organic phases were dried ($MgSO_4$) and concentrated in vacuo to give a yellow oil. Chromatography of the crude oil (40% EtOAc/hexanes) gave a microcrystalline solid (27 mg, 54%): mp 89–91 °C; $[\alpha]^{20}_D$ +5.27° (c 1.10, $CHCl_3$); IR (CH_2Cl_2) 1787 (lactone CO), 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.32 (dt, 1 H, J = 0.87, 4.82, H_2), 3.60 (s, 3 H), 3.75 (s, 6 H), 3.61 (s, 6 H), 3.84 (s, 3 H), 3.95 (t, 1 H, J = 5.08, H_3), 4.62 (d, 1 H, J = 4.69, H_1), 5.43 (d, 1 H, J = 4.90, H_4), 5.86 (s, 1 H), 5.97 (s, 2 H), 6.21 (s, 2 H), 6.43 (s, 1 H), 6.83 (s, 1 H), 7.32–7.42 (m, 5 H, Ar); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 44.45 (CH), 46.51 (CH), 49.72 (CH), 52.67 (CH_3), 56.20 (CH_3), 60.83 (CH_3), 75.04 (CH), 77.55 (CH), 101.38 (CH_2), 106.70 (CH), 108.22 (CH), 110.30 (CH), 127.56 (CH), 128.06 (C), 128.90 (CH), 129.61 (CH), 129.77 (C), 133.05 (C), 136.41 (C), 137.47 (C), 146.55 (C), 148.55 (C), 153.03, (C), 166.53 (C), 167.90 (C), 173.36 (C); MS m/z (relative intensity) 577 (M^+ + 1, 12), 576 (M^+, 33), 410 (23), 339 (36), 107 (100), 79 (55); HRMS, calcd for $C_{31}H_{28}O_{11}$ 576.1632, found 576.1633.

Lactone–Acid 11. Lactone 10 (27 mg, 0.047 mmol) and 5% Pd/C (15 mg) in EtOAc (10 mL) were stirred under H_2 (1 atm) at rt for 2 h. The mixture was filtered, the filtrate was evaporated, and the residue was dissolved in CH_2Cl_2 (20 mL). The solution was extracted with 5% aqueous $NaHCO_3$ (3 × 10 mL). The combined bicarbonate layers were acidified (10% HCl), saturated with NaCl, and extracted with EtOAc (3 × 10 mL). The organic extracts were dried ($MgSO_4$) and concentrated in vacuo to give a colorless solid (17.5 mg, 87%). Crystals from CH_2Cl_2/hexanes had the following: mp 209–211 °C; $[\alpha]^{20}_D$ –26.7° (c 0.43, $CHCl_3$); IR (CH_2Cl_2) 3400–2800 (br, CO_2H), 1787 (lactone CO), 1734 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.30 (t, 1 H, J = 4.75, H_2), 3.78 (s, 6 H, OCH_3), 3.85 (s, 3 H), 3.89 (t, 1 H, J = 5.05, H_3), 4.76 (d, 1 H, J = 4.77, H_1), 5.38 (d, 1 H, J = 5.12, H_4), 5.95, 5.97 (AB q, 2 H, J = 1.27, OCH_2O), 6.27 (s, 2 H, Ar H), 6.46 (s, 1 H, Ar H), 6.79 (s, 1 H, Ar H); MS m/z (relative intensity) 428 (M^+, 5), 382 (15), 338 (47), 323 (30), 81 (51), 73 (29), 69 (100); HRMS, calcd for $C_{22}H_{20}O_9$ 428.1107, found 428.1090.

(–)-Neopodophyllotoxin. Lactone–acid 11 (23.5 mg, 0.0549 mmol) in dry CH_2Cl_2 (3 mL, dried with 3-Å molecular sieves) and oxalyl chloride (5 mL) were stirred at rt for 4 days. The excess oxalyl chloride was evaporated; $NaBH_4$ (20 mg), dry THF (3 mL), and diglyme (1 mL) were added. The mixture was stirred for 2 h. Water (20 mL) was added and stirring continued for half an hour (until all the excess $NaBH_4$ was destroyed). The solution was saturated with NaCl and the organic phase separated. The aqueous phase was extracted with EtOAc (2 × 10 mL), and the combined extracts were dried ($MgSO_4$) and evaporated. Recrystallization of the crude product (EtOAc/hexanes) gave a colorless solid (20 mg, 88%): mp 232–234 °C (lit.[7] mp 230–231 °C); $[\alpha]^{20}_D$ –50.8° (c 0.26, $CHCl_3$), lit.[23] $[\alpha]^{20}_D$ –52.4°; IR (CH_2Cl_2) 3617 (OH), 3330 (OH), 1781 (lactone CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02 (t, 1 H, J = 4.38, H_2), 3.16 (m, 1 H, H_3), 3.66 (dd, 1 H, J = 7.69, 10.82), 3.75 (1 H, overlapped by OMe singlet), 3.78 (s, 6 H, OMe), 3.85 (s, 3 H, OMe), 4.25 (d, 1 H, J = 4.54, H_1), 5.19 (d, 1 H, J = 4.75, H_4), 5.95, 5.97 (AB q, 2 H, J = 1.30, OCH_2O), 6.28 (s, 2 H, Ar H), 6.49 (s, 1 H, Ar H), 6.74 (s, 1 H, Ar H); MS m/z (relative intensity) 415 (M^+ + 1, 11), 414 (M^+, 54), 394 (36) 339 (19), 98 (32), 69 (100); HRMS, calcd for $C_{22}H_{22}O_8$ 414.1315, found 414.1304. The ^1H NMR data are identical to those previously published.[7,23]

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Registry No. 6, 42123-15-9; 8, 138380-77-5; 9, 138234-54-5; 10, 138234-55-6; 11, 138234-56-7; fumaryl chloride, 627-63-4; (S)-methyl mandelate, 21210-43-5; (–)-neopodophyllotoxin, 1456-54-8.

Supplementary Material Available: ^1H NMR spectra for compounds 8–11 and (–)-neopodophyllotoxin (5 pages). Ordering information is given on any current masthead page.

Syntheses and Ion Selectivity of Conformational Isomers Derived from Calix[4]arene

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Three conformational isomers (cone, partial cone, and 1,3-alternate) of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-bis(2-pyridylmethoxy)calix[4]arene (3) were synthesized from 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(2-pyridylmethoxy)calix[4]arene (6). The examination of the metal selectivity in two-phase solvent extraction established that the cone conformer predominantly results when the base contains template metal cations, whereas the partial cone and 1,3-alternate conformers result when the base contains nontemplate metal cations. The solvent extraction data indicated that cone-3 shows the strong metal affinity as comparable with that of cone-5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (cone-2) and binds not only Na^+ but Li^+. On the other hand, partial-cone-2 shows a poor metal affinity. The difference was discussed on the basis of spectroscopic and X-ray crystallographic data. This paper demonstrates for the first time that the metal selectivity of ionophoric calix[*n*]arenes can be changed not only by the change in the ring size but also by the conformational change.

