Synthesis and Characterization of [3.3.3.3]Metacyclophane†

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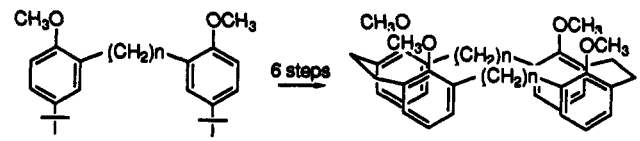
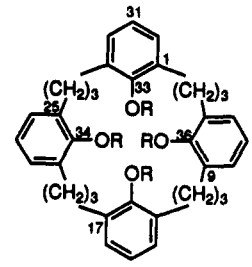
Because of their potential in host–guest chemistry cyclophanes have attracted much attention.[1] An important subgroup of this family, the metacyclophanes, have been dominated by the chemistry of the calixarenes ([1.1.1.1]metacyclophane).[2] Recently, interest has been shown in the synthesis of [2.*n*.2.*n*]metacyclophanes[3] (*n* = 1–3) **2** (Scheme I). Formation of **2** by cyclization of precursor dimers utilizing sulfur as a nucleophile and then ring contraction via SO_2 extrusion is a classic way to prepare cyclophanes.[4] However, use of this method limits one set of opposite methylene bridges to two carbons and requires six additional steps to synthesize **2** after preparation of the initial dimer **1**. Due to the needs of an ongoing project (whose goal is the preparation of synthetic blood substitutes), we required access to [3.3.3.3]metacyclophane **3**. We felt this structure would not be easily prepared by the SO_2 extrusion method, and we now report on a different strategy that leads to its successful five-step synthesis.

Our synthetic path is presented in Scheme II. Anisole **4** was prepared in 70–80% yields by reaction of 2-(1-methoxy)phenylmagnesium bromide with 1,3-dibromopropane using catalytic amounts of Li_2CuCl_4,[5] with little or no Wurtz product formation. In turn, **4** was added to lithiated anisole in THF at 0 °C, and the mixture was then allowed to warm to room temperature overnight, producing the dimer **5** with yields in excess of 70%.[6] Modification of Eaton's method[7] for halogenolysis of arylmercury compounds produced dibromo dimer **6** in 89–94% yield. When the dibromo dimer was reacted with magnesium, and then added to the same THF solution of dibromide and Li_2CuCl_4 as above, **7** was prepared in 43% yield. The dimer **7** was extremely hygroscopic, and it was necessary to first subject it to azeotropic distillation before continuing on to the next step.

Both the dianion of **5** (formed from **6** and 2 equiv of *t*-BuLi in Et_2O, −78 °C) and dimer **7** in THF were added slowly[8] to a THF solution at 0 °C over a 3-h period. After addition was complete, the reaction mixture was allowed to warm to room temperature and stirred an additional 24 h. Purification using a Chromatotron[9] yielded several products; identifiable compounds included small amounts of **5** and starting material **7**, linear tetramer **8** (M^+ = 672/674) (Figure 1), linear hexamer **9** (M^+ = 848), and a mixture

