Polyphosphoric Acid Catalyzed Conversion of 3-(Methoxyphenyl)propionic Acids to Derivatives of [3.3]Metacyclophane-1,10-diones and 1-Indanones

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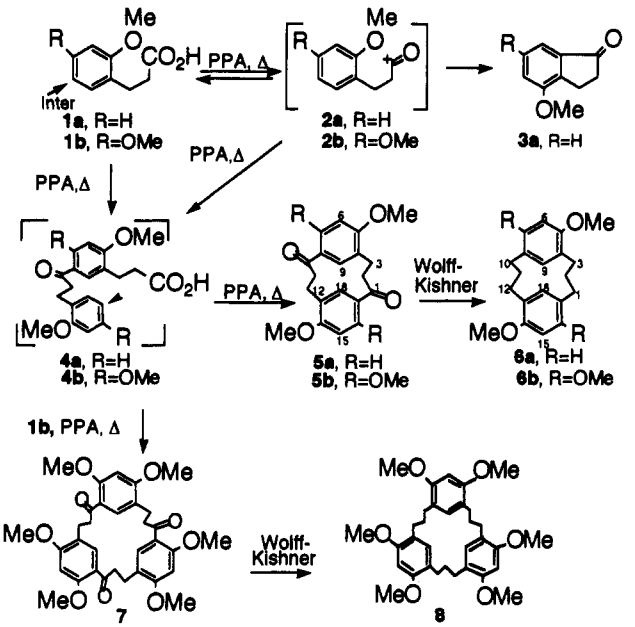
Polyphosphoric acid (PPA) catalyzed cycliacylation of 3-(2-methoxy- and 2,4-dimethoxyphenyl)-propionic acids (**1a,b**) results in dimeric products: 46 and 49% yields of 5,14-dimethoxy- and 5,7,-14,16-tetramethoxy[3.3]metacyclophane-1,10-diones (**5a,b**) and a 2.5% yield of 4-methoxy-1-indanone (**3a**), isolated by steam distillation. 3-(4-Methoxyphenyl)propionic acid (**1c**), depending upon the ratio of PPA/**1c**, gives 17–65% yields of steam-distilled 6-methoxy-1-indanone (**3c**). This latter reaction also gives low yields of 7,16-dimethoxy[3.3]metacyclophane-1,10-dione (**5c**) and an intermediate, dimeric keto acid *p*-methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (**4c**) ($C_{20}H_{22}O_5$). The latter was cyclized in PPA to **5c** in 44% yield. Wolff–Kishner reduction converts **5a** and **5c** to 5,14-dimethoxy[3.3]metacyclophane (**6a**) and **5b** to 5,7,14,16-tetramethoxy[3.3]-metacyclophane (**6b**). Single-crystal X-ray studies of **5a** show the aromatic rings are in the anti conformation whereas the solid-state structure of **6b** is in the syn conformation.

Introduction

Polyphosphoric acid (PPA) is currently the most widely used reagent for cycliacylation of 3-arylpropionic acids to the corresponding 1-indanones.[3a,b,c] We used the reaction to successfully prepare a broad series of alkyl-substituted indanones[3d] and more recently have prepared several known 1-indanones with mixed substitution of alkyl and methoxy groups. However, attempts to cyclize 3-(2-methoxyphenyl)propionic acid (**1a**) and 3-(2,4-dimethoxyphenyl)propionic acid (**1b**), in PPA,[3c,d] gave only a 2.5% yield of the expected 4-methoxy-1-indanone (**3a**) and none of 4,6-dimethoxy-1-indanone. Instead, colorless products, insoluble in ether but sparingly soluble in dichloromethane, were isolated. This unusual behavior initially prompted attempts to obtain even small yields of **3a** and **3b** but also to identify the unknown materials and learn about their formation.

