

ARTICLE

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 simultaneously in a cooperative fashion was synthesized. The binding model was investigated by using ¹H NMR titration experiments in CDCl₃-CD₃CN (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, simultaneously 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 metals, 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 C₃-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 ¹H 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 regulation⁵⁻⁷ of host-guest interactions with metal cations which play a major role in biological systems.

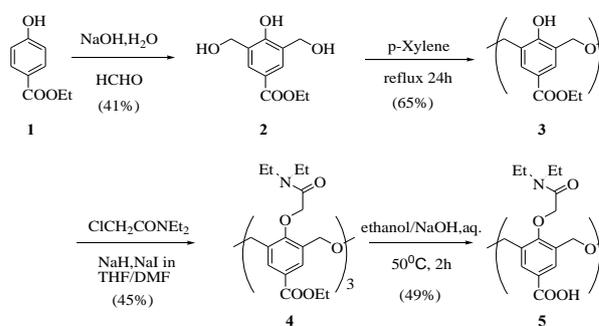
Moving from our interest in the synthesis of heteroditopic or heteropolytopic receptors that function as multiple types of cation binder, we introduced a 2,2'-bipyridyl group linked via a carbonyl group at the upper rim and diethylacetamides group at the lower rim of the hexahomotrioxacalix[3]arene. Herein, we report the synthesis

and complexation studies of these cone-hexahomotrioxacalix[3]arene triamide derivatives that serve as tritopic receptors simultaneously for Ag⁺, Li⁺ and Na⁺ ions. The recognition behaviour towards multiple types of cation was investigated by ¹H NMR experiments in CDCl₃-CD₃CN solution.

Results and discussion

Synthesis

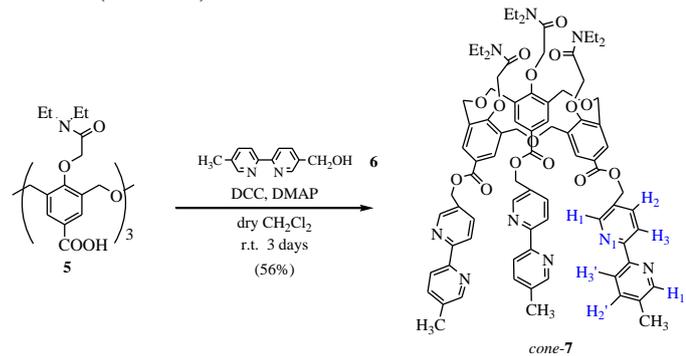
The preparation of cone-7,15,23-triethoxycarbonyl-25,26,27-tris-(*N,N*-diethylaminocarbonylmethoxy)-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (cone-4) is shown in Scheme 1. Thus, bis(hydroxymethylation) of ethyl 4-hydroxybenzoate (1) with formaldehyde in aqueous NaOH for one week afforded ethyl 3,5-bis(hydroxymethyl)-4-hydroxybenzoate (2)¹⁶ in 41 % yield. Heating compound (2) to reflux in *p*-xylene for 24 h 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*-diethylaminocarbonylmethoxy)hexahomotrioxacalix[3]arene cone-4¹⁷ 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

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

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-pyridine (DMAP) at room temperature for 3 days in dichloromethane (Scheme 2).

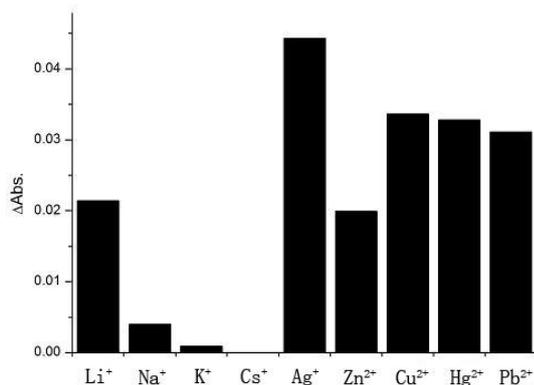


Scheme 2. Synthesis of hexahomotrioxacalix[3]arene *cone*-7.

