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Synthesis and Inclusion Properties of a Novel Thiacalix[4]arene-Based Hard–Soft Receptor with 1,3-*Alternate* Conformation

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Abstract

A novel ditopic receptor possessing two complexation sites and bearing 1,3-*alternate* conformation based on thiacalix[4]arene was prepared. The binding behaviors with alkali metals and silver ion have been examined by ^{1}H NMR titration experiment. Although the formation of the heterogeneous dinuclear complexes was not observed, the exclusive formation of mononuclear complexes of 1,3-*alternate*-**3** with metal cations is of particular interest in negative allosteric effect in the thiacalix[4]arene family. These findings demonstrate that preorganization, subtle conformational changes and affinity have a pronounced effect on the complexation process between the two different arms placed at the two edges of the thiacalix[4]arene cavity.

Introduction

A large variety of host–guest systems have been designed as selective cation, anion or neutral molecule receptors and carriers using three-demensional 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, Pappalardo *et al.* [7] reported the synthesis of calix[4]-arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals.

Recently, we reported the synthesis, conformation studies and inclusion properties of tetrakis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arene with *cone* and 1,2-*alternate* conformation, which show strong Ag^+ affinity [8]. We report herein the synthesis of the novel receptor **3** with 1,3-*alternate* conformation, having two different side arms and showing affinity to both alkali and soft heavy metal cations, and the study of their complexation behavior towards Na^+, K^+ and Ag^+ 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 Na^+, K^+ and Ag^+ by **3** is expected, owing to the presence of two ester moieties at one edge of the thiacalix[4]arene cavity [9] and two 2-pyridylmethyl moieties at the another edge.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. ^{1}H 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. Data of X-ray diffraction was collected on Bruker SMART 1000 CCD diffractometer. X-ray analysis was

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performed with SHELXTL program package and the structure was solved uneventfully by direct method.

Materials

5,11,17,23-Tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol **1** [2a] and *distal*-5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene *distal*-**2** were prepared according to the reported procedure [10].

Synthesis

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

A mixture of diester *distal*-**2** (370 mg, 0.413 mmol), Cs_2CO_3 (1.34 g, 4.13 mmol) in dry THF (6 ml) was refluxed for 1 h under nitrogen. Then a solution of 2-(chloromethyl)pyridine [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 added and the mixture heated for 17 h. After cooling, the reaction mixture was acidified with 1 M HCl (15 ml) and extracted with CH_2Cl_2 (2×50 ml). The combined extracts were washed with water (2×50 ml), dried (Mg_2SO_4) and condensed under reduced pressure to give 1,3-alternate-**3** (271 mg, 61%) as a colorless solid. Recrystallization from $CHCl_3$–MeOH afforded 1,3-*alternate*-**3** as colorless prisms. Mp 282–286 °C. IR ν (KBr)/cm^1 1766. ^{1}H NMR δ ($CDCl_3$) 0.81 (18H, s, *t*Bu), 1.22 (6H, t, *J* 7.4, CH_2CH_3), 1.28 (18H, s, *t*Bu), 4.13 (4H, q, *J* 7.4, CO_2CH_2), 4.53 (4H, s, OCH_2CO_2), 5.20 (4H, s, OCH_2Py), 6.84 (2H, d, *J* 7.3, PyH_3), 7.07 (4H, s, Ar*H*), 7.11 (2H, m, PyH_5), 7.31 (2H, m, PyH_4), 7.49 (4H, s, Ar*H*) and 8.51 (2H, d, *J* 4.4, PyH_6). MS *m*/*z* 1075.4 (M^+). Anal. Calcd. For $C_{60}H_{70}O_8S_4N_2$: C, 67.01; H, 6.56; N, 2.60. Found: C, 67.00; H, 6.57; N, 2.67%.

Similarly, *O*-alkylation of *distal*-**2** with 2-(chloromethyl)pyridine in the presence of K_2CO_3 afforded 1,3-*alternate*-**3** in 57% yield.

