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ORIGINAL ARTICLE

Allosteric bindings of thiacalix[4]arene-based receptors with 1,3-*alternate* conformation having two different side arms

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Abstract A novel ditopic receptor possessing two complexation sites such as crown ether and 2-pyridylmethyl groups bearing 1,3-*alternate* conformation based on thiacalix[4]arene was prepared. The binding behaviors with Li^+ and Ag^+ have been examined by ^1H NMR titration experiment. The exclusive formation of mononuclear complexes of 1,3-*alternate*-**5** with Li^+ and Ag^+ was observed even though the formation of the heterogeneous dinuclear complexes was expected. The decomplexation of Li^+ from the crown moiety of 1:1 complex 1,3-*alternate*-**5**⊃Li^+ to form the Ag^+⊂1,3-*alternate*-**5** complex by addition of $AgSO_3CF_3$ clearly shows that pyridyl moiety works as an efficient switch-off of the recognition ability of the crown moiety. We have also developed the construction of hydrogen-bonding self-assembly heterodimeric systems based on bis(4-pyridyl) and dicarboxylic acid thiacalix[4]arene derivatives in 1,3-*alternate* conformation. Their supramolecular behaviors are studied by ^1H NMR titration experiments with K^+ and Ag^+ ions. Although the values of the dimerization constants are relatively small, the stability of the dimers is strong enough to overcome only small conformational changes upon complex formation.

Keywords Thiacalix[4]arenas · Crownethers · Conformation · Metal complexation · Allosteric effect · Hydrogen bond · Self-assembly · Heterodimeric systems

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Introduction

A large variety of host–guest systems have been designed as selective cation, anion or neutral molecule receptors and carriers using three-dimensional calix[n]arenes as building blocks [1]. More recently, thiacalix[4]arenes [2], due to their novel features, have been used as potential platforms. Di- or polytopic receptors are those constructed with two or more binding subunits within the same macrocyclic structure [3]. It is well known that these systems are suitable candidates for the allosteric regulation [4] of host–guest interactions with metal cations that play a major role in biological systems [5].

From the literature it is known that the so-called 1,3-*alternate* conformation of calix[4]arene, which has D_{2h}-symmetry, tube-shape [6], etc., can be well adapted for the formation of 1:1 as well as 1:2 complexes owing to its symmetrical ditopic arrangement.

On the other hand, calixcrowns (crown ether calixarenes) have an extra intramolecular cavity formed by the crown ether bridge which displays significant levels of selectivity and avidity toward complexation with alkali metal ions. So far, the synthesis of 1,3-thiacalix[4]bis(crown-5) and -(crown-6) ethers have been reported [7, 8] as well as the studies of their complexation abilities toward Na^+, K^+, Rb^+ and Cs^+ which show lower extraction efficiencies that those of conventional calix[4]crowns [9–12]. Pappalardo et al. [13] reported the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals. Recently, we also reported the synthesis, conformation studies and inclusion properties of tris-[(2-pyridylmethyl)oxy]homocalix[3]arenes with cone and partial-cone conformation, which show strong Ag^+ affinity [14]. Thus there is substantially interest in the synthesis of the novel

receptors based on thicalix[4]arene framework with 1,3-*alternate* conformation, having two different side arms such as crown ethers and pyridyl groups and showing affinity to both alkali and soft heavy metal cations. In fact, some ditopic receptors based on thicalix[4]arene framework have been reported but there is no study concerning the presence of allosteric effect in such systems. Multi-recognition of Na^+, K^+ and Ag^+ by the receptor such as 1,3-*alternate*-bis[(2-pyridylmethyl)oxy]thiacalix[4]arene-mono (crown-4) ether **5** is expected, owing to the presence of crown moiety at one edge of the thiacalix[4]arene cavity [2] and two 2-pyridylmethyl moieties at the another edge.

On the other hand, the design of the molecular building blocks that form defined structures through noncovalent association, such as hydrogen bonds, aromatic π-stacking and van der Waal's interactions, is important for the development of large molecular arrays with higher forms of molecular behavior such as cooperativity, allostery and regulation. These materials find application in medicine, electronics, environmental science, etc. In particular, the use of hydrogen bonding on the generation of self-assembling supramolecular structures is due to its strong directional force and biological relevance and thus has been exploited by a number of research groups [15]. Numerous examples of hydrogen bonding, self-assembling calixarene homodimers have been reported [16] but heterodimeric systems are less common [17]. Nevertheless, very little effort has been done to study the supramolecular behavior of these kind of dimers.

Thus we designed the formation of two heterodimeric systems by intermolecular hydrogen bonding between two 4-pyridyl moieties and two carboxylic acid moieties of 1,3-*alternate*-thiacalix[4]arene derivatives having two different side arms, such as ester groups or 2-pyridyl methyl groups at the another edge. The present intermolecular hydrogen bonding supposed to be controlled by the complexation of the opposing side arms with alkali metal ions and Ag^+ ion.

We report, herein, the synthesis and complexation studies of thiacalix[4]arene-mono(crown-4) ether **5** and thiacalix[4]arene based hydrogen dimers **13** and **14** constraining 1,3-*alternate* conformation. The properties of these ionophores for application in the regulation of molecular recognition by external stimulus by ^1H NMR titration experiments are also described.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. ^1H NMR spectra were determined 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Elemental analyses were performed by Yanaco MT-5.

Materials

The 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis[(2-pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene *distal*-**4** was prepared from 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** in 3 steps according to our previous report [24f]. Triethyleneglycol ditosylate was prepared according to the reported procedure [25]. 5,11,17,23-Tetra-*tert*-butyl-25,27-bis(benzyloxy)-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene *distal*-**2** [24a] and 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene *distal*-**8a** [23a] and were prepared according to the reported procedure. The diester *distal*-**8a** was converted into the corresponding carboxylic acid *distal*-**8b** by using a reported procedure [29].

Synthesis

O-*Alkylation of distal-**4** with triethyleneglycol ditosylate*

To a solution of *distal*-**4** (2.44 g, 2.7 mmol), Cs_2CO_3 (4.40 g, 13.5 mmol) in dry acetone (20 mL) was added triethyleneglycol ditosylate (2.5 g, 5.5 mmol). After the mixture was refluxed for 48 h under Argon, it was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with 1 N HCl. The organic layer was separated, washed with brine (2 × 15 mL) and dried over $MgSO_4$. After filtration, the solvent was evaporated to dryness to obtain crude product which was subjected to column chromatography (150 g silica gel, 5:1 ethyl acetate:hexane) followed by recrystallization from $CHCl_3$–EtOH (3:1, v/v) to give 1.92 g (70%) of 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(2-pyridylmethyl)oxy]-2,8,14,20-tetra-thiacalix[4]arenemonocrown-4 (1,3-*alternate*-**5**) (1.92 g, 70%) as colorless prisms. Mp 255 °C. ^1H NMR δ_H ($CDCl_3$): 0.87 (18H, s, *t*Bu), 1.38 (18H, s, *t*Bu), 2.60 (4H, s, CH_2), 3.50–3.56 (4H, m, CH_2), 4.06–4.10 (4H, m, CH_2), 4.97 (4H, s, CH_2Py), 6.57 (2H, d, J = 8.80), Py–H_3), 7.12 (4H, s, Ar–*H*), 7.03 (2H, m, Py–H_5), 7.31 (4H, s, Ar–*H*), 7.35 (2H, m, Py-H_4), 8.45 (2H, m, Py–H_6). MS *m/z* 1016.20 (M^+). Anal. Calcd. For $C_{58}H_{68}N_2O_6S_4$ (1017.4): C, 68.47; H, 6.74; N, 2.75. Found: C, 68.45; H, 6.75; N, 2.73%.

*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 (2 × 100 mL). The combined extracts were washed with water (2 × 50 mL), dried (Na_2SO_4) and condensed under reduced pressure to give a yellow oil. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with methanol as an eluent to give 380 mg (63%) of **7** as a colorless oil; ^{1}H NMR δ_H ($CDCl_3$): 1.30 (9H, s, *t*Bu), 2.31 (6H, s, *CH*$_3$), 4.95 (2H, s, *CH*$_2$Py), 7.05 (2H, s, Ar–*H*), 7.20 (1H, m, Py-*H*$_5$), 7.74 (2H, m, Py-*H*$_3$ and Py-*H*$_4$), 8.58 (1H, dd, *J* = 0.9, 4.9, Py–*H*$_6$). MS *m/z* 269 (M^+). Anal. Calcd. For $C_{18}H_{23}NO$ (269.4): C, 80.26; H, 8.61; N, 5.2. Found: C, 80.55; H, 8.49; N, 4.98%.

*Synthesis of 1,3-alternate-5,11,17,23-tetra-tert-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-bis[(4-pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene (**9**)*

A mixture of diester *distal*-**8a** [23a] (407 mg, 0.413 mmol), Cs_2CO_3 (1.34 g, 4.13 mmol) in dry THF (6 mL) was heated at reflux for 1 h under nitrogen. Then a solution of 4-(chloromethyl)pyridine [prepared by neutralization of 4-(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 added and the mixture heated for 20 h. After cooling the reaction mixture to room temperature, it was acidified with 1 M HCl (15 mL) and extracted with CH_2Cl_2 (50 mL × 2). The combined extracts were washed with water (50 mL × 2), dried (Mg_2SO_4) and condensed under reduced pressure to give crude **9** (271 mg, 61%) as a white solid. Recrystallization from $CHCl_3$–MeOH (3:1) afforded colorless prisms. Mp 221–223 °C. IR ν_{max} (KBr)/cm^{-1}: 2961, 1769 (C=O), 1605, 1444, 1379, 1192, 1088, 879, 798. ^{1}H NMR δ_H ($CDCl_3$): 0.87 (18H, s, *t*Bu), 1.23 (6H, t, *J* = 7.5, CH_2CH_3), 1.29 (18H, s, *t*Bu), 4.17 (4H, q, *J* = 7.5, CO_2CH_2), 4.57 (4H, s, CH_2CO), 5.09 (4H, s, CH_2Py), 7.06 (4 H, s, Ar–*H*), 7.13 (4H, d, *J* = 5.6, *H*$_{3,5}$–Py), 7.53 (4H, s, Ar–*H*), 8.47 (4H, d, *J* = 5.6, *H*$_{2,6}$–Py). MS *m/z*: 1075.40 (M^+). Anal. calcd. for $C_{60}H_{70}N_2O_8S_4$ (1075.47): C, 67.01; H, 6.56; N, 2.6. Found: C, 67.00; H, 6.57; N, 2.51%.

