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Synthesis and inclusion behaviour of a heterotritopic receptor based on hexahomotrioxacalix[3]arene

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A heterotritopic hexahomotrioxacalix[3]arene receptor with the capability of binding two alkali metals and a transition metal in a cooperative fashion was synthesized. The binding model was investigated by using ^{1}H NMR titration experiments in $CDCl_3$-CD_3CN (10:1, v/v), and the results revealed that the transition metal was bound at the upper rim and the alkali metals at the lower and upper rims. Interestingly, the alkali metal ions Li^+ and Na^+ bind at the lower and upper rim respectively depending on the dimension of the alkali metal ions *versus* the size of the cavities formed by the calix[3]arene derivative. The hexahomotrioxacalix[3]arene receptor is acting as a heterotritopic receptor, binding with the transition metal ion Ag^+ and the alkali metals ions Li^+ and Na^+. These findings were not applicable to other different sized alkali, such as K^+ and Cs^+.

Introduction

Calixarenes and their derivatives are attractive compounds for use in host-guest and supramolecular chemistry. In particular, hexahomotrioxacalix[3]arene derivatives with C_3-symmetry can selectively bind ammonium ions which play important roles in both chemistry and biology.[1,2] Furthermore, the incorporation of two types of recognition sites via the introduction of different ionophores on the homotrioxacalix[3]arene will create potential heteroditopic receptors with the capability of binding cations and anions, eg. ammonium ions and halides.

Recently, we reported a novel ditopic receptor possessing two complexation sites and bearing a thiacalix[4]arene in the 1,3-alternate conformation. The binding behaviour with Na^+, K^+ and Ag^+ ions was examined by ^{1}H NMR titration experiments. Although the formation of a heterogeneous di-nuclear complex was not clearly observed, the exclusive formation of mononuclear complexes of the 1,3-alternate-derivative with metal cations is of particular interest with respect to the observation of positive/negative allosteric effects within the thiacalix[4]arene family.[3]

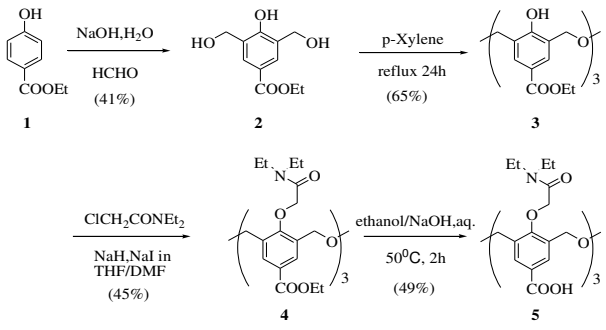
On the other hand, Nabeshima *et al.* reported a novel calix[4]arene derivative bearing two 2,2'-bipyridine moieties and two ester groups at the lower rim in the *cone* conformation to construct sophisticated molecular devices and systems.[4] Indeed, Bipyridyl containing calixarenes have been extensively used to complex various metal ions.[5–12] Di- or polytopic receptors are those constructed with two or more binding subunits within the same macrocyclic structure.[13–15] It is well known that these kinds of systems are suitable candidates for the allosteric regulation[5–7] of host–guest interactions with metal cations which play a major role in biological systems.

Moving from our interest in the synthesis of heteroditopic or heteropolytopic receptors that function as multiple types of cation binder, we introduced a 2,2'-bipyridyl group linked via a carbonyl group at the upper rim and diethylacetamide group at the lower rim of the hexahomotrioxacalix[3]arene. Herein, we report the synthesis and complexation studies of these *cone*-hexahomotrioxacalix[3]-arene triamide derivatives that serve as tritopic receptors for Ag^+, Li^+ and Na^+ ions in a cooperative fashion. The recognition behaviour towards multiple types of cation was investigated by ^{1}H NMR experiments in $CDCl_3$-CD_3CN solution.

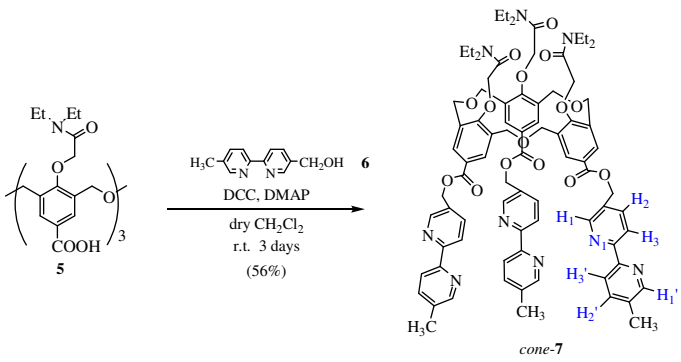
Results and discussion

Synthesis

The preparation of *cone*-7,15,23-triethoxycarbonyl-25,26,27-tris-(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-



Scheme 1. Synthesis of hexahomotrioxacalix[3]arene *cone*-**5.**



Scheme 2. Synthesis of hexahomotrioxacalix[3]arene *cone*-**7.**

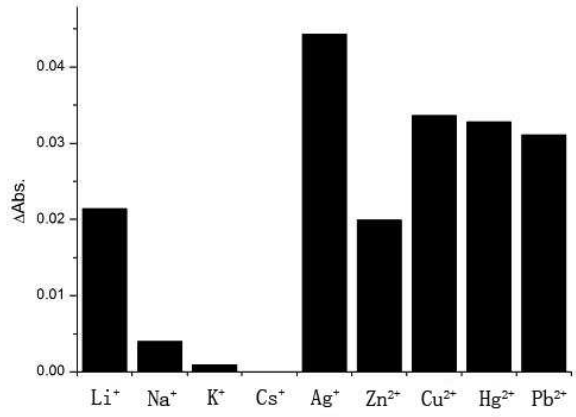


Fig. 1. UV-vis absorption spectra response of *cone*-**7** (1×10^{-6} M) in CH_2Cl_2-CH_3CN (10:1, v/v) to 1×10^{-5} M various tested metal ions. λ_{max} = 290 nm, ε = 1.89×10^5 $cm^{-1}M^{-1}$.

