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ORIGINAL ARTICLE

Synthesis and heteronuclear inclusion properties of a novel thiacalix[4]arene-based hard-soft receptor with 1,3-*alternate* conformation

Xin-long Ni · Hirotsugu Tomiyasu · Tomoe Shimizu · Carol Pérez-Casas · Zeng Xi · Takehiko Yamato

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Abstract A novel thiacalix[4]arene ditopic receptor with 1,3-*alternate* conformation and possessing two complexation sites for hard and soft cations, 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(*N,N*-diethylaminocarbonyl)methoxy]-26,28-bis[(pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene is prepared. Regioselective synthesis of *distal*-bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene is accomplished by a protection-deprotection method using benzyl groups as a protecting group. The deprotection of benzyl group was succeeded in the presence of solid superacid (Nafion-H) under refluxing benzene. Its complexation behavior is examined by ^{1}H-NMR titration experiments. The formation of 1:2 homo- and heteronuclear complexes demonstrates that the preorganization, subtle conformational changes and affinity have a pronounced effect on the complexation of the receptor.

Keywords Thiacalix[4]arene · *O*-alkylation · Conformation · Ionophores · Metal complexation · Hard-soft receptors

Introduction

Recently, thiacalix[4]arenes [1–3] have been used as potential platforms due to their novel features. It is well known that the conformation of the calix plays a very important role in the complexation process [4, 5]. In particular, the so-called calix[4]arene 1,3-*alternate* conformation, which has D_{2h}-symmetry, tube-shape can, be well adapted for the formation of 1:1 as well as 1:2 complexes owing to its symmetrical ditopic arrangement [6–8].

Papparlardo et al. [9] reported the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals [9–11].

We reported the synthesis, conformation studies and inclusion properties of tetrakis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes with *cone* and 1,2-a*lternate* conformation, which show strong Ag^+ affinity [12]. Furthermore, recently we reported similar studies of tetrakis[(*N,N*-diethylaminocarbonyl)methoxyl]tetrathiacalix[4]arene [13] with *cone* and 1,3-a*lternate* conformation, which show the ability to form 1:2 complexes. Di- or polytopic receptors are those constructed with two or more binding subunits within the same macrocyclic structure [14].

With this in mind we have designed the novel receptors with 1,3-*alternate* conformation, having two different sidearms and showing affinity not only toward alkali metal cations but also toward soft heavy metal cations. Thus, there is substantial interest in its synthesis and complexation behavior towards K^+ and Ag^+ ions. Multi-recognition of K^+ and Ag^+ owing to the presence of two amide moieties at one edge of the thiacalix[4]arene cavity and two 2-pyridylmethyl moieties at the other edge, is expected. Based on the fact that amide groups [15] show high affinity for Ag^+, a strong simultaneous and cooperative effect between the amide moiety and 2-pyridylmethyl groups during the binding with Ag^+ could be considered.

In this paper we report on the synthesis and inclusion properties of 1,3-*alternate*-5,11,17,23-tetra-*tert*-butyl-25,27-bis[(*N,N*-diethylaminocarbonyl)methoxy]-26,28-bis

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[(pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene from methoxyl]tetrathiacalix[4]arene with 2-(chloromethyl) pyridine.

Results and discussion

Synthesis

Attempted regioselective *O*-alkylation of hydroxy groups in calixarene **1** with *N,N*-diethylchloroacetamide to afford *distal*-bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene *distal*-**4** as following the reported procedure [15] failed. Although the desired bis-*O*-alkylation product *distal*-**4** was obtained along with the tetra-*O*-alkylation product, the isolation of *distal*-**4** in pure was quite difficult. On the other hand, recently, we have reported that regioselective synthesis of *distal*-di-*O*-alkoxythiacalix[4]arenes is accomplished by a protection-deprotection method using benzyl groups as a protecting group [16]. In fact, *O*-benzylation of tetrathiacalix[4]arene **1** carried out with 10 equiv. of benzyl bromide in the presence of Na_2CO_3 according to the reported procedure 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 *N,N*-diethylchloroacetamide in acetone in the presence of Cs_2CO_3 as base under reflux for 17 h yielded 1,3-*alternate*-**3** in 90% yield.

Attempted removal of the benzyl group in 1,3-*alternate*-**3** with Me_3SiBr [17–23] in $CHCl_3$ at room temperature for 3 h or hydrogenation in the presence of Pd–C [24, 25] at room temperature for 3 h to afford the desired bis[(*N,N*-diethylaminocarbonyl)methoxy] 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 [17–22]. It is possible that the sulfur atoms in the thiacalix[4]arene might deactivate the catalytic activity of Pd–C. 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 72%. The maximum yield was obtained in the presence of 5 equivalents of $AlCl_3$. The ring cleavage of the S–C bond in the thiacalixarene moiety as well as trans-*tert*-butylation was not observed under the conditions used. This result indicates that the protection-deprotection method is recommended as a useful strategy for the synthesis of *distal*-**4**.

