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Facile Preparation and Molecular Structure of a Novel Metacyclophane

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Abstract: A novel 1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane (**2**) was prepared in 25% yield by Friedel–Crafts cyclization of 4-(2-methoxyphenyl)-2-methylbutan-2-ol (**1**) at $-78\,^{\circ}C$ using $TiCl_4$ as Lewis acid catalyst in anhydrous dichloromethane. The structure of cyclophane **2** was determined by single-crystal X-ray diffraction, and the impact of substrate concentration on the yield of macrocycle **2** was also examined. The study on the effect of substituents at the phenyl ring showed that the methoxy group in **1** is crucial for its trimerization to give the hexamethyl[3.3.3]metacyclophane derivative. Demethylation of **2** with BBr_3 gave 1,1,10,10,19,19-hexamethyl-5,14,23-trihydroxy[3.3.3]metacyclophane (**4**) in 96% yield, and its three hydroxyl groups provide the possible modification sites for further construction of supramolecular assemblies.

Keywords: 1-(3-Chloro-3-methylbutyl)-2-methoxybenzene; Friedel-Crafts cyclization; 1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane; 4-(2-methoxyphenyl)-2-methylbutan-2-ol

INTRODUCTION

Host–guest chemistry has been developing rapidly in the past several decades.[1] Many macrocyclic compounds were employed as host molecules. Particularly, cyclodextrins and calixarenes have attracted major interest, because they can form inclusion complexes with various hydrophobic guests in aqueous solution. Calixarenes fundamentally consist of phenol

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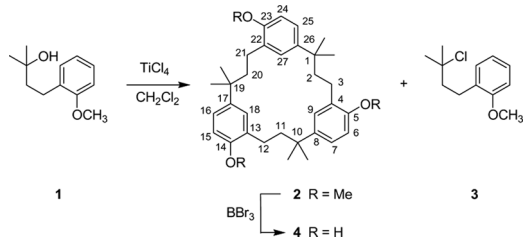
rings that are connected to each other by methylene bridges at meta positions of the ring, and thus, are considered as members of the metacyclophane (MCP) family. So far, there has been a lot of work on the syntheses, conformation and inclusion properties of macrocyclic cyclophanes[2] in which, the designing of artificial cavities of various sizes is possible. However, the preparations of macrocyclophanes are not easy, which usually contain several steps including oligomerization with low yields of 20% or less due to poor regiochemical control.[3,4] In this work, We report a one-step preparation of 1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane (**2**), its crystal structure and its demethylated derivative (**4**).

RESULTS AND DISCUSSION

1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane (**2**) was prepared in 25% yield from 4-(2-methoxyphenyl)-2-methylbutan-2-ol (**1**) by Friedel-Crafts cyclization using $TiCl_4$ as the catalyst[5] under $-78\,^{\circ}C$ in anhydrous dichloromethane. 1-(3-chloro-3-methylbutyl)-2-methoxybenzene (**3**) was also obtained in 14% yield due to nucleophilic substitution of hydroxyl group in **1** by chloridion. Demethylation of **2** was carried out by reaction with BBr_3 leading to 1,1,10,10,19,19-hexamethyl-5,14,23-trihydroxy[3.3.3]metacyclophane (**4**) in 96% yield. The three hydroxyl groups in **4** provide the possible modification sites for further construction of supramolecular assemblies.



The molecular structure of **2** was determined by single crystal X-ray crystallographic analysis (Fig. 1). Three phenyl rings incline into the cavity with different dihedral angles with the mean plane of the molecule and three methoxy groups pointing outward. Both molecules' bond angles and bond lengths are unexceptional.

