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Electrophilic Substitution of Deep Cavity Cavitands: Selective Exo Functionalization of Molecular Concavity

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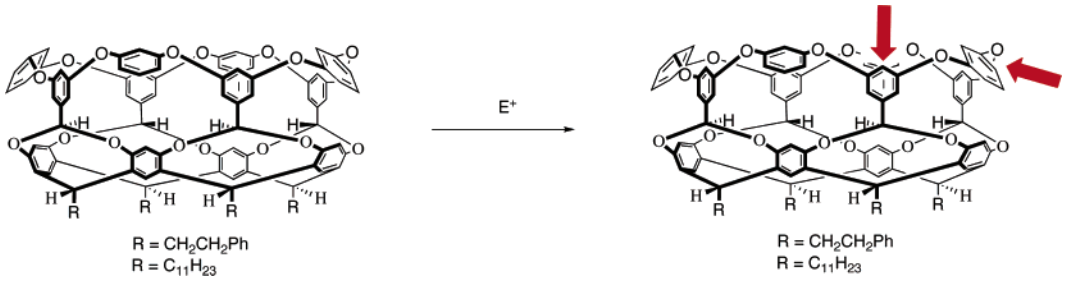
ABSTRACT



The functionalization of deep-cavity cavitands via electrophilic substitution was investigated. In the parent structures, substitution occurs both at the exo position of the bowl-shaped hosts and on the convex face. Little or no endo substitution was observed. In contrast, derivatives in which methyl groups blocked the reaction sites on the convex face reacted selectively at the exo positions.

Molecular concavity, and its corresponding supramolecular phenomenon, molecular encapsulation, lies at the heart of many chemical processes. The masters of chemical transformation—enzymes—rely on substrate encapsulation for their remarkable selectivities and rate accelerations. Although synthetic systems are some way from attaining the much sought after acceleration and oft sought after selectivity of enzymes, progress is being made, in terms of both catalyst developers increasingly building cavities around their catalytic centers of choice and host−guest chemists introducing catalytic centers into their cavities of choice. In regards to the latter, the pioneering work of Breslow[1] demonstrated the importance of having the binding cavity of a host and its catalytic machinery as proximate as possible. Building on this earlier work, considerable progress has recently been made using calixarenes[2] and resorcinarenes[3−5] in the development of single-portal hosts possessing concave functionality. Indeed, included in this list of endeavors are a range of resorcinarene-based hosts which possess not just exceptionally integrated binding sites and functionality but also reactive or catalytic properties.[5]

We have previously reported on the synthesis of deep-cavity cavitands such as **1** (Figure 1).[6] These hosts are readily available (three steps from commercially available materials)

(1) (a) Breslow, R.; Dong, S. D. *Chem. Rev.* **1998**, *98*, 1997. (b) Breslow, R. *Acc. Chem. Res.* **1995**, *28*, 146.

(2) (a) Darbost, U.; Rager, M.-N.; Petit, S.; Jabin, I.; Reinaud, O. *J. Am. Chem. Soc.* **2005**, *127*, 8517. (b) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Prangé, T.; Tomas, A.; Reinaud, O. *J. Am. Chem. Soc.* **2005**, *127*, 14833. (c) Rondelez, Y.; Rager, M. N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334. (d) Rondelez, Y.; Bertho, G.; Reinaud, O. *Angew. Chem., Int. Ed.* **2002**, *41*, 1044. (e) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2001**, *123*, 8442. (f) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183. (g) Blanchard, S.; Le Clainche, L.; Rager, M.-N.; Tuchagues, J.-P.; Dupart, A. F.; Le Mest, Y.; Reinaud, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2732. (h) Zeng, X.; Hucher, N.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 6886. (i) Darbost, U.; Giorgi, M.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 4879. (j) Jabin, I.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 3416.

(3) Laughrey, Z. R.; Gibb, B. C. *J. Org. Chem.* **2006**, *71*, 1289.

