Ditopic receptors of hexaamide derivatives derived from hexahomotrioxacalix[3]arene triacetic acid

Takehiko Yamato, Shofiur Rahman, Zeng Xi, Fumika Kitajima, and Jeong Tae Gil

Abstract: The lower rim functionalized hexahomotrioxacalix[3]arene hexaamide **7** having an amino acid moiety with cone conformation was synthesized from triol **1** by a stepwise reaction. The different extractability for alkali metal ions, transition metal ions, and alkylammonium ions from water into dichloromethane was discussed. Owing to the strong intramolecular hydrogen bond between the neighboring NH and CO groups in hexaamide **7**, its affinity to metal cations was weakened. Hexaamide **7** shows a single selectivity to n-$BuNH_3^+$. The anion complexation of hexaamide **7** was also studied by ^{1}H NMR titration experiments. Hexaamide **7** binds halides through the intermolecular hydrogen bond among the NH hydrogens of the amide in a 1:1 fashion in $CDCl_3$. Thus, hexaamide **7** serves as a heteroditopic receptor that can complex with halides (Cl^-, Br^-) and n-$BuNH_3^+$ at the same time. The association constants calculated from the chemical shift changes of the amide protons are K_a = 536 ± 32 $(mol/L)^{-1}$ for Cl^- and K_a = 230 ± 17 $(mol/L)^{-1}$ for Br^-.

Key words: hexahomotrioxacalix[3]arenes, ionophores, molecular recognition, ammonium ion, ditopic receptor.

Résumé : Utilisant le triol **1** comme produit de départ, on a réalisé la synthèse par étape de l'hexahomotrioxacalix[3]arène hexaamide **7** dont la ceinture inférieure fonctionnalisée porte une portion d'acide aminé avec conformation en cône. On discute des possibilités de l'extraire de solutions aqueuses vers du dichlorométhane à l'aide de divers ions métalliques alcalins ou métalliques et avec des ions alkylammonium. En raison de la forte liaison hydrogène intramoléculaire entre les groupes voisins NH et CO dans l'hexaamide **7**, son affinité pour les cations métalliques est réduite. L'hexaamide **7** présente une sélectivité particulière pour le n-$BuNH_3^+$. La complexation anionique de l'hexaamide **7** a aussi été étudiée par des expériences de titrage par RMN du ^{1}H. Dans le $CDCl_3$, l'hexaamide **7** se lie aux halogénures par le biais d'une liaison hydrogène intermoléculaire 1 : 1 avec les atomes d'hydrogène NH de l'amide. L'hexaamide **7** peut donc servir de récepteur hétéroditopique qui peut complexer en même temps les halogénures (Cl^-, Br^-) et le n-$BuNH_3^+$. Les constantes d'association obtenues à partir des changements du déplacement chimique des protons de l'amide sont K_a = 536 ± 32 $(mol/L)^{-1}$ pour Cl^- et K_a = 230 ± 17 $(mol/L)^{-1}$ pour Br^-.

Mots clés : hexahomotrioxacalix[3]arène, ionophores, reconnaissance moléculaire, ion ammonium, récepteur ditopique.

[Traduit par la Rédaction]

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 highly selective cation-binding properties (1). Shinkai and co-workers (2) reported the complexation of alkali metals to hexahomotrioxacalix[3]arene derivatives with alkylated phenolic oxygens. Hexahomotrioxacalix[3]arene derivatives with C_3 symmetry can selectively bind ammonium ions, which play important roles in both chemistry and biology (3). Thus, Takeshita and Shinkai (2*b*) reported the construction of C_3 symmetry pyrene-functionalized hexahomotrioxacalix[3]arenes, which selectively recognize primary ammonium ions.

On the other hand, the hydrogen bond plays an important role in the self-assembly of molecular recognition and has been investigated 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 (4). Arduini et al. (5) also described the formation of a hydrogen-bonded dimer in $CDCl_3$ based on the self-complementarity of carboxylic acid. The intramolecular hydrogen bonding also formed among opposing urea groups, which can bind anionic species, in calix[4]arene (6). Thus, the design of new ditopic ligands (7) 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 contain-

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Scheme 1.

