Journal of Inclusion Phenomena and Macrocyclic Chemistry **42:** 51–60, 2002.

Synthesis, Conformational Studies and Inclusion Properties of Tetrakis[(2-pyridylmethyl)oxy]thiacalix[4]arenes

TAKEHIKO YAMATO*, FENGLEI ZHANG, KENJI KUMAMARU and HIDETO YAMAMOTO
Department of Applied Chemistry, Faculty of Science and Engineering, Saga University, Honjo-machi 1, Saga-shi, Saga 840-8502, Japan
E-mail: yamatot@cc.saga-u.ac.jp

(Received: 19 December 2000; in final form: 8 October 2001)

Key words: thiacalixarenes, *O*-alkylation, template effect, conformation, ionophores, metal complexation

Abstract

An attempted *O*-alkylation of the flexible macrocycle **1** with 2-(chloromethyl)pyridine in the presence of Cs_2CO_3 under THF reflux afforded a mixture of two conformers of tetra-*O*-alkylated product **4a** in a ratio of 91:9 (*cone*-**4a**:1,2-*alternate*-**4a**) in 70% yield, while other possible isomers were not observed. In the case of Na_2CO_3, there was no reaction product, only the starting compound **1**, whereas only monoalkylated compound **3** was obtained when using K_2CO_3 as the base. The distribution of cone conformer decreased in the case of *O*-alkylation of tetraol **1** with 4-(chloromethyl)pyridine or benzyl bromide in the presence of Cs_2CO_3 in comparison with that of *O*-alkylation with 2-(chloromethyl)pyridine, while the 1,2-alternate conformer increased in the same sequence. The larger Cs^+ might increase the contribution of the metal template effect, which can hold the 2-pyridylmethyl group(s) and the oxide group(s) on the same side of the tetrathiacalix[4]arene **1** through the cation-O^- and -N-interaction in the case of *O*-alkylation of tetraol **1** with 2-(chloromethyl)pyridine. Only when the template metal can hold the 2-pyridyl group(s) and the oxide group(s) on the same side of the tetrathiacalix[4]arene is the conformation immobilized to the cone. The template effect of the cesium cation plays an important role in this alkylation reaction. The structural characterization of these products is also discussed. The two-phase solvent extraction data indicated that tetrakis[(2-pyridylmethyl)oxy]thiacalix[4]arenes **4a** show strong Ag^+ affinity and a high Ag^+ selectivity was observed for *cone*-**4a**. A good Job plot proves 1:1 coordination of *cone*-**4a** with Ag^+ cation. ^{1}H-NMR titration of *cone*-**4a** with $AgSO_3CF_3$ also clearly demonstrates that a 1:1 complex is formed with retention of the original symmetry. In contrast, the 1,2-*alternate*-**4a** can form a 2:1 metal/thiacalix[4]arene complex and the two metal-binding sites display positive allostericity. The conformational changes of pyridine moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the thiacalixarene cavity were observed in the process of Ag^+ complexation.

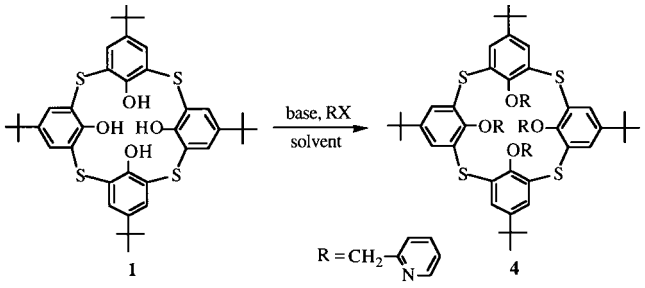
Introduction

Calixarenes, cyclic *p*-substituted phenol formaldehyde oligomers, are of current interest as versatile hosts and candidates for synthetic receptors and enzymes. Considerable efforts have been made on the modification to develop their potential; many "lower rim" and "upper rim" functionalized calixarenes have appeared in the literature [1]. Calixarene analogues containing elements other than carbon as bridge linkage are also of interest in this regard. The replacement of the carbon bridge with another element will have an effect on the conformational and complexation properties of the calixarenes by changing the mode of the circular intramolecular hydrogen bonding characteristic for the calixarenes.

Furthermore, some of the hetero atoms can serve as additional coordination sites with the aid of the lone electron pairs and undergo further modification easily. Recently, König *et al.* reported the silicon-bridged calix[4]arene [2]. Other kinds of calixarene analogues with hetero atoms were also reported, such as homoazacalix[n]arene with CH_2NRCH_2 as linkage [3], homooxacalix[n]arene with CH_2OCH_2 as linkage [4], and homothiacalixarene using CH_2SCH_2 as linkage [5]. All of these calixarene analogues have characteristics similar to those of calixarene. Moreover, with different linkages, they have the special properties brought by these linkage substituents, respectively.

The first synthesis of 5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene-25,26,27,28-tetraol was briefly reported by Sone *et al.* through acid catalyzed cyclization of an acyclic tetramer [6, 7]. Recently, a convenient and facile synthesis of thiacalix[4]arene in a satisfactory yield by simply heating *p*-*tert*-butylphenol with elemental sulfur in the presence of a base [8] was reported by Miyano and his coworkers. It has been found that thiacalix[4]arene has a very high ability to bind transition metal ions [9], which had been quite unexpected from the poor binding ability of calix[4]arene. Since 1998, many investigations were presented on the synthesis and properties of tetrathiacalix[4]arene with *O*-alkylation [10] and ester deriva-

* Author for correspondence.



Scheme 1.

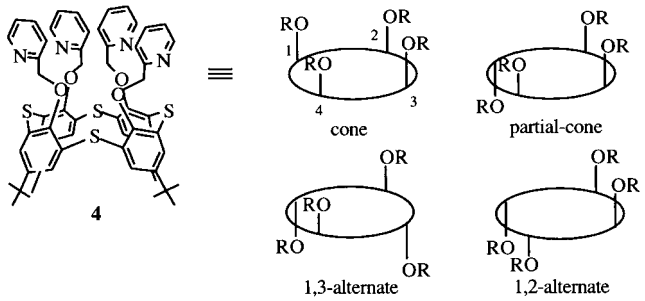


Figure 1. Possible conformers for *O*-tetrasubstitution of tetrathiacalix[4]arene **4**.

tives [11], as well as the oxidation of the bridge linkage S to SO and SO_2 [12].