(4) (a) Hooley, R. J.; Van Anda, H. J.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2006**, *128*, 3894. (b) Hooley, R. J.; Biros, S. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2006**, *45*, 3517.

(5) (a) Hooley, R. J.; Biros, S. M.; Rebek, J., Jr. *Chem. Commun.* **2006**, 509. (b) Purse, B. W.; Rebek, J., Jr. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 10777. (c) Purse, B. W.; Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2005**, *127*, 11222. (d) Richeter, S.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 16280. (e) Gissot, A.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2004**, *126*, 7424. (f) Purse, B. W.; Ballester, P.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2003**, *125*, 14682. (g) Gibson, C.; Rebek, J., Jr. *Org. Lett.* **2002**, *4*, 1887. (h) Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2000**, *39*, 3281. (i) Starnes, S. D.; Rudkevich, D. M.; Rebek, J., Jr. *J. Am. Chem. Soc.* **2001**, *123*, 4659. (j) Wash, P. L.; Renslo, A. R.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **2001**, *40*, 1221.

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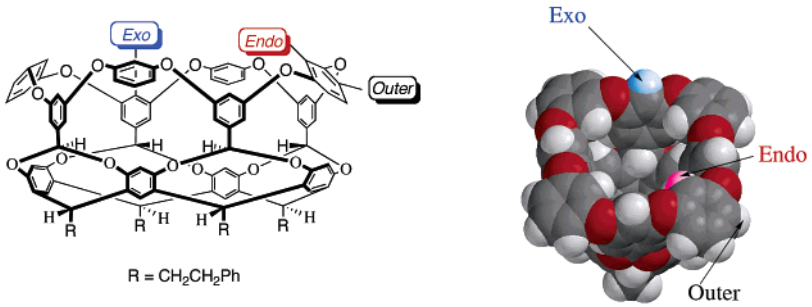


Figure 1. Chemical structure and space-filling model of cavitand **1**, showing the endo, exo, and outer positions.

and possess pseudoconical cavities 1 nm wide at their rim and approximately 1 nm deep. Toward the synthesis of examples of functionalized molecular concavity, we recently reported on the directed ortho metalation[3] of these deep-cavity cavitands.[6] Directed ortho metalation and quenching with DMF to form the corresponding formyl derivatives highlighted eight reactive positions at the rim: four positions pointing inward termed endo and four positions pointing with the cavity wall termed exo (Figure 1). There are 69 possible products arising from functionalizing between one and eight of these positions. However, a combination of host preorganization and reaction control constrains the overall number of products to 12: ten constitutional isomers, two of which exist as pairs of enantiomers. Within this range of products, there is a preference for exo functionalization; formylation led to only two products with solely endo groups, five with exo only, and five with both endo and exo.[3]

As an alternative to this metalation protocol, we report here on direct electrophilic aromatic substitution on **1** and related cavitands. As we described in detail below, this strategy leads to alternative patterning of functionalization. Whereas metalation is directed to the endo and exo positions because each is doubly activated by two *ortho*-oxygen atoms, electrophilic substitution can theoretically occur at three positions: the endo and exo positions and what we term the outer positions (Figure 1) that are doubly activated by *ortho*- and *para*-oxygen atoms.

Whereas a maximum of four groups could be simultaneously introduced via lithiation, electrophilic substitution was not limited by this constraint. For example, when phenethyl-footed cavitand **1** was treated with 10 equiv of Br_2, two kinds of products were observed: those with four or those with five bromine atoms (MS). Unfortunately, the low polarity of the C−Br bond meant that chromatographic separation of these products was not possible. Furthermore, adjusting the reaction conditions failed to identify a case where only one product was formed. As it was unclear from NMR precisely where **1** was brominated, and therefore reaction at the phenethyl "feet" could not be entirely eliminated, we opted to expose cavitand **5** to the same conditions. This new cavitand was synthesized following standard procedures (Scheme 1): stereoselective bridging[7] of the resorcinarene **2**[8] with 3,5-dibromobenzal bromide (**3**) gave the octabromide **4** in 40% yield, and a subsequent 8-fold Ullmann ether coupling of **4** with resorcinol afforded undecyl-footed **5** in 34% yield.