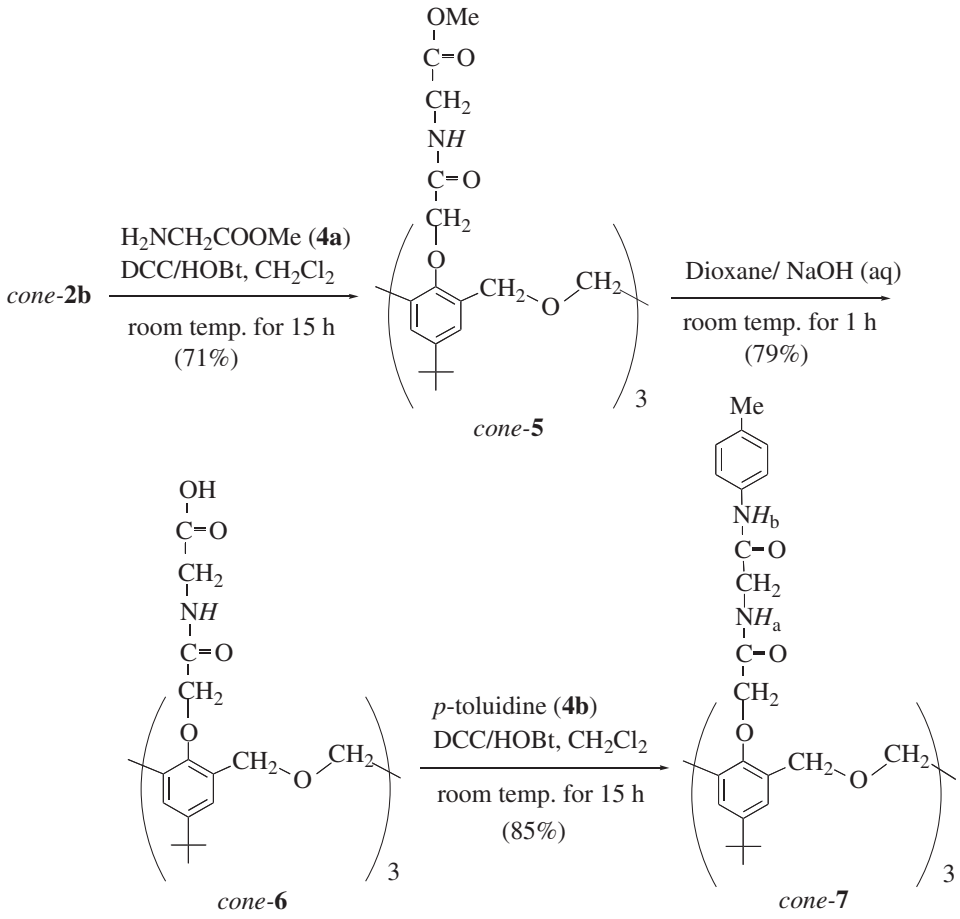
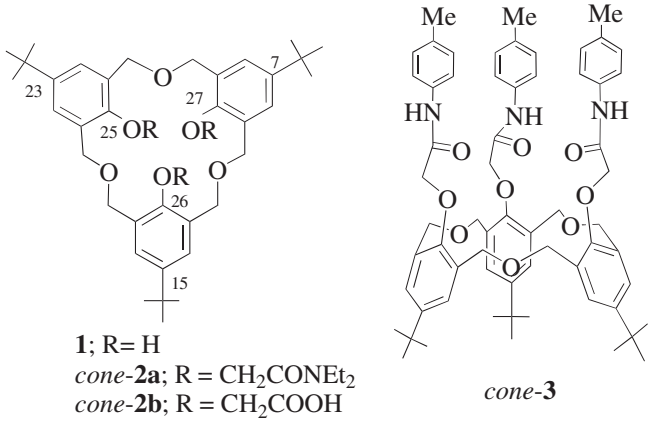


Chart 1.



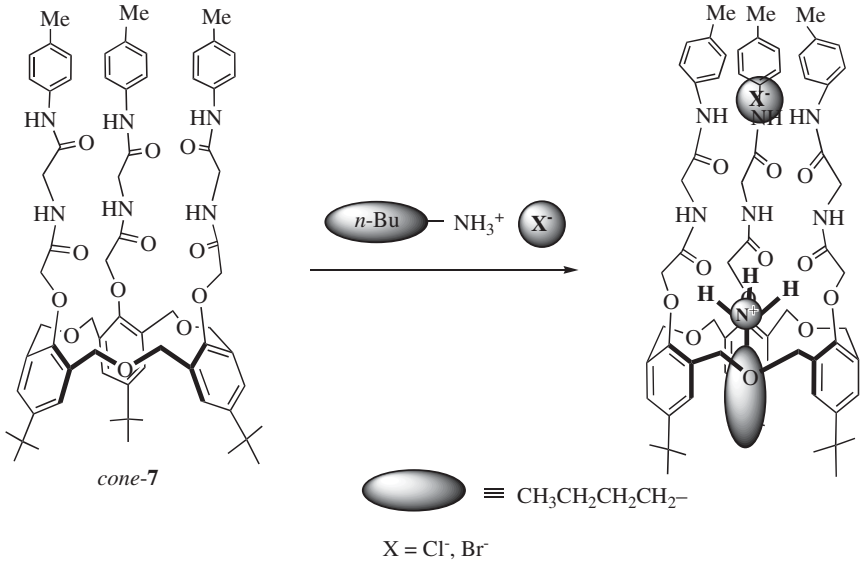
ing appropriate covalently linked binding sites for anions and cations include Lewis acidic boron (8), uranyl (9), polyammonium (10) centers combined with crown ether moieties, and crown ether or urea-functionalized calix[4]arene ionophores (11), which are capable of solubilizing alkali metal salts into organic media (Chart 1).