Introduction

Calixarenes have been used as useful basic skeletons for the synthesis of lipophilic,[1-3] water-soluble,[4] and ionophoric receptors.[5-8] For the design of these functionalized calixarenes, modification of OH groups arranged on the lower rim is convenient.[9,10] Among them, the ionophoric properties of calix[4]arene derivatives are of particular interest: for example, 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene with a cone conformation (cone-2), prepared by the reaction of

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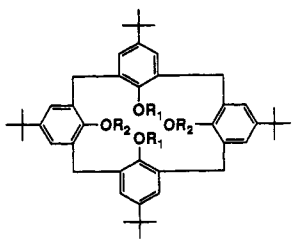
5,11,17,23-tetra-*tert*-butylcalix[4]arene-25,26,27,28-tetrol (1) and ethyl bromoacetate in the presence of NaH, shows the high Na^+ affinity and Na^+ selectivity comparable with those of cryptand 222.[5-8] Meanwhile, it is known that tetra-O-alkylation of 1 with alkyl bromides (e.g., *n*-PrBr) in the presence of NaH yields a mixture of conformational isomers.[10-13] In contrast, conformers other than cone are not known for 2.[14] Why does the reaction of 1 and ethyl bromoacetate yield only cone-2? It thus occurred to us that if one could synthesize ionophoric calix[4]arenes other than cone, they would show the different metal affinity and metal selectivity and further extend a calixarene-based receptor chemistry.[10c,d] We were interested in the synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)-methoxy]-26,28-bis(2-pyridylmethoxy)calix[4]arene (3) and 5,11,17,23,29,35-hexa-*tert*-butyl-37,40-bis[(ethoxycarbonyl)methoxy]-38,39,41,42-tetrakis(2-pyridylmethoxy)calix[6]arene (5). The original purpose of this research was the synthesis of universal ionophores which show the affinity not only toward alkali metal cations but also toward heavy metal cations. Compound 5 is conformationally mobile, allowing the oxygen-through-the-annulus rotation of each phenol unit whereas compound 3 is conformationally immobile because of steric hindrance of these substituents. Unexpectedly, we found that the product 3 is afforded as a mixture of three conformational isomers, which are eventually separated and identified to be cone-3, partial-cone-3, and 1,3-alternate-3.[15] This is the first example for the synthesis of ionophoric calix-[4]arenes other than cone. In this paper, we report the syntheses of these new ionophoric calixarenes, metal extraction properties, and the X-ray crystal structure of one of them.

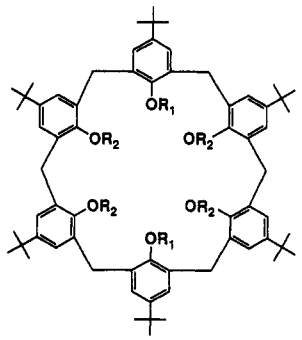


1 : $R_1 = R_2 = H$

2 : $R_1 = R_2 = CH_2CO_2Et$

3 : $R_1 = CH_2CO_2Et$, $R_2 =$ 

6 : $R_1 = H$, $R_2 =$



4 : $R_1 = R_2 = CH_2CO_2Et$

5 : $R_1 = CH_2CO_2Et$, $R_2 =$ 

7 : $R_1 = H$, $R_2 =$

Experimental Section

Materials. Compound 1 was synthesized according to Gutsche's method.[16] Preparations of 2 and 4 were described previously.[8]

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(2-pyridylmethoxy)calix[4]arene (6). Compound 1 (5.0 g; 7.7 mmol) was treated with 2-(chloromethyl)pyridine hydrochloride (10.1 g; 62 mmol) in the presence of K_2CO_3 (5.0 g) in anhydrous DMF (150 mL) at 70 °C for 16 h. After being cooled, the reaction mixture was poured into water and the precipitate was recovered by filtration. This was dissolved in chloroform, washed with water, and dried over $MgSO_4$. The solution was concentrated to dryness, the reside being recrystallized from methanol: mp 249–251 °C, yield 69%; IR (Nujol) ν_{OH} 3430 cm^{-1}, $\nu_{C=C}$ and $\nu_{C=N}$ 1590 and 1570 cm^{-1}; ^1H NMR ($CDCl_3$, 30 °C) δ 0.93 and 1.30 (*t*-Bu, s each, 18 H each), 3.34 and 4.31 ($ArCH_2Ar$, d each (J = 13 Hz), 4 H each), 5.19 (OCH_2, s, 4 H), 6.80 and 7.08 (ArH, s each, 4 H each), 7.21 (OH, s, 1 H), 7.28, 7.60, 8.29, and 8.61 (PyH, m, m, d, and d, respectively, 2 H each). Anal. Calcd for $C_{56}H_{66}N_2O_4$: C, 80.92; H, 8.00; N, 3.37. Found: C, 80.25; H, 7.93; H, 3.43. The splitting pattern for the $ArCH_2Ar$ protons (a pair of doublets with $\Delta\delta$ = 0.97 ppm) shows that compound 1 adopts a cone conformation.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)-methoxy]-26,28-bis(2-pyridylmethoxy)calix[4]arene (3). Compound 6 (1.5 g; 1.8 mmol) was treated with ethyl bromoacetate (3.0 g; 18 mmol) in the presence of K_2CO_3 (11 g) in anhydrous DMF at 75 °C for 14 h. After being cooled, the reaction mixture was poured into water, the precipitate being recovered by filtration. This was dissolved in chloroform, washed with water, and dried over $MgSO_4$. The solution was concentrated in vacuo, the residue being subjected to a TLC separation (silica gel, hexane:ethyl acetate = 3:2 v/v). Cone-3: R_f = 0.15, mp 144–145 °C, yield 32%; IR (CCl_4) $\nu_{C=O}$ 1740 and 1765 cm^{-1} (intensity ratio ca. 1:1); ^1H NMR ($CDCl_3$, 30 °C) δ 0.92 and 1.24 (*t*-Bu, s each, 18 H each), 1.13 (CH_3, t, 6 H), 3.16 and 4.68 ($ArCH_2Ar$, d each (J = 13 Hz), 4 H each), 3.95 ($COOCH_2$, q, 4 H), 4.76 (OCH_2CO, s, 4 H), 5.02 (OCH_2Py, s, 4 H), 6.58 and 6.99 (ArH, s each, 4 H each), 7.24, 7.68, 7.72, and 8.61 (PyH, m, m, d, d, respectively, 2 H each). Anal. Calcd for $C_{64}H_{78}N_2O_8$: C, 76.62; H, 7.84; N, 2.79. Found: C, 76.70; H, 7.88; N, 2.76. The splitting pattern (C_2 symmetry and a pair of doublets with $\Delta\delta$ for the $ArCH_2Ar$ protons) is commensurate with a cone structure. Partial-cone-3: R_f = 0.60, mp 211–213 °C, yield 7.7%; IR (CCl_4) $\nu_{C=O}$ 1740 and 1765 cm^{-1} (intensity ration ca. 1:3); ^1H NMR ($CDCl_3$, 30 °C) δ 0.95, 1.05, and 1.33 (*t*-Bu, s each, 9 H, 18 H, 9 H, respectively), 1.05 and 1.33 (CH_3, t each, 3 H each), 3.17, 3.76, 3.90, and 4.49 ($ArCH_2Ar$, d each (J = 13.1 ppm for 3.17 and 4.49 and 13.7 ppm for 3.76 and 3.90), 2 H each), 3.83 and 4.24 ($COOCH_2$, q each, 2 H each), 4.27 and 4.33 (OCH_2CO, s each, 2 H each), 4.76 and 4.89 (OCH_2Py, d each (J = 11.6 Hz), 2 H each), 6.55, 7.05, 7.06, and 7.09 (ArH, d, s, s, and d, respectively, 2 H each), 7.24, 7.57, 7.66, and 8.62 (PyH, m, d, m, d, respectively, 2 H each). Anal. Calcd for $C_{64}H_{78}N_2O_8$: C, 76.62; H, 7.84; N, 2.79. Found: C, 76.49; H, 7.86; N, 2.72. The partial cone ($EtOCOCH_2O$ inversed) structure

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is supported by (i) two pairs of doublets with a large $\Delta\delta$ (= 1.32 ppm) difference and a small $\Delta\delta$ (= 0.14 ppm) difference for the $ArCH_2Ar$ protons and (ii) the existence of two different $EtOCOCH_2O$ groups. On the other hand, a pair of doublets for the OCH_2Py methylene protons is ascribed to the geminal coupling caused by the restriction of the bond rotation. 1,3-Alternate-**3**: R_f = 0.75, mp 271–273 °C, yield 1.1%; IR (Nujol) $\nu_{C=O}$ 1770 cm^{-1}, no ν_{OH}; ^1H NMR ($CDCl_3$, 30 °C) δ 0.78 and 1.27 (*t*-Bu, s each, 18 H each), 1.17 (CH_3, t, 6 H), 3.40 (OCH_2CO, s, 4 H), 3.66 and 4.05 ($ArCH_2Ar$, d each (J = 16 Hz), 4 H each), 4.05 ($COOCH_2$, q, 4 H), 4.76 (OCH_2Py, s, 4 H), 6.71 and 7.13 (ArH, s each, 4 H each), 6.58, 7.17, 7.60, and 8.51 (PyH, m, d, m, d, respectively, 2 H each). Anal. Calcd for $C_{64}H_{78}N_2O_8$: C, 76.62; H, 7.84; N, 2.79. Found: C, 76.19; H, 7.93; H, 2.57. A pair of doublets with a small $\Delta\delta$ (= 0.39 ppm) difference for the $ArCH_2Ar$ protons and the existence of two equivalent $EtOCOCH_2O$ groups and $PyCH_2O$ groups are commensurate with a 1,3-alternate structure.

