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Selective functionalization of a resorcin[6]arene

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ABSTRACT

The Mannich-type condensation of hexaethylresorcin[6]arene with achiral primary amines results in S_6-symmetrical hexadihydro-1,3-oxazine derivatives, which are mesoforms. The reaction with individual enantiomers of α-phenylethylamine leads to C_3-symmetrical enantiomeric hexaoxazines, which crystallize from reaction mixtures in an analytically pure form.

1. Introduction

Resorcin[4]arenes **1**[1] (Fig. 1) are excellent building blocks for rational design of container molecules,[2] ion receptors,[3] self-assembling molecular capsules,[4] and hollow crystal structures.[5] Compounds **1** are readily available through the thermodynamically controlled acid-catalyzed condensation of resorcinol or its 2-substituted derivatives with various aldehydes.[6] In some cases, the reaction of 2-alkylresorcinol with formaldehyde affords resorcin[5]- and resorcin[6]arenes.[7] Acid-catalyzed condensation of resorcinol with propionic aldehyde resulted in resorcin[6]arene **2** as a minor product (5% yield),[8] which could be purified by simple crystallization.

Single crystal X-ray analysis revealed that compound **2** has *r-trans-cis-trans-cis-trans* (*r-tctct*) configuration and adopts a S_6-symmetrical wreath-like conformation in which the OH groups do not form intramolecular hydrogen bonds but are solvated by polar solvent molecules (acetone, DMSO). Only one derivative **3** was originally synthesized through the aminomethylation of **2** with *n*-dibutylamine and formaldehyde. In the crystalline state, compound **3** has *r-tctct* configuration and adopts a S_6-symmetrical wreath-like conformation stabilized through O–H···O and N···H–O intramolecular hydrogen bonds.

Regio- and stereoselective aminomethylation of resorcin[4]arenes **1** with primary amines and formaldehyde afforded a number of cyclochiral C_4-symmetrical tetraoxazine derivatives **4**[9] possessing extended molecular cavities stabilized by four intramolecular hydrogen bonds. The present research was undertaken in order to develop a method for a regioselective cyclocondensation of resorcin[6]arene **2** with primary amines and formaldehyde.

Reaction of *r-tctct* resorcin[6]arene **2** with primary amines and formaldehyde gives hexaoxazines **5** in a 40% yield (Scheme 1). Compounds **5** precipitate from the reaction mixtures and can be easily purified by simple recrystallization. Unlike the parent dodecaol **2**, hexaoxazines **5** are very soluble in nonpolar solvents, such as chloroform, dichloromethane, benzene, toluene, and insoluble in polar DMSO and methanol.

The ^{1}H NMR spectrum of compound **5a** measured in $CDCl_3$ at 295 K (500 MHz) contains one set of singlets for the protons of the resorcinol rings and hydroxyl groups, whereas the diastereotopic methylene protons of the oxazine rings emerge as pairs of ***AB*** doublets at 4.9 ppm (Fig. 2a). The signal centered at 4.1 ppm corresponds to the protons of the methine bridges. It arises as an ***ABB′*** quartet apparently due to the spin–spin coupling with diastereotopic protons of the adjacent methylene groups. The protons of the OH groups emerge as a sharp singlet at 7.4 ppm. The double doublet with J=23.0 Hz at 3.9 ppm appears to be a signal of an ***AB*** system of the diastereotopic hydrogen atoms of benzyl fragments of the dihydro-1,3-oxazine rings.

This pattern corresponds to S_6-symmetrical structure **A** (mesoform), in which the methine carbon atoms of the bridges have alternating *R*- and *S*-configurations (Fig. 3). The ^{13}C NMR spectrum of compound **4a** contains 14 sharp signals in accordance with the anticipated S_6-symmetrical structure **A**. Since the aminomethylation with *n*-dibutylamine does not change the conformation of the resorcin[6]arene skeleton it seems very likely that compounds **5** exist in a conformation similar to that of hexamine **3** (Figs. 1 and 3).