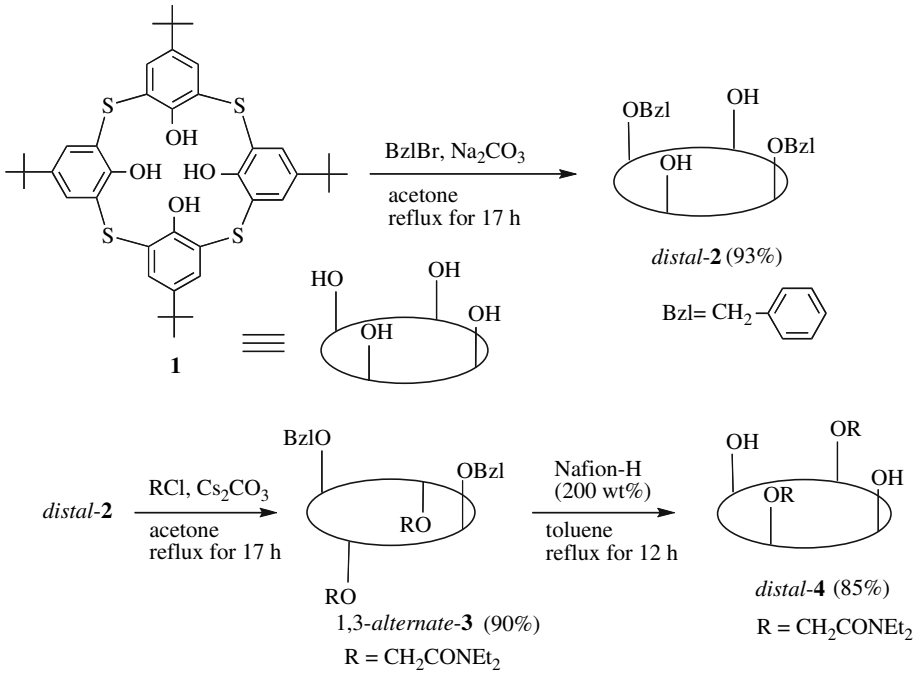
On the other hand, recently, we have found that the Nafion-H catalyst, a perfluorinated sulfonic acid resin [26, 27], is effective in a wide range of liquid and gas phase reactions, including electrophilic substitutions on aromatic nuclei, transalkylations, condensations and so on [28–33]. Debenzylation of 1,3-*alternate*-**3** in the presence of Nafion-H (100 wt%) as a catalyst, was carried out in boiling benzene for 24 h to afford the desired bis[(*N,N*-diethylaminocarbonyl)methoxy] derivative *distal*-**4** in 50% yield along with the recovery of the starting compound and diphenylmethane. Depending on the amount of Nafion-H and an acceptor for benzyl group, i.e. benzene or toluene, selective debenzylation was found to be possible. Thus, the maximum yield (85%) and the reduced reaction time to 12 h was achieved in the presence of 200 wt% equivalents of Nafion-H in the toluene as an acceptor for benzyl group (Scheme 1). The ring cleavage of the S–C bond in the thiacalixarene moiety as well as trans-*tert*-butylation was not also observed under the conditions used. The presently developed procedure provides excellent yield, easy isolation of the products, and ready regeneration of the catalyst without the loss of activity [26, 27].

The ^{1}H-NMR spectra of **3** show two singlets for the *tert*-butyl protons at δ 0.83 and δ 1.30 ppm, in which the former peak can be observed at a higher field due to the ring current effect arising from the two benzyl benzenes introduced. The singlet signals of the methylene protons (OCH_2Ph and OCH_2CONEt_2) in **3** were also observed at higher field (δ 4.70 and 4.95 ppm) than that for the methylene protons (OCH_2Ph) in *distal*-**2** (δ 5.49 ppm) due to the ring current effect arising from the two inverted calix benzene rings. These observations strongly suggest **3** adopts 1,3-alternate conformation [13].

The calixarenes show concentration-independent hydroxyl stretching bands in the 3,200 cm^{-1} region of the infrared spectrum and a signal at δ 9–10 ppm in the ^{1}H-NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes [4, 5]. The IR (KBr) spectrum of *distal*-**4** shows the absorption for the hydroxyl stretching vibration around 3363 cm^{-1}. The ^{1}H-NMR signal for hydroxyl group was observed at δ 8.54 ppm. Furthermore, the previously noted upfield shift for the methylene protons in the alkoxy groups in the ^{1}H-NMR spectra of 1,3-*alternate*-**3** has not been observed. Therefore, *distal*-bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene (*distal*-**4**) might adopt the *cone*-conformation due to the intramolecular hydrogen bonding between two hydroxy groups and alkoxy groups. Thus hydroxy groups and alkoxy groups of dialkoxytetrathiacalix[4]arenes have a tendency to orientate in the same direction and therefore favoured the adoption of the "cone" conformation.

Consequently, we have demonstrated for the first time that the regioselective synthesis of *distal*-bis[(*N,N*-diethylaminocarbonyl)methoxy]thiacalix[4]arene (*distal*-**4**) is accomplished by a protection-deprotection method using benzyl groups as a protecting group. Solid superacid (Nafion-H) was found to be a good catalyst for the present deprotection of benzyl group.