Literature reports of the PPA-catalyzed cyclization of the isomeric, monomethoxy, 3-phenylpropionic acids show wide variation in yield of the corresponding 1-indanones with no mention of unusual products such as shown in Scheme I. A subsequent literature search showed that 5-(2-methoxyphenyl)pentanoic acid has been converted in 30% yield to the homologous 7,18-dimethoxy[5.5]-metacyclophane-1,12-dione in PPA.[3e,f] While the meta isomer [3-(3-methoxyphenyl)propionic acid] readily cyclizes to a mixture of 5- and 7-methoxy-1-indanone in 85% yield,[4a] the ortho isomer **1a** failed to give **3a**.[4b] To account

Scheme I



for the failure to form **3a**, it has been suggested[4b] that the acyl cation, **2a** in Scheme I, interacts with the *o*-methoxy group, rendering the aromatic ring more electropositive and thus resistant to cyclization. Treatment of the para isomer **1c** with PPA gave low yields (30%,[4a] 4.5%,[4c] 43%,[4d] 11%[4e]) of 6-methoxy-1-indanone (**3c**). Cyclization of **1c** in HF gave a 36% yield of **3c**.[5]

When it became evident that metacyclophanes were being formed, the para isomer **1c** was included in the current study, as shown in Scheme II, to compare the influence of position of the methoxy group on the formation of these new products and to explore the utility of this one-step procedure for the synthesis of substituted [3.3]-metacyclophanes. In addition, the intermediate keto acids **4a–c** would be sought as obvious initial intermediates in the intermolecular cycliacylation process.

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(3) (a) Rowlands, D. A. In *Synthetic Reagents*; Pizey, J. S., Ed.; John Wiley & Sons, New York 1985; Vol. 6, Chapter 3, p 156. (b) Popp, F. D.; McEwen, W. E. *Chem. Rev.* **1958**, *58*, 321. (c) Koo, J.; Fish, M. S.; Walker, G. N.; Blake, J. *Organic Syntheses*; Wiley: New York, 1963; Collect. Vol. IV, p 327. (d) Boykin, D. W.; Hertzler, R. L.; Delphon, J. K.; Eisenbraun, E. J. *J. Org. Chem.* **1989**, *54*, 1418. (e) Bein, S. *J. Chem. Soc.* **1960**, 4015. (f) Bein, S. *Bull. Res. Council Isr.* **1960**, *9A*, 82.
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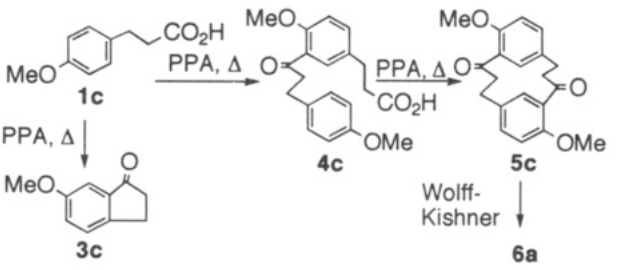
Scheme II



Results and Discussion

The above information prompted a high-dilution run (600 g of PPA, 2.2 g of **1a** in a Waring Blendor[6]) in an attempt to prepare some **3a**. The latter, identical with **3a** prepared by independent synthesis,[7] was isolated in 2.5% yield by steam distillation. The remaining material (95% weight) was an ether-insoluble, white solid. Similar dilution studies failed to give **3b** from **1b**. Addition of chlorobenzene as a solvent/diluent did not improve the yield of **3a** or **3b**.

Sublimation (235 °C/0.1 mm and 280 °C/0.1 mm) of the ether-insoluble products from **1a** and **1b** gave 46% and 49% yields, respectively, of colorless **5a** (EIMS 324, mp 234–235 °C) and **5b** (EIMS 384, mp 279–280 °C). The ^{1}H NMR spectra showed ratios of ArH:CH_2:OCH_3 of 3:4:3 and 1:2:3, respectively. The ^{13}C NMR spectra showed single carbonyl signals for both materials and one methoxy signal for **5a** but two methoxy signals for **5b**. These data suggested both products were highly symmetrical ketones and led to the conclusion that 5,14-dimethoxy[3.3]-metacyclophane-1,10-dione (**5a**) and 5,7,14,16-tetramethoxy[3.3]metacyclophane-1,10-dione (**5b**) had formed.[8a] Wolff–Kishner reduction[9a] of diones **5a** and **5b**, including remethylation[9c] to compensate for methoxy group cleavage, gave the methoxy-substituted [3.3]metacyclophanes **6a** and **6b**.[8a] The combined data (^{1}H and ^{13}C NMR, EIMS, and CH analyses) obtained from **6a** and **6b** also are consistent with the proposed structures and the symmetry suggested by NMR.

