Synthesis of the parent resorcin[4]arene

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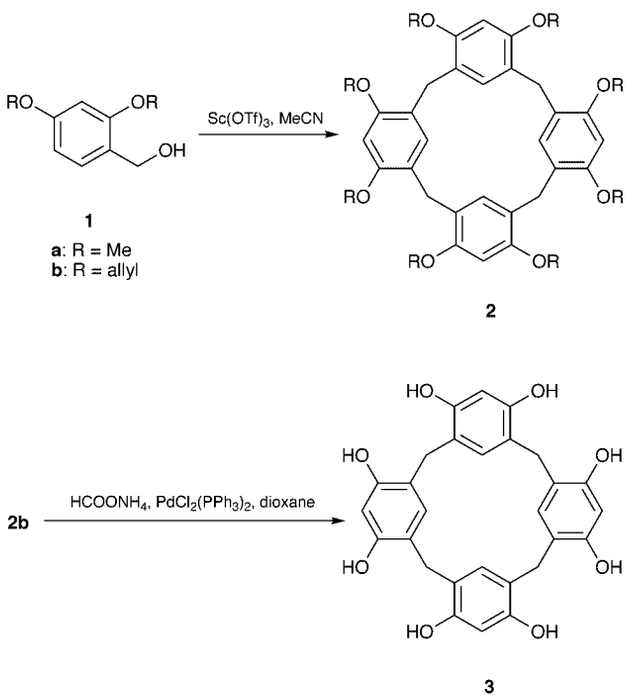
The treatment of 2,4-bis(allyloxy)benzyl alcohols with $Sc(OTf)_3$ in acetonitrile produced a cyclic tetramer as the major product, which was deallylated by ammonium formate and $PdCl_2(PPh_3)_2$ to produce the parent resorcin[4]arene.

Resorcinarenes are [1.*n*]metacyclophane compounds in which resorcinol units are linked *via* methylene bridges at their 4,6-positions.[1] Numerous potential applications of these resorcinarene derivatives as building blocks for supramolecular chemistry have been reported.[1–4] A variety of resorcin[4]arenes carrying alkyl or aryl substituents at the bridge positions are readily prepared by the acid-catalyzed condensation of resorcinols with aliphatic or aromatic aldehydes.[5,6] Analogously, the resorcin[*n*]arenes having no substituents at their methylene bridges were synthesized from 2-alkylresorcinols and formaldehyde.[7] Another procedure for preparing the unsubstituted-methylene bridged resorcin[4]arene involves the treatment of 2,4-dimethoxybenzyl alcohol **1a** with trifluoroacetic acid.[8] The resulting octamethyl ether **2a** was treated with BBr_3 to give a brick-red solid, which was presumed to be the parent resorcin[4]arene **3**. However, no spectroscopic characterization has been described in the literature. We would now like to describe a new synthetic method for resorcinarene octaethers, including the preparation of **3**. Its spectral properties have also been measured.

Due to the versatility of the allyl ether group as a phenolic hydroxy-protecting group in resorcinarene chemistry,[9] the octallyl ether **2b** was expected to be a promising starting material for the preparation of **3**. Thus, we attempted the condensation of 2,4-bis(allyloxy)benzyl alcohol **1b**.† However, the trifluoroacetic acid catalyzed reaction of **1b** did not produce any cyclic oligomers. Recently, it has been demonstrated that scandium trifluoromethanesulfonate, $Sc(OTf)_3$, promotes the Friedel–Crafts alkylation with benzyl alcohols as alkylating agents.[10] Furthermore, the $Sc(OTf)_3$ catalyst is not deactivated by water.[11] Therefore, we directed our efforts toward using this catalyst for the cyclocondensation of **1b**.

To a stirred solution of $Sc(OTf)_3$ (0.075 g, 0.15 mmol) in acetonitrile (100 ml) was added a solution of **1b** (3.3 g, 15 mmol) in acetonitrile (50 ml) over a period of 2 h at 30 °C. The reaction mixture immediately turned purple. After a further 3 h of stirring, most of the solvent was removed under reduced pressure. The residue was then dissolved in chloroform and washed with water. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo* to give the crude product from which the cyclic tetramer **2b**‡ was readily isolated by recrystallization from chloroform–hexane to give colorless crystals (mp 158–160 °C, 1.64 g, 54% yield). Analogously, the resorcinarene octamethyl ether **2a** was prepared from **1a** in 34% yield.§

The formation of metacyclophane structures was confirmed by their positive-ion FAB-mass spectra (*m*-nitrobenzyl alcohol matrix). In the 270 MHz ^{1}H NMR spectra at ambient temperature in $CDCl_3$, the resorcinarenes **2b** showed three singlets for the bridge methylene protons (3.79 ppm), extraannular aromatic protons (H_{ex}, 6.40 ppm) and intraannular aromatic protons (H_{in}, 6.30 ppm). The assignment of the aromatic protons was confirmed by an NOE observed between the H_{in} and the methylene protons. In addition, well-defined allylic multiplets were found. Furthermore, the ^{13}C NMR ($CDCl_3$, 30 °C) of **2b** showed eight signals as expected for the cyclic molecule.



