Synthesis, conformational studies and inclusion properties of *O*-benzylated calixarene analogues of trihydroxy[3.3.3]-metacyclophanes

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***O*-Benzylation of the flexible macrocycle 1 with benzyl bromide in the presence of NaH in THF under reflux afforded a mixture of two conformers of the tri-*O*-benzylated products, *cone*-2a and *partial-cone*-2a in a ratio of 20 : 80 in 80% yield. In contrast, *O*-alkylation of the triol 1 with 2-(chloromethyl)pyridine in the presence of NaH resulted in exclusive formation of *cone*-2b. Only when the template metal can hold the 2-pyridyl group(s) and the oxide group(s) on the same side of the [3.3.3]metacyclophane ring, is the conformation immobilized in the cone form. The template effect of the sodium cation plays an important role in this benzylation.**

The two-phase solvent extraction data indicated that tris(2-pyridylmethoxy)[3.3.3]metacyclophanes 2b show strong Ag^+ affinity, high Ag^+ selectivity being observed for both *cone*-2b and *partial-cone*-2b. ^1H NMR Titration of *cone*-2b with $AgSO_3CF_3$ clearly demonstrates that a 1 : 1 complex is formed with retention of the original symmetry. The pyridine moiety underwent conformational changes upon Ag^+ complexation with the original outward orientation of the ring nitrogen changing to an inside orientation toward the cyclophane cavity.

Introduction

Calixarene and related macrocycles have received considerable attention for their host–guest chemistry as ionophoric receptors and potential enzyme mimics in biology.[1] Chemical modification of calixarene represents an effective and versatile way of producing receptors with highly selective cation binding properties. Even minor changes in the regioselective functionalization or conformation of the chemically modified calixarene can be associated with drastic changes in the complexation properties.[2]

Recently, we reported on the influence of *O*-substituents on the conformational isomerism of 6,15,24-tri-*tert*-butyl-9,18,27-trihydroxy[3.3.3]MCP (MCP = metacyclophane) **1** in detail.[3] We have established that interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, is sterically allowed for methyl, ethyl and propyl groups whereas it is inhibited for butyl groups. There are only two possible conformations, 'cone' and 'partial-cone' for *O*-alkylation products in contrast to four possible conformations for calix[4]arenes.[1,2] Thus, the conformational isomerism is much simpler than that of *O*-alkylated calix[4]arenes such as hexahomotrioxacalix-[3]arenes.[4]

Pappalardo *et al.* reported[5] the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim as potential ligands for transition metals. Thus, both tris-2-picolyloxy-[3.3.3]MCPs with cone and partial-cone conformations derived from trihydroxy[3.3.3]MCPs are also supposed to bind selectively with soft metal ions, such as transition metal cations, Ag^+, or alkyl ammonium cations.

In this paper, we describe the synthesis, structures, and metal and ammonium ion complexation properties of tris(benzyloxy)- and tris(2-pyridylmethoxy)-[3.3.3]MCPs with cone- and partial-cone-conformations, which supposedly have encapsulating ionophilic cavities.

Results and discussion

6,15,24-Tri-*tert*-butyl-9,18,27-trihydroxy[3.3.3]MCP **1** was *O*-benzylated with benzyl bromide in the presence of Cs_2CO_3 to yield exclusively the tri-*O*-benzylated product *partial-cone*-**2a** (95%). No formation of the other possible cone-conformer as shown in Fig. 1 has been observed. Under the same reaction conditions a reaction in the presence of K_2CO_3 yielded *partial-cone*-**2a** (95%) along with recovery of the triol **1**. However, *O*-benzylation in the presence of Na_2CO_3 only resulted in the quantitative recovery of starting compound. A similar reaction was carried out in the presence of NaH to yield a mixture of two conformers of the tri-*O*-benzylated product **2a** in a ratio of 20 : 80 (*cone*-**2a**: *partial-cone*-**2a**) in 80% yield.

