Synthesis of a Shape-Persistent Macrocycle with Intraannular Sulfonate Groups

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The synthesis of a shape-persistent macrocycle with two intraannular sulfonate groups is described. The cylization step is the oxidative acetylene coupling of large phenylethynyl oligomers which are covalently connected to a template. The synthesis of the templated acetylenes at the template as well as the cyclization step give high product yields showing that the template-directed approach is superior to statistical oligocyclizations.

Introduction

Shape-persistent macrocycles with diameters in the nanometer range have attracted much interest during the last few years.[1−5] Apart from the synthetic challenge, the supramolecular organization of these compounds in solution as well as in the bulk is a topic of ongoing research.[6−11] Their interior offers the possibility of arranging functional groups at defined positions in a convergent arrangement, which is otherwise difficult to achieve.[12−14] Shape-persistent macrocycles with properly arranged functional groups allow the specific interaction with appropriate organic guest molecules or inorganic ions.[15−19] They may also be used as the basis for the formation of porous materials because their covalent construction avoids the problem of lattice interpenetration often observed with supramolecular 2- and 3-D aggregates.[20−28] Here again, the possibility to arrange functional groups at defined positions in a convergent arrangement may give rise to the construction of organic materials as functional analogues of zeolites. Although during the last years several shape-persistent macrocycles containing functional groups have been reported, ionic compounds are still relatively rare.[16,29] Since in this case the counterion can influence the solid-state and solution structure, it opens the possibility of controlling the supramolecular organization of these materials by simple ion exchange, keeping the molecular backbone and the functional groups unchanged. In addition, if the macrocycles are arranged in stacks and their interior is properly designed, one-dimensional ion conductance might be observed in the solid state.

Despite this possibly fascinating new application of shape-persistent macrocycles it should be mentioned that the combination of shape persistence of phenylene or phenylene-ethynylene macrocycles (Staab et al.)[30,31] and the concept of intraannular functional groups (Vögtle et al.)[32−34] can already be found in spherands (Cram et al.).[35−36]

One relatively easy synthetic route to shape-persistent macrocycles is the oxidative intermolecular oligomerization of rigid bis(acetylenes) under high-dilution conditions.[37] As we have shown previously, even higher yields can be obtained by coupling covalently templated tetra- or hexaacetylenes.[38−41] In this case, the local concentration of the terminal acetylenes is very high while their overall concentration in the solution is still low by using the pseudo-high-dilution technique. In addition, the template can act as a protective group for the polar functionalities of the molecule. Removing the template releases the functional groups, which can then be used as binding sites for the recognition of other molecules or can be further functionalized (Scheme 1).

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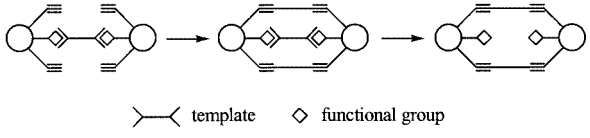
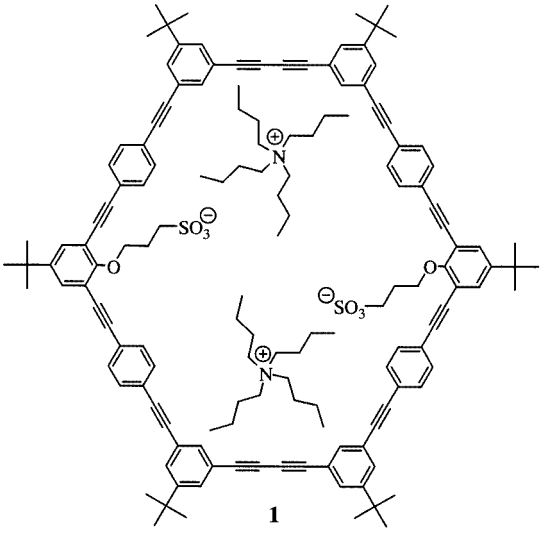


Scheme 1. Intraannular functionalized macrocycles by template-directed diacetylene formation and subsequent template removal

Here we report the synthesis of the shape-persistent macrocycle **1** with two intraannular sulfonate groups. The key step in this synthesis is the template-directed cyclization of rigid bis(acetylenes) in which a bis(phenol) acts as the covalent template and at the same time as a protective group for the polar sulfonate moieties of the macrocycle.