Recently, we reported a ditopic receptor (*cone*-**3**) incorporating these two types of recognition sites by introducing three amide groups to the phenolic oxygens of homotrioxacalix[3]arene, which can simultaneously bind alkyl ammonium ions and halides (12*a*). On the other hand, the introduction of multiple binding sites for cations and anions is important for the construction of the allosteric host–guest inclusion systems. In the present paper, we describe the synthesis, conformations, and metal and ammonium ion complexation properties of the additional amino acid linked cone *p*-methylphenyl amide derivative having two hydrogen-bonding systems and C_3-symmetric ionophoric cavities.

Results and discussion

cone-Hexahomotrioxacalix[3]arene tricarboxylic acid (*cone*-2**b**) was prepared by hydrolysis of *cone*-[(*N*,*N*-diethylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene (*cone*-**2a**) with aq. KOH 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 (2*d*, 12). *cone*-Hexahomotrioxacalix[3]arene triamide (*cone*-**5**) was prepared by a condensation reaction of *cone*-**2b** with glycine methyl ester (**4a**) in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBt) at room temperature for 15 h in CH_2Cl_2. *cone*-**5** was converted to triacid *cone*-**6** by hydrolysis with aq. NaOH in a mixture of dioxane and water at room temperature. *cone*-**6** was treated with *p*-toluidine (**4b**) in the presence of DCC and HOBt similar to that of *cone*-**5** to afford

Fig. 1. Binding mode of host *cone*-**7** and *n*-$BuNH_3X$.



the desired compound *cone*-hexahomotrioxacalix[3]arene hexaamide (*cone*-**7**) in 85% yield (Scheme 1).

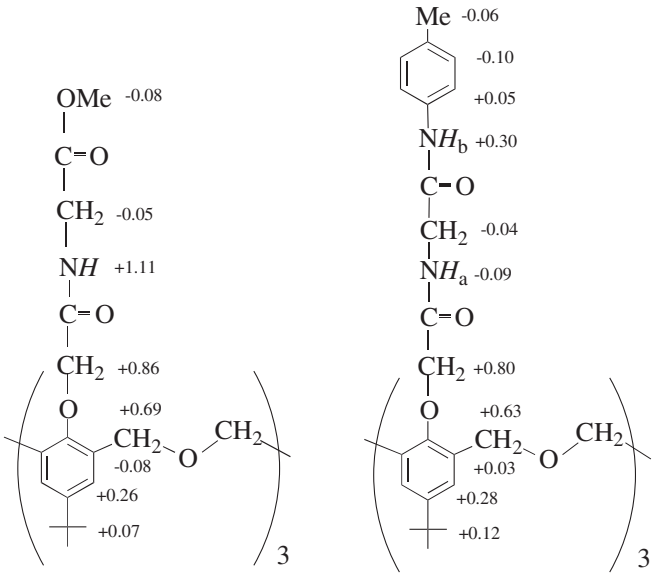
From the singlet peaks of *tert*-butyl protons and calix benzene protons for *cone*-**7**, it could be seen that the conformation remained in the desired compound with the cone conformation. To investigate the intramolecular hydrogen bond between the neighboring NH and CO groups of *cone*-**7** in detail, a reference compound **9c** was synthesized from 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid (**8**) following a method similar to that used in the preparation of *cone*-**7**.

Conformation assignment for the new hexahomotrioxacalix[3]arene hexaamide (*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 0.45 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 approximately 0.5 ppm with flattened cone or out orientation, and $\Delta\delta$ of 0 ppm with 1,3-alternate or anti orientation (13). The same findings were observed in hexahomotrioxacalix[3]arenes (2*a*). 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 the 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 with 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 was no change in the chemical shifts for both NH_a and NH_b protons, which is attributed to the concentration-independent intramolecular hydrogen bonds formed in this compound. Interestingly, the chemical shift of the NH_b protons in *cone*-**7** was shifted to a lower magnetic field to δ 9.91 ppm in DMSO-d_6 than in $CDCl_3$ (δ 9.21 ppm, $\Delta\delta$ = +0.70 ppm). This phenomenon was attributed to the intermolecular hydrogen bonding formed between the NH_b proton and DMSO-d_6. The intramolecular hydrogen bonding formed in compound *cone*-**7** was broken, and the new intermolecular hydrogen bonding was formed.

