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Regioselective Synthesis and Inclusion Properties of *distal*-Bis[(2-pyridylmethyl) oxy]tetrathiacalix[4]arenes

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Abstract

Regioselective synthesis of bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes was accomplished by a protection–deprotection method using benzyl groups as a protecting group. The conformational studies of *distal*-bis[(2-pyridylmethyl)oxy]thiacalix[4]arenes in solution and solid state are described. The two-phase solvent extraction data indicated that bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes show strong Ag^+ (E%, 97%) affinity. In contrast, no significant E% is observed for K^+. A good Job plots proves 1:1 coordination of 1,3-*alternate*-**3** with Ag^+ cation. ^{1}H-NMR Titration of 1,3-*alternate*-**3** with $AgSO_3CF_3$ also clearly demonstrates that a 1:1 complex is formed with retention of the original symmetry. The conformational changes of pyridine moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the thiacalixarene cavity were observed in the process of Ag^+ complexation. The down-field shifts of the benzene protons of the benzyl group were also observed and attributed to the conformational deviation from the original face to face overlapping.

Introduction

The introduction of larger alkyl groups on the phenolic oxygens of calix[4]arenes led to a situation where the OR groups within a cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation [1, 2]. There exist four possible conformational isomers in calix[4]-arenes; i.e. cone, partial-cone, 1,2-alternate and 1,3-alternate [1]. Similarly, four conformational isomers are possible in the case of tetrathiacalix[4]arenes. On the other hand, the regioselective *O*-alkylation of hydroxy groups in calixarenes is important for many purposes, in particular for the construction of multiple binding receptors or larger molecules starting from several calixarene building units [3]. Shinkai *et al*. reported the specific synthesis of calix[4]arene derivatives in a certain conformation using benzyl residues as protecting groups [4]. The different intramolecular hydrogen bonds among the hydroxy groups between the diarylsulfide units are expected to effect the regioselectivity of the *O*-alkylations of tetrathiacalix[4]arenes [5–7]. In fact, we previously reported [8] that 5,11,17.23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxytetrathiacalix[4]arene **1** when treated with 2-(chloromethyl)pyridine in the presence of Na_2CO_3 under acetone reflux yielded none of the pure regioselective isomers such as 1,2- or 1,3-di-*O*-substitution. Only a trace amount of a mixture of partial (2-pyridyl)methylation products were obtained along with the recovery of the starting compound. Recently, Miyano *et al*. reported the *O*-benzylation of the flexible tetrahydroxytetrathiacalix[4]arene to afford distal *O*-dibenzylated tetrathiacalix[4]arene [9]. This compound afforded convenient starting material for the attempted preparation of *distal*-bis[(2-pyridylmethyl)oxy]- tetrathiacalix[4]arenes. In this paper, we report on the regioselective synthesis of *distal*-bis[(2-pyridylmethyl)oxy] tetrathiacalix[4]arenes using benzyl residues as protecting groups. Conformational studies of *distal*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes in solution and in the solid state, as well as their inclusion properties are also described.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as

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an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

Materials

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** was prepared from *p*-*tert*-butylphenol according to the reported procedure [7b].

Synthesis

O-Benzylation of **1** *with benzyl bromide in the presence of* Na_2CO_3

A mixture of **1** (200 mg, 0.276 mmol) and Na_2CO_3 (293 mg, 2.8 mmol) in acetone (15 ml) was heated at reflux for 1 h. Benzyl bromide (0.34 ml, 2.8 mmol) was then added and the mixture heated at reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 ml × 2) and washed with water (50 ml × 2), and dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted benzyl bromide using a Kugelrohr apparatus. The residue was washed with methanol to give the crude *distal*-**2** (247 mg, 98%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 25, 27-dibenzyloxy-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-26,28-diol, *distal*-**2** as colorless prisms, m.p. 250–252 °C. IR (KBr) ν_{max}: 3383 (OH), 2962, 2867, 1478, 1448, 1437, 1363, 1260, 1244, 886, 756; ^{1}H-NMR ($CDCl_3$) $\delta = 0.79$ (18H, s, *t*Bu), 1.34 (18 H, s, *t*Bu), 5.49 (4 H, s, O*CH*$_2$ Ph), 6.96 (4 H, s, Ar–*H*), 7.24–7.36 (6 H, m, Ph–*H*), 7.61–7.64 (4 H, m, Ph–*H*), 7.68 (4 H, s, Ar–*H*) 7.98 (2 H, s, OH); *m*/*z*: 901 (M^+); Found: C 72.08, H 6.86. Calcd.: for $C_{54}H_{60}O_4S_4$ (901.28): C 71.96, H 6.71%.

*O-Alkylation of distal-***2** *with (chloromethyl)pyridine in the presence of* Cs_2CO_3

A mixture of *distal*-**2** (400 mg, 0.44 mmol) and Cs_2CO_3 (1.60 g, 4.92 mmol) in dry tetrahydrofuran (THF) (4 ml) was heated at reflux for 1 h under N_2. A solution of 2-(chloromethyl)pyridine (4.92 mmol) [prepared by neutralization of 2-(chloromethyl)-pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 ml) with a solution of triethylamine (0.68 ml, 4.92 mmol) in THF (8 ml) at room temperature] was then added and the mixture heated at reflux for an additional 17 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 ml) and extracted with CH_2Cl_2 (100 ml × 2). The combined extracts were washed with water (50 ml × 2), and dried (Na_2SO_4) and condensed under reduced pressure to give a yellow oil. The residue was washed with methanol to give a mixture of tetra-*O*-alkylated products as a colorless precipitate. The precipitate was washed with ether (5 ml) to give 1,3-*alternate*-**3** (340 mg, 73%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 1,3-*alternate*-**3** as a colorless prisms.

