DESIGN, SYNTHESIS AND GUEST BINDING OF NEW SYNTHETIC HOSTS

A thesis submitted for the degree of

Doctor of Philosophy

of

THE AUSTRALIAN NATIONAL UNIVERSITY

THANH VINH NGUYEN
August 2009

Research School of Chemistry
The Australian National University
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Declaration

I hereby declare that the material presented in this thesis, unless otherwise stated or referenced, represents the result of original work carried out by the author and has not been submitted for any other degree. This thesis is less than 100 000 words in length.

Portions of this research have been published previously in scientific journal, namely:


Thanh Vinh Nguyen
30th July 2009
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Abstract

The work described in this thesis is focused on the design, preparation and functionalization as well as host-guest chemistry studies of various host compounds, namely cavitands, deep cavity cavitands and superbowsls. Cavitands are compounds with a rigid concave π-basic surface, which bind guests of a complementary size and shape. These compounds are important building blocks for larger host-guest systems, most notably superbowsls. Superbowsls are composed of five methylene-linked cavitand units. They are arranged with one cavitand at the base and four cavitands orthogonal to the base, forming the surrounding wall and enclosing a relatively enormous internal volume. Deep cavity cavitands are newly developed host systems of intermediate size between cavitands and superbowsls. As part of the work, functionalizations of cavitands and superbowsls have been explored to investigate the effect of functional groups upon host-guest complexation. Binding of these new host compounds with biologically relevant guests was also studied.

Chapter 1 describes the synthesis and controlled interconversion of mono ortho-substituted aryl cavitands and the application of this system in the measurement of relative binding affinities of solvents to cavitands.
Chapter 2 focuses on the synthesis and structural manipulation of superbowl compounds, then describes the results of an investigation into the potential of these molecules in host-guest chemistry.

Work in Chapter 3 describes the functionalization of simple cavitands and the successful binding of a medicinal agent to these cavitands.

Chapter 4 reports the synthesis of a new deep-cavity cavitand system to serve as a host system of intermediate size between a simple cavitand and superbowl.
Chapter 5 describes attempts to synthesize the first aminoacid cavitands, new systems with potential in peptide chemistry.
Abbreviations

°C     degree/s Celsius
Ac     acetyl
AIBN   2,2'-azo-bis-isobutyronitrile
aq.    aqueous
Ar     argon
Bn     benzyl
Bz     benzoyl
br.    broad
Bu     butyl
Calcd. calculated
cat.   catalytic
cm⁻¹   wave number
conc.  concentrated or concentration
CPK   Corey-Pauling-Koltun
δ      chemical shift
d     day/s or doublet/s or deuterated
[D]   deuterated
DCM   dichloromethane
decomposed
DIBAL-H diisobutylaluminium hydride
DIPEA diisopropylethylamine
DMF   N,N-dimethylformamide
DMP   Dess-Martin periodinane
DMSO dimethylsulfoxide
DPPA   diphenyl phosphorly azide
E     electrophile
eq.   molar equivalent(s)
equil.  equilibrium
ESI    electron-spray isonization
Et     ethyl
h     hour(s)
HPLC  high pressure/performance liquid chromatography
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>ITC</td>
<td>Isothermal Titration Calorimetry</td>
</tr>
<tr>
<td>'Pr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (in Hz)</td>
</tr>
<tr>
<td>J</td>
<td>Joule</td>
</tr>
<tr>
<td>K</td>
<td>degrees Kelvin</td>
</tr>
<tr>
<td>$K_a$</td>
<td>association constant</td>
</tr>
<tr>
<td>m</td>
<td>milli or multiplet/s</td>
</tr>
<tr>
<td>M</td>
<td>molar or mega</td>
</tr>
<tr>
<td>$M^*$</td>
<td>molecular ion</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MEK</td>
<td>methyl ethyl ketone (2-butanone)</td>
</tr>
<tr>
<td>min</td>
<td>minute(s)</td>
</tr>
<tr>
<td>mol</td>
<td>mole</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethylene</td>
</tr>
<tr>
<td>MHz</td>
<td>megaHertz</td>
</tr>
<tr>
<td>mmHg</td>
<td>millimetres of mercury</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>$m/z$</td>
<td>mass to charge ratio</td>
</tr>
<tr>
<td>NBS</td>
<td>$N$-bromosuccinimide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>nOe</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear Overhauser effect spectroscopy</td>
</tr>
<tr>
<td>n.r.</td>
<td>not recorded</td>
</tr>
<tr>
<td>Nu</td>
<td>Nucleophile</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet</td>
</tr>
<tr>
<td>$R_f$</td>
<td>retention factor</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet</td>
</tr>
</tbody>
</table>
sat. saturated
sec second(s)
t time or triplet
T temperature
$t$ tert-
TBS tert-butyldimethylsilyl
TFA trifluoroacetic acid
THF tetrahydrofuran
TLC thin layer chromatography
VT variable temperature
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CHAPTER 1: MONO ORTHO-SUBSTITUTED ARYL CAVITANDS

R substituent blocks guest complexation

inside atropisomer

host-guest complex

outside atropisomer
1 Mono ortho-Substituted Aryl Cavitands

1.1 Introduction and Aims

Since the successful construction of the huge covalently linked superbowl molecules within the group (see Chapter 2 for more details), our interest has turned toward utilization of these giant bowls as modelling systems for catalysis and drug delivery. However, previous host-guest binding studies with superbowl molecules have proven that, although the superbowl's huge cavity is big enough to accommodate numerous small molecules, lack of strong host-guest binding forces often resulted in a poor capacity to bind important and valuable guest molecules. The majority of cavitand-based host-guest binding forces come from weak C-H···π interactions and hydrophobic effects. In order to increase the binding strength, it would be the best if an internal binding site could be installed somewhere inside superbowl molecules.

The positions most readily altered or functionalised on superbows are the upper-rim substituents around the portal. At these positions, the most operationally simple way to install a functional group/binding site internally is to incorporate a mono ortho-substituted aryl group. With the restricted rotation around the biaryl bond and a '20° angle from horizontal axis' orientation of superbowl upper-rim substituents, the substituent on the aryl group will be pointing downwards into the superbowl cavity, making it the internal functional group/site (Scheme 1.1.1).

Scheme 1.1.1. A superbowl with an internal binding site for stronger guest binding and a cavitand model system
Superbowl molecules, however, are precious, as the synthetic sequence to make the superbowl is lengthy; so the chemistry to make mono ortho-substituted aryl derivatives was first investigated on cavitands, the component units of superbowsls. It should be also noted that for mono ortho-substituted aryl cavitands or superbowsls, there would always be stereoisomerism, due to the possible inside- and outside-oriented (relative to the cavity) substituents. Obviously, only the inside-oriented substituent could serve as the targeting internal binding site. Rotation of the biaryl bond to interconvert inside/outside isomers could then act as an on/off switch for the binding capacity of the host molecule. Hence, the manipulation of the inside/outside ratio should also be studied.

The objectives of this project are, therefore:

- To investigate the chemistry for making mono ortho-substituted aryl cavitands via biaryl bond formation.
- To monitor and control the inside/outside stereoisomer ratio in order to identify the best conditions for inside isomer formation.

1.2 Review of the Literature Relevant to this Work

Cram’s cavitand bowls are rigid host compounds derived from resorcinarenes (Scheme 1.2.1 and Section 3.2). These hosts have enjoyed widespread application in supramolecular chemistry, particularly as building blocks for oligomers of cavitand molecules, such as hemicarcerands, carcerands and more recently, for larger covalent structures. Single cavitand bowls generally bind guests very weakly on their shallow, concave, \( \pi \)-basic surface. Indeed, solution-phase binding between simple cavitand bowls and (solvent) guests has only been detected by taking advantage of the hydrophobic effect, i.e. employing water-soluble cavitands in aqueous environments.

![Scheme 1.2.1. Cram’s methylene-bridged cavitands were derived from resorcinarenes](image-url)
As will be shown, the cavitand systems described in this chapter could be classified as host molecules with introverted functionality (see Section 1.2.1) or as cavitand host molecules with upper-rim aryl substituents (see Section 1.2.2). From another perspective, the restricted rotation around the biaryl bond and potential C-H⋯π interactions between the substituent and the concave π surface, to a great extent, recall the elegant molecular torsion balances prepared by Wilcox (see Section 1.2.3).

### 1.2.1 Host Systems with Similar Introverted Functionality

Due to the robust skeleton of cavitands, the most likely available sites for structural variation are the upper-rim positions. Since the nature of the upper-rim substituents has a significant effect on the chemical properties and guest binding capacity of cavitands, work in this area has mainly focused on manipulating the upper-rim functionality.\(^1\)\(^6\)

To be able to utilize the concave surface of the cavitand cavity to its best extent, the idea of placing one or more functional groups - acting as either binding site, directing anchor or reacting site - oriented directly into the cavity was first explored over a decade ago.\(^14\) As will be shown, many research groups have made landmark contributions to the development of this idea.

Dalcanale and co-workers have been working on the construction and configurational analysis of symmetrical or mixed-bridged phosphonate cavitands (Scheme 1.2.2).\(^14\)\(^,\)\(^15\) They later applied these systems to sensor studies.\(^16\)\(^,\)\(^17\) There are six possible stereoisomers for a simple symmetrically bridged phosphonate cavitand, due to the inside or outside orientation of the ‘oxide’ oxygen atoms on these bridges. Dalcanale’s group has demonstrated that placement of a fixed, inwardly-directed phosphonate binding substituent on a cavitand bridge leads to a sensor host capable of much stronger and more selective guest binding than Cram’s methylene-linked cavitands. This is due, in part, to the fact that Dalcanale’s hosts are capable of so-called two-point binding. Thus, they were able to selectively bind several organic molecules from among a pool of others based on the capacity to form both H-bonds at the ‘oxide’ oxygens as well as the more typical C-H⋯π interaction at the concave π surface of the cavitands simultaneously.
Scheme 1.2.2. (Top) synthesis of a symmetrical phosphonate-bridged cavitand and (bottom) six possible stereoisomers of Dalcanale’s symmetrical phosphonate bridged cavitand due to inside or outside orientation of the ‘oxide’ oxygen

This phosphonate cavitand system was also concurrently investigated by Dutasta’s research group to explore the possibility of sensing metal cations.\textsuperscript{17-20}

A Japanese research group led by Okazaki also reported the construction of interesting ‘lantern-shaped’ molecular bowl systems based on cavitand frameworks.\textsuperscript{21-23} These molecules have functional groups positioned over the top of the cavity that could be
either oriented outwardly to take an open-type ‘concave’ C-conformation or inwardly to take a collapsed-type ‘convex’ V-conformation (Figure 1.2.3).

![Diagram of concave (C) and convex (V) conformations](image)

**Figure 1.2.3.** Okazaki’s system with functional group \( R_1 \) pointing outwards (C) or inwards (V)

These two conformations are interconvertible and such changes drastically vary the guest binding ability of the cavity due to the orientation of the functional group mentioned above. These systems were created with a view to study the chemistry of the so-called inner space of the cavitand bowl in terms of both the complexing site and also of the potential reaction environment of the endohedral functionality. While Okazaki’s systems can be considered to be most relevant to the work described in this chapter, there has been no development reported after the initial studies.

In elegant studies, the Rebek research group has introduced deep cavity cavitands carrying fixed “introverted functionality”, in which one component of the host molecule is held inside the cavity. These systems exhibit interesting behavior by virtue of the shielding from the bulk phase afforded to a bound guest. Generally, the introverted functional group is attached to a cyclic substituent on the upper-rim of a deep cavity cavitand. The structure and geometry of the substituted cavitand place the functional group inside the cavity of the cavitand. With the deep wall surrounding the enclosed internal volume and separating it from the bulk medium, this functional group could
then operate as either a reaction catalytic site, a reacting site or an anchor point for guest binding (see example in Figure 1.2.4).

Figure 1.2.4. One example of Rebek’s deep cavity cavitand with introverted functionality (COOH)

Rebek and co-workers have also observed the formation of a stereoisomer of the introverted functionalised cavitands, where the functional group was oriented outwardly (Figure 1.2.5). These inward and outward isomers are not atropisomers and cannot be interchanged without covalent bond breaking/reforming.

Scheme 1.2.5. One of Rebek’s deep cavity cavitands with outwardly oriented functionality
Recently, Iwasawa, Kawamura and co-workers have synthesized cavitands that resemble hybrids of Dalcanale’s and Rebek’s systems and carry inwardly directed dialkylsilyl groups and phosphorus electron lone pairs (Figure 1.2.6). They are planning to utilize this system in the production of novel phosphorus ligands for transition metal catalysts.

![Figure 1.2.6. Iwasawa and Kawamura systems](image)

### 1.2.2 Cavitands with Aryl Substituents

A number of aryl and heteroaryl cavitands have been reported in the literature. A selection of distinguished work will now be described.

Cram’s group was the first to prepare cavitands carrying aryl groups at the bowl rim. Their approach involved the formation of the biaryl bond prior to resorcinarene formation. Thus, 2,6-dimethoxyphenylboronic acid was reacted with 1,4-dibromobenzene in the presence of Pd(PPh₃)₄ and Cs₂CO₃ in toluene/methanol at reflux in a statistical reaction to give the substituted biaryl in 50% yield. The biaryl was then converted into the tetra(4-bromophenyl) cavitand in three steps (Scheme 1.2.7).

While initially employing this procedure, the Rebek group also took a different approach to tetra-aryl cavitands. They firstly formed the tetrabromo cavitand, then conducted a four-fold Suzuki-Miyaura coupling with a boronic acid. Thus, the coupling reaction between a tetrabromo cavitand and (p-nitrophenyl)boronic acid in the presence of Pd(PPh₃)₄ and Na₂CO₃ in refluxing toluene/water gave a tetraaryl cavitand in 71% yield.
Scheme 1.2.7. Cram’s stepwise approach (top) and Rebek’s approach (bottom) to tetraaryl cavitands

Kobayashi and co-workers used a tetraiodocavitand to react with the pinacol esters of (4-pyridyl)- and (4-cyanophenyl)boronic acids in the presence of PdCl$_2$(PPh$_3$)$_2$, AsPh$_3$, and Cs$_2$CO$_3$ in dioxane/water at 110 °C to give the tetrasubstituted cavitands in 92% and 89% yields. Previous to this, two tetrabromocavitands (with different feet) were converted to the corresponding tetraboronic acids, then reacted with 3-bromopyridine in the presence of Pd(PPh$_3$)$_4$ and Na$_2$CO$_3$ in toluene/ethanol/water at reflux to give the tetrasubstituted cavitands in 23% and 20% yields after 2 steps (Scheme 1.2.8). It appears that by transposing the boronic acid and halide functional groups (relative to Rebek’s approach), the Suzuki coupling led to low yielding reactions. Meanwhile, replacement of bromide with iodide and repeating Rebek’s approach gave improved yields.
Similar to Kobayashi’s work, the Fukazawa research group coupled a tetraiodocavitand with a bipyridylphenylboronate in the presence of PdCl$_2$(PPh$_3$)$_2$, AsPh$_3$, and Cs$_2$CO$_3$ in refluxing dioxane to give the tetrasubstituted cavitand in 80% yield. Analogously, the Gramlich research group used two tetraiodocavitands (with different feet) to react with the pinacol ester of (3-cyanophenyl)boronic acid in the presence of PdCl$_2$(PPh$_3$)$_2$, AsPh$_3$, and Cs$_2$CO$_3$ in dioxane/water at 75°C to give the tetra-aryl cavitands in 80% and 85% yields, while a third cavitand coupled in the presence of PdCl$_2$(PhCN)$_2$, AsPh$_3$, and Cs$_2$CO$_3$ in dioxane/water at 70°C to give the tetra-aryl cavitand in 84% yield.

Tadokoro and co-workers produced heteroaryl cavitand using a Stille coupling reaction. A tetrabromocavitand was coupled with trimethylstannylpyrimidine in the presence of PdCl$_2$(PPh$_3$)$_2$ in refluxing toluene over six days to give the tetrasubstituted cavitand in 53% yield (Scheme 1.2.9).

Scheme 1.2.8. Two examples of Kobayashi’s approaches

Scheme 1.2.9. Tadokoro’s approach
The Lützen research group carried out a methodological study where monobromo or monoiodo cavitands were coupled with \( p \)-substituted aryl boronic acids to afford monoaryl cavitands in moderate to good yields (Scheme 1.2.10).\textsuperscript{36}

![Scheme 1.2.10. Lützen’s methodological study](image)

As has been shown, the majority of aryl and heteroaryl cavitands have been prepared using the Suzuki-Miyaura coupling reaction. The notable exception was a relatively low-yielding Stille reaction used by Tadokoro.\textsuperscript{35} Interestingly, studies on the synthesis of korupensamines and michellamines by Hoye and Chen suggested that the Suzuki reaction is superior to the Stille and Negishi reactions in the formation of sterically hindered biaryl bond.\textsuperscript{32,43}

To date, all cavitands prepared by these methods have been symmetrically tetrasubstituted, except for those prepared by the Lützen research group,\textsuperscript{36} who employed monoiodo and monobromo cavitands in their coupling reaction. No report of the use of the Suzuki reaction to selectively produce mono-aryl cavitand derivatives from tetrasubstituted cavitands have appeared in the literature. As described later in this chapter, we were interested in using our selective lithium-bromine exchange chemistry followed by Suzuki coupling reactions to enable the selective preparation of mono aryl cavitands.

1.2.3 Tröger’s base systems: measuring competing \( \text{C–H} \cdots \pi \) interactions between substituents

In 1994, Wilcox and co-workers reported the use of a Tröger’s base system to estimate weak molecular forces.\textsuperscript{36} Since then, the Wilcox and Diederich research groups have
been publishing fascinating work\textsuperscript{56-60} involving the employment of this biaryl system as molecular torsion balances (Scheme 1.2.11).

\textbf{Scheme 1.2.11.} One example of Wilcox’s systems

Due to the difference in strengths of the C-H\textcdots{\pi} interactions between the two substituents \textit{ortho} to the biaryl bond position and the ‘horizontal’ aromatic ring, equilibria are established between two dominant conformations (Scheme 1.2.11). These systems have been used to compare weak molecular forces such as C-H\textcdots{\pi} and van der Waals interactions, as well as predicting conformational selection,\textsuperscript{56} solid-state structure\textsuperscript{56} and protein folding preference.\textsuperscript{38}

The mono \textit{ortho}-substituted aryl cavitand system described in this chapter resembles Wilcox’s folding systems in that they both use non-covalent interactions between a substituent and an electron-rich \pi-surface to control atropisomerism around a biaryl bond. As we will see, the cavitand host platform is distinct from that derived from a Tröger’s base in the ability of the former to bind solvent molecules.

\subsection*{1.3 Suzuki-Miyaura Coupling Reaction to Make Mono \textit{ortho}-Substituted Aryl Cavitands}

Using the Suzuki coupling reaction, there are three different pathways by which a mono \textit{ortho}-substituted aryl cavitand can be synthesized, as detailed in Scheme 1.3.1 below:

\begin{itemize}
  \item Selective mono coupling reaction between an aryl boronate compound and tetrabromocavitand (route 1).
  \item Selective conversion of tetrabromocavitand to tribromo monoiodo cavitand followed by the coupling reaction with an aryl boronate compound (route 2).
\end{itemize}
Selective conversion of tetrabromocavitand to a boronate cavitand precursor followed by the coupling reaction with an aryl bromide or iodide (route 3).

Scheme 1.3.1. Possible synthetic routes towards mono \textit{ortho}-substituted aryl cavitands

Our group’s initial investigations into Suzuki-Miyaura coupling reaction on cavitands met with only moderate success. Reactions of bromo cavitands with phenylboronic acid (Scheme 1.3.1, route 1) were found to be slow and prone to stalling, while bromoiodo cavitands (Scheme 1.3.1, route 2) were difficult to purify, and the Suzuki coupling of incompletely purified bromoiodo cavitand products led to mixtures of arylated cavitands. Bromo cavitand boronate esters (Scheme 1.3.1, route 3), in contrast, proved to be much easier to purify than the corresponding iodides or boronic acids, and they reacted smoothly with iodobenzene under the conditions of Chaumeil.\textsuperscript{61} Hence, the third pathway was employed to approach the mono \textit{ortho}-substituted aryl cavitand family. Firstly, tetrabromocavitand 1.1 was converted to tribromo monoboronate pinacolyl ester cavitand 1.2 using the selective mono lithiation chemistry developed in the group some years ago.\textsuperscript{54,55} Then, stereoisomers 1.4 and 1.5 of mono \textit{ortho}-substituted aryl cavitands were readily prepared by Suzuki-Miyaura coupling of that cavitand boronate ester with various \textit{ortho}-iodoarenes 1.3 (Scheme 1.3.2).
Scheme 1.3.2. Synthesis of mono ortho-substituted aryl cavitands. Reagents and conditions: a) n-BuLi (1.1 eq.), THF, -78°C; then B(OMe)₃ (1.5 eq.), -78°C → 25°C; then pinacol (1.1 eq.), MgSO₄ (4.1 eq.), CH₂Cl₂, 25°C, 18 h. b) Iodoarene 1.3 (3.0 eq.), Ag₂CO₃ (2.0 eq.), Pd₂(dba)₃ (0.12 eq.), P(2-furyl)₃ (0.50 eq.), THF, 25°C, 18–72 h

The outcomes of Suzuki coupling reactions of cavitand boronic ester 1.2 with various iodoarenes were tabulated in Table 1.3.3
Table 1.3.3. Outcomes of Suzuki coupling between cavitand boronic ester 1.2 with various iodoarenes. [a] Average of two NMR runs, difference between runs = ±1%. [b] The cavitand substituent is a 1-naphthyl group in this case. [c] Not kinetic ratios: in these cases, thermodynamic interconversion between inside and outside forms occurs under the reaction conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Total isolated yield (%)</th>
<th>Kinetic ratio inside:outside (1.4:1.5)[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>70</td>
<td>86:14</td>
</tr>
<tr>
<td>b</td>
<td>1-naphthyl[b]</td>
<td>70</td>
<td>97:3</td>
</tr>
<tr>
<td>c</td>
<td>Br</td>
<td>85</td>
<td>98:2</td>
</tr>
<tr>
<td>d</td>
<td>CO₂Me</td>
<td>75</td>
<td>25:75[c]</td>
</tr>
<tr>
<td>e</td>
<td>CO₂Et</td>
<td>60</td>
<td>83:17</td>
</tr>
<tr>
<td>f</td>
<td>CO₂Pr</td>
<td>70</td>
<td>83:17</td>
</tr>
<tr>
<td>g</td>
<td>CO₂Bu</td>
<td>70</td>
<td>5:95[c]</td>
</tr>
<tr>
<td>h</td>
<td>CO₂Bu</td>
<td>65</td>
<td>99:1</td>
</tr>
</tbody>
</table>

Under optimized conditions, isolated yields for the 2,2',6-trisubstituted biaryl products 1.4 and 1.5 are in the 60–85% range. The procedure described here was, in our hands, superior to previously reported Suzuki-Miyaura or Stille coupling protocols for aryl cavitand formation. Reactions leading to the ortho-bromophenyl (1.4c/1.5c) and 1-naphthyl substituted cavitands (1.4b/1.5b) took considerably longer than the others. This could be explained by the obvious steric effect of bromo and 1-naphthyl substituents on the position ortho to these substituents. Intriguingly, all but two of these reactions furnish mixtures rich (83–99%) in the inside-stereoisomer 1.4. The kinetic preference for the inside-stereoisomer in the cross coupling reaction could be attributed to steric hindrance at play in the biaryl bond-forming step (Scheme 1.3.2, inside-stereoisomers are not always thermodynamically favored, see Section 1.6). Thus, in the three-centered transition state of the reductive elimination step, the Pd(Pfu₃)₂ group will occupy the less sterically hindered outside position and the R substituent will inexorably avoid the phosphine ligands, thereby adopting an orientation that leads to the formation of the inside isomer 1.4. Indeed, with a bulky substituent such as t-butyl group, the coupling reaction results in the formation of the inside-stereoisomer 1.4h exclusively. A
similar mechanism has been put forward to explain \( \pi \)-facial selectivities in Suzuki coupling reactions involving (arene)chromium complexes.\textsuperscript{62}Irrespective of the mechanism, the kinetic inside-stereoselectivity appears to be a general feature of these reactions: in the two systems furnishing mixtures rich in the outside cavitand isomer 1.5 (Table 1.3.3, entries d and g), the inside isomer 1.4 is atropisomerically unstable under the reaction conditions. Hence, the stereoisomer ratios recorded for entries d and g were not the kinetic ratios.

All of these newly-formed cavitands were fully characterized using common techniques, such as melting point measurement, \(^1\)H and \(^{13}\)C one-dimensional NMR, mass-spectroscopy, infra-red spectroscopy and elemental analysis. For further elucidation of stereochemistry, advanced techniques such as 2D-NMR, variable temperature NMR and single crystal X-Ray diffraction analysis were employed, as detailed in the following sections.

1.4 Stereochemistry Assignment for Mono ortho-Substituted Aryl Cavitands

The inside and outside atropisomers were readily separated by chromatography and the stereochemistry of each was assigned through \(^1\)H NMR chemical shifts and the results of interconversion experiments (\textit{vide infra}).

Informative regions of \(^1\)H NMR spectra of selected compounds are reproduced in Figure 1.4.1. All protons associated with the substituents of inside atropisomers of the methyl (1.4d), ethyl (1.4e), and \( n \)-propyl (1.4f) esters display upfield chemical shifts, by virtue of their close proximity to the shielding zone of the aromatic cavity. The upfield shift is greatest with the ethyl (1.4e) and \( n \)-propyl (1.4f) esters, the terminal methyl protons of which resonate at \( \delta \approx -2.05 \) and \(-2.71 \) ppm respectively, some 3–3.5 ppm upfield of the usual chemical shift for such protons. Surprisingly, the inside isomer of the corresponding \( n \)-butyl ester (1.4g) shows only small upfield chemical shifts. Presumably, whereas the ethyl and \( n \)-propyl groups are close to the ideal size to reach to the bottom of the cavity, the \( n \)-butyl group is prohibitively large for a snug fit.
Figure 1.4.1. Pertinent sections of $^1$H NMR spectra of *inside* and *outside* esters, 1.4d–h and 1.5d–g, respectively (300 MHz, CDCl$_3$, 25°C)

Additional X-ray crystallographic analysis (of 1.5f, Figure 1.4.2) and NOE experiments (of 1.4a-c and 1.5a-c, see examples in Figures 1.4.3 and 1.4.4) were also carried out to further confirm the orientation of substituents. All attempts to grow crystals of 1.4f for X-ray analysis failed due to the slow interconversion between 1.4f and 1.5f during recrystallization. It is quite interesting to see that one hexane solvent molecule was sitting inside the cavity of the cavitand of 1.5f in the crystalline form. Similar observation of alkanes coiling into the defined cavity of cavitands in the presence of other competitive solvents has been reported by Rebek and co-workers some years ago.$^{63}$
Figure 1.4.2. Anisotropic displacement ellipsoid plot of $\text{C}_{62}\text{H}_{71}\text{Br}_3\text{O}_{10}$ (1.5f) with the $n$-hexane molecule of inside the cavity. Minor sites of disordered atoms have been omitted. Ellipsoids show 30% probability levels. Hydrogen atoms have been deleted for clarity. Sample was crystallized from dichloromethane/hexane solution.
Figure 1.4.3. NOESY spectrum of compound 1.4a (500 MHz, CDCl₃, 25 °C)
Figure 1.4.4. NOESY spectrum of compound 1.5a (500 MHz, CDCl₃, 25 °C)
1.5 Variable Temperature NMR Studies with Compound 1.4h

The inside isomer of the iso-butyl ester (1.4h) can be viewed as a hybrid of the ethyl (1.4e) and n-propyl (1.4f) esters. The interesting NMR spectral properties (Figure 1.5.1) of this compound prompted us to undertake variable temperature (VT) NMR studies (Figure 1.5.2) in order to further understand the fascinating nature of this system.

![Diagram of compound 1.4h](image)

**Figure 1.5.1.** $^1$H NMR spectrum of compound 1.4h (top) in comparison with spectra of compound 1.4e (middle) and 1.4f (bottom) – The iso-butyl group of compound 1.4h is undergoing rapid rotation on the NMR time scale (300 MHz, CDCl$_3$, 25°C)

The iso-butyl group of inside isomer 1.4h is undergoing rapid interconversion between either “ethyl” down or “propyl” down conformations at room temperature. The triplet at $\delta$ -0.5 ppm and doublet at $\delta$ -1.1 ppm are the result of an averaging of the up and down
conformations of the “ethyl” CH$_3$ and the “propyl” CH$_3$ groups. The rate of interconversion between these two forms is too rapid, even at -90°C, to observe discrete conformations. Theoretically, if the temperature is low enough for the rotation to be slow on NMR timescale, the triplet and doublet should separate into at least two pairs of signals, representing the discrete up and down conformations for each terminal methyl group. Unfortunately, due to the limitation of our NMR facilities, only coalescence points of these two pairs - which incidentally overlap each other at -90 °C - can be observed. Interestingly, at 25 °C, a higher upfield shift is evident for the “ethyl” CH$_3$ than the “propyl” CH$_3$, a result that we interpret as a win for the ethyl over the propyl group as the more readily accommodated substituent.

Figure 1.5.2. Pertinent section of VT-¹H NMR spectra of compound 1.4h (500 MHz, CD$_2$Cl$_2$). Temperature range studied was from -20 °C to -90 °C.
1.6 Temperature and Substituent Effect on inside-outside Interconversions

Atropisomeric stability varies considerably throughout the series of compounds prepared for this study (Scheme 1.6.1). Thus, in [D₈]toluene solution, a pure sample of either atropisomer of the ortho-CO₂Me-phenyl-substituted cavitand 1.4d/1.5d interconverted to produce an equilibrium mixture at ambient temperature overnight, whereas the two atropisomers of the ortho-bromophenyl-cavitand (1.4c/1.5c) are kinetically stable at 100 °C for several days. A substituent’s influence upon the relative atropisomeric stability of an arylated cavitand (order of stability: ortho-Br phenyl > 1-naphthyl > ortho-Me phenyl >> ortho-CO₂R phenyl) is broadly consistent with substituent effects observed during racemization studies with chiral biphenyls. Nevertheless, within the ester substituent family, a curious atropisomeric stability order: CO₂Et > CO₂′Pr >> CO₂Me > CO₂′Bu is witnessed.