The impact of substrate concentration on the yield of macrocycle **2** was also examined. As shown in Table 1, the yields of product **2** did

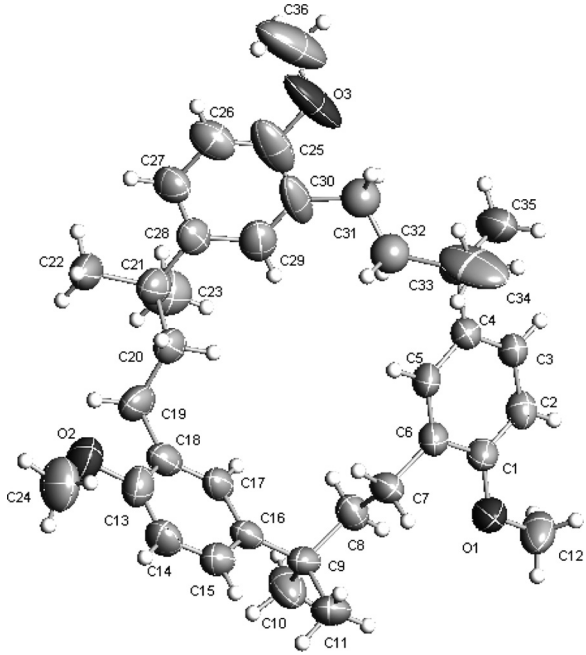


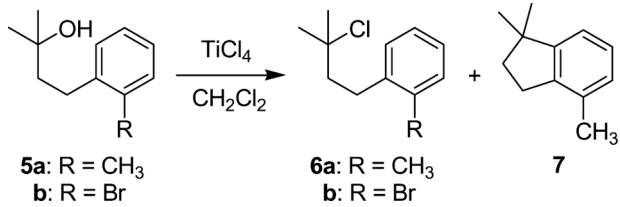
Figure 1. Molecular structure of compound **2**. Selected atom distances in Å: C(5)–C(17), 5.206; C(17)–C(29), 5.443; C(29)–C(5), 4.895; C(5)–C(20), 5.737; C(17)–C(32), 6.380; C(29)–C(8), 6.351; C(2)–C(14), 8.863; C(14)–C(26), 8.899; C(26)–C(2), 9.257; O(1)–O(2), 9.387; O(2)–O(3), 9.395; O(3)–O(1), 10.123; C(12)–C(24), 11.564; C(24)–C(36), 11.057; C(36)–C(12), 12.475.

not change very much with the concentration range of **1** from 1.1 to 2.7 mg/mL. However, further increasing of the substrate concentration to 3.6 mg/mL was obviously unfavorable to the formation of **2**, probably because of the easy formation of oligomers or polymers. A big spot with $R_f = 0$ (Eluent: petroleum ether-EtOAc (20:1 v/v)) was observed by TLC monitor in every case.

Table 1. Distributions of products **2** and **3** under different substrate concentration (HPLC yield%)

Substrate **1** / CH_2Cl_2 (mg / mL)	Product **2**	Product **3**
111/100 = 1.1	25%	16%
105/50 = 2.1	26%	13%
400/150 = 2.7	27%	15%
108/30 = 3.6	14%	16%

The scope of the present synthetic method was further investigated by taking 4-(2-substituted phenyl)-2-methylbutan-2-ol (**5a**,**b**) having a weak electron-donating (methyl) or electron withdrawing (bromo) group, as the reactants under the same conditions. The cyclization of **5a** gave the chlorinated product, 1-(3-chloro-3-methylbutyl)-2-methylbenzene (**6a**), and an intramolecular cyclization product, 1,1,4-trimethyl-2,3-dihydro-1*H*-indene (**7**), in 40% and 51% yields, respectively. In the reaction of **5b**, only a chlorinated product, 1-(3-chloro-3-methylbutyl)-2-bromobenzene (**6b**), was obtained in 43% yield, while some very polar unidentified matters were also observed on silica gel TLC plate (R_f value = 0 with ethyl acetate as eluent). No hexamethyl[3.3.3]metacyclophane derivatives were observed in the reactions of these two substrates with either methyl or bromo substituent at the benzene ring, which clearly showed that the methoxy group of **1** plays an important role in its trimerization to give the hexamethyl[3.3.3]metacyclophane derivative.



In summary, a facile synthesis of 1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane (**2**) and 1,1,10,10,19,19-hexamethyl-5,14,23-trihydroxy[3.3.3]metacyclophane (**4**) was realized from 4-(2-methoxyphenyl)-2-methylbutan-2-ol (**1**) by Friedel–Crafts cyclization and demethylation. The comparison of the substituent effect in the reactions of substrate **1** and **5a,b** clearly demonstrated that the methoxy group of **1** is crucial for its trimerization to give the corresponding hexamethyl[3.3.3]metacyclophane derivative. Further work will focus on the structural properties of these new macrocycles and utilizing them for the construction of supramolecular assemblies.

