

Reduced-Symmetry Deep-Cavity Cavitands

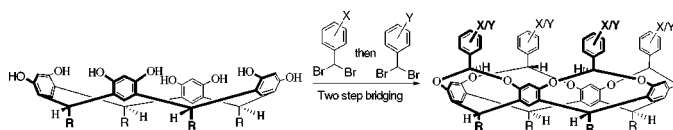
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ABSTRACT



The syntheses of reduced-symmetry deep-cavity cavitands by two-stage stereoselective bridging with substituted benzal bromides is reported. Conditions for the optimal formation of the trisbridged derivatives were readily established. However, it was not possible to determine conditions which selectively promoted formation of either one of the two bisbridged species, or the monobridged compound, above the other products. A comparison of yields for A/B bisbridged derivatives versus A/C bisbridged derivatives may indicate that the one-pot formation of deep-cavity cavitands occurs primarily through the former species.

In the development of new host–guest systems, two inter-related molecular information considerations exist, which necessitates an increase in the scale of host molecules. In the first instance, the host must simply be of sufficient scale to bind or encapsulate an increasing range of ever larger guests. Harder to attain perhaps is the need to pack information tightly into the binding site. Thus, precisely positioning the myriad of groups necessary for generating highly specific binding requires a deft touch that we are still not able to accomplish.

Investigations into the development of large host molecules with concave cavities have been underway for some time now and have focused on the use of calixarenes¹ and resorcinarenes.^{2,3} Enlarging the cavities of such molecules can be carried out by a variety of approaches. For example, bridging of resorcinarenes with 1,2-dihalo quinoxaline or pyrazine groups has led to the development of the velcrands, rigid molecules with deep, concave cavities.^{3–8} Taking the

host properties of these molecules further, Rebek et al. developed preorganized variants capable of kinetically stable guest binding in both organic^{9,10} and even aqueous media.¹¹ Furthermore, corresponding dimers of these molecules, be they held together by covalent¹² or noncovalent forces,¹³ have demonstrated a number of unusual binding properties such as novel stereochemical relationships between encapsulated guests.¹⁴

With a goal of forming large preorganized molecular cavities, we recently demonstrated the efficient formation of deep-cavity cavitands (DCCs) via the stereoselective bridging of resorcinarenes with benzal bromide.¹⁵ More recently, we noted that this process, involving the irreversible formation of eight new covalent bonds and the generation

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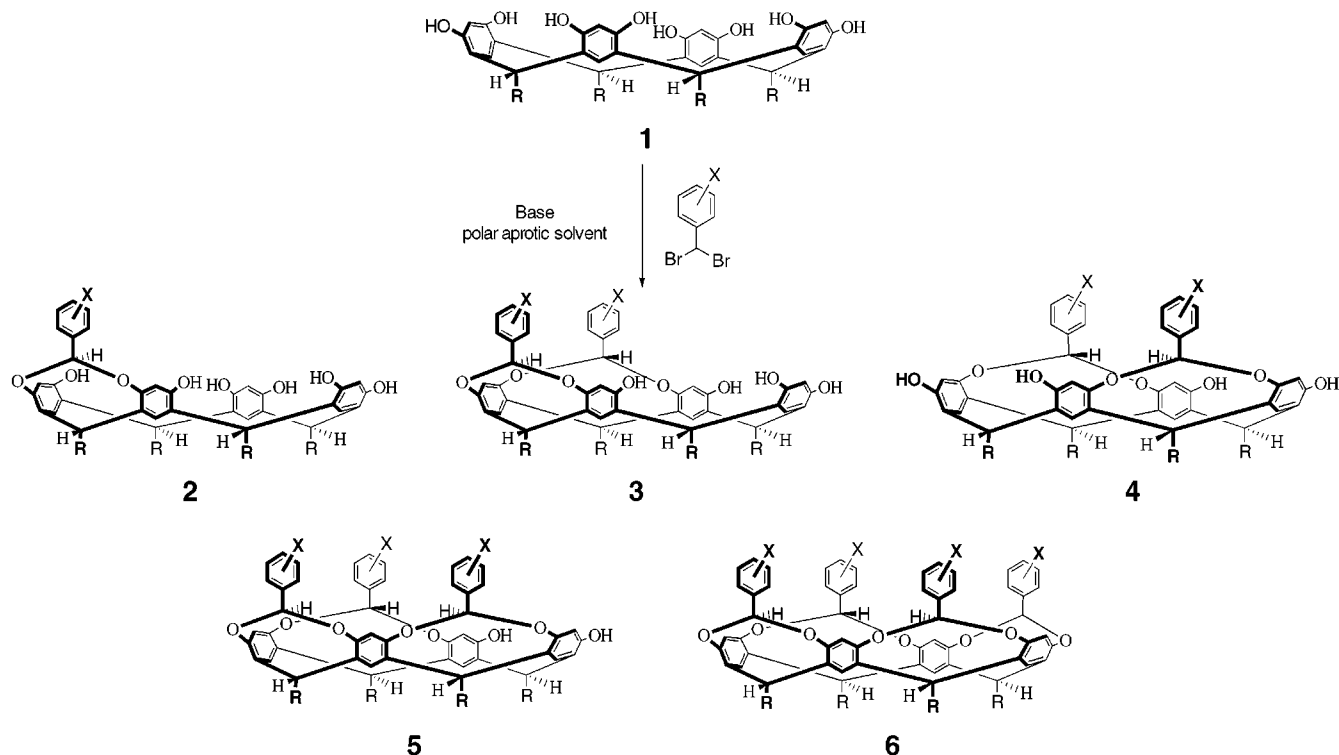
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Scheme 1. Possible Products from the Stereoselective Bridging of Resorcinarenes (Octols)^a

