Synthesis of Acetylenic Cyclophanes via Intramolecular Self-Assembly: Evidence of Perfluorophenyl-Phenyl Quadrupole Interactions in the Solution State

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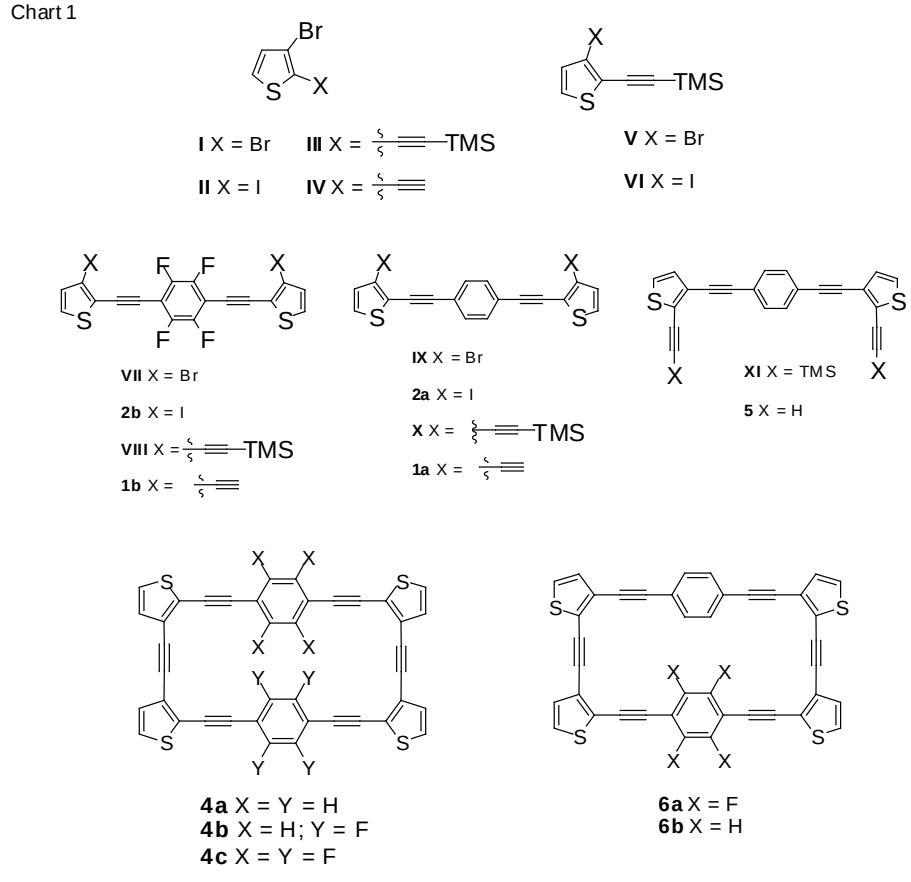
Experimental

General Considerations. All air and moisture-sensitive reactions were carried out in oven dried glassware using standard Schlenk techniques under an inert atmosphere of dry argon unless otherwise noted. Anhydrous solvents were used directly from Sure-Seal containers or dried over alumina. Reagents were used as received from Acros, Aldrich, and Lancaster unless otherwise noted. ^{1}H and ^{13}C NMR spectra were recorded with a GE QE-300 (300MHz) and Nova-500 (500MHz) spectrometer. Ultraviolet-visible spectra were recorded on a Hewlett-Packard 8452A diode-array spectrophotometer. Mass spectra and high-resolution mass spectra were performed at the Southern California Regional Mass Spectrometry Facility (University of California at Riverside).

Chart 1



General Lithium Halogen Exchange Procedure A. To a solution of bromothiophene (1 equiv.) in 0.2M of diethyl ether was added dropwise n-butyllithium (1.1 equiv) at -78˚C. The reaction mixture immediately turned dark red and stirred for an additional 45 min at -78˚C. A solution of iodine (1.1 equiv) in diethyl ether was added dropwise to the lithiated solution. The reaction mixture was slowly warmed to 0˚C. A saturated solution of sodium thiosulfate/water (100 ml) was added to the reaction mixture. The diethyl ether layer was collected and dried over anhydrous sodium sulfate. The crude product was obtained by removing the solvent in vacuo. Further purification was achieved by flash column chromatography.

