Synthesis and ion selectivity of conformers of tetraalkyl esters derived from 9,16,25,32-tetrahydroxy[3.1.3.1]metacyclophane

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Attempted *O*-alkylation of the flexible macrocycle **1** with alkyl bromoacetates in the presence of NaH or Cs_2CO_3 gave only one pure stereoisomer, **3a**–**c**, while other possible isomers were not observed. In contrast, a significant amount of 1,3-*O*-disubstituted product **2** was produced when Na_2CO_3 was used as the base. The structural characterization of these products is discussed. The two-phase solvent extraction data indicates that the tetraalkyl esters **3b**,**c** show strong Rb^+ affinities comparable with that for 18-crown-6, although the extractabilities are somewhat lower than that for the corresponding calix[6]arene tetraethyl ester **6**. A high Rb^+ selectivity was observed for tetraethyl ester **3b**. However, no significant high ion selectivity was observed with tetramethyl ester **3a**. ^{1}H NMR titration of tetra-*tert*-butyl ester **3c** with KSCN clearly demonstrates that a 1 : 1 complex is formed with retention of the original symmetry that is conformationally frozen on the NMR timescale.

Calix[*n*]arenes have attracted great attention as ionophoric receptors[1–4] and potential enzyme mimics[5] in host–guest chemistry. In calix[4]arenes there exists four possible conformational isomers: cone, partial cone, 1,2-alternate and 1,3-alternate, but the previous functionalized calix[4]arene-based ionophores have exclusively dealt with the cone and partial cone conformational isomers. Thus, Shinkai and coworkers have reported the preparation and ionophoric properties of four conformers of tetra-*tert*-butyltetrakis[(ethoxycarbonyl)-methoxy]calix[4]arene.[6–8] Cone and partial cone conformers are obtained by the metal template effect using sodium and caesium ions, respectively, but the 1,2- and 1,3-alternate conformers were synthesized by the protection-deprotection method.[8–10] They also found that the cone conformer shows a selectivity for sodium ion[6] and the other conformers show a selectivity for potassium ion.[8]

In particular, X-ray crystallographic studies of the 1,2-alternate conformer are very limited because of the extreme difficulty in synthesizing the 1,2-alternate conformer.[11] Therefore, it has been very difficult to obtain sufficient amounts of the above compound to investigate its chemical behaviour. On the other hand, we have found a convenient preparation of tetrakis[(alkoxycarbonyl)methoxy][3.1.3.1]MCPs (MCP = metacyclophane) in the 1,4-alternate conformation by the reaction of tetrahydroxy[3.1.3.1]MCP[12] and alkyl bromoacetate in the presence of K_2CO_3 or Cs_2CO_3. In this paper, we describe the convenient preparation and metal complexation properties of propane-bridged homocalix[4]arene tetraesters with the 1,4-alternate conformation, which are presumed to have encapsulated cavities.

Results and Discussion

Synthesis of the tetraalkyl esters

Introduction of larger alkyl groups on the phenolic oxygens of calix[4]arenes led to a situation where the OR groups within a cyclophane ring cannot pass each other by oxygen-through-the-annulus rotation. Although calix[4]arenes have four possible conformational isomers (see above), five different conformational isomers, of which the 1,4-alternate is new, appear due to the propane bridges in tetrahydroxy[3.1.3.1]MCPs (Fig. 1). Thus, in contrast to calix[4]arenes,[13] the conformational isomerism in the present system is slightly more complicated. Moreover, there are few reports concerning the introduction of substituents onto the hydroxy groups of dihomocalix[4]arenes.[12,14]

Alkylation of the flexible macrocycle **1** with ethyl bromoacetate in the presence of NaH under DMF–THF reflux

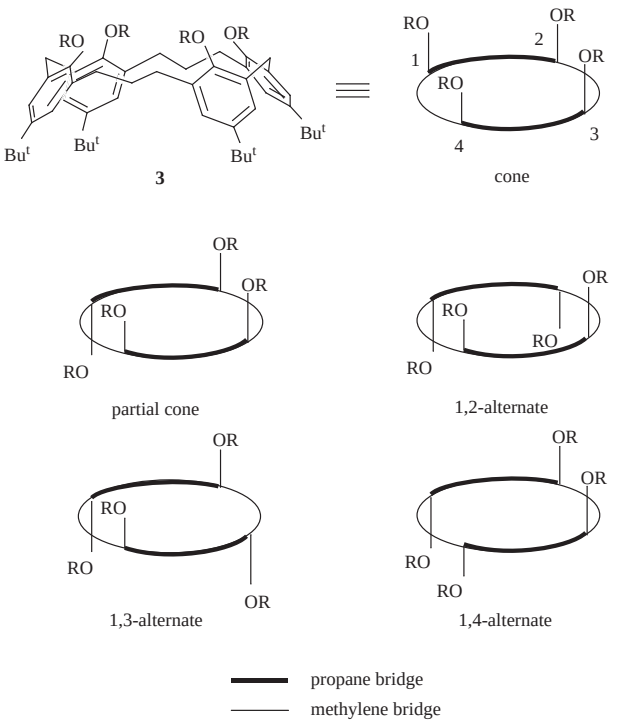

Fig. 1 Conformers possible from the *O*-tetrasubstitution of tetrahydroxyl[3.1.3.1]MCP, **1**

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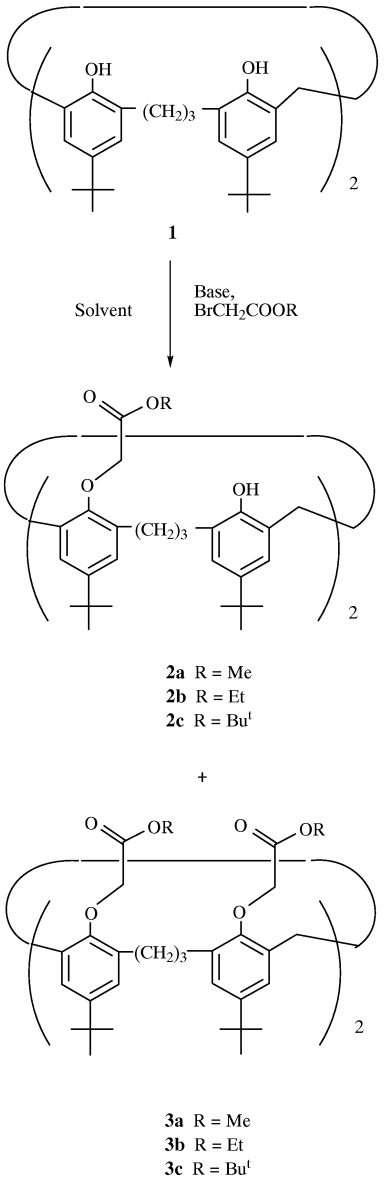


Scheme 1

(Scheme 1) gave only one pure stereoisomer **3b** in quantitative yield. Other possible isomers were not observed. Attempted *O*-alkylation of **1** with ethyl bromoacetate in the presence of Li_2CO_3 led to regioselective di-*O*-substitution to afford 1,3-disubstituted product **2b** in 28% yield along with the recovery of the starting compound. Similarly, when Na_2CO_3 was employed **2b** was obtained in quantitative yield even though a large excess of Na_2CO_3 was used. When K_2CO_3 or Cs_2CO_3 was used as a base, only tetrasubstituted product **3b** was obtained, while the 1,3-disubstituted product was not observed.

