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ORIGINAL ARTICLE

Heteroditopic receptors tris(2-pyridylamide) derivatives derived from hexahomotrioxacalix[3]arene triacetic acid

Masashi Takimoto · Xin-Long Ni · Shofuir Rahman · Zeng Xi · Takehiko Yamato

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Abstract The lower rim functionalized *cone*-hexahomotrioxacalix[3]arene tris(2-pyridylamide) derivatives *cone*-**3** and *cone*-**7** having the hydrogen bonding groups and 2-pyridyl groups 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. The complexation modes of *cone*-**3** and *cone*-**7** with *n*-$BuNH_3Cl$ and $AgSO_3CF_3$ were also demonstrated by ^1H NMR titration in $CDCl_3$. Tris(2-pyridylamide) derivatives *cone*-**3** and *cone*-**7** can complex with *n*-butyl ammonium ion and silver cation at the same time to form the heteroditopic complexation.

Keywords Macrocycles · Hexahomotrioxacalix[3]arenes · Ionophores · Molecular recognition · Ammonium ion · Ditopic receptors

Introduction

Calixarene and related macrocycles have received considerable attention for their host–guest chemistry as ionophoric receptors and potential enzyme mimics in biology. Chemical modification of calixarene represents a simple though effective and versatile way of producing receptors with high selective cation binding properties [1–4]. Shinkai and co-workers have reported the complexation of alkali metals to hexahomotrioxacalix[3]arene derivatives with alkylated phenolic oxygens [5–10]. Hexahomotrioxacalix[3]arene derivatives with C_3-symmetry can selectively bind ammonium ions which play important roles in both chemistry and biology [11, 12]. Thus, Shinkai et al. reported the construction of C_3-symmmetry pyrene functionalized hexahomotrioxacalix[3]arenes, which selectively recognize primary ammonium ions [6].

On the other hand, hydrogen bond plays an important role in the self-assembly of molecular recognition and has been aroused investigation in calixarene systems. 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 was reported [13]. Arduini et al. also described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acid [14]. The intramolecular hydrogen-bonding was also formed among opposing urea groups, which can bind anionic species, in calix[4]arene [15–17]. Thus, the design of new ditopic ligands [18] 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 [19], uranyl [20], polyammonium [21] centers combined with crown ether moieties and crown ether or urea functionalized calix[4]arene ionophores [15, 22] which are capable of

M. Takimoto · X.-L. Ni · S. Rahman · T. Yamato (✉)
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

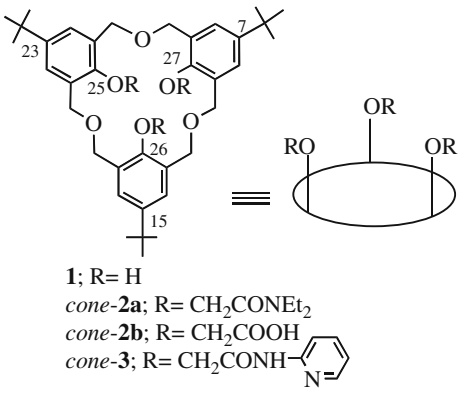
Z. Xi
Key Laboratory of Macrocyclic and Supramolecular Chemistry of Guizhou Province, Guizhou University, Guiyang 550025, Guizhou, China

solubilizing alkali metal salts into organic media (Chart 1).

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-pyridylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene *cone*-**3** derived from hexahomotrioxacalix[3]arene **1** [23–26], which show strong Ag^+ ion affinity. Therefore, 2-pyridylamide derivatives having the hydrogen-binding groups might show interesting complexation behavior for Ag^+ as well as anions and ammonium ions.

Hexahomooxacalix[3]arene is flexible compared to calix[4]arene due to its ethereal linkages, and has a C_3-symmetrical structure which is expected to be particularly useful in receptors of primary ammonium cations. Modified homooxacalix[3]arene with functional groups will have the potential as a flexible ditopic receptor. Thus, the introduction of multiple binding sites of cations and anions is important for the construction of the allosteric host–guest inclusion systems. Having the pyridyl groups on its alkylated moieties, compounds can complex with *n*-$BuNH_3^+$ and silver cation, respectively. Thus, the potential of them as the ditopic receptor to complex with *n*-$BuNH_3^+$ and silver cation will be great interesting in the coordination chemistry.

In the present paper, we describe the synthesis, conformations, and metal and ammonium ion complexation properties of the cone tris(2-pyridylamide) derivatives *cone*-**3** and *cone*-**7** having the hydrogen-binding groups derived from hexahomotrioxacalix[3]arene tricarboxylic acid, which are supposed to have C_3-symmetric ionophoric cavities.



1; R= H
cone-**2a**; R= CH_2CONEt_2
cone-**2b**; R= CH_2COOH
cone-**3**; R= CH_2CONH–

Chart 1 Synthesis of tris[(2-pyridylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene *cone*-**3**

