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# The Missing Member of the Partially *O*-Alkylated Resorcinarene Family: Synthesis and Conformation of Methyl Tetramethoxy Resorcinarene

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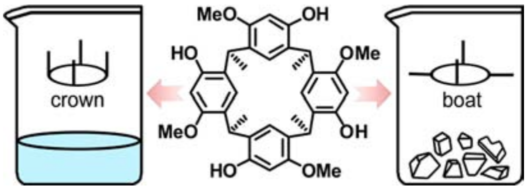
## ABSTRACT



**An improved Lewis acid catalyzed synthesis method for methyl tetramethoxy resorcinarene is described, which produced the missing lower rim methyl derivative of this partially *O*-alkylated resorcinarene family. Structural characterization by means of variable temperature NMR experiments and single crystal X-ray diffraction studies furthermore revealed that the resorcinarene core adopts different conformations in the solid state and in solution.**

Partially *O*-alkylated resorcinarene derivatives are particularly interesting due to their diverse possibilities in functionalization and potential for the preparation of enantiomerically pure chiral resorcinarene derivatives.[1] In 2000 McIldowie et al.[2] described a Lewis acid catalyzed synthesis of inherently chiral $C_4$ symmetric tetramethoxy resorcinarenes, a breakthrough in obtaining partially *O*-alkylated resorcinarenes in a convenient way. These derivatives have been advantageous platforms for example in the construction of Fréchet-type resorcinarene dendrimers,[3] resorcinarene mono- and bis-crowns,[4] and resorcinarene tetrapodands,[5] some of which have been shown to coordinate anions, alkaline and transition metal cations, and ammonium guests. The partial *O*-methylated resorcinarenes have also enabled the synthesis of other aromatic ring functionalized resorcinarene derivatives leading to tetrabiaryl cavity-extended resorcinarenes and resorcinarene tetrabenzoxazines.[6] Despite all the research carried out with tetramethoxy resorcinarenes to date, having the lower rim alkyl chain length varying from 2

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C-atoms (C2) up to 11 C-atoms (C11), the tetramethoxy resorcinarene family has lacked an efficient synthesis method for its smallest member, the one with methyl group (C1) at the lower rim.[7]

The *C*-methyl resorcinarenes have been shown to be conformationally remarkably flexible adopting at least crown, boat, chair, and scoop conformations in the solid state.[8] Both the adaptable scaffold and the free hydroxyl groups have enabled unique formations of various supramolecular assemblies, nanotubes, and capsules.[9] This encouraged us to look for a synthesis strategy for the preparation of C1-tetramethoxy resorcinarene, as it is not only an interesting structure on its own but also a platform for further functionalizations. Herein, we report a successful synthesis method for the preparation of C1-tetramethoxy resorcinarene (**1**). In addition, variable temperature (VT) NMR spectroscopy and single crystal X-ray diffraction (XRD) studies were used to investigate the structural characteristics that result from the short methyl group at the lower rim.

The standard protocol for the preparation of tetra-*O*-methylated resorcinarenes reported by McIldowie et al.[2] describes a one-pot reaction of an aldehyde[10] with 3-methoxy phenol in the presence of Lewis acid $BF_3{\bullet}Et_2O$ in dry dichloromethane at rt (Scheme 1). This protocol produces the C2- to C11-tetramethoxy resorcinarenes with good to excellent yields. However, when the reaction was repeated with acetaldehyde to produce C1-tetramethoxy resorcinarene, an unidentified polymeric product was obtained (Table 1, entry 1).[11]

**Scheme 1.** Synthesis of C1-Tetramethoxy Resorcinarene (**1**) with Crystallographic Numbering Shown for the Core; Schematic Presentations for the Boat and the Crown Conformations Are Shown at Bottom

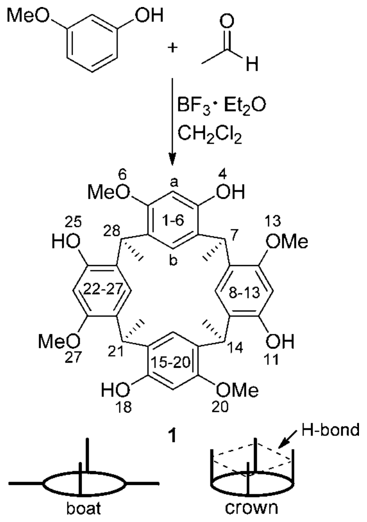

**Table 1.** Optimized Reaction Conditions for the Synthesis of Macrocycle **1**

| entry | *c* (mol/L)[a] | *t*[b] (°C) | *t*[c] (°C) | product (yield) |
|---|---|---|---|---|
| 1 | 1.64/1.72 | ~21 | reflux | polymer |
| 2 | 0.21/0.27 | 21 | <30 | macrocycle **1** + polymer |
| 3 | 1.64/1.72 | 1 | <20 | macrocycle **1** (33%) |
| 4 | 1.64/1.72 | −40 | −20 | macrocycle **1** (18%) |