In comparison with the structural characteristics of the calixarene family, thiacalix[4]arene is more attractive for the following reasons: (i) although both thiacalix[4]arene and calix[4]arene are composed of a 16-membered ring, the ring size of thiacalix[4]arene is larger than that of calix[4]arene because of the longer covalent bond length of C—S than C—C; (ii) ring linkages containing sulfurs may act cooperatively with phenolic oxygen upon the binding of metal ions, and (iii) because of the potential oxidation of S of the bridge linkage to SO and SO_2, it is possible to modify the linkage and change the properties of the cavity formed by the calix benzene rings, which is superior to any other calixarenes. Thus there is much more potential in investigating the derivatives of thiacalix[4]arene as artificial receptors or enzyme mimics.

On the other hand, Pappalardo *et al.* [13] reported on the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals. Recently, we have also reported the synthesis, conformational studies and inclusion properties of tris[(2-pyridylmethyl)oxy]homocalix[3]arenas [14], which show strong Ag^+ ion and *n*-butylammonium ion affinity. Thus, tetrathiacalix[4]arene derivatives bearing 2-picolyl groups on the phenolic oxygens are also assumed to selectively bind with soft metal ions, such as transition metal cations, Ag^+, or alkyl ammonium ions. In this paper, we describe the synthesis, structures, and metal ion complexation properties of tetrakis[(2-pyridylmethyl)oxy]tetrathiacalix[4]arenes with *cone*- and 1,2-*alternate*-conformation, which are assumed to have encapsuled ionophilic cavities.

Results and discussion

Although the first synthesis of tetrathiacalix[4]arene was reported by Sone and his coworkers via stepwise processes the analogues of *p-tert*-butylcalix[4]arene in which one to four of the methylene linkages were replaced by a sulfide bridge [6], the application was limited by the poor yield through cyclization of a linear tetramer [15] with sulfur dichloride. The systematic investigation of tetrathiacalix[4]arene was much appreciated to Miyano who introduced large scale synthesis through a convenient way of heating *p-tert*-butylphenol and sulfur element under basic condition [8].

Like other cyclic oligomer calixarenes, the strong intramolecular hydrogen bonding was also formed among the OH protons in thiacalix[4]arene **1**, which shows the OH stretching vibration at 3324 cm^{-1} in the IR spectrum and the signal for OH at 9.60 ppm in the ^1H NMR spectrum (in $CDCl_3$). Compared to that of the calix[4]arene, the intramolecular hydrogen bonding in **1** seems somewhat weaker, judged by the characteristic IR and NMR absorption. It is attributed to the large calix cavity contributed by C—S bonds, whereas the hydrogen bonding among hydroxyl protons in **1** seems somewhat stronger than that in homooxacalix[3]arene, because the latter has a 18-member ring and a much more flexible ethereal linkage [4]. Thus the reactivity of the hydroxyl protons in thiacalix[4]arene will be between that of calix[4]arene and hexahomotrioxacalix[3]arene [4].

It is known that tetrathiacalix[4]arene **1** exists in a cone conformation but the energy barrier of the ring inversion is somewhat lower than that of calix[4]arene due to the weaker intramolecular hydrogen bonding with the ring size slightly enlarged by replacing the methylene linkage with a sulfur bond. In calix[4]arenes there exist four possible conformational isomers: cone, partial-cone, 1,2-alternate and 1,3-alternate, but the previous functionalised calix[4]arene-based ionophores have exclusively dealt with the cone and partial-cone conformational isomers. In contrast, complete *O*-alkylation of the OH groups of tetrathiacalix[4]arene may produce all four possible isomers at most, each of which should be conformationally stable in the cone, 1,2-alternate, partial-cone, and 1,3-alternate conformations (Figure 1). *O*-alkylation of calixarenes have been applied on all kinds of calixarenes, and the template effect of metal cation was proven to play an important role on the conformational distribution of product [16]. In the present investigation, at first, several kinds of conditions were carried out on the *O*-alkylation of thiacalix[4]arene with 2-(chloromethyl)pyridine using NaH or alkali metal carbonates as the base. As molecular models suggest, the 2-pyridylmethyl group seems large enough to prevent the so-called oxygen-through-the-annulus rotation even in the case of thiacalix[4]arene. Therefore, complete *O*-alkylation of the OH groups of thiacalix[4]arene may produce all four possible isomers.

Tetrathiacalix[4]arene **1** [8] was *O*-alkylated with 2-(chloromethyl)pyridine **2a** in the presence of Cs_2CO_3 to yield a mixture of two conformers of tetra-*O*-alkylated

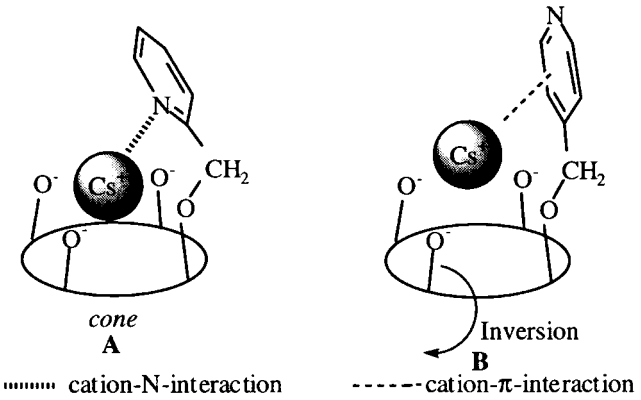
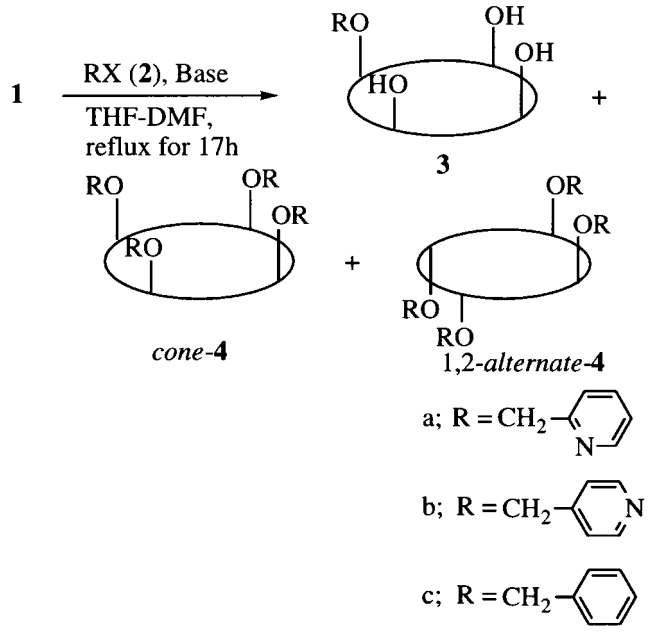


Figure 2. Ring inversion of *O*-alkylation intermediate of tetraol **1** and immobilization by metal template.



Scheme 2.