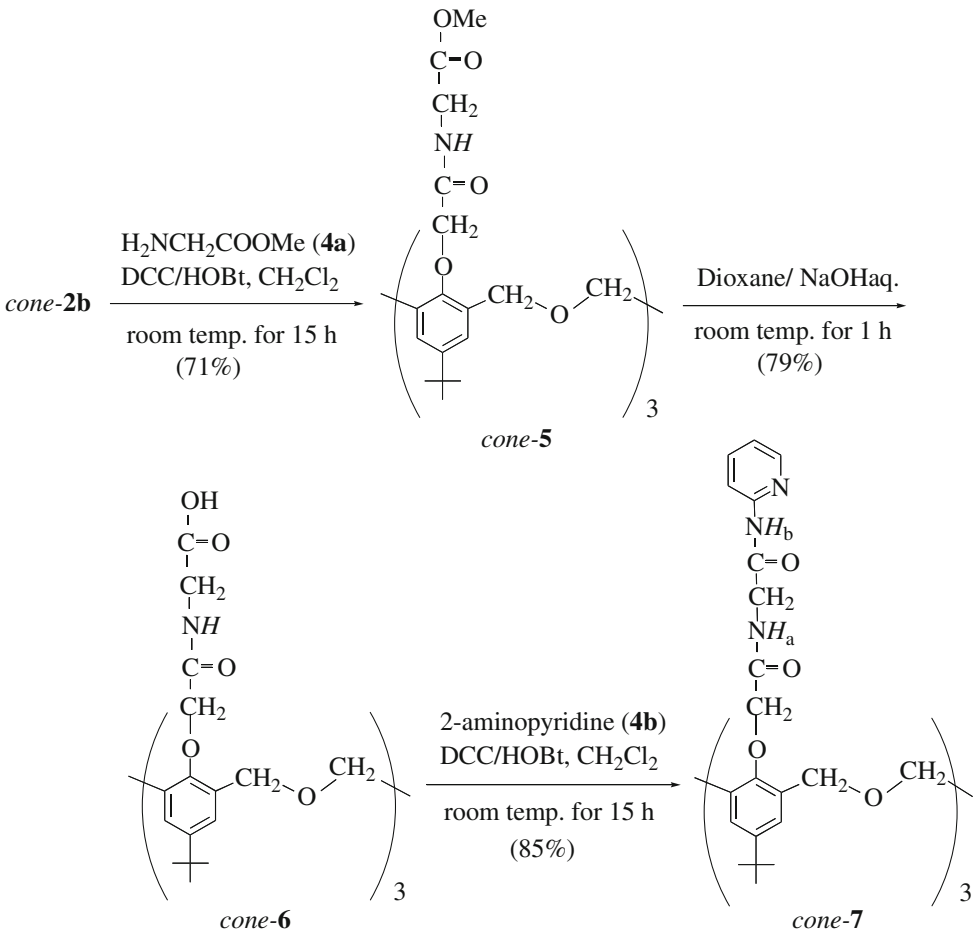
Results and discussion

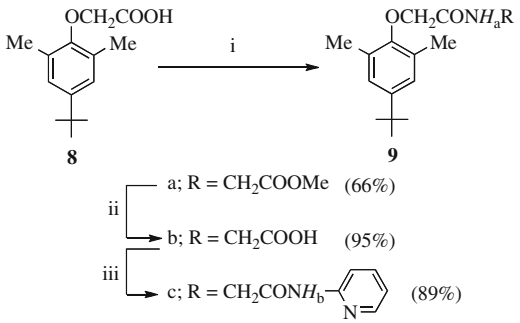
cone-Hexahomotrioxacalix[3]arene tricarboxylic acid *cone*-**2b** was prepared by hydrolysis of *cone*-[(*N,N*-diethylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene *cone*-**2a** with KOH aq. in a mixture of dioxane and water, which was prepared by *O*-alkylation of **1** with *N,N*-diethylchloroacetoamide in the presence of NaH according to the reported procedures [6, 23]. *cone*-Hexahomotrioxacalix[3]arene triamide *cone*-**5** was prepared by condensation reaction of *cone*-**2b** with glycine methyl easter (**4a**) in the presence of DCC (dicyclohexylcarbodiimide) and HOBt (1-hydroxybenzotriazole) at room temperature for 15 h in CH_2Cl_2. *cone*-**5** was converted to triacid *cone*-**6** by hydrolysis with NaOH aq. in the mixture of dioxane and water at room temperature. *cone*-**6** was reacted again with 2-aminopyridine (**4b**) in the presence of DCC and HOBt similar to that of *cone*-**5** to afford the desired compound *cone*-hexahomotrioxacalix[3]arene tris(2-pyridylamide) derivative *cone*-**7** in 85% yield (Scheme 1).

From the singlet peaks for *cone*-**7**, the conformation was remained in the desired compound with *cone*-conformation. In order to investigate the conformation of *cone*-**7** in detail, a reference compound **9c** was synthesized from 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid **8** following the similar method in the preparation of *cone*-**7** (Scheme 2).

Conformation assignment for the new *cone*-hexahomotrioxacalix[3]arene tris(2-pyridylamide) derivative *cone*-**7** is firmly established by the presence of AB quartets for the bridging methylene protons with a $\Delta\delta$ separation between H_{ax} and H_{eq} of δ 0.55 ppm in its ^{1}H NMR spectrum ($CDCl_3$). In the calix[4]arenes, the $\Delta\delta$ values of the ArCH_2Ar protons have been correlated to the orientation of adjacent aromatic rings, i.e. $\Delta\delta > 1$ ppm 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 [27]. The same findings were observed in hexahomotrioxacalix[3]arenes [5]. Thus, we can deduce that *cone*-**7** prefers a flattened cone conformation, in which hydrogen bonding can form. The intramolecular hydrogen bond was formed between neighboring NH and C=O groups which induced a large downfield shift for NH_a proton (δ 8.45 ppm, $\Delta\delta = +0.69$ ppm) and NH_b proton (δ 9.21 ppm, $\Delta\delta = +0.85$ ppm) in *cone*-**7** compared to compound **9c** (NH_a proton, δ 7.76 ppm; NH_b proton, δ 8.36 ppm). When the concentration of *cone*-**7** in $CDCl_3$ was diluted about 40 times, there is no change of the chemical shifts in both NH_a and NH_b protons, which was attributed to the concentration-independent intramolecular hydrogen bonding formed in this compound. Interestingly, the chemical shift of the NH_b protons in *cone*-**7** was shifted to lower field to δ 9.91 ppm in DMSO-d_6 than that in $CDCl_3$ (δ 9.21 ppm, $\Delta\delta = +0.70$ ppm). This phenomenon

Scheme 1 Synthesis of *cone*-hexahomotrioxacalix[3]arene tris(2-pyridylamide) derivative *cone*-**7**





Reagents and conditions: i) H_2NCH_2COOMe (**4a**), DCC/HOBt, CH_2Cl_2, room temp. for 15 h; ii) Dioxane/NaOHaq, room temp. for 1 h; iii) 2-aminopyridine (**4b**), DCC/HOBt, CH_2Cl_2, room temp. for 15 h.

Scheme 2 Synthesis of reference compound **9c**

was attributed to the intermolecular hydrogen bonding formed between the NH_b proton and solvent DMSO-d_6. The intramolecular hydrogen bonding formed in compound *cone*-**7** was broken and the new intermolecular hydrogen bonding was formed.

In the calix[*n*]arene series, the (δ values of the ArCH_2Ar protons have been correlated to the orientation of adjacent aromatic rings and it is applicable to homooxacalix[3]arene [28, 29]. We have deduced that compounds *cone*-**5**–*cone*-**7** prefer to the flatten-cone conformation for the intramolecular hydrogen bonding in $CDCl_3$. The difference of chemical shift between the proton H_{ax} and H_{eq} in the bridge methylene in compounds *cone*-**5**–*cone*-**7** was smaller in DMSO-d_6 (from δ 0.2 to 0.4 ppm) than that in $CDCl_3$ (from δ 0.4 to 0.6 ppm). The ethereal linkage in homooxacalix[3]arene is more flexible than the methylene group in calix[4]arene, when the NH proton was solvated by solvent in DMSO-d_6, the wobbling intensity of the calix benzene ring becomes much stronger than that in $CDCl_3$, and make the conformation more flatten. The CPK model was also proven that compounds *cone*-**5**–*cone*-**7** prefer to the flatten-cone conformation in order to reduce the steric energy.

