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ORIGINAL ARTICLE

Synthesis, structure and inclusion properties of *cone*-tris{[(5′-methyl-2,2′-bipyridyl)-5-yl] oxycarbonylmethoxy}hexahomotrioxacalix[3]arene

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Abstract Hexahomotrioxacalix[3]arene having [(5′-methyl-2,2′-bipyridyl)-5-yl]oxycarbonylmethoxy group with *cone* conformation was prepared, which shows strong Ag^+ affinity and acts as a ditopic receptor for Ag^+ and nBuNH$_3^+$. A conformational change of 2,2′-bipyridyl moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the thiacalixarene cavity was observed in the process of Ag^+ complexation.

Keywords Hexahomotrioxacalix[3]arene · 2,2′-Bipyridyl group · Ionophore · Metal complexation · Ditopic receptor

Introduction

Calixarene and related macrocycles have received considerable attention for their host–guest chemistry as ionophoric receptors [1–4] and potential enzyme mimics in biology [5–8]. Chemical modification of calixarene represents an effective and versatile way of producing receptors with highly selective cation binding properties [9–12]. Even minor changes in the regioselective functionalization [13] or conformation [14] of the chemical modified calixarene can be associated with drastic changes in the complexation properties. On the other hand, Shinkai et al. reported in detail on the influence of *O*-substituents on the conformational isomerism of hexahomotrioxacalix[3]arenes **1** [15–18]. They have established that interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, can be sterically allowed for methyl, ethyl, and propyl groups whereas it is inhibited for the butyl group [18]. In their studies on the conformer distribution of hexahomotrioxacalix[3]arene the partial-cone is sterically less crowded than the cone and therefore formed predominantly regardless of the choice of the *O*-alkylation conditions. On the other hand, the cone results as the single isomer, when a metal ion template, which strongly interacts with phenolic oxygens, such as ethoxycarbonylmethyl or *N,N*-diethylaminocarbonylmethyl group, is present in the reaction system [15, 18]. However, the selective introduction of alkoxycarbonylmethyl group on the phenolic groups has not yet been accomplished in spite of affording a convenient starting material for the *O*-functionalized hexahomotrioxacalix[3]arenes.

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 cone conformation to construct sophisticated molecular devices and systems [19]. Bipyridyl containing calixarenes have been extensively used to complex various metal ions [20–27]. Di- or polytopic receptors are those constructed with two or more binding subunits within the same macrocyclic structure [28–30]. It is well known that these kinds of systems are suitable candidates for the allosteric regulation [20–22] of host–guest interactions with metal cations which play a major role in biological systems. In this paper we report on the synthesis of *cone*-tris{[(5′-methyl-2,2′-bipyridyl)-5-yl]-oxycarbonylmethoxy}hexahomotrioxacalix[3]arene from condensation of *cone*-hexahomotrioxacalix[3]arene triacetic acid with 5-hydroxymethyl-5′-methyl-2,2′-bipyridine.

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Conformational studies of *cone*-tris{[(5′-methyl-2,2′-bipyridyl)-5-yl]oxycarbonyl methoxy}hexahomotrioxacalix[3]arene in solution and its inclusion properties are also described.

Results and discussion

5-Hydroxymethyl-5′-methyl-2,2′-bipyridine **5** was prepared by 3 steps from 5,5′-dimethyl-2,2′-bipyridine **2** as shown in Scheme 1. Thus, the reaction of **2** with *N*-bromosuccinimide in the presence of 2,2'-azobis(2,4-dimethylpentanenitrile (V_{65}) to afford **3** in 58% yield, from which compound **5** was obtained by the reaction with silver acetate, followed by hydrolysis of acetate **4**.