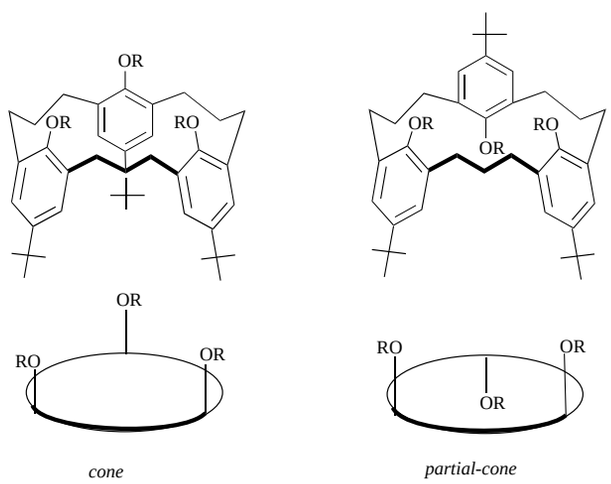


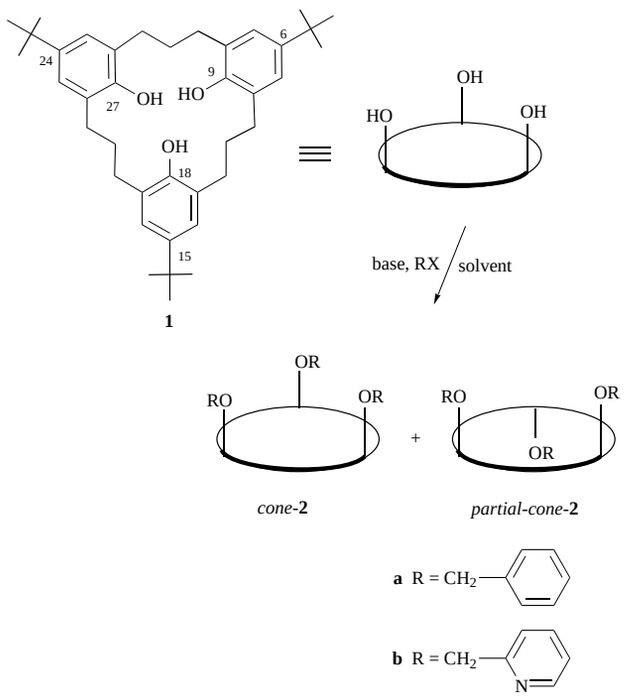
Fig. 1 Two possible conformers of *O*-alkylated trihydroxy[3.3.3]-metacyclophanes

On the other hand, we have reported[3] that tri-*O*-butylation of the triol **1** with butyl bromide in the presence of NaH exclusively yields a *partial-cone*-tri-*O*-butylated product. No formation of cone conformer was observed. These findings support the view that when substituents are introduced into trihydroxy[3.3.3]MCP **1** it prefers a partial-cone conformer to

Table 1 *O*-Substitution of the triol **1** with benzyl bromide and 2-(chloromethyl)pyridine

Run	RX	Base	Solvent	Distribution (%)[a,b] *cone*	*partial-cone*
1	BzlBr	NaH	THF-DMF	20 [10]	80 [70]
2	BzlBr	Na_2CO_3[c]	Acetone	0	0
3	BzlBr	K_2CO_3[d]	Acetone	0	96
4	BzlBr	Cs_2CO_3	Acetone	0	100 [95]
5	PicCl	NaH	THF–DMF	100 [80]	0
6	PicCl	Cs_2CO_3	Acetone	60 [50]	40 [17]

[a] Relative yields determined by ^{1}H NMR spectra. [b] Isolated yields are shown in parentheses. [c] Starting compound **1** was recovered in quantitative yield. [d] Starting compound **1** was recovered in 4% yield.



Scheme 1

reduce steric crowding. These results indicate that when benzyl bromide is used in the presence of NaH, the undissociated OH group forms intramolecular hydrogen bonds with the dissociated O^- group, which weakens the metal template effect arising from the $M^+ \cdots O^-$ interaction. Thus, ring inversion occurs to give the preferentially inverted partial-cone conformer as a result of the triol **1** having a much more flexible structure than the calix[4]arene.

In contrast, the preferential formation of *cone*-**2b** was observed in the reaction of the triol **1** with 2-(chloromethyl)-pyridine in the presence of Cs_2CO_3 (Table 1, run 6). Interestingly, the proportion of *cone*-**2b** dramatically increased, and in the *O*-substitution of trihydroxy[3.3.3]MCP **1** with 2-(chloromethyl)pyridine, when a stronger base was employed (*e.g.* NaH rather than Cs_2CO_3) the yield was almost quantitative. The template metal can hold the 2-pyridylmethyl group(s) and the oxide group(s) on the same side of the [3.3.3]MCP through the cation–N–interaction [Fig. 2 (A)]. Thus, the conformation is completely immobilized to the cone. Although a much larger contribution for Cs^+ to the template effect compound with Na^+ as reported by Harrowfield[6] can be expected, the larger Cs^+ may enlarge the cyclophane ring of the triol **1** sufficiently for ring inversion to occur and the thermodynamically stable partial-cone conformer [Fig. 2 (B)] to be formed.

The ^{1}H NMR spectrum of *cone*-**2a** shows a singlet for the *tert*-butyl protons at δ 1.19 and a singlet for ArOCH_2Ph and the aromatic protons at δ 4.76 and 6.74, respectively indicating a

Table 2 Chemical shifts of pyridine protons in *cone*-**2b** and reference compound **3**[a]

Compd.	Chemical shifts, δ (ppm) H-6	H-5	H-4	H-3
cone-**2b**	8.46	7.00[c]	7.13	7.70
3	8.58	7.20	7.74	7.74
$\Delta\delta$[b]	−0.12	−0.20	−0.61	−0.04

[a] $\Delta\delta$ Values are the difference of the chemical shift between *cone*-**2b** and reference compound **3** in $CDCl_3$ at 27 °C. [b] A plus sign (+) denotes a shift to lower magnetic field, whereas a minus sign (−) denotes a shift to higher magnetic field. [c] The midpoint value of multiplet.