*O-Alkylation of distal-25,27-dihydroxy-26,28-bis[(pyridylmethyl)oxy]-5,11,17,23-tetra-tert-butyl-2,8,14,20-tetrathiacalix[4]arene (distal-**4**) with bromoethyl acetate in the presence of Cs_2CO_3*

A mixture of *distal*-**4** (300 mg, 0.33 mmol) and Cs_2CO_3 (1.07 g, 3.30 mmol) in dry acetone (8 ml)) was heated at reflux for 1 h under nitrogen. Then bromoethyl acetate (550 mg, 3.30 mmol) was added and the mixture heated for 17 h. After cooling, the reaction mixture was acidified with 1 M HCl (10 ml) and extracted with CH_2Cl_2 (2×30 ml). The combined extracts were washed with water (2×50 ml), dried (Mg_2SO_4) and condensed under reduced pressure to give 1,3-*alternate*-**3** (209 mg, 59%) as a colorless solid.

Similarly, *O*-alkylation of *distal*-**4** with bromoethyl acetate in the presence of K_2CO_3 afforded 1,3-*alternate*-**3** in 56% yield.

Synthesis of 4-tert-butyl-2,6-dimethyl[(2-pyridyl methyl)oxy]benzene 6.

A mixture of 4-*tert*-butyl-2,6-dimethylphenol **5** (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 (2.0 ml, 14.5 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 on silica gel with methanol as an eluent to give the title compound **6** (380 mg, 63%) as a colorless oil. IR ν (NaCl)/cm^1: 2963, 2870, 1605, 1473, 1456, 1436, 1413, 1270, 804, 797; ^{1}H NMR δ ($CDCl_3$) 1.30 (9H, s, *t*Bu), 2.31 (6H, s, CH_3), 4.95 (2H, s, CH_2Py), 7.05 (2H, s, Ar*H*), 7.20 (1H, m, PyH_5), 7.74 (2H, m, Py-H_3 and PyH_4) and 8.58 (1H, dd, *J* 0.9, 4.9, PyH_6). MS *m*/*z*: 269 (M^+). Anal. Calcd. for $C_{18}H_{23}NO$ (269.39): C, 80.26; H, 8.61; N, 5.2. Found: C, 80.55; H, 8.49; N, 4.98%.

Stoichiometry of metal complexation

The method of continuous variation was employed to determine the stoichiometry of 1,3-*alternate*-**3** complexes. Two-phase solvent extraction was carried out between aqueous picrates (5 ml, [metal picrate] = 2×10^{-4} M, $AgNO_3$, 0.1 M, NaOH or KOH) 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/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.

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in $CDCl_3$:CD_3CN 1:1 v/v) at 298 °C using a concentration of 4×10^{-3} M and a varying guest concentration of 0.3–30 mM. The association constants

(K_{ass}) for the 1,3-*alternate*-**3** complexes were calculated by non-linear fitting analysis of the observed chemical shift of the methylene protons of OCH_2Py and OCH_2CO for $Ag^+\subset$1,3-*alternate*-**3** complex and 1,3-*alternate*-**3**$\supset Na^+$ or 1,3-*alternate*-**3**$\supset K^+$ complexes, respectively [11].

^{1}H NMR complexation experiments

To a $CDCl_3$ solution (4×10^{-3} M) of 1,3-*alternate*-**3** in the NMR tube was added a CD_3CN solution (4×10^{-3} M) of $AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$ [12]. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

The ^{1}H NMR data of the most representative complexes is given below.

$Ag^+\subset$1,3-*alternate*-**3**: δ_H ($CDCl_3$:CD_3CN, 1:1) 0.97 (18H, s, *t*Bu), 1.21 (6H, t, *J* 7.4, CH_2CH_3), 1.26 (18H, s, *t*Bu), 4.32 (4H, q, *J* 7.4, CH_2CH_3), 4.79 (4H, s, OCH_2CO_2), 4.72 (4H, broad s, OCH_2Py), 7.18 (4H, s, Ar*H*), 7.59 (2H, d, *J* 7.3, PyH_3), 7.61 (2H, m, PyH_5), 7.62 (4H, s, Ar*H*), 7.71 (2H, m, PyH_4) and 8.98 (2H, d, *J* 4.4, PyH_6).

