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Alkoxy-, Acyloxy-, and Bromomethylation of Resorcinarenes

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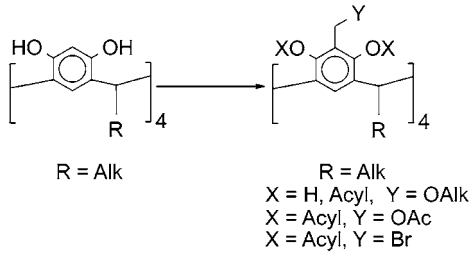
ABSTRACT



Reaction of resorcinarene octols with tris-hydroxymethylmethylamine (TRIS), formaldehyde, and alcohols results in tetraalkoxymethylation of the resorcinol rings. Harsh acylation of aminomethylated resorcinarenes with acid anhydrides leads to the complete acylation of eight hydroxyls and substitution of the amino versus acyloxy groups. Acyloxymethylated resorcinarene 6b can be transformed into a tetrabromomethylated derivative 7 through the reaction with HBr in acetic acid.

Resorcinarenes **1**[1] are easily available building blocks for the design of various supramolecular structures. To perform this design, various methods have been developed for complete and selective chemical modifications of **1**.[2] Acylations and alkylations of hydroxyl groups were used for the synthesis of cavitands, carcerands, hemicarcerands, velcrands,[3] and molecular capsules.[4] Chemical modifications of radicals attached to the bridging carbon atoms afforded water-soluble and polymer-attached receptors. Bromination,[5] diazo-coupling,[6] thiomethylation,[7] and aminomethylation with secondary and primary amines[8] at the 2-positions of the resorcinol rings gave completely or (and) partially substituted derivatives in preparative yields. Some of the compounds obtained were shown to be receptors for small organic molecules, cations, and anions.[9]

We have found conditions for alkoxy-, acyloxy-, and bromomethylation of rccc-resorcinarenes **1** at the 2-positions of their resorcinol rings.

The reaction of resorcinarene **1a** with CH_2O and tris-hydroxymethylmethylamine **2a** (TRIS) in EtOH, in the

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(2) For a recent review, see: Thondorf, I.; Shivanyuk, A.; Böhmer, V. Chemical Modifications of Calix[4]arenes and Resorcarenes. In *Calixarenes*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; pp 26−54.
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(5) (a) Cram, D. J.; Karbach, S.; Kim, H.-E.; Knobler, C. B.; Maverick, E. F.; Ericson, J. L.; Helgeson, R. C. *J. Am. Chem. Soc.* **1988**, *110*, 2229. (b) Konishi, H.; Nakamaru, H.; Nakatani, H.; Ueyama, T.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1997**, 185.
(6) Manabe, O.; Asakura, K.; Nishi, T.; Shinkai, S. *Chem. Lett.* **1990**, 1219.
(7) Konishi, H.; Yamaguchi, H.; Miyashiro, M.; Kobayashi, K.; Morikawa, O. *Tetrahedron Lett.* **1996**, *37*, 8547.
(8) (a) Schneider, U.; Schneider, H.-J. *Chem. Ber.* **1994**, *127*, 2455. (b) Airola, K.; Böhmer, V.; Paulus, E. F.; Rissanen, K.; Schmidt, C.; Thondorf, I.; Vogt, W. *Tetrahedron* **1997**, *53*, 10709. (c) Iwanek, W.; Mathay, J. *Lieb. Ann.* **1995**, 1463. (d) Shivanyuk, A.; Schmidt, C.; Paulus, E. F.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1998**, *120*, 4319. (e) Luostarinen, M.; Shivanyuk, A.; Rissanen, K. *Org. Lett.* **2001**, *3*, 4141.
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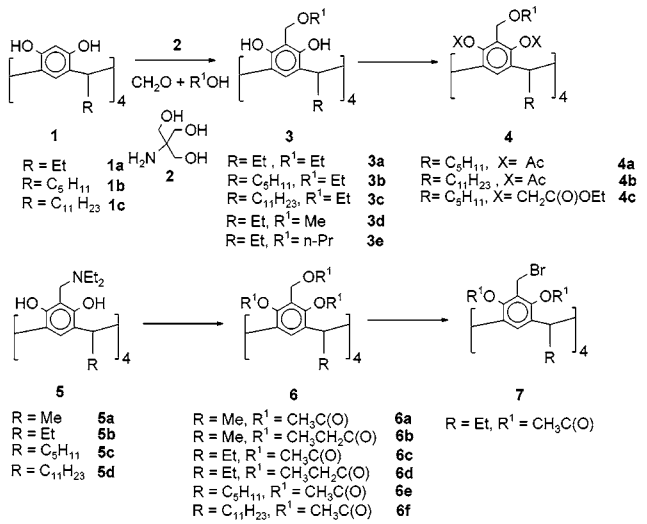
Scheme 1