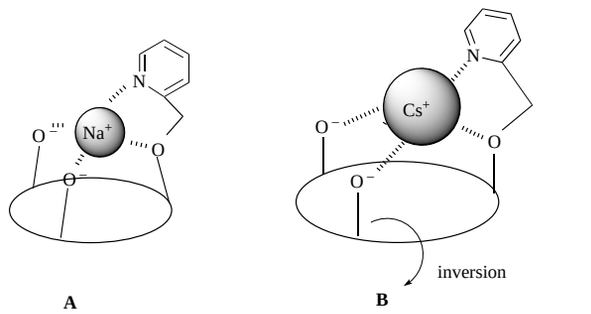


Fig. 2 Ring inversion of the triol **1** and immobilization by metal template

C_3-symmetrical structure for *cone*-**2a**. Similarly, the ^{1}H NMR spectrum of *partial-cone*-**2a** shows a singlet for the *tert*-butyl protons at δ 1.10 and 1.29 (relative intensity 2 : 1), a singlet at δ 3.93 and a pair of doublets for the diastereotopic ArOCH_2Ph methylene protons at δ 4.45 and 4.69 (J_{AB} = 11.7 Hz) (relative intensity 1 : 1) are observed. These signals are consistent with structure of *partial-cone*-**2a** having a C_2-symmetrical structure. Thus, in this conformation the two benzyl groups in the compound point up, while an inverted benzyl group is folded down into the π-cavity afforded by two benzene rings; it is thus greatly shielded. This gives upfield signals at δ 3.93 for the methylene protons and at δ 6.62 for the 2,6-aromatic protons.

Interestingly, the heteroaromatic protons of the pyridine rings of *cone*-**2b** are exposed to the ring current shielding effect[7,8] which results from the opposing pyridine ring among the diphenylpropane linkage, and resonate at higher fields with respect to those of the reference compound **3**; the latter was prepared by *O*-alkylation of 4-*tert*-butyl-2,6-dimethylphenol with 2-(chloromethyl)pyridine in the presence of NaH. Table 2 shows that the magnitude of this shielding, computed as the difference between the corresponding pyridine protons of *cone*-**2b** and reference compound **3**, increases significantly on H-4 and H-5. The remarkable shielding effect experienced by H-4 (−0.61 ppm) and H-5 (−0.20 ppm) of the pyridine ring suggests that these protons are located closer to the opposing pyridine ring than H-3 and H-6 because of the repulsion between the nitrogen atoms in the two pyridine rings separated by the diphenylpropane linkage. Thus, nitrogens in all of the pyridine rings were orientated outwards from the cyclophane cavity as shown in Fig. 3.

In contrast, the ^{1}H NMR spectrum of *partial-cone*-**2b** shows two singlets for the *tert*-butyl protons at δ 1.04, 1.26 (relative intensity 2 : 1), a singlet and a pair of doublets at δ 7.13 and 6.94, 6.96 for the aromatic protons. Furthermore, the resonance for the ArOCH_2Py methylene protons appeared as a singlet at δ 4.20 and a pair of doublets at δ 4.62, 4.83 (J_{AB} 14.16 Hz). Upfield shifts for the inverted pyridine ring protons were observed, in particular at δ 6.13 for H-3. These signals correspond to a C_2 symmetric structure similar to that for *partial-cone*-**2a**. On the basis of the ^{1}H NMR studies and a consideration of the CPK model of *partial-cone*-**2b**, it is clear that two 2-pyridylmethyl groups in the compound point upwards whilst

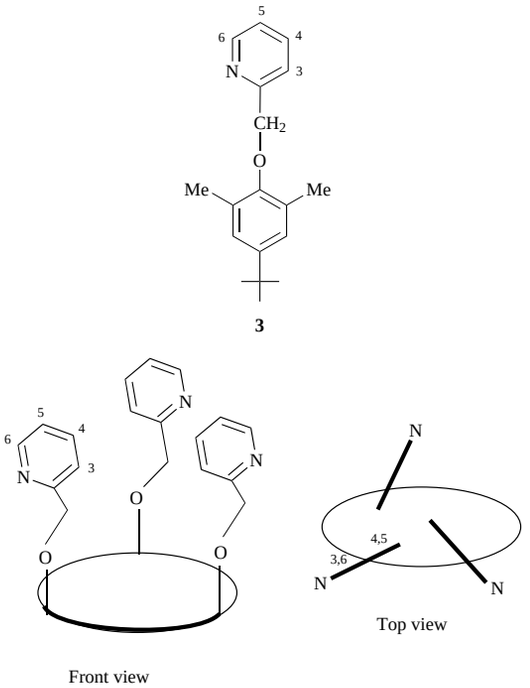


Fig. 3 Reference compound **3** and orientation of the pyridine N atoms in *cone*-**2b**

another one is folded into the π-cavity formed by two benzene rings so that its signals are shifted strongly upfield. The remarkable shielding effect experienced by H-3 of the inverted pyridine ring suggests that it is tightly accommodated inside the hydrophobic cavity in a type of self-inclusion complex, with the ring nitrogen orientated outwards from the cavity.[5]

It was also found that ring inversion by oxygen-through-the-annulus rotation is inhibited for tris(2-pyridylmethoxy) derivatives *cone*-**2b** and *partial-cone*-**2b** since it was noted that there was no change in the spectrum pattern for the ArCH_2-CH_2CH_2Ar methylene protons below 150 °C in [$^2H_6$]-DMSO.