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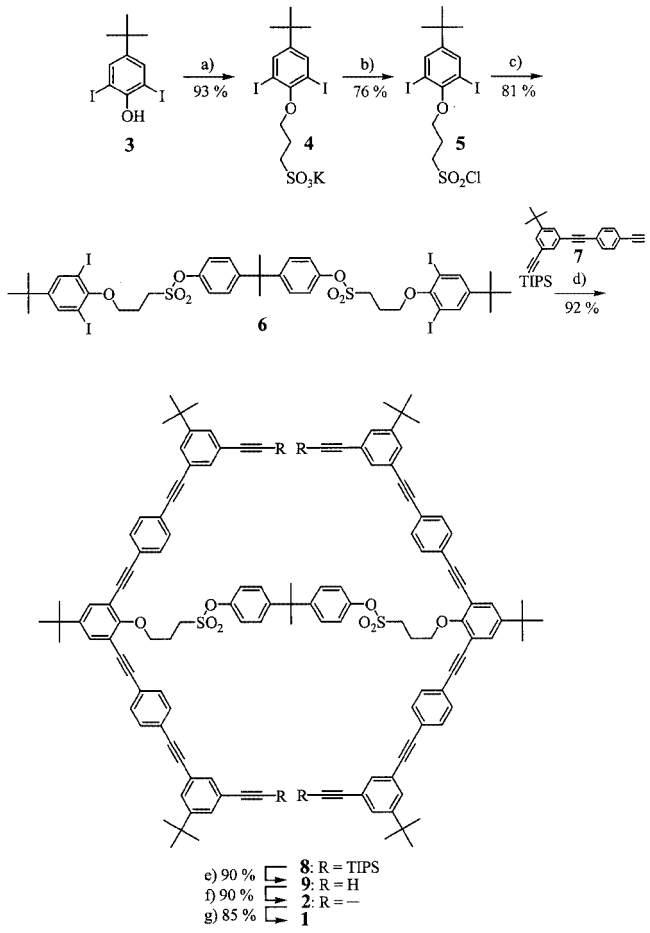
Results and Discussion

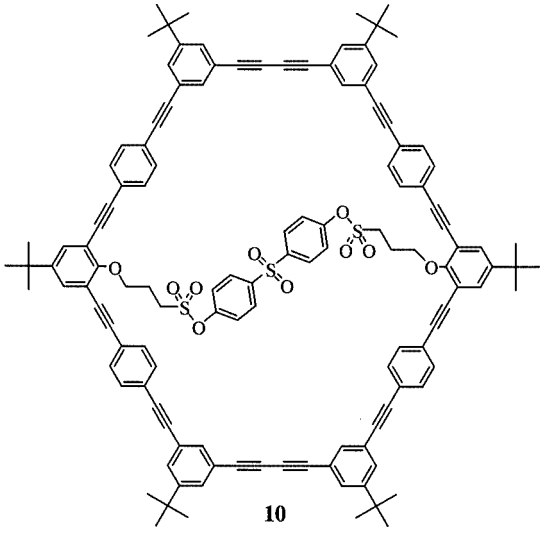
The synthesis of **1** is outlined in Scheme 2. Base-catalyzed alkylation of 4-*tert*-butyl-2,6-diiodophenol (**3**) with propanesultone gave the potassium sulfonate **4** in 93% yield. This compound was transformed into the corresponding sulfonyl chloride **5** in 76% yield with thionyl chloride/dimethylformamide. Reaction of **5** with 2,2-bis(4-hydroxyphenyl)propane under basic conditions gave the templated tetraiodide **6** (81%). Fourfold Hagihara–Sonogashira reaction of **6** with **7** formed the triisopropylsilyl-(TIPS-)protected tetraacetylene **8** in 92% yield. As we have shown before, the quadruple Pd-catalyzed coupling reaction leads to a product whose molecular weight and physical properties differ greatly from those of the starting materials and the by-products, so that **8** could be isolated in high yield.[39] Subsequently, the TIPS groups were removed by reaction with tetrabutylammonium fluoride to form the templated tetraacetylene **9** (90%).

