Synthesis and conformational studies of regio- and conformational isomers derived by *O*-alkylation of tetrahydroxy[3.1.3.1]-metacyclophane [1]

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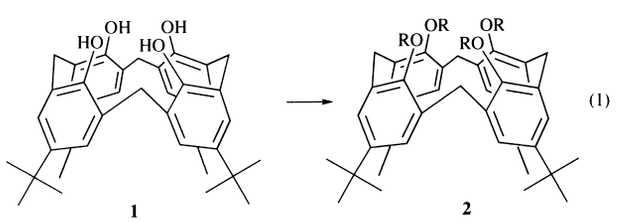
The synthesis and structure of *O*-alkylated tetrahydroxy[3.1.3.1]metacyclophanes are described. 6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]metacyclophane 3 was tetra-*O*-alkylated with alkyl bromides (RBr: R = Et, Pr and Bu) in the presence of Cs_2CO_3 to yield one pure stereoisomer in each case (*i.e.* the 1,4-alternate conformer) 5b–d as a major product; other possible isomers were not observed. Ring inversion by oxygen-through-the-annulus rotation is allowed for tetraethoxy and tetrapropoxy derivatives 5b,c (for 5c; coalescence temperature *ca.* 90 °C) but inhibited for the tetrabutoxy derivative 5d. In contrast, alkyl halides having larger alkyl groups than ethyl afforded poor yields of the corresponding tetra-*O*-alkylated compounds 5 although a significant amount of 1,3-di-*O*-substitution products 4 resulted when NaH was used as a base. On the other hand, the tetraol 3 was tetra-*O*-alkylated with benzyl bromide in the presence of NaH to yield exclusively the cone conformer *cone*-5f in quantitative yield. Only when the cation-π interactions between the alkali-metal cations and the π-electrons of the benzyl group(s) are able to hold the latter and the oxide group(s) on the same side of the [3.1.3.1]MCP is the conformation immobilized to the cone. The template effect of the sodium cation plays an important role in this benzylation. The ^{1}H NMR spectral behaviour of these macrocyclic metacyclophanes is also discussed.

Introduction

Gutsche,[2] Reinhoudt[3] and Shinkai[4] have reported that derivatization of the hydroxy groups of tetrahydroxy[1.1.1.1]MCP (MCP = metacyclophane) (calix[4]arene) led to conformationally rigid structures, *i.e.* fixed conformations such as 'cone', 'partial cone', '1,2-alternate' and '1,3-alternate'. A 'cone' shape conformation is shown in eqn. (1).



However, there were few reports of similar derivatization of the hydroxy groups of dihomocalix[4]arenes in spite of the formation of five conformers (*i.e.* cone- and partial-cone, 1,2-alternate, 1,3-alternate and 1,4-alternate conformers) being possible.[5]

In contrast to four possible conformations in calix[4]arenes,[2a] conformational isomerism in the system described here is slightly more complicated. Furthermore, the conformations of internally substituted tetrahydroxy[*n*.1.*n*.1]MCPs having more than three methylene bridges are, so far, unknown. Thus, there is substantial interest in investigating the effects of *O*-alkyl substituents on the conformations of the flexible higher tetrahydroxy[3.1.3.1]MCPs.

In this paper we report on the regioselective synthesis of conformers derived from the *O*-alkylation of tetrahydroxy-[3.1.3.1]MCP and an investigation of the ring inversion in these systems.

Results and discussion

Recently, Gutsche *et al.* reported on the influence of *O*-substituents on the conformational isomerism of calix[4]arenes in detail.[2a,2c] These authors have established that interconversion between conformers, which occurs by oxygen-through-the-annulus rotation, is sterically allowed for methyl and ethyl groups, but inhibited by *O*-substituents bulkier than a propyl group.

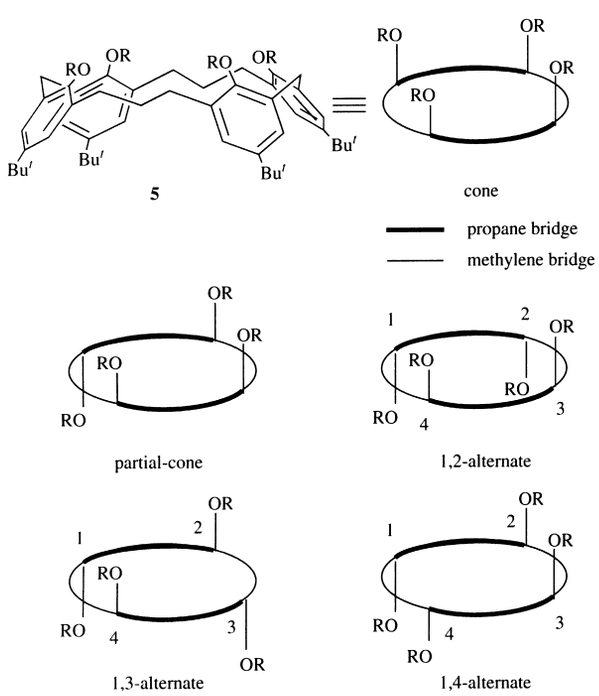
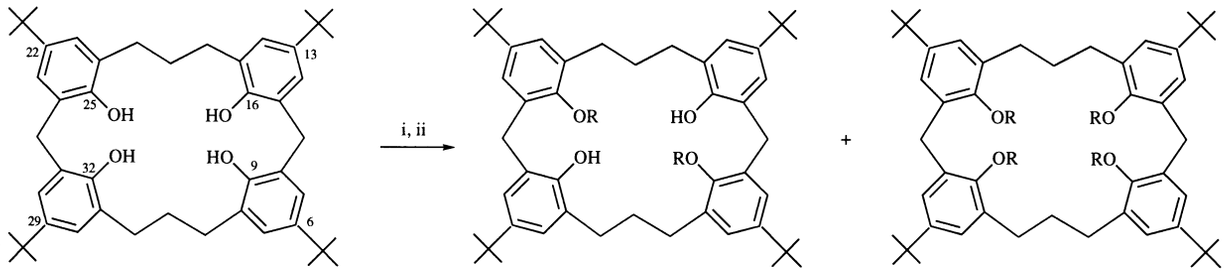