Table 1. O-Substitution reaction of thiacalix[4]arene **1** with 2-(chloromethyl)pyridine **2a**, 4-(chloromethyl)pyridine **2b**, and benzyl bromide **2c**

Run	RX	Base	Distribution (%)[a,b]			
			3	*Cone*-**4**	1,2-*Alternate*-**4**	Recovd. **1**
1	**2a**	NaH	0	0	0	100(92)
2	**2a**	Na_2CO_3	0	0	0	100(90)
3	**2a**	K_2CO_3	80(63)	0	0	20
4	**2a**	Cs_2CO_3	0	91(65)	9(5)	0
5	**2b**	Cs_2CO_3	0	81(73)	19(14)	0
6	**2c**	Cs_2CO_3	0	76(70)	24(20)	0

[a] Determined by ^{1}H NMR spectra.
[b] Isolated yields are shown in parentheses.

product **4a** in a ratio of 91:9 (*cone*-**4a**:1,2-*alternate*-**4a**) in 70% yield, while the other possible isomers were not observed. The degree of *O*-alkylation is governed by the nature of the alkali metal carbonates or NaH used as a base. Depending on the reaction conditions it was also found that the alkali metal cation can play an important role not only for the regioselectivity based on the template effect but also for the degree of *O*-alkylation. Table 1 shows the result of alkylation of thiacalix[4]arene with 2-(chloromethyl)pyridine using different bases. In the case of NaH and Na_2CO_3 under the same reaction conditions only the recovery of the starting compound **1** resulted, whereas, monoalkylated compound **3** was obtained when using potassium carbonate as the base. The exhaustive alkylation of thiacalix[4]arene was obtained in 70% yield when using the cesium carbonate as the base.

The larger Cs^+ might increase the contribution of the metal template effect, which can hold the 2-pyridylmethyl group(s) and the oxide group(s) on the same side of the tetrathiacalix[4]arene **1** through the cation-O^- and -N-interaction (Figure 2A).

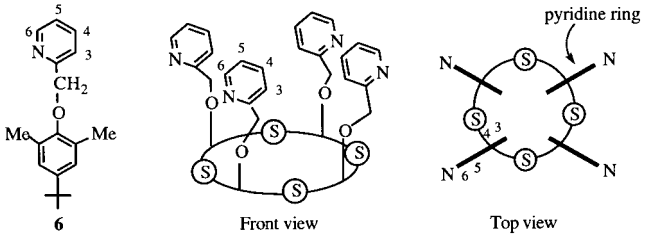
Furthermore, from Table 1 we can observe that the distribution of cone conformer decreased in the case of *O*-alkylation of tetraol **1** with 4-(chloromethyl)pyridine **2b** or benzyl bromide **2c** in the presence of Cs_2CO_3 in comparison with that of *O*-alkylation with 2-(chloromethyl)pyridine, while increasing the 1,2-alternate conformer in the same sequence. This finding suggests that the cation-π-interaction of the benzene ring or pyridine ring with Cs^+ does still exist in the process of *O*-alkylation. The distribution of cone conformer will be increased correspondingly in pyridylation. Whereas the position of the nitrogen atom in the pyridine ring will contribute a different template effect to the cation-π-interaction and affect the preferential formation of cone conformer. Due to the stronger cation-N-interaction in the 2-pyridine ring and less in the 4-pyridine ring, the more distribution of cone conformer in 2-pyridylation and the less in 4-pyridylation resulted.

Although the preferential formation of cone conformer of [(2-pyridylmethyl)oxy]calix[4]arene has been reported during *O*-alkylation of calix[4]arene with 2-(chloromethyl)pyridine using NaH as the base [13], it is not suitable for the *O*-alkylation of thiacalix[4]arene with 2-(chloromethyl)pyridine because of the large cavity and weaker intramolecular hydrogen bonding. Only when the template metal can hold the 2-pyridyl group(s) and the oxide groups attributed to the cation- π interaction [17] on the same side of the thiacalix[4]arene, is the conformation immobilized to the cone as shown in Figure 2. It has also been known that larger contribution of Cs^+ to the template effect than Na^+ can be expected [18]. Calix[4]arene has a suitable cavity for Na^+ and the strong intramolecular hydrogen bonding makes it prefer to the cone conformer in the presence of the stronger base NaH during the process of alkylation. But the ionic size of Na^+ is too small for thiacalix[4]arene so that no *O*-alkylated product was obtained in spite of using the condition of large excess sodium carbonate or even the stronger base NaH. Why did the *O*-alkylation of tetraol **1** in the presence of K_2CO_3 mainly afford monoalkylated product **3** instead of tetraalkylated product **4** in spite of the condition of large excess of K_2CO_3 and 2-(chloromethyl)pyridine? The larger potassium cation might be included strongly in a sufficient space in the alkylation process and result in slightly enlarging the cyclophane ring to destroy the intramolecular hydrogen bonds

among the hydroxyl groups of tetraol **1**. However, the three undissociated OH groups form intramolecular hydrogen bonds rather than the further dissociation to form the metal template intermediate different from the condition under the Cs_2CO_3 which led to the complete formation of four *O*-anions. Thus in the case of potassium carbonate the selective monoalkylation was observed due to the intramolecular hydrogen bonds between the hydroxyl groups and the (2-pyridylmethyl)oxy group. The much larger size of the cesium cation is suitable for the thiacalix[4]arene cavity and it contributes much more to the cation-π-interaction in the process of alkylation. Thus, the preferential formation of cone conformer was observed in the *O*-alkylation of thiacalix[4]arene with 2-(chloromethyl)pyridine in the presence of cesium carbonate.

In general, stereochemical assignments of calix[4]arenes with pendant pyridine groups followed unambiguously from distinctive ^{1}H NMR spectral patterns of the bridge methylene protons [19] and OC*H*$_2$Py protons, arising from the substitution pattern at the lower rim and from the conformation. For example, in tetra-*O*-alkylated calix[4]arenes, the ArC*H*$_2$ Ar show one pair of doublets in the cone conformer, two pairs of doublets in the partial-cone conformer, and one singlet in the 1,3-alternate conformer. Furthermore, the OC*H*$_2$ Py protons also display one singlet in the cone and 1,3-alternate conformers, while in the partial cone conformer, they give rise to two singlets and one pair of doublets (diastereotopic oxymethylenes) in the ratio 1:1:2. Unfortunately, because of the lack of bridge methylene protons, it seems difficult in judging the conformation of thiacalix[4]arene derivatives from the proton NMR patterns. While similar methods were also applicable to the conformational determination through the *tert*-butyl protons, OC*H*$_2$Py protons and aromatic protons, as well as the combination of these proton patterns. It was reported that both in the calix[4]arene and thiacalix[4]arene bearing ester functional groups, the chemical shift of the *tert*-butyl protons in the cone conformation were located at higher field than that in the 1,3-alternate conformation [11, 16a, 20a], whereas, in the calix[4]arene bearing pyridine groups, the chemical shift of *tert*-butyl protons in cone conformation was located at lower field than that in 1,3-alternate conformation [20b]. The cone conformation of [(2-pyridylmethyl)oxy]calix[4]arene *cone*-**4a** shows one singlet peak for the *tert*-butyl protons, the OC*H*$_2$Py proton and the aromatic protons at δ 0.85, 5.23 and 7.08 ppm, respectively. A pair of doublets peak at δ 4.75, 5.02 ppm for OC*H*$_2$Py with a 12.7 Hz coupling constant and one pair of doublets peak for aromatic protons at δ 7.42, 7.66 ppm with a 2.4 Hz coupling constant were also strongly in agreement with the 1,2-alternate conformation of [(2-pyridylmethyl)oxy]thiacalix[4]arene.