Compound II. 2,3-dibromothiophene (Compound **I**) was converted to Compound **II** via the lithium halogen exchange procedure A (97% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 6.90 (d, *J* = 5.4 Hz, 1H), 7.42 (d, *J* = 5.4 Hz, 1H). HRMS (EI): calcd for C_4H_2BrIS 287.8105, found 287.8101.

Compound 2a. Compound **IX** was subjected to the lithium halogen exchange procedure A yielding **2a** (90% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.09 (d, *J* = 5.4 Hz, 2H), 7.23 (d, *J* = 5.4 Hz, 2H), 7.56 (s, 4H). ^{13}C NMR ($CDCl_3$, 125Hz): δ 85.87, 87.76, 96.60, 123.26, 125.83, 129.16, 131.84, 135.56. HRMS (EI) calcd for $C_{18}H_8I_2S_2$ 541.8157, found 541.8159.

Compound 2b. Compound **VII** was converted to the title compound (92% yield) via lithium halogen exchange procedure A. ^{1}H NMR ($CDCl_3$, 300MHz): δ 7.14 (d, *J* = 5.4 Hz, 1H), 7.32 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 82.08, 89.62, 97.16, 124.35, 127.87, 130.94, 134.36, 136.02. HRMS (EI) calcd for $C_{18}H_4$ $F_4I_2S_2$ 613.7774, found 613.7780.

Compound VI. Compound **V** was converted to the title compound (97% yield) via lithium halogen exchange procedure A. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.29 (s, 9H, SiMe3), 7.01 (d, *J* = 5.4 Hz, 1H), 7.14 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 0.44, 87.98, 98.24, 103.38, 126.04, 128.74, 135.29. HRMS (EI) calcd for $C_9H_{11}ISSi$ 305.9395, found 305.9386.

General Acetylene Coupling Procedure B. A round-bottom flask was charged with iodoarene (1 equiv), bis(triphenylphosphine)palladium(II) chloride (0.01 equiv), copper(I) iodide (0.05 equiv), diisopropylamine (0.1M), and toluene (0.3M). The terminal acetylene (1.1-1.3 equiv) was added by syringe under an argon atmosphere. The reaction mixture was stirred at 70 ˚C overnight and was monitored by TLC. Upon completion, the reaction mixture was treated with 5% HCl/H_2O solution and washed with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel chromatography.

Compound V. Compound **II** (1 equiv) was converted to the title compound (98% yield) according to general acetylene coupling procedure B using trimethylsilylacetylene as the terminal acetylene. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.28 (s, 9H, SiMe3), 6.94 (d, *J* = 5.4 Hz, 1H), 7.17 (d, *J* = 5.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125Hz): δ 0.46, 86.37, 96.03, 103.86, 117.09, 127.47, 130.37. HRMS (EI) calcd for $C_9H_{11}BrSSi$ 259.2538, found 259.2537.

Compound IX. Compound **II** (2.1 equiv) was reacted with 1,4 diethynylbenzene (terminal acetylene) according to general acetylene coupling procedure B. (86% yield) ^{1}H NMR ($CDCl_3$, 300MHz): δ (d, *J* = 5.4 Hz, 1H); (d, *J* = 5.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125MHz): δ 83.73, 97.13, 116.96, 121.00, 123.22, 127.92, 130.65, 131.88. HRMS (EI) calcd for $C_{18}H_8Br_2S_2$ 445.8434, found 445.8444.

