Synthesis and conformational studies of tetrahydroxy-[3.1.3.1]metacyclophanes and electrophilic aromatic substitution of their tetramethoxy derivatives

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Base-catalysed condensation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane 5 with formaldehyde in xylene has been carried out to form the novel propane-bridged calixarene-type macrocyclic compound, tetrahydroxy[3.1.3.1]metacyclophane 6. The optimum yield (90%) of 6 is obtained with NaOH as the base, the use of other alkali-metal hydroxides giving lower yields. $AlCl_3$–$MeNO_2$-catalysed trans-*tert*-butylation of 6 in benzene affords 7 in 80% yield. Intramolecular hydrogen bonding has been observed in the tetraols 6 and 7 as comparable to calix[4]arene.

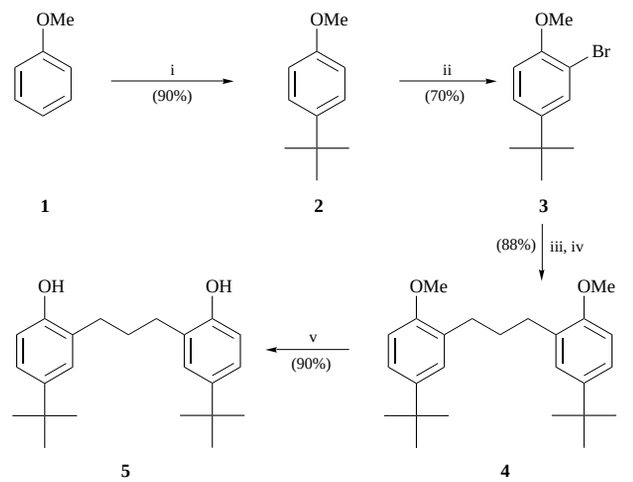
Methylation of 7 with MeI affords the tetramethoxy derivative 11a. The stability of multi-membered carbon skeletons permits the interconversion of functional groups at the lower and upper rims without special regard to ring-opening side-reactions on the upper rim. For example, the introduction of Br, formyl and acetyl substituents has been achieved by electrophilic aromatic substitution of the tetramethoxy derivative 11a. The ^{1}H NMR spectral behaviour of these macrocyclic metacyclophanes is also discussed.

Introduction

The calixarenes [1$_n$]MCPs (MCP = metacyclophane), prepared by base-catalysed condensation of *para*-substituted phenols with formaldehyde, are attractive matrices, their phenolic hydroxy groups being ordered in well-shaped cyclic arrays as a result of strong intramolecular hydrogen bonding,[1,2] which may be functionalized into novel guest inclusion blocks.[3,4] Because of our interest in calixarene-type host compounds having different cavities and several binding units, we have developed various functionalized host compounds with different bridged chains. It is surprising that there have been so few reports of the preparation of calixarenes containing bridges other than methylene groups and characterization of their hydrogen bonding.[5] We have recently demonstrated for the first time the convenient synthesis of the ethylene-bridged calixarene-analogous MCPs such as [(2.1)$_n$]MCPs by base-catalysed condensation of 1,2-bis(5-*tert*-butyl-2-hydroxyphenyl)ethane with formaldehyde in refluxing xylene and have disclosed their unique properties.[5e] However, the desired tetrahydroxy[(2.1)$_2$]MCP was not obtained by this method. Instead, a mixture of higher analogues, trimer and tetramers {*e.g.* hexahydroxy[(2.1)$_3$]MCP and octahydroxy[(2.1)$_4$]MCP} were obtained in good yield. This seems to be a result of tetrahydroxy[(2.1)$_2$]MCP having a much more strained structure than the higher analogues containing a larger ring. This strategy was thought likely to be useful for the preparation of tetrahydroxy[(3.1)$_2$]MCP, since the strain associated with the tetrahydroxy[(2.1)$_2$]MCP system was expected to be less because of the presence of two methylene bridges. In this paper, we describe the convenient preparation and conformational properties of propane-bridged calixarene-type macrocyclic MCPs, [3.1.3.1]MCPs, synthesized by a base-catalysed condensation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane **5** with formaldehyde.

Results and discussion

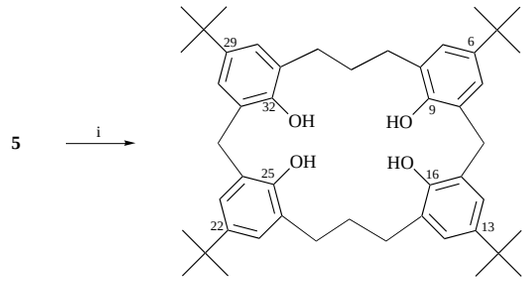
The starting compound, 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)-propane **5** was prepared in 4 steps (Scheme 1) from anisole **1** by using the *tert*-butyl group as a positional protective group on the aromatic ring.[6,7]



Scheme 1 *Reagents and conditions:* i, 2,6-di-*tert*-butyl-*p*-cresol, $AlCl_3$–$MeNO_2$; ii, Br_2, CCl_4; iii, Mg, THF; iv, $Br(CH_2)_3Br$, CuBr, HMPA, reflux for 17 h; v, BBr_3, CH_2Cl_2, room temp. for 24 h