Treatment of cavitand **5** with excess bromine also led to tetra- and pentabrominated products, strongly suggesting that the feet of **1** were not undergoing reaction. This supposition was confirmed by cocrystallizing the brominated mixture. X-ray crystallographic analysis of these crystals did not yield data of sufficient quality for deposition in the Cambridge Crystallographic Data Center (CCDC); however, it did clearly show (Supporting Information) that the predominant bromination sites were the exo positions and that bromination also occurred at the outer positions. No evidence of endo functionalization was apparent.

Substitution at the outer position was also highlighted by another common electrophile, SO_3. In our hands, the most successful sulfonating agent investigated was trimethylsilylchlorosulfonate ($TMSOSO_2Cl$).[9] Accordingly, when **5** was treated with 5 equiv in CCl_4, a monosulfonic acid was isolated in 25% yield. NMR analysis (^1H, COSY, and NOESY) confirmed that the cavitand had undergone monosulfonation at the outer position to yield sulfonic acid **6** (Figure 2). TLC and mass analysis indicated that the preponderance of the starting material was converted to higher sulfonic acids, although investigations using fewer equivalents of electrophile did not yield acceptable quantities of, for example, bissulfonic acids. This point is perhaps not surprising considering the low degree of control and increased reaction options. Thus, in the metalation protocol,[3] the first step is the generation of carbanionic species possessing between one and four charges. Creating a fifth

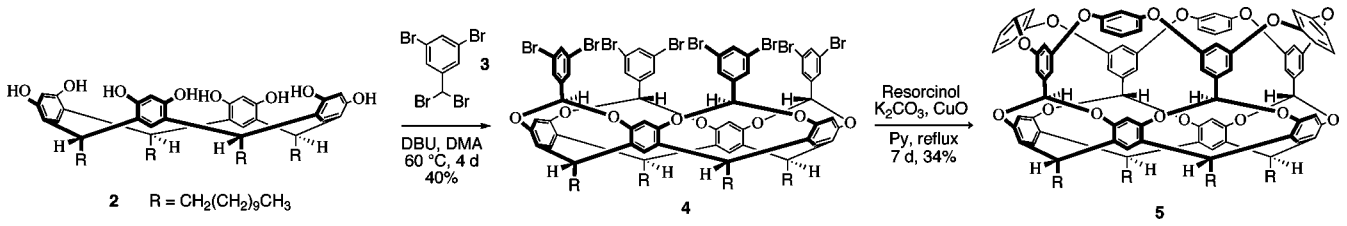
(6) (a) Laughrey, Z. R.; Upton, T.; Gibb, B. C. *Chem. Commun.* **2006**, 970. (b) Li, X.; Upton, T. G.; Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2003**, *125*, 650. (c) Laughrey, Z. R.; Gibb, C. L. D.; Senechal, T.; Gibb, B. C. *Chem.−Eur. J.* **2003**, *9*, 130. (d) Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2001**, *123*, 5849. (e) Gibb, C. L. D.; Xi, H.; Politzer, P. A.; Concha, M.; Gibb, B. C. *Tetrahedron* **2002**, *58*, 673.

(7) (a) Xi, H.; Gibb, C. L. D.; Stevens, E. D.; Gibb, B. C. *Chem. Commun.* **1998**, 1743. (b) Xi, H.; Gibb, C. L. D.; Gibb, B. C. *J. Org. Chem.* **1999**, *64*, 9286. (c) Green, J. O.; Baird, J.-H.; Gibb, B. C. *Org. Lett.* **2000**, *2*, 3845.

(8) Tunstad, L. M.; Tucker, J. A.; Dalcanale, E.; Weiser, J.; Bryant, J. A.; Sherman, J. C.; Helgeson, R. C.; Knobler, C. B.; Cram, D. J. *J. Org. Chem.* **1989**, *54*, 1305.

