Functionalized Deep-Cavity Cavitands

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In the development of efficient artificial enzymes[1−6] possessing preorganized catalytic machinery, a primary consideration for chemists is the choice of scaffold used to arrange and hold the requisite functional groups in the necessary three-dimensional array. This scaffold, acting as a surrogate for the bulk of the main chain of the target enzyme, must therefore possess three important aspects. First, the chemical architecture of the scaffold must afford it a reasonably high degree of rigidity while simultaneously providing the necessary scale for the orientation of the catalytic functional groups. Second, it should possess reasonable stability under a variety of reaction conditions. Finally, it should be readily available; in other words, its synthesis should be straightforward and readily scaled up. Bearing these criteria in mind, chemists have utilized cyclodextrins,[7−9] calixarenes,[1,10−12] porphyrins,[13−15] cyclophanes,[16] and a variety of other molecules[17] as scaffolds for "holding" the necessary catalytic groups.

We recently demonstrated the synthesis of a new family of deep-cavity cavitands (DCCs) formed by the stereoselective bridging of resorcinarenes (octols) with benzal bromide, a procedure that, although involving the formation of eight new covalent bonds and four stereogenic centers, proceeds in up to 58% yield.[18] As part of our research program directed toward the synthesis of enzyme mimics possessing preorganized catalytic machinery, we report here that this strategy can also be employed with a range of substituted benzal bromides. Thus, by using similar or slightly modified conditions, a range of functionalized DCCs can be synthesized in good yield. We believe these derivatives bode well for the formation of a broad range of potential concave hosts possessing catalytic machinery.

The general reaction utilized in the formation of the deep-cavity cavitands is shown in Scheme 1. Previously, we had demonstrated that the stereoselective bridging of octols with benzal bromide was highly dependent on both the solvent of the reaction and the feet (R groups) of the octols themselves. However, in an attempt to gain some understanding of the electronic or steric effects induced by the addition of the various functional groups, we chose to initially investigate the benzal bridging of phenethyl (PE) octol **1** (R = CH_2CH_2Ph) in dimethylacetamide (DMA) with K_2CO_3 as base. As the requisite benzal bromides were not commercially available, we chose two routes by which they could be readily accessed.[19] Thus, the bridging materials were synthesized by either treating the corresponding aldehyde with boron tribromide[20] or performing a free radical bromination with *N*-bromosuccinimide (NBS) on the respective tolyl derivative.[21] The former conditions were applied to aldehydes whose additional functional groups did not possess any lone pairs that may induce deleterious side reactions, and the latter NBS reaction was used for those that did. As expected, the kinetics of both approaches were found to be dependent on the substitution pattern of the particular aromatic derivative. However, by manipulation of temperature and/or time, a range of benzal bromides were synthesized in yields of ca. 70−100% yield from the aldehyde and 43−72% yield from the tolyl derivatives. One exception to these two approaches, 3,5-dibromobenzal bromide, was obtained via a two-step procedure starting from 1,3,5-tribromobenzene. Thus, monoformylation via metal−halogen exchange and quenching with dimethylformamide (DMF), followed by halogenation of the resulting aldehyde[22] with BBr_3, afforded the bridging material in 73% yield for the two steps. Generally these bridging materials were stable and required no special handling techniques. However, the *p*-Me derivative, with its electron-donating Me group, was noted to spontaneously hydrolyze in the presence of atmospheric moisture and as a consequence was isolated and manipulated only under anhydrous conditions.[23,24]

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(23) To the best of our knowledge, no systematic studies to determine σ values for the hydrolysis of benzal halides has been undertaken.