Similar to that of 2-pyridylation, only cone and 1,2-alternate conformers are obtained in the *O*-alkylation of thiacalix[4]arene **1** with 4-(chloromethyl)pyridine or benzyl bromide when using cesium carbonate as the base. Compared to that of [(2-pyridylmethyl)oxy]calix[4]arene, the same ^{1}H NMR patterns and similar chemical shift values of protons were observed in the cone and 1,2-alternate



6

Figure 3. Reference compound **6** and orientation of the pyridine N atoms in *cone*-**4a**.

Table 2. Chemical shift of pyridine protons in *cone*-**4a** and reference **6**[a,b]

Compound	Chemical shift, δ ppm			
	H_6	H_5	H_4	H_3
6	9.58	7.20[c]	7.74[c]	7.74[c]
Cone-**4a**	8.51	7.17	7.49[c]	6.68
$\Delta\delta$	−0.07	−0.03	−0.25	−1.06

[a] $\Delta\delta$ values are the difference of the chemical shift between *cone*-**4a** and reference **6** in $CDCl_3$ at 27 °C.
[b] A minus sign (−) denotes a shift to higher magnetic field.
[c] The midpoint values of the multiplet.

conformers of 4-pyridyl and benzyl thiacalix[4]arene derivatives. For example, in the case of 4-pyridylthiacalix[4]arene derivatives containing 4-pyridyl groups, there was a singlet peak for the *tert*-butyl protons, the OC*H*$_2$Py protons, the aromatic protons for *cone*-**4b** conformer at δ 0.87, 5.16, and 7.11 ppm, respectively. On the other hand, as for 1,2-*alternate*-**4b** conformer, singlet peaks for the *tert*-butyl protons, and OC*H*$_2$Py at δ 1.16, 4.67 ppm and one pair of doublets for the aromatic protons at δ 7.33, 7.76 ppm with a 2.4 Hz coupling constant, respectively.

The ^{1}H NMR spectrum pattern of *cone*-**4a** indicates a C_4-symmetrical structure. Interestingly, the hetero aromatic protons of the pyridine rings of *cone*-**4a** are exposed to the ring current shielding effect [21] operated by the opposing pyridine ring among the diaryl thiaether linkage, and resonate at higher fields with respect to those of the reference compound **6**, which was prepared by *O*-alkyaltion of 4-*tert*-butyl-2,6-dimethylphenol **5** with 2-(chloromethyl)pyridine in the presence of NaH. The magnitude of this shielding, computed as the difference between pertinent pyridine protons of *cone*-**4a** and reference compound **6**, increases significantly on the H_3 and H_4 protons (Table 2). The remarkable shielding effect experienced by the H_4 (−0.25 ppm) and H_3 (−1.06 ppm) protons of the pyridine suggest that these protons are located in a much closer environment toward the opposing pyridine ring than the H_5 and H_6 protons, due to the electron repulsion among the nitrogen atoms in the pyridine rings between the diaryl thiaether linkage. Thus, nitrogens in all of the pyridine rings were orientated outwards against the thiacalixarene cavity as shown in Figure 3.

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

by the *O*-alkylation with halomethyl *N*-heterocyclic reagents in the presence of the base has been recently introduced in order to obtain "universal" ligands for both hard and soft metal ions, which in principle should exhibit some advantages over amide and ester structures, because of a high stability in a wide pH range [22]. Recently, Pappalardo has reported on the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metal cations [13a]. A similar investigation was also carried out using hexahomotrioxacalix[3]arene and homocalix[3]arene as the platform [14]. Therefore, it is interesting to assess what kind of ionophoric cavity of tetrakis[(pyridylmethyl)oxy] derivatives **4** provide. At first, cation binding affinities of **4** were examined by liquid-liquid extraction.

Like other pyridyl calixarene derivatives, compounds **4a** and **4b** hardly extracted alkali metal cations in the present experimental system (less than 1%). *Cone*-**4a** and 1,2-*alternate*-**4a** show moderate affinities and selectivities to transition metal ions due to the nitrogen atom of the pyridine rings. Interestingly, the present developed ionophores **4a** exhibit not only superior extractabilities for Ag^+ (extraction %: 100% for *cone*-**4a** and 73% for 1,2-*alternate*-**4a**) but also high selectivities for Ag^+ than those of commercially available dibenzopyridino-18-crown-6 (extraction %: 65%) [23] or other Ag^+ ionophores. Ouchi and co-workers reported that a pair of polyether side chains attached at the same carbon atom of a crown ether can interact with various kinds of cations, but both side chains cannot work simultaneously with the crown ether ring, according to the consideration of bond-angles [24]. Therefore, our results mentioned above are considered due to the synergism of the thiacalixarene moiety and two or four lower-rim side chains having pyridyl groups play a significant role in the complexation of tetrakis[(2-pyridylmethyl)oxy] derivatives *cone*-**4a** and 1,2-*alternate*-**4a**. It was also found that the corresponding *cone*-tetrakis(benzyloxy) derivative *cone*-**4c** hardly extracted Ag^+ cation in these experimental conditions (extraction %: less than 1%). Interestingly, tetrakis[(4-pyridylmethyl)oxy] derivative *cone*-**4b** also showed moderate extractabilities for Ag^+ (extraction %: 52%). Due to the terminal position of the nitrogen atom in the pyridine ring, complexation between *cone*-**4b** and Ag^+ through intermolecular interaction might be proposed.

Usually, calixarenes form a 1:1 complex with guest molecules, but various types of complexation were observed depending on the calix ring size and introduced functional groups. A 1:2 complex of calix[8]arene to ammonium ions was reported by Shinkai [25]. The 1,3-alternate conformer of calix[4]arene derivatives can form also a 1:2 complex with metal cations [26]. While, the 2:1 complex of calixarenes with guest molecules was formed in some specially functionalized calixarenes [27]. Due to the existence of four metal-binding sites of pyridine moieties, there are several possibilities for the metal complexation mode of compound **2** with guest molecules and 1:1 or 1:2 metal complexation might be possible.