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 ¹H NMR spectra (CDCl₃). For the calix[4]arenes, the $\Delta\delta_H$ value of the ArCH₂Ar 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 hexahomotri-oxacalix[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, the UV-vis spectra of *cone*-7 displayed a typical absorption at around 290 nm in CH₂Cl₂-CH₃CN (10:1, v/v). The effects of the addition of various metal ions such as Li⁺, Na⁺, K⁺, Cs⁺, Ag⁺, Cu²⁺, Zn²⁺, Pb²⁺ and Hg²⁺ as their perchlorate salts in CH₂Cl₂-CH₃CN 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 metals Cu²⁺, Zn²⁺ and Hg²⁺, 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 upon the addition of K⁺ and Cs⁺ ions. Thus, it can be explained that the 2,2'-bipyridyl group acted as a



2

Fig. 1. UV-vis absorption spectra response of *cone*-7 (1×10^{-6} M) in CH₂Cl₂-CH₃CN (10:1, v/v) to 1×10^{-5} M various tested metal ions. $\lambda_{max} = 290$ nm, $\epsilon = 1.89 \times 10^5$ cm²M⁻¹.

chromophore displaying a red-shift absorption upon binding with transition metals. According to this observation, we can demonstrate that the transition metals bind with the 2,2'-bipyridyl group at the upper rim and the alkali metal binds with the other sites. This finding also can be proved by the ¹H NMR titration experiments.

¹H NMR titration studies

To investigate the binding behaviour of *cone*-7 with Li⁺, Na⁺ and Ag⁺ ions, ¹H NMR spectroscopic studies were carried out in CDCl₃/CD₃CN (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 ArCH₂O methylene protons changed from δ 0.39 ppm to δ 0.27 ppm. The $\Delta\delta_H$ value for the -NCH₂CH₃ methylene proton changed from δ 0.11 ppm to δ 0.30 ppm. In comparison with the complex *cone*-7 \supset Li⁺, in the spectra of *cone*-7 \supset Na⁺ complex, the $\Delta\delta_H$ value for the ArCH₂O methylene protons was barely changed, but the signals for the ArCH₂O methylene protons were both shifted upfield, i.e. δ 0.19 ppm. The $\Delta\delta_H$ value for the -NCH₂CH₃ 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-CH₂ (δ 0.11 ppm) were observed for the complex *cone*-7 \supset Na⁺.

The addition of an equiv. of AgClO₄ to *cone*-7 caused instant complexation at the upper rim as demonstrated by the downfield shifts of the 2,2'-bipyridyl protons (H_2 , $\Delta\delta = -0.08$ ppm, H_2' , $\Delta\delta = -0.10$ ppm,) and the upfield shifts of the 2,2'-bipyridyl protons (H_3 , $\Delta\delta = +0.10$ ppm, H_3' , $\Delta\delta = +0.10$ ppm) for the 1:1 complex of *cone*-7 \supset Ag⁺ ($K_a = 2.24 \times 10^5$ M⁻¹) as shown in Fig. 2d, whereas the lower rim protons were scarcely 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.

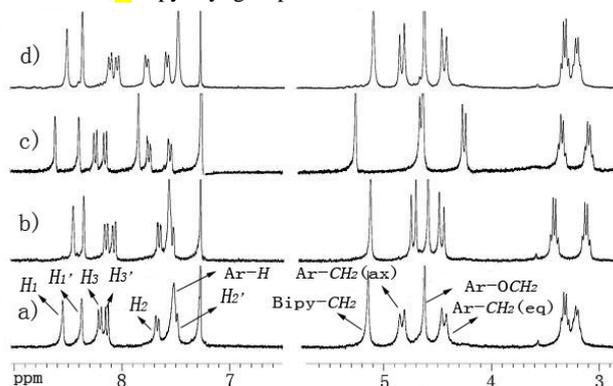


Fig. 2. Partial ¹H NMR titration of *cone*-7/guest complex (H/G = 1:1): a) free *cone*-7; b) *cone*-7 \supset Li⁺; c) *cone*-7 \supset Na⁺; d) *cone*-7 \supset Ag⁺; Solvent: CDCl₃/CD₃CN (10:1, v/v).

