

Deep-cavity cavitands: synthesis and solid state structure of host molecules possessing large bowl-shaped cavities

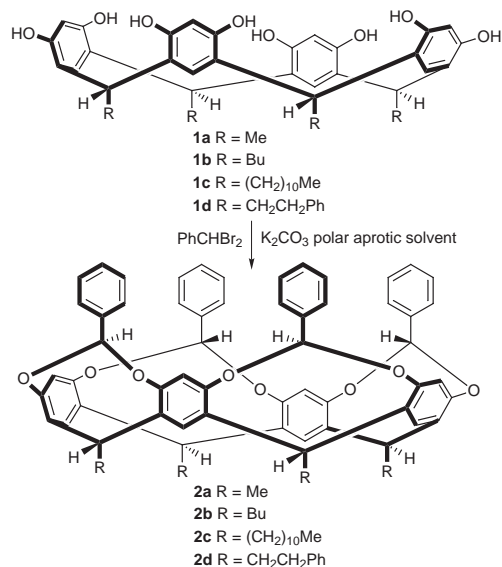
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A novel family of deep-cavity cavitands is prepared *via* the first examples of the stereoselective bridging of resorcin[4]arenes with carbon electrophiles.

Cavitands, molecules that contain a rigid enforced cavity, have a proven proclivity for a diverse range of applications; as molecular scaffolds,¹ as components in the formation of carceplexes,^{2–4} or as host molecules in their own right.^{2,5} In this later context, extending the paradigm to enzyme mimicry raises an important question; for a host with a necessarily large cavity, how do we incorporate both structural rigidity to its hydrophobic pocket while simultaneously imparting reasonable solubility on the system? This paper details our initial work towards addressing this question.

The most important factor contributing to the broad repertoire of cavitands as molecular hosts is undoubtedly the ease of synthesis of the corresponding resorcin[4]arenes (octols), *e.g.* **1a–d**.⁶ Accordingly, attempts to increase the size of a cavitand's



cavity have centered around the bridging of the phenolic pairs of these building blocks with a variety of moieties;^{7–9} an early example of cavitands with enlarged cavities being provided by Cram, with the formation of the conformationally flexible velcralexes.¹⁰ Here we demonstrate an important first step towards large, non-collapsing, hydrophobic pockets; the synthesis of deep-cavity cavitands¹¹ of the general structure **2**, *via* the stereoselective bridging of octols with benzyl bromides. We believe that this procedure will provide access to a significant range of rigid hosts possessing large hydrophobic cavities,¹² as well as a variety of novel molecular building-blocks for self-assembling systems.¹³

In the standard procedure for bridging octols, for example methylene bridging with BrClCH₂, there are a considerable number of variables that can be adjusted. Thus, to constrain our

investigations, and in an effort to more precisely define influences that may affect bridging reactions in general, we decided to modify arguably the two most influential parameters: the solvent and the rate of addition (*via* syringe pump) of the octol to the reaction. To monitor the influence of the pendent (R) groups of the octols we extended this syntheses matrix by examining the bridging of the four octols **1a–d**. Table 1 shows the yields of the deep-cavity cavitands **2a–d** from the corresponding octols using PhCHBr₂ as the bridging material and K₂CO₃ as base.‡ In all cases, although a total of six diastereomers could potentially be formed, only one isomer was isolated from the varying amounts of polymeric material.

The Me-octol **1a** proved resistant to benzal bridging for each of the solvents investigated;¹⁴ a maximum yield of 10% being obtained from bulk intractable polymer. The four-fold symmetry of the cavitand was evident from the ¹H NMR data, the most characteristic feature of which was a singlet at *ca.* 5.5 ppm for the protons on the bridging carbons. That the product was indeed cavitand **2a**, and not the diastereomer with the phenyl groups pointing into the cavity, was demonstrated by X-ray crystallography.¹⁵ Interestingly, the solid state structure (Fig. 1) also revealed that this cavitand dimerizes in a head to head fashion to generate cavities between the rigid dimers. Furthermore, the contiguous nature of these cavities results in the formation of channels (cross-section = 8.3 × 6.6 Å within a cavity, or 7.4 × 4.2 Å at the mouth of each cavity) that zigzag along a common axis.¹⁶

Similar low yields were obtained for **1b** in DMA and NMP. However, with the slow addition of the octol in DMPU, the deep-cavity cavitand, **2b**, was isolated in 58% yield; a remarkable yield when compared to either the statistical 6.25%, or the similar yields obtained for methylene bridging with CH₂ClBr.¹⁷ Encouraged by this disparity between **1a** and **1b**, we investigated the bridging of **1c**. For this compound we found that the reaction was successful in either DMA or DMPU, with maximum yields somewhat lower than for **1b**. Finally, we found

Table 1 Yields for the formation of deep-cavity cavitands **2a–d**^a

Entry	Octol	Product	Solvent ^b	Yield (%) <i>via</i> 4 h addn. of octol (2 d addn.)
1	1a	2a	DMA	<5 (<5)
2	1a	2a	NMP	<5 (<5)
3	1a	2a	DMPU	6 (10)
4	1b	2b	DMA	6 (<5)
5	1b	2b	NMP	6 (7)
6	1b	2b	DMPU	35 (58)
7	1c	2c	DMA	41 ^c (e)
8	1c	2c	NMP	<5 (<5)
9	1c	2c	DMPU	17 (40)
10	1d	2d	DMA	56 (51)
11	1d	2d	NMP	57 (55)
12	1d	2d	DMPU	31 (42)

^a These results relate to 250 mmol scale reactions. However, yields were essentially identical for multi-gram reactions. ^b See ref. 14. ^c Because of crystallization problems in DMA, octol **1c** was added over a 2 h period.

