more sensitive than calix[4]-mono-azacrown-5 (**1**). These results suggest that the source of the binding selectivity comes from the calixarene framework and azacrown ligand by controlling the fluorescence and PET mechanisms associated with the amine moiety. Those ligands may be employed successfully in the creation of selective and practical chemosensors for In³⁺ ion.

Experimental Section

Materials and Analytical Procedures. The two starting materials were prepared as described in the literature.^{3,15,16} ¹H NMR spectra (δ in ppm from TMS, J in Hz) in CDCl₃ were obtained from Bruker ARX-600 at Taejon (KBSI). FAB⁻ mass spectra was obtained from JEOL-JMS-HX 110A/110A High Resolution Tandem Mass Spectrometry in KBSI in Taejon, Korea. Fluorescence spectra were obtained from Model S-2100 (SINCO) spectrophotometer.

Syntheses.

N-(10-Bromo-9-antracenylnmethyl)-25,27-bis-(1-propyloxy)calix[4]arene azacrown-5 (1), 1,3-Alternate: Under nitrogen, to a solution of 0.50 g (0.75 mmol) of 25,27-bis-(1-propyloxy)calix[4]azacrown-5 and 0.26 mL (1.87 mmol) of triethylamine in 50 mL of THF was added dropwise 0.41 g (1.16 mmol) of 9-bromo-10-bromomethylanthracene 30 min at 0 °C. Upon complete addition, the reaction solution was stirred for 24 hr at 65 °C. Removal of THF in *vacuo* gave a yellow oil. The crude product was extracted several times with CH₂Cl₂ (100 mL) with water (100 mL). Column chromatography using methylene chloride as eluents on silica gel gave **1** as a pale yellowish solid in 44% yield. Mp 222.1-223.7 °C. IR (KBr pellet, cm⁻¹) 2965, 2942, 1454, 1382, 1206, 1095, 988, 903; ¹H NMR (CDCl₃): δ 8.65-7.60 (m, 8H, anthracene), 7.08-7.01 (dd, $J = 7.4$ Hz, 8H, Ar-H_{meta}), 6.79 (t, 4H, $J = 7.4$ Hz, Ar-H_{para}), 4.58 (s, 2H, N(CH₂-anthracene), 3.80 (s, 8H, Ar(CH₂Ar), 3.54 (t, 4H, $J = 4.52$ Hz, ArO(CH₂CH₂O), 3.38 (t, 6H, $J = 7.48$ Hz, O(CH₂CH₂CH₃), 3.30-3.23 (m, 8H, CH₂(CH₂O(CH₂CH₂), 2.73 (t, $J = 5.2$ Hz, 4H, (CH₂N(CH₂), 1.22-1.18 (m, 4H, OCH₂(CH₂CH₃), 0.69 (t, $J = 7.4$ Hz, 6H, OCH₂CH₂(CH₃). FAB MS m/z (M⁺) calcd 935.1, found 934.4.

25,27:26,28-Bis(N-10-bromo-9-anthracenemethyl)calix[4]azacrown-5 (2), 1,3-Alternate: Procedures are same as for synthesis of **1**. 54% yield. Mp 247-249 °C. IR (KBr pellet, cm⁻¹) 2965, 2942, 1454, 1382, 1206, 1095, 988, 903; ¹H NMR (CDCl₃): δ 8.62-7.59 (m, 16H, anthracene), 7.08 (d, $J = 7.4$ Hz, 8H, Ar-H_{meta}), 6.79 (t, 4H, $J = 7.4$ Hz, Ar-H_{para}), 4.56 (s, 4H, N(CH₂-anthracene), 3.83 (s, 8H, Ar(CH₂Ar), 3.53 (t, 8H, $J = 4.95$ Hz, ArO(CH₂CH₂O), 3.28 (t, 8H, $J = 5.32$ Hz, ArO(CH₂CH₂O), 3.16 (t, 8H, $J = 4.95$ Hz, O(CH₂CH₂N), 2.74 (t, 8H, $J = 5.3$ Hz, (CH₂N(CH₂)). FAB MS m/z (M) calcd 1277.18, found 1277.30

X-ray Crystal Structures. Crystallographic data and structure refinement parameters for **1** and **2** are shown in Table 1. Data were collected on a Siemens Smart CCD area-detector diffractometer (for **1**) and on an Enraf-Nonius CAD 4 diffractometer (for **2**). The structures were solved by direct methods and refined by full matrix least squares against F^2 for all data using SHELXTL software.¹⁹ All non-H atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in the calculated positions of their parent carbon atoms and refined using a riding model. In the refined structure **1**, one oxygen atom of azacrown moiety was disordered over two sites with occupancies 0.76 for O6 and 0.24 for O6'.

Preparation of Fluorometric Metal Ion Titration Solutions. We prepared two different stock solutions (1.0 mM) of the metal perchlorate salts. To measure the K_a of **1** and **2** we used ethanol and 1,2-dichloroethane/acetonitrile (1 : 1), respectively, because the ethanol could not dissolve **2** (soluble in above co-solvent) but **1**. Stock solutions of **1** and **2** were prepared in ethanol (0.01 mM) and in 1,2-dichloroethane/acetonitrile (1 : 1) (0.01 mM). The solutions were used on the day of preparation. Test solutions were prepared by placing 2.0 mL of the probe stock solution into a test tube, adding an appropriate aliquot (2.0 mL) of each metal stock. For all measurements, excitation was at 350 nm; excitation and emission slit widths were 4 nm.

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