^a R = CH₂CH₂Ph. For series **a**, X = 3,5-dibromo. For series **b**, X = 4-bromo.

of four stereogenic centers, is a general process applicable to a variety of substituted benzal bromides.¹⁶ The resulting functionalized deep-cavity cavitands, e.g., **6** (Scheme 1), allow access to novel molecular subunits for the study of irreversible self-assemblies¹⁷ and offer their large concave cavities to many aspects of the host–guest chemistry field. Here we demonstrate that this stereoselective bridging process can be applied in a stepwise manner to the formation of a variety of lower symmetry deep-cavity cavitands. We believe that such derivatives will be of considerable utility in the development of large molecular cavities possessing detailed and/or specific binding information within their structures.

In theory, the treatment of octol **1** with less than an excess of a benzal bromide bridging material can give rise to five products: the monobridged compound **2**, the A/B and A/C bisbridged species **3** and **4**, the trisbridged derivative **5**, and the fully bridged, C_{4v} DCC **6** (Scheme 1). With an excess of bridging material, yields of the tetrabridged DCCs are typically ca. 55% for benzal bromides whose substituents do not give rise to deleterious side reactions.¹⁶ These yields corresponds to an average of 86% diastereoselectivity per bridge¹⁸ and, assuming that this diastereoselectivity improves with each subsequent bridge, are indicative of a first bridging reaction occurring with at least 55% efficiency.

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(18) This value assumes no intermolecular bridging between the mono-, bis-, and trisbridged intermediates.

Initial investigations identified the stereoselective bridging of phenethyl octol **1** (R = CH₂CH₂Ph) with 3,5-dibromobenzal bromide as the reaction of choice for investigating partial bridging, primarily because the yield of DCC **6a** could be raised from the previously reported 43%¹⁶ to 67% with a slightly modified set of conditions. With an average of over 90% diastereoselectivity per bridging process, this reaction represented the most efficient benzal bromide bridging of an octol that we have observed to date.

With these experimental conditions in hand, we set out to investigate how at constant temperature (60 °C) yields of the various derivatives **2a–6a** were dependent on the equivalents of bridging material. The results are summarized in Table 1. Briefly, reducing the amount of bridging material

Table 1. Yields of Deep-Cavity Cavitands **2a–6a**^a

DCC	equiv of bridging material				
	8.8	4.4	3.3	2.2	1.1
2	trace	trace	3%	4%	2%
3	trace	trace	4%	9%	5%
4	trace	trace	2%	4%	2%
5	trace	trace	33%	33%	8%
6	67%	68%	28%	7%	trace

^a By bridging octol **1** with 3,5-dibromobenzal bromide, DMA, 60 °C, 24 h.

steadily decreased the yield of the tetrabridged species **6a** but without a concomitant increase in the yield of the partially

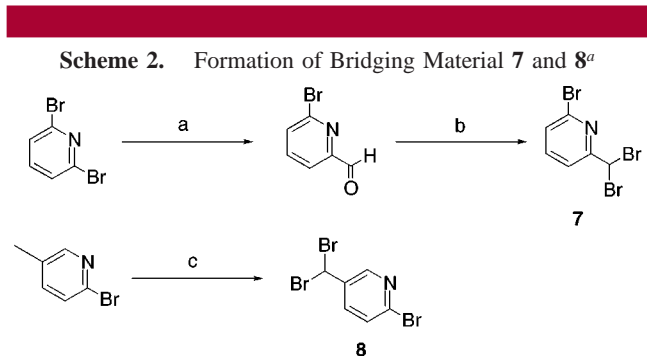
bridged intermediates **2a–5a**. In fact, even with only 2.2 or 1.1 equiv of bridging material there appeared to be a bias toward derivative **5a**. Particularly poor yields of the mono-bridged derivative **2a** and bis-A/C derivative **4a** (which is statistically half as likely to form as the bis-A/B derivative **3a**) were always observed.

