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Synthesis, Conformations and Inclusion Properties of Hexahomotrioxacalix[3]arene Triamide Derivatives having Hydrogen-bonding Groups

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Abstract

The lower rim functionalized hexahomotrioxacalix[3]arene triamide derivatives **4a** and **4b** were synthesized from triol **1** by a stepwise reaction. Extraction data for alkali metal ions, transition metal ions, and alkyl ammonium ions from water into dichloromethane are discussed. Due to the strong intramolecular hydrogen bonding between the neighboring NH and CO groups, their affinities to metal cations were weakened. *cone*-**4a** shows a single selectivity to *n*-$BuNH_3^+$ while *partial-cone*-**4a** almost has no affinity to cations. The anion complexation of *cone*-**4a** was studied by ^{1}H NMR titration experiments. *cone*-**4a** binds halides through the intermolecular hydrogen bonding among the NH hydrogens of amide in a 1 : 1 fashion in $CDCl_3$. The association constants calculated from these changes in chemical shifts of the amide protons are $K_a = 8520\ M^{-1}$ for Cl^- and $K_a = 1720\ M^{-1}$ for Br^-. *cone*-**4a** shows a preference for Cl^- complexation over Br^- complexation. In contrast, *cone*-**4b** has good selectivity and affinity to Ag^+ cation. A good Job plot proves 1:1 coordination of *cone*-**4b** with Ag^+ cation. The complexation mode of *cone*-**4a** with *n*-$BuNH_3Cl$ and *cone*-**4b** with $AgSO_3CF_3$ were also demonstrated by ^{1}H NMR titration in $CDCl_3$.

Introduction

Calixarenes and related macrocycles have received considerable attention for their host–guest chemistry as ionophoric receptors [1–4] and potential enzyme mimics in biology [5]. Chemical modification of calixarene represents a simple though effective and versatile way of producing receptors with highly selective cation binding properties [6–10]. When larger alkyl groups were introduced onto the phenolic oxygens of calixarene, which cannot pass each other by oxygen-through-the-annulus rotation, there exist four possible conformational isomers in calix[4]arene (i.e., cone, partial-cone, 1,2-alternate and 1,3-alternate) [11] and five conformational isomers for [3.1.3.1]metacyclophane adding 1,4-alternate due to the propane bridge [12]. However, there are only two possible conformers in homotrioxacalix[3]arene (i.e., cone and partial-cone), because of the three substituents on the phenolic oxygen positions [13–15].

Recently, Shinkai and co-workers have reported the complexation of alkali metals to homotrioxacalix[3]arene derivatives with alkylated phenolic oxygens [14, 15]. Homotrioxacalix[3]arene derivatives with C_3 symmetry can selectively bind ammonium ions which play important roles in both chemistry and biology [14–17]. Thus, Shinkai *et al*. reported the construction of C_3 symmmetry pyrene functionalized hexahomotrioxacalix[3]arenes, which selectively recognize primary ammonium ions [14b].

On the other hand, hydrogen bonding plays an important role in the self-assembly of molecular recognition and has aroused investigation in calixarene systems. Shinkai *et al*. reported that an intermolecular hydrogen-bonded duplex was formed through the interaction between a calix[4]arene with four carboxyl groups and a calix[4]arene with stilbazole moieties [18]. Arduini *et al*. also described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acid [19]. The intramolecular hydrogen-bonding was also formed among opposing urea groups, which can bind anionic species, in calix[4]arene [20]. Thus, the design of new ditopic ligands [21] for the simultaneous complexation of anionic and cationic guest species is a new exciting area of coordination chemistry of significant relevance to the selective extraction and/or transportation of metal salts across lipophilic membranes. Rare examples of receptors containing appropriate covalently linked binding sites for anions and cations include Lewis-acidic boron [22], uranyl [23] or polyammonium [24] centers combined with crown ether moieties and crown ether or urea functionalized calix[4]arene ionophores [25] which

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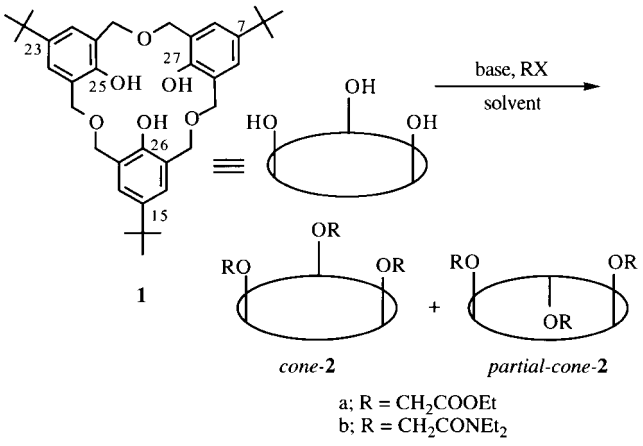
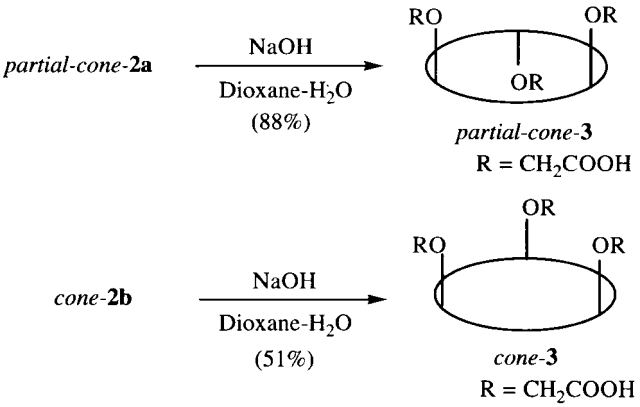


Scheme 1.



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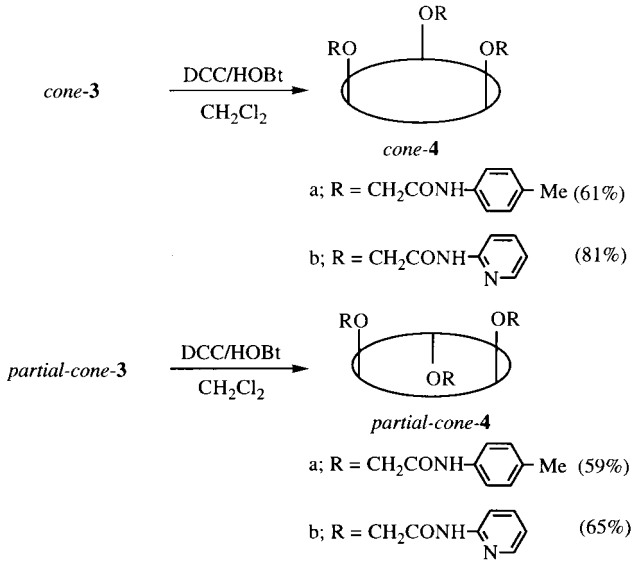


Scheme 3.

are capable of solubilizing alkali metal salts into organic media.