Rigorous proof for the correctness of structures **5a–c** and **6a,b** came from single-crystal, X-ray crystallographic studies of **5a** (Figure 1) and **6b** (Figure 2). In the solid state, **5a** exists with a crystallographic center of symmetry within the molecule, aromatic rings in anti conformation, and the methoxy group nearly coplanar with the aromatic ring. Tetramethoxy[3.3]metacyclophane, **6b**, crystallizes with syn conformation of aromatic rings (interplanar angles average 23.79 and 23.95°) and the three carbon bridging chains in the "chair" conformation. Each molecule shows the methoxy carbon atoms of one ring to be significantly distorted from the plane of the aromatic ring and oxygen atoms.

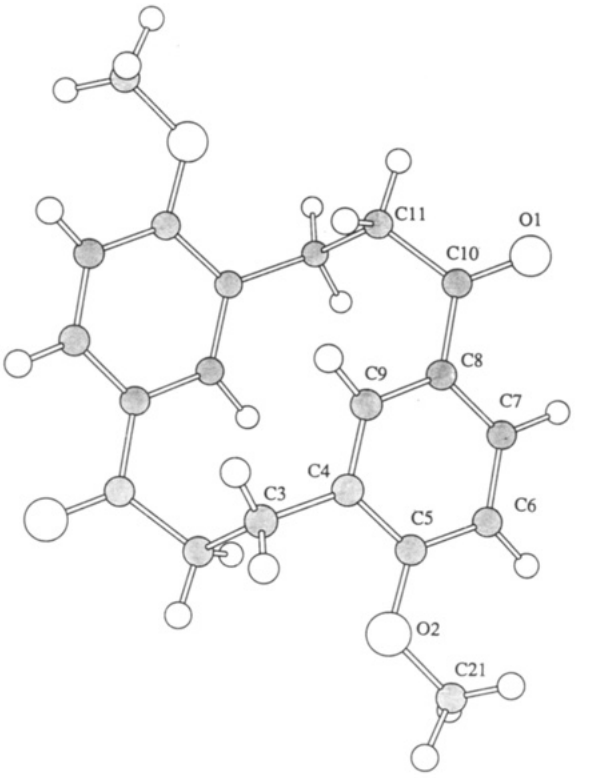


Figure 1. Projection view of **5a**.

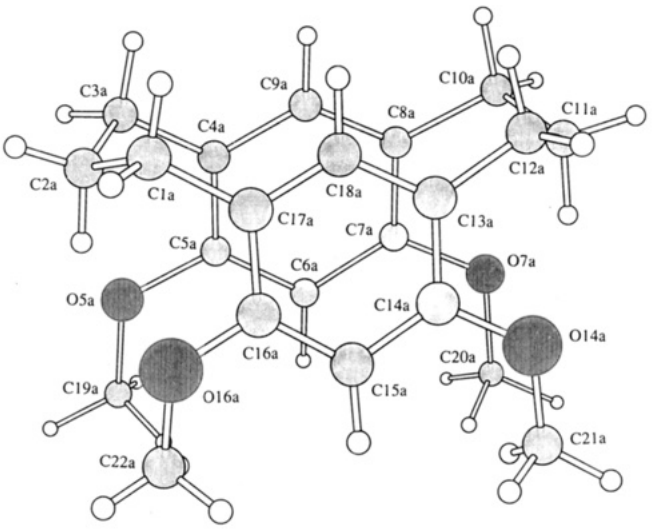


Figure 2. Projection view of **6b**, molecule **a**.

The effect of dilution on the cyclization of **1c** was studied by varying its concentration in 500 g of PPA (30.0, 14.4, 6.2, and 1.8 g of **1c** corresponding to a PPA/**1c** ratio of 17, 36, 81, and 278). The yield (17, 26, 40, and 65%) of steam-distilled **3c** increased progressively with dilution. The other reaction products (**4c** and **5c**) which could be extracted into dichloromethane weighed 16.1, 7.3, 3.3, and 0.43 g. The reaction mixture is heterogeneous, at least during the mixing stage, so that there is little control over concentration. However, this series of reactions demon-

(6) A household blender is not adequate to stir PPA at room temperature. Accordingly, a heavy-duty, Waring Blendor base, equipped with a small-jar adapter which permits use of a 946-mL, base-jacketed, stainless-steel container, was used. These items are shown as 14-509-7E, 14-509-16, and 14-509-22 respectively in the 92/93 Fisher Scientific Catalog. Since the base motor is rated at 15 A, a 110-V, 20-A Variac (W-20MT3) was used to precisely control the starting and operating speeds.