It was found by Ungaro *et al.*,[9] McKervey *et al.*,[10] Chang *et al.*,[11] and Shinkai *et al.*[12] that calix[*n*]arenes can be turned into neutral ligands by conversion of the OH groups into ester groups. Further, they demonstrated that metal selectivity is dependent on the calix[*n*]arene ring size and, in particular, calix[4]arylacetates and acetamides with a cone conformation show remarkably high Na^+ selectivity. There are differences in the ring size and ring flexibility of calix[4]arene and the present homocalixarene analogues of metacyclophanes. In addition, Pappalardo *et al.* have reported[5] the synthesis of calix[4]arenes bearing pendant pyridine groups at the lower rim which have potential as ligands for transition metals. Quite recently, Reinhoudt *et al.*[13] have also reported a well-defined hydrogen-bonded calix[4]arene duplex between the pyridylcalix[4]arenes and calix[4]arenetetracarboxylic acid. It was thus interesting to assess what kind of ionophoric cavity the tris(2-pyridylmethoxy) derivatives **2b** provide. To the best of our knowledge, however, no precedent exists for the molecular design of such propane-bridged calixarene analogues of metacyclophane-based ionophores. The cation binding properties of **2b** were examined by the liquid–liquid extraction method.

Although *cone*- (*cone*-**2b**) and *partial-cone*-tris(2-pyridylmethoxy)[3.3.3]MCP (*partial-cone*-**2b**) scarcely extract alkali-metal and butylammonium cations under the experimental conditions used, high extractability for Ag^+ was observed (Table 3). The present extractabilities for Ag^+ (extraction %: 78% for *cone*-**2b** and 76% for *partial-cone*-**2b**) are superior to that of commercially available dibenzopyridino-18-crown-6 (extraction %: 65%).[14] In contrast, the corresponding tris(benzyloxy) derivatives, *cone*-**2a** and *partial-cone*-**2a** scarcely extract Ag^+ cation under these experimental conditions (extraction %: < 1%). Therefore, the synergism of the cyclophane moiety and the two or three lower-rim side chains having pyridyl groups play a significant role on the complexation of tris(2-pyridylmethoxy) derivatives *cone*-**2b** and *partial-cone*-**2b** with Ag^+ cation.

Table 3 Extraction (%) of metal picrates in CH_2Cl_2[a]

Cation	Ionophore	
	cone-**2b**	*partial-cone*-**2b**
Li^+	1.4	0.1
Na^+	0.7	0.4
K^+	1.1	0.4
Cs^+	0.3	0
$BuNH_3^+$	2.2	1.4
Ag^+	77.8	75.6

[a] Extraction (%) of alkali-metal picrates by ionophores **2b** in CH_2Cl_2. Extraction conditions; 2.5×10^{-4} M of ionophore in CH_2Cl_2; 2.5×10^{-4} M of picric acid in 0.1 M of alkaline hydroxide at 25 °C. Ionophore solution (5.0 cm^3) was shaken for 2 h with picrate solution (5.0 cm^3) and the % extraction was measured by the absorbance of the picrate in CH_2Cl_2. The experimental error was ± 2%.

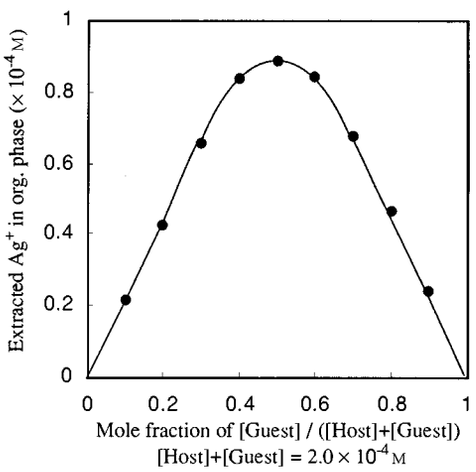


Fig. 4 Job plots of the extractions of Ag^+ with host *cone*-**2b**

Recently, Shinkai *et al.* reported that the 1,3-alternate conformer of the calix[4]arene tetraester can form both a 1 : 1 and a 2 : 1 metal/calixarene complex, with the two metal-binding sites displaying negative allostericity from ^{1}H NMR titration experiment.[12b] In the present systems, because of the existence of three metal-binding sites for the pyridine moiety there are several possibilities for metal complexation. Thus, both 1 : 1 and 2 : 1 metal complexation of *cone*-**2b** may be possible.

As shown in Fig. 4, the percent extractions reach a maximum at 0.5 mole fraction for this cation. This fact clearly indicates that Ag^+ forms a 1 : 1 complex with *cone*-**2b**. Thus, we established the synergism upon complexation of the cyclophane moiety and three pyridine-arms.