Incorporating these two types of recognition sites by introduction of three amide groups on the phenolic oxygens of homotrioxacalix[3]arene will create potential heteroditopic receptors capable of binding cations and anions, especially ammonium ions and halides. On the other hand, we have reported the synthesis, conformational studies and inclusion properties of tris[(2-pyridylmethyl)oxy]- hexahomotrioxacalix[3]arenes derived from hexahomotrioxacalix[3]arene [26], which show strong Ag^+ ion affinity. Therefore, 2-pyridylamide derivatives having hydrogen-bonding groups might show interesting complexation behaviour for Ag^+ as well as ammonium ions.

In the present paper, we describe the synthesis, conformations, and metal and ammonium ion complexation properties of the cone toluidinylamide derivatives as well as 2-pyridylamide derivatives having hydrogen-bonding groups derived from hexahomotrioxacalix[3]arene tricarboxylic acid, which are supposed to have C_3 symmetric ionophoric cavities.

Results and discussion

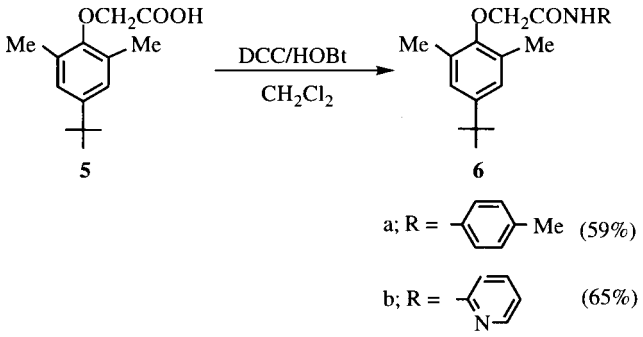
Partial-cone hexahomotrioxacalix[3]arene triethyl ester **2a** was prepared by alkylation of hexahomotrioxacalix[3]arene **1** [27] with ethyl bromoacetate in the presence of cesium carbonate as a base in refluxing acetone in 90% yield [14].

Hydrolysis of *partial-cone*-**2a** in a mixture of dioxane and water using NaOH as a base at room temperature afforded the corresponding *partial-cone*-hexahomotrioxacalix[3]arene tricarboxylic acid **3** in 88% yield. Although it is easy to get the cone triacid **3** by the same reaction from triethyl ester *cone*-**2a**, the yield is lower than 20% to get the cone conformation of triethyl ester **2a** in the alkylation process.

On the other hand, cone amide derivative **2b** was obtained almost quantitatively through the *O*-alkylation of triol **1** with *N*, *N*-diethyl chloroacetamide in the presence of NaH in refluxing THF [15]. Hydrolysis of cone amide **2b** in a refluxing mixture of dioxane and water afforded cone triacid **3** in 51% yield in the presence of NaOH. Although this method required a much longer time and elevated reaction temperature compared to that based on the ester derivative, it was more efficient and effective and produced enough amount of cone triacid **3**. ^{1}H-NMR spectra of **3** showed a single peak at δ 1.12 ppm for the *tert*-butyl protons in *cone*-**3** and two single peaks at δ 1.29 ppm and 1.33 ppm (intensity 2 : 1) for the *tert*-butyl protons in *partial-cone*-**3**, which are in agreement with their conformations. Reaction of triacid **3** with *p*-tuluidine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxy benzotriazole (HOBt) in CH_2Cl_2 afforded the corresponding compound **4a** in a yield of 61% for *cone*-**4a** and 59% for *partial-cone*-**4a**, respectively.

From the singlet peaks for *cone*-**4a** and the splitting patterns with a 1 : 2 integral intensity ratio for *partial-cone*-**4a**, the conformation remained in the desired compounds **4a**. In order to investigate the conformation of **4** in detail, a reference compound **6a** was synthesized from (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid **5** following a similar method in the preparation of **4a** (Scheme 4).

Conformation assignments for the new homotrioxacalix[3]arene amides **4a** followed from analysis of their ^{1}H NMR spectra. The *cone*-**4a** is firmly established by the pres-



Scheme 4.

ence of AB quartets for the bridging methylene protons with a $\Delta\delta$ separation between H_{ax} and H_{eq} of 0.60 ppm. In the calix[4]arenes, the $\Delta\delta$ values of the Ar*CH*$_2$Ar protons have been correlated to the orientation of adjacent aromatic rings, i.e., $\Delta\delta > 1$ with cone conformation or syn orientation, $\Delta\delta$ of about 0.5 with flattened cone or out orientation, $\Delta\delta$ of 0 ppm with 1,3-alternate or anti orientation [28, 29]. The same findings were observed in hexahomotrioxacalix[3]arenes [14a]. Thus, we can deduce that *cone*-**4a** prefers a flattened cone conformation, in which hydrogen bonding can form. On comparison with the chemical shift of relative protons between *cone*-**4a** and the reference compound **6a**, we can observe that the NH proton in *cone*-**4a** dramatically shifted down field ($\Delta\delta$ = 0.83 ppm) so that the intramolecular hydrogen bonding was formed between NH and the neighboring C=O moieties. On the other hand, *partial-cone*-**4a** exhibits two singlets for the *tert*-butyl protons at δ 0.94 and 1.08 ppm (integral intensity 2 : 1), singlets for ArO*CH*$_2$CO methylene protons at δ 3.35 and 4.37 ppm, these signals are consistent with the structure of *partial-cone*-**4a** having a C_2-symmetric structure. The two substituents were pointing up to the aromatic rings while the other one was inverted and tightly accommodated inside the hydrophobic cavity generated by the two aryl moieties, in a sort of self-inclusion complex. An intramolecular hydrogen bond was also formed between the two pointed up substituents so that a downfield shift of the NH proton ($\Delta\delta$ = 0.79 ppm) was observed compared to **6a**. Dramatic upfield shifts for the ArO*CH*$_2$CO proton ($\Delta\delta = -1.04$ ppm) and for the NH proton ($\Delta\delta = -0.65$ ppm) were observed in the inverted substituent, which strongly suggested that the inverted substituent folded into the hydrophobic cavity formed by two aromatic rings. A similar self-inclusion phenomenon was observed in the partial-cone structures such as other calix[4]arenes [30] and homocalix[3]arenes [31].

However, even minor changes in the regioselective functionalization [32] or conformation [33] of the chemically modified calixarene can introduce drastic changes in the complexation properties. N-heterocyclic reagents, such as pyridine moieties, or dipyridine moieties, have been introduced into calixarene in order to form ligands for both hard and soft metal ions, which should result in molecules superior to amide and ester structures because of the high stability in a wide pH range [34, 35]. Compound **4b** and its reference compound **6b** were prepared from the reaction of triacid **3** and **5** with 2-amino-pyridine similar to that of compound **4a**. Like *cone*-**4a**, *cone*-**4b** has a C_3-symmetrical conformation, which has an AB pattern for Ar*CH*$_2$O bridged protons with a $\Delta\delta$ separation of 0.42 ppm between H_{ax} and H_{eq}. The intramolecular hydrogen bond formed between the neighboring NH and CO groups induced a large downfield shift for the NH proton ($\Delta\delta$ = 0.46 ppm) in *cone*-**4b** compared to compound **6b**.