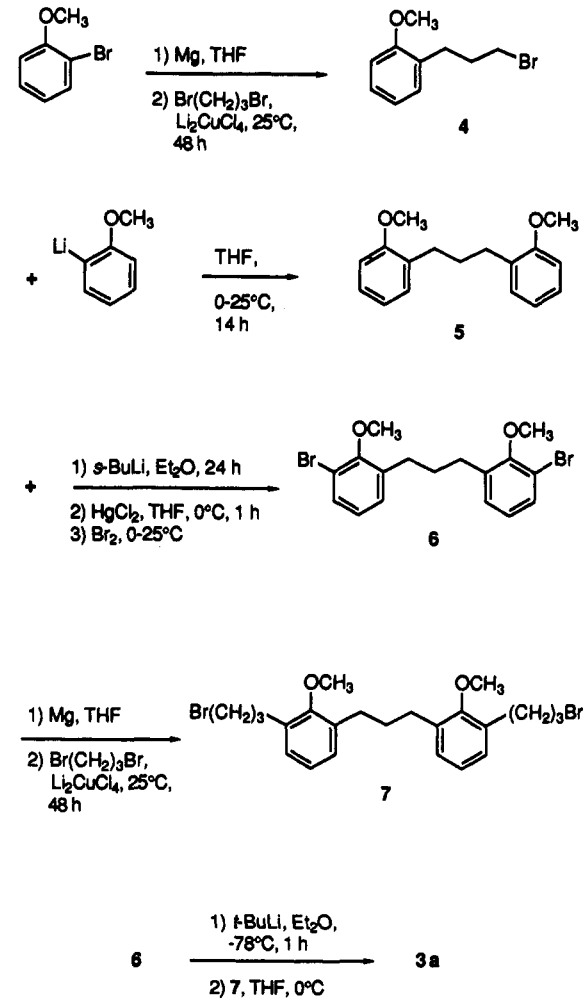
Scheme I





3a: R=CH_3
3b: R=H

Scheme II



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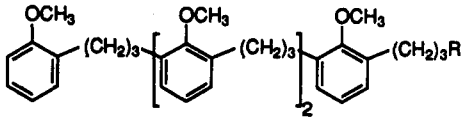

8 R=Br
10 R=H

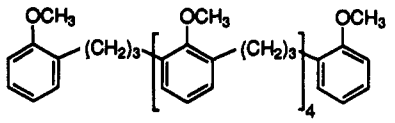

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Figure 1. Linear byproducts formed in the reaction of 6 and 7 to produce **3a**.

Table I. Minimization Calculations[a] for [3.3.3.3]Metacyclophanes 3a and 3b

isomer	conformation	energy (kcal)
3a (methoxymetacyclophane)		
	cone	11.06
	partial cone	20.29
	1,2 alternate	21.30
	1,3 alternate	27.14
3b (hydroxymetacyclophane)		
	cone	8.99
	partial cone	16.65
	1,2 alternate	12.11
	1,3 alternate	17.71

[a] ALCHEMY III force field calculations with gradient cutoff set at 0.01. Cone, partial cone, 1,2-alternates, and 1,3-alternates refer to the up and down orientations of ring oxygens as applied to calixarenes (see ref 13).

of cyclophane **3a** and linear tetramer **10**. While cyclophane **3a** could be purified from this mixture with the tedious application of analytical HPLC (**3a** was 15–20% of the total product mixture), we were unable to purify **10**. However, a 50/50 mixture (determined from ^{1}H NMR integration of the methoxy peaks) of **10** and **3a** gave a satisfactory elemental analysis, and its low-resolution mass spectra exhibited a large M^+ peak at 592 (**3a**), a small M^+ peak at 594 (**10**), and a large M – propyl peak at 552 (**10**), leading us to believe the structure of **10** is as shown in Figure 1 (the mass spectrum of pure **3a** does not exhibit the 552 peak, although it does exhibit a M + 2 peak at 594). Compounds **8** and **9** are simple alkylation products, and presumably **10** was formed via lithium–bromine exchange of (lithiated) **8** with excess *t*-BuLi present in the reaction mixture followed by protonation upon workup.

CPK analysis and ALCHEMY III[10] force field calculations (Table I) show the ring to be extremely flexible, and like the [2.3.2.3]metacyclophane **1c**,[3] **3a** exhibits only one methoxy resonance (methoxy[2.2.2.2]metacyclophane,[3] 2.9 ppm; **1c**, 3.2 ppm; **3a**, 3.45 ppm). In general, the structure of the low-energy conformation resembles a two-sided open-ended barrel with the oxygens all on one side (Table I).

