Resorcinarenes with Deepened Polyaromatic Lower Cavities: Synthesis and Structure

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In Nature, interactions derived from π-systems are of immense importance, influencing protein structure and molecular recognition.[1] Conjugated organic materials are the basis of the burgeoning field of molecular electronics.[2] Electronic organic materials embodying extended, semirigid, and well-defined π-cavities might thus find use as discriminating biomimetic molecular hosts for multipoint $\pi-\pi$, CH$-\pi$, and ion$-\pi$ interactions. Calixarenes are attractive synthetic receptors with preorganized, electron-rich π-cavities and versatile properties.[3] They have been employed as substrates for aryl−aryl coupling reactions to lengthen their aromatic cavities with the goal of promoting binding to larger guests.[4] X-ray structure analysis has shown, however, that severe conformational distortion occurs upon 4-fold coupling to a biphenyl substituent; the triphenyl arms exhibit skewed directionality, and a defined cavity is not attained.[4c]

Resorcinarenes have also been extensively studied as π-rich, hydrogen bonding molecular hosts.[5] Unlike calixarenes, which are typically obtained via formaldehyde condensations, resorcinarenes are synthesized from substituted aldehydes. The aldehyde-derived appendages reside on the lower rim of the macrocycles. Their steric bulk prevents conformational interconversion; therefore, resorcinarenes should embody ideal scaffolds for polyaromatic cavity enlargement without loss of structure. The functionalization of the resorcinarene lower rim has begun to attract attention as a means of enhancing the properties of the parent macrocycles,[6] but there is only one example describing conjugation extension of the lower rim.[6a] We previously reported the synthesis of a new series of resorcinarenes embodying boronic acid substituents.[7] Herein, we detail the first direct, 4-fold conjugation extension of the resorcinarene lower rim employing Suzuki couplings featuring both octol and cavitand macrocyclic substrates, including convenient, nonchromatographic product isolation. Importantly, the macrocycle conformation is preserved upon lower cavity extension, resulting in the creation of a deepened, polyaromatic lower rim cleft.

Suzuki coupling reactions have several advantages over related methodologies, including tolerance of a wide range of functionalities and relatively low toxicity.[8] Two resorcinarene substrates were chosen as Suzuki coupling partners (Figure 1). Compound **1** is synthesized in 72.4% yield via addition of a solution of the known precursor octol tetrabromide[6a] (5.00 g, 4.51 mmol), DMF (150 mL), and MeOH (10 mL) to a solution of K_2CO_3 (6.23 g, 45.1 mmol), DMF (100 mL), and CH_2BrCl (1.32 mL, 20.3 mmol) over the course of 30 h. The temperature is gradually increased from room temperature to 65 °C over 7 days, during which an additional 2 portions of CH_2-BrCl (1.32 mL, 20.3 mmol) is added. We observed that methanol improved the efficiency of the bridging reaction,[6d,9] presumably by aiding substrate solubility.

Compound **1** undergoes 4-fold Suzuki coupling (Scheme 1) with arylboronic acids containing electron-donating or -withdrawing groups to furnish the deepened lower cavity cavitands **3a**−**c** as the only observed macrocyclic reaction products.[10] A mixture of $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol), 20 mL of DMF, compound **1** (0.300 g, 0.259 mmol), K_2-CO_3 (0.286 g, 2.07 mmol), and $ArB(OH)_2$ (0.139 g, 1.14 mmol) in 30 mL of a 2:1 solution of DMF/H_2O is stirred under N_2 for 48 h at 65 °C. The solvent is removed in vacuo, and the residue is stirred in water and methanol