*1,3-alternate-25,27-Dibenzyloxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (1,3-alternate-***3***):* Colorless prisms [EtOH:$CHCl_3$ (3:1)], mp 269–272 °C. IR (KBr) ν_{max}: 2958, 2873, 1589, 1434, 1372, 1265, 1086, 1015, 750; ^{1}H-NMR ($CDCl_3$) $\delta = 0.87$ (18 H, s, tBu), 0.91 (18 H, s, tBu), 5.04 (4 H, s, Ar–O*CH*$_2$Ph), 5.10 (4 H, s, Ar–O*CH*$_2$Py), 6.65 (2 H, d, $J = 7.3$, Py–*H*$_3$), 6.91–7.03 (10 H, m, Ph-H), 7.01 (2 H, m, Py–H$_5$), 7.09 (4 H, s, Ar–*H*), 7.11 (4 H, s, Ar–*H*), 7.29 (2 H, d, $J = 7.3$, Py–*H*$_4$), 8.50 (2 H, d, $J = 4.4$, Py–*H*$_6$); *m*/*z*: 1082 (M^+); Found: C 72.93, H 6.47, N 2.51. Calcd.: for $C_{66}H_{70}N_2O_8S_4$ (1082.42): C 73.16, H 6.51, N 2.59%.

The splitting pattern in ^{1}H-NMR shows that the isolated compound is 1,3-*alternate*-**3**.

*Nafion-H catalyzed debenzylation of 1,3-alternate-***3** *in benzene*

A mixture of 1,3-*alternate*-**3** (200 mg, 0.222 mmol) and Nafion-H (200 mg) in benzene (6 ml) was heated at 100°C for 24 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated to give a yellow oil, which was washed with hexane to give the starting compound 1,3-*alternate*-**3** in quantitative yield.

*Aluminum chloride catalyzed debenzylation of 1,3-alternate-***3** *in toluene*

A mixture of $AlCl_3$ (250 mg, 1.88 mmol) in dry CH_2Cl_2 (1.5 ml) was stirred at room temperature for 30 min and then 1,3-*alternate*-**3** (340 mg, 0.31 mmol) dissolved in toluene (10 ml) was added. The reaction was vigorously stirred at room temperature for 5 h and then quenched with 1 M HCl, extracted with CH_2Cl_2. The organic layer was separated, washed twice with brine, dried (Na_2SO_4) and condensed under reduced pressure to give a colorless solid, which was recrystallized from chloroform–methanol to yield *distal*-**4** (218 mg, 78%) as a colorless prisms. 25,27-Bis[(2-pyridylmethyloxy]-5,11,17,23-tetra-*tert*-buty-2,8,14,20-tetrathiacalix[4]arene-26,28-diol(*distal*-**4**): Colorless prisms [MeOH:$CHCl_3$ (3:1)], m.p. 249–254 °C; IR (KBr) ν_{max}: 3373 (OH), 2955, 2865, 1463, 1272, 1089, 1004, 895; ^{1}H-NMR ($CDCl_3$) $\delta = 0.82$ (18 H, s, *t*Bu), 1.32 (18 H, s, *t*Bu), 5.74 (4 H, s, *CH*$_2$Py), 7.03 (4 H, s, Ar–*H*), 7.26 (2 H, d, $J = 7.8$, Py–*H*$_3$), 7.64 (4 H, s, Ar–*H*), 7.84 (2 H, m, Py–*H*$_5$), 7.91 (2 H, m, Py–*H*$_4$), 8.26 (2 H, s, O*H*), 8.62 (2 H, d, $J = 4.4$, Py–*H*$_6$); MS *m*/*z*: 902 (M^+); Found: C 69.07, H 6.37, N 2.90. Calcd.: for $C_{52}H_{58}O_4S_4N_2$ (903.29): C 69.14, H 6.47, N 3.17%.

*Alkylation of distal-***4** *with MeI in the presence of* Cs_2CO_3. A mixture of *distal*-**4** (200 mg, 0.222 mmol) and Cs_2CO_3 (342 mg, 1.78 mmol) in acetone (10 ml)