Interestingly, hexaamide *cone*-**7** shows low efficiency for metal cations compared with *cone*-**2a** (2*d*). The ionophoric activity of *cone*-**7** was almost absent. Hexaamide *cone*-**7** shows a single affinity only to *n*-butylammonium ion owing to the C_3-symmetric structure. However, no extractability for isobutyl- or *tert*-butyl-ammonium ion was observed under the conditions used. The ionophores usually form loose ion pairs with metal picrates, which produced the maximum absorption peak at 377 nm (14, 15). Interestingly, the hexaamide *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 a higher affinity to alkali metal ions (Na^+ (93.0% extraction) and K^+ (71.6%)), transition metal ions (Ag^+ (90.4%) and Cu^{2+} (27.5%)), and typical metal ion (Al^{3+} (19.1%)). Higher extractabilities of the *cone*-*N*,*N*-diethylamide derivative for *n*-butyl- (97.8%), isobutyl- (48.1%), and *tert*-butylammonium ion (35.4%) were observed and are attributable to the higher electron density of the oxygen of the carbonyl group by the electron donation ability of the amide group through conjugation N–C=O $\leftrightarrow$ N^+=C–O^- (2*d*, 12*a*, 12*b*). These findings clearly indicate that because of the strong hydrogen-bonding formation between NH and neighboring CO groups in hexaamide *cone*-**7**, there is no affinity shown for either hard or soft metal cations.

The present binding mode can be demonstrated more clearly by using ^{1}H NMR spectroscopy. There are two modes for *cone*-**7** to bind with *n*-butylammonium ion (Fig. 1), i.e., from the lower rim through substituent moieties or from the upper rim through the π cavity formed by three aromatic rings. As shown in Fig. 2, the chemical shifts of *cone*-**7** are different in the absence or presence of *n*-butylammonium ion. After adding an equivalent of *n*-$BuNH_3Cl$ to a solution of *cone*-**7** (5×10^{-3} (mol/L)$^{-1}$) in $CDCl_3$ at 27 °C, methylene protons of Ar$CH_2O CH_2$Ar and Ar′OCH_2CONHCH_2CONH$C_6H_4CH_3$ were dramatically shifted to a lower magnetic field, indicating that the binding mode is occurring through

Fig. 2. Chemical shift changes (Δδ) of *cone*-**5** and *cone*-**7** (5×10^{-3} mol/L) induced in the presence of *n*-$BuNH_3Cl$ (5×10^{-3} mol/L) in $CDCl_3$ at 27 °C. A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (–) denotes a shift to higher magnetic field.



the π cavity formed by the three aromatic rings. This binding is attributed to the π effect of aromatic rings on the C-H protons of the alkyl group because both the host and guest molecules have a C_3-symmetric conformation. With an excess of *n*-$BuNH_3Cl$, the free guest molecule and the encapsulated guest molecule were clearly observed by ^{1}H NMR spectroscopy in which the encapsulated one was shifted upfield: CH_3 (δ 0.95–0.26 ppm, Δδ = –0.69 ppm), CH_3CH_2 (δ 1.45–0.30 ppm, Δδ = –1.05 ppm), $CH_3CH_2CH_2$ (δ 1.77 to –0.25 ppm, Δδ = –2.02 ppm), and CH_2N (δ 3.00–0.30 ppm, Δδ = –2.70 ppm). The NH_b proton in *cone*-**7** was shifted to a lower magnetic field (δ 9.21–9.51 ppm, Δδ = +0.30 ppm) while NH_a was shifted to an upper field (δ 8.45–8.36 ppm, Δδ = –0.09 ppm). This observation indicates that the complexation of the anionic guest Cl^- occurred at the *p*-methylphenyl amide moiety but not at the glycine amide moiety. This is different from the observation that N*H* of the glycine amide in *cone*-**5** was shifted strongly to a lower magnetic field (δ 8.03–9.14 ppm, Δδ = +1.11 ppm).

As mentioned above, Δδ between H_{ax} and H_{eq} of the ArCH_2Ar methylene protons in calix[4]arene serves as a measure of the "flattening". The Δδ value increases from 0.37 to 0.92 ppm in *cone*-**7** upon the binding of *n*-$BuNH_3^+$. These findings imply that *cone*-**7** stands up when the guest is included because *n*-$BuNH_3^+$ enters into the π cavity formed by the three aromatic rings and Cl^- complexes with NH_b by hydrogen-bonding interaction. Similar findings were observed in the case of *cone*-**5** and *n*-$BuNH_3Cl$ (the Δδ value increases from 0.40 to 1.15 ppm).