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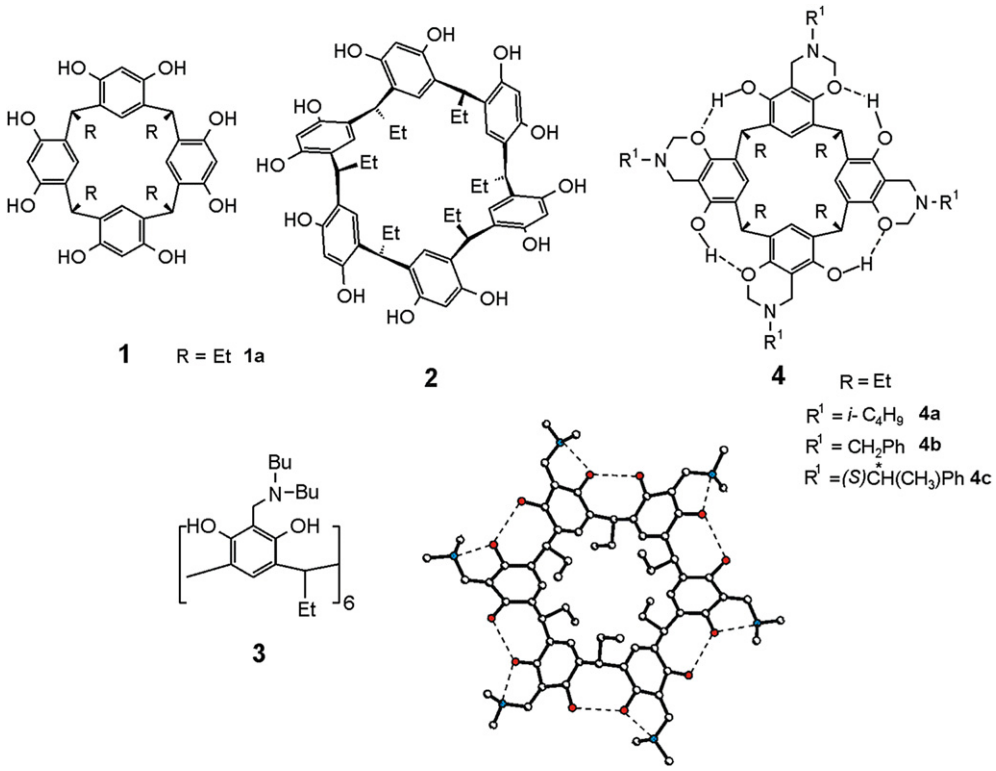
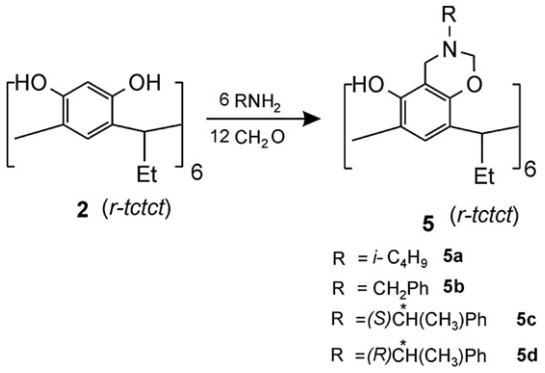


Fig. 1. Structures of compounds **1**–**4** and a molecular structure of hexaamine **3** in the crystalline state (bottom right). Hydrogen bonds are shown in dashed lines; disordered parts of *n*-butyl chains are omitted for clarity.



Scheme 1.

The ^{1}H NMR spectra of compounds **5a** and **5b** are nearly identical to those of tetraoxazines **4a** and **4b**. The protons in the 5-positions of the resorcinol rings emerge at 6.6 and 7.2 ppm for compounds **5** and **4**, respectively, apparently owing to different disposition of the resorcinol rings in the *r-cccc* crown and the *r-tctct* wreath conformations.

Molecular mechanics calculations suggested that the *r-tctct* wreath-like conformation of molecule **5** is likely to be stabilized by six intramolecular OH···O hydrogen bonds. This type of intramolecular hydrogen bonding was observed for resorcin[4]arenes **4** both in the crystalline state and in solution. Accordingly, the protons of the OH groups of compounds **4** and **5** emerge in ^{1}H NMR spectra as slightly broadened singlets at 7.4–7.45 ppm whose shape and position do not considerably depend on the concentration (10^{-2}–10^{-3} M, $CDCl_3$).