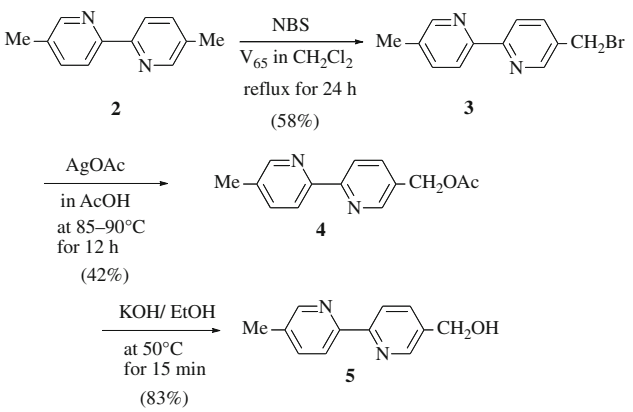
cone-Hexahomotrioxacalix[3]arene tricarboxylic acid *cone*-**7** was prepared by hydrolysis of *cone*-[(*N,N*-diethylaminocarbonyl)methoxy]hexahomotrioxacalix[3]arene *cone*-**6** with KOH aq. in a mixture of dioxane and water, which was prepared by *O*-alkylation of **1** with *N,N*-diethylchloroacetoamide in the presence of NaH according to the reported procedures [18, 31]. *cone*-Hexahomotrioxacalix[3]arene triester *cone*-**8** was prepared by condensation reaction of *cone*-**7** with 5-hydroxymethyl-5′-methyl-2,2′-bipyridine (**5**) in the presence of DCC (*N,N*-dicyclohexylcarbodiimide) and DMAP (4-dimethylaminopyridine) at room temperature for 35 h in CH_2Cl_2.

From the singlet peak of calix benzene protons for *cone*-**8**, the conformation was proven to have remained in the desired *cone*-conformation. In order to investigate the conformation of *cone*-**8** in detail, a reference compound **10** was synthesized from 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid **9** [32] following the similar method in the preparation of *cone*-**8**.

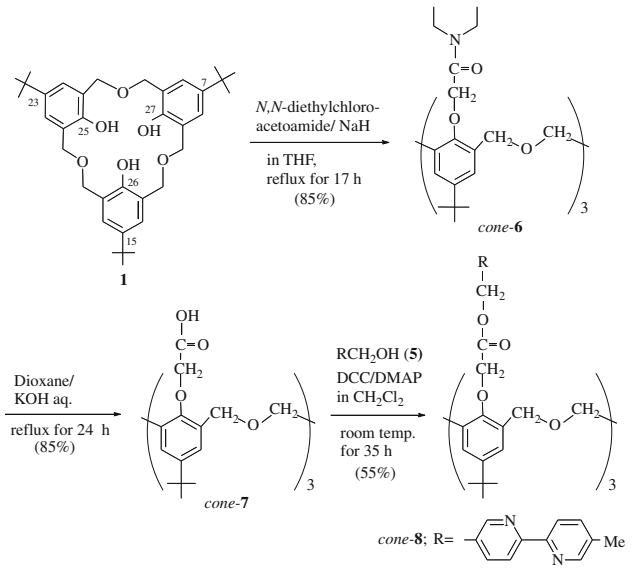
Conformation assignment for the new hexahomotrioxacalix[3]arene triester *cone*-**8** is firmly established by the presence of AB quartets for the bridging methylene protons with a $\Delta\delta$ separation between H_{ax} and H_{eq} of 0.39 ppm in its ^{1}H NMR spectrum ($CDCl_3$). In the calix[4]arenes, the $\Delta\delta$ values of the ArCH_2Ar protons have been correlated to the orientation of adjacent aromatic rings, i.e. $\Delta\delta > 1$ ppm with cone conformation or syn orientation, $\Delta\delta$ of about 0.5 with flattened cone or out orientation, $\Delta\delta$ of 0 ppm with *1,3-alternate* or anti orientation [33]. The same findings were observed in hexahomotrioxacalix[3]arenes [15]. Thus, we can deduce that *cone*-**8** prefers a flattened cone conformation.

Interestingly, the hetero aromatic protons of the bipyridine rings of *cone*-**8** are exposed to the ring current shielding effect [34–36] operating in the opposing bipyridine ring among the dibenzyl ether linkage, and resonate at higher fields with respect to those of the reference compound **10**. The magnitude of this shielding, computed as the difference between pertinent 2,2′-bipyridine protons of *cone*-**8** and reference compound **10**, increases significantly for the H_4, H_6 and $H_{3'}$ protons. The remarkable shielding effect experienced by the H_4 (−0.14 ppm), H_6 (−0.12 ppm) and $H_{3'}$ (−0.10 ppm) protons of the 2,2′-bipyridine suggest that these protons are located much closer to the neighboring bipyridine ring than the H_3 (+0.11 ppm) protons and are thus shifted stronger upfield. Thus, one nitrogen atom (N_1) in the 2,2′-bipyridine ring might be orientated outwards with respect to the hexahomotrioxacalix[3]arene cavity due to the electron repulsion between nitrogens at the neighboring positions. In contrary, the other nitrogen (N_1') oriented inwards due to the 2,2′-bipyridyl linkage (Scheme 2 and 3).