The oxidative acetylene coupling was carried out by slowly adding a solution of the tetraacetylene in pyridine to a slurry of $CuCl_2$/CuCl in the same solvent over a period of 4 d. The crude product of the reaction mixture was analyzed by gel permeation chromatography (GPC) indicating that the amount of **2** in the crude product exceeds 90% (Figure 1, a). Column-chromatographic purification gave **2** in an isolated yield of 90%.[42]

The deprotection of the aryl sulfonates turned out to be somewhat problematic initially. Dissolving **2** in THF and stirring with 10% aqueous NaOH solution at 90 °C did not cleave the ester to any significant degree. Attempts to prepare a macrocycle with a more labile template group (**10**) failed.[43]



Scheme 2. Synthesis of the macrocycle **1**: a) propanesultone, KO*t*Bu; b) SO_2Cl_2, DMF; c) bis(4-hydroxyphenyl)propane, NEt_3; d) Pd^0/Cu^I, NEt_3; e) Bu_4NF; f) Cu^I/Cu^{II}/pyridine; g) Bu_4NOH



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Therefore, the activity of the hydroxide was increased by reaction with tetrabutylammonium hydroxide (40 wt.% in H_2O) in THF to give the tetrabutylammonium disulfonate

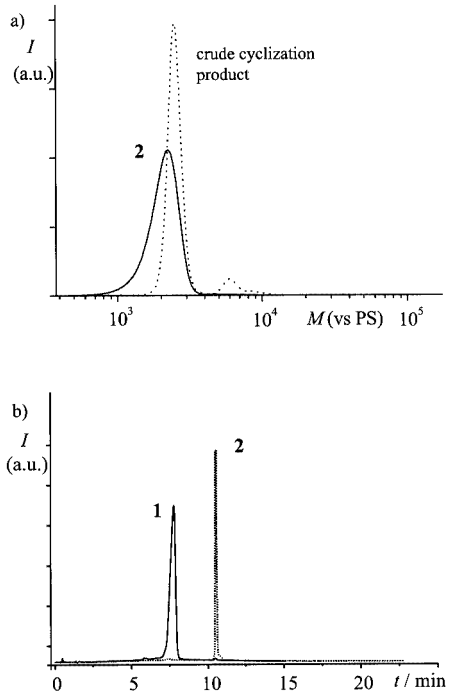

Figure 1. a) GPC of the crude cyclization product and of pure **2**; b) HPLC of **1** and **2**