*Synthesis of 5,11,17,23-tetra-tert-butyl-25,27-bis(benzyloxy)-26,28-bis[(4-pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene (**10**)*

The dibenzyl derivative *distal*-**2** [24a] (370 mg, 0.411 mmol) was treated with 4-(chloromethyl)pyridine in analogous manner for **9** to afford **10** in 63% (280 mg) yield as colorless prisms [$CHCl_3$–MeOH (3:1)]. Mp 248–251 °C. IR ν_{max} (KBr)/cm^{-1}: 2960, 1642, 1420, 1370, 1228, 789. ^{1}H NMR δ_H ($CDCl_3$): 0.85 (18H, s, *t*Bu), 1.25 (18H, s, *t*Bu), 5.07 (4H, s, C*H*$_2$Py), 5.27 (4 H, s, C*H*$_2$Ph), 6.89 (4H, d, *J* = 5.6, *H*$_{3,5}$–Py), 7.02–7.07(10H, m, Ar–*H*), 7.08–7.14 (8 H, m, Ar–*H*), 8.48 (4H, d, *J* = 5.6, *H*$_{2,6}$–Py). MS *m/z*: 1083.49 (M^+). Anal. calcd. for $C_{66}H_{70}N_2O_4S_4$ (1083.54): C, 73.16; H, 6.51; N, 2.59. Found: C, 73.02; H, 6.69; N, 2.47%.

*Synthesis of 5,11,17,23-tetra-tert-butyl-25,27-bis[(hydroxycarboxy)methoxy]-26,28-bis-[(2-pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene (**11**)*

The dicarboxylic acid *distal*-**8b** [29] (346 mg, 0.413 mmol) was treated with 2-(chloromethyl)pyridine in analogous manner for **9** to afford **11** in 64% (270 mg) yield as colorless prisms [$CHCl_3$–MeOH (3:1)]. Mp 222–225 °C. IR ν_{max} (KBr)/cm^{-1}: 3500–3200 (OH), 2960, 1755 (C=O), 1573, 1432, 1362, 1326, 1267, 1089, 879, 761. ^{1}H NMR δ_H ($CDCl_3$): 0.84 (18H, s, tBu), 1.27 (18H, s, tBu), 4.60 (4H, s, C*H*$_2$CO), 5.23 (4H, s, C*H*$_2$Py), 6.58 (2H, d, J = 5.6, *H*$_3$–Py), 7.08 (4H, s, Ar–*H*), 7.15 (2H, m, *H*$_5$–Py), 7.31 (2H, m, *H*$_4$-Py), 7.43 (4H, s, Ar–*H*), 8.53 (2H, d, *J* = 5.2, *H*$_6$–Py). MS m/z: 1019.38 (M^+). Anal. calcd. for $C_{56}H_{62}N_2O_8S_4$ (1019.36): C, 65.98; H, 6.13; N, 2.75. Found: C, 65.71; H, 6.09; N, 2.65%.

*Synthesis of 5,11,17,23-tetra-tert-butyl-26,28-bis(benzyloxy)-25,27-bis-[(hydroxycarboxy)methoxy]-2,8,14,20-tetrathiacalix[4]arene (**12**)*

The dicarboxylic acid *distal*-**8b** [29] (346 mg, 0.413 mmol) was treated with benzyl bromide by using a reported procedure [24a] to afford **12** in 67% (281 mg) yield as colorless prisms [$CHCl_3$–MeOH (3:1)]. IR ν_{max} (KBr)/cm^{-1}: 3500–3250 (OH), 2951, 1758 (C=O), 1579, 1365, 1271, 888, 743. Mp 218–222 °C. ^{1}H NMR δ_H ($CDCl_3$): 0.82 (18H, s, *t*Bu), 1.28 (18H, s, *t*Bu), 4.60 (4H, s, C*H*$_2$CO), 4.97(4H, s, C*H*$_2$Ph), 7.21 (10H, s, Ar–*H*), 7.56

(4H, s, Ar–*H*), 7.93 (4H, s, Ar–*H*). MS *m/z*: 1017.28 (M^+). Anal. calcd. for $C_{58}H_{64}O_8S_4$ (1017.39): C, 68.47; H, 6.34. Found: C, 68.46; H, 6.40%.

Preparation of dimer ***13***

A chloroform solution of **11** (10 mM) 5 mL was added to a chloroform solution of **9** (10 mM) 5 mL. The solvent of the equimolar mixture solution was removed under reduced pressure to give a white solid.

Dimer **13**: IR ν_{max} (KBr)/cm^{-1}: 3500–3250 (OH), 2964, 1960 (OH···N), 1770 (C=O), 1746 (C=O), 1606, 1573, 1446, 1431, 1380, 1363, 1322, 1267, 1190, 1088, 877, 796, 764. ^{1}H NMR δ_H ($CDCl_3$): 0.86 (18H, s, *t*Bu), 0.90 (18H, s, *t*Bu), 1.21 (6H, q, J = 7.5, CH_2CH_3), 1.28 (18H, s, *t*Bu), 1.30 (18H, s, *t*Bu), 4.16 (4H, q, J = 7.5, CO_2CH_2), 4.55 (4H, s, CH_2CO), 4.58 (4 H, s, CH_2CO), 5.09 (4H, s, CH_2Py), 5.25 (4H, s, CH_2Py), 6.58 (2H, d, J = 5.7, H_3–Py), 6.97 (4 H, s, Ar–*H*), 7.11 (4H, s, Ar–*H*), 7.40 (4H, s, Ar–*H*), 7.54 (4H, s, Ar–*H*), 8.53 (4H, d, J = 5.7, $H_{2,6}$–Py), 8.55 (2H, d, J = 5.2 H_6–Py), 12.82 (2H, broad s, OH).

The overlap of the signals of H_5–Py, $H_{3,5}$–Py, H_4–Py protons together with the slight broad signals avoided the assignment for such a protons.

Preparation of dimer ***14***

Dimer **14** was prepared in analogous manner to dimer **13** as a white solid. IR ν_{max} (KBr)/cm^{-1}: 3500–3200 (OH), 2950, 1963 (OH···N), 1750 (C=O), 1640, 1579, 1421, 1369, 1366, 1268, 1230, 886, 789, 743. ^{1}H NMR δ_H ($CDCl_3$): 0.84 (18H, s, *t*Bu), 0.87 (18H, s, *t*Bu), 1.26 (18H, s, *t*Bu), 1.30 (18H, s, *t*Bu), 4.56 (4H, s, CH_2CO), 4.97 (4H, s, CH_2Ph), 5.08 (4H, s, CH_2Py), 5.27 (4 H, s, CH_2Ph), 6.91 (4H, d, J = 5.7, $H_{3,5}$–Py), 7.23 (10H, s, Ar–*H*), 7.03–7.07 (10H, m, Ar–*H*), 7.10–7.15 (8H, m, Ar–*H*), 7.59 (4H, s, Ar–*H*), 7.90 (4H, s, Ar–*H*), 8.54 (4H, d, J = 5.7, $H_{2,6}$–Py), 12.78 (2H, broad s, OH).

^{1}H NMR complexation experiment

To a $CDCl_3$ solution (5×10^{-3} M) of 1,3-*alternate*-**5** in the NMR tube was added a CD_3CN solution (5×10^{-3} M) of $AgSO_3CF_3$ and $LiSO_3CF_3$, separately. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

The ^{1}H NMR data of the complexes are given below.

$Ag^+\subset$1,3-*alternate*-**5**: ^{1}H NMR ($CDCl_3$:CD_3CN, 1:1) δ_H: 1.35 (18H, s, *t*Bu), 1.34 (18H, s, *t*Bu), 2.55 (4H, s, CH_2), 3.54–3.58. (4H, m, CH_2), 3.82–3.87 (4H, m, CH_2), 3.85 (4H, s, CH_2Py), 7.19 (4H, s, Ar–*H*), 7.34 (4H, s, Ar–*H*), 7.43 (2H, m, Py–H_3), 7.72 (2H, m, Py–H_5), 7.94 (2H, m, Py–H_4), 8.73 (2H, m, Py–H_6).

1,3-*alternate*-**5**$\supset Li^+$: ^{1}H NMR ($CDCl_3$:CD_3CN, 1:1) δ_H: 0.89 (18H, s, *t*Bu), 1.38 (18H, s, *t*Bu), 2.86 (4H, s, CH_2), 3.56–3.60 (4H, m, CH_2), 4.28–4.32 (4H, m, CH_2), 4.83 (4H, s, CH_2Py), 6.67 (2H, d, J = 8.80, Py–H_3), 7.09 (2H, m, Py–H_5), 7.13 (4H, s, Ar–*H*), 7.33 (2H, m, Py–H_4), 7.34 (4H, s, Ar–*H*), 8.42 (2H, m, Py–H_6).

Stoichiometry of metal complexation

The method of continuous variation was employed to determine the stoichiometry of 1,3-*alternate*-**5**. Metal picrates (2.5×10^{-4} M) were prepared in situ by dissolving the lithium hydroxide (0.01 mol) or silver nitrate (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 metal picrates (5 mL, [metal picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 mL, [1,3-*alternate*-**5**] = 2.5×10^{-4} M). The molar ratios of the both 1,3-*alternate*-**5** and metal picrate were varied from 0 to 1 while their total concentration were 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 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^+] or [Li^+] versus the mole fraction of metal.