Intramolecular hydrogen bonding in *cone*-**7** weakens the affinity of *cone*-**7** to metal ions, which were encapsulated through the lower rim of the homotrioxacalix[3]arene derivative. When *cone*-**7** was complexed with *n*-$BuNH_3^+$ through the π cavity, the conformation was changed and intramolecular hydrogen bonding was broken. Thus, the complexation of the anionic guest Cl^- through hydrogen bonding is possible (16). Upon the addition of *n*-Bu_4NI and $PhMe_3NCl$ to a solution of *cone*-**7** in $CDCl_3$ (5×10^{-3} (mol/L)$^{-1}$), no complexation of halide anions was observed. This is due to the strong intramolecular hydrogen bonding, which breaks the anion binding site.

Table 1. Association constants (K_a, (mol/L)$^{-1}$) and free energies of association (ΔG, kJ mol^{-1}) of hosts *cone*-**3**, *cone*-**5**, and *cone*-**7** with halide anions.

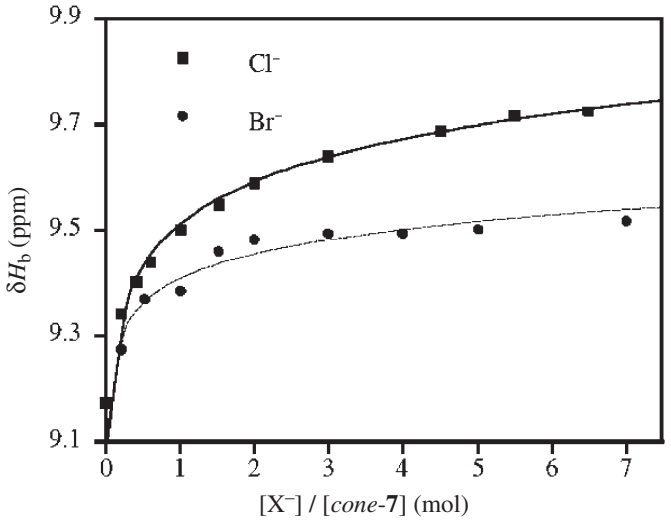
	Cl^-		Br^-	
Hosts	K_a	$-\Delta G°$	K_a	$-\Delta G°$
cone-**3**	8520±510	22.6	1731±122	18.6
cone-**5**	1060±60	17.4	220±16	13.4
cone-**7**	536±32	15.7	230±17	13.6

Note: In $CDCl_3$ at 27 °C; host concentration was 5 mmol/L.

Based on this observation, we investigated the complexation of *cone*-**7** with *n*-butylammonium halide counterions. With the addition of ammonium halide counterions, the proton peaks in *cone*-**7** were separated into complex and uncomplex. The downfield shift of NH_b might be attributed to the presence of the anionic guest close to the NH_b group by the intramolecular hydrogen bonding. The chloride anion induces a larger downfield shift for the amide hydrogen of *cone*-**7** than the bromide anion does. For example, significant downfield shifts of Δδ = +0.60 ppm for the NH_b proton in the case of Cl^- and Δδ = +0.40 ppm in the case of Br^- were observed. As the electronegativity of the halogen atom decreased with the series of Cl, Br, and I atoms, the intensity of hydrogen bonding formed between their anions and N*H* protons should be decreased following the same order. In fact, in ^{1}H NMR spectrum of a mixture of *cone*-**7** and *n*-$BuNH_3^+X^-$, a larger downfield chemical shift in the complex of NH_b with Cl^- was observed as compared with Br^- and I^-. The association constants calculated from these changes in chemical shifts of the amide protons are K_a = 536 ± 32 (mol/L)$^{-1}$ ($\Delta G°$ = 15.7 kJ mol^{-1}) for Cl^- and K_a = 230 ± 17 (mol/L)$^{-1}$ ($-\Delta G°$ = 13.6 kJ mol^{-1}) for Br^-. The smaller K_a values for the halide anions than for those of *cone*-**3** and *cone*-**5** might be attributable to the reduced electrostatic attractive interaction between *n*-butylammonium ion and the halide anions arising from the longer distance (Table 1).

Similar to triamide *cone*-**3**, hexaamide *cone*-**7** shows a preference for Cl^- over Br^- complexation (Fig. 3). This finding suggests that the cavity formed by the threefold amide moieties is more complementary to the size of the Cl^- than to that of Br^-, as well as the higher electronegativity of Cl^- than that of Br^-. In the case of tri(urea)-functionalized calix[6]arene, the anion complexation is prefered for Br^- because it has a large calix cavity and the three functionalized moieties in the 1, 3, and 5 positions of calix[6]arene are more complementary to the size of Br^- than to that of Cl^- (16*b*). Calix[5]arene derivatives were reported to complex with alkylammonium ions and to display an enzymelike selectivity (17) towards biologically important ammonium substrates. Since hexahomotrioxacalix[3]arenes and their de-

Fig. 3. Dependence of halide anion on chemical shift values of proton NH_b in *cone*-**7**.



rivatives have the C_3-symmetric conformation, they can bind with primary ammonium ions, having a potential function not only in chemical but also in biological systems (3).