We later found that the reaction of **6** and ethyl bromoacetate in the presence of Cs_2CO_3 in acetone at the reflux temperature for 1 h yields 11.4% of 1,3-alternate-**3** and 4.6% of partial-cone-**3**. Thus, 1,3-alternate-**3** used for solvent extraction was synthesized by this method.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,40-dihydroxy-38,39,41,42-tetrakis(2-pyridylmethoxy)calix[6]arene (7). 2-(Chloromethyl)pyridine hydrochloride (8.36 g; 50 mmol) in 50 mL of DMF and triethylamine (5.06 g; 50 mmol) in 100 mL of THF were mixed, and the precipitate (triethylamine hydrochloride) was removed by filtration under a nitrogen stream. 5,11,17,23,29,35-Hexa-*tert*-butylcalix[6]arene-37,38,39,40,41,42-hexol (5.00 g; 5.1 mmol) was treated with oil-dispersed NaH (2.80 g; 70 mmol) in 100 mL of THF. To this solution was added the 2-(chloromethyl)pyridine solution dropwise at room temperature. The reaction mixture was stirred at reflux temperature for 17 h under a nitrogen stream. After the mixture was cooled, excess NaH was decomposed with methanol. The reaction mixture was concentrated under reduced pressure, the residue being poured into water (200 mL). The precipitate was collected by filtration and washed with water. Then, the product was refluxed in methanol for 1 h, the insoluble material being recovered by filtration. Finally, the product was recrystallized from chloroform–methanol: mp >300 °C, yield 41%; IR (Nujol) ν_{OH} 3360 cm^{-1}, $\nu_{C=C}$ and $\nu_{C=N}$ in pyridine 1565 and 1590 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 0.85 and 1.36 (18 H and 36 H (respectively), s each, *t*-Bu), 3.6–4.8 (12 H, d-d × 2, $ArCH_2Ar$), 4.17 (8 H, s, OCH_2), 6.09–8.10 (28 H, m, BzH and PyH). Anal. Calcd for $C_{90}H_{104}N_4O_6$: C, 80.80; H, 7.83; N, 4.18. Found: C, 80.16; H, 7.80; N, 4.12.

5,11,17,23,29,35-Hexa-*tert*-butyl-37,38-bis[(ethoxycarbonyl)methoxy]-38,39,41,42-tetrakis(2-pyridylmethoxy)calix[6]arene (5). This compound was synthesized from **4** and ethyl bromoacetate in a manner similar to that described for **3**: mp 280–282 °C, yield 58%; IR (Nujol) no ν_{OH}, $\nu_{C=O}$ 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 50 °C) δ 1.04 (60 H, m, *t*-Bu and CH_3), 3.78 (4 H, q, OCH_2C), 3.93 (4 H, s, OCH_2CO), 4.13 (12 H, s, $ArCH_2Ar$), 4.87 (8 H, s, $PyCH_2$), 7.01–8.42 (28 H, m, BzH and PyH). Anal. Calcd for $C_{98}H_{116}N_4O_{10}$: C, 77.95; H, 7.74; N, 3.71. Found: C, 77.73; H, 7.71; N, 3.68.

X-ray Crystal Structure Determination of 3. Colorless crystals from acetonitrile. A 0.10 × 0.33 × 0.46 mm crystal was used for all X-ray measurements: Enraf-Nonius CAD4 diffractometer with Cu source and incident beam graphite monochromator (CuKα, λ = 1.5418 Å); crystal orientation from 25 automatically centered reflections in the range 10. $5 < \theta < 40.4°$; triclinic space group, $P\bar{1}$; a = 11.117 (2) Å, b = 13.970 (3) Å, c = 21.682 (5) Å, α = 72.78 (2)°, β = 76.97 (2)°, γ = 68.16 (2)°; ρcalc = 1.17 g cm^{-3} for Z = 2 ($C_{64}H_{78}N_2O_8 \cdot CH_3CN$, MW 1044.4); 2θ–θ scans over θ range of 1.5 (0.5 + 0.14 tan θ)°; θ scan speed of 8.24° min^{-1}; each scan recorded in ca. 0.01° increments and subjected to on-line reflection profile processing; diffractometer controlled with Digital Equipment Corp. MicroVax II computer and NRCCAD program;[17] nine standard reflections monitored at 1-h intervals of X-ray exposure, −4.9 to 0.1% intensity variation, −1.4% average, correction applied; intensity decline may be attributed to loss of the acetonitrile included in the crystal, but a second crystal sealed in a capillary with excess solvent showed the same intensity decrease; μ = 5.7 cm1^{-1}; maximum θ of 55°; 8043 total data measured, 7656 data without standards, 7416 unique data, 6056 data with $I > 3\sigma(I)$, R_{int} = 0.014 for 240 twice-measured data. All crystallographic calculations performed with the TEXSAN program system[18] on D. E. C. MicroVax II or VaxStation II computers; structure solved with the MITHRIL direct-methods program[19] incorporated in TEXSAN. Full-matrix least-squares refinement, $\sum[1/\sigma^2(F_o)(F_o - F_c)^2]$ minimized, reflections with $I < 3\sigma(I)$ excluded from refinement; anisotropic temperature factors for C, O, and N; H atoms positioned from the C-atom framework, H temperature factors and coordinates were not varied; 695 variables; atomic scattering factors from *International Tables for X-ray Crystallography*;[20] Δ/σ of 0.31 in final 1.s. cycle; final min and max $\Delta\rho$ of −0.37, 0.55 e $Å^{-3}$; R, R_w, and S of 0.094, 0.137, 3.60. Atomic coordinates are listed in Table I. The PLOTMD program[21] was used to display the ball-and-stick ORTEP drawing[22] on a VaxStation II monitor, label the drawing, and prepare a print file for a Hewlett-Packard Laser-Jet II printer.

Table I. Conformer Distribution for the Reaction of 6 and Ethyl Bromoacetate[a]

solvent	temp/°C	base	yield/%	distribution of 3[b]/% cone	partial cone	1,3-alternate
DMF	80	Li_2CO_3	35	100	0	0
DMF	80	K_2CO_3	100	79	16	5
DMF	80	Cs_2CO_3	74[c]	0	69	31
acetone	56 (reflux)	Li_2CO_3	100	100	0	0
acetone	56 (reflux)	K_2CO_3	98	0	100	0
acetone	56 (reflux)	Cs_2CO_3	95	0	37	63
dioxane	80	Cs_2CO_3	100	0	56	44

[a] The reaction was continued for 14 h. In every case, the fourth peak which might be assigned to 1,2-alternate-**3** was not observed. [b] The conformer distribution was estimated by HPLC analysis. [c] After 2 h. When the reaction was continued more than 2 h, further decomposition of **3** took place.

HPLC Analysis. The reaction of **6** and ethyl bromoacetate was followed by a HPLC method: column Zorbax ODS (ϕ 4.6 × 250 mm), chloroform: methanol = 1:4 v/v, flow rate 1 mL min^{-1}. Three peaks for 1,3-alternate-**3**, partial-cone-**3**, and cone-**3** appeared in this order. This order is reversely correlated with the order of the R_f values on the silica gel TLC plate.