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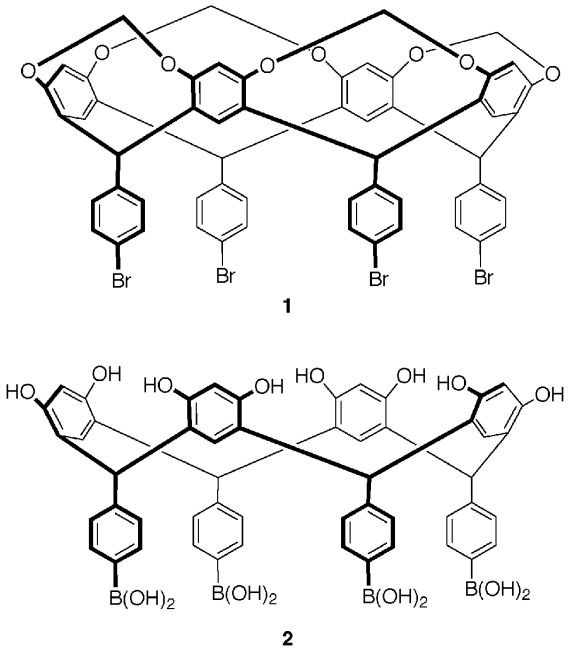
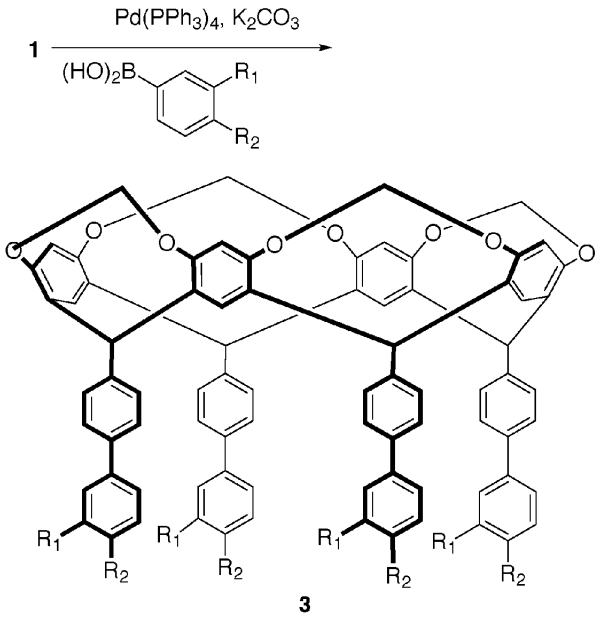


Figure 1.

and then filtered and dried. The resultant solid is then stirred in ether, filtered, and dried, furnishing **3a** in 71% yield. In a similar fashion, compounds **3b** and **3c** are synthesized in 79 and 42% yields, respectively.

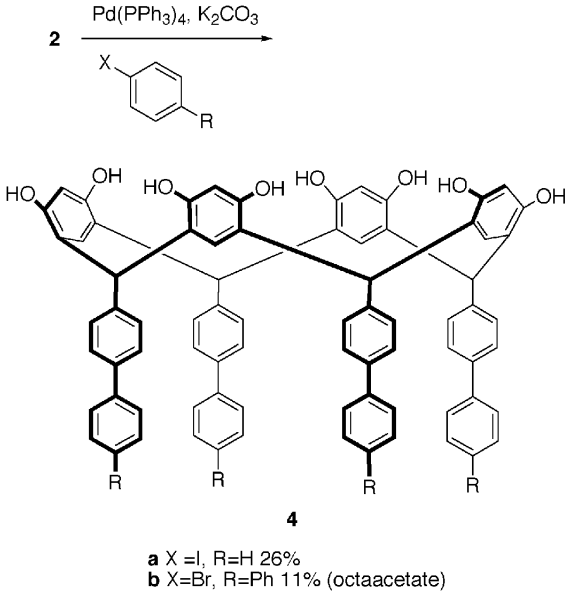
Scheme 1



a R_1=H, R_2=H 71%
b R_1=H, R_2=OCH_3 79%
c R_1=NO_2, R_2=H 42%

The great diversity of readily available aryl halides is an advantage of employing tetraaryl boronic acid **2** and congeners[7] as Suzuki coupling substrates. Compound **2** undergoes 4-fold Suzuki coupling (Scheme 2) with iodobenzene to furnish a sole macrocyclic product as evidenced by ^{1}H NMR. $Pd(PPh_3)_4$ (0.107 g, 0.093 mmol), compound **2** (0.750 g, 0.774 mmol), K_2CO_3 (0.856 g, 6.19 mmol), and iodobenzene (0.38 mL, 3.41 mmol) in 50 mL of a 4:1 solution of DMF/H_2O are stirred under N_2 for 48

Scheme 2



a X =I, R=H 26%
b X=Br, R=Ph 11% (octaacetate)

h at 65 °C. The solvent is removed in vacuo, and the resultant residue is stirred in water and then methanol, filtered, and dried. The solid is stirred in ether, filtered, and dried, yielding compound **4a** in 26% yield. This compound was previously reported as a reaction mixture component along with a stereoisomer via direct resorcinol condensation with 4-biphenylcarboxaldehyde.[11] The ^{1}H NMR spectrum of **4a** obtained via Suzuki coupling is identical to that of the crown stereoisomer component of the condensation reaction.