presence of catalytic amounts of acetic acid, was carried out in order to obtain the corresponding aminomethylated product, tetrabenzoxazine or (and) oxazolidine.[10] After the mixture was stirred for 5 days at room temperature, a precipitate formed, which, to our surprise, was not a product of aminomethylation. The ^{1}H NMR spectrum of this compound contains one triplet for the methine protons of the bridges and one singlet for the protons of the resorcinol rings at 7.14 ppm. The disappearance of the singlet for the protons in the 2-positions of the resorcinol rings suggests that the complete substitution occurred at the wide rim of the resorcinarene. In addition, three new signals emerged: a singlet at $\delta = 4.79$, corresponding to 8 protons, and a quartet at $\delta = 3.61$ ppm and a triplet at $\delta = 1.21$ ppm, corresponding to 8 and 12 protons, respectively. This spectrum can be attributed to the structure of tetraethoxymethylated product **3a** (Scheme 1).[11] Accordingly, the main peak in the MALDI-TOF mass spectrum (m/z = 855.99) is in accordance with the proposed structure (M + Na = 856.0).

At room temperature the reaction gave poor yields of **3a** (~20%); however, under reflux the product precipitated after 1−1.5 h and its yield increased to 55%. To avoid precipitation and to ensure the completeness of the reaction, $CHCl_3$ was added to the reaction mixture. Compounds **1b** and **1c** were ethoxymethylated in 42−69% yields under the same conditions. The reaction of resorcarcinarene **1a** with CH_2O and TRIS in MeOH or PrOH afforded tetraethers **3d** and **3e**, respectively.

The alkoxymethylation of resorcinarenes *does not occur without* **2**, suggesting that the aminomethylation could be the first step of the alkoxymethylation. The second step might involve nucleophilic attack of the alcohol on the amino residues in the tetraaminomethylated product. Although nucleophilic substitution of the aminoresidues in resorcinarene tetramines of type **5** by other amines (the retro Mannich reaction) is known,[12] the TRIS-assisted alkoxymethylation[13] described above is unprecedented.

(10) Iwanek, W.; Wolf, C.; Mattay, J. *Tetrahedron Lett.* **1995**, *36*, 8969.

Acylation of hydroxy groups of **3** by acetic anhydride (pyridine, rt) or alkylation with ethylbromoacetate (K_2CO_3, MeCN) afforded octa-O-substituted derivatives **4a**−**c** in 49−98% yields.

Aminomethylated derivatives **5** were prepared by Mannich reaction of resorcinarenes **1** with diethylamine and formaldehyde in EtOH.[7] Acylation of tetraamines **5** with boiling acetic or propionic anhydride resulted in complete acylation of the hydroxy groups and substitution of diethylamino versus acyloxy fragments.[14] This procedure afforded dodecaesters **6** in 19−57% yield.[15] The reaction of tetraacetoxymethylated resorcinarenes **6c** with HBr[16] in AcOH gave tetrabromomethylated derivarive **7**.[17]

Recrystallization of resorcinarene **3b** from EtOH/CH_2Cl_2 resulted in diffraction-quality crystals.[18,19] The resorcinarene