In order to confirm the synergism between the cyclophane moiety and the three lower-rim side chains having pyridyl groups, we examined the ^{1}H NMR chemical-shift differences between these both before and after the addition of an equimolar aliquot of $AgSO_3CF_3$; we have also examined the composition of the ion–ionophore complex.

In fact, the chemical shifts of the aromatic protons of *cone*-**2b** underwent a change upon titration of the compound with $AgSO_3CF_3$ in $CDCl_3$–CD_3OD (1 : 1, v/v): *i.e.*, a 1 : 1 mixture of *cone*-**2b** and $AgSO_3CF_3$ showed a completely different ^{1}H NMR spectrum with sharp aromatic proton signals being evident (Fig. 5). The methylene proton ArOCH_2Py resonates at lower field (δ 5.07, $\Delta\delta$ = +0.19 ppm) compared with its position in the metal-free spectrum. As shown in Fig. 6, the pyridine moieties show considerable shifts to lower field ($\Delta\delta$ = +0.72 ppm for H-4, 0.48 ppm for H-5 and 0.53 ppm for H-6), similar to that

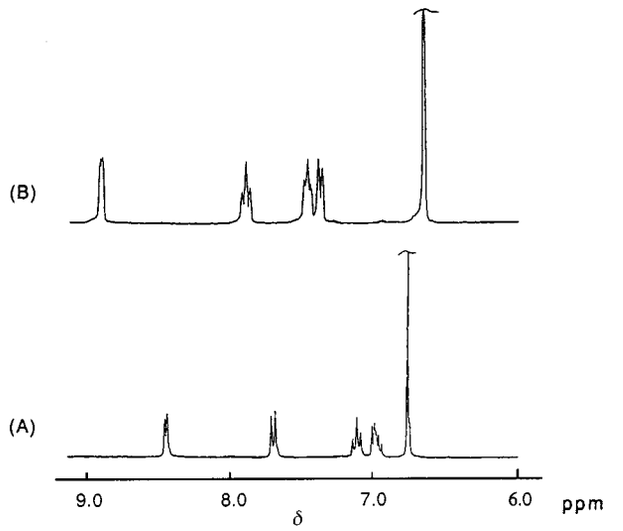


Fig. 5 Partial ^{1}H NMR titration spectra of *cone*-**2b** (5×10^{-4} M), $CDCl_3$: [$^2H_4$]methanol = 1:1 v/v, 270 MHz. (A) in the absence of $AgSO_3CF_3$ and (B) in the presence of $AgSO_3CF_3$ (5×10^{-4} M).

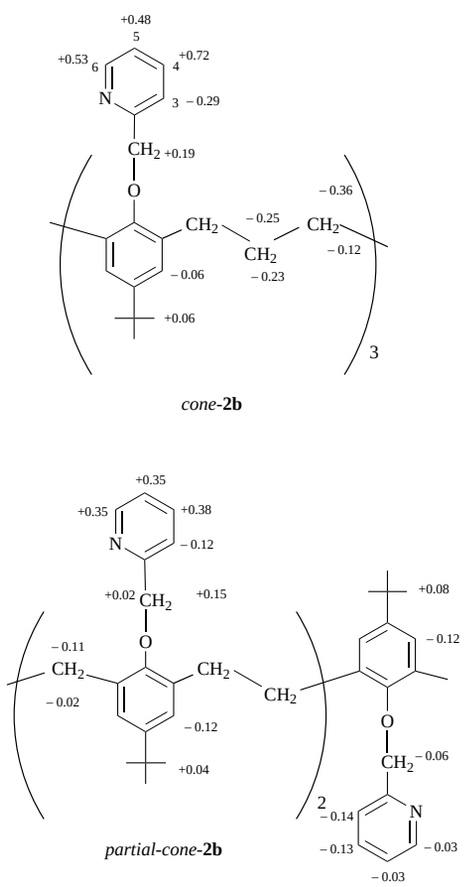


Fig. 6 Chemical shift changes of *cone*-**2b** and *partial-cone*-**2b** induced in the presence of $AgSO_3CF_3$; + denotes the downfield and − denotes the upfield shift

reported for a related complex (with two pyridine arms, one crown ether ring, and one Ag^+ ion).[15] In contrast to these observations, the signals for the aromatic and *tert*-butyl protons failed to appear separately ($\Delta\delta = -0.06$ and $+0.06$ ppm, respectively).