Scheme 1



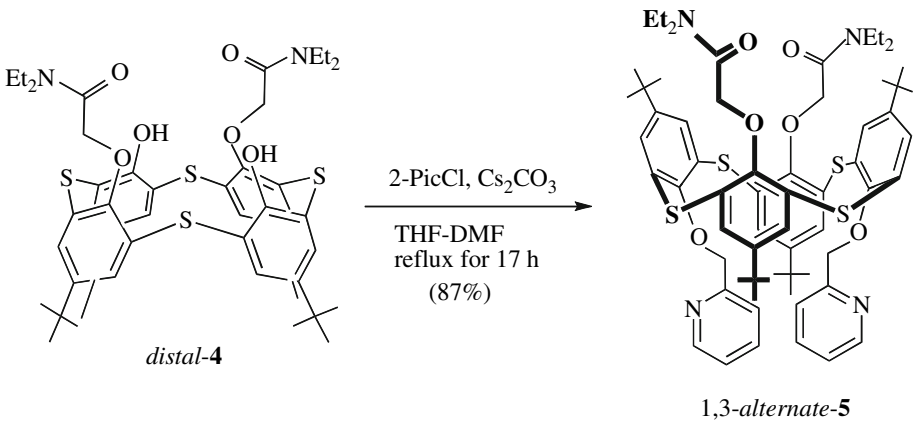
Compound **5** is obtained in 87% yield by the stereoselective *O*-alkylation of the amide *distal*-**4** with 2-(chloromethyl)pyridine in dry THF-DMF in the presence of Cs_2CO_3 (Scheme 2). Similar yield was obtained by *O*-alkylation in the presence of K_2CO_3. However, use of Na_2CO_3 as a base resulted in the recovery of the starting compound.

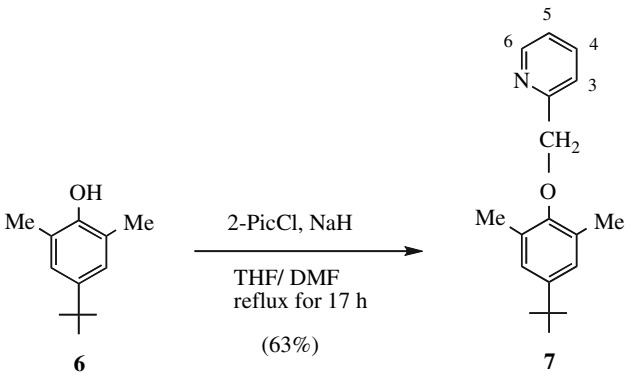
The ^{1}H-NMR spectrum of **5** shows two singlets for the *tert*-butyl protons at δ 0.83 and 1.30 ppm, in which the former peak can be observed at a higher field due to the ring current effect arising from the two pyridine rings introduced. Similarly, the OCH_2Py and OCH_2CO protons resonances appear at δ 5.15 and 4.65 ppm, respectively. These chemical shift values together with the examples reported in the literature [12, 13, 34–37] strongly suggest that the **5** adopts a "1,3-*alternate* conformation".

The magnitude of this shielding, calculated as the difference between pertinent 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 in 63% yield (Scheme 3).

Interestingly, the hetero aromatic protons of the pyridine rings of 1,3-*alternate*-**5** are exposed to the ring current shielding effect [38–41] operating in facing pyridine ring and the diaryl thiaether linkage, and resonate at higher fields with respect to those of pyridine protons of 1,3-*alternate*-**5** and reference compound **7**, increases significantly for the H_3 and H_4 protons. The remarkable shielding effects experienced by the H_4 (δ −0.36 ppm) and H_3 (δ −1.02 ppm) (Table 1) protons of the pyridine rings suggest that these protons are located much closer to the opposing pyridine ring than are the H_5 and H_6 protons and folded

Scheme 2





Scheme 3

Table 1 Chemical shift of pyridine protons in 1,3-*alternate*-**5** and reference **7**[a,b]

Compd.	Chemical shift, δ pm			
	H_6	H_5	H_4	H_3
7	8.58	7.20[c]	7.74[c]	7.74[c]
1,3-alternate-**5**	8.50	7.13	7.38[c]	6.72
$\Delta\delta$	−0.08	−0.07	−0.36	−1.02

[a] $\Delta\delta$ Values are the difference of the chemcial shift between 1,3-*alternate*-**5** and reference **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

into the π-cavity [12, 13] 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 inboth pyridine rings were orientated outwards with respect to the thiacalixarene cavity. The preoganization of 1,3-*alternate*-**5** might provide the possibility to act as ditopic receptor, Fig. 1.

