Host–Guest Systems

Simple Synthetic Receptors for Aspirin

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Abstract: Shallow methylene-bridged cavitands appended with simple H-bond donor/acceptor groups are shown to bind aspirin. The structural features needed in a synthetic receptor for aspirin binding are defined.

We have previously shown that certain deep cavity hosts termed superbowl molecules serve as the first—and only—synthetic receptors for aspirin.^[1] Based upon observations that aspirin was bound: a) selectively over other compounds with different arrangements of functional groups, and b) in a 1:1 stoichiometry with the host, a two-point binding mode was proposed (Figure 1).^[1] The suggested binding involved a hydrogen bond between aspirin's $-\text{CO}_2\text{H}$ group and the ether group of the base-wall linker, and $\text{C}-\text{H}\cdots\pi$ interactions between the drug's acetoxy methyl group and the aromatic rings of the base bowl of the host.

This binding mode represents a full encapsulation of the drug by the covalently linked penta-cavitand receptor. Nevertheless, since only one of the five cavitands of the superbowl (and only one of this cavitand's four substituents) appeared to be involved in the synthetic receptor-drug binding,^[1] we won-

dered if the remainder of the superbowl structure was necessary. Specifically, we aimed to find out if a shallow cavitand carrying a simple functional group could bind aspirin.

Prior work in this area was not encouraging. Despite their immense historical importance in the development of host–guest chemistry, monomeric versions of Cram's shallow cavitands^[2] have been only rarely employed as receptors, due to their weak binding ability.^[3] In contrast, larger—and necessarily more synthetically convoluted—deep cavity cavitands^[4] and multi-cavitand systems have been used extensively.^[5] These larger hosts are invariably used to *encapsulate* their guests. Encapsulation would naturally offer protection—hence stabilization—of a host–guest complex.

To our knowledge, the only shallow cavitands previously shown to bind guests are the phosphonate-bridged resorcin-arenes introduced by the Dalcanale group.^[6] This elegant work has established phosphono-cavitands as effective and selective hosts for a wide variety of guests including alcohols and ammonium salts of α -amino acids. In the Dalcanale work, the phosphonate ester groups are intimately involved in the binding.^[6] Herein, we show that a family of simple methylene-linked cavitands^[7]—which lack either phosphonate binding groups or the possibility of encapsulation—exhibit detectable binding of aspirin.

The base cavitand of the superbowl structure **1** carries four $-\text{CH}_2\text{O}-$ (*wall cavitand*) substituents and the first group of compounds prepared represent “pared back” versions of this host (Figure 2). Thus, four simple tetra-substituted cavitands **2**, **3**, **4**, and **5** were prepared, which carry progressively smaller groups in place of the four wall cavitands of the superbowl, while keeping a π -basic cavity and a hydrogen bond acceptor in the same locations as the superbowl.^[1] The tetra(2,6-dimethoxyphenoxy)methylene cavitand **2** would mimic the superbowl structure most closely, followed by the tetra(phenoxy)methylene cavitand **3**, the tetra(methoxymethylene) derivative **4**, with the tetra(hydroxymethylene) derivative **5** being the furthest removed from the superbowl host, at least in terms of size and functional group content. These cavitands were conveniently produced by four-fold nucleophilic substitution reactions between tetra(bromomethylene) cavitand and oxygen-based nucleophiles.^[8]

Disappointingly, cavitands **2–4** showed no detectable binding with aspirin, using both ^1H NMR and isothermal titration calorimetry (ITC)^[9] techniques.^[8] Evidently, the presence of a π -basic cavity and a hydrogen bond acceptor in the same locations as the superbowl is not enough for successful binding. If our two-point model for aspirin binding is correct then these findings seem to indicate that there is a special affinity of the drug for the superbowl. The obvious difference between these

Figure 1. The proposed two point binding mode of aspirin (green) inside a superbowl (front wall-cavitand omitted for clarity).

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Figure 2. Simple tetra-substituted cavitands mimicking the superbowl base fragment. [*] Front wall-cavitant omitted for clarity.

simple cavitands and the superbowl structure is that the latter is an encapsulating host. We wondered if the ability to fully encapsulate would be a pre-requisite for detectable aspirin binding.