The ratio of the products bis[(ethoxycarbonyl)methoxy]-[3.1.3.1]MCP, **2b**, to tetrakis[(ethoxycarbonyl)methoxy]-[3.1.3.1]MCP, **3b**, in the *O*-alkylation of **1** is governed by the nature of the alkali metal carbonate used as a catalyst. Thus, the smaller alkali metal ions Li^+ and Na^+ obviously give rise to the yield of a dialkylation product **2b**, while the action of the much larger K^+ and Cs^+ leads to complete *O*-tetraalkylation. These results indicate that the alkali metal cation can play an important role, not only for the regioselectivity based on the template effect, but also on the extent of the *O*-alkylation, as previously observed in the *O*-alkylation of calix[4]arenes.[8,9,11,15]

When a weak base is used (M_2CO_3), the undissociated OH group forms intramolecular hydrogen bonds with the dissociated O^- group rather than further dissociating to form the metal template intermediate; that is different from what is observed when a strong base (*e.g.* NaH) is used, which leads to the complete formation of two O^- anions. The same phenomenon might occur in the di-*O*-alkylated product **2b**. Thus, complete *O*-tetraalkylation was not observed due to the intramolecular hydrogen bonds formed with the (ethoxycarbonyl)methoxy groups when bases such as Li_2CO_3 or Na_2CO_3 are used. In contrast, the larger K^+ and Cs^+ might enlarge the cyclophane ring and disturb the intramolecular hydrogen bonding between the undissociated OH group and the dissociated O^- group by the template effect, which then leads to the complete formation of O^- anions like NaH.

The present template effect was also confirmed by the observation of the *O*-alkylation of bis[(ethoxycarbonyl)-methoxy][3.1.3.1]MCP, **2b**, with ethyl bromoacetate using NaH or Cs_2CO_3 to give exclusive formation of tetrakis-[(ethoxycarbonyl)methoxy][3.1.3.1]MCP, **3b**.

Similar results were obtained in the *O*-alkylation of **1** with methyl and *tert*-butyl bromoacetate in the presence of various bases and are listed in Table 1. Thus, alkylation of **1** with methyl bromo acetate or *tert*-butyl bromoacetate in the presence of NaH under DMF–THF reflux also gave only one pure stereoisomer, **3a** or **3c**, in quantitative yield, respectively. Attempted *O*-alkylation of **1** with methyl bromoacetate in the presence of Li_2CO_3 led to mono-*O*-substitution to afford the mono[(methoxycarbonyl)methoxy] derivative **4a** in 28% yield along with the recovery of the starting compound. However, when Na_2CO_3 is employed for *O*-alkylation with methyl bromoacetate only an intractable mixture was obtained. In contrast, in the case of *O*-alkylation with *tert*-butyl bromoacetate the 1,3-disubstituted product **2c** was obtained in 55% yield.

Table 1 *O*-Substitution reactions of tetraol **1** with alkyl bromoacetates.

Run	R	Base	Solvent	Time/h	Product yield/%[a,b]	
1	Me	NaH	THF, DMF	1	**2a** 0	**3a** 100 (89)
2	Me	Li_2CO_3	DMF	24	**2a** 0	**3a** 0[c]
3	Me	K_2CO_3	Acetone	24	**2a** 0	**3a** 100 (92)
4	Me	Cs_2CO_3	Acetone	3	**2a** 0	**3a** 100 (86)
5	Et	NaH	THF, DMF	1	**2b** 0	**3b** 100 (76)
6	Et	Li_2CO_3	DMF	24	**2b** 28 (20)	**3b** 0[d]
7	Et	Na_2CO_3	Acetone	24	**2b** 100 (64)	**3b** 0
8	Et	K_2CO_3	Acetone	3	**2b** 0	**3b** 100 (79)
9	Et	Cs_2CO_3	Acetone	3	**2b** 0	**3b** 100 (81)
10	Bu^t	NaH	THF, DMF	1	**2c** 0	**3c** 100 (60)
11	Bu^t	Na_2CO_3	Acetone	24	**2c** 100 (55)	**3c** 0
12	Bu^t	K_2CO_3	Acetone	3	**2c** 0	**3c** 100 (81)[e]
13	Bu^t	Cs_2CO_3	Acetone	3	**2c** 0	**3c** 100 (81)[e]

a Relative yields determined by ^{1}H NMR spectrometry. *b* Isolated yields are shown in parentheses. *c* Mono[(methoxycarbonyl)methoxy] derivative **4a** was obtained in 28% yield. *d* Starting compound **1** was recovered in 72% yield. *e* *O*-Alkylation product **3c** was obtained as a mixture of free **3c** and the 1 : 1 complex with K_2CO_3 or Cs_2CO_3 (1 : 1 ratio).

Use of K_2CO_3 or Cs_2CO_3 for *O*-alkylation with methyl bromoacetate or ethyl bromoacetate gave only the tetra-substituted product **3a** or **3b** in quantitative yield. Interestingly, *O*-alkylation of **1** with *tert*-butyl bromoacetate in the presence of K_2CO_3 or Cs_2CO_3 gave a mixture of tetra-substituted product **3c** and unknown compound **A** (50 : 50 ratio), whose ^{1}H NMR pattern was quite similar to that of the 1 : 1 complex of **3c** with KSCN mentioned below. The physical properties of these compounds were very similar to each other, and isolation by column chromatography or preparative TLC was extremely difficult. However, the present mixture was treated with dilute hydrochloric acid to afford pure **3c** in quantitative yield. These findings strongly suggest that unknown compound **A** might be a 1 : 1 complex with the K_2CO_3 or Cs_2CO_3 used in the *O*-alkylation reaction. This clearly indicates the high ionophilic abilities of the tetrakis[(alkoxycarbonyl)methoxy] derivatives **3** for K^+ or Cs^+.