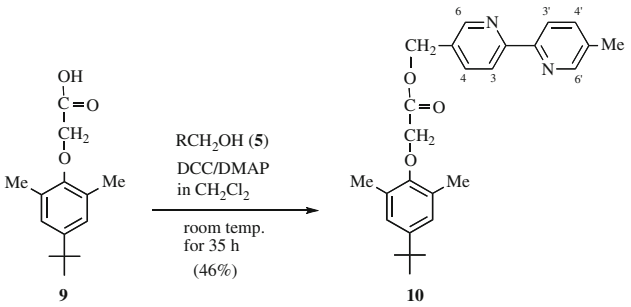
As a concave ionophore, that is, cavity-shaped molecules with an inwardly-directed functionality embedded in the concave position, compound *cone*-**8** was enabled to



Scheme 1 Synthesis of 5-hydroxymethyl-5′-methyl-2,2′-bipyridine **5**



Scheme 2 Synthesis of *cone*-hexahomotrioxacalix[3]arene triester *cone*-**8**



Scheme 3 Synthesis of the reference compound **10**

bind with metal cations and primary ammonium ions. The complexation mode was elucidated quantitatively by the NMR titration of nuclear magnetic resonance. Interestingly, depending on the ionic size, complexing behavior was different in the complex of compound *cone*-**8** with these cations.

The C_3-symmetrical conformation of compound *cone*-**8** makes it possible to bind with primary ammonium ions [16, 18]. The present ammonium ions binding mode can be also demonstrated more clearly by using ^{1}H NMR spectroscopy. There are two modes for *cone*-**8** to bind with *n*-butyl ammonium ions, i.e. from the lower rim through substituents moieties or from the upper rim through the π-cavity formed by three aromatic rings. After adding an equivalent of *n*-$BuNH_3^+Pic^-$ to a solution of *cone*-**8** (5×10^{-3} M) in $CDCl_3$ at 27 °C, peak signals of compound *cone*-**8** appeared both of complex and of free host, respectively. With increasing the amount of ammonium ion excessively, the signals of compound *cone*-**8** decreased and finally only the complex signals were observed. In comparison with the free host, in the complex, the protons of calix benzene rings shifted to lower field (from δ 6.91 to 7.32 ppm), while the chemical shift changes of the 2,2′-bipyridyl (*Bipy)* protons were negligibly small in the *cone*-**8** complexes *n*-butyl ammonium ion. These findings suggest the conformational change in the 2,2′-bipyridyl moiety might be small after complexation with *n*-butyl ammonium. Furthermore, the axial protons in the bridge methylene, which was related to the conformation of calixarene, were shifted to lower magnetic field (from δ 4.85 to 5.20 ppm), while the equatorial protons shifted to upper field (from δ 4.46 to 4.30 ppm). The methylene protons of ArO*CH*$_2$ were also shifted to lower field (from δ 4.55 to 4.95 ppm). With excess of *n*-$BuNH_3^+Pic^-$, the free guest molecules and the encapsulated molecules were clearly observed by the proton ^{1}H NMR spectroscopy, in which the encapsulated one was shifted to upfield, *CH*$_3$ (0.95 to 0.26, $\Delta\delta = -0.69$ ppm), CH_3CH_2 (1.45 to 0.30, $\Delta\delta = -1.05$ ppm), $CH_3CH_2CH_2$ (1.77 to −0.30, $\Delta\delta = -2.07$ ppm) and *CH*$_2$N (3.00 to 0.30, $\Delta\delta = -2.70$ ppm). The chemical shift of *NH* in *n*-$BuNH_3^+Pic^-$ was shifted to upper field (δ 8.30 to 5.85; $\Delta\delta = -2.45$ ppm). These phenomena were also proven the *n*-butyl ammonium ion was encapsulated into the cavity formed by the benzene rings and changed the conformaton of compound *cone*-**8**.

