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Resorcin[6]arene as a building block for tubular crystalline state architectures

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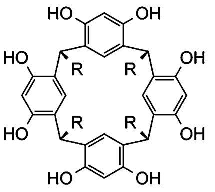
A resorcin[6]arene with an *r-trans-cis-trans-cis-trans* configuration of the pendant ethyl groups forms tubular crystal structures.

Resorcinarenes are synthesized in high yields by acid-catalyzed condensation of resorcinol and its derivatives with aldehydes.[1] Cyclic tetramers are particularly well studied:[2] the bowl-shaped *r-cis-cis-cis* crown isomers of type **1** were the hemispheres for the construction of cavitands, carcerands[3] and molecular capsules.[4] They also self-assemble to surround suitable guests as dimeric[5] and hexameric[6] capsules in solution, and provide excellent modules for crystal design.[7] Cyclic hexamers,[8] obtained from 2-alkylresorcinols, are less common, but extended cavitands[9] derived from them are known.



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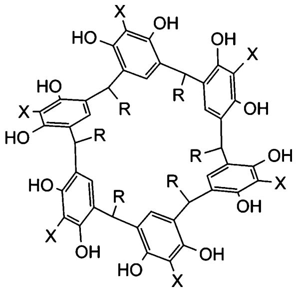

R = Et **2,3**

X = H **2**
X = CH_2NBu_2 **3**

We report here the synthesis, characterization and chemical derivatization of a new hexamer, the *r-trans-cis-trans-cis-trans* (*r-tctct*) resorcin[6]arene **2** bearing ethyl chains at its bridging atoms. This structure forms tubular arrangements in the solid state.

Acid-catalyzed condensation of resorcinol with propionaldehyde under conditions of thermodynamic control[10] gave the known cyclic tetramer (90%) and a minor product that precipitated from the reaction solution. Trituration of the solid with hot THF left the insoluble product in pure form.† The ^{1}H-NMR spectrum in methanol-d_4 indicated high symmetry: one triplet for the methine protons of the bridges and two singlets for the protons of resorcinol rings and the pendant ethyl groups give one multiplet and one triplet. The MALDI-TOF mass spectrum showed a major peak at 923.3977 D corresponding to the sodium salt of hexamer **2**.

Slow crystallization from a three component solvent (DMSO–MeCN–EtOH) afforded diffraction quality crystals.‡ Single crystal X-ray analysis revealed the structure shown in Fig. 1. The conformation has S_6-symmetry with the pendant ethyl groups assuming axial positions; they alternate above and below the plane defined by the six bridging methine groups. Neighboring resorcinol rings assume a dihedral angle of 94.5°. The distance between oxygen atoms of the neighboring hydroxy groups (3.57 Å) excludes intramolecular hydrogen bonds. Instead, one well-ordered DMSO molecule forms an intermolecular hydrogen bond with each hydroxy group of **2** (Fig. 1). This amount of DMSO corresponds to 51% of the crystal mass, a value somewhat lower than characteristic of quasi-solutions formed by *rctt* isomers of tetrameric resorcinarenes.[11] Along the crystallographic c-axis, the molecules are arranged into infinite tubes that are stabilized by van der Waals interactions (Fig. 2). These tubes are isolated from each other by layers of hydrogen-bonded DMSO molecules.

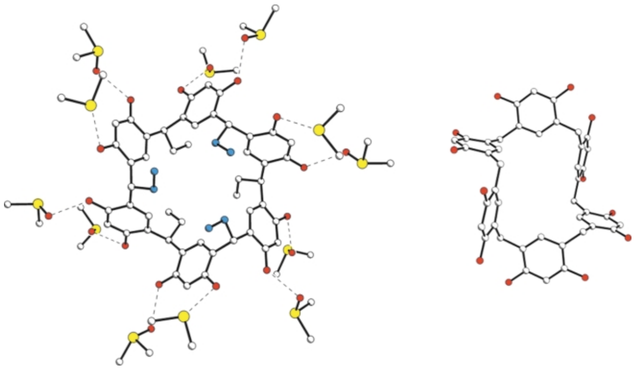

Fig. 1 Crystal structure of **2**·12DMSO. Hydrogen atoms are omitted for clarity. Left: Top view. Ethyl groups above the plane of the macrocycle are shown in blue. Hydrogen bonds are shown in dotted lines; Right: Tilted view. Pendant groups and DMSO molecules are omitted for clarity.

Slow crystallization of **2** from acetone afforded diffraction quality crystals of the composition **2**·6acetone. The molecule **2** exists in nearly the same conformation as in **2**·12DMSO (Fig. 3, top left) and the resorcinarene molecules form infinite tubes along crystallographic c-axis (Fig. 3, bottom). The acetone molecules are hydrogen bonded to the alternating hydroxy groups on the perimeter of the resorcinarene. The non-solvated hydroxy groups form intermolecular hydrogen bonds to adjacent molecules of **2**. The change of crystallization solvent from DMSO to acetone does not affect the formation of the tubular arrangements but fine tunes the interactions between them.