Due to the repulsion effect between heteroatom nitrogens in the pyridine rings, they were orientated outward against the cavity, wherein the protons in the pyridine rings were subjected to the ring current shielding effects from the adjacent pyridine rings. The protons were accordingly shifted to high magnetic field compared to those in a single unit of reference compound **6b**. On the other hand, the intramolecular hydrogen bond makes the free-fold chains, OCH_2CONH, approach each other so that the twisted orientation of pyridine rings is observed. Therefore, proton H_3 is located closer in space than other protons in the pyridine rings and the largest upfield shift was observed ($\Delta\delta = -0.4$ ppm). A similar tendency is also found for *partial-cone*-**4b**. An intramolecular hydrogen bond was formed between the two pointed-up substituents, the nitrogen atoms in the pyridine rings were orientated outward against the cavity and a large upfield shift was observed for H_3 ($\Delta\delta = -0.25$ ppm) in the pyridine rings. The inverted substituent was folded down into the cavity formed by two aryl moieties. In comparison with compound **6b**, in the inverted substituent, the protons of diastereomethylene, NH and H_3 in the pyridine ring were largely shifted upfield by $\Delta\delta$ 1.55, 0.50 and 0.25 ppm, respectively, while other protons in the pyridine ring are little changed. This observation indicates that the nitrogen atom is also orientated outward even in the inverted substituent.

The alkyloxy calixarene can bind cations, neutral molecules or anions to form complexes, which has been investigated by several groups through different types of calixarenes [1–4, 11]. The two-phase solvent extraction is an efficient and available method to investigate how host molecules bind metal cations [2, 3]. Extraction studies were conducted by the standard two phase procedure whereby dilute solutions of each calixarene derivative in dichloromethane were shaken with neutral aqueous metal picrate solutions, following which the equilibrium distribution of the picrate was measured spectrophotometrically.

Interestingly, amides **4a** and **4b** show low efficiency for metal cations compared to *N*, *N*-diethylamide **2b**[14a, 15]. The ionophoric activity of compound **4** was almost absent. *cone*-**4a** shows a single affinity to *n*-butyl ammonium ion because of the C_3-symmetry as discussed later. The ionophores usually form loose ion pairs with metal picrates, which produced the maximum absorption peak at 377 nm [36]. As to Cu^{2+} and Al^{3+}, they form contact ion pairs with *partial-cone*-**2b** and *cone*-**4b**, which shows the maximum absorption peak at 365 nm. Interestingly, *cone*-**4a** also forms contact ion pairs with *n*-$BuNH_3^+$ and shows the maximum absorption peak at 365 nm. As to *partial-cone*-**4b**, a contact ion pair was formed with Ag^+. In comparison with *cone*-**4a**, *cone*-**4b** has high affinity to transition metal ions, Ag^+ and

Cu^{2+} and the typical metal ion Al^{3+}. These findings clearly indicate that the lower-rim side chains having pyridyl groups play a significant role in the complexation with transition metal ions. Thus, the cations might be encapsulated into the cavity formed by pyridine rings. Due to the strong hydrogen bonding formation between the NH and neighboring CO groups in *cone*-**4a**, it shows no affinity to either hard or soft metal cations. On the other hand, *cone*-**4b** can bind transition metal cations because of having the pyridyl groups which can bind soft metal cations.

The present binding mode can be demonstrated more clearly by using ^{1}H NMR spectroscopy. There are two modes for *cone*-**4a** to bind with *n*-butyl ammonium ions, i.e., from the lower rim through substituent moieties or from the upper rim through the π-cavity formed by three aromatic rings. As listed in Table 2, the chemical shifts of *cone*-**4a** are different in the absence and presence of *n*-butyl ammonium ion. After adding an equivalent of *n*-$BuNH_3Cl$ to a solution of *cone*-**4a** (5×10^{-3} mol/L) in $CDCl_3$ at 27 °C, the protons on aromatic rings, ArCH_2O, ArOCH_2 were dramatically shifted to lower magnetic field, which indicate that the binding mode occurred through the π-cavity formed by three aromatic rings. This binding is attributed to the π-effect of aromatic rings because both the host and the guest molecules have a C_3-symmetric conformation. With excess of *n*-$BuNH_3Cl$, the free guest molecules and the encapsulated molecules were clearly observed by proton ^{1}H NMR spectroscopy, in which the encapsulated one was shifted upfield, CH_3(0.95 to 0.26, $\Delta\delta = -0.69$ ppm), CH_3CH_2 (1.45 to 0.30, $\Delta\delta = -1.05$ ppm), $CH_3CH_2CH_2$(1.77 to -0.25, $\Delta\delta = -2.02$ ppm) and CH_2N (3.00 to 0.30, $\Delta\delta = -2.70$ ppm). The chemical shift of the NH proton in *cone*-**4a** was shifted to lower magnetic field (δ 9.43 to 10.52; $\Delta\delta$ = 1.09 ppm) while the NH in *n*-$BuNH_3Cl$ was shifted to higher field (δ 8.30 to 5.93; $\Delta\delta = -2.37$ ppm). Intramolecular hydrogen bonding in *cone*-**4a** weakens the affinity of *cone*-**4a** to metal ions which were encapsulated through the lower rim of homotrioxacalix[3]arene derivatives. When *cone*-**4a** was complexed with *n*-$BuNH_3^+$ through the π-cavity, the conformation of *cone*-**4a** was changed and intramolecular hydrogen bonding was impossible in this conformation, the NH protons in *cone*-**4a** were shifted to lower magnetic field to indicate complexation of the anionic guest Cl^-, through hydrogen bonding (Figure 1) [37]. On addition of *n*-Bu_4NI and $PhMe_3NCl$ to a solution of *cone*-**4a** in $CDCl_3$(5×10^{-3} mol/L), no complexation of halide anions was observed. Due to the strong intramolecular hydrogen bonding, the anion binding site is blocked.

Based on this observation, we investigated the complexation of *cone*-**4a** with *n*-butyl ammonium halide counterions. With addition of ammonium halide counterions the proton peaks in *cone*-**4a** were separated into complexed and uncomplexed ones. The integral intensity of the proton peaks of the complex was increased with increasing amount of ammonium halide counterions, and changed completely to the complex.

Furthermore, the ortho protons of the phenyl substituents at the amide groups show a downfield shift (0.05–0.1 ppm)

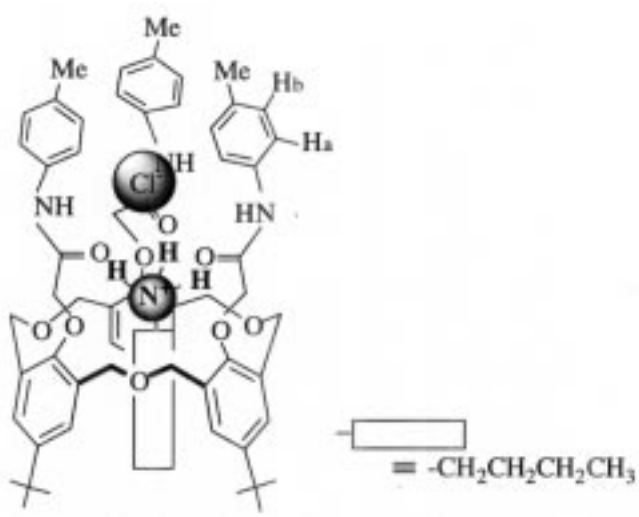


Figure 1. Binding mode of tris[(4-methylphenyl)aminocarbonyl)methoxy] hexahomotrioxacalix[3]arene *cone*-**4a** and *n*-$BuNH_3Cl$.

while the meta protons shift to higher field (0.05–0.1 ppm) in complexes, this effect may be attributed to a different electron density at the ortho and the meta positions of the aromatic ring due to the presence of the anionic guest.

