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Partial Aminomethylation of Resorcarenes

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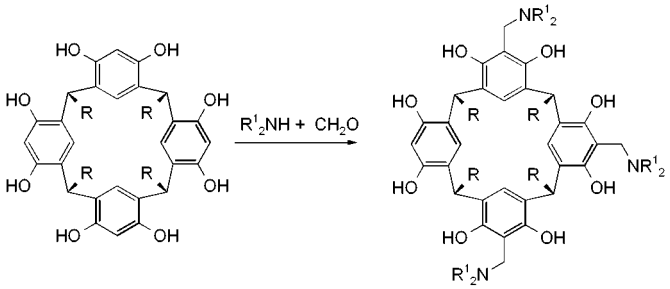
ABSTRACT



Aminomethylation of resorcarenes at the wider rim with bulky diisopropylamine and formaline leads to trisubstituted derivatives. Analogous reaction with C_{2v}-symmetrical resorcarene tetratosylate gives the monoaminomethylated compound. Further reactions of remaining unsubstituted resorcinol rings result in new resorcarene derivatives.

Resorcarenes[1] **1** (Figure 1) are readily available by acid-catalyzed condensation of resorcinol with various aldehydes. Chemical modifications of bowl-shaped rccc-conformers of resorcarenes have been used for the synthesis of cavitands, carcerands, and hemicarcerands[2] as well as molecular capsules.[3] Especially promising are partial reactions that allow the attachment of several different functional groups to the resorcarene core. Partial O-alkylations and acylations of resorcarenes have been used for the construction of functional cavitands and hemicarcerands,[4] various self-folding cavitand hybrids,[5] chiral hosts,[6] and guest-controlled molecular capsules.[7] In contrast, partial reactions of **1** at 2-positions of the resorcinol rings are much less explored. It was reported that partial bromination of **1a** with NBS leads selectively to 1,3-dibromo derivative,[8] while partial 1,3-diaminomethylated resorcarenes could be prepared through protection-deprotection strategies starting from C_{2v}-symmetrical tetraesters.

We have found conditions for partial aminomethylation of resorcarenes **1** with diisopropylamine. Herein we report on the first direct syntheses of tris- and monoaminomethylated resorcarenes and their chemical and conformational properties.

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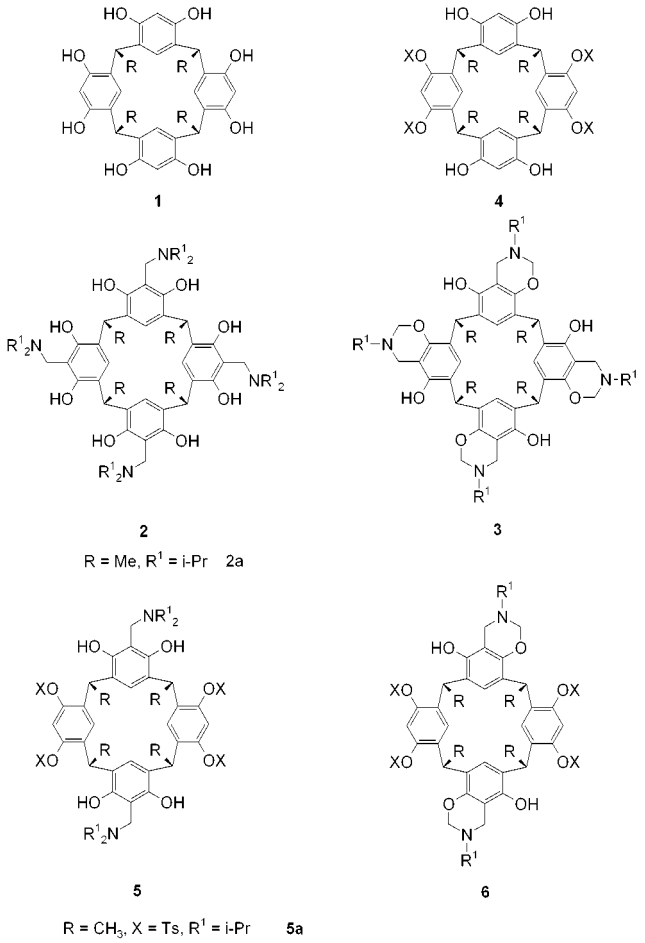
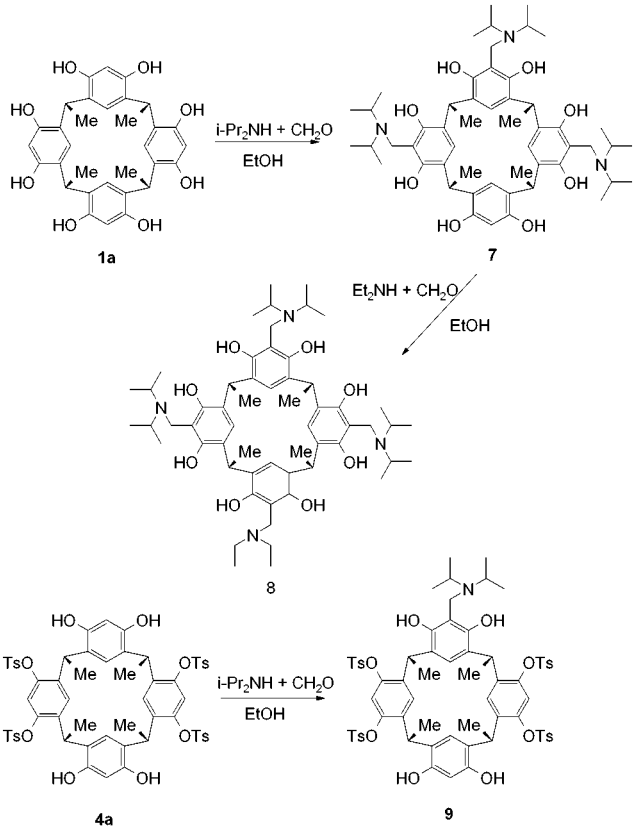


