Quadruple Decker [3.3][3.3][3.3]Orthocyclophane Acetal—An Orthocyclophane Ladder

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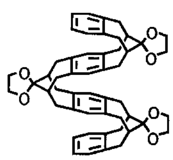
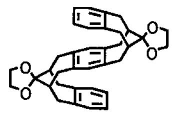
Nonbonding interactions between aromatic units play a fundamental role in the behavior of many molecules, with some of them being important to natural processes.[1] Of these, $\pi-\pi$ interactions between closely layered π systems have been a subject of ongoing interest.[2] For benzene, the difference in the energy of a stacked dimer with a face-to-face geometry to that with an offset geometry or that with an edge-on geometry is well known.[3] A variety of compounds have been synthesized in which aromatic rings are held rigidly at a short distance in a face-to-face geometry. Typically, ring-substituted or complexed cyclophanes with small ring-sizes[4] have been used to demonstrate the effects arising from the through-space interaction of π orbitals. The π systems in smaller meta- and paracyclophanes, however, often suffer high distortion.[5] Thus, it is not always easy to differentiate effects[6, 7] from a through-space $\pi-\pi$ interaction from any effects caused by the distortion of the π system. For the most part, the aromatic units of orthocyclophanes are nondistorted or at most slightly distorted. Orthocyclophanes are often flexible structures and exhibit a less interesting topology.[8] Through clever bridging, however, rigid orthocyclophanes may be formed with layered π systems, which have only a slight degree of distortion.[9] One such class of molecules[10] is made up of [3.3]orthocyclophanes, in which arene units are linked by a bicyclo[4.4.1]undecane group. The introduction of bulky substituents onto the central bridge in these molecules[11] forces the arene units into a facing position. In this way, starting from the flexible orthocyclophane ketones, rigid, layered [3.3]orthocyclophanes (for example **1**–**5**) can be synthesized. In principle, because of the possibility of a "saw-tooth" or byobulike stacking mode (a byobu is a traditional Japanese folding screen), it is possible to build orthocyclophane ladders in which $\pi-\pi$ interactions over longer distances can be expected.



λ_{max} = 310 nm

1



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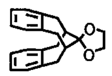
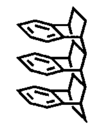
2

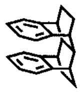


λ_{max} = 286 nm

3

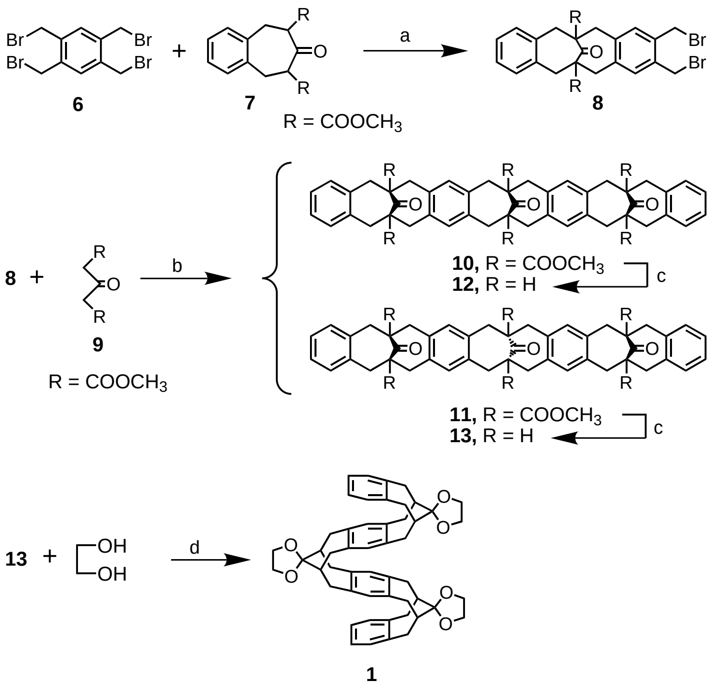


4[9c]



5[9c]

The strategy used for the preparation of quadruple layered **1** is shown in Scheme 1. Dibromide **8** was prepared by treating 1,2,4,5-tetrakis(bromomethyl)benzene (**6**) with dimethyl 1,2-benzo-1-cyclohepten-5-one-4,6-dicarboxylate **7**. The reaction of **8** with dimethyl acetonedicarboxylate (**9**) afforded a 1:4 mixture of diastereoisomeric hexacarboxylates **10** and **11**, which could be separated by column chromatography. The compounds were transformed separately to their corresponding triketones **12** and **13** through a sequence of hydrolysis and thermally induced decarboxylation. The X-ray structure of **12**[13] showed it to have its three carbonyl groups on the same side of the molecular plane. However, diastereoisomeric **13**



