

Xanthene[n]arenes: Exceptionally Large, Bowl-Shaped Macrocyclic Building Blocks Suitable for Self-Assembly

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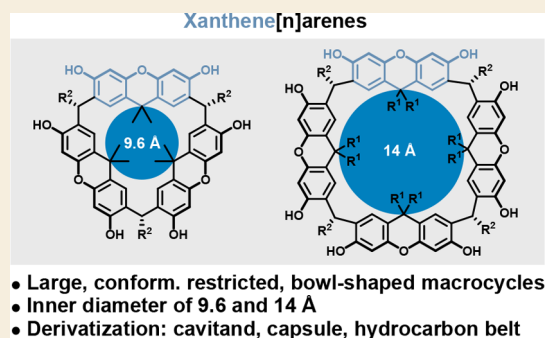
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Supporting Information

ABSTRACT: A new class of macrocycles denoted as “xanthene[n]arenes” was synthesized. In contrast to most other macrocycles, they feature a conformationally restricted bowl shape due to the attached alkyl groups at the linking methylene units. This facilitates the synthesis of cavitands and the self-assembly to molecular capsules via noncovalent interactions. The derivatization potential of the novel macrocycles was demonstrated on the xanthene[3]arene scaffold. Besides a deep cavitand and an oxygen-embedded zigzag hydrocarbon belt[12]arene, a modified macrocycle was synthesized that self-assembles into a hydrogen-bonded tetrameric capsule, demonstrating the potential of xanthene[n]arenes as a new set of macrocyclic building blocks.

KEYWORDS: macrocycle, macrocyclization, self-assembly, molecular capsule, host–guest chemistry, calixarene, hydrocarbon belt, deep cavitand



Macrocycles have been a cornerstone in supramolecular chemistry since its beginning, which was marked by the discovery of crown ethers.^{1,2} A wide variety of macrocycles featuring different degrees of conformational freedom and sizes has been developed and explored intensively ever since.^{3–10} An important subset of these macrocycles is comprised of conformationally restricted bowl-shaped derivatives, which are required for the construction of cavitands^{11,12} and closed host structures like (hemi)carcerands.^{5,6,13–17} Moreover, the self-assembly of molecular capsules via noncovalent interactions depends on such bowl-shaped macrocycles.^{18–24} Macrocycles utilized for self-assemblies mainly comprise phenol-based systems like the calixarene family of compounds,^{25–27} with the two widely used members resorcinarene (**1**, Figure 1a) and pyrogallolarene (**2**).²⁸ The key features of these bowl-shaped molecules are (1) the crown conformation is highly favored due to the preference of the R substituents for the axial orientation and the hydrogen bond pattern of the free phenols²⁸ and (2) the R residues are essential for increasing the solubility of the free phenol compounds. This enhanced solubility facilitates self-assembly processes via hydrogen bonds and the facile derivatization of the macrocycles as low solubility is often a challenge for synthetic work.²⁹ Naturally, it was attempted to broaden this specific subclass of macrocycles by replacing the benzene-based building blocks with larger ones, for instance, naphthalene-derived ones. Unfortunately, all attempts have failed to deliver size-extended bowl-shaped resorcinarene-like macrocycles as of yet.^{30–33} During the past decade, many new large phenol-based macrocycles, including 3–8 (Figure 1b),^{34–41} have been reported.^{42–48} Importantly,

in contrast to **1** and **2**, they do not feature R residues at the linking methylene units that conformationally restrict the crown conformation, and increase the solubility of the free phenol derivatives. The higher conformational freedom of the CH₂-linked macrocycles is revealed in the ¹H NMR spectra. For instance, the calix[n]carbazoles (**6**) and the fluoren[3]-arenes (**7**) feature magnetically equivalent hydrogens at the methylene linkages. Such a high symmetry originates from a fast inversion of the macrocyclic ring. In contrast, macrocycles **1** and **2** feature a conformationally restricted bowl shape that does not invert due to the presence of the R substituents.