was heated at reflux for 1 h. Methyl iodide (250 mg, 1.78 mmol) was then added and the mixture heated at reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (100 ml × 2) and washed with water (50 ml × 2), and dried (Na_2SO_4). The filtrate was concentrated to give a yellow oil, which was washed with methanol to give 1,3-*alternate*-**5** (101 mg, 66.9%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 1,3-*alternate*-**5** (180 mg, 76%) as a colorless prisms. *1,3-alternate-25,27-Dimethoxy-26,28-bis[(2-pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (1,3-al-ternate-**5**):* Colorless prisms [MeOH:$CHCl_3$ (3:1)], m.p. 271–274 °C; IR (KBr) ν_{max}: 2970, 2858, 1588, 1362, 1272, 1082, 1026, 784; ^{1}H-NMR ($CDCl_3$) δ = 0.83 (18 H, s, *t*Bu), 1.29 (18 H, s, *t*Bu), 3.53 (6 H, s, *CH*$_3$), 5.23 (4 H, s, *CH*$_2$Py), 6.84 (2 H, d *J* = 8.8, Py–*H*$_3$), 7.06 (4 H, s, Ar–H), 7.10 (2 H, m, Py–*H*$_5$), 7.35 (2 H, m, Py–*H*$_4$), 7.54 (4 H, s, Ar–*H*), 8.52 (2 H, d, *J* = 4.9, Py–H$_6$); MS *m*/*z*: 930 (M^+); Found: C 69.12, H 6.73, N 2.98. Calcd.: for $C_{54}H_{62}O_4S_4N_2$ (931.35): C 69.36, H 6.71, N 3.01%.

Preparation of 4-tert-butyl-2,6-dimethyl[(2-pyridylmethyl)oxy]benzene **7**

A mixture of 4-*tert*-butyl-2,6-dimethylphenol **6** (400 mg, 2.25 mmol) and NaH (580 mg, 14.5 mmol, 60%) in dry THF (20 ml) was heated at reflux for 1 h under N_2. Then a solution of 2-(chloromethyl)pyridine (14.5 mmol) [prepared by neutralization of 2-(chloromethyl) pyridine hydrochloride (2.38 g, 14.5 mmol) in DMF (15 ml) with a solution of triethylamine (2.02 ml, 14.52 mmol) in THF (25 ml) at room temperature] was added and the mixture heated at reflux for an additional 17 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (10 ml) and extracted with CH_2Cl_2 (100 ml × 2). The combined extracts were washed with water (50 ml × 2), dried (Na_2SO_4) and condensed under reduced pressure to give a yellow oil. The residue was chromatographed on silica gel with methanol as an eluent to give the title compound **7** (380 mg, 63%) as a colorless oil; IR (KBr) ν_{max}: 2963, 2870, 1605, 1473, 1456, 1436, 1413, 1270, 804, 797; ^{1}H-NMR ($CDCl_3$) δ = 1.30 (9 H, s, *t*Bu), 2.31 (6 H, s, *CH*$_3$), 4.95 (2 H, s, *CH*$_2$Py), 7.05 (2 H, s, Ar–*H*), 7.20 (1 H, m, Py–*H*$_5$), 7.74 (2 H, m, Py–*H*$_3$ and Py–*H*$_4$), 8.58 (1 H, dd, J = 0.9,4.9, Py–*H*$_6$); *m*/*z*: 269 (M^+); Found: C 80.55, H 8.49, N 4.98. Calcd.: for $C_{18}H_{23}NO$ (269.39): C 80.26, H 8.61, N, 5.2.

Stoichiometry of metal complexation

The method of continuous variation was employed to determine the stoichiometry of *1,3-alternate*-**3**. Two-phase solvent extraction was carried out between aqueous picrates (5 ml, [silver picrate] = 2×10^{-4} M) and *1,3-alternate*-**3** (5 ml, [*1,3-alternate*-**3**] = 2×10^{-4} M in CH_2Cl_2). The molar ratios of the both *1,3-alternate*-**3** and metal picrate were varied from 0 to 1, while the total concentration was kept at several constant levels. The two-phase mixture in a glass tube immersed in a thermostated water bath at 25 °C was shaken at 300 strokes per min for 1 h and then kept, at the same temperature, for 2 h, allowing the complete separation of the two phases. The absorbance of each solution was determined by UV spectroscopy (λ = 290 nm). Job plots were generated by plotting the extracted [Ag^+] *versus* the mole fraction of metal.

^{1}H-NMR complexation experiments

To a $CDCl_3$ solution (5×10^{-3} M) of *1,3-alternate*-**3** and **5** in the NMR tube was added a CD_3CN solution (5×10^{-3} M) of $AgSO_3CF_3$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C. The association constant K_{ass} was calculated by non-linear fitting analysis of the observed chemical shift changes of O*CH*$_2$Py protons [10].

Extraction experiments

Metal picrates (2.5×10^{-4} M) were prepared *in situ* by dissolving the metal hydroxide (0.01 mol) in 2.5×10^{-4} M picric acid (100 ml); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between water (5 ml, [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 ml, [ionophore] = 2.5×10^{-4} M). The two-phase mixture was shaken in a stoppered flask for 2 h at 25 °C. We confirmed that this period is sufficient to attain the distribution equilibrium. This was repeated three times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen [11].