Scheme 1. a) 5% NaOH/CH_2Cl_2, TBABr, room temperature, 6 h, 80%; b) 20% NaOH/CH_2Cl_2, TBABr, room temperature, 24 h; separation by column chromatography (**10** (R = $COOCH_3$): 16%; **11** (R = $COOCH_3$): 44%); c) 1. 10% KOH/EtOH (70 mL), reflux, 4 h, (**10** (R = COOH): 88%; **11** (R = COOH): 91%); 2. 320°C, (**12**: 56%; **13**: 70%); d) benzene/nitrobenzene (6 mL, 1/1), *p*-toluenesulfonic acid, reflux, 48 h, 68%.

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1433-7851/98/3718-2532 $ 17.50+.50/0

could be acetalized easily to yield the quadruple layered [3.3][3.3][3.3]orthocyclophane tris(acetal) **1**.

The symmetric structure of **1** is reflected in its ^1H NMR spectrum. An upfield shift of the aromatic protons in the two middle stacks of the structure ($\delta = 5.77$ in $CDCl_3$) is more pronounced than those of the two outer stacks ($\delta = 6.40-6.62$). Interestingly, however, this upfield shift cannot be explained sufficiently by a simple addition of effects arising from the anisotropy of two isolated facing benzene units, as evidenced by a comparison with the shift of the aromatic protons of the inner stack of the triple layered analogue **2** ($\delta = 5.90$ in $CDCl_3$).

The UV/Vis spectroscopic data gives the first evidence for a $\pi-\pi$ interaction in **1**. The rigid layered orthocyclophane acetal **1** ($\lambda_{max} = 310$ nm) shows an absorption at a much longer wavelength than the corresponding flexible orthocyclophane ketone **13** (280 nm, which corresponds exactly to the λ_{max} value of 1,2,4,5-tetramethylbenzene). A comparison of the electronic spectra of the corresponding double-layered [3.3]orthocyclophane **3** ($\lambda_{max} = 286$ nm) and the triple-layered [3.3]orthocyclophane **2** ($\lambda_{max} = 300$ nm) with that of **1** shows a progressive, albeit small bathochromic shift in the absorption maxima. This is in contrast to the sesqui- and sesterbicyclo[2.2.2]octanes **4** and **5**, where the stacking of an additional benzene unit leads to no further shift of the absorption maximum.[9c] Multilayered paracyclophanes, however, do show more pronounced bathochromic shifts.[6]

A very intriguing feature of **1** which arises from the $\pi-\pi$ through-space interaction in **1** can be found in its cyclovoltammogram. Thus, at $-40\,°C$, it can be oxidized reversibly to its monocation radical ($E_1 = 0.80$ V versus [Ag | $AgNO_3$, 10^{-2} M in CH_3CN[14]]) followed by the reversible formation of its dication ($E_2 = 1.29$ V) (Figure 1). Under the conditions used ($c = 5 \times 10^{-5}$ M in CH_2Cl_2, 0.1 M Bu_4NPF_6, $V = 100$ mV s^{-1}), the monocation radical is also formed reversibly at room temperature. Benzene itself cannot be oxidized reversibly, but instead undergoes polymerization upon oxidation.[15] In fact, only with the oxidation of the sesterbenzobicyclo[2.2.2]octane **4** was the first reversible oxidation of a hydrocarbon consisting of only benzene π systems observed.[9c] Both the radical cation as well as the dication of **1** were generated at similar potentials to the corresponding cations of **4**. Moreover, consecutive stacking of benzene units in [3.3]orthocyclophanes leads to the stabilization of cationic charges, with the higher stacked systems undergoing oxidation more readily. Thus, triple-layered [3.3][3.3]orthocyclophane **2** shows a reversible oxidation wave at 1.02 V and a nonreversible oxidation to an instable dication at 1.66 V. Double-layered [3.3]orthocyclophane **3** only shows one nonreversible oxidation wave at 1.52 V, which corresponds to the monocation radical.