The alkyloxy calixarene can bind cations, neutral molecules or anions to form complexes, which had been investigated by several groups through different types of calixarenes [1–4, 30, 31]. The two phase solvent extraction is an efficient and available method to investigate the host molecules bind metal cations [5–12]. Extraction studies were conducted by the standard two phase procedure whereby dilute solutions of each calixarene derivatives in dichloromethane were shaken with neutral aqueous metal

Table 1 Extraction (%) of metal and ammonium picrates in CH_2Cl_2

Ionophore	Na^+	K^+	Ag^+	Cu^{2+}	Al^{3+}	*n*-$BuNH_3^+$	*i*-$BuNH_3^+$	*t*-$BuNH_3^+$
cone-**3**	0	0	76.9	16.6	11.5	38.1	1.9	0.8
cone-**7**	0	0	53.3	8.9	14.7	13.2	1.2	1.2
cone-**5**	0	0	0	0	0	9.2	<0	<0
cone-**2a**	93.0	71.6	90.4	27.5	19.2	97.8	48.1	35.4

Extraction (%) of metal and ammonium picrates by ionophores 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%

picrate solutions, following which the equilibrium distribution of the picrate was measured spectrophotometrically.

Interestingly, tris(2-pyridylamide) derivatives *cone*-**3** and *cone*-**7** show low efficiency for alkali metal ions and alkyl ammonium ions compared to *N,N*-diethylamide derivative *cone*-**2a** [8, 23, 24]. The ionophoric activity of compound *cone*-**5** was almost absent, but *cone*-**5** shows a single affinity to *n*-butyl ammonium ion. The ionophores usually form a loose ion pairs with metal picrates, which produced the maximum absorption peak at 377 nm [32–34]. As to Cu^{2+} and Al^{3+}, they form a contact ion pairs with *cone*-**3** and *cone*-**7**, which showed the maximum absorption peak at 365 nm. Interestingly, the tris(2-pyridylamide) derivative *cone*-**7** also forms a contact ion pair with *n*-$BuNH_3^+$ and shows the maximum absorption peak at 365 nm. In comparison with *cone*-**7**, *N,N*-diethylamide derivative *cone*-**2a** has higher affinity to alkali metal ions, Na^+, K^+, transition metal ions, Ag^+ and Cu^{2+} and typical metal ion Al^{3+} [35–38]. Higher extractabilities of *cone*-*N,N*-diethylamide derivative *cone*-**2a** for *n*-butyl (97.8%), *i*-butyl (48.1%) and *t*-butyl ammonium ion (35.4%) are also observed and are attributable to the higher electron density of oxygen of carbonyl group by electron-donationg ability of the amide group through conjugation N–C=O ↔ N^+=C–O^- [8, 23, 24]. These findings clearly indicate that due to the strong hydrogen bonding formation between NH and neighboring CO groups in hexaamide *cone*-**7**, it shows no affinity for alkali metal ions. In contrast, *cone*-**3** and *cone*-**7** has high affinity to transition metal ions, Ag^+ and Cu^{2+} and typical metal ion Al^{3+}. These findings clearly indicate that the lower-rim side chains having pyridyl groups play a significant role on the complexation with soft transition metal ions. Thus, the cations might be encapsulated into the cavity formed by pyridine rings (Table 1).

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 ^{1}H NMR titration experiment [39]. In the present system, due to the existence of three metal-binding sites of pyridine moiety there are several possibilities for metal complexation mode. Thus, a 1:1 and a 2:1 metal complexation of *cone*-**7** might be possible.

As shown in Fig. 1, the percent extractions reach maximum at 0.5 mol fraction for this cation. The fact clearly indicates that Ag^+ forms 1:1 complex with *cone*-**7**. It was also found that the corresponding *cone*-**5** hardly extracted Ag^+ cation in this experimental conditions (extraction %: less than 1%). Thus, Ag^+ should be completely bound by soft pyridine cavity of *cone*-**7** and 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 ^{1}H NMR chemical shift differences between those before and after the addition of an equimolar $AgSO_3CF_3$, and composition of the ion–ionophore complex.

After titration with an equivalent of $AgSO_3CF_3$, the protons in pyridine rings in *cone*-**7** were shifted to lower magnetic field except H_3 shifted to upper field ($\Delta\delta = -0.20$ ppm). This indicates that the nitrogen atoms turned to inside the cavity and interact with Ag^+, which makes great downfield shift for H_4, H_5 and H_6 induced by the

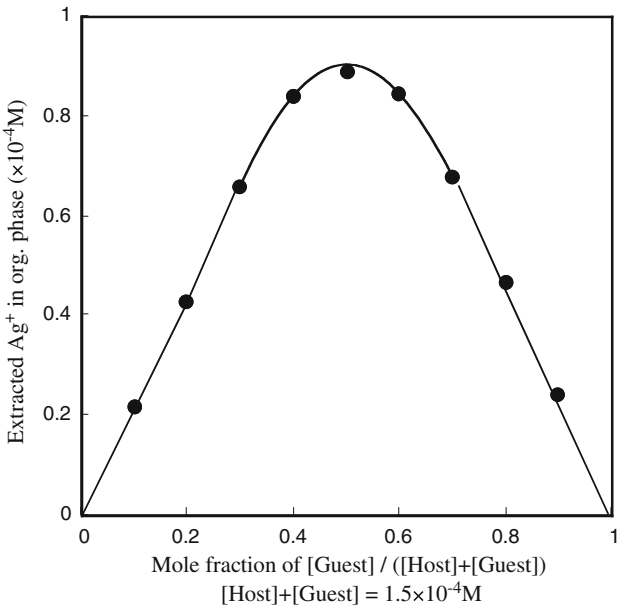


Fig. 1 Job plots of the extractions of Ag^+ with host *cone*-**7**

inductive effect arising for the N–Ag^+ interaction present in this cavity. Almost no change was observed for other protons in *cone*-**7** after complexation. After complexation with Ag^+, *cone*-**7** still remains the C_3-symmetrical conformation and NH_a proton is also shifted to lower field ($\Delta\delta = +0.03$ ppm) due to the increased intramolecular hydrogen bonding formed with the neighboring C=O group (Fig. 2).

Similar phenomena were also observed in the case of complex of *cone*-**3** with Ag^+. The protons in pyridyl rings were shifted to lower magnetic field except H_3 to upper field ($\Delta\delta$: −0.01 ppm). Thus, silver cation was complex with three pyridine groups through the N–Ag^+ interaction and affected the pyridyl protons shifted to lower magnetic field. In comparison with *cone*-**7**, the larger chemical shift changes for other protons in *cone*-**3** after complexation were observed. For example, in the case of *cone*-**3**, the *tert*-butyl proton and the calix benzene proton, located on the upper rim of the structure, were changed very little with +0.03 and −0.05 ppm, respectively.

