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Regioselective Complexation of Metal Ion in Chromogenic Calix[4]biscrowns

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Abstract: A series of 1,3-alternate chromogenic azo-coupled calix[4]biscrowns in which the crown size varied with crown-5 and crown-6 have been synthesized. From the results of UV/vis band shift upon metal ion complexation, metal ions were entrapped only by the upper crown loop, causing the hypsochromic shift on the UV/vis spectra. Calix[4]bis(crown-5)(crown-6) revealed K^+ ion selectivity while calix[4]bis(crown-6)(crown-6) showed Cs^+ ion selectivity caused by a size complementarity between hosts and guest ions. From the UV band shift of **4** in which the NO_2 group is replaced by the NH_2 group, we observed bathochromic shift upon the metal ion addition, indicating that the metal ion is encapsulated in the lower crown ring because of strengthened π-cation interaction by introducing the electron-donating NH_2 unit regardless of the steric hindrance between two azo-phenyl groups adjacent to the crown ring.

Calixarenes have been utilized as excellent platforms of shaping units for creating attractive host molecules with ion-sensing properties.[1,2] As one of the calixarene derivatives, calixcrown compounds in which one or two crown ether units are incorporated into the lower rim of a calix[4]arene skeleton are also well documented because of their high selectivity toward alkali metal ions.[2] In particular, 1,3-alternate calix[4]crown-6 has been extensively investigated for selective separation of radioactive ^{137}Cs isotope from aqueous nuclear wastes.[3-5] With this 1,3-alternate conformation, the cesium ion is selectively encapsulated not only by the crown ether unit but also by the two aromatic rings (cation/π-interaction).

Chromoionophores[6] have been intensively investigated as a specific metal ion indicator since Pedersen[7] reported salt-dependent UV/vis measurement for the characterization of the complexation process with the crown ether containing aromatic conjugated system. It was reported that a calix[4]arene with triamide and monoalkylated azophenol units on the lower rim gave a UV/vis band shift, in which the direction of the shift was dependent on the conformation of the calixarene.[8,9] Recently, we also reported that the absorbance bands of the partial cone (azo)calix[4]crown-6 (**1**) having two OR groups (R = methyl, *n*-propyl, and *n*-octyl) on the lower rim shifted by the addition of Ca^{2+} ion.[10] Electrostatic interaction between the oxygen atom of OR and a metal ion gave a hypsochromical (blue) band shift while π-metal complexation between the rotated phenyl unit and a metal ion resulted in a bathochromical (red) band shift.

With these observations in mind, we have prepared *p*-nitrophenyl azo-coupled 1,3-alternate calix[4]biscrown-5;6 (**2**), biscrown-6 (**3**), and *p*-aminophenyl azo-coupled 1,3-alternate calix[4]biscrown-5;6 (**4**) and then herein have compared their selectivity toward metal cations and determined the regioselectivity between the two crown rings in each compound by UV band shift.

Syntheses of compounds **2**−**4** are shown in Scheme 1. Compounds **5** and **6** as starting materials were prepared by adaptation of the published procedures.[10] Cyclization of **6** with a tetra- and a pentaethyleneglycol ditosylate in the presence of K_2CO_3 or Cs_2CO_3 as a base gave **2** and **3** in moderate yields, respectively. From the singlet at around δ 3.6 in the ^{1}H NMR spectra and a resonance at about 38 ppm in the ^{13}C NMR spectra for **2** and **3**, they were found to be in the rigid 1,3-alternate conformation. Reduction of **2** by $SnCl_2$ gave compound **4** in 70% yield with retained 1,3-alternate conformation.