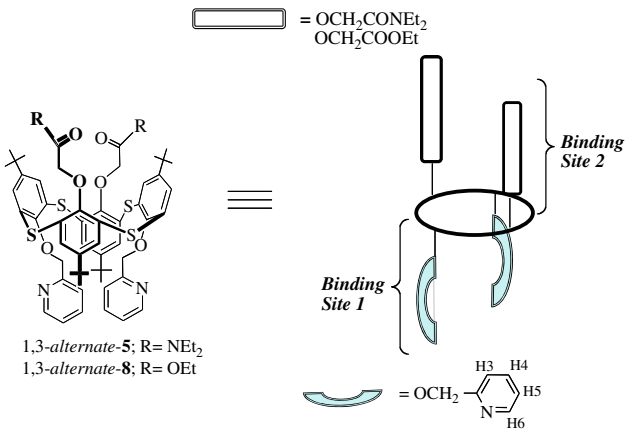


Fig. 1 Structures of ditopic receptors based on thiacalix[4]arenes

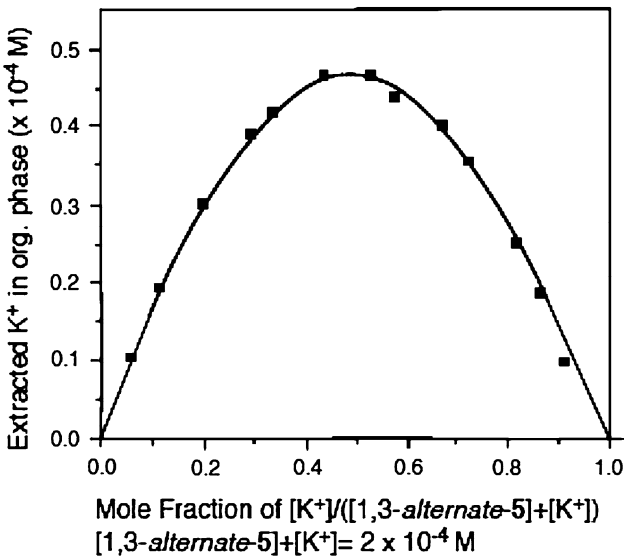


Fig. 2 Job Plot of the extraction of K^+ with 1,3-*alternate*-**5**

Stoichiometry

The stoichiometry of the 1,3-*alternate*-**5** complexes with Na^+, K^+ and Ag^+ is determined by a two phase-extraction experiment (H_2O/CH_2Cl_2), using the continuous variation method. The percent extractions for Na^+ and K^+ complex (Job plots) support the exclusive formation of the 1:1 complex (Fig. 2). In the case of Ag^+ the percent extraction reaches maximum at 0.7 mol when change the **5** and silver cation systematically, which indicates that 1,3-*alternate*-**5** forms 1:2 complex with Ag^+, fact also confirmed by ^{1}H-NMR (Fig. 3).

^{1}H-NMR titration experiments with KSO_3CF_3, $NaClO_4$ and $AgSO_3CF_3$ are carried out. ^{1}H-NMR titration

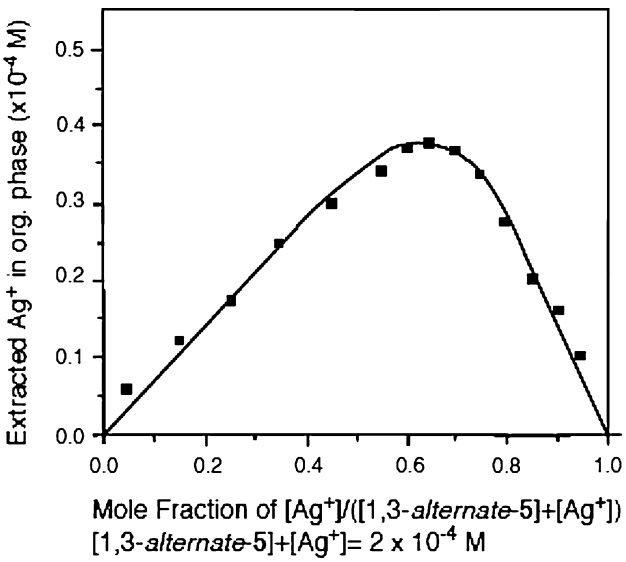


Fig. 3 Job Plot of the extraction of Ag^+ with 1,3-*alternate*-**5**

experiments of 1,3-*alternate*-**5** with KSO_3CF_3 two distinct signals for free 1,3-*alternate*-**5** and 1:1 1,3-*alternate*-**5** $\supset$ $\mathbf{K^+}$ complex are observed when up to 1 equiv. of KSO_3CF_3 is titrated, which implies ligand exchange is slow on the NMR time scale (Fig. 4). Only the 1:11,3-*alternate*-**5** $\supset$ $\mathbf{K^+}$ [Fig. 4c] are formed even with a large excess of KSO_3CF_3. The addition of an equiv. of KSO_3CF_3 to 1,3-*alternate*-**5** causes immediate complexation as demonstrated by the downfield shift of the both methylene protons (OCH_2CONEt_2, $\Delta\delta = +0.12$ ppm; OCH_2Py, $\Delta\delta = +0.09$ ppm), whereas the pyridine protons were scarcely affected (H_3, $\Delta\delta = -0.02$ ppm). Titration with $NaClO_4$ afforded similar results (OCH_2CONEt_2, $\Delta\delta = +0.10$ ppm; OCH_2Py, $\Delta\delta = +0.10$ ppm). The results confirm that the two amides compose an ionophoric cavity stronger for K^+ and Na^+ than the two 2-pyridine moieties [6, 34].

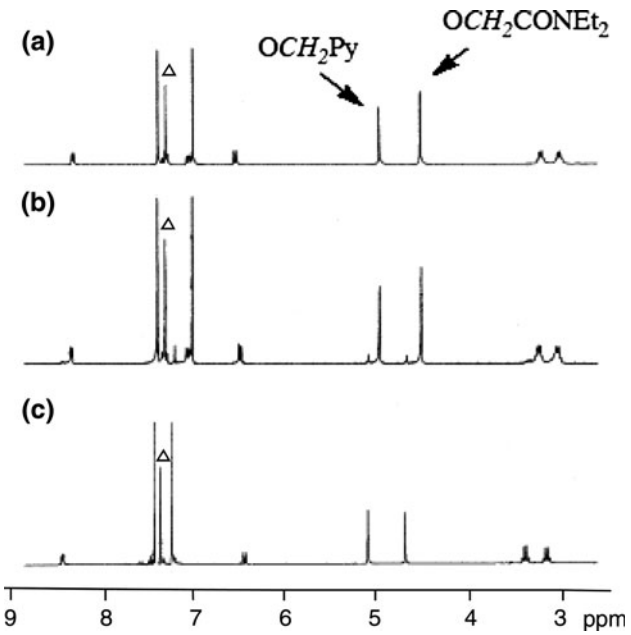


Fig. 4 Partial ^{1}H-NMR of 1,3-*alternate*-**5** (4×10^{-3} M) at 300 MHz in $CDCl_3$:CD_3CN 2:1 v/v. **a** Free ligand, **b** Addition of 1 equiv. of KSO_3CF_3 after 5 min. **c** after 3 h. Δ denotes solvent signal