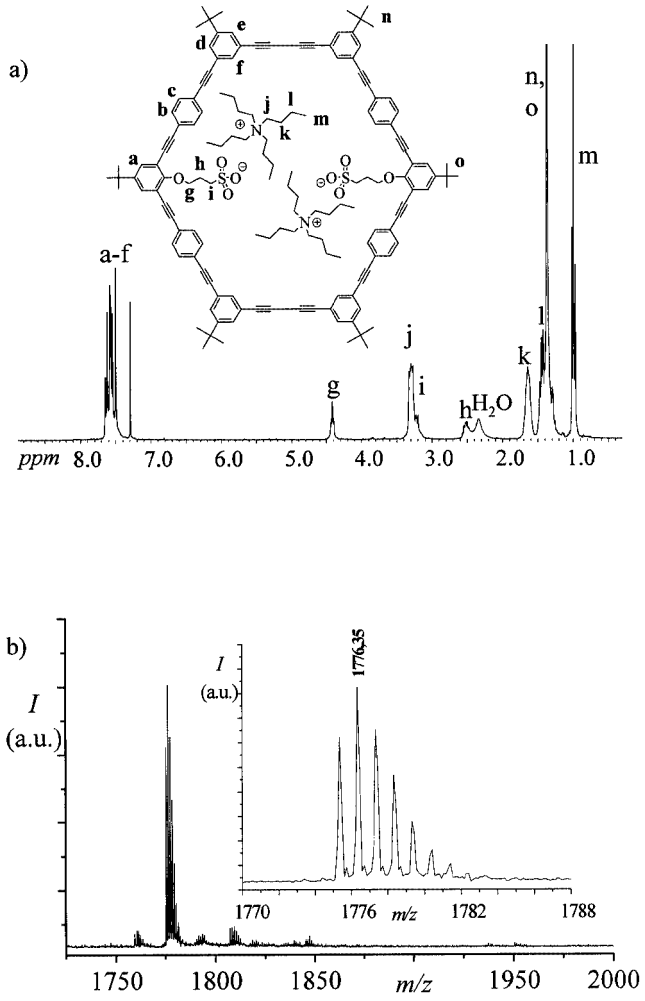

Figure 2. a) ^{1}H NMR spectrum of **1**; b) MALDI-TOF spectrum of **1**

1 in 85% yield.[44] The ^{1}H NMR spectrum of **1** (Figure 2, a) shows the signals of the macrocyclic backbone at δ = 7.4−7.7 (a−f) and 1.3 ppm (n,o) and the aliphatic CH_2 groups of the spacer between the rigid backbone of the molecule and the sulfonate group at δ = 4.4 (g), 3.2 (i) and 2.5 (h) ppm. The signals of the tetrabutylammonium group are found at δ = 3.4 (j), 1.7 (k), 1.4 (l) and 1.0 (m) ppm. The signals of the template are absent, indicating that the deprotection is complete. Quantitative deprotection could also be confirmed by analytical high performance liquid chromatography(HPLC) (Figure 1, b). Mass spectrometric analysis (MALDI-TOF) of **1** shows an isotope-resolved signal pattern at m/z = 1776.4, corresponding to the mass of the macrocyclic sulfonate and 3 K^+ (Figure 2, b). Not surprisingly for a sulfonate, elemental analysis indicates the presence of four water molecules per macrocycle, even after drying in vacuo.

Compound **1** is stable in air at room temperature and dissolves well in organic solvents like 1,2-dichloroethane or dimethylformamide. Within the investigated concentration regime (0.25−20 mg/ml) no concentration-dependent signal shift could be observed, thus there is no indication for any aggregation of the macrocycles in these solvents.

Due to our interest in tubular stacks of macrocycles with possible Li-ion conductivity, we investigated if an exchange of the counterion would lead to new functional materials, eventually by further addition of Li salts. However, exchange of the organic cation by lithium decreased the solubility of the macrocycle dramatically and did not lead to a completely cation-exchanged product. Even repeated heating of the product with LiCl in DMF was unsuccessful.[45] A possible explanation for the low solubility of the Li compound is that the metal cation is coordinated by several sulfonate groups of different macrocycles leading to a physically crosslinked network. Future experiments with analogous macrocycles containing additional oligoalkyl substituents at the exterior will show if this 3-D network formation can be avoided and tractable ion-conductive materials can be obtained.

In conclusion, we have synthesized the first shape-persistent macrocycle consisting of two intraannular sulfonate groups in a large internal void. Due to the use of a covalently bound template in the cyclization reaction and during the preparation of the precursors, the yields in each reaction step are very high. These results show again that the template-directed synthesis of shape-persistent macrocycles is superior to statistical cyclooligomerization reactions. In addition, the deprotection of the aryl sulfonate moieties has been optimized and works now under mild conditions leading to soluble ionic shape-persistent macrocycles.

Experimental Section

General Remarks: Reactions requiring an inert gas environment were conducted under argon, and the glassware was oven-dried (140 °C). THF was distilled from potassium prior to use. Triethylamine and pyridine were distilled from CaH_2 and stored under argon. Commercially available chemicals were used as received. Compounds **3** and **7** are described elsewhere.[39,46] ^1H and ^{13}C NMR spectra were recorded with a Bruker DPX 250 or AC 300 spectrometer (250 and 300 MHz for ^1H, 62.5 and 75.48 MHz for ^{13}C). Chemical shifts are given in ppm, referenced to residual proton resonances of the solvents. Thin-layer chromatography was performed on aluminum plates precoated with Merck 5735 silica gel 60 F_{254}. Column chromatography was performed with Merck silica gel 60 (230−400 mesh). The gel permeation chromatograms were measured in THF (flow rate 1 mL min^{-1}) at room temperature, using a combination of three styragel columns (porosity 10^3, 10^5, 10^6) and a UV detector operating at λ = 254 nm. The molecular weight was obtained from polystyrene-calibrated SEC columns. RP-HPLC was performed using an HP 1100 gradient chromatography system. The chromatograms were measured in methanol/water (80:20) over 20 min (start phase: methanol; flow rate 1 mL min^{-1}) at room temperature, using a reversed-phase column and a UV detector operating at λ = 340 nm. The matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry measurements were carried out with a Bruker reflex spectrometer (Bruker, Bremen), which incorporates a 337-nm nitrogen laser with a 3-ns pulse duration (10^6−10^7 W/cm, 100 mm spot diameter). The instrument was operated in a linear mode with an accelerating potential of 33.65 kV. The mass scale was calibrated with polystyrene (M_p = 2300), using a number of resolved oligomers. Samples were prepared by dissolving the macrocycle in THF at a concentration of 10^{-4} mol/L. In all cases, 1,8,9-trihydroxyanthracene (Aldrich, Steinheim) was used as the matrix. Field desorption spectra were recorded with a VG ZAB 2-SE FPD machine. Microanalyses were performed by the University of Mainz. Melting points were measured with a Reichert hot-stage apparatus and are uncorrected.