Studies on the resorcinarene framework have furthermore demonstrated that the synthetic access to methylene-linked systems is more facile than the R-substituted ones, giving more facile access to the unsubstituted larger penta-, hexa-, and heptameric resorcinarenes.^{49–53} This might explain the prevalence of methylene-linked macrocycles over R-substituted ones (Figure 1).

Herein, we report the synthesis of new, exceptionally large, conformationally restricted bowl-shaped macrocycles X-3 and X-4 (Figure 1c), composed of three or four xanthene units, respectively, and propose the name “xanthene[n]arenes” (X-n). In contrast to the known large macrocycles (Figure 1b), they

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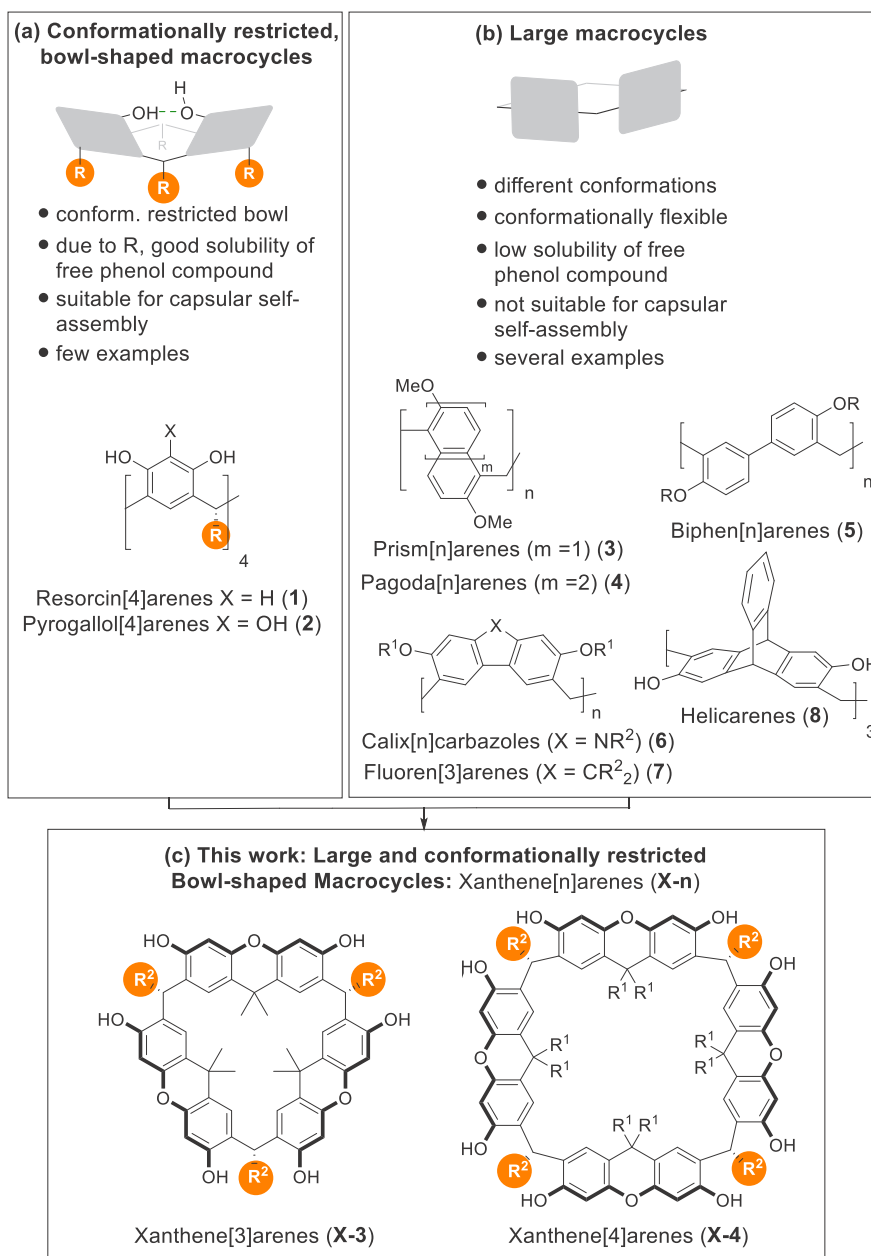


