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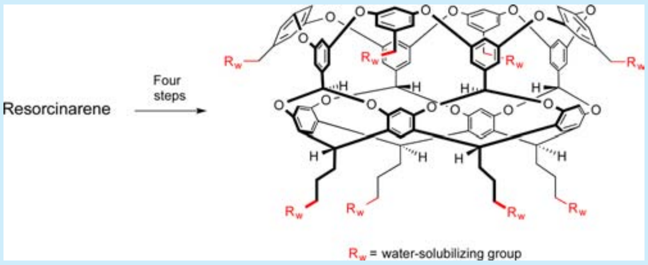
Synthesis of Water-Soluble Deep-Cavity Cavitands

Matthew B. Hillyer, Corinne L. D. Gibb, Punidha Sokkalingam, Jacobs H. Jordan, Sarah E. Ioup, and Bruce C. Gibb*

Department of Chemistry, Tulane University, New Orleans, Louisiana 70118, United States

Supporting Information

ABSTRACT: An efficient, four-step synthesis of a range of water-soluble, deep-cavity cavitands is presented. Key to this approach are octahalide derivatives (**4**, X = Cl or Br) that allow a range of water-solubilizing groups to be added to the outer surface of the core host structure. In many cases, the conversion of the starting dodecol (**1**) resorcinarene to the different cavitands avoids any chromatographic procedures.



Recent work with water-soluble hosts such as cucurbiturils[1−4] and pillararenes[5,6] have greatly expanded the realm of aqueous supramolecular chemistry and our understanding of noncovalent forces in water. Likewise, the deep-cavity cavitand, octa-acid (OA) **1** (Scheme 1) has proven useful to a number of research groups because of its ability to bind guests within its hydrophobic pocket to form 1:1 complexes and for its propensity to undergo self-assembly.[7] For example, the orientation-specific 1:1 complexes formed between **1** and amphiphiles have proven useful to the predictive challenges of computational chemists such as the statistical assessment of modeling of proteins and ligands exercise.[8] Additionally, small (partially hydrated) anions are also observed to bind to **1**, a fact that engenders the Hofmeister effect within stronger host−guest complexes formed by this host.[9−11] OA **1** has also been shown to readily self-assemble via the hydrophobic effect to form dimeric capsules possessing dry, inner nanospaces. The resulting 2:*n* host−guest complexes have been used for physical separations[12] and kinetic resolutions,[13] the control of redox-active guests,[14−16] and as yocto-liter reaction flasks for the precise control of a range of photochemical reactions.[17−20] The Ramamurthy group continues to study this last line of investigation.[21,22]

Two features of **1** likely contribute to this diverse application: (1) its ready accessibility—it is available in five linear steps from resorcinarene **2**, only one of which requires chromatographic purification; (2) its well-behaved nature; thus under basic conditions, the free host does not aggregate in the mM range (although this is buffer-dependent), while it readily forms monodispersed dimeric capsules in the presence of suitable guests. We attribute this excellent behavior to the pseudo, square antiprism array of carboxylate groups that lead to the water-solubilizing groups being spread evenly around its outer surface.[23] These points noted, the carboxylate coating on the outer surface of the host limits studies of the host to basic conditions. Consequently, we sought a short and efficient route for the synthesis of a broad range of cavitands with different water-solubilizing "coats". To that end, we report here on a general synthesis of a range of cavitands with cationic, anionic, and uncharged coats in as few as four linear (chromatographic free) steps from resorcinarene **2**.

Key to the synthesis of water-soluble deep-cavity cavitands is octol **3**, and we considered a range of approaches for introducing eight electrophilic sites on the surface of this host (**4**, X = various). Unfortunately, many proved unsuitable. For example, tosylation in pyridine was complicated by the formation of cavitand pyridinium salts, and even in the absence of this solvent, a complex mixture of randomly tosylated and chlorinated products was obtained with tosyl chloride. Mesyl anhydride avoided this nucleofuge replacement issue, but this reaction suffered other issues that limited the yield of **4** (X = OMs). During this time, the partial characterization of octabromide **4** (X = Br) was reported,[24] and we found that modifications to the Appel procedure used in its synthesis worked efficiently in our hands. Initially, this synthesis of octabromide **4** (X = Br) was optimized from pure octol **3**. However, as the latter is insoluble in most solvents and only available from crude **3** via acetylation (acetic anhydride), chromatographic separation, and hydrolysis (LiOH),[25] we were interested in developing a chromatography-free procedure for the formation of pure **4** (both X = Br and Cl) from crude **3**. Ultimately, we identified conditions, and octahalides **4** (X = Br and Cl) were efficiently synthesized on the multigram scale in 56 and 62%, respectively (Supporting Information). The conversion of octol **3** to octabromide **4** (X = Br) was complete within 16 h, while the octachloride **4** (X = Cl) required 3 days for complete reaction. The yields for these reactions correspond to very reasonable conversions, taking into account that crude octol **3** is typically only ∼75% pure and that eight reactions occur in each conversion. Thus, in the case of the octabromide **4** (X = Br), this equates to a 75% yield and a 96% yield per reaction site for the octol **3** within the crude starting material.