[a] Concentrations of 3-methoxyphenol/acetaldehyde in the reaction mixture. [b] Temperature of the reaction mixture before the addition of $BF_3{\cdot}Et_2O$. [c] Temperature of the reaction mixture during the addition of $BF_3{\cdot}Et_2O$.

Intrigued by this we set out to test whether different reaction conditions would favor the production of the macrocycle **1** over the polymeric product obtained under the standard reaction conditions (Table 1). First, high dilution conditions were used resulting in a mixture that contained both the macrocycle **1** and the polymeric product (entry 2). The foremost difference to the standard protocol was that the reaction was less exothermic as the temperature rose to its highest at 30 °C, whereas in the standard protocol a higher increase in temperature (> 40 °C) was observed. This indicated that for C1-tetramethoxy resorcinarene a slower reaction rate might be more optimal for the macrocycle formation, thus hinting to be a kinetic reaction, whereas the formation of a polymer would indicate a thermodynamic reaction. The reaction was repeated with a standard concentration at lower temperatures in an ice bath and at an explicitly lower temperature of −40 °C to slow down the reaction (entries 3 and 4). Both of these experiments produced the pure macrocycle **1** with moderate yields of 18−33%. These results indicate that the temperature of the reaction mixture has a more pronounced role in obtaining the pure macrocycle **1** than the high-dilution conditions.

The $^1H$ NMR spectra of macrocycle **1** at rt shows one set of resonances to the protons of the resorcinarene core, which is indicative of a $C_4$ symmetric crown conformation (Figure 1, 30 °C).[2]

However, the resorcinarene core could also adopt less symmetric conformations giving rise to multiple signals of the resorcinarene core, but due to fast interconversion between the conformations on the NMR time scale this might not be detected at rt.[12] Therefore, VT NMR

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(7) We have found a Japanese patent mentioning the structure of C1-tetramethoxy resorcinarene in an application for heat-resistant flat films. However, no details of the synthesis appear to be reported. Momota, J.; Onishi, H. Jpn. Kokai Tokkyo Koho, JP 2004018421 A 20040122, 2004.

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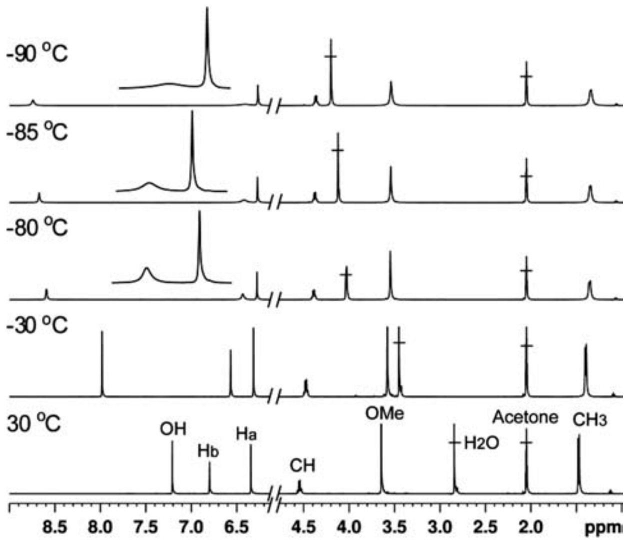

**Figure 1.** $^1$H NMR variable temperature experiment of compound **1** in acetone-$d_6$ showing the spectra measured at a temperature range of 30 to −90 °C. A close-up of the region 6.30−6.60 ppm is shown for the spectra of −80 to −90 °C.