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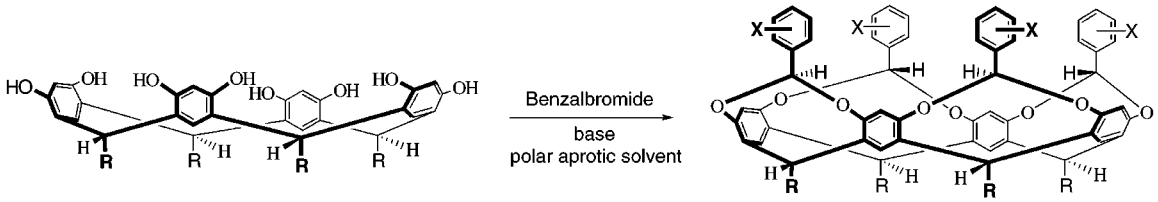
Scheme 1



1: R = CH_2CH_2PH **2a-o:** R = CH_2CH_2PH

Table 1. Yields of Functionalized Deep-Cavity Cavitands

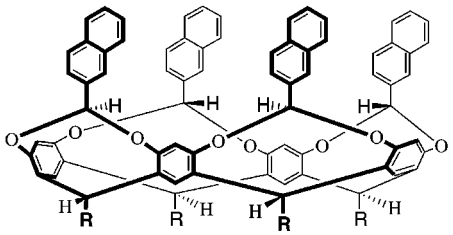
deep-cavity cavitand	yield[a] (%)
2a X = H[b]	56
2b X = 2-Br	48
2c X = 3-Br	25 (31)[c]
2d X = 3-Me	39
2e X = 3-OCH_2OEt	25
2f X = 3-NO_2	10 (8)[c]
2g X = 3-CN	15 (23)[c]
2h X = 4-Br	43
2i X = 4-I	43
2j X = 4-Me	51
2k X = 4-Ph	55
2l X = NO_2	trace
2m X = 4-CN	6 (9)[c]
2n X = 4-CO_2Et	0 (40)[c]
2o X = 3-Br, 5-Br	5 (43)[c]
3 2-naphthal bridged	53

[a] Yields are for standardized bridging in DMA with K_2CO_3 as base (see Experimental Section). [b] See ref 18. [c] Reaction modified by using homogeneous base (diazabicyclo[5.4.0]undec-7-ene, slower addition of benzal bromide, and longer reaction time (see Supporting Information).

Under the conditions outlined above, a series of new deep-cavity cavitands were readily synthesized with the various benzal bromides (Table 1). As was noted in the formation of the unsubstituted DCC **2a**,[18] only the desired C_{4v} isomer was isolated from the varying but ubiquitous amounts of polymer.

Evident from this series of reactions is the following. First, functional groups at the 4-position that are not strongly electron-donating or -withdrawing ($-0.14 < \sigma < 0.26$)[25] have little influence on the reaction when compared to the parent DCC **2a**, whereas much stronger electron-withdrawing substituents have a significantly detrimental effect on the reaction outcome. Lower yields were also generally obtained for those DCCs with a functional group at the 3-position of the second row of aromatic rings, an observation reinforced by the much lower yield of DCC **2o**. However, for these compounds and those with strongly electron-withdrawing groups at the 4-position, further investigations revealed that yields could generally be improved when a combination of the stronger (and homogeneous) base diazabicyclo[5.4.0]-undec-7-ene (DBU), slower addition of the bridging material, and increased reaction time were implemented (Table 1). These improvements suggest that a significant, although by no means singular, contributor to the observed yields is a competing hydrolysis of the bridging material by water generated from the K_2CO_3.[26]

Although the range of DCCs listed in Table 1 allows access to a variety of further DCC derivatives, several of them are worthy of brief mention here. Thus, the synthesis of the 2-, 3-, and 4-bromo derivatives (**2b**, **2c**, and **2h**) provides an approach to a range of isomeric cavitands via 4-fold metal−halogen exchange reactions.[27] Likewise, cavitand **2o** may provide access to a parallel series of molecules if 8-fold metal−halogen exchange reactions prove viable. Finally, although not directly amenable to the formation of enzyme-mimicking derivatives, the ca. 14 Å deep cavities of cavitands **2j** and **3** may engender them with interesting inclusion properties.



R = CH_2CH_2PH

3

Two types of functional groups proved antagonistic to the bridging process: the nitro- and cyanobenzal bromides. We attribute the reduced yields for the bridging reactions of the latter to hydrolysis of the cyano groups[28] and subsequent reaction with the remaining benzal bromide. In the case of the nitro compounds, their poor bridging ability is possibly due to the propensity of such compounds to undergo electron-transfer processes,[29] with the usefulness of the 4-nitro derivative as a bridging material further impeded by the relatively high acidity of its benzal proton.[30]

Rationalization of these results is complicated by a lack of understanding of the bridging mechanism in general;

(24) Our efforts to examine the effects of strongly electron-donating groups *para* to the benzal halide were thwarted by the instability of *p*-phenoxybenzal bromide. Thus although it is readily synthesized from the corresponding aldehyde, all attempts to isolate this bridging material met with failure.