Solvent Extraction. Two-phase solvent-extraction was carried out between water (5 mL, [alkali picrate] = 2.50 × 10^{-4} M, [MOH] = 0.10 M, [MCl] = 0.50 M) and dichloromethane (5 mL, [**3** or **5**] = 2.50 × 10^{-3} M). The two-phase mixture was shaken at 25 °C for 30 min. We confirmed that this period is enough to attain the distribution equilibrium. The extractability was determined spectrophotometrically from the decrease in the absorbance of the picrate ion in the aqueous phase.

Results and Discussion

On the Synthesis and Characterization of Conformational Isomers. The conformational characteristics of calix[*n*]arenes are conveniently estimated by the splitting pattern of the $ArCH_2Ar$ methylene protons in ^1H NMR spectroscopy.[11] The $ArCH_2Ar$ methylene protons of **5** appeared as a singlet at 50 °C in $CDCl_3$. This indicates

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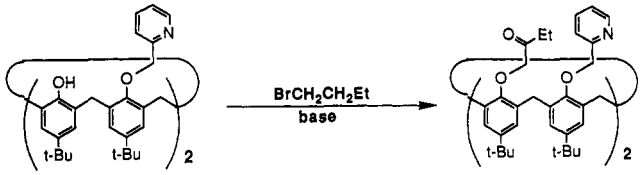
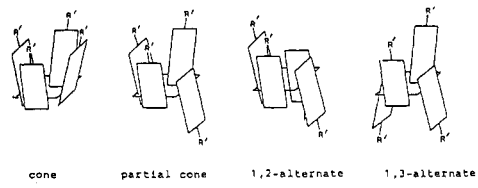
(21) Luo, J.; Ammon, H. L.; Gilliland, G. L. *J. Appl. Crystallogr.* **1989**, *22*, 186.

(22) Johnson, C. K. *ORTEP, A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations*; Report ORNL-3794; Oak Ridge National Laboratory, Oak Ridge, TN; 1965.

that the conformation of **5** is not immobilized. It is known that the reaction of **1** and ethyl bromoacetate in the presence of NaH as base yields cone-**2** in 100% selectivity.[5-8,14] On the other hand, the reaction of **1** and alkyl bromides (RBr: R should be larger than Et to inhibit the oxygen-through-the-annulus rotation[12,13]) yields not only tetra-O-substituted cone but also partial cone and 1,3-alternate.[12,13] The origin of this difference is not yet explained clearly. In the reaction of **6** and ethyl bromo-





acetate in the presence of K_2CO_3, we recognized three spots on the TLC plate. On the basis of the ^1H NMR spectra, we could assign these three compounds to cone-**3**, $EtOCOCH_2O$-inversed partial-cone-**3**, and 1,3-alternate-**3** (the yields determined by HPLC analysis were 79%, 16%, and 5%, respectively). This implies that one can synthesize ionophoric calix[4]arenes other than cone by this method. We considered that the "perfect" cone selectivity observed for the synthesis of cone-**2** from **1** and ethyl bromoacetate is attributed to the strong metal (Na^+) template effect because cone-**2** strongly associates with Na^+.[5-8] This suggests that the formation of conformers (other than cone) is favored when non-template metal cations are used as base.[14] We thus used M_2CO_3 (M^+ = Li^+, K^+, and Cs^+) as base for the reaction of **6** and ethyl bromoacetate and examined the conformer distribution by an HPLC method. The results are summarized in Table I.

It is seen from Table I that the conformer distribution is surprisingly affected by metal cations: the reaction in the presence of Li_2CO_3 yields cone-**3** in 100% selectivity whereas that in the presence of K_2CO_3 or Cs_2CO_3 yields partial-cone-**3** and 1,3-alternate-**3**. In particular, the conformer distribution in acetone changes from 100% selectivity for cone-**3** in the presence of Li_2CO_3 to 100% selectivity for partial-cone-**3** in the presence of K_2CO_3.

Three conformers of **3** were reasonably assigned to cone, partial cone, and 1,3-alternate on the basis of the splitting pattern of the $ArCH_2Ar$ protons in ^1H NMR spectroscopy. In partial-cone-**3** two OCH_2Py groups are equivalent whereas two $EtOCOCH_2O$ groups are inequivalent. This indicates that one of the two $EtOCOCH_2O$ groups is inversed. We previously calculated dipole moments of 5,11,17,23-tetra-*tert*-butyl-24,26,27,28-tetramethoxycalix[4]arene conformers by MM2PP.[23] The order of the dipole moment is cone > partial cone ≫ 1,2-alternate > 1,3-alternate; that is, the dipole moment is increased by a syn conformation and decreased by an anti conformation. As recorded in Experimental Section, the R_f values on the

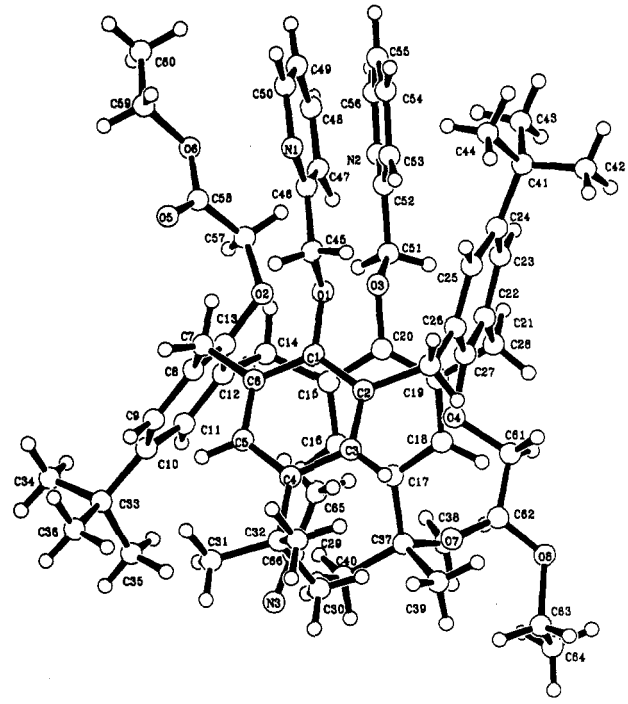


Figure 1. Ball-and-stick drawing of partial-cone-**3**. The trapped acetonitrile molecule is at the bottom and inside and may be identified with the N3 label.

TLC plate were in the order of 1,3-alternate > partial cone > cone. Since the stationary phase is silica gel, the R_f value should be inversely correlated with the polarity of **3**. Thus, cone-**3** is most polar and partial-cone-**3** is the next. Interestingly, the OCH_2Py methylene protons in cone-**3** and 1,3-alternate-**3** appeared as a singlet whereas those in partial-cone-**3** appeared as a pair of doublets because of geminal coupling. This implies that the rotation of the OCH_2Py bonds in partial-cone-**3** is most restricted: that is, the space around the OCH_2Py groups in partial-cone-**3** is more sterically-crowded than other two conformers (even than that in cone-**3**). This problem will be discussed more in detail on the basis of the X-ray crystallographic studies.