Same protons in *cone*-**7**, having the longer distance between pyridine rings and calix benzene rings, were only +0.01 and −0.01 ppm. This is attributable to the longer alkylated chain in *cone*-**7** between the pyridyl moieties and phenolic oxygens than that in *cone*-**3**. When complex was formed by the pyridine rings and silver cation, the complex position was located only into the cavity of N atom in pyridine rings. The pyridine rings rotated around the NH_b–C(pyridyl) linkage to make the coordination while little conformation was changed for the whole structure.

The present ammonium ions binding mode can be also demonstrated more clearly by using ^{1}H NMR spectroscopy. There are two modes for *cone*-**7** to bind with *n*-butyl ammonium ions, i.e. from the lower rim through substituents moieties or from the upper rim through the π-cavity formed by three aromatic rings. The chemical shift differences in the absence and presence of *n*-butyl ammonium ion are shown in Fig. 3. After adding an equivalent of *n*-$BuNH_3Cl$ to solution of *cone*-**7** (5×10^{-3} M) in $CDCl_3$ at 27 °C, protons on aromatic rings, ArCH_2O, ArOCH_2 were dramatically shifted to lower magnetic field, which indicate that the binding mode is 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 the proton ^{1}H NMR spectroscopy, in which the encapsulated one was shifted to upfield, CH_3 (0.95–0.26, $\Delta\delta = -0.69$ ppm), CH_3CH_2 (1.45–0.30, $\Delta\delta = -1.05$ ppm), $CH_3CH_2CH_2$ (1.77 to −0.25, $\Delta\delta = -2.02$ ppm) and CH_2N (3.00–0.30, $\Delta\delta = -2.70$ ppm). The chemical shift of NH protons in *cone*-**7** was shifted to lower magnetic field (δ 8.32–9.07 ppm; $\Delta\delta = +0.75$ ppm for NH_a

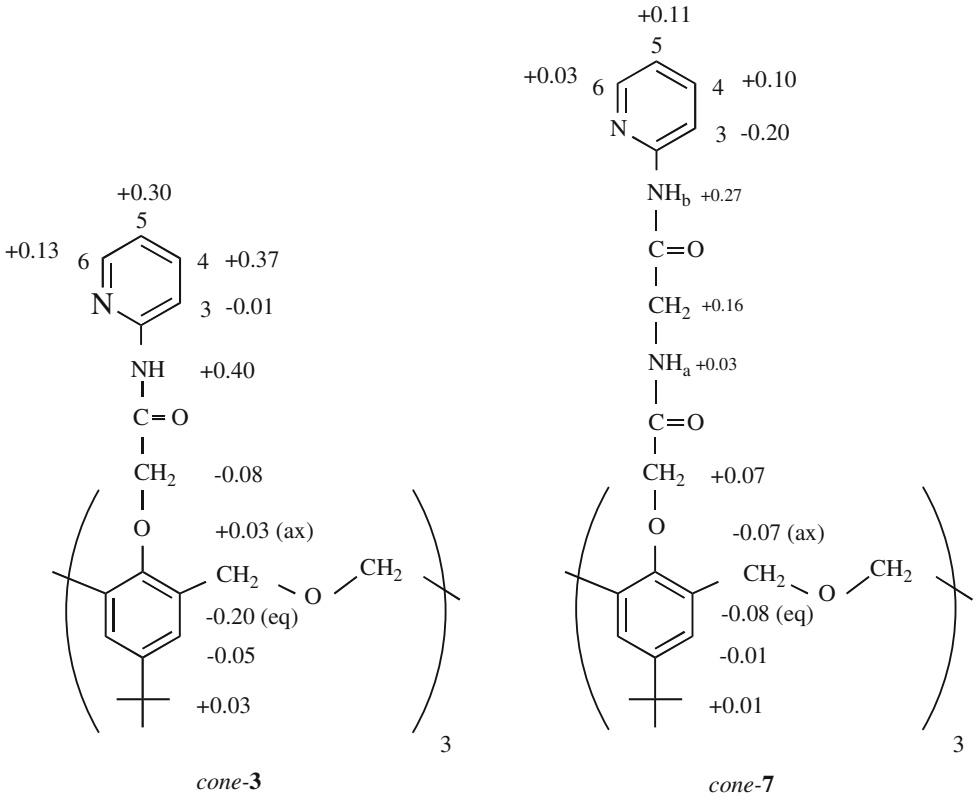


Fig. 2 Chemical shift changes of *cone*-**3** and *cone*-**7** induced in the presence of $AgSO_3CF_3$; (+) denotes the down-field and (−) denotes the up-field shift (300 MHz, $CDCl_3$:CD_3CN, 30:1 v/v, 27 °C)

