Higher Analogues of Resorcinarenes and Pyrogallolarenes: Bricks for Supramolecular Chemistry

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ABSTRACT: Easy scalable and eco-friendly syntheses of resorcin[5]arene, pyrogallol[5]arene, (2-nitro)resorcin[5]arene, (2-carboxyl)resorcin[5]arene, and resorcin[7]arene are presented and a wide range of upper-rim modifications is demonstrated. The macrocycles open the door toward expanding the rich covalent and supramolecular chemistry of [4]arenes with analogues having unique 5-fold and 7-fold symmetry.

Various classes of (poly)phenolic macrocycles1–6 feature a prominent role in supramolecular chemistry serving as platforms for construction of effective ion receptors,7,8 molecular switches,9 porous materials,10,11 supramolecular catalysts,12,13 nanoscale architectures,14,15 and receptors for biological applications.16 It is apparent that the size of a macrocyclic ring controls recognition selectivity and conformational lability and defines molecular symmetry. Among these features, symmetry is a crucial factor that affects the formation of higher-order structures from these macrocycles, especially closed-shell structures (capsules and cages). For example, [4]arenes featuring 4-fold symmetry form dimeric,17 tetrameric, and hexameric16 capsules and cages, while other geometries are disfavored. The 5-fold symmetry is unique in this regard, because it enables the construction of exceptionally large dodecahedron-type capsules. This symmetry is widely exploited in Nature to construct viral capsids.19 However, only a single dodecahedron structure has been reported thus far; it was based on 4-carboxylatocalix[5]arene coordinating to UO$_2^{2-}$.20

In this paper, we present the synthesis, effective isolation and structural properties of a series of resorcin[5]arenes, pyrogallol[5]arene, and resorcin[7]arenes with modifiable upper rims. Despite the fact that, for some classes of polyphenolic macrocycles (e.g., for calixarenes), numerous analogues having various ring sizes are known,21 for resorcin[4]arenes and pyrogallol[4]arenes, examples of higher analogues remain rare. Synthesis of 2-methyl resorcin[7]arenes in the form of O-methylene bridged cavitands was reported for $n = 5$ in 3.6% yield, $n = 6$ in 13.9% yield, and $n = 7$ in 1.1% yield.22 None of these compounds has found widespread applications thus far, most likely because of blockage of their reactive upper rim positions by methyl groups. Prorse, Shivanyuk and Rebek reported the synthesis of a single derivative of an upper-rim unsubstituted $S_c$-symmetric r-tctct isomer of resorcin[6]arene in ~5% yield,23 and its modifications24 and applications13 have been demonstrated. Resorcinarenes or pyrogallolarenes with unique 5-fold symmetry and with unsubstituted upper rims, beside a single notice of their detection via mass spectroscopy (MS),25 remain unknown.

A typical procedure for the synthesis of resorcinarenes and pyrogallolarenes involves a reversible acid-catalyzed condensation reaction that leads to thermodynamically most stable [4]arenes as the sole isolable products.26,27 Intramolecular hydrogen bonds are claimed to be the reason for thermodynamic preference toward [4]arenes. We put forward the hypothesis that deprotonation of phenolic protons or application of reaction condition under which the reaction is irreversible may lead to the formation of higher analogues of resorcinarenes or pyrogallolarenes. Therefore, we tested the reaction between resorcinol and formaldehyde (to avoid regioselectivity problems) under basic conditions. Similar conditions have been previously applied for the synthesis of resorcinarenes; however, the authors isolated only [4]arenes.28

Aqueous NaOH solution was used as a reaction medium for the reaction of resorcinol 1 and formaldehyde at room temperature (Figure 1). Under such conditions, the reaction gives resorcin[4]arene 4 as a main product, but resorcin[5]-
arene 9 and resorcin[7]arene 13 were also detected. We tested the influence of various factors, such as concentration, temperature, addition of organic solvents and the type of a base (organic and inorganic bases) on the reaction yield (Table S1 in the Supporting Information). The detailed studies on the influence of reaction time on the yield of the macrocyclic products were performed (HPLC monitoring every hour; see Figure S40 in the Supporting Information). We have found that the reaction time is a crucial parameter: the best results were obtained after 24 h, and reaction times that are either too short and too long lead to a reduction in the amount of higher resorcinarenes. Resorcin[5]arene 9 was isolated in 4.3% yield, using NaOH as a base after 24 h. Although the yield remains low, considering the availability of reagents, and the easy, mild, repeatable, and scalable synthetic procedure, the resorcin[5]arene can be obtained in gram scale at relatively low cost. For example, we tested the procedure on a larger scale and isolated 1.05 g of 9 in one batch. We have found that this synthetic procedure is quite general, because it enables the synthesis of respective [5]arenes for a wide range of 2-substituted resorcinols with even higher yields. Thus, pyrogallol[5]arene 10 was obtained in 8.7% yield, pentanitroresorcin[5]arene 11 was obtained in 9.9% yield, and pentacarboxyresorcin[5]arene 12 was obtained in 5.4% yield. The purification procedure in most cases requires the initial removal of [4]arenes (that are the main products in all reactions) and chromatographic resolution of higher analogues. Pentanitroresorcin[5]arene 11 is a notable exception here, because it can be isolated without chromatography. This was possible due to substantial differences in solubility of the products ([5]arene is soluble in THF, while [4]arene is not) and relatively high yield.