Similarly, titration with 1 equiv. of $AgSO_3CF_3$ to 1,3-*alternate*-**5** also causes immediate complexation as demonstrated by the downfield shift of the amide protons (OCH_2CONEt_2, $\Delta\delta = +0.12$ ppm) and the OCH_2Py protons (OCH_2Py, $\Delta\delta = +0.10$ ppm, Table 2), whereas the *Py* protons were scarcely affected. These findings together with the slow ligand exchange process observed could suggest that Ag^+ is bound in the cavity delineated by the amide moiety (1:1 1,3-*alternate*-**5** $\supset$ $\mathbf{Ag^+}$ complex). Interestingly, additional peaks appeared in the 1,3-*alternate*-**5** $\supset$ $\mathbf{Ag^+}$ complex spectrum which prove the formation of the dinuclear complex $\mathbf{Ag^+}\subset$1,3-*alternate*-**5** $\supset$ $\mathbf{Ag^+}$. The OCH_2Py and H_3 protons appear as broad signals at δ 5.15 and 6.53 ppm, respectively.

We have already reported [13] that in the case of the corresponding ester derivative, 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(ethoxycarbonyl)methoxy]-26,28-bis[(pyridylmethyl)oxy]-2,8,14,20-tetrathiacalix[4]arene only the 1:1 complexe 1,3-*alternate*-**8** $\supset$ K^+ was formed even with a large excess of KSO_3CF_3. The results confirm that the two ester moieties of 1,3-*alternate*-**8** compose an ionophoric cavity stronger for K^+ and Na^+ than the two pyridyl moieties. On the other hand, titration with 1 equiv. of $AgSO_3CF_3$ to 1,3-*alternate*-**8** causes a dramatic upfield shift for the methylene protons of OCH_2Py in 1,3-*alternate*-**8** ($\Delta\delta = -0.48$ 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*-**8** complex). Spectral changes of the 1:1 $Ag^+\subset$1,3-*alternate*-**8** 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*-**8** complex. The exclusive formation of mononuclear complexes of 1,3-*alternate*-**8** with Na^+, K^+ and Ag^+ was observed even through the formation of the heterogeneous dinuclear complexes was expected.

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*-**5** $\Delta\delta$ (ppm)[b] in the presence of metal			1,3-*alternate*-**8** $\Delta\delta$ (ppm)[b] in the presence of metal		
	Na^+	K^+	Ag^+	Na^+	K^+	Ag^+
H_6	+0.05	+0.09	+0.04	+0.02	+0.04	+0.47
H_3	−0.25	−0.02	−0.26	−0.24	−0.26	+0.75
OCH_2Py	+0.10	+0.09	+0.10	+0.06	+0.08	−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

Complexation of 1,3-*alternate*-**5** with both alkali metals is very similar to that of 1,3-*alternate*-**8**, but the $\Delta\ \delta$ of H_3 with K^+ significantly decreases. Noticeable differences are observed in 1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ complex. The up field of the protons H_3 and the down field shift of the OCH_2Py are the most remarkable difference when compare with $\mathbf{Ag^+}$⊂1,3-*alternate*-**8** complex; thus, the hypothesis that Ag^+ complexes with the amide moieties is confirmed.

Allosteric studies

The presence of allosteric effect in 1,3-*alternate*-**5** is studied by three sets of ^{1}H-NMR titration. In the first set of experiments, 5 equiv. $AgSO_3CF_3$ were added into the solution containing 1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ and 1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$. The ^{1}H-NMR resonance significantly differed from that of the 1:1 1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ and 1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ complexes. Thus, new peaks are observed in 1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ and 1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ assignable to the 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ complex ($K_{ass} = 2.88 \times 10^3\ M^{-1}$) and $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ ($K_{ass} = 2.75 \times 10^3\ M^{-1}$). The association constant values for the complexation of Ag^+ by the pyridine moiety remain virtually unchanged which proves the existence of strong positive cooperativity. The ^{1}H-NMR spectra of 1,3-*alternate*-**5** complexes are repeatedly scanned at various time intervals (1 h to 5 h). After 3 h, only the signals for 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ and $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ complexes could be observed, indicating that the equilibrium was reached. Table 3 shows the essential chemical shift of pyridine protons of 1:2 complexes of 1,3-*alternate*-**5**.

The complexation of 1,3-*alternate*-**5** with the first ion (K^+, Na^+ or Ag^+), does not affect the induced-fit recognition of a second ion which implies a positive cooperativity between the two sides which favors the formation of the 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$, and $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ complexes. The chemical shift of OCH_2Py protons as well as that of H_3 and H_6 protons of pyridine ring shift to up field, being the most remarkable shift in those of $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ complex. These results indicated that the Ag^+ complexes through the metal–oxygen electrostatic interactions and metal-nitrogen interaction.

