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Chromogenic Indoaniline Armed-Calix[4]azacrowns

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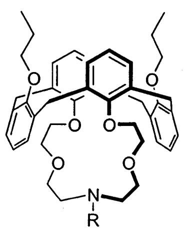
Two novel chromogenic 1,3-alternate calix[4]azacrown (**1**) and calix[4]-bis-azacrown (**2**) in which an indoaniline chromophore was attached on the nitrogen atom of the azacrown unit with one methylene spacer were synthesized. The ^{1}H NMR spectrum of the ligand **1** and Ca^{2+} proved that the metal ion is entrapped by the calix[4]azacrown unit and by the conjugated indoaniline system. From the UV/vis band shifts upon metal ion complexation, Zn^{2+} ion was found to give the largest band shifts compared to other metal cations, indicating that Zn^{2+} ion ($K_a = 18\,760$ M^{-1} for **1** and $K_a = 19\,930$ M^{-1} for **2**) was selectively encapsulated by the calix[4]azacrown cavity with assistance of the pendent indoaniline sidearm.

Introduction

Over the past few decades, a considerable number of *N*-pivot azacrown ethers have been investigated because they selectively entrap the specific metal cations not only through an electrostatic interaction between the heteroatoms of the azacrown loop and the target metal ions but also through three-dimensional encapsulating assistance of the appended sidearm on the nitrogen atom.[1] Previously, we have reported the synthesis of *N*-pivot azacrowns combining a calix[4]arene framework, so to speak, calix[4]azacrown ethers, and their selective recognition toward certain metal cations.[2−4] Those calix[4]azacrowns have attracted intense interest as certain metal ion-selective extractants, due to the complexation of the metal ion by the azacrown ether unit as well as by the two aromatic rings (cation/π-interaction)[5−7] when fixed in the 1,3-alternate conformation.

Chromoionophores have long been studied as specific metal ion indicators since Perdersen reported salt-dependent UV measurements for the characterization of complexation processes with crown ethers containing aromatic structure units.[8] Diazo-chromophores bearing azacrown ether unit were reported to give a color change upon specific metal ion complexation.[9,10] The amine nitrogen atoms simultaneously possess an electron-donor function to complexed cations as well as to the chromophore. Then we reported that the absorption bands of the *N*-chromogenic calix[4]azacrown having a diazo functional group on the nitrogen atom of the azacrown unit were hypsochromically shifted by complexation of alkali and alkaline earth metal ions.[11]

The indoaniline chromophore system prepared by condensing phenol derivatives with (*N*,*N*-dialkylamino)-aniline is important in color-changing systems, because its optical properties can be perturbed significantly by chemical stimuli.[12] Kubo reported that the quinone carbonyl group of the indoaniline-type ligands interacts with divalent metal ions to cause a pronounced color change.[12] In accordance with the ion−dipole concept regarding the color change mentioned above, we have synthesized another series of calix[4]azacrown ethers **1** and **2** in which double bond conjugated indoaniline chromophore is appended to the nitrogen atom of the calix[4]azacrown and calix[4]-bis-azacrown, respectively.



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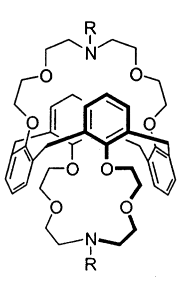

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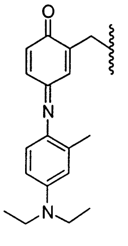

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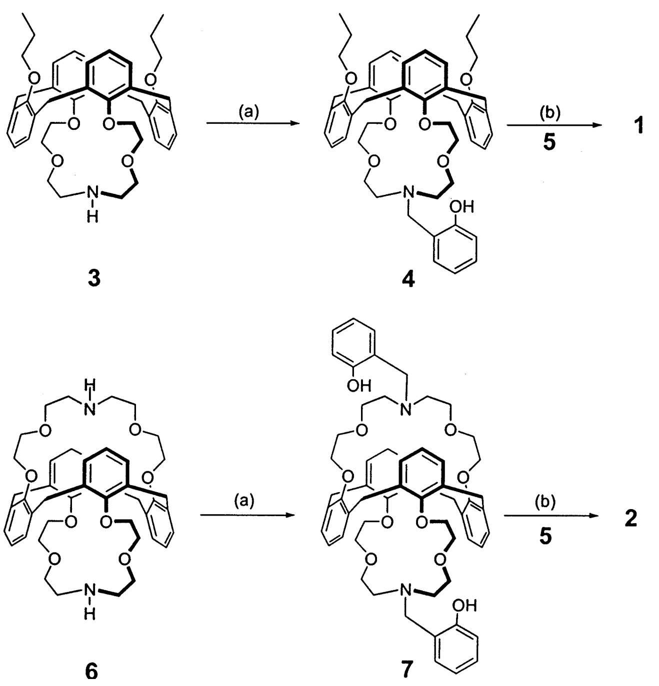
SCHEME 1. Synthetic Routes for Indoaniline-Derived Calixazacrown Ethers[a]