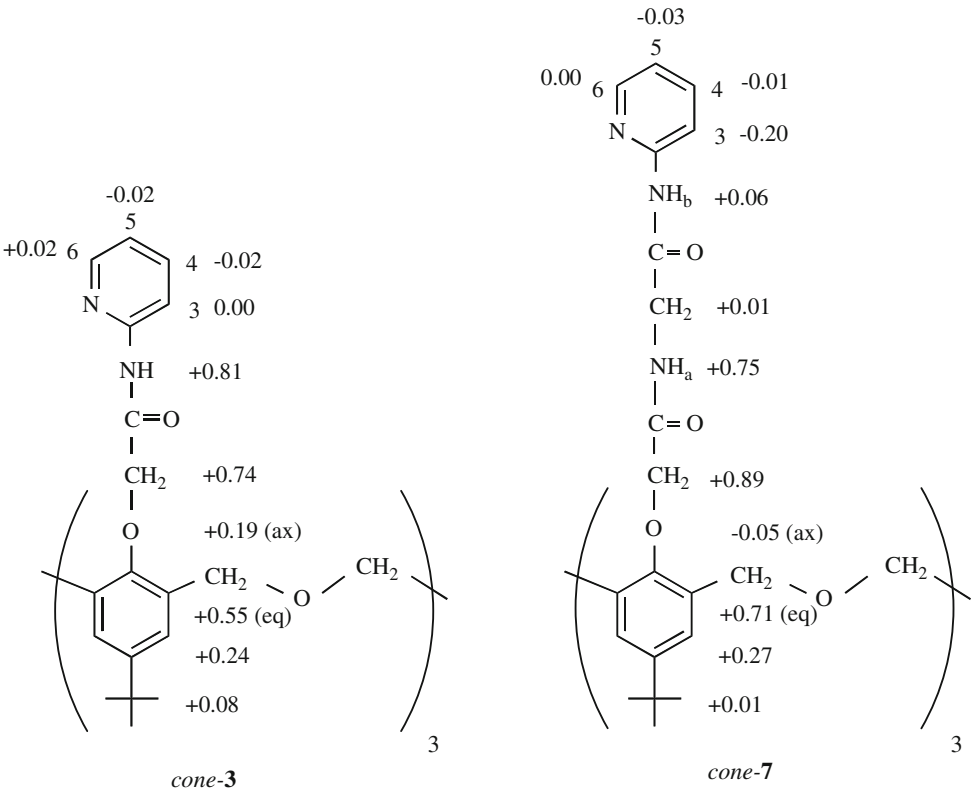


Fig. 3 Chemical shift changes of *cone*-**3** and *cone*-**7** induced in the presence of *n*-$BuNH_3Cl$; (+) denotes the down-field and (−) denotes the up-field shift (300 MHz, $CDCl_3$:CD_3CN, 30:1 v/v, 27 °C)

(δ 9.41–9.47 ppm; $\Delta\delta = +0.06$ ppm for NH_b) while NH in *n*-$BuNH_3Cl$ was shifted to upper field (δ 8.30–5.93; $\Delta\delta = -2.37$ ppm). As mentioned above, intramolecular hydrogen bonding in *cone*-**7** weakens the affinity of *cone*-**7** to metal ions which were encapsulated through the lower rim of homotrioxacalix[3]arene derivatives. When *cone*-**7** was complexed with *n*-$BuNH_3^+$ through π-cavity, the conformation of *cone*-**7** was changed and intramolecular hydrogen bonding was impossible in this conformation. As a result, the NH_a proton in *cone*-**7** was shifted to lower magnetic field to indicate complexation of the anionic guest Cl^- through hydrogen bonging. Similar phenomena were also observed in the case of complex of *cone*-**3** with *n*-$BuNH_3Cl$. It was also found that addition of *n*-Bu_4NI and $PhMe_3NCl$ to a solution of *cone*-**3** and *cone*-**7** in $CDCl_3$ (5×10^{-3} M), no complexation of halide anions was observed. Due to the strong intramolecular hydrogen bonding, the anion binding site is blocked.

As mentioned previously, $\Delta\delta$ between H_{ax} and H_{eq} of the ArCH_2Ar methylene protons in calix[4]arene serves as a measure of the 'flattening'. $\Delta\delta$ increases from δ 0.43 to δ 1.17 ppm in *cone*-**3** upon the binding of *n*-$BuNH_3^+$ and from δ 0.58 to δ 1.08 ppm in *cone*-**7** upon the binding of *n*-$BuNH_3^+$, respectively. These findings imply that both *cone*-**3** and *cone*-**7** 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 pyridine rings.

Modified homooxacalix[3]arene with functional groups will have the potential as a flexible ditopic receptor. Compounds *cone*-**3** and *cone*-**7** have been proven to complex with alkylammonium ion and silver cation simultaneously. Thus, the potential of them as the ditopic receptor to complex with *n*-$BuNH_3^+$ and silver cation will be great interesting in the coordination chemistry.

Compounds *cone*-**3** and *cone*-**7** were determined with silver cation and *n*-butyl ammonium ion through ^{1}H NMR titration to investigate the possibility as the ditopicreceptors. At first, with adding two equivalents of silver cation, the chemical shift of protons peaks was changed as described above. The further investigation was continued by adding two equivalent of *n*-butyl ammonium picrate to the solution of compounds *cone*-**3** and *cone*-**7** in the presence of silver cation. The results were shown in Table 2. The induced chemical shift to upper field of *n*-butyl ammonium protons strongly suggested the complexation of *cone*-**7** $\supset$ Ag^+ with *n*-butyl ammonium ion. Furthermore, the conformation of the host was changed too. Both *tert*-butyl protons and calix benzene protons were shifted to the lower field under the complexation with *n*-butyl ammonium ions. The chemical shift difference between the axial proton and equatorial proton in bridge methylene was increased upper to δ 0.93 ppm under the presence of both *n*-butyl ammonium ion and silver cation, which was mostly contributed by the complexation with *n*-butyl ammonium ion. Furthermore, the chemical shift of protons on pyridine

Table 2 Selected proton chemical shifts (δ, ppm) (300 MHz, $CDCl_3$:CD_3CN, 30:1 v/v, 27 °C) of *cone*-**3** and *cone*-**7** complexed with Ag^+ and *n*-$BuNH_3^+$

	*t*Bu	Ar-*H*	ArO*CH*$_2$ (N*CH*$_2$)	Ar*CH*$_2$O	Py-*H*			
					H_3	H_4	H_5	H_6
cone-**3**	1.15	6.99	4.49	4.95, 4.53	7.89	7.49	6.90	8.17
$+Ag^+$	1.18	6.94	4.41	4.97, 4.33	7.88	7.86	7.20	8.30
$Ag^+ + n\text{-}BuNH_3^+$	1.24	7.28	5.01	5.32, 4.35	7.91	7.62	7.05	8.21
cone-**7**	1.11	6.96	4.11 (4.21)	4.92, 4.37	8.20	7.69	7.04	8.30
$+Ag^+$	1.12	6.95	4.18 (4.37)	4.85, 4.29	8.00	7.79	7.15	8.33
$Ag^+ + n\text{-}BuNH_3^+$	1.21	7.26	4.82 (4.22)	5.26, 4.33	7.96	7.73	7.10	8.23

rings showed small changes (0.04–0.10 ppm) proving that the complex with silver cation was remained after *cone*-**7** ⊃ Ag^+ complex with *n*-butyl ammonium ion. The chemical shift of protons in pyridine in the complex of *cone*-**3** ⊃ Ag^+ has also a little change after it complex with *n*-butyl ammonium ion. Compared to the values of chemical shift on the complex of *cone*-**7** ⊃ Ag^+ with *n*-butyl ammonium ion, the similar tendency as that of *cone*-**3** ⊃ Ag^+ gave the same result as that of *cone*-**7** ⊃ Ag^+. Thus, compounds *cone*-**3** and *cone*-**7** can complex with *n*-butyl ammonium ions and silver cation at the same time to form the heteroditopic complexation (Fig. 4).

The anion complexation of *cone*-**7** ⊃ Ag^+ as a ditopic receptor was studied by ^{1}H NMR titration experiments [33, 34, 40–42]. However, we have not yet succeeded to get an evidence for *cone*-**7** ⊃ Ag^+ binding halide through the intermolecular hydrogen bonding among the N*H*$_a$ hydrogens of amide in a 1:1 fashion in $CDCl_3$.