As mentioned previously, $\Delta\delta$ between H_{ax} and H_{eq} of the Ar*CH*$_2$Ar methylene protons in calix[4]arene serves as a measure of the 'flattening'. $\Delta\delta$ increases from δ 0.41 ppm to δ 0.86 ppm in *cone*-**8** upon the binding of *n*-$BuNH_3^+$ upon the binding of *n*-$BuNH_3^+$, respectively. These findings imply that *cone*-**8** stands up when the guest is included because *n*-$BuNH_3^+$ enters into the π-cavity formed by three aromatic rings.

Due to the existence of the three potential metal-binding sites, namely the bipyridine moieties, two ester moieties and calix benzene rings, there are several possibilities for metal complexation for compound *cone*-**8** with guest molecules. Either 1:1 or 1:2 metal complexation might be possible attributable to the electrostatic interactions as well as cation-π interactions. The Job plots of compound *cone*-**8** were carried out in the H_2O/CH_2Cl_2 phases. The percent extractions reach maximum at 0.5 mol fraction when the *cone*-**8** and silver cation are changed systematically. This fact clearly indicates that the Ag^+ cation forms a 1:1 complex with *cone*-**8**. This result suggests the major contribution is from the nitrogen of 2,2′-bipyridine ring to Ag^+ binding, but not a cation–π-interaction with calix benzene rings or the oxygen on the bridged linkage.

In order to explore the binding mode of three lower-rim side chains having pyridyl groups, we examined the ^{1}H NMR chemical shift differences between those before and after the addition of an equiv. KSO_3CF_3 or $AgSO_3CF_3$ in $CDCl_3$–CD_3CN, and composition of the ion–ionophore complex. The addition of an equiv. of KSO_3CF_3 to *cone*-**8** causes negligible chemical shift. On the other hand, titration with an equivalent of $AgSO_3CF_3$ causes a low field shift for the 2,2′-bipyridyl (*Bipy)* protons shifted with δ +0.24, +0.34 ppm for H_4, H_4' protons, and shifted to upper field with −0.17, −0.10, −0.13 ppm for H_3, H_3', H_6 protons, respectively (Fig. 1c). These observations might be attributed to the conformational change of the bipyridyl moieties in *cone*-**8** upon complexation. Thus, the *cone*-**8** complexes Ag^+ through the both metal-nitrogen electrostatic interactions of bipyridyl group by tetrahedral Ag^+/heterocycle complex. Interestingly, contrary to the observation of chemical shift changes of the bipyridyl protons, the chemical shift changes of the methylene protons of O*CH*$_2$Bipy moiety and Ar*CH*$_2$O were negligibly small in the *cone*-**8** complexes Ag^+. These findings suggest the conformational changes in calix benzene and ester moieties might be small after complexation with Ag^+.

Compound *cone*-**8** was treated with silver cation and *n*-butyl ammonium ion in a ^{1}H NMR titration to investigate the behavior as a ditopicreceptors. At first, with adding an

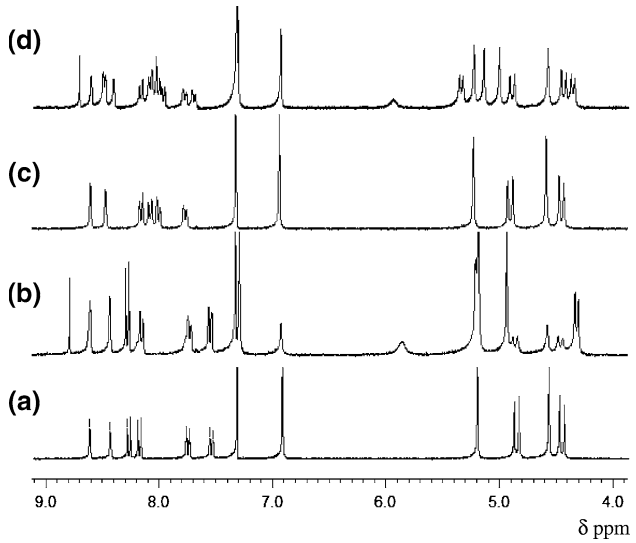


Fig. 1 Partial ^{1}H NMR spectra of *cone*-**8** ($CDCl_3$:CD_3CN, 2×10^{-3} M) a) Free *cone*-**8**,b) *cone*-**8** ⊂ *n*-$BuNH_3^+Pic^-$ (1:1); c) Ag^+⊃*cone*-**8** (1:1); d) [Ag^+⊃*cone*-**8** ⊂ *n*-$BuNH_3^+Pic^-$]