1,3-*alternate*-**3**$\supset Na^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 0.83 (18H, s, *t*Bu), 1.24 (6H, t, *J* 7.4, CH_2CH_3), 1.26 (18H, s, *t*Bu), 4.32 (4H, q, *J* 7.4, CH_2CH_3), 4.79 (4H, s, OCH_2CO_2), 5.28 (4H, s, OCH_2Py), 6.62 (2H, broad d, *J* 7.3, PyH_3), 7.19 (4H, s, Ar*H*), 7.22 (2H, m, PyH_5), 7.30 (2H, m, PyH_4), 7.33 (4H, s, Ar*H*) and 8.55 (2H, d, *J* 4.4, PyH_6).

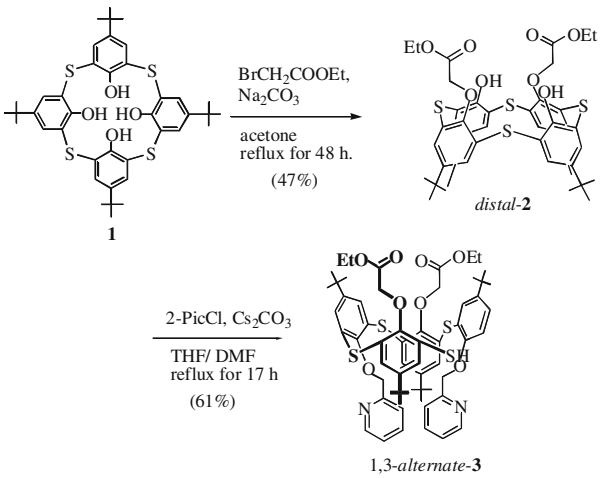
1,3-*alternate*-**3**$\supset K^+$: δ_H ($CDCl_3$:CD_3CN, 1:1) 0.84 (18H, s, *t*Bu), 1.28 (18H, s, *t*Bu), 1.33 (6H, t, *J* 7.4, CH_2CH_3), 4.38 (4H, q, *J* 7.4, CH_2CH_3), 4.81 (4H, s, OCH_2CO_2), 5.26 (4H, s, OCH_2Py), 6.60 (2H, broad d, *J* 7.3, PyH_3), 7.15 (4H, s, Ar*H*), 7.18 (2H, m, PyH_5), 7.30 (2H, m, PyH_4), 7.49 (4H, s, Ar*H*) and 8.53 (2H, d, *J* 4.4, PyH_6).

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

Crystal data for 1,3-*alternate*-**3**: $C_{60}H_{70}N_2O_8S_4$, M = 1075.4, orthorhombic, *Pccn*, a = 19.1059 (9), b = 34.6127 (16), c = 17.3499 (8) Å, V = 11473.6 (9) Å^3, Z = 8, D_c = 1.245 g cm^{-3}, μ(MoK$_\alpha$) = 0.22 mm^{-1}, T = 150(2) K, colourless prisms; 10106 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} = 0.079, structure solved by direct methods, F^2 refinement, R_1 = 0.05560 for 6498 data with $F^2 > 2\sigma(F^2)$, wR_2 = 0.1618 for all data, 751 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 245504. 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].

