Selective Derivatizations of Resorcarenes. 4. General Methods for the Synthesis of C_{2v}-Symmetrical Derivatives

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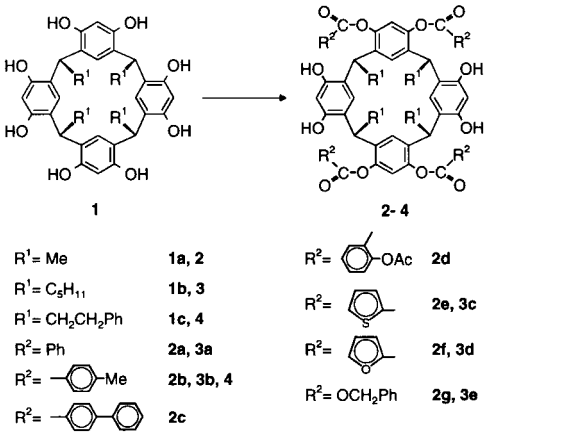
Resorcarenes **1**[1] are easily prepared by acid-catalyzed condensation of resorcinol with various aldehydes. The bowl-shaped all-cis isomers have been frequently used as building blocks for the synthesis of covalently linked container molecules[2] as well as for the construction of self-assembled structures.[3] Although many complete and some partial derivatizations of resorcinol units have been described for compounds **1**,[4] truly regioselective partial conversions[5] are scarce. For example, the tetraphosphorylation and tetrasulfonylation lead to C_{2v}-symmetrical derivatives[6] in reasonable yields. However, neither phosphoryl nor sulfonyl groups are suitable protecting groups due to difficulties with their removal.

We have now found conditions for the regioselective tetraacylation of resorcarenes **1** that are applicable to various aroyl and heteroaroyl chlorides as well as benzyl chloroformate. The tetraesters obtained are promising intermediates for the synthesis of C_{2v}-symmetrical tetraethers, aliphatic tetraesters, and resorcarene derivatives that are selectively substituted in the 2-positions of opposite resorcinol rings.

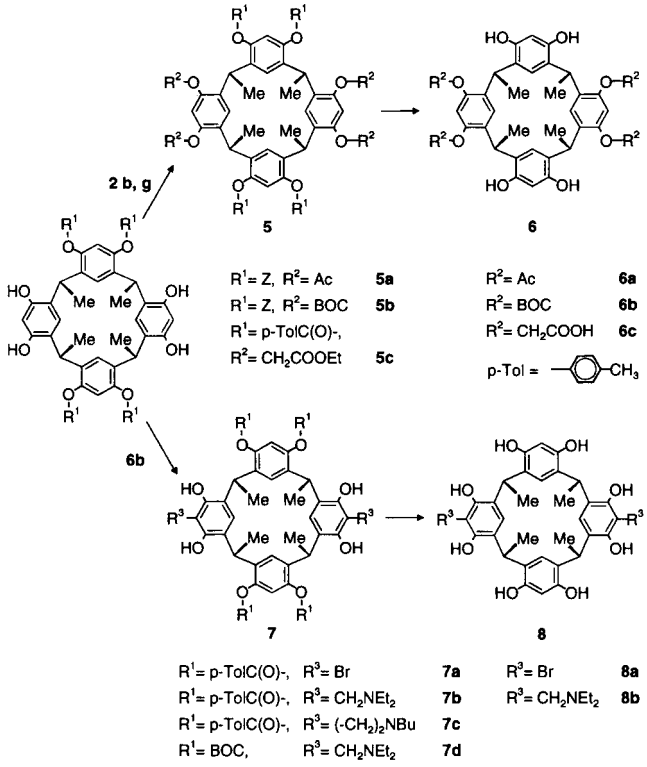
Typically, the reaction of octaols **1a**−**c** with acid chlorides was performed in MeCN in the presence of Et_3N as base (molar ratio 1:4:4). The addition of Et_3N to a solution of **1** caused the formation of a pink precipitate, most probably the complex of **1** with Et_3N.[7] After addition of the acid chloride, this complex immediately dissolved, and later a white precipitate of **2**·2Et_3NHCl was formed. Fast addition of the acid chloride with vigorous stirring of the reaction mixture is crucial for the purity of the products. A slow, dropwise addition of the acylating agent usually resulted in the formation of complicated mixtures that could not be separated. Tetraesters **2**−**4** were isolated in 30−50% yield by simple recrystallization.[8] Their structures were unambiguously proved by ^1H and ^{13}C NMR spectroscopy, by FD-mass spectrometry, and by single-crystal X-ray analysis (see below).[9] The ^1H NMR spectra of compounds **2**−**4** show four singlets for the aromatic protons of the calixarene skeleton, one signal for the hydroxy and methine protons, and one set of signals for the acyl fragments in accordance with the C_{2v}-symmetrical structure.