^{1}H NMR spectrometry

The ^{1}H NMR spectrum of **3b** shows a singlet for the *tert*-butyl protons and a set of doublets with equal intensity for the aromatic protons. Furthermore, the resonance for the ArCH_2Ar methylene protons appeared as a pair of doublets (δ 3.27 and 4.63, J_{AB} 13.7 Hz), corresponding to a symmetric structure (C_{2v} symmetry). On consideration of the ^{1}H NMR spectrum, there are two possible structures for **3b**: cone or 1,4-alternate. Fortunately, we have succeeded in measuring the X-ray diffraction of **3b** and its crystal structure is shown in Fig. 2. It is clear that the 'stepped conformation' of diphenylmethane moieties like *anti*-[3.3]metacyclophane is possible.[16] The lack of change in the spectral pattern of the ArCH_2Ar methylene protons below 150 °C in DMSO-d_6 confirms that ring inversion by oxygen-through-the-annulus rotation is inhibited for the tetrakis[(ethoxycarbonyl)methoxy] derivative **3b**.

In contrast, the ^{1}H NMR spectrum of **2b** shows resonances for the *tert*-butyl protons at δ 1.21 and 1.22 as singlets, for the methylene protons at δ 3.45 and 4.35 (J_{AB} 13.7 Hz) as doublets, for the aromatic protons at δ 6.88, 7.04, 7.05 and 7.16 (*J* 2.4 Hz) as doublets, and for the hydroxy proton at δ 7.32 as a singlet, indicating a 1,3-di-*O*-substituted structure.[12d,e] Although these signals in the ^{1}H NMR spectrum also correspond to cone or 1,4-alternate conformers, the υ_{OH} (3453 cm^{-1}) and δ_{OH} (7.32) values in **2b**, in which two hydroxy groups are located in distal positions, show a slightly lower frequency and an upfield shift, which implies that the hydrogen bond is weaker than that in the parent tetraol **1** (υ_{OH} = 3254 cm^{-1} and δ_{OH} = 9.35).[12a,b] Therefore, bis[(ethoxycarbonyl)methoxy)][3.1.3.1]MCP, **2b**, might adopt an *anti*-oriented 1,4-alternate conformation but not a *syn*-oriented cone conformation.

The present assignment is also supported by the result from the exhaustive *O*-alkylation of **2b** with bromo ethylacetate to exclusively afford the 1,4-alternate conformer **3b**. Since we have already shown that the oxygen-through-the-annulus rotation in the present system is suppressed with substituents larger than the *n*-propyl group,[12c] the ring inversion of benzene rings having (ethoxycarbonyl)methoxy groups should be impossible during the *O*-alkylation of **2b**.

Similarly, the ^{1}H NMR spectrum of the *tert*-butyl ester **3c** shows a singlet for the *tert*-butyl protons at δ 1.26, a set of doublets (*J* 15.2 Hz) for ArOCH_2COOBu^t at δ 4.20 and 4.50, and two doublets of equal intensity for the aromatic protons at δ 6.72 and 6.91. Furthermore, the resonance for the ArCH_2Ar methylene protons appears as a pair of doublets (δ 3.31 and 4.70, J_{AB} 14.2 Hz, relative intensity 1 : 1). Since these signals in the ^{1}H NMR spectrum were observed at slightly different chemical shifts than those for the corresponding ethyl ester **3b**, the cone conformation might be expected for *tert*-butyl ester **3c**. However, the middle methylene protons in the propane bridge Ar$CH_2CH_2CH_2$Ar are observed as only one multiplet at δ 1.50–1.65; this pattern corresponds to the 1,4-alternate conformer because these protons are in the same environment. In contrast, a split multiplet pattern for the same protons, due to different environments, was observed at δ 1.32–1.48 and 1.61–1.88 (relative intensity 1 : 1) in the ^{1}H NMR spectrum of cone-9,16,25,32-tetrabenzyloxy-6,13,22,29-tetra-*tert*-butyl[3.1.3.1]metacyclophane.[12c] Therefore, *tert*-butyl ester **3c** could also adopt an *anti*-oriented 1,4-alternate conformation but not a *syn*-oriented cone conformation.

The same finding was observed in mono[(methoxycarbonyl)methoxy][3.1.3.1]MCP, **4a**. In a ^{1}H NMR spectrum (in $CDCl_3$) of triol **4a** the δ_{OH} values resonating at higher field (δ_{OH} = 4.92, 5.70, 6.75) than that in the parent tetraol **1** (δ_{OH} = 9.35) and the low Δδ value (Δδ = 0.38) for one of the geminal methylene protons in ArCH_2Ar resonating at δ 3.24 and 3.62 might suggest the *anti*-oriented conformation as shown in Fig. 3.

Metal ion selectivity

Many groups[1a–d,6–8,17] have shown that calix[*n*]arenes can be converted to neutral ligands by the introduction of ester groups onto the OH groups. They demonstrated that metal selectivity is dependent on the calix[*n*]arene ring size and, in

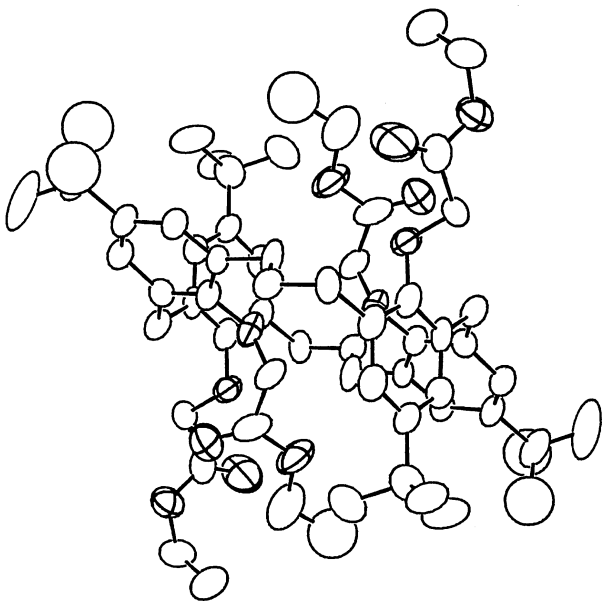
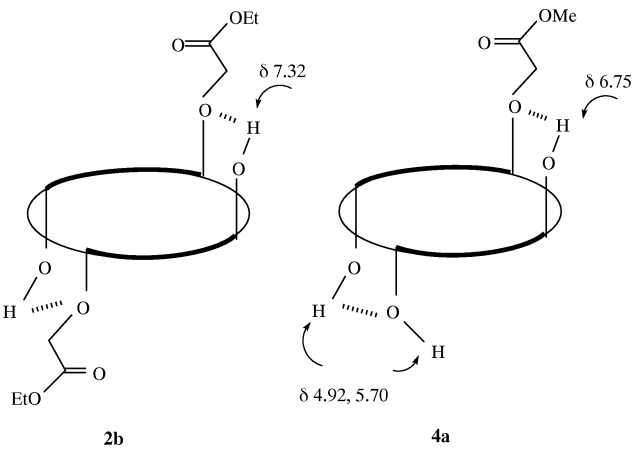