3,11,19-trioxacalix[3]arene (*cone*-**4**) is shown in Scheme 1. Thus, bis(hydroxymethylation) of ethyl 4-hydroxybenzoate (**1**) with formaldehyde in aqueous NaOH for one week afforded ethyl 3,5-hydroxymethyl)-4-hydroxybenzoate (**2**)[16] in 41 % yield. Heating compound (**2**) to reflux in *p*-xylene for 24 h hours afforded hexahomotrioxacalix[3]arene (**3**).[17] The *O*-alkylation of compound (**3**) with *N,N*-diethylchloroacetamide in the presence of NaI/NaH in refluxing THF/DMF（v/v = 5/1）gave *cone*-tris(*N,N*-diethylamino-carbonylmethoxy)hexahomotrioxacalix[3]arene *cone*-**4**[17] in 45 % yield. Hydrolysis of the *O*-alkylated compound, *cone*-**4**, was carried out with NaOH in a mixture of ethanol/water (4:1) at 50 °C for 2 h to yield the *cone*-hexahomotrioxacalix[3]arene tricarboxylic acid *cone*-**5**. [17]

Cone-hexahomotrioxacalix[3]arene triamide derivative (*cone*-**7**) was prepared by a condensation reaction of *cone*-**5** with **6** in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylamino-pryidine (DMAP) at room temperature for 3 days in dichloro-methane (Scheme 2).

Cone-**7** immobilised in a 'flattened *cone*' conformation (in which the phenolic rings are tilted to open up the calixarene cavity), was obtained in moderate yield. Conformational assignments for *cone*-**7** were firmly established by the presence of the bridging methylene protons with a $\Delta\delta_H$ separation between H_{ax} and H_{eq} of 0.41 ppm in the ^{1}H NMR spectra ($CDCl_3$). For the calix[4]arenes, the $\Delta\delta_H$ value of the ArCH_2Ar protons has been correlated with the orientation of adjacent aromatic rings.[2d-e,18,19] The same findings were observed for homotrioxacalix[3]arenes.[20]

UV-vis spectroscopy studies

Cone-**7** as a tritopic hexahomotrioxacalix[3]arene ligand was synthesized, which possessed *N,N*-diethylacetamide group at the lower rim and 2,2'-bipyridyl group at the upper rim linked by carbonyl group. Consequently, the binding behaviour of *cone*-**7** towards different metal cations can be investigated by UV-vis absorption spectroscopy. As shown in Fig. 1 and Fig. S4, the UV-vis spectra of *cone*-**7** displayed a typical absorption at around 290 nm in CH_2Cl_2- CH_3CN (10:1, v/v). The effects of the addition of various metal ions such as Li^+, Na^+, K^+, Cs^+, Ag^+, Cu^{2+}, Zn^{2+}, Pb^{2+} and Hg^{2+} as their perchlorate salts in CH_2Cl_2-CH_3CN solution have been studied. As can be seen, an obvious absorption change in the UV-vis spectrum occurred upon addition of Li^+, Na^+ and transition metal ions. The electronic absorption spectrum of *cone*-**7** exhibited a red shift in the presence of transition metals, whereas only an intensity change was observed for alkali metals. For the metal of Zn^{2+}, it was noticed that the absorption band was split into two absorption bands at around 310 nm and 320 nm, respectively. No significant UV-vis absorption changes were observed shown upon the addition of K^+ and Cs^+ ions. Thus, it can be explained that the 2,2'-bipyridyl group acted as a chromophore displaying a red-shift absorption after binding with transition metals. According to this observation, we can demonstrate the transition metals bound with 2,2'-bipyridyl group at the upper rim and alkali metals bound with other sites respectively. This finding also can be proved by the ^{1}H NMR titration experiments.

^{1}H NMR titration studies

To investigate the binding behaviour between *cone*-**7** with Li^+, Na^+ and Ag^+ ions, ^{1}H NMR spectroscopic studies were carried out in $CDCl_3/CD_3CN$ (10:1, v/v). The spectral differences are shown in Fig. 2. In the presence of an equivalent of Li^+, for example, the $\Delta\delta_H$ value for H_{ax} and H_{eq} for the ArCH_2O methylene protons changed from δ 0.39 ppm to δ 0.27 ppm, The $\Delta\delta_{H'}$ value for the –N$CH_2$$CH_3$ methylene proton changed from δ 0.11 ppm to δ 0.30 ppm. In comparison with the complex *cone*-**7** ⊃ Li^+, in the spectra of *cone*-**7** ⊃ Na^+ complex, the $\Delta\delta_H$ value for the ArCH_2O methylene protons was barely changed but the signals for the ArCH_2O methylene protons both were both shifted upfield, i.e δ 0.19 ppm. The $\Delta\delta_{H'}$ value for the –N$CH_2$$CH_3$ methylene proton was changed from δ 0.11 ppm to δ 0.25 ppm. In addition, obvious downfield chemical shifts for Ar-*H* (δ 0.33 ppm) and bipy-CH_2 (δ 0.11 ppm) were observed for the complex *cone*-**7** ⊃ Na^+.