Figure 1. Xanthene[*n*]arenes extend the narrow field of conformationally restricted, bowl-shaped macrocycles as its largest representative.

carry R residues on the linking methylene units and, therefore, feature the two main advantages mentioned in the introduction: (1) the conformationally restricted crown conformation and (2) the good solubility of the free phenol compounds. We demonstrate that they are well-suited for the construction of deeper cavitands, hydrocarbon belts, and the self-assembly of hydrogen bond-based molecular capsules.

The known xanthene **9** can easily be obtained on the decagram scale from acetone and resorcinol in the presence of the Lewis acid ZnCl₂ (Scheme 1).⁵⁴ In analogy to the calixarene/resorcinarene syntheses, a direct macrocyclization of **9** and different aldehydes under acidic conditions was attempted. However, no traces of xanthene[*n*]arenes were detected via ¹H NMR and ESI-MS analysis. Therefore, we decided to attempt macrocyclization in a head-to-tail manner from the prefunctionalized monomer **15** equipped with the side chain and the reactive benzylic alcohol moiety.

Compound **15** is accessible via a simple four-step procedure. After benzyl protection in high yield (92%), selective monoformylation was achieved using Vilsmeier–Haack conditions in excellent yield (96%).

Subsequently, the benzyl groups were removed using TFA to deliver aldehyde **12** (62%). Finally, Grignard-addition yielded the desired benzylic alcohol **15** (90%). Extensive screening of cyclization conditions using different acids, solvents, and concentrations resulted in very low yields (<5%) of the macrocyclic products in most cases (see Supporting Information, Chapter 3). Gratifyingly, under optimized conditions (25 mM **15**, 15 vol % TFA:CH₂Cl₂, 20 h, 0 °C to rt), the xanthene[3]arene **19** was obtained as the major macrocyclic product in 21% isolated yield. The even larger X-4 was only observed in traces via MALDI-MS. Attempts to increase the amount of X-4 by changing the reaction conditions failed. We speculated that the product

corresponding ketone using hydrochloric acid instead of the zinc chloride utilized for **9**. They were converted to the benzylic alcohols **17** and **18** in good yields utilizing the chemistry developed for **15**. Indeed, utilizing the cyclization conditions optimized for the conversion of **15** to **19**, conversion of **17** and **18** led to the tetrameric **X-4** structures **21** and **22** as the only defined cyclization products, albeit in very low yields (<1%). Although the yield was terrible, the selective formation of **X-4** over **X-3** was promising. Furthermore, it was found that the product **X-4** decomposes during the extended reaction time (20 h). After extensive optimizations, shorter and milder reaction conditions were found (64 mM **17/18**, 1:9 TFA:DCE, 60 min, 0 °C) that yielded the **X-4**-derivatives **21** and **22** in at least useful yields of 7 and 4%, respectively (see Supporting Information, Chapter 4).

All macrocycles synthesized (**19**, **21**, and **22**) were characterized by ^1H -, ^{13}C -, and 2D-NMR spectroscopy as well as ESI-HRMS measurements. Additionally, the crystalline xanthene[3]arene derivative **20**, featuring *i*-Bu instead of *n*-Dec feet, was synthesized via alcohol **16**. Single crystals suitable for X-ray crystallography were obtained by slow evaporation of a solution of **20** in THF. The crystal structure analysis of **20** (space group: $P4/n$) confirms the crown conformation (C_{3v} -symmetry, Scheme 1). While the tetrahedral angles between two adjacent xanthene units remain at 109.4° , interestingly, the dihedral angles between the two aromatic units of each xanthene are 16.5° , induced by the strain of the macrocycle.