The perchlorate salts of Li^+, Na^+, K^+, Rb^+, Cs^+, Ag^+, Ca^{2+}, Mg^{2+}, Pb^{2+}, Zn^{2+}, Cu^{2+}, Hg^{2+}, Al^{3+}, and In^{3+} ions were tested to evaluate the metal ion binding properties of **2**−**4**. Ligand concentration in all titration experiments was fixed by 10^{-5} M in CH_3CN. Free **2** and **3** exhibited absorption bands at 368 and 370 nm in CH_3CN, respectively. Addition of metal ions in the ligand solution gave a hypsochromical color change in all cases, indicating that the metal ion is entrapped exclusively by the upper crown loop not by the lower crown ring, as shown in Figures 2 and 3. The λ_{max} changes ($\Delta\lambda_{max}$) upon the metal ion addition are listed in Table 1 as well.

To obtain the association constants (K_a) of the complexes, various amounts of metal perchlorate were added stepwise to **2** and **3**, respectively. Figure 4 and Figure S1 represent the wavelength changes of **3** and **2** upon the addition of Cs^+ and K^+ ion, respectively. The titration profiles of other metal cations for **2** and **3** are also depicted in Figures S3 and S4. By using the computer program ENZFITTER,[11] the association constant (K_a) and the free energy change for the addition of each metal ion were obtained and are listed in Table 2. Metal ion affinities of **2** and **3** are in the order of $K^+ > Rb^+ > Cs^+$

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(1) Gutsche, C. D. *Calixarenes*; The Royal Society of Chemistry: Cambridge, U.K., 1989.

(2) Casnati, A.; Ungaro, R.; Asfari, Z.; Vicens, J. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, Holland, 2001; pp 365−384.

(3) Casnati, A.; Pochini, A.; Ungaro, R.; Ugozzoli, F.; Arnaud-Neu, F.; Fanni, S.; Schwing, M.-J.; Egberink, R. J. M.; de Jong, F.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1995**, *117*, 2767.

(4) Kim, J. S.; Lee, W. K.; Kim, J. G.; Suh, I. H.; Yoon, J. Y.; Lee, J. H. *J. Org. Chem.* **2000**, *65*, 7215.

(5) Nijenhuis, W. F.; Buitenhuis, E. G.; de Jong, F.; Sudhölter, E. J. R.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1991**, *113*, 7963.

(6) (a) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1980**, *113*, 457. (b) Dix, J. P.; Vögtle, F. *Chem. Ber.* **1981**, *114*, 638.

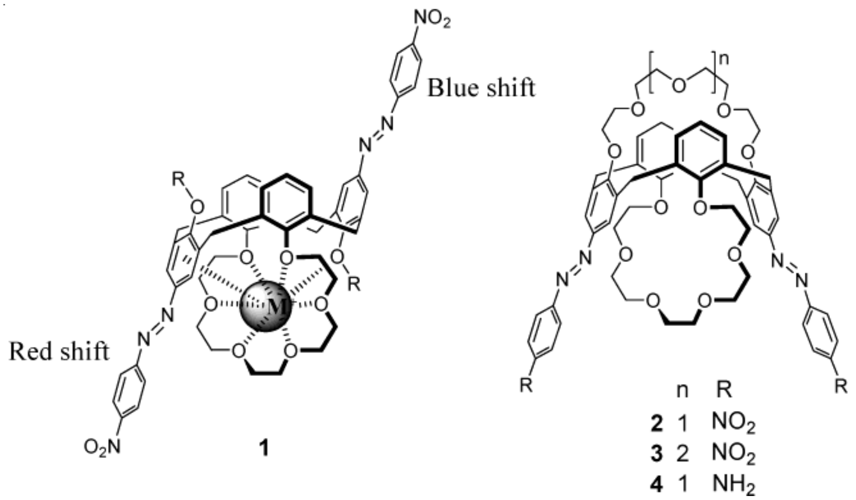
(7) Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 2495.

(8) Kim, J. S.; Shon, O. J.; Lee, J. K.; Lee, S. H.; Kim, J. Y.; Park, K. M.; Lee, S. S. *J. Org. Chem.* **2002**, *67*, 1372.

(9) Cobben, P. L. H. M.; Egberink, R. J. M.; Böhmer, J. R.; Bergveld, P.; Verboom, W.; Reinhoudt, D. N. *J. Am. Chem. Soc.* **1992**, *114*, 10573.