Fig. 2 X-ray structure of 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrakis[(ethoxycarbonyl)methoxy][3.1.3.1]metacyclophane, **3b**



2b **4a**

Fig. 3 Intramolecular hydrogen bonds in *distal*-**2b** and **4a**.

particular, calix[4]arylacetates and acetamides with a cone conformation (Fig. 4) show remarkably high Na^+ selectivity.

Arduini *et al.*[1a] and Inoue *et al.*[18] suggested an interesting idea: the bathochromic shift of the absorption band of the picrate anion, extracted into the organic phase with a macrocyclic ligand from aqueous metal picrate solutions, serves as a convenient measure for evaluating the ion pair tightness in solution. Also, one can estimate the association constants (K) and stoichiometry from the spectral change. Recently, Arimura *et al.* reported that the calix[4]arene tetraethyl ester with cone conformation forms 1 : 1 complexes with alkali metal cations and the bathochromic shift for sodium picrate amounts to 31 nm.[6] This shift is equal to that induced by cryptand 222, indicating that the ion pair is considerably solvent-separated.[19] These findings are rationalized in terms of the 'encapsulation' effect of ionophores having an ionophoric cavity deep in the molecule.

To obtain quantitative insights into the metal affinity of the 1,4-alternate form of [3.1.3.1]MCP tetraalkyl esters **3** and to compare it with that of the confomers of calix[4]arene tetraethyl ester **5**, we have determined the association constants by absorption spectroscopy. It is known that the absorption maxima (λ_{max}) of alkali picrates shift to longer wavelength when they form 1 : 1 complexes with calix[*n*]arene derivatives.[6] In THF, for example, the λ_{max} of sodium picrate appears at 352 nm and shifts with an isosbestic point (358 nm) to 380 nm with increasing 1,4-alternate-**3** concentration. By using a simple method applied to the plots one can estimate the K for 1 : 1 complexes. The spectral change induced by 1,4-alternate-**3b** for Na^+ was too small to estimate the stoichiometry and K. The results are summarized in Table 2, together with those for calix[4]arene tetraethyl ester, **5**, 18-crown-6 and cryptand 222.

Examination of Table 2 reveals that the tetraethyl ester, 1,4-alternate-**3b**, shows a higher affinity for large metal ions such as K^+ and Rb^+ than for a small ion, Na^+. In contrast, the tetra-*tert*-butyl ester **3c** has a higher ionophoricity than tetraethyl ester **3b**: for example, K for tetra-*tert*-butyl ester **3c** and K^+ is greater by about tenfold than that for tetraethyl ester **3b** and K^+. The highest K value was obtained for tetra-*tert*-butyl ester **3b** and Rb^+ ($K = 5.18$), as comparable to that for 18-crown-6 and K^+ ($K = 5.33$).

Comparing K for tetra-*tert*-butyl ester **3c** with those for the conformers of the calix[4]arene derivative **5**, **3c** shows higher values than those of cone-**5** and partial-cone-**5** and the same value as that of 1,3-alternate-**5**. These findings are rationalized in terms of the 'encapsulation' effect of 1,4-alternate-**3c**, which has an ionophoric cavity deep in the molecule. Interestingly, higher K^+, Cs^+ and Rb^+ affinities of the [3.1.3.1]MCP 1,4-alternate-**3b** than those of the calix[4]arene 1,2-alternate-**5** were observed, in spite of the fact that both adopt the same conformation. This result can be easily explained by the much larger inner ionophilic cavity of [3.1.3.1]MCP tetraalkyl esters than that of calix[4]arene tetraethyl ester, due to the introduction of two propane bridges into the two methylene bridges of the calix[4]arene skeleton.

The ring size and the ring flexibility are different between calix[4]arene and the analogous uncompleted homocalixarene metacyclophanes. It is thus interesting to assess what kind of ionophoric cavity the tetraalkyl esters **3** provide. To the best of our knowledge, however, no precedent exists for the molecular design of such propane-bridged calixarene-type ionophores. We estimated this through two-phase solvent extraction of alkali metal picrates and compared these data with those for calix[*n*]arene aryl acetates. The results are summarized in Table 3.

It is already known that the cone conformer of a calix[4]arene tetraethyl ester shows Na^+ selectivity whereas the partial cone conformer of calix[4]arene tetraethyl ester shows K^+ selectivity. The two-phase solvent extraction data indicate that tetraethyl ester **3b** and tetra-*tert*-butyl ester **3c** (extraction %: 72.0% for **3b** and 76.3% for **3c**) show a strong Rb^+ affinity comparable with that for 18-crown-6 (extraction %: 77.3%) although the extraction % is somewhat lower than that for the corresponding calix[6]arene tetraethyl ester **6** (extraction %: 88.7%). However, no significant high ion selectivity was observed with tetramethyl ester **3a**. Thus, the metal selectivity of ionophoric [3.1.3.1]MCP tetraalkyl esters can be varied by changing the size of the ester alkyl groups and this variation is different from that of the corresponding calix[*n*]arene tetraesters. The increase of the restricted 'encapsulation' effect in the 1,4-alternate structure by introduction of the bulkier alkyl groups into the ester groups, in spite of the larger ring size compared to a calix[4]arene, clearly appears in the ion selectivity; tetraethyl ester **3b** extracted large ions like Rb^+ more efficiently than small ones like Li^+, Na^+ and K^+. This behaviour makes a remarkable

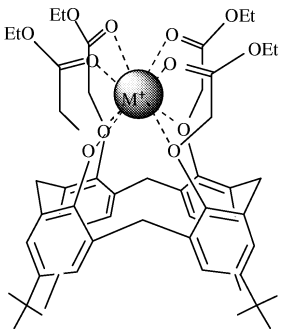


Fig. 4 Complexation of cone-calix[4]arene tetraethyl ester, cone-**5**, with metal cations

Table 2 Association constants (K)[a] for M^+Pic^-

	log K			
Ionophore	Na^+	K^+	Rb^+	Cs^+
1,4-Alternate-**3b**	—[b]	3.51	4.57	3.41
1,4-Alternate-**3c**	4.30	4.84	5.18	4.48
Cone-**5**	3.95	3.08		1.60
Partial-cone-**5**	4.26	3.52		2.12
1,2-Alternate-**5**	—[b]	—[b]		—[b]
1,3-Alternate-**5**	4.10	4.98		4.41
18-Crown-6	4.27	5.33		4.91
Cryptand 222	6.69	8.38		6.61

[a] $K = [M^+Pic^-, Ester]/[M^+Pic^-][Ester]$. [b] The spectral change was too small to determine K.