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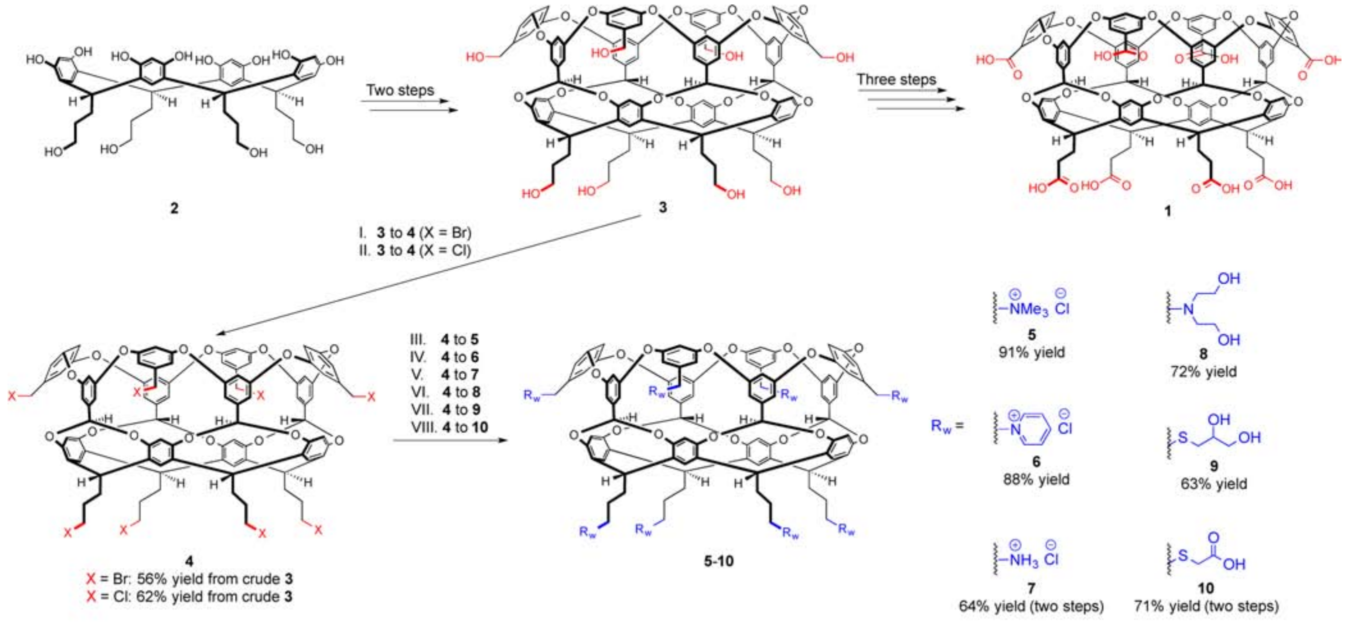
Scheme 1. Synthesis of Water-Soluble Cavitands from Resorcin[4]arene 2



	Compound	Reagents	Solvent	Temp (°C)	Rxn Time (h)	Product	Yield (%)
I	**3**	PPh_3 (12 equiv) CBr_4 (12 equiv)	DCM	rt	16	**4** (X = Br)	56
II	**3**	PPh_3 (12 equiv) CCl_4 (12 equiv)	DCM	rt	72	**4** (X = Cl)	62
III	**4**[a]	NMe_3 (12 equiv)	DMF	50	48	**5**	60
IV	**4**[a]	pyridine (large excess)	pyridine	80	16	**6**	88
V[b]	**4**[a]	NaN_3 (12 equiv)	DMF	rt	3	**7a**	98
V[b]	**7a**	PPh_3 (12 equiv) H_2O (80 equiv)	THF	50	48	**7**	65
VI	**4**[a]	DIPEA (16 equiv) diethanolamine (16 equiv)	DMF	50	48	**8**	72
VII	**4**[a]	DIPEA (16 equiv) 1-thioglycerol (48 equiv)	DMF	50	24	**9**	63
VIII[b]	**4**[a]	DIPEA (16 equiv) methyl thioglycolate (16 equiv)	DMF	50	24	**10a**	80
VIII[b]	**10a**	LiOH (60 equiv)	acetone	rt	48	**10**	89

[a] Compound **4** (X = Br). [b] Two-step syntheses.

Octabromide **4** (X = Br) was fully characterized and its structure confirmed by single-crystal X-ray crystallography. The crystals obtained from chloroform contained two cavitands in the unit cell, one of which was slightly disordered around its rim (Figure 1). The unit cell also contained multiple, disordered chloroform molecules, with the cavity of both cavitands containing one disordered chloroform. For these guests, the chlorine atom located toward the base of the pocket was highly ordered, emphasizing the attractive C−H···Cl−R hydrogen bonds between host and guest.[26]

Cavitand **4** (X = Br) proved to be an ideal intermediate for the synthesis of the different cavitands by reacting quickly and smoothly with a range of nucleophiles. Thus, the syntheses of novel, positively charged cavitands **5** and **6** by treatment with trimethyl amine and pyridine, respectively, were both uneventful. Furthermore, in both cases, product isolation was a straightforward precipitation. Anion exchange converted the bromide salts to the corresponding chlorides.