Cyclophane **3a** was subjected to BBr_3·$(CH_3)_2S$ in refluxing 1,2-dichloroethane[11] resulting in phenolic [3.3.3.3]-metacyclophane **3b** in 65–80% yield. Since the mixture of **3a** and **10** was impossible to purify without the extensive use of analytical HPLC (normal phase, 97/3 hexane/ethyl acetate), the usual procedure was to directly demethylate the crude mixture collected from the chromatotron, which was then easily purified by preparative HPLC (C18, 70/30 acetonitrile/water).[12] The ^{1}H NMR spectrum of **3b** exhibits the phenolic hydrogens as a broad singlet at 6.01 ppm in $CDCl_3$, resonances far enough downfield to be suggestive of some intramolecular hydrogen bonding. The demethylated counterpart of dimer **5** (**5**, BBr_3 in CH_2Cl_2 overnight, 80% yield) exhibits phenolic hydrogens at 4.1 ppm in $CDCl_3$, and when the solvent is replaced by acetone-d_6 the phenolic resonances are shifted downfield to 8.1 ppm, as are the phenolic hydrogens in **3b**, showing intermolecular hydrogen bonding with the solvent. This correlates with ALCHEMY III force field calculations that describe **3b**'s low-energy form as a "flattened barrel" with all four phenolic hydrogens pointed in the same direction. In this form, CPK analysis shows one and possibly two of the phenolic hydrogens could engage in intramolecular hydrogen bonding, producing the averaged phenolic ^{1}H NMR signal.

Extending the above method to the preparation of [*n.n.n.n*]metacyclophanes where $n > 3$, along with the binding of these cyclophanes to other macrocycles for the preparation of unique molecular receptors, is currently in progress.

Experimental Section

All melting and boiling points are uncorrected. ^{1}H NMR spectra were recorded at 300 MHz in $CDCl_3$ with Me_4Si as an internal reference unless otherwise specified. Low-resolution mass spectra were obtained at 70 eV using a Finnigan Incos direct inlet system. HRMS utilized a VG ZAB system. Column chromatography was carried out on silica gel (Davisil 633). HPLC utilized an Analtech analytical econosphere silica and C_{18} column, 4.6-mm i.d., 250-mm length, and an Analtech preparative econosphere silica and C_{18} column, 22.5-mm i.d., 250-mm length. Lithium reagents were assayed utilizing 1,10-phenanthroline according to a literature procedure.[14]

1-Bromo-3-(2-methoxyphenyl)propane (4). 2-Bromoanisole (6.0 g, 32.1 mmol) was added at a rate of 0.75 mL/min to a solution of Mg turnings (0.86 g, 35.3 mmol) in 12 mL of THF and the resulting mixture allowed to reflux for 1 h. The reaction mixture was then cannulated into a stirred solution containing 1,3-dibromopropane (6.48 g, 32.1 mmol) and 4.0 mL of 0.1 M Li_2CuCl_4/THF cooled to 0 °C. The mixture was allowed to gradually warm to rt, and after 3 h another 4.0 mL of 0.1 M Li_2CuCl_4/THF was added. After 6 h a third portion of 2.0 mL of 0.1 M Li_2CuCl_4/THF was added. After 48 h the reaction was quenched with H_2O (100 mL) and then extracted with CH_2Cl_2 (3 × 100 mL). The organic portion was washed with 10% HCl (100 mL), H_2O (100 mL), and brine (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was fractionally distilled using a 10-cm Vigreux column under reduced pressure to yield 5.9 g (80%) of **4**: bp 102 °C (1.0 mmHg), (lit.[15] 145 °C (5.0 mmHg)); UV (CH_2Cl_2) λ_{max} (ϵ) 230 (2058), 272 (2499); ^{1}H NMR δ 2.08–2.20 (m, 2H), 2.75 (t, 2H, J = 7.4 Hz), 3.38 (t, 2H, J = 6.8 Hz), 3.79 (s, 3H), 6.80–6.91 (m, 2H), 7.10–7.23 (m, 2H); HRMS *m/z* calcd for $C_{10}H_{13}BrO$ 228.0150, found 228.0151.

1,3-Bis(2-methoxyphenyl)propane (5). A 36.3-mL sample of 1.67 M *t*-BuLi (60.6 mmol) was added to a −78 °C solution of