(9) Petit, P.; Bourgeois, P. *J. Chem. Res.* **2004**, 194.

Scheme 1



negative charge on a cavitand is thermodynamically difficult because the charge density would be exceptionally high. Likewise, when two to four anionic centers are initially formed, they are patterned in selective ways that minimize charge density. Added electrophiles therefore quench a limited pool of carbanions. No such charge control is in operation in electrophilic substitution. This point, combined with the fact that reaction occurs primarily at the exo and outer positions (12 sites) rather than at the endo and exo positions (8 sites), means that it is difficult to isolate cavitands with distinct patterns of functionality. For example, there are 22 constitutional and stereoisomers of bis-functionalized cavitands with functional groups spread around the exo and outer positions.

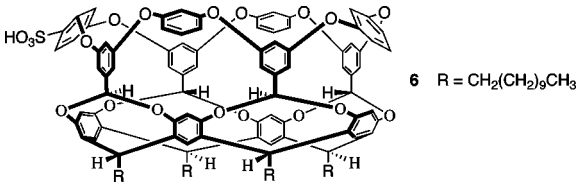
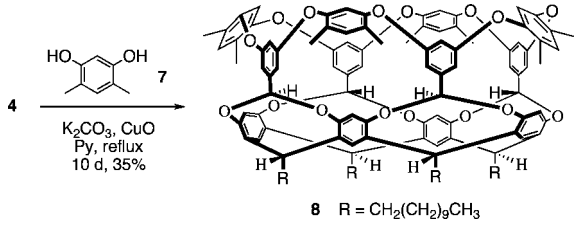


Figure 2. Chemical structure of **6**.

Adding functional groups to the outer positions has some interesting possibilities in regards to controlling the solubility of these hosts,[10] but enzyme mimetics require ready access to the endo and exo positions. To eliminate the possibility of outer substitution, we sought cavitand **8** in which the outer positions are blocked (Scheme 2). The required material for

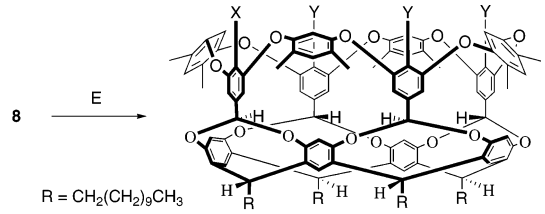
Scheme 2



the 8-fold Ullmann reaction of cavitand **4**, 4,6-dimethylresorcinol **7**, was easily prepared according to the published procedure.[11] Reaction of **4** with **7** afforded the undecyl-footed octamethyl cavitand **8** in 35% yield.

Octamethyl cavitand **8** was then subjected to various electrophilic substitution reactions (Scheme 3). For example,

Scheme 3



9 E: Br_2, $CHCl_3$, rt, 12 h, > 99%; X = Y = Br
10 E: $TMSOSO_2Cl$, CCl_4, rt, 12 h, 18%; X = SO_3H, Y = H
11 E: CH_3OCH_2Cl, $ZnCl_2$, $CHCl_3$, rt, 24 h, 96%; X = Y = CH_2Cl
12 E: CH_3OCHCl_2, $SnCl_4$, $CHCl_3$, rt, 1 h, 82%; X = Y = CHO

reaction with 10 equiv of Br_2 afforded the tetra-*exo*-bromide **9** in quantitative yield. Surprisingly, even with no possibility of reaction at the outer positions, no evidence of bromination of the endo positions was observed, even after treatment at elevated temperatures. There is obviously a significant kinetic barrier to reaction at the endo position, a phenomenon that allows good yields of the tetra-*exo*-bromide. Again, however, the low polarity of the C−Br bond inhibited isolation of the three mono- to trisubstituted derivatives when fewer equivalents of bromine were used. In contrast, sulfonation of **8** with $TMSOSO_2Cl$ readily gave the mono-*exo*-sulfonic acid **10** in 18% yield, but the higher substituted sulfonic acids, including the tetrasubstituted derivative, proved exceptionally difficult to handle and could not be isolated. Chloromethylation[12] of **8** also proved successful. Treatment with a large excess of CH_3OCH_2Cl in the presence of anhydrous $ZnCl_2$ furnished the tetra-*exo*-chloromethylated compound **11** in 96% yield. Again, no endo functionalization was observed. Finally, Gross formylation[13] of **8**, with a large excess of CH_3OCHCl_2 in the presence of $SnCl_4$ (or $TiCl_4$), also proved efficient,