Chloride anion induces a larger downfield shift for the amide hydrogen of *cone*-**4a** than bromide anion does. For example, significant downfield shifts of $\Delta\delta$ 1.09 ppm for the NH proton in the case of Cl^- and $\Delta\delta$ 0.71 ppm in the case of Br^-, respectively, were observed (Figure 2). As the electron negativity of the halogen atom decreased with the series of Cl, Br to I atom, the intensity of hydrogen bonding formed between their anions and NH protons should be decreased following the same order. In fact, in the proton NMR spectrum of a mixture of *cone*-**4a** and *n*-$BuNH_3^+X^-$, the larger downfield chemical shift in the complex of NH with Cl^- than that with Br^- and I^- was observed. The association constants calculated from these changes in chemical shifts of the amide protons are K_a = 8520 M^{-1} ($-\Delta G^\circ$ = 22.6 KJmol^{-1}) for Cl^- and K_a = 1720 M^{-1} ($-\Delta G^\circ$= 18.6 KJ mol^{-1}) for Br^-. *cone*-**4a** shows a preference for Cl^- complexation rather than Br^- complexation. This finding suggests that the cavity formed by the three-fold amide moieties is more complementary to the size of Cl^- than to that of Br^- as well as the higher electronegativity of Cl^- rather than that of Br^-. In the case of tri(urea)-functionalized calix[6]arene, the anion complexation is preference for Br^- because it has a large calix cavity and the three functionalized moieties in the 1,3,5-positions of calix[6]arene is more complementary to the size of the Br^- than to that of Cl^- [37b].

Calix[5]arene derivatives were reported to complex with alkylammonium ions and display an enzymelike selectivity [38] towards biologically important ammonium substrates. Since hexahomotrioxacalix[3]arenes and their derivatives have the C_3-symmetrical conformation, they can bind with primary ammonium ions having potential function not only in chemical but in biological system [14–17]. The ammonium ions form complexes with *cone*-**4** entering the cavity formed by the calix benzene rings from the upper rim.

Table 1. Extraction (%) of metal and ammonium picrates in CH_2Cl_2[a]

Ionophore	Na^+	K^+	Ag^+	Cu^{2+}	Al^{3+}	*n*-$BuNH_3^+$	*i*-$BuNH_3^+$	*t*-$BuNH_3^+$
cone-**2b**	93.0	71.6	90.4	27.5	19.0	97.8	48.0	35.4
partial-cone-**2b**	27.9	72.9	77.1	24.0	8.9	93.2	36.8	14.2
cone-**4a**	0	0	0	0	0	18.7	0	0
partial-cone-**4a**	0	0	0	0	0	0	0	0
cone-**4b**	0	0	76.9	16.6	11.5	38.1	1.9	0.8
partial-cone-**4b**	0	0	31.1	3.1	2.6	2.2	0.4	0.4

[a] Extraction (%) of metal and ammonium picrates by ionophores **2** and **4** in CH_2Cl_2. Extraction conditions; 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-4} M of picric acid in 0.1 M of alkali hydroxide or metallic nitrate at 25 °C. Ionophore solution (5.0 mL) was shaken for 24 h with picrate solution (5.0 mL) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ±2%.

Table 2. Chemical shift changes of *cone*-**4a** induced in the presence of *n*-$BuNH_3Cl$[a]

Compound	Ph		Ph—CH_3	NH	$ArOCH_2$	$ArCH_2O$	Ar–H	t-Bu
	H_a	H_b						
cone-**4a**	7.44	6.95	2.25	9.43	4.39	4.27, 4.86	6.92	1.14
cone-**4a** + *n*-$BuNH_3Cl$	7.53	6.90	2.21	10.52	5.14	4.30, 5.50	7.22	1.23
$\Delta\delta$[b]	+0.09	−0.04	−0.04	+1.09	+0.75	+0.03, +0.64	+0.30	+0.09

[a] $\Delta\delta$ values are the difference of the chemical shift of *cone*-**4a** (5×10^{-3} M) induced in the presence of *n*-$BuNH_3Cl$ (5×10^{-3} M) in $CDCl_3$ at 27 °C.
[b] A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (−) denotes a shift to higher magnetic field.

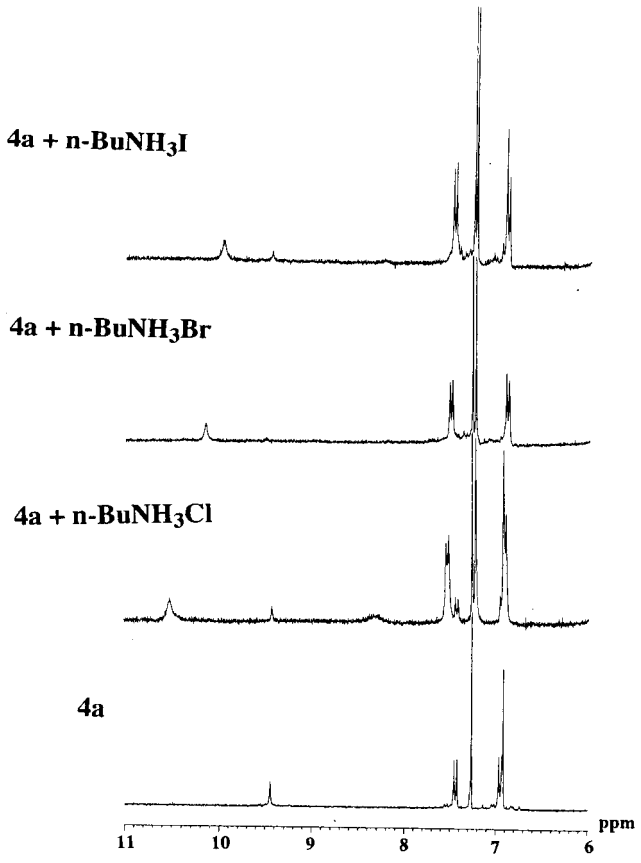


Figure 2. Partial ^1H NMR spectrum of *cone*-**4a** with *n*-$BuNH_3^+X^-$ (in $CDCl_3$, 270 MHz, at 27 °C).

Thus the alkylated substituents remain in the cavity and are shielded under the resonance of the calix benzene rings, the protons on the alkylated ammonium ion will be shifted to the upper rim correspondingly compared to their free protons. In fact, three kinds of alkylated substituents were examined by the ^1H NMR titration experiments. The results are listed in Table 3.