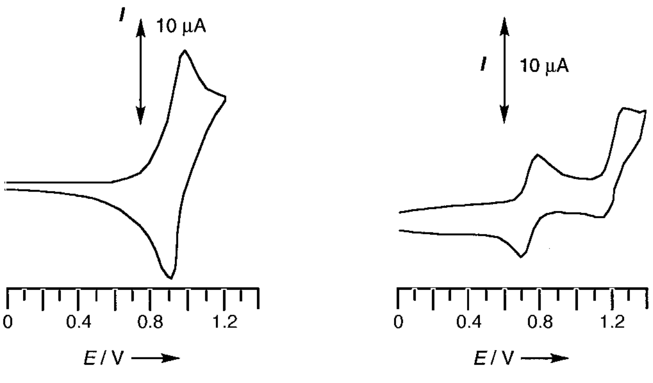

Figure 1. Cyclovoltammogram of orthocyclophanes **1** and **2**. Conditions: $c = 5 \times 10^{-5}$ M for **1** and 1×10^{-4} M for **2** in CH_2Cl_2/0.1 M Bu_4NPF_6, glassy carbon anode, $T = -40\,°C$, $V = 100$ mV s^{-1}, E versus Ag | $AgNO_3$.[14]

The physical and chemical properties of the quadruple-layered [3.3]orthocyclophane **1** indicate that for this "saw-tooth" mode of stacking benzene units, the upper limit of exploiting $\pi-\pi$ interaction in these molecules has not yet been reached. Further stacking of π systems in [3.3]orthocyclophane ladders of this type may well lead to stable cations of higher electronic charge.

Experimental Section

8: A mixture of **6** (810 mg, 1.8 mmol) and **7** (165 mg, 0.6 mmol) was added dropwise to a well stirred mixture of tetrabutylammonium bromide (TBABr; 97 mg, 0.3 mmol) in 5% aqueous NaOH (200 mL) and CH_2Cl_2 (25 mL). The resulting mixture was stirred for 6 h at room temperature, and then it was extracted with water (2 × 50 mL). The separated organic phase was dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/ethyl acetate, 4/1) to yield **8** (270 mg, 80%) as colorless crystals; m.p. 225–228 °C; IR (KBr): $\tilde{\nu} = 1740$ (C=O), 1700 cm^{-1} (C=O); ^1H NMR (270 MHz, CD_2Cl_2): $\delta =$ 1.05–1.90 (br, 4H), 2.60–3.20 (br, 4H, CH_2), 3.60–3.95 (br, 6H, $COOCH_3$), 4.40–4.70 (br, 4H), 7.08–7.35 (br, 6H, aryl); EI-MS (70 eV): m/z (%): 566 (26) {[$^{81}Br_2$]M}$^+$, 564 (52) {[$^{79}Br^{81}Br$]M}$^+$, 562 (27) {[$^{79}Br_2$]M}$^+$; elemental analysis calcd for $C_{25}H_{24}Br_2O_5$ (564.27): C 53.25, H 4.25; found: C 53.50, H 4.37.

10 and **11**: A solution of **8** (282 mg, 0.5 mmol) and **9** (140 mg, 0.8 mmol) in CH_2Cl_2 (50 mL) was added dropwise to a well-stirred mixture of TBABr (64 mg, 0.2 mmol) in 20% aqueous NaOH (100 mL) and CH_2Cl_2 (50 mL). The resulting mixture was stirred for 24 h at room temperature. Water (2 × 50 mL) was then added, and the organic phase dried over anhydrous $MgSO_4$ and concentrated in vacuo. The residue was separated by column chromatography on silica gel (CH_2Cl_2/ethyl acetate, 4/1) to give hexamethyl *syn*-triketohexacarboxylate (**10**; 40 mg, 16%) and hexamethyl *anti*-triketohexacarboxylate **11** (110 mg, 44%).

10: M.p. 241–244 °C; IR (KBr) 1740 (C=O), 1700 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.68-3.58$ (br, 24H, CH_2), 3.65 (brs, 18H, $COOCH_3$), 7.22–7.36 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 978 (97) $[M]^+$; elemental analysis calcd for $C_{57}H_{54}O_{15} \cdot H_2O$ (997.05): C 68.69, H 5.42; found: C 68.86, H 5.94.

11: M.p. 300–320 °C; IR (KBr): $\tilde{\nu} = 1742$ (C=O), 1699 cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.78-3.69$ (br, 42H), 7.15–7.25 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 978 (16) $[M]^+$; elemental analysis calcd for $C_{57}H_{54}O_{15}$ (979.04): C 69.96, H 5.52; found: C 69.74, H 5.59.