(10) For water-soluble derivatives, see: (a) Gibb, C. L. D.; Gibb, B. C. *J. Am. Chem. Soc.* **2004**, *126*, 11408. (b) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2005**, *127*, 3674. (c) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *J. Am. Chem. Soc.* **2004**, *126*, 14366.

(11) Cram, D. J.; Cranz, F. W. *J. Am. Chem. Soc.* **1950**, *72*, 595.

(12) Hamada, F.; Ito, S.; Narita, M.; Nashirozawa, N. *Tetrahedron Lett.* **1999**, *40*, 1527.

(13) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, *60*, 1448.

with the tetra-*exo*-aldehyde **12** being formed in 82% yield (Scheme 3). We were fortunate enough to obtain the crystal structure of cavitand **12** (Figure 3 and Supporting Information). This gave the first absolute confirmation of our NMR-based assignment of endo vs exo functionalization. As predicted by models, the four C−CHO bonds point with the cavity wall so that the formyl groups increase the depth of the cavity somewhat. The cavity itself was found to contain two disordered solvent (ethyl acetate) molecules, and no evidence of inclusion of the alkyl feet was observed.

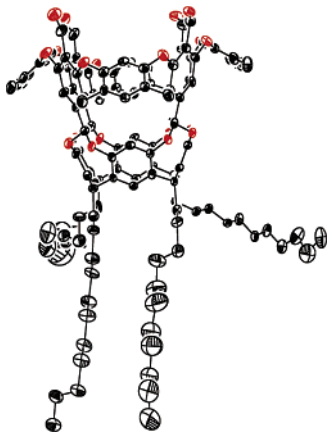
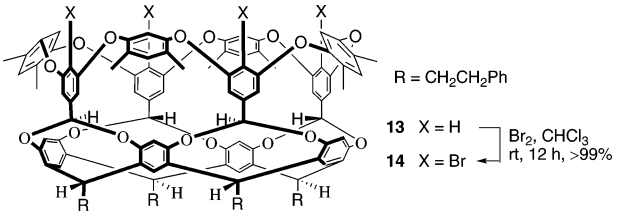


Figure 3. Crystal structure of **12** (displacement parameters are drawn to the 30% probability level).

The generality of this electrophilic substitution was confirmed by the synthesis of a second octamethyl cavitand **13**, formed in an analogous fashion to **8**. Thus, when phenethyl-footed cavitand **13** was subjected to bromination, it readily afforded the tetra-*exo*-bromide **14** in quantitative yield (Scheme 4).

In summary, our preliminary results reveal that parent deep-cavity cavitands such as **1** undergo electrophilic substitution at both the exo and the outer positions. No reaction was observed to occur at the endo positions.

Scheme 4



This is in contrast to metalation strategies that lead to either endo or exo functionalization. Our studies also revealed that direct electrophilic substitution is under less control than metalation.[3] As a result, no distinct patterning of functionalization is observed. Be that as it may, this strategy "opens up" the outer positions of these cavitands, which may be used to modulate the solubility properties of these molecules. For deep-cavity cavitands such as **8**, in which the outer positions are blocked, electrophilic substitution constitutes an efficient method of exo functionalization. We are currently exploring some of the myriad of possibilities that arise from metalation and direct electrophilic substitution of these cavitands and in particular the synthesis of molecules that possess functionality capable of bringing about guest transformation. We will report on these results in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (PDF) and X-ray structural information of **12** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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