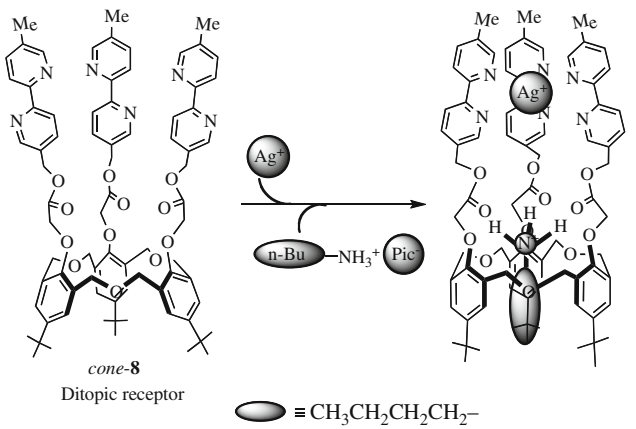


Fig. 2 Plausible binding mode of *cone*-**8** with Ag^+ and *n*-$BuNH_3Pic$

equivalent of silver cation, the chemical shift of protons peaks was changed as described above. The further investigation was complex Ag^+⊃*cone*-**8** in the presence of *n*-butyl ammonium ion. The results were shown in Fig. 1d. The induced chemical shift to upper field of *n*-butyl ammonium protons strongly suggested the complexation of Ag^+⊃*cone*-**8** with *n*-butyl ammonium ion. Furthermore, the conformation of the host was changed too. The chemical shift difference between the axial proton and equatorial proton in bridge methylene was increased upper to δ 0.92 ppm under the presence of both *n*-butyl ammonium ion and silver cation, which was mostly contributed by the complexation with *n*-butyl ammonium ion. Furthermore, the chemical shift of protons on pyridine rings showed small changes (0.04–0.10 ppm) proving that the complex with silver cation remained intact after the Ag^+⊃*cone*-**8** complex was treated with the *n*-butyl ammonium ion. Thus, compound *cone*-**8** can complex with *n*-butyl ammonium ions and silver cation at the same time to form the heteroditopic complexation. Compound *cone*-**8** shows association constant for *n*-butylammonium ion ($K_a = 18.25 \times 10^3$ M^{-1} in $CDCl_3$–CD_3CN 10:1). The complex ability decreases in the presence of Ag^+ ion ($K_a = 7.55 \times 10^3$ M^{-1} in $CDCl_3$–CD_3CN 10:1) due to strong electrostatic repulsion between *n*-butylammonium ion and silver ion included in the cavity of *cone*-**8**.

As shown in Fig. 2, the nitrogen atom (N_1) in the bipyridine ring points away from the calix cavity in the free *cone*-**8** because of the electron repulsion between nitrogens. After complexation, the nitrogen turns inwards towards the cavity to complexwith Ag^+ and thus affects H_4, H_4' protons which shift to lower field and H_3, H_3', H_6 protons which shift to upper field due to the tetrahedral interaction of N—Ag^+. Furthermore, the C_3-symmetrical conformation of *cone*-**8** is still retained after complexation with both *n*-butyl ammonium ion and silver ion.

Conclusions

For the first time, the relationship between properties of soft-hard ionophore hosts and alkyl ammonium ion was taken into account in C_3-symmetric conformation. *cone*-**8** can bind *n*-butyl ammonium ions through the π-cavity formed by three aryl rings, which can provide functional moieties in biologic systems with good affinity and high selectivity. As C_3-symmetrical bipyridyl-substituted calixarene, ionophore *cone*-**8** can also bind Ag^+ ion and the complexation mode was elucidated clearly in this paper. Thus, ionophore *cone*-**8** acts as a heteroditopic receptor which can complex with Ag^+ and *n*-$BuNH_3^+$ at the same time. The nitrogen atom in the bipyridine rings turned from outward from the cavity to inside the cavity to interact with Ag^+. After complexation of *cone*-**8** with Ag^+, the original C_3-symmetry has been remained for *cone*-**8**. To the best of our knowledge the present result is the first example of heterogeneous dinuclear complex in the hexahomotrioxacalix[3]arene family. These results give some insight into the molecular design of new synthetic receptors for use in anion controlled of biomimetic systems.