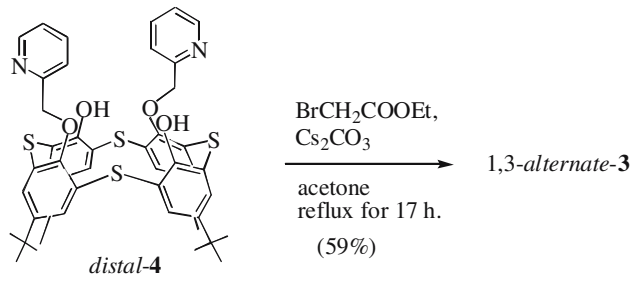
Results and discussion

O-Alkylation of tetrathiacalix[4]arene **1** carried out with 2 equiv. of bromoethyl acetate in the presence of an equiv. of Na_2CO_3 according to the reported procedure produces exclusively the disubstituted product *distal*-**2** [10]. *O*-alkylation of *distal*-**2** with 2-(chloromethyl)pyridine in the presence of Cs_2CO_3 in dry THF-DMF afforded the desired disubstitution product 1,3-*alternate*-**3** in 61% yield. Similar yield was obtained by *O*-alkylation in the presence of K_2CO_3. However, use of Na_2CO_3 as a base resulted in the recovery of the starting compound. On the other hand, we have reported regioselective synthesis of *distal*-bis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arene *distal*-**4** that was accomplished by a protection–deprotection method using benzyl as a protecting group [13]. Thus, *O*-alkylations of *distal*-**4** with bromoethyl acetate to obtain the different conformers of **3** in the presence of K_2CO_3 or Cs_2CO_3 as base were carried out. Unfortunately, the same product, 1,3-*alternate*-**3** in 56 and 59% yields, respectively, was obtained. These results are quite different from the conformer distribution of *O*-alkylation of calix[4]arenes [7c] (Schemes 1 and 2).



Scheme 1.

The structure of 1,3-*alternate*-**3** has been assigned by ^{1}H NMR spectroscopy and confirmed by X-ray analysis. The ^{1}H NMR spectrum of 1,3-*alternate*-**3** shows two singlets for the *tert*-butyl protons at δ 0.81 and 1.28 ppm, in which the former peak was observed at a higher field due to the ring current effect arising from two adjacent pyridine rings. 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, recrystallization from MeOH and $CHCl_3$ produces X-ray quality color-

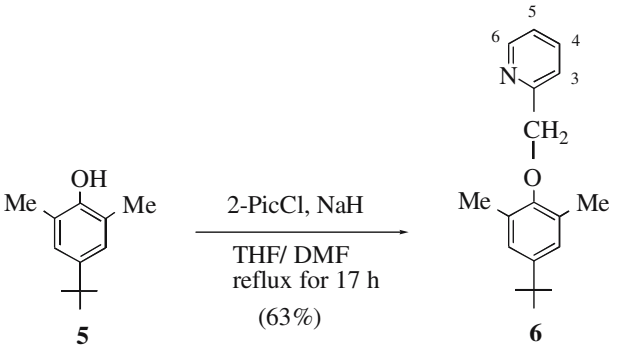


Scheme 2.

less crystals of 1,3-*alternate*-**3**. The ORTEP drawing of 1,3-*alternate*-**3** analyzed by single crystal X-ray diffraction is shown in Figure 1. In the solid state, it is clear that compound **3** adopts a '1,3-*alternate* conformation' as well as the orientation of the ring nitrogens which are outward of the cavity because of the electron repulsion between nitrogens.

Interestingly, the hetero aromatic protons of the pyridine rings of 1,3-*alternate*-**3** are exposed to the ring current shielding effect [14, 15] operating in facing pyridine ring and the diaryl thiaether linkage, and resonate at higher fields with respect to those of the reference compound **6**, which was prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol **5** with 2-(chloromethyl)pyridine in the presence of NaH in 63% yield.

The magnitude of this shielding, calculated as the difference between pertinent pyridine protons of 1,3-*alternate*-**3** and reference compound **6**, increases significantly for the H_3 and H_4 protons. The remarkable shielding effect experienced by the H_4 (δ −0.43 ppm) and H_3 (δ −0.90 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 3, Table 1).



Scheme 3.

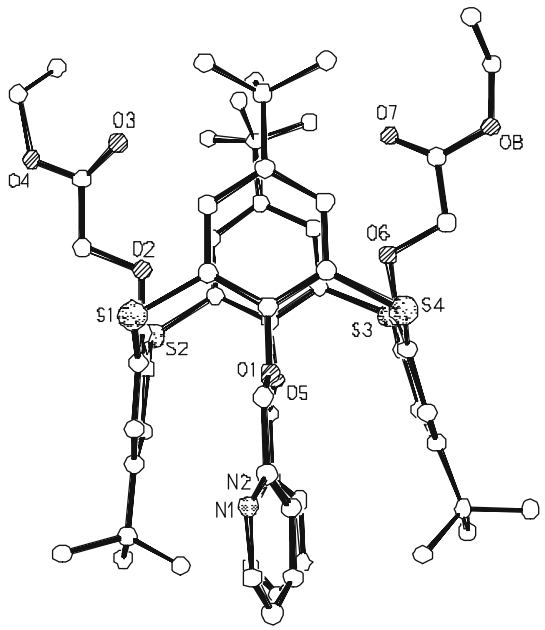


Figure 1. Ball and stick drawing of 1,3-*alternate*-**3**.

