Preparation and Conformational Properties of Tetrahydroxy[3.1.3.1]metacyclophanes

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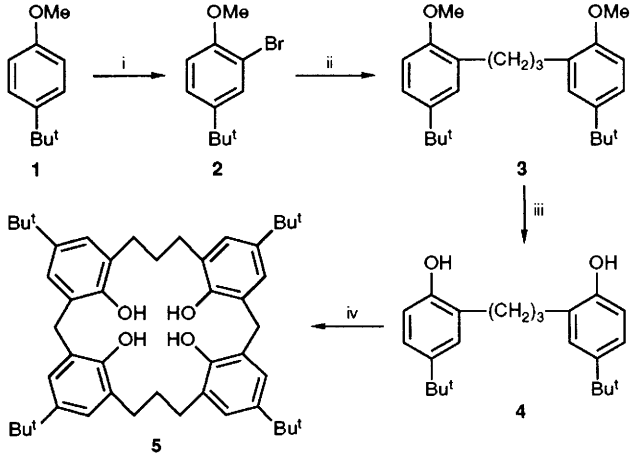
The preparation of a novel macrocyclic compound, tetrahydroxy[3.1.3.1]metacyclophane **5** by base-catalysed condensation of 1,3-(2,2′-dihydroxy-5,5′-di-*tert*-butyldiphenyl) propane **4** with formaldehyde in xylene in 90% yield is described and its conformational properties are discussed.

The calixarenes, [1$_n$]metacyclophanes prepared by base catalysed condensation of *p*-substituted phenols with formaldehyde are attractive matrices, their phenolic hydroxy groups being ordered in well shaped cyclic arrays due to strong intramolecular hydrogen bonds,[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 further binding units, we have developed a method to introduce functional groups into the bridged chains of calixarenes. In this communication, we report the preparation of propane-bridged calixarene-analogous macrocyclic metacyclophanes such as tetrahydroxy[3.1.3.1]metacyclophanes **5** and **7**.

The starting compound, 1,3-(2,2′-dihydroxy-5,5′-di-*tert*-butyldiphenyl)propane **4**† was prepared in three steps from *p*-*tert*-butylanisole **1** by using the *tert*-butyl group as a positional protecting group on the aromatic ring (Scheme 1).[5–9] Condensation of **4** with formaldehyde in xylene under basic conditions, using the same procedure that Gutsche used for the preparation of calix[6]arene,[1] to afford 6,13,22,29-tetra-*tert*-butyl-9,16,25,32-tetrahydroxy[3.1.3.1]metacyclophane **5**.‡ The optimum yield (90%) of **5** was obtained with NaOH as the base, whereas the use of other alkali metal hydroxides, *c.f.* LiOH, KOH, CsOH and RbOH, gave lower yields of 10, 36, 26 and 10%, respectively. This result suggests that Na^+ acts as a template alkaline metal for the formation of [3.1.3.1]metacyclophane **5**.

The ^{1}H NMR spectrum of macrocycle **5** shows single peaks for *tert*-butyl, methylene, aromatic and phenolic OH protons at room temperature due to rapid conformational flipping. However, at −40 °C in $CDCl_3$ the singlet signal of the methylene protons of $ArCH_2Ar$ splits into two sets of doublets (AB system, J_{AB} = 14 Hz) at δ 3.46 and 4.36 and the benzyl methylene protons of the propane bridge are also observed as a split pattern at δ 2.32 and 3.27. This behaviour is rationalized by the conformational inversion of macrocycle **5** in the same manner as Gutsche's tetrahydroxy[1.1.1.1]metacyclophane, that is calix[4]arene.[2] The temperature of coalescence is 0 °C and the free energy of activation for inversion is estimated to be 52.3 kJ mol^{-1} (T_c = 0 °C, Δν = 243.65 Hz). The value of the free energy of activation for inversion is smaller than that



Scheme 1 *Reagents*: i, Br_2, CCl_4 (74%); ii, (a) Mg, tetrahydrofuran (THF); (b) $Br(CH_2)_3Br$, hexamethylphosphoramide (HMPA), CuBr (62%); iii, BBr_3, CH_2Cl_2 (81%); iv, NaOH, $(HCHO)_n$, *p*-xylene (90%)

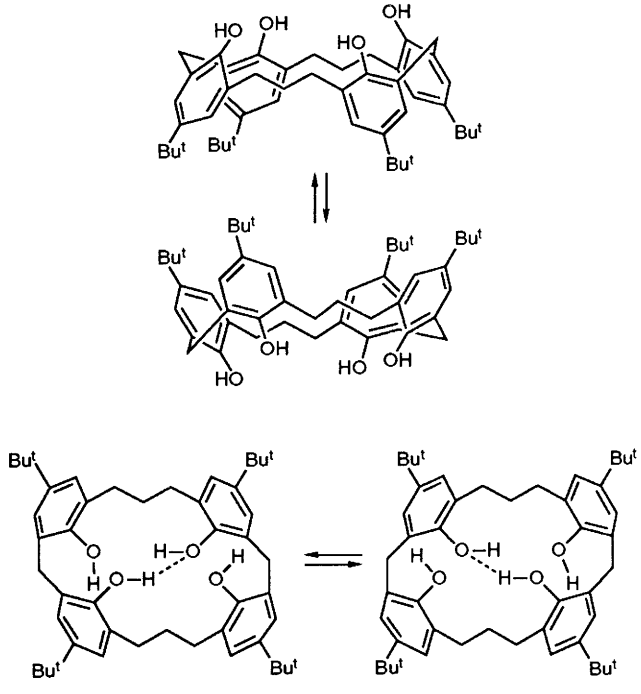
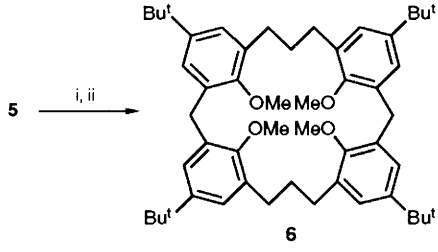