(10) Kim, J. Y.; Kim, G. C.; Kim, C. R.; Lee, S. H.; Lee, J. H.; Kim, J. S. *J. Org. Chem.* **2003**, *68*, 1372.

10.1021/jo049954o CCC: $27.50



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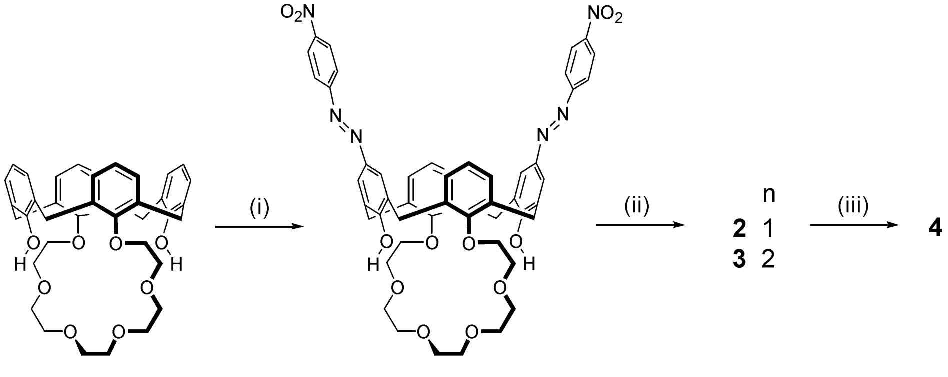
	n	R
2	1	NO$_2$
3	2	NO$_2$
4	1	NH$_2$

FIGURE 1. Azo-coupled calix[4]mono- and biscrown compounds.

SCHEME 1[a]



5 **6**

[a] Reagents: (i) 4-Nitrobenzenediazonium tetrafluoroborate, pyridine, THF. (ii) **2**: tetraethyleneglycol ditosylate, K_2CO_3, CH_3CN; **3**: pentaethyleneglycol ditosylate, Cs_2CO_3, CH_3CN. (iii) EtOH, tin(II) chloride dihydrate.

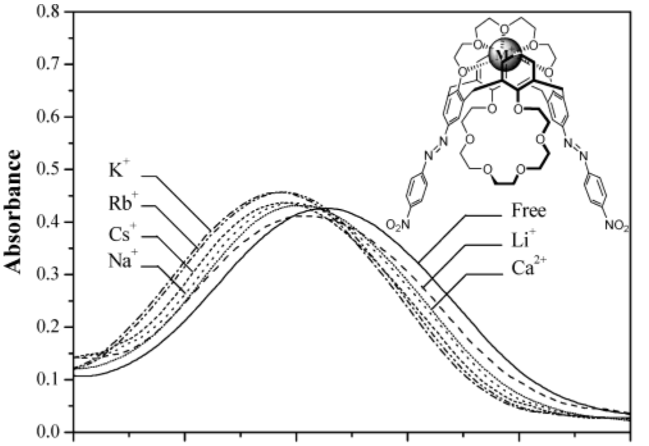


FIGURE 2. Wavelength changes of **2** upon the addition of metal cations. Conditions: **2** (0.01 mM)/CH_3CN; metal cations (1000 equiv)/CH_3CN.

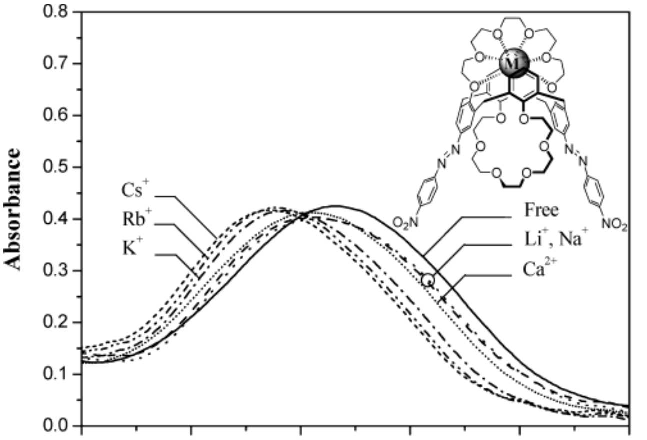


FIGURE 3. Wavelength changes of **3** upon the addition of metal cations. Conditions: **3** (0.01 mM)/CH_3CN; metal cations (1000 equiv)/CH_3CN.