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2-bromoanisole (5.3 g, 28.3 mmol) in 85 mL of THF at a rate of 0.67 mL/min. The solution was stirred at −78 °C for 1.5 h. In a separate flask, 85 mL of THF, TMED (3.3 g, 28.4 mmol), and 4 (7.5 g, 32.8 mmol) were cooled to 0 °C. The lithiated species was then cannulated into this solution. The mixture was stirred for 16 h, gradually allowed to warm to rt, and then quenched with H_2O (100 mL) and extracted with Et_2O (2 × 75 mL). The organic portion was washed with 10% HCl (100 mL), H_2O (100 mL), and saturated NaCl (100 mL), dried over Na_2SO_4, and concentrated under vacuum to yield a yellow solid. Recrystallization from EtOH yielded 5.18 g of 5 (20.2 mmol, 72%) as white crystals: mp 53–54 °C; UV (CH_2Cl_2) λ_{max} (ϵ) 230 (6550), 272 (4588); ^1H NMR δ 1.86–1.95 (m, 2H), 2.67 (t, 4H, J = 7.83 Hz), 3.80 (s, 6H), 6.8–6.9 (m, 4H), 7.10–7.23 (m, 4H); HRMS m/z calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1461. Anal. Calcd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.86. Found: C, 79.53; H, 8.01.

1,3-Bis(3-bromo-2-methoxyphenyl)propane (6). Compound 5 (2.0 g, 7.8 mmol) and TMED (1.95 g, 16.8 mmol) in 8.0 mL of Et_2O were cooled to 0 °C, and 16.4 mL of 1.27 M s-BuLi in cyclohexane (20.8 mmol) was added at a rate of 0.18 mL/min. The solution was stirred for 24 h at rt and cooled to 0 °C, at which time $HgCl_2$ (5.75 g, 21.2 mmol) dissolved in 20 mL of THF was added at a rate of 0.5 mL/min. The solution was stirred at 0 °C for 1.5 h, and then bromine (1.56 g, 19.5 mmol) was added slowly and the solution was stirred for 1 h. At this time another 1.56 g of bromine was added and the solution again stirred for 1 h, this time gradually warming to rt. A third portion of bromine (3.1 g, 39 mmol) was added to the mixture, and it was stirred for another 1 h. The reaction was quenched with 10% Na_2SO_3 (100 mL) and extracted with CH_2Cl_2 (3 × 100 mL), and the combined organic layer was washed with 10% sodium sulfide solution. The solution was filtered through a Celite pad and washed with 10% HCl (200 mL), H_2O (200 mL), and saturated NaCl (200 mL), dried over Na_2SO_4, and concentrated under vacuum to yield a tan oil. The crude product was purified by chromatography (98:2 ratio of hexanes/ethyl acetate) to yield 6 (3.03 g, 94%) as a clear oil: UV (CH_2Cl_2) λ_{max} (ϵ), 234 (3104), 276 (1177); ^1H NMR δ 1.87–1.98 (m, 2H), 2.71 (t, 4H, J = 7.83 Hz), 3.78 (s, 6H), 6.89 (t, 2H, J = 7.74 Hz), 7.12 (dd, 2H, J_1 = 7.9 Hz, J_2 = 1.5 Hz), 7.36 (dd, 2H, J_1 = 8.3 Hz, J_2 = 1.5 Hz); HRMS m/z calcd for $C_{17}H_{18}Br_2O_2$ 411.9676, found 411.9674. Anal. Calcd for $C_{17}H_{18}Br_2O_2$: C, 49.30; H, 4.39. Found: C, 49.47; H, 4.50.

1,3-Bis[3-(3-bromopropyl)-2-methoxyphenyl]propane (7). Compound 6 (1.82 g, 4.4 mmol) in 6.0 mL of THF was added at a rate of 0.33 mL/min to Mg turnings (1.0 g, 41 mmol) in 6.0 mL of THF. The mixture was heated to reflux for 1.5 h and then cannulated into a stirred solution of 1,3 dibromopropane (13.3 g, 66 mmol) and 1.5 mL of 0.1 M Li_2CuCl_4/THF while the temperature was maintained at 0 °C. The solution was stirred for 24 h while it gradually warmed to rt, and then an additional 1.5 mL of 0.1 M Li_2CuCl_4/THF was added. After 12 h the reaction was quenched with water (200 mL) and extracted with CH_2Cl_2 (2 × 100 mL). The organic layer was washed with 10% HCl (100 mL), water (100 mL), and saturated NaCl solution (100 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude product was vacuum distilled to remove excess 1,3 dibromopropane (30 °C, 1.0 mmHg). The remaining product was purified by chromatography (98:2 ratio of hexanes/ethyl acetate) to yield 7 (0.94 g, 43%) as a clear oil: UV (CH_2Cl_2) λ_{max} (ϵ) 232 (1880), 272 (2790); ^1H NMR δ 1.85–2.00 (m, 2H), 2.10–2.22 (m, 4H), 2.69–2.78 (m, 8H), 3.42 (t, 4H, J = 6.63 Hz), 3.71 (s, 6H), 6.90–7.10 (m, 6H); HRMS m/z calcd for $C_{23}H_{30}Br_2O_2$ 496.0613, found 496.0611. Anal. Calcd for $C_{23}H_{30}Br_2O_2$: C, 55.44; H, 6.07. Found: C, 55.63; H, 6.30.