The crystal for the X-ray analysis was grown up from acetonitrile. Fractional coordinates (with equivalent isotropic temperature factors) are summarized in Table II. Anisotropic temperature factors, bond lengths, and bond angles are stored as Supplementary Material (Tables A, B, and C, respectively). A ball and stick drawing of **3** from the X-ray crystallographic investigation is shown in Figure 1. In agreement with the NMR data, the structure has the partial cone conformation; three of the calix[4]arene *tert*-butylphenyls and an (ethoxycarbonyl)methyl are down and constitute the walls of the partial cone; an (ethoxycarbonyl)methyl and two 2-pyridylmethyl substituents and a *tert*-butylphenyl are up. The down *tert*-butylphenyls are splayed out from the central axis and somewhat resemble a skirt. The molecule may be described as having an hourglass shape, with upper and lower bulges separated by a narrow waist or belt. The alkoxy oxygen atoms associated with the three up substituents (and the three down *tert*-butylphenyls) form the central belt; these oxygens would be hydroxyls in an unsubstituted calixarene. The planes of the two pyridine rings are approximately parallel to the long axis of the molecule with the pyridine nitrogen atoms pointed outward away from the center. The pyridine rings' inward pointing hydrogen atoms are in van der Waals contact (shortest H···H = 2.38 Å). The (ethoxycarbonyl)methyl and *tert*-butylphenyl neighbors of the up pyridine rings appear to hinder free rotation of

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Table II. Fractional Coordinates, Equivalent Isotropic Temperature Factors (Å²), and Estimated Standard Deviations (Parentheses)

atom	x	y	z	B_{eq}	atom	x	y	z	B_{eq}
O(1)	0.8065 (3)	0.2457 (2)	0.1640 (1)	4.3 (3)	C(29)	0.6375 (5)	−0.0615 (4)	0.1163 (2)	4.6 (4)
O(2)	1.0895 (3)	0.1178 (2)	0.1921 (2)	4.5 (3)	C(30)	0.6102 (7)	−0.1424 (5)	0.1780 (3)	7.5 (7)
O(3)	1.0673 (3)	0.1029 (2)	0.3398 (1)	3.9 (3)	C(31)	0.7285 (7)	−0.1186 (6)	0.0657 (4)	8.4 (8)
O(4)	0.6964 (3)	0.0507 (2)	0.3418 (2)	4.5 (3)	C(32)	0.5070 (7)	0.0010 (5)	0.0905 (4)	7.5 (7)
O(5)	1.1841 (6)	0.2302 (4)	0.0721 (2)	9.9 (6)	C(33)	1.2903 (6)	−0.2757 (4)	0.1164 (3)	5.3 (5)
O(6)	1.2910 (6)	0.2815 (4)	0.1222 (2)	9.3 (6)	C(34)	1.4358 (9)	−0.2965 (7)	0.0954 (5)	12 (1)
O(7)	0.597 (1)	−0.0963 (8)	0.3389 (4)	20 (1)	C(35)	1.287 (1)	−0.3706 (5)	0.1725 (4)	12 (1)
O(8)	0.5113 (6)	−0.1101 (4)	0.4365 (3)	10.8 (6)	C(36)	1.230 (1)	−0.2797 (5)	0.0639 (4)	12 (1)
N(1)	0.8009 (8)	0.5024 (5)	0.0702 (4)	11.2 (8)	C(37)	1.0217 (5)	−0.3096 (3)	0.4408 (2)	4.4 (4)
N(2)	1.2799 (4)	0.2102 (4)	0.3796 (3)	6.2 (5)	C(38)	1.0524 (9)	−0.3382 (5)	0.5090 (3)	8.8 (7)
N(3)	0.943 (1)	−0.3216 (6)	0.2504 (5)	14 (1)	C(39)	0.8823 (8)	−0.3122 (5)	0.4463 (4)	9.0 (8)
C(1)	0.7711 (4)	0.1642 (3)	0.1568 (2)	3.8 (4)	C(40)	1.1132 (8)	−0.3924 (4)	0.4046 (3)	8.3 (7)
C(2)	0.6551 (4)	0.1481 (3)	0.1913 (2)	3.7 (4)	C(41)	0.6407 (5)	0.4772 (4)	0.3305 (3)	5.2 (5)
C(3)	0.6177 (4)	0.0732 (4)	0.1785 (2)	4.0 (4)	C(42)	0.520 (1)	0.511 (1)	0.370 (1)	28 (3)
C(4)	0.6888 (4)	0.0139 (3)	0.1324 (2)	3.7 (4)	C(43)	0.737 (1)	0.4969 (5)	0.3535 (7)	16 (1)
C(5)	0.8086 (4)	0.0278 (3)	0.1027 (2)	3.8 (4)	C(44)	0.624 (2)	0.5505 (7)	0.2661 (6)	20 (2)
C(6)	0.8529 (4)	0.1004 (3)	0.1148 (2)	3.6 (4)	C(45)	0.7606 (5)	0.3415 (4)	0.1171 (3)	5.5 (5)
C(7)	0.9874 (4)	0.1061 (4)	0.0852 (2)	4.0 (4)	C(46)	0.8271 (6)	0.4168 (4)	0.1150 (3)	5.5 (5)
C(8)	1.0929 (4)	0.0142 (4)	0.1217 (2)	3.7 (4)	C(47)	0.9122 (8)	0.3968 (5)	0.1584 (4)	8.4 (8)
C(9)	1.1426 (5)	−0.0818 (4)	0.1034 (2)	4.1 (4)	C(48)	0.973 (1)	0.4705 (8)	0.1519 (5)	11 (1)
C(10)	1.2307 (5)	−0.1720 (4)	0.1379 (2)	4.2 (4)	C(49)	0.943 (1)	0.5585 (7)	0.1072 (5)	11 (1)
C(11)	1.2625 (4)	−0.1607 (3)	0.1938 (2)	4.0 (4)	C(50)	0.863 (1)	0.5731 (7)	0.0674 (6)	14 (1)
C(12)	1.2164 (4)	−0.0676 (3)	0.2136 (2)	3.5 (4)	C(51)	1.1544 (5)	0.1064 (4)	0.3780 (3)	5.1 (5)
C(13)	1.1347 (4)	0.0223 (3)	0.1748 (2)	3.5 (4)	C(52)	1.1760 (5)	0.2107 (4)	0.3581 (2)	4.5 (4)
C(14)	1.2473 (4)	−0.0650 (3)	0.2777 (2)	4.2 (4)	C(53)	1.0932 (6)	0.3006 (4)	0.3232 (3)	5.4 (5)
C(15)	1.1402 (4)	−0.0798 (3)	0.3324 (2)	3.4 (4)	C(54)	1.1230 (8)	0.3940 (5)	0.3084 (3)	7.5 (7)
C(16)	1.1277 (4)	−0.1799 (3)	0.3589 (2)	3.8 (4)	C(55)	1.2304 (8)	0.3936 (6)	0.3294 (4)	7.5 (7)
C(17)	1.0284 (5)	−0.1986 (3)	0.4078 (2)	3.8 (4)	C(56)	1.3048 (6)	0.3013 (6)	0.3644 (4)	7.4 (7)
C(18)	0.9353 (4)	−0.1103 (3)	0.4277 (2)	3.7 (4)	C(57)	1.1869 (8)	0.1661 (5)	0.1876 (3)	7.7 (7)
C(19)	0.9435 (4)	−0.0082 (3)	0.4032 (2)	3.5 (4)	C(58)	1.2209 (7)	0.2276 (5)	0.1239 (3)	6.9 (6)
C(20)	1.0492 (4)	0.0046 (3)	0.3585 (2)	3.3 (3)	C(59)	1.339 (1)	0.342 (1)	0.0638 (5)	14 (1)
C(21)	0.8382 (5)	0.0853 (3)	0.4270 (2)	4.1 (4)	C(60)	1.411 (1)	0.3937 (7)	0.0717 (4)	10 (1)
C(22)	0.7601 (4)	0.1729 (3)	0.3763 (2)	3.6 (4)	C(61)	0.5999 (5)	0.0221 (4)	0.3929 (3)	5.6 (5)
C(23)	0.7449 (5)	0.2774 (3)	0.3716 (2)	4.0 (4)	C(62)	0.5701 (7)	−0.0645 (6)	0.3853 (4)	7.6 (7)
C(24)	0.6705 (5)	0.3632 (3)	0.3288 (2)	4.2 (4)	C(63)	0.448 (2)	−0.194 (1)	0.4293 (6)	15 (2)
C(25)	0.6171 (5)	0.3368 (4)	0.2852 (2)	4.4 (4)	C(64)	0.502 (1)	−0.259 (1)	0.4726 (7)	17 (2)
C(26)	0.6298 (4)	0.2345 (3)	0.2868 (2)	3.7 (4)	C(65)	0.8979 (6)	−0.1305 (5)	0.2559 (3)	6.2 (5)
C(27)	0.6953 (4)	0.1529 (3)	0.3352 (2)	3.7 (4)	C(66)	0.9235 (7)	−0.2369 (7)	0.2533 (4)	8.3 (8)
C(28)	0.5672 (5)	0.2129 (4)	0.2401 (2)	4.6 (4)					

the 2-pyridylmethyl substituents and presumably give rise to the nonequivalent methylene hydrogens in the NMR. In the crystal, there is one molecule of acetonitrile per molecule of **3** located in the bottom skirt section with the hydrophobic methyl end closest to the three *tert*-butylphenyls. The acetonitrile nitrogen atom is even with the *tert*-butyl methyl hydrogens at the very bottom of the molecule.