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in a varying guest concentration of 0–50 mM and a constant concentration of host receptors with 5 mM. After each addition and mixing, the chemical shift change in the methylene protons [Ar–OCH_2Py] and [Ar–OCH_2 CH_2O–] was recorded during each titration. The result of the experiment was a plot of displacement in chemical shift as a function of the amount of added cation, which was subjected to analysis according to the literature [37].

^{1}H NMR titration experiment

The dimerization process was investigated by quantitative ^{1}H NMR dilution studies (50 mM–60 μM, $CDCl_3$). Association constants reported are the average of two or more replicate experiments and were obtained by fitting

chemical shift data to 1:1 binding isotherms using standard, nonlinear curve-fitting procedures [33].

Results and discussion

Synthesis and inclusion properties of 1,3-*alternate*-bis[(2-pyridylmethyl)oxy]thiacalix[4]arene-mono(crown-4) ether

Since the pioneering work of Pedersen [18], crown ethers and their complexes with metal cations have attracted considerable attentions. Calixarenes have been widely used as three-dimensional molecular platforms with specific properties [1]. The calixcrowns family (macro-polycycles) constructed from calix[4]arene units and polyethylene glycolic units is one of the most studied supramolecular receptors [12]. They show binding properties towards alkali metal, alkaline earth metal and ammonium cations which can be turned by selecting the most appropriate conformation of the calix[4]arene and the crown ether size [9, 10]. Probably the main interest in these ligands derives from their application as selective cesium extractants in radioactive waste treatment [11].

The highest selectivities towards the cesium cation have been observed for 1,3-calix[4]crowns-6 ("1,3-" refers to the bridging of the polyethylene glycolic units onto the calix[4]arene skeleton) in the 1,3-*alternate* conformation in which the crown moiety bears six oxygen atoms. In such a molecular topology binding of cesium involves not only ether-oxygen donors but also the calixarene aromatic cation tunneling through the π-basic tube of the calix units. As mentioned previously, calixcrowns have an extra intramolecular cavity formed by the crown ether bridge which displays significant levels of selectivity and avidity toward complexation with alkali metal ions (Fig. 1).

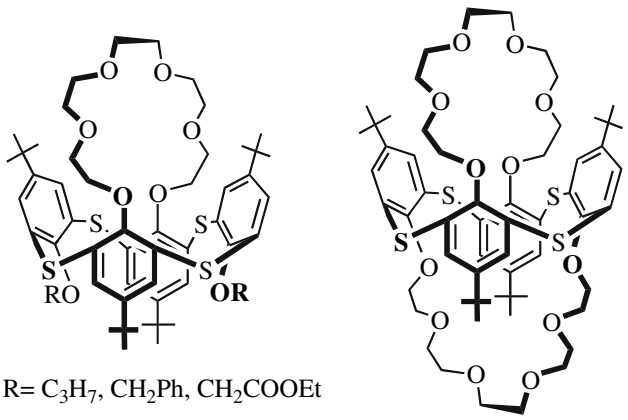


Fig. 1 Structures of 1,3-*alternate*-thiacalix[4]arene-monocrown-6 and -biscrown-6

Lithium complexes of crown ethers are of great interest due to their applications as anionic conductors in manufacturing lithium-based rechargeable batteries [19] and electrolytes [20] and as anion activators in organic synthesis [21]. Despite of the importance of lithium complexes no detailed investigation on the extraction of lithium by calixcrowns-4 has been carried out. It is expected that the cavity delineated by the crown-4 matches well with Li^+ [22], and the other cavity delineated by pyridine moieties can work as a switch for complexation and decomplexation in the crown site.

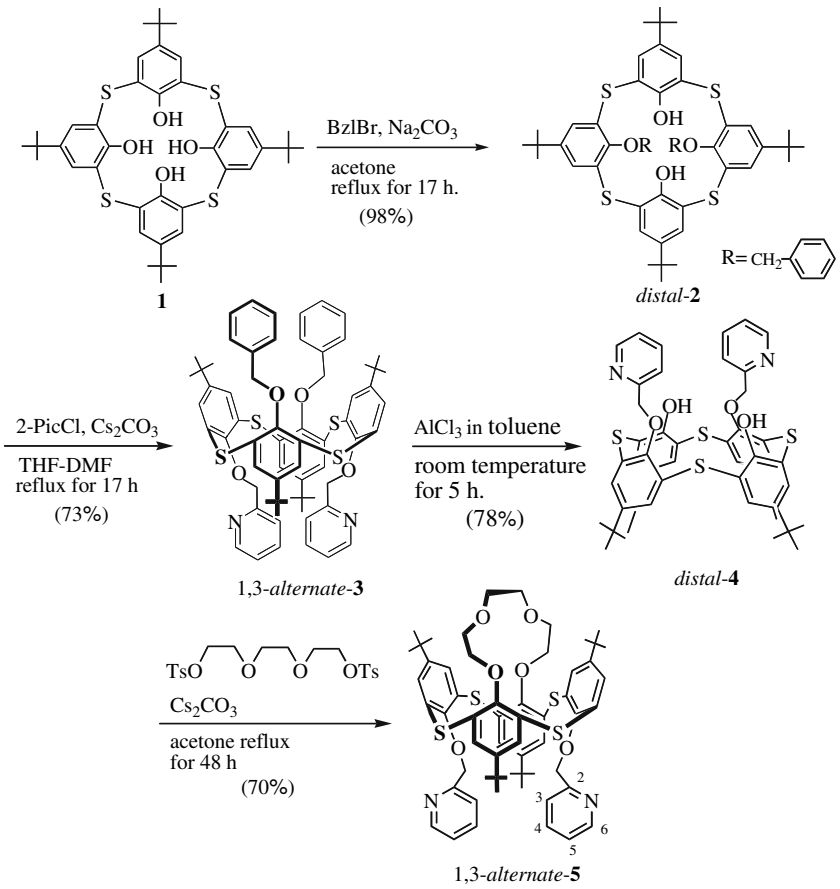
We have designed a novel receptor bis[(2-pyridyl methyl)oxy]thiacalix[4]arene-mono(crown-4) ether 1,3-*alternate*-**5** constraining 1,3-*alternate* conformation, having two different side arms and showing affinity to both alkali metal cations, and the study of their complexation behavior towards Li^+ and K^+ ions. In fact, some ditopic receptors based on thicalix[4]arene framework have been reported but there is no study concerning the presence of allosteric effect in such systems. Multi-recognition of Li^+ and K^+ by 1,3-*alternate*-**5** is expected, owing to the presence of two 2-pyridylmethyl moieties at one edge of the thiacalix[4]arene cavity [2] and a crown-4 ether moiety at the another edge. Distal binding moiety, such as 2-pyridyl group, is efficient for larger alkali metals or Ag^+.

Regioselective synthesis of 1,3-*alternate*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arene-mono(crown-4) ether 1,3-*alternate*-**5** was accomplished by a protection–deprotection method using benzyl groups as a protecting group as shown in Scheme 1. Thus, *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 98% yield [23c, 24a]. 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. 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** [24e] in 78%. Finally, *O*-alkylation of *distal*-**4** carried out with 2 equiv. of triethyleneglycol ditosylate [25] in the presence of an equiv. of Cs_2CO_3 according to the reported procedure [24] afforded the desired 1,3-*alternate*-**5** in 70% yield.

The structure of 1,3-*alternate*-**5** was supported by their spectral and analytical data. The ^1H NMR spectrum of 1,3-*alternate*-**5** shows two singlets for the *tert*-butyl protons at δ 0.87 and 1.38 ppm, in which the former peak can be observed at a higher field due to the ring current effect arising from the inverted two pyridine rings [26]. This observation strongly suggests **5** adopts 1,3-*alternate* conformation.

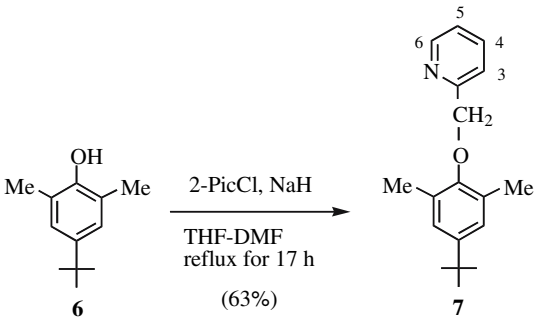
Interestingly, the hetero aromatic protons of the pyridine rings of 1,3-*alternate*-**5** are exposed to the ring current

Scheme 1



shielding effect [27] operated by the opposing pyridine ring among the diaryl thiaether linkage, and resonate at higher fields with respect to those of the reference compound **7**, which was prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol **6** with 2-(chloromethyl)pyridine in the presence of NaH. The magnitude of this shielding, calculated as the difference between pertinent pyridine protons of 1,3-*alternate*-**5** and reference compound, 4-*tert*-butyl-2,6-dimethyl[(2-pyridylmethyl)oxy]benzene **7**, increases significantly for the H_3 and H_4 protons. The remarkable shielding effect experienced by the H_4 (δ –0.39 ppm) and H_3 (δ –1.17 ppm) protons of the pyridine rings suggests 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 both pyridine rings were orientated outwards with respect to the thiacalixarene cavity (Scheme 2, Table 1).

The heteroditopic receptor 1,3-*alternate*-**5** displays affinity toward alkali as well as transition metals. The complexation abilities of 1,3-*alternate*-**5** was assessed by two phase solvent extraction experiments and ^{1}H NMR



Scheme 2

spectroscopy. Due to the existence of the two potential metal-binding sites, namely the one crown moiety and two pyridyl moieties, the formation of 1:1 and 1:2 metal complexes attributable to the electrostatic interactions can be expected.