Crystallographic data for 1,3-alternate-**3**

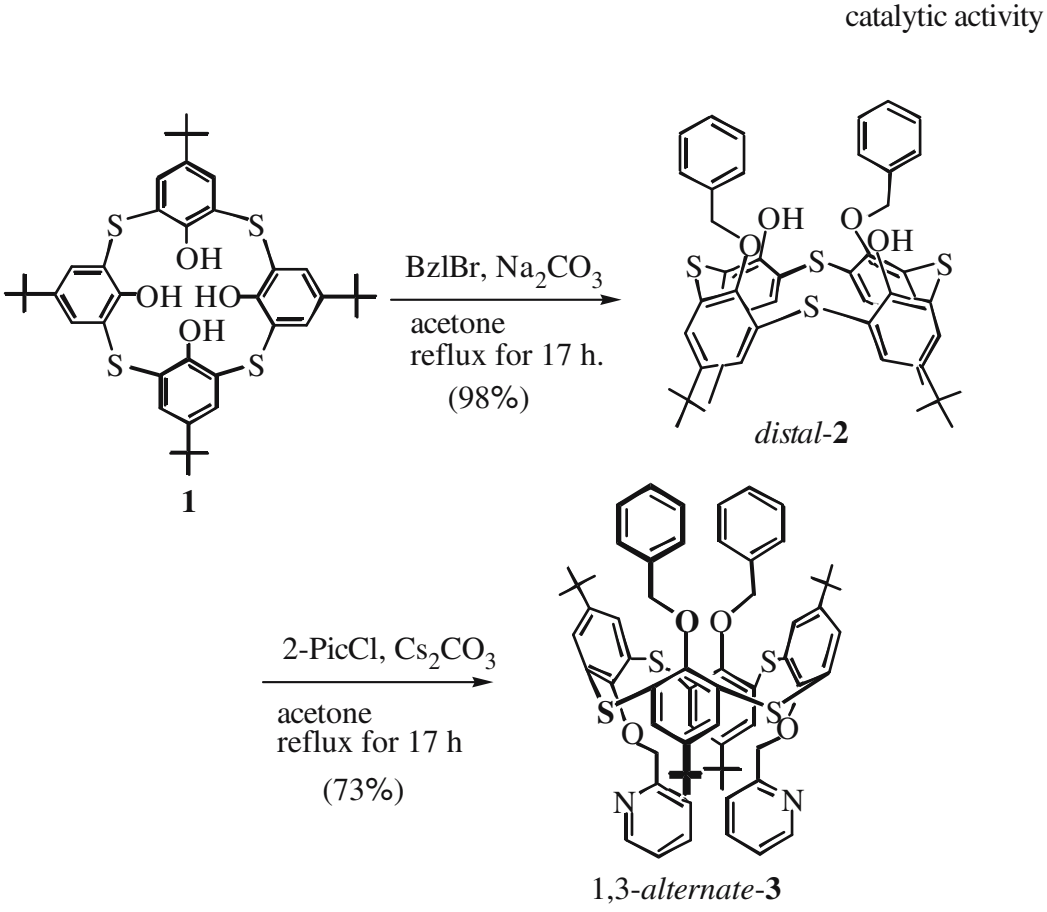
Crystal data for 1,3-*alternate*-**3**: $C_{66}H_{70}N_2O_4S_4$, $M = 1083.48$, orthorhombic, $Pmn2_1$, a = 15.265(2), b = 14.818(2), c = 12.8185(19) Å, V = 2899.5(7) Å^3, Z = 2, D_c = 1.241 g cm^{-3}, μ(Mo-K$_\alpha$) = 0.214 mm^{-1}, T = 150(2) K, colourless tablets; 25144 reflections measured on a Bruker SMART 1000 CCD diffractometer, of which 7203 were independent, data corrected for absorption on the basis of symmetry equivalent and repeated data (min and max transmission factors: 0.906, 0.987) and Lp effects, $R_{int} = 0.052$, structure solved by direct methods, F^2 refinement, $R_1 = 0.044$ for 5152 data with $F^2 > 2s(F^2)$, $wR_2 = 0.086$ for all data, 399 parameters. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 245644. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2

1EZ, UK [fax: +144-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

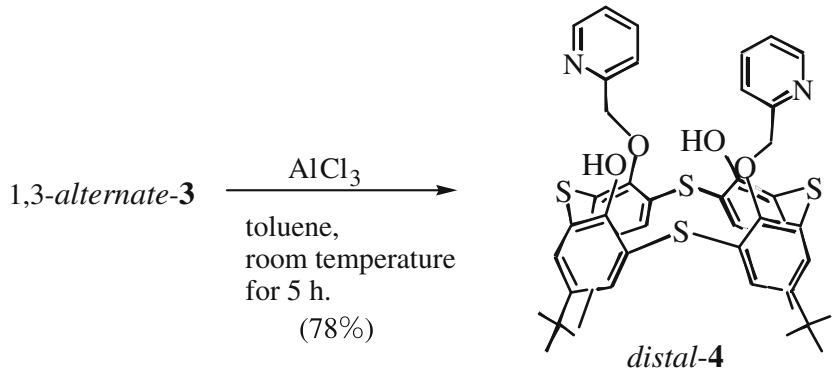
Results and discussion

O-Benzylation of tetrathiacalix[4]arene **1** carried out with 10 equiv. of benzyl bromide in the presence of Na_2CO_3 furnished exclusively the formation of the disubstituted product *distal*-**2** in spite of the use of a large excess of benzyl bromide. The reaction of bisbenzylated compound *distal*-**2** with 2-(chloromethyl)pyridine in THF-DMF in the presence of Cs_2CO_3 as base yielded 1,3-*alternate*-**3** in 73% yield (Scheme 1). Attempted removal of the benzyl group in 1,3-*alternate*-**3** with Me_3SiBr [12] in $CHCl_3$ at room temperture for 3 h or hydrogenation in the presence of Pd-C [13] at room temperature for 3 h to afford the desired *distal*-bis(2-pyridylmethyl)oxy derivative *distal*-**4** was unsuccessful. Only the recovery of the starting compound was obtained which is different from the results affording the debenzylated products in quantitative yield in the case of calix[4]arenes. It is possible that the sulfur atoms in the thiacalix[4]arene might deactivate the catalytic activity of Pd–C.