Fig. 1 Conformers possible for *O*-tetrasubstitution of tetrahydroxy-[3.1.3.1]MCPs

In studies on the conformer distribution of calix[4]arenes Shinkai *et al.* reported that the partial-cone is sterically less crowded than the cone and, therefore, is formed preferentially.[6] On the other hand, the cone results only when the template



3

distal-**4** **a** R = Me
b R = Et
c R = Pr
d R = Bu
e R = Allyl
f R = $PhCH_2$

5 **a** R = Me
b R = Et
c R = Pr
d R = Bu
e R = Allyl
f R = $PhCH_2$

Scheme 1 (see Table 1) *Reagents and conditions:* i, NaH, DMF–THF, room temp. for 1 h; ii, RX, reflux for 3 h

Table 1 *O*-Alkylation of tetraol **3** with alkyl halide in the presence of NaH

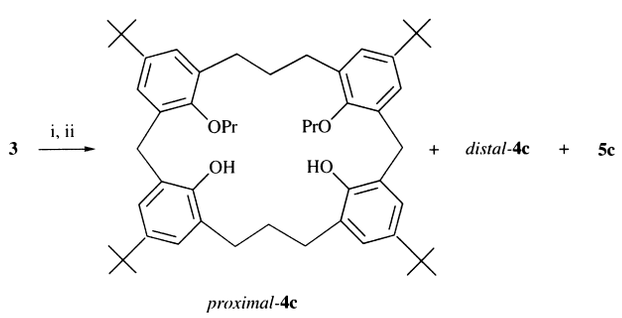
Run	RX	Time (*t*/h)	Products yield (%)[a]	
1	MeI	0.25	*distal*-**4a** (80) [72][b]	**5a** (20)
2	MeI	1	*distal*-**4a** (0)	**5a** (100) [96][b]
3	EtBr	1	*distal*-**4b** (100) [90]	**5b** (0)
4	EtBr	3	*distal*-**4b** (50)	**5b** (50)
5	EtBr	6	*distal*-**4b** (20)	**5b** (80) [70]
6	PrBr	3	*distal*-**4c** (84) [74][c]	**5c** (7)
7	BuBr	3	*distal*-**4d** (100) [95]	**5d** (0)
8	Allyl bromide	3	*distal*-**4e** (0)	**5e** (100) [95]
9	$PhCH_2Br$	3	*distal*-**4f** (0)	**5f** (100) [90]

[a] Relative yields determined by ^{1}H NMR spectroscopy. [b] Isolated yields are shown in square brackets. [c] *proximal*-**4c** was obtained in 9% yield.

Table 2 *O*-Substitution of tetraol **3** with propyl bromide in the presence of M_2CO_3

		Products yield (%)[a,b]		
Run	Base	*proximal*-**4c**	*distal*-**4c**	**5c**
1	Li_2CO_3[c]	0	0	0
2	Na_2CO_3[d]	20	30	0
3	K_2CO_3	50	50	0
4	Cs_2CO_3	12 (9)	12 (9)	76 (60)

[a] Relative yields determined by ^{1}H NMR spectroscopy. [b] Isolated yields are shown in parentheses. [c] Starting compound **3** was recovered in almost quantitative yield. [d] Starting compound **3** was recovered in 50% yield.



proximal-**4c**

Scheme 2 (see Table 2) *Reagents and conditions:* i, M_2CO_3, acetone, room temp. for 1 h; ii, PrBr, reflux for 3 h

metal, which strongly interacts with phenolic oxygens, is present in the reaction system. In particular, formation of the 1,2-alternate conformer is very limited because of the extreme difficulty of direct *O*-alkylation.[3b,7]

In fact, 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy-[3.1.3.1]MCP **3** was *O*-alkylated with MeI in the presence of NaH under reflux in DMF–THF for 15 min to yield one pure regioselective isomer, the 1,3-di-*O*-substitution product *distal*-**4a** as a major product along with the tetramethoxy derivative **5a**; other possible isomers were not observed. Prolonged reaction times led to complete *O*-methylation, affording tetramethoxy derivative **5a** in quantitative yield. Similar results were obtained in the *O*-ethylation of **3** with ethyl bromide. Interestingly, *O*-alkylation with alkyl bromides such as propyl bromide and butyl bromide having larger alkyl groups than ethyl afforded poor yields of the corresponding tetra-*O*-alkylated compounds **5**; however, a significant amount of 1,3-di-*O*-substitution products **4** results when NaH is used as a base. On the other hand, in spite of having larger alkyl groups than ethyl, *O*-alkylation with allyl bromide and benzyl bromide exclusively afforded tetra-*O*-substitution products **5e** and **5f** under the same reaction conditions. This result can be easily explained by the higher reactivities of allyl bromide and benzyl bromide than those of propyl bromide and butyl bromide. The *O*-alkylation described here was found to be strongly affected not only by the bulkiness of the alkyl halide but also by its reactivity.

Attempted *O*-alkylation of 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **3** with propyl bromide in the presence of Li_2CO_3 failed, starting compound being recovered in almost quantitative yield. When K_2CO_3 or Na_2CO_3 was used as a base, a mixture of 1,2-disubstituted product *proximal*-**4c** and the 1,3-disubstituted product *distal*-**4c** was obtained; other possible isomeric 1,4-disubstituted products were not observed. In contrast, Cs_2CO_3 led to tetra-*O*-substitution to afford **5c** as a major product.