The stoichiometry of the 1,3-*alternate*-**5** complexes with Li^+ and Ag^+ was determined by a two phase-extraction experiment (H_2O/CH_2Cl_2), using the continuous variation method. The percent extractions for Ag^+ reach maximum at 0.5 mole fraction when the 1,3-*alternate*-**5** and Ag^+ were changed systematically, indicating the formation of 1:1 complex (Fig. 2). Similar results were obtained in the case of Li^+.

Table 1 Chemical shift of pyridine protons in 1,3-*alternate*-**5** and reference compound **7**

Compd.	Chemical shift, δ ppm[a, b]			
	H_6	H_5	H_4	H_3
1,3-*alternate*-**5**	8.58	7.20[c]	7.74[c]	7.74[c]
	8.45	7.03	7.35[c]	6.57
$\Delta\delta$	–0.13	–0.17	–0.39	–1.17

[a] $\Delta\delta$ Values are the difference of the chemical shift between 1,3-*alternate*-**5** and reference compound **7** in $CDCl_3$ at 27 °C

[b] A minus sign (–) denotes a shift to higher magnetic field

[c] The midpoint values of multiplet are indicated

^{1}H NMR titration experiments with $LiSO_3CF_3$ and $AgSO_3CF_3$ were carried out. The addition of an equiv. of $LiSO_3CF_3$, separately, to 1,3-*alternate*-**5** caused immediate complexation as demonstrated by the down field shift of the crown protons (i.e. 1,3-*alternate*-**5**⊃Li^+; ArOCH_2, $\Delta\delta$ = +0.26; K_{ass} = 1.5 × 10^3 M^{-1}), whereas the OCH_2Py and thiacalixarene protons were scarcely affected. Only the 1:1 complex 1,3-*alternate*-**5**⊃Li^+ was formed even with a large excess of $LiSO_3CF_3$. The results confirm that the crown moiety of 1,3-*alternate*-**5** composes a stronger ionophoric cavity for Li^+ than the two pyridyl moieties. It is clear that Li^+ does not enter into the cavity of the thiacalix[4]arene. It must be noted that there is a large difference between the K_{ass} reported in the literature for 12-crown-4 and lithium (K_{ass} = 8.1 × 10^3 M^{-1}) in acetonitrile [28]. The steric hindrance by the *tert*-butyl groups and low flexibility of the crown may not contribute to the stabilization of the lithium complex. On the other hand, titration with 1 equiv. of $AgSO_3CF_3$ to 1,3-*alternate*-**5** causes a dramatic upfield shift for the methylene protons of OCH_2Py in 1,3-*alternate*-**5** ($\Delta\delta$ = –1.12 ppm) 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 Ag^+⊂1,3-*alternate*-**5** complex). Spectral changes of the 1:1 Ag^+⊂1,3-*alternate*-**5** complex in the presence of an excess of $AgSO_3CF_3$ were not detectable, which supports the exclusive formation of the 1:1 Ag^+⊂1,3-*alternate*-**5** complex. The results of the chemical shift changes ($\Delta\delta$) of OCH_2Py protons are summarized in Figs. 3 and 4.

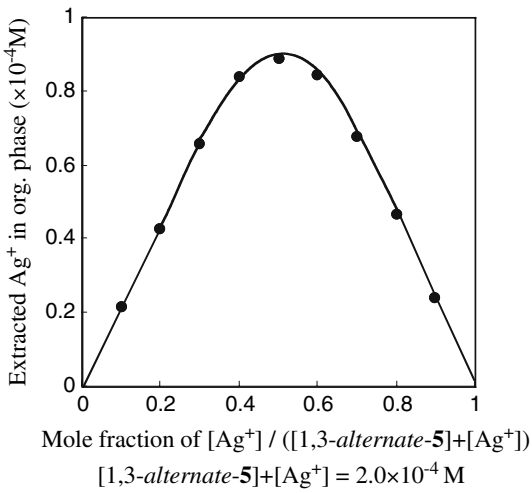


Fig. 2 Job plots of the extractions of Ag^+ with host 1,3-*alternate*-**5**

From Fig. 4, it is clear that in the case of 1,3-*alternate*-**5** upon complexation with Ag^+ (K_{ass} = 4.9 × 10^3 M^{-1}) the nitrogen turned inward to the cavity and the H_6, H_5 and H_4 protons shifted to down field. Contrary to the observation of upfield shift of H_3 protons in the classical calixarenes, the protons H_3 in the present thiacalix[4]arene shifted to down field which might be affected by the sulfur atom in the diarylthiaether linkage. The H_6 protons shifted to down field while the methylene protons of OCH_2Py shifted in opposite site direction due to the ring current effect of the benzene moiety.

The possible switch on–off of the recognition behavior of 1,3-*alternate*-**5** upon complexation was studied by a set of ^{1}H NMR titration experiments. First, from 1 up to 5 equiv. of $AgSO_3CF_3$ were added to the solution containing 1,3-*alternate*-**5**⊃Li^+. The ^{1}H NMR spectra of complex completely changed to that of Ag^+⊂1,3-*alternate*-**5** complex. In contrast, when Ag^+⊂1,3-*alternate*-**5** was titrated with Li^+ no spectra change was observed. These findings

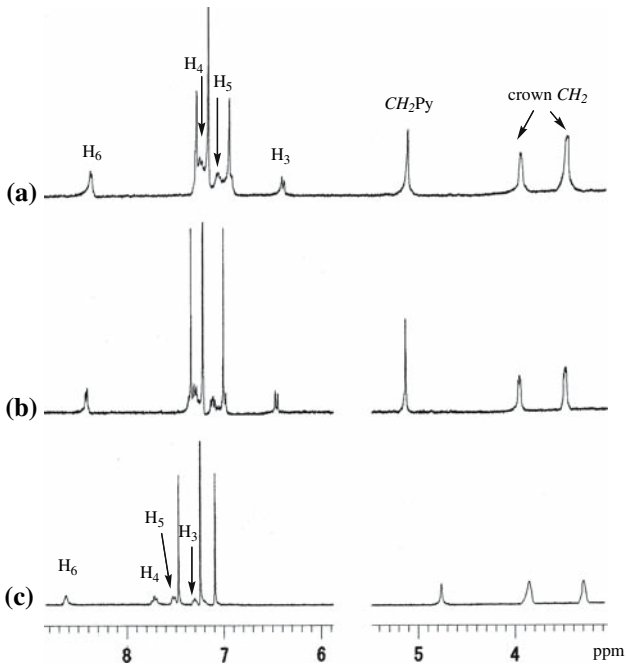


Fig. 3 Partial ^{1}H NMR titration spectra of 1,3-*alternate*-**5** (5 × 10^{-3} M, in $CDCl_3$:CD_3CN, 1:1, v/v). (**a**) Free ligand; (**b**) in the presence of 1 equiv. of $LiSO_3CF_3$; (**c**) in the presence of 1 equiv. of $AgSO_3CF_3$

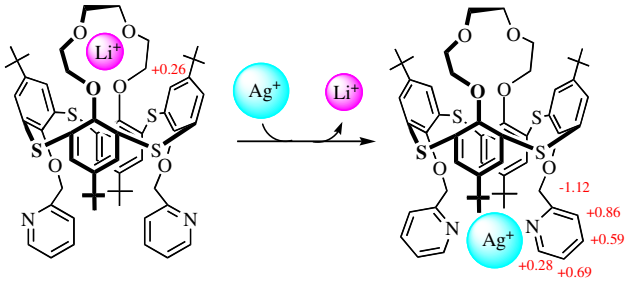


Fig. 4 Binding mode and chemical shift changes of 1,3-*alternate*-**5** upon complexation with Ag^+ [300 MHz, in $CDCl_3$:CD_3CN 1:1, 27 °C]. $\Delta\delta = \delta$ (metal)–δ (free ligand). (–) denotes a shift to up field. (+) denotes a shift to down field

suggest not only the release of Li^+ from the crown moiety but also complete suppression of the recognition of Li^+ derived from the crown moiety upon formation of the $Ag^+\subset$1,3-*alternate*-**5** complex. The observed switch-off might be ascribed to great conformational changes upon complexation of Ag^+ at the pyridyl moieties, which is supported by the remarkable chemical shift changes of the methylene protons of OCH_2Py and pyridine ring protons.

Self-assembly of 1,3-*alternate*-thiacalix[4]arene by hydrogen bonding

Synthesis

Compounds **9** and **10** were obtained in 61 and 63% yield, respectively, by the stereoselective *O*-alkylation of the distal-diester *distal*-**8a** [23a] and distal-dibenzyl derivative *distal*-**2** [23c, 24a] with 4-(chloromethyl)pyridine, respectively, in dry THF-DMF in the presence of Cs_2CO_3 to assure the 1,3-*alternate* conformation [24]. Compounds **11** and **12** were synthesized in 64 and 67% yield by the reaction of dicarboxylic acid *distal*-**8b** [29] with 2-(chloromethyl)pyridine and benzyl bromide, respectively, in dry THF-DMF in the presence of Cs_2CO_3 (Scheme 3).

The product structures were supported by their spectral and analytical data. The ^{1}H NMR spectra of **9** shows two singlets for the *tert*-butyl protons at δ 0.87 and 1.29 ppm, in which the former peak can be observed at a higher field due to the ring current effect arising from the two pyridine rings introduced. Similar upfields of the *tert*-butyl protons of **10–12** were observed. These observations strongly suggest **10–12** adopt 1,3-*alternate* conformation.