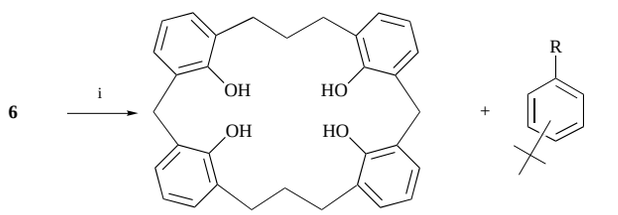
Condensation of **5** with formaldehyde in xylene under basic conditions the same as the procedure that Gutsche used for the preparation of calix[6]arene[2] afforded 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]MCP **6**. The optimum yield (90%) of **6** was obtained with NaOH as the base; the use of other alkali-metal hydroxides, *cf*. LiOH, KOH, CsOH and RbOH, giving lower yields: 10, 36, 26 and 10%, respectively. These results suggest that Na^+ serves as a template alkali metal for the formation of [3.1.3.1]MCP **6** (Scheme 2).

The $AlCl_3$–$MeNO_2$-catalysed trans-*tert*-butylation of **6** in benzene at 20 °C for 24 h afforded the desired de-*tert*-butylated product **7** (30%) along with recovery of the starting compound and the formation of incompletely de-*tert*-butylated products. The prolonged reaction time of 48 h led to complete trans-*tert*-butylation to afford **7** (80%). However, use of toluene as an acceptor for the *tert*-butyl group failed, only ring-cleavage as a result of the transbenzylation occurring. Thus, ring-cleavage as a result of transbenzylation rather than trans-*tert*-butylation was favourable under the conditions used (Table 2).



6

Scheme 2 (See Table 1). *Reagents and conditions:* i, $(HCHO)_x$, MOH, xylene, reflux for 16 h.



8a R = H
b R = Me

7

Scheme 3 (See Table 2). *Reagents and conditions:* i, $AlCl_3$–$MeNO_2$, ArH.

Table 1 Condensation of **5** with paraformaldehyde in the presence of alkali-metal hydroxides

Run	Alkali hydroxide	Product yield (%)[a] **6**
1	LiOH	10
2	NaOH	90
3	KOH	36
4	RbOH	26
5	CsOH	10

[a] Isolated yields are shown.

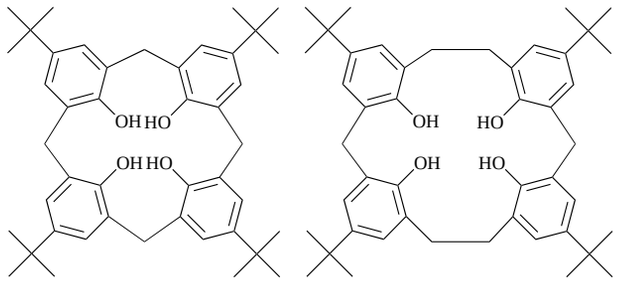
Table 2 $AlCl_3$–$MeNO_2$-catalysed trans-*tert*-butylation of tetrahydroxy[3.1.3.1]MCP **6**

Run	ArH	$AlCl_3$/**6** (mol/mol)	Temp. (T/°C)	Time (t/h)	Products yield (%)[a]
1	Benzene	3.8	20	1	0[b]
2	Benzene	3.8	20	24	30[c]
3	Benzene	3.8	20	48	80
4	Benzene[c]	3.8	Reflux	6	60
5	Toluene	3.8	Reflux	1	0[b]
6	Toluene	7.2	Reflux	3	20[d]

[a] Isolated yields are shown. [b] Starting compound **6** was recovered in 100% yield. [c] Recovery of **6** and formation of incompletely debutylated products were observed. [d] Formation of ring-cleavage reaction products due to the transbenzylation was observed.

The calixarenes show concentration-independent hydroxy stretching bands in the 3200 cm^{-1} region of their IR spectra and a signal at δ = 9–10 in their ^{1}H NMR spectra, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes.[1] The IR spectrum of the tetraol **6** shows the absorption of the hydroxy stretching vibration around 3254 cm^{-1}. The ^{1}H NMR spectra (in $CDCl_3$) exhibit signals for hydroxy groups around δ = 9.35. The ν_{OH} and δ_{OH} values for the tetraol **6** in which four hydroxy groups are close neighbours, show both a slightly higher frequency and upfield shift; this implies that the hydrogen bond is weaker than that in the corresponding calix[4]arene **9** (ν_{OH} = 3160 cm^{-1} and δ_{OH} = 10.2 in $CDCl_3$) and calix[6]arene (ν_{OH} = 3150 cm^{-1} and δ_{OH} = 10.5 in $CDCl_3$).[8] These results strongly suggest that the intramolecular hydrogen bonding associated with the hydroxy groups attached to diarylpropane units is weaker than that for those attached to diarylmethane units in the corresponding

Table 3 Selected ^{1}H NMR and IR spectral data for *p-tert*-butylcalix[4]arene **9**, *p-tert*-butyltetrahydroxy[2.1.2.1]MCP **10** and tetrahydroxy[3.1.3.1]MCPs **6** and **7**[a]