On the other hand, recently, we have found that the Nafion-H catalyst, a perfluorinated sulfonic acid resin [14], is effective in a wide range of liquid and gas phase reactions, including electrophilic substitutions on aromatic nuclei, transalkylations, condensations and so on [15]. Several attempts of debenzylation of *distal*-bis(2-pyridylmethyl)oxy derivative 1,3-*alternate*-**3** failed in the presence of Nafion-H (100 wt%) as a catalyst under the various conditions. Only the recovery of the starting compounds resulted. Finally, we have succeeded the debenzylation of 1,3-*alternate*-**3** in the presence of $AlCl_3$ in toluene at room temperature for 5 h to afford the desired diol *distal*-**4** in 78% yield (Scheme 2). The maximum yield was obtained in the presence of five equivalents of $AlCl_3$. The cleavage of the O–C bond in the pyridylmethyloxy group was not observed under the conditions used. The complexation with the nitrogen atom in the pyridyl group might deactivate the cleavage of the O–C bond in the pyridylmethyloxy group. The ring cleavage of the S–C bond in the thiacalixarene moiety as well as trans-*tert*-butylation were not also observed. However, a large excess of $AlCl_3$ was required to complete the present debenzylation. These results indicate that the protection–deprotection method is recommended as a useful strategy for the synthesis of *distal*-bis(2-pyridylmethyl)oxy derivative. In fact, *O*-Alkylation of *distal*-**4** with methyl iodide in acetone in the presence of Cs_2CO_3 as base yielded 1,3-*alternate*-**5** in 76% yield. (Scheme 3)



Scheme 1.



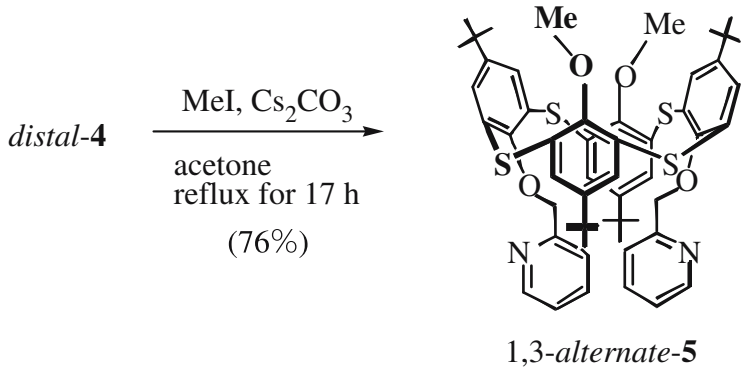
Scheme 2.

The ^{1}H-NMR spectrum of 1,3-*alternate*-**3** shows two singlet peaks for *tert*-butyl protons, in which both *tert*-butyl protons were observed to higher field at δ 0.87 and 0.91 ppm due to the ring current effect arising from the two benzyl benzene rings and the two pyridine rings introduced. Other signals in the ^{1}H-NMR spectrum may correspond to both the *cone* or 1,3-*alternate* conformer differing only slightly in their observed chemical shifts. Fortunately, we have managed to obtain X-ray quality colorless crystals of 1,3-*alternate*-25,27-dibenzyloxy-26,28-bis[(pyridylmethyl)oxy]-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene (1,3-*alternate*-**3**) by recrystallization from MeOH and $CHCl_3$. The ORTEP drawing of the 1,3-*alternate*-**3** analyzed by single crystal X-ray diffraction is shown in Figure 1. It is clear that **3** adopts a '1,3-*alternate* conformation'.

The ^{1}H-NMR spectrum of diol *distal*-**4** shows two singlets for the *tert*-butyl protons at δ 0.82, 1.32 ppm (relative intensity 1:1), two singlets of equal intensity for the aromatic protons at δ 7.03, 7.64 ppm and a singlet for the ArOCH_2Py methylene protons at δ 5.74 ppm. These findings strongly suggests the structure of *distal*-**4** is *distal*-*O*-pyridylmethyl thiacalixarene. The IR (KBr) spectrum of *distal*-**4** shows the absorption for the hydroxyl stretching vibration around 3373 cm^{-1}. The ^{1}H-NMR spectrum (in $CDCl_3$) exhibits the signals for hydroxy groups at δ 8.26, which shows the existence of the intramolecular hydrogen bonding between the hydroxy groups and benzyloxy groups of cyclic structure, which may fix in position the '*cone*' conformation [1, 6].