To demonstrate that these unusually large, conformationally restricted, bowl-shaped macrocycles indeed feature the same advantages as their much smaller resorcinarene (**1**) counterparts, several derivatives were prepared. We demonstrate that (1) they are a suitable platform to synthesize large and well-soluble cavitands, (2) derivatives of **X-3** self-assemble to unusually large tetrameric supramolecular capsules, and (3) they enable the synthesis of a well-soluble oxygen-embedded zigzag hydrocarbon belt.

First, quinoxaline walls⁵⁵ were introduced by nucleophilic aromatic substitution to deliver cavitand **23** in good yield (48%, 88% yield per substitution, Scheme 2). **23** displays a high selectivity for binding adamantanemethanol (**24**) (see Supporting Information, Chapter 7.2). Interestingly, a series of other adamantane derivatives, ammonium salts, and fullerenes did not show uptake.

Second, derivatization at the upper rim of **X-3** was conducted in analogy to a literature procedure on resorcinarene.⁵⁶ After NBS-bromination (89%) and subsequent permethylation (88%), the aryl bromides were converted into phenolic moieties via halogen/lithium exchange, followed by quenching with trimethyl borate and subsequent oxidation. Product **25** was obtained in good yield considering that six positions were functionalized (27%, 80% yield per functionality). Macrocycle **25** was characterized by ^1H -, ^{13}C -, and 2D-NMR spectroscopy as well as ESI-HRMS measurements. In apolar solvents such as chloroform and toluene, **25** self-assembles to defined larger structures. Interestingly, this is in contrast to the unmodified **X-3** and **X-4** that did not form assemblies in apolar solvents. Whereas the signals of the ^1H NMR spectra are broad at room temperature, the signals sharpen upon cooling (Figure 2). At 228 K, the phenol signals resonate as sharp peaks at 12.9 and 8.8 ppm, while the signals for the aromatic C–H groups and the methoxy groups split into two sharp singlets each.

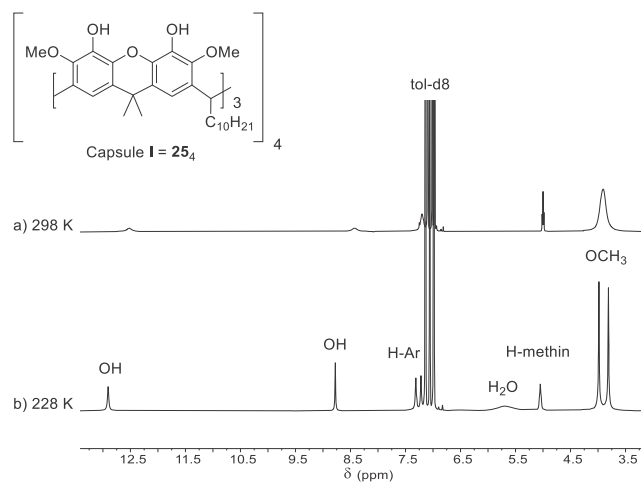


Figure 2. ^1H NMR spectra of capsule **I** in toluene- d_8 (1.25 mM) at (a) 298 K and (b) 228 K.

The geometric requirements of the C_3 -symmetric macrocycle **25** would, in principle, enable the self-assembly to dimeric, tetrameric, and octameric structures. These options can be differentiated via DOSY-NMR measurements. DOSY-NMR has been established as a reliable tool for the size determination of supramolecular assemblies.⁵⁷ This technique is very valuable as well-soluble derivatives usually do not crystallize well to enable X-ray structure determination. Moreover, the in-solution analysis is of high interest, as the crystal packing in the solid-state may change the assembly size and shape. DOSY-NMR experiments at 298 K in toluene- d_8 provided a diffusion value of $D = 0.23 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$. According to a well-established procedure involving the modified Stokes–Einstein equation,⁵⁸ this value corresponds to a hydrodynamic radius of $r_h = 1.7 \text{ nm}$ for the supramolecular assembly (see Supporting Information, Chapter 5.2). The hydrodynamic radius determined from the respective diffusion coefficient only correlates well with the molecular model of a tetrameric assembly ($r_{\text{dimer}} = 1.30 \text{ nm}$, $r_{\text{tetramer}} = 1.6 \text{ nm}$, $r_{\text{octamer}} = 2.10 \text{ nm}$, see Supporting Information, Chapter 5.3). Accordingly, the dimeric and octameric assembly can be reliably excluded. Additionally, substrate uptake studies with C_{60} and C_{70} fullerene provided further convincing evidence for the tetrameric size.