![Scheme 1.6.1. Temperature and substituent effects on atropisomer ratio.](image)

```
<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>t₁/₂ at 65°Cᵃ</th>
<th>t₁/₂ at 100°Cᵃ</th>
<th>Equil. ratio in:out at 65°Cᵇ</th>
<th>Equil. ratio in:out at 100°Cᵇ</th>
<th>Isomer favored at higher T</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Me</td>
<td>28 h</td>
<td>20 min</td>
<td>13:87 ±3</td>
<td>6:94 ±2</td>
<td>outside</td>
</tr>
<tr>
<td>b</td>
<td>1-naphthylᶜ</td>
<td>400 h</td>
<td>4 h</td>
<td>28:72 ±1</td>
<td>17:83 ±2</td>
<td>outside</td>
</tr>
<tr>
<td>d</td>
<td>CO₂Me</td>
<td>5 min</td>
<td>2 min</td>
<td>30:70 ±2</td>
<td>43:57 ±2</td>
<td>inside</td>
</tr>
<tr>
<td>e</td>
<td>CO₂Et</td>
<td>50 min</td>
<td>2 min</td>
<td>83:17 ±2</td>
<td>86:14 ±1</td>
<td>inside</td>
</tr>
<tr>
<td>f</td>
<td>CO₂′Pr</td>
<td>40 min</td>
<td>2 min</td>
<td>75:25 ±1</td>
<td>77:23 ±2</td>
<td>inside</td>
</tr>
<tr>
<td>g</td>
<td>CO₂′Bu</td>
<td>10 min</td>
<td>20 sec</td>
<td>16:84 ±2</td>
<td>23:77 ±2</td>
<td>inside</td>
</tr>
</tbody>
</table>
```

**Scheme 1.6.1.** Temperature and substituent effects on atropisomer ratio. [ᵃ] Starting from outside atropisomer. [ᵇ] in:out ratios are the average of 4–8 runs and standard deviations are quoted. [ᶜ] The cavitand substituent is a 1-naphthyl group in this case. [ᵈ] No measurable change after 1000 h. [ᵉ] Equil. ratio at 120°C. [ᶠ] Equil. ratio at 140°C.
Further unexpected and unprecedented properties begin to emerge during more detailed investigations into the thermodynamic equilibration of these compounds (Scheme 1.6.1). In general, the thermodynamically more stable isomer in toluene is the *outside* form. The exceptions are the CO₂Et and CO₂"Pr substituted compounds (Scheme 1.6.1, entries e and f), which favor the *inside* isomer. Interestingly, the equilibrium ratios of atropisomers are temperature dependent: the majority of derivatives examined (Scheme 1.6.1, entries c–g) display an enhanced preference for the *inside* isomer as the temperature is increased. The exceptions to this trend are the o-tolyl (1.4a/1.5a) and 1-naphthyl (1.4b/1.5b) substituted cavitands. The strange behaviour of these two compounds cannot be easily explained but the electronic and structural similarity of the cavitand aryl substituents to the solvent used in the study could possibly play some role to alter these thermodynamic equilibria.

These results are best explained by the equilibrium depicted in Scheme 1.6.2, which takes into account the influence of solvation upon the relative stabilities of the *inside* and *outside* atropisomers. The cavity of the *inside* isomer 1.4 is occupied by the ortho-substituent of the aryl group, which precludes guest (i.e. solvent) binding. In contrast, the *outside* isomer 1.5 is free to serve as a host for a complementary guest molecule. The increased preference for the *inside* isomer 1.4 at higher temperatures (Scheme 1.6.1) now becomes evident: *outside → inside* switching leads to the expulsion of a guest molecule, an entropically driven process.

![Scheme 1.6.2. Solvent (guest) role in atropisomerism](image.png)
At first glance, the atropisomeric stability order CO$_2$Et $>$ CO$_2$nPr $>$ CO$_2$Bu $>$ CO$_2$Me (Scheme 1.6.1, $t_{1/2}$ times) appears curious. If steric effects alone were determining the magnitude of the energetic barrier towards rotation about the biaryl bond, one would expect that as the size of the ester substituent is increased, atropisomeric stability would increase. We suggest an additional (Goldilocks) factor at play here, which relates to how well the ester substituent fits into the cavity: the methyl ester is too small for the cavity and the $n$-butyl is too large, whereas the ethyl and $n$-propyl esters are within the correct size range (but the ethyl is just right). Evidently, the self-fulfilling$^{64}$ nature of the inside ethyl and $n$-propyl groups causes a ground state stabilization which increases the barrier towards biaryl bond rotation. The methyl and $n$-butyl groups have a lower interconversion barrier since the inside isomers lack such a high degree of stabilization. The complementary fit of the ethyl and $n$-propyl substituents in the cavitand bowl not only affects the barrier towards atropisomerization, it is sufficiently strong to override the usual thermodynamic preference for the outside form in toluene (Scheme 1.6.1, in:out equilibrium ratios).

Mixtures of compounds 1.4d/1.5d were subjected to thermodynamic equilibration in [D$_6$]toluene at different temperatures, ranging from 25 °C to 200 °C (Figure 1.6.3). Obviously, increasing the temperature generally drives the equilibrium to the inside atropisomer. So, at very high temperature, something remarkable happens with the methyl ester atropisomers 1.4d/1.5d: the inside isomer becomes dominant (inside 1.4d : outside 1.5d thermodynamic ratio at 200 °C in [D$_6$]toluene = 54:46, Figure 1.6.3). Thus, it is possible to prepare a mixture rich in either atropisomer by simply holding a solution of the mixture at a particular temperature.

A van’t Hoff analysis (Figure 1.6.3) was carried out to obtain information about the enthalpy and entropy changes associated with this equilibrium, assuming that these two thermodynamic parameters are independent of temperature change. Based on this analysis, the thermodynamic parameters of this equilibrium are: $\Delta H = 8.8 \pm 0.3$ kJ mol$^{-1}$ and $\Delta S = 20.3 \pm 0.6$ J mol$^{-1}$ K$^{-1}$.
<table>
<thead>
<tr>
<th>Ratio 1.4d/1.5d</th>
<th>K</th>
<th>T</th>
<th>1/T</th>
<th>ln(K)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25/75</td>
<td>0.333</td>
<td>298.15</td>
<td>3.35 x 10^{-3}</td>
<td>-1.099</td>
</tr>
<tr>
<td>30/70</td>
<td>0.429</td>
<td>338.15</td>
<td>2.96 x 10^{-3}</td>
<td>-0.847</td>
</tr>
<tr>
<td>43/57</td>
<td>0.754</td>
<td>373.15</td>
<td>2.68 x 10^{-3}</td>
<td>-0.282</td>
</tr>
<tr>
<td>54/46</td>
<td>1.174</td>
<td>473.15</td>
<td>2.11 x 10^{-3}</td>
<td>0.160</td>
</tr>
</tbody>
</table>

**Figure 1.6.3.** van’t Hoff analysis of 1.4d/1.5d atropisomerism in [D₆]toluene

Hence, it may be concluded that temperature and the nature of substituent on the aryl group have significant effect on the atropisomerism of these mono aryl cavitands.

### 1.7 Solvent Effect on inside-outside Interconversions

Since solvent, acting as a guest, plays an important role in the inside-outside thermodynamic isomerization, a further investigation into the effect of solvent on this interconversion was carried out with a view to fully understand and then manipulate these systems. A mixture of compounds 1.4e/1.5e was dissolved in different solvents, then the solutions were equilibrated at 50 °C. The stereoisomer ratios were determined using ^1^H NMR spectroscopy, providing a fascinating range of ratios as tabulated in Scheme 1.7.1.
Scheme 1.7.1. Relative guest binding affinities measured via atropisomer ratios. [a] Average of three \(^1\)H NMR runs, difference between runs = \(\pm 1\%\). [b] The solid 1.4e/1.5e mixture was heated to 50°C, then immediately dissolved in CDCl\(_3\) at 25°C and a \(^1\)H NMR spectrum was recorded. [c] Non-deuterated solvent NMR technique was used.

The results depicted in Scheme 1.7.1 demonstrate that changing the solvent causes a change in the thermodynamic stereoisomer ratios. Indeed, the major isomer at equilibrium is different in different solvents. This unique system offers a very convenient method for the measurement of relative solvent guest binding strengths. This remarkable solvent influence upon the inside:outside atropisomer ratio is the result of competition between the ortho-CO\(_2\)Et substituent and the solvent for the cavitand bowl cavity. In the absence of solvent, or in poorly binding solvents, the equilibrium is dominated by the inside isomer 1.4e. In contrast, a solvent that binds strongly in the cavity (i.e. ethyl acetate) is signaled by an equilibrium dominated by the outside isomer 1.5e. The equilibrium ratio in a particular solvent is, therefore, a direct measure of relative solvent guest binding affinity for cavitands.
<table>
<thead>
<tr>
<th>Solvent</th>
<th>in:out ((1.4e:1.5e))</th>
<th>Dipole (D)</th>
<th>Dielectric constant</th>
<th>Sherman’s water soluble complex K∞ (M⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>no solvent</td>
<td>99:1 ± 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me₂NCHO</td>
<td>98:2 ± 1</td>
<td>3.86</td>
<td>36.70</td>
<td></td>
</tr>
<tr>
<td>CCl₄</td>
<td>85:15 ± 2</td>
<td>0.00</td>
<td>2.24</td>
<td></td>
</tr>
<tr>
<td>PhMe</td>
<td>81:19 ± 1</td>
<td>0.43</td>
<td>2.38</td>
<td>30±6</td>
</tr>
<tr>
<td>Me₂CO</td>
<td>80:20 ± 1</td>
<td>2.85</td>
<td>20.70</td>
<td>19±1</td>
</tr>
<tr>
<td>PhH</td>
<td>76:24 ± 2</td>
<td>0.00</td>
<td>2.27</td>
<td>55±16</td>
</tr>
<tr>
<td>CHCl₃</td>
<td>73:27 ± 1</td>
<td>1.15</td>
<td>4.81</td>
<td>120±4</td>
</tr>
<tr>
<td>Me₃SO</td>
<td>69:31 ± 1</td>
<td>3.90</td>
<td>46.70</td>
<td></td>
</tr>
<tr>
<td>EtOAc</td>
<td>41:59 ± 3</td>
<td>1.88</td>
<td>6.02</td>
<td>200±40</td>
</tr>
</tbody>
</table>

Table 1.7.2. 1.4e/1.5e ratios in different solvents. These data show that there is no correlation between inside/outside ratios and solvent polarities.

A simple explanation of different atropisomer ratios resulting from solvent polarity effects can be ruled out, since there is no correlation between atropisomer ratios and solvent dipoles or dielectric constants (Table 1.7.2) In contrast, the relative solvent binding affinities determined by studies of the switchable inside/outside cavitands 1.4e/1.5e display an excellent correlation with the association constants (Table 1.7.2) reported by Sherman. Sherman’s studies employed an ammonium phosphate–derivatized cavitand (Figure 1.7.3) in aqueous solution. The same relative binding strengths can be observed: PhMe < PhH < CHCl₃ < EtOAc in both Sherman’s and our own work. Sherman obtained a much lower binding affinity for acetone, a result that is likely due to competitive H-bonding between acetone and water in the studied system. Since such competitive H-bonding is absent in our system, this new data is believed to provide a better value for the relative binding affinity of acetone to the cavitand cavity.

![Figure 1.7.3. Sherman’s water-soluble cavitand was employed to measure binding affinity of organic solvents towards the hydrophobic cavity in aqueous solution.](image_url)
The ability of this new method to measure relative guest binding strengths of organic solvents in an operationally straightforward manner, i.e. by simply measuring atropisomer ratios, and without recourse to the hydrophobic effect, clearly demonstrates an unprecedented simplicity and sensitivity. A future goal of this work is the development of a system that can provide a quantitative measurement of association constants.

1.8 Enhancing the outside Isomer Population by Complexation with Third-party Molecules

By equilibrating at elevated temperature (Scheme 1.6.1) and/or using suitable solvents (Scheme 1.7.1), the inside isomer 1.4e of mono ortho-(carboxymethylphenyl) cavitand can be exclusively formed from a mixture of inside/outside isomers 1.4e/1.5e (solid state or DMF solution, 50 °C). However, to date, the highest outside isomer 1.5e population obtained was only 59% (ethyl acetate solution, 50 °C). Despite significant efforts, no organic solvent tested could completely drive the equilibrium to the outside form.

Scheme 1.8.1. Coordination of Lewis acid to the ester group of the substituted aryl cavitand

We proposed that complexing the Lewis-basic COOEt group with a Lewis acid would increase the size of the ortho-substituent, which will disfavour the inside form. Lewis acids (AlCl₃, EtAlCl₂, Et₂AlCl) were added to a chloroform solution of mixture 1.4e/1.5e in order to attempt to push the equilibrium to the expected outside form.
Unfortunately, no isomer ratio change was observed at room temperature after several days. Upon warming to 50 °C, decomposition of the cavitand substrate was observed.

These preliminary studies are somewhat unpromising. Nevertheless, it is possible that a more exhaustive survey of Lewis acids would achieve the desired outcome. Due to time constraints, this task will be re-investigated in future studies.

1.9 Summary, Conclusions and Future Work

The initial objectives of this project were to:

- Investigate the chemistry for making mono ortho-substituted aryl cavitands via biaryl bond formation.
- Monitor and control the inside/outside stereoisomer ratio in order to identify the best conditions for inside isomer formation.

The goals to build mono ortho-substituted aryl cavitands and to explore the possibility of manipulation of the inside/outside isomer ratios of these cavitands were successfully achieved. Furthermore, the study led to interesting and valuable information about systems that could enjoy widespread future application in host-guest chemistry, namely:

- The Suzuki-Miyaura coupling reaction using the optimised conditions reported in this work is a powerful tool to create biaryl bonds in sterically hindered and electron-rich systems like cavitands (Scheme 1.9.1).

![Scheme 1.9.1. Synthesis of mono ortho-subsituted aryl cavitands](image-url)
The *inside/outside* stereoisomer ratio is temperature, solvent and substituent dependent. One or other of these two stereoisomers predomnates in the mixture, subject to the conditions of the equilibrium. This study provides the methods to control the stereoisomer ratio in this and related systems (Scheme 1.9.2).

**Scheme 1.9.2.** Stereoisomer interconversion is R group, temperature and solvent dependent.

- Mono ortho-substituted aryl cavitands can serve as tools to measure the relative binding affinities of solvent/guest molecules to cavitand cavities (Scheme 1.9.3).

**Scheme 1.9.2.** Mono ortho-substituted aryl cavitands as qualitative meters for binding affinities of solvents within cavitand cavities.

Future development of the work described in this chapter would be to apply the knowledge from these cavitand systems to the incorporation of internal binding sites within the superbowl structure, which will be discussed in more details in Section 2.7 of Chapter 2. A similar cavitand system that can provide a quantitative measurement of guest association constants will also be investigated.
CHAPTER 2: PRACTICAL SYNTHESIS AND HOST-GUEST BINDING STUDIES OF SUPERBOWL MOLECULES

Aspirin

Two-point binding: H-bonding and C-H/π interaction
2 Practical Synthesis and Host-guest Binding Studies of Superbowl Molecules

2.1 Overview of Relevant Literature and Objectives of this Work

Superbowls are huge synthetic molecules composed of five covalently linked cavitand units, taking the form of a spherical cage with a portal. They have potential application in host-guest chemistry, for examples as models for drug delivery, catalysis and molecular sensing/recognition.

2.1.1 Inspiration for Superbowl Molecule Construction

In 1997, when trying to co-crystallize C-methyl calix[4]resorcinarene with H-bond acceptors in aromatic solvents, Atwood and MacGillivray discovered the formation of a solid state spherical hexamer. Single crystal X-ray diffraction analysis revealed a self-assembled array comprising six C-methyl calix[4]resorcinarene and eight water molecules held together by 60 hydrogen bonds (Figure 2.1.1), enclosing a huge internal volume of ~1375 Å³, 4.5 times larger than the next biggest cavity reported at that time.

![Figure 2.1.1. Space-filling and stick models of Atwood's hexameric capsule. Water molecules are highlighted in purple.](image)

The hexameric capsule, with its ability to encapsulate several solvent molecules, enjoyed widespread interest from host-guest chemistry and drug delivery researchers around the world. Following the initial report by Atwood and MacGillivray, a similar
pyrogallolarene hexamer was reported by the Mattay\textsuperscript{71} research group in 1999. Single crystal X-ray analysis revealed that this hexameric capsule differed from the Atwood’s structure in that it was formed without the participation water. Since then, the Atwood,\textsuperscript{72,80} Rebek,\textsuperscript{81-84} Cohen,\textsuperscript{66-70} and Kaifer\textsuperscript{85} research groups have been publishing evidence for the presence of the same types of hexameric assemblies in the solution phase and reversible encapsulation of relatively large molecules such as tetraalkyl ammonium and phosphonium salts, antimony (V) salts and ferrocenium ions inside the assemblies.

Atwood filed a patent in 2001\textsuperscript{86} describing the preparation of hexameric capsules containing either methanol or pharmaceutically active agents. While providing explicit evidence for the presence of methanol molecules within some hexameric capsules, no evidence for the hexamer-pharmaceutically active agent complexes were reported. The patent also suggests potential applications in drug delivery for the hexameric system. There has been, however, no further report since then.

The 1997 report by Atwood and MacGillivray inspired our research group to design and build a covalently-linked analogue of the hexameric capsule. The purpose of this work was to obtain a non-collapsible structure with greater stability, the possibility of wider structural variation and superior solubility in organic solvents.\textsuperscript{87} Cavitands, conformationally rigid derivatives of resorcinarenes, were used as building blocks for this structure in place of resorcinarenes.

![Scheme 2.1.2. Dissociation of hexameric capsule required for guest exchange](image)

We decided to build a pentameric cage with a portal on top for guest entry and egress, instead of a completely closed hexameric capsule, which could be valueless to host-
guest chemistry. While this work was underway, the Rebek research group reported elegant studies, proving that dissociation of one resorcinarene molecule from Atwood’s hexamer is required for guest exchange (Scheme 2.1.2). This report supported the potential advantages of our approach.

2.1.2 Synthesis of Superbowl Molecules within the Sherburn Group

After a few years of development, in 2004, our research group reported the synthesis of the target pentameric structures, which we named superbowl molecules. Superbowls are built by the assembly of five cavitand units, comprising four wall cavitands and one base cavitand. They are held together using –OCH₂O- (wall-wall) and –CH₂O- (base-wall) linkages (Scheme 2.1.3). This structure can be considered as a big, deep cage with a portal on top, bearing four functional groups of choice around the portal. This portal is the doorway for guest entry and egress.

Scheme 2.1.3. Retrosynthetic analysis of superbowl molecule

There are two types of cavitand building blocks for superbowls. As indicated above, there are four identical cavitands substituted by three different upper-rim functional groups, the so-called wall cavitands. The symmetrically tetrasubstituted cavitand at the
bottom is called the base cavitand (Scheme 2.1.3). Four wall cavitands were connected to the base cavitand to make the cavitand cruciform pentamer. After two functional group interconversions, the wall cavitand units are connected together to form the superbowl molecule (Scheme 2.1.3).

2.1.2.1 Previous Synthesis of the Base Cavitand

In the reported synthesis of superbowl, the base cavitand was made in three steps from 2-methyl resorcinol. Firstly, a tetrameric cyclocondensation reaction with hexanal resulted in the C-pentyl tetramethyl calix[4]resorcinarene. This resorcinarene was then closed to make tetramethyl cavitand and finally a free radical bromination with NBS/AIBN in refluxing CCl₄ gave the C-pentyl tetra(bromomethyl) cavitand, which is the base cavitand (Scheme 2.1.4).

![Scheme 2.1.4. Reported synthesis of the base cavitand](image)

2.1.2.2 Previous Synthesis of the Wall Cavitand

The synthesis of the wall cavitand was somewhat lengthier than the base cavitand. Resorcinol was reacted with hexanal to give C-pentyl calix[4]resorcinarene, followed by an four-fold electrophilic aromatic bromination with NBS and then a cavitand formation reaction with base and bromochloromethane to provide C-pentyl tetrabromo cavitand (Scheme 2.1.5).

The tetrabromo cavitand was then selectively distally disubstituted (a so-called A,C-selective di-functionalization) using our previously reported lithium-bromine exchange protocol. Thus, treatment with 2.2 equivalents of n-BuLi followed by sequential quenching with trimethyl borate and oxidative hydrolysis provided the A,C-dibromo dihydroxy cavitand. The phenol groups were protected as MOM ethers, and then similar
chemistry to the previous step was done to selectively convert one of the remaining two bromines to a third, unprotected phenol group, which afforded the wall cavitand (C-pentyl monobromo, monohydroxy, A,C-di(methoxymethyleneoxy) cavitand) (Scheme 2.1.5).^{2,87}

**Scheme 2.1.5.** Reported synthesis of the wall cavitand

The kinetic A,C-selectivity of the lithium-bromine exchange may be explained as shown in Scheme 2.1.6. The first lithium-bromine exchange takes place at one of the four bromines. Then, the second n-butyl lithium (aggregate) approaches the tribromo monolithic cavitand (aggregate) at the side distal from the first lithium to avoid Coulombic. Hence, the distal approach is more favoured, leading to the preferred formation of A,C-dilithio intermediate.^{2,87}

**Scheme 2.1.6.** The kinetic selectivity of A,C-difunctionalization
2.1.2.3 **Previous Synthesis of Tetrabromo Superbowl**

An excess (five molar equivalents) of wall cavitand (a mono phenol) was then reacted with the base cavitand (a tetra benzyl bromide) in a four-fold $S_N2$ reaction to give the MOM protected cruciform pentamer. This was then treated with trifluoroacetic acid to cleave the MOM ethers to form the octaphenol cruciform pentamer. Finally, the phenol groups were connected by acetal bridge formation to provide the superbowl, in a analogous fashion to cavitand formation (Scheme 2.1.7).\(^ {39}\)

![Diagram of the synthesis process](image)

**Scheme 2.1.7.** Synthesis of tetrabromo superbowl from wall and base cavitands

2.1.2.4 **Synthesis of other Superbowl Molecules**
Tetrabromo superbowl, as can be seen in Scheme 2.1.7, has four bromines around the portal. These bromines are obvious positions for further functionalization. Initial attempts to directly convert these bromines to other functionalities met with failure. Hence, the reported tetraprotio and tetraphenol superbowls (Scheme 2.1.8) were prepared not through the manipulation of tetrabromo superbowl but through the manipulation of the requisite wall cavitands, before using those cavitands to build the superbowl molecules (Scheme 2.1.8).  

**Scheme 2.1.8.** Other reported superbowls were produced using different wall cavitands. 

---

**Diagram:**

- **Tetrabromo superbowl:**
  - Initial state: 4 bromines around the portal
  - Functionalization:
    1. n-BuLi (1.1 eq)
    2. PrOH (1.1 eq)
    3. n-BuLi (1.1 eq)
    4. B(OMe)₃ (1.5 eq)
    5. H₂O₂, NaOH
  - Result: Tetraprotio superbowl

- **Tetraprotio superbowl:**
  - Preparation:
    1. n-BuLi (2.2 eq)
    2. B(OMe)₃ (3.0 eq)
    3. H₂O₂, NaOH
  - Result: Tetraphenol superbowl

- **Wall-cavitand for tetraprotio superbowl:**
  - Preparation:
    1. n-BuLi (1.1 eq)
    2. PrOH (1.1 eq)
    3. n-BuLi (1.1 eq)
    4. B(OMe)₃ (1.5 eq)
    5. H₂O₂, NaOH

- **Wall-cavitand for tetraphenol superbowl:**
  - Preparation:
    1. n-BuLi (1.1 eq)
    2. B(OMe)₃ (1.5 eq)
    3. H₂O₂, NaOH

---

2,87
Generally, the reported syntheses of superbowl molecules were 6-8 steps in length from the known and commercially available tetrabromo cavand. The overall yield varied between 10-20%.

### 2.1.2.5 Previous Host-guest Binding Studies of Superbowl Molecules

The large non-collapsible cavities of superbowl molecules were expected to offer new opportunities in guest binding. As a starting point for binding studies, the guests that were encapsulated successfully in the hexameric resorcinarene and pyrogallolarene capsules were examined (Section 2.1.1). A range of tertiary amines and bromide salts were thus surveyed for their binding affinities with the tetrabromo and tetraprotio superbows using the $^1$H NMR titration technique. Tetrahexyl ammonium bromide ($K = 460 \text{ M}^{-1}$) and tetraoctyl ammonium bromide ($K = 120 \text{ M}^{-1}$) were shown to bind within tetraprotio superbowl (Scheme 2.1.8). No binding was observed for either trihexyl amine or tetrabutylantimony bromide within the tetraprotio superbowl. Furthermore, none of these four compounds showed binding within tetrabromo superbowl (Scheme 2.1.7).  

### 2.1.2.6 Failed Attempts to Cap the Superbowl

At that time, investigations into placing one more cavitand on top of the superbowl to cap it and thus make the closed covalently-bonded hexameric capsule were also carried out without success (Scheme 2.1.9).  

---

**Scheme 2.1.9.** Attempts to close the hexameric capsule
2.1.3 Studies towards Hexameric Capsule from other Research Groups

In 2005, one year after our publication of the superbowl synthesis, Sherman and a co-worker reported a short synthetic route towards a hexameric capsule that involving statistical and low yielding reactions (Scheme 2.1.10)\textsuperscript{10}. The hexameric capsule isolated from the reaction was shown by NMR to encapsulate seven DMSO molecules and varied number of water molecules inside its cavity.

![Scheme 2.1.10. Sherman’s hexameric capsule](image)

According to Sherman, the hexameric capsule could be considered a hemicarcerand\textsuperscript{3} to water, since the water molecules inside could be exchanged with a conformational change of the hexameric capsule. No evidence for DMSO exchange was observed.

One year after that, in 2006, the Warmuth research group reported a ‘one-pot synthesis’ of a hexameric nano-container built from cavitands with diimine linkages (Scheme 2.1.11).\textsuperscript{12}
Scheme 2.1.11. Warmuth’s hexameric nanocontainer

The one-step self-assembly of six tetraformyl cavitands to form the hexameric nanocontainer was impressive. However, the lengthy diimine bridges render this structure more akin to an open cage than a container molecule. Thus, solvent (guest) molecules can enter and exit the cage freely through the big gaps between the cavitand units.

In summary, the hexameric structures of Sherman and Warmuth can be prepared through short synthetic sequences, they have limited value in host-guest chemistry. Sherman’s hexameric capsule can only exchange water molecules and Warmuth’s hexameric structure allows free guest exchange through a cage structure with eight wide-open portals. Atwood’s hexameric capsule is superior in terms of guest binding ability.

Regarding our work prior to this study, the original synthesis of superbowl was indeed a significant achievement. The lengthy and scale-limited synthetic sequence, however, only allowed access to ~ 100 mg of superbowl. Clearly, a more practical synthesis is required. Furthermore, each different rim-substituted superbowl (Schemes 2.1.7 and 2.1.8) requires a different synthesis. A much more effective approach would involve the generation of various superbows from the tetrabromo superbowl precursor. We also have very limited knowledge of superbowl host-guest chemistry (Section 2.1.2.5). It should be noted that despite the great interest in this area, no one, to the best of our knowledge, has reported evidence for the binding of any biologically relevant guests within cavitand-derived hosts.
2.1.4 Objectives of this Project

The project described in this chapter was carried out with aims to:

• Optimize the synthesis of tetrabromo superbowl so it could be produced in practical amounts.
• Develop a convenient method to functionalize tetrabromo superbowl so various rim-substituted superbows could be easily accessed.
• Study the effect of rim-substitution on the guest-binding ability of superbowl molecules
• Seek evidence that the superbows will bind biologically relevant guests

It was anticipated that these studies would promote future applications of superbows in molecular recognition, catalysis and drug delivery.

2.2 Towards a Practical Synthesis of Tetrabromo Superbowl

Several steps in the synthetic sequence to make tetrabromo superbowl were optimised and modified to achieve higher yields or simpler purification methods. The work described in Sections 2.2.1 and 2.2.2 were carried out in collaboration with Mr. Hiroshi Yoshida, another PhD candidate in our research group with 50% contribution from each party. The collaborative work is illustrated by an asterisk in brackets (*).

2.2.1 Modified Synthesis of Tetrabromo Cavitand (*)

The modifications from the previously reported synthesis within the group² (Scheme 2.1.5) of tetrabromo cavitand 2.3 are depicted in Scheme 2.2.1 below:
Scheme 2.2.1. Modified synthesis of tetrabromo cavitand 2.3

For the conversion of C-pentyl calix[4]resorcinarene 2.1 to C-pentyl tetrabromo calix[4]resorcinarene 2.2, the previous method used slow addition of N-bromosuccinimide to a 2-butanone solution of the resorcinarene to carry out the electrophilic aromatic bromination. This reaction was done with external cooling to 0 °C over 18-24 hours in the dark. A newly developed method allowed this transformation to take place at room temperature over 2-4 hours by not moderating the reaction exotherm. N-bromosuccinimide was added rapidly to a 2-butanone solution of resorcinarene without cooling, and the reaction proceeded much faster with comparable outcomes. It was rationalized that the exothermic nature of the aromatic bromination reaction made it a self-heated reaction. The higher temperature did not negatively affect the bromination but facilitated it to go faster instead. Furthermore, the irritant 2-butanone solvent could be replaced with tetrahydrofuran or acetone with comparable yields.

Tetrabromo cavitand 2.3 was previously synthesized by a simple reaction with excess bromochloromethane (more than 300 molar equivalents) and potassium carbonate (more than 30 molar equivalents) in N,N'-dimethyl formamide solution. However, since bromochloromethane was recently listed as an ozone-depleting reagent, it is not easily accessible in Australia and the consumption of large amounts could have a negative impact on the natural environment. Hence, the replacement of this reagent with other chemicals as well as attempts to reduce the amount used were examined during this project. Based on a report of an improved synthesis of cavitands, dichloromethane was used to good effect for this cavitand formation reaction on small scale (less than 3
grams) at high temperature (90 °C) and high-pressure conditions, providing a very good yield (~ 90%). Due to the low boiling point of dichloromethane, a sealed tube or a high-pressure reactor are required, thus limiting the scale of the reaction. Dibromomethane was also tested but gave a lower yield for cavitand formation (~ 55-65%), although there was no scale limitation for the reaction.