[a] Conditions: (a) phenol, *p*-formaldehyde, benzene; (b) *N*,*N*-diethyl-2-methyl-1,4-phenylenediamine (**5**), $K_3[Fe(CN)_6]$, NaOH, acetone/ethanol.

Results and Discussion

For **1** and **2**, synthesis began with 1,3-alternate 1,3-bis(1-propyloxy)calix[4]azacrown-5 (**3**)[3] and calix[4]-bis-azacrown-5 (**6**)[2], respectively, as described in Scheme 1. Reaction of **3** and **6** with phenol and *p*-formaldehyde gave **4** and **7** in 40 and 27% yields, respectively. For these phenolic azacrown compounds, Lagow reported that one-pot synthesis using 1,10-diaza-18-crown-6 and para-substituted phenol in the presence of *p*-formaldehyde yielded the Mannich reaction product.[13] Subsequently, oxidation of **4** and **7** using $K_3[Fe(CN)_6]$ followed by coupling with *N*,*N*-diethyl-2-methyl-1,4-phenylenediamine (**5**) in the presence of NaOH in acetone/ethanol gave **1** and **2** in 27 and 33% yields, respectively. According to the presence of a singlet peak at around 3.8 ppm in the ^{1}H NMR as well as the presence of a single peak at about 38 ppm in the ^{13}C NMR spectra, both **1** and **2** were confirmed to be in the 1,3-alternate conformations.

A crystal of **7** suitable for X-ray study was grown by slow evaporation of a methanol/CH_2CH_2 (1:4) solution. It crystallized in the triclinic space group *P*-1. The structure is a saddle-shaped 1,3-alternate conformation: the aromatic rings are tilted up and down alternately. The ORTEP drawing and the crystal data are shown in Figure S1 and Table S1, respectively (Supporting Information). Compound **7** exhibited poor complexation ability for metal cations. As indicated in Figure S1, there is intramolecular hydrogen bonding between the hydrogen atom of the phenolic OH and the nitrogen atom of the azacrown unit. The N(1)H···O(1) and N(2)H···O(6) distances are 1.84 and 1.78 Å, respectively. The N(1)−H−O(1) and N(2)−H−O(6) angles are 146.5° and 148.2 °, respectively. This H-bonding decreases the electron-donating capability of the nitrogen atom to a metal cation. Detailed studies on metal ion complexation of **7** at high pH that will produce the deprotonated phenoxide system are in progress and will be reported elsewhere.

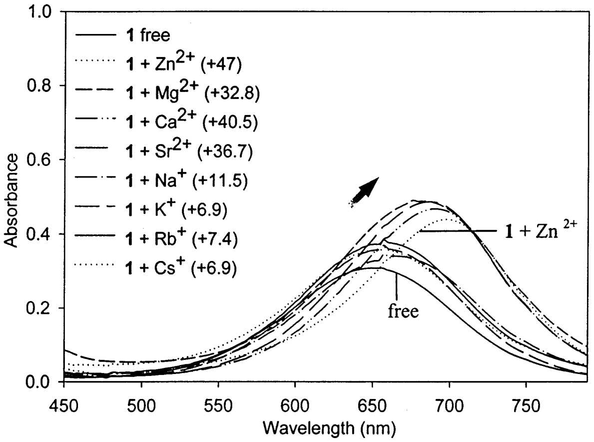


FIGURE 1. UV/vis changes of indoaniline-derived calixazacrown ether **1** upon the addition of metal ions. Conditions: ligand, 0.025 mM; metal perchlorate, 500 equiv. The number in the parenthesis is $\Delta\lambda_{max} = \lambda_{max}{}^{complex} - \lambda_{max}{}^{free}$ in the presence of metal ion.