Experimental

All mps (Yanagimoto MP-S_1) are uncorrected. NMR spectra were determined at 300 MHz with a Nippon Denshi JEOL FT-300 NMR spectrometer with $SiMe_4$ as an internal reference: J-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl

plates in a Nipon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by Shimadzu 240 spectrophotometer. Mass spectra were obtained on a Nippon Denshi JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system through GLC. Elemental analysis: Yanaco MT-5.

Materials. Hexahomotrioxacalix[3]arene **1** was prepared according to the literature [15, 16]. *cone*-Hexahomotrioxacalix[3]arene triacetic acid *cone*-**7** was prepared according to the literature [18, 31].

Synthesis

*Synthesis of 5-monobromomethyl-5′-methyl-2,2′-bipyridine (**3**)*

A solution of 5,5′-dimethyl-2,2′-bipyridine **2** (500 mg, 2.71 mmol), *N*-bromosuccinimide (NBS) (531 mg, 2.98 mmol) and 2,2′-azobis(2,4-dimethyl-pentanenitrile) (V_{65}) (300 mg, 1.20 mmol) in CH_2Cl_2 (100 mL) refluxed 12 h under argon protect. The reaction mixture was cooled to room temperature and then solvent was evaporated. The residue dissolved in hot hexane and the solid part off out. The filtrate solution keep 4 h at room temperature, dibromomethyl derivatives was precipitated and separated by filtration. The filtrate part again reduced one-third volume and put 12 h at room temperature to afford white solid, which was recrystallization from ethylacetate/hexane(1:1) to give pure product **3** (410 mg, 58%) as a white powder, Mp 85–87 °C. ^{1}H NMR δ ($CDCl_3$) 2.39 (3H, s, bipy–CH_3), 4.53 (2H, s, –CH_2Br), 7.62 (1H, d, J 7.8 Hz, bipy–H_4'), 7.83(1H, d, J 6.0 Hz, bipy–H_4), 8.28 (1H, d, J 7 .8 Hz, bipy–H_3'), 8.35 (1H, d, J 8.4 Hz, Bipy–H_3), 8.49 (1H, s, Bipy–H_6') and 8.65 (1H, s, Bipy–H_6). ^{13}C NMR (75 MHz) δ 156.08, 150.05, 138.32, 134.59, 121.87 and 30.22. MS *m/z* 264 (M^+). Anal. Calcd for $C_{12}H_{11}BrN_2$ (263.14): C, 54.77; H, 4.21; N, 10.65. Found: C, 54.97; H, 4.42; N, 10.88%.

*Synthesis of 5′-methyl-2,2′-bipyridinyl-5-yl-methyl ester (**4**)*

A solution of 5-bromomethyl-5′-methyl-2,2′-bipyridinyl (**3**) (300 mg, 1.14 mmol) and silver acetate (951 mg, 5.7 mmol) in acetic acid(30 mL) was heated at 85–90 °C for 20 h. The reaction mixture was allowed to cool to room temperature and acetic acid was evaporated. The residue extracted with CH_2Cl_2 (2 × 50 mL), and washed with 10% Na_2CO_3 (20 mL) and water (2 × 30 mL), the organic layer was separated and dried over with $MgSO_4$, then condensed under reduced pressure. The residue was recrystallization from hexane to give pure product 5′-methyl-2,2′-bipyridinyl-5-yl-methyl ester **4** (116 mg, 42%) as colourless prisms, Mp 62–63 °C. ^{1}H NMR δ ($CDCl_3$) 2.12 (3H, s, –COCH_3), 2.40 (3H, s, Bipy–CH_3), 5.17 (2H, s, Bipy–CH_2–), 7.62 (1H, d, J 6.3 Hz, Bipy–H_4'), 7.80 (1H, d, J = 5.7 Hz, Bipy–H_4'), 8.28(1H, d, J 7.8 Hz, Bipy–H_3'), 8.36 (1H, d, J 8.4 Hz, Bipy–H_3), 8.50 (1H, s, Bipy–H_6') and 8.65 (1H, s, Bipy–H_6). MS *m/z* 242 (M^+). Anal. Calcd for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.61; H, 5.72; N, 11.48%.