(11) **Tetraethoxymethylresorcinarene 3a.** To a vigorously stirred solution of **1a** (1.5 g, 2.5 mmol), formaldehyde (37%) (4.2 mL, 51.3 mmol), and acetic acid (0.5 mL) in EtOH (50 mL) was added a solution of tris(hydroxymethyl)aminomethane **2** (2.70 g, 22.3 mmol) in H_2O (20 mL) in one portion. After 1 h of stirring at ambient temperature, the reaction mixture was brought to reflux. After 1−2 h, the reaction mixture became turbid, and $CHCl_3$ (50 mL) was added after cooling to about 50 °C. The transparent reaction mixture was refluxed for the next 8 h. The solvent was removed *in vacuo*, and the solid formed was recrystallized from EtOH/CH_2Cl_2: yield 1.15 g (55%); mp 138−139 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (s, 8H), 7.16 (s, 4H), 4.80 (s, 8H), 4.19 (t, J = 7.9 Hz, 4H), 3.61 (q, J = 14.1 Hz, 8H), 2.18−2.25 (m, 8H), 1.26 (t, J = 7.0 Hz, 12H), 0.93 (t, J = 7.2 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.60, 14.91, 26.76, 35.18, 66.81, 68.01, 109.33, 122.36, 124.04, 149.91; MALDI-MS m/z 856.0 [M +Na$^+$, calcd 856.0]. Anal. Calcd for $C_{48}H_{64}O_{12}$·0.5 CH_2Cl_2: C, 66.54; H, 7.48; Found: C, 66.71; H, 7.41. **Tetramethoxymethylresorcinarene 3d.** To a solution of **1a** (600 mg, 1.0 mmol) in MeOH (80 mL) were added formaldehyde (37%) (1.7 mL, 20.5 mmol) and acetic acid (0.3 mL) followed by a solution of **2** (1.08 g, 8.9 mmol) in H_2O (10 mL). The reaction mixture was stirred for 1 h at room temperature and for 8 h at reflux. The precipitate was filtered off and analytically pure product crystallized from the filtrate upon cooling: slightly pink solid; yield 380 mg (49%); mp 239−242 °C (decomp); ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.66 (s, 8H), 7.15 (s, 4H), 4.77 (s, 8H), 4.18 (t, J = 7.9 Hz, 4H), 3.44 (s, 12H), 2.21 (m, 8H), 0.92 (t, J = 7.1 Hz, 12H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 12.58, 26.75, 35.16, 58.76, 70.15, 109.08, 122.43, 124.04, 149.88; FD-MS m/z 776.9 [M$^+$, calcd 776.9]. **Tetrapropoxymethylresorcinarene 3e.** The compound was prepared in the same way as **3d** using propanol (80 mL) as solvent. The reaction mixture was evaporated, and crude product was recrystallized from PrOH: white solid; yield 373 mg (42%); mp 191−192 °C; ^{1}H NMR (250 MHz, $CDCl_3$) δ 8.80 (s, 8H), 7.15 (s, 4H), 4.80 (s, 8H), 4.19 (t, J = 7.9 Hz, 4H), 3.50 (t, J = 6.6 Hz, 8H), 2.14−2.26 (m, 8H), 1.56−1.69 (m, 8H), 0.88−1.02 (m, 24H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 10.43, 12.61, 22.62, 26.74, 35.17, 68.28, 73.06, 109.35, 122.35, 124.03, 149.91. FD-MS m/z 889.1 [M$^+$, calcd 889.1]. **Tetramethoxymethyloctaacetylresorcinarene 4c.** To a vigorously stirred suspension of **3c** (500 mg, 0.5 mmol) and K_2CO_3 (1.21 g, 8.8 mmol) in dry MeCN (30 mL) and THF (5 mL) was added ethyl bromoacetate (1.34 g, 8.0 mmol) in one portion at ambient temperature. The reaction mixture was brought to reflux and stirred overnight. The precipitate was filtered off and washed with MeCN (10 mL). The filtrate was evaporated to afford the crude product as a dark yellow oil, which was dissolved in EtOH. Reprecipitation with water and repetition of this procedure three times resulted in complete removal of the ethylbromoacetate. An analytically pure sample of **4c** was obtained by recrystallization from aqueous EtOH: white solid; yield 491 mg (58%); mp 115−116 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (s, 4H), 4.50−4.56 (m, 12H), 4.47 (s, 8H), 4.16−4.29 (m, 24H), 3.47 (q, J = 14.0 Hz, 8H), 1.82−1.90 (m, 8H), 1.28 (t, J = 7.1 Hz, 24H), 1.21−1.32 (m, 24H), 1.13 (t, J = 7.0 Hz, 12H), 0.82 (t, J = 6.9 Hz, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.05, 14.15, 15.01, 22.62, 27.91, 31.98, 35.40, 37.62, 60.65, 63.13, 66.09, 71.85, 124.74, 127.08, 133.86, 155.44, 169.14; FD-MS m/z 1690.8 [M$^+$, calcd 1690.0]. Anal. Calcd for $C_{92}H_{136}O_{28}$: C, 65.38; H, 8.11; Found: C, 65.36, H, 8.22.