In donor−acceptor chromophores, electronic excitation is mostly accompanied by a charge density shift in the direction of the acceptor substituents of the chromoionophore; i.e., increases in the dipole moments take place.[14] Since it can be postulated that when the well-matched metal cation comes into the calixazacrown cavity the amine nitrogen atoms of the chromoionophores (**1** and **2**) become positively polarized, in such a manner, the quinone changes to a phenoxide by a mesomeric effect. Thus, upon the metal ion complexation, the excited states are more strongly stabilized than the ground states and a bathochromic shift results.[15] Figure 1 shows the color change of the chromophore **1** upon the addition of metal ions. The metal ion causes a significant ion−dipole interaction of the quinone carbonyl group and that induces an absorption spectral change. The maximum wavelength and the molecular extinction coefficient for **1** are λ_{max} 648.9 nm (blue color) and 14 840 dm^3 mol^{-1} cm^{-1}, respectively. With ClO_4^- as the counteranion, among the tested ions of Na^+, K^+, Rb^+, Cs^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, and Zn^{2+}, Zn^{2+} had the greatest effect and gave the largest bathochromical UV band shift ($\Delta\lambda_{max} = 47$ nm). The sensitivity order is found to be $Zn^{2+} > Ca^{2+} > Sr^{2+} > Mg^{2+} > Na^+ > Rb^+ > K^+ = Cs^+$. Judging from the magnitude of this bathochromic shift, it is concluded that the Zn^{2+} is best encapsulated in the calixazacrown cavity with aid of the conjugated indoaniline system as a three-dimensional encapsulating sidearm.

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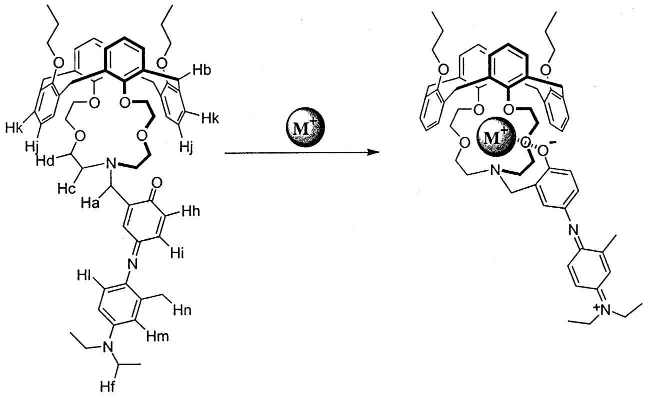
TABLE 1. Metal-Induced Change in ^1H NMR Chemical Shifts of Lariat Calixazacrown Ether 1



	absorptions in the ^1H NMR spectra (ppm)											
	a	b	c	d	f	h	i	j	k	l	m	n
1	3.82	3.78	2.68	3.40 3.29	3.38	7.49	7.29	6.79	7.02	6.53	6.64	2.38
1 + Ca^{2+}	4.40	3.81	3.74	3.48 3.35	3.41	7.62 7.48	7.35 (br)	6.89	7.04 (br)	6.77 6.70	6.82	2.45

To verify that the metal ion is encapsulated within the azacrown cavity, we took ^1H NMR spectrum of **1**$-Zn^{2+}$ in $CDCl_3$. Unfortunately, the NMR peaks were so broad that we could not properly assign the peak changes probably, because the conformational interconversion is somewhat slow on the NMR time scale. However, the complex with Ca^{2+}, which showed the second largest band shift, was assignable for the ^1H NMR spectrum, and the corresponding peak assignments are listed in Table 1. Considering metal ion-induced chemical shift changes ($\Delta\delta$), H_c of the azacrown part was shifted downfield by 1.06 ppm, indicating that metal ion is coordinated by the heteroatoms of the azacrown part. Another interesting feature is the Ar-H_{meta} and Ar-H_{para} resonances of the calix[4]arene. Triplet peaks for Ar-H_{para} (H_j) shifted downfield by 0.10 ppm. These NMR change imply that the para-carbons for the two pairs of the downward-benzene rings participate in the cation-π interactions.[3,5,7,11] In addition, H_a (methylene spacer), H_h and H_i (quinone), and H_l and H_m (aniline part) showed metal-induced downfield chemical shifts of 0.58, 0.13, 0.06, 0.24, 0.18 ppm, respectively. This ^1H NMR investigation clearly demonstrates that the metal ion is encapsulated by the distally located azacrown ring (ion−dipole interaction) of the calix[4]arene, by the two rotated benzene rings (π-metal interaction), and by the associated indoaniline sidearm having a mesomeric conjugate system.