Condensation of resorcinol with acetaldehyde or butyraldehyde under the same conditions used for propionaldehyde

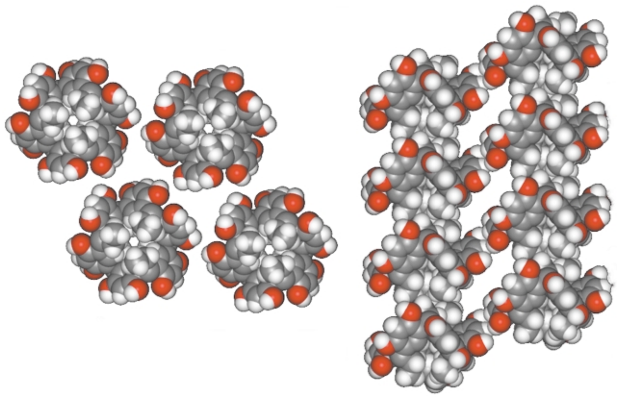

Fig. 2 Crystal packing of **2**·12DMSO in space-filling representation. DMSO-molecules are omitted for clarity. Left: View along crystallographic c-axis; Right: View along crystallographic a-axis.

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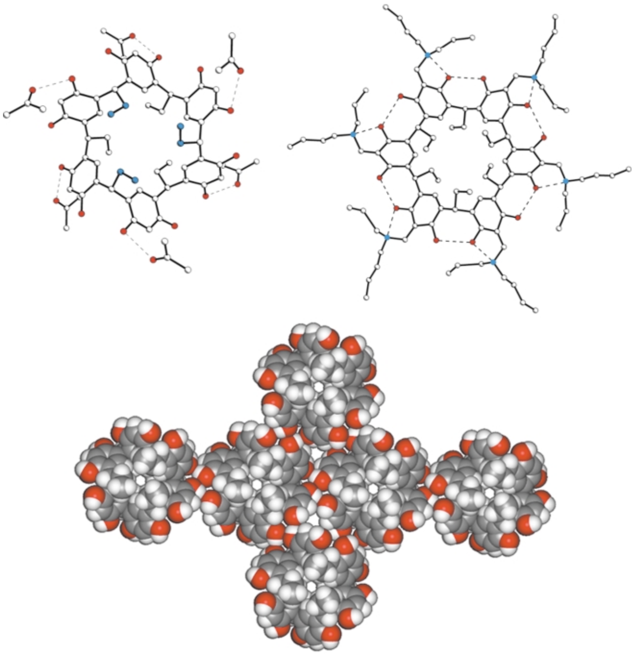

Fig. 3 Top left: Molecular structure of **2**·6acetone. Top right: Molecular structure of **3**. Hydrogen atoms are omitted for clarity. Hydrogen bonds are shown in dotted lines. Bottom: Crystal packing of **2**·6acetone (space filling representation). Acetone molecules are omitted for clarity.

afforded only the cyclic tetramers. The formation of hexamer **2** results from its precipitation from the reaction mixture. When either **1** or **2** are subjected to the reaction conditions for 24 hours, they neither interconvert nor equilibrate. The low solubility is most probably caused by the ideal shape of molecules **2** for crystal packing (Fig. 2, 3).

Aminomethylation of **2** with dibutylamine and formaldehyde in ethanol affords hexaaminomethylated derivative **3**. The ^{1}H NMR spectrum of **3** in $CDCl_3$ at 295 K contains two multiplets for the diastereotopic methylene protons of pendant ethyl groups and the benzyl methylene protons emerge as an AB quartet. The protons of the resorcinol rings and methine bridges give one singlet and one triplet, respectively. This pattern corresponds to an inherently chiral conformation with clock- or counterclockwise orientation of hydrogen bonding dibutylamino groups.[12] A preliminary X-ray crystallographic investigation revealed such a conformation (Fig 3, top right). Strong intramolecular hydrogen bonds were found between amino groups and neighboring hydroxy groups (N–O distances 2.6 Å). The remaining hydroxy groups of **3** form intramolecular hydrogen bonds (O–O distances 2.9 Å).

In conclusion, **2** is available in multigram amounts. The favorable packing of the pendant ethyl groups appears to direct the formation of tubular architectures. Acylated, alkylated and aminomethylated derivatives of **2** are currently under examination as building blocks for crystal engineering.

