Calix[6]resorcinarenes: The First Examples of [1$_6$]Metacyclophanes derived from Resorcinols

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The cyclocondensation of 2-alkylresorcinols with 1,3,5-trioxane in ethanol–conc. HCl (4:1 v/v) produced calix[4]resorcinarene and calix[6]resorcinarene; the latter was isomerized to the former on prolonged heating in the reaction media.

4-Alkylphenols react with formaldehyde under basic conditions to afford cyclic oligomers, calix[*n*]arenes (*n* = 4–8).[1] On the other hand, the acid-catalysed cyclocondensation of resorcinols with aldehydes produces calix[4]resorcinarenes as the only isolatable cyclic oligomer.[2–5] In a previous communication, the preparation of a series of calix[4]resorcinarenes derived from 2-alkylresorcinols was described.[6] Further examination of the reaction mixture has now resulted in the isolation of the hexameric macrocycles, calix[6]resorcinarenes. The [1$_6$]metacyclophanes derived from resorcinols are hitherto unknown. We now report the isolation and spectral properties of the cyclic hexamers.

2-Propylresorcinol (2.31 g, 0.015 mol) and 1,3,5-trioxane (0.454 g, 0.005 mol) were dissolved in a mixture of ethanol (20 ml) and conc. HCl (5 ml). This solution was gently refluxed for 3 h with stirring, diluted with water, and then added to diethyl ether. The organic layer was separated and evaporated *in vacuo*. The resulting material was thoroughly washed with methanol to leave an off-white solid, which was recrystallized from acetonitrile–methanol to yield cyclic tetramer **2**† (mp 254–258 °C, 45% yield). The washings were evaporated to dryness, and the residue was triturated with diethyl ether several times to leave a white powder, which was purified by recrystallization from acetone–hexane to yield the hexamer **5**† [mp 300 °C (decomp.), 22% yield]. The condensation of 2-methylresorcinol with 1,3,5-trioxane under similar conditions gave the cyclic tetramer **1**[7] and the cyclic hexamer **4**,† which are less soluble in common solvents than the propyl derivatives.‡ On the other hand, **3**[6] and **6**† derived from 2-hexylresorcinol have good solubility in nonpolar solvents.§ The cyclic oligomers were characterized by FAB mass, IR, ^{1}H and ^{13}C NMR spectroscopies. The hexameric structures of **4**, **5** and **6** were confirmed by FAB mass spectra (diethanolamine matrix). Due to the high symmetry of the cyclic oligomers, their ^{1}H NMR spectra in $(CD_3)_2SO$ showed three singlets for the bridge CH_2, aromatic H and OH protons.

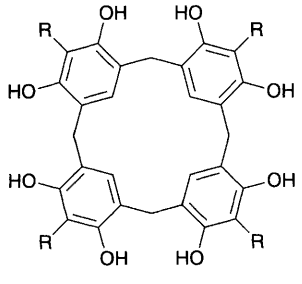
The hexyl derivative **6** has good solubility in $CDCl_3$ for variable-temperature NMR spectroscopy. At −60 °C in this solvent its ^{1}H NMR spectrum displayed three singlets (1:1:1 ratio) at δ 6.32, 6.58 and 6.61 for OH protons, two singlets (2:1 ratio) at δ 7.19 and 7.56 for aromatic protons and two AB systems (2:1 ratio) at δ 3.222 and 3.913 (*J* 14.5 Hz) and δ 3.639 and 4.148 (*J* 14.1 Hz) for the bridging methylene. The Δδ values (0.69 and 0.51 ppm), the chemical shift differences between the geminal protons of the bridging methylene groups, rule out the *anti*-orientation of adjacent aromatic rings. These spectroscopic characteristics indicate that at −60 °C **6** exists in a winged cone conformation with effective C_{2v} symmetry (out–up–up–out–up–up).[1] At ambient temperature, the spectrum showed that the six resorcinol rings are equivalent on the NMR timescale.

The presence of intramolecular hydrogen bonding between the OH groups on the adjacent resorcinol rings was confirmed by IR spectroscopy. In $CDCl_3$, **5** and **6** show the hydrogen-bonded ν_{OH} at 3432 and 3430 cm^{-1}, respectively. A small shift to a higher wavenumber in ν_{OH} compared with **3** (3420 cm^{-1}) suggests that the intramolecular hydrogen bonding in the cyclic hexamer is slightly weaker than that in the cyclic tetramer. However, it is noted that the hydrogen bonding in the calix[*n*]resorcinarene system is much weaker than that in the calix[*n*]arene system.[8]

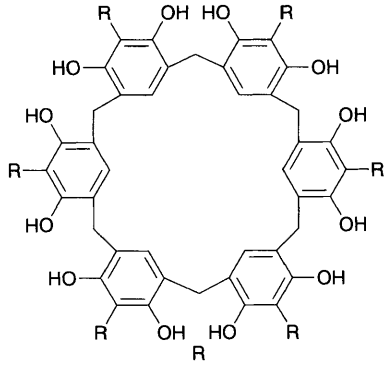
The reaction of 2-propylresorcinol with 1,3,5-trioxane is homogeneous, and the yields of **2**, **5** vary with reaction time. Periodic analysis of the reaction mixture by ^{1}H NMR revealed that several linear and cyclic oligomers are first to form and **5** develops as the major product with increasing time. Furthermore, under refluxing conditions, **5** was completely converted to **2** within 24 h.¶ These experiments clearly established that the tetramer is thermodynamically a more stable product.