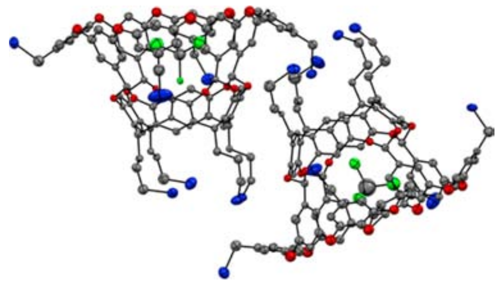


Figure 1. X-ray crystal structure unit cell of octabromide **4** (X = Br), showing the two hosts each with a bound chloroform guest within its cavity. Hydrogens and noncavity solvent molecules are omitted for clarity.

That these hosts possess the expected properties was demonstrated by positively charged cavitand **5**, which readily formed the expected host−guest complex with *n*-dodecane.

Thus, the addition of an excess of *n*-dodecane (~26 equiv) to a 0.8 mM solution of **5** in D_2O and vortexing the sample for 5 min led to the quantitative formation of the corresponding 2:1 host—guest complex with the characteristic upfield shifted guest signals between 0 and −3.4 ppm (Figure S15).

In contrast, treatment of **4** (X = Br) with ammonia led to significant amounts of polymer contaminating the desired octaamine **7**. Consequently, to form this cavitand, the octabromide **4** (X = Br) was first treated with NaN_3 to give the corresponding octaazide **7a** (not shown) in near quantitative yield. The subsequent Staudinger reduction gave the octaamine **7** in 65% yield. In both steps, the product was isolated by simple precipitation.

Building on this range of amine/ammonium-coated cavitands, the diethanolamine-coated cavitand **8** was targeted because the 16 hydroxy groups were expected to augment the water solubility provided by the ionizable ammonium groups. Moreover, the hydroxyethyl groups were expected to attenuate the frequently observed strong hydrogen bonding between free primary amines (such as **7**) and their protonated conjugate acid forms. Cavitand **8** was isolated in 65% yield by treating **4** (X = Br) with diethanolamine and precipitation.

Analogous to **8** but devoid of basic protonation sites, hexadecaalcohol **9** was also synthesized to determine if the dihydroxy propylthioether coating could bestow water solubility. This cavitand was formed from **4** (X = Br) in 63% yield by treatment with thioglycerol. Again, the pure product was isolated via precipitation rather than chromatography.

Finally, we also wanted to have access to anionic coated cavitands using **4** (X = Br). With this in mind, we targeted host **10**. Conceivably this could be synthesized by directly treating **4** (X = Br) with thioglycolic acid. However, in our initial studies, we found it better to use thioglycolate methyl ester and isolate the corresponding octaester (80% yield) and then hydrolyze this to the target **10** (89% yield). Although this approach gives **10** in the same number of steps as OA **3**, it both demonstrates a general approach to other anionic cavitands and avoids any trace impurities that can arise in the synthesis of **3**.[25]

OA **1** is soluble in neutral solutions to the extent of tens of micromolar. However, in basic conditions, depending on the buffer, it is soluble to several hundred millimolar concentrations. We determined that the trimethylammonium-coated **5** and pyridinium-coated **6** are equally as soluble across the pH range. The protic octaamines, **7** and **8**, are freely soluble in acidic to slightly basic solutions but precipitate from solution in highly basic media. Hexadecaalcohol **9** was synthesized with inspiration from a previously reported [G3] dendronized cavitand,[27] whose binding and assembly properties were handicapped somewhat by self-intercalation. However, neutral cavitand **9** proved to be soluble in only polar aprotic solvents. Finally, like octaacid **1**, thioglycolic acid **10** was found to be freely water-soluble in basic solutions.

In conclusion, we have found that octa-halogenated cavitand **4** (X = Br) is a synthetically versatile cavitand that provides easy access to a library of water-soluble hosts. These new hosts expand the scope of deep-cavity cavitands, and an array of studies can now be explored to investigate how the charged coating on these hosts and the medium they are dissolved in influence their properties. We will report on these hosts and their properties in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01903.

> Experimental procedures, characterization details, and ^1H, ^{13}C, ESI/MALDI mass spectra, and X-ray crystallographic data of new compounds (PDF)
>
> Crystal structure of octahalide **4** (X = Br) (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: bgibb@tulane.edu.

Notes

The authors declare no competing financial interest.

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(23) Evenly distributing and maximizing the distance between eight points on the surface of a sphere defines the apexes of a square antiprism.
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Moreover, we were unable to reproduce the reported NMR data, and the reported MS data (calculated molecular formula, molecular weight, and obtained molecular weight) were incorrect.

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