

Rational Synthesis of Resorcarenes with Alternating Substituents at Their Bridging Methine Carbons

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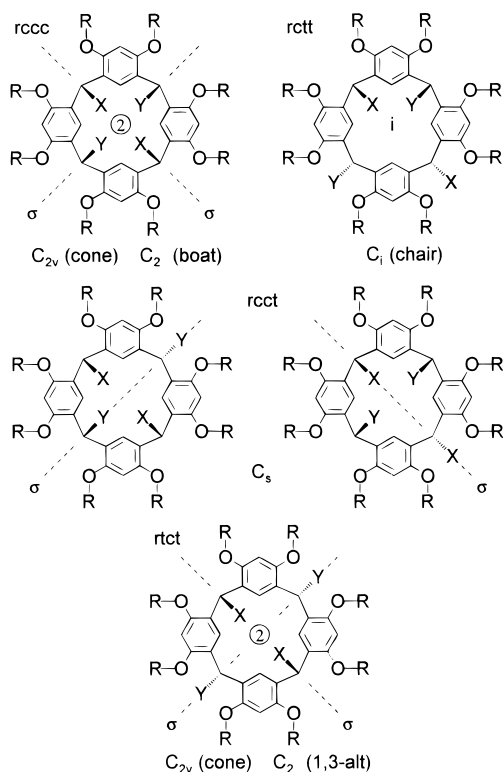
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Resorcarenes^{1,2} are macrocyclic compounds that are easily obtained by acid-catalyzed condensation of resorcinol with a variety of aliphatic as well as aromatic aldehydes in a simple one-pot reaction. Of the four possible stereoisomers (rccc, rctt, rctc, rtct), the all-cis isomer (rccc) is often the main product (Scheme 1). This isomer has been widely used to synthesize further elaborated molecules such as cavitands^{2,3} (hemi)carcerands^{2,4} or even larger systems.⁵ The rctt isomer, sometimes a kinetically controlled product that can be isomerized to the thermodynamically stable rccc-isomer, has attracted less attention,⁶ while only a few examples of the rctc isomer have been reported.⁷

In all these cases, a single aldehyde has been used and consequently the four resorcinol units are linked via the same –CHR bridge. We report here the first controlled synthesis of resorcarenes in which two different aldehydes are incorporated in alternating order.^{8,9}

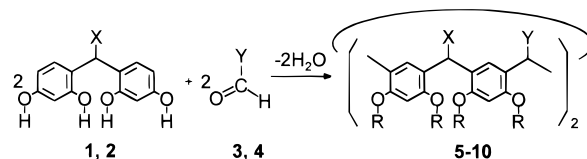
Acid-catalyzed condensation of dimer **1**, available in a rational way through condensation of 4-bromoresorcinol with phenylpropionaldehyde (60%) and subsequent dehalogenation (100%), with *p*-hydroxybenzaldehyde **3** gave a condensation product in quantitative yield. After complete acetylation (acetic anhydride/pyridine), the product was separated (crystallization from methanol, column chromatography (CHCl₃/ethyl acetate 7/3)) into three fractions (**a**, 10%; **b**, 15%; **c**, 34%; isolated yields), which on the basis of MS and NMR evidence, are isomeric decaacetates **8** of the desired alternating resorcarene **5** (Scheme 2).

Scheme 1. Possible Stereoisomers of Alternating Resorcarenes with Their Symmetry Elements^a



^a The σ -plane in the rccc and rtct isomer exists only in a cone conformation. On the basis of the present general experience, the formation of the rctc isomer is highly unlikely.

Scheme 2. Synthesis of Alternating Resorcarenes



- 1 X = $-(CH_2)_2-C_6H_5$ 3 Y = *p*-C₆H₄-OH
2 X = *p*-C₆H₄-NO₂ 4 Y = $-CH_2-CH_3$

	X	Y	R
5	$-(CH_2)_2-C_6H_5$	<i>p</i> -C ₆ H ₄ -OH	H
6	<i>p</i> -C ₆ H ₄ -NO ₂	<i>p</i> -C ₆ H ₄ -OH	H
7	$-(CH_2)_2-C_6H_5$	$-CH_2-CH_3$	H
8	$-(CH_2)_2-C_6H_5$	<i>p</i> -C ₆ H ₄ -O-CO-CH ₃	-CO-CH ₃
9	<i>p</i> -C ₆ H ₄ -NO ₂	<i>p</i> -C ₆ H ₄ -O-CO-CH ₃	-CO-CH ₃
10	$-(CH_2)_2-C_6H_5$	$-CH_2-CH_3$	-CO-CH ₃

A preliminary structural assignment was possible by ¹H NMR spectroscopy. A singlet (5.66 ppm) and a triplet (3.99 ppm) for the methine protons of **8a** are compatible with the rccc isomer, although the rctt isomer cannot be entirely excluded. Three triaryl methine signals (1:2:1) for **8b** suggest a 1:1 mixture of the two possible rctc isomers (which in fact can be separated by further chromatography with CHCl₃/ethyl acetate/*n*-hexane 8/1/1). The rctc configuration of **8c** is suggested by a doublet of doublets (instead of a triplet)

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(1) For a review see: Timmerman, P.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1996**, *52*, 2663.