*Synthesis of (5′-methyl-2,2′-bipyridinyl-5-yl)methanol (**5**)*

A solution of 5′-methyl-2,2′-bipyridinyl-5-yl-methyl ester (**4**) (140 mg, 0.58 mmol) aq.KOH (335 mg, 5.97 mmol in 2 mL of H_2O) in ethanol (10 mL) was heated and stirred for 25 min at 50 °C. The reaction mixture then cooled to room temperature and solvent was evaporated. The residue extracted with CH_2Cl_2 (2 × 50 mL) and washed with water (2 × 50 mL). The organic phase dried over with $MgSO_4$, and condensed under reduced pressure. The residue was recrystallization from hexane to give pure product (5′-methyl-2,2′-bipyridinyl-5-yl)methanol **5** (97 mg, 83%) as colourless prisms, Mp 110–111 °C. ^{1}H NMR δ ($CDCl_3$) 2.40 (3H, s, Bipy–CH_3), 4.79 (2H, d, J = 5.4 Hz, Bipy–CH_2–), 7.82 (1H, d, J 8.4 Hz, Bipy–H_4'), 7.82 (1H, d, J 6.0 Hz, Bipy–H_4), 8.27 (1H, d, J 7.8 Hz, Bipy–H_3'), 8.36 (1H, d, J = 8.1 Hz, Bipy–H_3), 8.50 (1H, s, Bipy–H_6') and 8.65 (1H, s, Bipy–H_6). MS m/z 200 (M^+). Anal. Calcd for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.99. Found: C, 71.73; H, 6.12; N, 13.68%.

*Preparation of cone-hexahomotrioxacalix[3]arene triacetic acid (cone-**7**)*

A mixture of *cone*-**6** (1.0 g, 1.14 mmol) in dioxane (35 ml), was added 1 N KOH aqueous solution (40 mL). After the mixture was refluxed for 24 h, it was condensed under reduced pressure, and then acidified by hydrochloric acid to pH 1–2. The dispersion was extracted with ethyl acetate (2 × 20 mL). The combined extracts were washed with water (2 × 20 mL), saturated brine (20 mL), dried ($MgSO_4$) and condensed under reduce pressure. The residue was washed with small amount of diethyl ether to give the crude *cone*-**7** as a colorless solid. Recrystallization from methanol to give *cone*-**7** (730 mg, 85%) as colorless powder; Mp 227–229 °C (lit. [31] Mp 227–229 °C).

*Synthesis of cone-7,15,23-tri-tert-butyl-25,26,27-tris {[(5′-methyl-2,2′- bipyridinyl)-5-yl]methoxy}-2,4,10,12,18,20-hexahomo-3,11,19-trioxacalix[3]arene (cone-**8**)*

(5′-Methyl-2,2′-bipyridinyl-5-yl)methanol **5** (85 mg, 0.42 mmol) and 4-dimethylaminopyridine (DMAP) (52 mg, 0.42 mmol) were added to a solution of *cone*-**7** (50 mg, 0.066 mmol) in CH_2Cl_2 (6 mL). The mixture was stirred at 0 °C while a solution of *N,N*-dicyclohexylcarbodiimide