There was also no detectable binding upon ITC monitoring of mixing solutions of tetra(hydroxymethylene) cavitant **5** and aspirin. Unexpectedly, the titration profile displayed an endotherm upon injections of the guest solution into the host solution. A similar endotherm was observed in the absence of guest, by titrating solutions of tetra(hydroxymethylene) cavitant **5** into blank chloroform solution,^[8] a result that we ascribe to the dissociation of hydrogen-bonded dimers/oligomers of this cavitant, perhaps in a similar manner to those reported by the Sherman group.^[10]

To avoid the issue of dimer/oligomer formation witnessed with tetra(hydroxymethyl) cavitant **5**, its mono-substituted analogue, hydroxymethylene cavitant **6** was prepared.^[8] We were delighted to find that cavitant **6** exhibits 1:1 binding with aspirin by ITC titration (exothermic peaks, Scheme 1).^[8] We postulate that aspirin is bound by this receptor by way of: 1) a double H-bond between the carboxylic acid group of aspirin and the hydroxyl group attached to the upper-rim of the cavitant, and 2) a C–H... π interaction between the aspirin acetyl methyl group and the electron-rich cavity of the cavitant (Scheme 1).^[11] The binding of methyl groups of solvent guests within the cavity of cavitands is well established, and X-ray crystal structures of cavitant complexes of toluene, acetone and acetonitrile demonstrate that the methyl hydrogens of the guest reside just above a plane defined by the cavitant acetal oxygens.^[3a] With aspirin as guest, such an arrangement places aspirin's carboxylic acid group close to the binding rim-sub-

Scheme 1. Aspirin binds to mono-hydroxymethylene cavitant **6**.

stituent (see the table of contents graphic for a rendering based upon X-ray crystal structures of both aspirin and cavitant complexes of solvents). On face value, it is surprising that cavitant **5**, with four H-bonding sites, exhibits no detectable binding of aspirin whereas cavitant **6**, with only one H-bonding site, does show binding. Inter-cavitant hydrogen bonding in mono(hydroxymethylene) cavitant **6** is presumably much weaker than in tetra(hydroxymethyl) cavitant **5**. Thus, aspirin can successfully compete for H-bonding between molecules of the former but not with those of the latter.

The association of mono(hydroxymethyl)cavitant **6** and aspirin is also observable by ¹H NMR spectroscopy. Upon mixing solutions of aspirin and cavitant **6** in [D₄]1,2-dichlorobenzene as solvent (a poor competing guest for the cavitant cavity), a significant upfield change in chemical shift of the aspirin acetyl methyl group was witnessed (see Figure 3; maximum $\Delta\delta = 0.94$ ppm at 1:1 stoichiometry).^[8]

To our knowledge, this is the first report of a biologically relevant guest binding in a simple, shallow cavitant. Prior to this observation, shallow methylene-bridged cavitands had been shown to bind only small solvent molecules.^[3] What other structural variations in shallow cavitands would lead to aspirin binding? A systematic investigation was carried out answer this question.

Figure 3. ^1H NMR spectroscopic evidence for binding of aspirin by cavitand **6** (400 MHz, 25°C).

We wondered whether binding would be seen in related receptors, whereupon the distance between the cavitand and the $-\text{OH}$ group was decreased or increased. Cavitand phenol **7** lacks the methylene spacer and cavitand alcohol **8** carries an additional methylene spacer (Figure 4). The former exhibited aspirin binding but with a slightly lower association constant than hydroxymethylene cavitand **6**, whereas no binding was detected in the latter. It is possible that the spacing between the cavity and the hydroxy group is optimal for two-point binding in cavitand **6**, with the distance a little shorter than optimal in **7** and too long (or geometrically challenged) in **8**.