From Table 3, we see that the NH protons on alkylammonium ions were shifted to higher field when they were encapsulated into the calix cavity. The maximum up field shift was observed among the protons of $CH_2CH_2NH_3^+$ and then decreased with the sequence of alkyl length. For example, in the case of *n*-butylammonium ion, the protons in $CH_2CH_2NH_3^+$ were shifted to higher field more than 2.0 ppm while protons in CH_3CH_2 shifted to higher field only by 0.69 ppm and 1.05 ppm, respectively. The calix cavity of homooxacalix[3]arene can enclose the *n*-butyl ammonium ion totally, the terminal $CH_2CH_2NH_3^+$ was located deeply into the cavity, while CH_3CH_2 was located on the edge of the cavity. Very close chemical shift values were observed for encapsulated NH among the different alkylammonium ions, as well as their two linked methylene protons. This finding indicates that the protons of $CH_2CH_2NH_3^+$(or $CH_3CH_2NH_3^+$, $(CH_3)_3CNH_3^+$) were located in a similar position in the cavity of the calix benzene rings, and were under a similar intensity of resonance shielding.

Recently, Shinkai *et al.* reported that the 1,3-alternate conformer of calix[4]arene tetraester can form both a 1 : 1 and a 2 : 1 metal/calixarene complex and the two metal-binding sites display negative allostericity by ^1H NMR titration experiments [39]. In the present system, due to the existence of three metal-binding sites of the pyridine moiety

Table 3. Chemical shift changes of RNH_3Cl included in *cone*-**4a**[a]

		Chemical shift of proton				
		CH$_3$	CH$_3$*CH*$_2$	CH$_3$CH$_2$*CH*$_2$	*CH*$_2$	N*H*
	Free	0.95	1.45	1.77	3.00	8.30
n-BuNH$_3^+$	Complex	0.26	0.30	−0.25	0.30	5.93
	$\Delta\delta$	−0.69	−1.05	−2.02	−2.70	−2.37
	Free	1.32			3.04	8.24
EtNH$_3^+$	Complex	−0.49			0.43	5.94
	$\Delta\delta$	−1.81			−2.61	−2.30
	Free	1.50				8.16
tert-BuNH$_3^+$	Complex	−0.36				5.94
	$\Delta\delta$	−1.86				−2.22

[a] Determined in $CDCl_3$, 270 MHz, 27 °C; chemical shift (δ): ppm. $\Delta\delta = \delta_{complex} - \delta_{free}$.

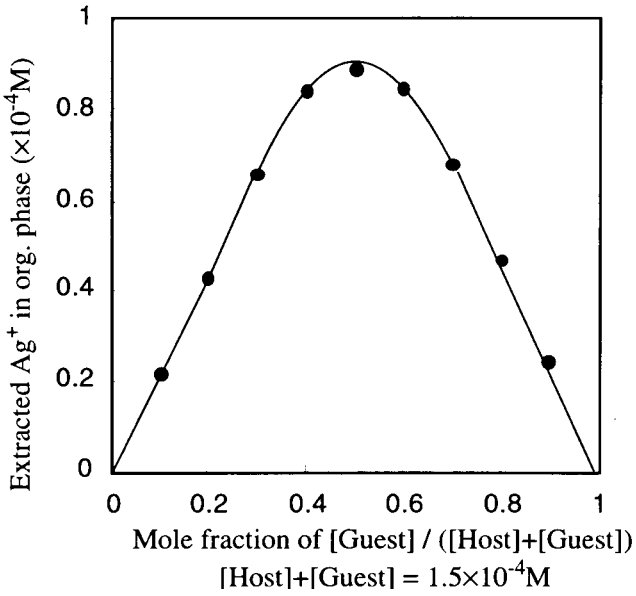


Figure 3. Job plots of the extraction of Ag^+ with host *cone*-**4b**.

there are several possibilities for metal complexation modes. Thus, a 1 : 1 and a 2 : 1 metal complexation of *cone*-**4b** might be possible.

As shown in Figure 3, the percent extractions reach a maximum at 0.5 mole fraction for this cation. The fact clearly indicates that Ag^+ forms a 1 : 1 complex with *cone*-**4b**. It was also found that the corresponding *cone*-**4a** hardly extracted Ag^+ cation in these experimental conditions (extraction %: less than 1%). Thus, Ag^+ should be completely bound by the soft pyridine cavity of *cone*-**4b** and the homotrioxacalix[3]arene cavity does not participate in the complexation. In order to explore the binding mode of three lower-rim side chains having pyridyl groups, we examined the ^1H NMR chemical shift differences between those before and after the addition of equimolar $AgSO_3CF_3$, and the composition of the ion-ionophore complex.

After titration with an equivalent of $AgSO_3CF_3$, the protons in the pyridine rings in *cone*-**4b** were shifted to lower magnetic field except H_3 which shifted to upper field ($\Delta\delta = -0.12$ ppm). This indicates that the nitrogen atoms turned inside the cavity and interact with Ag^+, which makes a large downfield shift for H_4, H_5 and H_6 induced by the inductive effect arising for the N—Ag^+ interaction present in this cavity. After complexation with Ag^+, *cone*-**4b** still retains the C_3-symmetrical conformation and the NH proton is also shifted to lower field due to the increased intramolecular hydrogen bonding formed with the neighboring C=O group.

Similar results were obtained when *partial-cone*-**4b** was titrated with an equivalent of $AgSO_3CF_3$, the nitrogen atoms in the pyridine rings of the two pointed-up substituents turned inside the cavity and coordinated with Ag^+ (Figure 5), as well as the much stronger hydrogen bonding formed between the NH protons and C=O (a lower magnetic field shift of $\Delta\delta = +0.43$ ppm for the NH proton). The protons in the two pyridine rings in the ordinary phenyl units shifted to lower magnetic field ($\Delta\delta$ = + 0.28–+ 0.40 ppm) except H_3 which shifted to higher field ($\Delta\delta = -0.15$ ppm). This fact suggests that Ag^+ ion is mainly bound to the nitrogens of the pyridine rings in the two ordinary phenyl units and the pyridyl group in the inverted phenyl unit rotates into the cavity. Probably, this rotation is induced by steric repulsion between the bound Ag^+ ion and the *tert*-butyl group in the inverted phenyl unit. Furthermore, the complexation of *partial-cone*-**4b** with Ag^+ makes the flattened aromatic rings stand up so the shielding effect formed by the two aryl rings became stronger. In the inverted substituent, both the NH proton and H_3 in the pyridine ring were shifted upfield ($\Delta\delta = -0.34$ ppm for NH and -0.14 ppm for H_3, respectively) because they were under the shielding current caused by the two aryl rings. Due to the complicated patterns of diastereomethylene protons and bridged methylene protons in the presence of Ag^+ as well as lower solubility of the complex in $CDCl_3$, it seems difficult to detect the changes of these methylene protons in the inverted substituent in the complex with Ag^+ ion. We also observed a precipitate during the NMR titration experiments. Although the reason for formation of the precipitate is not clear at the present stage, one might assume the intermolecular complexation between Ag^+ and inverted pyridyl groups.