EXPERIMENTAL

Melting points were uncorrected. Reactions were monitored by TLC on 0.2-mm silica-gel plates, and the spots were visualized by ultraviolet light. Flash-column chromatography was performed on silica gel (300–400 mesh). ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer at 300.13 and 75.47 MHz, respectively, and the solvent used was $CDCl_3$ unless indicated. All chemical shifts were reported in δ units with reference to TMS (^{1}H) or the signals of the solvent (^{13}C).

Mass spectra were taken on an HP5989A, Agilent 5973N MSD (EI), or Agilent LC/MSD spectrometer (ESI). High resoultion mass spectra (HRMS) data were determined on a Waters Micromass GCT spectrometer.

Cyclization of Compound 1 with $TiCl_4$

A solution of **1** (400 mg, 2.06 mmol) in 150 mL of anhydrous CH_2Cl_2 was added dropwise over a period 1.5 h to a solution of $TiCl_4$ (0.8 mL, 1.376 g, 7.25 mmol) in 8 mL of anhydrous CH_2Cl_2 with stirring at $-78\,^{\circ}C$ under an argon atmosphere. The reaction mixture changed into red gradually and was stirred at room temperature overnight after addition was complete. Then it was poured into saturated aqueous $NaHCO_3$, and the layers were separated. The aqueous layer was extracted with EtOAc (3×30 mL), and the combined organic phase was washed with H_2O (3×20 mL) and brine (20 mL) and dried over Na_2SO_4. After removal of the volatiles in vacuo, the residue was purified by flash column chromatography on silica gel (petroleum ether, petroleum ether-AcOEt (20:1 v/v)) to give compound **3** as a clear oil (60 mg, 14%): ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.65 (s, 6H, CH_3), 2.01 (t, $J = 7.8$ Hz, 2H, 3-H), 2.80 (t, $J = 8.4$ Hz, 2H, 4-H), 3.82 (s, 3H, OCH_3), 6.83–6.89 (m, 2H, 3′-H, 5′-H), 7.14–7.20 (m, 2H, 4′-H, 6′-H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 157.39, 130.12, 129.73, 127.18, 120.45, 110.20, 71.047, 55.22, 45.98, 32.34, 29.69, 26.24. MS (EI) m/z (%): 212 (M^+, 9.44), 176 (9.84), 161 (16.31), 121 (68.89), 91 (100.00). HRMS: Calcd for $C_{12}H_{17}OCl$: 212.0968; Found: 212.0974. Compound **2** as white prisms (90 mg, 25%): mp: 144–146 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.30 (s, 18H), 1.92–1.98 (m, 6H), 2.42–2.48 (m, 6H), 3.82 (s, 9H), 6.77 (d, $J = 8.1$ Hz, 3H), 7.13–7.16 (m, 6H).^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.15, 141.41, 131.12, 126.62, 123.57, 108.39, 60.40, 55.28, 43.65, 37.21, 29.47, 25.43, 21.07, 14.19. ESI-MS m/z (%): 546.40 ($M + NH_4^+$, 100).

X-ray Crystal Structure Determination of 1,1,10,10,19,19-hexamethyl-5,14,23-trimethoxy[3.3.3]metacyclophane (2)

Crystals of compound **2** suitable for single-crystal X-ray diffraction were grown by slow evaporation of an ethyl acetate solution of **2**. Crystal with dimensions of 0.497 mm × 0.236 mm × 0.135 mm was selected and mounted on a Bruker Smart CCD diffractometer with graphite monochromatized Mo $K\alpha$ radiation ($\lambda = 0.071073$ nm). Diffraction data were collected using ω-2θ scans at room temperature (293 K). A perspective view of the structure is depicted in Figure 1. Empirical formula: $C_{36}H_{48}O_3$. Formula weight: 528.74. Crystal system: orthorhombic. Space

group: Pca2(1). Unit cell dimensions: $a = 24.763\ (4)$ Å, $b = 11.0549\ (17)$ Å, $c = 11.5301\ (18)$ Å, $V = 3156.4\ (8)$ Å^3. Theta range for data collection is from 1.64 to 25.49°. $Z = 4$. $Dc = 1.113\,g/cm^3$. $F(000) = 1152$. Refinement method: full-matrix least-squares on F^2. Goodness-of-fit on F^2: 0.851. Final R indices [$I > 2\sigma\ (I)$]: 0.0786, 0.2028. R indices (all data): 0.1425, 0.2301. Largest diff. peak and hole: 0.667 and $-0.294\,e/nm^3$.