Fig. 1

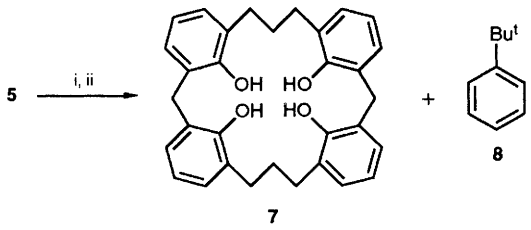


Scheme 2 *Reagents*: i, NaH, THF, dimethylformamide (DMF); ii, MeI (50%)

† **3**: Colourless prisms (from light petroleum) m.p. 62–65 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (18 H, s), 1.87–1.96 (2 H, m), 2.69 (4 H, t, *J* 7.8 Hz), 3.79 (6 H, s), 6.77 (2 H, d, *J* 8.3 Hz), 7.17 (2 H, dd, *J* 2.4 and 8.3 Hz) and 7.20 (2 H, d, *J* 2.4 Hz).

4: Colourless prisms (from hexane) m.p. 107–110 °C; IR (KBr) ν_{OH}/cm^{-1} 3853; ^{1}H NMR ($CDCl_3$) δ 1.29 (18 H, s), 1.94–2.03 (2 H, m), 2.69 (4 H, t, *J* 7.8 Hz), 4.96 (2 H, s), 6.71 (2 H, d, *J* 8.3 Hz), 7.09 (2 H, dd, J 2.4 and 8.3 Hz) and 7.16 (2 H, d, *J* 2.4 Hz).

‡ **5**: Colourless prisms (hexane) m.p. 260 °C; IR (KBr) ν_{OH}/cm^{-1} 3254; ^{1}H NMR ($CDCl_3$) δ 1.24 (36 H, s), 1.78 (4 H, m), 2.85 (8 H, br s), 4.01 (4 H, s), 6.94 (4 H, d, *J* 2.4 Hz), 7.15 (4 H, d, *J* 2.4 Hz) and 9.40 (4 H, s); *m*/*z* 704 (M^+).



Scheme 3 *Reagents*: i, $AlCl_3$–$MeNO_2$, benzene (80%)

of calix[4]arene (65.7 kJ mol^{-1}).[10] This is attributed to the increase of ring size by the introduction of the two propane-bridges into the two methylene bridges of calix[4]arene.

It was also found that below −40 °C, the singlet signal of the phenolic-OH at δ 9.40 splits into two singlets at δ 9.15 and 10.12. This phenomenon seems to be attributable to the formation of two sets of non-equivalent phenolic-OHs these are formed because the conformational fluctuation of the cyclophane ring is frozen below this temperature by the intramolecular hydrogen bonding between the two OH groups substituted on the benzene rings opposite to each other as shown in Fig. 1. The estimated free energy for fluctuation is 43.9 kJ mol^{-1} (T_c = −40 °C, Δν = 261.72 Hz).

From the dynamic ^1H NMR studies and considering the Corey–Pauling–Koltun (CPK) model of macrocycle **5**, it is concluded that below 0 °C the conformation of macrocycle **5** would be expected to be the 'flattened 1,3-alternate form' owing to intramolecular hydrogen bonding between the OH groups below 0 °C.

On the other hand, in the spectra of tetramethoxy derivative **6**,§ which was prepared by methylation of **5** with MeI (Scheme 2), protons of *tert*-butyl and methoxy groups and methylene bridges appeared each as singlets even below −60 °C. This indicates a much more flexible structure for **6** than macrocycle **5**. It is concluded that the calix[4]arene-like intramolecular hydrogen bonds can fix the conformation of tetrahydroxy[3.1.3.1]metacyclophane **5**.

It was also found that the $AlCl_3$–$MeNO_2$ catalysed *trans-tert*-butylation of **5** in benzene gave the desired tetrahydroxy[3.1.3.1]metacyclophane **7**¶ in 80% yield along with *tert*-butylbenzene **8**. However, using toluene as an acceptor for the *tert*-butyl groups failed. In this case ring cleavage reactions due to the transbenzylation occurred rather than trans-*tert*-butylation.

In conclusion, the propane-bridged metacyclophanes **5** and **7** could be useful sources of new types of host compounds.

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§ **6**: Colourless prisms (benzene) m.p. >300 °C; ^1H NMR ($CDCl_3$) δ 1.214 (36 H, s), 1.72–1.83 (4 H, m), 2.53 (8 H, t, *J* 7.3 Hz), 3.14 (12 H, s), 3.82 (4 H, s), 6.96 (4 H, d, *J* 2.4 Hz) and 7.01 (4 H, d, *J* 2.4 Hz); *m/z* 761 (M^+).

¶ **7**: Colourless prisms (hexane); m.p. 170–175 °C; IR (KBr) ν_{OH}/cm^{-1} 3529 and 3485; ^1H NMR ($CDCl_3$) δ 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 Hz), 6.96 (4 H, dd, *J* 1.5 and 7.3 Hz), 7.15 (4 H, dd, *J* 1.5 and 7.3 Hz) and 9.50 (4 H, s).

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