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The Synthesis and Probable Conformation of *m*-Xylenyl Capped Homocalix[3]arenes derived from a Trihydroxy[3.3.3]metacyclophane†

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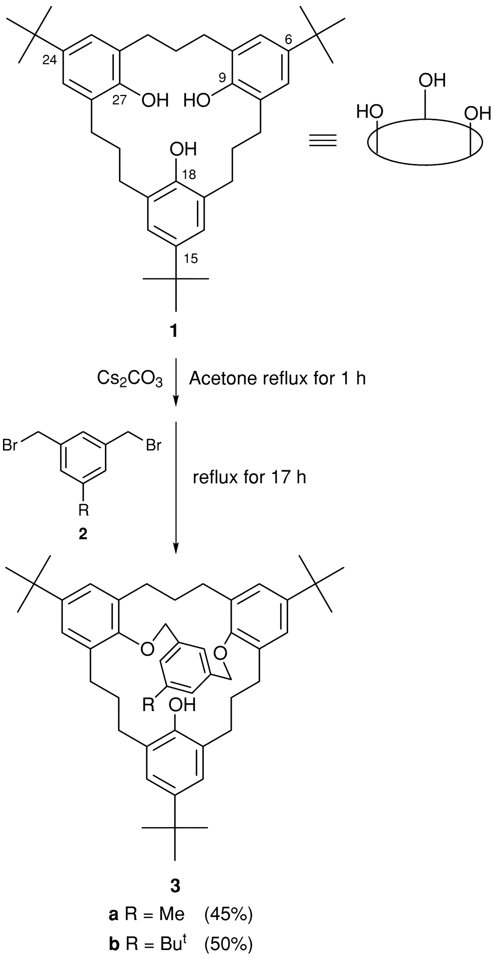
O-Benzylation of trihydroxy[3.3.3]metacyclophane with 3,5-bis(bromomethyl)toluene in the presence of Cs_2CO_3 affords a doubly-bridged macrocycle in 45% yield, in which structural characterization is also discussed.

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

In 1993, Biali and coworkers succeeded in the immobilization using two dialkyl phosphates which can react with six phenol groups of calix[6]arenes.[4] Later, Shinkai and coworkers reported the synthesis of doubly- and triply-bridged calix[6]arenes at the lower rim side by *O*-benzylation of phenolic hydroxyl groups with bis- and tris-(bromomethyl) reagents.[5,6]

However, there were few reports on the synthesis and the conformations regarding the doubly- and triply-bridged homocalix[3]arenes at the lower rim side by *O*-benzylations in spite of the construction of novel capsule type host molecules.[7] Thus, there is substantial interest in investigating the *O*-benzylation of the flexible [3.3.3]MCPs. Here, we describe the synthesis and structure of doubly-bridged [3.3.3]MCPs at the lower rim side by *O*-benzylation of phenolic hydroxyl groups with bis(bromomethyl) reagents.

O-Benzylation of the flexible macrocycle **1** with 1 equiv. of 3,5-bis(bromomethyl)toluene **2a** in the presence of NaH under THF reflux did not afford any product and the starting material **1** was returned quantitatively. However, when Cs_2CO_3 was used as base under acetone reflux, the desired 1,2-capped [3.3.3]MCP **3a** was obtained in 45% yield. Similarly, compound **3b** was prepared by *O*-benzylation of **1** with 3,5-bis(bromomethyl)-*tert*-butylbenzene **2b** in 50% yield (Scheme 1).



Scheme 1

The structures of **3a** and **3b** have been elucidated on the basis of their elemental analyses and spectral data. For instance, the mass spectral data for **3a** ($M^+ = 686$) strongly support an *m*-xylenyl capped [3.3.3]MCP macrocyclic structure. The ^1H NMR spectrum of **3a** shows resonances for the *tert*-butyl protons at δ 1.21 and 1.26 (relative intensity, 1:2) as a singlet, for the aromatic protons at δ 6.85 as a singlet and at δ 6.96, 7.01 as a doublet (J 2.4 Hz), and the hydroxy proton at δ 8.86 as a singlet indicating a di-*O*-substituted structure. Interestingly, a greater upfield shift for the aromatic internal proton of the *m*-xylenyl moiety at δ 4.95 was observed. This observation strongly suggests that in the actual conformation, the internal *m*-xylenyl aromatic proton is shielded by the opposite inverted benzene ring as shown in Fig. 1.