As mentioned above, $\Delta\delta$ between H_{ax} and H_{eq} of the Ar*CH*$_2$Ar methylene protons in calix[4]arene serves as a

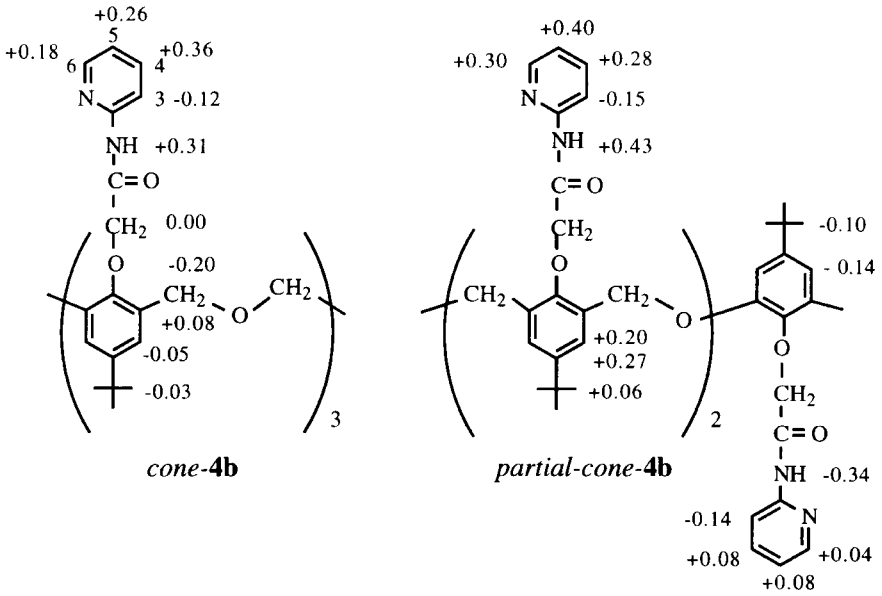


Figure 4. Chemical shift changes of *cone*-**4b** and *partial-cone*-**4b** induced in the presence of $AgSO_3CF_3$; (+) denotes the down-field and (−) denotes the up-field shift.

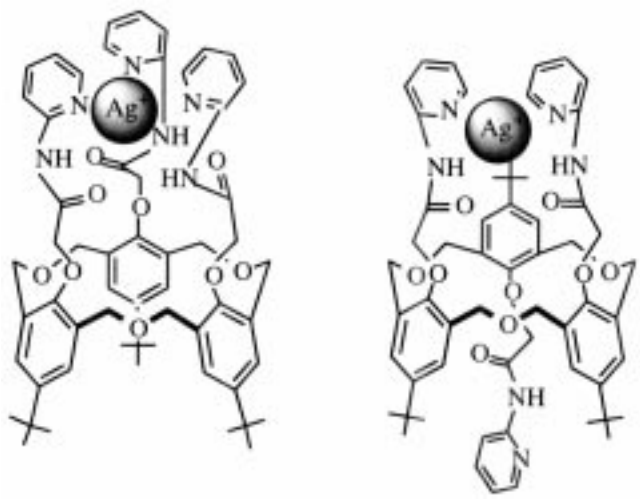


Figure 5. Binding mode of tris[(2-pyridylaminocarbonyl)methoxy] hexahomotrioxacalix[3]arenes *cone*-**4b**, and *partial-cone*-**4b** and Ag^+.

measure of the 'flattening'. $\Delta\delta$ increases from 0.60 ppm to 1.20 ppm in *cone*-**4a** upon the binding of *n*-$BuNH_3^+$ and from 0.42 ppm to 0.69 ppm in *cone*-**4b** upon the binding of Ag^+, respectively. These findings imply that *cone*-**4a** stands up when the guest is included because *n*-$BuNH_3^+$ enters into the π-cavity formed by three aromatic rings. On the other hand, Ag^+ was encapsulated into the cavity formed by the pyridine rings.

Conclusion

For the first time, the relationship between the properties of ionophore hosts and their intramolecular hydrogen bonding was taken into account in the C_3-symmetric conformation. Due to the intramolecular hydrogen bonding, the affinities of ionophores **4a** and **4b** to metal ions were weakened, they do not bind alkali metal ions because the binding site was blocked. Both *cone*-**4a** and *cone*-**4b** can bind *n*-butyl ammonium ions through the π-cavity formed by the three aryl rings, which can provide functional moieties in biological systems with good affinity and high selectivity. The anion complexation of *cone*-**4a** was studied by ^1H NMR titration experiments. *cone*-**4a** binds halide through intermolecular hydrogen bonding among the NH hydrogens of amide in a 1 : 1 fashion in $CDCl_3$. *cone*-**4a** shows a preference for Cl^- complexation rather than Br^- complexation.

As a C_3-symmetrical pyridyl-substituted calixarene, compound **4b** 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^+ while another one in the inverted substituent in *partial-cone*-**4b** still remained. After complexation of amides **4b** with Ag^+, the original C_3-symmetry and C_2-symmetry have been retained for *cone*-**4b** and *partial-cone*-**4b**, respectively. The oxygen in the ethereal linkage did not take part in the complex procedure.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 270MHz 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 spectrophotometer. 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: *partial-cone*-7,15,23-Tri-*tert*-butyl-25,26,27-tris[(ethoxycarbonyl)methoxy]-2,3,10,11,18,19-

hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**2a**) and *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(*N*, *N*-diethylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11, 19-trioxacalix[3]arene (*cone*-**2b**) were prepared according to the literature [14, 15].

Synthesis

*Preparation of cone-hexahomotrioxacalix[3]arene triacetic acid (cone-***3***)*

To a mixture of *cone*-**2b** (1.0 g, 1.14 mmol) in dioxane (30 mL) was added 1N NaOH aqueous solution (30 mL). After the mixture was refluxed for three days, it was condensed under reduced pressure, then acidified to pH 1–2. The dispersion was extracted with ethyl acetate (2 × 3 mL). The combined extracts were washed with water (2 × 20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduced pressure. The residue was washed with a small amount of diethyl ether to give the crude *cone*-**3** as a colorless solid. Recrystallization from methanol gave *cone*-**3** (440 mg, 51.2%) as a colorless powder; m.p. 227-229 °C; υ_{max} (KBr)/cm^{-1} 3400, 2975, 2915, 2867, 1758, 1483, 1456, 1363, 1234, 1199, 1094, 1058; δ_H ($CDCl_3$) 1.12 (27 H, s, *t*-Bu), 4.44 (6 H, d, *J* 12.7, Ar*CH*$_2$O), 4.92 (6 H, d, 12.7, Ar*CH*$_2$O), 4.46 (6 H, s, ArO*CH*$_2$) and 6.95 (6 H, s, Ar-*H*); *m/z*: 750 (M^+); *Found*: C, 67.36; H, 7.40. *Calcd.* for $C_{42}H_{54}O_{12}$: C, 67.18; H, 7.25%.

