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Facile Lewis Acid Catalyzed Synthesis of C_4 Symmetric Resorcinarenes

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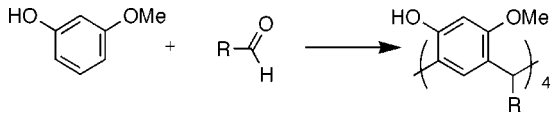
ABSTRACT



The Lewis acid catalyzed condensation of 3-methoxyphenol with octanal produced the C_4 symmetric calix[4]resorcinarene 2, in high yield. Of the numerous stereo- and regioisomers possible, the rccc isomer with C_4 symmetry was the only product isolated (as a racemate). The structure has been established by single-crystal X-ray structure analysis.

Calixarenes are readily functionalized macrocyclic compounds that can include ions and neutral molecules within their cavity.[1] Calixarene derivatives have been employed in a variety of industrial applications,[2] and in recent years the applications of chiral calixarenes have attracted considerable interest.[3] Consequently, many elegant syntheses of chiral calixarenes have been developed. These have included the attachment of chiral moieties,[4] controlled regioselective substitution with a chiral auxiliary,[5] asymmetric substitution on the calixarene skeleton,[6] and condensation of *meta*-substituted phenols.[7]

The aesthetic simplicity and molecular recognition potential of the C_4 symmetric calixarenes inspired us to develop a practical "one-pot" synthesis of C_4 symmetric resorcin[4]-arenes. It has been reported that resorcinol derivatives in which the hydroxyl groups are (partially) alkylated do not give cyclomeric products on condensation with aldehydes in the presence of mineral acids in alcoholic solvents.[8] However, octamethylresorcinarenes have been prepared by employing a Lewis acid catalyst,[9] and this prompted us to investigate the use of Lewis acids in the reaction of 3-methoxyphenol (**1**) with octanal (Scheme 1).

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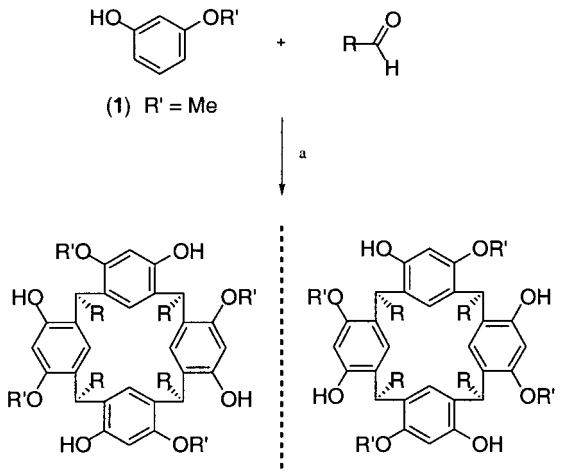
Scheme 1



a. $BF_3.Et_2O$ 2 eq., CH_2Cl_2, rt, 2 h.

(**2**) R = C_7H_{15}, R' = Me, (**3**) R = $C_{11}H_{23}$, R' = Me
(**4**) R = $C_{11}H_{23}$, R' = *n*-Pr

Resorcinarenes can be formed in four principal isomeric configurations: rccc, rcct, rctt, and rtct.[8a] Numerous regioisomers are possible for each of these configurations when resorcinol monoethers are used as the precursor. For example, four regioisomers having the rccc configuration are possible (Figure 1).

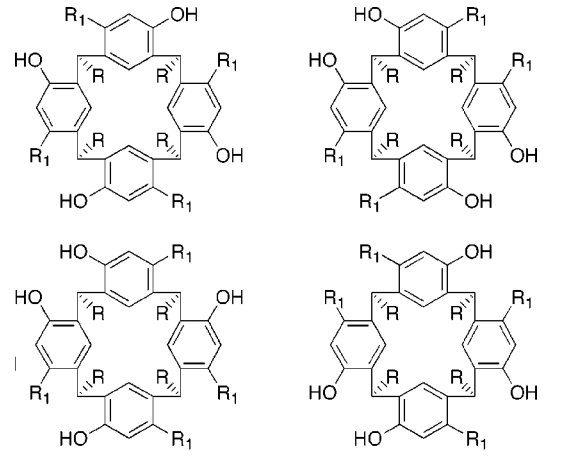


Figure 1. Four regioisomers possible for the rccc configuration.