Figure 1. Resorcarenes and their aminomethylated derivatives.

Reaction of resorcarenes **1** with secondary amines and formaldehyde leads to the complete tetraaminomethylation of resorcinol rings to give tetraamines **2**.[9] Aminomethylation with primary amines resulted in a regioselective formation of inherently chiral C_4-symmetrical tetrabenzoxazines **3**.[10] Analogous reactions of tetrasulfonates **4** gave, respectively, distal diaminomethylated products **5** and **6**.[11] All attempts to react resorcarenes **1** and tetrasulfonate **4a** with less than, respectively, 4 or 2 equiv of diethylamine or butylamine and excess of formaline failed to give any individual partially aminomethylated derivatives. To attain the selectivity we have used bulky primary and secondary amines.

The reaction of octol **1a** with diisopropylamine and formaldehyde in 1:3:6 molar ratio resulted in triaminomethylation (Scheme 1). Compound **7** precipitated from the

Scheme 1. Partial Aminomethylation of Resorcarenes



reaction mixture together with tetraamine **2a** and could be purified by flash column chromatography in 41% yield. The reaction with the excess of *i*-Pr_2NH and CH_2O (1:8:16 ratio) leads under the same conditions to the tetraaminomethylated derivative **2a**. The reaction between **1a** and dicyclohexylamine resulted in an unseparable mixture of partially aminomethylated products, whereas with dibenzylamine only the corresponding tetraaminomethylated derivative could be isolated.

The structure and composition of compounds **7** and **8** were confirmed by NMR spectroscopy, mass spectrometry and elemental analysis. The ^{1}H NMR spectrum of triamine **7** in CD_2Cl_2 at 303 K (Figure 2) contains one singlet at 6.2 ppm corresponding to one proton in the 2-position of the unsubstituted resorcinol ring, while four other protons of resorcinol rings emerge as three singlets (1:2:1 ratio) between 7.20 and 7.33 ppm. Two quartets correspond to the methine protons of the bridges, while next to them methyl protons emerge as two doublets. No signals of hydroxy groups could be found in the spectrum, most probably as a result of the fast exchange with water molecules. In the ^{13}C NMR spectrum two singlets are observed for the carbon atoms of the bridges, benzylic methylene groups, and methyne atoms of the diisopropylamino fragments.

The unsubstituted resorcinol ring of **7** could be aminomethylated with diethylamine and formaldehyde to give a mixed derivative **8** in 82% yield (Scheme 1).