(12) Page, P. C. B.; Heaney, H.; McGrath, M. J. Sampler, E. P.; Wilkins, R. F. *Tetrahedron Lett.* **2003**, *44*, 2965.

(13) Reaction of phenol or resorcinol with TRIS and formaline in EtOH led to the formation of phenol formaldehyde polymers.

(14) (a) Tiffenau, M.; Fuhrer, K.;*Bull. Soc. Chim. France* **1914**, 162. (b) Moran, W. J.; Schreiber, E. C.; Engel, E.; Behn, D. C.; Yamins, J. L. *J. Am. Chem. Soc*. **1952**, *74*, 127. (c) Da Re, P.; Verlichi, L.; Setnikar, I. *J. Org. Chem.* **1960**, *25*, 1097.

molecule adopts the rccc-crown conformation stabilized by four intramolecular hydrogen bonds (Figure 1a). Ethoxy group O109-Et forms a short intramolecular hydrogen bond to O105H (Figure 1, top left), while the distances O111−O105 and O112−O108 are considerably longer and reflect relatively weaker hydrogen bonding. No intramolecular hydrogen bonds are possible for ethoxy group O110Et since the neighboring hydroxyls O103H and O104H are H-donors to O102 and O105. Two molecules of **3b** form a dimer through intermolecular hydrogen bonds between the ethoxy groups and the hydroxyls (Figure 1, bottom). The resorcinarene concavities are filled with the ethoxy groups so that no solvent is included in the crystal. Tetrapropoxymethylated derivative **3e** has a similar crystal structure (Figure 1, middle).

Diffraction-quality crystals of dodecaacetate **6c** and tetrabromide **7** were obtained from ethanol and CH_2Cl_2, respectively.[20] The molecule of **6c** exists in a boat conformation (Figure 2, top) which is distorted in a propeller-like manner. The carbonyl groups of the acetoxymethyl fragments

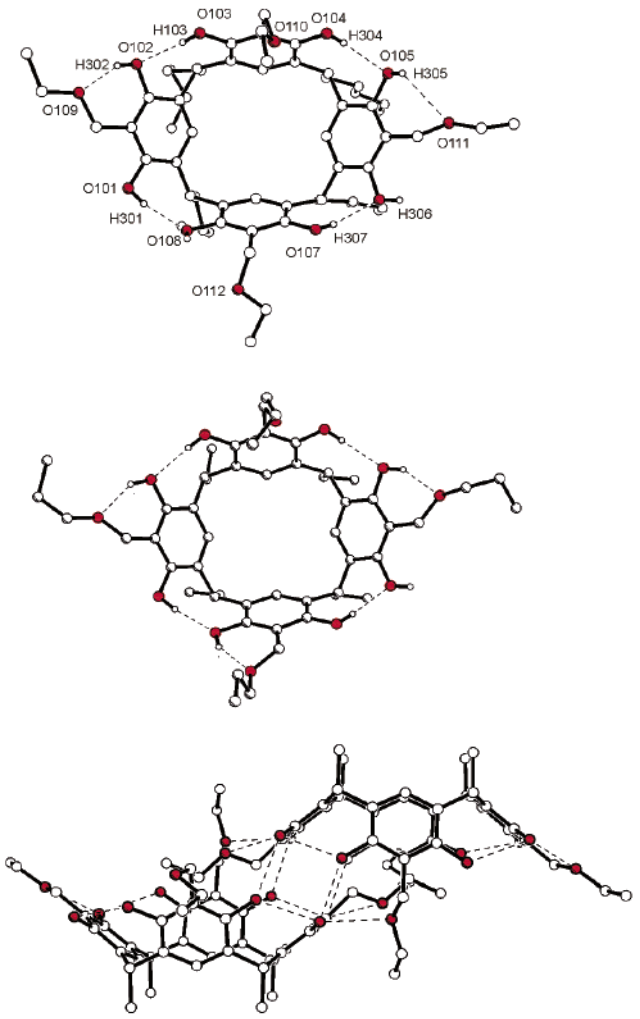


Figure 1. Crystal structures of alkoxymethylated resorcinarenes: **3b** (top); **3e** (middle). Bottom: packing of **3b** in the crystal. CH hydrogen atoms are omitted for clarity; hydrogen bonds are indicated with dotted lines.