Potassium 3-(4-*tert*-Butyl-2,6-diiodophenoxy)propanesulfonate (4): 4-*tert*-Butyl-2,5-diiodophenol (**3**) (30.8 g, 76.6 mmol) was dissolved in *t*BuOH (100 mL) at 35 °C. KO*t*Bu (1 M in *t*BuOH, 76.6 mL, 76.6 mmol) and then propanesultone (6.7 mL, 76.6 mmol) were added. A fine precipitate formed immediately. The mixture became slowly more viscous and could not be stirred after 15 min. After an additional hour at 35 °C, the solvent was removed under reduced pressure and the residue was recrystallized from methanol (250 mL) to give **4** (37.5 g, 93%) as a colorless solid. M.p. 262 °C (dec.). ^1H NMR (250 MHz, [D$_6$]DMSO): δ = 7.75 (s, 2 H), 3.87 (t, *J*= 6.3 Hz, 2 H), 2.65 (m, 2 H), 2.09 (m, 2 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (62.5 MHz, [D$_6$]DMSO): δ = 155.23, 150.91, 136.69, 91.67, 72.52, 48.83, 34.01, 31.04, 26.28 ppm. MS (FD): *m*/*z* = 561.8 [M$^+$]. $C_{13}H_{17}I_2KO_4S$ (562.25): calcd. C 27.77, H 3.05; found C 27.48, H 2.95.

3-(4-*tert*-Butyl-2,6-diiodophenoxy)propane-1-sulfonyl Chloride (5): SO_2Cl_2 (3.0 g, 24.9 mmol, 1.8 mL) was slowly added to a suspension of **4** (14.0 g, 24.9 mmol) in THF/DMF (2:1, 300 mL) at room temperature. The solid dissolved and, after the heat evolution had stopped (approx. 1 h), the solution was heated to 60 °C for 2 h. After cooling to room temperature, the mixture was poured slowly onto ice/water (1 L). The product was then filtered off and washed three times with ice-cold water and then with petroleum ether. After drying, **5** (10.3 g, 76%) was obtained as a fawn powder sufficiently pure for the next step. An analytical sample was obtained by chromatography on silica gel eluting with ethyl acetate (R_f = 0.69). M.p. 94 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.71 (s, 2 H), 4.12 (m, 4 H), 2.59 (m, 2 H), 1.25 (s, 9 H) ppm. ^{13}C NMR (62.5 MHz, $CDCl_3$): δ = 155.28, 151.09, 136.72, 91.93, 72.11, 48.89, 34.08, 31.12, 26.03 ppm. MS (FD): *m*/*z* = 542.2 [M$^+$], 1084.1 [2 M$^+$]. $C_{13}H_{17}ClI_2O_3S$ (542.60): calcd. C 28.78, H 3.16; found C 28.73, H 2.96.

Compound 6: Triethylamine (0.6 mL, 8.3 mmol) was slowly added to a solution of **5** (2.3 g, 4.3 mmol) and 2,2-bis(4-hydroxyphenyl)-propane (0.5 g, 2.1 mmol) in THF (10 mL) at 0 °C. The solution was stirred for 1 h at 0 °C and then at room temperature overnight. The formed precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The yellow, oily residue was purified by chromatography on silica gel eluting with CH_2Cl_2/hexanes (2:1) (R_f = 0.51) to give **6** (2.2 g, 81%) as yellow solid. M.p. 77−80 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.70 (s, 4 H), 7.22 (br. s, 8 H) 4.07 (t, *J*= 5.7 Hz, 4 H), 3.67 (m, 4 H), 2.53 (m, 4 H), 1.65 (s, 6 H), 1.25 (s, 18 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 154.67, 150.87, 138.45, 136.28, 129.62, 127.51, 123.09, 120.91, 90.61, 71.88, 70.07, 47.98, 32.21, 30.54, 24.81 ppm. MS (FD): *m*/*z* = 1242.5 [M$^+$], 2485.2 [2 M$^+$]. $C_{41}H_{48}I_4O_8S_2$ (1240.58): calcd. C 39.70, H 3.90; found C 40.04, H 3.93.