Interestingly, the hetero aromatic protons of the pyridine rings of 1,3-*alternate*-**3** are exposed to the ring current shielding effect [16, 17] operating in the opposing pyridine ring among the diaryl thiaether linkage, and resonate at higher fields with respect to those of the reference compound **7** [8], which was prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol **6** with 2-(chloromethyl)pyridine in the presence of NaH (Scheme 4). The magnitude of this shielding, computed as the difference between pertinent pyridine protons of 1,3-*alternate*-**3** and reference compound **7**, increases significantly for the H_3 and H_4 protons (Table 1). The remarkable shielding effect experienced by the H_4 (−0.45 ppm) and H_3 (−1.09 ppm) protons of the pyridine suggest that these protons are located much closer to the opposing pyridine ring than are the H_5 and H_6 protons and folded into the π-cavity formed by two thiacalix benzene rings and are thus shifted stronger upfield. This is doubtless due to the electron repulsion between the nitrogen atoms in the pyridine rings and the diaryl thiaether linkages. Thus, nitrogens in all of the pyridine rings were orientated outwards with respect to the thiacalixarene cavity. (Table 1, Scheme 4)

Calixarene can be converted to neutral ligands by introduction of ester or amide groups into the OH groups. The metal selectivity is dependent on the ring size and the *O*-alkylated substituents present. The ring size and the ring flexibility of thiacalix[4]arene are different from both calix[4]arene and hexahomotrioxacalix[3]arene. Functionalization of calix[4]arene by

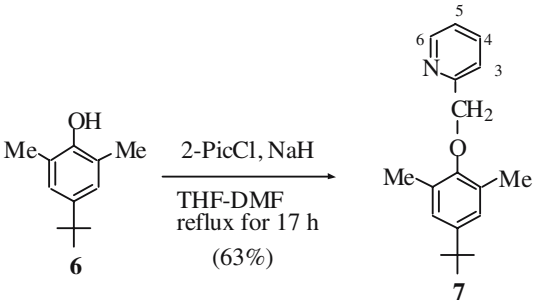


Scheme 3.

Table 1. Chemical shift of pyridine protons in 1,3-*alternate*-**3** and reference compound **7**[a]

Compd.	Chemical shift, δ ppm			
	H_6	H_5	H_4	H_3
7	8.58	7.20[b]	7.74[b]	7.74[b]
1,3-*alternate*-**3**	8.50	7.01	7.29[c]	6.65
Δδ	−0.08	−0.19	−0.45	−1.09

[a]Δδ values are the difference of the chemical shift between 1,3-*alternate*-**3** and reference compound 7 in $CDCl_3$ at 27 °C.
[b]A minus sign (−) denotes a shift higher magnetic field.
[c]the midpoint values of multiplet.



Scheme 4.

O-alkylation with halomethyl *N*-heterocyclic reagents in the presence of the base has been recently introduced in order to obtain 'universal' ligands for both hard and soft metal ions, which in principle should exhibit some advantages over ester and amide structures, because of a high stability over a wide pH range [18]. Recently, Pappalardo has reported the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metal cations [18, 19]. Similar investigation was also carried out using hexahomotrioxacalix[3]arene and homocalix[3]arene as the platform [20]. Therefore, it is interesting to assess the type of ionophoric cavity provided by the bis[(pyridylmethyl)oxy] derivatives 1,3-*alternate*-**3** and **5**. Usually, calixarenes form a 1:1 complex with guest molecules, but various other types of complexation were observed depending on the calix ring size and functional groups present. A 1:2 complex of calix[8]arene with ammonium ions was reported by Shinkai *et al.* [21]. The 1,3-*alternate* conformer of calix[4]arene derivatives can also form a 1:2 complex with metal cations [12e]. While, the 2:1 complex of calixarenes with guest molecules was formed in some specially functionalized calixarenes [22].

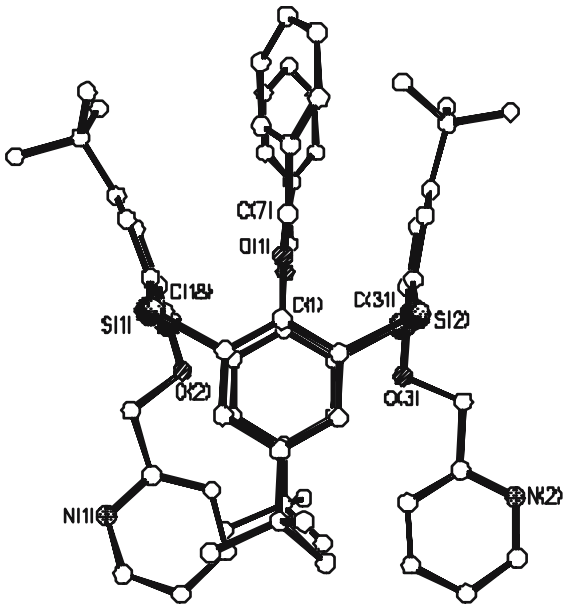


Figure 1. Crystal structure of 1,3-*alternate*-25,27-dibenzyloxy-26,28-bis[(pyridylmethyl)oxy]-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene (1,3-*alternate*-**3**).

Due to the existence of the two potential metal-binding sites, namely the pyridine moieties and two benzyl moieties, there are several possibilities for metal complexation for compound 1,3-*alternate*-**3** with guest molecules. Both 1:1 or 1:2 metal complexation might be possible attributable to the electrostatic interactions as well as cation–π interactions. As shown in Figure 2, the Job plots of compound 1,3-*alternate*-**3** were carried out in the H_2O/CH_2Cl_2 phases. The percent extractions reach maximum at 0.5 mol fraction when the 1,3-*alternate*-**3** and silver cation are changed systematically. This fact clearly indicates that the Ag^+ forms a 1:1 complex with 1,3-*alternate*-**3**. This result suggests the major contribution is from the nitrogen of pyridine ring to Ag^+ binding, and not a cation–π-interaction. This demonstrates the high Ag^+ affinity of the 1,3-*alternate*-calix[4]arene [23], similar findings were observed in the case of 1,3-*alternate*-**5**.