The ratio of the products dipropoxy[3.1.3.1]MCP **4c** and tetrapropoxy[3.1.3.1]MCP **5c** in the *O*-propylation of tetrahydroxy[3.1.3.1]MCP **3** is governed by the nature of the alkali-metal carbonate used as a catalyst, as revealed by the results listed in Table 2. Thus, use of lithium carbonate in this reaction gave only recovery of the starting compound. Use of sodium carbonate however gave the dipropylated products *proximal*-**4c** and *distal*-**4c** (40:60) in 50% yield with recovery of starting compound; this was in spite of use of a large excess of sodium carbonate. However, use of potassium carbonate gave selective dipropylation, the larger alkaline metal K^+ obviously gives rise to a higher yield of the dipropylation product **4c**; use of the larger Cs^+ cation leads to a decreased product yield. These results indicate that the alkali-metal cation plays an important role not only for the regioselectivity, based on the template effect, but also for the product yield of the *O*-alkylation. This behaviour has been previously observed in the *O*-alkylation of calixarenes.[4,6]

When a weak base is used (M_2CO_3), the undissociated OH group forms intramolecular hydrogen bonds with the dissociated O^- group (intermediate **A**, **B** in Fig. 2) rather than leading to further dissociation to form the metal template intermediate **C**, **D**. These results differ from those observed under the influence of a strong base (*e.g.* NaH) which gave rise to complete formation of two O^- anions. The same phenomenon

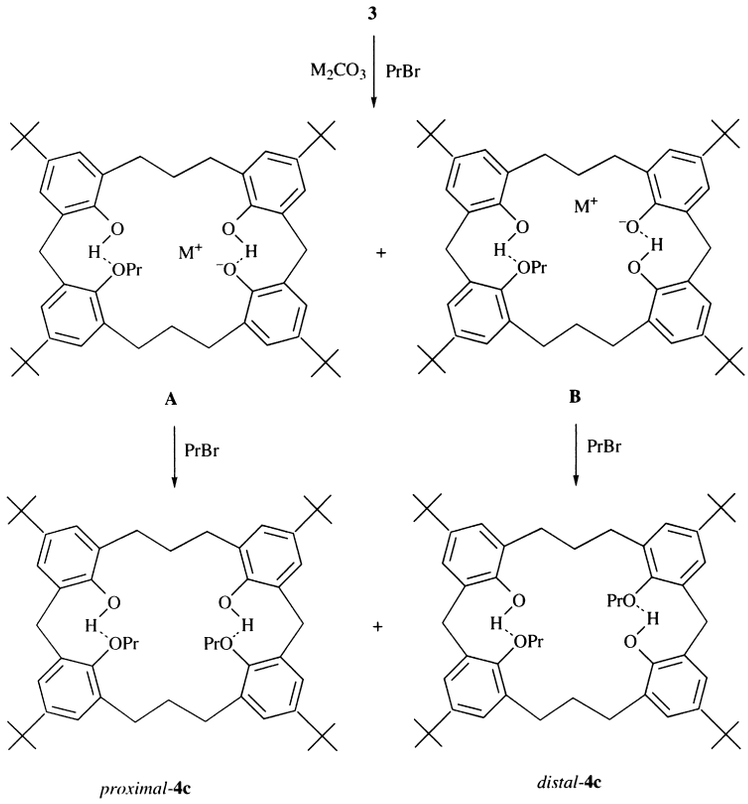


Fig. 2 Possible intramolecular hydrogen bonds with the dissociated O^- groups

might occur in the dipropylated product **4**. Thus, double alkylation was not observed due to intramolecular hydrogen bond formation with the propoxy groups.

The present template effect was also confirmed by the *O*-propylation of dipropoxy[3.1.3.1]MCP *proximal*-**4c** and *distal*-**4c** with NaH as a base to furnish exclusive formation of tetrapropoxy[3.1.3.1]MCP **5c** *via* the intermediates **C** and **D** (see Fig. 3).

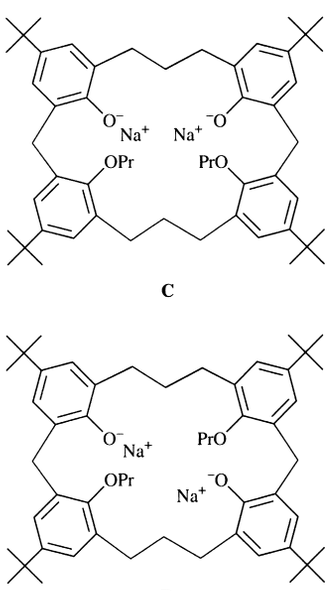


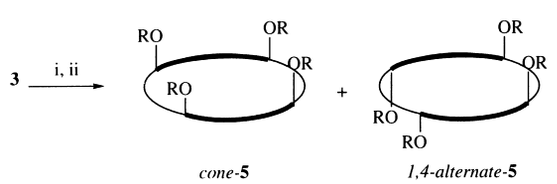
Fig. 3 Possible intermediates for formation of tetra-*O*-propylation

As mentioned previously, 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **3** was tetra-*O*-benzylated with benzyl bromide in the presence of NaH to yield exclusively the tetra-*O*-benzylated product *cone*-**5f** in quantitative yield. No formation of other possible conformers (see Fig. 1) has been observed. A similar reaction was carried out in the presence of Cs_2CO_3 to yield a mixture of two conformers of the tetra-*O*-benzylated product **5f** (ratio of 80:20 for *cone*-**5f**:1,4-*alternate*-**5f**) in quantitative yield.

Table 3 *O*-Substitution of tetraol **3** with butyl bromide and benzyl bromide in the presence of NaH and Cs_2CO_3

			Product yields (%)[a,b]	
Run	RX	Base	*cone*-**5**	1,4-*alternate*-**5**
1	BuBr	Cs_2CO_3	0	100 (90)
2	BzlBr	NaH	100 (90)	0
3	BzlBr	Cs_2CO_3	80 (70)	20 (13)

[a] Relative yields determined by ^{1}H NMR spectroscopy. [b] Isolated yields are shown in parentheses.



Scheme 3 (see Table 3) *Reagents and conditions:* i, NaH, DMF–THF, room temp. for 1 h or Cs_2CO_3, acetone, room temp. for 1 h; ii, BuBr or BzlBr, reflux for 3 h

The ^{1}H NMR spectrum of *cone*-**5f** shows a singlet for the *tert*-butyl protons at δ 1.12, and two doublets (J 2.0 Hz) of equal intensity for the aromatic protons at δ 6.78 and 6.97. Furthermore, the resonance for the ArCH_2Ar methylene protons appeared as a pair of doublets (δ 3.08 and 4.36, J_{AB} = 13.4 Hz) (relative intensity 1:1).