Table 3 Extraction of alkali metal picrates by [3.1.3.1]MCP tetraalkyl esters **3** in CH_2Cl_2[a]

	Extractability/%				
Ionophore	Li^+	Na^+	K^+	Rb^+	Cs^+
1,4-Alternate-**3a**	0	3.0	37.0	29.0	11.0
1,4-Alternate-**3b**	7.6	9.1	11.6	72.0	19.1
1,4-Alternate-**3c**	37.2	45.0	50.0	76.3	32.0
Cone-**5**	15.0	94.6	49.1	23.6	48.9
6	11.4	50.1	85.9	88.7	100
18-Crown-6	8.7	23.1	77.9	77.3	62.9

[a] 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 mL) was shaken for 2 h with picrate solution (5.0 mL) and % extraction was measured by the absorbance of picrate in CH_2Cl_2. Experimental error was ±2%.

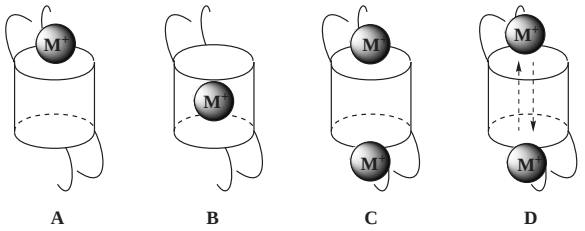


Fig. 5 Possible metal complexation modes for [3.1.3.1]MCP tetraalkyl esters **3**

contrast to that of the cone conformer of calix[4]arene tetraethyl ester, which has a rather smaller ionophoric cavity than the partial cone conformer of calix[4]arene tetraethyl ester that shows notable K^+ selectivity.[8]

Metal ion complexes

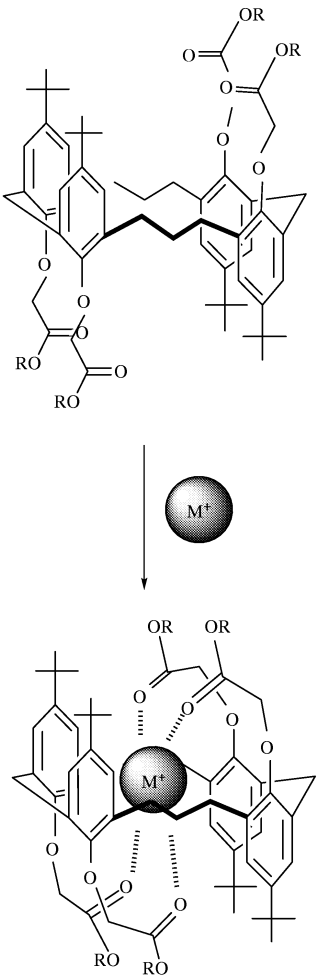
In 1992, Iwamoto and Shinkai reported that the 1,3-alternate conformer of calix[4]arene tetraethyl ester can form both 1 : 1 and 2 : 1 metal : calixarene complexes and the two metal binding sites display negative allostericity by ^{1}H NMR titration experiments.[8] In the present systems, due to the existence of two metal binding sites, there are several possibilities for the metal complexation mode, as shown in Fig. 5. Thus, 1 : 1 and a 2 : 1 metal complexation by the 1,4-alternate conformer of tetraalkyl ester **3** might be possible.

The chemical shifts of the ArCH_2Ar methylene protons of tetraethyl ester **3b** were altered by titration with KSCN in $CDCl_3$–CD_3OD (1 : 1 v/v): a 1 : 1 mixture of **3b** and KSCN showed a completely different ^{1}H NMR spectrum with sharp lines becoming evident for these protons. Their methylene proton peaks were shifted downfield to δ 3.48 and 4.92 (J_{AB} 12.7 Hz) as a pair of doublets, in comparison to those in the metal-free spectrum (δ 3.27 and 4.63, J_{AB} 13.7 Hz). The ^{1}H NMR titration experiment clearly indicates a 1 : 1 stoichiometry for the KSCN complex with **3b**, since all signals remain essentially unchanged after the tetraethyl ester **3b** : KSCN ratio has reached a value of unity. In addition to this observation, the signals for the aromatic protons are slightly downfield-shifted and the phenoxy methylene protons and the protons of ethyl groups also showed different chemical shifts.

These findings might be attributable to the conformational changes of the binding site in the process of metal complexation. No changes arising from the formation of two sets of non-equivalent aromatic protons and two sets of non-equivalent *tert*-butyl protons, due to asymmetric metal cation complexation on one side of the tetra-*tert*-butyl ester **3c**, were observed. These results strongly suggest that the original C_{2v} symmetry might remain after complete metal cation complexation, as shown in Fig. 6.

Thus, the K^+ ion might complex in either mode **B** or **D**. In the latter case, the rate of an intramolecular hopping between two possible metal-binding sites might be faster than the NMR timescale at room temperature. Despite lowering the temperature to −80 °C, no clear evidence for the intramolecular hopping behaviour was obtained, as with biscalix[4]arenes.[3e,20]

A more detailed examination of the chemical shift change suggests that K^+ should be bound to the ionophoric cavity, which is composed of four phenolic oxygens and four carbonyl group oxygens, because large downfield shifts were observed for the neighbouring methylene protons of ArOCH_2COOEt (Δδ from +0.34 to +0.39) and ArCH_2Ar (Δδ from +0.21 to +0.29). Similar findings were observed in the ^{1}H NMR titration experiment of tetra-*tert*-butyl ester **3c** with KSCN. However, these signals were observed at slightly different chemical shifts than those for the corresponding tetraethyl ester **3b**. Especially, the methylene proton peaks for