(7) The synthesis from dihydrocoumarin included hydrolysis, benzoylation, cycliacylation of the acid chloride with $AlCl_3$, hydrolysis, and methylation to **3a**. (a) Barco, A.; Benetti, S.; Pollini, G. P. *Org. Prep. Proc. Int.* **1976**, *8*, 7. (b) Cannon, J. G.; Dushin, R. G.; Long, J. P.; Ilhan, M.; Jones, N. D.; Swartzendruber, J. K. *J. Med. Chem.* **1985**, *28*, 515.

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strates some control over intra- and intermolecular reaction. The reactivity of the aromatic ring, as influenced by position and number of methoxy groups, is probably more important in determining the ratio of indanone/metacyclophane since the yield of indanone from **1a** and **1b** was not significantly influenced by changing the concentration of starting material in PPA.

The intermediate keto acids **4a**, **4b**, and **4c** are direct precursors of cyclic diones **5a**, **5b**, and **5c**. The terminal ring of each keto acid remains reactive whereas the remaining ring is deactivated by the attached ketone carbonyl group. Keto acids **4a** and **4b** appear to be too reactive to survive since they were not found. However, keto acid **4c**[4e] (Scheme II) was isolated in 14% yield, purified by sublimation and recrystallization, characterized, and cyclized at 80 °C for 30 min in PPA, to a mixture of **5c** (30%) and recovered **4c** (35%). A ^{13}C NMR spectrum of the crude product showed the carbonyl and other absorptions characteristic of **5c**. A second cyclization of **4c** for 1 h at 80 °C gave 28% recovery of **4c** and 44% yield of **5c**. The residue after removal of **5c** by sublimination was shown to contain a cyclic tetraone $C_{44}H_{48}O_{12}$ (EIMS 648; +LSIMS 649). Wolff-Kishner reduction[9a] of **5c** gave **6a** in 67% yield.

Evidence for the formation of other higher cyclic polyones was found. A mass spectrum (mol wt 810, *m/z* 811 using +LSIMS) of the sublimation residue from **5a** showed the presence of a cyclic pentamer. This cyclic polyone also has a highly symmetrical structure showing single peaks in the methoxy and carbonyl regions of the ^{13}C NMR spectrum.

Trione **7** (mol wt 576, *m/z* 577 using +LSIMS) was isolated in about 10% yield as a residue from the sublimation of the dione **5b**. A ^{13}C NMR spectrum showed a single carbonyl and two methoxy absorptions. It was reduced (Wolff-Kishner,[9a] including remethylation[9c]) to the hexamethoxy[3.3.3]metacyclophane **8**.[8a] The ^{13}C NMR spectrum of **8** showed a single methoxy signal and MS of the expected mol wt (534 EIMS).

The conversion of **1c** and keto acid **4c** in PPA to **5c** establishes that the presence of an *o*-methoxy group, as in **1a,b**, and 5-(2-methoxyphenyl)pentanoic acid[3e,f] is not a necessary condition for the formation of a metacyclophane polyone and suggests that other PPA-catalyzed reactions of aryl-substituted alkanoic acids may provide a convenient and direct route to substituted metacyclophanes.

Experimental Section

Procedures for MS and NMR Studies. Liquid secondary ion mass spectrometry (LSIMS) analyses were performed on a high-resolution spectrometer tuned to a resolution of 1000 (fwhm definition) and operated at 8 kV accelerating voltage with a cesium ion gun potential of 35 kV. Data were acquired over the mass range of 100–1000 using a scan time of 15 s. The matrix consisted of thioglycerol with 1% trifluoroacetic acid. The HRMS analyses employed an electron energy of 70 eV and a 8kV accelerating potential. The instrument was tuned to a resolution of 10000 (fwhm), and data were acquired over the range of 50–500 Da at 15 s/scan. Direct-probe (DP) electron impact (EI) MS data were obtained at 4 kV accelerating potential and 70 eV electron energy. NMR spectra were recorded in $CDCl_3$ referenced to tetramethylsilane.