are oriented in the same direction, making the conformation chiral; however, the crystal is a racemate (space group C2/*c*). The molecule of **7** exists in an undistorted boat conformation (Figure 2, bottom). Three bromine atoms are pointing outward, and one is pointing toward the macrocycle. The voids in the crystal are filled with numerous dichloromethane molecules.

The ^{1}H NMR spectrum of **3b** measured at 303 K in $CDCl_3$ and CD_2Cl_2 corresponds to a C_{4V} -symmetric structure of the crown (cone) conformer. The high chemical shift of the OH resonance suggests that the cone conformation of **3b** is stabilized by intramolecular hydrogen bonds as it is found in the crystalline state. At 193 K (CD_2Cl_2, 500 MHz) the OH resonance splits into two sharp singlets positioned at 8.4 and 9.6 ppm. The singlet for the protons of the benzyl methylene groups transforms into an AB-quartet, while none of the other resonances change considerably. The ^{1}H NMR spectrum at 193 K can be attributed to a chiral C_4-symmetrical structure with left- or right-handed orientation

(15) **Resorcinarene Dodecapropionate 6d.** Resorcinarenetetraamine **5b** (1 g, 1.13 mmol) was dissolved in propionic anhydride. The reaction mixture was stirred and refluxed for 16 h. The solvent was evaporated *in vacuo*, and the residue was recrystallized from MeOH/CH_2Cl_2 (1:1). The precipitate was filtered off and crystallized from Et_2O/CH_2Cl_2 (1:1) to afford an analytically pure sample of **6d**: yield 27% (not optimized); mp 223 °C; ^{1}H NMR (500 MHz, $C_2D_2Cl_4$, 303 K) δ 7.47 (br s, 2H), 6.05 (br s, 2H), 4.97 (br s, 4H), 4.65 (br s, 4H), 4.14 (br m, 4H), 2.69 (q, J = 7.5 Hz, 8H), 2.43 (q, J = 7.2 Hz, 8H), 2.31 (m, 4H), 2.13 (q, J = 7.6 Hz, 4H), 1.47 (d, J = 6.7 Hz, 12H), 1.34 (t, J = 7.6 Hz, 12H), 1.15−1.00 (m, 24H). MS (ESI-TOF): m/z 1359.19 $[M + Na]^+$; Anal. Calcd for $C_{78}H_{88}O_{24}$: C, 64.66; H, 6.63. Found: C, 64.56, H, 6.72.

(16) Fields, D. L.; Miller, J. B.; Reynolds, D. D. *J. Org. Chem.* **1964**, *29*, 9, 2640−2647.

(17) **Tetrabromoresorcinarene 7.** Dodecaacetate **6c** (1.5 g, mmol) was dissolved in a solution of HBr in acetic acid (25 mL, 33%). The reaction mixture was stirred at ambient temperature for 10 h followed by the addition of CH_2Cl_2 until the precipitate was dissolved. The reaction mixture was stirred for 2 h, and the solvent was evaporated in vacuo. The residue was triturated with acetone (4 × 5 mL), and the remaining powder was crystallized from CH_2Cl_2: white crystals; yield 15%; mp > 300 °C; ^{1}H NMR (500 MHz, $CDCl_3$, 303 K) δ 7.50, 6.00 (two br s, 2H each), 4.12 (br s, 8H), 3.96 (br m, 4H), 2.36 (br s, 24H), 1.88 (br m, 8H), 0.94 (br m, 12H); MS (ESI-TOF) m/z 1330.87 (M + Na). Anal. Calcd for $C_{56}H_{60}Br_4O_{16}$: C, 52.40; H, 4.62; Found: C, 50.89, H, 4.68.