Similarly, the ^{1}H NMR spectrum of 1,4-*alternate*-**5f** shows a singlet for the *tert*-butyl protons at δ 1.08, a set of doublets (J = 11.5 Hz) for benzyl protons at δ 4.35 and 4.45, and two doublets of equal intensity for the aromatic protons at δ 7.00 and 7.12. Furthermore, the resonance for the ArCH_2Ar methylene protons appeared as a pair of doublets (δ 3.29 and 4.54, J_{AB} = 13.4 Hz) (relative intensity 1:1).

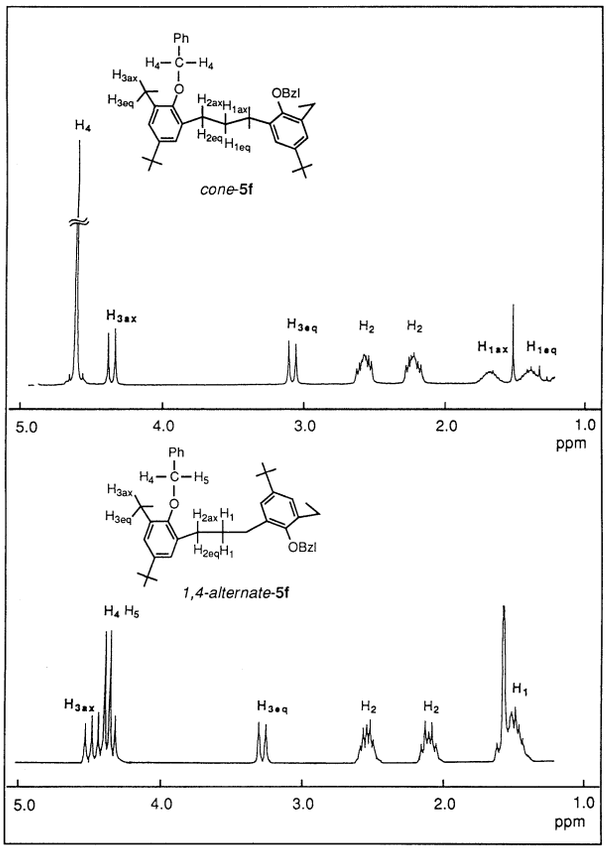


Fig. 4 Partial ^{1}H NMR spectra for *cone*-**5f** and 1,4-*alternate*-**5f**

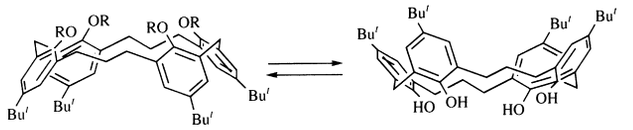
Although these ^{1}H NMR signals are consonant with both the cone and 1,4-alternate conformers, the middle methylene protons for the propane bridge $ArCH_2CH_2CH_2Ar$ are observed as a split multiplet pattern for *cone*-**5f** at δ 1.32–1.48 and 1.61–1.88 (relative intensity 1:1), whilst for the 1,4-*alternate*-**5f** only a single multiplet is observed at 1.40–1.59. The former pattern corresponds to the cone conformer because the middle methylene protons for the propane bridge $ArCH_2CH_2CH_2Ar$ are in different environments, whilst the latter pattern corresponds to the 1,4-alternate conformer where the protons are in the same environment (Fig. 4).

Tetra-*O*-butylation of the tetraol **3** with butyl bromide in the presence of Cs_2CO_3, however, exclusively yields the tetra-*O*-butylated product 1,4-*alternate*-**5d** in quantitative yield. These findings support the view that when substituents are introduced into tetrahydroxy[3.1.3.1]MCP **3** a 1,4-alternate conformer is preferred to reduce steric crowding.

The preferential formation of *cone*-**5f** was observed in the reaction of the tetraol **3** with benzyl bromide in the presence of Cs_2CO_3 along with the 1,4-alternate conformer 1,4-*alternate*-**5f** (20%) (Table 3). It was further found that the proportion of *cone*-**5f** dramatically increased, almost to exclusive formation, in the *O*-substitution of tetrahydroxy[3.1.3.1]MCP **3** with benzyl bromide when a stronger base was employed (*e.g.* NaH rather than Cs_2CO_3). *O*-Alkylation with butyl bromide, however, failed to give a similar result, only the 1,4-*alternate*-**5f** being obtained even in the presence of NaH.

These results indicate that when butyl bromide is used in the presence of Cs_2CO_3, 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 (Fig. 5). Thus, it seems that a ring inversion occurs as a result of the tetraol **3** having a more flexible structure than calix[4]arene, thus giving rise to the completely inverted 1,4-alternate conformer. In constrast, only when the template metal can hold the benzyl group(s) and the oxide group(s) attributable to the cation-π-interactions[9] on the same side of the [3.1.3.1]MCP, is the conformation immobilized to the cone. Although the much larger contribution of Cs^+ to the template effect than Na^+ as reported by Harrowfield[10] can be expected, the larger Cs^+ might enlarge the cyclophane ring of tetraol **3** to form sufficient space for ring inversion to afford a 1,4-alternate conformer.

Table 4 Influence of *O*-substituents on the oxygen-through-the-annulus rotation in [3.1.3.1]metacyclophanes **4** and **5**



O-Substituent	**4**	**5**
Me	Mobile ($T_c < -60$ °C)	Mobile ($T_c < -60$ °C)
Et	Mobile ($T_c = 10$ °C, $\Delta G_c^{\ddagger} = 13.3$)	Mobile ($T_c < -60$ °C)
Pr	Immobile[b]	Mobile ($T_c = 90$ °C, $\Delta G_c^{\ddagger} = 14.7$)[b]
Bu	Immobile[b]	Immobile[b]
Bzl	Immobile[b]	Immobile[b]

[a] T_c: [°C]; $\Delta G_c^{\ddagger}$: [kcal mol^{-1}]. T_c and $\Delta G_c^{\ddagger}$: were determined in $CDCl_3$–CS_2 (1:3) by using $SiMe_4$ as reference unless otherwise indicated. [b] Solvent: $CDBr_3$–$CDCl_3$ (6:1).