The ^{1}H NMR spectra of compounds **5c** and **5d** bearing six chiral (*S*) and (*R*)-α-phenyl-ethylamino groups, respectively, are identical and contain a double set of signals for the protons at the 5-positions of the resorcinol rings and *N*-acetal methylene protons of the dihydro-1,3-oxazine rings (Fig. 2b). The other protons emerge as a complicated set of signals. The ^{13}C NMR spectra of **5c** and **5d** contain a double set of sharp signals in 1:1 ratio for all the carbon atoms in keeping with C_3-symmetrical structure **B** (Fig. 3) whose

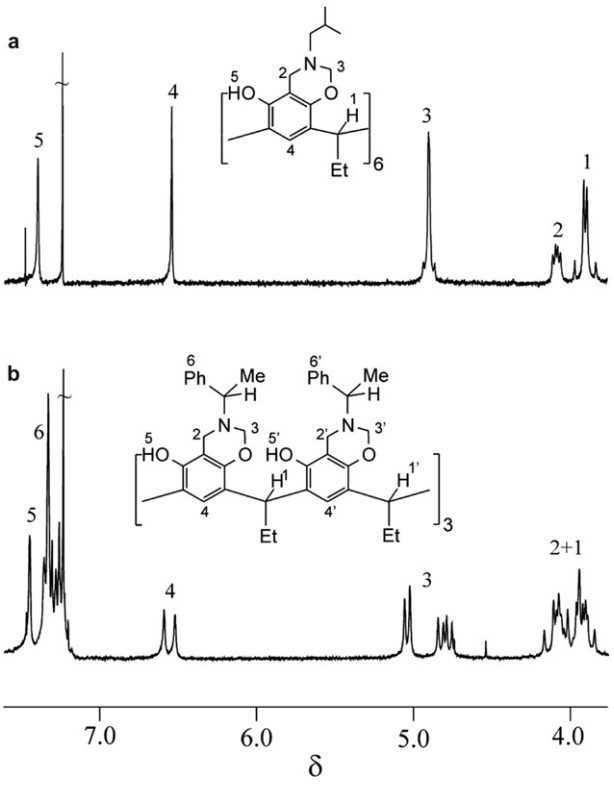


Fig. 2. The ^{1}H NMR spectra (500 MHz, $CDCl_3$, 295 K) of: (a) **5a**; (b) **5c** and **5d**.

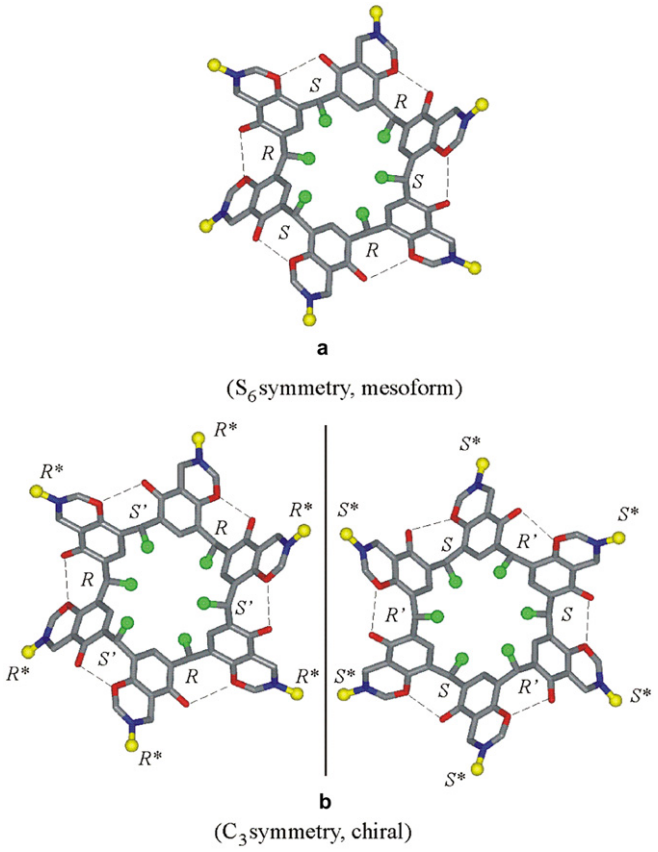


Fig. 3. Energy-minimized structures of compounds **5a**, **b** (A) and **5c**, **d** (B). Time averaged conformations of dihydro-1,3-oxazine rings are shown. Hydrogen bonds are indicated by broken lines.