Wishing to improve upon the yields of these bridged compounds, we investigated the bridging process at reduced temperatures. As anticipated, a general trend of increasing yields for the partially bridged derivatives was observed as the reaction temperature was decreased. Again however the corresponding decrease in tetrabridged DCC **6a** was not matched by a concomitant increase in yield of the lower species. More specifically, yields for the trisbridged species **5a** was optimized at 34% (48 h at 35 °C), 3% for the bis-A/C derivative **4a** (48 h at 35 °C), 13% for the bis-A/B derivative **3a** (48 h at rt), and 13% for the monobridged derivative **2a** (48 h at rt). Interestingly, in all ten reactions investigated that shared the same solvent and base, the ratio of **3a** to **4a** was found to be 5.38 ($\pm\sigma = 2.8$); a range considerably greater than the statistically expected 2:1 ratio.¹⁹ Also worthy of note was the relative ease at which the trisbridged derivative **5a** was isolated in reasonable 20–35% yields, but conditions for isolating each of the lower species in similar yields could not be determined.²⁰ In these cases optimum conditions gave broad overall product distributions (e.g., **2a** 13%, **3a** 13%, **4a** 3%, **5a** 15%; 48 h reaction at 25 °C) and no conditions could be determined that favored one of these product over the others.

To investigate the generality of these conclusions, we also investigated the bridging of octols with 4-bromobenzal bromide. Briefly, similar trends were observed for the formation of the intermediate bridged derivatives **2b–5b**. For example, optimum yields for the formation of the trisbridged **5b** were around 35% (24 h at 47 °C), 2% and 14% for the bis-A/C **4b** and bis-A/B **3b** derivatives respectively²¹ (48 h at 25 °C), and 11% for the monobridged derivative **2b** (48 h at 25 °C).

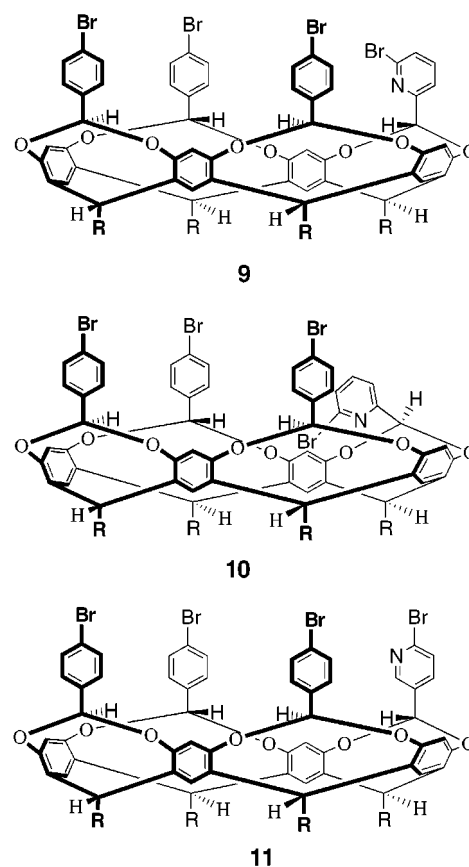
With various partially bridged intermediates now in hand, we investigated the formation of a number of reduced symmetry DCCs. Diol **5b** can be bridged a fourth time with a variety of molecules, but with little to go wrong in terms of inadvertent side reactions, we opted to investigate for the first time the suitability of pyridine compounds as bridging compounds. The formation of the requisite bridging materials **7** and **8** was relatively straightforward and is shown in Scheme 2. Thus, in the first instance, 2,6-dibromopyridine was monoformylated²² and the aldehyde converted to the α,α -dihalopicoline. We initially attempted this latter conversion with BBR_3 ²³ without success. However, treatment of the aldehyde with a triphenylphosphite/bromine mixture²⁴ resulted in the formation of **7**. Bridging material **8** was readily synthesized by treating 5-methyl-2-bromopyridine with *N*-bromosuccinimide.