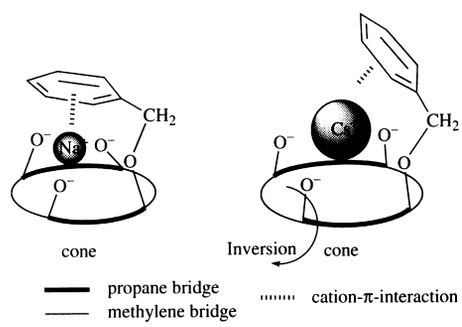


Fig. 5 Ring inversion of the tetraol **3** and immobilization by metal template

As mentioned previously, it is known that four different conformers (cone, partial-cone, 1,2-alternate and 1,3-alternate) can exist in conformationally immobile calix[4]arenes.[6] In *O*-alkylated [3.1.3.1]MCPs **4** and **5**, on the other hand, several conformations can exist as in *O*-alkylated calix[4]arenes. Thus, the conformational complexity in the *O*-alkylated [3.1.3.1]-MCPs **4** and **5** must be considered.

The influence of *O*-substituents on the oxygen-through-the-annulus rotation of di-*O*-alkylated [3.1.3.1]MCPs **4** is compared with that in the corresponding tetra-*O*-alkylated [3.1.3.1]MCPs **5** in Table 4. The observation of a singlet signal for each proton even at the lower temperature (−60 °C in $CDCl_3$–CS_2, 1:3) in the ^{1}H NMR spectrum of dimethoxy[3.1.3.1]MCP (*distal*-**4a**) and tetramethoxy[3.1.3.1]MCP **5a** indicates that the methoxy groups in *distal*-**4a** and **5a** rotate rapidly through the annulus.

Although the same phenomenon was observed in tetraethoxy[3.1.3.1]MCP **5b** even at a lower temperature (−60 °C in $CDCl_3$–CS_2, 1:3), in diethoxy[3.1.3.1]MCP (*distal*-**4b**) at 0 °C the methylene protons of $ArCH_2Ar$ and $ArCH_2CH_2CH_2Ar$ are observed to be split into two sets of doublets (AB system, J_{AB} 13.4 Hz) at δ 3.35 and 3.90 and multiplets at δ 2.66 and 2.84, respectively. The coalescence temperature of the methylene protons of $ArCH_2Ar$ is 10 °C and the free energy of activation for inversion is estimated to be 13.3 kcal mol^{-1} (1 cal = 4.184 J). This difference may be attributed mainly to a higher barrier for diethoxy[3.1.3.1]MCP (*distal*-**4b**) to conformational ring flip-

ping than that for tetraethoxy[3.1.3.1]MCP **5b** by the introduction of two ethyl groups onto the phenolic oxygens. From the coalescence temperature of the ArCH_2Ar methylene protons in $CDBr_3$ the barrier for ring inversion was calculated as 13.3 kcal mol^{-1} ($T_c = 10$ °C) indicating that the introduction of the two ethyl groups slightly increases the rigidity of the system by about 0.8 kcal mol^{-1} {$\Delta G_c^{\ddagger} = 12.5$ kcal mol^{-1} ($T_c = 0$ °C, $\Delta\nu = 243.65$ Hz) for tetrahydroxy[3.1.3.1]MCP **3** in $CDCl_3$}. While the four hydroxy groups in tetrahydroxy[3.1.3.1]MCP **3** can serve as a donor or an acceptor of hydrogen bonds, the OEt groups in diethoxy[3.1.3.1]MCP (*distal*-**4b**) can serve only as a donor. The decreased rigidity of tetraethoxy[3.1.3.1]MCP **5b** may be attributed to the loss of an OH · · · O hydrogen bond in spite of the much bulkier OEt substituent than the OH group.

Ring inversion by oxygen-through-the-annulus rotation is allowed for tetraethoxy and tetrapropoxy derivatives **5b**,**c** (for **5c**; coalescence temperature *ca.* 90 °C) but inhibited for the tributoxy derivative **5d** and benzyloxy derivative **5f**.

Shinkai *et al.* reported that in the calix[4]arenes the ethyl group only introduces some steric hindrance and that the rotation is completely inhibited by the bulkier propyl group.[6] In [3.1.3.1]MCP **5**, on the other hand, the propyl group is also bulky enough to inhibit the rotation, but the conformational ring inversion can still occur above 90 °C. The results consistently reveal that it is slightly more difficult to inhibit the rotation in [3.1.3.1]MCP **5** than in *O*-alkylated calix[4]arenes: in other words, the inner cavity of **5** is apparently larger due to the two propane bridges than that of *O*-alkylated calix[4]arenes.

The ArCH_2Ar methylene protons and aromatic protons for tetrapropoxy[3.1.3.1]MCP **5c** appeared as a set of doublets at $\delta = 3.30$, 4.40 ($J = 13.2$ Hz) and as a set of doublets at $\delta = 6.98$, 7.10 ($J = 2.4$ Hz) (relative intensity 1:1) at −20 °C in $CDCl_3$–CS_2 (1:3). The middle methylene protons for the propane bridge Ar$CH_2CH_2CH_2$Ar are observed as a multiplet at δ 1.92–1.98. This pattern corresponds to a 1,4-alternate conformer similar to the corresponding tetrabenzyloxy derivative 1,4-*alternate*-**5f** mentioned previously. The methyl protons in the propyl groups appear as a triplet to higher field at $\delta = 0.60$. On the basis of the Corey–Pauling–Koltun (CPK) model of 1,4-*alternate*-**5c**, the '*anti*-stepped conformation' of diphenylmethane moeties like [3.3]metacyclophane[11–13] are possible. Thus four propoxy groups are located in the shielded region by the ring current effect of the opposing benzene rings. These findings strongly support the view that **5c** adopts a 1,4-alternate conformation. Similar findings have been observed in the conformationally rigid tetrabutoxy[3.1.3.1]MCP **5d**. Thus, **5d** also adopts a 1,4-alternate conformation.