When *cone*-**7** ⊃ Ag^+ complexed with *n*-$BuNH_3^+$ through π-cavity, intramolecular hydrogen bonding broken and the conformations of *cone*-**7** ⊃ Ag^+ changed into a symmetrical cone conformation. Thus, the complexation of the anionic guest Cl^- through hydrogen bonding is possible [33, 34]. Upon addition of Bu_4NCl or Bu_4NBr to a 5×10^{-3} M solution of *cone*-**7** ⊃ Ag^+ $CDCl_3/CD_3CN$, no complexations of halide anions were observed. Owing to intramolecular hydrogen bonding between N*H*$_a$ proton and neighboring CO moieties of *cone*-**7** ⊃ Ag^+, the anion-binding site is blocked. Base on this observation, we investigated the complexation of *cone*-**7** ⊃ Ag^+ with *n*-butylammonium halide counterions. After adding an equivalent of *n*-$BuNH_3Cl$ to a solution of *cone*-**7** ⊃ Ag^+ (5×10^{-3} M) in $CDCl_3/CD_3CN$ (10:1 v/v) at 27 °C, the protons on aromatic rings, Ar*CH*$_2$O, ArO*CH*$_2$ were dramatically shifted to lower magnetic field, which indicate that the binding mode are occurred through the π-cavity formed by three aromatic

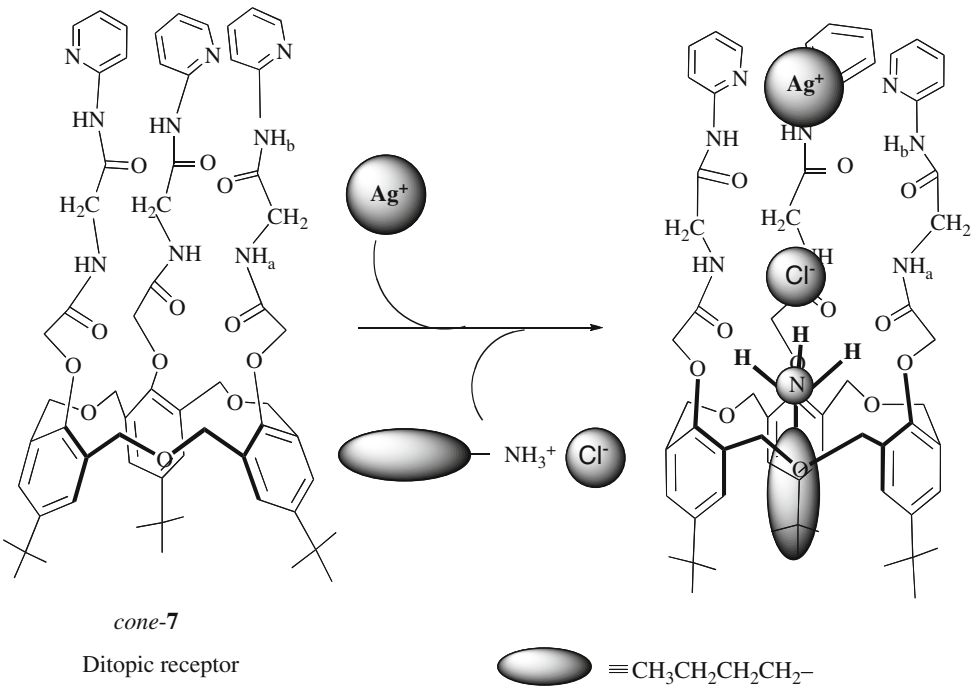


Fig. 4 Binding mode of *cone*-hexahomotrioxacalix[3]arene tris(2-pyridylamide) derivative *cone*-**7** with Ag^+ and *n*-$BuNH_3Cl$

rings. Intramolecular hydrogen bonding between NH_a protons and CO moieties were impossible in this conformation due to the rigidification of the hexahomotrioxacalix[3]arene skeleton. This is evident from the large downfield shift of the ^{1}H NMR signal for the aromatic hydrogens from $\delta = 6.96$ to $\delta = 7.26$ ppm. Additionally, larger downfield shift of the NH_a protons from $\delta = 8.32$ to $\delta = 9.07$ ppm ($\Delta\delta = +0.75$ ppm) to indicating complexation with the anionic guest through hydrogen bonding. Similar finding were also observed for the complexation of *cone*-**7** $\supset$ Ag^+ with *n*-$BuNH_3Br$. As the electronegativity of the halogen atom decreased with the series of Cl and Br atoms, the intensity of hydrogen bonding formed between their anions and NH_a protons should be decreased following the same order. In fact, in ^{1}H NMR spectrum of a mixture of *cone*-**7** $\supset$ Ag^+ and *n*-$BuNH_3{}^+X^-$, a larger downfield of chemical shift in the complex of NH_a with Cl^- was observed as compared with Br^-. The association constants of *cone*-**3** and *cone*-**7** with *n*-$BuNH_3{}^+$ ions in the absence and presence of Ag^+ calculated from the chemical shift changes of ArCH_2O are summarized in Table 3.

Interestingly, the association constant K_a for the complexation of *cone*-**7** with *n*-$BuNH_3Cl$ ($K_a = 2570 \pm 250$) is much larger than that with *n*-$BuNH_3$pic ($K_a = 2250 \pm 130$). Similar finding was observed in the complexation of *cone*-**3** ($K_a = 3690 \pm 310$ for *n*-$BuNH_3Cl$ and $K_a = 2675 \pm 155$ for *n*-$BuNH_3$pic). Thus, in the presence of chloride ion the complexation of *n*-butylammonium ion increases compared to picrate counterions, due to strong electrostatic interaction between *n*-butylammonium and Cl^- ions included in the cavity of *cone*-**7**. In contrast, in the presence of Ag^+ the complexation of *cone*-**7** with *n*-butylammonium chloride decreases compared to *n*-butylammonium picrate due to strong electrostatic interaction between Ag^+ and Cl^- ions. These results show that *cone*-**7** can simultaneously complex with Ag^+, *n*-$BuNH_3{}^+$ and Cl^- or Br^- ions and that *n*-$BuNH_3{}^+$ complexation induces a structural change that is prerequisite for anion complexation. This process resembles a heterotopic allosteric effect [43].