measurements were undertaken in a nonpolar $CDCl_3$ solvent and in a polar acetone-$d_6$ solvent at a temperature range of 30 to −60 or −90 °C, respectively, in order to confirm the conformation of macrocycle **1** in solution. Even at the remarkably low temperature of −60 °C in the nonpolar $CDCl_3$ solvent all the signals remained sharp (Figure S1). This observation indicated that no boat-to-boat interconversion or other less symmetric conformations occurred, as no extensive broadening or splitting of the signals was observed, confirming the crown conformation of macrocycle **1**. This was expected since macrocycle **1** cannot form intermolecular H-bonds with the nonpolar $CDCl_3$ solvent. Instead, macrocycle **1** forms an intramolecular H-bonding network on the upper rim, stabilizing the crown conformation.[13] The only significant difference observed in the spectra measured at different temperatures was the downfield shift of the hydroxyl protons by 0.40 ppm, which was due to the OH signal shifting upon the change in temperature.[14]

The VT NMR spectra measured in the polar acetone-$d_6$ also indicated a crown conformation. Even though some signals broadened at lower temperatures, no splitting occurred (Figure 1). All but the OH-proton signal of macrocycle **1** was observed to shift somewhat upfield by 0.08/$H_a$−0.38/$H_b$ ppm. The signal of the OH group on the other hand had a substantial downfield shift of 1.53 ppm, and in addition, the residual water signal in the solution was observed to have a similar downfield shift of 1.36 ppm. It is likely that the methoxy and hydroxyl groups at the upper rim interact with the residual water and acetone-$d_6$, but intermolecular H-bonds do not seem to break the intramolecular H-bonding network of macrocycle **1**, which ultimately keeps the macrocycle in the crown conformation.

The structural properties of **1** were also studied in the solid state by XRD. Single crystals of compound **1** suitable for crystal structure analysis were grown by vapor diffusion (solute/antisolvent) from ethyl acetate/hexane (structure **I**) and methanol/water (structure **II**). Structure **I** crystallized in a monoclinic space group $P2_1/n$ as a 1:1 water solvate. Structure **II** was obtained in a triclinic space group $P\overline{1}$ having one methanol and one water molecule per compound **1**. In both structures **I** and **II**, the resorcinarene core is in a boat conformation, despite the capacity of the upper rim to form intramolecular H-bonds stabilizing the core into a crown conformation (Figure S2).[15] All previously reported structures of tetramethoxy resorcinarenes with varying alkyl chain lengths have the resorcinarene cores more or less in the H-bond stabilized crown conformation.[2,3,15,16] However, the boat conformation is not uncommon with the solid state structures of octahydroxyl *C*-methyl resorcinarenes.[8b,17] In those reported structures the boat conformations are generally in "brick"-like rows stabilized by intermolecular H-bonds and $\pi-\pi$ interactions between the resorcinarene molecules. The basis for why the boat conformation is more common with the short alkyl chain resorcinarenes was reasoned to be due to the ideal close packing compared to the longer alkyl chain resorcinarenes, which tend to crystallize into lipid-like bilayers with the resorcinarene core in a crown conformation.[18]

In the case of macrocycle **1**, the crystal packing is likewise clearly affected by the intermolecular H-bonds formed in the crystal lattice, which also explains the preferred boat conformation of macrocycle **1** in the solid state. In structure **I** a bridging water molecule connects two same-handed adjacent resorcinarene enantiomers **1** (A and B) together via three intermolecular H-bonds (2.03−2.38 Å, Figure 2) by having two differerent roles acting as both a H-bond donor and acceptor. With the water molecule as the acceptor, intermolecular H-bonds are formed with the hydroxyl groups of the two adjacent resorcinarenes (O20/upright-A and O13/horizontal-B), while the other role of water as the donor leads to formation of H-bonds to the resorcinarene methoxy group (O18). Two additional direct intermolecular H-bonds (2.22 Å) are formed via the remaining hydroxyl groups of each resorcinarene (O6/upright-A, and O27/horizontal-A) with the respective hydroxyl groups of two neighboring different handed resorcinarene molecules (Figure 2).

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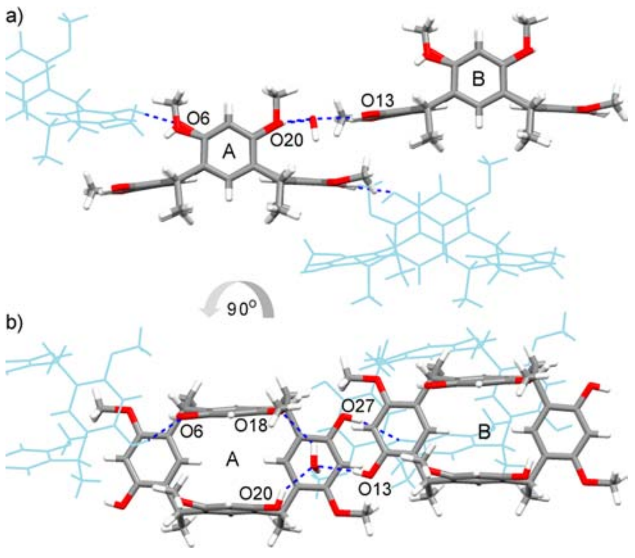

**Figure 2.** H-bonding network of structure **I** of macrocycle **1**, shown from side (a) and top views (b). Resorcinares A and B joined together via a water molecule are presented with elemental colors and acceptor/donor of direct H-bonds between resorcinarenes with light blue. The H-bonds are shown as blue dotted lines.