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(7) (a) Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Org. Chem.* **1988**, *53*, 5475. (b) Abis, L.; Dalcanale, E.; Du vosel, A.; Spera, S. *J. Chem. Soc., Perkin Trans. 2* **1990**, 2075.

(8) A recent publication describes a statistical approach using a mixture of two aldehydes: Hayashi, Y.; Maruyama, T.; Yachi, T.; Kudo, K.; Ichimura, K. *J. Chem. Soc., Perkin Trans. 2* **1998**, 981–987.

(9) Resorcarenes consisting of different resorcinol units were recently also described: Cortes-Lopez, G.; Gutierrez Tunstad, L. M. *Synlett* **1998**, 139

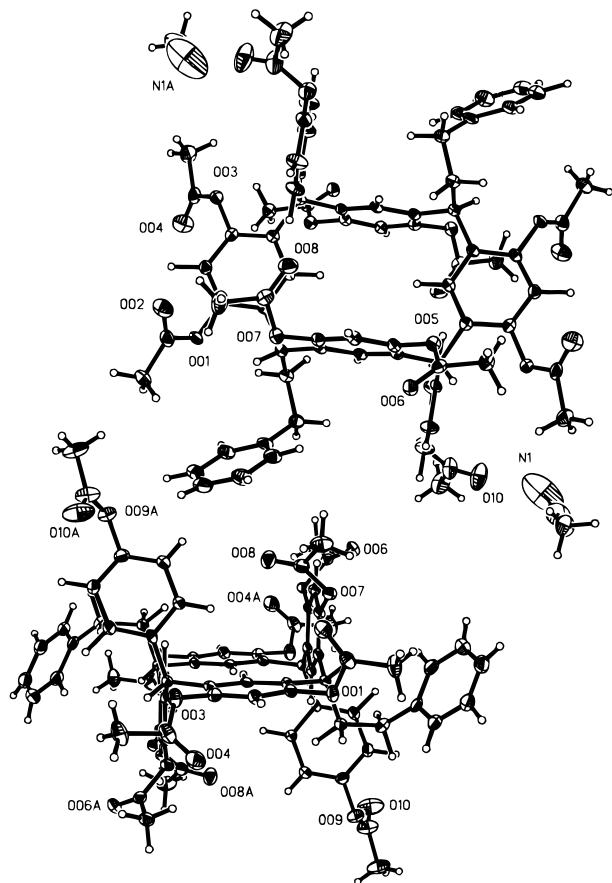


Figure 1. Molecular conformation of **8c** seen from two different directions, showing the alternating order of the methine bridge residues (above) and the chair conformation of the rctt isomer (below).

for the methine protons at 4.08 ppm (in addition to the singlet at 5.58 ppm), as the diastereotopicity of the adjacent CH_2 protons is much more pronounced than for the boat conformation of **8a**, thus leading to different coupling constants. The stronger separation of the singlets of the *endo*-aryl protons (6.11 and 6.68 ppm) is also expected for the chair conformation of the rctt isomer.

Both the general structure of the resorcarenene skeleton with alternating substituents at the methine bridges and the configurational/conformational assignment for **8c** were confirmed by the single-crystal X-ray analysis¹⁰ shown in Figure 1.

Condensation of the dimer **2** with *p*-hydroxybenzaldehyde **3** was also quantitative, and three different isomers (**a**, 40%;