Scheme 1

The parent resorcin[4]arene **3** was prepared from **2b** by deallylation.[12] A mixture of **2b** (1.21 g, 1.5 mmol), $PdCl_2(PPh_3)_2$ (0.17 g, 0.24 mmol), and ammonium formate (3.02 g, 0.48 mmol) in dioxane (90 ml) was refluxed for 6.5 h under an atmosphere of argon. The white solid that precipitated during the reaction was collected and dissolved in methanol. After removal of the methanol and insoluble material, the solvent was evaporated to leave almost pure **3**‡ in 52% yield. A sample for analysis was obtained by recrystallization from methanol as needles, mp 235 °C (decomp.). Its ^{1}H NMR spectrum in methanol-d_4 at 30 °C showed that **3** possesses a highly symmetrical structure. One singlet for the methylene protons (3.63 ppm), two singlets for the aromatic protons (6.25 and 6.87 ppm), and a singlet for the OH protons (8.53 ppm) are compatible with a time-averaged D_{4h} conformation. When a few drops of trifluoroacetic acid-d_1 were added to this methanol sample, the signal at 6.25 ppm gradually decreased, which is ascribed to the aromatic electrophilic deuteration at the *ortho* position to the OH groups at the extraannular positions (H_{ex}). Therefore, the singlet at 6.87 ppm was assigned to the H_{in}. This assignment was also supported by NOE experiments.

To gain insight into the conformational behavior of the resorcinarenes **2b** and **3**, we performed dynamic ^{1}H NMR experiments.¶ In $CDCl_3$, the ^{1}H NMR spectra of **2b** showed the bridging methylene signal as a sharp singlet and the H_{in} as a singlet (6.30 ppm) in the range −50 to 50 °C, indicating that **2b** exists in a 1,3-alternate conformation or is at a fast equilibrium among the conformational flexible species on the NMR

timescale. The high-field shift of the H_{in} is remarkable and could be due to shielding of the adjacent aromatic rings. Thus, it is suggested that the preferred conformation of **2b** is a 1,3-alternate conformation. On the other hand, in the ^{1}H NMR spectrum of **3** in methanol-d_4, the singlet for H_{in} (6.87 ppm at 30 °C) moved to a higher field upon cooling, and resonated at 6.41 ppm at −70 °C. In addition, the bridge methylene appeared as a singlet at 3.55 ppm. These findings suggest that the conformational freezing did not occur in this solvent and the preferred conformation of **3** may be a 1,3-alternate conformation. In conclusion, the hydrogen bonding interaction between the neighboring resorcinol rings is weakened in protic solvents and the steric hindrance due to the solvated hydroxy groups plays an important role in controlling the conformational behavior.

Notes and references

† 2,4-Dihydroxybenzaldehyde was treated with allyl bromide in acetone in the presence of K_2CO_3 **3** to give 2,4-bis(allyloxy)benzaldehyde, and then the reduction of the aldehyde function with $NaBH_4$ produced the benzyl alcohol **1b**.

‡ *Selected data* for **2b**: MS (FAB$^+$, *m*-NBA) *m*/*z* 808.4 (M+). δ_H (270 MHz, $CDCl_3$, 30 °C) 3.769 (8H, s), 4.423 (16H, d, *J* 5), 5.183 (8H, dd, *J* 10.5 and 1.6), 5.329 (8H, dd, *J* 17.3 and 1.6), 5.978 (8H, m), 6.302 (4H, s, H_{in}), 6.399 (4H, s, H_{ex}). δ_C (67.8 MHz, $CDCl_3$, 30 °C) 28.2 (t), 69.7 (t), 98.8 (d), 116.6 (t), 122.1 (s), 131.1 (d), 133.9 (d), 155.3 (s). ν_{max}(KBr)/cm^{-1} 3014, 1651, 1611, 1299, 997, 917. **3**: MS (FAB$^+$, *m*-NBA) *m*/*z* 488.2 (M$^+$). δ_H (270 MHz, methanol-d_4, 30 °C) 3.626 (8H, s, CH_2), 6.254 (4H, s, H_{ex}), 6.866 (4H, s, H_{in}), 8.530 (8H, br s, OH). δ_C (67.8 MHz, methanol-d_4, 30 °C) 29.9 (t), 103.8 (d), 121.6 (s), 132.3 (d), 155.1 (s). ν_{max}(KBr)/cm^{-1} 3188, 2798, 1631, 1446.

§ Recrystallization from DMSO gave colorless crystals, mp 300 °C (decomp.).

¶ In calixarene systems, the *syn*- or *anti*-orientation of the adjacent aromatic rings is predicted on the basis of the ^{13}C chemical shift of the bridging methylene carbons.[13] However, this rule is inapplicable to the present resorcinarene systems. In all experiments, the methylene carbons resonate in the range of 28–30 ppm.

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