33,34,35,36-Tetramethoxy[3.3.3.3]metacyclophane (3a). A 2.5-mL sample of 1.7 M t-BuLi in pentane (4.2 mmol) was added at a rate of 5 mL/h to a solution containing 6 (0.43 g, 1.04 mmol) in 2 mL of dry Et_2O cooled to −78 °C. After 1 h the solution was placed in a syringe and added simultaneously with a second solution of 7 (0.47 g, 0.94 mmol) in 3.5 mL of THF to a receiver flask containing 3.0 mL of THF maintained at 0 °C. The addition was complete after 4 h, and the mixture was stirred for 24 h while it gradually warmed to rt. The reaction was then quenched with water (100 mL) and extracted with CH_2Cl_2 (2 × 100 mL), and the combined organics were washed with 10% HCl (100 mL), water (100 mL), and saturated NaCl (100 mL). The organic portion was dried over Na_2SO_4 and concentrated under vacuum. The crude product mixture was purified by chromatography using a Chromatotron (98:2 hexanes/ethyl acetate) yielding 5, 7, 8, 9, and a mixture of 3a and 10. Metacyclophane 3a was further purified by analytical HPLC (97:3 ratio of hexanes/ethyl acetate) to yield a white solid. Recrystallization from EtOH produced 3a (0.12 g, 21%) as a white crystalline solid: mp 169–170 °C; UV (CH_2Cl_2) λ_{max} (ϵ) 232 (6070), 268 (4150); ^1H NMR δ 1.75–1.87 (m, 8H), 2.66 (t, 16H, J = 7.6 Hz), 3.45 (s, 12H), 6.9–7.1 (m, 12H); HRMS m/z calcd for $C_{40}H_{48}O_4$ 592.3553, found 592.3535. Anal. Calcd for $C_{40}H_{48}O_4$: C, 81.04; H, 8.16. Found: C, 80.85; H, 8.16.

33,34,35,36-Tetrahydroxy[3.3.3.3]metacyclophane (3b). A 0.118-g (0.38 mmol) sample of BBr_3·$S(Me)_2$ was added to a solution of 3a (0.028 mg, 0.047 mmol) in 1.5 mL of 1,2-dichloroethane and refluxed for 27 h. The reaction mixture was then quenched with 5.0 mL of water and allowed to stir for 30 min. To this was added 50 mL of CH_2Cl_2, and the mixture was extracted with 2.5 M NaOH (2 × 100 mL). The combined basic extract was acidified to pH 2 with 3 M HCl and extracted with Et_2O (2 × 50 mL). The organic portion was dried over Na_2SO_4, concentrated under vacuum to yield a crude tan solid, and purified by HPLC (C18, 70:30 acetonitrile/water) to produce a white solid. Recrystallization from light petroleum ether yielded 3b (0.018 g, 71%) as a white solid: mp 189–194 °C; UV (CH_2Cl_2) λ_{max} (ϵ) 228 (6973), 274 (4406); ^1H NMR δ 1.90–2.10 (m, 8H), 2.67 (t, 16H, J = 6.7 Hz), 6.05 (s, 4H), 6.81–6.85 (m, 4H), 7.00 (d, 8H, J = 7.3 Hz); HRMS m/z calcd for $C_{36}H_{40}O_4$ 536.2927, found 536.2916.

Supplementary Material Available: ^1H NMR for compounds 4-7, 3a, and 3b, ^{13}C NMR for compounds 4-7 and 3a, and ALCHEMY III structures for the low-energy forms of 3a and 3b printed in Table I (13 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.