The Li⁺ formed a complex with the *N,N*-diethylmethoxycarbonylmethoxy group of *cone*-7 and adopted the more-upright C₃-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 ArCH₂ 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⁺ cation 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 ArCH₂ protons (i.e. δ 0.19 ppm), the downfield chemical shifts for the Ar-H (δ 0.33 ppm) and bipy-CH₂ (δ 0.11 ppm). When Na⁺ ion is bound in the cavity formed by the three benzene rings with oxygen atoms framework, had intermolecular electron transfer from the upper rim to binding sites and caused the corresponding chemical shifts – cannot understand the English here.

We also carried out ¹H NMR titration experiments for cone-7 with K⁺ and Cs⁺ ions (Figures S4 and S5). An equivalent of KClO₄ and CsClO₄ 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 ¹H NMR spectroscopy. The addition of an equiv. of AgClO₄ to cone-7 caused instant complexation at the upper rim as demonstrated in Fig. 3b.

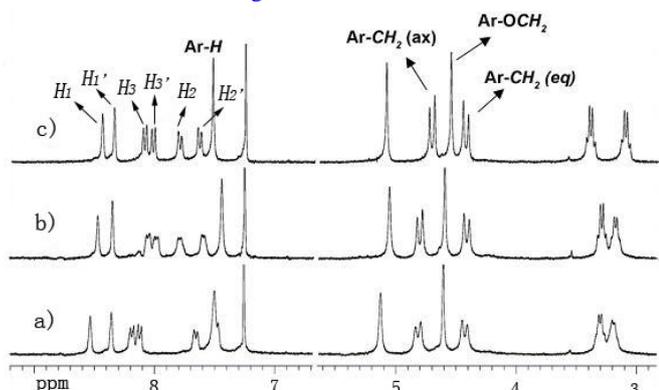
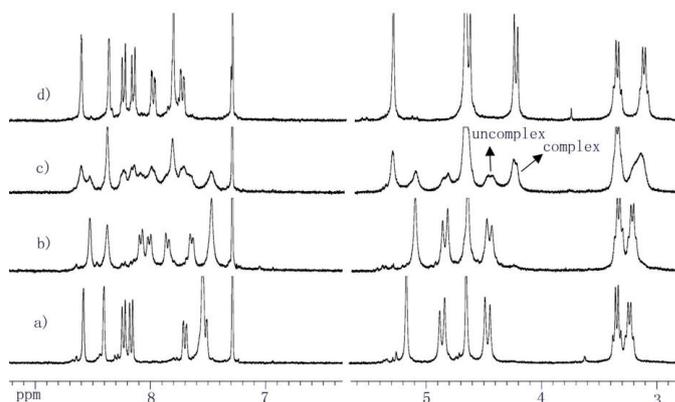


Fig. 3. Partial ¹H NMR titration of cone-7/guest complex (H/G = 1:1); a) free cone-7; b) cone-7 + AgClO₄; c) LiClO₄ + [cone-7 + Ag⁺]; Solvent: CDCl₃/CD₃CN (10:1, v/v).