'asymmetric unit' contains two diastereomeric fragments. Specific optical rotations of compounds **5c** and **5d** are equal in amount and opposite in sign. The above results indicate that dihydro-1,3-oxazines **5c** and **5d** are individual enantiomers.

The HPLC chromatograms of **5c** and **5d** (silica gel, hexane–*i*-PrOH) were identical and contained one broad signal with retention time 4.6 min. Unfortunately all attempts to analyze compounds **5c** and **5d** on chiral cellulose column have failed (see Experimental part).

The reaction of compound **2** with formaldehyde and racemic α-phenylethylamine gave a 1:1 mixture of compounds **5c** and **5d**. The solution of the product did not rotate the plane of polarized light and had ^{1}H and ^{13}C NMR spectra identical to those of individual enantiomers **5c** and **5d**. These results indicate the remarkable diastereoselectivity of the reaction between **2**, α-phenylethylamine, and formaldehyde.

Compounds **5b** and **5c** were also prepared from compound **2** and the corresponding bisaminol ethers.[10] They were postulated to exist as 1:1 mixtures of enantiomers or diastereoisomers, respectively, differing in a clock- and anti-clockwise orientation of dihydro-1,3-oxazine fragments. It should be noted that the *r-ctctct* wreath-like structures of **5b** and **5c** have only one concerted orientation of the dihydro-1,3-oxazine rings . It is in contrast to C_4-symmetrical *rccc* resorcin[4]arenes **4a** and **4c** in which the clock and anti-clockwise orientations of the dihydro-1,3-oxazine rings are enantio- and diastereomeric, respectively.

The regioselective formation of compounds **5** can be explained by intramolecular hydrogen bonding involving six aminomethyl groups in the intermediate hexaminomethylated resorcin[6]arenes (like in hexaamine **3**) that preorganize the amino and hydroxyl groups for the ring closing reaction with formaldehyde to give a concerted orientation of the six dihydro-1,3-oxazine rings.

In conclusion, a Mannich-type aminomethylation of *r-tctct* resorcin[6]arenedodecaol **2** with primary amines and formaldehyde results in the formation of the hexadihydro-1,3-oxazine derivatives whose conformations are stabilized by intramolecular hydrogen bonds between hydroxyl groups and oxygen atoms of dihydro-1,3-oxazine rings. This reaction results in complete functionalization of the resorcinol rings at the 5-position and a selective alkylation of six OH-groups. Apparently, this procedure can be used for synthesis of wreath-like *r-tctct* resorcin[6]arenes bearing six functional groups attached to the 5-positions or (and) to the oxygen atoms of the resorcinol rings.[11]

2. Experimental part

2.1. General

All reactions were carried out under open atmosphere with no precautions taken to exclude ambient moisture. Melting points measured with a Buchi melting points apparatus are uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a Bruker Avance DRX 500 (500 and 125 MHz, respectively) with TMS as an internal standard. IR spectra were measured on a Vertex 70 spectrometer. HPLC analyses were carried out on Agilent 1100, column EC 125/4.6 Nucleosil 100-5 (Macherey-Nagel), eluent hexane–isopropanol 85:15 v/v. Chiral HPLC analyses were carried out on CHIRALPAK IB 0.46×25 cm, cellulose tris (3,5-dimethylphenylcarbamate immobilized on 15 μ silica) eluent hexane–*i*-PrOH (gradient 85:15 up to 70:30).