The addition of an equiv. of $AgClO_4$ to *cone*-**7** caused instant complexation at the upper rim as demonstrated by the downfield shifts of the 2,2'-bipyridyl protons ($H_{2'}$, Δδ = -0.08 ppm, H_2, Δδ = -0.10 ppm), and the upfield shifts of the 2,2'-bipyridyl protons ($H_{3'}$,

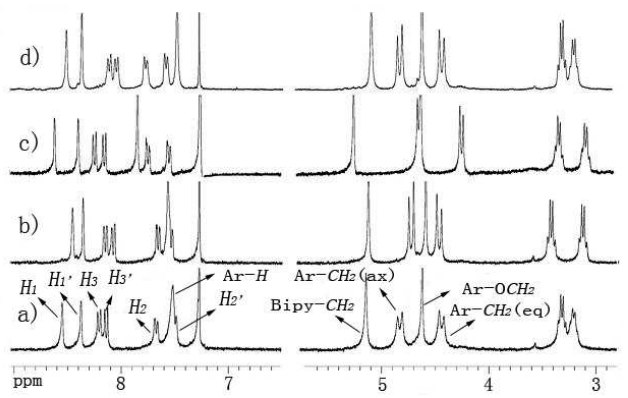


Fig. 2. Partial ^{1}H NMR titration of *cone*-**7**/guest complex (H/G = 1:1); a) free *cone*-**7**; b) *cone*-**7** ⊃ Li^+; c) *cone*-**7** ⊃ Na^+; d) *cone*-**7** ⊃ Ag^+; Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).

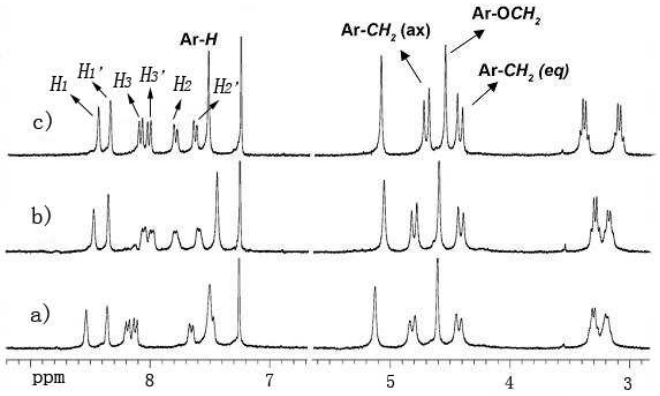


Fig. 3. Partial ^{1}H NMR titration of *cone*-**7**/guest complex (H/G = 1:1); a) free *cone*-**7**; b) *cone*-**7** ⊃ $AgClO_4$; c) $LiClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+]; Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).

Δδ = +0.10 ppm, H_3, Δδ = +0.10 ppm) for the 1:1 complex of *cone*-**7** ⊃ Ag^+ ($K_a = 2.24 \times 10^5\ M^{-1}$) as shown in Fig. 2d, whereas the lower rim protons were scarely affected in the presence of Ag^+. This results strongly suggested that Ag^+ can be selectively bound by the nitrogen atoms of the 2, 2'-bipyridyl group.

The Li^+ formed a complex with the *N,N*-diethylmethoxy-carbonylmethoxy group of *cone*-**7** and adopted the more-upright C_3-symmetric form. It is known that the introduction of bulky substituents onto the OH groups forces the phenol units to stand upright from the calixarene ring plane.[1] This inclination was reflected by the chemical-shift difference ($\Delta\delta_H$) between the axial and equatorial Ar*CH*$_2$ protons, the small $\Delta\delta_H$ value for H_{ax} and H_{eq} indicated that the phenol groups in the complex are positioned in a more-upright orientation. We have already reported that when a Li^+ ions was bound to the ionophoric group at the lower rim, the calix cavity changed from a "flattened cone" to a more-upright form.[21] The Na^+ ion was bound in the cavity formed by the three phenoxy rings, as evidenced by the upfield chemical shift of the axial and equatorial Ar*CH*$_2$ protons (*i.e.* δ 0.19 ppm), the downfield chemical shifts for the Ar-*H* (δ 0.33 ppm) and bipy-*CH*$_2$ (δ 0.11 ppm).

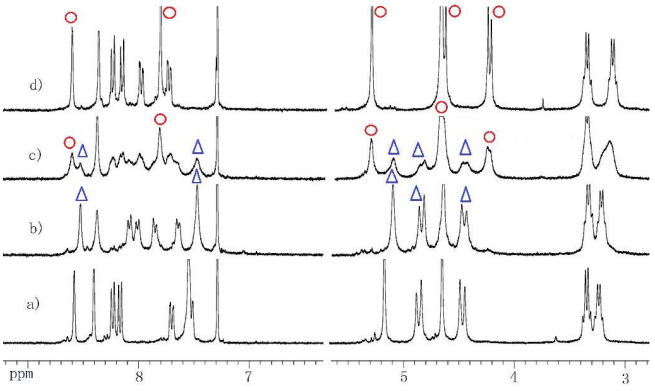


Fig. 4. Partial ^{1}H NMR titration of *cone*-**7**/guest complex (H/G = 1:1); a) free *cone*-**7**; b) *cone*-**7** ⊃ $AgClO_4$; c) $NaClO_4$ (0.4 equiv.) ⊂ [*cone*-**7** ⊃ Ag^+], blue triangles for free and red circles for complexed; d) $NaClO_4$ (1 equiv.) ⊂ [*cone*-**7** ⊃ Ag^+]; Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).