In contrast, in di-*O*-alkylated derivatives **4c** and **4d**, for example, the above described upfield shift for the methyl protons in the propyl and butyl groups has not been observed. Therefore, dipropoxy[3.1.3.1]MCP **4c** and dibutoxy[3.1.3.1]MCP **4d** might adopt a cone-conformation due to the intramolecular hydrogen bonding between two hydroxy groups and the alkoxy groups. Thus the hydroxy groups and the alkoxy groups can be held strongly on the same side of the [3.1.3.1]MCP.

Conclusions

An interesting result was obtained by alkylation of the hydroxy groups of the tetraol **3**. We have demonstrated inhibition of interconversion between conformers derived from the tetraol **3** by *O*-substitution different from the calix[4]arenes as a result of the intramolecular hydrogen bonding between the hydroxy groups and the 1,3-diarylpropane units being weaker than the corresponding bonding for the diarylmethane units. Thus, the weaker intramolecular hydrogen bonding in the tetraol **3** compound with that in the corresponding calix[4]arenes gives rise to flexibility of the propane linkages.

In conclusion, the presently prepared propane-bridged calixarenes analogous to the metacyclophanes **4** and **5** have potential as rich sources of new types of host compounds.

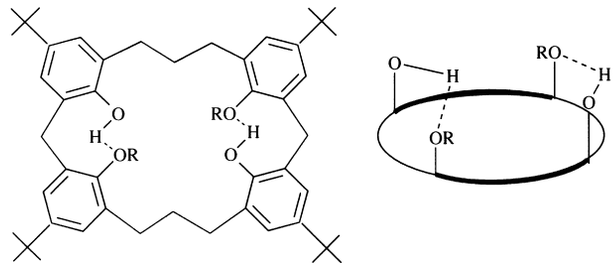


Fig. 6 Intramolecular hydrogen bonds in *distal*-**4**

Experimental

All mps 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. 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 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]metacylophane **3** has been described.[1,14]

Alkylation of 3 with alkyl halide in the presence of NaH

Typical procedure. A mixture of **3** (400 mg, 0.567 mmol) and NaH (454.0 mg, 11.35 mmol) in dry tetrahydrofuran (36 cm^3) and DMF (9 cm^3) was stirred at room temperature for 1 h under nitrogen. Propyl bromide (0.515 cm^3, 5.67 mmol) was then added to the mixture after which it was heated at reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was acidified with 1 M 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 evaporated under reduced pressure to give a yellow oil. This was then distilled *in vacuo* to remove the excess of unchanged propyl bromide using a Kugelrohr apparatus to give a brown oil. The ^{1}H NMR spectrum of this oil was in accord with its being a mixture of three components; **5c**, *distal*-**4c** and *proximal*-**4c** in the ratio of 7:84:9. The residue was chromatographed on silica gel with hexane and hexane–benzene (1:1) as eluents to give **5c** (28 mg, 5.7%), *distal*-**4c** (333 mg, 74.4%) and *proximal*-**4c** (37 mg, 8.3%), respectively.

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrapropoxy[3.1.3.1]-metacyclophane 5c. *Prisms* [from hexane–benzene (1:1)], mp 234–236 °C; ν_{max}(KBr)/cm^{-1} 2992, 2874, 1481, 1197, 1008 and 956; δ_H($CDCl_3$) 0.60 (12 H, br t), 1.27 (36 H, s), 1.20–1.30 (8 H, m), 1.92–1.98 (4 H, m), 2.20 (4 H, br s), 2.73 (4 H, br s), 3.30 (10 H, br s), 4.40 (2 H, br s), 6.98 (4 H, d, *J* 2.4) and 7.10 (4 H, d, *J* 2.4); *m*/*z* 872 (M^+) (Found: C, 82.00; H, 10.27. $C_{60}H_{88}O_4$ requires C, 82.52; H, 10.16%).

6,13,22,29-Tetra-*tert*-butyl-9,25-dihydroxy-16,32-dipropoxy-[3.1.3.1]metacyclophane *distal*-4c. *Prisms* [from $CHCl_3$–MeOH (1:1)], mp 285–287 °C; ν_{max}(KBr)/cm^{-1} 3331 (OH), 2962, 2862, 1601, 1486, 1458, 1387, 1363, 1298, 1248, 1208, 1192, 1140, 1124, 1091, 1060, 995, 959, 881 and 868; δ_H($CDCl_3$) 1.15–1.27 (4 H, m), 1.20 (18 H, s), 1.24 (18 H, s), 1.32 (6 H, t, *J* 7.3), 1.93–2.23 (2 H, m), 2.24–2.44 (4 H, m), 2.84–3.07 (4 H, m), 3.48 (2 H, d, *J* 13.4), 3.91–4.00 (2 H, m), 4.05 (2 H, d, *J* 13.4), 4.05–4.16 (2 H, m), 6.90 (2 H, d, *J* 2.4), 6.97 (2 H, d, *J* 2.4), 7.06 (2 H, d, *J* 2.4), 7.14 (2 H, d, *J* 2.4) and 8.05 (2 H, s, replaced by D_2O); *m*/*z* 788 (M^+) (Found: C, 82.08; H, 9.72. $C_{54}H_{76}O_4$ requires C, 82.18; H, 9.71%).