Preliminar studies of the binding ability of 1,3-*alternate*-**3** and 1,3-*alternate*-**5** are carried out by ion-pair extraction [M^+Pic^- ($M^+ = Ag^+$ or K^+)]. The E% values of 97 and 99% for 1,3-*alternate*-**3** and 1,3-*alternate*-**5**, respectively, show that both 1,3-*alternate*-**3** and 1,3-*alternate*-**5** strongly extract Ag^+. In contrast, no significant E% is observed for K^+ (1.3 and 1.5%, respectively). The association constant K_{ass} for the 1,3-*alternate*-**3**⊃Ag^+ and 1,3-*alternate*-**5**⊃Ag^+ are $K_{ass} = 2.88 \times 10^3\ M^{-1}$ and $K_{ass} = 3.45 \times 10^3\ M^{-1}$, respectively, were calculated by non-linear fitting analysis of the observed chemical shift changes of O*CH*$_2$Py protons. However, The accurate association constant of 1,3-*alternate*-**3**⊃K^+ and 1,3-*alternate*-**5**⊃K^+ could not be calculated due to the chemical shift scarcely change.

^{1}H NMR titration experiments in $CDCl_3$–CD_3CN and with KSO_3CF_3 and $AgSO_3CF_3$ are carried out. The addition of an equiv. of KSO_3CF_3 to either 1,3-*alternate*-**3** or 1,3-*alternate*-**5** causes negligible chemical shift. On the other hand, titration with 1 equiv. of $AgSO_3CF_3$ causes a dramatic upfield shift for the methylene protons of O*CH*$_2$Py (1,3-*alternate*-**3**, $\Delta\delta = -0.46$ ppm: 1,3-*alternate*-**5**, $\Delta\delta = -0.57$ ppm) of 1,3-*alternate*-**3** and 1,3-*alternate*-**5** while the *Py* protons display a downfield shift, strongly suggesting that Ag^+ is bound to the nitrogen atoms of pyridine and phenolic oxygens which affects the H_6, H_5, H_4, H_3 protons in pyridine rings (1:1 1,3-*alternate*-**3**⊃Ag^+ complex).

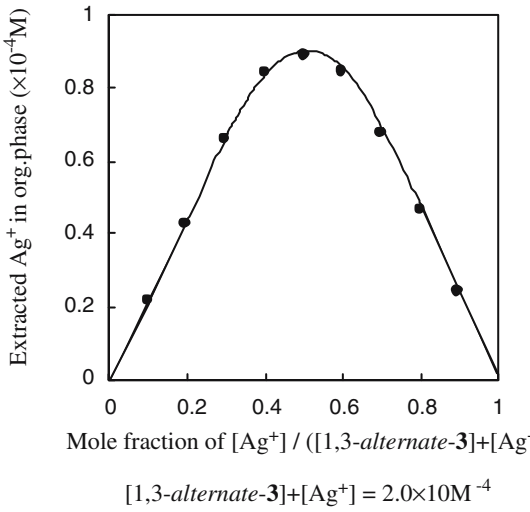


Figure 2. Job plots of the extractions of Ag^+ with host 1,3-*alternate*-**3**.

Further investigation of the complexation behaviour of 1,3-*alternate*-**3** towards Ag^+ was carried using ^{1}H-NMR spectral titration. Upon complexation of 1,3-*alternate*-**3** with Ag^+ in $CDCl_3$:CD_3CN (1:1, v/v), the chemical shift of all signals moved to lower field.

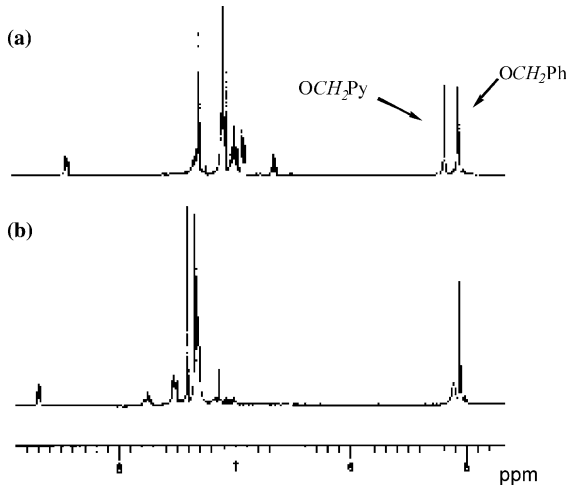


Figure 3. Partial ^{1}H-NMR titration spectra of 1,3-*alternate*-**3** (5×10^{-3} M, in $CDCl_3$:CD_3CN, 1:1, v/v). (a) in the absence of $AgSO_3CF_3$; (b) in the presence of $AgSO_3CF_3$ (3×10^{-2} M).