We also carried out ^{1}H NMR titration experiments for *cone*-**7** with K^+ and Cs^+ ions (Figures S5 and S6). An equivalent of $KClO_4$ and $CsClO_4$ were added to the solution of *cone*-**7**, and no obvious chemical shift change was observed. Because of the size of K^+ and Cs^+ ions, they are not suitable for binding with the lower rim or upper rim cavities.

The complexation modes of receptor *cone*-**7** with Ag^+ and Li^+ were investigated by ^{1}H NMR spectroscopy. The addition of an equiv. of $AgClO_4$ to *cone*-**7** caused instant complexation at the upper rim as demonstrated in Fig. 3b. Fig. 3c showed the ^{1}H NMR spectrum after the addition of Li^+ ion to the *cone*-**7** ⊃ Ag^+ complex. When an equivalent of $LiClO_4$ was added, the $\Delta\delta_H$ value for H_{ax} and H_{eq} for the Ar*CH*$_2$O methylene protons changed, the $\Delta\delta_H$ value (from peaks around δ 4.42–4.69 ppm) for the $LiClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] (δ 0.27 ppm) was smaller than that of the *cone*-**7** ⊃ Ag^+ (from peaks around δ 4.42–4.80 ppm) (δ 0.38 ppm). The $\Delta\delta_{H'}$ value for the –N*CH*$_2$CH$_3$ methylene protons (δ 0.29 ppm) of $LiClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] was larger than that of the *cone*-**7** ⊃ Ag^+ (δ 0.12 ppm). This result implied that Li^+ formed a complex with the *N,N*-diethylmethoxy-carbonylmethoxy group after *cone*-**7** complexed with Ag^+ and adopted the more-upright C_3-symmetric form. This result was also observed after changing the binding sequence of metal ions, first to form the complex *cone*-**7** ⊃ Li^+ and then to form the complex $AgClO_4$ ⊂ [*cone*-**7** ⊃ Li^+] (Figure S7). Thus, the *cone*-hexahomotrioxacalix[3]arene triamide derivative *cone*-**7** can serve as a receptor for Ag^+ and Li^+ in a cooperative fashion. Similar findings were observed for the $NaClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] complex.

^{1}H NMR titration experiments were also carried out with the Na^+ ion and solutions of *cone*-**7** ⊃ Ag^+ as shown in Fig. 4c and 4d. When 0.4 equivalents of $NaClO_4$ was added, the complex $NaClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] and the free species [*cone*-**7** ⊃ Ag^+] both existed in the system. However, when 1 equivalent of $NaClO_4$ was added to the solution of *cone*-**7** ⊃ Ag^+, the free species [*cone*-**7** ⊃ Ag^+] gradually disappeared and only the complex Na^+ ⊂ [*cone*-**7** ⊃ Ag^+], as shown in Fig. 4d, was observed. The corresponding protons shifts were given by ^{1}H NMR complexation experiments. Thus, *cone*-**7** first bound with Ag^+ at the upper rim, then bound with Na^+

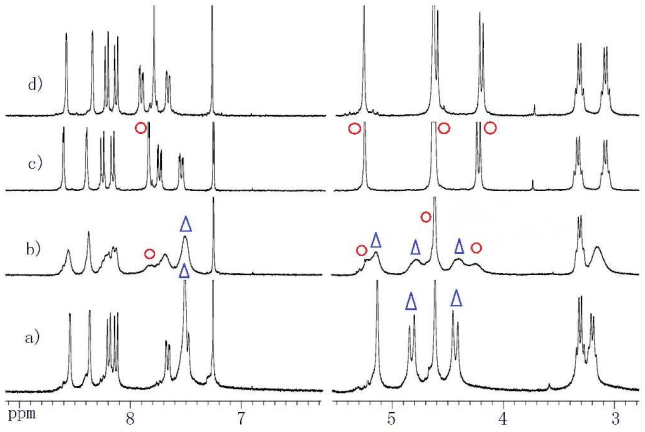


Fig. 5. Partial ^{1}H NMR titration of *cone*-**7** /guest complex (H/G = 1:1); a) free *cone*-**7**; b) *cone*-**7** ⊃ $NaClO_4$; c) *cone*-**7** ⊃ $NaClO_4$ (0.4 equiv.), blue triangles for free and red circles for complexed; d) $AgClO_4$ ⊂ [*cone*-**7** ⊃ Na^+]; Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).

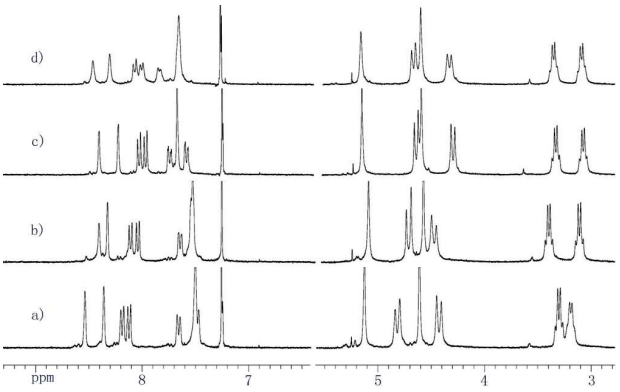


Fig. 6. Partial ^{1}H NMR titration of *cone*-**7** /guest complex (H/G = 1:1); a) free *cone*-**7**; b) *cone*-**7** ⊃ $LiClO_4$; c) $NaClO_4$ ⊂ [*cone*-**7** ⊃ Li^+]; d) Ag^+ ⊂ {Na^+ ⊂ [*cone*-**7** ⊃ Li^+]}; Solvent: $CDCl_3/CD_3CN$ (10:1, v/v).