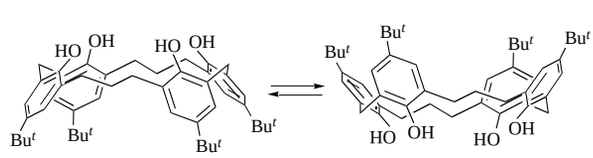
9 **10**

Compds	ν_{OH}(KBr)/cm^{-1}	δ_H($CDCl_3$) OH	T_c ($\Delta G_c^{\ddagger}$)
9	3160	10.2	52 (15.7)
10	3418	8.8	< -40[b]
6	3254	9.35	0 (12.5)
7	3485, 3529	9.5	0 (13.7)

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

tetrahydroxy[1.1.1.1]MCP (calix[4]arene). *p-tert*-Butyltetrahydroxy[2.1.2.1]MCP **10**,[5a] on the other hand, exhibits a higher frequency and upfield shift (ν_{OH} = 3418 cm^{-1} and δ_{OH} = 8.8 in $CDCl_3$) and much lower coalescence temperature value ($T_c < -40$ °C in $CDCl_3$–CS_2 1:3) than those in tetrahydroxy-[3.1.3.1]MCP **6** (T_c = 0 °C in $CDCl_3$). It is expected to be slightly more difficult to inhibit the rotation in tetrahydroxy-[3.1.3.1]MCP **6** than in **10** in spite of the inner cavity of **6** being apparently larger than that of tetrahydroxy[2.1.2.1]MCP **10** due to the diarylpropane linkage. This finding is easily rationalized by the staggered conformation of the diarylpropane-like [3.3]MCPs, which adopt a *syn*-conformation.[9] Hence the ring of tetrahydroxy[3.1.3.1]MCP **6** is more rigid than that of tetrahydroxy[2.1.2.1]MCP **10** because of the stronger intramolecular hydrogen bonding.

In comparison with the structural characteristics of a calix[4]arene whose cyclophane ring is composed of a 16-membered ring, the tetraol **6** has a cavity composed of a 20-membered ring. Gutsche and his co-workers[1a] have reported that the strong intramolecular hydrogen bond of calix[4]arene may fix the 'cone' shape conformation. A conformational inversion has also been observed in this system [free energy of activation for inversion $\Delta G^{\ddagger}$ = 15.7 kcal mol^{-1} (1 cal = 4.184 J)].[8] In the ^{1}H NMR spectrum for the macrocycle **6**, signals for *tert*-butyls, methylenes, aromatics and phenolic-OH are singlets at room temperature because of rapid conformational flipping. However, at −40 °C in $CDCl_3$ the singlet signal for methylene protons of $ArCH_2Ar$ splits into two sets of doublets (AB system, J_{AB} = 14 Hz) at δ 3.46 and 4.36; similarly, the benzyl methylene protons of the propane bridge are also observed to be split at δ 2.32 and 3.27. This behaviour is rationalized by the conformational inversion of the macrocycle **6** in the same way as Gutsche's tetrahydroxy[1.1.1.1]MCPs (calix[4]arenes).[8] The

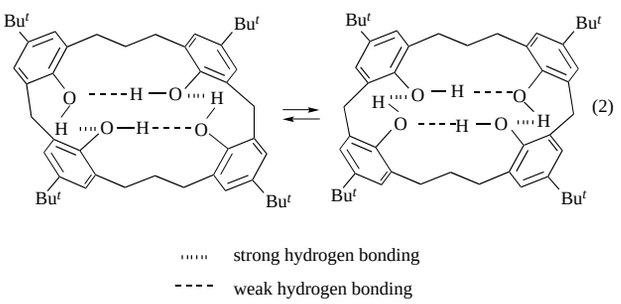


(1)

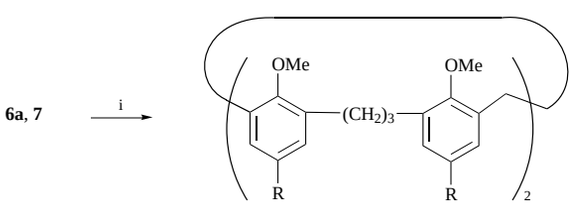
temperature of coalescence is 0 °C and the free energy of activation for inversion is estimated to be 12.5 kcal mol^{-1} (T_c = 0 °C, $\Delta\nu$ = 243.65 Hz). The rate of conformational ring flipping of **6** is faster than the NMR time-scale above this temperature. The value of the free energy of activation for inversion

is smaller than that of calix[4]arene (15.7 kcal mol^{-1}).[8] Thus, this indicates that the tetraol **6** is much more flexible than the calix[4]arene. This is attributed to the increase in ring size by the introduction of two propane-bridges in place of two methylene-bridges in the calix[4]arene.

It was also found that below −40 °C, the singlet signal for phenolic-OH at δ 9.35 splits into two sets of singlets at δ 9.15 and 10.12. This phenomenon seems to be attributed to the formation of two sets of non-equivalent phenolic-OHs because the conformational fluctuation of the cyclophane ring is frozen below this temperature by the intramolecular hydrogen bonding between the OH groups on facing benzene rings [see eqn. (2)]. The estimated free energy for fluctuation is 10.5 kcal mol^{-1} (T_c = −40 °C, $\Delta\nu$ = 261.72 Hz).