*Preparation of partial-cone-hexahomotrioxacalix[3]arene triacetic acid (partial-cone-***3***)*

To a mixture of *partial-cone*-**2a** (1.0 g, 1.20 mmol) in dioxane (30 mL) was added 1N NaOH aqueous solution (30 mL). After the mixture was stirred for 1 h at room temperature, it was condensed under reduced pressure, then acidified to pH 1–2. The dispersion was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with water (2 × 20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduced pressure. The residue was washed with a small amount of hexane to give the crude *partial-cone*-**3** as a colorless solid. Recrystallization from methanol gave *partial-cone*-**3** (790 mg, 87.8%) as a colorless powder; m.p. 158-160 °C; υ_{max} (KBr)/cm^{-1} 3400, 2961, 2873, 1786, 1738, 1365, 1195, 1065, 1056, 886; δ_H ($CDCl_3$) 1.29 (18 H, s, *t*-Bu), 1.33 (9 H, s, *t*-Bu), 2.61 (2 H, s, ArO*CH*$_2$), 3.15, 4.27, 4.34, 4.45, 4.95, 5.17 (each 2 H, d,*J* 12.7, Ar*CH*$_2$O), 4.60 (4 H, s, ArO*CH*$_2$), 7.30 (2 H, d, *J* 2.4, Ar-*H*), 7.38 (2 H, d, *J* 2.4, Ar-*H*) and 7.43 (2 H, s, Ar-*H*); *m/z*: 750 (M^+); *Found*: C, 67.32; H, 7.35. *Calcd.* for $C_{42}H_{54}O_{12}$: C, 67.18; H, 7.25%.

*Preparation of cone-7,15,23-tri-tert-butyl-25,26,27-tris-[(4-methylphenylaminocarbonyl)methoxy]-2,3,10,11,18, 19-hexahomo-3, 11, 19-trioxacalix[3]arene (cone-***4a***)*

To a solution of *cone*-**3** (100 mg, 0.133 mmol), *p*-toluidine (130 mg, 1.17 mmol) and 1-hydroxy-benzotriazole (HOBt) (23 mg, 0.17 mmol) in CH_2Cl_2 (12 mL) were added dropwise into a solution of dicyclohexylcarbodiimide (DCC) (171 mg) in CH_2Cl_2 (5 mL) at 0 °C. After the mixture was stirred for 15 h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with 10% citric acid (2 × 20 mL), 5% sodium bicarbonate (20 mL), water (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduced pressure. The residue recrystallized from methanol gave *cone*-**4a** (83 mg, 61.2%) as colorless prisms; m.p. 234-236 °C; υ_{max} (KBr)/cm^{-1} 3333, 2921, 2860, 1632, 1580, 1539, 1437, 1312, 1244, 1230, 1089, 1068, 1045, 1020, 802, 657, 641; δ_H ($CDCl_3$) 1.14 (27 H, s, *t*-Bu), 2.25 (9 H, s, Ph-*CH*$_3$), 4.27 (6 H, d, *J* 12.7, Ar*CH*$_2$O), 4.39 (6 H, s, ArO*CH*$_2$), 4.86 (6 H, d, *J* 12.7, Ar*CH*$_2$O), 6.92 (6 H, s, Ar-*H*), 6.95 (6 H, d, *J* 8.8, Ph-*Ha*), 7.44 (6 H, d, *J* 8.8, Ph-*Hb*) and 9.42 (3 H, s, N*H*); *m/z*: 1018 (M^+); *Found*: C, 74.52; H, 7.53; N, 4.30. *Calcd.* for $C_{63}H_{75}O_9N_3$: C, 74.31; H, 7.42; N, 4.13%.

Similarly, *partial-cone*-**4a**,*cone*-**4b** and *partial-cone*-**4b** were prepared in 59.0, 80.1 and 65.2% yields, respectively.

Partial-cone-7,15,23-tri-*tert*-butyl-25,26,27-tris[(4-methylphenylamino- carbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**4a**): Colorless prisms (from methanol); m.p. 254-255 °C; υ_{max} (KBr)/cm^{-1} 3362, 3322, 2962, 2867, 1696, 1606, 1526, 1483, 1458, 1407, 1312, 1249, 1197, 1060, 885, 817; δ_H ($CDCl_3$) 0.94 (18 H, s, *t*-Bu), 1.08 (9 H, s, *t*-Bu), 2.32 (6 H, s, Ph-*CH*$_3$), 2.34 (3 H, s, Ph-*CH*$_3$), 3.35 (2 H, s, ArO*CH*$_2$), 4.01, 4.38, 4.45, 4.53, 4.87, 4.92 (each 2 H, d, *J* 12.7, Ar*CH*$_2$O), 4.37 (4 H, s, ArO*CH*$_2$), 6.98 (2 H, d, *J* 8.8, Ph-*Ha*), 7.08 (4 H, d, *J* 8.8, Ph-*Ha*), 7.14, 7.27 (each 2 H, d, *J* 2.4, Ar-*H*), 7.35 (2 H, s, Ar-*H*), 7.46 (2 H, d, *J* 8.8, Ph-H_b), 7.49 (4 H, d, *J* 8.8, Ph-H_b), 7.95 (1 H, s, NH), 9.40 (2 H, s, NH); *m/z*: 1018 (M^+); *Found*: C, 74.59; H, 7.40; N, 3.98. *Calcd.* for $C_{63}H_{75}O_9N_3$: C, 74.31; H, 7.42; N, 4.13%.

Cone-7,15,23-tri-*tert*-butyl-25,26,27-tris[(2-pyridyl-aminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11, 19-trioxacalix[3]arene (*cone*-**4b**): Colorless prisms (from methanol); m.p. 124-126 °C; υ_{max} (KBr)/cm^{-1} 3395, 3304, 2957, 2909, 1701, 1696, 1595, 1575, 1516, 1483, 1461, 1433, 1303, 1196, 1094, 777; δ_H ($CDCl_3$) 1.15 (27 H, s, *t*-Bu), 4.53 (6 H, d, *J* 12.7, ArO*CH*$_2$), 4.49 (6 H, s, ArO*CH*$_2$), 4.94 (6 H, d, *J* 12.7, ArO*CH*$_2$), 6.99 (6 H, s, Ar-H), 6.89 (3 H, m, pyridine-H_5), 7.45 (3 H, m, pyridine-H_4), 7.89 (3 H, d, *J* 8.8, pyridine-H_3), 8.18(3 H, m, pyridine-H_6), 9.71 (3 H, s, NH); *m/z*: 979 (M^+); *Found*: C, 69.65; H, 6.73; N, 8.30. *Calcd.* for $C_{57}H_{66}O_9N_6$: C, 69.92; H, 6.79; N, 8.58%.

Partial-cone-7,15,23-tri-*tert*-butyl-25,26,27-tris[(2-pyridylaminocarbonyl) methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*partial-cone*-**4b**): Colorless prisms (from methanol); m.p. 216-218 °C; υ_{max} (KBr)/cm^{-1} 3326, 2918, 2851, 1702, 1628, 1577, 1524, 1483, 1460, 1433, 1302, 1197, 1086, 1052, 779; δ_H ($CDCl_3$) 0.92 (18 H, s, *t*-Bu), 1.10 (9 H, s, *t*-Bu), 2.86 (2 H, s, ArO*CH*$_2$), 3.99, 4.40, 4.57, 4.62, 5.00, 5.08 (each 2 H, d, *J* 12.7, Ar*CH*$_2$O), 4.42 (4 H, s, ArO*CH*$_2$), 6.98 (2 H, m, pyridine-H_5), 7.03 (1 H, m, pyridine-$H_{5'}$), 7.12 (2 H, d, *J* 2.4, Ar-H), 7.35 (2 H, d, *J* 2.4, Ar-H), 7.43 (2 H, s, Ar-H), 7.58 (2 H, m, pyridine-H_4), 7.62 (1 H, m, pyridine-$H_{4'}$), 8.03 (2 H, d, *J* 8.8, pyridine-H_3), 8.06 (1 H, d, *J* 8.8,

pyridine-$H_{3'}$), 8.31 (2 H, m, pyridine-H_6), 8.46 (1 H, m, pyridine-$H_{6'}$), 8.76 (1 H, s, NH), 9.42 (2 H, s, NH); *m/z*: 979 (M^+); *Found*: C, 69.77; H, 6.91; N, 8.34. *Calcd.* for $C_{57}H_{66}O_9N_6$: C, 69.92; H, 6.79; N, 8.58%.