The aminomethylation of resorcarene tetratosylate **4a** with CH_2O and diisopropylamine in 1:4:4 molar ratio in EtOH

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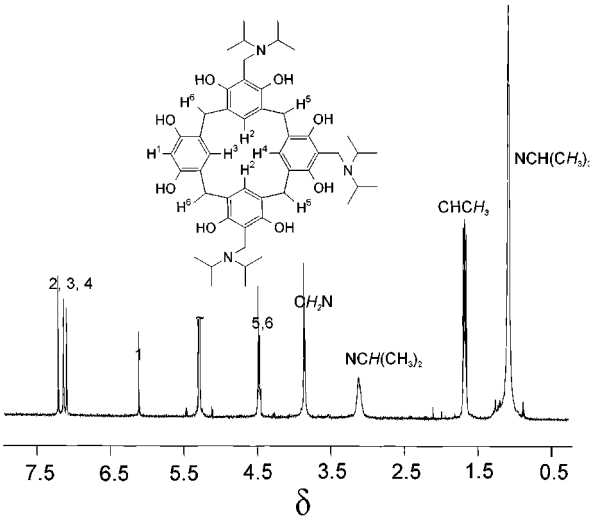

Figure 2. ^{1}H NMR spectrum of **7** in CD_2Cl_2 (500 MHz, 303 K)

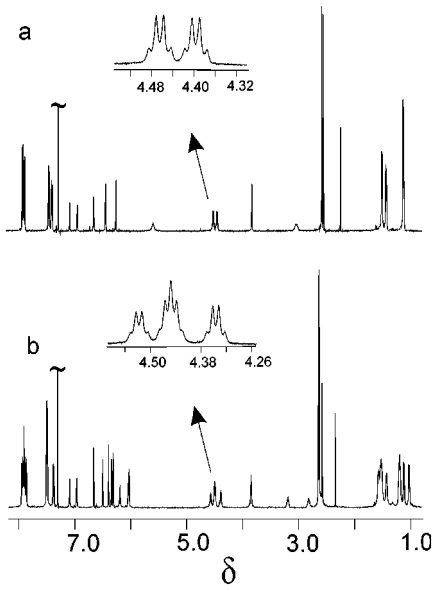

Figure 3. ^{1}H NMR spectra of monoamine **9** (500 MHz, $CDCl_3$): (a) at 303 K; (b) at 223 K. Signals for the methine protons of the bridges are enlarged.

resulted in precipitation of white solid, which was the 1:1 mixture of starting material and monosubstituted derivative **9**[12] (Scheme 1). This mixture could be readily separated by flash column chromatography to give **9** in 28% yield. If under otherwise identical conditions the ratio **1a**:*i*-Pr_2NH:CH_2O was 1:8:8, a 1:1 mixture of monoamine **9** and diamine **5a** was formed. The addition of CH_2Cl_2 prevented the precipitation of monosubstituted derivative and resulted in the complete aminomethylation of the unsubstituted resorcinol rings. The structure of this product was unambiguously proved by NMR spectroscopy, mass spectrometry, and elemental analysis.

The ^{1}H NMR spectrum of compound **9** (Figure 3) contains a double set of signals for the protons of tosyl fragments, as well as two quartets and two doublets for the methine and methyl protons of the bridges, respectively. One set of signals is found for the protons of methylene diisopropylamino fragments and one broadened singlet positioned at 5.53 ppm corresponds to the protons of hydroxy groups. In the aromatic region five signals in a 2:2:2:1:1 ratio are observed for the protons of the resorcinol rings in accordance with C_s-symmetric structure of monosubstituted derivative **2**. The 2D-NOESY and long-range COSY techniques allow an unambiguous assignment of all these resonances. The large difference between chemical shifts of the protons at the