The factors responsible for the selective formation of cyclic tetramers in the reaction of resorcinols with aldehydes are attributed to the strong intramolecular hydrogen bonding between the OH groups of adjacent resorcinol units and the steric repulsion between the OH groups and the substituents on the bridge methylene.[5] However these two factors are lacking in our cases. A detailed study of the selective formation of the tetramer is currently in progress.

Received, 9th August 1994; Com. 4/04876H



R
1 Me
2 Pr^n
3 *n*-C$_6$H$_{13}$



R
4 Me
5 Pr^n
6 *n*-C$_6$H$_{13}$

Footnotes

† *Spectroscopic data*: NMR spectra were obtained at 50 °C in $(CD_3)_2SO$. **1**: ^1H NMR (270 MHz) δ 1.997 (s, 12H, CH_3), 3.589 (s, 8H, bridge CH_2), 6.756 (s, 4H, aromatic), 8.48 (s, 8H, OH); ^{13}C NMR (67.5 MHz) δ 9.9, 30.0 (bridge CH_2), 112.2 (2-Ar), 120.7 (4,6-Ar), 127.7 (5-Ar), 150.0 (1,3-Ar). **2**: ^1H NMR (270 MHz) δ 0.882 (t, 12H, CH_3), 1.385 (m, 8H, $CH_2CH_2CH_3$), 2.5 (m, 8H, $ArCH_2$), 3.562 (s, 8H, bridge CH_2), 6.680 (s, 4H, aromatic), 8.42 (s, 8H, OH); ^{13}C NMR (67.5 MHz) δ 13.9, 21.9, 25.5, 29.9 (bridge CH_2), 116.9 (2-Ar), 120.4 (4,6-Ar), 127.7 (5-Ar), 149.8 (1,3-Ar). **3**: ^1H NMR (270 MHz) δ 0.850 (m, 12H, CH_3), 1.26 [br s, 32H, $CH_2(CH_2)_4CH_3$], 2.55 (m, 8H, $ArCH_2$), 3.564 (s, 8H, bridge CH_2), 6.633 (s, 4H, aromatic), 8.292 (s, 8H, OH); ^{13}C NMR (67.5 MHz) δ 13.9, 22.0, 23.6, 28.9, 30.0, 31.2, 117.4 (2-Ar), 120.5 (4,6-Ar), 127.7 (5-Ar), 149.9 (1,3-Ar). **4**: ^1H NMR (270 MHz) δ 2.037 (s, 18H, CH_3), 3.605 (s, 12H, bridge CH_2), 6.990 (s, 6H, aromatic), 8.51 (s, 12H, OH); ^{13}C NMR (67.5 MHz) δ 9.7, 30.2 (bridge CH_2), 112.2 (2-Ar), 120.6 (4,6-Ar), 127.8 (5-Ar), 150.1 (1,3-Ar). **5**: ^1H NMR (270 MHz) δ 0.885 (t, 18H, CH_3), 1.41 (m, 12H, $CH_2CH_2CH_3$), 2.5 (m, 12H, $ArCH_2$), 3.585 (s, 12H, bridge CH_2), 6.923 (s, 6H, aromatic), 8.44 (s, 12H, OH); ^{13}C NMR (67.5 MHz) δ 13.4, 21.6, 25.2, 29.9 (bridge CH_2), 117.0 (2-Ar), 120.3 (4,6-Ar), 127.6 (5-Ar), 149.7 (1,3-Ar). **6**: ^1H NMR (270 MHz) δ 0.838 (t, 18H, CH_3), 1.25 [br s, 48H, $CH_2(CH_2)_4CH_3$], 2.585 (t, 12H, $ArCH_2$), 3.592 (s, 12H, bridge CH_2), 6.990 (s, 6H, aromatic), 8.44 (s, 12H, OH); ^{13}C NMR (67.5 MHz) δ 13.9, 22.0, 23.6, 28.8, 30.5, 31.1, 117.5 (2-Ar), 120.7 (4,6-Ar), 128.0 (5-Ar), 149.9 (1,3-Ar).

‡ ^1H NMR analysis of the reaction mixture showed that **1** and **4** are the major products. The reaction mixture was acylated with propionic anhydride and pyridine, and the resulting dodecapropionate of **4** was isolated as a insoluble fraction and converted to **4** by treatment with $LiAlH_4$. **4**: mp 230 °C (decomp.), 13% total yield. Isolation of **1** from the reaction mixture was not attempted.

§ The condensation of 2-hexylresorcinol with 1,3,5-trioxane gave a complex mixture, from which **6** was isolated by repeated TLC separation (silica gel, ethyl acetate–hexane 1:4 *v/v*). **6**: mp 200 °C (decomp.), 9% yield.

¶ A solution of 100 mg of **5** in 2.0 ml of a mixture (4:1 *v/v*) of ethanol and conc. HCl was heated at 80 °C for 24 h. The solvent was removed *in vacuo*, and the resulting tetramer was analysed by TLC and ^1H NMR.

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