(25) Reference 21, p 280

(26) Hydrolysis of 2-Br, 3-Br, 4-Br, and 4-CO_2Et benzal bromides, in the presence of K_2CO_3 (d_6-DMSO) showed that, after 1 day at 60 °C, 26%, 28%, 49%, and 54% of the halide had been converted to the corresponding aldehyde.

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(28) Exposure of 4-CN benzal bromide to approximate reaction conditions (K_2CO_3, d_6-DMSO, 1 day, 60 °C) resulted in hydrolysis of 75% of the original benzal bromide to the cyanobenzladehyde, the corresponding acid derivative, and the 4-HO_2C benzal bromide.

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(30) Nitro-substituted benzyl halides have a propensity to undergo SET reactions when treated with base.[29] Thus, in the case of 4-nitrobenzal bromide under the reaction conditions, both the bridging material and its conjugate base may undergo SET processes. Furthermore, the nucleophilicity of the latter carbanion may promote further deleterious reaction pathways and reduce the yield of DCC **2l** considerably. For example, in the absence of octol, ^1H NMR showed that the 4-NO_2 benzal bromide rapidly formed (one diastereomer of) the corresponding stilbene *p*-$NO_2C_6H_4CBrCBrC_6H_4$-*p*-NO_2 in essentially quantitative yield. For further details of this chemistry see ref 35.

does it occur via a double S_N2 mechanism or a process whereby the second step is an S_N1 mechanism on an oxonium intermediate? Furthermore, as is observed for a variety of solvolyses of different benzyl halides or sulfonates,[31−33] the precise mechanism of benzal bridging is likely to be dictated by the aromatic ring's substituents. Unfortunately therefore, the above data offer little opportunity for gleaning mechanistic details of bridging reactions in general.

In an effort to establish criteria for the optimization of these bridging reactions, we examined the stereoselective bridging of phenethyl octol with 4-Br benzal bromide under a variety of conditions. For example, a series of reactions using varying amounts of benzal bromide bridging material showed that the reaction yield with only 1.1 equiv per bridging site was reduced to 31% but that a maximum yield of ca. 50% was attained with only 1.3 equiv of bridging material per reaction site. We also investigated whether, as was observed for unsubstituted deep-cavity cavitands,[18] reaction yield was dependent on the solvent and the pendant group of the octol. Briefly, by carrying out a matrix of reactions investigating the R group (Me, Bu, and PE) crossed-referenced with solvent [DMA, 1-methyl-2-pyrrolidinone (NMP), and 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU)] for the 4-bromo DCC **2h**, we observed the same trends as previously observed[18] (see Supporting Information). Thus, DCC formation improved, and the yields became less solvent-dependent as the size of the pendant (R) groups increased. Finally, another series of experiments investigating time showed that this particular bridging reaction was essentially complete after only 1 day at room temperature and 2 days at 60 °C. Combining these optimizations gave a yield of 54% for the formation of **2h**.

In summary, we have demonstrated that the stereoselective bridging of octols with benzal bromides is a general process that can be applied to a range of bridging materials. Thus, by judicious choice of base, solvent, and octol pendant group, a range of functionalized deep-cavity cavitands can be synthesized. Efforts to introduce catalytic machinery within the cavities of these deep-cavity cavitands are now underway.

Experimental Section

The following syntheses are representative. See the Supporting Information for the synthesis of the remaining bridging materials and deep-cavity cavitands.