(12) **Resorcarenetriamine 7.** A solution of resorcarene **1a** (1.0 g, 1.8 mmol), diisopropylamine (0.78 mL, 5.4 mmol), and formaldehyde (1.5 mL, 18.5 mmol) in 50 mL of ethanol was stirred overnight. The precipitate was filtered off and washed with ethanol. The remaining residue was chromatographically separated by flash column chromatography (ethyl acetate/THF, 1:2): mp >300 °C; yield 660 mg (41%); ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 36H), 1.71 (d, 7, 04, 12H), 3.13 (q, J = 6.34 Hz, 6H), 3.88 (s, 6H), 4, 55 (q, J = 6.92 Hz, 4H), 6.24 (s, 1H), 7.21 (s, 3H), 7.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.58, 27.63, 43.09, 45.85, 48.19, 107.29, 121.23, 124.56, 150.29, 153.17; MS (ESI-TOF) 884.5 $[M + H]^+$. Anal. Calcd for $C_{53}H_{77}N_3O_8 \cdot 3H_2O$: C, 67.83; H, 8.84, N, 4.47. Found: C, 68.18, H, 8.80, N, 4.31. **Resorcarenetetraamine 2a.** A solution of resorcarene **1a** (1.0 g, 1.8 mmol), diisopropylamine (2.1 mL, 14.7 mmol), and formaldehyde (5.0 mL, 61.6 mmol) in ethanol (55 mL) was stirred overnight. The precipitate was filtered off, washed with ethanol, and dried in a vacuum to yield a white solid: yield, 700 mg (38%); mp >300 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.10 (s, 48H), 1.71 (d, J = 7.3 Hz, 12H), 3.15 (s, 8H), 3.89 (s, 8H), 4.53 (q, J = 7.1 Hz, 4H), 7.21 (s, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.13, 19.60, 27.74, 43.45, 49.12, 107.70, 116.17, 121.24, 124.82; MS (ESI-TOF) *m*/*z* 998.7 $[M + H]^+$. Anal. Calcd for $C_{53}H_{77}N_3O_8 \cdot 3H_2O$: C, 67.83, H, 8.84, N, 4.47. Found: C, 68.18, H, 8.80, N, 4.31. **Resorcarenetetratosylatemonoamine 9.** A solution of tetratosylate **4a** (1.0 g, 0.7 mmol), diisopropylamine (0.39 mL, 2.8 mmol), and formaldehyde (0.45 mL, 5.6 mmol) in 100 mL of ethanol was stirred overnight. The precipitate was filtered off and washed with ethanol. The remaining residue was chromatographically separated by flash column chromatography (EtOAc/$CHCl_3$, 1:1): yield 310 mg (28%); mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 1.02 (d, J = 6.46 Hz, 12H,), 1.35 (d, J = 7.03 Hz, 12H), 1.41 (d, J = 6.94 Hz, 12H), 2.47 (s, 6H), 2.50 (s, 6H), 3.76 (s, 2H), 4.38 (q, J = 7.15 Hz, 2H), 4.45 (q, J = 6.86 Hz, 2H), 5.55 (s, 1H), 6.21 (s, 1H), 6.40 (s, 1H), 6.61 (s, 1H), 6.91 (s, 1H), 7.05 (s, 1H), 7.36 (d, J = 8.11 Hz, 4H), 7.41 (d, J = 8.11 Hz, 4H), 7.86 (d, J = 8.31 Hz, 4H), 7.89 (d, J = 8.34 Hz, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.57, 20.19, 20.61, 21.77, 21.81, 30.88, 32.02, 32.23, 42.41, 48.40, 78.47, 104.17, 109.08, 115.56, 117.92, 118.64, 122.79, 125.30, 127.32, 128.47, 128.50, 130.08, 130.31, 130.68, 132.17, 132.85, 139.07, 140.98, 144.46, 145.46, 145.70, 146.16, 154.28; MS (ESI-TOF) *m*/*z* 1274.35 $[M + H]^+$. Anal. Calcd for $C_{67}H_{71}NO_{16}S_4 \cdot 2H_2O$: C, 61.39, H, 5.72, N, 1.06, S, 9.78. Found: C, 61.93, H, 5.57, N, 1.02, S, 10.18. **Resorcarenetetratosylatediamine 5a.** A solution of **4a** (0.5 g, 0.41 mmol), diisopropylamine (0.48 mL, 3.4 mmol), and formaldehyde (1.0 mL, 12.3 mmol) in ethanol (25 mL) was stirred for 8 h. The precipitate was filtered off, washed with ethano,l and recrystallized from MeCN: white solid; yield 400 mg (66.9%); mp 267.5 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.93 (d, J = 6.32 Hz, 24H), 1.31 (d, J = 6.77 Hz, 12H), 2.49 (s, 12H), 2.92 (m, 4H), 3.69 (s, 4H), 4.41 (q, J = 6.99 Hz, 4H), 6.48 (s, 2H), 6.61 (s, 2H), 6.99 (s, 2H), 7.35 (d, J = 8.11 Hz, 8H), 7.85 (d, J = 8.19 Hz, 8H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.43, 21.24, 21.75, 31.33, 108.92, 114.50, 122.87, 127.22, 128.50, 129.98, 130.29, 132.89, 140.26, 144.55, 145.55; MS (ESI-TOF) *m*/*z* 1388.2 $[M + H]^+$. Anal. Calcd for $C_{74}H_{86}N_2O_{16}S_4$: C, 64.05, H, 6.25, N, 2.02, S, 9.24. Found: C, 63.93, H, 6.36, N, 2.04, S 9.45. **Resorcarenetetraamine 8.** A solution of the **7** (150 mg, 0.17 mmol), diethylamine (0.053 mL, 0.51 mmol), and formaldehyde (0.2 mL, 2.5 mmol) in 10 mL of ethanol and 10 mL of CH_2Cl_2 was stirred overnight. The solution were evaporated. The crude product was then treated with CH_2Cl_2 and hexane, filtered off, and washed with hexane: mp >300 °C; yield 135 mg (82%); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 1.06 (m, 42H), 1.72 (d, J = 7.19 Hz, 12H), 2.60 (s, 4H), 3.16 (s, 6H), 3.89 (s, 8H), 4.53 (q, J = 7.12 Hz, 4H), 7.24 (s, 3H), 7.27 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 10.94, 19.58, 27.51, 43.08, 46.31, 48.19, 51.34, 107.42, 121.27, 124.80, 150.34, 152.68, 153.64. MS (ESI-TOF) *m*/*z* 968.7 $[M]^+$, 969.8 $[M + H]^+$. Anal. Calcd for $C_{58}H_{88}N_4O_8 \cdot 2H_2O$: C, 69.28, H, 9.15, N, 5.57. Found: C, 69.07; H, 9.39; N, 5.40.