Reactions of 1a–c, Dione 5c, and Keto Acid 4c with PPA Using a Waring Blendor. PPA (500 g, Stauffer Chemical Co.) was weighed into a base-jacketed blender vessel attached, using a size-reduction adapter, to a 3 hp, Waring Blendor base.[6] Stirring was initiated cautiously through use of an auxillary 20-A Variac.[6] The voltage was gradually increased to avoid spattering and held at 70 V until the temperature of the PPA rose to about 50 °C. A test run showed that stirring friction warms the PPA. Cooling water was passed through the base of the vessel, as needed, to aid in maintaining the selected reaction temperature and to protect the impeller bearing. The carboxylic acid (e.g. 5 g of **1c**) was added in portions during 1–2 min, and the voltage was reduced (to 50–60 V) to maintain a reaction temperature of 70–80 °C. Stirring was continued for 30 min (except for one 60-min run of **4c**), and color changes from pale yellow to orange or red were observed. The stirrer was stopped, crushed ice was added until the vessel was at least $^3/_4$ full, and stirring was cautiously resumed to hydrolyze the PPA with addition of more ice and water as needed. The hydrolyzed mixture was transferred to a 6-L separatory funnel, and water (4 L) was added. The product was extracted (CH_2Cl_2, 4 × 500 mL), and the combined extracts were washed with water (3 × 500 mL) and brine (500 mL). The water layer was neutralized with Na_2CO_3 or alkali before disposal. The dried ($MgSO_4$) extract was distilled to recover CH_2Cl_2. The residue, on steam distillation and extraction, gave 1-indanones **3a** and **3c**. The pot residue from the steam distillation was dissolved in CH_2Cl_2, extracted repeatedly with saturated $NaHCO_3$ solution to remove keto acid, dried, and stripped to yield the nonvolatile neutral products shown in Schemes I and II. The bicarbonate extract was acidified, and the precipitated **4c** was isolated by extraction with CH_2Cl_2.

The stability of dione **5a** was tested by heating 0.93 g in 500 g of stirred PPA at 70–80 °C for 30 min. A pink color developed, but no bicarbonate soluble product was found, and the recovered **5a** (97%) was not altered as shown by comparison (mmp, ^1H and ^{13}C NMR) with the original sample.

For the larger cyclization runs, it was convenient to filter the reaction mixture through a bed of Dicalite filter-aid and wash the filter cake thoroughly with saturated $NaHCO_3$ solution and with water. If keto acid or starting acid is present, the product and Dicalite are first thoroughly mixed with saturated $NaHCO_3$ solution in a blender. The filter cake and recovered Dicalite, dried under an infrared heat lamp and then under vacuum, was extracted with CH_2Cl_2 in a modified Soxhlet extractor[9d] to obtain the neutral product(s).

Wolff-Kishner Reductions: 5a and 5c to 6a, 5b to 6b, and 7 to 8. These reductions[9a] were carried out using a small-scale version of a stainless-steel vessel and stainless-steel condenser.[9a,b] Samples of **5a–c** and **7** (1.77, 2.19, 1.73, 0.93 g), diethylene glycol (250 mL), KOH (10 g), and hydrazine hydrate (25 mL) were added, and the reaction mixture was heated at reflux under a N_2 atmosphere for 60 min. The products were isolated and remethylated[9c] using dimethyl sulfate (2.5, 5.3, 3.0, 3.0 mL), NaOH (0.80, 1.68, 0.80, 1.00 g), tetrabutylammonium bromide (0.43, 0.90, 0.43, 0.50 g), and water (10 mL) in refluxing CH_2Cl_2 (100 mL) to give **6a,b** and **8**. The yields are given below.