Compound X. Compound 2a (1 equiv) was converted to the title compound (86% yield) using the general acetylene coupling procedure A with (trimethylsily)acetylene as the terminal acetylene. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.29 (s, 18H), 7.04 (d, *J* = 5.4 Hz, 2H); 7.18 (d, *J* = 5.4 Hz, 2H), 7.51 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 0.62, 84.611, 97.73, 99.32, 99.65, 123.37, 126.67, 127.35, 127.52, 130.10, 131.76. HRMS (EI) calcd for $C_{28}H_{26}S_2Si_2$ 482.1015, found 482.1024.

Compound VIII. Compound 2b (1 equiv) was converted to the title compound (82% yield) using the general acetylene coupling procedure A with (trimethylsilyl)acetylene as the terminal acetylene. ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.29 (s, 18H), 7.08 (d, *J* = 5.4 Hz, 2H), 7.29 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 0.62,

97.73, 99.32, 99.65, 126.67, 126.70, 127.35, 127.52, 130.10, 131.76. HRMS (EI) calcd for $C_{28}H_{22}F_4S_2Si_2$ 554.0955, found 409.9840 (M^+-2TMS).

Compound XI. Compound **VI** (2.1 equiv) was reacted with 1,4-diethynylbenzene according to the general acetylene coupling procedure A to give the aforementioned compound (88% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 0.27 (s, 18H), 7.05 (d, *J* = 5.1 Hz, 2H), 7.18 (d, *J* = 5.1 Hz, 2H), 7.51 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 0.52, 86.40, 93.96, 96.96, 104.31, 123.52, 126.64, 126.90, 127.70, 129.51, 131.93. HRMS (EI) calcd for $C_{28}H_{26}S_2Si_2$ 482.1015, found 482.1006.

General Desilylation Procedure C. [(Trimethylsilyl) ethynyl]thiophene (1 equiv) and K_2CO_3 (6 equiv) were dissolved in a mixture of MeOH (0.2M) and THF (0.2M) under an atmosphere of argon. The resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with diethyl ether and washed with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was concentrated under reduced pressure and then purified by silica gel column chromatography.

Compound IV. Compound **III** was converted to the title compound (90% yield) according to the general desilylation procedure C. ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.62 (s, 1H), 6.94 (d, *J* = 5.3 Hz, 1H), 7.16 (d, *J* = 5.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125MHz): 85.74, 117.40, 127.91, 127.98, 130.40, 130.44. HRMS (EI) calcd for $C_9H_{11}BrSSi$ 259.2538, found 259.2537.

Compound (1a). The bis(trimethylsily) protected precursor to the title compound was subjected to the general desilylation procedure C yielding **1a** (84% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.36 (s, 2H), 7.07 (d, *J* = 5.4 Hz, 2H), 7.21 (d, *J* = 5.4 Hz, 2H), 7.52 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): 81.98, 84.06, 97.59, 99.32, 123.27, 126.060, 127.89, 127.702, 130.42, 131.91. HRMS (EI) calcd for $C_{28}H_{10}S_2$ 338.0224, found 338.0214.

Compound (1b). The di(trimethylsily) protected precursor to the title compound was subjected to the general desilylation procedure C yielding **1b** (82% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.42 (s, 2H); 7.11 (d, *J* = 5.4 Hz, 2H); 7.33 (d, *J* = 5.4 Hz, 2H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 97.73, 126.70, 127.24, 130.10, 131.76 (remainder obscured). HRMS (EI) calcd for $C_{22}H_6F_4S_2$ 409.9877, found 409.9840.

Compound (5). The di(trimethylsily) protected precursor to the title compound was subjected to the general desilylation procedure C yielding **5** (82% yield). ^{1}H NMR ($CDCl_3$, 300MHz): δ 3.65 (s, 2H), 7.07 (d, *J* = 5.4 Hz, 2H), 7.21 (d, *J* = 5.4 Hz, 2H), 7.52 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 85.81, 86.05, 93.58, 123.41, 125.46, 126.92,127.95, 129.77, 129.81, 132.03. HRMS (EI) calcd for $C_{28}H_{10}S_2$ 338.0224, found 338.0217.