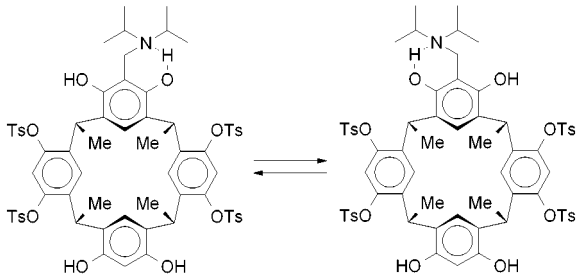

Figure 4. Two enantiomeric structures of **9**.

narrow rim of resorcarene suggests that compound **2** exists in a boat conformation. It was found that in the boat conformation the acylated resorcinol rings are coplanar and nonacylated ones are parallel, similarly to parent tetratosylate **4a**.[13]

Decrease of the temperature to 223 K results in a dramatic change of the ^{1}H NMR spectrum. The two multiplets and four doublets correspond to the CH and CH_3 protons of the isopropyl groups, and the methine and methyl protons of the bridges emerge as four quartets and four doublets, respectively. In the aromatic region seven singlets are found for the protons of resorcinol rings and four doublets for the ortho protons of the sulfonyl groups. This pattern corresponds to a C_1-symmetrical chiral structure in which the amino group forms hydrogen bonds to the neighboring hydroxyl (Figure 4). Thus the C_s-symmetrical pattern observed at 303 K reflects the fast interconcversion between two enantiomeric conformations (compare with ref 11a). The $\Delta G^{\ddagger}$ value of this process, based upon the coalescence data for the methine signals of isopropyl fragments, is 13.0 kcal/mol at $T_c = 280.5$ K.

In summary, the aminomethylation of resorcarenes with bulky diisopropylamine results in partial substitution at the wider rim. The remaining unsubstituted resorcinol rings can be substituted to give novel resorcarene derivatives. The trisaminomethylated compounds are promising building blocks that can be further employed for synthesis of oligoresorcarenes, as well as resorcarenes bearing different functional groups at the wide rim.

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