From dynamic ^{1}H NMR studies and considering the Corey–Pauling–Koltun (CPK) model of the macrocycle **6**, it is concluded that below 0 °C the conformation of the macrocycle **6** would be expected to be in a 'flattened 1,3-alternate form' as a result of calix[4]arene-like intramolecular hydrogen bonding between the OH groups. The same results have been obtained for the tetraol **7**. However, in comparison with **6**, **7** adopts a slightly more rigid conformation. These results seem to indicate that the bulky *tert*-butyl groups in **6** may weaken the intramolecular hydrogen bonding by creating a sterically crowded environment in the fixed conformation.



Scheme 4 *Reagents and conditions:* i, NaH–DMF–THF, room temp. for 1 h; ii, MeI, reflux for 3 h

On the other hand, in the spectra of the tetramethoxy derivative **11b**, which was prepared by methylation of **6** with MeI in the presence of NaH, the protons for the *tert*-butyl and methoxy groups, together with those of the methylene bridges, appeared as singlets even below −60 °C. The same phenomenon has been also observed for tetramethoxy derivative **11a** derived from the tetraol **7**. These findings suggest that **11** has a much more flexible structure than the macrocycles **6** and **7**.

Consideration of the structures of **6** and **7** based on CPK models suggests that the diphenylmethane moieties may have a 'stepped conformation' like *anti*-[2.2]metacyclophane.[10] The intramolecular hydrogen bonding is apparently much shorter for the diphenylmethane linkage than that for the diphenylpropane linkage, although weaker hydrogen bonding is still possible. It is concluded that the calix[4]arene-like intramolecular hydrogen bonds could fix the conformation of the tetrahydroxy-[3.1.3.1]MCPs **6** and **7** in a 'stepped-flattened 1,3-alternate form'.

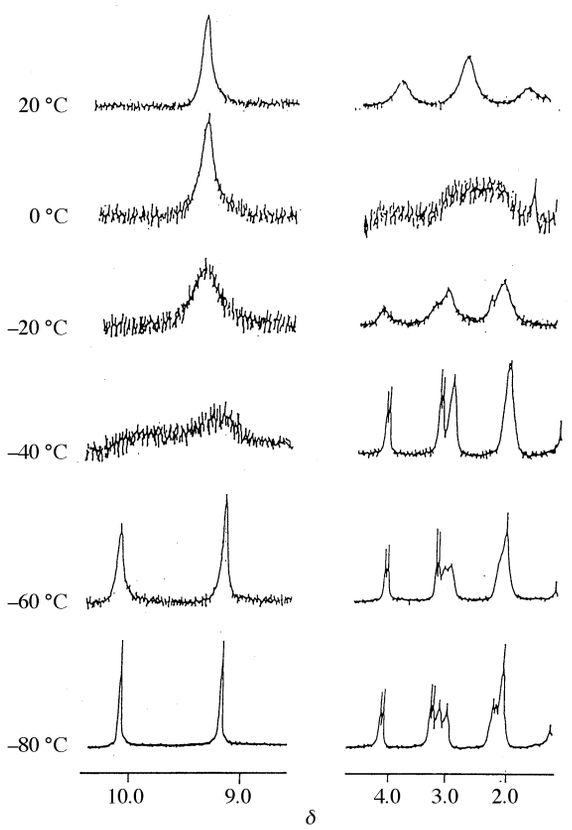
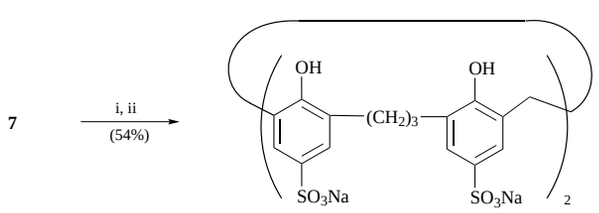


Fig. 1 Partial dynamic ^{1}H NMR spectra of the tetraol **6** in $CDCl_3$–CS_2 (1:3) at 270 MHz

One of the principal reasons for an interest in calixarenes is their potential for serving as enzyme mimics. If they are to operate in this capacity, however, it is necessary that they should carry functional groups of various types. Gutsche *et al.* reported that the *p*-*tert*-butylcalixarenes have proved to be excellent precursors for the introduction of functional groups into the *para*-position, since the *tert*-butyl group is easily removed by trans-alkylation.[1,11] For example, Shinkai *et al.* succeeded in preparing water-soluble calixarenes by introduction of sulfonate groups.[12] Initially, they prepared the corresponding *p*-nitro compound by treatment of *p*-sulfonatocalixarenes with nitric acid.[13] More recently, efficient direct nitration and ipso-nitration of *tert*-butylcalixarenes have been reported.[14] Thus, there is substantial interest in investigating the introduction of substituents at the *para*-position into tetrahydroxy[3.1.3.1]-MCP **7** in order to prepare novel host compounds.

In fact, the selective introduction of four sulfonate groups at the *para*-position of the tetraol **7** by electrophilic aromatic sulfonation has been shown to afford the desired compound **12** without rupture of the macrocyclic ring. The stability of multi-membered carbon skeletons was found to be an advantage. It permits the interconversion of functional groups without ring-opening side reactions such as those occurring with hexahomotrioxacalix[3]arenes and their ethereal linkages.[15] The inclusion properties of **12** for various guests will be reported in detail in the near future.