More detailed examination of the chemical-shift change suggests that Ag^+ should be bound to the lower rim of the cavity, which is composed of three phenolic oxygens and three pyridine nitrogens, because the large downfield shifts were observed for H-4, H-5 and H-6 on a pyridine ring due to the inductive effect arising from the N···Ag^+ interaction present around this cavity. A similar downfield shift of the methylene protons of ArOCH_2Py was also observed as a result of interaction of the oxygen atoms in these phenyl units with Ag^+. Furthermore, in this complex the downfield shifts for the ArCH_2CH_2CH_2Ar methylene protons are also observed ($\Delta\delta$ from -0.12 to -0.36 ppm). These results are explicable in terms of 'interaction' of Ag^+ with the benzene rings: that is, Ag^+ is trapped in a cavity composed of three phenolic oxygens and three pyridine nitrogens, by both metal–oxygen electrostatic interactions and metal–nitrogen interactions. However, since, as mentioned earlier, the corresponding *cone*-tris(benzyloxy) derivative *cone*-**2a** failed to exhibit any extraction behaviour for Ag^+, this finding strongly supports the contribution of the pyridine nitrogen to Ag^+-binding, but not the cation-π interaction demonstrated by Shinkai *et al*. in the high affinity of Ag^+ for 1,3-alternate-calix[4]-arene.[16]

In the *partial-cone*-**2b**·Ag^+ complex, the ArOCH_2*Py* methyl-

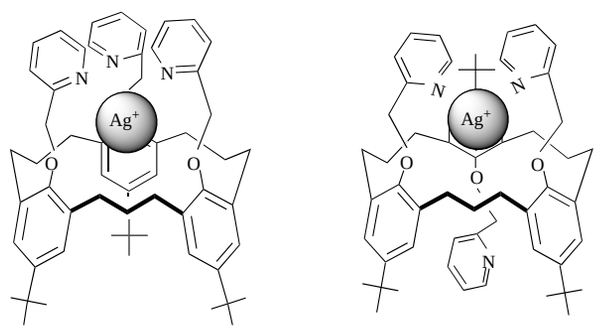


Fig. 7 Binding mode of tris(2-pyridylmethoxy)[3.3.3]MCPs *cone*-**2b**, *partial-cone*-**2b** and Ag^+

ene protons and the pyridine ring protons (H-4, H-5, H-6) in the ordinary phenyl units shift to lower magnetic field (by $+0.15$ and from $+0.35$ to $+0.38$ ppm), whereas those in the one inverted phenyl unit shift to higher magnetic field (by -0.06, from -0.03 to -0.14 ppm). This fact suggests that the Ag^+ ion is mainly bound to the phenolic oxygens and the pyridine nitrogens in the two ordinary phenyl units and the picolyl group in the inverted phenyl unit rotates into the cavity. Probably, this rotation is induced by steric repulsion between the bound Ag^+ ion and the *tert*-butyl group in the inverted phenyl unit. In this complex the splitting pattern for the ArCH_2CH_2CH_2Ar methylene protons is very complicated. Hence, it is difficult to obtain useful information from the δ values for the propane bridge protons.

The conformational changes of the pyridine moiety from the original outward orientation of the ring nitrogen to the inside orientation toward the cyclophane cavity was observed in the process of Ag^+ complexation. This result strongly suggests that the original C_3 and C_2 symmetry might remain after the complete metal cation complexation. Further experiments on these metal complexations are currently in progress in our laboratory.

Conclusions

Interesting results have been obtained by derivatization of the hydroxy groups of the triol **1** into the corresponding benzyl and 2-picolyl compounds. We have demonstrated for the first time that *O*-benzylation of the flexible macrocycle **1** with benzyl bromide or 2-(chloromethyl)pyridine gave tri-*O*-benzylated products with a cone or partial-cone conformation. The alkali-metal cation can play an important role for the conformer distribution based on the template effect. The two-phase solvent extraction data indicated that tris(2-pyridylmethoxy)[3.3.3]-MCPs **2b** show a strong affinity for Ag^+. ^{1}H NMR Titration of *cone*- and *partial-cone*-**2b** with $AgSO_3CF_3$ clearly demonstrates that a 1:1 complex is formed with retention of the original symmetry. Thus, the synergism of the cyclophane moiety and two or three lower-rim side chains having pyridyl groups play a

significant role on the complexation of tris(2-pyridylmethoxy) derivatives *cone*-**2b** and *partial-cone*-**2b** with Ag^+ cation.

Experimental

Mps (Yanagimoto MP-S1) and bps are uncorrected. NMR spectra were determined at 270 MHz with a Nippon Denshi JEOL FT-270 NMR spectrometer with $SiMe_4$ as an internal reference: *J*-values are given in Hz. IR spectra were measured for samples as KBr pellets or a liquid film on NaCl plates in a Nippon 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.

Materials

The preparation of 6,15,24-tri-*tert*-butyl-9,18,27-trihydroxy-[3.3.3]metacyclophane **1** has been previously described.[3]