The reaction of **1** with 1 equiv of octanal, in the presence of 2 equiv of $BF_3{\cdot}Et_2O$ in anhydrous dichloromethane gave a high yield (80%) of the C_4 symmetric chiral resorcin[4]-arene **2**. The mass spectrum (M^+ = 936.6) confirmed that the product was tetrameric. This coupled with the ^{1}H NMR spectrum clearly supported a resorcinarene with C_4 symmetry as there was only one signal for the methoxy groups, one for the bridging methines, and only two signals for the upper and lower rim aromatic protons.[10] Evidence that the resorcinarene **2** was a racemic mixture was obtained by measurement of the ^{1}H NMR spectrum in the presence of the chiral shift reagent europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate]. This resulted in a doubling of the phenolic, aromatic, and methine signals (Figure 2),

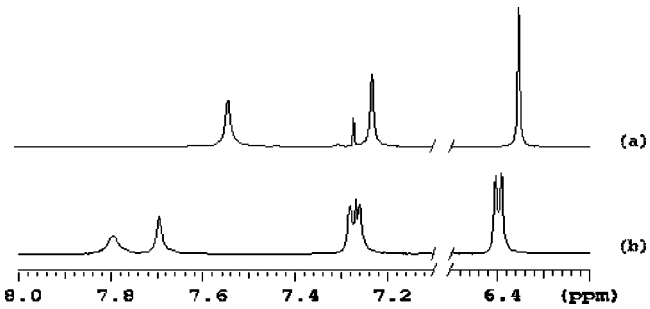


Figure 2. ^{1}H NMR spectrum of the aromatic region of the resorcinarene (**2**) without (a) and with (b) the chiral shift reagent, europium tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate].

demonstrating that the product was a mixture of enantiomers in a ratio of 1:1,[11] consistent with its crystallization in the centrosymmetric triclinic space group $P\bar{1}$, with one molecule and accompanying THF solvent comprising the asymmetric unit of the structure.[12] Taking the C_4 "plane" of the bridging methylene groups as datum, the C_6 aromatic ring planes exhibit alternately steep and shallow inclinations, with the totality of the molecule including substituent dispositions approaching C_2 in symmetry. Interestingly, the phenolic hydrogen atoms do not conform to this symmetry; three are engaged in OH···OMe interactions between neighboring rings cyclically but the fourth in an intermolecular hydrogen bond (Figure 3). The crystal packing is of interest with molecules approaching pairwise across crystallographic

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(10) Selected data for **2**: mp 160 °C. ^{1}H NMR ($CDCl_3$) δ 0.90 (br t, 12 H, CH_2CH_3), 1.20−1.42 (m, 40 H, CH_2), 2.20 (m, 8 H, CH_2CH), 3.84 (s, 12 H, OCH_3), 4.28 (t, 4 H, J = 7.8 Hz, $CHCH_2$), 6.36, 7.23, (s, 2 × 4 H, Ar), 7.52 (s, 4 H, OH). ^{13}C NMR ($CDCl_3$) δ 14.7 (CH_3), 23.2, 28.7, 30.0, 30.3, 32.5, 34.6 (CH_2), 33.7 (CH), 56.5 (OCH_3), 100.7, 124.4, 125.3, 125.4, 153.7, 154.4 (Ar). Found: C, 76.8; H, 9.4; $C_{60}H_{88}O_8$; requires C, 76.9; H, 9.5%.

(11) Chiral HPLC on a Chiralpak AD column gave partial resolution of the enantiomers using hexane/2-propanol (98:2) as eluent.

(12) $C_{60}H_{88}O_8{\cdot}$thf, M_r = 1009.5. Triclinic $P\bar{1}$, a = 12.218(1), b = 13.820(1), c = 17.532(2) Å, α = 80.400(1), β = 86.126(1), γ = 80.06(1)°, V = 2907 Å^3. D_C = 1.153 g cm^{-3}. T ca. 153 K. 32861 CCD diffractometer reflections (monochromatic Mo Kα radiation, λ = 0.7107$_3$ Å; $2\theta_{max}$ = 58°) merged to 13899 unique (R_{int} = 0.013), 11056 with $F > 4\sigma(F)$ being considered "observed" and used in the full matrix least squares refinement, refining undisordered and disordered major component non-hydrogen atom thermal parameter forms anisotropically, and associated (x, y, z, U_{iso})$_H$. Chain C(10n) (etc.) was modelled as disordered over two sets of sites, occupancies refining to 0.697(4) and complement. The (nonincluded) THF solvent was modelled with CH_2 groups disordered over two sets of sites of equal occupancy. Final R, R_w (statistical weights) at convergence: 0.043, 0.057, $|\Delta\rho_{max}|$ = 0.88(1) e Å^{-3}. CCDC 151370.