Molecular modeling clearly indicated that the dimeric capsule would be too small for uptake of either fullerene, while the tetrameric assembly would accommodate one C_{60} very well (see Supporting Information, Chapter 7.4). The octameric capsule on the other hand would easily accommodate several fullerenes at once. The experiments revealed (1) a selective uptake of C_{60} , where no interactions with C_{70} were observed, and (2) that uptake was limited to 1 equiv of C_{60} (Figure 3, Supporting Information, 7.4). DOSY-NMR experiments further provided a diffusion value of $D = 0.24 \times 10^{-5} \text{ cm}^2 \text{ s}^{-1}$ for the host–guest complex, confirming the structural stability of assembly **I** upon guest uptake. The binding constant K_a was found to be approximately $7 \times 10^5 \text{ M}^{-1}$ (see Supporting Information, Chapter 7.4). Accordingly, the dimeric and octameric assembly can be reliably excluded based not only on the analysis of the diffusion value but also on this guest uptake study.

With an internal cavity volume of approximately 1400 \AA^3 , this tetrameric capsule **I** (Scheme 2b) is more than five times

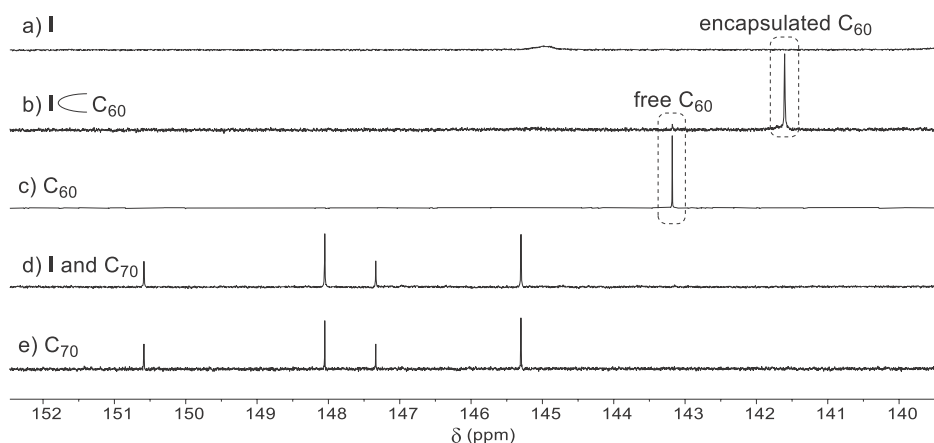


Figure 3. ^{13}C NMR spectra in toluene- d_8 of (a) capsule **I** (1.25 mM), (b) capsule **I** and C_{60} fullerene (both 0.85 mM), (c) C_{60} (2.50 mM), (d) capsule **I** and C_{70} (both 0.85 mM), and (e) C_{70} (1.00 mM).

larger than the largest tetrameric hydrogen bond-based supramolecular capsule reported so far (270 \AA^3).^{59–61} Further guest uptake studies with alkyl ammonium guests indicated that the assembly displays a similar uptake behavior as the pyrogallol[4]arene (**2**) capsule with these guests.⁶² With Et_4NBr , a dimeric precipitate was observed. Dimeric assemblies of pyrogallolarene (**2**) containing ammonium species were previously observed to form in solid-state and as precipitates from solution.^{63–65} The addition of larger ammonium, terpene, and polyaromatic guests did not interfere with the formation of the tetrameric capsule. However, no host–guest complexes could be observed (see [Supporting Information, Chapter 7.3](#)).