ion in the cavity formed by the three phenoxy rings of the oxacalix[3]arene. $\Delta\delta_H$ value for H_{ax} and H_{eq} for ArCH_2O methylene protons mostly did not change, however the signals for the ArCH_2O methylene protons were both shifted upfield, *i.e.* δ 0.20 ppm (H_{eq}, δ 4.45 ppm to δ 4.23 ppm and H_{ax}, δ 4.84 ppm to δ 4.64 ppm, respectively). The $\Delta\delta_{H'}$ value for the –N$CH_2$$CH_3$ methylene protons (δ 0.24 ppm) for $NaClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] was larger than that of the *cone*-**7** ⊃ Ag^+ (δ 0.11 ppm). The Ar-*H* proton was downfield chemical shift (δ 0.32 ppm) and the bipy-CH_2 proton was shifted downfield (δ 0.20 ppm). When 0.4 equivalents of $NaClO_4$ was added to the complex *cone*-**7** ⊃ Ag^+, the complex $NaClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+] and the free species [*cone*-**7** ⊃ Ag^+] both existed in the system. It was necessary to consider whether the negative allosteric effect caused by the binding of Ag^+ existed or not, so the sequence of metal ions addition was changed, *viz* initially bind with Na^+ ion, then to the Ag^+ ion as shown in Fig. 5. However, when 0.4 equivalents of $NaClO_4$ was added to *cone*-**7**, the complex *cone*-**7** ⊃ Na^+ and the free species *cone*-**7** were both observed as shown in Fig. 5c. On further addition of the metal ion Na^+ (1 equiv.), the free species

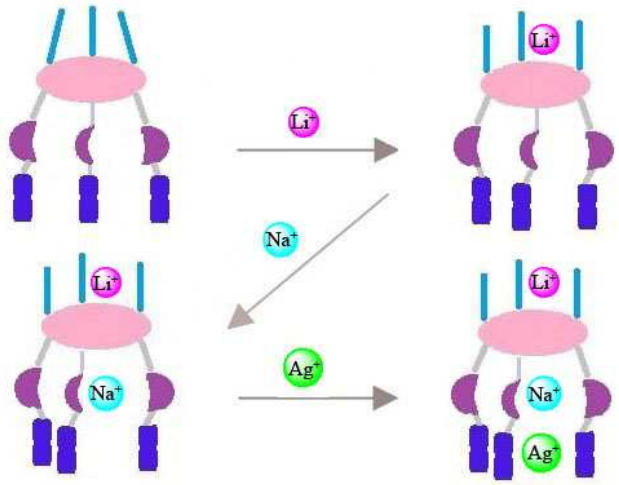


Fig. 7. Plaussible complexation mode of host *cone*-**7** with Li^+, Na^+ and Ag^+ ions.

disappeared and only the complex *cone*-**7** ⊃ Na^+ existed. In most other work, a passive/negative allosteric effect was caused by the binding with Ag^+, but here, there was no observation of the allosteric effect.

Until now, the ability of the *cone*-**7** to serve as a heteroditopic receptor has been demonstrated, but now to illustrate that *cone*-**7** can serve as a heterotritopic receptor, *cone*-**7** was to complex with Li^+, Na^+ and Ag^+ metal ions in a cooperative fashion, ^{1}H NMR spectroscopic titration experiments were carried out by addition of Li^+ ions to the solution of *cone*-**7**, by Na^+ ions to the solution of *cone*-**7** ⊃ Li^+ and by Ag^+ ions to the solution of Na^+ ⊂ [*cone*-**7** ⊃ Li^+] as shown in Fig. 6. In the presence of an equivalent of Li^+, the $\Delta\delta_H$ values for H_{ax} and H_{eq} for the ArCH_2O methylene protons changed from δ 0.40 ppm to δ 0.24 ppm, and the $\Delta\delta_{H'}$ value for the –N$CH_2$$CH_3$ methylene protons changed from δ 0.11 ppm to δ 0.28 ppm. When 1 equiv. of $NaClO_4$ was added to the solution of *cone*-**7** ⊃ Li^+, the $\Delta\delta_H$ value for H_{ax} and H_{eq} of the ArCH_2O methylene protons changed from δ 0.24 ppm to δ 0.34 ppm, and the signals for the ArCH_2O methylene protons were both shifted upfield, i.e δ 0.18 ppm (H_{eq}, δ 4.48 ppm to δ 4.30 ppm and H_{ax}, δ 4.72 ppm to δ 4.64 ppm, respectively), indicating that binding mode was occurring between the *cone*-**7** ⊃ Li^+ and Na^+; the corresponding chemical shift changes were attributable to the cooperative effects by the Li^+ and Na^+ ions. The Ar-*H* proton was downfield chemical shift (δ 0.15 ppm) and the bipy-CH_2 proton was shifted downfield (δ 0.06 ppm). After addition of Ag^+ ion to the solution of Na^+ ⊂ [*cone*-**7** ⊃ Li^+], we also observed the same downfield shifts for the 2,2'-bipyridyl protons ($H_{2'}$, $\Delta\delta$ = -0.08 ppm, H_2, $\Delta\delta$ = -0.10 ppm,). Thus, *cone*-**7** can serve as a heterotritopic receptor. This result was also observed after changing the binding sequence of the metal ions. Firstly, the complex of *cone*-**7** ⊃ Ag^+ was formed, then the complex $LiClO_4$ ⊂ [*cone*-**7** ⊃ Ag^+], Na^+ ⊂ {Li^+ ⊂ [*cone*-**7** ⊃ Ag^+]} (Figure S8) was formed. We observed the same ^{1}H NMR spectrum as shown in

Table 1 Chemical shift of pyridine protons in *cone*-**7**.