$> Na^+ > Ca^{2+} > Li^+$ and $Cs^+ > Rb^+ > K^+ > Ca^{2+} > Li^+ > Na^+$, respectively.

The hypsochromic shifts on the UV spectra are attributable to the fact that the phenolic oxygen atoms of the upward crown loop are positively polarized when the ligands complex with metal ion with the result that the excited states are more destablized by cations than the ground states.[8] Among the metal ions tested for compound **2**, the K^+ ion was the most selective with respect to the blue shift. Similarly, compound **3** having both crown-6 rings showed a Cs^+ ion selectivity in hypso-

TABLE 1. Optical Responses of 2−4 (10^{-5} M) to Different Metal Perchlorate Salts (10^{-2} M) in CH_3CN

compd	λ_{max} (nm)	ϵ (cm^{-1} M^{-1})	metal-induced wavelength changes ($\Delta\lambda_{max}$/nm)[a] Li^+	Na^+	K^+	Rb^+	Cs^+	Ag^+	Ca^{2+}	Mg^{2+}	Pb^{2+}	Zn^{2+}	Hg^{2+}
2	368	42 600	−6	−9	**−13**	−12	−11	−13	−8	−9	−7	−8	−9
3	370	42 500	−6	−5	−15	−17	**−19**	−5	−7	−9	−10	−5	−4
4	396	43 500	0	0	+3	+7	**+9**	−1	0	0	0	0	0

[a] (+) and (−) in wavelength changes denote red and blue shift, respectively. The samples were prepared by mixing equal volumes of stock solutions of **2**−**4** and the metal perchlorate salts.

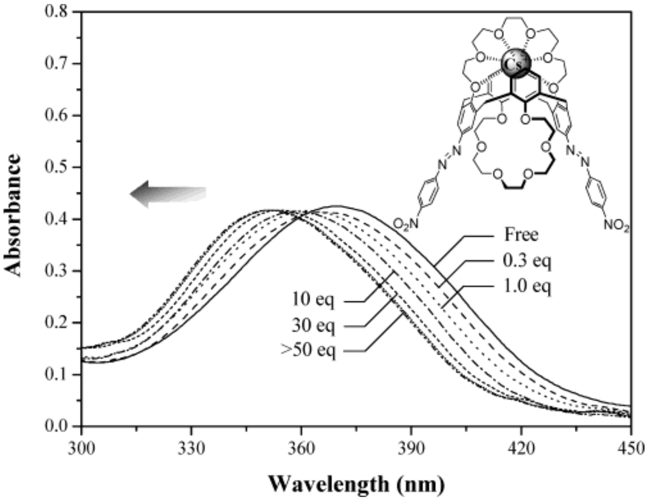


FIGURE 4. Wavelength changes of **3** upon the addition of various amounts of $CsClO_4$. Titration conditions: **3** (0.01 mM)/CH_3CN; $CsClO_4$ (0.3→100 equiv)/CH_3CN.