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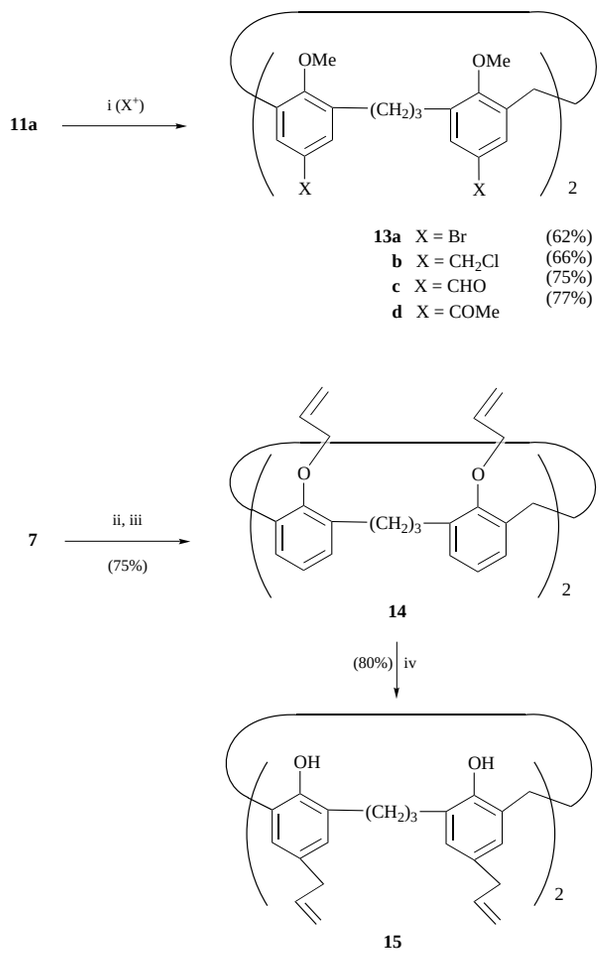
Scheme 5 *Reagents and conditions:* i, H_2SO_4, 60 °C for 6 h; ii, $Ba(OH)_2$, Na_2CO_3

Bromination of the tetramethyl ether **11a** with bromine in the presence of iron powder proceeds smoothly, affording the tetrabromo compound **13a** (62%). In a similar fashion, $TiCl_4$-catalysed Friedel–Crafts reactions such as chloromethylation with chloromethyl methyl ether, formylation with dichloromethyl methyl ether and acetylation with acetic anhydride yield the corresponding *para*-substituted [3.1.3.1]MCPs **13b–d** in good yield. These results seem to reflect the highly regioselective nature of the tetramethyl ether **11a** towards electrophilic aromatic substitution.

An alternative reaction sequence for the introduction of functional groups into the tetrahydroxy[3.1.3.1]MCPs has been developed which involves the conversion of the tetraol **7** into the tetraallyl ether **14**. When heated in diethylaniline, **14** undergoes a four-fold *para*-Claisen rearrangement to afford the *p*-allyl tetraol **15** (80%) as in the preparation of *p*-allylcalixarenes.[16]



Scheme 6 *Reagents and conditions:* i, *a*, Br_2, CCl_4, room temp. for 1 h; *b*, $ClCH_2OMe$, $TiCl_4$, CH_2Cl_2, room temp. for 24 h; *c*, Cl_2CHOMe, $TiCl_4$, CH_2Cl_2, room temp. for 24 h; *d*, Ac_2O, $TiCl_4$, CH_2Cl_2, room temp. for 24 h; ii, NaH, DMF, THF, room temp. for 1 h; iii, allyl bromide, reflux for 3 h; iv, *N*,*N*-diethylaniline, reflux (250 °C) for 6 h

Conclusions

We have prepared 9,16,25,32-tetrahydroxy[3.1.3.1]MCP **7** in 6 steps from anisole with the *tert*-butyl group as a positional protecting group in 27% overall yield using base-catalysed condensation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane **5** with formaldehyde in xylene. Intramolecular hydrogen bonding has been observed in the tetraols **6** and **7**, although it is slightly weaker than that in the corresponding calix[4]arenes because of the flexibility of the propane linkages.

We have also demonstrated de-*tert*-butylation of *tert*-butyl-[3.1.3.1]MCP **6** and the introduction of sulfonate groups on the upper rim of the tetraol **7** by direct four-fold sulfonation using sulfonic acid. Various substituents have been introduced at the *para*-positions of [3.1.3.1]MCP by direct electrophilic aromatic substitution of the tetramethoxy derivative **11a**. The *p*-allyl tetraol **15** was obtained in 80% yield by a four-fold *p*-Claisen rearrangement of the tetraallyl ether **14**. The stability of the multi-membered carbon skeletons was found to be an advantage in that it permits the interconversion of functional groups without ring-opening side reactions. The results consistently suggest that the metacyclophanes **6** and **7** are rich sources of a new type of host compounds. We are now presently testing their behaviour in this role.

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 GC.