General Macrocyclization Procedure D. Over the course of 10 hours, a dilute solution (0.01M) of a diiodo component (1 equiv.) and a diacetylene component (1 equiv.) in diisopropylamine and THF was slowly added to a solution of diisopropylamine (2 ml) containing copper (I) iodide (0.05 equiv.) and *trans*-dichlorobis-(triphenylphosphine)palladium(II) (0.01 equiv.) at 80 ˚C. The mixture was cooled, diluted with ether, treated with 5% HCl solution, and washed with brine. The organic layer was dried over sodium sulfate and concentrated in vacuo. The crude product was purified by silica gel chromatography.

Compound 4a. Compounds **1a** and **2a** were reacted together according to the general macrocyclization procedure D to give **4a** (12%). ^{1}H NMR (CD_3COCD_3, 500MHz): δ 7.23 (d, *J* = 5.4 Hz, 4H), 7.27 (d, *J* = 5.4 Hz, 4H), 7.62 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 88.21, 97.23, 126.35, 129.59, 131.41 (remainder obscured). HRMS (EI) calcd for $C_{40}H_{16}S_4$ 624.0135, found 624.0130.

Compound 4b. Compounds **1a** and **2b** were reacted together according to the general macrocyclization procedure D to give **4c** (30%). ^{1}H NMR (CD_3COCD_3, 500MHz): δ 7.24 (d, *J* = 5.6 Hz, 2H), 7.30 (d, *J* = 5.6 Hz, 2H), 7.63 (d, *J* = 5.6 Hz, 2H), 7.79 (d, *J* = 5.6 Hz, 2H), 7.42 (s, 4H). ^{13}C-NMR ($CDCl_3$, 125MHz): δ 89.10, 97.63, 126.67, 129.72, 131.76 (remainder obscured). ^{19}F-NMR (THF-d_8, 125Hz): δ -137.79. HRMS (EI) calcd for $C_{40}H_{12}F_4S_4$ 695.9758, found 695.9756.

Compound 4c. Compounds **1b** and **2b** were reacted together according to the general macrocyclization procedure D to give **4b** (ca. 10%) contaminated by an unidentified impurity that could not be readily removed. ^{1}H-NMR (CD_3COCD_3, 500MHz): δ 7.23 (d, *J* = 5.2 Hz, 4H), 7.63 (d, *J* = 5.2 Hz, 4H). ^{19}F-NMR (THF-d_8, 125Hz): δ -140.30. MS (EI) calcd for $C_{40}H_8F_8S_4$ 767.93824, found 768.0192 (31.15%), 767.0414 (M-1H; 42.16%), 766.0219 (M-2H; 100%).

Compound 6a. Compounds **5** and **2b** were reacted together according to the general macrocyclization procedure D to give **6** (26%). ^{1}H NMR (CD_3COCD_3, 500MHz): δ 7.24 (d, *J* = 5.4Hz, 2H), 7.34 (d, *J* = 5.4Hz, 2H), 7.64 (d, *J* = 5.4Hz, 2H), 7.80 (d, *J* = 5Hz, 2H), 7.41 (s, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 89.25, 97.68, 126.77, 129.79, 131.72 (remainder obscured). ^{19}F-NMR (THF-d_8, 125Hz): δ -138.27. HRMS (EI) calcd for $C_{40}H_{12}F_4S_4$ 695.9758, found 695.9751.

Compound 6b. Compounds **5** and **2a** were reacted together according to the general macrocyclization procedure D to give **6b** (10%). ^{1}H NMR (CD_3COCD_3, 500MHz): δ 7.11 (d, *J* = 5.4Hz, 2H), 7.14 (d, *J* = 5.4Hz, 2H), 7.19 (s, 8H), 7.24 – 7.26 (br, 4H). ^{13}C NMR ($CDCl_3$, 125MHz): δ 120.72, 124.46, 127.56, 127.95, 129.26, 129.35 (remainder obscured). HRMS (EI) calcd for $C_{40}H_{16}S_4$ 624.0135, found 624.0164.