3 R = Me, Et, Bu^t

Fig. 6 Metal complexation of [3.1.3.1]MCP tetraalkyl esters **3**

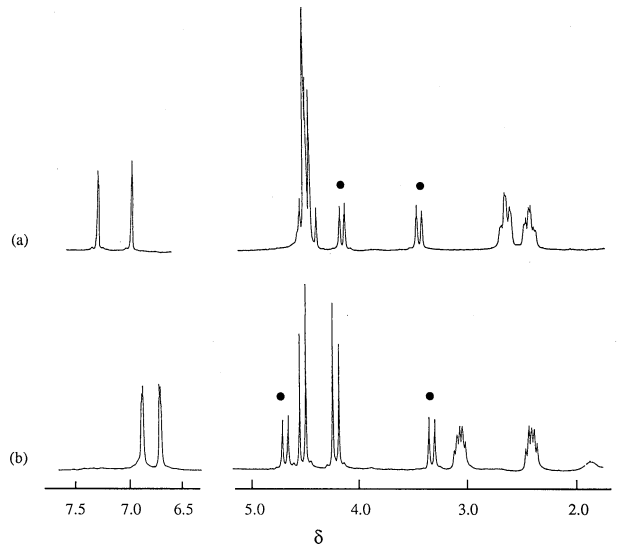


Fig. 7 Partial ^{1}H NMR titration spectra of tetra-*tert*-butyl ester **3c** (5×10^{-4} M) with KSCN in $CDCl_3$–CD_3OD (1 : 1 v/v), 270 MHz. (*a*) In the presence of KSCN (5×10^{-4} M) and (*b*) in the absence of KSCN

ArCH_2Ar were concentrated at δ 3.48 and 4.18 (J_{AB} 12.2 Hz) as a pair of doublets in comparison to those in the metal-free spectrum (δ 3.31 and 4.70, J_{AB} 14.2 Hz), as shown in Fig. 7.

This result might suggest that the conformational change of the binding site during the metal complexation of **3c** is slightly different from that for **3b**, attributable to the steric bulkiness of *tert*-butyl group. Thus, **3c** shows a different behaviour in the extraction experiment and a loss of selectivity in comparison with **3a**,**b**. However, from the presently available data we cannot yet completely explain the different extractabilities arising from the size of the ester alkyl groups. Further experiments on these metal complexations are currently in progress in our laboratory.

Conclusions

An attempted alkylation of the flexible macrocycle 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **1** with alkyl bromoacetates in the presence of NaH or Cs_2CO_3 gave only one pure stereoisomer, the 1,4-alternate conformers **3a**–**c**, while other possible isomers were not observed. In contrast, a significant amount of the 1,3-*O*-disubstituted product **2** was produced when Na_2CO_3 was used as the base. Only when the template metal ion can hold the ester group(s) and the oxide group(s) on different sides of the propane bridges of [3.1.3.1]MCP is the conformation immobilized to the thermodynamically stable 1,4-alternate conformer.

The two-phase solvent extraction data indicate that tetraethyl ester **3b** shows a strong Rb^+ affinity, comparable with that for 18-crown-6, although the extraction percentage is somewhat lower than that for the corresponding calix[6]arene tetraethyl ester **6**. ^{1}H NMR titration of the *tert*-butyl ester **3c** with KSCN clearly demonstrates that a 1 : 1 complex is formed that is conformationally frozen on the NMR timescale.

We have demonstrated for the first time that the derivatives of the propane-bridged homocalixarenes formed by *O*-alkylation with alkyl bromoacetates give ionophores with promising complexation properties and interesting stereochemistry. While to date only one stereoisomer has been obtained, variation of the alkylation conditions and reagents could lead to derivatives with the cone conformation, which will serve as interesting building blocks for larger potential host molecule.

Experimental

All melting points (Yanagimoto MP-S1) and boiling points are uncorrected. NMR spectra were determined at 270 M Hz 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 as liquid films on NaCl plates in a Nippon Denshi JIR-AQ2OM spectrophotometer. UV spectra were measured by a 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

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]-metacyclophane **1** was prepared from anisole according to the reported procedure.[12a,b]

Alkylation of 1 with alkyl bromoacetate in the presence of NaH to afford 3

Typical Procedure. A mixture of **1** (400 mg, 0.57 mmol) and NaH (454 mg, 11.35 mmol, 60%) in dry THF (90 mL) and DMF (9 mL) was heated at reflux for 1 h under N_2. Then ethyl bromoacetate (0.628 mL, 5.67 mmol) was added and the mixture heated at reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove excess unreacted ethyl bromoacetate using a Kugelrohr apparatus. The residue was treated with hexane (5 mL) and the precipitate was filtered to give 454 mg (76%) of **3b** as a colourless solid. Recrystallization from MeOH–$CHCl_3$ (3 : 1) afforded 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrakis[(ethoxycarbonyl)methoxy]-[3.1.3.1]metacyclophane **3b** as colourless prisms, mp 176–180 °C; υ_{max}(KBr)/cm^{-1}: 2962, 2870, 1736 (C=O), 1480, 1445, 1394, 1381, 1297, 1265, 1185, 1123, 1064, 1044 and 876; δ_H($CDCl_3$) 1.03 (12H, t, *J* 7.33), 1.24 (36H, s), 1.83–1.94 (4H, m), 2.20–2.30 (4H, m), 2.79–2.89 (4H, m), 3.27 (2H, d, *J* 13.7), 3.91 (4H, d, *J* 15.1), 3.75–4.00 (8H, m), 4.06 (4H, d, *J* 15.1), 4.63 (2H, d, *J* 13.7 Hz), 7.00 (4H, d, *J* 2.4) and 7.06 (4H, d, *J* 2.4); *m*/*z* 1048 (M^+). Anal. calcd. for $C_{64}H_{88}O_{12}$ (1049.4) C, 73.25; H 8.45. Found: C, 73.20; H, 8.39.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrakis[(methoxycarbonyl)methoxy][3.1.3.1]metacyclophane, 3a. 3a was prepared as described above, yield 89%; colourless prisms (MeOH–$CHCl_3$, 3 : 1), mp 234–236 °C; υ_{max}(KBr)/cm^{-1}: 2957, 1765, 1741 (C=O), 1480, 1439, 1393, 1363, 1288, 1194, 1116, 1068, 1021 and 880; δ_H($CDCl_3$) 1.27 (36H, s), 1.90–2.00 (4H, m), 2.15–2.25 (4H, m), 2.75–2.85 (4H, m), 3.14 (12H, s), 3.27 (2H, d, *J* 13.4), 3.91 (4H, d, *J* 15.1 Hz), 4.05 (4H, d, *J* 15.1), 4.45 (2H, d, *J* 13.4), 7.06 (4H, d, *J* 2.4) and 7.16 (4H, d, *J* 2.4); *m*/*z* 992 (M^+). Anal. calcd. for $C_{60}H_{80}O_{12}$ (993.3): C, 72.55; H, 8.12. Found: C, 72.57; H, 8.34.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrakis[(*tert*-butoxycarbonyl)methoxy[3.1.3.1]metacyclophane, 3c. 3c was prepared as described above, yield 60%; colourless prisms (MeOH–$CHCl_3$, 3 : 1), mp 195–200 °C; υ_{max}(KBr)/cm^{-1}: 2965, 2867, 1757, 1725 (C=O), 1478, 1435, 1418, 1366, 1228, 1194, 1157 and 1126; δ_H($CDCl_3$) 1.26 (36H, s), 1.50 (36H, s), 1.50–1.65 (4H, m), 2.30–2.50 (4H, m), 3.00–3.17 (4H, m), 3.31 (2H, d, *J* 14.2), 4.20 (4H, d, *J* 15.2), 4.50 (4H, d, *J* 15.2), 4.70 (2H, d, *J* 14.2), 6.72 (4H, d, *J* 2.4) and 6.91 (4H, d, *J* 2.4); *m*/*z* 1160 (M^+). Anal. calcd. for $C_{72}H_{104}O_{12}\cdot CH_3OH$ (1193.7): C, 73.46, H, 9.12. Found: C, 73.07; H, 8.98.