Furthermore, the resonance for the benzyl methylene protons of the *m*-xylenyl moiety appeared as a pair of doublets (δ 4.72 and 5.50, $J_{AB} = 13.7$ Hz) (relative intensity 1:1) and do not coalesce below 130 °C in $CDBr_3$. The energy barrier to flipping is > 25 kcal mol^{-1}. On the other hand, in the spectrum of the corresponding reference compound **5**, which was prepared by *O*-benzylation of 1,3-bis(5-*tert*-butyl-2-hydroxy-3-methylphenyl)propane **4** with 3,5-bis(bromomethyl)toluene **2a** in the presence of Cs_2CO_3 in 91% yield (Scheme 2), the benzyl methylene protons of the *m*-xylenyl moiety appeared each as a singlet even below –60 °C. A greater downfield shift for the aromatic internal proton of the *m*-xylenyl moiety at δ 7.85 was observed. These findings suggest that the conformation of the *m*-xylenyl moiety of **3a** is different from that of **5** and conformationally rigid below 130 °C due to the sterically crowded environment arising

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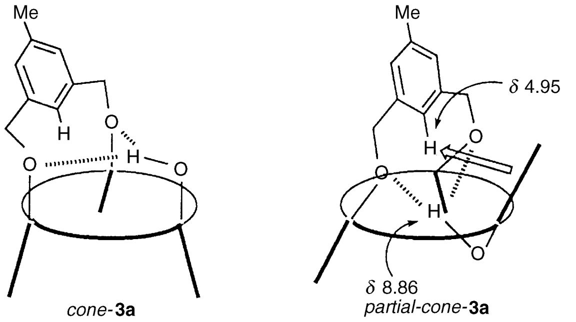


cone-**3a** *partial-cone*-**3a**

Fig. 1 Intramolecular hydrogen bonding in partially capped [3.3.3]metacyclophane **3a**

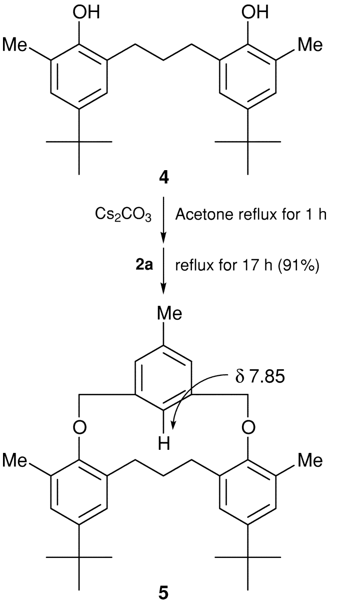
from the opposite inverted benzene ring and the intramolecular hydrogen bonding between the hydroxy group and two benzyloxy groups of **3a**.

The calixarenes show concentration-independent hydroxy stretching bands in the 3200 cm^{-1} region of the IR spectrum and a signal at δ 9–10 in the ^{1}H NMR spectrum, indicative of very strong intramolecular hydrogen bonding and the cyclic nature of calixarenes.[2] The IR (KBr) spectrum of **3a** shows the absorption for the hydroxy stretching vibration around 3410 cm^{-1}. The signals for ^{1}H NMR spectrum both correspond to cone or partial-cone conformer. Although the signal for hydroxy groups around δ 8.86 might strongly suggest a cone conformation, a greater upfield shift for the aromatic internal proton of the *m*-xylenyl moiety at δ 4.95 was observed. Similar findings were observed in the corresponding *tert*-butyl analog **3b**. Therefore, partially capped [3.3.3]MCPs **3a** and **3b** might adopt 'partial-cone' conformations.

In conclusion, an interesting result was obtained by the reaction of **1** with 3,5-bis(bromomethyl)benzenes **2** in the presence of Cs_2CO_3 affording a doubly-bridged [3.3.3]MCP **3** in moderate yield. Further studies of the structural and chemical properties of **3** are in progress.

Experimental

^{1}H NMR spectra were recorded at 270 MHz on a Nippon Denshi JEOL FT-270 NMR spectrometer in deuteriochloroform with Me_4Si as an internal reference. IR spectra were measured as KBr pellets on a Nippon Denshi JIR-AQ2OM spectrometer. Mass spectra were obtained on a Nippon JMS-01SA-2 spectrometer at 75 eV using a direct-inlet system.