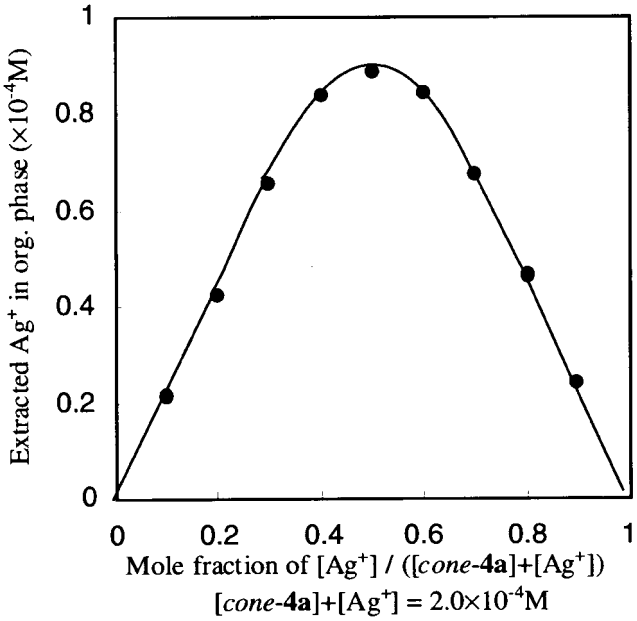


Figure 4. Job plots of the extractions of Ag^+ with host *cone*-**4a**.

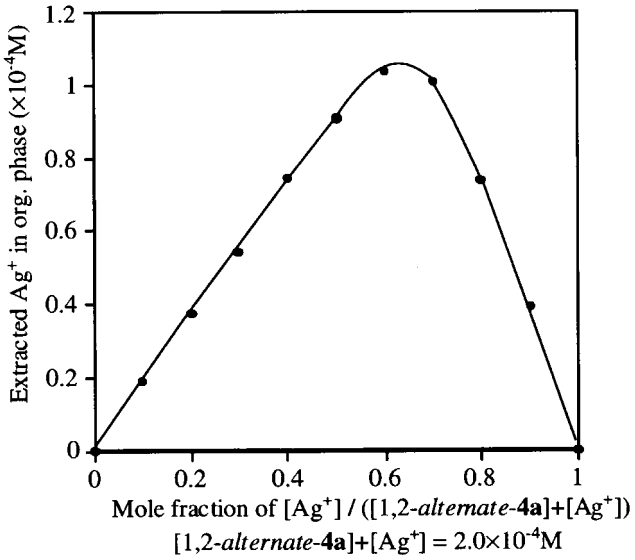


Figure 5. Job plots of the extractions of Ag^+ with host 1,2-*alternate*-**4a**.

As shown in Figure 4, the Job plots of compound *cone*-**4a** were carried out in the H_2O/CH_2Cl_2 phases. The percent extractions reach a maximum at 0.5 mole fraction. This fact clearly indicates that Ag^+ forms a 1:1 complex with *cone*-**4a**, while the percent extractions reach a maximum between 0.6 and 0.7 mole in the 1,2-*alternate*-**4a** and silver cation system, which indicates that 1,2-*alternate*-**4a** forms a 1:2 complex with Ag^+ (Figure 5).

Further investigation of the complex of compound **4a** with Ag^+ was carried out using ^1H NMR spectra titration. Upon complexation of *cone*-**4a** with Ag^+ in $CDCl_3$:CD_3OD (1:1, v/v), the chemical shift of all signals changed to lower magnetic fields. As shown in Figure 6 both protons in the pyridine rings were shifted to lower field by 0.15, 0.36, 0.46 and 0.20 ppm for H_6, H_5, H_4, and H_3 protons, respectively. It has been proven when calixarenes bearing pendant pyrid-

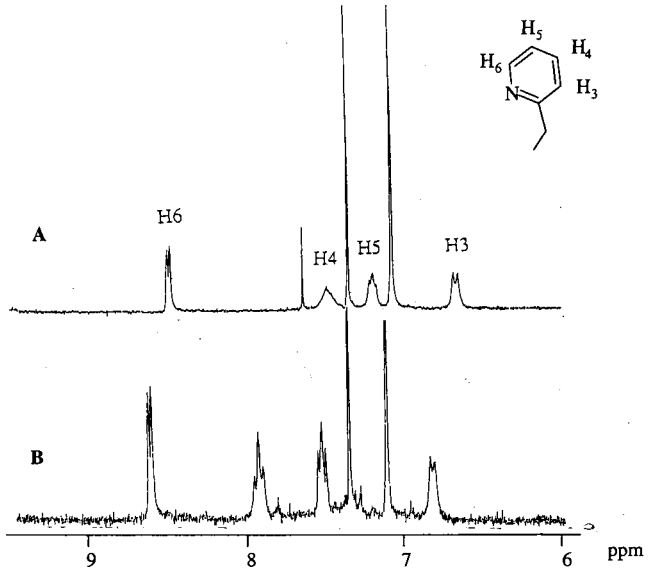


Figure 6. Partial ^{1}H NMR titration spectra of *cone*-**4a** (5×10^{-3} M, in $CDCl_3$:CD_3OD, 1:1, v/v). (A) In the absence of $AgSO_3CF_3$; (B) in the presence of $AgSO_3CF_3$ (3×10^{-2} M).

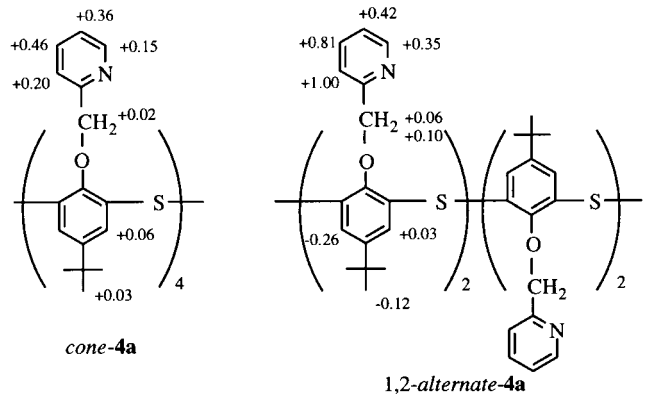


Figure 7. Chemical shift changes of *cone*-**4a** and 1,2-*alternate*-**4a** induced in the presence of $AgSO_3CF_3$; + denotes the downfield and − denotes the upfield shift.

ine rings complex with Ag^+, the Ag^+ was trapped into the cavity formed by nitrogen atoms in pyridine and phenolic oxygens, and affected the H_6, H_5 and H_4 protons in pyridine rings to shift to lower field [13, 14]. Similar phenomena were also observed in the complex of *cone*-**4a** with Ag^+. Due to the interaction of N—Ag^+, protons H_6, H_5 and H_4 in the pyridine rings shifted to lower fields, as well as the ArO*CH*$_2$Py protons attributed by the involvement of phenolic oxygens. Thus, *cone*-**4a** complexes Ag^+ through the metal-oxygen electrostatic interactions and metal-nitrogen interactions. Furthermore, as mentioned above, the corresponding *cone*-tetrakis(benzyloxy)thiacalix[4]arene derivative *cone*-**4c** exhibited no extraction behavior for Ag^+ at all, this strongly supports the contribution of the nitrogen of the pyridine ring to Ag^+ binding, but not the cation-π-interaction, demonstrated by the high Ag^+ affinity to 1,3-alternate calix[4]arene [28]. The down field shift of the *tert*-butyl and aromatic protons ($\Delta\delta$: less than 0.1 ppm) may be attributed to the conformation change of *cone*-**4a** after complexation.