***p*-Methoxy-3-(*p*-methoxyhydrocinnamoyl)hydrocinnamic acid (4c):** 0.67 g (14%) from 5.0 g of **1c** in 500 g of PPA; mp 121.5–122.5 °C (lit.[4e] mp 119–120.5 °C); ^1H NMR δ 10.86 (s, 1 H), 7.51 (d, 1 H, *J* = 2.4 Hz), 7.32 (dd, 1 H, *J* = 8.4, 2.4 Hz), 7.16 (d, 2 H, *J* = 8.7 Hz), 6.87 (m, 3 H), 3.85 (s, 3 H), 3.78 (s, 3 H), 3.26 (t, 2 H, *J* = 7.7 Hz), 2.93 (m, 4 H), 2.66 (t, 2 H, *J* = 7.8 Hz); ^{13}C NMR δ 202.0, 178.8, 157.8, 157.2, 133.7, 133.5, 132.4, 130.0, 129.4, 128.2, 113.8, 111.8, 55.6, 55.3, 45.7, 35.6, 29.7, 29.5; HRMS (+EI) calcd for $C_{20}H_{22}O_5$ 342.1467, found 342.1467; EIMS *m/z* (rel intensity) 342 (30), 269 (7), 207 (100), 134 (10), 121 (60). Anal. Calcd: C, 70.16; H, 6.48. Found: C, 70.16; H, 6.51.

5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (5a): 0.83 g (46%) from 2 g of **1a** in 500 g of PPA; mp 234–235 °C; ^1H NMR δ 7.38 (dd, 2 H, *J* = 8.7, 2.1 Hz), 6.89 (d, 2 H, *J* = 2.1 Hz), 6.59 (d, 2 H, *J* = 8.4 Hz), 3.82 (s, 6 H, OMe), 2.96 (broad s, 8 H); ^{13}C NMR δ 203.3, 160.1, 134.5, 132.1, 128.3, 127.7, 109.9, 55.6, 40.4, 27.8; HRMS (+EI) calcd for $C_{20}H_{20}O_4$ 324.1362, found 324.1355; EIMS *m/z* (rel intensity) 324 (100), 161 (76), 145 (17), 91 (10), 77 (7.5). Anal. Calcd: C, 74.05; H, 6.22. Found: C, 74.34; H, 6.37.

5,7,14,16-Tetramethoxy[3.3]metacyclophane-1,10-dione (5b): 0.90 g (49%) from 2 g of **1b** in 500 g of PPA; mp 279–280 °C; ^1H NMR δ 6.49 (s, 2 H), 6.08 (s, 2 H), 3.82 (s, 6 H), 3.76 (s, 6 H), 3.05 (t, 4 H, *J* = 3.5 Hz), 2.83 (t, 4 H, *J* = 6.3 Hz); ^{13}C NMR

δ 206.4, 160.5, 158.3, 135.3, 124.3, 120.1, 94.4, 55.8, 55.5, 41.3, 29.1; HRMS (+EI) calcd for $C_{22}H_{24}O_6$ 384.1573, found 384.1566; EIMS *m/z* (rel intensity) 384 (100), 355 (10), 191 (41), 164 (12), 91 (5). Anal. Calcd: C, 68.73; H, 6.29. Found: C, 68.44; H, 6.02.

7,16-Dimethoxy[3.3]metacyclophane-1,10-dione (5c): 0.60 g (14%) from 5 g of 1c in 500 g of PPA; mp 181–182 °C; ^{1}H NMR δ 7.07 (dd, 2 H, *J* = 8.4, 2.4 Hz), 6.60 (d, 2 H, *J* = 8.4 Hz), 6.35 (d, 2 H, *J* = 2.1 Hz), 3.76 (s, 6 H), 3.04 (t, 4 H, *J* = 6.6 Hz), 2.84 (t, 4 H, *J* = 6.5 Hz); ^{13}C NMR δ 207.1, 155.9, 132.8, 131.9, 131.5, 131.3, 111.2, 55.6, 44.1, 33.1; HRMS (+EI) calcd for $C_{20}H_{20}O_4$ 324.1361, found 324.1360; EIMS *m/z* (rel intensity) 324 (30), 202 (100), 187 (70), 168 (80), 134 (51). Anal. Calcd: C, 74.05; H, 6.22. Found: C, 74.40; H, 6.30.