All [5]arenes 9−12 exhibit high conformational flexibility of the macrocyclic rings. 1H NMR spectra at room temperature in acetone-d6 reveal D5h symmetry for all derivatives (see Figure 2). Such high symmetry must originate from dynamically averaged structures (rearrangements within hydrogen bonding system and fast inversion of the macrocyclic ring). VT 1H NMR spectra show no signal splitting down to 213 K for all compounds, indicating that conformational lability is preserved in this temperature range. In order to gain insight into the conformational preferences, we have performed quantum mechanical calculations (DFT, B3LYP functional, employing the 6-31g basis set, in acetone). The initial models were constructed using calix[5]arenes conformations retrieved from the CSD database (the 15 most abundant conformations were retrieved, which, after optimization, converged to 7 conformations; see Figure S41 in the Supporting Information). It has been found that the lowest energy conformation in acetone

Figure 1. Synthesis of [n]arenes.
is the conelike conformation with static C₅ symmetry (Figure 2). The second most stable conformation has C₄ static symmetry and an energy that is 32 kJ/mol higher, which translates to a negligible Boltzmann population at 298 K (with a ratio of 1:2.59 × 10⁻⁸). These calculations and experimental results suggest that, most likely, in solution, dynamically averaged D₅₅ symmetric conformation comes from two C₅ symmetric conformations (all other conformations have negligible populations).

The applicability of [5]arenes 9–12 in supramolecular chemistry can be greatly expanded by restriction of their conformational lability and by possible chemical modifications of their upper rims (Figure 3). Toward this end, we tested the possibility of locking the cavitand-like conformations by linking hydroxyl group with methylene bridges. Reaction of 9 with bromochloromethane in DMA gives -methylene bridged resorcin[5]arene 14. ¹H NMR spectrum confirms that the ring has been locked in C₅ᵥ-symmetric vase conformation: lower rim and bridging methylene protons (H₆ and H₇) appear in the spectrum as two doublets each with characteristic vicinal coupling constants (δ(H₆) = 3.525 and 4.245 ppm and J = 12 Hz; δ(H₇) = 4.52 and 5.795 ppm and J = 8 Hz).

Furthermore, we have also examined the possibility of modification of an upper rim of resorcin[5]arenes at the 2-position of the resorcinol rings. We tested the reactivity of 9 in the Mannich reaction, that is widely known for resorcin[4]arenes. Reaction between 9, aniline (6 equiv), and an excess of formaldehyde (12 equiv) resulted in the formation of pentabenzoxazine 15. The product is formed regioselectively—a single isomer was isolated in 51% yield via a chromatography-free procedure. The C₅ᵥ symmetry of this isomer was confirmed by ¹H and ¹³C NMR spectra in CDCl₃ that exhibit a single set of sharp signals for only one symmetry-independent repeating unit (Figure 4). Regioselectivity in benzoxazine formation reaction is typical for resorcin[4]arenes, for which the lower rim alkyl substituents stabilize a cone conformation and promote the formation of four hydrogen bonds for a C₄ᵥ-symmetric isomer (isomers of lower symmetry would have fewer hydrogen bonds). However, it is nontrivial that similar regioselectivity will also be observed for 9, which has a different ring size and exhibits fast ring inversion because of a lack of lower rim substituents. Apparently, the dynamic character of the macrocyclic ring does not preclude preferences toward C₅ᵥ symmetric structure. VT ¹H NMR spectra show that not only substrate 9 but also benzoxazine 15 is dynamic. Inversion of a macrocyclic ring and inversions of within six-membered benzoxazine rings are fast on the NMR timescale. This was deduced based on the signals of methylene bridges that appear as singlets at 293 K, and they are only slightly broadened upon lowering of the temperature down to 213 K. The Mannich reaction was also used to introduce chiral substituents at the upper rim to obtain chiral amine 20.

In conclusion, we have shown easy and scalable syntheses of various substituted resorcin[5]arenes (including pyrogallol[5]-arene) and resorcin[7]-arenes. Considering the unique symmetry and proven tuneability of [5]arenes, we foresee their applications in applications in the construction of various sensing molecules and molecular capsules and cages. In fact, our preliminary results confirm unique self-assembly properties of these compounds, e.g., their ability to form large self-assembled capsules.

**ASSOCIATED CONTENT**

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02357.

Experimental details, additional information and NMR spectra of new compounds, details of theoretical
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calculations, along with Cartesian coordinates of optimized structures (PDF)

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Author Contributions

M.C. performed all the synthetic experimental work, analyzed NMR data and suggested crucial modifications. A.S. conceived and directed the project, supervised data interpretation, and wrote the manuscript.

Notes

The authors declare no competing financial interest.

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