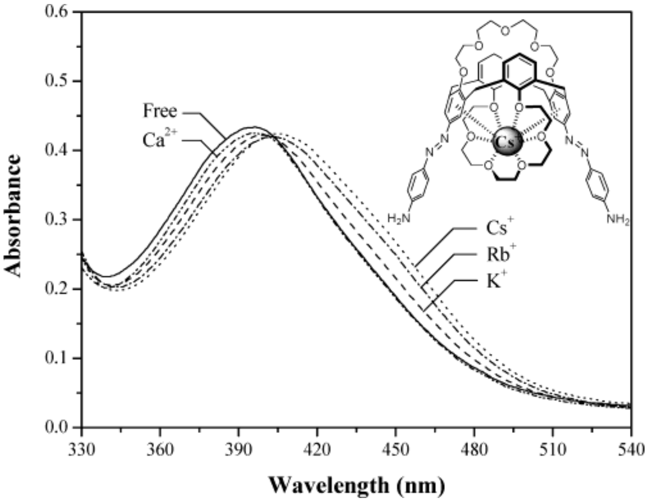


FIGURE 5. Wavelength changes of **4** upon the addition of metal cations. Conditions: **4** (0.01 mM), metal cations (1000 equiv); solvent, CH_3CN/DMSO (9:1, v/v).

TABLE 2. Association Constants (K_a)[a] and Free Energy of 2 and 3 for Metal Cations

compd	property	Li^+	Na^+	K^+	Rb^+	Cs^+	Ca^{2+}
2	K_a (10^3)	0.85	2.46	822.1	652.5	48.5	1.72
	$-\Delta G^b$	16.7	19.3	33.7	33.1	26.7	18.4
3	K_a (10^3)	1.20	0.98	5.86	6.58	223.6	2.41
	$-\Delta G^b$	17.5	17.0	21.5	21.7	30.5	19.3

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

chromical band shift. This selectivity is obviously because the calix[4]crown-5 and calix[4]crown-6 are suitable for potassium and cesium ions, respectively. In our earlier report,[10] we described that for partial cone **1**, (a) the metal ion entrapped in the downward crown ring interacts with the propyloxy (−OR) oxygen atom of the distal azophenyl unit, leading to the 22-nm blue shift, and (b) interacts with the aromatic ring of the proximal azophenol group by the π-metal complexation mode, then giving an 18-nm red shift. So, for **2** and **3**, one can make the inference that the metal ion is encapsulated not in the downward crown ring unlike in the case of **1** but in the upper crown ring because no bathochromic band shift was observed in all cases upon the metal ion addition.

To prove the regioselective binding of metal ion toward the upper crown part of both **2** and **3**, leading to hypsochromic band shifts, we obtained ^1H NMR spectra of complex **3**·Cs^+ (Figure S4). H_d (meta) and H_e (para) moved downfield by 0.11 and 0.21 ppm, which are driven by π-metal interaction between the cesium ion and the two rotated benzene rings. The 0.08-ppm downfield shift of H_c, however, is not due to π-metal interaction but to the strong electrostatic interaction of the phenyloxy oxygen of the upper loop with the Cs^+ ion.

Then, for **2** and **3**, why does the metal ion choose the upper crown part rather than the lower crown part as the better binding partner? We initially assumed that when the metal ion approaches the ligand there might be steric hindrance between the two phenylazo groups and downward crown-6 or a weak π-cation complexation by the electron-withdrawing NO_2 group on the benzene ring. To support this postulate, **4** in which a nitro unit of the phenylazo group was reduced to an amino group was investigated with respect to UV-band change upon the metal ion complexation. Surprisingly, we could not observe any blue shift, but exclusively a red shift as shown in Figure 5 and Table 1 although the assumed steric hindrance between two azo-coupled phenyl groups and the crown loop may be still occur upon the metal ion entrapping. Wavelength changes of **4** for the metal ion binding were $\Delta\lambda_{max} = 3$, 7, and 9 nm for the K^+, Rb^+, and Cs^+ ions, respectively, ensuring that the cesium ion is selectively encapsulated in the crown-6 ring, which supports the fact that the 1,3-alternate calix[4]crown-6 selectively captures the cesium ion not only due to an electrostatic interaction between the cesium ion and the crown-6 loop but also due to the π-cesium complexation between the cesium ion and two rotated benzene rings.[3,4] So, it should be noteworthy that the cesium ion selectivity based on the red shift in this study is ascribed to a

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(11) (a) Association constants were obtained with use of the computer program ENZFITTER, available from Elsevier-BIOSOFT, 68 Hills Road, Cambridge CB2 1LA, United Kingdom. (b) Connors, K. A. *Binding Constants*; Wiley: New York, 1987.

suitable crown size for the cesium ion together with strengthened π-cation interaction driven by the electron-donating NH_2 group on the phenylazo unit to result in a regioselectivity in metal ion complexation.