Benzylation of 1 with benzyl bromide in the presence of NaH

To a suspension of NaH (227 mg, 5.25 mmol) in dry tetrahydrofuran (THF) (5 cm^3) was added a solution of **1** (100 mg, 0.174 mmol) in a mixture of DMF (2 cm^3) and THF (3 cm^3) under nitrogen. The reaction mixture was stirred under gentle reflux for 1 h after which it was treated with benzyl bromide (0.21 cm^3, 1.74 mmol) and further heated at reflux for 17 h. After cooling of the reaction mixture to room temperature, it was quenched with water and extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure. ^1H NMR analyses of the residue were in accord with its being a mixture of *cone*-**2a** and *partial-cone*-**2a** in the ratio of 20 : 80. The residue was washed with methanol to give crude *partial-cone*-**2a** as a colourless solid (102 mg, 70%). Recrystallization of this from methanol–$CHCl_3$ (3 : 1) gave partial-cone-9,18,27-*tribenzyloxy*-6,15,24-*tri*-tert-*butyl*[3.3.3]*metacyclophane partial-cone*-**2a** as *prisms* [from methanol–$CHCl_3$ 3 : 1)]; mp 208–210 °C; δ_H-($CDCl_3$) 1.10 (18 H, s), 1.29 (9 H, s), 1.67–3.01 (18 H, m), 3.93 (2 H, s), 4.45 (2 H, d, *J* 11.72), 4.69 (2 H, d, *J* 11.72), 6.38–6.44 (2 H, m) and 6.90–7.18 (19 H, m); *m*/*z* 840 (M^+) (Found: C, 85.53; H, 8.73. $C_{60}H_{72}O_3$ requires C, 85.67; H, 8.63%). The splitting pattern in ^1H NMR showed that the isolated compound was *partial-cone*-**2a**.

The filtrate was concentrated under reduced pressure and the residue was chromatographed on silica gel (Wako, C-300; 100 g) with benzene as eluent to give crude *cone*-**2a** as a colourless oil (15 mg, 10%). Recrystallization of this from methanol–$CHCl_3$ (3 : 1) gave cone-9,18,27-*tribenzyloxy*-6,15,24-*tri*-tert-*butyl*-[3.3.3]*metacyclophane cone*-**2a** as *prisms* (from methanol–$CHCl_3$, 3 : 1); mp 121–123 °C; $\delta_H(CDCl_3)$ 1.19 (27 H, s), 2.31–2.82 (18 H, m), 4.76 (6 H, s), 6.74 (6 H, s) and 7.16–7.36 (15 H, m); *m*/*z* 840 (M^+) (Found: C, 85.73; H, 8.53. $C_{60}H_{72}O_3$ requires C, 85.67; H, 8.63%). The splitting pattern in ^1H NMR showed that the isolated compound was *cone*-**2a**.

Benzylation of 1 with benzyl bromide in the presence of Cs_2CO_3

A mixture of **1** (100 mg, 0.174 mmol) and Cs_2CO_3 (567 mg, 1.74 mmol) in acetone (10 cm^3) was heated at reflux for 1 h, after which it was treated with benzyl bromide (0.21 cm^3, 1.74 mmol). The mixture was heated at reflux for 17 h and then cooled to room temperature and filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (2 × 100 cm^3). The compound extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure; ^1H NMR analyses of the residue were consistent with its being *partial-cone*-**2a**. The residue was washed with methanol to give crude *partial-cone*-**2a** (139 mg, 95%) as a colourless solid.

Alkylation of 1 with 2-(chloromethyl)pyridine in the presence of NaH

A mixture of **1** (200 mg, 0.35 mmol) and NaH (60%; 420 mg, 10.5 mmol) in dry THF (18 cm^3) was heated at reflux for 1 h under N_2 after which it was treated with a solution of 2-(chloromethyl)pyridine (7.87 mmol) [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (1.29 g, 7.87 mmol) in DMF (8 cm^3) with a solution of triethylamine (1.10 cm^3, 7.87 mmol) in THF (15 cm^3) at room temperature]. The mixture was heated at reflux for an additional 17 h, after which it was cooled to room temperature, acidified with 1 M aq. HCl (10 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (50 cm^3 × 2), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil; ^1H NMR analyses of the residue were in accord with its being *cone*-**2b**. The residue was chromatographed on silica gel with methanol as an eluent to give *cone*-**2b** (236 mg, 80%). This was recrystallized from MeOH–$CHCl_3$ (3 : 1) to afford cone-6,15,24-*tri*-tert-*butyl*-9,18,27-*tris*(2-*pyridylmethoxy*)[3.3.3]*metacyclophane cone*-**2b** as prisms (from methanol–$CHCl_3$, 3 : 1); mp 200–203 °C; $\delta_H(CDCl_3)$ 1.18 (27 H, s), 1.63–1.75 (3 H, m), 1.88–1.99 (3 H, m), 2.34–2.44 (6 H, m), 2.78–2.88 (6 H, m), 4.88 (6 H, s), 6.77 (6 H, s), 6.95–7.05 (3 H, m, H-5), 7.13 (3 H, ddd, *J* 7.81, 7.69 and 1.47, H-4), 7.70 (3 H, d, *J* 7.81, H-3), 8.46 (3 H, dd, *J* 1.47 and 4.89, H-6); *m*/*z* 843 (M^+) (Found: C, 81.52; H, 8.09; N, 4.57. $C_{57}H_{69}O_3N_3$ requires C, 81.62; H, 8.01; N, 4.84%). The splitting pattern in ^1H NMR showed that the isolated compound was *cone*-**2b**.