Conclusions

We have demonstrated that the relationship between the properties of ionophore hosts and their intramolecular hydrogen bonding was taken into account in C_3-symmetric conformation. Owing to the intramolecular hydrogen bonding, the affinities of ionophore *cone*-**7** to metal ions were weakened; *cone*-**7** does not bind alkali metal ions because the binding site was blocked. However, hexaamide *cone*-**7** can bind *n*-butylammonium ion through the π cavity formed by three aryl rings, which can provide functional moieties in biological systems with good affinity and high selectivity. Interestingly, hexaamide *cone*-**7** binds a halide through the intermolecular hydrogen bonding among the NH_b hydrogens of *p*-methyphenyl amide in a 1:1 fashion in $CDCl_3$ in spite of the reduced electrostatic attractive interaction between *n*-butylammonium ions and the halide anions arising from the longer distance. Thus, hexaamide *cone*-**7** serves as a heteroditopic receptor that can complex with Cl^- and *n*-$BuNH_3^+$ at the same time. These results give some insight into the molecular design of new synthetic receptors for use in anion-controlled biomimetic systems.

Experimental

All melting points (Yanagimoto MP-S1) were uncorrected. ^{1}H NMR spectra were recorded on a Nippon Denshi JEOL FT-270 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Nippon Denshi JMS-01SG-2 mass spectrometer at an ionization energy of 70 eV using a direct inlet system through GLC; *m*/*z* values reported include the parent ion peak. IR spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Elemental analyses were performed using a Yanaco MT-5. UV spectra were measured by a Hitachi 220A spectrophotometer.

Materials

cone-Hexahomotrioxacalix[3]arene triacetic acid (*cone*-**2b**) and (4-*tert*-butyl-2,6-dimethyl)phenoxyacetic acid (**8**) were prepared according to the previously reported procedures (2*d*, 12*a*, 12*b*).

Preparation of *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(methoxyacetylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-5)

To a solution of *cone*-hexahomotrioxacalix[3]arene triacetic acid (*cone*-**2b**) (400 mg, 0.532 mmol) and glycine methyl ester (**4a**) (427 mg, 4.80 mmol) in CH_2Cl_2 (30 mL) was added 1-hydroxybenzotriazole (HOBt) (94 mg, 0.697 mmol). To the mixture was added a solution of dicyclohexylcarbodiimide (DCC) (684 mg) in CH_2Cl_2 (10 mL) dropwise at 0 °C. Then the solution was stirred for 15 h at room temperature. After reaction, the solvent was removed; then the residue was dissolved with AcOEt and filtered; the filtrate was washed with 10% citric acid, water, 5% sodium bicarbonate, water, and brine, dried with Na_2SO_4, and condensed under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with AcOEt as the 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 (KBr) ν_{max}: 3350, 2958, 2871, 1752, 1678, 1540, 1484, 1200, 1076. ^{1}H NMR ($CDCl_3$) δ: 1.13 (27H, s, *t*-Bu), 3.78 (9H, s, *CH*$_3$), 4.15 (6H, d, *J* = 5.86 Hz, N-*CH*$_2$), 4.38 (6H, d, *J* = 12.7 Hz, Ar*CH*$_2$O), 4.78 (6H, d, *J* = 12.7 Hz, Ar*CH*$_2$O), 4.23 (6H, s, ArO*CH*$_2$), 6.95 (6H, s, Ar-*H*), 8.03 (3H, s, N*H*). *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.

Preparation of *cone*-7,15,23-tri-*tert*-butyl-25,26,27-tris[(hydroxyacetylaminocarbonyl)methoxy]-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]arene (*cone*-6)

To a mixture of *cone*-**5** (225 mg, 0.23 mmol) in dioxane (35 mL) was added an aqueous 1 mol/L NaOH solution (25 mL), the mixture was stirred at room temperature for 1 h, then the solvent was removed under reduced pressure. The residue was acidified to neutral pH. The dispersion 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), and saturated brine (20 mL), dried with Na_2SO_4, and condensed under reduced pressure. The residue was washed with hexane to give *cone*-**6** (170 mg, 79%) as a colorless solid, mp 215–217 °C. IR (KBr) ν_{max}: 3500–3250, 2958, 2867, 1736, 1661, 1540, 1457, 1363, 1231, 1197, 1093. ^{1}H NMR ($CDCl_3$–MeOH[D_4], 3:1 *v*/*v*) δ: 1.13 (27H, s, *t*-Bu), 4.13 (6H, s, ArO*CH*$_2$), 4.20 (6H, d, *J* = 5.86 Hz, N-*CH*$_2$), 4.42 (6H, d, *J* = 12.7 Hz, Ar*CH*$_2$O), 4.80 (6H, d, *J* = 12.7 Hz, Ar*CH*$_2$O), 6.97 (6H, s, Ar-*H*), 8.18 (3H, t, *J* = 5.86 Hz, *NH*). *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.