Compd.	Chemical shift,δ_{ppm} [a,b]					
	H_1	H_2	H_3	H_1'	H_2'	H_3'
cone-**7**	8.55	7.67[c]	8.21[c]	8.37	7.50[c]	8.14[c]
cone-**7**⊃ Ag+	8.51	7.77	8.11	8.36	7.58	8.04
$\Delta\delta$	+0.04	-0.10	+0.10	+0.01	-0.08	+0.10

[a] Δδ values are the difference of the chemical shift between *cone*-**7** in $CDCl_3$-CD_3CN at 27°C. [b] A minus sign (–) denotes a shift to lower magnetic field, a plus sign (+) denotes a shift to higher magnetic. [c] The midpoint values of multiplet are indicated.

Figure 6d and Figure S8d, and thus it was proved that *cone*-**7** can serve as a heterotritopic receptor for the Ag^+, Li^+ and Na^+ ions in a cooperative fashion (Fig. 7).

As shown in Table 1, the nitrogen atom N_1 in the bipyridine ring pointed away from the calix cavity in free *cone*-**7** because of the electron repulsion between the nitrogens. After complexation, the nitrogen turned inwards towards the cavity to complex with the Ag^+ and thus affected the 2,2'-bipyridyl protons with downfield shifts for $H_{2'}$ (Δδ = -0.08 ppm) and H_2 (Δδ = -0.10 ppm), upfield shifts for $H_{3'}$ (Δδ = +0.10 ppm), H_3 (Δδ = +0.10 ppm) and H_1 (Δδ = +0.04 ppm) (Table 1) due to the tetrahedral interaction of the N—Ag^+ motif. Furthermore, after complexation, $H_{3'}$ and H_3, $H_{2'}$ and H_2 have the similar magnetic environments, and therefore the downfield/upfield shifts were similar.

Complexation studies

The stoichiometries of the *cone*-**7** complexes with Ag^+ and Li^+ were determined by UV-vis absorption spectra [CH_2Cl_2/CH_3CN (10:1, v/v)], using the continuous variation method, the absorption reached a maximum at around 0.5 mol fraction for this cation (Fig. 8), which clearly indicated that the Ag^+ formed 1:1 complex with *cone*-**7**. Thus, Ag^+ was completely bound by the soft bipyridine cavity of *cone*-**7** and the homotrioxacalix[3]arene cavity did not participate in the complexation. The stoichiometry of the *cone*-**7** complexes with Li^+ was also determined by UV-vis absorption spectra [CH_2Cl_2/CH_3CN (10:1, v/v)] (Figure S9), using the continuous variation method. The absorption also reached maximum at 0.5 mol fraction for this cation, indicating that the Li^+ ion formed a 1:1 complex with *cone*-**7**, and the Li^+ ion was completely bound by the *N,N*-diethylaminocarbonyl-methoxy groups. The molar ratio method was used to determine the stoichiometry of *cone*-**7** complexed with Na^+ by UV-vis absorption spectra [CH_2Cl_2/CH_3CN (10:1, v/v)] (Figure S10), which also indicated that the Na^+ ion formed a 1:1 complex with *cone*-**7**.

UV-vis spectrophotometric analysis was employed to detemine the association constant of the inclusion complex of *cone*-**7** and Ag^+. The decrease in absorbance at 290 nm *versus* the increase in concentration of The Ag^+ was fitted to a 1:1 binding model to determine the association constant, which was found to be 2.24×10^5 M^{-1}. The association constant for *cone*-**7** and Li^+ was 2.58×10^5 M^{-1} and for *cone*-**7** and Na^+, which was found to be 1.55×10^5 M^{-1} (Figures S11–13).

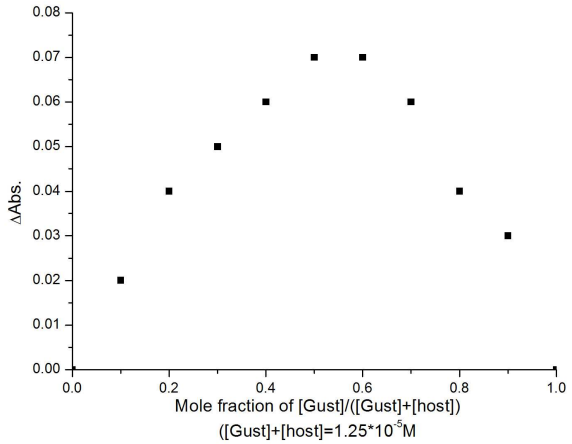


Fig. 8. Job plot of the extractions of Ag^+ with host *cone*-**7**.

Conclusions

A *cone*-hexahomotrioxacalix[3]arene receptor *cone*-**7** bearing 2,2'-bipyridyl linked via a carbonyl group at the its upper rim and *N,N*-diethylacetamide chains at the lower rim, respectively, has been synthesized. The receptor *cone*-**7** can serve as a heterotritopic hexahomotrioxacalix[3]arene receptor with capability for binding two type of cations in a cooperative fashion. The binding of the alkali metal ion Li^+ took place at the lower rim, and the alkali metal ion Na^+ and transition metal ion Ag^+ at the upper rim, respectively. In addition, given the Na^+ ion is larger than the Li^+ ion, the Li^+ ion bound with the lower rim cavity through the oxygens whereas the Na^+ ion chose to bind with the larger cavity formed by the three phenoxy rings of the oxacalix[3]arene, which was verified by ^1H NMR titration experiments.