Alkylation of 1 with 2-(chloromethyl)pyridine in the presence of Cs_2CO_3

A mixture of **1** (200 mg, 0.35 mmol) and Cs_2CO_3 (2.43 g, 10.5 mmol) in dry THF (18 cm^3) was heated at reflux for 1 h under N_2, after which it was treated with a solution of 2-(chloromethyl)pyridine (7.87 mmol) [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (1.29 g, 7.87 mmol) in DMF (8 cm^3) with a solution of triethylamine (1.10 cm^3, 7.87 mmol) in THF (15 cm^3) at room temperature]. The mixture was heated at reflux for an additional 17 h and then cooled to room temperature and filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (2 × 100 cm^3). The combined extracts were washed with water (2 × 50 cm^3), dried (Na_2SO_4) and concentrated under reduced pressure; ^1H NMR analyses of the residue were in accord with its being a mixture of *cone*-**2a** and *partial-cone*-**2a** in the ratio of 60 : 40. The residue was chromatographed on silica gel with methanol as eluent to give *cone*-**2b** (148 mg, 50%) and *partial-cone*-**2b** (50 mg, 17%), respectively. Recrystallization of latter fraction from MeOH–$CHCl_3$ (3 : 1) afforded partial-cone-6,15,24-*tri*-tert-*butyl*-9,18,27-*tris*(2-*pyridylmethoxy*)[3.3.3]*metacyclophane partial-cone*-**2b** as prisms [from methanol–$CHCl_3$ (3 : 1)]; mp 278–280 °C; $\delta_H(CDCl_3)$ 1.04 (18 H, s), 1.26 (9 H, s), 2.00–3.00 (18 H, m), 4.20 (2 H, s), 4.62 (2 H, d, *J* 14.16), 4.83 (2 H, d, *J* 14.16), 6.13 (1 H, d, *J* 7.81, H-3′), 6.81 (2 H, d, *J* 7.81, H-3), 6.94 (2 H, d, *J* 2.44), 6.96 (2 H, d, *J* 2.44), 6.69–7.07 (3 H, m, H-5, H-5′), 7.13 (2 H, s), 7.30 (2 H, ddd, *J* 7.81, 7.69 and 1.47, H-4), 7.46 (1 H, ddd, *J* 7.81, 7.69 and 1.47, H-4′), 8.32 (1 H, dd, *J* 4.88 and 1.47, H-6′) and 8.41 (2 H, dd, *J* 4.88 and 1.47, H-6); *m*/*z* 843 (M^+) (Found: C, 81.79; H, 8.08; N, 4.68. $C_{57}H_{69}O_3N_3$ requires C, 81.62; H, 8.01; N, 4.84%). The splitting pattern in ^1H NMR showed that the isolated compound was *partial-cone*-**2b**.

Preparation of 4-*tert*-butyl-2,6-dimethyl(2-pyridylmethoxy)-benzene 3

A mixture of 4-*tert*-butyl-2,6-dimethylphenol (400 mg, 2.25 mmol) and NaH (60%; 580 mg, 14.5 mmol) in dry THF (20 cm^3) was heated at reflux for 1 h under N_2, after which it was treated with a solution of 2-(chloromethyl)pyridine (14.5 mmol) [prepared by neutralization of 2-(chloromethyl)pyridine hydrochloride (2.38 g, 14.5 mmol) in DMF (15 cm^3) with a solution of triethylamine (2.02 cm^3, 14.52 mmol) in THF (25 cm^3) at room temperature]. The mixture was heated at reflux for

an additional 17 h after which it was cooled to room temperature, acidified with 1 M aq. HCl (10 cm^3) and extracted with CH_2Cl_2 (100 $cm^3 \times 2$). The combined extracts were washed with water (50 $cm^3 \times 2$), dried (Na_2SO_4) and concentrated under reduced pressure to give a yellow oil. This was chromatographed on silica gel with methanol as an eluent to give the *title compound* **3** (380 mg, 63%) as a colourless oil; $\delta_H(CDCl_3)$ 1.30 (9 H, s), 2.31 (6 H, s), 4.95 (2 H, s), 7.05 (2 H, s), 7.20 (1 H, m), 7.74 (2 H, m) and 8.58 (1 H, dd, *J* 0.89 and 4.89); *m/z* 269 (M^+) (Found: C, 80.55; H, 8.49; N, 4.98. $C_{18}H_{23}ON$ requires C, 80.26; H, 8.61; N, 5.2%).

Picrate extraction measurements

Metal picrates (2.5×10^{-4} M) were prepared *in situ* by dissolving the appropriate metal hydroxide (0.01 mol) in 2.5×10^{-4} M picric acid (100 cm^3); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between water (5 cm^3 [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 cm^3, [ionophore] = 2.5×10^{-4} M). The two-phase mixture was shaken in a stoppered flask for 2 h at 25 °C. We confirmed that this period was sufficient to achieve the distribution equilibrium. This was repeated 3 times, the solutions being stored until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen.[17]

^{1}H NMR complexation experiment

To a $CDCl_3$ solution (5×10^{-4} M) of *cone*-**2b** in the NMR tube was added a [$^2H_4$]methanol solution (5×10^{-4} M) of $AgSO_3CF_3$. The spectrum was registered after addition, the temperature of the NMR probe being kept constant at 27 °C.

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