Preparation of the hexaamide derivative of homooxacalix[3]arene (*cone*-7)

To a solution of cone triacid homocalix[3]arene (*cone*-**6**) (491 mg, 0.532 mmol) and *p*-toluidine (**4b**) (514 mg, 4.80 mmol) in CH_2Cl_2 (30 mL) was added HOBt (94 mg,

0.697 mmol). To the mixture was added a solution of DCC (684 mg) in CH_2Cl_2 (10 mL) dropwise at 0 °C. Then the solution was stirred for 15 h at room temperature. After reaction, the solvent was removed; then the residue was dissolved with AcOEt and filtered; the filtrate was washed with 10% citric acid, water, 5% sodium bicarbonate, water, and brine, dried with Na_2SO_4, and condensed under reduced pressure. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with AcOEt as the eluent to give a colorless solid. The solid was recrystallized from methanol to give *cone*-**7** (538 mg, 85%) as colorless prisms, mp 147–149 °C. IR (KBr) ν_{max}: 3476, 3410, 3312, 2958, 2867, 1664, 1609, 1541, 1516, 1482, 1197, 818. ^{1}H NMR ($CDCl_3$) δ: 1.11 (27H, s, *t*-Bu), 2.29 (9H, s, Ar′-CH_3), 4.09 (6H, s, ArOCH_2), 4.20 (6H, d, *J* = 5.86 Hz, N-CH_2), 4.34 (6H, d, *J* = 12.7 Hz, ArCH_2O), 4.79 (6H, d, *J* = 12.7 Hz, ArCH_2O), 6.95 (6H, s, Ar-*H*), 7.08 (6H, d, *J* = 8.8 Hz, Ar′-H_a), 7.43 (6H, d, *J* = 8.8 Hz, Ar′-H_b), 8.45 (3H, t, *J* = 5.86 Hz, NH_a), 9.21 (3H, s, NH_b); (DMSO-d_6) δ: 1.23 (27H, s, *t*-Bu), 2.23 (9H, s, Ar′-CH_3), 4.01 (6H, d, *J* = 5.86 Hz, N-CH_2), 4.19 (6H, s, ArOCH_2), 4.47 (6H, d, *J* = 12.7 Hz, ArCH_2O), 4.77 (6H, d, *J* = 12.7 Hz, ArCH_2O), 6.94 (6H, s, Ar-*H*), 7.06 (6H, d, *J* = 8.8 Hz, Ar′-H_a), 7.39 (6H, d, *J* = 8.8 Hz, Ar′-H_b), 8.25 (3H, t, *J* = 5.86 Hz, NH_a), 9.91 (3H, s, NH_b). ^{13}C NMR ($CDCl_3$) δ: 20.89, 31.44, 34.28, 43.98, 70.28, 73.26, 120.20, 127.79, 129.52, 129.52, 131.05, 134.18, 135.16, 147.39, 153.51, 167.74, 170.99. *m*/*z*: 1189 ([M]$^+$). Anal. calcd. for $C_{69}H_{84}O_{12}N_6$ (1189.47): C 69.68, H 7.12, N 7.07; found: C 69.51, H 7.23, N 7.14.

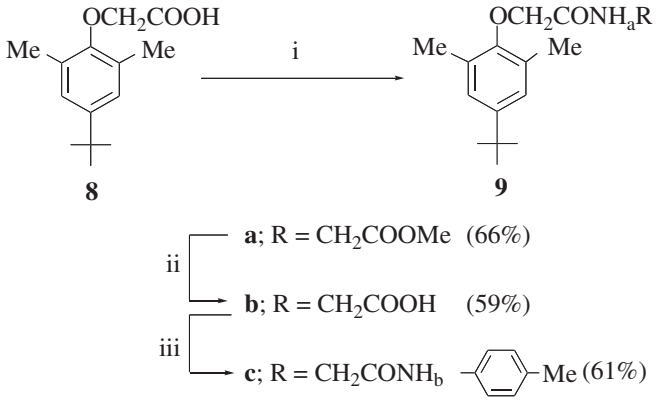
Preparation of 4-*tert*-butyl-2,6-dimethyl[(methoxyacetylaminocarbonyl)methoxy]benzene (9a)