2.2. General procedure for the synthesis of compounds 5

To a solution of resorcin[6]arene **2** (0.5 g, 0.56 mmol) in ethanol (20 ml), formaldehyde (1 ml, 37% in H_2O, 14 mmol CH_2O) and amine (5 mmol) were added upon stirring. The reaction mixture was stirred for 8 h at ambient temperature, the precipitate was filtered off, washed with ethanol, recrystallized from CH_2Cl_2·MeOH, and dried in vacuo. Yields are not optimized. Analytical data for **5b**–**d** are consistent with the previously reported data.[10]

Compound **5a**: yield 48%. Mp >300 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.39 (s, 6H, OH), 6.53 (s, 6H, CH), 4.90–4.80 (m, 6H, OCH_2N), 4.08 (dd, *J* 9.4 Hz, 6H, CH), 3.89 (dd, *J* 23.0 Hz, 12H, NCH_2), 2.55–2.42 (m, 12H, NCH_2), 2.23–2.09 (m, 6H, CH), 2.00–1.84 (m, 6H, CH), 1.84–1.70 (m, 6H, CH), 0.95–0.84 (m, 36H, $CHMe_2$), 0.74 (t, *J* 7.5 Hz, 18H, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.29, 149.01, 124.24, 122.86, 121.64, 107.83, 83.95, 59.72, 46.51, 34.12, 28.85, 26.76, 20.60, 20.55, 12.71. IR (KBr): 3379.09 (83%), 3072.22 (82%), 2964.42 (68%), 2929.23 (73%), 2670.48 (%), 1971.09 (86%), 1601.05 (75%), 1470.37 (55%). Anal. found %: C, 72.64; H, 8.50; N, 5. 67; anal. calcd for $C_{90}H_{126}O_{12}N_6$%: C, 72.87; H, 8.65; N, 5.52.

Compound **5b**: yield 32%. Mp >300 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.47 (s, 6H, OH), 7.40–7.20 (m, 30H, Ph), 6.55 (m, 6H, CH), 4.87 (s, 12H, OCH_2N), 4.13 (q, *J* 5.0 Hz, 6H, CH), 4.00 (s, 12H, NCH_2), 3.88 (s, 12H, NCH_2Ph), 2.31–2.15 (m, 6H, CH), 2.08–1.93 (m, 6H, CH), 0.82 (t, *J* 7.2 Hz, 18H, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.43, 148.79, 137.92, 129.06, 128.54, 127.47, 124.54, 122.94, 121.85, 107.55, 82.13, 55.84, 46.63, 34.20, 28.95, 12.86. Anal. found %: C, 76.72; H, 6.84; N, 4. 98; anal. calcd for $C_{108}H_{114}O_{12}N_6$%: C, 76.86; H, 6.76; N, 4.81.

Compounds **5c** and **5d**: yield 40%. Mp 160–163 °C (dec). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm): 7.45 (s, 6H, OH), 7.39–7.15 (m, 30H, Ph), 6.59 (s, 3H, CH), 6.52 (s, 3H, CH), 5.03 (d, *J*=9.8 Hz, 6H, OCH_2N), 4.81 and 4.78 (d, *J* 16.2 Hz, 6H, OCH_2N), 4.16–3.84 (m, 24H, CH, NCH_2, *CH*Ph), 2.30–2.12 (m, 6H, *CH*H), 2.06–1.90 (m, 6H, CH*H*), 1.42 (m, 18H, Me), 0.87–0.73 (m, 18H, Me). ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm): 149.37, 149.32, 149.34, 144.26, 144.16, 128.56, 128.50, 127.44, 127.32,

127.25, 124.27, 123.13, 122.85, 121.67, 121.50, 107.96, 107.86, 81.05, 80.91, 58.02, 57.99, 44.54, 44.33, 34.19, 28.93, 28.82, 21.72, 21.62, 12.99, 12.90; **5c** $[\alpha]_D^{293K}$ −81±1 (*c* 0.03, $CHCl_3$). Anal. found %: C, 77.13; H, 6.98; N, 4. 63; anal. calcd for $C_{114}H_{126}O_{12}N_6$%: C, 77.28; H, 7.12; N, 4.75. **5d** $[\alpha]_D^{293K}$ 82±2 (*c* 0.03, $CHCl_3$). Anal. found %: C, 77.23; H, 7.04; N, 4, 58; anal. calcd for $C_{114}H_{126}O_{12}N_6$%: C, 77.28; H, 7.12; N, 4.75.

3. Molecular mechanics calculations

MMX force field was used as implemented in PCMODEL 7.50.00.[12] Crystallographic coordinates of hexamine **3** were used for generating the initial structures.

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