Self-assembly of heterodimers

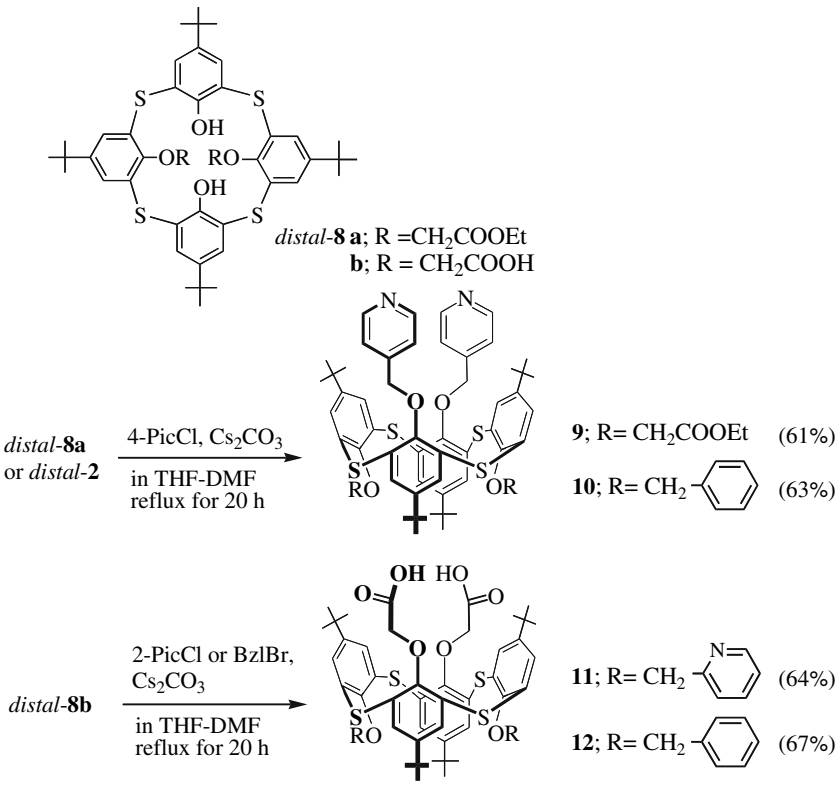
The tetrasubstituted compounds **9** and **10** bearing two 4-pyridyl moieties [17], and **11** and **12** bearing two carboxylic acid moieties [30], might permit dimerization through hydrogen bonding to afford dimers **13** and **14**, respectively, as shown in Fig. 5.

Evidence of the formation of the dimers **13** and **14** was obtained by ^{1}H NMR and IR spectroscopy. Figure 6c shows the ^{1}H NMR spectrum of the equimolar (50 mM) mixture of **9** and **11** in $CDCl_3$ solution. The assembly process occurred rapidly and was completed within minutes of mixing. It is worth mentioning that **11** was partially soluble in chloroform but after mixing with **9** a clear solution was obtained. The ^{1}H NMR spectrum is highly symmetrical and fairly well resolved. Compared with the ^{1}H NMR spectra of the precursors **9** and **11**, the spectrum of the mixture showed a signal at δ 12.82 ppm which can be attributed to an intermolecular hydrogen bond formed by the carboxylic acid protons. In addition, the different chemical shift for the 4-pyridylmethyl protons [CH_2 (4-Py) $\Delta\delta$ = +0.06, $H_{2,6}$ $\Delta\delta$ = +0.18 ppm] and for the methylene protons of carboxylic acid moiety (CH_2CO_2 $\Delta\delta$ = –0.11 ppm) strongly suggested the formation of the dimer **13**. The chemical shift slightly changed even in the presence of an excess of **9**, presumably, due to the formation of a dimer rather than a polymer, further corroborate by Job Plot (Fig. 7).

Furthermore, the IR spectrum confirms the formation of the dimer **13**. One of the most important features is the appearance of a broad band [17, 31] with a low intensity at 1960 cm^{-1}, representing the $\nu_{OH\cdots N}$ vibration band. The vibration mode of $\nu_{C=O}$ of the carboxylic moiety slightly shifted toward low wave number to 1746 cm^{-1} in comparison with the normal vibration around 1755 cm^{-1}. This clearly suggested that the dimer **13** is formed by hydrogen bonding between the carboxylic acid protons and the nitrogen of the 4-pyridyl ring [32]. Similar findings were observed for the dimer **14** composed by **10** and **12**.

The concentration-dependent (50 mM–60 μM, $CDCl_3$) ^{1}H NMR measurement of the equimolar **9/11** and **10/12** mixtures showed only significant shift for the protons 4-pyridyl protons and CH_2CO_2 protons while the CO_2H protons slightly shift and disappeared gradually. Thus, the determination of the dimerization constants was made only using the 4-pyridyl ($H_{2,6}$) signal due to CH_2CO_2 protons signal shifted less than the other and would give a more inaccurate result. These data fitted reasonably well to a 1:1 binding isotherm, as shown in Figs. 7 and 8. From these data association constants [33] of K_{ass} = 389 ± 9 M^{-1} and 342 ± 12 M^{-1} for **13** and **14**, respectively, were calculated. The dimerization constants of **13** and **14** are 19 times smaller than that of parent calix[4]arene dimer [17] might be due to the number of donor and/or acceptor moieties of the precursors and steric hindrance caused by the *tert*-butyl groups.

Scheme 3 Synthesis of bis(4-pyridyl) and dicarboxylic acid thiacalix[4]arene derivatives



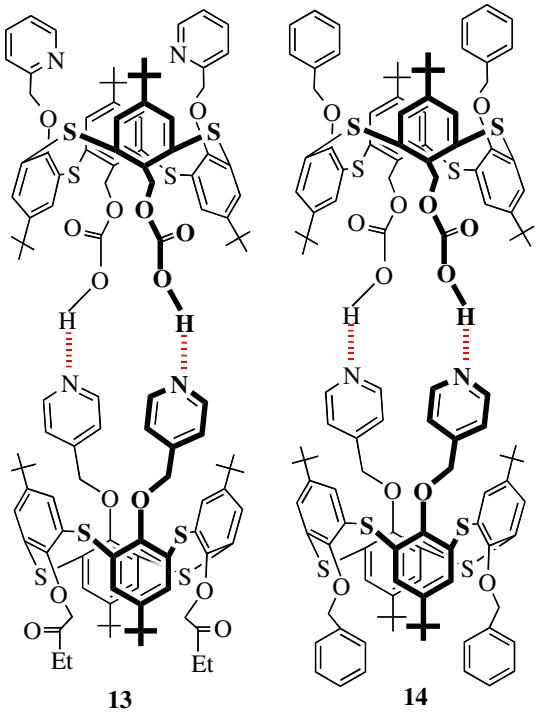


Fig. 5 Heterodimers derived from intermolecular hydrogen bonding

^{1}H NMR titration experiments

In addition to the self-assembly studies, we also investigated the molecular behavior of the dimers **13** and **14** by ^{1}H

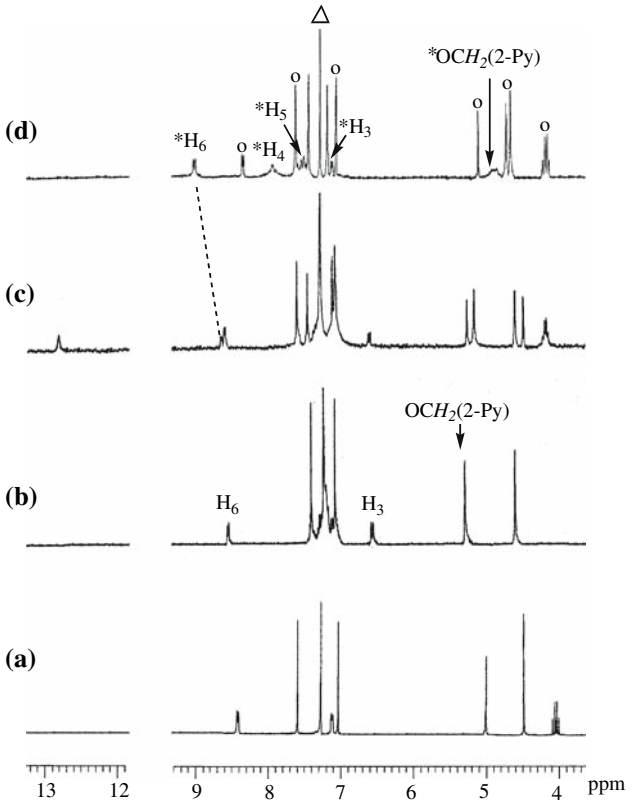


Fig. 6 Partial ^{1}H NMR at 300 MHz in $CDCl_3$ of; (**a**) free **9**, (**b**) free **11**, (**c**) dimer **13**, (**d**) after addition of an equiv. of $AgSO_3CF_3$ into (**c**). *$\mathbf{11}\supset Ag^+$, ° free **9**, Δ solvent

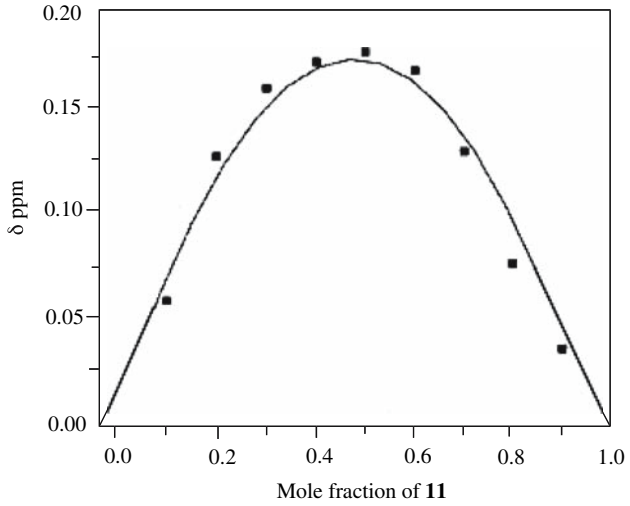


Fig. 7 Job plot of **9** with **11** ([**9**]+[**11**] = 2 mM)