Fig. 3c showed the ¹H NMR spectrum after the addition of Li⁺ ion to the cone-7 + Ag⁺ complex. When an equivalent of LiClO₄ was added, the Δδ_H value for H_{ax} and H_{eq} for the ArCH₂O methylene protons changed, the Δδ_H value (from peaks around δ 4.42–4.69 ppm) for the LiClO₄ + [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 Δδ_H value for the –NCH₂CH₃ methylene protons (δ 0.29 ppm) of LiClO₄ + [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*-diethylmethoxycarbonylmethoxy group after cone-7 complexed with Ag⁺ and adopted the more-upright C₃-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 AgClO₄ + [cone-7 + Li⁺] (Figure S6). Thus, the cone-hexahomotrioxacalix[3]arene triamide derivative cone-7 can serve as a receptor for Ag⁺ and Li⁺ simultaneously. Similar findings were observed for the NaClO₄ + [cone-7 + Ag⁺] complex.

¹H 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 NaClO₄ was added, the complex NaClO₄ + [cone-7 + Ag⁺] and the uncomplexed species [cone-7 + Ag⁺] both existed in the system. However, when 1



equivalent of NaClO₄ was added to the solution of cone-7 + Ag⁺, the uncomplex species [cone-7 + Ag⁺] gradually disappeared and only the complex Na⁺ + [cone-7 + Ag⁺], as shown in Fig. 4d, was observed. The corresponding proton shifts were given by ¹H NMR complexation experiments. Thus, cone-7 first bound with Ag⁺ at the upper rim, then bound with Na⁺ ion in the cavity formed by the three phenoxy rings of the oxacalix[3]arene. Δδ_H value for H_{ax} and H_{eq} for ArCH₂O

Fig. 4. Partial ¹H NMR titration of cone-7/guest complex (H/G = 1:1); a) free cone-7; b) cone-7 + AgClO₄; c) NaClO₄ (0.4 equiv) + [cone-7 + Ag⁺]; d) NaClO₄ (1 equiv) + [cone-7 + Ag⁺]; Solvent: CDCl₃/CD₃CN (10:1, v/v).

methylene protons mostly did not change, however the signals for the ArCH₂O 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 Δδ_H value for the –NCH₂CH₃ methylene protons (δ 0.24 ppm) for NaClO₄ + [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-CH₂ proton was shifted downfield (δ 0.20 ppm).

When 0.4 equivalents of NaClO₄ was added to the complex cone-7 + Ag⁺, the complex NaClO₄ + [cone-7 + Ag⁺] and the uncomplexed 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. However, when 0.4 equivalents of NaClO₄ was added to cone-7, the complex cone-7 + Na⁺ and the uncomplexed species cone-7 were both observed. On further addition of the metal ion Na⁺ (1 equiv.), the uncomplexed species 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.

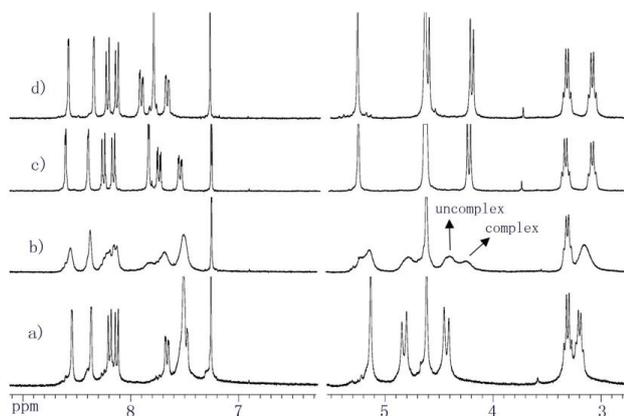


Fig. 5. Partial ^1H NMR titration of *cone-7* /guest complex (H/G = 1:1); a) free *cone-7*; b) *cone-7* \supset NaClO_4 ; c) $\text{AgClO}_4 \subset [\text{cone-7} \supset \text{Na}^+]$; Solvent: $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v).