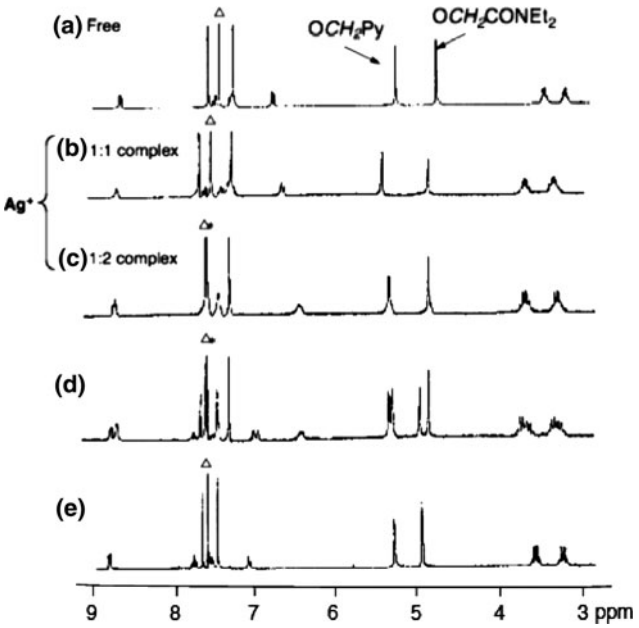


Fig. 5 Partial ^{1}H-NMR of 1,3-*alternate*-**5** (4×10^{-3} M) at 300 MHz in $CDCl_3$:CD_3CN 2:1 v/v. **a** Free ligand, **b** in the presence of 1 equiv. of $AgSO_3CF_3$, **c** in the presence of 5 equiv. of $AgSO_3CF_3$, **d** Addition of KSO_3CF_3 into **c** solution, **e** After 3 h Ag^+⊂1,3-*alternate*-**5** ⊃ K^+ complex, Δ denotes solvent signal

In contrast, the ^{1}H-NMR resonance upon titration of 1:1 1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ with K^+, once the equilibrium was reached, is very similar to that observed in the reverse titration, already described. Interestingly, the ^{1}H-NMR pattern of the 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ upon addition of an excess of K^+ and after a short time (30 min) turn out to be that of the 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$, Fig. 5e. The released of Ag^+ in $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ and the captured of K^+ instead ($\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$) can be ascribed to the preorganization of 1,3-*alternate*-**5**. The affinity of amide moiety to K^+ ($K_{ass} = 3.12 \times 10^4\ M^{-1}$) is higher than to Ag^+ ($K_{ass} = 2.08 \times 10^4\ M^{-1}$), which is uncommon, Scheme 4B; thus the formation of $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ is realized, presumably, through two steps Scheme 4A.

Finally, the addition of 5 equiv. of $NaClO_4$ into the solution of 1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ separately, does not cause any change in the spectra, only the signals for 1:1 complex are presented. Contrary to what is observed in the previous titration, the 1:2 complex of $\mathbf{Ag^+}$⊂1,3-*alternate*-

Table 3 ^{1}H-NMR chemical shift ($\Delta\delta$) of pyridine protons and methylene protons of OCH_2Py of 1:2 complexes of 1,3-*alternate*-**5**[a,c,d]

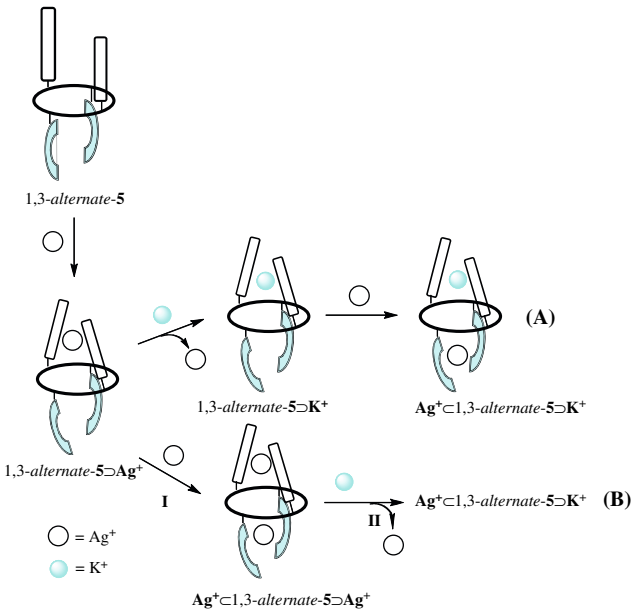
Complex	$\Delta\delta$ (ppm)[b] in of 1:2 complexes		
	OCH_2Py	H_3	H_6
$\mathbf{Ag^+}$⊂ 1,3-*alternate*-**5**⊃$\mathbf{Ag^+}$	−0.09	+0.07	+0.08
$\mathbf{Ag^+}$⊂ 1,3-*alternate*-**5**⊃$\mathbf{K^+}$	−0.13	−0.20	−0.25
$\mathbf{Ag^+}$⊂ 1,3-*alternate*-**5**⊃$\mathbf{Na^+}$	−0.07	+0.08	+0.06

[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



Scheme 4 Complexation process in 1,3-*alternate*-**5**: **a** Affinity effect. **b I**. Positive allosteric effect, **II**. Affinity effect

5 ⊃ $\mathbf{Na^+}$ is not formed. Comparison among the K_{ass} of Na^+ ($K_{ass} = 1.9 \times 10^4$ M^{-1}), K^+, and Ag^+ could explain why the $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ is formed only in one path: 1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$ + $\mathbf{Ag^+}$ → $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Na^+}$. The presence of Na^+ does not cause the realized of Ag^+ from the amide moiety, so the interchange of metals Ag^+→ Na^+ does not occur.