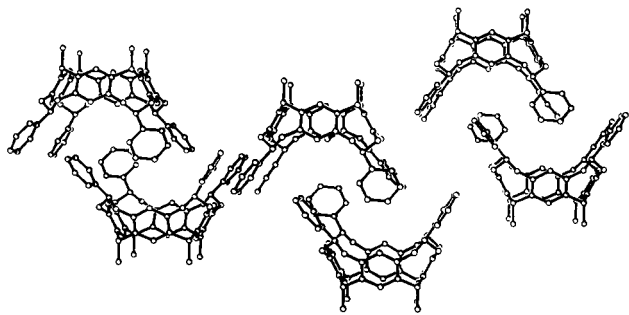


Fig. 1 Ball and stick diagram showing a view perpendicular to the direction of the channel. The central dimeric pair of deep-cavity cavitands is behind the plane formed by its adjacent neighbors. For clarity, the hydrogen atoms and the disordered solvents have been omitted.

benzal bridging of **1d** to be relatively solvent independent, with the highest yields again comparable with methylene bridging.

These results, in conjunction with uniformly poor yields obtained when the octol was added as a solid (data not shown), highlight the importance of a constant, slow rate of addition of the octol to the reaction. Equally as important, the apparently capricious nature of the solvent/R group relationship highlights the need to investigate these reactions in a variety of solvents. To gain more insight into influences that affect benzal bridging, a further series of experiments were undertaken (data not shown). Briefly, for the DMA solvated reaction with **1d**, we observed no significant dependence of the yield on reaction scale or concentration, but that the use of caesium carbonate as base, or PhCHCl₂ as bridging material, had a pronounced, detrimental effect on the yield.

The most significant observation from these results is that bridging is more favored for octols with larger pendent groups; a reflection, we believe, of a propensity for large groups to preorganise the octol into a bowl shaped conformation suitable for bridging. In a related issue, we attribute the apparent reduction in solvent-dependent yield with increasing size of the R group to a stronger association between such groups which pushes the equilibrium between favorable and unfavorable conformations towards the former.

Pin-pointing the precise cause of this stereoselective bridging is complicated by a lack of knowledge of the bridging mechanism in general. However, regardless of the pathway, the overall reaction is clearly highly diastereoselective, as steric demands induce a remarkable average of at least 87% stereoselectivity for each bridge.

In conclusion, we have demonstrated an approach to extending the π -surface of cavitands in a manner that should allow formation of a range of host molecules possessing large enforced cavities. With the concept of catalytic machinery preorganized within hydrophobic pockets our long term goal, we are currently extending our studies to the formation of a variety of functionalized deep-cavity cavitands.

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Notes and References

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‡ The following general procedure is illustrative: the octol (0.275 mmol) was added as a solution in the respective solvent (5 ml) to a stirred mixture of 450 mg of K₂CO₃ and 200 μ l (1.25 mmol) benzal bromide (PhCHBr₂) in 12 ml of solvent. After stirring for 2 days at 25 °C, an additional 67 μ l (0.42 mmol) of PhCHBr₂ was added and the reaction mixture warmed to 40 °C.

After 1 day, a further 67 μ l (0.42 mmol) of PhCHBr₂ was added and the temperature increased to 50 °C. This temperature was maintained for a further day, when an additional 67 μ l (0.42 mmol) of PhCHBr₂ was added, and the reaction heated to 60 °C for 3 days. The reaction was then cooled, and the solvent removed under reduced pressure. The crude mixture was partitioned between water and CHCl₃, the CHCl₃ layer separated and the aqueous layer extracted twice with CHCl₃. The organic layers were then combined, dried with anhydrous MgSO₄, and the solvent removed under reduced pressure. Column chromatography (silica gel, CHCl₃-hexane, 1 : 1) afforded the corresponding deep-cavity cavitand which was dried (0.1 mmHg, 110 °C) overnight. All compounds gave satisfactory NMR, MS and elemental analysis (\pm 0.4%).

Selected data for 2a: mp > 300 °C; δ (300 MHz, CDCl₃) 1.86 (d, 12 H, *J* 7.5), 5.20 (q, 4 H, *J* 7.5), 5.50 (s, 4 H), 6.69 (s, 4 H), 7.42 (m, 16 H), 7.68 (d, 8 H, *J* 7.8); *m/z* 897.13 (M + H⁺), 919.11 (M + Na⁺) (Calc. for C₆₀H₄₈O₈: C, 80.33; H, 5.40. Found: C, 80.05; H, 5.45%).

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- Solvents employed were dimethylacetamide (DMA), 1-methyl-2-pyrrolidinone (NMP) and 1,3-dimethyl-3,4,5,6-tetrahydropyrimidin-2(1H)-one (DMPU).
- Crystal data for 2a:* C₆₀H₄₈O₈·1.5CHCl₃·0.5C₆H₁₄·0.5H₂O, *M* 1021, monoclinic, space group *P*2₁/*c*, *a* = 15.1106(7), *b* = 28.6654(14), *c* = 14.6484(7) Å; β = 109.1515(10)°, *V* = 5993.8(5) Å³, *Z* = 4, *T* = 113(2) K, μ = 0.275 mm⁻¹. 46 542 reflections measured, 12 707 unique reflections (*R*₁ = 0.0680), *R*(*F*) = 0.0817 and *wR*(*F*²) = 0.1481 and *S* = 1.197 for 8773 reflections with *I* > 6 σ (*I*). CCDC 182/899.
- Given distances are atom-to-atom.
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