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 heterotripotic

Fig. 6. Partial ^1H NMR titration of *cone-7* /guest complex (H/G = 1:1); a) free *cone-7*; b) *cone-7* \supset LiClO_4 ; c) $\text{NaClO}_4 \subset [\text{cone-7} \supset \text{Li}^+]$; d) $\text{Ag}^+ \subset \{\text{Na}^+ \subset [\text{cone-7} \supset \text{Li}^+]\}$; Solvent: $\text{CDCl}_3/\text{CD}_3\text{CN}$ (10:1, v/v).

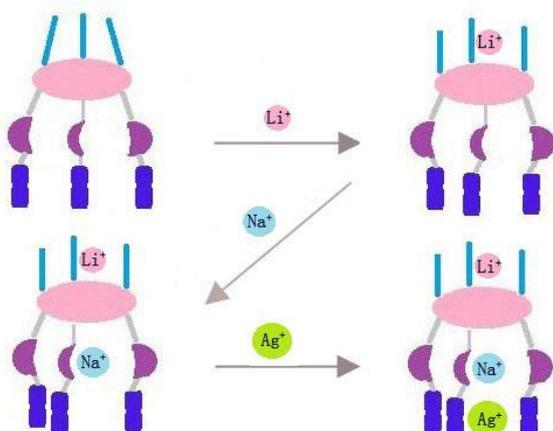
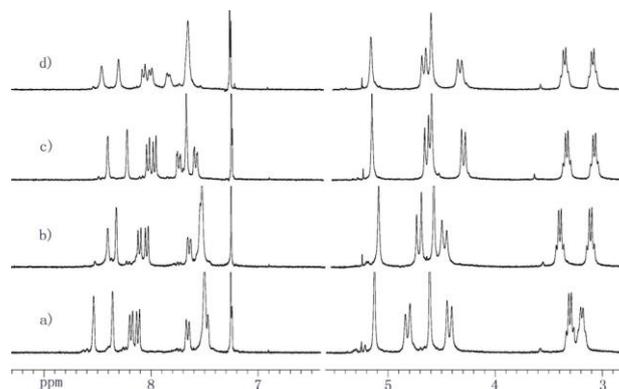


Fig. 7. Plausible complexation mode of host *cone-7* with Li^+ , Na^+ and Ag^+ ions.

receptor, *cone-7* was to complex with Li^+ , Na^+ and Ag^+ metal ions simultaneously, ^1H 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* \supset Li^+ and by Ag^+ ions to the solution of $\text{Na}^+ \subset [\text{cone-7} \supset \text{Li}^+]$ as shown in Fig. 6. In the presence of an equivalent of Li^+ , the $\Delta\delta_{\text{H}}$ 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 $\Delta\delta_{\text{H}}$ value for $-\text{NCH}_2\text{CH}_3$ 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* \supset Li^+ , the $\Delta\delta_{\text{H}}$ 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 was occurring between the *cone-7* \supset Li^+ and Na^+ , corresponding chemical shifts were the coefficient 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 $\text{Na}^+ \subset [\text{cone-7} \supset \text{Li}^+]$, 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, the *cone-7* can serve as a heterotripotic receptor. This result was also observed after changing the binding sequence of the metal ions. Firstly, the complex of *cone-7* \supset Ag^+ was formed, then the complex

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

Compd.	Chemical shift, $\delta_{\text{ppm}}^{\text{a,b}}$					
	H_1	H_2	H_3	H_1'	H_2'	H_3'
<i>cone-7</i>	8.55	7.67 ^c	8.21 ^c	8.37	7.50 ^c	8.14 ^c
<i>cone-7</i> \supset Ag^+	8.51	7.77	8.11	8.36	7.58	8.04
Dd	+0.04	-0.10	+0.10	+0.01	-0.08	+0.10

^a $\Delta\delta$ values are the difference of the chemical shift between *cone-7* in $\text{CDCl}_3/\text{CD}_3\text{CN}$ at 27°C. ^bA minus sign (–) denotes a shift to lower magnetic field, a plus sign (+) denotes a shift to higher magnetic. ^cThe midpoint values of multiplet are indicated.