Lastly, macrocycle **19** was converted to the O_6 -belt[12]arene **26** ([Scheme 2c](#)). This O -beltarene is 1.5 times wider than any previously reported O -derivative. The conversion was achieved using conditions reported recently on the resorcinarene (**1**) framework.⁶⁶ After triflation (99%), a partial hydrolysis followed by aromatic substitution under basic reaction conditions yielded the O_6 -belt[12]arene **26** in 76% isolated yield. The photophysical properties of **26** were investigated ([Scheme 2c](#)). The UV–vis absorption spectrum in CH_2Cl_2 at 293 K shows two bands with maxima at 227 and 275 nm ($\epsilon \approx 2500\text{--}6000 \text{ M}^{-1} \text{ cm}^{-1}$), which we attribute to spin-allowed transitions into singlet excited states. Furthermore, a broad (and considerably weaker) absorption feature between 300 and 375 nm is observed and is tentatively attributed to a spin-forbidden transition into a triplet excited state. When a CH_2Cl_2 solution of O_6 -belt **26** is excited at 293 K at 275 nm, a broad, featureless emission band with a maximum $\lambda_{\text{max, em}}$ at 350 nm and a luminescence lifetime τ of 1.6 ns is observed. Emission measurements at 77 K in 2-methyl-THF with excitation at 275 nm reveal some fine structure of this emission band, including progressions in a $\sim 1600 \text{ cm}^{-1}$ mode ([Scheme 2c](#), right inset). Following excitation at 350 nm, a weak emission band with a maximum at 462 nm, which we attribute to phosphorescence, was observed (see [Supporting Information, Chapter 8](#) for details). In cyclic voltammetry, no reduction or oxidation within the potential window between -2.2 and 1.9 V vs Fc^+/Fc was detectable. This is in contrast to related O_4 -belt[8]arenes which have been shown to undergo irreversible oxidation at a potential of 1.3 V vs Fc^+/Fc .⁶⁶

In summary, we have developed a novel class of exceptionally large, conformationally restricted, bowl-shaped macro-

cycles denoted xanthene[n]arenes. The selective synthesis of xanthene[3]arenes or xanthene[4]arenes was achieved through modulation of the steric hindrance at the C9-position of the monomer (methyl, ethyl, *n*-propyl). The macrocycles are amenable to further modifications as demonstrated for **X-3**. Cavitand **23**, hydrocarbon belt **26**, and macrocycle **25**, which is able to self-assemble to a tetrameric capsule, were synthesized in one, two, and three steps, respectively. Both supramolecular hosts displayed guest binding properties. Macrocycles with an intrinsic curvature are essential for the construction of closed container molecules like molecular capsules. Only very few suitable building blocks are available as of yet. Importantly, all available macrocycles are rather small with a diameter of approximately 7 \AA . In contrast, the developed macrocycles **X-3** and **X-4** feature a diameter of 9.6 and even 14 \AA , respectively. Conformationally restricted, bowl-shaped macrocycles of this size are unprecedented. Considering the current interest directed to the synthesis of novel macrocyclic hosts and self-assembling systems, we are convinced that they will serve as valuable platforms for the construction of a wide range of host structures, far beyond the examples we report in this Letter.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/jacsau.1c00343>.

Experimental details and NMR spectra of new compounds ([PDF](#))

X-ray crystallographic data for **20** ([CIF](#))

Accession Codes

CCDC 2108499 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

K.T. supervised and conceived the project. J.P.R. and K.T. planned the project. J.P.R. carried out all synthetic work and supramolecular studies. L.S. performed and interpreted the photophysical and electrochemical measurements of belt **26**. A.P. carried out the crystallographic analysis of **20**. The first draft of the manuscript was compiled by J.P.R. and K.T. All authors contributed to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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