Materials

Preparation of 1,3-bis(5-*tert*-butyl-2-methoxyphenyl)propane **4** has been previously described.[6c]

Preparation of 1,3-bis(5-*tert*-butyl-2-hydroxyphenyl)propane 5. To a solution of 1,3-bis(5-*tert*-butyl-2-methoxyphenyl)-propane **4** (10.0 g, 27.1 mmol) in dry CH_2Cl_2 (180 cm^3) at 0 °C was gradually added a solution of BBr_3 (4.6 cm^3, 48.7 mmol) in CH_2Cl_2 (120 cm^3) over a period of 30 min. After the reaction mixture had been stirred at room temp. for 24 h, it was poured into ice–water (200 cm^3) and extracted with CH_2Cl_2 (100 cm^3 × 2). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to afford crude **5** as a colourless solid. Recrystallization of this from hexane gave the *title compound* **5** (8.3 g, 90%) as prisms; mp 107–110 °C; ν_{max}(KBr)/cm^{-1} 3317 (OH); δ_H($CDCl_3$) 1.28 (18 H, s), 1.91–2.02 (2 H, m), 2.68 (4 H, t, *J* 7.6), 4.96 (2 H, s, exchangeable with D_2O), 6.70 (2 H, d, *J* 8.3), 7.07 (2 H, dd, *J* 2.4/8.3) and 7.15 (2 H, d, *J* 2.4); *m*/*z* 340 (M^+) (Found: C, 81.20; H, 9.40. $C_{23}H_{32}O_2$ requires C, 81.13; H, 9.47%).

Base-catalysed condensation: typical procedure

To a vigorously stirred mixture of **5** (5 g, 14.77 mmol) and paraformaldehyde (895 mg, 29.8 mmol) in *p*-xylene (150 cm^3) was added under nitrogen 5 M aq. NaOH (3 cm^3). After the reaction mixture had been heated at 80 °C for 3 h and refluxed for 16 h, it was cooled to room temp., acidified with 1 M aq. HCl (50 cm^3) and extracted with CH_2Cl_2 (2 × 300 cm^3). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo*. The residue was washed with hexane (50 cm^3 × 2) to afford crude **6** (4.69 g, 90%) as a colourless solid. Recrystallization of this from toluene gave 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]-metacyclophane **6** as *prisms*; mp 260 °C; ν_{max}(KBr)/cm^{-1} 3254 (OH); δ_H($CDCl_3$) 1.24 (36 H, s), 1.78 (4 H, br s), 2.85 (8 H, br s), 4.01 (4 H, s), 6.94 (4 H, d, *J* 2.4), 7.15 (4 H, d, *J* 2.4) and 9.35 (4 H, s, exchangeable with D_2O); *m*/*z* 704 (M^+) (Found: C, 81.70; H, 9.15. $C_{48}H_{64}O_4$ requires C, 81.77; H, 9.15%).

Trans-*tert*-butylation of 6: typical procedure

To a solution of **6** (2.0 g, 2.84 mmol) in benzene (80 cm^3) was added a solution of $AlCl_3$ (1.44 g, 10.80 mmol) in nitromethane (3.0 cm^3) at 20 °C. After being stirred at 20 °C for 48 h, the reaction mixture was poured into ice–water (100 cm^3) and extracted with benzene (100 cm^3 × 2). The combined extracts were washed with water (100 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue. This was chromato-

graphed on SiO_2 with benzene as the eluent to give 9,16,25,32-tetrahydroxy[3.1.3.1]metacyclophane **7** (1.09 g, 80%) as *prisms* (from $CHCl_3$–MeOH, 1:1); mp 170–175 °C; ν_{max}(KBr)/cm^{-1} 3529 and 3485 (OH); δ_H($CDCl_3$) 1.86 (4 H, br s), 2.90 (8 H, br s), 4.07 (4 H, s), 6.80 (4 H, t, *J* 7.3), 6.96 (4 H, dd, *J* 2.4 and 7.3), 7.14 (4 H, dd, *J* 2.4 and 7.3) and 9.50 (4 H, s, exchangeable with D_2O); *m*/*z* 480 (M^+) (Found: C, 79.43; H, 6.75. $C_{32}H_{32}O_4$ requires C, 79.97; H, 6.71%).

Similar treatment of **6** with toluene in the presence of $AlCl_3$–$MeNO_2$ afforded **7**. The yields and reaction conditions are given in Table 2. The formation of *tert*-butylbenzene **8a** and *tert*-butyltoluene **8b** was confirmed by GLC (conditions: Shimadzu gas chromatography, GC-14A, Silicone OV-1, 2 m, programmed temperature rise 12 °C min^{-1}; carrier gas nitrogen 25 ml min^{-1}).

Methylation of 7 with methyl iodide in the presence of NaH

A mixture of **7** (400 mg, 0.832 mmol) and 60% NaH (640.0 mg, 16.0 mmol) in dry tetrahydrofuran (36 cm^3) and DMF (9 cm^3) was stirred at room temperature for 1 h under nitrogen. Methyl iodide (1.29 cm^3, 14.18 mmol) was then added to the mixture after which it was heated under reflux for an additional 3 h. After cooling to room temperature, the reaction mixture was 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 evaporated *in vacuo* to afford crude **11a** as a colourless solid. Recrystallization from hexane–benzene (1:1) gave 9,16,25,32-tetramethoxy[3.1.3.1]metacyclophane **11a** (380 mg, 85%) as *prisms*; mp 263–266 °C; δ_H($CDCl_3$) 1.79 (4 H, m), 2.57 (8 H, t, *J* 7.3), 3.19 (12 H, s), 3.86 (4 H, s), 6.91 (4 H, d, *J* 7.3), 6.92 (4 H, dd, *J* 2.0 and 7.3) and 7.03 (4 H, dd, *J* 2.0 and 7.3); *m*/*z* 536 (M^+) (Found: C, 80.60; H, 7.46. $C_{36}H_{40}O_4$ requires C, 80.56; H, 7.51%).