In an attempt to reduce the bromochloromethane loading for cavitand formation, a temperature programmed reaction profile was developed. Since the boiling point of bromochloromethane is quite low (68 °C), most of it was lost to evaporation during the reaction at 65 °C. It was also known that the first three bridges of cavitand molecule are much easier to form than the last (fourth) one. Hence, the modified reaction was run at 40-45 °C to form the first three acetal bridges, then heated to 65 °C with additional bromochloromethane to finalize the cavitand formation. This temperature-controlled method helped to reduce the amount of bromochloromethane used to less than 70 equivalents while still resulting in yields (~ 70%) comparable to the original procedure.

The purification of tetrabromo cavitand was significantly improved. The previous method required column chromatography to isolate the tetrabromo cavitand from the crude product. This limited the amount of the crude product that could be practically purified to less than 30 grams. A few other purification methods were employed successfully, creating opportunities to scale up the reaction. For example, Sohxlet extraction of crude product with suitable solvent systems (normally 10% EtOAc or 10% dichloromethane in hexane) gave the tetrabromo cavitand with up to 95-98% purity with scale between 50-80 grams. Fractional recrystallization of tetrabromo cavitand from DMF solution of the crude product, followed by a short silica-plug filtration to remove DMF, was done successfully on 100-200 gram scale, giving the product with purity up to 99%.

In summary, the synthesis of tetrabromo cavitand was improved so that the reactions can be scaled up to hundred gram syntheses without any column chromatography involved, making the synthesis feasible in industry.

2.2.2 Modified Synthesis of the Wall Cavitand (*)
In the previous reported method, the wall cavitand was synthesized in a three-step sequence from tetrabromo cavitand (Scheme 2.1.5). Column chromatography was employed for product purification in all three steps. Modifications of that procedure are depicted in Scheme 2.2.2.

Scheme 2.2.2. Modified synthesis of wall cavitand 2.6

No significant modification was done to improve the synthesis of wall-cavitand 2.6, since the first and third steps in this sequence with lithium-bromine exchange were scale-limited. The yields quoted are optimised yields for 10-15 mmol (~ 11-16 grams) scale for the first reaction and 5-7 mmol (~ 5-7 grams) scale for the third reaction. When the reaction was scaled up, the yield was dramatically decreased, especially for the A,C-difunctionalization step to give other over- and under-hydroxylated cavitands. This could possibly be rationalized by the effect of local n-BuLi concentration on the selectivity of the A,C-difunctionalization. When the reaction scale was larger than 10 mmol and the stirring was not controlled well, added n-BuLi has a high local concentration (higher than 2 equivalents relative to the cavitand) at some points in the bulk solution. The lithium-bromine exchange is very fast (experimental result showed that 5-30 seconds were enough for reaction to finish on 1-3 mmol scale) so the high local concentration caused the selectivity for two distal lithium-bromine exchanges to decrease.
Some minor improvements, however, were made in the second step. The previous method used pure methoxymethyl chloride (MOMCl). This reagent is not commercially available in Australia. The previous synthesis of this reagent required a potentially hazardous protocol involving prolonged heating fractional distillation to purify this volatile carcinogenic and moisture-sensitive reagent. During this project, a simple and convenient synthesis of MOMCl solution in toluene was successfully carried out based on a synthetic route reported by Berliner and co-workers. The synthesis was much shorter without any purification steps and the crude MOMCl solution could be used directly to protect the A,C-dibromo diphenol cavitand 2.4, resulting in a product mixture from which cavitand 2.5 can be recrystallised cleanly with yields of up to 92%.

2.2.3 Modified Synthesis of the Base Cavitand

The previous synthesis of the base cavitand was a three-step sequence without any column chromatography (Scheme 2.1.4). Though the previous synthesis of the base cavitand was effective, an issue arose that required modification of the reaction conditions. Carbon tetrachloride was listed as an ozone depleting agent and is thus not accessible in Australia. Thus, other solvents were examined to achieve the four-fold free radical bromination in high yield. After some experimentation, it was found that the free radical bromination could be carried out in dichloromethane solvent with comparable results as in carbon tetrachloride. The new reaction conditions required radiation from a tungsten lamp (Scheme 2.2.3, see Experimental Section for more details).

Scheme 2.2.3. Modified synthesis of the base cavitand 2.8

2.2.4 Modified Synthesis of Tetrabromo Superbowl

From the wall and base cavitands, three more steps were required to synthesize tetrabromo superbowl, as depicted in Scheme 2.1.7. No change was made to the first
and the third of these steps but the second step was modified as depicted in 
**Scheme 2.2.4.** The previous synthesis\(^2\) involved three cycles of trifluoroacetic acid in 
MeOH/DCM solvent system for complete removal of the MOM ethers. New reaction 
conditions were developed where all MOM ethers could be cleaved by a trace amount 
of concentrated aqueous HCl (36.5\%) in MeOH/DCM solution at 40 °C, giving a 
comparable yield (~ 95\%) in a much shorter period of time than the original protocol.

**Scheme 2.2.4.** Modified synthesis of tetrabromo superbowl 2.11
All of these three reactions were also scaled up without any decrease in yield and without increased complexity of purification. In that manner, this linear synthetic sequence was used to synthesize tetrabromo superbowl on 1-3 gram scale. (Mr Hiroshi Yoshida further scaled up this sequence to prepare 5-6 gram batches of tetrabromo superbowl).

2.3 Attempts to Functionalize Tetrabromo Superbowl

After successfully modifying the synthetic sequence to make tetrabromo superbowl on gram scale, the attention of this project was turned towards developing methods for the direct conversion of tetrabromo superbowl into new members of the superbowl family.

Previous reports within the group\(^2,8^7\) have already demonstrated the ability of superbowsls to accommodate numerous small solvent molecules. Tetraprotio superbowl also showed relatively strong binding with bulky tetraalkyl ammonium bromide species. Interestingly, tetrabromo superbowl showed no detectable binding with these guests. This observation encouraged us to vary the structure and functional groups of superbowsls and to investigate how these changes affect their ability to bind guest molecules.

It was concluded from the previous studies\(^2\) that lithium-bromine exchange with n-BuLi was not a useful means to functionalize tetrabromo superbowl. The earlier studies\(^2\) reported that treatment of tetrabromo superbowl with n-BuLi followed by quenching with electrophiles usually gave complex mixtures of products. Hence, the initial goal of this project was to re-investigate this method and develop an alternative method to perform functionalization of tetrabromo superbowl.

2.3.1 Free Radical Chemistry to Access the Family of Partially Brominated Superbowl Molecules

Since tetraprotio superbowl showed relatively strong 1:1 binding with some tetraalkyl ammonium salts while tetrabromo analogue showed no binding, it is obvious that the bromine substituents either sterically and/or electronically hindered guest binding.
examine this effect more closely, a family of superbowl molecules with different numbers of bromines around the portal (2.12-2.16, Scheme 2.3.1) was produced using free radical chemistry in a statistical debromination reaction of tetrabromosuperbowl.

**Scheme 2.3.1.** Free radical reductive debromination of tetrabromo superbowl 2.11

A brief summary of reaction outcomes using different stoichiometries of tributyl tin hydride is listed in Table 2.3.2.

<table>
<thead>
<tr>
<th>Superbowl derivatives</th>
<th>Molar equivalent of Bu₃SnH</th>
<th>1.1 eq (*)</th>
<th>2.2 eq (*)</th>
<th>3.3 eq (*)</th>
<th>4.4 eq (*)</th>
<th>16 eq (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Br (2.11)</td>
<td>30%</td>
<td>3%</td>
<td>1%</td>
<td></td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3Br1H (2.12)</td>
<td>44%</td>
<td>21%</td>
<td>12%</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A,B-2Br2H (2.13)</td>
<td>3%</td>
<td>18%</td>
<td>15%</td>
<td>11%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A,C-2Br2H (2.14)</td>
<td>7%</td>
<td>25%</td>
<td>18%</td>
<td>9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1Br3H (2.15)</td>
<td>1%</td>
<td>12%</td>
<td>28%</td>
<td>12%</td>
<td>3%</td>
<td></td>
</tr>
<tr>
<td>4H (2.16)</td>
<td>3%</td>
<td>7%</td>
<td>43%</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.3.2.** Free radical debromination of tetrabromo superbowl 2.11. (*) Percentage ratios obtained from HPLC peak area integration. (#) Percentage ratios obtained from ¹H NMR integration.

Flash column chromatographic separation of the product mixtures is possible but a lengthy process. Separation by HPLC was found to be more convenient. Since the
purpose of this statistical free radical reductive debromination was solely to obtain the partially brominated family of superbowsls, these reactions were not optimised. This family of partially brominated superbowsls were then subjected to binding studies with various guests (Sections 2.4 and 2.5)

2.3.2 Magnesium-Bromine Exchange with Knochel’s Reagent

Knochel’s reagent, iso-propyl magnesium chloride.lithium chloride (iPrMgCl.LiCl), is a much milder organometallic reagent than n-BuLi for the metal-halogen exchange reactions of aryl halides. The results of reactions between Knochel’s reagent and tetrabromo superbowl are listed in Scheme 2.3.3.

![Scheme 2.3.3. Reductive Knochel’s debromination of tetrabromo superbowl 2.11 through organomagnesium intermediates. (*) Percentage ratios obtained from HPLC peak area integration. (#) Percentage ratios obtained from 1H NMR integration.](attachment:image.png)
Figure 2.3.4. Family of brominated superbowsls
The reductive debromination of tetrabromo superbowl using Knochel’s reagent worked well if a large excess of reagent was employed (Scheme 2.3.3). This represents an alternative method to the free radical debromination for production of the brominated superbowl family (Scheme 2.3.4).

Attempts to convert tetrabromo superbowl into tetraphenol superbowl using Knochel’s reagent were unsuccessful. In all cases, a mixture of partially hydroxylated superbows was always obtained, even with 50 molar equivalents of Knochel’s reagent.

It is possible that the big and deep cavity of the superbowl contained several molecules of protic solvents that later consumed Knochel’s reagent during the reaction. It is also possible that due to the aggregation of organomagnesium intermediates formed, steric hindrance around the portal of the superbowl molecule prevented the complete exchange of all four bromines with Knochel’s reagent.

In a concurrent study, Mr. Hiroshi Yoshida was able to use t-BuLi as the organometallic reagent for functionalization of tetrabromo superbowl in a clean, simple and high-yielding method. Hence, the studies with Knochel’s reagent were not pursued further.

2.3.3 Concurrent Superbowl Functionalization Study with tert-Butyl Lithium (method developed by Hiroshi Yoshida)

At the same time as the attempts to functionalize tetrabromo superbowl were being made, another PhD candidate in the group, Mr. Hiroshi Yoshida, was successful in employing t-BuLi to carry out the lithium-bromine exchange on tetrabromo superbowl. The presumed tetralithiated superbowl intermediate was then converted to other tetrasubstituted superbows by quenching with suitable electrophiles. t-BuLi was superior to n-BuLi in this type of reaction for tetrabromo superbowl. More details about this method will be reported by Mr. Hiroshi Yoshida in due course.

Employing the method developed by Mr. Hiroshi Yoshida, a few superbowl derivatives (Scheme 2.3.5) were synthesized within this project to serve as host molecules in guest binding studies (see Sections 2.4, 2.5 and 2.6).
Scheme 2.3.5. Synthesis of various tetrasubstituted superbowsls using methods developed by Mr. Hiroshi Yoshida (2.16, 2.17, 2.18) and the author (2.19)

To more conveniently represent superbowsls in various roles, the superbowl structure will be depicted in several schematic versions as illustrated in Figure 2.3.6.
Figure 2.3.5. Superbowl structure (top), schematic (middle) and stick model (bottom) from side-view and top-view (feet are omitted for clarity)
2.4 Host-Guest Binding Studies with Tetraalkyl Ammonium Bromides

The superbowl molecules were subjected to binding studies with guests, with the first guest candidates being tetraalkyl ammonium bromides. Since this is the first description of this type of work in this thesis, a general discussion about the methods used to investigate the binding of a guest by a host is included in Section 2.4.1.

2.4.1 General Binding Study Methods

The synthetic hosts discussed in this thesis are cavitands and superbows. Cavitands are compounds with a rigid concave $\pi$-basic surface, which bind guests of complementary size and shape. Superbows are composed of five covalently-linked cavitand units and can be considered as a deep cage with a large $\pi$-basic cavity. Hence, any guest that binds inside these hosts has either part of or the whole molecule inside the cavitand/superbowl cavity, which is a $\pi$-electron-rich environment by virtue of the component aromatic rings. The atoms of the guest molecule will be shielded from an external magnetic field, which will make their nuclei resonate at higher field than the free guest. Hence, it is convenient to determine whether or not a guest binds inside a cavitand or superbowl by recording the $^1$H NMR spectrum of the host-guest mixture solution and then comparing this to the spectra of the free guest and free host solutions.

When examining potential binding activity between a host and a guest, one of three possible outcomes will be observed:

- **NO observable binding**: no upfield chemical shift movement of the guest signals.
- **BINDING with slow guest exchange on the NMR timescale**: two sets of the guest signals will appear. One at the usual chemical shifts for the free guest and another with upfield chemical shifts for the guest bound within the cavity.
- **BINDING with fast guest exchange on the NMR timescale**: the guest signals will appear upfield of their 'free' chemical shift due to the averaging of rapidly exchanging bound and unbound guest environments.
Following the initial qualitative binding screen, the magnitude of the binding was then quantified either by a $^1$H NMR titration method or by Isothermal Titration Calorimetry (ITC). Since ITC generally gives much more accurate results for the stoichiometry (binding ratio) and association constant (binding strength) of the binding than does the NMR titration method, it was used as the main method for quantitative binding studies in the work described in this thesis (see Experimental Section for more details on ITC binding studies). ITC also gives results for thermodynamic parameters such as enthalpy and entropy changes of the binding, information not readily obtained by the NMR titration technique.

For each binding study discussed in this thesis, there is always an initial qualitative and a secondary quantitative binding study. It means that a host-guest pair was always checked for Yes/No binding with $^1$H NMR first. If it was a ‘No’ result, then no further binding study was carried out. If it was a ‘Yes’ result, the ITC experiment was then carried out to determine the stoichiometry and the binding constant (see Section 3.3 for further discussion on ITC experiment). In principle, it is possible that the binding could occur without any observable movement of the guest signals. A few host-guest pairs that showed no evidence of binding by $^1$H NMR were selected for re-examination by ITC. The ITC results were consistent with $^1$H NMR binding studies. Hence, the aforementioned possibility can be ruled out.

2.4.2 Previous Binding Studies with Related Hosts

Prior to these studies, the only reported host-guest binding studies with superbowsls were the associations of tetrahexyl and tetraoctyl ammonium bromide guests with tetrabromo (2.11) and tetraprotio superbowl (2.16) hosts. It was interesting to see that in chloroform solutions, tetraprotio superbowl (2.16) showed relatively strong 1:1 binding with tetrahexyl (K ~ 460 M$^{-1}$) and tetraoctyl (K ~ 120 M$^{-1}$) ammonium bromides in CDCl$_3$ while tetrabromo superbowl (2.11) showed no detectable binding with these two alkyl ammonium salts.$^2$

Tetraalkyl ammonium bromide salts are common guests in cavitand-based host-guest chemistry.$^{88}$ They usually show relatively strong binding inside these hosts due to cation-$\pi$ interaction.$^{87,88}$ In a study carried out by the Rebek research group,$^{88}$ the guests
tetrahexyl ammonium bromide and tetraoctyl ammonium bromide were found to bind inside Atwood’s hexameric structure slightly more strongly than in the tetraprotio superbowl, with association constants of 1200 M$^{-1}$ and 150 M$^{-1}$ respectively in water-saturated CDCl$_3$. These higher binding constants are not surprising, given that in the hexameric capsule, hydrogen bonds have to be broken to undergo guest exchange. The water-saturated solution could also strengthen the binding by an additional hydrophobic effect of the alkyl chains.

Rebek and co-workers have published a series of reports$^{83,84,88}$ of binding studies between several guest molecules and Atwood’s hexameric resorcinarene assembly. Notably, tetraheptyl ammonium bromide bound within the H-bonding hexameric capsule with an association constant of 450 M$^{-1}$.$^{88}$

2.4.3 Binding with Superbowls

The superbowl can be considered as a big, deep cage with a portal on top bearing four functional groups of choice. This portal is the doorway for guest entry and egress. While cavitand upper-rim substituents orientate away from the cavity aperture, superbowl upper-rim functional groups orientate towards the aperture at about 20° from the horizontal axis. This leads to the anticipation that varying these functional groups will have great influence on the guest binding of the superbows.

To learn more about the binding of guests within superbows, binding studies of a family of tetra($n$-alkyl) ammonium bromides with linear $n$-alkyl chains varying from 2-8 carbons in length within tetraprotio superbowl 2.16 were carried out (Figure 2.4.1). All of these ammonium salts showed 1:1 binding with tetraprotio superbowl 2.16. Although these guests do not completely fill the internal volume of the superbowl, there are always solvent molecules competing to get inside as well. Presumably, the close proximity of guest molecules inside the superbowl cavity prevents more than one tetra($n$-alkyl) ammonium species to get in at the same time. It should also be noted that the association constants observed by ITC for tetrahexyl ammonium bromide (467 M$^{-1}$) and tetraoctyl ammonium bromide (139 M$^{-1}$) are in agreement with the previously reported values (460 and 120 M$^{-1}$, respectively) obtained from $^1$H NMR titration technique.$^{2,87}$
Figure 2.4.1. Association constants and best-fit stoichiometry ratios for binding between tetraprotio superbowl 2.16 and the family of tetra(n-alkyl) ammonium bromides (ITC, chloroform, 25 °C).

From these binding studies, it is clear that tetrahexyl ammonium bromide is the best guest among this tetra(n-alkyl) ammonium bromide family. There are two factors at play here that can affect the binding strength: 1) how easily the guest can get past the portal to get inside/outside the superbowl and 2) how strong the binding interactions are. Tetrahexyl ammonium bromide among this family is probably the one that has the best combination of molecular size and binding interactions with the host.

Tetrahexyl ammonium bromide was hence used as the guest for binding studies in a series of superbowl molecules with different upper-rim functionalities (Table 2.4.2). Mr. Hiroshi Yoshida in the group provided samples of some tetrafunctionalized superbowl hosts (2.20, 2.21). Dr. Nicholas Kanizaj, another member of the group also provided samples of other superbows with ethylene inter-wall linkers as extended cavitand bridges (2.22-2.27). These expanded superbows were examined to see if conformational change (due to flexibility of these molecules) has any effect on guest binding. These binding studies, as well as all other host-guest binding studies discussed
in this thesis, were carried out qualitatively by $^1$H NMR titration and quantitatively (stoichiometry, association constant, thermodynamic parameters) by the ITC titration method (see Experimental Section – Chapter 6 for more details).

<table>
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<th>P</th>
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</tr>
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</tr>
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</tr>
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</tr>
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<td>CH$_2$</td>
<td>OH</td>
<td>No binding</td>
</tr>
</tbody>
</table>

Table 2.4.2. Association constants (ITC, chloroform, 25 °C) of (1:1) binding between different superbowl molecules with tetrahexyl ammonium bromide in chloroform at 25 °C. (*) compounds provided by Dr. Nicholas Kanizaj. (#) compounds provided by Mr. Hiroshi Yoshida.

Most of these superbows did not show any detectable binding with tetrahexyl ammonium bromide. It can be noticed that any superbowl with four bulky and/or polar
functional groups such as bromines (2.11, 2.22, 2.24, 2.26), methoxy groups (2.19), carbomethoxy groups (2.21) or ethyls (2.18) showed no binding with this guest. It could easily be rationalized that steric and/or electronic effect of these substituents prevented the tetrahexyl ammonium salt from bypassing the upper-rim portal. Among the expanded (ethylene-bridged) superbowls, those with flexible base cavitands (base cavitand having ethylene bridges, 2.25 and 2.27) may be distorted so much in solution that they could not accommodate this large guest. Only the tetraprotio superbowl 2.23 with a robust base cavitand and extended wall-wall linkages (hence bigger guest exchange portal) showed binding with this tetrahexyl ammonium salt. The binding was, however, weaker than that for its analogous methylene-bridged tetraprotio superbowl 2.16, probably also due to the effect of conformational flexibility.

It is very interesting to look at the superbowls that bind the ammonium salt guest (Figure 2.4.3). Evidently, four bromines (2.11) or three bromines (2.12) are too much of a hindrance to guest binding. Two bromines seemed to be the threshold where guest molecules can get past for entry and egress (2.13, 2.14, 2.15 and 2.16). It is instructive to compare superbowl 2.11 and 2.20. While the electron-rich bromine and the 'neutral' methyl group are known to be similar in size, the tetramethyl superbowl 2.20 showed binding whereas tetrabromo superbowl 2.11 did not. This clearly indicates that the electronic effect of bromine has greater impact than does the steric effect. When the alkyl substituents were longer than one carbon (tetraethyl superbowl 2.18), the magnitude of the steric effect, however, becomes more significant as evidenced by the absence of binding of tetrahexyl ammonium bromide (Figure 2.4.3).

Tetraphenol superbowl 2.17 showed no detectable binding with tetrahexyl ammonium bromide. ITC titration of the guest into this superbowl host solution resulted in endothermic signals. This is possibly the evidence of tetraphenol superbowl 2.17 forming dimers/oligomers in the solution phase, due to good ability to form intermolecular H-bonds of the OH groups. Further discussion about this observation will be detailed in Section 2.5.4.
Figure 2.4.3. Interesting binding trends of superbowsls with tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

In summary, the binding studies between superbowsls and tetraalkyl ammonium bromides have provided a deeper understanding of the effect of guest size, electronic and steric hindrance of substituents as well as the number of substituents around the portal on the binding strength. This knowledge will be very useful for future investigations into applications of superbowsls as models for drug delivery, molecular recognition and catalysis.

2.5 Host-guest Binding Studies with Medicinal Agents

The project moved on to investigate the binding of biologically relevant guests to superbowl molecules. Small molecule medicinal agents likely to be encapsulated within the binding cavity were examined.

2.5.1 Binding Screens with Common Drugs
Numerous small over-the-counter (OTC) medicinal agents (Table 2.5.1) were screened for binding with superbows. The preliminary binding studies were done by the $^1$H NMR technique between these drugs and tetrabromo superbowl 2.11 as well as tetraprotio superbowl 2.16. Interestingly, only the aspirin/tetraprotio superbowl 2.16 pair showed binding out of thirteen different drugs and two hosts tested (Table 2.5.1). This is the very first report of a medicinal agent binding inside cavitand-related hosts.

Table 2.5.1. OTC drugs tested for binding with superbows 2.11 and 2.16 in chloroform. Binding was confirmed by upfield chemical shift movement of the guest signals in the $^1$H NMR spectrum
The binding of aspirin within tetraprotio superbowl 2.16 was then further examined using VT-NMR. Based on VT-NMR studies of binding with tetraprotio superbowl 2.16 (Figure 2.5.2), aspirin undergoes fast exchange at 25 °C and slow exchange at -50 °C on the NMR timescale. At 25 °C, all observable aspirin 'H NMR signals are broad due to the exchange between the bound and unbound/free forms. At -50 °C, the bound aspirin signals appear at almost 4 ppm upfield from their original unbound chemical shifts, due to the shielding effect of the electron rich superbowl cavity. The presence of these two bound and unbound sets of signals at low temperature is strong evidence for the binding of aspirin inside the superbowl cage. The proton signals for the superbowl host also changed slightly with guest encapsulation.

![NMR Spectra](image)

**Figure 2.5.2.** VT-NMR studies of aspirin binding inside tetraprotio superbowl 2.16 (500 MHz, CDCl₃)

Although the volume of the superbowl’s inner cavity is large enough to encapsulate several aspirin molecules, only 1:1 binding is observed (binding ratio is confirmed by an ITC experiment). While it is geometrically possible for another aspirin molecule to
enter the cavity, no evidence of more than one aspirin molecule encapsulated within the superbowl was obtained. It appears that the presence of one aspirin molecule inside the cavity has an inhibiting effect upon binding by a second one. The high binding affinity of chloroform solvent within the π-basic cavity (Section 1.7) could also play some role in this complexation. The ratio of chloroform solvent to aspirin guest is approximately 1000:1 in the solution under scrutiny. This aspect reveals the superior binding ability of the aspirin molecule compared to chloroform. On the other hand, the binding competition from solvent molecules might prevent the second aspirin molecule to get inside the superbowl. This requires further examination in future studies.

Aspirin comprises two functional groups attached to a benzene ring: a carboxylic acid and an acetoxy group. It is interesting that while aspirin shows relatively strong 1:1 binding with superbowsls, neither of the two compounds containing only one functional group - benzoic acid and phenyl acetate (Figure 2.5.3) - shows detectable binding within tetraprotio superbowl 2.16. Apparently, both functional groups are required for binding. It is even more interesting that the meta and para isomers of aspirin (2.28 and 2.29, Figure 2.5.3) do not show binding with tetraprotio superbowl 2.16. It appears that the two functionalities have to be arranged ortho to one another for the binding event to occur.

![Chemical structures](image)

Figure 2.5.3. Structures of aspirin-related compounds. The known compounds 2.28 and 2.29 were synthesized for binding studies (See Experimental Section for more details)

From these results and inspection of CPK models, we propose a two-point binding mode for the special complexation of aspirin within superbowl. This proposal is supported by experimental evidence from NMR and additional binding studies (vide infra) (Section 2.5.3). The binding mainly involves the electron rich base cavittand cavity and the -CH₃O- linkages between the base and wall cavittands of the superbowl.
One aspect of this binding is a H-bonding interaction between the carboxylic proton of aspirin and the oxygen atom on the aforementioned -CH₂O- linkages. The other involves a C-H⋯π interaction between the acetyl methyl group of the aspirin molecule and the electron rich cavity of the base cavitand (Figure 2.5.4).

![Proposed two-point binding mode of aspirin inside tetraprotio superbowl](image)

**Figure 2.5.4.** Proposed two-point binding mode of aspirin inside tetraprotio superbowl

### 2.5.3 Proving the Two-Point Binding Mode by NMR Studies

Initial evidence for the two-point binding mode was revealed in the VT-NMR studies (Figure 2.5.2). From the spectrum of aspirin/tetraprotio superbowl mixture at -50 °C, it can be seen that the signals for the bound aspirin protons appear upfield from those of unbound aspirin, due to the shielding effect of the superbowl aromatic rings:

- The bound acetyl methyl protons appear about 4.3 ppm upfield of those in the free guest.
- The bound carboxylic acid proton appears about 3.7 ppm upfield of those in the free guest.
- The bound aromatic protons appear about 1.5-3 ppm upfield of those in the free guest.
Hence, it is clear that the carboxylic acid group and the acetyl methyl group are much closer to the shielding zone of the superbowl than is the aromatic ring of the guest, which is consistent with the two-point binding mode depicted in Figure 2.5.4.

NOESY NMR spectroscopy is generally a useful technique to obtain information about guest orientation inside a host. In this particular case, however, the complexity of the NMR spectrum (Figure 2.5.2 (d)) precludes the identification of noe signals between host and guest. Therefore, NOESY NMR study was not performed for this system.

To derive more evidence for the two-point binding mode, a line-broadening NMR technique was employed. Line-broadening NMR techniques are powerful methods to study the structure and conformational changes of proteins.100,101 The line-broadening NMR technique used in this project is an operationally simple method of adding a very small amount of the host (superbowl) to the guest (aspirin) solution. Due to the fast interconversion between the bound and unbound guest at room temperature (Figure 2.5.2 (c)), the NMR signals for the guest will be broadened. By correlating the magnitude of the guest signal line-broadening with the amount of added host, useful information about the orientation of the guest relative to the host can be obtained (See Experimental Section for more details). The more broadened the signal, the closer the proton associated with that signal to the shielding zone of the superbowl cavity.

In Figure 2.5.5, linewidth changes (ratio of broadened linewidth relative to original free aspirin linewidth) for individual protons were plotted against the aspirin/host ratio. It is clear that the acetyl methyl of the aspirin is the closest to the shielding zone of the superbowl cavity.
Figure 2.5.5. Line-broadening NMR studies of aspirin/superbowl 2.16 host mixture (500 MHz, CDCl₃, 25 °C)

Among the aromatic protons, the line-broadening levels decrease in the order: H1 ~ H3 > H2 ~ H4. This order is consistent with the two-point binding mode depicted in Figure 2.5.6.

2-point binding: Hydrogen bonding and C-H/π interaction

Figure 2.5.6. A two-point binding mode can rationalize the observed line-broadening effects of the superbowl upon aspirin 'H-NMR signals.
2.5.4  Binding of Aspirin within other Superbowls

Aspirin is a relatively small and almost planar species (Scheme 2.5.7). It is proposed that the binding of aspirin inside superbows involves a two-point binding mode (vide supra).

![Diagram: Postulated binding of aspirin within superbowl cavity in chloroform solution](image)

**Scheme 2.5.7.** Postulated binding of aspirin within superbowl cavity in chloroform solution

From these geometrical considerations, it is predicted that the steric effects of the superbowl upper-rim substituents on the binding of aspirin would be smaller than those effects on the binding of the bulky tetrahexyl ammonium bromide. In order to probe the effects of upper-rim substitution and conformational mobility on the binding affinity towards aspirin of the superbowl hosts, we screened a family of structurally diverse superbows. The results of these aspirin binding studies are summarized in **Table 2.5.8**. The results of binding studies with the bulky, non-planar guest tetrahexyl ammonium bromide are also included for comparison purposes.
Data in Table 2.5.8 reveals several distinct trends. Firstly, the superbowl molecules that bind tetrahexyl ammonium bromide generally bind aspirin as well, with the notable exception of hosts 2.25 and 2.27. Secondly, aspirin usually binds more strongly within superbowls than does tetrahexyl ammonium bromide. We suggest that this superior binding ability of aspirin is related to both size and shape complementarity of the guest.