(18) Selected crystallographic data. **3b**: crystal size 0.2 × 0.14 × 0.1 mm^3, triclinic, P-*1*, a = 16.3988(4) Å, b = 17.0717(4) Å, c = 22.1524(5) Å, α = 97.988(1) Å, β = 109.672(1)°, γ = 96.773(1)°, V = 5692.1(2) Å^3, Z = 2, D = 1.38 g cm^{-3}, μ = 0.092 mm^{-1} , $2\theta_{max}$ = 50.82°, 1409 parameters, S = 1.023, R_1 = 0.0918, wR_2 = 0.1780 (for 10 347 reflections $I > 2\sigma(I)$), R_1 = 0.1935, wR_2 = 0.2202 (for 20 712 independent reflections), $\Delta\rho$ (min/max) = −0.27/0.42 e Å^{-3} . **3e**: crystal size 0.5 × 0.3 × 0.15 mm^3, triclinic, P-*1*, a = 11.2747(4) Å, b = 17.9814(4) Å, c = 16.4661(4) Å, α= 79.582 (1) Å, β = 85.451(1)°, γ = 85.545(1)°, V = 2357.87(8) Å^3, Z = 2, D = 1.252 g cm^{-3}, μ = 0.088 mm^{-1} , 2 θ_{max} = 51.11°, 628 parameters, S = 1.014, R_1 = 0.0521, wR_2 = 0.1349 (for 6925 reflections $I > 2\sigma(I)$), R_1 = 0.0632, wR_2 = 0.1433 (for 8222 independent reflections), $\Delta\rho$ (min/max)= −0.30/ 0.84 e Å^{-3}.

(19) (a) Sheldrick, G. M. *Acta Crystallogr., Sect. A* **1990**, *46*, 467. Sheldrick, G. M. *SHELXL-97, Program for the Refinement of Crystal Structures*; Universität Göttingen, Göttingen, Germany, 1997.

(20) Selected crystallographic data. **6c**: crystal size 0.3 × 0.2 × 0.2 mm^3, monoclinic, C2/*c*, a =17.9079(4) Å, b = 16.9690(4) Å, c = 22.4574(3) Å, β = 103.240(1)°, V = 6642.9(2) Å^3, Z = 4, D = 1.291 g cm^{-3}, μ = 0.092 mm^{-1}, 2 θ_{max}= 50.82°, 1409 parameters, S = 1.023, R_1 = 0.0918, wR_2 = 0.1780 (for 5230 reflections $I > 2\sigma(I)$), R_1 = 0.1935, wR_2 = 0.2202 (for 7552 independent reflections), $\Delta\rho$ (min/max)= −0.27/0.42 e Å^{-3} . **7** 5.25 CH_2Cl_2: crystal size 0.2 × 0.2 × 0.1 mm^3, orthorombic, $P2_12_12_1$, a = 18.0215 (2) Å, b = 24.0218(3) Å, c = 36.5073 (4) Å, V = 15804.3(3) Å^3, Z = 4, D = 1.506 g cm^{-3}, μ = 0.138 mm^{-1} , $2\theta_{max}$ = 54.92°, 454 parameters, S = 1.046, R_1 = 0.0633, wR_2 = 0.1745 (for 20 462 reflections $I > 2\sigma(I)$), R_1 = 0.0975, wR_2 = 0.1975 (for 27 843 independent reflections), $\Delta\rho$ (min/max) = −0.28/0.76 e Å^{-3}.

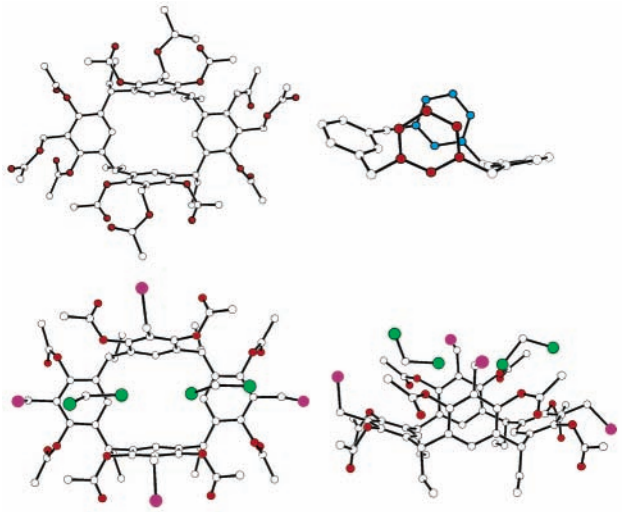


Figure 2. Crystal structures of dodecaacetate **6c** (top) and tetrabromide **7** (bottom).