5,14-Dimethoxy[3.3]metacyclophane (6a): 1.15 g (70%) from 1.77 g of **5a**, 1.05 g (67%) from 1.73 g of **5c**; mp 136–137 °C; ^{1}H NMR δ 6.72 (d, 2 H, *J* = 2.1 Hz), 6.63 (dd, 2 H, *J* = 8.4, 2.4 Hz), 6.32 (d, 2 H, *J* = 8.1 Hz), 3.67 (s, 6 H), 2.65 (m, 8 H), 2.02 (m, 2 H); ^{13}C NMR δ 154.8, 135.8, 132.8, 128.0, 125.9, 110.2, 55.4, 35.9, 32.0, 28.0; HRMS (+EI) calcd for $C_{20}H_{24}O_2$ 296.1776, found 296.1793; EIMS *m/z* (rel intensity) 296 (100), 161 (15), 147 (30), 135 (15), 90 (10). Anal. Calcd: C, 81.04; H, 8.16. Found: C, 81.05; H, 8.32.

5,7,14,16-Tetramethoxy[3.3]metacyclophane (6b): 1.25 g (88%) from 2.19 g of **5b**; mp 200–201 °C; ^{1}H NMR δ 6.64 (s, 2 H), 6.01 (s, 2 H), 3.68 (s, 12 H), 2.65 (broad s, 8 H), 2.01 (m, 4 H); ^{13}C NMR δ 156.0, 137.1, 120.6, 95.3, 55.5, 31.8, 25.1; HRMS (+EI) calcd for $C_{22}H_{28}O_4$ 356.1988, found 356.2016; EIMS *m/z* (rel intensity) 356 (100), 191 (5), 177 (10), 165 (15), 91 (8). Anal. Calcd: C, 74.13; H, 7.92. Found: C, 73.93; H, 7.83.

5,7,14,16,23,25-Hexamethoxy[3.3.3]metacyclophane-1,10,-18-trione (7):[8a] 0.19 g (10%) from 2.0 g of **1b**; mp 236–237 °C; ^{1}H NMR δ 7.27 (s, 3 H), 6.37 (s, 3 H), 3.90 (s, 18 H), 3.22 (t, 6 H, *J* = 5.1 Hz), 2.91 (t, 6 H, *J* = 6.2 Hz); ^{13}C NMR δ 199.5, 161.9, 159.1, 131.2, 121.9, 120.0, 94.4, 55.6, 55.5, 42.0, 23.2; +LSIMS calcd for $C_{33}H_{36}O_9$ 576, found M + H 577.

5,7,14,16,23,25-Hexamethoxy[3.3.3]metacyclophane (8):[8a] 0.73 g (84‰) crude yield from 0.93 g of **7**, 0.45 g (52%) after extraction through acidic/basic alumina with toluene; mp 144–146 °C; ^{1}H NMR δ 7.02 (s, 3 H), 6.46 (s, 3 H), 3.84 (s, 18 H), 2.55 (t, 12 H, *J* = 7.6 Hz), 1.97 (m, 6 H); ^{13}C NMR δ 156.3, 130.7, 122.2, 95.6, 55.7, 30.2, 27.3; EIMS *m/z* (rel intensity) 534 (10), 296 (20), 202 (45), 69 (68), 57 (100); HRMS calcd for $C_{33}H_{42}O_6$ 534.2981, found 534.2977. Anal. Calcd: C, 74.13; H, 7.92. Found: C, 74.28; H, 7.92.

Single-Crystal X-ray Diffraction. Single crystals of **5a** and **6b** (from acetonitrile) were measured on a syntex P3 automated diffractometer. [**5a**, monoclinic space group $P2_1/a$, 8.106 (4), 11.724 (6), 8.499 (5) Å, 103.14 (4)°; **6b** triclinic space group *P*1 bar, 12.046 (3), 17.955 (12), 9.280 (3), 83.33 (4), 90.28 (4), 103.52 (2)]. *R* = 4.8% **5a** and 7.6% **6b** [676, **5a**, and 2164, **6b**, points $I > 3.0\sigma(I)$].

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Supplementary Material Available: Description of X-ray diffraction and crystallographic data for **5a** and **6b** and NMR spectra (^{1}H and ^{13}C) for **7** (4 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.