6,13,22,29-Tetra-*tert*-butyl-9,16,25,32-tetramethoxy[3.1.3.1]-metacyclophane **11b** was prepared in a similar manner to that described above in 96% yield as *prisms* (hexane–benzene, 1:1); mp >300 °C; δ_H($CDCl_3$) 1.24 (36 H, s), 1.75–1.81 (4 H, m), 2.53 (8 H, t, *J* 7.3), 3.14 (12 H, s), 3.83 (4 H, s), 6.97 (4 H, d, *J* 2.4) and 7.01 (4 H, d, *J* 2.4); *m*/*z* 760 (M^+) (Found: C, 81.86; H, 9.44. $C_{52}H_{72}O_4$ requires C, 82.06; H, 9.53%).

Preparation of tetrasodium 9,16,25,32-tetrahydroxy[3.1.3.1]-metacyclophane-6,13,22,29-tetrasulfonate 12

Compound **7** (1.0 g, 2.08 mmol) was mixed with concentrated H_2SO_4 (10 cm^3) and the mixture was heated at 60 °C for 6 h, after which it was cooled and filtered. The precipitate recovered was dissolved in water (50 cm^3), and the solution was neutralized by $BaCO_3$. Precipitated $BaSO_4$ was filtered off and Na_2CO_3 was added to the filtrate to bring it to pH 8–9; the reaction mixture was then left overnight at room temperature. The precipitate was filtered to afford the *title compound* **12** (1.0 g, 54%) as a colourless powder; mp >300 °C; ν_{max}(KBr)/cm^{-1} 3425, 1601, 1592, 1486, 1297, 1163, 1119, 1049, 675, 667, 657, 639 and 620; δ_H(D_2O) 1.55 (4 H, m), 2.63 (8 H, t, *J* 8.4), 3.90 (4 H, s), 7.37 (4 H, d, *J* 2.4) and 7.38 (4 H, d, *J* 2.4).

Preparation of 6,13,22,29-tetrabromo-9,16,25,32-tetramethoxy-[3.1.3.1]metacyclophane 13a

To a solution of **11a** (100 mg, 0.19 mmol) in CCl_4 (10 cm^3) was added a small amount of iron powder and a solution of Br_2 (0.2 cm^3, 3.6 mmol) in CCl_4 (2 cm^3) at room temperature. After the reaction mixture had been stirred for 1 h, it was poured into water (10 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 2). The combined organic layer and extracts were washed with water (10 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue, which was washed with hexane (5 cm^3) to afford the *title compound* **13a** (100 mg, 62%) as a colourless solid. Recrystallization of this from benzene gave **13a** as *prisms*; mp 130–135 °C; δ_H($CDCl_3$) 1.79 (4 H, m), 2.50 (8 H, t, *J* 7.3), 3.22 (12 H, s), 4.20 (4 H, s), 7.07 (4 H, d, *J* 2.4) and 7.18 (4 H, d, *J* 2.4); *m*/*z* 848, 850 and 852 (M^+) (Found: C, 50.60; H, 4.46. $C_{36}H_{36}O_4Br_4$ requires C, 50.73; H, 4.26%).

Preparation of 6,13,22,29-tetrakis(chloromethyl)-9,16,25,32-tetramethoxy[3.1.3.1]metacyclophane 13b

To a solution of **11a** (100 mg, 0.19 mmol) and $ClCH_2OMe$ (0.1 cm^3, 1.44 mmol) in CH_2Cl_2 (10 cm^3) was added a solution of $TiCl_4$ (0.2 cm^3, 1.44 mmol) in CH_2Cl_2 (2 cm^3) at room temperature. After the reaction mixture had been stirred for 24 h, it was poured into ice–water (10 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 2). The combined organic layer and extracts were washed with water (10 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which, after column chromatography on silica gel (Wako, C-300; 50 g) with benzene–$CHCl_3$ (1:1) as eluent, afforded the *title compound* **13b** (92 mg, 66%) as a colourless solid. Recrystallization of this from benzene gave **13b** as *prisms*; mp >300 °C; δ_H($CDCl_3$) 1.80 (4 H, m), 2.55 (8 H, t, *J* 7.0), 3.19 (12 H, s), 3.83 (4 H, s), 4.50 (8 H, s), 6.97 (4 H, d, *J* 2.4) and 7.08 (4 H, d, *J* 2.4); *m*/*z* 728, 730, 732, 734 and 736 (M^+) (Found: C, 67.93; H, 6.22. $C_{40}H_{44}O_4Cl_4 \cdot C_6H_6$ requires C, 68.32; H, 6.23%).