Table 2.5.8: Association constants (ITC, chloroform, 25 °C) of (1:1) binding between different superbowl molecules and aspirin (K) or tetrahexyl ammonium bromide (K'). (*) compounds provided by Dr. Nicholas Kanizaj. (#) compounds provided by Mr. Hiroshi Yoshida.

<table>
<thead>
<tr>
<th>Host</th>
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<th>Y</th>
<th>Z</th>
<th>P</th>
<th>K2(M-')</th>
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<td></td>
</tr>
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</tr>
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(*) compounds provided by Dr. Nicholas Kanizaj. (#) compounds provided by Mr. Hiroshi Yoshida.
as well as the two-point binding mechanism within the superbowl cavity. In turn, we will discuss superbowl hosts that do not bind either of the guests under examination, followed by hosts that selectively bind aspirin. Finally, we will discuss the instructive examples of hosts that bind both guests.

As was observed with the tetraalkyl ammonium guest (Section 2.4.3), an examination of Table 2.5.8 shows that superbowl hosts with more than two bromine substituents on the upper-rim (2.11, 2.12, 2.22, 2.24, 2.26, Table 2.5.8) show no detectable binding with aspirin. It is clear that bromine substituents again seem to be of electronic and/or steric impediment to the complexation of aspirin. Similar results are observed for the superbowl hosts with four bulky substituents such as ethyl groups (2.18), methoxy groups (2.19) and carbomethoxy groups (2.21).

A definitive explanation of why hosts 2.25 and 2.27 bind aspirin but show no detectable binding with tetrahexyl ammonium bromide eludes us. It is, however, possible that hosts 2.25 and 2.27, with their extended ethylene bridging units (Figure 2.5.9), are conformationally distorted in the solution phase. We suggest, therefore, that the encapsulation of a small molecule like aspirin is possible but that the bulky tetrahexyl ammonium bromide cannot be accommodated within the geometrically constrained cavities of these two hosts.

![Figure 2.5.9. Structures of superbows 2.23, 2.25, 2.27, ethylene bridging units highlighted](image)

Host 2.23 with a similar methylene-bridged base cavitand to tetraprotio superbowl 2.16 but having a bigger portal (due to the ethylene inter-wall linkages, Figure 2.5.9) showed stronger binding ($K_2 = 470 \text{ M}^{-1}$) with aspirin than did tetraprotio superbowl 2.16.
(K₂ = 309 M⁻¹). It could be rationalized that a bigger portal facilitates aspirin entry into the superbowl cavity. In contrast, hosts 2.25 and 2.27 (Figure 2.5.9), with increased conformational mobility at the base cavitand, conferred by ethylene linkages, showed significantly weaker binding (K₂ = 138 M⁻¹ and 130 M⁻¹, respectively) with aspirin than did prototype tetraprotio superbowl 2.16. These observations are in harmony with the two-point binding mode where the binding predominantly involves the base cavitand unit and base-wall linkages (Figure 2.5.4). We conclude, therefore, that the presence of a more flexible base cavitand unit (in hosts 2.25 and 2.27) weakens the binding forces with aspirin.

Again, the brominated superbowl (2.11-2.16) and the tetraalkyl superbowl (2.16, 2.18, 2.20) families showed interesting binding trends with aspirin (Figure 2.5.10). The portal substituent effects on binding ability threshold are similar to that for tetrahexyl ammonium bromide (Figure 2.4.3).

![Figure 2.5.10. Interesting binding trends of superbowsls with aspirin](image)

The different steric effects of upper-rim substituents on the binding of tetrahexyl ammonium bromide and aspirin are most obvious when we consider the examples of
A,B-dibromo diprotio superbowl 2.13 and A,C-dibromo diprotio superbowl 2.14. Tetrahexyl ammonium bromide binds more weakly in A,C-dibromo diprotio superbowl 2.14 ($K_1 = 49 \text{ M}^{-1}$) than in A,B-dibromo diprotio superbowl 2.13 ($K_1 = 79 \text{ M}^{-1}$). We propose that the distal positioning of two bromines (2.14, Figure 2.5.11) hinders the entry of the bulky tetrahexyl ammonium bromide more so than does the proximal arrangement of upper-rim bromines (2.13, Figure 2.5.11). If this argument is sound, the arrangement of two bromine substituents will have insignificant effect on the entry and egress of the relatively small aspirin guest. Indeed, the two superbowl hosts 2.13 and 2.14 exhibit comparable binding strengths to aspirin ($K_2 = 94 \text{ M}^{-1}$ for 2.13 and $K_2 = 96 \text{ M}^{-1}$ for 2.14, Table 2.5.8).

The most curious case among all these binding studies is the unexpectedly strong binding of aspirin by host 2.20 ($K_2 = 485 \text{ M}^{-1}$) while this superbowl only showed relatively weak binding with tetrahexyl ammonium bromide ($K_1 = 89 \text{ M}^{-1}$). This result
may be rationalized as follows: the binding of bulky tetrahexyl ammonium bromide is inhibited by the steric hindrance of four methyl groups. This effect is much reduced for a small guest like aspirin (Figure 2.5.11). We also propose that extra C-H⋯π interactions between the methyl groups around the portal and the electron poor aromatic ring of the aspirin may take place during guest entry and egress, thus strengthening the binding.

Tetraphenol superbowl 2.17 (Figure 2.5.11) binds neither guest. Its ability to form inter-host H-bonds between hydroxy groups, suggested by inspection of CPK models, might lead to the existence of tetraphenol superbowl H-bonded dimers/oligomers in solution phase. This hypothesized dimerization prevents the binding and/or detection of guest binding using NMR and/or ITC techniques, despite the fact that the small size of hydroxyl substituents (comparable to the methyl group) was not anticipated to hinder guest binding. While evidence for the disassociation of this postulated H-bonding dimer was observed during ITC studies (endothermic peaks); attempts to form charged-hydrogen-bonded complexes in solution to prove the presence of this dimer by NMR failed. Similar observations for the simple cavitands that can form H-bonding dimers/oligomers are discussed in Chapter 3.

In summary, several types of superbows bind the aspirin guest. This suggests potential applications of superbows in the modelling of drug delivery systems. Insight into the effects of portal substituents and conformational mobility on aspirin binding will inspire future structural variation of the superbowl for the purposes of molecular recognition and catalysis.

2.5.5 Investigation of Constrictive Guest Binding within the Superbowl Cavity

Inspection of CPK models reveals that it is geometrically possible for tetrahexyl ammonium bromide and aspirin to pass the portal of tetrabromo superbowl 2.11 to enter the cavity. This superbowl, however, does not show binding with either guest under the studied conditions (chloroform, 25 °C) as reported in Sections 2.4 and 2.5.1. It is suggested that, under these conditions, the guests cannot overcome the energetic barrier, sterically and/or electronically caused by the bromine substituents around the portal, to get inside the cavity. We believe that if the guests get inside the tetrabromo superbowl
under more forcing conditions, it will not be easy for them to get out. These predictions were inspired by Cram’s concept of ‘constrictive binding’ of guests in some host molecules, where forcing conditions such as elevated temperature were required to get the guest inside/outside the host.\(^1\)

Attempts to ‘squeeze’ the guests inside the superbowl cavity were made by heating mixtures of tetrabromo superbowl \textbf{2.11} with guests such as tetrahexyl ammonium bromide or aspirin in DMF solution. DMF was selected as the solvent for these studies since it is known to be a poor guest for cavitand cavities (see \textbf{Section 1.7 in Chapter 1} for more details). In another study, solutions of host/guest mixtures in chloroform were evaporated to dryness at elevated temperature under high vacuum, attempting to vacate the superbowl cavity so the guest(s) could enter. Unfortunately, no evidence of guests encapsulated inside this tetrabromo superbowl \textbf{2.11} was found using these binding methods. Due to time constraints, this will be re-investigated in future studies.

\section{Attempts to Expand the Binding with Superbowl to other Medicinal Agents}

After learning about the special binding of aspirin molecules inside superbowl cavities, several attempts were made to utilize superbowl molecules for binding of other, more exotic biologically relevant guests (\textbf{Figure 2.6.1}). During the course of this project, the biological significance of the aspirin hybrid-drug (\textbf{2.30}) and its analogue (\textbf{2.31}) was noted.\(^{102}\) Although these structures lack the carboxylic acid group for the two-point binding, their biological value prompted us to examine the binding of these compounds within the superbowl cavity (\textbf{Section 2.6.1}). On the other hand, a recent study\(^{103}\) revealed that nicotine molecule has suitable functionalities for an analogous two-point binding mode (\textbf{Section 2.6.2}). Hence, nicotine was also tested for binding with superbows.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{fig261.png}
\caption{Other biologically relevant guests tested for binding with superbows}
\end{figure}
2.6.1 Synthesis and Binding Studies with Superbowls of Aspirin Hybrid Drugs

Aspirin (acetyl salicylic acid - ASA) is a common non-steroidal anti-inflammatory drug used widely because of its therapeutic analgesic, anti-inflammatory and antipyretic effects. Nevertheless, there is little interest in studying drug delivery for medicines like aspirin owing to its ubiquity and ease of ingestion. The idea of combining the structural motifs of aspirin with those of other drugs in order to increase the potency of both in a synergistic manner has been of interest for some time. Such so-called aspirin hybrid drugs were next examined by us.

The syntheses of an anti-cancer candidate drug as a NO-ASA (Nitric Oxide - Acetyl Salicylic Acid) hybrid drug of aspirin (2.30, Scheme 2.6.2) and one of its analogues (2.31) were repeated (Scheme 2.6.3). The potential binding of those drugs inside superbowsls was studied.

![Scheme 2.6.2. NO-ASA hybrid drug of aspirin (2.30), its analogue (2.31) and mechanism of potential anti-cancer activity](image)

Hybrid drug 2.30 (NO-ASA) consists of aspirin (ASA) and a -ONO₂ (NO) group connected through a spacer and is in preclinical development as an antitumor drug. Neither ASA nor NO contributes to this antitumor effect but an unsubstituted quinone methide metabolite was identified as the sole cytotoxic agent. The quinone methide forms in a 1,6-elimination of nitrate anion after an enzymic ester hydrolysis. Analogue
2.31 lacking ASA is, surprisingly, 10 times more effective than 2.30 due to the same mechanism (Scheme 2.6.2).

\[
\text{Scheme 2.6.3. Synthesis of 2.30 and 2.31}
\]

Based on the synthetic route reported, both of these anti-cancer candidates were synthesized with little modification (Scheme 2.6.3, see Experimental Section for detailed syntheses of these compounds).

Unfortunately, these two drugs 2.30 and 2.31 did not show any detectable binding with tetrabromo superbowl 2.11, tetraprotio superbowl 2.16 or tetraphenol superbowl 2.17. Due to time constraints, further binding studies of these anti-cancer agents with other superbows were not performed but it is anticipated that with suitable structural variation, a superbowl could be identified to accommodate these aspirin-hybrid compounds inside its cavity.

2.6.2 Binding Studies with Nicotine and its Hydrochloride Salt
During the course of this project, a 2009 publication from Dougherty and co-workers\(^{103}\) reported evidence for a two-point binding mode of nicotine to brain receptors. That this two-point binding mode involves a cation-\(\pi\) interaction and H-bonding is the possible explanation of why nicotine binds tightly in brain but not in muscle receptors (Figure 2.6.4).

This interesting report encouraged us to investigate the binding of nicotine inside superbowsls, which previously showed binding with aspirin in a similar two-point binding mode.

![Figure 2.6.4](image)

**Figure 2.6.4.** (Left) Image courtesy of Dennis Dougherty) Nicotine forms a cation-\(\pi\) interaction with a tryptophan residue in the binding site of acetylcholine receptors in the brain. A hydrogen bond involving a lysine residue shapes the binding site so that the cation-\(\pi\) interaction can happen.\(^{103}\)

Unfortunately, free-base nicotine did not show any binding with tetraprotio superbowl 2.16. Its hydrochloride salt was prepared to mimic the biologically relevant form of nicotine (Figure 2.6.4), however, this also did not show any binding with 2.16. Probably, the distance between two binding centres on nicotine was too short to allow binding inside superbowl in a similar fashion to aspirin. Due to time constraints, no further binding studies for nicotine and other superbowsls were carried out.

### 2.7 Further Manipulation of Tetraphenol Superbowl Molecule 2.17
After obtaining insightful knowledge about superbowl portal substituents and their effects on guest binding, studies focused on performing further manipulations of tetraphenol superbowl 2.17, based on a synthetic challenge described in Section 2.1.2.6.

2.7.1 Portal Bridges – Revolving Doors at the Guest Entrance

The challenge to make the closed hexameric capsule from tetraphenol superbowl 2.17 (Section 2.1.2.6) has been met in a concurrent study by Mr. Hiroshi Yoshida within the group. The four-fold etherification of one tetraphenol superbowl 2.17 by one base cavitand 2.8 proceeded smoothly to give closed hexameric capsule (Scheme 2.7.1) with several solvent molecules encapsulated inside. This synthesis will be reported by Mr. Hiroshi Yoshida in due course. The successful capping of superbowl by one cavitand by Mr Hiroshi Yoshida. (Bottom) Alternative capping candidates for superbowl
Examination of a tetraphenol superbowl 2.17 CPK molecular model, however, suggested that it does not require a cavitand to cap the superbowl portal. As depicted in **Scheme 2.7.1**, it is possible to use much smaller capping agents to close the superbowl upper-rim aperture. Two capping candidates (2.38 and 2.39) were selected from CPK modelling studies (Figure 2.7.1). Although modelling studies revealed that the capped systems with these candidates would be somewhat strained, it is still possible to construct the molecules.

Tetra(bromomethyl) benzene 2.39 is commercially available. 3,3',5,5'-Tetra(bromomethyl)biphenyl 2.38 was synthesized within this project by an efficient route that was inspired by a literature report (Scheme 2.7.2, see Experimental Section for more details):

![Scheme 2.7.2. Synthesis of capping candidate 2.38](image)

Several attempts to make the capped superbowls using compound 2.38 or 2.39 (Scheme 2.7.1) as caps, however, met with limited success. Only traces (less than 3%) of what could likely be the capped superbowls were observed in the complex reaction mixtures.

**2.7.1.1 From Capping to Bridging the Superbowl**
To better understand the etherification of tetraphenol superbowl 2.17 with bromomethyl arenes, a range of different α,α'-dibromo xylene regioisomers were chosen to react with tetraphenol superbowl under the same reaction conditions as those used in capping attempts (Scheme 2.7.1). It was surprising and exciting to see that all three para, meta and ortho isomers reacted cleanly with tetraphenol superbowl 2.17 and in high yield to give a family of interesting upper-rim bridged superbows (2.43-2.45, Scheme 2.7.3). It is also worth noting that these bridged superbows were always the major products of the reactions, independent of the number of molar equivalents of α,α'-dibromo xylene reagents (two equivalents to more than 100 equivalents). Hence, it is clear that following the first etherification, intramolecular substitution happens much faster than do competing intermolecular processes. This characteristic feature could be very useful for future plans to vary the superbowl structure.

Scheme 2.7.3. Xylyl-bridging of superbowl molecules at the upper-rim with para (2.43), meta (2.44) and ortho (2.45) xylyl linkages
2.7.1.2 Conformational Studies of Bridged-Superbowls

Inspection of CPK models suggests that the rotation of the newly-introduced aromatic rings about the $\text{OCH}_2$ linkages is possible. These 'xylyl' aromatic rings could rotate around at the portal and hence serve as 'revolving doors' at the guest entrance of the superbowl structure. These CPK models indicate that the energy barrier towards rotation decreases from \textit{ortho} (2.45) > \textit{meta} (2.44) >> \textit{para} (2.43) isomers. These predictions were confirmed by VT-NMR studies as depicted in Figure 2.7.4. Figure 2.7.4 clearly shows that in all three cases, broadening of the $^1\text{H}$ NMR signals is observed at low temperature (-50 °C). In addition, changes in the chemical shifts of the proton signals are witnessed. Levels of line-broadening are consistent with the following rotation energy barrier order: \textit{ortho} (2.45) > \textit{meta} (2.44) >> \textit{para} (2.43)

Figure 2.7.4. Pertinent sections of VT-NMR spectra for xyyl-bridged superbows 2.43-2.45 at 25 and -50 °C (CDCl$_3$, 500MHz): level of line-broadening is proportional to the energy barrier for bridge rotation (CHCl$_3$ signals at 7.26 ppm remain sharp at low temperature)
NOESY NMR studies suggest that the dominant conformation of these xylyl-bridged superbowsls are as drawn in **Scheme 2.7.3**. For example, the NOESY-NMR spectrum of compound **2.44** (Figure 2.7.5), with *meta*-xylyl bridges, showed an nOe interaction between the protons on the acetal bridges of the wall cavitands and 2-H (conformer **2.44b**) of the *m*-xylyl aromatic rings. In contrast, the same interaction with other protons on the *m*-xylyl aromatic rings (4-H, 5-H, 6-H - conformer **2.44a**), were not observable (Figure 2.7.5). This is consistent with CPK models, in that the xylyl-benzene rings of conformer **2.44a** experience a steric clash with the acetal bridges of the wall cavitands. Such clashes are absent in conformer **2.44b**.

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Figure 2.7.5. Conformation studies by NOESY-NMR of compound 2.44
Reconsidering the capping of tetraphenol superbowl 2.17 with tetra(bromomethyl) arenes 2.38 and 2.39 (Scheme 2.7.1), it is possible that, after forming two –OCH₂-linkages, the energy barrier for the transition state to form the third (and fourth) –OCH₂-linkage would be very high. The formation of the capped superbowl structure, hence, is disfavoured. In principle, this problem could be overcome by using more flexible tetra(bromomethyl) arene capping agents. Due to time constraints, however, this possibility was not pursued further.

2.7.1.3 Guest Binding of Bridged-Superbowls

The novel xylyl-bridged superbowl compounds 2.43-2.45 were then subjected to binding studies with both tetrahexyl ammonium bromide and aspirin in order to explore their value in host-guest chemistry. The binding studies were carried out using ¹H NMR and ITC techniques, as described in Section 2.4.1.

None of these xylyl-bridged superbowl compounds 2.43-2.45 showed any detectable binding with tetrahexyl ammonium bromide. In certain cases, the xylyl-bridges presumably exhibit significant steric hindrance to guest entry through the now much narrower portals of the superbowl derivatives (Figure 2.7.6). We postulate that a bulky guest like tetrahexyl ammonium bromide does not get past these portals. It is, however, of obvious value to see whether a smaller tetraalkyl ammonium salt could bind inside the superbowl cavities. Due to time constraints, this will be explored in future studies.
Figure 2.7.6. Space-filling (CPK) models of tetraphenol superbowl (2.17, top-left), para-xylyl bridged superbowl (2.43, top-right), meta-xylyl bridged superbowl (2.44, bottom-left) and ortho-xylyl bridged superbowl (2.45, bottom-right). The portal sizes in the ortho and meta xylyl-bridged derivatives are visibly smaller than that in the tetraphenol superbowl (2.17) precursor, whereas portal narrowing is less significant for the para isomer. H atom = white, O atom = red and C atom = black. The pentyl feet are omitted for clarity.

Neither the meta-xylyl bridged superbowl (2.44) nor ortho-xylyl bridged superbowl (2.45) showed any detectable binding with aspirin. Pleasingly, the para-xylyl bridged superbowl (2.43) showed obvious slow exchange (on the NMR timescale) encapsulation of an aspirin molecule at room temperature, as observed in the $^1$H NMR spectrum of a mixture of this host (2.43) and guest (aspirin) in CDCl$_3$ (Figure 2.7.7). Two sets of bound and unbound aspirin signals are clearly visible. The bound aspirin signals appear significantly upfield from the unbound aspirin signals, due to the shielding effect of the superbowl’s cavity. The chemical shift difference is most dramatic for the acetyl methyl...
group of aspirin, where the bound signal appears almost 4 ppm upfield relative to the unbound signal (Figure 2.7.7). The superbowl signals become broad due to some exchange occurring. An ITC experiment for this binding was also carried out, which gave a binding stoichiometry of 1:1 2.43/aspirin with an association constant of 314 M$^{-1}$, which is comparable to the binding constant of aspirin inside the tetraprotio superbowl 2.16.

![NMR spectra](image)

**Figure 2.7.7.** Pertinent sections of $^1$H NMR spectra for free aspirin (top), free host 2.43 (middle) and a mixture of these host/guest (bottom) solutions (300 MHz, CDCl$_3$, 25 °C): the presence of both bound and unbound aspirin signal indicates the relatively slow exchange on the NMR timescale at room temperature.

It is interesting that only the para-xylyl bridged superbowl 2.43 out of the three isomers showed binding with aspirin. The binding is different than that of the simple (i.e unbridged) superbowl derivatives (Section 2.5) in that slow exchange on the NMR timescale is witnessed here. These fascinating features of host 2.43 could be rationalized through inspection of CPK models of these xylyl-bridged superbowl derivatives (Scheme 2.7.6). For the meta and ortho isomers (2.44 and 2.45), the rotation of –OCH$_2$- linkages is somewhat restricted. Hence the ‘xylyl’ aromatic rings cause huge steric hindrance at the cavity portals such that aspirin molecule cannot bypass to enter the cavity as shown in Figure 2.7.6. The para-xylyl bridges in compound 2.43,
however, are freer to rotate. The two conformations that the aromatic rings cover the portal the most (2.43a) and the least (2.43b) are depicted in Scheme 2.7.8. The portal is wide open for entry and egress of aspirin molecules in both of these extreme conformers. Consider the orientation when the ‘xylyl’ aromatic rings are oriented vertically to face each other in parallel (2.43b, Scheme 2.7.8). We suggest that these electron rich aromatic rings could possibly participate in π-π stacking interactions with the electron poor aromatic ring of the aspirin molecule. This hypothesis explains the relatively strong binding of aspirin inside the para-xylyl bridged superbowl 2.43 and the slowly exchanging nature of this binding at room temperature.

Scheme 2.7.8. Space-filling (CPK) models of two possible dominant conformations of the para-xylyl bridged superbowl 2.43 due to the rotation of of –OCH₂⁻ linkages.

The host-guest chemistry of these systems was not further examined. The interesting ability to bind aspirin of the para-xylyl bridged superbowl 2.43, however, promises spectacular application in the modelling of devices for drug delivery.

2.7.2 Installation of an Internal Binding Site into the Superbowl Structure

Although superbowl’s huge cavity is large enough to accommodate numerous small molecules, they usually bind guests quite weakly with the exception of the special case of aspirin. It happens by chance that the base-wall –CH₂O⁻ linkage can serve as an internal H-bonding site for aspirin. In order to purposely control the guest binding, it
would be ideal if a functional group could be installed \textit{inside} the superbowl molecules as an \textit{active} binding site. The most operationally simple positions for functionalization in the superbowl structure are the upper-rim substituents around the portal. At those positions, one possible way to install such a functional group/binding site internally is by way of a mono \textit{ortho}-substituted aryl group. With restricted rotation about the biaryl bond and a $20^\circ$ angle from horizontal axis orientation of superbowl upper-rims, the \textit{ortho}-substituent on the aryl group will either be pointing inside or outside the superbowl cavity (Scheme 2.7.9). The inside orientation of the ortho-substituent affords the targeted internal functionality. A cavitand model study has been described in \textbf{Section 1.3} in \textbf{Chapter 1} of this thesis.

\begin{center}
\includegraphics[width=\textwidth]{schema.png}
\end{center}

\textbf{Scheme 2.7.9.} A superbowl with an internal binding site for stronger guest binding and a cavitand model system

In the superbowl series (Scheme 2.7.10), this task could be achieved by using the same chemistry developed for mono \textit{ortho}-substituted aryl cavitands (\textbf{Chapter 1, Section 1.3}).

\begin{center}
\includegraphics[width=\textwidth]{schema_2.png}
\end{center}

\textbf{Scheme 2.7.10.} Synthetic plan for mono \textit{ortho}-substituted aryl superbowl 2.47
Several attempts to selectively mono-functionalize tetrabromo superbowl 2.11 using \( t\)-BuLi (which is superior to \( n\)-BuLi for this type of transformation, see Section 2.3.3 for more details), however, have failed (Scheme 2.7.11). These attempts generally resulted in complex reaction mixtures with no selectivity witnessed. We attribute these poor results to technical difficulties associated with the small scale of these reactions, due to the limited amount of superbowl precursor available. Increasing the scale of this reaction should overcome this problem.

**Scheme 2.7.11.** Failed attempts to mono-functionalize tetrabromo superbowl 2.11

### 2.8 Summary, Conclusions and Future Work

In this chapter, the practical synthesis and functionalization, as well as the guest binding ability, of superbowl molecules have been investigated.

The work described in this chapter included:

- An optimisation of the superbowl synthesis so it could be practically used in other synthetic laboratories (Scheme 2.8.1).
Scheme 2.8.1. Practical synthesis of superbowl from cavitand building blocks

- The development of different pathways to functionalise tetrabromo superbowl, so various types of novel superbows could be easily accessed (Scheme 2.8.2).

Scheme 2.8.2. Investigation of superbowl functionalization

- Interesting binding trends of tetra(n-alkyl) ammonium bromides to superbows (Figure 2.8.3).
Figure 2.8.3. Binding studies between tetraprotio superbowl 2.16 and the family of tetraalkyl ammonium bromides (ITC, chloroform, 25 °C).

- The first report of a medicinal agent binding inside cavitand-related hosts (Scheme 2.8.4).

Scheme 2.8.4. Binding of aspirin inside superbows in chloroform

- The synthesis of xylyl-bridged superbows, among those the para-xylyl bridged superbowl 2.43 shows relatively strong and slow exchange binding with aspirin at room temperature (Figure 2.8.5).
There is a bright future for the application of superbowl molecules in host-guest chemistry, molecular recognition as well as modelling drug delivery systems. This is evidenced by both the versatile functionalization methods of superbows, as well as their ability to selectively bind guests.

Future developments of work discussed in this chapter will include the investigation of using superbows to bind other bioactive guests, which will have obvious potential applications in drug delivery. The superbowl structure will be further modified using the synthetic pathway discussed in Section 2.7 to incorporate internal functionality, which will greatly enhance the binding abilities of superbowl molecules (Scheme 2.8.6). Furthermore, the exterior surface of superbowl (i.e. the feet) should be modified such that the superbowl is soluble in aqueous solution. This feature will promote guest binding ability as well as applications of the superbowl system in modelling drug-delivery.
CHAPTER 3: THE BINDING OF A MEDICINAL AGENT BY SIMPLE CAVITANDS
CHAPTER 3: THE BINDING OF A MEDICINAL AGENT
BY SIMPLE CAVITANDS

\[ H \stackrel{X}{\longrightarrow} (CH_2)_n \]

\[ \text{Aspirin} \]

\[ n = 0-2; \; X = \text{hetero atom} \]
3 The Binding of a Medicinal Agent by Simple Cavitands

3.1 Introduction and Objectives of this Work

In the previous chapter, it was shown that superbowl molecules selectively bind aspirin, over several other medicinal agents. CPK molecular modelling and various NMR studies are consistent with the two-point binding mode between superbowl and aspirin (Scheme 3.1.1).

![Two-point binding: H-bonding and C-H/π interaction]

**Figure 3.1.1.** The proposed two-point binding mode of aspirin (A) inside superbows

Based on the two-point binding hypothesis, only the base cavitand, with its four \(-\text{CH}_2\text{O-}\) base-wall bridges, is involved in the binding of aspirin (**Figure 3.1.1**). Hence, it is predicted that a *simple* cavitand with similar functionality will also exhibit binding of aspirin. Further investigations of this idea were carried out to gain a deeper insight into this two-point binding mode. A family of cavitands having similar structural and electronic properties to the base fragment of the superbowl (**Figure 3.1.2**) were produced for a series of systematic studies. These studies aim at deconstructing the superbowl framework to further investigate what it takes to bind an aspirin molecule.
3.2 Cavitands Mimicking the Superbowl Base

A number of cavitands having similar structural and electronic properties to the base fragment of the superbowl (Figure 3.1.2) were produced. The cavitands described in this section (3.1-3.4) have the general structure shown in Figure 3.2.1 with \( R \) varying from bulky aryl groups to simple alkyl groups and hydrogen atoms.

![Figure 3.1.2. Highlighted base fragment of superbowl molecule in molecular structure (top) and schematic (bottom) presentations](image)

![Figure 3.2.1. General structure of cavitands mimicking the superbowl base fragment](image)
3.2.1 A Cavitand with (2,6-Dimethoxy phenoxy)methyl Substituents

Cavitand 3.1 with (2,6-dimethoxy phenoxy)methyl substituents is the structure most closely related to the superbowl base fragment, since the 2,6-dimethoxy phenyl group is similar to the wall cavitand unit in terms of electronic and steric aromatic ring properties at the location of the two-point binding. Cavitand 3.1 was conveniently produced from a four-fold nucleophilic substitution reaction between the base cavitand 2.8 and 2,6-dimethoxy phenol (Scheme 3.2.2) under reaction conditions similar to the formation of the cruciform cavitand pentamer (Section 2.2.4, Chapter 2). The optimised reaction provided an 80% isolated yield with five molar equivalents of 2,6-dimethoxy phenol and excess potassium carbonate (50 molar equivalents) in refluxing acetone over 18 hours.

![Scheme 3.2.2. Synthesis of cavitand 3.1](image)

3.2.2 A Cavitand with Phenoxy methyl Substituents

Tetra(phenoxymethyl) cavitand 3.2 is a simplified analogue of cavitand 3.1 (Scheme 3.2.2) with the methoxy groups on the aromatic substituents removed. Instead of being appended by electron-rich and bulky alkoxy groups, the substituents are equipped with hydrogens, and are hence, more electron-neutral and much less sterically hindered. Similarly to cavitand 3.1, cavitand 3.2 was produced via a substitution reaction between the base cavitand 2.8 and phenol with an optimised yield of 82% (Scheme 3.2.3).
Scheme 3.2.3. Synthesis of cavitand 3.2

3.2.3 Cavitands with Methoxymethyl and Hydroxymethyl Substituents

Tetra(methoxymethyl) cavitand 3.3 has more electron-rich and less sterically hindered α-oxygen atoms on the substituents than does tetra(phenoxymethyl) cavitand 3.2 (Scheme 3.2.3). Meanwhile, tetra(hydroxymethyl) cavitand 3.4 is the simplest member of this series, with only hydrogen atoms attached to the α-oxygen atoms of the substituents. These substituents can be either a H-bonding acceptor or a H-bonding donor. This feature distinguishes cavitand 3.4 from its analogues, cavitands 3.1-3.3, because the substituents on cavitands 3.1-3.3 can only serve as H-bonding acceptors.