NMR titration experiments in $CDCl_3$. Firstly, control titration experiments of **9** with $AgSO_3CF_3$ and/or KSO_3CF_3 were carried out. The addition of an equiv. of $AgSO_3CF_3$ to **9** caused a complex formation **9**⊃Ag^+ (K_{ass} = 153.4 ± 8 M^{-1}) [34a] as demonstrated by the downfield shift of the 4-pyridyl protons [CH_2(4-Py) $\Delta\delta$ = +0.08, $H_{2,6}$ $\Delta\delta$ = +0.21 and $H_{3,5}$ $\Delta\delta$ = +0.10 ppm], whereas the ester protons were scarcely affected (CH_2CO_2 $\Delta\delta$ = +0.003 ppm). These findings suggest that the Ag^+ must be coordinated by the two nitrogens of the 4-pyridyl moiety and two triflate oxygens to saturate the requirements of the Ag^+ coordination sphere [35]. Titration of **9** with an equiv. of KSO_3CF_3 caused negligible shifts of pyridyl protons [CH_2(4-Py) $\Delta\delta$ = +0.01, $H_{2,6}$ $\Delta\delta$ = –0.03 ppm and $H_{3,5}$ $\Delta\delta$ = +0.002 ppm] and moderate shift of the protons in the cavity composed by the ester moieties (i.e. CH_2CO_2 $\Delta\delta$ = +0.11 ppm). These findings suggest the formation of

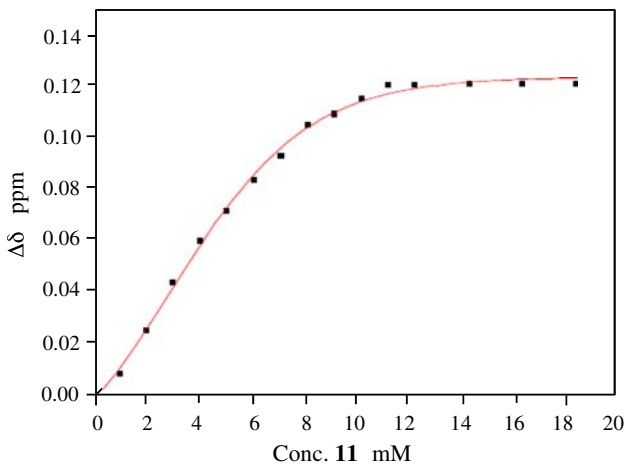


Fig. 8 $H_{2,6}$ measured change chemical shift ($\Delta\delta$) of **9** (2 mM) as a function of **11** concentration in $CDCl_3$ at 293 K

K^+⊂**9** complex at the ester moieties. Addition of an excess of $AgSO_3CF_3$ and KSO_3CF_3 into the solutions of **9**⊃Ag^+ and K^+⊂**9** complexes, respectively, did not cause any significant chemical shift [34b] (Table 2).

Finally, titration experiments of the dimers **13** and **14** with $AgSO_3CF_3$ and/or KSO_3CF_3 were carried out. Addition of an equiv. of $AgSO_3CF_3$ caused the immediate disassembly of the dimer **13** as demonstrated by the disappearance of the signal of CO_2H protons and chemical shift of the rest of the protons, Fig. 6d. The disassembly is attributed to conformational changes produced by the formation of **11**⊃Ag^+ (K_{ass} = 1.28 × 10^4 M^{-1}) [36] (Scheme 4). We assumed that the Ag^+ ion has to be complexed by the nitrogen atoms of 2-pyridyl moiety and phenolic oxygens. The methylene protons of CH_2 (2-Py) shifted to upfield ($\Delta\delta$ = –0.44 ppm) due to the ring current of the benzene moiety, while the 2-pyridyl protons displayed a downfield shift. Contrary to that observed in the classical calixarenes, the protons H_3 shift to down field which might be affected by the sulfur atom in the diarylthiaether linkage. Titration of **13** with an equiv. of KSO_3CF_3 caused moderate shift of protons of the ester cavity (i.e. CH_2CO_2 $\Delta\delta$ = +0.10 ppm) and negligible shift of the rest of protons. These results strongly suggest that the hydrogen bonding was not altered substantially upon complexation of K^+ by the ester moiety.

In contrast, similar titration experiments of **14** showed that the presence of an equiv. of $AgSO_3CF_3$ or KSO_3CF_3 does not cause disassembly of the dimer **14**. This result corroborated the disassembly process of **13** in the presence of Ag^+ ion. However, after 30 min. the disassembly of the dimer **14** and formation **10**⊃Ag^+ complex was observed. These results together with the association constants reveal that the two hydrogen bonding system is strong enough to stabilize the dimers **13** and **14**, but not to compete effectively with the Ag^+ ion.

Conclusion

A novel ditopic receptor 1,3-*alternate*-**5** possessing two complexation sites, crown-4 moiety and 2-pyridyl groups in 1,3-*alternate* conformation based on thiacalix[4]arene has been prepared. The exclusive formation of mononuclear complexes of 1,3-*alternate*-**5** with Li^+ and Ag^+ was observed even though the formation of the heterogeneous dinuclear complexes was expected. The decomplexation of Li^+ from the crown moiety of 1:1 complex 1,3-*alternate*-**5**⊃Li^+ to form the Ag^+⊂1,3-*alternate*-**5** complex by addition of $AgSO_3CF_3$ clearly shows that pyridyl moiety works as an efficient switch-off of the recognition ability of the crown moiety. These results give some insight into the

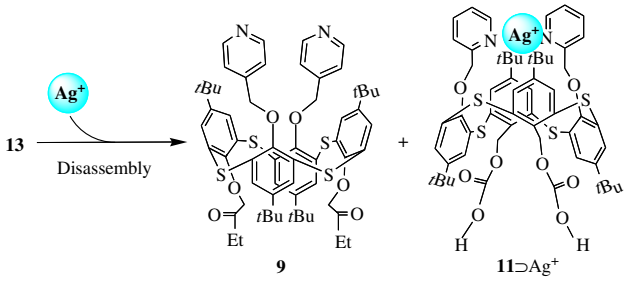
Table 2 Chemical shift of pyridine protons in free and silver complex of **9** and **11**, respectively

Compound	Chemical shift, δ ppm[a,b]		
	H6	H3	OCH_2Py
9	8.47[c]	7.13[c]	4.57
$\Delta\delta$ (**9**⊃Ag^+)	0.21	0.10	0.08
11	8.58[c]	6.57[c]	5.23
$\Delta\delta$ (**11**⊃Ag^+)	0.37	0.49	–0.44

[a] $\Delta\delta$ Values are the difference of the chemical shift between 1,3-*alternate*-**9** or **11** and the complex **9**⊃Ag^+ and **11**⊃Ag^+, respectively, in $CDCl_3$ at 27 °C

[b] A minus sign (–) denotes a shift to higher magnetic field

[c] The midpoint values of multiplet are indicated



Scheme 4 Disassembly of dimer **13** by addition of an equiv. of $AgSO_3CF_3$

molecular design of new synthetic receptors for use in metal controlled biomimetic systems.

We have also found that the formation of the heterodimers **13** and **14** was detected by ^{1}H NMR and IR. The disassembly of the heterodimers **13** and **14** depends on both the degree of conformational changes produced by complex formation and competition between the Ag^+ ion and carboxylic acid protons for the lone pair of nitrogen of 4-pyridyl moieties. These results open new doors for the use of heterodimeric systems driven by the formation of hydrogen bonding for the regulation of molecular recognition which has biological and environmental relevance. We are currently preparing more sophisticated molecular building block for the formation of dimeric systems.

Acknowledgement We would like to thank the OTEC at Saga University for financial support.