Interestingly, the reaction of **5b** with bridging material **7** resulted in the isolation of two isomeric DCCs: the expected cavitand **9** and its isomer **10** in 54% yield and 16% yield, respectively. This latter DCC is the first example we have



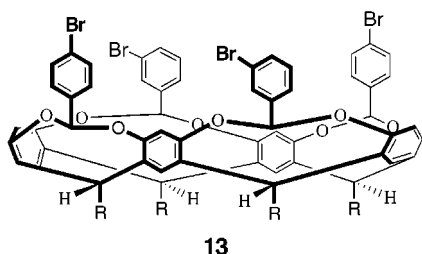
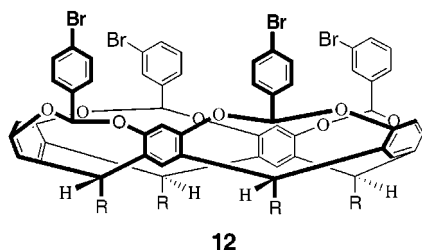
^a Key: (a) (i) *n*-BuLi, then DMF then H_3O^+ , 65%. (b) $(\text{PhO})_3\text{P}/\text{Br}_2$, 50%. (c) NBS, benzoyl peroxide, benzene. 41%.

observed where the stereogenicity of a benzal bridge ensures that the aromatic ring of the bridge essentially fills the cavity of the molecule. In contrast to bridging with **7**, reaction with bridging material **8** gave DCC **11** in 64% yield and no indication of any “miss-bridging”.



For both the formation of **9(+10)** and **11** it is interesting to note that the yields are less than the theoretical 86% for each step in a “normal” ca. 55% 4-fold bridging process. Put another way, translating the efficiency of the above one-step bridging processes into theoretical four-step processes (octol **1** to respective tetrapyrindyl derivative) would result in yields of 8.5% and 18% for reactions with **7** and **8**, respectively. Is this because the pyridyl bridging materials are not very efficient? To investigate this we once again took

trisbridged DCC **5b** but this time treated it with 4-bromobenzal bromide. Under identical conditions the known DCC **6b**¹⁶ was isolated in 84% yield. This corresponds to a theoretical yield of 50% for the transformation of **1** to **6b** which is close to the actual yield of 54%. Consequently, it would appear that the nucleophilic centers of **7** and **8** do indeed interfere with their bridging ability.



Finally, having also noted an apparent preference for the formation of A/B-bisbridged **3b** over A/C-bisbridged **4b**, we investigated the efficiency of bridging these compounds to form tetrabridged DCCs. When treated with 4- and 3-bromobenzal bromide, the bis-A/B derivative **3b** gave DCCs **6b** and **12** in 61% and 65% yields, respectively. These values correspond to an average 80% yield for each bridging reaction and again are in line with theoretical values derived

(19) These findings may indicate that the bridging route from octol to DCC primarily involves an A/B-bisbridged intermediate. Such an apparent preference could be attributed to the degree of preorganization of the resorcinol rings. Thus, the introduction of the first bridge, e.g., to form **2a**, results in the preorganization of one of the resorcinol rings if the next bridge is to go to the B position (e.g., to form **3a**) but does not preorganize the resorcinol rings involved with the second bridge going in to the C position (e.g., to form **4a**). Alternatively, these results might indicate different rates of decomposition of **3a** and **4a** in the reaction medium. However if this were the case then it would be expected that yields for the conversion of **3b** into **6b/12** and **4b** into **6b/13** (see text) would differ. This was not observed.

from 4-fold bridging processes. Similar results were obtained with the A/C tetrol **4b**. Thus, treatment with the same bridging materials gave DCCs **6b** and **13** in 62% and 59% yields, respectively. Consequently, although it may be the case that formation of the A/B-bisbridged intermediate is favored over the formation of the A/C species, it would appear that both tetrols **3b** and **4b** are equally efficient in generating tetrabridged species.

We have demonstrated here the partial stereoselective bridging of resorcinarenes with benzal bromides. By this stepwise process we have noted the first example of miss-bridged DCCs in which the cavity of the cavitand is filled by one of the benzal bridging units. We have also noted a statistically significant bias in favor of formation of the bis-A/B over the bis-A/C derivative. Further investigations into the described protocols, as well as the utilization of these and other non- C_{4v} DCCs, are currently underway and will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization data, and ¹H NMR spectra of all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) The isolation of comparable yields of tris-bridged products arising from nonstereospecific bridging processes has been attributed to a relatively high energy barrier when introducing the fourth bridge. See ref 6.

(21) Thirteen reactions gave an average ratio of **3b** to **4b** of 7.55 ($\pm\sigma = 3.0$). For the six reactions that share the same solvent and base similar, statistically significant results were noted (**3b:4b** ratio of 6.11 $\pm\sigma = 1.3$). Both of these results are statistically significantly greater than the expected 2:1 ratio.

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