Scheme 3.2.4. Tetra(methoxymethyl) cavitand 3.3 and tetra(hydroxymethyl) cavitand 3.4

Cavitand 3.4 was obtained from a two-stage, one-pot substitution reaction of the base cavitand 2.8 (Scheme 3.2.5), based on a procedure reported by the Plenio research group.⁶⁶ The reaction proceeded via the formation of the tetrakis(acetoxymethyl) cavitand intermediate followed by hydrolysis of the ester groups to form cavitand 3.4 in good yield.
A simple four-fold methylation reaction of the cavitand 3.4 hydroxy groups afforded tetra(methoxymethyl) cavitand 3.3 in high yield (Scheme 3.2.6).

Scheme 3.2.6. Synthesis of cavitand 3.3

3.2.4 Binding Studies with Aspirin

A series of cavitands (3.1-3.4) mimicking the base moiety of the superbowl structure were produced, with varied electronic and steric properties. It was postulated that the more electron-rich and less sterically hindered the α-oxygen atoms of the substituents would participate better in H-bonding. The cavitands in this series were subjected to binding studies with aspirin, using $^1$H NMR and ITC titration techniques as discussed in Section 2.4.1 (see Experimental Section for Chapter 3 for more details). These results are summarized in Table 3.2.7.

Interestingly, most of these cavitands (3.1-3.3) showed no detectable binding with aspirin. Startled by the experimental results, we also investigated the binding of aspirin with the MOM protected cruciform pentamer 2.9. Perceiving four wall cavitands as ‘substituents’, this cruciform pentamer is considered as structurally analogous to the cavitands in this series. Strangely enough, this open-form precursor of the superbowl did not show any detectable binding with aspirin either (Table 3.2.7). It is clear, therefore, that functionality capable of forming H-bonds is an important but not decisive
factor to aspirin binding among these cavitand-derived hosts. The superbowl structure, with a confined cavity to isolate the guest from the bulk medium, allows the weak interactions such as the H-bonding and C-H···π interactions to effectively hold the aspirin guest inside. For cavitands 3.1-3.3 and the cruciform pentamer 2.9, it could be postulated that while the H-bonding and C-H···π interactions with the aspirin molecules do take place, they are too weak to compete with other processes such as solvation by solvent molecules.

For cavitand 3.4, positive evidence of the binding could be deduced from examination of \(^1\)H NMR spectra, where the signals of aspirin in the mixture with cavitand host appeared at \(~0.13\) ppm upfield from their original chemical shifts. An ITC experiment, however, did not provide evidence of binding. The ITC titration profile displayed strong endothermic signals upon the injections of the guest solution into the host solution. This phenomenon will be discussed in more details in Section 3.3.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.9</td>
<td>No binding observed by both NMR and ITC</td>
</tr>
<tr>
<td>3.1</td>
<td>No binding observed by both NMR and ITC</td>
</tr>
</tbody>
</table>
Table 3.2.7. Binding studies of cavitands 3.1-3.4 and cruciform pentamer 2.9 with aspirin (chloroform, 25 °C)

The conclusion drawn from this cavitand series is that the binding of aspirin within superbowl is special. Not only having the functionalities to form binding interactions (H-bond and C-H···π interaction) with aspirin, the superbowl structure itself provides an isolated space to stabilize these binding interactions. In the two-point binding mode, the four wall cavitands of the superbowl are not directly involved but they indirectly act as a barricade to isolate the aspirin guest from the bulk solution.

3.3 Re-investigating the Binding Studies of Hydroxymethyl Substituted Cavitands with Aspirin

For the quantitative ITC binding studies described in this chapter, a 1-5 mM solution of the cavitand host and 50-100 mM solution of the aspirin guest were prepared for each ITC experiment. A reference baseline was established with titration of the aspirin guest solution into blank chloroform solvent to eliminate the dilution effect of aspirin (see Experimental Section for more details regarding ITC experiments). Evidence for binding was the observation of exothermic signals during injections of guest solution into host solution.
Reconsidering the ITC binding study between tetra(hydroxymethyl) cavitand 3.4 and aspirin, the endothermic signals can be rationalized by the H-bonding interactions in the host. Since there are four hydroxy groups on the cavitand upper-rim, it is possible that they form cavitand dimers/oligomers by intermolecular H-bonds (Scheme 3.3.1), similar to those reported by the Sherman research group.\(^{107}\) The endothermic signals could be attributed to the dissociation of these postulated dimers/oligomers. To confirm this hypothesis, two reference ITC experiments were performed, where cavitand 3.3 (10 mM solution) or cavitand 3.4 (10 mM solution) were titrated into blank chloroform solvent. Very weak endothermic signals were observed for tetra(methoxymethyl) cavitand 3.3 (unable to form dimer/oligomer). Titration of cavitand 3.4 (able to form dimer/oligomer), however, showed strong endothermic signals. This is evidence for the dissociation of dimers/oligomers of cavitand 3.4 upon dilution. The dissociation constant of this dimer/oligomers was determined by ITC (see pages 285-286 for more details) to be \(K_{\text{dissociation}} = 0.0149 \pm 0.0008 \text{ M}\). As can be seen later, the self-association of cavitand 3.4 \((K_{\text{association}} = 1/K_{\text{dissociation}} \sim 67 \text{ M}^{-1})\) has the same order of magnitude with the complexation of aspirin with the simple cavitands studied in this Chapter.

![Scheme 3.3.1. Postulated formation/dissociation of cavitand 3.4 H-bonding dimers](image)

The ability to form dimers/oligomers could be generalized for any cavitand with functional groups having both H-bond accepting and H-bond donating characteristics. There are four factors that we will need to consider when the aspirin guest solution is injected into a solution containing such a cavitand:

- Diluting the concentrations of aspirin and the cavitand host: the dilution effect of the cavitand is negligible since the initial concentration is low (1-5 mM) and the amount of the guest solution added is very small compared to the bulk volume.
The dilution effect of aspirin, while significant, is accounted for by the reference titration of the guest into blank solvent \textit{(vide supra)}.

- The dissociation of aspirin dimers: aspirin and other carboxylic acids are known to equilibrate between the monomer and the dimer forms in the solution phase.\textsuperscript{108} This effect is eliminated by the blank titration. If binding between aspirin and the cavitand host occurs, however, aspirin dimers will have to further dissociate to maintain the equilibrium, since the monomer is consumed in the binding event. This will be an endothermic process.

- The dissociation of cavitand host dimers/oligomers: cavitand hosts with H-bonding functionalities could possibly form dimers/oligomers in the solution phase. The binding event between cavitand and aspirin requires the dissociation of these (hypothetical) cavitand dimers/oligomers, which would also be an endothermic process \textit{(vide supra)}.

- The binding of aspirin into the cavitand host: presumably via the two-point binding mode. This would be an exothermic process.

What is observed on ITC titration profiles is a combination of all four processes. A cavitand host that shows binding with aspirin in ITC is one that has the exothermic process overcoming any other endothermic processes.

From the work described in Section 3.2.5, we postulate that a functional group such as hydroxymethyl group is sufficient to hold the aspirin molecule inside the cavity, due to its good ability to donate and/or accept H-bonding interactions. To avoid the issue of dimer/oligomer formation as for the tetra(hydroxymethyl) cavitand 3.4 compound, its mono substituted analogue - cavitand 3.7 - was prepared (Section 3.3.1).

### 3.3.1 Synthesis of Mono(Hydroxymethyl) Triprotio Cavitand 3.7

Mono(hydroxymethyl) triprotio cavitand 3.7 was synthesized from tetrabromo cavitand 2.3 in a three-step sequence (Scheme 3.3.2). Firstly, tetrabromo cavitand 2.3 was converted to monobromo triprotio cavitand 3.5 \textit{via} a stepwise reductive debromination employing lithium-bromine exchange chemistry. Cavitand 3.5 was then converted to monoformyl triprotio cavitand 3.6 using a standard lithium-bromine exchange followed by addition of DMF. These procedures were developed based upon the chemistry.
previously reported within the group. The newly formed monoformyl cavitand 3.6 was then reduced with sodium borohydride to obtain mono(hydroxymethyl) triprotio cavitand 3.7.

Scheme 3.3.2. Synthesis of cavitand 3.7

Several attempts have been made to convert 3.5 directly into 3.7, using the synthetic plan outlined in Scheme 3.3.3. Formaldehyde, however, seemed to be a weak electrophile in its commercially available (anhydrous) paraformaldehyde form, such that the reactions did not proceed under standard reaction conditions (temperature below 25 °C). When the reactions were carried out at elevated temperature to facilitate the dissociation of paraformaldehyde to its monomer form, side-reactions such as non-selective deprotonation of solvent by the cavitand lithio intermediate often occurred, resulting in complex reaction mixtures. Therefore, although the synthesis in Scheme 3.3.2 is somewhat lengthy, it is still the most practical method in hand to produce cavitand 3.7.

Scheme 3.3.3. Attempts at a direct synthesis of cavitand 3.7
### 3.3.2 Binding Studies of Cavitand 3.7 with Aspirin

Cavitand 3.7 was then subjected to binding studies with aspirin using $^1$H NMR and ITC titration techniques. These results are summarized in Table 3.3.4, in comparison with cavitand 3.4.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="cavitand_3_4.png" alt="" /></td>
<td>Binding observed by NMR but not by ITC (strong endothermic signals in ITC)</td>
</tr>
<tr>
<td><img src="cavitand_3_7.png" alt="" /></td>
<td>Binding observed by both NMR and ITC. Association constant = $68 \pm 4$ (M$^{-1}$). Binding stoichiometry = 1:1</td>
</tr>
</tbody>
</table>

**Table 3.3.4.** Binding studies of cavitands 3.4 and 3.7 with aspirin (chloroform, 25 °C)

Gratifyingly, cavitand 3.7 showed evidence of binding with aspirin by both $^1$H NMR (aspirin signals, in the presence of cavitand host, appear ~ 0.1 ppm upfield from their original chemical shifts) and ITC titration (exothermic peaks) methods. Based on the two-point binding mode of aspirin in the superbowl, it is postulated that aspirin is bound inside this cavitand due to the contribution of:

- The ‘double’ (cyclic) H-bond between the carboxyl group of aspirin and the hydroxy group on the upper-rim of the cavitand. This superior H-bonding interaction is absent in cavitands 3.1-3.3.
- The C-H···π interaction between the aspirin acetyl methyl group and the electron-rich cavity of the cavitand (Figure 3.3.5).
This observation represents very solid evidence for the two-point binding hypothesis. It also proves that it is possible to bind aspirin with simple cavitand hosts such as 3.7 by simply incorporating suitable H-bonding functionalities on the upper rims of the cavitands. It should be noted here that the simple methylene bridged cavitands, first reported by Cram, have generally been shown to bind only small solvent molecules.\(^3\) The binding event between mono(hydroxymethyl) cavitand 3.7 and aspirin discussed in this section is, to the best of the author’s knowledge, the first report of a biologically relevant guest/medicinal agent binding in a simple cavitand.

### 3.4 The Influence of Substituent Structural Variation on Guest Binding Ability

To further explore the scope of simple cavitands binding aspirin, a systematic investigation was carried out to synthesize a series of cavitands with functional groups that can potentially form H-bonds with the carboxylic acid group of aspirin. The effects of structural variation at these functionalities on the aspirin binding ability of the cavitand hosts were examined.
3.4.1 Tetra and Mono-Substituted Cavitands – the Effect of Substituent Number on Binding Ability

Four substituents - all of which can potentially form H-bonds - around the cavitand cavity are not necessarily suitable for aspirin binding, as shown by the example of cavitand 3.4 and 3.7 (Section 3.3). This intriguing result prompts further investigations into the effect of the number of cavitand upper-rim substituents on the binding strength with aspirin. Cavitands with tetra (3.8) or mono (3.9) substituted phenol groups were selected as candidates for this study.

3.4.1.1 Tetra and Mono-Hydroxy Cavitands

The incorporation of hydroxy groups on the cavitand upper-rim has been previously carried out within the group.254,55,89 Employing these synthetic procedures, tetrahydroxy cavitand 3.8 was produced via the exhaustive lithium-bromine exchange of tetrabromo cavitand 2.3 followed by quenching with trimethyl borate and subsequent oxidative hydrolysis. Similar chemistry was carried out on monobromo triprotio cavitand 3.5 to afford the monohydroxy triprotio cavitand 3.9 (Scheme 3.4.1).

Scheme 3.4.1. Synthesis of cavitand 3.8 and 3.9

3.4.1.2 Binding Studies with Aspirin
These two cavitands were then subjected to binding studies with aspirin, using $^1$H NMR and ITC titration techniques. These results are summarized in Table 3.4.2, in comparison with tetra and mono(hydroxymethyl) cavitands 3.4 and 3.7.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.4.png" alt="Image 3.4" /></td>
<td>Binding observed by NMR but not by ITC (strong endothermic signals in ITC)</td>
</tr>
<tr>
<td><img src="image3.7.png" alt="Image 3.7" /></td>
<td>Binding observed by both NMR and ITC. Association constant $= 68 \pm 4$ (M$^{-1}$). Binding stoichiometry $= 1:1$</td>
</tr>
<tr>
<td><img src="image3.8.png" alt="Image 3.8" /></td>
<td>Binding observed by both NMR and ITC. Association constant $= 25 \pm 3$ (M$^{-1}$). Binding stoichiometry $= 1:1$</td>
</tr>
<tr>
<td><img src="image3.9.png" alt="Image 3.9" /></td>
<td>Binding observed by both NMR and ITC. Association constant $= 53 \pm 3$ (M$^{-1}$). Binding stoichiometry $= 1:1$</td>
</tr>
</tbody>
</table>

**Table 3.4.2.** Binding studies of cavitands 3.4, 3.7, 3.8, 3.9 with aspirin (chloroform, 25 °C)

It should be noted that these hydroxy functional groups on the cavitand upper-rims could possibly form 'double' H-bonds with aspirin, similar to those depicted in Figure 3.3.5. As can be seen in Table 3.3.2, there are two binding trends among these four cavitand hosts:

- The tetrafunctionalized cavitands (3.4, 3.8) bind aspirin more weakly than do their monofunctionalized analogues (3.7, 3.9). We assume that the dissociation of cavitand dimers/oligomers during the binding event contributes to weaken the
observed binding strengths of the tetrafunctionalized analogues. The monofunctionalized cavitands would form much less strongly bound dimers/oligomers, thus leading to the observation of stronger aspirin binding.

- Cavitand 3.7, with one hydroxymethyl group, binds aspirin more strongly than does cavitand 3.9, with one hydroxy group. This is very interesting, given the similarity of these two functional groups. It is possible that the spacing between the cavity and the hydroxy group in cavitand 3.7 is optimal for the two-point binding. This effect will be further examined in Section 3.4.3.

3.4.2 Mono-Functionalized Cavitands – the Effect of Substituent Type on Binding Ability

There are several types of functional groups that are able to form H-bonds with the aspirin carboxylic acid group, since this COOH group can act as both H-bonding acceptor and H-bonding donor. Installation of these functionalities on cavitand upper-rims would obviously influence the binding strength of the cavitand host with aspirin. This effect will be investigated in this section by examination of a cavitand family with various upper-rim functionalities. For convenient comparison purposes, only mono-substituted triprotio cavitands were produced for binding studies with aspirin.

3.4.2.1 Triprotio Monocarboxylic Acid Cavitand

Neither triprotio monocarboxylic acid cavitand 3.11 nor its corresponding methyl ester 3.10 were previously prepared. Their undecyl-footed analogues, however, were recently reported. Thus, monobromo triprotio cavitand 3.5 was converted, in a similar manner, to the methyl ester cavitand 3.10, which was then hydrolyzed to afford the target triprotio monocarboxylic acid cavitand 3.11 in good yield (Scheme 3.4.3).
Scheme 3.4.3. Synthesis of cavitand 3.11

3.4.2.2 Monoamino Triprotio Cavitand

The previously unreported monoamino triprotio cavitand 3.12 was synthesized using chemistry developed by the Shiori research group (Scheme 3.4.4). Details of the development of the very first cavitand amination and other related transformation are described in Chapter 5. In brief, the lithium-bromine exchange of monobromo cavitand 3.5 was carried out with $n$-BuLi, then the reaction mixture was quenched with the electrophilic nitrogen-source: diphenylphosphoryl azide. Subsequent reduction of the intermediate with lithium aluminium hydride afforded the monoamino triprotio cavitand 3.12 in good overall yield (Scheme 3.4.4).

Scheme 3.4.4. Synthesis of cavitand 3.12 using diphenyl phosphoryl azide (DPPA)

3.4.2.3 Triprotio Monoboronic Acid Cavitand
The triprotio monoboronic acid cavitand 3.13 has been previously prepared within the group.\(^2\) The experimental procedure was reproduced without difficulty to convert monobromo triprotio cavitand 3.5 to triprotio monoboronic acid cavitand 3.13 in good yield (Scheme 3.4.5).

\[
\begin{align*}
\text{3.5} & \xrightarrow{1. \text{n-BuLi (1.1 eq)}} \xrightarrow{2. \text{B(OMe)}_3 (1.5 \text{eq})} \xrightarrow{3. \text{HCl}} \text{74\%} \text{3.13}
\end{align*}
\]

Scheme 3.4.5. Synthesis of cavitand 3.13

3.4.2.4 Binding Studies with Aspirin

The cavitands in this series were then subjected to binding studies with aspirin, using \(^1\)H NMR and ITC titration techniques. The results are summarized in Table 3.4.6, in comparison with results from binding studies of previously prepared cavitands 3.6, 3.7 and 3.9.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Image of 3.6" /></td>
<td>No binding observed by both NMR and ITC</td>
</tr>
<tr>
<td><img src="image" alt="Image of 3.7" /></td>
<td>Binding observed by both NMR and ITC. Association constant = (68 \pm 4) (M(^1)). Binding stoichiometry = 1:1</td>
</tr>
<tr>
<td><img src="image" alt="Image of 3.9" /></td>
<td>Binding observed by both NMR and ITC. Association constant = (53 \pm 3) (M(^1)). Binding stoichiometry = 1:1</td>
</tr>
</tbody>
</table>
Table 3.4.6. Binding studies between aspirin and cavitands with different functionalities (chloroform, 25 °C)

Cavitand aldehyde 3.6 did not show binding with aspirin by both detection methods. Presumably, H-bonding between the formyl group and aspirin cannot compete with the process of aspirin forming H-bonds with itself.

Upfield chemical shift movements (~0.05-0.10 ppm from the original positions) of the aspirin signals in the mixtures with cavitand hosts 3.11 and 3.13 could be observed in 'H NMR spectra. Binding, however, could not be detected in the ITC titration profiles. Endothermic ITC signals, similar to those witnessed with cavitand 3.4, were observed. Although the monofunctionalized cavitands were anticipated to be less likely to form dimers/oligomers, carboxylic and boronic acid functionalities have good capacity to form relatively strong intermolecular cyclic H-bonds and condensation products, respectively. This would possibly lead to the formation of cavitand dimers/oligomers as well. We postulate that the lack of observed binding of aspirin to these cavitands is due to this effect. This hypothesis was supported by endothermic signals during ITC titrations of cavitand 3.11 and 3.13 into blank chloroform solvent.

Gratifyingly, monoamino cavitand 3.12 showed relatively strong binding with aspirin. Presumably, this is due to H-bonding and/or Coulombic interactions between the...
carboxylic acid group of aspirin and the amino group of cavitand 3.12 as well as the C-H-π interaction between the aspirin acetyl methyl group and the π-electron rich cavity of the cavitand (Scheme 3.4.7).

![Scheme 3.4.7. Two-point binding mode between aspirin and cavitand 3.12](image)

In summary, it is clear that although every cavitand functionality studied in this section can, in principle, form H-bonds with aspirin, in practice, only a few of them show binding.

### 3.4.3 Effect of the Substituent Chain Length on Binding Ability

Apart from the effect of the type and the number of upper-rim substituent on the aspirin binding ability of cavitands, it was also of interest to explore how far away from the cavity the H-bonding substituents can be, yet still bind aspirin and/or other guests. From the interesting observation in Section 3.4.1.2, the hydroxy group was selected as the fixed functionality for chain length variation. The syntheses and binding studies of cavitands bearing this functionality either directly attached (i.e. 3.9) or one methylene group removed (i.e. 3.7) have been reported in the previous sections. The chain length was then extended (cavitand 3.14, Scheme 3.4.9) to see how this would affect the aspirin binding ability.

The synthesis of the cavitand with two carbons in the substituent chain, namely the mono(2-hydroxyethyl) triprotio cavitand 3.14, was not easily accomplished. The first strategy to make this compound was to lithiate the monobromo cavitand 3.5 and then quench that lithio cavitand with ethylene oxide to yield the target compound. This
transformation has been successfully reported for several aromatic substrates in the literature.\textsuperscript{10-115} When similar procedures were applied to the lithio cavitand derived from 3.5, however, they met with failure and generally gave complex mixtures under various reaction conditions (Scheme 3.4.8).

Scheme 3.4.8. Failed attempts at a direct synthesis of cavitand 3.14

An alternative approach was, therefore, developed and carried out. Monoformyl triprotio cavitand 3.6 was reacted with the ylide derived from triphenyl(methoxymethyl)phosphonium bromide in a Wittig reaction to form enol ether cavitand 3.15. Hydrolysis under acidic conditions gave cavitand aldehyde 3.16, which was subsequently reduced to afford mono(2-hydroxyethyl) cavitand 3.14 in good yield (Scheme 3.4.9). This homologation process was inspired by a literature procedure reported by the Enders research group on a much simpler aromatic substrate.\textsuperscript{116}

Scheme 3.4.9. Synthesis of cavitand 3.14
Cavitands 3.7, 3.9, 3.14 were then subjected to binding studies with aspirin, using $^1$H MR and ITC titration techniques. These results are summarized in Table 3.4.10.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="3.9" /></td>
<td>Binding observed by both NMR and ITC. Association constant = $53 \pm 3$ (M$^{-1}$). Binding stoichiometry = 1:1</td>
</tr>
<tr>
<td><img src="image" alt="3.7" /></td>
<td>Binding observed by both NMR and ITC. Association constant = $68 \pm 4$ (M$^{-1}$). Binding stoichiometry = 1:1</td>
</tr>
<tr>
<td><img src="image" alt="3.14" /></td>
<td>No binding observed by both NMR and ITC</td>
</tr>
</tbody>
</table>

Table 3.4.10. Binding studies with aspirin of cavitands with different functional group chain length (chloroform, 25 °C)

As discussed in Section 3.4.1.2, it is possible that the spacing between the cavity and the hydroxy group in cavitand 3.7 is optimal for the two-point binding. The functional group in cavitand 3.9 is possibly a bit shorter than the optimal length such that the aspirin binding strength for this cavitand is lower than for cavitand 3.7. With increasing chain length in cavitand 3.14, however, the functional group is presumably too distant from the cavity such that the H-bond formed could not cooperate with the C-H...π interaction in a two-point binding mode anymore. Lacking the capacity to participate in the two-point binding mode, cavitand 3.14 cannot bind aspirin. In conclusion, the functional group chain length has a significant impact on the binding ability of the simple cavitands.

3.4.4 Effect of other Substituents around the Cavity on Binding Ability
A new series of substituted cavitands was produced for comparison with selected members of those series described in Section 3.4.1 to Section 3.4.3, namely cavitands 3.7 and 3.9. These cavitands have other functionalities on the upper-rims rather than just hydrogen atoms.

### 3.4.4.1 Tribromo Monohydroxy Cavitand

Tribromo monohydroxy cavitand 3.17 was prepared for comparison with monohydroxy triprotio cavitand 3.9. From the binding strength of these two compounds with aspirin, the effect of three extra bromines around the cavitand cavity would be deduced. Bromine substitution was shown to have a negative influence on guest binding ability of cavitand-derived superbowl hosts (see Sections 2.4-2.5 in Chapter 2 for more details).

The tribromo monohydroxy cavitand 3.17 has been previously prepared within the group. The experimental procedure was reproduced without difficulty to convert tetrabromo triprotio cavitand 2.3 to cavitand 3.17 in good yield (Scheme 3.4.11).

![Scheme 3.4.11. Synthesis of cavitand 3.17](image)

### 3.4.4.2 Monohydroxy Trimethyl Cavitand

Monohydroxy trimethyl cavitand 3.18 was prepared for comparison with monohydroxy triprotio cavitand 3.9 and tribromo monohydroxy cavitand 3.17 described above. In the superbowl series (Section 2.5, Chapter 2), methyl substitution around the portal gives rise to host compounds that bind aspirin, while bromine substitution inhibits binding. It would be interesting to compare the effect of methyl and bromine substitutions in the cavitand series.
The synthesis of monohydroxy trimethyl cavitand 3.18 from tetrabromo cavitand 2.3 was carried out in good yield, in a one-pot process (Scheme 3.4.12). Firstly, three bromines of cavitand 2.3 were selectively converted to methyl groups by means of lithium-bromine exchange followed by substitution reaction with methyl iodide. Then, the fourth bromine was converted to a hydroxy group in the usual manner (Section 3.4.1.1) to afford monohydroxy trimethyl cavitand 3.18 (Scheme 3.4.12).

![Scheme 3.4.12. Synthesis of cavitand 3.18](image)

**Scheme 3.4.12.** Synthesis of cavitand 3.18

### 3.4.4.3 Tribromo Mono(hydroxymethyl) Cavitand

Tribromo mono(hydroxymethyl) cavitand 3.20 was prepared for comparison with mono(hydroxymethyl) tripotio cavitand 3.7. From the binding strength of these two compounds with the aspirin guest, the effect of bromine substitution around the cavitand cavity will be further explored.

Analogous to the conversion of monobromo cavitand 3.5 to mono(hydroxymethyl) cavitand 3.7, tribromo mono(hydroxymethyl) cavitand 3.20 was produced from tetrabromo cavitand 2.3 in two steps in good overall yield (Scheme 3.4.13).
Scheme 3.4.13. Synthesis of cavitand 3.20

3.4.4.4 Binding Studies with Aspirin

These cavitands were then subjected to binding studies with aspirin, using $^1$H NMR and ITC titration techniques. These results are summarized in Table 3.4.14.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="3.9" alt="Image" /></td>
<td>Binding observed by both NMR and ITC. Association constant = $53 \pm 3$ (M$^{-1}$). Binding stoichiometry = 1:1</td>
</tr>
<tr>
<td><img src="3.17" alt="Image" /></td>
<td>No binding observed by both NMR and ITC</td>
</tr>
<tr>
<td><img src="3.18" alt="Image" /></td>
<td>Binding observed by both NMR and ITC. Association constant = $49 \pm 3$ (M$^{-1}$). Binding stoichiometry = 1:1</td>
</tr>
</tbody>
</table>
It is interesting to see that tribromo mono-substituted cavitands 3.17 and 3.20 showed no detectable binding with aspirin, despite having a cavity and a hydroxy group in the suitable location for binding. It is even more interesting to note that mono(hydroxymethyl) trimethyl cavitand 3.18 binds aspirin with a comparable binding strength to cavitand 3.9. It is clear that substituents have an inhibitive effect on aspirin binding. That this effect is not steric in nature is demonstrated by the successful aspirin binding of the trimethyl mono-substituted analogue. It is possible that the electron withdrawing nature of bromine substituents decreases the electron density in the $\pi$-cavity, hence weakening the C-H-$\cdots\pi$ interaction of the two-point binding. The observations described here agree well with the experimental data discussed in Section 2.5 for the effect of substituents on the superbowl upper-rims.

**3.4.5 The Effect of Conformational Mobility on Binding Ability**

To investigate the effect of conformational flexibility on the guest binding ability of the cavitand structure, ethylene-bridged tetrahydroxy cavitand 3.22 was subjected to binding studies with aspirin to compare with (methylene-bridged) tetrahydroxy cavitand 3.8. Cavitand 3.22 was previously produced within our group by Dr. Nicholas Kanizaj (Scheme 3.4.15).\(^{117}\)
Scheme 3.4.15. Synthesis of cavitand 3.22

With the ethylene bridges connecting the phenolic hydroxy groups, cavitand 3.22 has a much more conformationally mobile structure than does the methylene-bridged cavitand 3.8. The cavity of cavitand 3.22 is, thus, likely to be distorted due to this flexibility. The binding studies with aspirin of this compound are summarized in Table 3.4.16, in comparison with cavitand 3.8.

<table>
<thead>
<tr>
<th>Cavitand host</th>
<th>Binding studies result</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="" /> 3.8</td>
<td>Binding observed by both NMR and ITC. Association constant = (25 \pm 3) (M(^{-1})). Binding stoichiometry = 1:1</td>
</tr>
<tr>
<td><img src="image" alt="" /> 3.22</td>
<td>No binding observed by both NMR and ITC</td>
</tr>
</tbody>
</table>

Table 3.4.16. Binding studies of cavitands 3.8 and 3.22 with aspirin

Cavitand 3.22, although having analogous functionalities to cavitand 3.8, did not show any detectable binding with aspirin. We therefore conclude that the conformational mobility of the cavitand cavity also has effect on the guest binding ability. The non-binding character of cavitand 3.22 may tentatively be attributed to a weakened C-H⋯π interaction between the aspirin acetyl methyl group and the cavitand cavity, one of the two contributors to the two-point binding mode. This is also in agreement with the decrease in binding ability of the expanded (ethylene-bridged) superbowl hosts.
described in Sections 2.4-2.5. To further investigate this effect, the mono(hydroxy) cavitand analogues of 3.8 and 3.22 will be examined in future studies to rule out the possible interference of cavitand dimer/oligomer formation.