6,13,22,29-Tetra-*tert*-butyl-9,32-dipropoxy-16,25-dihydroxy-[3.1.3.1]metacyclophane *proximal*-4c. *Prisms* [from $CHCl_3$–MeOH (1:1)], mp 274–276 °C; ν_{max}(KBr)/cm^{-1} 3291 (OH), 2961, 2883, 1486, 1458, 1391, 1363, 1302, 1248, 1208, 1124, 1061, 990, 957, 880 and 870; δ_H($CDCl_3$) 1.21 (18 H, s), 1.23 (18 H, s), 1.21–1.23 (6 H, CH_3 proton signal overlaps with *tert*-butyl proton signals), 1.71–1.89 (4 H, br s), 2.02–2.17 (4 H, m), 2.19–2.46 (4 H, m), 2.86–3.09 (4 H, m), 3.48 (2 H, d, *J* 13.2), 3.84–4.02 (4 H, m), 4.06 (2 H, d, *J* 13.2), 6.90 (2 H, d, *J* 2.4), 6.97 (2 H, d, *J* 2.4), 7.03 (2 H, d, *J* 2.4), 7.15 (2 H, d, *J* 2.4) and 7.82 (2 H, s, replaced by D_2O); *m*/*z* 788 (M^+) (Found: C, 82.10; H, 9.65. $C_{54}H_{76}O_4$ requires C, 82.18; H, 9.71%).

Compounds *distal*-**4a**, **4b**, **4d** and **5a**, **5b**, **5e**, **5f** were prepared in a similar manner to that described above. The yields are given in Table 1.

6,13,22,29-Tetra-*tert*-butyl-16,32-dihydroxy-9,25-dimethoxy-[3.1.3.1]metacyclophane *distal*-4a. *Prisms* [from $CHCl_3$–MeOH (1:1)], mp >300 °C; ν_{max}(KBr)/cm^{-1} 3413 (OH), 2960, 2866, 1482, 1459, 1363, 1298, 1208, 1169, 1105, 990 and 880; δ_H($CDCl_3$) 1.20 (18 H, s), 1.25 (18 H, s), 1.43–1.61 (4 H, m), 2.61–2.69 (8 H, m), 3.78 (4 H, s), 3.98 (6 H, s), 6.92 (2 H, d, *J* 2.4), 6.98 (2 H, d, *J* 2.4), 7.06 (2 H, d, *J* 2.4), 7.11 (2 H, d, *J* 2.4) and 7.97 (2 H, s); *m*/*z* 732 (M^+) (Found: C, 82.06; H, 9.34. $C_{50}H_{68}O_4$ requires C, 81.92; H, 9.35%).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetramethoxy-[3.1.3.1]metacyclophane 5a. *Prisms* (from benzene), mp >300 °C (lit.,[14] mp >300 °C).

6,13,22,29-Tetra-*tert*-butyl-9,25-diethoxy-16,32-dihydroxy-[3.1.3.1]metacyclophane *distal*-4b. *Prisms* (from benzene), mp >300 °C; ν_{max}(KBr)/cm^{-1} 3339 (OH), 2960, 1486, 1363, 1207 and 1030; δ_H($CDCl_3$, 27 °C) 1.22 (18 H, s), 1.25 (18 H, s), 1.32 (6 H, t, *J* 7.3), 1.55–1.65 (4 H, m), 2.63 (8 H, br s), 3.74 (4 H, br s), 4.12 (4 H, q, *J* 7.3), 6.91 (2 H, d, *J* 2.4), 6.97 (2 H, d, *J* 2.4), 7.07 (2 H, d, *J* 2.4), 7.15 (2 H, d, *J* 2.4) and 8.04 (2 H, s, replaced by D_2O); δ_H($CDCl_3$, −40 °C) 1.22 (18 H, s), 1.25 (18 H, s), 1.32 (6 H, t, *J* 7.3), 1.55–1.65 (2 H, m), 2.00–2.40 (6 H, m), 2.70–3.00 (4 H, m), 3.35 (2 H, d, *J* 13.4), 3.90 (2 H, d, *J* 13.4), 4.12 (4 H, q, *J* 7.3), 6.91 (2 H, d, *J* 2.4), 6.97 (2 H, d, *J* 2.4), 7.07 (2 H, d, *J* 2.4), 7.15 (2 H, d, *J* 2.4) and 8.04 (2 H, s, replaced by D_2O); *m*/*z* 760 (M^+) (Found: C, 82.28; H, 9.42. $C_{52}H_{72}O_4$ requires C, 82.06; H, 9.53%).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetraethoxy[3.1.3.1]-metacyclophane 5b. *Prisms* [from $CHCl_3$–MeOH (1:1)], mp 256–258 °C; ν_{max}(KBr)/cm^{-1} 2957, 2933, 2862, 1486, 1458, 1389, 1360, 1208, 1193, 1111 and 1031; δ_H($CDCl_3$) 0.85 (12 H, t, *J* 6.7), 1.26 (36 H, s), 1.60 (4 H, br s), 2.49 (8 H, br s), 3.33 (8 H, d, *J* 6.7), 3.82 (4 H, br s), 6.99 (4 H, d, *J* 2.4) and 7.06 (4 H, d, *J* 2.4); *m*/*z* 816 (M^+) (Found: C, 73.14; H, 8.84. $C_{56}H_{80}O_4 \cdot CHCl_3$ requires C, 73.10; H, 8.72%).