Synthesis of 2-Bromobenzal Bromide[34] from the Corresponding Aldehyde. 2-Bromobenzaldehyde (9.6 g, 51.9 mmol) was dissolved in 200 mL of dry dichloromethane. To this stirring solution was added, over a 5 min period, 49.6 mL of 1.15 M BBr_3 in dichloromethane (57.1 mmol). After stirring at room temperature for 1 day, the mixture was run through a silica plug, and the silica was then washed with hexane. Combining the organic solutions and removing the solvent under reduced pressure gave the crude benzal bromide. Flash chromatography (mobile phase, 3:1 hexane/$CHCl_3$) and drying (overnight, 0.1 mmHg, 25 °C) gave the benzal bromide as a colorless oil in quantitative yield: bp 102 °C, 0.7 mmHg (lit. 100−102 °C (1.0 mmHg)); ^{1}H NMR (400 MHz) δ 7.07 (s, 1H), 7.16 (ddd, 1H, J = 8.0, 7.2, 1.6 Hz), 7.39 (m, 1H), 7.48 (dd, 1H, J = 8.0, 1.2 Hz), 8.00 (dd, 1H, J = 8.0 and 1.6 Hz); MS m/z $(M)^+$ 329.

Synthesis of 4-Cyanobenzal Bromide[36] from the Corresponding Tolyl Derivative. 4-Cyanotoluene (1 g, 8.5 mmol), NBS (3.11 g, 17.5 mmol), and benzoyl peroxide (423 mg, 1.75 mmol) were dissolved in 40 mL of dry CCl_4. The solution was heated to reflux for 2 days. After this time the solvent was removed under reduced pressure, and the crude reaction mixture was partitioned between water and chloroform. Washing the organic layer twice with water, drying with anhydrous magnesium sulfate, and removing the solvent under reduced pressure gave the crude product. Flash chromatography (mobile phase, of 3:1, hexane/$CHCl_3$) and drying (overnight, 0.1 mmHg, 25 °C) gave a 72% yield of the benzal bromide as a colorless solid: mp 56−58 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.27 (s, 1H), 7.88 (s, 4H); MS m/z 309.7 $(M + Cl^-)^-$. Anal. Calcd for $C_8H_5Br_2N$: C, 34.94; H, 1.83. Found: C, 34.94; H, 1.85.

Synthesis of Deep-Cavity Cavitands 2b. A solution of the phenethyl octol **1** (R = CH_2CH_2Ph; 250 mg, 0.275 mmol) in 5 mL of DMA was added (syringe pump, 4 h) to a stirred mixture of K_2CO_3 (450 mg, 3.2 mmol) and 1.65 mmol of the respective benzal bromide in 12 mL of DMA. After 2 days of stirring at room temperature, an additional 0.55 mmol of the benzal bromide was added, and the reaction mixture was warmed to 60 °C. This temperature was maintained for 5 days. The reaction mixture was then cooled, and the solvent was removed under reduced pressure. The crude reaction mixture was partitioned between water and chloroform, the chloroform layer was separated, and the aqueous layer was extracted twice with chloroform. The organic layers were then combined and dried with anhydrous magnesium sulfate, and the solvent was removed under reduced pressure. Flash chromatography (1:3 $CHCl_3$/hexane), removal of the solvent under reduced pressure, and drying (overnight, 0.1 mmHg, 110 °C) afforded a 48% yield of cavitand **2b**: mp 295 °C; ^{1}H NMR (400 MHz) δ 2.60 (m, 8H), 2.73 (m, 8H), 5.05 (t, 4H, J = 8 Hz), 5.89 (s, 4H), 6.99 (s, 4H), 7.22 (m, 28H), 7.40 (td, 4H, J = 7.6 Hz, J = 1.2 Hz), 7.56 (doublet of doublets (dd), 4H, J = 8 Hz, J = 0.8 Hz), 7.94 (dd, 4H, J = 8 Hz, J = 1.8 Hz); MS m/z 1608.5 $(M + Cl^-)^-$. Anal. Calcd for $C_{88}H_{68}O_8Br_4$: C, 67.18; H, 4.33. Found: C, 67.33; H, 4.49.

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Supporting Information Available: Synthesis of all bridging materials (except 2-bromo- and 4-cyanobenzal bromides, see Experimental Section) and deep-cavity cavitands **2c**−**o** and **3**, plus the ^{1}H and ^{13}C NMR spectra of 3-hydroxybenzal bromide ethoxy methyl ether and deep-cavity cavitands **2g** and **2m**. This material is available free of charge via the Internet at http://pubs.acs.org.

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