Two-Phase Solvent Extraction of Alkali Metal Cations. Solvent extraction and transport of alkali metal cations by calix[*n*]arenes was first investigated Izatt et al.[24,25] who showed that all calix[*n*]arenes (*n* = 4, 6, and 8) have Cs^+ selectivity.[24,25] It was later demonstrated by Ungaro et al.,[5] McKervey et al.,[7] and Chang et al.[6] that calix[*n*]arenes can be converted to neutral ligands for alkali metal cations by introduction of ester or amide groups into the OH groups. They showed that the metal selectivity is dependent on the calix[*n*]arene ring size which governs the spherical recognition pattern as observed for crown-metal interactions.[5-8] In particular, conformationally-immobile calix[4]aryl acetates and acetoamides with a cone conformation show the remarkably high Na^+ selectivity.[5-8] This implies that the ionophoric cavity composed of four esters or amides fits the size of Na^+ ion. Here, we discuss if the metal selectivity is affected not only by the ring size of calix[*n*]arenes but also by the conformational difference.

(24) Izatt, R. M.; Lamb, J. D.; Hawkins, R. T.; Brown, P. R.; Izatt, S. R.; Christensen, J. J. *J. Am. Chem. Soc.* **1983**, *105*, 1782.
(25) Izatt, S. R.; Hawkins, R. T.; Christeneen, J. J.; Izatt, R. M. *J. Am. Chem. Soc.* **1985**, *107*, 63.

Table III. % Extraction of Alkali Metal Picrates in CH_2Cl_2 at 25 °C[a]

calixarene	extractability/%			
	$M^+ = Li^+$	Na^+	K^+	Cs^+
cone-2	17.6	100	86.1	24.6
cone-3	62.4	98.7	70.9	9.8
partial-cone-3	0.2	11.4	41.8	26.8
1,3-alternate-3	3.6	90.8	97.7	66.7
4	14.1	64.4	91.2	100
5	6.5	45.4	51.4	74.6

[a] Aqueous phase (5 mL) contains M^+Pic^- (2.50×10^{-4} M), MOH (0.10 M), and MCl (0.50 M). Organic phase (CH_2Cl_2, 5 mL) contains calixarene ionophores (2.50×10^{-3} M).

Solvent extraction of alkali metal cations with the picrate ion into dichloromethane was performed at 25 °C. The results obtained are summarized in Table III. As can be seen from the table, the extraction efficiencies of **3** are significantly affected by the conformational difference. Cone-**3** shows the Na^+ selectivity and the Ex% is comparable with that of cone-**2**. In addition, cone-**3** can extract Li^+ ion which is scarcely extracted by other ionophoric calix[n]arenes. Thus, the order of the Ex% for cone-**3** is $Na^+ > K^+ > Li^+ > Cs^+$ whereas that for cone-**2** is $Na^+ > K^+ > Cs^+ > Li^+$. The results suggest that the ionophoric cavity composed in cone-**3** of two esters and two pyridines is somewhat smaller than that composed in cone-**2** of four esters. On the other hand, compound **5**, the ionophoric cavity of which is composed of two esters and four pyridines, showed the selectivity toward Cs^+. This selectivity is similar to that of compound **4**, the ionophoric cavity of

Table IV. ^{1}H NMR Chemical Shifts (δ) of the Metal-Coordination Groups in Cone-3 and 1,3-Alternate-3[a]

proton	δ/ppm for cone-3			δ/ppm for 1,3-alternate-3		
	no metal	with Li^+	$\delta\Delta$[b]	no metal	with Na^+	$\delta\Delta$[b]
CH_3	1.14	1.36	+0.22	1.17	1.39	+0.22
$ArCH_2Ar$	3.16	3.15	+0.11	3.68	3.79	+0.11
$COOCH_2$	3.94	4.30	+0.36	4.04	4.34	+0.30
$ArCH_2Ar$	4.62	4.21	+0.41	4.07	3.89	−0.18
OCH_2CO	4.73	4.78	+0.05	3.35	4.41	+1.06
OCH_2Py	5.04	5.32	+0.28	4.76	4.80	+0.04

[a] 400 MHz, $CDCl_3$–CD_3OD (9:1 v/v), 30 °C, [3] = 5.0×10^{-3} M, $[MClO_4] = 5.0 \times 10^{-2}$ M. [b] $\Delta\delta = \delta$ (with M^+) − δ (no metal).

which is composed of six esters.[7] The results indicate that the ionophoric cavity designed from calix[6]arene generally shows the selectivity toward large alkali metal cations, regardless of the ligand group.

To clarify how Li^+ ion is bound to the ionophoric cavity in cone-3, we measured the ^{1}H NMR spectra. The results are summarized in Table IV. It is seen from Table IV that $\Delta\delta$ values for the OCH_2CO_2Et and OCH_2Py protons shift to lower magnetic field: for example, the $COOCH_2$ methylene protons and the OCH_2Py methylene protons shift to lower magnetic field by 0.36 and 0.28 ppm, respectively. This established that not only the ester groups but also the pyridine groups operate for the binding of Li^+ ion. We observed the similar down-field shift for the δ in the presence of $NaClO_4$, although the magnitude of the down-field shift was somewhat smaller than that in the presence of $LiClO_4$. Also significant is $\Delta\delta$ for the $ArCH_2Ar$ protons. In a cone-shaped calix[4]arene, the $ArCH_2Ar$ protons appear as a pair of doublets because of geminal coupling between H_{exo} and H_{endo} and $\Delta\delta$ between H_{exo} and H_{endo} serves as a measure of the "flattening": $\Delta\delta$ is generally 0.9 ppm for a system in the cone conformation and in the flattened, $\Delta\delta$ is significantly decreased.[26] The $\Delta\delta$ value for cone-3 is 1.46 ppm. Although this value is smaller than that for cone-2 ($\Delta\delta$ = 1.80 ppm[27]), it is significantly greater than 0.9 ppm for cone-1.[26] The result indicates that phenol units in cone-2 and cone-3 become more parallel to each other by the introduction of "bulky" OCH_2CO_2Et or OCH_2Py groups. Interestingly, the $\Delta\delta$ value for the cone-3·Li^+ complex is 1.06 ppm. This change implies that phenol units in cone-3 are flattened, as a shell closes, when the OCH_2CO_2Et and OCH_2Py groups coordinate to Li^+ cation.

When we unexpectedly isolated 1,3-alternate-3, we considered that this conformer would not show the metal affinity because it has only two esters (or pyridines) on the one side. Contrary to our expectation, 1,3-alternate-3 extracted $K^+ > Na^+ > Cs^+$ in this order and the Ex% for K^+ was highest among four ionophoric calix[4]arenes tested herein. Where does 1,3-alternate-3 bind metal cations? To specify the binding site in 1,3-alternate-3, we measured the ^{1}H NMR spectra of 1,3-alternate-3 in the absence and the presence of $NaClO_4$. The essential chemical shifts (δ) are summarized in Table IV. It is seen from Table IV that the δ values of the protons in the OCH_2CO_2Et groups move to lower magnetic field (0.22 ppm for CH_3, 1.06 ppm for OCH_2CO, and 0.30 ppm for $COOCH_2$) whereas those of the protons in the OCH_2Py groups are scarcely affected (e.g., only 0.04 ppm for CH_2).[28] The difference clearly indicates that the two esters compose an ionophoric cavity stronger than the two pyridines and Na^+ is primarily bound to the cavity composed of the two ester groups.