Alkylation of 1 with alkyl bromoacetate in the presence of Na_2CO_3 to afford 2

Typical procedure. A mixture of **1** (400 mg, 0.57 mmol) and sodium carbonate (1.20 g, 11.4 mmol) in dry acetone (36 mL) was heated at reflux for 1 h under N_2. Then ethyl bromoacetate (0.63 mL, 5.7 mmol) was added and the mixture heated at reflux for an additional 3 h. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted ethyl bromoacetate using a Kugelrohr apparatus. The residue was treated with hexane (5 mL) and the precipitate was filtered to give 382 mg (64%) of **2b** as a colourless solid. Recrystallization from MeOH–$CHCl_3$ (3:1) afforded 6,13,22,29-tetra-*tert*-butyl-9,25-bis[(ethoxycarbonyl)]methoxy]-16,32-dihydroxy[3.1.3.1]metacyclophane **2b** as colourless prisms, mp 212–215 °C; υ_{max}(KBr)/cm^{-1}: 3453 (OH), 2962, 1756, 1495, 1458, 1363, 1298, 1208, 1187, 1127 and 1068; δ_H($CDCl_3$) 1.21 (18H, s), 1.22 (18H, s), 1.40 (6H, t, *J* 7.32), 1.85 (4H, broad s), 2.24–2.53 (4H, m), 2.81–3.07 (4H, m), 3.45 (2H, d, *J* 13.7), 4.31–4.41 (4H, m), 4.35 (2H, d, *J* 13.7), 4.49 (2H, d, *J* 15.4), 4.85 (2H, d, *J* 15.4), 6.88 (2H, d, *J* 2.4), 7.04 (2H, d, *J* 2.4), 7.05 (2H, d, *J* 2.4), 7.16 (2H, d, *J* 2.4) and 7.32 (2H, s, OH, H/D exchange with D_2O); *m*/*z* 876 (M^+). Anal. calcd. for $C_{56}H_{76}O_8$ (877.2): C, 76.68; H, 8.73. Found: C, 76.57; H 8.81.

6,13,22,29-Tetra-*tert*-butyl-9,25-bis[(*tert*-butoxycarbonyl)-methoxy]-16,32-dihydroxy[3.1.3.1]metacyclophane, 2c. **2c** was prepared as described above, yield 55%; colourless prisms (MeOH–$CHCl_3$, 3:1), mp 218–220 °C; υ_{max}(KBr)/cm^{-1}: 3454 (OH), 2965, 2867, 1757, 1727, 1479, 1393, 1367, 1310, 1294, 1227, 1157, 1125 and 1059; δ_H($CDCl_3$): 1.19 (18H, s), 1.20 (18H, s), 1.59 (18H, s), 1.90–2.05 (4H, m), 2.35–2.50 (4H, m), 2.80–3.10 (4H, m), 3.42 (2H, d, *J* 13.2), 4.23 (2H, d, *J* 15.6), 4.36 (2H, d, *J* 15.6), 4.77 (2H, d, *J* 15.6), 7.01 (2H, d, *J* 2.4), 7.03 (2H, d, *J* 2.4), 7.11 (2H, d, *J* 2.4), 7.14 (2H, d, *J* 2.4) and 7.46 (2H, s, OH, H/D exchange with D_2O); *m/z* 932 (M^+). Anal. calcd. for $C_{60}H_{84}O_8$ (933.3): C, 77.21; H, 9.07. Found: C, 77.07; H, 9.18.

Alkylation of 1 with alkyl bromoacetate in the presence of Cs_2CO_3 to afford 3

Typical procedure. A mixture of **1** (400 mg, 0.57 mmol) and caesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 mL) was heated at reflux for 1 h under N_2. Then ethyl bromoacetate (0.63 mL, 5.7 mmol) was added and the mixture heated at reflux for an additional 3 h. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted ethyl bromoacetate using a Kugelrohr apparatus. The residue was treated with hexane (5 mL) and the precipitate was filtered to give 482.2 mg (81%) of **3b** as a colourless solid.

Compounds **3a** and **3c** were similarly prepared. The yields are listed in Table 1.

Alkylation of 1 with methyl bromoacetate in the presence of Li_2CO_3 to afford 4a