We also carried out the UV/vis spectroscopic experiments for **2**, which has two binding sites as well as two chromophore sites with a symmetrical array. The maximum wavelength and molecular extinction coefficient of **2** are λ_{max} 648 nm and 18 384 $dm^3\ mol^{-1}\ cm^{-1}$, respectively. Because it has two binding sites, we used a Job plot experiment to determine the complex ratio.[16] In view of difficulty in obtaining zinc picrate, we used strontium picrate instead. Two-phase extraction of strontium picrate by **2** under conditions of invariant total concentration was carried out. Figure 2 illustrates that **2**$-Sr^{2+}$ complex concentration approaches a maximum when the molar fraction of [**2**]/([**2**] + [Sr^{2+}]) is about 0.5, meaning that it forms 1:1 complex of **2** and Sr^{2+}, although it has two binding cavities. This is not only because there is an electrostatic repulsion between the two metal ions in the case of 1:2 complex in solution but also because there is an induced conformation change that does not favor binding of the second metal ion.[17,18] Like **1**, compound **2** showed UV band shifts upon the metal perchlorate complexation. Among the tested metal cations, Zn^{2+} ion also gave a selective band shift, as shown in Figure 3.

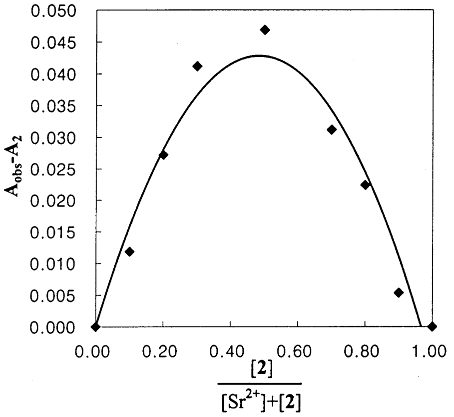


FIGURE 2. Job plot for 1:1 complexation of **2** with Sr^{2+} ion.

To obtain the association constants (K_a) of the complex, various amounts of metal perchlorate were added stepwise to **1** and **2**, respectively. The titration profiles for **1** are depicted in Figure 4. As the metal salt was gradually added, λ_{max} of the ligand **1** bathochromically shifted with an increase of absorption intensity. With about 40 equiv of the metal salt, no further band shifting was observed. These saturation points from which the association constant can be calculated were dependent on the metal ion species, as shown in Figure 5. We tested all metal

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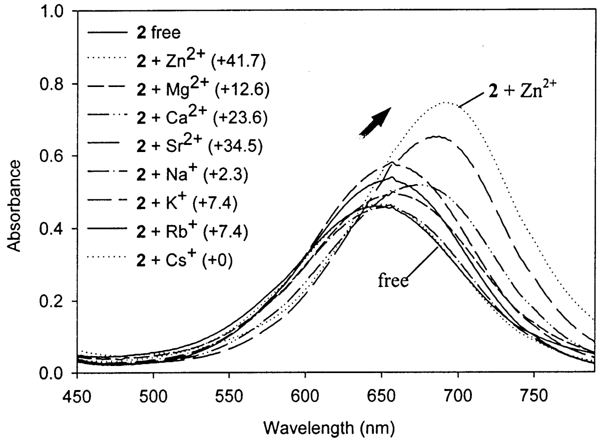

FIGURE 3. UV/vis changes of indoaniline-derived calixazacrown ether **2** upon the addition of metal ions. Conditions: ligand, 0.025 mM; metal perchlorate, 500 equiv. The number in the parenthesis is $\Delta\lambda_{max} = \lambda_{max}^{complex} - \lambda_{max}^{free}$ in the presence of metal ion.