Compound **2** also undergoes Suzuki coupling with 4-bromobiphenyl, affording compound **4b** which was conveniently purified and characterized as the corresponding octaacetate. In contrast to that for the triphenyl calixarene analogue,[4c] ^{1}H NMR evidence indicates that all four resorcinarene triphenyl appendages reside on the lower face of the macrocycle and that the macrocycle conformation is preserved. The octaacetate displays the well-known, characteristic chemical shift pattern of a typical acylated resorcinarene [acetate protons (2.12 and 2.14 ppm, 24 H), methine protons (5.66 ppm, 4 H), and aromatic protons (6.52 and 6.62 ppm, 4 H; 7.07 and 7.21 ppm, 4 H)[12] directly derived from a C_{4v} crown octol.[13]

In conclusion, we have demonstrated the utility of resorcinarenes with aryl halide or boronic acid lower appendages as versatile 4-fold Suzuki coupling substrates. Importantly, the integrity of the macrocyclic conformation is preserved upon lower cavity deepening. The upper rim is left free for host−guest interactions or chemical modification. The extended compounds described herein might not otherwise be readily attainable via direct resorcinol/aldehyde condensation conditions which are often sensitive to functionality and can afford unfavorable or intractable stereoisomeric mixtures.[5] The Suzuki coupling strategy described herein should also be amenable to the coupling of larger oligomers as well as

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(13) The isolated yields reported have not been optimized. We are curently investigating variations in coupling methodology (e.g., solvent, catalyst, base, and temperature) as well as further improvements in the isolation of the products.

heteroaromatics and polyenes. The fabrication of conjugated π-cavities of increased complexity and the detailed study of their properties are currently in progress in our laboratory.

Experimental Procedures

General. All solvents used for Suzuki coupling reactions were degassed. All other chemicals were reagent grade (Aldrich or Lancaster) and were used without further purification. General methods of characterization have been described previously.[7]

Cavitand 1. The tetrabromo octol[6a] (5.00 g, 4.51 mmol) in 50 mL of DMF and 10 mL MeOH was added to a solution of potassium carbonate (6.23 g, 45.1 mmol), 100 mL of DMF, and bromochloromethane (1.32 mL, 20.3 mmol) via a syringe pump over the course of 30 h. The reaction mixture was then stirred at room temperature under nitrogen for 2 days. An additional 1.32 mL (20.3 mmol) of bromochloromethane was added. The reaction mixture was heated to 45 °C and stirred for 24 h. An additional 1.32 mL (20.3 mmol) of bromochloromethane was added and the mixture heated for 2 days at 65 °C. The reaction mixture was filtered and the resulting solid dried in vacuo and stirred in 50 mL of water and 50 mL of ethyl ether. A total of 3.78 g (73.4%) of product was obtained: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.58 and 5.86 (d, J = 7.2 Hz, 8 H), 6.31 (s, 4 H), 6.70 (s, 4 H), 6.83 (s, 4 H), 7.18 (d, J = 8.3 Hz, 8 H), 7.42 (d, J = 8.4 Hz, 8 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.5, 99.8, 117.2, 121.0, 126.4, 130.5, 131.4, 137.7, 138.6, 156.2; UV λ_{max} 288.5 nm (DMSO); FAB-MS m/z (m-NBA matrix) calcd for $C_{56}H_{36}Br_4O_8$ 1156.5, found 1156.1 (M^+).

Procedure A. Cavitand 3a. To a three-neck 100 mL round-bottom flask were added $Pd(PPh_3)_4$ (0.036 g, 0.031 mmol) and 20 mL of DMF under N_2. Cavitand **1** (0.300 g, 0.259 mmol) dissolved in 10 mL of DMF, potassium carbonate (0.286 g, 2.07 mmol) dissolved in 10 mL of water, and phenylboronic acid (0.139 g, 1.14 mmol) dissolved in 10 mL of DMF were added stepwise via a syringe to the reaction mixture. The reaction mixture was stirred under N_2 for 2 days at 65 °C. The solvent was removed in vacuo, and the resultant solid was stirred in 50 mL of MeOH and 50 mL of ether. The solid was filtered and dried, yielding 0.210 g (71%) of product: mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.65 and 5.90 (d, J = 7.1 Hz, 8 H), 6.48 (s, 4 H), 6.74 (s, 4 H), 7.13 (s, 4 H), 7.13−7.53 (m, 36 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 99.9, 117.0, 127.1, 127.3, 127.4, 128.9, 138.0, 138.9, 139.5, 140.8, 156.2; UV λ_{max} 289 nm (DMSO); FAB-MS m/z (m-NBA matrix) calcd for $C_{80}H_{56}O_8$ 1145.3, found 1145.9 M^+.