Compound 8: [Pd(PPh$_3$)$_2$Cl$_2$] (30 mg) and CuI (22 mg) were added to a solution of **6** (0.92 g, 0.74 mmol) and **7** (1.47 g, 3.33 mmol) in triethylamine (12 mL) under argon. The mixture turned dark after a few minutes and was stirred overnight at room temperature and then at 50 °C for 1 h. After cooling to room temperature, diethyl ether (150 mL) and water (150 mL) were added, the organic phase was separated and extracted with water (2 × 75 mL), 10% acetic acid (5 × 75 mL), water (2 × 75 mL), 10% aqueous NaOH (3 × 75 mL), water (2 × 75 mL) and brine (75 mL). Drying with $MgSO_4$ and evaporation of the solvent yielded an oily residue, which was purified by chromatography on silica gel eluting with CH_2Cl_2/hexanes (1:2) (R_f = 0.36) to give **8** (1.68 g, 92%) as a light yellow foamy solid. M.p. 167 °C. ^1H NMR (250 MHz, $CDCl_3$): δ = 7.11 (d, *J*= 8.8 Hz, 4 H), 7.04 (d, *J*= 8.8 Hz, 4 H), 7.42−7.48 (m, 32 H), 4.44 (t, *J*= 5.4 Hz, 4 H), 3.69 (m, 4 H), 2.50 (m, 4 H), 1.55 (br. s, 6 H), 1.32 (s, 18 H), 1.31 (s, 36 H), 1.13 (s, 28 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 157.91, 151.75, 149.26, 147.20, 147.16, 133.01, 132.61, 131.93, 131.66, 131.46, 129.32, 129.01, 128.48, 123.73, 123.58, 122.95, 122.89, 121.83, 116.90, 106.87, 93.53, 91.47, 90.88, 89.12, 87.71, 71.47, 48.16, 42.78, 34.90, 34.63, 31.40, 31.31, 30.98, 25.21, 23.55, 18.91, 11.54 ppm. MS (FD): *m*/*z* = 2483.5 [M$^+$]. $C_{165}H_{196}O_8S_2Si_2$ (2483.87): calcd. C 79.79, H 7.95; found C 79.69, H 8.00.

Compound 9: Tetrabutylammonium fluoride (1 M solution in THF, 9.3 mL, 9.3 mmol) was added to a solution of **8** (1.65 g, 0.66 mmol) in THF/water (39:1, 40 mL). The solution was stirred at room temperature for 4 h. After evaporation of most of the solvent, diethyl ether (300 mL) and water (200 mL) were added and the organic phase was extracted with water (3 × 100 mL) and brine (100 mL). Drying with $MgSO_4$ and evaporation of the solvent yielded an oily residue which was treated several times with small portions of methanol to give **9** (1.11 g, 90%), after drying in vacuo, as a light-yellow foamy solid. M.p. 155 °C. ^1H NMR (250 MHz, CD_2Cl_2): δ = 7.12 and 7.05 (d, *J*= 8.8 Hz, each 4 H), 7.42−7.48 (m, 32 H), 4.42 (t, *J*= 5.4 Hz, 4 H), 3.67 (m, 4 H), 2.88 (s, 4 H), 2.46 (m, 4 H), 1.55 (br. s, 6 H), 1.31 (s, 18 H), 1.30 (s, 36 H) ppm. ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ = 158.32, 152.76, 149.98, 147.93, 147.82, 133.49, 133.00, 132.29, 132.07, 131.87, 129.32, 129.40, 128.85, 124.01, 123.68, 122.91, 122.89, 121.83, 117.40, 106.87, 93.90, 91.66,

90.88, 89.70, 88.35, 77.88, 72.19, 48.72, 43.32, 35.38, 35.09, 31.40, 31.31, 30.98, 25.81, 23.55, 18.91 ppm. MS (FD): *m/z* = 1859.6 [M^+], 929.0 [M^{2+}], 619.7 [M^{3+}]. $C_{129}H_{116}O_8S_2$ (1858.49): calcd. C 83.37, H 6.29; found C 82.98, H 6.38.