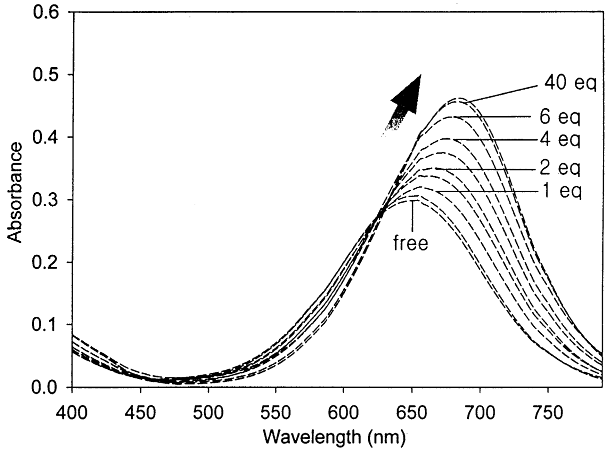

FIGURE 4. Bathochromic shifting upon the addition of $Zn(ClO_4)_2$ to calixazacrown **1**. $[\mathbf{1}]_{int} = 0.025$ mM; $[Zn^{2+}] = 0.2 \rightarrow 100$ equiv.

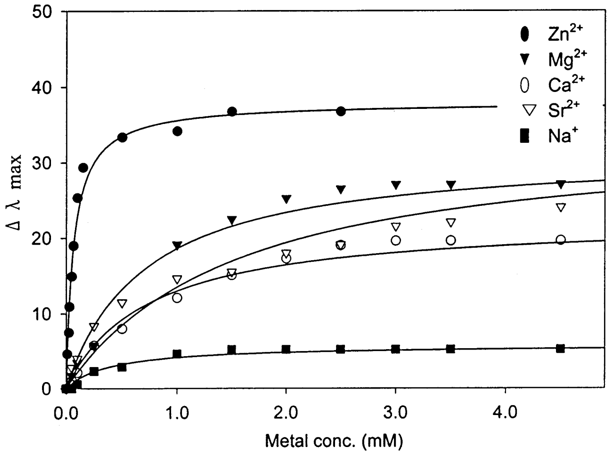

FIGURE 5. Wavelength changes ($\Delta\lambda_{max}$) upon the addition of $MClO_4$ to **1** in 99% ethanol; $[\mathbf{1}]_{int} = 0.025$ mM.

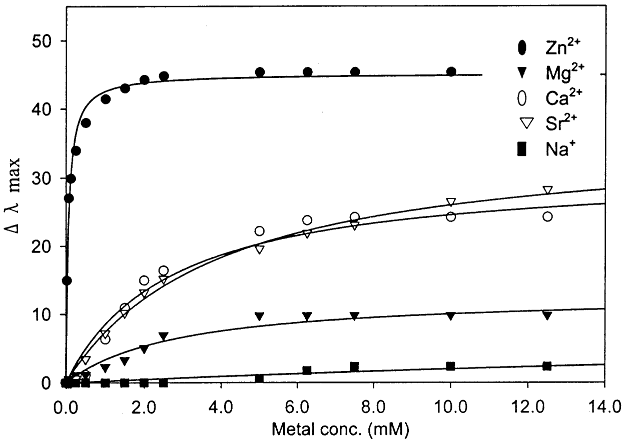

FIGURE 6. Wavelength changes ($\Delta\lambda_{max}$) upon the addition of $MClO_4$ to **2** in 99% ethanol; $[\mathbf{2}]_{int} = 0.025$ mM

TABLE 2. Association Constants (K_a)[a] and Free Energy of 1 and 2 for Metal Cations

compd	property	Zn^{2+}	Sr^{2+}	Ca^{2+}	Mg^{2+}	Na^+
1	K_a (10^3)	18.76	0.76	0.93	1.28	1.28
	$-\Delta G^b$ (10^3)	24.39	16.45	16.95	17.74	18.33
2	K_a (10^3)	19.93	0.41	0.25	0.20	0.12
	$-\Delta G^b$ (10^3)	24.54	14.94	13.69	13.19	12.00

[a] The K_a (M^{-1}) values were obtained from ENZFITTER program. [b] J/mol·K.

ions mentioned above, but have selected only some of them for presentation in this paper. Wavelength changes ($\Delta\lambda_{max} = \lambda_{max}^{complex} - \lambda_{max}^{free}$ in the presence of metal ion) for **1** and **2** derived from the bathochromic shifts are illustrated in Figures 5 and 6, respectively. Most alkali metal ions scarcely gave the color change. For alkaline earth metal ions, we have observed remarkable changes, but not more than that for Zn^{2+} ion. Using the computer program ENZFITTER,[19] the association constant (K_a) and free energy change for each metal ion were obtained and are listed in Table 2. Metal ion sensing orders for **1** and **2** as determined by the association constants are $Zn^{2+} \gg Mg^{2+} = Na^+ > Ca^{2+} > Sr^{2+}$ and $Zn^{2+} \gg Sr^{2+} > Ca^{2+}\ Mg^{2+} > Na^+$, respectively. Compound **2** showed a little better selectivity for Zn^{2+} over other metal ions than did **1**.