Unlike in structure **I**, in structure **II** a three-molecule unit is formed by one water molecule connecting three neighboring resorcinarene molecules **1** (A, B, and C) via three H-bonds to two horizontal (O13-A and O27-C) and to one upright hydroxyl (O6-B) groups (1.98−2.08 Å, Figure 3). A horizontal methoxy group oxygen (O25-B) of the resorcinarene B in the unit acts also as an acceptor for the fourth intermolecular H-bond formed by the bridging water molecule (2.00 Å). Solvent methanol molecules fill up the remaining voids between the two adjacent three-resorcinarene assemblies. The repeating three-molecule units form layer-like structures, which are piled on top of each other in the crystal lattice.

Even with different kinds of H-bond networks both structures **I** and **II** form with a similar packing style. The chains (structure **I**, Figure S3) are positioned over each other forming a slightly oblique "brick wall" while the layers (structure **II**, Figure S4) are piled straight. The shortest possible alkyl chain on the lower rim enables this very close packing of resorcinarene **1** since the methyl group requires only a small volume. Due to this unique structural characteristic of the C1 derivative, the lower rim alkyl chain does not seem to be the major contributor in the crystal packing as generally is the case with the longer alkyl chain derivatives. The major role therefore in the formation of crystal packing interactions falls to the upper rim functionalities. This property together with the "brick" form of the macrocycle will enable various supramolecular assemblies (e.g., nanorod, nanotube, and hexameric capsules)[9] via further derivatizations and cocrystallizations that can be useful in making crystal engineered materials.

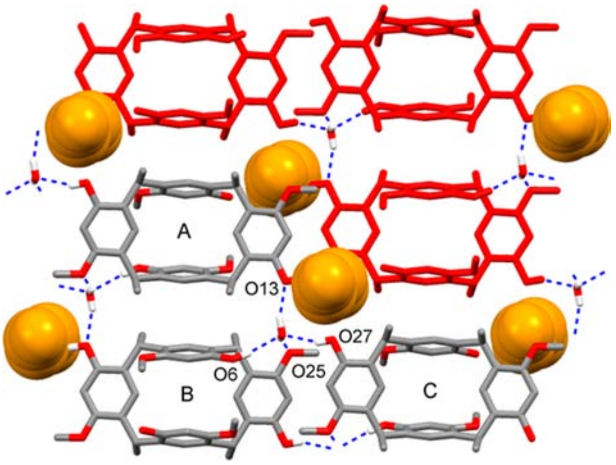

**Figure 3.** H-bonding network of structure **II** showing solvent methanol as a space fill model. The adjacent three-resorcinarene unit is shown in red, and the resorcinarenes connected with the water molecule are labeled A−C. Noncoordinating hydrogens have been omitted for clarity, and H-bonds are shown as blue dotted lines.

In conclusion, C1-tetramethoxy resorcinarene having methyl chains on its lower rim was successfully synthesized from 3-methoxyphenol and acetaldehyde by an improved synthesis method. The pure macrocycle was achieved at a reaction temperature below 0 °C as opposed to the unidentified polymeric product obtained when the reaction was performed using standard reaction conditions at room temperature. VT NMR measurements showed that the resorcinarene core adapts a crown conformation in both polar and nonpolar solvents. In contrast, in the crystal structures obtained the core adopts a boat conformation as the intramolecular H-bonds of the upper rim are replaced with intermolecular interactions. These unique structural characteristics of the up-to-now missing C1-tetramethoxy resorcinarene will add new possibilities to the macrocyclic family of tetramethoxy resorcinarenes in terms of supramolecular self-assembly, crystal engineering, and further functionalization.

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**Supporting Information Available.** Experimental procedures and characterization for compound **1**; two additional structures **III** and **IV**; additional figures of XRD structures and a scatter plot presentation of the results of a CCDC structure search; crystal data and CIF for all structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.