Conclusion

The compound 1,3-*alternate*-**5** presents high affinity for K^+ and Ag^+ ions due to the 1,3-*alternate* conformation, as expected, but showed a remarkable opposite cooperative behavior which is ascribed to the presence of allosteric effect which is strongly impacted by preorganization, complexation mode and functional affinity. But, most importantly, a cooperative behavior between the two edges of the thiacalix[4]arene cavity favors the 1:2 $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{Ag^+}$ and $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ complexes formation. The unexpected high affinity of the amide groups to K^+ ion is an important example of how the preorganization impacts the complexation behavior. To the best of our knowledge the formation of 1:2 complex $\mathbf{Ag^+}$⊂1,3-*alternate*-**5** ⊃ $\mathbf{K^+}$ is the first example of heterogeneous dinuclear complex in the thiacalix[4]arene family. These results give some insight into the molecular design of new synthetic receptors for use in metal controlled of biomimetic systems.

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 were measured for samples as KBr pellets in a Nippon Denshi JIR-AQ2OM spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. UV spectra were measured by Shimadzu 240 spectrophotometer. 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 according to the reported procedure [1].

Synthesis

*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 20 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** (230 mg, 93%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 25,27-bis(benzyloxy)-26,28-dihydroxy-5,11,17,23-tetra*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene, *distal*-**2** as colourless prisms. Mp 250–252 °C. IR *v* (KBr)/cm^{-1} 3383 (OH), 2962, 2867, 1478, 1448, 1437, 1363, 1260, 1244, 886 and 756. ^{1}H-NMR δ ($CDCl_3$) 0.79 (18H, s, *t*Bu), 1.34 (18H, s, *t*Bu), 5.49 (4H, s, OCH_2Ph), 6.96 (4H, s, Ar–*H*), 7.24–7.36 (6H, m, Ph-*H*), 7.61–7.64 (4H, m, Ph-*H*), 7.68 (4H, s, Ar–*H*) and 7.98 (2H, s, *OH*). MS *m/z* 901 (M^+). Anal. Calcd. For $C_{54}H_{60}O_4S_4$ (901.34) C, 71.97; H, 6.72. Found: C, 72.08; H, 6.86.

*O-Alkylation of distal-**2** with N,N-diethylchloroacetamide in the presence of Cs_2CO_3*

A mixture of *distal*-**2** (680 mg, 0.754 mmol) and Cs_2CO_3 (2.46 g, 7.54 mmol) in dry acetone (30 mL) was heated at

reflux for 1 h under N_2. A solution of *N*,*N*-diethylchloroacetamide (1.13 g, 7.54 mmol) 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 1,3-*alternate*-**3** (510 mg, 60%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 1,3-*alternate*-25,27-bis(benzyloxy)-26,28-bis[(*N*,*N*-diethylaminocarbonyl)methoxy]-5,11,17,23-tetra- *tert*-butyl-2,8,14,20-tetrathiacalix[4]arene, 1,3-*alternate*-**3** as a colourless prisms. Mp 255–256 °C. IR *v* (KBr)/cm^{-1} 1664 (C = O). ^{1}H-NMR δ ($CDCl_3$) 0.83 (18H, s, *t*Bu), 0.89–1.00 (6H, m, CH_2CH_3), 1.10–1.20 (6H, m, CH_2CH_3), 1.30 (18H, s, *t*Bu), 3.12–3.19 (4H, m, $CONCH_2$), 3.35–3.42 (4H, m, $CONCH_2$), 4.70 (4H, s, CH_2CON), 4.95 (4H, s, CH_2Ph), 7.18 (4H, s, Ar–*H*), 7.17–7.23 (10H, m, Ph-*H*) and 7.62 (4H, s, Ar–*H*). MS *m/z* 1127.5 (M^+). Anal. Calcd. For $C_{66}H_{82}N_2O_6S_4$ (1127.64) C, 70.3; H, 7.33; N, 2.48. Found: C, 70.25; H, 7.28; N, 2.44.