Table 3 Association constants (K_a, M^{-1}) of *cone*-**3** and *cone*-**7** with *n*-$BuNH_3{}^+$ ions in $CDCl_3$:CD_3CN = 10:1 (v/v) at 27 °C

Guest	Association constant K_a (M^{-1})	
	cone-**3**	*cone*-**7**
n-$BuNH_3$pic	2675 ± 155	2250 ± 130
Ag^+ + *n*-$BuNH_3$pic	1075 ± 65	1355 ± 65
n-$BuNH_3Cl$	3690 ± 310	2570 ± 250
Ag^+ + *n*-$BuNH_3Cl$	570 ± 40	985 ± 50

Measured in $CDCl_3$:CD_3CN = 10:1 (v/v) at 27 °C by the ^{1}H NMR titration method of the chemical shift change of the *NH* proton and ArCH_2O, host concentration was 5×10^{-3} M. Guest were used as $AgSO_3CF_3$, *n*-butylammonium picrate and *n*-butylammonium chloride

Conclusion

For the first time, the relationship between properties of ionophore hosts and their intramolecular hydrogen bonding was taken into account in C_3-symmetric conformation. Due to the intramolecular hydrogen bonding, the affinities of ionophores *cone*-**3** and *cone*-**7** to metal ions were weakened, it does not bind alkali metal ions because the binding site was blocked. Both *cone*-**3** and *cone*-**7** can bind *n*-butyl ammonium ions through the π-cavity formed by three aryl rings, which can provide functional moieties in biologic systems with good affinity and high selectivity. As C_3-symmetrical pyridyl-substituted calixarene, ionophores *cone*-**3** and *cone*-**7** can bind Ag^+ ion and the complexation mode was elucidated clearly in this paper. Thus, ionophores *cone*-**3** and *cone*-**7** serve as a heteroditopic receptor which can complex with Ag^+ and *n*-$BuNH_3{}^+$ at the same time. The nitrogen atom in pyridine ring turned from outward against the cavity to inside the cavity to interact with Ag^+. After complexation of tris(2-pyridylamide) derivative *cone*-**7** with Ag^+, the original C_3-symmetry has been remained for *cone*-**7**. Although we have not yet succeeded to get an evidence for *cone*-**7** binding halide through the intermolecular hydrogen bonding among the NH_a hydrogens of amide, *cone*-**7** can simultaneously complex with Ag^+, *n*-$BuNH_3{}^+$ and Cl^- ion from the consideration of the association constants K_a in the presence of different counteranions. To the best of our knowledge the present result is the first example of heterogeneous dinuclear complex in the hexahomooxacalix[3]arene family. These results give some insight into the molecular design of new synthetic receptors for use in anion controlled of biomimetic systems.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. 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 Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

Materials

cone-Hexahomotrioxacalix[3]arene triacetic acid (*cone*-**2b**), *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(2-pyridylaminocarbonyl)methoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-**3**) and (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid (**8**) were prepared according to the previously reported procedures [8, 23, 24].

Synthesis

*Synthesis of cone conformation of 7,15,23-tri-tert-butyl-25,26,27-tris[(methoxyacetyl)amino]carbonylmethoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (cone-**5**)*

To a solution of cone triacid homocalix[3]arene (*cone*-**2b**) (400 mg, 0.532 mmol) in CH_2Cl_2 (30 mL) with glycine methyl ester (**4a**) (427 mg, 4.80 mmol) was added HOBt (94 mg, 0.697 mmol), then the mixture solution was stirred at 0 °C while adding a solution of DCC (684 mg) in CH_2Cl_2 (10 mL) by dropwise. Then the solution was stirred for 15 h at room temperature. After reaction, remove solvent, then the residue was dissolved with AcOEt and filtered, the filtrate was washed orderly with 10% citric acid, water, 5% sodium bicarbonate, water and brine. Dried with Na_2SO_4 then removed solvent under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with AcOEt as eluent to give a colorless solid. The solid was recrystallized from methanol to give *cone*-**5** (365 mg, 70.5%) as colorless prisms. Mp 90–92 °C. IR ν_{max} (KBr)/cm^{-1} 3350, 2958, 2871, 1752, 1678, 1540, 1484, 1200, 1076. ^{1}H NMR δ ($CDCl_3$) 1.13 (27H, s, *t*Bu), 3.78 (9H, s, CH_3), 4.15 (6H, d, *J* 5.86, N-CH_2), 4.38 (6H, d, *J* 12.7, ArCH_2O), 4.78 (6H, d, *J* 12.7, ArCH_2O), 4.23 (6H, s, ArOCH_2), 6.95 (6H, s, Ar-*H*), 8.03 (3H, s, N*H*). MS *m/z* 964 (M^+). Anal. Calcd. for $C_{51}H_{69}O_{15}N_3$ (964.12): C, 63.54; H, 7.21; N, 4.36. Found: C, 63.75; H, 7.35; N, 4.26%.

*Synthesis of cone conformation of 7,15,23-tri-tert-butyl-25,26,27-tris[(hydroxyacetyl)amino]carbonylmethoxy]-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (cone-**6**)*

To a mixture of *cone*-**5** (225 mg) in dioxane (35 mL) was added 1 M NaOH aqueous solution (25 mL), the mixture was stirred at room temperature for 1 h, then the solution was removed dioxane under reduced pressure. The residue was acidified to neutral condition. The dispersion 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 reduce pressure. The residue was washed with hexane to give *cone*-**6** (170 mg, 79%) as colorless solid. Mp 215–217 °C. IR ν_{max} (KBr)/cm^{-1} 3500–3250, 2958, 2867, 1736, 1661, 1540, 1457, 1363, 1231, 1197, 1093. ^{1}H NMR δ ($CDCl_3$-MeOH[D_4], 3:1, v/v) 1.13 (27H, s, *t*Bu), 4.13 (6H, s, ArOCH_2), 4.20 (6H, d, *J* 5.86, N-CH_2), 4.42 (6H, d, *J* 12.7, ArCH_2O), 4.80 (6H, d, *J* 12.7, ArCH_2O), 6.97 (6H, s, Ar-H), 8.18 (3H, t, *NH*). MS *m/z* 922 (M^+). Anal. Calcd. for $C_{48}H_{63}O_{15}N_3$ (922.05): C, 62.53; H, 6.89; N, 4.56. Found: C, 62.72; H, 6.73; N, 4.40%.