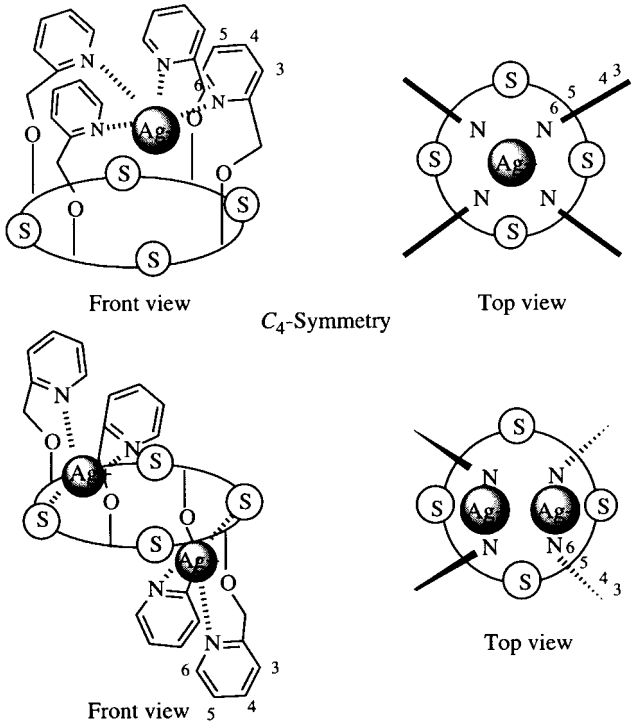


Figure 8. Binding mode of tetrakis[(2-pyridylmethyl)oxy]thiacalix[4]arene *cone*-**4a**, 1,2-*alternate*-**4a** and Ag^+.

In all the cases of complexes of calixarenes bearing 2-pyridine rings with Ag^+, the chemical shift of proton H_3 in the pyridine rings shifted to higher field after complexation [13, 14], whereas, the chemical shift of proton H_3 in the pyridine rings in *cone*-**4a** shifted to lower field after complexation (0.20 ppm), which might be deshielded due to the sulfur atom of the diaryl thiaether linkage. As shown in Figure 8, the nitrogen atom in the pyridine ring is located outward against the calix cavity in the free *cone*-**4a** because of the electron repulsion among nitrogens. After complexation, the nitrogen turned inward to the cavity to complex with Ag^+ and affect H_6, H_5 and H_4 shift to lower field. Proton H_3 might be affected by the sulfur atom in the diarylthiaether linkage and shifted to lower field, not like in other cases having the methylene linkage. Furthermore, the C_4-symmetrical conformation of *cone*-**4a** still remained after complexation.

With addition of an equivalent of Ag^+ to the solution of 1,2-*alternate*-**4a**, the peaks of 1,2-*alternate*-**4a** become considerably broadened, indicating that complexation with Ag^+ was occurring. This phenomenon still remained with 2 equivalents of Ag^+, but a clear complex pattern different from the free host was obtained with excess of guest molecule up to 6 equivalent moles and a long time was required for complex equilibrium. Similar to that in *cone*-**4a**, all the protons in the pyridine rings shifted to lower field, but the magnitudes of the shifts are much larger than those for *cone*-**4a** as shown in Figure 7. The pair of doublets peak of the aromatic protons in 1,2-*alternate*-**4a** approach each other and appear at the same value after complexation, namely, one doublet peak moves to higher field by 0.26 ppm while another doublet moves to lower field by 0.03 ppm. It has

been known that 1,2-*alternate*-**4a** complex with Ag^+ with 1:2 ratio from the Job plot of extraction (Figure 5). It seems the calix benzene ring in 1,2-*alternate*-**4a** stands up and gives the aromatic proton the same chemical environment after complexation with Ag^+.

After complexation of 4-pyridylthiacalix[4]arene derivative *cone*-**4b** and Ag^+, the chemical shift in the pyridine rings shifted to lower field by 0.05 ppm and 0.21 ppm, but the signals for the methylene protons ArO*CH*$_2$Py, the *tert*-butyl protons and the aromatic protons did not appear separately changed (less than 0.1 ppm). However, we observed a precipitate during NMR titration experiments. Although the reason for formation of the precipitate is not clear in the present stage, one might assume the intermolecular complexation between Ag^+ and 4-pyridyl groups. We also observed a precipitate in the process of the solvent extraction experiment to determine the complexation ratio by the Job plots and cannot get accurate data. Due to the terminal position of the nitrogen atom in the pyridine ring, it seems that the complex formed between *cone*-**4b** and Ag^+ through the intermolecular interaction involving two molecular hosts *cone*-**4b**. In the case of the complex of 1,2-*alternate*-**4b** with Ag^+, a large amount of precipitate from solution was observed after complexation and no signal in solution remained again, thus, the coordination of 1,2-*alternate*-**4b** with Ag^+ may form a polymer in which Ag^+ act as a "bead" between 4-pyridine in two host 1,2-*alternate*-**4b**, like the 1D polyrotaxane coordination polymer between Ag^+ and 4,4′-bipyridine derivatives [29].