*$AlCl_3$ catalyzed debenzylation of 1,3-alternate-**3** in toluene*

A mixture of $AlCl_3$ (246 mg, 1.85 mmol) in dry CH_2Cl_2 (1.5 mL) was stirred at room temperature for 30 min and then 1,3-*alternate*-**3** (350 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 N HCl, extracted with CH_2Cl_2. The organic layer was separated, washed twice with brine, dried with $MgSO_4$ and evaporated to dryness to obtain 5,11,17,23-tetra-*tert*-butyl-25,27-bis-[(*N*,*N*-diethylaminocarbonyl)methoxy]-26,28-dihydroxy-2,8,14,20-tetrathiacalix[4]arene, *distal*-**4** (211 mg, 72%) as colorless solid. Recrystallization from $CHCl_3$–MeOH afforded *dital*-**4** as colorless prisms. Mp 259–264 °C. IR *v* (KBr)/cm^{-1} 3363, 1666; ^{1}H-NMR δ ($CDCl_3$) 0.82 (18H, s, *t*Bu), 1.24 (12H, t, $J = 7.4$ Hz, CH_2CH_3), 1.35 (18H, s, *t*Bu), 3.38 (4H, q, $J = 7.4$ Hz, CH_2CH_3), 3.55 (4H, q, $J = 7.4$ Hz, CH_2CH_3), 5.37 (4H, s, OCH_2CO), 6.88 (4H, s, Ar*H*), 7.63 (4H, s, Ar*H*), 8.54 (2H, s, *OH*). MS *m/z:* 947.5 (M^+). Anal. Calcd. for $C_{52}H_{70}O_6S_4N_2$ (947.39): C, 65.93; H, 7.45; N, 2.96. Found: C, 65.67; H, 7.41; N, 2.96.

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

A mixture of 1,3-*alternate*-**3** (200 mg, 0.177 mmol) and Nafion-H (400 mg) in toluene (6 mL) was heated at 100 °C for 12 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 *distal*-**4** (142 mg, 85%) as a colorless solid.

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

A mixture of amide *distal*-**4** (370 mg, 0.390 mmol), Cs_2CO_3 (1.26 g, 3.90 mmol) in dry THF (6 mL) was heated at reflux for 1 h under nitrogen. Then a solution of 2-(chloromethyl)pyridine [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (639 mg, 3.90 mmol) in DMF (8 mL) with a solution of triethylamine (0.53 mL, 3.90 mmol) in THF (8 mL) at room temperature]was added and the mixture heated for 17 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 condense under reduced pressure to give 1,3-*alternate*-**5** (250 mg, 57%) as a colorless solid. Recrystallization from $CHCl_3$–MeOH afforded 5,11,17,23-tetra-*tert*-butyl-25,27-bis[(*N*,*N*-diethylaminocarbonyl)methoxy]-26,28-bis[(pyridyl-methyl)oxy]-2,8,14,20-tetrathiacalix[4]arene, 1,3-*alternate*-**5** as colorless prisms. Mp 246–251 °C. IR *v* (KBr)/cm^{-1}: 1674 (C = O); ^{1}H-NMR δ ($CDCl_3$) 0.83 (18H, s, *t*Bu), 1.2 (12H, t, $J = 7.4$, CH_2CH_3), 1.30 (18H, s, *t*Bu), 3.08 (4H, q, $J = 7.4$ Hz, CH_2CH_3), 3.33 (4H, q, $J = 7.4$ Hz, CH_2CH_3), 4.65 (4H, s, OCH_2CO), 5.15 (4H, s, OCH_2Py), 6.72 (2H, d, $J = 7.3$ Hz, PyH_3), 7.11 (4H, s, Ar*H*), 7.13 (2H, m, PyH_5), 7.38 (2H, m, PyH_4), 7.49 (4H, s, Ar*H*) and 8.50 (2H, d, $J = 4.4$ Hz, PyH_6). MS *m/z:* 1129.4 (M^+). Anal. Calcd. for $C_{64}H_{80}O_6S_4N_4$ (1129,61): C, 68.05; H, 7.14; N, 4.96. Found: C, 68.04; H, 7.13; N, 4.92.

*Synthesis 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 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*$_2$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 $C_{18}H_{23}NO$ (269.39): 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-a*lternate*-**5**. 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-a*lternate*-**5** (5 mL, [1,3-a*lternate*-**5**] = 2×10^{-4} M in CH_2Cl_2). The molar ratios of the both 1,3-a*lternate*-**5** 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.

Determination of association constants

A solution of the receptor 1,3-*alternate*-**5** was prepared at a concentration typically on the order of 0.01 mol dm^{-3} in 1:1 (v/v) $CDCl_3$-CD_3CN. The initial ^{1}H-NMR spectrum was recorded, and aliquots of cation solution ($AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$ in the same solvent mixture) were added. The solution was made such that from 1 M equiv to 2 M equiv was added in 20 μL. The association constant values were calculated by the integral intensity of C*H*$_2$CON methylene protons in the complex and free host molecules.

Under similar procedure the association constants for 1,3-a*lternate*-**5** were calculated but with addition of aliquots of cation from 0–50 mM. After each addition and mixing, the change in shift of *CH*$_2$CON singlet 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 [42].

The accurate association constant of **Ag**$^+$⊂1,3-a*lternate*-**5** ⊃ **Ag**$^+$ could not be calculated due to the chemical shift scarcely change. The association constant K_{ass} for 1:2 complexes of 1,3-a*lternate*-**5** were calculated by non-linear fitting analysis of the observed chemical shift changes of O*CH*$_2$Py protons, maintaining the concentration of 1:1 complex constant (4.0 mM in $CDCl_3$-CD_3CN) and adding aliquots of cation ($AgSO_3CF_3$ and/or KSO_3CF_3) from 0–50 mM in the same solvent mixture.

^{1}H-NMR complexation experiments

To a $CDCl_3$ solution (4×10^{-3} M) of the receptor 1,3-a*lternate*-**5** in the NMR tube was added a CD_3CN solution (4×10^{-3} M) of $AgSO_3CF_3$, KSO_3CF_3 and $NaClO_4$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

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