As demonstrated earlier (cavitands **5** and **6**), the presence of four potential hydrogen-bonding substituents is not necessarily better than one, at least in the realm of aspirin binding by cavitands. Is this a general rule? The answer to this question appears to be yes. Cavitand tetraphenol **9** binds aspirin with an association constant around one half of that of monophenol **7** (Figure 4). Once again, we assume that the problem with tetraphenol host **9** is a stronger inter-cavitand association through multiple H-bonding. Only one inter-cavitand H-bond is possible for monophenol **7**, thus leading to the observation of stronger aspirin binding.^[12]

Increasing the length of the *intra*-cavitand bridging chain from a methylene to an ethylene unit (**7** vs. **10**; **9** vs. **11**) was accompanied by a loss in detectable aspirin binding. The conformationally more flexible ethylene-bridged cavitands are known to bind solvent guests.^[13] Nevertheless, to our knowledge, the *relative* binding capacities of methylene and ethylene bridged cavitands have not been previously reported. Our findings suggest that the latter are more weakly binding hosts.

Figure 4. Effect of substituent spacer length, number of binding substituents and bridge length on binding ability of simple cavitands with aspirin.

Presumably, the energetic penalty imposed upon ethylene-bridged receptors by guest binding in the π -basic cavity—specifically, a conformational lock—is too high a price to pay.

Aspirin-binding receptors **6** and **8** carry one binding group at and three hydrogens at the four rim positions. Are spectator groups other than hydrogens allowed? To answer this question, cavitands **12**, **13**, and **14** were prepared, carrying methyl-, bromo-, and methoxy-substituents, respectively (Figure 5).^[8,14] Interestingly, whereas the cavitand phenol with three methyl

Figure 5. Effect of 'spectator' substituents and the type of binding group on cavitand binding with aspirin.

spectator rim substituents **12** exhibited aspirin binding with essentially the same association constant as the triprotio-analogue **7**, tribromo-cavitand **13**, and trimethoxy-cavitand **14** showed no detectable binding. On steric grounds alone, guest binding must be more challenging with these three cavitands than it is with triprotio-host **7**. Despite their electron-donating nature, the methoxy groups are presumably too large to allow detectable binding. The problem with the bromines, with a similar van der Waals radius to a methyl group,^[15] must be electronic in nature: they would be expected to withdraw electron density and result in a significant weakening of the C–H... π component of the two-point binding.

A final set of potential aspirin receptors were prepared in order to find out if binding groups other than a hydroxyl could be successfully employed (Figure 5).^[8,14] Specifically, aldehyde **15**, carboxylic acid **16**, boronic acid **17**, and amine **18** were synthesized and subjected to binding assays with aspirin. Intriguingly, only amino-cavitand **18** showed detectable aspirin binding. Carboxylic acid **16** and boronic acid **17** exhibited the same endothermic response to dilution as did cavitand **5**. Evidently, H-bonded dimers of these cavitands (and anhydrides, in the case of the boronic acid) successfully compete with the cavitand-aspirin complex so that the latter is not observed. The complex between the cavitand aldehyde and aspirin would involve only a *single* H-bond and a C–H... π interaction. It would appear that this interaction is insufficiently strong to outweigh the aspirin carboxylic acid H-bonded dimer.^[16]

The binding between monoamino cavitand **18** and aspirin could be either a two point H-bond and C–H... π interaction or the former could be replaced with a Coulombic interaction between a tight ion pair if an acid-base reaction occurs. That a cavitand is needed at all for this interaction was demonstrated by a control titration between 2-amino-1,6-dimethoxybenzene and aspirin under the same conditions, which gave a negligibly small exothermic response on ITC.^[17]

In summary (Figure 6), this study has shown for the first time that simple, shallow cavitands bind a biologically relevant guest. The drug–synthetic receptor association appears to involve a two point binding mode comprising both a double H-bond to a rim-appended substituent and C–H... π interaction to the cavity. Both the nature of the rim substituent and its distance from the cavity are important. The size and shape of the cavity and the identities of the non-binding, “spectator” substituents also contribute to the ability of the receptor to

bind the drug. Intriguingly, the presence of more rim binding groups has a deleterious effect upon guest binding, since self-association of the host is too strong for the guest to compete. These findings represent a new direction of inquiry in the quest for devices based upon simple, shallow cavitands.

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Figure 6. A summary of cavitand structural features required for aspirin binding.

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