The nitrogen atom in the bipyridine ring pointed away from the calix cavity in the *cone*-**7** because of the electronic repulsion between the nitrogens. After complexation, the nitrogen atom in the bipyridine ring turned inwards towards the cavity to complex with Ag^+ to allow for the tetrahedral disposition of the N---Ag^+ motif.

Further studies on the synthesis of tritopic receptors based on the hexahomotrioxacalix[3]arene are also underway in our laboratory.

Experimental

General

All melting points (Yanagimoto MP-S1) are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and Varian-400MR-vnmrs400 with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrophotometer. Mass spectra were obtained with a Nippon Denshi JMS-HX110A Ultrahigh Performance mass

spectrometer at 75 eV by using a direct-inlet system. UV-vis spectra were recorded using a Shimadzu UV-3150UV-vis-NIR spectrophotometer. Elemental analyses were performed by a Yanaco MT-5.

Materials

cone-7,15,23-Tris(hydroxycarbonyl)-25,26,27-tris(*N,N*-diethyl-aminocarbonylmethoxy)-3,11,19-trioxacalix[3]arene triacid (*cone*-**5**) was synthesized from *cone*-7,15,23-tris(ethoxycarbonyl)-25,26,27-trihydroxy-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene *cone*-**3** as following the reported procedure.[21] 5'-Methyl-2,2'-bipyridyl-5-ylmethanol **6** was prepared according to the reported procedure.[22]

Synthesis of 7,15,23-tris(5'-methyl-2,2'-bipyridyl-5-yl-methyl-oxycarbonyl)-25,26,27-tris(*N,N*-diethylaminocarbonyl-methoxy)-3,11,19-trioxacalix[3]arene (*cone*-7)

To a solution of *cone*-**5** (100 mg, 0.11 mmol), 5'-methyl-2,2'-bipyridyl-5-ylmethanol **6** (110 mg, 0.55 mmol) and 1-hydroxybenzotriazole (DMAP) (67.2 mg, 0.55 mmol) in CH_2Cl_2 (10 mL), was added dropwise a solution of dicyclohexylcarbodiimide (DCC) (190 mg, 0.92 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred for 3 days at room temperature then 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) and saturated brine (20 mL); the solution was dried ($MgSO_4$) and condensed under reduced pressure. The *cone*-**7** was obtained from column chromatography [($CHCl_3$-MeOH (5:1, v/v)) (88 mg, 56 %) as colorless prisms. M.p. 84.5–85 °C. IR: υ_{max}(KBr)/cm^{-1}= 1723 (COOR) and 1650 (CONRR'). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.11–1.12 (18H, m, -CH_2CH_3), 2.40 (9H, s, Bipy-CH_3), 3.30–3.41 (12H, m, -NCH_2), 4.50 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.67 (6H, s, Ar-OCH_2), 4.92 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.21 (6H, s, Bipy-CH_2), 7.57 (3H, dd, *J* = 6.7 Hz, *J* =1.2 Hz, Bipy-*H*), 7.58 (6H, s, Ar-*H*), 7.74 (3H, dd, *J* = 10.2, *J* = 2.0 Hz, Bipy-*H*), 8.21 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.28 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.45 (3H, s, Bipy-*H*) and 8.62 (3H, s, Bipy-*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5 (CH_3), 18.5 (CH_3), 40.5 (CH_2), 63.5 (CH_2), 67.0 (CH_2), 72.5 (CH_2), 120.7–160.1 (Ar-*C*, Bipy-*C*), 165.0 (*C*=O) and 167.0 (*C*=O) ppm. FABMS: *m/z*: 1426.78 (M^+). $C_{81}H_{87}O_{15}N_9$ (1426.61): calcd C 68.19, H 6.15; N 8.84. Found: C 68.31, H 6.24, N 8.93.

^{1}H NMR complexation experiments

To a $CDCl_3$ solution (500 μL, 5 × 10^{-3} M) of *cone*-**7** in an NMR tube was added a CD_3CN solution (50 μL, 5 × 10^{-3} M) of $LiClO_4$, $NaClO_4$, $KClO_4$, $CsClO_4$ and $AgClO_4$. The spectrum for each was recorded after the addition metal ions. The temperature of the ^{1}H NMR probe was kept constant at 27 °C. The ^{1}H NMR data of the most representative complexes are given below.

The ^{1}H NMR data of the most representative complexes was given below:

cone-**7** ⊃ Li^+ (1:1): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.12–3.42 (12H, m, -NCH_2), 4.46 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.59 (6H, s, Ar-OCH_2), 4.73 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.12 (6H, s, Bipy-CH_2), 7.54 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.56 (6H, s, Ar-*H*), 7.66 (3H, dd, *J* = 10.2 Hz, *J* = 1.2 Hz, Bipy-*H*), 8.08 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.15 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.35 (3H, s, Bipy-*H*) and 8.45 (3H, s, Bipy-*H*) ppm.

cone-**7** ⊃ Na^+ (1:1): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.10–3.35 (12H, m, -NCH_2), 4.26 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.64 (6H, s, Ar-OCH_2), 4.66 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.26 (6H, s, Bipy-CH_2), 7.56 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.85 (6H, s, Ar-*H*), 7.75 (3H, dd, *J* = 10.2 Hz, *J* = 1.2 Hz, Bipy-*H*), 8.16 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.25 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.40 (3H, s, Bipy-*H*) and 8.63 (3H, s, Bipy-*H*) ppm.

cone-**7** ⊃ Ag^+ (1:1): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.21–3.32 (12H, m, -NCH_2), 4.45 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.62 (6H, s, Ar-OCH_2), 4.84 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.10 (6H, s, Bipy-CH_2), 7.58 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.47 (6H, s, Ar-*H*), 7.77 (3H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, Bipy-*H*), 8.04 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.11 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.36 (3H, s, Bipy-*H*) and 8.51 (3H, s, Bipy-*H*) ppm.