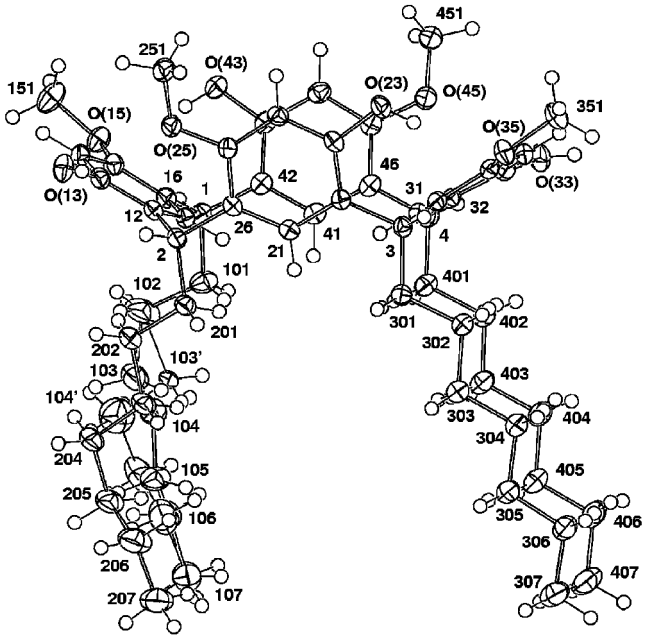

Figure 3. Projection of a single molecule, showing 50% thermal envelopes for the non-hydrogen atoms, hydrogen atoms having arbitrary radii of 0.1 Å. H(13,23,43) have intramolecular hydrogen bonds to O(25,35,15) (O,H···O: 2.946(2), 2.34(2); 3.050(1), 2.22(2); 2.934(2), 2.13(2) Å, respectively), H(33) intermolecular to THF O(01) (O,H···O ($x-1, y, z$) 2.736(2), 1.96(2) Å). Dihedral angles of the C_6 ring planes ($n = 1-4$) to the C(1,2,3,4) datum (χ^2 10^4; δC(n) −0.083(2), 0.080(2), −0.078(2), 0.084(2) Å) are 32.54(4), 73.29(3), 28.89(3), 76.11(4)°. The sequence C(103−106) of tail 1 is disordered.

inversion centers in a somewhat staggered interlocking approach so as to mesh rim substituents mutually. The alkane "tails" to the other side of the molecule are all quite reasonably planar; for the arrays C(n,n01−7) deviations lie in the range $n = 1,1'$ −0.36−0.55, −0.35−0.79; $n = 2$ −0.34−0.44, $n = 3$ −0.03−0.04, $n = 4$ −0.05−0.07 Å, i.e., tails 3 and 4 in particular are very planar indeed. Tails 2, 3, and 4 in particular are quasiparallel (interplanar dihedrals 2/3,4; 3/4 23.9(1), 13.7(1); 11.0(1)°) and pack together with their inversion images in a swarm about the center of the cell, with the less intimately involved tail 1 disordered at the periphery (figure available as Supporting Information).

A possible rationale for such remarkable regioselectivity would involve the complete formation of the intermediate, 2-(1-hydroxyoctyl)-5-methoxyphenol, prior to subsequent condensation with like molecules to ultimately produce the tetrameric product. Although it may be argued that this C_4 symmetry was due to a reversible reaction with the formation of four intramolecular O−H···OMe hydrogen bonds as the driving force, we believe that this is not the case as it has been reported by Botta et al.[9a] that the Lewis acid catalyzed isomerization of resorcinarenes required heating for several hours at reflux.

The reaction of dodecanal with 3-methoxyphenol and 3-propoxyphenol[13] yields the corresponding C_4 symmetric resorcinarenes **3** and **4**, respectively. Thus, the reaction appears to be general with respect to the aliphatic aldehyde and 3-alkoxyphenol.

In conclusion, this work is an important advance in the high-yield preparation of C_4 symmetric resorcinarenes and provides potential for new axially chiral resorcinarenes.

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Supporting Information Available: Experimental procedures and characterization for compounds **2**−**4**; the unit cell packing arrangement and crystallographic data in cif format. This information is available free of charge via the Internet at http://pubs.acs.org.

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