$\text{LiClO}_4 \subset [\text{cone-7} \supset \text{Ag}^+]$, $\text{Na}^+ \subset \{\text{Li}^+ \subset [\text{cone-7} \supset \text{Ag}^+]\}$ (Figure S7) was formed. We observed the same ^1H NMR spectrum as shown in Figure 6d and Figure S7d, and thus it was proved that *cone-7* can serve as a heterotripotic receptor for the Ag^+ , Li^+ and Na^+ ions simultaneously (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' ($\Delta\delta = -0.08$ ppm) and H_2 ($\Delta\delta = -0.10$ ppm), upfield shifts for H_3' ($\Delta\delta = +0.10$ ppm), H_3 ($\Delta\delta = +0.10$ ppm) and H_1 ($\Delta\delta = +0.04$ ppm) (Table 1) due to the tetrahedral interaction of the $\text{N}-\text{Ag}^+$ motif. Furthermore, after complexation, H_3' and H_3 , H_2' and H_2 have 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 [in $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (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 a 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 [$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (10:1, v/v)] (Figure S8), using the continuous variation method. The absorption also reached a maximum at 0.5 mol fraction for this cation, indicating that the Li^+ ion formed

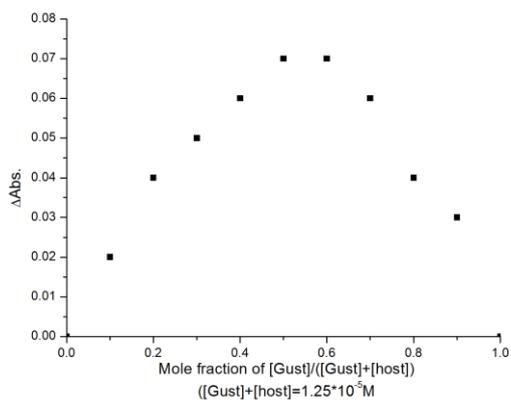


Fig. 8. Job plots of the extractions of Ag^+ with host *cone-7*.

a 1:1 complex with *cone-7*, and the Li^+ ion was completely bound by the *N,N*-diethylaminocarbonylmethoxy groups. The molar ratio method was used to determine the stoichiometry of *cone-7* complexed with Na^+ by UV-vis absorption spectra [$\text{CH}_2\text{Cl}_2/\text{CH}_3\text{CN}$ (10:1, v/v)] (Figure S9), which also indicated that the Na^+ ion formed a 1:1 complex with *cone-7*.

UV-vis spectrophotometric analysis was employed to determine 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 Ag^+ was fitted to a 1:1 binding model to determine the association constant, which was found to be $2.24 \times 10^5 \text{ M}^{-1}$. The association constant for *cone-7* and Li^+ was $2.58 \times 10^5 \text{ M}^{-1}$ and for *cone-7* and Na^+ , which was found to be $1.55 \times 10^5 \text{ M}^{-1}$ (Figures S10–12).

Conclusions

A *cone*-hexahomotrioxacalix[3]arene receptor *cone-7* bearing 2,2'-bipyridyl linked via a carbonyl group at the upper rim and *N,N*-diethylacetamide chains at the lower rim, respectively, has been synthesized. The receptor *cone-7* can serve as a heterotropic hexahomotrioxacalix[3]arene receptor with capability for binding two types of cation simultaneously 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 $\text{N} \cdots \text{Ag}^+$ 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-AQ20M 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*-diethylaminocarbonylmethoxy)-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*-diethylaminocarbonylmethoxy)-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 [$(\text{CHCl}_3\text{-MeOH})$ (5:1, v/v)] (88 mg, 56 %) as colorless prisms. M.p. 84.5–85 °C. ^1H NMR δ (CDCl_3) 1.11–1.12 (18H, m, $-\text{CH}_2\text{CH}_3$), 2.40 (9H, s, Bipy- CH_3), 3.30–3.41 (12H, m, $-\text{NCH}_2$), 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. IR: $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1} = 1723$ (COOR) and 1650 (CONRR'). ^{13}C NMR δ (CDCl_3) 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^+). $\text{C}_{81}\text{H}_{87}\text{O}_{15}\text{N}_9$ (1426.61): calcd C 68.19, H 6.15; N 8.84. Found: C 68.31, H 6.24, N 8.93.