Table V. ^{1}H NMR Chemical Shifts (δ) of the Metal-Coordination Groups in Partial-Cone-3[a]

proton	δ/ppm		
	no metal	with Na^+	$\Delta\delta$[b]
$OCH_2(CH_3)$	3.76	4.02	+0.26
$OCH_2(CH_3)$(inversed)	4.23	4.29	+0.06
OCH_2CO	4.29	3.16	−1.13[c]
OCH_2CO(inversed)	4.31	4.30	−0.01
OCH_2Py[d]	4.77	5.02	+0.25
	4.92	5.20	+0.28

[a] 400 MHz, $CDCl_3$–CD_3OD (9:1 v/v), 30 °C, [partial-cone-3] = 5.0×10^{-3} M, $[NaClO_4] = 5.0 \times 10^{-2}$ M. [b] $\Delta\delta = \delta$ (with Na^+) − δ (no metal). [c] For the reason of unusual upfield shift, see ref 28. [d] The OCH_2Py methylene protons appear as a pair of doublets because of geminal coupling.

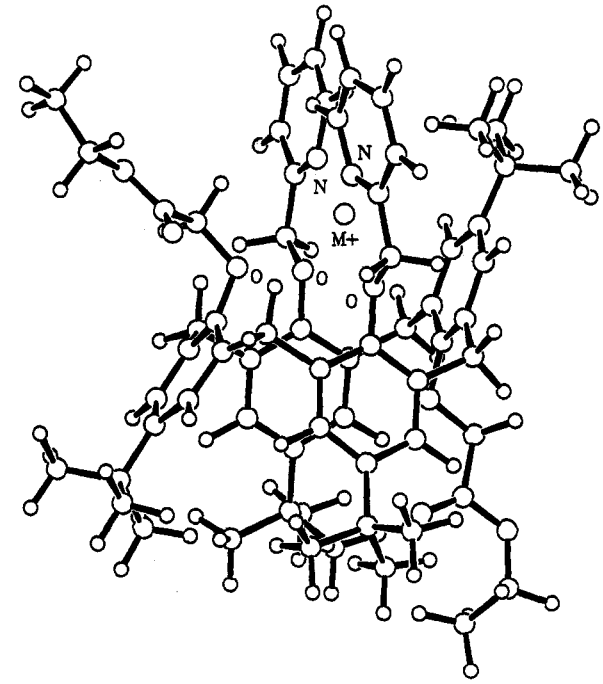

Figure 2. Ball-and-stick model of possible cation (e.g., K^+) complex of partial-cone-3. A 2.0-Å van der Waals radius was used for the cation in the MM2 structure refinement.

Partial-cone-3 shows enhanced K^+ selectivity, although the Ex% values generally are lower than those for other two isomers (Table V). In the ^{1}H NMR spectra, the protons in two OCH_2Py groups and one OCH_2CO_2Et group composing a partial-cone structure specifically shifted to lower magnetic field in the presence of Na^+ ion (Table V). This supports the idea that Na^+ is bound to an ionophoric cavity composed of these three groups. The X-ray structure of partial-cone-3 is in accord with the solution data that indicate the molecule is a rather poor host for cation complexation. The three waist oxygen atoms are arranged in the form of an equilateral triangle (distances of O1···O2 = 3.08, O2···O3 = 3.10, O1···O3 = 4.80 Å); cations presum-

(26) See page 111 in ref 9b.

(27) Yamada, A.; Murase, T.; Kikukawa, K.; Arimura, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 793.

(28) We previously found that upon complexation of cone-2 and Na^+ the ^{1}H NMR peaks generally shift to lower magnetic field while that for the OCH_2CO protons exceptionally shifts to higher magnetic field.[27] The OCH_2CO groups freely rotate in the absence of Na^+, but the protons are enforced to be located on the benzene ring when the two oxygens coordinate to Na^+. This also explains the exceptionally small down-field shift (+0.05 ppm) for the OCH_2CO protons in cone-3 (Table IV): that is, the down-field shift induced by complexation with Na^+ is partially offset by the up-field shift induced by the anisotropic effect of the benzene ring current.

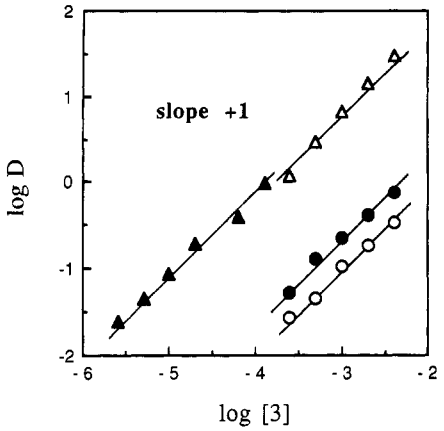

Figure 3. Plots of log D vs log [3]: extraction of Na^+ with partial-cone-3 (○), K^+ with partial-cone-3 (●), Na^+ with 1,3-alternate-3 (△), and K^+ with 1,3-alternate-3 (▲).

ably enter from the top and sit above and to one side of the triangle. A model of a possible cation···3 complex has been constructed with the MACROMODEL system[29] and refined with an extended MM2 force field. In the initial mode, the two pyridine rings were rotated approximately 180° to bring the nitrogen atoms into the cavity for cation binding and a putative cation was positioned about 2.8 Å from the three alkoxy oxygens. The refined model structure is shown in Figure 2. The O···M^+ and N···M^+ distances are 2.85–2.91 and 2.52–2.56 Å, respectively. The shortest cross-cavity pyridine H···H distance is 2.43 Å. In potassium···18-crown-6 and cryptand complexes, K^+···O distances of 2.74–2.91 Å and K^+···N distances of 2.96–3.03 Å are observed. It is unlikely that either of the ester oxygen atoms in the up CH_2CO_2Et group are involved in complexation because the necessary conformational changes to bring these atoms into the cavity would result in very close contacts between the cation and ester oxygens. In addition, steric interactions between the CH_2CO_2Et and the flanking pyridines become a problem if an ester oxygen (presumably the carbonyl) is brought into the cavity. It is probable that the pyridines must rotate approximately 180° to bring the ring nitrogen atoms into the cavity and, equally important, to eliminate the inward pointing aromatic hydrogen which, before rotation, would be impossibly close to a cation. The pyridine nitrogens cannot point directly at the cation because cation···N distances are too short in this orientation and H···H distances as small as 1.5 Å occur between the pyridine rings across the cavity. Overall, these various factors suggest that cation complexation would be weak.

Stoichiometry and Association Constants. We previously reported that cone-2 forms 1:1 complexes with all alkali metal cations and does not form 1:2 metal/calixarene sandwich complexes (as in metal/crown complexes).[8] This ionophoric characteristic of the calixaryl esters is attributed to the deep encapsulation of alkali metal cations in the cavity. To estimate the stoichiometry of the 3·metal complexes we measured the distribution ratio (D = [M^+ in the dichloromethane phase]/[M^+ in the aqueous phase]; M^+ = Na^+ and K^+) as a function of the calix[4]arene concentration. The typical examples are illustrated in Figure 3. We thus found that the log D – log [3] plots all result in slopes with unity, indicating the formation of the 1:1 complexes with Na^+ and K^+. The slope of the plot for 1,3-alternate-3 is worth remarking again: the slope with unity indicates that metal cations are bound only to the ionophoric cavity composed of two esters forming a 1:1 complex.