Due to the existence of the two potential metal-binding sites, namely the two ester moieties 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*-**3** complexes with Na^+, K^+ and Ag^+ was determined by a two phase-extraction experiment (H_2O/CH_2Cl_2), using the continuous variation method. The percent extractions for K^+ reach maximum at 0.5 mol fraction when the 1,3-*alternate*-**3** and K^+ were changed systematically, indicating the formation of 1:1 complex. Similar results were obtained in the case of Na^+ and Ag^+.

^{1}H NMR titration experiments with KSO_3CF_3, $NaClO_4$ and $AgSO_3CF_3$ were carried out. The results of the chemical shifts ($\Delta\delta$) of OCH_2Py protons are summarized in Table 2. The addition of an equiv. of KSO_3CF_3 or $NaClO_4$, separately, to 1,3-*alternate*-**3** caused immediate complexation as demonstrated by the down field shift of the ester protons (i.e., 1,3-*alternate*-**3**$\supset K^+$; OCH_2CO, $\Delta\delta = +0.26$; $K_{ass} = 2.5 \times 10^3$ M^{-1} and 1,3-*alternate*-**3**$\supset Na^+$ OCH_2CO, $\Delta\delta = +0.24$; $K_{ass} = 2.2 \times 10^3$ M^{-1}), whereas the OCH_2Py protons were scarcely affected. Only the 1:1 complexes 1,3-*alternate*-**3**$\supset K^+$ (Figure 2c) or 1,3-*alternate*-**3**$\supset Na^+$ were formed even with a large excess of KSO_3CF_3. The results

Table 1. Chemical shift of pyridine protons in 1,3-*alternate*-**3** and reference compound **6**[a,b]

Compd.	Chemical shift, δ ppm			
	H_6	H_5	H_4	H_3
6	8.58	7.20[c]	7.74[c]	7.74[c]
1,3-*alternate*-**3**	8.51	7.11	7.31[c]	6.84
$\Delta\delta$	−0.07	−0.09	−0.43	−0.90

[a]$\Delta\delta$ Values are the difference of the chemcial shift between 1,3-*alternate*-**3** and reference compound **6** 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.

Table 2. ^{1}H NMR chemical shift ($\Delta\delta$) of pyridine protons and methylene protons of OCH_2Py of 1:1 complexes[a,c,d]

Proton	1,3-*alternate*-**3** $\Delta\delta$ (ppm)[b] in the presence of metal		
	K^+	Na^+	Ag^+
H_6	+0.04	+0.02	+0.47
H_3	−0.22	−0.24	+0.75
OCH_2Py	+0.08	+0.06	−0.48

[a]300 MHz, in $CDCl_3$:CD_3CN 2:1, 26 °C.
[b]$\Delta\delta = \delta$ (metal) − δ (free ligand).
[c](−) Denotes a shift to up field. (+) denotes a shift to down field.
[d]The signals of H_4 and H_5 overlap with other signals.

confirm that the two ester moieties of 1,3-*alternate*-**3** compose an ionophoric cavity stronger for K^+ and Na^+ than the two pyridyl moieties [6a, 9].

On the other hand, titration with 1 equiv. of $AgSO_3CF_3$ to 1,3-*alternate*-**3** causes a dramatic upfield shift for the methylene protons of OCH_2Py in 1,3-*alternate*-**3** ($\Delta\delta = -0.48$ 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^+\subset$1,3-*alternate*-**3** complex). Spectral changes of the 1:1 $Ag^+\subset$1,3-*alternate*-**3** complex in the presence of an excess of $AgSO_3CF_3$ were not detectable, which supports the exclusive formation of the 1:1 $Ag^+\subset$1,3-*alternate*-**3** complex.

From Table 2, it is clear that in the case of 1,3-*alternate*-**3** upon complexation with Ag^+ ($K_{ass} = 2.9 \times 10^3$ M^{-1}) [11] 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. Both Na^+ and K^+ caused a shift to down field of H_6 protons and OCH_2Py protons while the H_3 protons shifted to up field [15]. This implies that only the H_3 protons move closer to the benzene ring upon the complaxation of Na^+ or K^+.