(DCC) (96 mg, 0.46 mmol) in CH_2Cl_2 (6 mL) was added drop wise. The solution was stirred 1 h at 0 °C and 35 h at room temperature. After completion, filtering of the insoluble solid, CH_2Cl_2 was removed under reduce pressure. The residue was dissolved in AcOEt and filtrated. The filtrate was washed sequentially with 10% citric acid (2 × 25 mL), water (2 × 25 mL), 5% sodium bicarbonate (2′ 25 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), and concentrated. The residue was washed several times with hexane, and recrystalization from methanol to give the product *cone*-**8** (47 mg, 55%) as colourless prisms, Mp 95–97 °C. IR ν_{max} (KBr)/cm^{-1} 3431, 2955, 2863, 1760, 1610, 1557, 1470, 1362, 1188, 1068, 883, 830, 741 and 651 cm^{-1}. ^{1}H NMR δ ($CDCl_3$) 1.07 (27H, s, *t*Bu), 2.35 (9H, s, Bipy–CH_3), 4.46 (6H, d, *J* 12.9 Hz, ArCH_2O–), 4.55 (6H, s, ArOCH_2–), 4.85 (6H, d, *J* 12.9 Hz, ArCH_2O–), 5.21 (6H, s, Bipy–CH_2O–), 6.91 (6H, s, Ar–*H*), 7.54 (3H, d, *J* 6.0 Hz, Bipy–H_4'), 7.76 (3H, d, *J* 6.0 Hz, Bipy–H_4), 8.20 (3H, d, *J* 8.1 Hz, Bipy–H_3'), 8.29 (3H, d, *J* 8.1 Hz, Bipy–H_3), 8.62 (3H, s, Bipy–H_6') and 8.63 (3H, s, Bipy–H_6). MS m/z 1297.57 (M^+). Anal. Calcd for $C_{78}H_{84}N_6O_{12}$ + CH_3OH (1329.61): C, 71.37; H, 6.67; N, 6.32. Found: C, 71.39; H, 6.50; N, 6.43%.

*Preparation of 4-tert-butyl-2,6-dimethyl{[(5′-methyl-2,2′-bipyridinyl)-5-yl]methoxy}benzene (**10**)*

(5′-Methyl-2,2′-bipyridinyl-5-yl)-methanol **5** (85 mg, 0.42 mmol) and 4-dimethyl-aminopyridine (DMAP) (52 mg, 0.42 mmol) were added to a solution of 4-*tert*-butyl-2,6-dimethylphenoxyacetic acid **9** [33] (50 mg, 0.22 mmol) in CH_2Cl_2 (6 mL). The mixture was then stirred at 0 °C while a solution of *N,N*-dicyclohexyl- carbodiimide (DCC) (96 mg, 0.45 mmol) in CH_2Cl_2 (6 mL) was added drop wise. The solution was stirred 1 h at 0 °C and 35 h at room temperature. After completion, filtering of the insoluble solid, CH_2Cl_2 was removed under reduced pressure. The residue was dissolved in AcOEt and filtrated. The filtrate was washed sequentially with 10% citric acid (2 × 25 mL), water (2 × 25 mL), 5% sodium bicarbonate (2 × 25 mL), and brine (30 mL). The organic layer was dried ($MgSO_4$), and concentrated under reduced pressure to give a yellow oil. The residue was treated with MeOH (5 mL) to give the crude **10** (37 mg, 46%) as a white solid. Recrystallization from $CHCl_3$/MeOH (3:1) to give **10** as colourless prisms, Mp 81–82 °C. ^{1}H NMR δ ($CDCl_3$) 1.30 (9H, s, *t*Bu), 2.30 (6H, s, CH_3), 2.40 (3H, s, Bipy–CH_3), 4.87 (2H, s, OCH_2), 7.04 (2H, s, Ar–*H*), 7.63 (1H, dd, *J* = 8.1, 1.8 Hz, Bipy–$H_{4'}$), 7.91 (1H, dd, *J* 8.1, 1.8 Hz, Bipy–H_4), 8.30 (1H, d, *J* 8.1 Hz, Bipy–$H_{3'}$), 8.39 (1H, d, *J* 8.1 Hz, Bipy–H_3), 8.51 (1H, d, *J* 1.8 Hz, Bipy–$H_{6'}$) and 8.75 (1H, d, *J* 1.8, Bipy–H_6). MS *m/z* 360 (M^+). Anal. Calcd for $C_{24}H_{28}N_2O$ (360.50): C, 79.95; H, 7.83; N, 7.77. Found: C, 80.05; H, 7.79; N, 7.68%.

^{1}H NMR complexation experiment

A $CDCl_3$ solution (1.53×10^{-3} M, 400 μL) of *cone*-**8** in the NMR tube, was added a CD_3CN solution (1.53×10^{-2} M, 40 μL) of an equivalent of *n*-$BuNH_3^+Pic^-$. The spectrum was recorded after addition and the temperature of NMR tube kept constant at 27 °C. The association constants values were calculated by the integral intensity of CH_2 protons [ArOCH_2Bipy] in the complex and free host molecules according to the literature [37].

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