The regioselectivity observed depends strongly on the solvent, the base, and the acylating agent. No selective acylation took place, for instance, with acetyl chloride (as well as acetic anhydride), acryloyl, pivaloyl, and *p*-nitroben-

Scheme 1



Scheme 2



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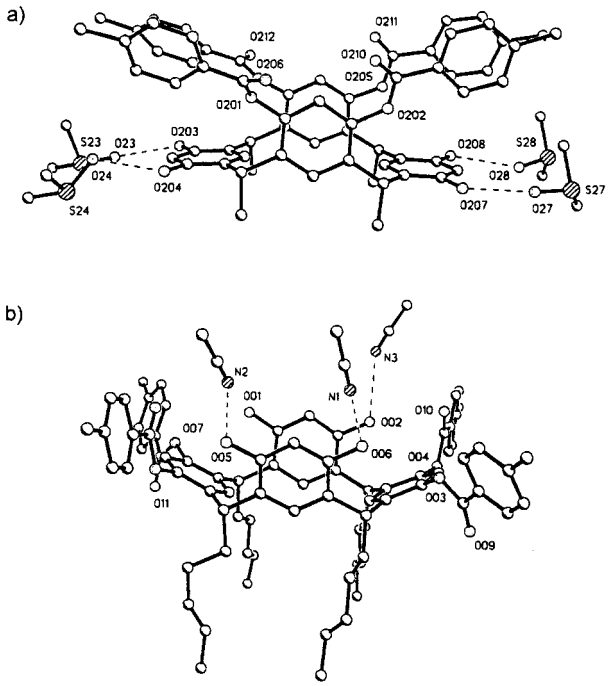

Figure 1. (a) Molecular structure of **2b**·5DMSO. Hydrogen bonds are shown by dotted lines. The non-hydrogen-bonded DMSO molecule is omitted for clarity. O203−O23 = 2.604 Å; O204−O24 = 2.642 Å; O207−O27 = 2.580 Å; O208−O28 = 2.726 Å. (b) Molecular structure of **3b**·3MeCN·H_2O. The disordered water molecule is not shown. O02−N3 = 2.851 Å, O05−N2 = 2.850 Å, O06−N1 = 2.836 Å.

zoyl chlorides, 1-adamantylcarbonyl chloride, and isobutyl chloroformate. The tetraacylation with aroyl chlorides was also regioselective when *i*-Pr_2NEt was used as the base in contrast to *i*-Bu_3N or pyridine. Although a definite reason for the selectivity remains as yet unknown, it is clear that complexation with R_3NHCl plays a crucial role.[10]

It is important that the analogous acylation with benzylchloroformate allows the *regioselective protection*[11] of four hydroxy groups. The four remaining hydroxy groups can be further acylated, for instance, with acetic and BOC anhydrides to give the octaesters **5a,b**. The mild removal of the Z groups by catalytic hydrogenation (Pd/C, dioxane, rt) resulted in tetraesters **6a,b** (90%), which are not available by direct acylation (Scheme 2). Similarly, the alkylation of **2b** with ethyl bromoacetate (K_2CO_3, MeCN) led to the tetraether **5c** (68%), which on hydrolysis (MeOH/H_2O, KOH) gave quantitatively the resorcarene tetraacid **6c**.[12]

The tetraesters **2** undergo selective electrophilic substitutions in the free resorcinol rings (bromination with NBS, aminomethylation with primary and secondary amines) to give derivatives **7a**−**c** in 70−80% yield.[13] The alkaline hydrolysis of the dibromo derivative **7a** (MeOH/H_2O, KOH, 60 °C) gave the corresponding dibromo resorcarene **8a**,[14] but all attempts to cleave the ester groups in compounds **7b** and **7c** have failed. However, the regioselective aminomethylation of the tetracarbonate **6b** gave the diamine **7d** (78%), which by cleavage of the BOC groups (TFA, CH_2Cl_2, rt) was quantitatively transformed into the 1,3-bis-aminomethylated resorcarene **8b**.[15] These results demonstrate the potential of using the ester functions as protecting groups in the *rational* syntheses of C_{2v}-symmetrical resorcarenes.

Single crystals of the *p*-methylbenzoates **2b** and **3b** were obtained from DMSO and MeCN, respectively. Surprisingly, their molecular conformation is significantly different.

The molecules of **2b** assume a boat conformation in which the acylated resorcinol rings are nearly parallel (dihedral angle 5.6°) and the unsubstituted rings are coplanar (dihedral angle 168.9°). Each of the four hydroxy groups forms a hydrogen bond to an individual DMSO molecule (Figure 1a), while a fifth DMSO molecule fills the voids in the crystalline lattice.