Conclusion

As a C_4-symmetrical tetrapyridyl-substituted thiacalix[4]arene, compound *cone*-**4a** can bind Ag^+ ion and the complexation mode was elucidated clearly in this paper. The nitrogen atom in the pyridine ring turned from outward against the cavity to inside the cavity to interact with Ag^+ in *cone*-**4a**. After complexation of *cone*-**4a** with Ag^+, the original C_4-symmetry has been retained. In contrast, the 1,2-alternate conformer 1,2-*alternate*-**4a** can form a 2:1 metal/thiacalix[4]arene complex and the two metal-binding sites display positive allostericity. While to date the sulfur in the diarylthia ether linkage did not take part in the complexation procedure for alkali metal cations or Ag^+, variation of the alkylation conditions and reagents could lead to derivatives, which will serve as interesting building blocks for larger potential host molecules.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. ^{1}H NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a Shimadzu 240 spectrophoto- meter. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

Materials

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

Synthesis

Alkylation of **1** *with 2-(chloromethyl)pyridine* **2a** *in the presence of* Cs_2CO_3

A mixture of **1** (300 mg, 0.41 mmol) and Cs_2CO_3 (1.60 g, 4.92 mmol) in dry tetrahydrofuran (THF) (4 ml) was heated at reflux for 1 h under N_2. Then a solution of 2-(chloromethyl)pyridine **2a** (10.40 mmol) [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 ml) with a solution of triethylamine (0.68 mL, 4.92 mmol) in THF (8 ml) at room temperature] was added and the mixture heated at reflux for an additional 20 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 washed with methanol to give a mixture of tetra-*O*-alkylated products as a colorless precipitate. The precipitate was washed with ether (5 ml) to give 1,2-*alternate*-**4a** (22 mg, 5%) as a colorless solid. The ethereal filtrate was concentrated to give *cone*-**4a** (290 mg, 65%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 1,2-*alternate*-**4a** and *cone*-**4a** as a colorless prisms, respectively.

Cone-25,26,27,28-tetra[(2-pyridylmethyl)oxy]-5,11,17, 23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix-[4]arene, *cone*-**4a**. *cone*-**4a** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp 278–281 °C; ν_{max} (KBr)/cm^{-1}: 2962, 2868, 1476, 1432, 1265, 1086, 1026, 759; δ_H ($CDCl_3$): 0.85 (36 H, s, t-Bu), 5.23 (8 H, s, ArO*CH*$_2$), 6.68 (4 H, d, *J* 7.8, Py-*H*), 7.08 (8 H, s, Ar-*H*), 7.17 (4 H, t, *J* 2.4, Py-*H*), 7.48 (4H, m, Py-*H*), 8.51 (4 H, d, *J* 4.4, Py-*H*); *m/z*: 1084 (M^+). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.82; H, 6.31; N, 5.16. Found: C, 70.63; H, 6.15; N, 4.92.

The splitting pattern in ^{1}H NMR shows that the isolated compound is *cone*-**4a**.

1,2-*alternate*-25,26,27,28-tetra[(2-pyridylmethyl)oxy]-5, 11,17, 23-tetra-*tert*-butyl-2, 8, 14, 20-tetrathiacalix[4]arene,1,2-*alternate*-**4a**. 1,2-*alternate*-**4a** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp >300 °C; ν_{max} (KBr)/cm^{-1}: 2961, 2869, 1593, 1476, 1431, 1094, 778; δ_H ($CDCl_3$): 1.14 (36 H, s, t-Bu), 4.76 (4 H, d, *J* 12.7, ArO*CH*$_2$), 5.00 (4 H, d, *J* 12.7, ArO*CH*$_2$, 6.52 (4 H, d, *J* 7.8, Py-*H*), 7.10 (8 H, m, Py-*H*), 7.42 (4 H, d, *J* 2.4, Ar-*H*), 7.67 (4 H, d, *J* 2.4, Ar-*H*), 8.37 (4 H, d, *J* 4.4, Py-*H*); *m/z*:

1084 (M^+). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.82; H, 6.31; N, 5.16. Found: C, 70.71; H, 6.09; N, 5.05.

The splitting pattern in ^1H NMR shows that the isolated compound is 1,2-*alternate*-**4a**.

Alkylation of **1** *with 2-(chloromethyl)pyridine* **2a** *in the presence of* K_2CO_3

A mixture of **1** (300 mg, 0.41 mmol) and K_2CO_3 (680 mg, 4.92 mmol) in dry tetrahydrofuran (THF) (4 ml) was heated at reflux for 1 h under N_2. Then a solution of 2-(chloromethyl)pyridine **2a** (10.4 mmol) [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (807 mg, 4.92 mmol) in DMF (8 ml) with a solution of triethylamine (0.68 ml, 4.92 mmol) in THF (8 ml) at room temperature] was added and the mixture heated at reflux for an additional 20 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 washed with methanol to give a mixture of mono-*O*-benzylated product and the starting compound **1** as a colorless precipitate. The precipitate was washed with ether (5 ml) to give mono-*O*-alkylated product **3** (280 mg, 63%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave **3** as a colorless prisms.

5, 11, 17, 23-Tetra-*tert*-butyl-26, 27, 28-trihydroxy-25-[(2-pyridylmethyl)oxy]-2, 8, 14, 20-tetrathiacalix[4]arene, **3**. **3** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp 283–285 °C; ν_{max} (KBr)/cm^{-1}: 3373, 3313, 2962, 2868, 1476, 1432, 1265, 1086, 1026, 759; δ_H ($CDCl_3$): 1.07 (9 H, s, t-Bu), 1.20 (18 H, s, t-Bu), 1.21 (9 H, s, t-Bu), 5.55 (2 H, s, ArO*CH*$_2$, 7.25 (1 H, s, *OH*), 7.33–7.37 (1 H, t, *J* 2.4, Py-*H*), 7.45 (2 H, s, *OH*), 7.56 (2 H, d, *J* 2.4, Ar-*H*), 7.59 (4 H, s, Ar-*H*), 7.61 (2 H, d, *J* 2.4, Ar-*H*), 7.85 (1 H, d, *J* 2.4, Py-*H*), 7.97 (1 H, d, *J* 2.4, Py-*H*), 8.65 (1 H, d, J 4.4, Py-*H*); *m/z*: 811 (M^+). Anal. calcd. for $C_{46}H_{53}O_4NS_4$ (812.18): C, 68.03; H, 6.58; N, 1.72. Found: C, 68.24; H, 6.41; N, 1.86.

Alkylation of **1** *with 4-(chloromethyl)pyridine* **2b** *in the presence of* Cs_2CO_3

A mixture of **1** (300 mg, 0.41 mmol) and Cs_2CO_3 (1600 mg, 4.92 mmol) in dry tetrahydrofuran (THF) (4 ml) was heated at reflux for 1 h under N_2. Then a solution of 4-(chloromethyl)pyridine **2b** (10.4 mmol) [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 at reflux for an additional 20 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 washed with methanol to give a mixture of tetra-*O*-alkylated products as a colorless precipitate. The precipitate was washed with ether (5 ml) to give 1,2-*alternate*-**4b** (62 mg, 14%) as a colorless solid. The ethereal filtrate was concentrated to give *cone*-**4b** (325 mg, 73%) as a colorless solid. Recrystallization from MeOH:$CHCl_3$ (3:1) gave 1,2-*alternate*-**4b** and *cone*-**4b** as a colorless prisms, respectively.