In conclusion, new chromogenic 1,3-alternate calix[4]-azacrown and calix[4]-bis-crown in which an indoaniline chromophore is attached on the nitrogen atom of the azacrown unit with one methylene spacer were synthesized. From the UV/vis band shifts of the indoaniline chromophore part upon the metal ion complexation, Zn^{2+} produced the largest effect, revealing that Zn^{2+} (K_a = 18 760 M^{-1} for **1** and K_a = 19 930 M^{-1} for **2**) was selectively encapsulated within the calix[4]azacrown cavity (ion−dipole interaction and π−metal interaction) with assistance of the pendent indoaniline sidearm.

Experimental Section

Syntheses. Starting materials **3** and **6** were prepared as described in the literature.[2,3]

***N*-((((4-(*N*,*N*-Diethylamino)-2-methyl)iminophenyl)-quinone)methyl)-25,27-bis(1-propyloxy)calixazacrown-5 (1).** To a solution of **4** (100 mg, 0.13 mmol) in acetone:ethanol (15 mL:10 mL) were added 3 mL of 60% NaOH solution, 2

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[19] Association constants were obtained using the computer program ENZFITTER, available from Elsevier-BIOSOFT, 68 Hills Road, Cambridge CB2 1LA, United Kingdom.

mL of aqueous **5** (30 mg, 0.14 mmol), and 5 mL of aqueous $K_3[Fe(CN)_6]$ (170 mg, 0.52 mmol). The solution was stirred for 40 min at room temperature and then extracted with 100 mL of ethyl acetate. The organic layer was washed several times with 100 mL of H_2O, dried over $MgSO_4$, and was evaporated in vacuo. Column chromatography on silica gel with ethyl acetate:hexane (1:1) as eluents ($R_f = 0.325$) provided 34.0 mg (26% yield) of **1** as a blue solid. Mp: 90.8−92.5 °C. FAB MS: m/z ($M^+ + 1$) calcd 945.1, found 946.2.

Bis(*N*-((((4-(*N*,*N*-diethylamino)-2-methyl)iminophenyl)-quinone)methyl))-25,27:26,28-bis(3,9-dioxa-6-aza-undecane-1,11-dioxy)calix[4]arene (2). Compound **2** was prepared by adapting the method given for **1**. Mp: 173.9−177.3 °C. FAB MS: m/z ($M^+ + 1$) calcd 1299.2, found 1300.1.

***N*-(2-Hydroxybenzyl)-25,27-bis(1-propyloxy)calix[4]-azacrown-5 (4).** To a solution of 25,27-bis(1-propyloxy)calix-[4]azacrown-5 (**3**) (1.00 g, 1.50 mmol) in 100 mL of dry benzene were added 160 mg (1.64 mmol) of phenol and 58 mg (1.94 mmol) of *p*-formaldehyde. The mixture was refluxed for 48 h and the solvent was evaporated in vacuo. The residue was extracted with 50 mL of chloroform. The organic layer was washed with 50 mL of water, dried over $MgSO_4$, and evaporated in vacuo. The residual yellowish oil was purified by column chromatography on silica gel with ethyl acetate:hexane (1:3) as eluents. The pure product was obtained as a white solid in 40% yield. Mp: 81.9−84.6 °C. FAB MS: m/z (M^+) calcd 771.9, found 772.0.

***N*-(2-Hydroxybenzyl)calix[4]-bis-azacrown-5 (7).** Compound **7** was prepared by adaptation of the method given for **4**. 27% yield. Mp: 178.1−185.1 °C. FAB MS: m/z ($M^+ + 1$) calcd 951.2, found 952.1.

Two-Phase Picrate Extraction for Job Plot. Compound **2** (0.025 mM) in chloroform and strontium picrate (0.025 mM) in water were prepared as stock solutions. The concentrations in organic and aqueous phase were varied, but their volumes were fixed at 2 mL. After shaking for 2 h, followed by centrifuging, the UV/vis absorbance at 653 nm was recorded.

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Supporting Information Available: Additional Table (Table S1) and ORTEP crystal structure (Figure S1) for **7** and IR, ^1H, and ^{13}C NMR data of **1**, **2**, **4**, and **7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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