The presence of allosteric effect in 1,3-*alternate*-**3** was studied by a set of ^{1}H NMR titration experiments. First, 5 equiv. of $AgSO_3CF_3$ were added to the solution containing 1,3-*alternate*-**3**$\supset K^+$ and 1,3-*alternate*-**3**$\supset Na^+$, separately. The ^{1}H NMR spectrum of both complexes completely changed to that of $Ag^+\subset$1,3-*alternate*-**3** complex. These findings suggest the release of K^+ or Na^+ from the ester moieties and complexation with Ag^+ at the pyridyl moieties to form the $Ag^+\subset$1,3-*alternate*-**3** complex. The observed negative allosteric effect 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. On the contrary, the spectral pattern of the 1:1 $Ag^+\subset$1,3-*alternate*-**3** complex did not show any significant change upon addition of 5 equiv. of KSO_3CF_3 or $NaClO_4$. Only the original signals for 1:1

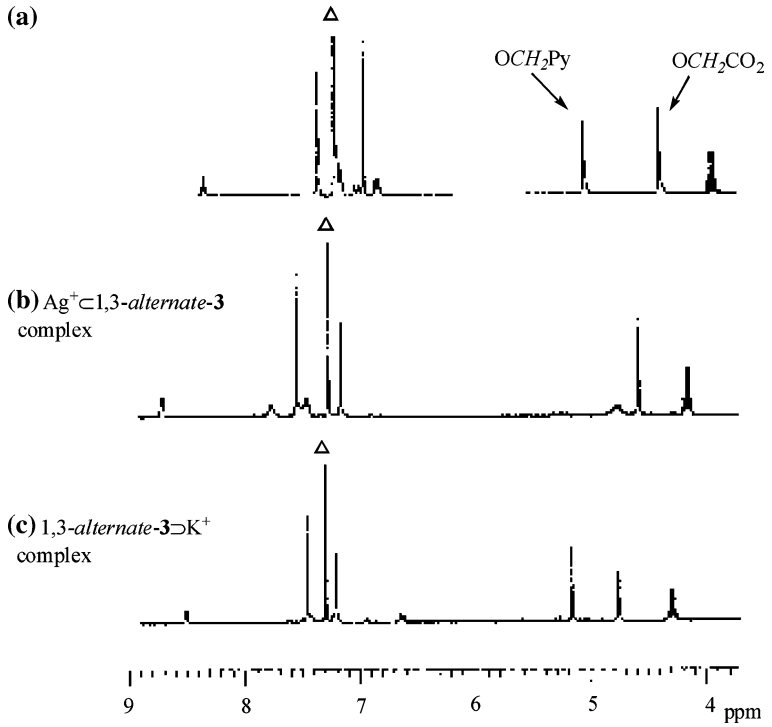


Figure 2. Partial ^{1}H NMR of 1,3-*alternate*-**3** (4×10^{-3} M) at 300 MHz in $CDCl_3$:CD_3CN 2:1 v/v. (a) Free ligand, (b) in the presence of 1 equiv. of $AgSO_3CF_3$, (c) in the presence of 1 equiv. of KSO_3CF_3. Δ denotes solvent signal.

complex remained. These results indicate that complexation of Ag^+ completely suppresses the recognition of K^+ or Na^+ derived from the ester moieties.

Conclusion

A novel ditopic receptor 1,3-*alternate*-**3** possessing two complexation sites: ester moieties and 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*-**3** with Na^+, K^+ and Ag^+ was observed even through the formation of the heterogeneous dinuclear complexes was expected. To the best of our knowledge the decomplexation of K^+ from the ester sites of 1:1 complex 1,3-*alternate*-**3**$\supset K^+$ to form the $Ag^+\subset$1,3-*alternate*-**3** complex by addition of $AgSO_3CF_3$ is the first example of negative allosteric effect in the thiacalix[4]arene family. These results give some insight into the molecular design of new synthetic receptors for use in metal controlled biomimetic systems.

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