3.5 Binding Studies with Reference Compounds

Control binding studies were carried out with simple aromatic substrates to ensure that the observations that we took as evidence for binding, namely NMR upfield chemical shift movements and ITC exothermic signals, were not just the result of simple H-bond formation between aspirin and the cavitand functional groups. The aromatic substrates 3.23-3.27 generally have the H-bond donating/accepting functional groups attached to a 2,6-dimethoxy phenyl group (Scheme 3.5.1), which is analogous to the H-bonding segments of cavitand hosts. These compounds were either commercially available (3.24-3.26) or could be easily synthesized by quenching lithiated 2,6-dimethoxy benzene with suitable electrophiles (3.23 and 3.27). Although direct functionalization of 1,3-dimethoxy benzene is possible, it was much more operationally simple to use 2,6-dimethoxy bromobenzene 3.28 as the starting material for these model compounds (see Experimental Section for detailed syntheses of these compounds).

![Scheme 3.5.1. Reference compounds for NMR and ITC binding studies](image-url)
Gratifyingly, none of these compounds showed any detectable evidence of aspirin binding by either NMR or ITC methods. In other words, the conclusions drawn regarding the binding of aspirin into the cavitands via a two-point binding mode described in Section 3.4 are supported.

3.6 Summary, Conclusions and Future Work

In summary, several new families of cavitands, with incorporated simple functional groups, have been designed and synthesized (Figure 3.6.1). Several of these cavitands show 1:1 binding with aspirin. Although the binding was usually weaker than that of the superbowsls, we are pleased to report the first binding of a medicinal agent into simply functionalized cavitands. These cavitand hosts are much more accessible than the far more complex superbowsls.

Figure 3.6.1. Simple functionalised cavitands

The work described in this chapter proved that with suitable design and incorporation of functionality, simple cavitands could specifically bind a biologically relevant guest. The two-point binding mode theory for the binding of aspirin within the superbowl cavity is
also supported by the binding trends of these cavitands. Conclusions drawn from this work could be applied to model other cavitand-based host molecules for future applications. These include:

- Both a functional group that can form sufficiently strong H-bonds and an electron rich π-cavity are required for aspirin binding in the cavitand hosts.
- Tetrafunctionalized cavitands are not superior to monofunctionalized analogues in term of guest binding ability.
- Functional group chain length, other upper-rim substituents and the conformational flexibility of the cavitand cavity all have a significant influence on the binding ability of the cavitands.

To better understand the effect of functional group variation on guest binding, a few more cavitand derivatives will be prepared in future studies to compare with existing members of the cavitand family discussed in this chapter (Figure 3.6.2).

**Figure 3.6.2.** Future work – cavitand derivatives for study of the effect of functional groups on guest binding ability.

Triethyl monohydroxy cavitand will be compared with tribromo monohydroxy cavitand 3.17 and trimethyl monohydroxy cavitand 3.18 to further study the steric effect of side substituents on guest binding. Similarly, trimethoxy monohydroxy cavitand will be compared with tribromo monohydroxy cavitand 3.17 to study the electronic effect, since
the methoxy group has electron-donating character compared with electron withdrawing bromines. Ethylene-linked monohydroxy cavitand will be compared with methylene-linked monohydroxy cavitand 3.9 to re-investigate the effect of conformational mobility on guest binding ability (Section 3.4.5).

Future work will also include investigations into the binding of other biologically relevant guests to the simple cavitands.
CHAPTER 4: NEW DEEP CAVITY CAVITANDS
4 New Deep Cavity Cavitands

4.1 Overview of this Work

The first generation of cavitands was Cram’s methylene-bridged derivatives of resorcinarenes (Section 1.2, Chapter 1). They are molecules with a concave π-basic surface that can accommodate guests of complementary size and shape.5 Prior to the studies described in this thesis, however, cavitands generally have been shown to weakly bind only small solvent molecules.3 Hence, many research groups in the cavitand area have been trying to create a new generation of cavitand with a deeper cavity/concave surface, with a view to bind larger molecules.120 This chapter will describe efforts to design and construct a new deep cavitand system (Figure 4.1.1) based on fundamental methodology that differs from the previous reported attempts by other research groups. It also reports the advantageous properties and values of this new deep cavity cavitand system and its potential applications in host-guest chemistry.

Figure 4.1.1. Proposed structure of a new deep cavity cavitand system with bridging unit (X) of choice.

4.2 Review of the Literature Relevant to this Work

A few research groups have reported the construction of larger or deeper cavity systems from resorcinarene related compounds. Since the time when Cram and co-workers created the heterophenylene-bridged cavitands and proved that one of the conformations was possessed of a deeper cavity than original cavitands (Figure 4.2.1),121 research
groups led by Rebek, Gibb and Sherman have been inspired to build other deep cavity cavitand systems, as detailed later in this section.

The first generation cavitand with methylene-bridges has a cavity depth of roughly 4 Å, so a deep-cavity cavitand may be defined as a cavitand with a cavity deeper than 4 Å. This section will only review the fundamental contributions to the development of deeper cavity cavitands; host systems assembled from several cavitand units or particular derivatives of fundamental deep cavitand systems will be excluded.

### 4.2.1 Cram’s Vase and Kite Cavitands

Cram and co-workers implemented the idea of creating a bigger cavity by replacing the original methylene bridges with aromatic spacers to link the resorcinarene phenol groups. Several examples were prepared; the most notable of them all is the cavitand made with 2,3-dichloroquinoxaline. The quinoxaline bridges could adopt either the axial (a) or equatorial (e) positions. The newly formed cavitand was found to exist in two major exchangeable conformations: vase (aaaa) or kite (eeee) in the solution state (Figure 4.2.1). Generally, there is higher degree of interaction with solvent in the kite conformation (higher surface area for solvation); hence, the vase conformation is entropically stabilized, while the kite conformation is enthalpically stabilized. In solution, therefore, the vase conformation is the dominant form at higher temperature and vice versa.

![Vase and Kite Conformations](image-url)

**Figure 4.2.1.** Two conformations of Cram’s heterophenylene-bridged cavitand
Based on modelling studies, Cram and co-workers suggested that the vase conformation is also less strained than the kite form. With the extended aromatic wall oriented upwards, the vase conformation has a much deeper π electron-rich cavity. This molecule and its analogues have inspired other research groups to develop more stable deep cavity systems with a view to expand the application of cavitands in host-guest chemistry.

4.2.2 Rebek’s Deep Cavity Cavitands

In the last decade, Rebek and co-workers have been developing several deep cavity systems in this area. In principle, most of these are elaborated forms of Cram’s vase cavitand. These cavitands were generally produced by the bridging of resorcinarenes with phenylene or heterophenylene linkages (Figure 4.2.2). The major advantage of Rebek’s systems is the installation of functional groups with H-bonding ability on the aromatic bridges. Adjacent functional groups can form H-bonds intramolecularly and support the deep cavity aromatic wall in a stable ‘vase’ conformation. In some cases, other sources of non-covalent interactions such as dipole-dipole or metal coordination have also been employed to stabilize the deep cavity.

Numerous deep cavitands developed by the Rebek group have interesting properties such as introverted functionality (see Section 1.2 for more details) or high solubility in aqueous solutions (by the incorporation of hydrophilic functional groups).

Figure 4.2.2. Two examples of Rebek’s H-bonded deep cavity cavitands
In summary, Rebek’s deep cavity cavitands are improved versions of Cram’s vase-form deep cavity system with extra non-covalent interactions to stabilize the vase conformation. Their host-guest properties are superior to Cram’s systems, owing to the presence of incorporated functional groups.

4.2.3 Gibb’s Deep Cavity Cavitands

For the last decade, Gibb’s research group has been working on the development of a new deep cavity cavitand system that, while also built from the phenol bridges, is structurally distinct from Cram’s deep cavity vases. First, Gibb and co-workers used functionalized benzal bridges to connect the phenol groups of resorcinarene together, forming another layer of four aromatic rings on top of the cavitand. These four aromatic rings were then linked together with aromatic spacers to close the upper layer, enclosing a much deeper and wider internal cavity (Scheme 4.2.3).

Scheme 4.2.3. A typical two-stage synthesis of Gibb’s deep cavity cavitand

By incorporating functional groups on the resorcinol bridges in the second stage, several types of functionality can be installed on the new deep cavity cavitand, conferring different physical properties and guest binding abilities.

Gibb and co-workers have also been trying to carry out direct functionalization of these deep cavity cavitand using organometallic chemistry. These reactions, however, normally resulted in only moderate yields and with limited regio- and chemo-selectivities. Notably, Gibb’s deep-cavity cavitand system has provided interesting results in photo-catalyzed nano-scale reactor studies. This work has been continued by Ramamurthy, a previous member of the Gibb research group.
4.2.4 Sherman’s \(\sigma\)-Xylyl Bridged Cavitands

In an attempt to create a new deep cavity cavitand system, Sherman and co-workers have also investigated the modification of resorcinarene bridges approach, conceptually similar to the work of Cram/Rebek and Gibb. Sherman et al used \(\sigma\)-xylyl bridges to link resorcinarene phenolic substituents to obtain a new deeper cavity system (Figure 4.2.4). The conformational freedom of this system, however, compromised its value in host-guest chemistry. Since then, no development has been reported for this system.

\[\text{Figure 4.2.4. One example of Sherman’s } \sigma\text{-xylyl bridged cavitands}\]

Again, it should be emphatically noted here that these previous deep cavity cavitands were synthesized by modifying the bridges connecting phenol groups of resorcinarenes.

4.2.5 A Related Structure

To the best of the author’s knowledge, there is no previous report of a deep cavity cavitand built up from the cavitand upper-rim (i.e aromatic ring) substituents. Nevertheless, there is an example of a ‘macrocavitand’ system, where the deep wall was constructed on upper-rim substituents of a calixarene, and is hence related to the work described in this chapter.

This system, first reported by the Ungaro research group fourteen years ago, was built by placement of a calix[8]arene on top of a calix[4]arene. The two calixarene units were linked by four \(-\text{CH}_2\text{O}\)- bridges. This head-to-tail connection imposed some conformational restriction upon both macrocyclic layers to result in a system that can be considered a big and deep cavity similar to deep cavitands (Scheme 4.2.5).
Scheme 4.2.5. ‘Macrocavitand’ formed by the combination of a calix[4]arene and a calix[8]arene

4.3 Design of a New Deep Cavity Cavitand System – Objectives of this Work

Inspired by the design and construction of the superbowl molecules within the group (Chapter 2), a new deep cavity system was proposed (4.1, Scheme 4.3.1). This structure is analogous to the superbowl structure but instead of four wall cavitands, four much simpler phloroglucinol units were built on top of the base cavitand to form the surrounding wall. The second aromatic layer is built from the upper rim substituents, not from the bridges of the base cavitand.

Scheme 4.3.1. Top view and side view of new deep cavity cavitand system bearing bridging units (X) of choice

The synthetic plans to approach this deep cavity cavitand system are outlined in Scheme 4.3.2. In the first proposed synthetic pathway (Route I, Scheme 4.3.2), four
phloroglucinol units are connected to the base cavitand via substitution reaction to form the substituted-cavitand octol 4.2. The phenol groups can then be connected together in an analogous fashion to cavitand formation from resorcinarenes to afford the deep-cavity cavitand 4.1. Synthetic Route 1 is quite similar to what has been done to build up the superbowl molecules, except that synthetically complex wall cavitands are replaced by commercially available phloroglucinol units. Several types of bridges can, in principle, be installed on structure 4.2 to make various kinds of deep-cavity cavitands 4.1.

**Figure 4.3.2.** Synthetic plans for a new deep cavity system

In principle, the deep-cavity cavitand 4.1 can also be made by a four-fold substitution reaction of the base-cavitand 2.8 with a cyclic tetramer 4.3 (Route 2, Scheme 4.3.2). Cyclic tetramer 4.3 can, in turn, be made from phloroglucinol.

There are potential issues associated with both of these approaches. The first steps of these two approaches might require partial protection of the phloroglucinol units to work. There also would be competitive intermolecular processes in both of the second steps (i.e from 4.2 to 4.1 and 4.3 reacts with 2.8 to produce 4.1). The first approach (Route 1, Scheme 4.3.2) is, however, preferred to the second approach (Route 2,
Scheme 4.3.2) because the formation of a tetrameric phloroglucinol cycle such as 4.3 is hard to achieve. Phloroglucinol units can potentially form other linear and cyclic oligomers as well. For example, a preliminary study to make the intermediate 4.5 (Scheme 4.3.3) via tetrameric cyclocondensation reactions of compound 4.4 met with failure. Reactions between 4.4 and a bridging reagent such as ethylene ditosylate generally gave complex mixtures of different linear and cyclic oligomers. Hence, synthetic Route 1 (Scheme 4.3.2) was selected as the pathway to construct the new deep cavity cavitand system 4.1.

Scheme 4.3.3. Failed attempts to make cyclic tetramer 4.6

4.4 Attempts to Synthesize Substituted-Cavitand Octol 4.2

To synthesize the substituted-cavitand octol 4.2, the obvious route is to substitute the bromines on tetra(bromomethyl) cavitand 2.8 with phloroglucinol units in a S_N2 approach.

4.4.1 Substitution with Unprotected Phloroglucinol

It would be convenient if a substitution reaction between unprotected phloroglucinol and the tetra(bromomethyl) cavitand 2.8 could readily occur to produce the substituted-cavitand octol 4.2 in one single step (Scheme 4.4.1). There are, however, several possible impediments to the success of this reaction. These include the optimistic selection of reaction at just one phenoxy group out of the three and the possible oligomer formation from intermolecular substitutions.

To address these problems, several reaction conditions were investigated but unfortunately, none of these gave adequate results. These reaction conditions included various bases (NaOH, K_2CO_3 or Cs_2CO_3), various solvents (THF, DMF or acetone), various temperatures (0 °C, room temperature, refluxing temperature of the solvent),
various reaction times and various reaction stoichiometries (tetra(bromomethyl) cavitand 2.8 reacting with 10-30 molar equivalents of phloroglucinol or slow addition of tetra(bromomethyl) cavitand 2.8 to a solution containing an excess amount of phloroglucinol). These reactions generally gave complex mixtures of products with desired product 4.2 formed in only low yield (5-10% by NMR). It was also difficult to separate the target material from the crude products, as they are very polar compounds. Hence, the direct substitution with phloroglucinol, although being convenient in principle, is not a practical pathway to approach the substituted-cavitand octol 4.2.

Scheme 4.4.1. Attempts to form 4.2 directly from unprotected phloroglucinol

4.4.2 Substitution with Protected Phloroglucinol

Due to failure of the direct substitution of tetra(bromomethyl) cavitand 2.8 with phloroglucinol, a revised strategy was developed: two hydroxy groups of phloroglucinol would be protected with a suitable protecting group. This di-protected species 4.7 would then react with tetra(bromomethyl) cavitand 2.8 to form protected substituted-cavitand octol 4.8. The protecting groups would then be removed to produce the substituted-cavitand octol 4.2 (Scheme 4.4.2).
Scheme 4.4.2. Revised synthetic plan for substituted-cavitand octol 4.2. P = suitable protecting groups

The protecting group employed should be easy to install and should be stable during the S_N2 reaction to provide intermediate 4.8. It should also be easy to cleave such that the acetal bridges on the base cavitand and the benzyl ether on the linkages between the cavitand and phloroglucinol units of intermediate 4.8 are undisturbed.

After screening selections of commonly used protecting groups for phenol, there are only a few candidates suitable for this synthetic route:\textsuperscript{191}

- Methoxymethyl (MOM) ether: can be easily formed by treating the phenol group with base then quenching the resulting phenoxide with methoxymethyl chloride (MOMCl). It is stable under the proposed reaction conditions (potassium/cesium carbonate, acetone) to form intermediate 4.8 and can be cleaved with mild acidic conditions, which do not affect the –OCH₂O- and Ar-OCH₂-Ar linkages on the cavitand.

- Silyl ethers, especially tert-butyldimethylsilyl (TBS group): can be easily formed by treating the phenol with a weak organic base and the appropriate silyl chloride. It is normally stable under the proposed reaction conditions (potassium/cesium carbonate, acetone) to form intermediate 4.8 and can be easily cleaved with tetraalkyl ammonium fluoride, a deprotecting reagent that is harmless to cavitands.
• Benzoyl (Bz) group: can be formed by treatment with organic base and benzoyl chloride. It is moderately stable under the proposed reaction conditions (potassium/cesium carbonate, acetone) to form intermediate 4.8 and cleavage can be achieved by hydrolysis of the ester groups.

4.4.2.1 Utilizing the MOM Protecting Group

To protect two of the three phenoxy groups on a phloroglucinol molecule, a weak organic base (such as Hüning's base, ~ 2.2 molar equivalents) and MOMCl (~ 2.5 molar equivalents) were employed (see Experimental Section for more details). This statistical reaction is moderate-yielding, but still a convenient method to produce the di-protected phloroglucinol unit 4.9 (Scheme 4.4.2). Interestingly, this simple compound was not reported in the literature before.

Scheme 4.4.2. Synthesis of MOM protected substituted-cavitand octol 4.10

The four-fold substitution reaction between 4.9 and 2.8 proceeded smoothly to give the MOM protected substituted-cavitand octol 4.10 in a clean and high yielding reaction (Scheme 4.4.2). Disappointingly, removal of the MOM groups was problematic under all tested reaction conditions. The reactions were either incomplete under mild conditions or unwanted by-products were formed under forcing conditions. The latter
outcome was tentatively explained by the electron-rich nature of the phloroglucinol units, which are expected to participate in unwanted side reactions. For example, under the studied reaction conditions, they could presumably undergo electrophilic aromatic substitution with formaldehyde by-product (Scheme 4.4.3).

Scheme 4.4.3. Failed attempts to deprotect MOM ethers

Many reaction conditions and deprotecting agents were investigated without formation of the substituted-cavitand octol 4.2, so the employment of the MOM protecting group was abandoned.

4.4.2.2 Utilizing the TBS Protecting Group

Attention was then turned towards using the t-butyldimethylsilyl (TBS) unit as protecting group. The di-protected phloroglucinol unit 4.11 was easily formed by treating phloroglucinol with two molar equivalents of n-BuLi, followed by addition of TBSCl (Scheme 4.4.4, see Experimental Section for more details). This compound has been prepared in the literature using imidazole (3 molar equivalents) and TBSCl (2 molar equivalents) in a yield of approximately 35%. Our method resulted in significantly higher yield, presumably due to the lithium diphenoxide intermediate formed by reaction between phloroglucinol and 2 molar equivalents of n-BuLi.
Scheme 4.4.4. Attempts to form TBS protected substituted-cavitand octol 4.12

Unfortunately, the substitution reaction between 4.11 and 2.8 under various reaction conditions (Scheme 4.4.4) did not result in the formation of target product 4.12. Based on analyses of the crude reaction mixtures, under reaction conditions (a) and (c) (Scheme 4.4.4) the cavitand acetal -OCH₂O- bridges appeared to be cleaved. This mysterious problem was left unsolved; investigation of an alternative protecting group was examined instead.

4.4.2.3 Utilizing the Benzoyl Protecting Group

The benzoyl protecting group was the least favoured of the three candidates, since we feared that it might be readily cleaved under the conditions of the substitution reaction. To our surprise and delight, although the benzoyl esters were partially unmasked during the base-mediated substitution reaction, it did not prevent the successful production of substituted-cavitand octol 4.2, as detailed in this section.

3,5-Di(benzoyloxy) phenol 4.13 was easily isolated by column chromatography from a statistical esterification reaction of phloroglucinol with benzoyl chloride. This procedure was developed from a literature report. The reaction produced a mixture of...
the mono (4.15, ~ 15-25%), di (4.13, 50-55%) and tri (4.14, 20-35%) benzoyl protected phloroglucinols (Scheme 4.4.5).

Scheme 4.4.5. Production of benzoyl protected phloroglucinols.

A mixture of predominantly (more than 98%) di (4.13) and tri (4.14) benzoyl protected phloroglucinols could be separated from the crude product mixture using chlorinated solvents such as dichloromethane or chloroform. This operation relies on the sparing solubility of 4.15 in dichloromethane or chloroform. The product ratio of this isolate was approximately 4.13:4.14 = 2:1 (see Experimental Section for more details). This mixture is very useful for the substitution reaction (vide infra).

The substitution reaction between an excess of 3,5-di(benzoyloxy) phenol 4.13 and tetra(bromomethyl) cavitand 2.8 proceeded smoothly, producing the benzoyl protected substituted-cavitand octol 4.16 in 50-55% yield (Scheme 4.4.6).

Scheme 4.4.6. Synthesis of benzoyl protected substituted-cavitand octol 4.16

An initial examination of this reaction suggests a low yield for the substitution reaction. Closer examination of the isolated products, however, reveals the presence of a mixture
of partially deprotected substituted-cavitand octols (25-35%). Thus, it is clear that the benzoyl protecting group is partially labile under these reaction conditions. In any case, partially deprotected material can be combined with the pure target product 4.16 and carried through the next deprotection step. Hence, the yield of the substitution step may be considered to be 75-90%.

Interestingly, products 4.14 and 4.15, the products of transesterification between two molecules of 3,5-di(benzoyloxy) phenol 4.13 were also observed (Scheme 4.4.7). This side reaction inspired the idea of using the aforementioned 2:1 mixture of 4.13 and 4.14 (Scheme 4.4.5) to react with the tetra(bromomethyl) cavitand 2.8. Le Chatelier’s principle shows us that such a mixture suppresses the transesterification side reaction by virtue of the initial presence of 4.14 (Scheme 4.4.7). Such a modification also operationally simplifies the purification process for the preceding step (vide supra). Pleasingly, the use of this mixture generally increases the isolated yield of the pure target product 4.16 by 5-7% (without taking into account the partially deprotected octols mixture), based on the limiting reagent 2.8.

Scheme 4.4.7. Side reactions during the production of compound 4.16
In summary, a mixture of fully benzoyl protected substituted-cavitand octol 4.16 and its partially deprotected derivatives could be conveniently produced by a simple base-mediated substitution reaction between a mixture of benzoyl protected phloroglucinols (4.13 and 4.14) and tetra(bromomethyl) cavitand 2.8 in good yield (80-90%).

4.4.3 Deprotection Step to Produce Substituted-Cavitand Octol 4.2

Global hydrolytic deprotection of the mixture of fully and partially benzoyl protected substituted-cavitand octols (Section 4.4.2) produces substituted-cavitand octol 4.2. The reaction proceeded smoothly with sodium hydroxide in a THF/water (1:1) mixture to give the deprotected substituted-cavitand octol 4.2 (Scheme 4.4.8) in good yield (78-85%).

Scheme 4.4.8. Deprotection to form the substituted-cavitand octol 4.2

Interestingly, while 4.2 dissolves in THF, EtOAc, Et₂O, acetone, DMF and DMSO, it is insoluble in chlorinated solvents. In this respect, its solubility behaviour is more akin to calix[4]resorcinarenes than to cavitands. Furthermore, while the substituted-cavitand octol 4.2 is not soluble in water, addition of only three molar equivalents of sodium hydroxide renders the resulting triphenoxide water-soluble. This observation will be useful in future studies towards a water-soluble host systems based on compound 4.2.

4.5 Guest Binding Studies with Substituted-Cavitand Octol 4.2
The substituted-cavitand octol 4.2 has a rigid bowl at the bottom and eight phenolic groups around the cavity (Figure 4.5.1), somewhat analogous with resorcinarenes. The abilities of resorcinarenes to self-assemble and complex with guests (Section 2.1, Chapter 2) have been previously reported. Inspections of CPK models show that substituted-cavitand octol 4.2 is also conformationally mobile like resorcinarenes. The vase-like conformation depicted in Figure 4.5.1 is just one possible conformation that this molecule can take.

Figure 4.5.1. A resorcinarene and a vase-like conformation of the substituted-cavitand octol 4.2

CPK molecular models suggest that the substituted-cavitand octol 4.2 encloses a much larger interior volume than does a resorcinarene (Figure 4.5.2). Thus, it would be interesting to look at the substituted-cavitand octol 4.2 to see if this ‘extended version’ of resorcinarene could show guest binding ability as well.
Binding studies between the substituted-cavitand octol 4.2 and a series of different tetraalkyl ammonium halides were carried out using the ITC titration technique to explore this intriguing idea. Tetraalkyl ammonium halides were chosen as the initial guests because of their good binding ability towards similar resorcinarene-derived systems. Interestingly, the substituted-cavitand octol 4.2 showed strong 2:1 binding with several tetraalkyl ammonium halides in acetone solution (Scheme 4.5.3). We postulate that two molecules of the substituted-cavitand octol 4.2 form a H-bonding dimeric capsule, possibly with assistance from some solvent molecules (acetone). This capsule might accommodate one tetraalkyl ammonium halide molecule inside. The driving force for these binding events is presumably due to cation-π interactions. The H-bonding dimerization of conformationally flexible ‘deep-cavity’ resorcinarenes analogous to octol 4.2 system has been previously reported by the Rebek research group. Since ITC data only reveal the host/guest binding ratio, we cannot rule out the
possibility that the host/guest complex is formed from six substituted-cavitand octols 4.2 and three tetraalkyl ammonium halides (6:3) or four substituted-cavitand octols 4.2 and two tetraalkyl ammonium halides (4:2). This is reasonable since resorcinarenes are known to self-assemble as hexamers rather than dimeric capsules. To solve this puzzle, attempts to grow crystals of these (substituted-cavitand octols 4.2 and tetraalkyl ammonium ammonium halide) complexes for single crystal X-Ray analysis are ongoing.

Scheme 4.5.3. Binding studies between host 4.2 and guest R₄NHal

Among the tetrabutyl ammonium halide series, the binding strength increases from iodide to bromide to chloride (Scheme 4.5.3). Among the three tetraalkyl ammonium bromides studied, the tetrahexyl ammonium salt is the one binding most strongly inside the H-bonded capsule (Scheme 4.5.3). We attribute both of these binding trends to complementarity of the guest and the host, the guest that shows strongest binding is the one that fits best in the H-bonded dimeric capsule.

4.2 itself assembles in solution, with the dissociation constant of this assembly (probably dimer) determined by ITC to be $K_{\text{dissociation of 4.2 dimer}} = 0.0014 \pm 0.0002$ M, see pages 302-303 for more details). This indicates the promising potential of this ‘resorcinarene analogue’ in host-guest chemistry. Unfortunately, the limited solubilities of the lower and higher tetraalkyl ammonium bromides in acetone solvent prevented a complete survey of this interesting binding trend. The successful binding events with
the aforementioned guests, however, promise future applications of the substituted-cavitand octol system 4.2 in host-guest chemistry.

4.6 Failed Attempts to Close the Deep-Cavity Cavitand with Methylene and Ethylene Bridges

Several attempts to connect the adjacent phenol groups of substituted-cavitand octol 4.2 using either one carbon (CH$_2$) or two carbon (CH$_2$CH$_2$) bridges met with failure (Scheme 4.6.1). CPK molecular models of deep-cavity cavitand 4.1 with CH$_2$ or CH$_2$CH$_2$ bridges can be made but are conformationally restricted. It is postulated that this conformational restriction manifested itself in a high energy barrier towards ring closure. Thus, formation of deep-cavity cavitand 4.1 with longer linkers was explored.

Scheme 4.6.1. Failed attempts to form the deep-cavity cavitand 4.1 with one or two carbon linkers

4.7 Formation of Deep-Cavity Cavitands with Xylyl Bridges

Since the deep-cavity cavitand systems with the ‘short’ methylene or ethylene linkers are possibly too strained to be formed, the use of ‘longer’ xylyl bridges$^{189}$ to close the deep-cavity cavitand was investigated.

4.7.1 Closing Deep-Cavity Cavitand with para and meta Xylyl Bridges

All attempts to install p-xylyl bridges on the substituted-cavitand octol 4.2 met with failure. Various reaction conditions were examined, as detailed in Scheme 4.7.1, with no observed formation of the target compound 4.17. Molecular models suggested that
such a system as 4.17 might perhaps be too conformationally mobile to be formed. It seemed that intramolecular processes to close the deep-cavity cavitand were not able to effectively compete with intermolecular processes, resulting in a complex mixture of oligomers. The construction of this molecule was not pursued further.

Scheme 4.7.1. Failed attempts to approach $p$-xylyl bridged deep-cavity cavitand 4.17

We then turned our attention towards analogous $m$-xylyl bridges to close the deep-cavity cavitand. All attempts to produce $m$-xylyl bridged deep-cavity cavitand 4.18 (Scheme 4.7.2), however, met with the same lack of success.

Scheme 4.7.2. Failed attempts to approach $m$-xylyl bridged deep-cavity cavitand 4.18

4.7.2 Synthesis of Deep-Cavity Cavitand with $o$-Xylyl Bridges

Initial attempts to construct $o$-xylyl bridged deep-cavity cavitand 4.19 were successful but low yielding: substituted-cavitand octol 4.2 was reacted with 4.4 molar equivalents
of α,α’-dibromo o-xylene in the presence of cesium carbonate at 65 °C to afford the o-xylyl bridged deep-cavity cavitand 4.19 in 20-25% yield (Scheme 4.7.3). This interesting compound comprises three layers of aromatic rings as depicted in Scheme 4.7.3 and Figure 4.7.4.

Scheme 4.7.3. Synthesis the of o-xylyl bridged deep-cavity cavitand 4.19

Our attention was next focused on achieving a higher yield for this deep-cavity cavitand formation. After several modifications of reaction conditions, it was found that a room temperature reaction with an excess amount (10 molar equivalents) of α,α’-dibromo o-xylene produced the o-xylyl bridged deep-cavity cavitand 4.19 in an improved yield of 37%.

Figure 4.7.4. Space-filling (CPK) models of the deep-cavity cavitand 4.19 from side-view (left), top-view (middle) and a simple methene-bridged cavitand (right). H atom = white, O atom = red and C atom = black.
The target o-xylyl bridged deep-cavity cavitand 4.19 was easily isolated from the crude product mixture by column chromatography. Characterization by $^1$H and $^{13}$C NMR and IR spectroscopies as well as mass spectrometry and elemental analysis all gave results corresponding to the expected structure of this new deep-cavity cavitand. Attempts to grow crystals suitable for single crystal X-Ray diffraction analysis are ongoing.