References

1. (a) Gutsche, C.D.: In: Stoddart, J. F. (ed.) Calixarenes revisited, Monographs in Supramolecular Chemistry, vol. 6. The Royal Society, Cambridge (1998); (b) Asfari, Z., Böhmer, V. Harrowfield, J., Vicens, J.: Calixarenes 2001. Kluwer Academic, Dordrecht (2001); (c) Vögtle, F.: Supramolecular Chemistry: An Introduction. J. Wiley, New York (1991).
2. (a) Lhoták, P.: Chemistry of Thiacalixarenes. Eur. J. Org. Chem. 1675–1692 (2004); (b) Morohashi, N., Narumi, F., Iki, N., Hattori, T., Miyano, S.: Thiacalixarenes. Chem. Rev. **106**, 5291–5316 (2006); (c) Kumagai, J., Hasegawa, M., Miyanari, S., Sugawa, Y., Sato, Y., Hori, T., Ueda, S., Kamiyama, H., Miyano, S.: Facile synthesis of *p-tert*-butylthiacalix[4]arene by the reaction of *p-tert*-butylphenol with elemental sulfur in the presence of a base. Tetrahedron Lett. **38**, 3971–3972 (1997); (d) Iki, N., Kabuto, C., Fukushima, T., Kumagai, H., Takeya, H., Miyanari, S., Miyashi, T., Miyano, S.: Synthesis of *p-tert*-butylthiacalix[4]arene and its inclusion property. Tetrahedron **56**, 1437–1443 (2000).
3. Lehn, J.M.: Supramolecular Chemistry: Concepts and Perspectives. VCH, Weinheim, Germany (1995).
4. (a) Nabeshima, T., Saiki, T., Sumitomo, K.: Modulation of metal recognition by a novel calix[4]arene bearing two bipyridine units as a molecular gate. Org. Lett. **4**, 3207–3209 (2002); (b) Nabeshima, T., Yoshihira, Y., Saiki, T., Akine, S., Horn, E.: Remarkably large positive and negative allosteric effects on ion recognition by the formation of a novel helical pseudocryptand. J. Am. Chem. Soc. **125**, 28–29 (2003).
5. Hammes, G.G., Wu, C.W.: Kinetics of allosteric enzymes. Annu. Rev. Biophys. Bioeng. **3**, 1–33 (1974).
6. (a) Iwamoto, K., Shinkai, S.: Synthesis and ion selectivity of all conformational isomers of tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene. J. Org. Chem. **57**, 7066–7073 (1992); (b) Ikeda, A., Shinkai, S.: On the origin of high ionophoricity of 1,3-*alternate* calix[4]arenes: pi-donor participation in complexation of cations and evidence for metal-tunneling through the calix[4]arene cavity. J. Am. Chem. Soc. **116**, 3102–3110 (1994); (c) Koh, K.N., Araki, K., Shinkai, S., Asfari, Z., Vicens, J.: Cation binding properties of a novel 1,3-*alternate* calix[4]biscrown. Formation of 1:1 and 1:2 complexes and unique cation tunneling across a calix[4]arene cavity. Tetrahedron Lett. **36**, 6095–6098 (1995).
7. (a) van Leeuwen, F.W.B., Beijleveld, H., Kooijiman, H., Spek, A.L., Verboom, W., Reinhoudt, D.N.: Synthesis and conformational evaluation of *p-tert*-butylthiacalix[4]arene-crowns. J. Org. Chem. **69**, 3928–3936 (2004); (b) Lamare, V., Dozol, J.F., Thuéry, P., Nierlich, M., Asfari, Z., Vicens, J.: Experimental and theoretical study of the first thiacalixcrowns and their alkali metal ion complexes. J. Chem. Soc., Perkin Trans. **2**, 1920–1926 (2001).
8. (a) Grün, A., Csokai, V., Parlagh, G., Bitter, I.: Synthesis and alkali cation extraction ability of 1,3-alt-thiacalix[4]bis(crown) ethers. Tetrahedron Lett. **43**, 4153–4156 (2002); (b) Csokai, V., Grün, A., Parlagh, G., Bitter, I.: Synthesis and alkali cation extraction ability of 1,3-alt-thiacalix[4]mono(crown) ethers. Tetrahedron Lett. **43**, 7627–7629 (2002).
9. (a) Kubo, Y., Maeda, S., Tokita, S., Kubo, M.: Colorimetric chiral recognition by a molecular sensor. Nature **382**, 522–524 (1996); (b) Zheng, Q.Y., Chen, C.F., Huang, Z.T.: Synthesis of new chromogenic calix[4]crowns and molecular recognition of alkylamines. Tetrahedron **53**, 10345–10356 (1997); (c) Arnaud-Neu, F., Caccamese, S., Fuangswasdi, S., Pappalardo, S., Parisi, M.F., Petringa, A., Principato, G.: Synthesis, optical resolution and complexation properties of inherently chiral monoalkylated *p-tert*-butyl-(1,2)-calix[4]crown ethers. J. Org. Chem. **62**, 8041–8048 (1997).
10. (a) Ungaro, R., Casnati, A., Ugozzoli, F., Pochini, A., Dozol, J.-F., Hill, C., Pouquette, H.: 1,3-Dialkoxycalix[4]arenecrowns-6 in 1,3-*alternate* conformation: cesium-selective ligands that exploit cation–arene interactions. Angew. Chem., Int. Ed. Engl. **33**, 1506–1509 (1994); (b) Lamare, V., Dozol, J.F., Fuangswasdi, S., Arnaud-Neu, F., Thuéry, P., Nierlich, M., Asfari, Z., Vicens, J.: A new calix[4]arene-bis(crown ether) derivative displaying an

improved caesium over sodium selectivity: molecular dynamics and experimental investigation of alkali-metal ion complexation. J. Chem. Soc., Perkin Trans **2**, 271–284 (1999).

11. (a) Thuéry, P., Nierlinch, M., Lamare, V., Dozol, J.F., Asfari, Z., Vicens, J.: Bis(crown ether) and azobenzocrown derivatives of calix[4]arene. A review of structural information from crystallographic and modelling studies. J. Incl. Phenom. Macrocyclic Chem. **36**, 375–408 (2000); (b) Blanda, M.T., Farmer, D.F., Brpdbelt, J.S., Goolsby, B. J.: Synthesis and alkali metal ion binding properties of two rigid sterochemical isomers of calix[6]arene bis-crown-4. J. Am. Chem. Soc. **122**, 1486–1491 (2000); (c) Izatt, R.M., Pawlak, K., Bradshaw, J.S., Bruening, R.L.: Thermodynamic and kinetic data for macrocycle interactions with cations and anions. Chem. Rev. **91**, 1721–2085 (1991); (d) Arena, G.. Contino, A., Magri, A., Scioto, D., Spoto, G., Torrisi, A.: Strategies based on calixcrowns for the detection and removal of cesium ions from alkali-containing solutions. Ind. Eng. Chem. Res. **39**, 3605–3610 (2000); (e) Luo, H., Dai, S., Bonnesen, P.V., Buchana, A.C., Holbrey, J.D., Bridges, N.J., Rogers, R.D.: Extraction of cesium ions from aqueous solutions using calix[4]arene-bis(*tert*-octylbenzo-crown-6) in ionic liquids. Anal. Chem. **76**, 3078–3083 (2004); (f) Casnati, A., Della Ca', N., Sansone, F., Ugozzoli, F., Ungaro, R.: Enlarging the size of calix[4]arene-crowns-6 to improve Cs^+/K^+ selectivity: a theoretical and experimental study. Tetrahedron **60**, 7869–7876 (2004).
12. (a) Casnati, A., Pochini, A., Ignaro, R., Ugozzoli, F., Arnaud, F., Fanni, S., Schwing, M.-J., Egberink, R.J.M., de Jong, F., Reinhoudt, D.N.: Synthesis, complexation, and membrane transport studies of 1,3-*alternate* calix[4]arene-crown-6 conformers: a new class of cesium selective ionophores. J. Am. Chem. Soc. **117**, 2767–2777 (1995); (b) Kim, J.S., Suh, I.H., Kim, J.K., Cho, M.H.: Selective sensing of caesium ions by novel calix[4]arene bis-(dibenzocrown) ethers in an aqueous environment. J. Chem. Soc., Perkin Trans. **1**, 2307–2312 (1998); (c) Asfari, Z., Weiss, J., Papparlardo, S., Vicens, J.: Synthesis and properties of double-calix[4]arenes, doubly-crowned calix[4]arenes, and double-calix-crowns. Pure Appl. Chem. **65**, 585–590 (1993); (d) Stephan, H., Gloe, K., Paulus, E.F., Saadioui, M., Böhmer, V.: Calix crowns derived from *para*-bridged calix[4]arenas. Org. Lett. **2**, 839–841 (2000).
13. (a) Ferguson, G., Gallagher, J.F., Giunta, L., Neri, P., Pappalardo, S., Parisi, M.: Synthetic strategies to inherently chiral calix[4]-arenes with mixed ligating functionalities at the lower rim. J. Org. Chem. **59**, 42–53 (1994); (b) Pappalardo, S., Ferguson, G., Neri, P., Rocco, C.: Synthesis and complexation studies of regioisomers and conformational isomers of *p-tert*-butylcalix[4]arene bearing pyridine or pyridine *N*-oxide pendant groups at the lower rim. J. Org. Chem. **60**, 4576–4584 (1995); (c) Pappalardo, S.: Self-filled partial cone pyridinocalix[4]arenes. New J. Chem. 465–472 (1996); (d) De Danil, N., Angela, F., Piro, O.E., Pulcha, S., Lupe, E., Aguilar, C., Adolfo, F., Al-Rawi, N., Catellano, E.E., Sueros, V., Felix, J.: Solution thermodynamics of geometrical isomers of pyridino calix(4)arenes and their interaction with the silver cation. The X-ray structure of a 1:1 complex of silver perchlorate and acetonitrile with 5,11,17,23-tetra-*tert*-butyl-[25,26,27,28-tetrakis(2-pyridylmethyl)oxy]calix[4]arene. J. Chem. Soc. Faraday Trans. **94**, 3097–3104 (1998); (e) Shinkai, S., Fujimoto, K., Otsuka, T., Ammon, H.-L.: Syntheses and ion selectivity of conformational isomers derived from calix[4]arene. J. Org. Chem. **57**, 1516–1523 (1992).
14. (a) Yamato, T., Haraguchi, M., Iwasa, T., Tsuzuki, H.: Synthesis and inclusion propeties of tetrakis[(2-pyridylmethyl)oxy]homocalix[4]arenas. Anales de Química Int. Ed. **93**, 301–309 (1997); (b) Yamato, T., Haraguchi, M., Nishikawa, J., Ide, S., Tsuzuki, H.: Synthesis, conformational studies and inclusion properties of tris[(2-pyridylmethyl)oxy]hexahomotrioxacalix[3]arenes. Can. J. Chem. **76**, 989–996 (1998); (c) Yamato, T., Haraguchi, M., Nishikawa, J., Ide, S.: Synthesis, conformational studies and inclusion properties of *O*-benzylated calixarene-analogous trihydroxy[3.3.3]metacyclophanes. J. Chem. Soc., Perkin Trans. **1**, 609–614 (1998); (d) Yamato, T., Zhang, F.: Synthesis, structures and inclusion properties of hexahomotrioxacalix[3]arene triamide derivatives having the hydrogen-bonding groups. J. Incl. Phenom. 55–64 (2001); (e) Yamato, T., Kitajima, F., Gil, J.T.: Alkyl ammonium ion selectivity of hexahomotrioxacalix[3]arene triamide derivative having the intramolecular hydrogen-bonding group. J. Incl. Phenom. **53**, 257–262 (2005); (f) Yamato, T., Rahman, S., Xi, Z., Kitajima, F., Gil, J.T.: Ditopic receptors of hexaamide derivatives derived from hexahomotrioxacalix[3]arene triacetic acid. Can. J. Chem. **84**, 58–64 (2006).
15. Selected reviews. (a) Lehn, J.-M.: Perspectives in supramolecular chemistry – from molecular recognition towards molecular information processing and self-organization. Angew. Chem., Int. Ed. Engl. **29**, 1304–1319 (1990); (b) Whitesides, G.M., Simanek, E.E., Mathias, J.P., Seto, C.T., Chin, D.N., Mammen, M., Gordon, D.M.: Noncovalent synthesis: using physical-organic chemistry to make aggregates. Acc. Chem. Res. **28**, 37–44 (1995); (c) Hamann, B.C., Shimizu, K.D., Rebek, J. Jr.: Reversible encapsulation of guest molecules in a calixarene dimmer. Angew. Chem. Int. Ed. Engl. **35**, 1326–1329 (1996); (d) Iwanek, W.: Chiral calixarenes derived from resorcinol. Part 3: functionalization of octaester derivatives with chiral amines and amino alcohols. Tetrahedron Asymm. **9**, 3171–3174 (1998); (e) Prints, L.J., Reinhoudt, D.N., Timmerman, P.: Noncovalent synthesis using hydrogen bonding. Angew. Chem., Int. Ed. Engl. **40**, 2382–2426 (2001); (f) Archer, E.A., Krische, M.J.: Hydrogen bonding in noncovalent synthesis: selectivity and the directed organization of molecular strands. Tetrahedron **57**, 1139–1159 (2001).
16. Conn, M.M., Rebek, J. Jr.: Self-assembling capsules. Chem. Rev. **97**, 1647–1668 (1997) and references therein.
17. Vreekamp, R.H., Verboom, W., Reinhoudt, D.N.: Lower rim-upper rim hydrogen-bonded adducts of calix[4]arenes, J. Org. Chem. **61**, 4282–4288 (1996).
18. Pedersen, C.J.: Cyclic polyethers and their complexes with metal salts. J. Am. Chem. Soc. **89**, 7017–7036 (1967).
19. Xu, K.: Nonaqueous liquid electrolytes for lithium-based rechargeable batteries. Chem. Rev. **104**, 4303–4418 (2004).
20. (a) Fujimoto, M., Nogami, T., Mikawa, H.: New anionic conductors: crown ether complexes of alkali-metal iodides and alkaline-earth metal iodides. Chem. Lett. 547–550 (1982); (b) Lee, H.S., Yang, X.Q., McBreen, J., Choi, L.S., Okamoto, Y.: The synthesis of a new family of anion receptors and the studies of their effect on ion pair dissociation and conductivity of lithium salts in nonaqueous solutions. J. Electrochem. Soc. **143**, 3825–3829 (1996).
21. Bajaj, A.V., Poonia, N.S.: Comprehensive coordination chemistry of alkali and alkaline earth cations with macrocyclic multidentates: latest position. Coord. Chem. Rev. **87**, 55–213 (1988).
22. (a) Hilgenfeld, R., Saenger, W.: Structural chemistry of natural and synthetic ionophores and their complexes with cations. Top. Curr. Chem. **101**, 1–82 (1982); (b) Akutagawa, T., Hasewaga, T., Nakamura, T., Takeda, S., Inabe, T., Sugiura, K., Sakata, Y., Underhill, A.E.: M^+(12-crown-4) supramolecular cations (M^+ = Na^+, K^+, Rb^+, and NH_4^+) within Ni(2-thioxo-1,3-dithiole-4,5-dithiolate)$_2$ molecular conductor. Inorg. Chem. **39**, 2645–2651 (2000).
23. (a) Iki, N., Narumi, F., Fujimoto, T., Morohashi, N., Miyano, S.: Selective synthesis of three conformational isomers of tetrakis[(ethoxycarbonyl)methoxy]thiacalix[4]arene and their complexation properties towards alkali metal ion. J. Chem. Soc., Perkin Trans. **2**, 2745–2750 (1998); (b) Morohashi, N., Iki, N.,