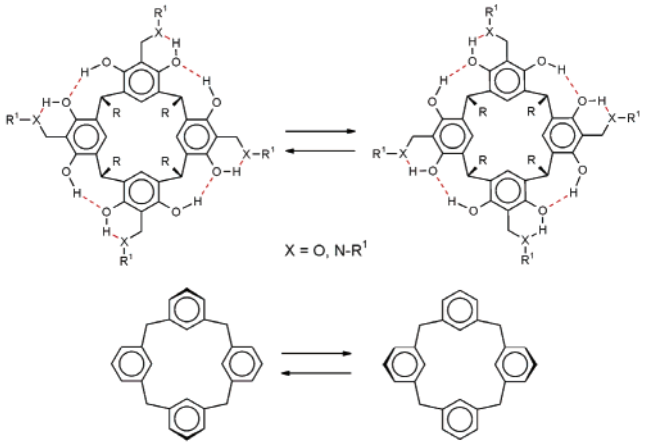


Figure 3. Conformational equilibrium of resorcinarenes. Top: racemization. Bottom: boat−boat interconversion. Hydrogen bonds are shown in red.

of the six-membered hydrogen-bonded rings (Figure 3, top). This structure should be the most stable since it allows the highest possible number of intramolecular hydrogen bonds.[21] Thus, the C_{4V} -symmetrical NMR pattern observed at 303 K is a result of fast interconversion between two chiral C_4-symmetrical conformations. The $\Delta G^{\ddagger}$ of this process at the coalescence temperature of the OH signals (T_c = 223 K) is 9.7 kcal/mol. A comparable value was obtained for the benzyl methylene protons ($\Delta G^{\ddagger}$ = 10.1 kcal/mol, T_c = 213 K). A much higher barrier for a similar inversion was found for tetraamine **5c** ($\Delta G^{\ddagger}$ of 15.9 kcal/mol, at 314 K). Apparently, this difference is caused by stronger O−H···N (compared to O−H···O) hydrogen bonds, which stabilize the entire hydrogen-bonded pattern.

The ^{1}H NMR spectrum of **4b** measured at 303 K in $CDCl_3$, CD_2Cl_2, and CD_2Cl_4 is broad and featureless due to some hindered dynamic process. This dynamic behavior becomes fast on the NMR time scale at 373 K so that the ^{1}H NMR spectrum corresponds to an average C_{4V} -symmetrical structure. Decreasing the temperature to 223 K leads to a doubling of the signals for the protons of resorcinol rings and the methylene protons of the benzyl and ethyl fragments. This pattern can be ascribed to the C_{2V}-symmetric boat conformation with two parallel and two coplanar resorcinol rings. Thus, the C_4-symmetrical pattern observed at 373 K reflects fast boat−boat interconversion (Figure 3, bottom), which becomes slow at lower temperatures. The $\Delta G^{\ddagger}$ value of this process is 13.7 kcal/mol at T_c = 308 K. Similar conformational behavior was observed also for dodecaesters **6** and tetrabromoresorcinarene **7**.

In conclusion, we have developed simple and efficient methods for the introduction of alkoxymethyl, acetoxymethyl, and bromomethyl groups at the wide rim of resorcinarenes. The novel resorcinarenes are easily available and will be used as building blocks for the design of functional resorcinarenes. Tetrabromoresorcinarene **7**, which can potentially be involved in various nucleophilic substitutions, seems especially promising in this regard.

Acknowledgment. This work was financially supported by the Finnish Academy (Project 63018) and National Technology Agency of Finland (TEKES, Project 40328). We are grateful to Mr. R. Kauppinen for assistance with measuring the variable-temperature NMR spectra.

Supporting Information Available: Crystallographic details in CIF format, as well as experimental procedures and analytical data for compounds **3b**, **3c**, **4a**, **4b**, **6a**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) This has been verified by molecular mechanics calculations using MMX force field as implemented in the PCModel package: *PCMODEL for Windows V. 7.50.00*; Serena Software: Bloomington, IN, 2000.