### 4.7.3 Conformational Studies of the Deep-Cavity Cavitand 4.19

Previous studies\textsuperscript{194,195} revealed that the tetra(n-propoxy) calix[4]arene can exist in several conformations. Among those, the cone and pinched-cone conformations (Figure 4.7.5) can interconvert. Generally, the cone conformation is the predominant form in the presence of a suitable guest for the calix[4]arene cavity.\textsuperscript{118} Based on inspections of CPK molecular models, it is predicted that the deep-cavity cavitand 4.19 would similarly exist in one of two predominant conformations in the solution phase (Scheme 4.7.6). The first conformation is similar to the pinched-cone form of tetra(n-propoxy) calix[4]arene.\textsuperscript{118} This conformation is presumably stabilized by π-π stacking\textsuperscript{196} interactions of two opposite aromatic rings on the third aromatic layer and also the two pairs of aromatic rings on the second aromatic layers. The second form is a vase-like (also cone-like, but it is deeper) conformation, similar to the vase conformation of Cram’s deep cavity cavitand\textsuperscript{121} (Section 4.2.1). This conformation is likely stabilized by solvation with solvent molecules sitting inside and around the cavity. Similar conformational stabilization was also suggested by Cram and co-workers in their report of cavitand vases and kites (Section 4.2.1).\textsuperscript{121}
Figure 4.7.5. Pinched-cone (top) and cone (bottom) conformations of tetra(n-prooxy) calix[4]arene. Feet are truncated and hydrogen atoms are omitted for clarity.

These pinched-cone and vase-like conformations would rapidly interconvert in the solution phase at room temperature as depicted in Scheme 4.7.6. Furthermore, it is predicted that changing temperature or solvent will affect the interconversion rate and the position of equilibrium between these two forms.

Scheme 4.7.6. Postulated rapid conformational interconversion of the deep-cavity cavitand 4.19 in solution phase. Two pinched-cone conformations are equivalent.

The deep-cavity cavitand 4.19 was, therefore, subjected to conformational change studies using the variable temperature NMR method (Figure 4.7.7). The ¹H NMR spectrum of this compound in CDCl₃ solution at 25 °C reveals that all proton signals are
sharp, suggesting fast conformational interconversion at this temperature. Cooling of the cavitand solution to low temperature (-50 °C) would slow the postulated conformational exchange between vase-like and pinched-cone conformers, resulting in different environments for the protons. Indeed, notable changes are observed in the 1H NMR spectrum of the deep-cavity cavitand 4.19 upon cooling to -50 °C in terms of chemical shifts, multiplicity and broadness (Figure 4.7.7).

![Diagram of the deep-cavity cavitand 4.19](image)

**Figure 4.7.7.** Conformational change studies of the deep-cavity cavitand 4.19 by VT-NMR (500 MHz, CDCl₃), only pertinent sections of the spectra are shown for clarity. Note that the CHCl₃ signal at 7.26 ppm remains sharp at -50 °C.

Subsequent to the VT-NMR studies, the effect of solvation on the conformational mobility of the deep-cavity cavitand 4.19 was investigated. 1H NMR spectra of the
deep-cavity cavitand 4.19 solutions in CDCl₃ and in [D]₆benzene were recorded at 25 °C. Comparison of corresponding signals in the two solutions provides insight into the conformation of the deep-cavity cavitand 4.19 in the solution phase (Figure 4.7.8). Indeed, significant differences in signal chemical shifts can be observed (especially for H₃ and H₆). The signals of the deep-cavity cavitand 4.19 in benzene solution are also much broader than in chloroform solution (Figure 4.7.8).

![Figure 4.7.8. Pertinent sections of ¹H NMR spectra (500 MHz, 25 °C) of the deep-cavity cavitand 4.19 in CDCl₃ (top) and [D]₆benzene (bottom). The signals are much broader in [D]₆benzene than in CDCl₃.](image)

The observation of broader signals in [D]₆benzene is consistent with slower conformational exchange in benzene solution relative to chloroform solution. This may indicate either a higher energy barrier (for conformational exchange) or increased stabilization of at least one of these different conformations in benzene solution. Similar effects of solvents on conformational mobility of cavitands were noted in a 2006 report by Dalcanale and Diederich research groups.¹⁹⁷

In conclusion, the conformational studies of the deep-cavity cavitand 4.19 by VT-NMR as well as ¹H NMR in different solvents are consistent with the proposed conformational flexibility of this deep-cavity structure (Scheme 4.7.6). The effects of temperature and solvent on conformational interconversion of the deep-cavity cavitand 4.19 will be further investigated in future studies.
4.7.4 Guest Binding of Deep-Cavity Cavitand 4.19

Turning our attention now towards the host-guest chemistry of this compound, deep-cavity cavitand 4.19 unfortunately showed no binding with aspirin in chloroform, despite having a similar substitution pattern at the base cavitand to the superbowl, which binds aspirin. Deep-cavity cavitand 4.19 presumably binds chloroform solvent more strongly than aspirin. The limited aspirin binding ability of the deep-cavity cavitand 4.19 may also be somehow associated with its conformational mobility, as described in Section 4.7.3. This issue could be overcome in future studies by incorporating appropriate functional groups on the upper aromatic layer (See Section 4.8 for more details).

Excitingly, deep-cavity cavitand 4.19 shows 1:1 binding with tetrabutyl, tetrahexyl and tetraoctyl ammonium bromides with association constants of approximately 69, 50 and 25 M$^{-1}$ (ITC, chloroform, 25 °C, Table 4.7.9), respectively. While these binding constants could be considered fairly weak in host-guest chemistry, they show a huge improvement from the simple methylene bridged cavitands, considering the sizes of these bulky quaternary ammonium salts. No simple cavitands (Chapter 3 and Chapter 5) showed evidence of binding with these tetraalkyl ammonium salts. In comparison with tetraprotio superbowl 2.16 and tetraprotio cavitand 5.3, deep-cavity cavitand 4.19 indeed shows the expected binding strength of an intermediate size host between the simple methylene bridged cavitands and the superbows (Table 4.7.9).

It should be noted that the binding strength of tetra($n$-alkyl) ammonium bromide in tetraprotio superbowl 2.16 peaks for tetrahexyl ammonium bromide, while deep-cavity cavitand 4.19 binds smaller tetra($n$-alkyl) ammonium bromide more strongly (Table 4.7.9). This is attributed to the difference in size complementarity of the guests in big (2.16) and medium sized (4.19) cavities. Binding studies of other tetra($n$-alkyl) ammonium bromides within deep-cavity cavitand 4.19 will be examined in future work to investigate this effect further.
<table>
<thead>
<tr>
<th>Host</th>
<th>&quot;Bu$_4$NBr</th>
<th>&quot;Hex$_4$NBr</th>
<th>&quot;Oct$_4$NBr</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Diagram" /></td>
<td>329 M$^{-1}$</td>
<td>467 M$^{-1}$</td>
<td>139 M$^{-1}$</td>
</tr>
<tr>
<td><img src="image2.png" alt="Diagram" /></td>
<td>69 M$^{-1}$</td>
<td>50 M$^{-1}$</td>
<td>25 M$^{-1}$</td>
</tr>
<tr>
<td><img src="image3.png" alt="Diagram" /></td>
<td>No binding</td>
<td>No binding</td>
<td>No binding</td>
</tr>
</tbody>
</table>

**Table 4.7.9.** Association constants of hosts 2.16, 4.19 and 5.3 with tetrabutyl, tetrahexyl and tetraoctyl ammonium bromides (ITC, chloroform, 25 °C)

### 4.8 Summary and Conclusions

In summary, a new substituted-cavitand octol (4.2) has been designed and prepared by a synthetic sequence of only three steps from readily available starting materials. It has interesting guest binding ability towards tetra(n-alkyl) ammonium halides (Scheme 4.8.1).
Scheme 4.8.1. 2:1 binding of tetra(n-alkyl) ammonium halides by the substituted-cavitand octol 4.2 and

This versatile substituted-cavitand octol 4.2 was manipulated to create a new deep-cavity cavitand system with o-xylyl bridging units (4.19, Figure 4.8.2). The synthesis of deep-cavity cavitand 4.19 will be further optimised in future studies. Preliminary guest binding studies with tetra(n-alkyl) ammonium bromides promise applications of deep-cavity cavitand 4.19 in host-guest chemistry.

Figure 4.8.2. Synthesis of the deep-cavity cavitand 4.19

The new design for a deep-cavity cavitand system described in this chapter has broad scope for substitution and structural variation. Future developments of this new approach to deep-cavity cavitand systems will include modifications of the bridging units to improve the guest binding ability of these cavitands. For example, xylyl bridges could be replaced by other arene units (naphthalene, quinoxaline, etc) to provide even
deeper cavities. Incorporation of functional groups on the second and third aromatic layers could also enhance the guest binding ability of this system (Figure 4.10.3).

**Figure 4.10.3.** Modification of the deep-cavity cavitand bridges is anticipated to provide superior guest binding ability.
The synthesis of [formula] and its biological evaluation are presented in Figure 4.18. Preliminary results indicate promising activity against certain cancer cell lines. Further studies are necessary to confirm these findings and explore potential applications of [drug name].
CHAPTER 5: TOWARDS THE SYNTHESIS OF AMINOACID CAVITANDS

\[
\begin{align*}
&\text{HOOC} \\
&\text{H} \\
&\text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \\
&\text{A,C-aminoacid cavitand} \\
&\text{COOH} \quad \text{H} \\
&\text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \\
&\text{(1) A,B-aminoacid cavitand}
\end{align*}
\]
5 Towards the Synthesis of Aminoacid Cavitands

5.1 Introduction and Objectives of this Work

Aminoacids are molecules containing both amine and carboxylic acid functional groups. α-Aminoacids are critical building blocks of life (proteins) and have a variety of roles in metabolism (for example, in enzymes). Natural α-aminoacids combine in condensation reactions to form linear polypeptide chains, which are the primary structures of proteins (Figure 5.1.1). Each protein is defined by the unique sequence of aminoacids; twenty-two natural α-aminoacids can be linked in various orders to form an enormous array of proteins. Changing certain aminoacids in the linear chains can greatly affect the physical and chemical nature of proteins. Hence, there is growing interest in the synthesis of unnatural aminoacids to modify polypeptide/protein properties for specific purposes. In this chapter, synthetic efforts towards aminoacid cavitands, special members of artificial aminoacids, will be reported.

Figure 5.1.1. α-Aminoacids and a polypeptide chain. α-Aminoacids are enantiomeric due to the α-carbon stereocenters.

A family of simple functionalised cavitands was designed and synthesized for the specific purpose of aspirin binding (Chapter 3). Thus, many different functional groups were incorporated onto the upper-rims of methylene-bridged cavitands. Most of this chemistry was well described (either within the group or by other research groups in the cavitand area), with the exception of the amination leading to monoamino triprotio
cavitand 3.12 (Scheme 5.1.2). This is the first report of direct installation of the amino
group on the upper-rim of cavitands.

Scheme 5.1.2. Synthesis of cavitand 3.12 with diphenyl phosphoryl azide (DPPA)

Triprotio monocarboxylic acid cavitand 3.11 (Scheme 5.1.3) was also reported in
Chapter 3.

Scheme 5.1.3. Synthesis of triprotio monocarboxylic acid cavitand 3.11

The successful syntheses of the monoamino triprotio cavitand 3.12 and triprotio
monocarboxylic acid cavitand 3.11 inspired us to examine the incorporation of both the
carboxylic acid and amino groups directly onto the upper-rims of the same cavitand.
Such an investigation would:

• Offer new synthetic challenges in cavitand chemistry.
• Provide cavitand systems with carboxylic acid and amino functionalities, which
could be exploited to construct cavitand oligomers via amide linkages.
• Provide an unnatural (cavitand) aminoacid with a cavity available for guest
docking within novel polypeptides, with obvious value for modelling new
enzyme systems.
There are three possible isomeric aminoacid cavitands with both amino and carboxylic acid groups present on the upper-rims of a cavitand (Figure 5.1.4). The A,C-aminoacid cavitand is an achiral compound while the A,B-aminoacid cavitand is a chiral compound with two enantiomers.

The objective of the work described in this chapter, therefore, is to investigate the synthesis of these aminoacid cavitands.

5.2 Review of the Literature Relevant to this Work

In this section, previous literature examples of carboxylic acid cavitands are described. Additionally, the attachment of cavitands to polypeptide chains is also discussed.

5.2.1 Incorporation of Carboxylic Acid Groups on Cavitands

While there has been no report of the direct amination of cavitand upper-rims, Cram and co-workers first reported the carboxylation of cavitands twenty years ago. By simply reacting tetrabromo cavitand with an excess of organolithium reagent, then quenching that lithiated cavitand with methyl chloroformate, tetra(carbomethoxy) cavitand was produced in good yield. The methyl ester could be easily hydrolysed to afford the cavitand tetra carboxylic acid (Scheme 5.2.1). The Lützen research group recently reported the employment of the same chemistry on monobromo cavitand substrate to produce monocarboxylic acid cavitand (see Section 3.4.2.1 for more details).
Scheme 5.2.1. Cram’s approach to incorporate the carboxylic acid group on the cavitand upper-rims.

Cram and co-workers also reported an interesting rearrangement of the tetracarboxylic acid cavitand in the presence of Brönsted acids\(^{201}\) (Scheme 5.2.2).

Alternatively, carbon dioxide could be used as the electrophile for reaction with lithiated cavitands to furnish cavitand tetracarboxylic acids.\(^{37}\) Generally, after the lithium-bromine exchange, \(\text{CO}_2\) was bubbled into the reaction mixture to facilitate the nucleophilic addition of lithiated cavitand to carbon dioxide. Acidic work-up then furnished the carboxyl cavitands (Scheme 5.2.3). Usually, however, the transformation
using CO₂ gas is more operationally complicated than that using methyl chloroformate.\textsuperscript{37,200}

Scheme 5.2.3. An example of incorporating carboxylic acid group on cavitand upper-rims using CO₂\textsuperscript{37}

To the best of the author’s knowledge, there has been no report for the use of carbonylative transition metal catalyzed coupling chemistry to install the carboxylic acid group on cavitand upper-rims.

### 5.2.2 Attaching Cavitands to Polypeptide Chains

There are relatively few reports involving the attachment of cavitand units to polypeptides. Sherman and co-workers were the first to publish in this area. These researchers attached helical polypeptide chains to thiol functional groups on cavitand upper-rims. The work was carried out to investigate protein-folding of polypeptide chains on cavitands (Scheme 5.2.4).\textsuperscript{202-206}

Scheme 5.2.4. Sherman’s approach to attach polypeptides to cavitands
Later, Feigel and co-workers synthesized cavitands with upper-rim polypeptide chains from tetra(aminomethyl) cavitand (Scheme 5.2.5). The nature of benzylic amino groups in this cavitand is clearly different from the cavitand aryl amino group targeted in the work reported in this chapter.

Scheme 5.2.5. Feigel’s approach to attach polypeptides to cavitands

The Sherman and Feigel research groups used different approaches but obtained similar results. Their work on tetra(polypeptide-substituted) cavitands is distinct from the work described in this chapter. Our work focuses on transforming cavitands into discrete aminoacid units with one amino and one carboxylic acid functionality. These units could be then incorporated in to a single linear polypeptide chain.

5.3 Development of Direct Cavitand Upper-Rim Amination

Prior to the work discussed in this chapter, there have been no reports of direct amination of the cavitand upper-rims to form cavitands with structures analogous to 3.12 (Figure 5.3.1). The only related examples in the literature refer to the attachment of amino groups to upper-rim side-chains, similar to the previously-described work by Feigel et al (Section 5.2.2). An investigation was, therefore, carried out to identify the best synthetic processes to achieve direct upper-rim amination.

Figure 5.3.1. Structure of (aryl) amino cavitand 3.12
Several attempts, using both Buchwald-Hartwig\textsuperscript{210} and Ullman\textsuperscript{211} methodologies, to achieve the installation of the amino group at the cavitand upper-rims, met with failure (Scheme 5.3.2). This is not surprising, since extensive work, reported in Chapter 1, has demonstrated that direct transition-metal catalyzed cross coupling reactions with cavitand bromides are very sluggish. This is presumably due to the electron rich and sterically hindered nature of the cavitand aromatic rings. The C-N cross coupling reaction is known to be more difficult than C-C cross coupling reaction.\textsuperscript{212}

Scheme 5.3.2. Failed attempts to install amino groups on cavitand upper-rims using C-N coupling reactions and Curtius rearrangement.

The amino group could also be derived from rearrangement of various amine derivatives such as amides or carboxylic azides. The most popular methods for this type of conversion are Hofmann\textsuperscript{213} and Curtius\textsuperscript{214} rearrangements. Due to the observed sensitivity of the cavitand structure to halogen oxidants – which are generally required for the Hofmann rearrangement - only the Curtius rearrangement was investigated in this work. Unfortunately, attempts to carry out this rearrangement on azide derivatives of monocarboxylic acid cavitand 3.11 met with failure under various reaction conditions (Scheme 5.3.2).
Attention was then turned towards using the lithium-bromine exchange chemistry to perform this amination process. In principle, many different electrophilic nitrogen sources could be used to aminate the lithio cavitand intermediates, such as organic azides or hydroxylamine derivatives. After initial screening, diphenyl phosphoryl azide (DPPA) was identified as the electrophilic agent of choice for the amination process on cavitands. Shioiri and co-workers first reported the use of this reagent to install the amino group on simple aryl halide substrates more than twenty years ago.

The initial attempt to convert monobromo cavitand 3.5 to monoamino cavitand 3.12 using the standard one-pot reaction conditions reported by the Shioiri group met with moderate success. Firstly, cavitand 3.5 was treated with 1.1 molar equivalents of n-BuLi to form the monolithio cavitand intermediate 5.1. This was then quenched with diphenyl phosphoryl azide (DPPA, 1.0 molar equivalent) to yield triaza intermediate 5.2. This was then reduced by sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al, 4.4 molar equivalents) to give monoamino cavitand 3.12 in approximately 40% yield (Scheme 5.3.3).

Encouraged by this success, several modifications to the reaction conditions were made in order to optimise the yield of this process. These included lengthening the reaction.

Scheme 5.3.3. First synthesis of a cavitand with an amino group directly attached to the upper-rim with organolithium reagent and DPPA.
time, using excess DPPA, as well as replacing Red-Al with LiAlH₄ for easier work up. The optimised reaction conditions (Scheme 5.3.4) worked smoothly to give monoamino cavitand 3.12 in 63% yield (see Experimental Section for more details). The characterization data of the product corresponded to the target monoamino cavitand 3.12. Since this is the first cavitand with direct incorporation of an amino group at the upper-rim, single crystal X-Ray analysis of this compound was also carried out (Figure 5.3.6).

Scheme 5.3.4. The optimized reaction conditions to synthesize monoamino cavitand 3.12

Additional investigations were carried out to further optimise the synthesis of this cavitand. Inspired by the monolithiation of cavitands first reported by Irwin et al., and further developed by the Lützen research group, tetraprotio cavitand 5.3 was made and then converted to monoamino cavitand 3.12 (see Experimental Section for more details) in comparable yield (Scheme 5.3.5) to the amination of monobromo cavitand 3.5.

Scheme 5.3.5. Alternative synthesis of monoamino cavitand 3.12
With a practical method for direct amination of the cavitand upper-rim in hand, attention was then turned towards applying this knowledge, in conjunction with the already known carboxylic acid chemistry, to construct the targeted aminoacid cavitands.

Figure 5.3.6. Anisotropic displacement ellipsoid plot of $C_{52}H_{68}NO_8$ (3.12) with a diethylether molecule inside the cavity (two cavitands share one diethyl ether molecule) with labelling of selected atoms. Ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii; the minor sites of disordered atoms have been omitted. Crystals were obtained from diethyl ether/hexane solution.
5.4 Towards the Synthesis of Aminoacid Cavitands

Initially, A,C-aminoacid cavitand 5.5 was targeted (Scheme 5.4.1). A,C-dibromo cavitand 5.4 (Scheme 5.4.1a) was employed as the starting material such that manipulation of the bromine groups would lead to A,C-aminoacid cavitand 5.5 (Scheme 5.4.1b). Since neither amino nor carboxylic acid groups could yet be installed on cavitands using traditional transition-metal catalyzed cross-coupling reactions (vide supra), the approach to aminoacid cavitands is forced to rely on organolithium chemistry. It is, however, not feasible to install both amino and carboxylic acid groups at the same time using organolithium chemistry since each of these functional groups is sensitive to organolithium reagents. In order to carry out the installation of both functionalities by organolithium chemistry, it was decided that a step-wise approach utilizing protecting groups should be employed. This can be carried out by installing either the carboxylic acid group first (Route A, Scheme 5.4.1b) or the amino group first (Route B, Scheme 5.4.1b). Introduction of the other functionality would then follow after protection of the first one.

![Scheme 5.4.1](image-url)
The initial attempts following synthetic Route B (Section 5.4.1b) met with failure. Based on analyses of crude product mixtures, the presence of strong reductant (LiAlH₄ or Red-Al) during the amination process resulted in the reduction of the other bromine atom as well. This reduction has been previously reported in the literature for simple aryl bromides.²¹⁷-²¹⁹

5.4.1 Protecting the Carboxylic Acid Group in the Form of Ester Derivatives

Attention was then turned towards introducing the carboxylic acid group first (Route A, Scheme 5.4.1b) and then protecting this group to allow further lithium-bromine exchange. Conceptually, protection could take the form of protected carboxylic acid groups or the installation of insensitive and stable precursors to the carboxylic acid functionality.

Examples from the literature²²⁰ suggested that a methyl ester could be stable in the presence of t-BuLi. We utilized this moiety in our first attempt (Scheme 5.4.2). A,C-monobromo mono(carbomethoxy) cavitand 5.6 was successfully produced in good yield from A,C-dibromo cavitand 5.4. Unfortunately, treatment of cavitand 5.6 with t-BuLi and DPPA followed by reduction with LiAlH₄ did not yield the desired product 5.7. Analysis of the complicated reaction mixture revealed that the organolithium reagent also underwent nucleophilic addition to the ester group. A similar addition to a carboxyl group with n-BuLi has previously been observed within the group.²²¹ Furthermore, the reduction of the methyl ester by LiAlH₄ was also observed.
Scheme 5.4.2. Methyl ester fails to survive amination process

This synthetic plan was revised by protecting the carboxylic acid group as the much bulkier t-butyl ester\(^\text{232}\) (Scheme 5.4.3). Using t-BuLi as the organometallic reagent and replacing LiAlH\(_4\) with the bulky DIBAL-H, it was expected that there would be neither nucleophilic addition nor reduction at the t-butyl ester. A,C-dibromo cavitand 5.5 was converted to A,C-monobromo mono(carbo tert-butoxy) cavitand 5.8 in respectable yield. Unfortunately, we again observed that the conversion of the other bromine on cavitand 5.8 to the amino group did not proceed cleanly. Only traces of what may have been cavitand 5.9 were found in the reaction mixtures. While predicting that the reaction could be improved, this synthetic route was not further investigated.
Scheme 5.4.3. Unsuccessful attempts to protect the carboxylic acid group in the form of $t$-butyl ester

5.4.2 First Revised Strategy – Protecting the Carboxylic Acid Group in the Form of Protected Aldehyde Derivatives

Since the aforementioned attempts to protect carboxyl groups from organolithium reagents had failed, a revised strategy to pseudo-protect the carboxyl group in its derivative form was proposed as detailed in Scheme 5.4.4. This route started from the aldehyde group, an immediate precursor to the carboxylic acid functionality.

The formylation step in this synthetic plan was carried out easily by lithium-bromine exchange, followed by quenching with DMF to convert one of the bromines on A,C-dibromo cavitand 5.4 to the aldehyde group (Scheme 5.4.4). In principle, the aldehyde group could be protected from organometallic reagents by forming acetal derivatives (Scheme 5.4.5). There have been literature examples of acetal protected 2,6-dimethoxy benzaldehyde systems, very similar to the cavitand aldehyde.\(^{223}\)
Scheme 5.4.4. First revised strategy to produce A,C-aminoacid cavitand 5.5

Unfortunately, all attempts to protect the aldehyde group on cavitand 5.10 by the formation of acetal species were unsuccessful (Scheme 5.4.5). While the reactions progressed well to form the acetal derivatives (based on TLC and $^1$H NMR monitoring), these acetals proved labile during the purification process. This was most likely due to the weak acidity of the silica used in column chromatography.

While it is difficult to definitively explain why stable acetal derivatives of the aldehyde cavitand 5.10 could not be formed, it could possibly be attributed to steric and electronic effects of the cavitand on the side chain of the aldehyde.
Scheme 5.4.5. Attempts to acetal-protect the aldehyde cavitand 5.12

In principle, the aldehyde functionality could be protected in the form of an vinyl group. This vinyl group may eventually be converted back to the aldehyde group by an oxidative cleavage (Scheme 5.4.6). A Wittig olefination of cavitand aldehyde 5.10 proceeded in good yield to give A,C-monobromo monovinyl cavitand 5.12. This encouraging work was set aside in the face of success of an operationally simpler and safer, though longer, synthetic route to A,C-aminoacid cavitand (Section 5.4.3).

Scheme 5.4.6. Synthetic plan employing a vinyl group as a protected aldehyde functionality
5.4.3 Second Revised Strategy – Protecting the Carboxylic Acid Group in the Form of Protected Benzylic Alcohol Derivatives

In the first revised synthetic plan, there were issues associated with protection of the aldehyde group on cavitand 5.10. Hence, a second revised synthetic plan, in which the carboxylic acid group is protected in the form of benzylic alcohol derivative (Scheme 5.4.7), was proposed and executed.

![Scheme 5.4.7. Second revised strategy to produce A,C-aminoacid cavitand 5.5](image)

As previously described (Section 5.4.2), A,C-monobromo monoformyl cavitand 5.10 was easily produced by selective monoformylation of A,C-dibromo cavitand 5.4. After reduction of the aldehyde group, cavitand 5.14 was produced in good yield. MOM protection of the newly-formed benzylic alcohol cleanly afforded cavitand 5.15. Amination of cavitand 5.15 using the developed procedure (Section 5.3), followed by subsequent cleavage of the MOM ether gave A,C-monoamino mono(hydroxymethyl) cavitand 5.16 in moderate yield. It simply remains to selectively oxidize the benzylic alcohol to the carboxylic acid group to produce A,C-aminoacid cavitand 5.5.
Preliminary investigations have been carried out to address this challenge. Stepwise treatment with Dess-Martin periodinane and Pinnick oxidation as well as direct oxidation using silica-supported Jones reagent\textsuperscript{224,225} of A,C-monoamino mono(hydroxymethyl) cavitand 5.16 showed promising results (Scheme 5.4.8). Due to time constraints and the limited amount of the precursor cavitand 5.16 available, these encouraging result will be re-investigated in future studies.

Scheme 5.4.8. Selective oxidation of 5.16 to 5.5

5.5 Host-Guest Chemistry of the Cavitand Intermediate 5.16

It is interesting to examine the host-guest chemistry of A,C-monoamino mono(hydroxymethyl) cavitand 5.16, the hybrid of compound 3.1 and 3.12. Preliminary binding studies with aspirin showed that cavitand 5.16 also binds aspirin in a 1:1 ratio with an association constant of 58 ± 2 M\textsuperscript{-1} (Figure 5.5.1)

Figure 5.5.1. Association constants with aspirin of cavitands 3.1, 3.12 and 5.16 (ITC, chloroform, 25 °C)
While at first glance, it is surprising to see that cavitand 5.16, a hybrid of the two cavitands that bind aspirin most strongly among the simple cavitands studied in Chapter 3, showed relatively weaker binding than either component cavitand. It does, however, not contradict the observations discussed in Chapter 3. Since both the amino and the hydroxy methyl groups can potentially participate in H-bonding interactions, it is likely that the formation of H-bonding cavitand dimers/oligomers competes with the aspirin binding process. It can be concluded that the incorporation of two functional groups with similar guest binding potential on a host molecule will not necessarily result in a better host with enhanced binding ability.

5.6 Summary and Future Work

The development of the first practical direct amination of the cavitand upper-rims is described in this chapter. The amination process was then employed towards the synthesis of the first aminoacid cavitands. Due to time limits, the ultimate goal to make all three isomers of cavitand compounds with both amino and carboxylic acid functionalities on the upper-rims was not reached. With A,C-monoamino mono(hydroxymethyl) cavitand 5.16 in hand, the final target A,C-aminoacid cavitand is just one oxidation step away (Scheme 5.6.1).

![Scheme 5.6.1. Future work to obtain A,C-aminoacid cavitand](image)

When the A,C-aminoacid cavitand is produced, there should be no impediment to using a synthetic sequence analogous to Scheme 5.4.7 to functionalize the readily available A,B-dibromo cavitand 5.17 to provide a racemic mixture of A,B-aminoacid cavitands (Scheme 5.6.2).
Scheme 5.6.2. Synthetic plan towards A,B-aminoacid cavitands

In the future, when all targeted aminoacid cavitands are made, they will be interesting representatives of cavitand systems that may be reasonably anticipated to bind a wider variety of biologically active compounds than any of the individual simple cavitands reported previously (Chapter 3). These cavitands also offer the opportunity to assemble larger cavitand based host systems by exploiting carboxyl and amino functionalities in amide linkages. It furthermore presents the prospect of using these newly-created cavitand systems as unnatural aminoacids with cavities available for C-H⋯π interactions in polypeptides, with clear applications in the modelling of new enzyme systems.
CHAPTER 6: EXPERIMENTAL DATA
General Methods

Reactions, unless otherwise stated, were conducted under a positive pressure of dry nitrogen in oven-dried glassware. Tetrahydrofuran (THF), benzene, toluene and diethyl ether were dried over sodium wire and distilled from sodium benzophenone ketyl. Dichloromethane was dried by distillation from calcium hydride. B(OMe)$_3$ was dried by distillation from sodium metal. Magnesium sulfate was dried at 140 °C for 12 h prior to use. Commercially available reagents were used as purchased unless otherwise noted. Analytical thin layer chromatography was performed using silica gel plates precoated with silica gel 60 F$_{254}$ (0.2 mm). Flash chromatography employed 230-400 mesh silica gel. Solvents used for chromatography are quoted as volume/volume ratios.

HPLC was performed using a Shimadzu CLASS-VP LC-10AD chromatography pump monitored by a Shimadzu SPD-10A VP UV detector and a Shimadzu RID-10A refractive index detector. Preparative HPLC employed an RTI Zorbax SIL column of pore size 7 μm, of internal diameter 21.2 mm and 25 cm length.