Kabuto, C., Miyano, S.: Stereocontrolled oxidation of a thiacalix[4]arene to the sulfinyl counterpart of a defined S=O configuration. Tetrahedron Lett. **41**, 2933–2937 (2000); (c) Morohashi, N., Katagiri, H., Iki, N., Yamane, Y., Kabuto, C., Hattori, T., Miyano, S.: Synthesis of all stereoisomers of sulfinylcalix[4]arenes. J. Org. Chem. **68**, 2324–2333 (2003).

24. (a) Yamato, T., Zhang, F., Kumamaru, K., Yamamoto, H.: Synthesis, conformational studies and inclusion properties of tetrakis[(2-pyridylmethyl)oxy]thiacalix[4]arenes. J. Incl. Phenom. Macrocyclic Chem. **42**, 51–60 (2002); (b) Pérez-Casas, C., Yamato, T.: Hard–Soft receptors, tetrakis[(*N*,*N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene derivatives with *cone* and 1,3-*alternate* conformation. J. Incl. Phenom. Macrocyclic Chem. **53**, 1–8 (2005); (c) Pérez-Casas, C., Yamamoto, H., Yamato, T.: Regioselective synthesis of distal-bisalkoxytetrathiacalix[4]arenes by a protection–deprotection method using benzyl gropus. J. Chem. Res. 694–696 (2005); (d) Yamato, T., Pérez-Casas, C., Gil, J.T., Elsegood, M.R.J., Dale, S.H., Redshaw, C.: Synthesis, structures and inclusion properties of *distal*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes. J. Chem. Res. 270–273 (2006); (e) Yamato, T., Pérez-Casas, C., Yamamoto, H., Elsegood, M.R.J., Dale, S.H., Redshaw, C.: Regioselective synthesis and inclusion properties of *distal*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes. J. Incl. Phenom. Macrocyclic Chem. **54**, 261–269 (2006); (f) Yamato, T., Pérez-Casas, C., Elsegood, M.R.J., Dale, S.H., Redshaw, C.: Synthesis and inclusion properties of a novel thiacalix[4]arene-based hard–soft receptor with 1,3-*alternate* conformation. J. Incl. Phenom. Macrocyclic Chem. **55**, 31–36 (2006).
25. Ashton, P., Huff, J., Menzer, S., Parsons, I.W., Preece, J.A., Stoddart, J.F., Tolley, M.S., White, A.J.P., Williams, D.J.: Bis[2]catenanes and a bis[2]rotaxane-model compounds for polymers with mechanically interlocked components. Chem. Eur. J. **2**, 31–44 (1996).
26. Narumi, F., Masumura, N., Morohashi, N., Kameyama, H., Miyano, S.: First synthesis of 25,26-bridged thiacalix[4]crowns by the use of a 25,26-*O*-disiloxane-diyl-capped *p*-*tert*-butylthiacalix[4]arene. J. Chem. Soc., Perkin Trans. **1**, 1843–1844 (2002).
27. (a) Tashiro, M., Yamato, T.: Metacyclophanes and related compounds. 1. Preparation and nuclear magnetic resonance spectra of 8,16-disubstituted [2.2]metacyclophanes. J. Org. Chem. **46**, 4556–4562 (1981); (b) Tashiro, M., Yamato, T.: Metacyclophanes and related compounds. 8. Preparation and reactions of 8,16-diformyl[2.2]metacyclophanes. J. Org. Chem. **48**, 1461–1468 (1983).
28. Danil de Namor, A.F., Llosa Tanco, M.A., Ng, J.C.Y., Salomón, M.: Lithium-coronand electrolytes: thermodynamic and electrochemical aspects. Pure Appl. Chem. **67**, 1095–1102 (1995).
29. Iki, N., Morohashi, N., Narumi, F., Fujimoto, T., Suzuki, T., Miyano, S.: Novel molecular receptors based on a thiacalix[4]arene platform. Preparations of the di- and tetracarboxylic acid derivatives and their binding properties towards transition metal ions. Tetrahedron Lett. **40**, 7337–7341 (1999).
30. (a) IR spectra of **11** and **12** show an intense band at 1755 and 1758 cm^{-1} ($\nu_{C=O}$), respectively, suggesting their monomeric form. (b) ^1H NMR of **11** and/or **12** in DMSO-d_6 showed a signal at δ 12.55 and 12.61 ppm, respectively, might be due to an intermolecular hydrogen bonding between CO_2H protons and DMSO. (c) Titration of **11** with $AgSO_3CF_3$ and/or KSO_3CF_3 did not cause any change in the ^1H NMR spectra.
31. Johnson, S.L., Rumon, K.A.: Infrared spectra of solid 1:1 pyridine-benzoic acid complexes; the nature of the hydrogen bond as a function of the acid–base levels in the complex. J. Phys. Chem. **69**, 74–86 (1965).
32. The possible hydrogen bonding formation between the carboxylic acid protons and the nitrogen of the 2-pyridyl ring was ruled out since the unfavorable orientation of the 2-pyridyl moieties.
33. (a) Schneider, H.J., Durr, H. (eds.): Frontiers in Supramolecular Organic Chemistry and Photochemistry, pp. 123–143. VCH, New York (1991); (b) Binding Constants: The Measurement of Molecular Complex stability. Wiley, New York, Chapter 5 (1987).
34. (a) The association constants (K_{ass}) for **9**$\supset Ag^+$ and $K^+\subset$**9** were calculated by non-linear fitting analysis of the observed chemical shift changes of 4-pyridyl ($H_{2,6}$) protons of **9**, respectively, as a function of increased of cations. (b) The stoichiometry of cation complexes was determined by Job plots from ^1H NMR titration data.
35. Munakata, M., Ning, G.L., Suenega, Y., Kuroda-Sowa, T., Mackawa, M., Ohta, T.: A one-dimensional metallocyclophane with columnar aromatic stacking: the silver(i) (2-coordination complex of 1,2-benztriphenylene. Angew. Chem. Int. Ed. Engl. **39**, 4555–4557 (2000).
36. The K_{ass} of **11**$\supset Ag^+$ was calculated base on the chemical shift of the CH_2 (2-Py) protons upon titration of dimer **13** with $AgSO_3CF_3$. Similar value was obtained for the formation of **11**$\supset Ag^+$ in the independent titration experiment of **11** with $AgSO_3CF_3$ ($K_{ass} = 1.46 \times 10^4$ M^{-1}).
37. Benesi, H.A., Hildebrand, J.H.: A spectrophotometric investigation of the interaction of iodine with aromatic hydrocarbons. J. Am. Chem. Soc. **41**, 2073–2707 (1949).