Preparation of 6,13,22,29-tetraformyl-9,16,25,32-tetramethoxy[3.1.3.1]metacyclophane 13c

To a solution of **11a** (100 mg, 0.19 mmol) and Cl_2CHOMe (0.3 cm^3, 2.53 mmol) in CH_2Cl_2 (10 cm^3) was added a solution of $TiCl_4$ (0.2 cm^3, 1.44 mmol) in CH_2Cl_2 (2 cm^3) at room temperature. After the reaction mixture had been stirred for 24 h, it was poured into ice–water (10 cm^3). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 2). The combined organic layer and extracts were washed with water (10 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue which, after column chromatography on silica gel (Wako, C-300; 50 g) with benzene–$CHCl_3$ (1:1) as eluent, afforded the *title compound* **13c** (92 mg, 75%) as a colourless solid. Recrystallization of this from $CHCl_3$–MeOH (1:1) gave **13c** as *prisms*; mp >300 °C; ν_{max}(KBr)/cm^{-1} 1690 (C=O); δ_H($CDCl_3$) 1.83 (4 H, m), 2.57 (8 H, t, *J* 7.0), 3.23 (12 H, s), 3.93 (4 H, s), 7.47 (4 H, d, *J* 2.4), 7.57 (4 H, d, *J* 2.4) and 9.81 (4 H, s); *m*/*z* 648 (M^+) (Found: C, 72.03; H, 6.30. $C_{40}H_{40}O_8 \cdot$MeOH requires C, 72.33; H, 6.51%).

Preparation of 6,13,22,29-tetraacetyl-9,16,25,32-tetramethoxy-[3.1.3.1]metacyclophane 13d

To a solution of **11a** (200 mg, 0.37 mmol) and acetic anhydride (0.4 cm^3, 2.16 mmol) in CH_2Cl_2 (20 cm^3) was added a solution of $TiCl_4$ (1.0 cm^3, 8.64 mmol) in CH_2Cl_2 (3 cm^3) at room temperature. After the reaction mixture had been stirred for 24 h, it was poured into ice–water (10 cm^3) and the layers separated. The aqueous layer was extracted with CH_2Cl_2 (10 cm^3 × 2) and the combined organic layer and extracts were washed with water (10 cm^3 × 2), dried (Na_2SO_4) and evaporated *in vacuo* to leave a residue. This, when column chromatographed on silica gel (Wako, C-300; 50 g) with benzene–$CHCl_3$ (1:1) as eluent, afforded the *title compound* **13d** (200 mg, 77%) as a colourless solid. Recrystallization of this from $CHCl_3$–MeOH (1:1) gave **13d** as *prisms*; mp >300 °C; ν_{max}(KBr)/cm^{-1} 1690 (C=O); δ_H($CDCl_3$) 1.88 (4 H, m), 2.53 (12 H, s), 2.63 (8 H, t, *J* 7.0), 3.27 (12 H, s), 3.95 (4 H, s), 7.62 (4 H, d, *J* 2.4) and 7.69 (4 H, d, *J* 2.4); *m*/*z* 704 (M^+) (Found: C, 75.03; H, 6.70. $C_{44}H_{48}O_8$ requires C, 74.98; H, 6.86%).

Preparation of 9,16,25,32-tetraallyloxy[3.1.3.1]metacyclophane 14

A mixture of **7** (400 mg, 0.567 mmol) and 60% NaH (640.0 mg, 16.0 mmol) in dry tetrahydrofuran (36 cm^3) and DMF (9 cm^3) was stirred at room temperature for 1 h under nitrogen. Allyl bromide (1.20 cm^3, 14.18 mmol) was then added to the mixture after which it was heated under reflux for an additional 3 h.

After cooling to room temperature, the mixture was 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 evaporated *in vacuo* to afford a yellow oil. The excess of unchanged allyl bromide was removed from this by distillation under reduced pressure using a Kugelrohr apparatus and the residue was washed with hexane to afford the *title compound* **14** (400 mg, 75%) as a colourless solid. Recrystallization of this from $CHCl_3$–MeOH (1:1) gave **14** as *prisms*; mp 185–190 °C; $\delta_H(CDCl_3)$ 1.82 (4 H, br s), 2.51 (8 H, br s), 3.85 (8 H, d, *J* 5.5), 3.86 (4 H, br s), 4.78 (4 H, dd, *J* 1.8 and 10.4), 5.04 (4 H, dd, *J* 1.83 and 17.7), 5.46–5.62 (4 H, m), 6.89 (4 H, t, *J* 7.3), 6.92 (4 H, dd, *J* 1.2 and 7.3) and 7.02 (4 H, dd, *J* 1.2 and 7.3); *m*/*z* 640 (M^+) (Found: C, 82.63; H, 7.55. $C_{44}H_{48}O_4$ requires C, 82.46; H, 7.55%).

Preparation of 6,13,22,29-tetraallyl-9,16,25,32-tetrahydroxy-[3.1.3.1]metacyclophane 15

A solution of **14** (500 mg, 0.780 mmol) in *N*,*N*-diethylaniline (50 cm^3) was heated under reflux (250 °C) for 6 h in a flow of nitrogen after which it was cooled. Excess of *N*,*N*-diethylaniline was removed by distillation under reduced pressure (1 mmHg) to leave a residue which was washed with hexane (10 cm^3) to afford the *title compound* **15** (400 mg, 80%) as a colourless solid. Recrystallization of this from $CHCl_3$–MeOH (1:1) gave **15** as *prisms*; mp 95–100 °C; $\delta_H(CDCl_3)$ 1.80 (4 H, br s), 2.80 (8 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), 6.76 (4 H, d, *J* 2.0), 6.95 (4 H, d, *J* 2.0) and 9.31 (4 H, s); *m*/*z* 640 (M^+) (Found: C, 82.50; H, 7.39. $C_{44}H_{48}O_4$ requires C, 82.46; H, 7.55%).

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