^1H 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 ^1H NMR probe was kept constant at 27 °C. The ^1H NMR data of the most representative complexes are given below.

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

cone-7 \supset Li⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.12–3.42 (12H, m, -NCH₂), 4.46 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.59 (6H, s, Ar-OCH₂), 4.73 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.12 (6H, s, Bipy-CH₂), 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 \supset Na⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.10–3.35 (12H, m, -NCH₂), 4.26 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.64 (6H, s, Ar-OCH₂), 4.66 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.26 (6H, s, Bipy-CH₂), 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 \supset Ag⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.21–3.32 (12H, m, -NCH₂), 4.45 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.62 (6H, s, Ar-OCH₂), 4.84 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.10 (6H, s, Bipy-CH₂), 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* \supset Ag⁺] \supset Li⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.08–3.37 (12H, m, -NCH₂), 4.42 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.54 (6H, s, Ar-OCH₂), 4.69 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.08 (6H, s, Bipy-CH₂), 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* \supset Ag⁺] \supset Na⁺ (1:0.4): 3.13–3.35 (12H, m, -NCH₂), 4.23 (6H, d, J = 13.2 Hz, Ar-CH₂) complex, 4.45 (6H, d, J = 13.2 Hz, Ar-CH₂) uncomplex, 4.64 (6H, s, Ar-OCH₂), 4.64 (6H, d, J = 12.6 Hz, Ar-CH₂) complex, 4.84 (6H, d, J = 12.6 Hz, Ar-CH₂) uncomplex, 5.29 (6H, s, Bipy-CH₂) complex, 5.09 (6H, s, Bipy-CH₂) uncomplex, 7.64 (3H, dd, J = 6.7 Hz, J = 1.2 Hz, Bipy-H) uncomplex, 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) uncomplex, 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) uncomplex, 8.37 (3H, s, Bipy-H) and 8.59 (3H, s, Bipy-H) complex and 8.53 (3H, s, Bipy-H) uncomplex ppm.

[*cone-7* \supset Ag⁺] \supset Na⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.11–3.35 (12H, m, -NCH₂), 4.23 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.65 (6H, s, Ar-OCH₂), 4.64 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.29 (6H, s, Bipy-CH₂), 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 \supset Na⁺ (1:0.4): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.15–3.31 (12H, m, -NCH₂), 4.25 (6H, d, J = 13.2 Hz, Ar-CH₂) complex, 4.40 (6H, d, J = 13.2 Hz, Ar-CH₂) uncomplex, 4.62 (6H, s, Ar-OCH₂), 4.62 (6H, d, J = 12.6 Hz, Ar-CH₂) complex, 4.79 (6H, d, J = 12.6 Hz, Ar-CH₂) uncomplex, 5.24 (6H, s, Bipy-CH₂) complex, 5.14 (6H, s, Bipy-CH₂) uncomplex, 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) uncomplex, 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* \supset Na⁺] \supset Ag⁺ (1:1): δ_{H} (CDCl₃/CD₃CN, 10:1, v/v): 3.06–3.31 (12H, m, -NCH₂), 4.19 (6H, d, J = 13.2 Hz, Ar-CH₂), 4.62 (6H, s, Ar-OCH₂), 4.60 (6H, d, J = 12.6 Hz, Ar-CH₂), 5.26 (6H, s, Bipy-CH₂), 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 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/¹³C NMR spectra of *cone-7* and the detailed ¹H NMR titration spectra data.

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