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Notes and references

† **Hexaethylresorcin[6]arene 2**. Resorcinol (55 g, 5.0 × 10^2 mmol) was dissolved in absolute ethanol (100 mL) in a 500 mL round bottom flask under nitrogen. Water (100 mL) was added, followed by the slow addition of concentrated hydrochloric acid (50 mL). The solution was stirred at 0 °C, and propionaldehyde (36 mL, 5.0 × 10^2 mmol) was added over 8 h by syringe pump. The reaction mixture was allowed to warm to room temperature and stirred for 12 h after which it was heated to 75 °C and stirred at this temperature for another 24 h. The precipitate was then filtered and washed with 150 mL 1 : 1 ethanol–water. The crude product was then allowed to dry under ambient conditions for 12 h, after which it was suspended in 400 mL tetrahydrofuran and heated to boiling. This procedure dissolves resorcin[4]arene **1**, and leaves resorcin[6]arene **2** as a suspended solid. The mixture was then allowed to cool to room temperature and filtered. A drying pistol was used to remove residual tetrahydrofuran yielding an off–white solid (5.5 g, 4.9% yield). M.p. > 300 °C (decomp.). R_f = 0.40 (4 : 1 DCM : MeOH). ^{1}H NMR (MeOH-d_4, 600 MHz) δ 7.42 (s, 6H, Ar*H meta* to OH), 6.29 (s, 6H, Ar*H ortho* to OH), 4.33 (t, *J* = 8, 6H, ArC*H*RAr), 2.04 (m, 12H, $Ar_2CHCH_2CH_3$), 0.77 (t, *J* = 7, 18H, $Ar_2CHCH_2CH_3$). ^{13}C NMR (MeOH-d_4, 150 MHz) δ 153.54, 126.07, 125.54, 103.54, 36.37, 30.36, 13.47. MS (MALDI-FTMS: MNa^+) calcd. for $C_{54}H_{60}O_{12}Na^+$ 923.3977, found 923.3962.

Hexaamine 3. To a solution of **2** (0.2 g, 0.22 mmol) and formaldehyde (1.5 ml, 40%) in EtOH (10 ml) dibutylamine (1.0 g, 7.8 mmol) was added with vigorous stirring. The reaction mixture was stirred at ambient temperature for 8 h, after which the precipitate formed was filtered and washed with ethanol to give hexamine **3** as a white solid (0.3 g, Yield 79%). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 7.06 (s, 6H, Ar*H meta* to OH), 3.99 (t, *J* = 7.3, 6 H, ArC*H*RAr), 3.72–3.64 (m, 12H, $ArCH_2N$), 2.39–2.27 (m, 24H, NCH_2), 2.08–1.98 (m, 6H, $Ar_2CHCH_2CH_3$), 1.86–1.75 (m, 6H, $Ar_2CHCH_2CH_3$), 1.38–1.29 (m, 24H, NCH_2CH_2), 1.15–1.07 (m, 24H, $NCH_2CH_2CH_2$), 0.69 (t, *J* = 7.3, 36H, $NCH_2CH_2CH_2CH_3$), 0.57 (t, *J* = 7.3, 18H, $Ar_2CHCH_2CH_3$). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.52, 150.30, 124.47, 123.76, 122.63, 107.95, 53.76, 52.67, 35.05, 29.16, 28.85, 20.94, 14.35, 13.34. MS (ESI MS: $[M-H]^-$) calcd. for $C_{108}H_{137}N_6O_{12}$ 1746, found 1746.

‡ *X-Ray crystal structure analysis*. Measurements were made on a Bruker Smart diffractometer with CCD-detector, graphite monochromatized MoKα radiation [λ(MoK$_\alpha$) = 0.71073 Å] at 173 K. The crystal was covered by inert FOMBLIN® oil and mounted in the nylon loop. The structures were solved by direct methods (SHELXS-97 [G. M. Sheldrick, *Acta Cryst.* 1990, **A46**, 467]) and refinement, based on F^2, was made by full-matrix least-squares techniques (SHELXL-97 [G. M. Sheldrick, SHELXL-97 - *A program for crystal structure refinement*, 1997, University of Göttingen, Germany]).

2·12DMSO: measurements at 173.0(2) K, crystal size 0.3 × 0.3 × 0.1 mm^3, hexagonal, $R\bar{3}$, a = 11.455(1) Å, c = 10.024(2) Å, V = 2360.0(4) Å^3, Z = 18, ρ_{calcd} = 1.301 g cm^{-3}, 2θ_{max} = 56.12°, μ = 0.348 mm^{-1}, F(000) = 2934, 9 parameters, $R1$ = 0.0684, $wR2$ = 0.1663 (for 1841 refl. $I > 2\sigma(I)$), $R1$ = 0.1532 , $wR2$ = 0.2056 (for 3760 unique reflections), S = 1.022 , $\Delta\rho$ (min/max) = −0.46 / 0.55 e Å^{-3}. CCDC 193890. See http://www.rsc.org/suppdata/cc/b2/b208189j/ for crystallographic files in CIF or other electronic format.

2·6Me$_2$CO: measurements at 173.0(2) K, crystal size 0.3 × 0.3 × 0.2 mm^3, hexagonal, $R\bar{3}$, a = 24.786(2) Å, c = 9.775(1) Å, V = 5201.0(7) Å^3, Z = 18, ρ_{calcd} = 1.197 g cm^{-3}, 2θ_{max} = 56.12°, μ = 0.085 mm^{-1}, F(000) = 2016, 145 parameters, $R1$ = 0.0479, $wR2$ = 0.1194 (for 2338 refl. $I > 2\sigma(I)$), $R1$ = 0.0579, $wR2$ = 0.1266 (for 2796 unique reflections), S = 1.045 , $\Delta\rho$ (min/max) = −0.2/0.4 e Å^{-3}. CCDC 193891.

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