Full crystallographic details have been deposited at Cambridge Crystallographic Data Centre (CCDC). Any request to the CCDC for this material should quote the full literature citation and the reference number CCDC 653771.

1,1,10,10,19,19-hexamethyl-5,14,23-trihydroxy[3.3.3]metacyclophane (4)

To a solution of **2** (80 mg, 0.15 mmol) in 2 mL of dry CH_2Cl_2, BBr_3 (0.3 mL, 3 M in CH_2Cl_2) was added dropwise with stirring at − 78 °C under an argon atmosphere. After addition was complete, the reaction mixture was warmed to room temperature and stirred for another 2.5 h. The mixture was then added to ice water, and the precipitate was filtered. The aqueous mixture was extracted with CH_2Cl_2 (3×20 mL). The organic layer was washed with water and brine, dried over Na_2SO_4, and evaporated to leave compound **4** as a pale yellow solid (70 mg, 96%): mp 118–120 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 6H, CH_3), 1.98 (t, $J = 8.2$ Hz, 6H), 2.44 (t, $J = 8.2$ Hz, 6H), 4.57 (br, 3H), 6.70 (d, $J = 8.2$ Hz, 3H), 7.07 (d, $J = 13.3$ Hz, 6H). MS (EI) m/z (%): 486 (M^+, 18.46), 323 (44.04), 203 (30.95), 163 (100.00), 155 (24.70), 147 (62.56). HRMS: calcd. for $C_{33}H_{42}O_3$: 486.3134; found: 486.3114.

Reaction of Compound 5a with $TiCl_4$

Following a similar procedure for the cyclization of compound **1** with $TiCl_4$, **6a** and **7** ($R_f = 0.6$ and 0.8, on silica-gel plate with petroleum ether as the eluent) were afforded from **5a** as colorless liquids in 40% and 51% yields respectively. **6a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.27 (s, 6H, CH_3), 1.94 (t, $J = 7.1$ Hz, 2H, 2′-H), 2.31 (s, 3H, CH_3), 2.83 (t, $J = 7.3$ Hz, 2H, 1′-H), 6.98–7.01 (m, 2H, 3-H, 5-H), 7.11–7.16 (m, 2H, 4-H, 6-H). MS (EI) m/z (%): 196 (M^+, 5.61), 145 (39.28), 85 (45.36), 71 (70.03), 69 (43.33), 57 (100.00), 55 (49.78), 43 (75.40), 41 (59.99). **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.26 (s, 6H, 1-CH_3), 1.93 (t, $J = 7.5$ Hz, 2H, 2-H), 2.27 (s, 3H, 4-CH_3), 2.82 (t, $J = 7.4$ Hz, 2H, 3-H), 6.98–7.00 (m, 2H, 7-H, 5-H), 7.10–7.14 (m, 1H, 6-H).[6]

Reaction of Compound 5b with $TiCl_4$

Following a similar procedure for the cyclization of compound **1** with $TiCl_4$, **6b** was obtained from **5b** as a colorless liquid in 43% yield: ^1H NMR (400 MHz, $CDCl_3$) δ: 1.70 (s, 6H, CH_3), 2.09–2.13 (m, 2H, 2′-H), 2.87–2.91 (m, 2H, 1′-H), 7.24–7.28 (m, 2H, 3-H, 5-H), 7.34–7.37 (m, 2H, 4-H, 6-H). MS (EI) m/z (%): 260 (M^+, 1.00), 91 (30.98), 85 (44.95), 83 (25.76), 71 (78.93), 69 (26.35), 57 (100.00), 55 (35.69), 43 (54.23).

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