As shown in Figures 3 and 4, protons in the pyridine rings were shifted to lower field with δ 0.21, 0.25, 0.37 and 0.20 ppm for H_6, H_5, H_4, and H_3 protons, respectively. It has been shown that when calixarenes bearing pendant pyridine rings complex with Ag^+, the Ag^+ is trapped in the cavity formed by the nitrogen atoms in pyridine and the phenolic oxygens. This affects the protons H_6, H_5 and H_4 of the pyridine rings, which shift to lower field [16, 17]. Similar phenomena were also observed in the complexation of 1,3-*alternate*-**5** with Ag^+. Due to the interaction of N–Ag^+, protons H_6, H_5 and H_4 of the pyridine rings shift to lower fields. Thus, the 1,3-*alternate*-**3** complexes Ag^+ through the metal–oxygen electrostatic interactions and metal–nitrogen interactions. The chemical shift changes of the thiacalixarene benzene protons (Δδ:−0.19 and +0.20 ppm) may be attributed to the conformational change of the 1,3-*alternate*-**3** upon complexation. The down-field shift of the benzene protons of the benzyl group (Δδ: +0.29 for 2,6-protons) were also observed and attributed to the conformational deviation from the original face to face overlapping.

In all the cases of complexation of calixarenes bearing 2-pyridine rings with Ag^+, the chemical shift of proton H_3 in pyridine rings shifted up field upon complexation [16, 17], whereas, the chemical shift of proton H_3 in the pyridine rings in the 1,3-*alternate*-**3** shifted to lower field after complexation (Δδ + 0.20 ppm), which might be deshielded due to the sulfur atom of the diaryl thiaether linkage.

As shown in Figure 5, the nitrogen atom in the pyridine ring points away from the calix cavity in the free 1,3-*alternate*-**3** because of the electron repulsion between nitrogens.

After complexation, the nitrogen turns inwards towards the cavity to complex with Ag^+ and thus affects H_6, H_5 and H_4, which shift to lower field. Proton H_3 might be affected by the sulfur atom of the diarylthiaether linkage and shifts to lower field, unlike in other cases having the methylene linkage. Furthermore, the

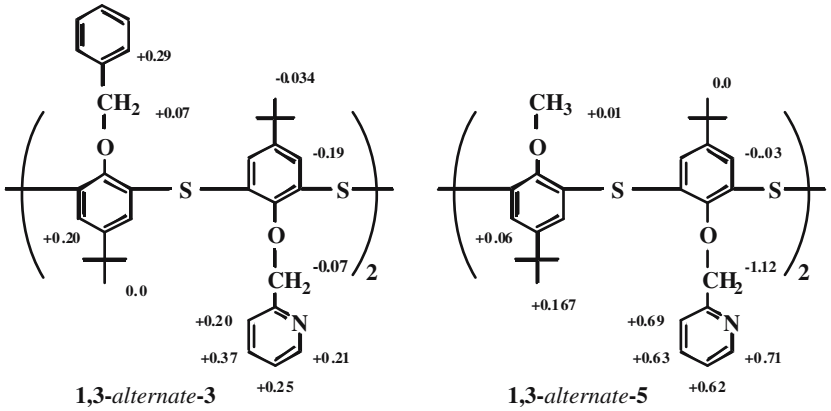
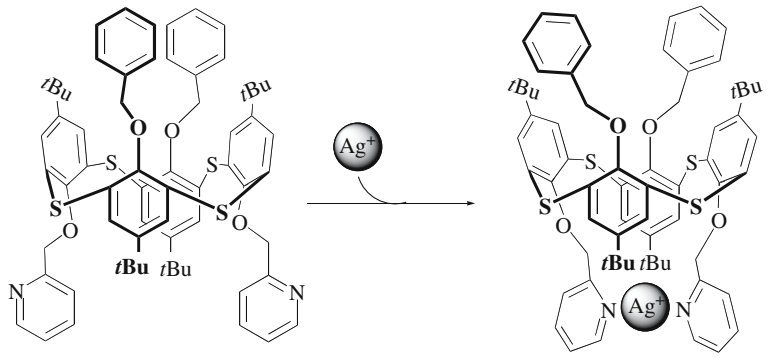


Figure 4. Chemical shift changes of 1,3-*alternate*-**3** and 1,3-alternate-**5** induced in the presence of $AgSO_3CF_3$; + denotes the downfield and – denotes the upfield shift.



1,3-*alternate*-**3** 1,3-*alternate*-**3**-Ag^+ complex

Figure 5. Binding mode of 1,3-*alternate*-**3** and Ag^+ complex.

C_{2V}-symmetrical conformation of 1,3-*alternate*-**3** is still retained after complexation.

Conclusion

We have demonstrated for the first time that the regioselective synthesis of *distal*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes 1,3-*alternate*-**3** and 1,3-*alternate*-**5** are accomplished by a protection–deprotection method using benzyl groups as a protecting group. As C_{2V}-symmetrical dipyridyl-substituted thiacalix[4]arenes, 1,3-*alternate*-**3** and 1,3-*alternate*-**5** can bind Ag^+ ion and the complexation mode was elucidated clearly in this paper. The nitrogen atom in pyridine ring turned from outward against the cavity to inside the cavity to interact with Ag^+ in 1,3-*alternate*-**3**. After complexation of 1,3-*alternate*-**3** with Ag^+, the original C_{2V}-symmetry has been remained. Further studies on the possibility for application to the regioselective synthesis of substituted tetrathiacalix[4]arenes using benzyl residues as protecting groups are now in progress.

Acknowledgements

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