Cavitand 3b. Procedure A was used employing cavitand **1** (1.00 g, 0.865 mmol) and (4-methoxyphenyl)boronic acid (0.577 g, 3.80 mmol): yield 0.865 g (79%); mp >300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 12 H), 4.64 and 5.89 (d, J = 6.9 Hz, 8 H), 6.46 (s, 4 H), 6.73 (s, 4 H), 6.86 (d, J = 8.4 Hz, 8 H), 7.11 (s, 4 H), 7.37−7.47 (m, 24 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 41.7, 55.5, 99.9, 114.3, 116.9, 126.7, 127.1, 128.4, 129.3, 133.4, 138.1, 138.2, 139.1, 156.2, 159.2; UV λ_{max} 341.0 nm (DMSO); MALDI m/z (anthracene matrix) calcd for $C_{84}H_{64}O_{12}$ 1265.4, found 1265.4 (M^+).

Cavitand 3c. Procedure A was used employing cavitand **1** (0.600 g, 0.518 mmol) and (3-nitrophenyl)boronic acid (0.380 g, 2.28 mmol): yield 0.286 g (42%); mp >300 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 4.70 and 5.97 (d, J = 7.6 Hz, 8 H), 6.40 (s, 4 H), 6.89 (s, 4 H), 7.60−8.45 (m, 36 H); ^{13}C NMR (100 MHz, (DMF-d_7) δ 42.7, 117.8, 121.8, 123.0, 127.6, 129.8, 130.8, 131.4, 133.8, 136.6, 138.7, 142.5, 149.9, 157.0; IR (KBr) NO_2 1533 and 1340 cm^{-1}; UV λ_{max} 277.5 nm (DMF); MALDI m/z (dithranol matrix) calcd for $C_{80}H_{52}O_{16}N_4$ 1325.3, found 1365.8 [$(M + K)^+$].

Procedure B. Octol 4a. To a three-neck 100 mL round-bottom flask were added $Pd(PPh_3)_4$ (0.107 g, 0.093 mmol) and 20 mL of DMF under N_2. Iodobenzene (0.38 mL, 3.41 mmol), potassium carbonate (0.856 g, 6.19 mmol) dissolved in 10 mL of water, and octol **2** (0.750 g, 0.774 mmol) dissolved in 20 mL of DMF were added stepwise via a syringe to the reaction mixture. The reaction mixture was stirred under N_2 for 2 days at 65 °C. The solvent was removed in vacuo, and the resultant solid was stirred in 100 mL of water, 100 mL of MeOH, and 150 mL of ether. The solid was filtered and dried, yielding 0.220 g (26%) of product: mp >300 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 5.72 (s, 4 H), 6.18 (s, 4 H), 6.86 (d, J = 8.0 Hz, 8 H), 7.20 (d, J = 8.0 Hz, 8 H), 7.28−7.34 (m, 24 H), 8.67 (s, 8 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 41.0, 102.2, 120.2, 125.5, 126.3, 126.7, 128.8, 129.1, 136.7, 140.4, 145.4, 152.8; UV λ_{max} 279.5 nm (DMF); MALDI m/z (anthracene matrix) calcd for $C_{76}H_{56}O_8$ 1097.3, found 1098.0 (M^+).

Octaacetate of 4b. Procedure B was used employing octol **2** (0.500 g, 0.517 mmol) and 4-bromobiphenyl (0.530 g, 2.27 mmol). Compound **4b** was characterized as the corresponding octaacetate; after being stirred in 150 mL of MeOH, the solid purified by crystallization as detailed for octol **4a** was refluxed in 50 mL of Ac_2O for 8 h. The solvent was removed in vacuo, and the resultant solid was stirred in 100 mL of water, filtered, dried, and recrystallized by slow diffusion from $CHCl_3$ in an acetonitrile atmosphere: yield of first crop of crystalline **4b** 0.095 g (11%); mp >300 °C; ^{1}H NMR (400 MHz, DMF-d_7) δ 2.12 (s, 12 H), 2.14 (s, 12 H), 5.66 (s, 4 H), 6.52 (s, 2 H), 6.62 (s, 2 H), 7.07 (s, 2 H), 7.15 (d, J = 8.3 Hz, 8 H), 7.21 (s, 2 H), 7.40−7.45 (m, 12 H), 7.58−7.65 (m, 32 H); ^{13}C NMR (100 MHz, DMF-d_7) δ 45.6, 127.7, 127.8, 128.2, 128.3, 128.5, 130.1, 130.7, 131.5, 133.8, 139.6, 140.2, 140.3, 141.1, 148.4, 148.6, 148.6, 169.4, 169.6; IR (KBr) ν_{CO} 1771; UV λ_{max} 284.0 nm (DMF); MALDI m/z (anthracene matrix) calcd for $C_{116}H_{88}O_{16}$ 1736.6, found 1758.2 [$(M + Na)^+$].

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Supporting Information Available: ^{1}H NMR,^{13}C NMR, and mass spectra of compounds **1**, **3a**−**c**, **4a**, and **4b** (octaacetate) (18 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.

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