Table VI. Bathochromic Shifts (Δλ) and Association Constants (K_{ass}) of Alkali Picrates (M^+Pic^-)[a]

	Δλ/nm			log K_{ass}/M^{-1}		
ionophore	M^+ = Li^+	Na^+	K^+	M^+ = Li^+	Na^+	K^+
cone-3	33	22	20	3.64	4.26	4.23
partial-cone-3	4	2	2	*c*	*c*	*c*
1,3-alternate-3	21	15	14	2.95	3.95	3.08
cone-2[b]	1	31	2	3.00	3.95	3.08
18-crown-6[b]	1	29	13	3.72	4.29	5.33
cryptand 222[b]	–	31	29	–	6.69	8.38

[a] 30 °C, [M^+Pic^-] = 5.00×10^{-6} M, [3] = 0–5×10^{-4} M. The λ_{max} values of M^+Pic^- in the absence of the ionophore are 345 nm for Li^+, 351 nm for Na^+, and 357 nm for K^+. [b] Cited from ref 8. [c] The spectral change was too small to determine the K_{ass} accurately.

Inoue et al.[30] suggested an interesting idea that the bathochromic shift of the absorption band of the picrate anion, extracted into the organic phase with a macrocyclic ligand from aqueous metal picrate solutions, serves as a convenient measure for evaluating the ion pair tightness in solution. Also, one can estimate the association constants (K_{ass}) and stoichiometry from the spectral change.[8] Previously, we found on the basis of the spectral measurements that cone-2 forms 1:1 complexes with alkali metal cations and the bathochromic shift for sodium picrate amounts to 31 nm.[8] This shift is equal to that induced by cryptand 222, indicating that the ion pair is considerably solvent-separated. These findings are rationalized in terms of the "encapsulation" effect of cone-2 having an ionophoric cavity deeply in the molecule. We measured the absorption spectra of alkali picrates in THF in the presence of 3. The results are summarized in Table VI together with those for cone-2, 18-crown-6, and cryptand 222. Partial-cone-3, which was classified as a poor extractant, induced the spectral shifts (Δλ) of only 2–6 nm. On the other hand, cone-3 and 1,3-alternate-3 induced the spectral shifts of 14–33 nm, which are well comparable with those for cone-2 and crown compounds. In particular, cone-3 having a deep cavity composed of two esters and two pyridines induced the largest spectral shift. Thus, the solvent separation of alkali picrates occurs in the order of cone-3 > 1,3-alternate-3 > partial-cone-3.

The K_{ass} values were determined from the spectral change induced by the addition of 3. Since compounds 3 form only 1:1 complexes with alkali metal cations, we analyzed the plots of the absorbance vs [3] by a Benesi–Hildebrand equation for a 1:1 complex.[31] Although the K_{ass} values for cone-3 and 1,3-alternate-3 were smaller than those for cryptand 222 (by about 2–4 log units), they are comparable with those for 18-crown-6 and better than those for cone-2. Instead, they did not show the sharp metal selectivity as observed for cone-2 + Na^+.

Concluding Remarks

The present paper demonstrates that new, ionophoric conformational isomers can be synthesized from calix[4]arenes by skillfully choosing metal cations in base. The comparison of the conformer distribution with the solvent extraction data established that the cone conformer predominantly results when the carbonate salt contains a template metal cation whereas the partial cone and 1,3-alternate conformers result when the carbonate salt con-

(29) Still, C. MACROMODE<<l, v. 3.0, Columbia University, New York, NY, 1990.

(30) Inoue, Y.; Fujiwara, C.; Wada, K.; Tai, A.; Hakushi, T. *J. Chem. Soc., Chem. Commun.* **1987**, 393.

(31) Benesi, H. A.; Hildebrand, H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.

tains a nontemplate metal cation. The conclusion reminds us of the correlation lying between the metal template effect in the synthesis of and the solvent extraction with crown compounds. We believe that the methodology for metal recognition with calix[n]arenes can be exploited not only on the basis of the change in the ring size but also on the basis of the conformational change.

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Supplementary Material Available: Tables A–C containing anisotropic temperature factors, bond lengths, and bond angles of a single crystal of partial-cone-3 (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Pyridoacridine Alkaloids from Deep-Water Marine Sponges of the Family Pachastrellidae: Structure Revision of Dercitin and Related Compounds and Correlation with the Kuanoniamines

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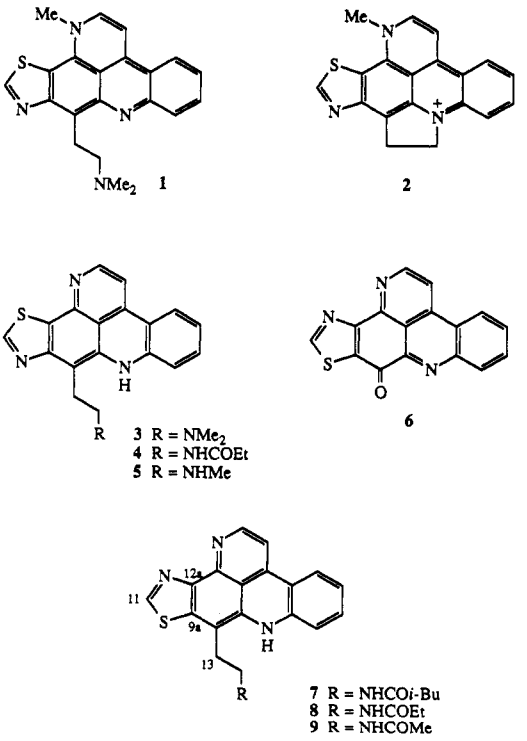
The single-crystal X-ray diffraction of a novel alkaloid, stellettamine (**15**), together with long-range ^{1}H–^{13}C coupling constants obtained by inverse detection methods, and metal chelation studies have shown that the previously reported regiochemistry of the thiazole moiety of dercitin (**1**) and four other related alkaloids **2–5** has to be revised. The corrected structures **10–14** are related to, and in one case identical to, those of the kuanoniamines **6–9**.

The structure of dercitin (**1**), a DNA interacting alkaloid from a deep-water marine sponge *Dercitus* sp. was deduced by a combination of long-range ^{1}H–^{13}C (COLOC) and ^{13}C–^{13}C (2D INADEQUATE) correlation information on the parent compound and its tetrahydro derivative.[2] Although the carbon skeleton of dercitin was established unambiguously from these data, the regiochemistry of the thiazole moiety was incorrectly assigned by comparison of the ^{13}C NMR chemical shifts of C-9a and C-12a with those of the respective carbons in simple thiazoles. Several attempts were made to establish the regiochemistry of the thiazole ring by desulfuration, but the various metal catalysts used for this reaction caused hydrogenation of the aromatic rings to give complex mixtures of products. Subsequently, cyclodercitin (**2**), which is a minor metabolite of the sponge *Dercitus* sp., and nordercitin (**3**), dercitamide (**4**), and dercitamine (**5**), which are metabolites of another deep-water sponge, *Stelletta* sp., were isolated and their structures proposed based on long-range ^{1}H–^{13}C (HMBC) correlation information and spectral comparison to dercitin (**1**).[3] The regiochemistry of the thiazole ring in these compounds was assumed to be the same as that of dercitin.

While the present work was in progress, kuanoiamines A–D (**6–9**) were obtained from an unidentified tunicate and its mollusc predator *Chelynotus semperi* by Carroll and Scheuer.[4] The carbon skeleton of the kuanoniamines was established by interpretation of spectral data, and the regiochemistry of the thiazole moiety was correctly assigned by interpretation of the HMBC experiment, which shows the large difference in the three-bond ^{1}H–^{13}C coupling constants across the thiazole ring caused by the difference in electron delocalization through C–N and C–S bonds. The value of $^{3}J_{H\text{-}C\text{-}N\text{-}C}$ is 12–16 Hz while $^{3}J_{H\text{-}C\text{-}S\text{-}C}$



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(2) (a) Gunawardana, G. P.; Kohmoto, S.; Gunasekara, S. P.; McConnell, O. J.; Koehn, F. E. *J. Am. Chem. Soc.* **1988**, *110*, 4856–4858. (b) Burres, N. S.; Sazesh, S.; Gunawardana, G. P.; Clement, J. J. *Cancer Res.* **1989**, *49*, 5267–5274.

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