The distortion of the crown (cone) conformation of molecule **3b** is less pronounced and in the opposite direction (Figure 1b). Here the two *unsubstituted* resorcinol units are bent inward, including a dihedral angle of 33.0°, while the two acylated resorcinol units assume an interplanar angle of 127.9°. No intramolecular hydrogen bonds were found between neighboring hydroxy and carboxy groups. Three hydroxyl groups of **3b** are involved in intermolecular hydrogen bonds with three acetonitrile molecules, and the one remaining is hydrogen bonded to the carboxy group of the next resorcarene molecule (O01−O09A = 2.857 Å). In this way, infinite chains of hydrogen bonded molecules **3b** are formed.

This result of the X-ray analysis suggests that the energy difference between the two possible boat conformations of tetrabenzoates **2** is rather small. A conformation with either parallel or coplanar resorcinol units can be "selected" to build up the crystal depending on packing and solvation effects.[16]

In conlusion, C_{2v}-symmetrical tetraesters of resorcarenes are readily available in gram quantities by simple synthetic and purification procedures. Not only are these compounds interesting building blocks themselves, but they also open up the way to synthesize further C_{2v}-symmetrical derivatives via protection/deprotection strategies.

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Supporting Information Available: Characterization data and crystallographic details (48 pages).

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(8) General Procedure for the tetraacylation. To a vigorously stirred suspension or solution of octanol **1** (10 mmol) in dry MeCN (100 mL) was added Et_3N (40 mmol) in one portion. The suspension formed was stirred at room temperature for 10−15 min, and then the solution of acid chloride (40 mmol) was added in one portion. The precipitate was completely dissolved (assistance by vigorous stirring), and within 3−20 min a colorless precipitate was formed again. The reaction mixture was stirred at room temperature overnight. The precipitate was filtered off, washed with MeCN (2 × 10 mL) and H_2O (3 × 10 mL), and recrystallized from MeCN, DMSO, DMSO/H_2O, and DMF/H_2O.

(9) Selected Crystallographic Data. **2b**·5DMSO: orthorhombic, space group *Pna*2(1), a = 23.547(5) Å, b = 15.871(3) Å, c = 40.116 (8) Å, V = 14992(5) Å^3, Z = 8, D_c = 1.247 g/cm^3, R = 0.0630 (for 10261 reflections $I > 2((I))$), $wR(F^2)$ = 0.1266 (for all 15802 unique reflections), S = 1.14. **3b**·3MeCN·H_2O: monoclinic, space group *C*2/*c*, a = 43.1478(3) Å, b = 16.330 Å, c = 23.0436 (2) Å, β = 92.0436 (2)°, V = 16226.3(3) Å^3, Z = 8, D_c = 1.132 g/cm^3, R = 0.1280 (for 5883 reflections $I > 2((I))$, $wR(F^2)$ = 0.2412 (for all 12873 unique reflections), S = 1.14.

(10) It has been shown that resorcarenes **1** and their tetraanions are able to complex tri- and tetraalkylammonium salts: (a) Murayama, K.; Aoki, K. *Chem. Commun.* **1997**, 119−120. (b) Lippmann, T.; Wilde, H.; Pink, M.; Schäfer, A.; Hesse, M.; Mann, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1195−1197. (c) Schneider, H.-J.; Güttes, D.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6449−6454.

(11) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, New York, 1994.

(12) The tetraalkylation of **1a** by ethyl bromoacetate was possible only in a rather poor yield of about 10%. The C_{2v}-symmetrical structure of this tetraether was confirmed by single-crystal X-ray analysis of its tetraacetate: Shivanyuk, A.; Böhmer, V.; Paulus E. F. Unpublished results.

(13) Bis-benzoxazine **7c** has a C_2-symmetrical structure similar to the analogous derivative from a resorcarene tetratosylate; see: Shivanyuk, A., Schmidt, C.; Böhmer, V.; Paulus, E. F.; Lukin, O. V.; Vogt, W. *J. Am. Chem. Soc.* **1998,** *120*, 4319−4326.

(14) This compound was recently prepared by partial bromination of **1a**: Konishi, H.; Nakamaru, H.; Nakatani, H.; Ueyama, T.; Kobayashi, K.; Morikawa, O. *Chem. Lett.* **1997**, 185−186.

(15) All attempts to synthesize compound **8b** by reaction of **1a** with 2 equiv of Et_2NH and CH_2O were unsuccessful.

(16) Tetraester **2d** adopts in the crystalline state the boat conformation with coplanar acylated resorcinol rings, similar to **3b**: Paulus, E. F.; Shivanyuk, A.; Böhmer, V. Unpublished results.