In conclusion, we now demonstrate that *p*-nitrophenylazo-coupled 1,3-alternate calix[4]biscrown **2** and **3** encapsulates the metal ions in the upper part of the crown ring, showing a blue shift on the UV/vis spectra. However, changing the nitro group to the amino group in the phenylazo unit gave a red shift, implying that the metal ion is encapsulated in the lower crown part with the aid of enhanced π-cation interaction. Therefore, for the metal ion binding one can ensure that the π-metal complexation plays the most important role in the determination of the regioselectivity in the 1,3-alternate calix[4]biscrown system.

Experimental Section

Syntheses. Compounds **5** and **6** were prepared in 50−70% yield as described in the literature.[10]

General Method for the Synthesis of Calix[4]biscrowns. A solution of **6** (1.08 mmol) in dried acetonitrile (50 mL) was treated with anhydrous metal carbonate (3.0 equiv). To this suspension was added a poly(ethylene glycol) ditosylate (1.1 equiv) dissolved in CH_3CN (10 mL), and the reaction mixture was then refluxed for 48 h. After removal of the solvent in vacuo, the residue was acidified with 10% aqueous HCl solution (50 mL), and then extracted with CH_2Cl_2 (50 mL). The organic layer was separated and washed with 10% HCl solution, then dried over anhydrous $MgSO_4$, and the solvent was evaporated to yield a reddish solid. The pure product was isolated by column chromatography, using ethyl acetate:hexane (3:1) as eluent in silica gel.

5,17-Bis[(4-nitrophenyl)(azo)phenyl]-26,28:25,27-calix[4]-crown-5-crown-6 (2). Tetraethyleneglycol ditosylate and K_2CO_3 were used. Yield: 65%. Mp: 313−314 °C. Anal. Calcd for $C_{58}H_{62}N_6O_{15}$: C, 64.32; H, 5.73. Found: C, 64.35; H, 5.70.

5,17-Bis[(4-nitrophenyl)(azo)phenyl]-26,28:25,27-calix[4]-biscrown-6 (3). Pentaethyleneglycol ditosylate and Cs_2CO_3 were used. Yield: 52%. Mp: 240−241 °C. Anal. Calcd for $C_{60}H_{66}N_6O_{16}$: C, 63.94; H, 5.86. Found: C, 63.97; H, 5.84.

5,17-Bis[(4-aminophenyl)(azo)phenyl]-26,28:25,27-calix-[4]crown-5-crown-6 (4). To a solution of **2** (200 mg, 0.18 mmol) in ethyl alcohol (20 mL) was added tin(II) chloride dihydrate (70.0 mg, 0.37 mmol), and the reaction mixture was then refluxed for 12 h. After removal of the solvent in vacuo, the residue was washed with $NaHCO_3$ solution (50 mL) and then extracted with CH_2Cl_2 (50 mL). The organic layer was separated, washed with H_2O solution, and dried over anhydrous $MgSO_4$, and the solvent was evaporated to yield a reddish solid. The pure product was isolated by recrystallization with AcOEt:CH_2Cl_2 (5/1). Yield: 70%. Mp: 253−254 °C. FAB MS *m/z* (M^+): calcd 1023.18; found 1023.00. Anal. Calcd for $C_{58}H_{66}N_6O_{11}$: C, 68.08; H, 6.50. Found: C, 68.12; H, 6.48.

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Supporting Information Available: Additional UV/vis and ^1H NMR spectra (Figure S1−S4). This material is available free of charge via the Internet at http://pubs.acs.org.

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