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 a solution of DCC (560 mg) in CH_2Cl_2 (5 mL) dropwise 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), and saturated brine (20 mL), dried with Na_2SO_4, and condensed under reduced pressure. The residue was recrystallized from methanol to give the title compound **9a** (Scheme 2) (87 mg, 66%) as colorless prisms, mp 101 to 102 °C. IR (KBr) ν_{max}: 3337, 3320, 2968, 2865, 1755, 1734, 1667, 1534, 1488, 1277, 1197, 1182, 1056. ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s, *t*-Bu), 2.27 (6H, s, CH_3), 3.80 (3H, s, OCH_3), 4.20 (2H, d, *J* = 5.37 Hz, N-CH_2), 4.33 (2H, s, ArOCH_2), 7.03 (2H, s, Ar-*H*), 7.46 (1H, t, *J* = 5.37 Hz, *NH*). *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) in dioxane (30 mL) was added an aqueous 1 mol/L NaOH 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 orderly with water (20 mL) and saturated brine (20 mL), dried with Na_2SO_4, and condensed under reduced pressure. The residue was washed with hexane to give **9b** (Scheme 2) (81 mg, 59%) as a colorless solid, mp 193–195 °C. IR (KBr) ν_{max}: 3383, 2963, 2925, 2867, 1730, 1635, 1540, 1436, 1245, 1229, 1124. ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s, *t*-Bu), 2.27 (6H, s, CH_3), 3.10 (1H, broad, COO*H*), 4.25 (2H, d, *J* = 5.37 Hz, N-CH_2), 4.35 (2H, s, ArOCH_2), 7.03 (2H, s, Ar-*H*), 7.46 (1H, t, *J* = 5.37 Hz, *NH*). *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.

Scheme 2. Reagents and conditions: (*i*) H_2NCH_2COOMe (**4a**), DCC–HOBt, CH_2Cl_2, room temp. for 15 h; (*ii*) Dioxane–NaOH(aq), room temp. for 1 h; (*iii*) *p*-toluidine (**4b**), DCC–HOBt, CH_2Cl_2, room temp. for 15 h.



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

To a solution of **9b** (50 mg, 0.17 mmol), *p*-toluidine (**4b**) (55 mg, 0.51 mmol), and HOBt (23 mg, 0.17 mmol) in CH_2Cl_2 (12 mL) was added a solution of DCC (171 mg) in CH_2Cl_2 (5 mL) dropwise 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 (30 mL × 2). The combined extracts were washed with 10% citric acid (20 cm^3 × 2), 5% sodium bicarbonate (20 mL), water (20 mL), and saturated brine (20 mL), dried with Na_2SO_4, and condensed under reduced pressure. The residue was recrystallized from hexane–CH_2Cl_2 (3:1) to give **9c** (Scheme 3) (83 mg, 61.2%) as colorless prisms, mp 233 to 234 °C. IR (KBr) ν_{max}: 3383, 3320, 3289, 2962, 2948, 2851, 1699, 1609, 1526, 1312, 1195. ^{1}H NMR ($CDCl_3$) δ: 1.29 (9H, s, *t*-Bu), 2.27 (6H, s, CH_3), 2.31 (3H, s, ArCH_3), 4.25 (2H, d, *J* = 5.37 Hz, N-CH_2), 4.36 (2H, s, ArOCH_2), 7.02 (2H, s, Ar-*H*), 7.13, 7.42 (each 2H, d, *J* = 8.8 Hz, Ar-H_a, Ar-H_b), 7.76 (1H, t, *J* = 5.37 Hz, NH_a), 8.36 (1H, s, NH_b). *m*/*z*: 382 ([M]$^+$). Anal. calcd. for $C_{23}H_{30}O_3N_2$ (382.51): C 72.22, H 7.91, N 7.32; found: C 72.45, H 7.73, N 7.48.

Picrate extraction measurements

Alkali metal picrates (2.5×10^{-4} mol/L) were prepared in situ by dissolving 0.1 mol/L of alkali metal hydroxide in 2.5×10^{-4} mol/L of picric acid; triply distilled water was used for all aqueous solutions. Similarly, metallic picrates

were prepared in situ by dissolving 0.1 mol/L of metallic nitrate ($AgNO_3$, $Cu(NO_3)_2{\cdot}3H_2O$, $Al(NO_3)_3{\cdot}9H_2O$) in 2.5×10^{-4} mol/L of picric acid. Alkyl ammonium picrates were prepared by mixing an equimolar amount of alkylamine and picric acid in methanol.

Two-phase solvent extraction was carried out between water (5 mL, [alkali picrate] = 2.5×10^{-4} mol/L) and CH_2Cl_2 (5 mL, [ionophore] = 2.5×10^{-4} mol/L). 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 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 (18).

Determination of association constants

The measurements were performed by ^{1}H NMR titration experiments in a varying guest concentration of 0–50 mmol/L and a constant concentration of host receptors (5 mmol/L). 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 (19).

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