6,13,22,29-Tetra-*tert*-butyl-9,25-dibutoxy-16,32-dihydroxy-[3.1.3.1]metacyclophane *distal*-4d. *Prisms* (from hexane), mp 279–282 °C; ν_{max}(KBr)/cm^{-1} 3353 (OH), 2962, 2870, 1122, 880, 819, 667 and 656; δ_H($CDCl_3$) 1.10 (6 H, t, *J* 6.7), 1.19 (18 H, s), 1.24 (18 H, s), 1.67–1.79 (4 H, m), 1.91–2.01 (4 H, m), 2.08–2.20 (4 H, m), 2.23–2.45 (4 H, m), 2.82–3.09 (4 H, m), 3.47 (2 H, d, *J* 13.7), 3.95–4.13 (4 H, m), 4.05 (2 H, d, *J* 13.7), 6.90 (2 H, d, *J* 2.4), 6.95 (2 H, d, *J* 2.4), 7.05 (2 H, d, *J* 2.4), 7.12 (2 H, d, *J* 2.4) and 7.99 (2 H, s, replaced by D_2O); *m*/*z* 816 (M^+) (Found: C, 82.38; H, 9.64. $C_{56}H_{80}O_4$ requires C, 82.3; H, 9.87%).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetraallyloxy[3.1.3.1]-metacyclophane 5e. *Prisms* (from benzene), mp 218–222 °C; ν_{max}(KBr)/cm^{-1} 3075, 3015, 2958, 2862, 1479, 1458, 1420, 1392, 1363, 1292, 1202, 1115, 992, 917 and 873; δ_H($CDCl_3$) 1.23 (36 H, s), 2.80 (8 H, br s), 3.85–3.87 (4 H, br s), 3.23 (8 H, d, *J* 6.4), 3.96 (4 H, br s), 5.02 (4 H, dd, *J* 1.8 and 10.4), 5.06 (4 H, dd, *J* 1.8 and 17.7), 5.8–6.0 (4 H, m), 6.90 (4 H, d, *J* 2.4) and 6.95 (4 H, d, *J* 2.4); *m*/*z* 864 (M^+) (Found: C, 83.38; H, 9.54. $C_{60}H_{80}O_4$ requires C, 83.29; H, 9.32%).

9,16,25,32-Tetrabenzyloxy-6,13,22,29-tetra-*tert*-butyl-[3.1.3.1]metacyclophane cone-5f. *Prisms* [from $CHCl_3$–MeOH (1:1)], mp 156–158 °C; ν_{max}(KBr)/cm^{-1} 3063, 3030, 2962, 1479, 1453, 1194, 758, 729 and 696; δ_H($CDCl_3$) 1.12 (36 H, s), 1.32–1.48 (2 H, m), 1.61–1.88 (2 H, m), 2.18–2.28 (4 H, m), 2.53–2.63 (4 H, m), 3.08 (2 H, d, *J* 13.4), 4.36 (2 H, d, *J* 13.4), 4.61 (8 H, s), 6.78 (4 H, d, *J* 2.0), 6.97 (4 H, d, *J* 2.0) and 7.21–7.25 (20 H, m); *m*/*z* 1064 (M^+) (Found: C, 85.89; H, 8.54. $C_{76}H_{88}O_4$ requires C, 85.67; H, 8.32%).

Alkylation of 3 with propyl bromide in the presence of metal carbonates

Typical procedure. A mixture of **3** (400 mg, 0.567 mmol) and caesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 cm^3) was heated at reflux for 1 h under nitrogen. Propyl bromide (0.52 cm^3, 5.67 mmol) was then added to the mixture after which it was heated at reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under reduced pressure to remove the excess of unchanged propyl bromide using a Kugelrohr apparatus to give a brown oil. The ^{1}H NMR spectrum of this oil was in accord with its being a mixture of three components: **5c**, *distal*-**4c** and *proximal*-**4c** in the ratio of 76:12:12. The residue was chromatographed on silica gel with hexane and hexane–benzene (1:1) as eluents to give **5c** (292 mg, 58.9%), *distal*-**4c** (41 mg, 9.2%) and *proximal*-**4c** (42 mg, 9.4%), respectively.

Alkylation of 3 with alkyl halide in the presence of Cs_2CO_3

Typical procedure. A mixture of **3** (400 mg, 0.567 mmol) and caesium carbonate (3.70 g, 11.4 mmol) in dry acetone (36 cm^3) was heated at reflux for 1 h under nitrogen. Butyl bromide (1.52 cm^3, 14.19 mmol) was then added to the mixture after which it was heated at reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was filtered. The filtrate was concentrated and distilled under reduced pressure to remove the excess of unchanged butyl bromide using a Kugelrohr apparatus. The residue was chromatographed on silica gel with hexane and hexane–benzene (1:1) as eluents to give **5d** (638 mg, 90%).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetrabutoxy[3.1.3.1]-metacyclophane 1,4-*alternate*-5d. *Prisms* (benzene), mp 287–290 °C; δ_H($CDCl_3$) 0.60 (12 H, t, *J* 6.7), 1.23–1.28 (8 H, m), 1.27 (36 H, s), 1.75–1.78 (8 H, m), 1.92–1.94 (4 H, m), 2.16–2.24 (4 H, m), 2.68–2.78 (4 H, m), 3.20 (2 H, d, *J* 13.2), 3.25–3.35 (8 H, m), 4.44 (2 H, d, *J* 13.2), 7.00 (4 H, d, *J* 2.4) and 7.12 (4 H, d, *J* 2.4); *m*/*z* 928 (M^+) (Found: C, 82.58; H, 10.64. $C_{64}H_{96}O_4$ requires C, 82.7; H, 10.41%).

Compounds *cone*-**5f** and 1,4-*alternate*-**5f** were prepared in a similar manner to that described above. The yields and reaction conditions are shown in Table 3.

9,16,25,32-Tetrabenzyloxy-6,13,22,29-tetra-*tert*-butyl-[3.1.3.1]metacyclophane 1,4-*alternate*-5f. *Prisms* [from $CHCl_3$-MeOH (1:1)], mp 286–292 °C; ν_{max}(KBr)/cm^{-1} 2865, 2904, 1479, 1454, 1362, 1195, 1020, 728 and 594; δ_H($CDCl_3$) 1.08 (36 H, s), 1.40–1.59 (4 H, m), 2.03–2.14 (4 H, m), 2.49–2.58 (4 H, m), 3.29 (2 H, d, *J* 13.4), 4.35 (4 H, d, *J* 11.5), 4.45 (4 H, d, *J* 11.5), 4.54 (2 H, d, *J* 13.4), 6.91 (4 H, d, *J* 2.0), 6.63–6.73 (16 H, m), 7.00 (4 H, d, *J* 2.0) and 7.12 (4 H, d, *J* 2.0); *m*/*z* 1064 (M^+) (Found: C, 85.88; H, 8.21. $C_{76}H_{88}O_4$ requires C, 85.67; H, 8.32%).

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