Cone-25, 26, 27, 28-tetra[(4-pyridylmethyl)oxy]-5, 11, 17, 23-tetra-*tert*-butyl-2, 8, 14, 20-tetrathiacalix[4]arene, *cone*-**4b**. *Cone*-**4b** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp 285–287 °C; ν_{max} (KBr)/cm^{-1}: 2963, 2872, 1605, 1437, 1413, 1379, 1021, 794; δ_H ($CDCl_3$): 0.87 (36 H, s, t-Bu), 5.16 (8 H, s, ArO*CH*$_2$), 6.95 (8 H, d, *J* 5.9, Py-*H*), 7.11 (8 H, s, Ar-*H*), 8.42 (8 H, d, *J* 5.9, Py-*H*); *m/z*: 1084 (M^+). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.82; H, 6.31; N, 5.16. Found: C, 70.56; H, 6.46; N, 4.94.

The splitting pattern in ^1H NMR shows that the isolated compound is *cone*-**4b**.

1, 2-*Alternate*-25, 26, 27, 28-Tetra[(4-pyridylmethyl)-oxy]-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]-arene, 1,2-*alternate*-**4b**. 1,2-*alternate*-**4b** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp >300 °C; ν_{max} (KBr)/cm^{-1}: 2963, 2870, 1605, 1473, 1456, 1436, 1413, 1270, 804, 797; δ_H ($CDCl_3$): 1.16 (36 H, s, t-Bu), 4.67 (8 H, s, ArO*CH*$_2$), 6.52 (8 H, d, *J* 5.9, Py-*H*), 7.33 (4 H, d, *J* 2.4, Ar-*H*), 7.76 (4 H, d, *J* 2.4, Ar-*H*), 8.11 (8 H, d, *J* 5.9, Py-*H*); *m/z*: 1084 (M^+). Anal. calcd. for $C_{64}H_{68}O_4N_4S_4$ (1085.51): C, 70.82; H, 6.31; N, 5.16. Found: C, 70.97; H, 6.42; N, 4.88.

The splitting pattern in ^1H NMR shows that the isolated compound is 1,2-*alternate*-**4b**.

Benzylation of **1** *with benzyl bromide* **2c** *in the presence of* Cs_2CO_3

A mixture of **1** (200 mg, 0.28 mmol) and Cs_2CO_3 (1820 mg, 5.60 mmol) in acetone (18 ml) was heated at reflux for 1 h. Then benzyl bromide **2c** (0.31 ml, 2.8 mmol) was 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), 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 a mixture of tetra-*O*-benzylated products as a colorless precipitate (290 mg). The precipitate was washed with ether to give *cone*-**4c** (212 mg, 70%) as a colorless solid. The ethereal filtrate was concentrated to give 1,2-*alternate*-**4c** (61 mg, 20%) as a colorless solid. Recrystallization from methanol:$CHCl_3$ (3:1) gave *cone*-**4c** and 1,2-*alternate*-**4c** as a colorless prisms, respectively.

Cone-25, 26, 27, 28-tetrabenzyloxy-5, 11, 17, 23-tetra-*tert*-butyl-2, 8, 14, 20-tetrathiacalix[4]arene, *cone*-**4c**. *Cone*-**4c** was obtained as colorless prisms [MeOH:$CHCl_2$ (3:1)]; mp 239-241 °C; ν_{max} (KBr)/cm^{-1}: 2962, 2870, 1771, 1455, 1435, 1264, 966, 877; δ_H ($CDCl_3$): 0.84 (36 H, s, t-Bu), 5.07 (8 H, s, OCH_2), 6.86–7.67 (20 H, m, Ph-*H*), 7.14 (8 H, s, Ar-*H*); *m/z*: 1080 (M^+). Anal. calcd. for $C_{68}H_{72}O_4S_4$ (1081.57): C, 75.52; H, 6.71. Found: C, 75.73; H, 6.66.

The splitting pattern in ^{1}H NMR shows that the isolated compound is *cone*-**4c**.

1,2-*Alternate*-25,26,27,28-Tetrabenzyloxy-5,11,17,23-tetra-*tert*-butyl-2,8,14,20-tetrathiacalix[4]arene, 1,2-*alternate*-**4c**. 1,2-*alternate*-**4c** was obtained as colorless prisms [MeOH:$CHCl_3$ (3:1)]; mp 283-285 °C; ν_{max} (KBr)/cm^{-1}: 2962, 2868, 1576, 1435, 1248, 1019, 884; δ_H ($CDCl_3$): 1.13 (36 H, s, t-Bu), 4.49 (4 H, d, *J* 11.7, ArO*CH*$_2$), 4.69 (4 H, d, *J* 11.7, ArO*CH*$_2$), 6.57 (8 H, d, J 7.3, Ph-*H*), 6.93 (8 H, dd, *J* 7.3 and 7.3, Ph-*H*), 7.05 (4 H, t, *J* 7.3, Ph-*H*), 7.31 (4 H, d, *J* 2.4, Ar-*H*), 7.67 (4 H, d, *J* 2.4, Ar-*H*); *m/z*: 1080 (M^+). Anal. calcd. for $C_{68}H_{72}O_4S_4$ (1081.57): C, 75.52; H, 6.71. Found: C, 75.69; H, 6.78.

The splitting pattern in ^{1}H NMR shows that the isolated compound is 1,2-*alternate*-**4c**.

Preparation of
4-tert-*butyl-2,6-dimethyl[(2-pyridylmethyl)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 (2.02 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 **6** (380 mg, 63%) as a colorless oil; ν_{max} (KBr)/cm^{-1}: 2963, 2870, 1605, 1473, 1456, 1436, 1413, 1270, 804, 797; δ_H ($CDCl_3$): 1.30 (9 H, s), 2.31 (6 H, s), 4.95 (2 H, s), 7.05 (2 H, s), 7.20 (1 H, m, H_5), 7.74 (2 H, m, H_3 and H_4), 8.58 (1 H, dd, *J* 0.9,4.9, H_6); *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.

Picrate extraction measurements

Metal picrates (2.5×10^{-4} M) were prepared *in situ* by dissolving the metal hydroxide (0.01 mol) in 2.5×10^{-4} M picric acid (100 ml); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between water (5 ml, [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 ml, [ionophore] = 2.5×10^{-4} M). The two-phase mixture was shaken in a stoppered flask for 2 h at 25 °C. We confirmed that this period is sufficient to attain the distribution equilibrium. This was repeated 3 times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen [30].

^{1}H NMR complexation experiment

To a $CDCl_3$ solution (5×10^{-3} M) of *cone*-**4a** in the NMR tube was added a [D_4]methanol solution (3×10^{-2} M) of $AgSO_3CF_3$. The spectrum was registered after addition and the temperature of NMR probe kept constant at 27 °C.

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