(10) Crystal data for **8c**: $\text{C}_{76}\text{H}_{88}\text{O}_{20} \cdot 2\text{CH}_3\text{CN}$; $M_r = 1383.41$, triclinic, space group $P-1$, $Z = 1$, $a = 10.745(1) \text{ \AA}$, $b = 12.450(1) \text{ \AA}$, $c = 14.244(1) \text{ \AA}$; $\alpha = 76.49(1)^\circ$, $\beta = 85.39(1)^\circ$, $\gamma = 83.87(1)^\circ$, $V = 1839.1(3) \text{ \AA}^3$, $D_c = 1.249 \text{ g cm}^{-3}$; crystals from $\text{CH}_3\text{CN}/\text{CH}_2\text{Cl}_2$, dimensions $0.35 \times 0.1 \times 0.07 \text{ mm}$; computer-controlled four-circle diffractometer with CCD area detector and low-temperature device, X-ray generator with rotating anode (Siemens), λ (Mo $K\alpha$) = 0.71073 \AA , $\mu = 0.090 \text{ mm}^{-1}$, $F(000) = 728$, $T = 238(2) \text{ K}$; 6894 reflections measured, 4066 of which were unique ($R_{\text{int}} = 0.0465$, $R_\sigma = 0.1026$) and used for the structure determination. Direct methods (SHELXS-90), refinement by least-squares methods (SHELXS-90, SHELXL-93), minimization of $(F_o^2 - F_c^2)^2$; $R = 0.0811$ and $R_w = 0.2022$ for 2351 reflections with $I > 2\sigma(I)$, $R = 0.1408$ and $R_w = 0.2417$ for all unique CCD data; the coordinates of the H-atoms were calculated, $S = 1.021$, $\Delta\rho_{\text{min}} = -0.270$, $\Delta\rho_{\text{max}} = 0.517 \text{ e \AA}^{-3}$.

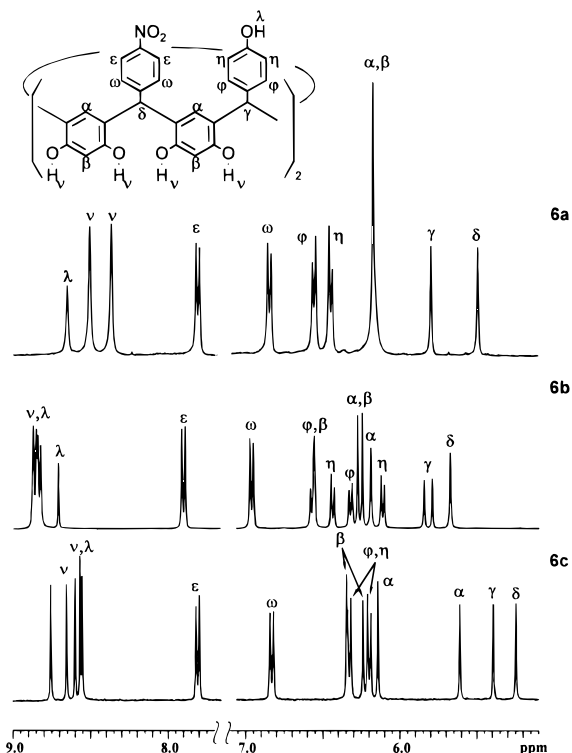


Figure 2. Section of the ^1H NMR spectra of the three isomeric resorcarenenes **6a–c** (400 MHz, CDCl_3). The assignment of α/β , δ/γ , and η/ϕ is sometimes tentative (**6a** at 60°C , **6b,c** at rt).

b, 7%; **c**, 40%; isolated yields) were separated chromatographically from the mixtures **6a–c** or **9a–c**, respectively. In this case, only one rctt isomer (**6b**), with two identical *p*-nitrophenyl groups, was observed, in addition to the rccc (**6a**) and rctt (**6c**) isomers. Its ^1H NMR spectrum is shown and interpreted in Figure 2, and this structural assignment is confirmed by its decaacetate **9b**, showing six methyl singlets in the ratio of 1:1:2:2:2:2.

The less reactive propionaldehyde **4** gave with **1** only 15% of a condensation product **7**, which after acetylation could be split into four isomeric compounds **10**, namely the rccc, the rctt, and the two rctt isomers.

In conclusion, we have shown for the first time that resorcarenenes bearing aldehyde residues in alternating order can be prepared by fragment condensation of resorcinol derived dimers with a second aldehyde. Further analogous compounds should be available, using various aldehydes in various combinations.

Thus far, the condensations were carried out under mild conditions, while the rccc isomer often forms preferably at high temperatures. Such an acid-catalyzed isomerization $\text{rctt} \rightarrow \text{rccc}$ requires the cleavage of $\text{Ar}-\text{CHR}$ bonds, a reaction that could lead to a "scrambling" of residues X and Y. However, no compounds with a different composition could be detected, and we are presently attempting to modify the conditions in order to shift the product distribution toward the rccc isomer.

Supporting Information Available: Crystallographic details of compound **8c** and preparation and characterization of compounds **6** and **9** (14 pages).

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