*Preparation of (4-tert-butyl-2,6-dimethyl)phenoxyacetic acid (**5**)*

To a solution of 2,6-dimethyl-4-*tert*-butylphenol (400 mg, 2.24 mmol) in dry THF (25 mL) was added NaH (177 mg, 7.38 mmol), then the solution was refluxed for one hour under N_2 avoiding light. To the mixing solution was added methyl bromoacetate (2.60 g, 17.0 mmol). The mixture was refluxed under N_2 for an additional 17 h. Removing most of the solvent the residue was treated with water, then acidified and extracted with ethyl acetate. The combined organic solution was washed with water and then saturated brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure to afford methyl (4-*tert*-butyl-2,6-dimethyl)phenoxyacetate as a yellow oil: δ_H ($CDCl_3$) 1.28 (9 H, s, *t*-Bu), 2.28 (6 H, s, *CH*$_3$), 3.89 (3 H, s, O*CH*$_3$), 4.41 (2 H, s, ArO*CH*$_2$), 7.00 (2 H, s, Ar-H). The oily residue was used for the following hydrolysis reaction without purification.

To a mixture of crude methyl (4-*tert*-butyl-2,6-dimethyl)phenoxyacetate in dioxane (30 mL) was added 1N NaOH aqueous solution (30 mL) at room temperature. After the mixture was stirred at room temperature for 1 h, it was condensed under reduced pressure. The residue was then acidified to neutral condition. The precipitate was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with water (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduced pressure to afford the title compound **5** (423 mg, 80%) as a colorless solid; m.p. 85–86 °C; υ_{max} (KBr)/cm^{-1} 3510, 2953, 2857, 1732, 1691, 1489, 1266, 1197, 1126; δ_H ($CDCl_3$) 1.28 (9 H, s, *t*-Bu), 2.28 (6 H, s, *CH*$_3$), 4.45 (2 H, s, ArO*CH*$_2$), 7.02 (2 H, s, Ar-H).

*Preparation of 4-tert-butyl-2,6-dimethyl[(4-methylphenyl)-aminocarbonyl)methoxy]benzene (**6a**)*

To a solution of (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid **5** (100 mg, 0.43 mmol), *p*-toluidine (137 mg, 1.28 mmol) and HOBt (75 mg, 0.17 mmol) in CH_2Cl_2 (12 mL) was added dropwise a solution of DCC (560 mg) in CH_2Cl_2 (5 mL) at 0 °C. After the mixture was stirred for 7 h at room temperature, it was condensed under reduced pressure. The residue was extracted with ethyl acetate (2 × 30 mL). The combined extracts were washed with 10% citric acid (2 × 20 mL), 5% sodium bicarbonate (20 mL), water (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduced pressure. The residue recrystallized from methanol gave the title compound **6a** (81 mg, 59%) as colorless prisms; m.p. 204-206 °C; υ_{max} (KBr)/cm^{-1} 3277, 2950, 2928, 2865, 1667, 1533, 1515, 1484, 1458, 1443, 1408, 1360, 1322, 1310, 1195, 1124, 1050, 870, 819, 753; δ_H ($CDCl_3$) 1.30 (9 H, s, *t*-Bu), 2.30 (6 H, s, Ph-*CH*$_3$), 2.35 (3 H, s, Ph-*CH*$_3$), 4.39 (2 H, s, ArO*CH*$_2$), 7.05 (2 H, s, Ar-H), 7.18 (2 H, d, *J* 8.8, Ph-*H*a), 7.52 (2 H, d, *J* 8.8, Ph-*H*b), 8.60 (1 H, s, NH); *m/z*: 325 (M^+); *Found*: C, 77.36; H, 8.33; N, 4.27. *Calcd.* for $C_{21}H_{27}O_2N$: C, 77.50; H, 8.36; N, 4.31%.

Similarly, compound **6b** was prepared in 65.3% yield.

4-*tert*-Butyl-2,6-dimethyl[(2-pyridylaminocarbonyl)-methoxy]benzene (**6b**): colorless prisms; m.p. 118-120 °C; υ_{max} (KBr)/cm^{-1} 3397, 3323, 2926, 2851, 1714, 1703, 1627, 1572, 1518, 1435, 1310, 1304, 1244, 1047, 774; δ_H ($CDCl_3$) 1.30 (9 H, s, *t*-Bu), 2.30 (6 H, s, Ph-*CH*$_3$), 4.41 (2 H, s, ArO*CH*$_2$), 7.04 (2 H, s, Ar-H), 7.10 (1 H, m, pyridine-H_5), 7.75 (1 H, m, pyridine-H_4), 8.31 (1 H, m, pyridine-H_3), 8.35 (1 H, m, pyridine-H_6), 9.25 (1 H, s, NH); *m/z*: 312 (M^+); *Found*: C, 73.23; H, 7.35; N, 8.72. *Calcd.* for $C_{19}H_{24}O_2N_2$: C, 73.05; H, 7.74; N, 8.97%.

Picrate extraction measurements

Alkali metal picrates (2.5×10^{-4} M) were prepared in situ by dissolving 0.1 M of alkali metal hydroxide in 2.5×10^{-4} M of picric acid; triply distilled water was used for all aqueous solutions. Similarly, metallic picrates were prepared in situ by dissolving 0.1 M of metallic nitrate [$AgNO_3$, $Cu(NO_3)_2 3H_2O$, $Al(NO_3)_3 9H_2O$] in 2.5×10^{-4} M of picric acid. Alkyl ammonium picrates were prepared by mixing an equimolar mixture of alkylamine and picric acid in methanol.

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 24 h at 25 °C. We confirmed that this period was 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 spectrophotometrically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen [40].

^{1}H NMR complexation experiment

To a $CDCl_3 : CD_3OD$ (3 : 1 v/v) solution (5×10^{-4} M) of *cone*-**4b** in the NMR tube was added a $CDCl_3 : CD_3OD$ (1 : 1 v/v) solution (5×10^{-3} M) of $AgSO_3CF_3$. The spectrum was registered after addition and the temperature of the NMR probe kept constant at 27 °C.

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in a varying guest concentration of 0-50 mM and a constant concentration of host receptors of 5 mM. As a probe the chemical shift of the amide protons [C(O)N*H*] signal was used. The association constant values were calculated by the integral intensity of the NH protons in the complex and free host molecules according to the literature [41].

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