[*cone*-**7** ⊃ Ag^+] ⊃ Li^+ (1:1): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.08–3.37 (12H, m, -NCH_2), 4.42 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.54 (6H, s, Ar-OCH_2), 4.69 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.08 (6H, s, Bipy-CH_2), 7.62 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.51 (6H, s, Ar-*H*), 7.78 (3H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, Bipy-*H*), 8.01 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.08 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.33 (3H, s, Bipy-*H*) and 8.43 (3H, s, Bipy-*H*) ppm.

[*cone*-**7** ⊃ Ag^+] ⊃ Na^+ (1:0.4): 3.13–3.35 (12H, m, -NCH_2), 4.23 (6H, d, *J* = 13.2 Hz, Ar-CH_2) complex, 4.45 (6H, d, *J* = 13.2 Hz, Ar-CH_2) free, 4.64 (6H, s, Ar-OCH_2), 4.64 (6H, d, *J* = 12.6 Hz, Ar-CH_2) complex, 4.84 (6H, d, *J* = 12.6 Hz, Ar-CH_2) free, 5.29 (6H, s, Bipy-CH_2) complex, 5.09 (6H, s, Bipy-CH_2) free, 7.64 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*) free, 7.72 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*) complex, 7.81 (6H, s, Ar-*H*) complex, 7.48 (6H, s, Ar-*H*) free, 7.99 (3H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, Bipy-*H*), 8.15 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.23 (3H, d, *J* = 8.1 Hz, Bipy-*H*) complex, 8.09 (3H, d, *J* = 8.1 Hz, Bipy-*H*) free, 8.37 (3H, s, Bipy-*H*) and 8.59 (3H, s, Bipy-*H*) complex and 8.53 (3H, s, Bipy-*H*) free ppm.

[*cone*-**7** ⊃ Ag^+] ⊃ Na^+ (1:1): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.11–3.35 (12H, m, -NCH_2), 4.23 (6H, d, *J* = 13.2 Hz, Ar-CH_2), 4.65 (6H, s, Ar-OCH_2), 4.64 (6H, d, *J* = 12.6 Hz, Ar-CH_2), 5.29 (6H, s, Bipy-CH_2), 7.72 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.80 (6H, s, Ar-*H*), 7.97 (3H, dd, *J* = 10.2 Hz, *J* = 2.0 Hz, Bipy-*H*), 8.15 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.23 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.35 (3H, s, Bipy-*H*) and 8.59 (3H, s, Bipy-*H*) ppm.

cone-**7** ⊃ Na^+ (1:0.4): δ_H ($CDCl_3$/CD_3CN, 10:1, v/v): 3.15–3.31 (12H, m, -NCH_2), 4.25 (6H, d, *J* = 13.2 Hz, Ar-CH_2) complex, 4.40 (6H, d, *J* = 13.2 Hz, Ar-CH_2) free, 4.62 (6H, s, Ar-OCH_2), 4.62 (6H, d, *J* = 12.6 Hz, Ar-CH_2) complex, 4.79 (6H, d, *J* = 12.6 Hz, Ar-CH_2) free, 5.24 (6H, s, Bipy-CH_2) complex, 5.14 (6H, s, Bipy-CH_2) free, 7.50 (3H, dd, *J* = 6.7 Hz, *J* = 1.2 Hz, Bipy-*H*), 7.83 (6H, s, Ar-*H*) complex, 7.50 (6H, s, Ar-*H*) free, 7.68 (3H, dd, *J* = 10.2 Hz, *J* = 1.2 Hz, Bipy-*H*), 8.14 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.20 (3H, d, *J* = 8.1 Hz, Bipy-*H*), 8.39 (3H, s, Bipy-*H*) and 8.56 (3H, s, Bipy-*H*) ppm.

[*cone*-**7** ⊃ Na^+] ⊃ Ag^+ (1:1): δ_H ($CDCl_3/CD_3CN$, 10:1, v/v): 3.06–3.31 (12H, m, -NCH_2), 4.19 (6H, d, J = 13.2 Hz, Ar-CH_2), 4.62 (6H, s, Ar-OCH_2), 4.60 (6H, d, J = 12.6 Hz, Ar-CH_2), 5.26 (6H, s, Bipy-CH_2), 7.65 (3H, dd, J = 6.7 Hz, J = 1.2 Hz, Bipy-*H*), 7.78 (6H, s, Ar-*H*), 7.90 (3H, dd, J = 10.2 Hz, J = 1.2 Hz, Bipy-*H*), 8.13 (3H, d, J = 8.1 Hz, Bipy-*H*), 8.21 (3H, d, J = 8.1 Hz, Bipy-*H*), 8.32 (3H, s, Bipy-*H*) and 8.56 (3H, s, Bipy-*H*) ppm.

Stoichiometry of metal complexation and determination of association constants

Job's plot experiment was carried out using the absorption spectrum, make the volume fixed and the concentration of [Host]+[Guest] = 1.25×10^{-5} M, [Guest]/([Host]+[Guest]) changed from 0.1 to 0.9, and the association constants also determined by the absorption spectrum in a varying guest concentration of 0–1.25 μM and a constant concentration of host receptors with 1 μM. As a probe the absorption intensity signal was used. The association constant values were calculated by the intensity changes in the complex and the free host molecules.

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† Electronic Supplementary Information (ESI) available: $^1H/^{13}C$ NMR spectra of *cone*-**7** and the detailed ^1H NMR titration spectra data.

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