12: A mixture of **10** (50 mg, 5.1×10^{-2} mmol) in ethanolic 10% KOH (70 mL, 1:1) was refluxed for 4 h. The reaction mixture was cooled, and then water (70 mL) and 3 N HCl (140 mL) were added sequentially. The resulting mixture was left at 4 °C for 12 h. The precipitate formed was filtered off and washed carefully with water to give the corresponding hexacarboxylic acid **10** (R = COOH, 40 mg, 88%). This diacid was heated in a pyrex tube at 320 °C to give **12** (15 mg, 56%) as colorless crystals; m.p. 198–223 °C; IR (KBr): $\tilde{\nu} = 1700$ cm^{-1} (C=O); ^1H NMR (270 MHz, $CDCl_3$): $\delta = 2.60-2.95$ (br, 24H, CH_2), 2.95–3.16 (br, 6H, CH), 6.95–7.15 (br, 12H, aryl); EI-MS (70 eV): m/z (%): 630 (100) $[M]^+$; elemental analysis calcd for $C_{45}H_{42}O_3$ (630.82): C 85.72, H 6.66; found: C 85.40, H 6.70.

13: Compound **11** (50 mg, 5.1×10^{-2} mmol) was treated using the same procedure as for **12** to give **13** (21 mg, 64% yield for the two steps); m.p. 214–216 °C; IR (KBr): $\tilde{\nu} = 1700$ (C=O), 1490, 1444 cm^{-1}; ^1H NMR

(270 MHz, CDCl$_3$): $\delta = 2.60-3.11$ (br, 30H), 7.00 (brs, 4H, aryl), 7.17 (brs, 8H, aryl); EI-MS (70 eV): m/z (%): 630 (100) [M]$^+$; elemental analysis calcd for $C_{45}H_{42}O_3 \cdot 0.5\,H_2O$ (639.83): C 84.52, H 6.57; found: C 84.68, H 6.66.

1: A mixture of **13** (50 mg, $8.0 \cdot 10^{-2}$ mmol), *p*-toluenesulfonic acid (5 mg), and ethylene glycol (31 mg, 0.5 mmol) in a mixture of benzene/nitrobenzene (6 mL, 1/1) were refluxed for 48 h. The reaction mixture was then cooled, and the resulting precipitate was collected and washed carefully with hexane to give **1** (42 mg, 68%); m.p. 345–347 °C; IR (KBr): $\tilde{\nu} = 1103$ cm^{-1} (C–O); ^{1}H NMR (270 MHz, CDCl$_3$): $\delta = 1.91-2.56$ (m, 18H), 2.83–3.31 (m, 8H), 3.93–4.09 (m, 12H, OCH$_2$), 5.77 (s, 4H, aryl), 6.40–6.62 (m, 8H, aryl); EI-MS (70 eV): m/z (%): 762 (17) [M]$^+$; elemental analysis calcd for $C_{51}H_{54}O_6 \times H_2O$ (781.00): C 78.48, H 6.92; found: C 78.46, H 7.02.

Received: February 24, 1998 [Z11512IE]
German version: *Angew. Chem.* **1998**, *110*, 2626–2628

Keywords: cations · cyclic voltammetry · cyclophanes · stacking interactions

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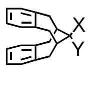
[11] Apart from the acetalization of the keto group, a 1,2-addition of a Grignard reagent to the keto group (**14**, X = OH, Y = CH$_3$, C$_6$H$_5$)[10a] and the reduction of the spirocyclopropane substituted compound[12] to a bis-*gem*-dimethyl bridged compound (**14**, X = Y = CH$_3$) both lead to rigid layered [3.3]orthocyclophanes.



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Solid-Phase Synthesis of Macrocyclic Systems by a Cyclorelease Strategy: Application of the Stille Coupling to a Synthesis of (*S*)-Zearalenone

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In recent years combinatorial chemistry and solid-phase synthesis have emerged as powerful tools for the drug discovery process.[1] Sold-phase synthesis is particularly useful for the construction of combinatorial libraries by virtue of the opportunity to adopt the powerful and elegant encoded split-pool methods[2] as well as convenient purification procedures. Considering the importance of natural products to chemistry, biology, and medicine, we initiated a program directed at the development of solid-phase technologies suitable for the total synthesis of such molecules and of directed libraries of their analogues.[3] Herein, we report a new solid-phase method for the construction of macrocycles by a novel cyclorelease mechanism[4] that employs the Stille coupling,[5] and its application to the total synthesis of (*S*)-zearalenone,[6, 7] a biologically active natural product.[8] Currently, most solid-

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[**] We thank Dr. D. H. Huang and Dr. G. Suizdak for assistance with the NMR spectroscopy and mass spectrometry, respectively. This work was supported by The Skaggs Institute for Chemical Biology, the National Institutes of Health USA, a fellowship from the Ministerio de Educación y Ciencia (Spain) (to J.P.), and grants from Merck, DuPont-Merck, and Schering Plough.