*Synthesis of tris(2-pyridylamide) derivative of homooxacalix[3]arene (cone-**7**)*

To a solution of cone triacid homocalix[3]arene (*cone*-**6**) (491 mg, 0.532 mmol) in CH_2Cl_2 (30 mL) with 2-aminopyridine (514 mg, 4.80 mmol) was added HOBt (94 mg, 0.697 mmol), then the mixture solution was stirred at 0 °C while adding a solution of DCC (684 mg) in CH_2Cl_2 (10 mL) by dropwise. Then the solution was stirred for 15 h at room temperature. After reaction, remove solvent, then the residue was dissolved with AcOEt and filtered, the filtrate was washed orderly with 10% citric acid, water, 5% sodium bicarbonate, water and brine. Dried with Na_2SO_4 then removed solvent under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with AcOEt as eluent to give a colorless solid. The solid was recrystallized from methanol to give *cone*-**7** (538 mg, 85%) as colorless prisms. Mp 152–154 °C. IR ν_{max} (KBr)/cm^{-1} 3476, 3410, 3312, 2958, 2867, 1664, 1609, 1541, 1516, 1482, 1197, 818. ^{1}H NMR δ ($CDCl_3$) 1.12 (27H, s, *t*Bu), 4.13 (6H, s, ArOCH_2), 4.23 (6H, d, *J* 5.86, N-CH_2), 4.35 (6H, d, *J* 12.7, ArCH_2O), 4.90 (6H, d, *J* 12.7, ArCH_2O), 6.96 (6H, s, Ar-*H*), 7.04 (3H, m, pyridine-H_5), 7.69 (m, 3H, pyridine-H_4), 8.20 (3H, d, *J* 8.30, pyridine-H_3), 8.30 (3H, dd, *J* 3.90, 2.44, pyridine-H_6), 8.45 (3H, t, NH_a), 9.21 (3H, s, NH_b). MS *m/z* 1150 (M^+). Anal. Calcd. for $C_{63}H_{75}O_{12}N_9$ (1150.35): C, 65.76; H, 6.57; N, 10.96. Found: C, 65.61; H, 6.38; N, 10.04%.

*Preparation of 4-tert-butyl-2,6-dimethyl[(methoxyacetylaminocarbonyl)methoxy]benzene (**9a**)*

To a solution of (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid **8** (100 mg, 0.43 mmol), glycine methyl ester **4a** (114 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 (30 mL × 2). The combined extracts were washed with 10% citric acid (20 mL × 2), 5% sodium bicarbonate

(20 mL), water (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduce pressure. The residue was recrystallized from methanol to give the *title compound* **9a** (87 mg, 66%) as colorless prisms. Mp 101–102 °C. IR ν_{max} (KBr)/cm^{-1} 3337, 3320, 2968, 2865, 1755, 1734, 1667, 1534, 1488, 1277, 1197, 1182, 1056. ^{1}H NMR δ ($CDCl_3$) 1.29 (9H, s, *t*Bu), 2.27 (6H, s, *CH*$_3$), 3.80 (3H, s, O*CH*$_3$), 4.20 (2H, d, *J* 5.37, N-*CH*$_2$), 4.33 (2H, s, ArO*CH*$_2$), 7.03 (2H, s, Ar-*H*), 7.46 (1H, t, *NH*). MS *m/z* 307 (M^+). Anal. Calcd. for $C_{17}H_{25}O_4N$ (307.39): C, 66.43; H, 8.2; N, 4.56. Found: C, 66.23; H, 8.35; N, 4.68%.

*Preparation of 4-tert-butyl-2,6-dimethyl [(hydroxyacetylaminocarbonyl)methoxy]benzene (**9b**)*

To a solution of **9a** (150 mg, 0.49 mmol) in dioxane (30 mL) was added 1 M 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 (30 mL × 2). The combined extracts were washed with water (20 mL), saturated brine (20 mL), dried (Na_2SO_4) and condensed under reduce pressure. The residue was washed with hexane to give **9b** (136 mg, 95%) as a colorless solid. Mp 193–195 °C. IR ν_{max} (KBr)/cm^{-1} 3383, 2963, 2925, 2867, 1730, 1635, 1540, 1436, 1245, 1229, 1124. ^{1}H NMR δ ($CDCl_3$) 1.29 (9H, s, *t*Bu), 2.27(6H, s, *CH*$_3$), 4.25 (2H, d, *J* 5.37 Hz, N-*CH*$_2$), 4.35 (2H, s, ArO*CH*$_2$), 7.03 (2H, s, Ar-*H*), 7.46 (1H, t, *J* 5.37 Hz, *NH*). MS *m/z* 293 (M^+). Anal. Calcd. for $C_{16}H_{23}O_4N$ (293.37): C, 65.51; H, 7.9; N, 4.77. Found: C, 65.63; H, 7.87; N, 4.64%.

*Preparation of 4-tert-butyl-2,6-dimethyl[(2-pyridylaminocarbonyl)methoxy]benzene (**9c**)*

To a solution of **9b** (50 mg, 0.17 mmol), 2-aminopyridine (55 mg, 0.51 mmol) and 1-hydroxybenzotriazole (HOBt) (23 mg, 0.17 mmol) in CH_2Cl_2 (12 mL) was added dropwise 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 reduce pressure. The residue was recrystallized from hexane-CH_2Cl_2 (3:1) gave **9c** (56 mg, 89%) as colorless prisms. Mp 217–219 °C; IR ν_{max} (KBr)/cm^{-1} 3407, 3268, 2960, 2950, 2867, 1699, 1665, 1577, 1541, 1518, 1432, 1300, 1192. ^{1}H NMR δ ($CDCl_3$) 1.29 (9H, s, *t*Bu), 2.28 (6H, s, *CH*$_3$), 4.30 (2H, d, *J* 5.37 Hz, N-*CH*$_2$), 4.38 (2H, s, ArO*CH*$_2$), 7.03 (2H, s, Ar-*H*), 7.09 (1H, m, pyridine-*H*$_5$), 7.75 (1H, m, pyridine-*H*$_4$), 8.21 (1H, d, *J* 8.30, pyridine-*H*$_3$), 8.30 (1H, dd, *J* 3.90, 2.44, pyridine-*H*$_6$), 7.76 (1H, t, *NH*$_a$), 8.36 (1H, s, *NH*$_b$). MS *m/z* 369 (M^+). Anal. Calcd. for $C_{21}H_{27}O_3N_3$ (369.46): C, 68.27; H, 7.37; N, 11.37. Found: C, 68.45; H, 7.53; N, 11.48%.

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 [$AgNO_3$, $Cu(NO_3)_2{\cdot}3H_2O$, $Al(NO_3)_3{\cdot}9H_2O$] in 2.5×10^{-4} M of picric acid. Alkyl ammonium picrates were prepared by mixing an equimolar 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 is sufficient to attain the distribution equilibrium. This was repeated three 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 [44].

^{1}H NMR complexation experiment

To a $CDCl_3$ solution (5×10^{-3} M) of *cone*-**3** and *cone*-**7** in the NMR tube was added an equivalent of *n*-$BuNH_3X$. The spectrum was registered after addition and the temperature of 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 with 5 mM. As a probe the chemical shift of the amide protons [C(O)NH_b] signal was used. The association constant values were calculated by the integral intensity of NH protons in the complex and free host molecules according to the literature [45].

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