Scheme 2

Materials.—The preparation of 6,15,24-tri-*tert*-butyl-9,18,27-trihydroxy[3.3.3]metacyclophane **1** was previously described.[1] 1,3-Bis(5-*tert*-butyl-2-hydroxy-3-methylphenyl)propane **4** was prepared by demethylation of 1,3-bis(5-*tert*-butyl-2-methoxy-3-methylphenyl)-propane[8] with BBr_3 in CH_2Cl_2 in 80% yield.

O-Benzylation of **1** *with* 3,5-*bis*(*bromomethyl*)*toluene* **2a** *in the presence of* Cs_2CO_3.—A mixture of **1** (100 mg, 0.174 mmol) and Cs_2CO_3 (567 mg, 1.74 mmol) in acetone (10 cm^3) was heated at reflux for 1 h. Then 3,5-bis(bromomethyl)toluene **2a** (49 mg, 0.174 mmol) was added and the mixture heated at reflux for 17 h. After cooling the reaction mixture to room temperature, it was filtered. The filtrate was concentrated and the residue was extracted with CH_2Cl_2 (2 × 100 cm^3) and washed with water (2 × 50 cm^3), dried (Na_2SO_4) and condensed under reduced pressure. The residue was washed with benzene to give crude **3a** (54 mg, 45%) as a colorless solid. Recrystallization from methanol–$CHCl_3$ (3:1) gave partially capped [3.3.3]metacyclophane **3a** as *prisms*; mp 155–158 °C; ν_{max} (KBr)/cm^{-1} 3410 (OH), 2980, 2867, 1484, 1363, 1262, 1187 and 1078; δ_H ($CDCl_3$) 1.21 (9 H, s), 1.26 (18 H, s), 1.55–1.75 (2 H, m), 2.15–2.6 (14 H, m), 2.40 (3 H, s), 3.20–3.25 (2 H, m), 4.72 (2 H, d, *J* 13.7 Hz), 4.95 (1 H, s), 5.50 (2 H, d, *J* 13.7 Hz), 6.85 (4 H, s), 6.96 (2 H, d, *J* 2.4 Hz), 7.01 (2 H, d, *J* 2.4 Hz) and 8.86 (1 H, s); *m*/*z* 686 (M$^+$) (Found C, 83.73; H, 8.83. $C_{48}H_{62}O_3$ requires C, 83.92; H, 9.1%).

Similarly compound **3b** was prepared by *O*-benzylation of **1** with 3,5-bis(bromomethyl)-*tert*-butylbenzene **2b** in the presence of Cs_2CO_3 in 50% yield as *prisms* [from methanol–$CHCl_3$(3:1)]; mp 185–187 °C; ν_{max} (KBr)/cm^{-1} 3478 (OH), 2965, 2935, 2902, 2863, 1481, 1463, 1362, 1192, 1021 and 874; δ_H ($CDCl_3$) 1.20 (9 H, s), 1.27 (18 H, s), 1.33 (9 H, s), 1.5–1.75 (2 H, m), 2.1–2.6 (14 H, m), 3.20–3.26 (2 H, m), 4.73 (2 H, , *J* 13.7 Hz), 5.00 (1 H, s), 5.48 (2 H, d, *J* 13.7 Hz), 6.83 (2 H, s), 6.97 (2 H, d, *J* 2.4 Hz), 7.02 (2 H, d, *J* 2.4 Hz), 7.06 (2 H, s) and 8.87 (1 H, s); *m*/*z* 728 (M$^+$) (Found C, 83.83; H, 9.23. $C_{51}H_{68}O_3$ requires C, 84.02; H, 9.4%).

Similarly compound **5** was prepared by *O*-benzylation of 1,3-bis(5-*tert*-butyl-2-hydroxyl-3-methylphenyl)propane **4** with **2a** in the presence of Cs_2CO_3 in 91% yield as *prisms* (from methanol); mp 174–176 °C; ν_{max} (KBr)/cm^{-1} 2962, 2903, 2864, 1483, 1462, 1361, 1300, 1195, 1121 and 871; δ_H($CDCl_3$) 1.29 (18 H, s), 1.7–1.85 (2 H, m), 2.33 (3 H, s), 2.39 (6 H, s), 2.37–2.45 (4 H, m), 4.97 (4 H, s), 6.97 (2 H, s), 7.02 (4 H, s) and 7.80 (1 H, s); *m*/*z* 484 (M$^+$) (Found C, 84.37; H, 9.23. $C_{34}H_{44}O_2$ requires C, 84.25; H, 9.15%).

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