A mixture of **1** (400 mg, 0.57 mmol) and lithium carbonate (828 mg, 11.4 mmol) in dry DMF (36 mL) was heated at reflux for 24 h under N_2 Then methyl bromoacetate (0.523 mL, 5.7 mmol) was added and the mixture heated at 70 °C for an additional 3 h. After cooling to room temperature, the mixture was filtered. The filtrate was concentrated to give a yellow oil, which was then distilled under reduced pressure to remove the excess unreacted methyl bromoacetate using a Kugelrohr apparatus. The residue was chromatographed over silica gel (Wako, C-300; 100 g) with benzene as eluent to give 124.0 mg (28%) of **4a** as a colourless solid. Recrystallization from MeOH–$CHCl_3$ (3:1) afforded 6,13,22,29-tetra-*tert*-butyl-9,16,25-trihydroxy-32-[(methoxycarbonyl)methoxy][3.1.3.1]-metacyclophane **4a** as colourless prisms, mp 168–171 °C; υ_{max}(KBr)/cm^{-1} 3447 (OH), 2963, 2863, 1765, 1664, 1559, 1484, 1457, 1364, 1300, 1220, 1205, 1174, 1124, 1095, 1059, 987 and 884; δ_H($CDCl_3$) 1.166 (9H, s), 1.169 (9H, s), 1.30 (9H, s), 1.32 (9H, s), 1.89–2.27 (8H, m), 2.65–2.71 (2H, m), 2.98–3.21 (2H, m), 3.24 (1H, d, *J* 14.4), 3.62 (1H, d, *J* 14.4), 3.68 (1H, d, *J* 12.7), 3.85 (3H, s), 4.53 (1H, d, *J* 12.7), 4.64 (1H, d, *J* 15.9), 4.92 (1H, s, OH, H/D exchange with D_2O), 4.97 (1H, d, *J* 15.9), 5.70 (1H, s, OH, H/D exchange with D_2O), 6.75 (1H, s, OH, H/D exchange with D_2O), 6.82 (1H, d, *J* 2.4), 6.83 (1H, d, *J* 2.4), 6.86 (1H, d, *J* 2.4), 6.92 (1H, d, *J* 2.4), 6.96 (1H, d, *J* 2.4), 7.15 (1H, d, *J* 2.4), 7.18 (1H, d, *J* 2.4) and 7.20 (1H, d, *J* 2.4); *m/z* 776 (M^+). Anal. calcd. for $C_{51}H_{68}O_6$ (777.1): C, 78.83; H, 8.82. Found: C, 78.57; H, 8.53.

Picrate extraction measurements

Metal picrates (2.5×10^{-4} M) were prepared *in situ* by dissolving the metal hydroxide (0.01 mol) in 2.5×10^{-4} M picric acid (100 mL); triply distilled water was used for all aqueous solutions. Two-phase solvent extraction was carried out between water (5 mL, [alkali picrate] = 2.5×10^{-4} M) and CH_2Cl_2 (5 mL, [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 is sufficient to attain the distribution equilibrium. This was repeated 3 times, and the solutions were left standing until phase separation was complete. The extractability was determined spectrophotochemically from the decrease in the absorbance of the picrate ion in the aqueous phase as described by Pedersen.[21]

^{1}H NMR Complexation experiments

To a $CDCl_3$ solution (5×10^{-4} M) of the tetraalkyl esters **3b** and **3c** in the NMR tube was added a methanol-d_4 solution (5×10^{-4} M) of KSCN. The spectrum was registered after addition and the temperature of the NMR probe kept constant at 27 °C.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrakis[(ethoxycarbonyl)methoxy][3.1.3.1]metacyclophane (3b)-KSCN complex. δ_H ($CDCl_3$–methanol-d_4, 1 : 1 v/v): 1.06 (12H, t, *J* 7.33), 1.25 (36H, s), 1.93–2.04 (4H, m), 2.40–2.50 (4H, m), 2.70–2.80 (4H, m), 3.48 (2H, d, *J* 12.7), 4.28–4.46 (8H, m), 4.30 (4H, d, *J* 15.1), 4.40 (2H, d, *J* 15.1 Hz), 4.92 (4H, d, *J* 12.7), 7.00 (4H, d, *J* 2.4) and 7.42 (4H, d, *J* 2.4).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrakis[(*tert*-butoxycarbonyl)methoxy][3.1.3.1]metacyclophane (3c)-KSCN complex. δ_H ($CDCl_3$–methanol-d_4, 1 : 1 v/v): 1.25 (36H, s), 1.30–1.70 (4H, m), 1.61 (36H, s), 2.40–2.55 (4H, m), 2.60–2.78 (4H, m), 3.48 (4H, d, *J* 12.2), 4.18 (4H, d, *J* 12.2), 4.46 (2H, d, *J* 16.6), 4.56 (2H, d, *J* 16.6), 7.02 (4H, d, *J* 2.4) and 7.41 (4H, d, *J* 2.4).

Crystal data and refinement details for 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrakis[(ethoxycarbonyl)methoxy]-[3.1.3.1]metacyclophane, 3b

Crystallographic data for **3b** are given in Table 4. The unit cell constants were derived from least-squares analysis of the settings of a CAD4 FR 586 diffractometer for 25 reflections, in the range of $43.4° < 2\theta < 84.2°$. The intensities of all independent reflections with $5.4° < 2\theta < 148.6°$ were measured with ω scan width (0.81 + 0.76 tan θ), Ni-filtered Cu K_α radiation (λ = 1.54184 Å) was used.

The X-ray analysis was performed with the MolEN program package[22] and the structure was solved uneventfully by direct methods (MULTAN 11/82).[23] The refinement

Table 4 Crystallographic data for 6,13,22,29-tetra-*tert*-9,16,25,32-tetrakis[(ethoxycarbonyl)methoxy][3.1.3.1]metacyclophane, 1,4-alternate-**3b**

Formula	$C_{64}H_{88}O_{12}$
FW	1049.41
Size/mm	0.03 × 0.025 × 0.02
Space group	$P\bar{1}$ (No. 2)
a/Å	13.5602 (8)
b/Å	13.980 (8)
c/Å	9.8338 (4)
α/°	105.59 (4)
β/°	91.311 (4)
γ/°	60.60 (4)
U/Å^3	1550.98
Z	1
ρ_{calcd}/gm^{-3}	1.125
T/K	294
Radiation	Cu K_α
λ/Å	1.54184
μ/cm^{-1}	5.8
No. of reflections	6705
Unique reflections	5941
R	0.153
R_w	0.195
S	3.36

method used was full-matrix least squares and the 458 parameters refined were atomic coordinates, temperature factors (anisotropic for carbon atoms in part isotropic), scale factors and secondary extinction coefficients. No corrections were made for absorption. The 38 independent non-hydrogen atoms (except for C_9, C_{10}, and C_{28}) were refined anisotropically. Although the final agreement factor R value (0.153) was high, in the residual electron density no polyatomic molecules such as water or solvent molecules were observed. Large thermal parameters for C_9, C_{10}, and C_{28} during solution of the structure suggested disorder in the conformation of the terminal positions of the molecule, but attempts to resolve two sets of positions for these atoms were unsuccessful. Thus, thermal parameters of C_9, C_{10}, and C_{28} were isotropically fixed at 12.0 Å^3. The 44 independent hydrogen atoms were included in the refinement as isotropically fixed at 4.0 Å^3. Unfortunately, it was very difficult to improve the R value using several techniques such as mentioned above, but the ORTEP drawing[24] depicted in Fig. 2 offers sufficient information in order to discuss the conformation of **3b**.

CCDC reference number 440/064

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