Compound 2: A solution of **9** (1.10 g, 0.59 mmol) in pyridine (50 mL) was added to a suspension of CuCl (8.44 g, 85.2 mmol) and $CuCl_2$ (1.68 g, 7.4 mmol) in pyridine (300 mL) over 96 h at room temperature. After completion of the addition, the mixture was stirred for an additional day, then poured into CH_2Cl_2 (300 mL) and water (200 mL). The organic phase was extracted with water, 25% NH_3 solution (in order to remove the copper salts), water, 10% acetic acid, water, 10% aqueous NaOH and, finally, brine. After drying with $MgSO_4$, the solvent was evaporated to about 20 mL, and the coupling products precipitated by the addition of methanol (200 mL) and collected by filtration. Recrystallization from ethyl acetate followed by chromatography on silica gel eluting with CH_2Cl_2/hexanes (1:1) (R_f = 0.74) gave **2** (0.99 g, 90%) as slightly yellow solid. M.p. > 220 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.51−7.56 (m, 32 H), 7.28 (d, *J*= 8.8 Hz, 4 H), 7.20 (d, *J*= 8.8 Hz, 4 H), 4.42 (t, *J*= 5.4 Hz, 4 H), 3.75 (m, 4 H), 2.56 (m, 4 H), 1.72 (s, 6 H) 1.34 (s, 18 H), 1.32 (s, 36 H) ppm. ^{13}C NMR (75.5 MHz, CD_2Cl_2): δ = 159.05, 152.98, 150.18, 148.11, 147.41, 133.39, 133.03, 132.19, 132.05, 131.85, 129.21, 128.85, 123.99, 123.94, 123.78, 122.44, 121.83, 117.61, 93.85, 91.46, 89.99, 88.28, 81.97, 74.40, 72.24, 49.34, 43.49, 35.48, 35.13, 31.40, 31.31, 30.98, 25.94 ppm. MS (MALDI-TOF): *m/z* = 1964.3 [M + Ag]$^+$; 1878.1 [M + Na]$^+$. $C_{129}H_{112}O_8S_2$ (1854.45): calcd. C 83.55, H 6.09; found C 83.38, H 5.99.

Compound 1: Tetrabutylammonium hydroxide (1.6 mL, 40% in water) was added to a solution of **2** (220 mg, 0.12 mmol) in THF (20 mL). The mixture was stirred overnight at 40 °C and then the solution was concentrated to a small volume. Methanol was added to the oily residue (10 mL), the suspension stirred for 4 h and the product collected by filtration to give **1** (190 mg, 85%) as a yellow solid. M.p. > 220 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 7.61−7.44 (m, 32 H), 4.37 (t, *J*= 5.7 Hz, 4 H), 3.30 (m, 16 H) 3.17 (m, 4 H), 2.48 (m, 4 H), 1.61 (m, 16 H), 1.41 (m, 16 H) 1.32 (s, 18 H), 1.31 (s, 36 H) 0.97 (t, *J*= 7.2 Hz, 24 H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 158.16, 152.34, 149.56, 148.17, 147.50, 133.48, 132.97, 132.06, 131.94, 131.80, 129.14, 128.76, 123.59, 123.29, 122.49, 121.78, 116.97, 93.47, 91.23, 89.27, 87.93, 81.97, 77.47, 71.77, 48.31, 42.89, 34.95, 34.66, 31.40, 31.31, 25.38, 16.93, 13.08, 11.29 ppm. MS (MALDI-TOF): *m/z* = 1776.3 [$M_{Dianion}$+ 3 K^+]$^+$. $C_{146}H_{170}N_2O_8S_2$·4 H_2O (2217.2): calcd. C 79.08 H 8.11; found C 79.11 H 8.38.

Acknowledgments

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[42] We also performed the statistical dimerization of the *p*-cresol-protected bis(acetylenes) and obtained the corresponding macrocyclic dimer in 30% isolated yield after recrystallization (the crude cyclization product contained about 60−70% of the macrocyclic dimer).
[43] The electron-withdrawing effect of the sulfone group led to a cleavage of the aryl sulfonate group by fluoride ions when we tried to prepare the template-free tetraacetylene.
[44] Attempts to use a mixture of NaOH and 18-crown-6 led to undefined side products.
[45] High-temperature ^{1}H NMR spectra of the soluble parts of the material in DMSO still showed the presence of about 20−30% of the signal intensity of the initial tetrabutylammonium ions.
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