$^1$H NMR spectra were recorded at 298 K unless otherwise stated using Varian Unity INOVA 300 MHz and 500 MHz spectrometers. Data is expressed in parts per million (ppm) downfield shift from tetramethylsilane with residual solvent as an internal reference (δ 7.26 ppm for chloroform, 2.04 ppm for acetone and 2.09 ppm for the toluene methyl group) and is reported as position (δ in ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (J in Hz) and integration (number of protons).

$^{13}$C NMR spectra were recorded at 298 K unless otherwise stated using Varian Unity INOVA 75 MHz and 125 MHz spectrometers with complete proton decoupling. Data is expressed in parts per million (ppm) downfield shift relative to the internal reference (δ 77.2 ppm for the central peak of deuterated chloroform, 29.8 and 206.8 ppm for the central peaks of deuterated acetone) and is reported as position (δ in ppm).

Compounds were prepared for IR spectroscopic analysis as mixtures in KBr pressed disks (solids) or thin films between NaCl plates (oils) and the spectra were collected.
using a Perkin-Elmer Spectrum One spectrophotometer. All compounds were dried before analysis at ca. 50 °C and 0.1 mm Hg for 24 h.

Elemental analyses were obtained at the Microanalytical Unit at the Research School of Chemistry, Australian National University. All compounds were dried at ca. 50 °C and 0.1 mmHg for 24-120 h before analysis.

Mass spectra were recorded on Micromass ZMD and Bruker Alrex 3 FTICR instruments. Melting points were recorded on a Reichert heating stage with a microscope and are uncorrected.

ITC binding studies were carried out using a MicroCal VP-ITC Isothermal Titration Calorimeter. See ‘General Methods for Host-Guest Binding Studies’ for more details.
Standard Drying Procedures for Organometallic Reactions

To a two-necked round-bottomed flask, fitted with a septum and stir bar, containing the cavitand or superbowl starting material, was added dry, freshly distilled THF (10 mL per 1 mmol of starting material). The resulting solution was evaporated to dryness and then heated at 80 °C at 0.1 mmHg for 1 h. The vacuum was replaced with Ar, and the procedure was repeated two more times.
General Methods for Host-Guest Binding Studies

For $^1$H NMR studies, unless otherwise stated, a solution of 1:1 mixture of the host (1 mM) and the guest (1 mM) in CDCl$_3$ was prepared for each cavitand/superbowl host. The spectrum of the mixture was then recorded and compared with the spectra of the free cavitand host and the free aspirin in the same solvent. Evidence of binding would be either the appearance of bound guest signals upfield from the free guest chemical shifts and/or splitting of the signals of unbound guest/host and the bound guest+host complex.

ITC binding studies were carried out using a MicroCal VP-ITC Isothermal Titration Calorimeter. All binding studies, unless otherwise stated, were carried out in chloroform (AR grade, degassed) or acetone (AR grade, degassed) solvents with the initial host concentrations varying from 0.5 to 3 mM and the initial guest concentrations varying from 50 to 100 mM. The initial guest concentrations were always maintained more than 10 times higher than the initial host concentrations to ensure accuracy of the weak-binding association constants. The host solutions were placed in the cell and the guest solutions were injected from the syringe. Baselines were corrected with titration of solutions of guests into blank solvents. Evidence for binding would be exothermic signals during injections of guest solution into host solution.

The rate of enthalpy change $\delta H$ (µcal/sec) was monitored and plotted against time (sec or min). From that, the relationship between enthalpy change $\Delta H$ and molar ratio of the guest to the host can be deduced and plotted. Based on these two plots, the association constant $K$, binding stoichiometry $N$, enthalpy change $\Delta H$ and entropy change $\Delta S$ can be derived. Data were automatically processed by One Set of Sites model of Origin 7.0 software with manual integration adjustment if necessary, in the case of thermal overcompensating. All experiments were performed in duplicate.

The ITC titration set-up was used throughout as:

- Cell volume = 1.4365 mL;
- Syringe volume = 297 µL;
- Cell temperature = 25 °C;
Reference power = 30 μcal/sec;
Stirring speed = 300 rpm;
Initial delay = 300 sec;
Total number of injections = 42;
1st injection = 1 μL during 2.5 sec with spacing from the next injection = 240 sec;
Each of 2nd – 42nd injections = 7 μL during 14 sec with spacing from the next injection = 180 sec.

ITC data output (rounding up to significant figures):

N = binding stoichiometry [Guest:Host] (binding ratio);
K = association constant (M⁻¹);
ΔH (or H) = enthalpy change (cal mol⁻¹);
ΔS (or S) = entropy change (cal mol⁻¹K⁻¹).
CHAPTER 1 - EXPERIMENTAL DATA

R substituent blocks guest complexation

host-guest complex

inside atropisomer

outside atropisomer
C-pentyl tribromocavitandboronate pinacolyl ester 1.2

Tetrabromocavitand 2.3 (2.00 g, 1.77 mmol) was dried according to the standard procedures. The dried tetrabromocavitand was then dissolved in dry tetrahydrofuran (90 mL) and the resulting solution cooled to -78 °C. n-Butyllithium (1.30 M in hexane, 1.50 mL, 1.94 mmol) was added rapidly and the solution was stirred for 20 minutes, then trimethoxyborane (300 µL, 2.65 mmol) was added rapidly. The reaction mixture was allowed to warm to room temperature, quenched with 1M aq. HCl (100 mL) then stirred for a further 40 minutes before THF was removed in vacuo. The mixture was extracted with dichloromethane (3 x 50 mL) then the combined organic phases were dried over MgSO₄ and the solvent was removed in vacuo. The residue was dissolved in dichloromethane (90 mL) then pinacol (230 mg, 1.94 mmol, 1.1 mol eq.) and MgSO₄ (880 mg) were added. The mixture was stirred overnight, then filtered and the solvent was removed in vacuo. The crude product was purified by flash chromatography (200 g silica, 6:4 dichloromethane/hexane) to afford compound 1.2 as a white solid (1.59 g, 76%): \( R_f = 0.54 \) (6:4 dichloromethane/hexane); m.p. 168-170 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.12 (s, 1H), 7.02 (s, 3H), 5.95 (d, \( J = 7.2 \) Hz, 2H), 5.78 (d, \( J = 7.5 \) Hz, 2H), 4.83 (t, \( J = 8.1 \) Hz, 2H), 4.79 (t, \( J = 8.3 \) Hz, 2H), 4.45 (d, \( J = 7.2 \) Hz, 2H), 4.36 (d, \( J = 7.5 \) Hz, 2H), 2.35-2.10 (m, 8H), 1.50-1.25 (m, 36H), 0.98-0.90 (m, 12H) ppm; \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 157.5, 152.4, 152.2, 139.9, 139.4, 139.3, 138.0, 119.3, 119.1, 113.8, 99.2, 98.7, 84.7, 38.0, 37.9, 37.2, 32.1, 30.1, 30.0, 27.7, 25.0, 22.9, 14.3 ppm; IR (KBr) 2929, 2862, 1642, 1590 cm⁻¹; LSIMS-MS \( m/z \) 1179 ([M+H]⁺, 100%); Anal. Calcd. for C₉₈H₇₂BBr₅O₁₀: C, 59.05; H, 6.15; found C, 59.06; H, 6.11.
General procedures for the synthesis of mono ortho-substituted aryl cavitands

An oven-dried round-bottom flask was placed under a nitrogen atmosphere and charged with C-pentyltribromocavitandboronate pinacolyl ester 1.2 (100 mg; 84.8 µmol), ortho-substituted iodobenzene 1.3 (254 µmol, 3.0 mol eq.), silver carbonate (46.1 mg, 170 µmol, 2.0 mol eq.), tris(dibenzylideneacetone)dipalladium(0) (10.0 mg, 10.0 µmol, 0.12 mol eq.), and tri-2-furylphosphine (10.0 mg, 42.0 µmol, 0.5 mol eq.). The flask was evacuated and refilled with nitrogen three times then dry tetrahydrofuran (5 mL) was added. The reaction mixture was stirred at 25-30 °C in the dark for 18-72 h then filtered through a short plug of celite, washed with several portions of dichloromethane and the solvent was evaporated to afford the crude product, which was purified by flash chromatography.

General procedures for characterizing mono ortho-substituted aryl cavitands

For the inside/outside cavitand isomers, the interconversion between inside and outside forms happens with heating or changing solvent and results in a mixture of both isomers. Hence, mass spectrometric, IR spectroscopic and elemental analyses as well as melting point determinations, which require handling compounds in different solvents and/or at high temperature, are reported as for the mixture of inside/outside isomers.
General procedures for thermodynamic interconversion studies of mono ortho-substituted aryl cavitands

1 mM solutions (1 mL) of the inside stereoisomers in suitable deuterated solvents were placed inside standard NMR tubes. These NMR tubes were equilibrated inside a multi-neck reaction flask equipped with a condenser containing suitable heating medium (THF for 65 °C experiments and water for 50 °C and 120 °C). For experiments with compounds 1.4c/1.5c, sealed tube was used instead of standard NMR tubes. Time of experiments was monitor using a standard clock timer. \( t_{1/2} \) was determined as the time when the concentrations/ratios of the inside stereoisomers were half the differences between the initial and final (equilibrium) concentrations/ratios.

\(^1\)H NMR spectra for stereoisomer ratios were recorded at 298 K using a Varian Unity INOVA 300 MHz spectrometer in the solvent specified. Stereoisomer ratios were calculated from integrations of characteristic proton signals for inside and outside isomers. Each ratio was the average of 2 runs (for inside/outside ratios of Suzuki coupling reactions) or 4-8 runs (for thermodynamic equilibria). Standard deviations are quoted. T1 values for these characteristic protons were determined, then the delay time \( d1 \) was set to 5 times the maximum T1 value to minimize integration error to less than 1%.

For equilibria of compounds 1.4e/1.5e in ethyl acetate and carbon tetrachloride, non-D NMR technique was employed to records spectra and measure stereoisomer ratios.
Inside-C-pentyl-(2-methylphenyl) tribromo cavitand 1.4a and outside-C-pentyl-(2-methylphenyl) tribromo cavitand 1.5a

These compounds were synthesized using the general procedure with 2-iodotoluene as electrophile 1.3. The reaction time was 18 h. NMR of the crude product indicated a 86:14 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4a (58 mg, 60%) and outside isomer 1.5a (9 mg, 10%).

The inside isomer 1.4a was obtained as a white solid: $R_f = 0.30$ (3:7 dichloromethane/hexane); m.p. 130-135 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.18-7.30 (m, 4H), 7.16 (s, 1H), 7.11 (s, 2H), 6.90 (d, $J = 6.9$ Hz, 1H), 6.00 (d, $J = 7.5$ Hz, 2H), 5.55 (d, $J = 7.5$ Hz, 2H), 4.88 (t, $J = 8.1$ Hz, 2H), 4.78 (t, $J = 7.2$ Hz, 2H), 4.39 (d, $J = 9.3$ Hz, 2H), 4.36 (d, $J = 7.5$ Hz, 2H), 2.40-2.10 (m, 8H), 2.09 (s, 3H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.1, 152.8, 152.1 (two coincident resonances), 140.1, 139.6, 139.1, 138.4, 134.7, 134.3, 130.5, 130.1, 129.8, 128.0, 126.0, 120.0, 119.2, 113.6, 112.7, 99.1, 98.9, 38.0, 37.6, 32.2, 32.1, 30.5, 30.1, 29.9, 27.7, 22.9, 22.5, 14.3 ppm; IR (KBr) 2929, 2866, 1465, 1447 cm$^{-1}$; ESI-MS $m/z$: 1168.2 ([M+Na]$^+$, 100%), 1143.5 ([M]$^+$, 10%); Anal. Calcd. for C$_{59}$H$_{97}$Br$_3$O$_8$: C, 61.95; H, 5.90; found C, 61.84; H, 5.92.

The outside isomer 1.5a was obtained as a white solid: $R_f = 0.42$ (3:7 dichloromethane/hexane); m.p. 130-135 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.28 (d, $J = 6.0$ Hz, 1H), 7.24 (t, $J = 4.2$ Hz, 1H), 7.16 (t, $J = 5.7$ Hz, 1H), 7.15 (s, 1H), 7.11 (s, 1H), 7.09 (s, 2H), 6.77 (d, $J = 7.2$ Hz, 1H), 5.99 (d, $J = 7.5$ Hz, 2H), 5.42 (d, $J = 7.5$ Hz, 2H), 4.87 (t, $J = 8.1$ Hz, 2H), 4.82 (t, $J = 8.7$ Hz, 2H), 4.37
Inside-C-pentyl-(1-naphthyl) tribromo cavitand 1.4b and outside-C-pentyl-(1-naphthyl) tribromo cavitand 1.5b

These compounds were synthesized using the general procedure with 1-iodonaphthalene as electrophile 1.3. The reaction time was 48 h. NMR of the crude product indicated a 97:3 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4b (67 mg, 68%) and outside isomer 1.5b (2 mg, 2%).

The inside isomer 1.4b was obtained as a white solid: $R_f = 0.64$ (6:4 dichloromethane/hexane); m.p. 122-126 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.94 (d, $J = 5.4$ Hz, 1H), 7.90 (d, $J = 8.7$ Hz, 1H), 7.56 (d, $J = 7.2$ Hz, 1H), 7.51 (t, $J = 0.6$ Hz, 1H), 7.50 (t, $J = 0.6$ Hz, 1H), 7.36 (t, $J = 4.5$ Hz, 1H), 7.22 (s, 1H), 7.19 (s, 1H), 7.17 (d, $J = 6.0$ Hz, 1H), 7.16 (s, 2H), 6.04 (d, $J = 7.5$ Hz, 2H), 5.17 (d, $J = 7.5$ Hz, 2H), 4.93 (t, $J = 8.1$ Hz, 2H), 4.81 (t, $J = 8.0$ Hz, 2H), 4.47 (d, $J = 7.5$ Hz, 2H), 4.34 (d, $J = 7.5$ Hz, 2H), 2.40-2.10 (m, 8H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 153.8, 152.8, 152.2, 152.1, 140.3, 139.7,
The outside isomer 1.5b was obtained as a white solid: $R_f = 0.68$ (6:4 dichloromethane/hexane); m.p. 122-126 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J = 7.8$ Hz, 1H), 7.86 (d, $J = 8.7$ Hz, 1H), 7.50 (t, $J = 8.1$ Hz, 1H), 7.46 (t, $J = 4.2$ Hz, 1H), 7.43 (t, $J = 7.2$ Hz, 1H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.21 (s, 1H), 7.14 (s, 1H), 7.11 (s, 2H), 7.00 (d, $J = 7.2$ Hz, 1H), 6.00 (d, $J = 7.2$ Hz, 2H), 5.32 (d, $J = 7.5$ Hz, 2H), 4.91 (t, $J = 8.1$ Hz, 2H), 4.85 (t, $J = 8.7$ Hz, 2H), 4.39 (d, $J = 7.2$ Hz, 2H), 4.34 (d, $J = 7.2$ Hz, 2H), 2.40-2.10 (m, 8H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 152.9, 152.8, 152.2, 152.1, 140.5, 139.7, 139.1, 138.4, 133.8, 132.6, 132.3, 128.9, 128.8, 128.3 two coincident resonances), 126.9, 125.9, 125.4, 120.4, 120.2, 119.2, 113.9, 112.5, 99.7, 98.8, 38.0, 37.6, 32.1, 30.5, 30.1, 27.8, 22.8, 14.4 ppm; IR (KBr) 2928, 2860, 1466, 1448 cm$^{-1}$; ESI-MS $m/z$: 1198.7 ([M+NH$_3$]$^+$, 90%), 1179.7 ([M]$^+$, 100%); Anal. Calcd. for C$_{62}$H$_{56}$Br$_3$O$_8$: C, 63.11; H, 5.72; found C, 63.46; H, 5.68.

**Inside-C-pentyl-(2-bromophenyl) tribromo cavitand 1.4c and outside-C-pentyl-(2-bromophenyl) tribromo cavitand 1.5c**

These compounds were synthesized using the general procedure with 2-bromoiodobenzene as electrophile 1.3. The reaction time was 72 h. NMR of the crude product indicated a 98:2 mixture of inside:outside isomers. The crude product was...
purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give **inside** isomer 1.4c (85 mg, 83%) and **outside** isomer 5c (2 mg, 2%).

The **inside** isomer 1.4c was obtained as a white solid: \( R_f = 0.40 \) (6:4 dichloromethane/hexane); m.p. 202-204 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.62 \) (dd, \( J = 7.8, 0.9 \) Hz, 1H), 7.35 (td, \( J = 7.2, 0.9 \) Hz, 1H), 7.24 (td, \( J = 6.6, 1.8 \) Hz, 1H), 7.15 (s, 1H), 7.14 (s, 1H), 7.11 (s, 2H), 7.01 (dd, \( J = 7.5, 1.8 \) Hz, 1H), 5.98 (d, \( J = 7.5 \) Hz, 2H), 5.58 (d, \( J = 7.2 \) Hz, 2H), 4.89 (t, \( J = 7.9 \) Hz, 2H), 4.77 (t, \( J = 8.1 \) Hz, 2H), 4.69 (d, \( J = 7.5 \) Hz, 2H), 4.42 (d, \( J = 7.8 \) Hz, 2H), 2.40-2.10 (m, 8H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 152.9, 152.8, 152.2, 152.1, 140.0, 139.3, 139.1, 138.2, 136.5, 132.4, 132.3, 129.7, 129.4, 127.7, 122.9, 120.8, 120.0, 119.1, 113.7, 112.7, 99.7, 99.0, 38.0, 37.6, 32.2 (two coincident resonances), 30.5, 30.1, 27.7 (two coincident resonances), 22.9, 14.4 ppm; IR (KBr) 2929, 2861, 1467, 1449 cm\(^{-1}\); ESI-MS m/z: 1226.2 ([M+NH\(_4\)]\(^+\), 100%), 1208.2 ([M]\(^+\), 35%); Anal. Calcd. for C\(_{58}\)H\(_{64}\)Br\(_4\)O\(_8\): C, 57.63; H, 5.34; found C, 57.67; H, 5.28.

The **outside** isomer 1.5c was obtained as a white solid: \( R_f = 0.36 \) (6:4 dichloromethane/hexane); m.p. 203-204 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta 7.68 \) (dd, \( J = 7.8, 1.5 \) Hz, 1H), 7.26 (t, \( J = 8.2 \) Hz, 1H), 7.24 (t, \( J = 8.4 \) Hz, 1H), 7.15 (s, 1H), 7.12 (s, 1H), 7.09 (s, 2H), 6.91 (dd, \( J = 5.4, 1.5 \) Hz, 1H), 6.00 (d, \( J = 7.2 \) Hz, 2H), 5.45 (d, \( J = 7.5 \) Hz, 2H), 4.87 (t, \( J = 8.4 \) Hz, 2H), 4.84 (t, \( J = 9.0 \) Hz, 2H), 4.36 (d, \( J = 7.5 \) Hz, 2H), 4.30 (d, \( J = 7.2 \) Hz, 2H), 2.40-2.10 (m, 8H), 1.55-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; \(^13\)C NMR (125 MHz, CDCl\(_3\)) \( \delta 152.7, 152.3, 152.1 \) (two coincident resonances), 140.7, 140.0, 139.8, 139.2, 138.7, 138.5, 136.2, 133.2, 132.4, 130.1, 129.4, 127.0, 124.8, 120.4, 119.8, 119.3, 113.8, 112.9, 111.4, 99.1, 98.9, 38.0, 37.4, 32.1 (two coincident resonances), 30.5, 30.0, 29.9, 29.7, 29.4, 29.2, 27.7, 22.9, 21.3, 14.4, 14.3 ppm; IR (KBr) 2929, 2861, 1467, 1449 cm\(^{-1}\); ESI-MS m/z: 1226.2 ([M+NH\(_4\)]\(^+\), 100%), 1208.2 ([M]\(^+\), 35%); Anal. Calcd. for C\(_{58}\)H\(_{64}\)Br\(_4\)O\(_8\): C, 57.63; H, 5.34; found C, 57.67; H, 5.28.
Inside-C-pentyl-(2-carbomethoxyphenyl) tribromo cavitand 1.4d and outside-C-pentyl-(2-carbomethoxyphenyl) tribromo cavitand 1.5d

These compounds were synthesized using the general procedure with methyl 2-iodobenzoate as electrophile 1.3. The reaction time was 18 h. NMR of the crude product indicated a 25:75 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4d (19 mg, 19%) and outside isomer 1.5d (57 mg, 56%).

The inside isomer 1.4d was obtained as a white solid: $R_f = 0.31$ (1:9 ethyl acetate/hexane); m.p. 120-127 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.99 (d, $J = 7.8$ Hz, 1H), 7.76 (d, $J = 16.2$ Hz, 1H), 7.63 (t, $J = 3.3$ Hz, 1H), 7.43 (t, $J = 3.6$ Hz, 1H), 7.15 (s, 2H), 7.14 (s, 1H), 7.13 (s, 1H), 5.98 (d, $J = 7.5$ Hz, 2H), 5.40 (d, $J = 7.2$ Hz, 2H), 4.89 (t, $J = 8.1$ Hz, 2H), 4.80 (t, $J = 8.1$ Hz, 2H), 4.49 (d, $J = 7.5$ Hz, 2H), 4.18 (d, $J = 7.2$ Hz, 2H), 2.73 (s, 3H), 2.40-2.10 (m, 8H), 1.50-1.25 (m, 24H), 1.00-0.90 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.1, 152.7, 152.4, 152.2, 151.6, 143.6, 139.7, 139.6, 139.3, 137.9, 135.0, 132.9, 130.8, 129.2, 128.7, 128.3, 128.1, 125.7, 119.2, 113.7, 113.4, 99.0 (two coincident resonances), 50.7, 38.0, 37.6, 32.2 (two coincident resonances), 30.3 (two coincident resonances), 27.8, 27.7, 24.1, 22.9, 21.0, 14.3 ppm; IR (KBr) 2928, 2857, 1752, 1621, 1467 cm$^{-1}$; ESI-MS $m/z$: 1209.3 ([M+Na]$^+$, 100%), 1187.3 ([M]$^+$, 15%); Anal. Calcd. for C$_{68}$H$_{67}$Br$_3$O$_{10}$: C, 60.67; H, 5.68; found C, 60.83; H, 5.67.

The outside isomer 1.5d was obtained as a white solid: $R_f = 0.26$ (1:9 ethyl acetate/hexane); m.p. 120-127 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.06 (d, $J = 7.5$ Hz, 1H), 7.48 (t, $J = 7.5$ Hz, 1H), 7.42 (t, $J = 6.0$ Hz, 1H), 7.12 (s, 1H), 7.10 (s, 1H), 7.08 (s, 2H), 6.91 (d, $J = 7.5$ Hz, 1H), 5.99 (d, $J = 7.2$ Hz,
Inside-C-pentyl-(2-carboethoxyphenyl) tribromo cavitand 1.4e and outside-C-pentyl-(2-carboethoxyphenyl) tribromo cavitand 1.5e

These compounds were synthesized using the general procedure with ethyl 2-iodobenzoate as electrophile 1.3. The reaction time was 18 h. NMR of the crude product indicated a 83:17 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4e (50 mg, 50%) and outside isomer 1.5e (10 mg, 10%).
MHz, CDCl₃) δ 166.9, 152.6, 152.3, 152.1, 151.0, 140.1, 139.8, 139.4, 138.1, 135.9, 133.1, 131.9, 131.8, 131.7, 128.7, 128.2, 119.7, 119.5 (two coincident resonances), 113.5 (two coincident resonances), 98.9, 97.8, 83.2, 59.5, 41.1, 37.9, 37.5, 34.0, 32.2, 32.1, 30.1, 29.9, 28.6, 27.8, 27.7, 24.0, 22.9, 21.0, 17.7, 17.5, 14.9, 14.4, 14.3 (two coincident resonances), 8.2 ppm; IR (KBr) 2929, 2868, 1714, 1621, 1467, 1449 cm⁻¹; ESI-MS m/z: 1225.3 ([M+Na]⁺, 100%), 1201.3 ([M]⁺, 5%); Anal. Calcd. for C₆₀H₆₀Br₃O₁₀: C, 60.96; H, 5.79; found C, 61.12; H, 5.88.

The outside isomer 1.5e was obtained as a white solid: Rf = 0.15 (1:9 ethyl acetate/hexane); m.p. 109-113 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 8.08 (d, J = 7.5 Hz, 1H), 7.48 (t, J = 7.5 Hz, 1H), 7.43 (t, J = 6.6 Hz, 1H), 7.13 (s, 1H), 7.11 (s, 1H), 7.08 (s, 2H), 6.91 (d, J = 6.9 Hz, 1H), 5.99 (d, J = 7.5 Hz, 2H), 5.40 (d, J = 7.2 Hz, 2H), 4.87 (t, J = 8.1 Hz, 2H), 4.82 (t, J = 8.1 Hz, 2H), 4.35 (d, J = 7.2 Hz, 2H), 4.29 (d, J = 6.9 Hz, 2H), 4.07 (q, J = 7.2 Hz, 2H), 2.40-2.10 (m, 8H), 1.50-1.25 (m, 27H), 1.00-0.90 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 167.2, 152.6, 152.3, 152.2, 140.1, 140.0, 139.7, 139.4, 139.1, 138.1, 138.0, 135.2, 131.8, 131.4, 131.1, 130.2, 128.0, 119.8, 119.5, 119.3, 119.1, 113.7, 113.5, 112.8, 99.1, 98.9, 83.2, 61.0, 41.1, 38.0, 37.5, 37.4, 34.0, 32.2, 30.2, 28.6, 27.8, 27.7, 24.1, 22.9, 21.0, 20.8, 17.7, 17.5, 14.9, 14.3, 13.9, 8.2 ppm; IR (KBr) 2929, 2868, 1714, 1621, 1467, 1449 cm⁻¹; ESI-MS m/z: 1225.3 ([M+Na]⁺, 100%), 1201.3 ([M]⁺, 5%); Anal. Calcd. for C₆₀H₆₀Br₃O₁₀: C, 60.96; H, 5.79; found C, 61.12; H, 5.88.

Inside-C-pentyl-(2-carbo-n-propoxyphenyl) tribromo cavitand 1.4f and outside-C-pentyl-(2-carbo-n-propoxyphenyl) tribromo cavitand 1.5f

These compounds were synthesized using the general procedure with n-propyl 2-iodobenzoate as electrophile 1.3. The reaction time was 18 h. NMR of the crude product
indicated a 83:17 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4f (58 mg, 58%) and outside isomer 1.5f (12 mg, 12%).

The inside isomer 1.4f was obtained as a white solid: \( R_f = 0.28 \) (1:9 ethyl acetate/hexane); m.p. 99-105 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.01 (d, \( J = 7.8 \) Hz, 1H), 7.54 (t, \( J = 7.5 \) Hz, 1H), 7.43 (t, \( J = 7.5 \) Hz, 1H), 7.12 (s, 2H), 7.11 (s, 1H), 7.08 (s, 1H), 7.06 (d, \( J = 7.8 \) Hz, 1H), 5.98 (d, \( J = 7.2 \) Hz, 2H), 5.46 (d, \( J = 7.2 \) Hz, 2H), 4.89 (t, \( J = 8.1 \) Hz, 2H), 4.82 (t, \( J = 8.4 \) Hz, 2H), 4.19 (d, \( J = 7.2 \) Hz, 2H), 4.16 (d, \( J = 10.5 \) Hz, 2H), 3.55 (t, \( J = 7.8 \) Hz, 1H), 5.98 (d, \( J = 7.2 \) Hz, 2H), 4.89 (t, \( J = 8.4 \) Hz, 2H), 4.82 (t, \( J = 8.4 \) Hz, 2H), 4.19 (d, \( J = 7.2 \) Hz, 2H), 4.16 (d, \( J = 10.5 \) Hz, 2H), 3.55 (t, \( J = 7.8 \) Hz, 1H), 2.40-2.10 (m, 8H), 1.50-1.10 (m, 24H), 1.00-0.80 (m, 12H), 0.79 (t, \( J = 7.2 \) Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 168.3, 152.6, 152.4, 152.1, 151.6, 139.7, 139.6, 139.2, 138.5, 134.7, 132.4, 131.7, 131.5, 130.0, 128.0, 120.3, 119.8, 119.7, 113.8, 113.7, 98.8, 98.5, 85.7, 85.3, 83.1, 67.5, 41.1, 38.0, 37.6, 34.0, 32.2, 32.1, 30.1, 30.0, 28.6, 27.7 (two coincident resonances), 24.1, 22.9, 21.4, 21.0, 20.8, 17.7, 17.5, 14.9, 14.3, 8.2, 5.5 ppm; IR (KBr) 2929, 2870, 1720, 1615, 1468, 1448 cm\(^{-1}\); ESI-MS \( m/z: 1239.6 ([M+Na]^{+}, 100\%), 1215.7 ([M]^{+}, 40\%); \) Anal. Calcd. for \( C_{62}H_{71}Br_3O_{10} \): C, 61.24; H, 5.89; found C, 61.40; H, 6.22.

The outside isomer 1.5f was obtained as a white solid: \( R_f = 0.16 \) (1:9 ethyl acetate/hexane); m.p. 99-105 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.09 (d, \( J = 9.3 \) Hz, 1H), 7.47 (t, \( J = 6.9 \) Hz, 1H), 7.43 (t, \( J = 7.5 \) Hz, 1H), 7.13 (s, 1H), 7.09 (s, 1H), 7.08 (s, 2H), 6.90 (d, \( J = 7.2 \) Hz, 1H), 5.99 (d, \( J = 7.5 \) Hz, 2H), 5.38 (d, \( J = 6.9 \) Hz, 2H), 4.87 (t, \( J = 8.4 \) Hz, 2H), 4.81 (t, \( J = 7.8 \) Hz, 2H), 4.35 (d, \( J = 7.2 \) Hz, 2H), 4.28 (d, \( J = 7.2 \) Hz, 2H), 3.98 (t, \( J = 6.9 \) Hz, 2H), 2.35-2.10 (m, 8H), 1.50-1.05 (m, 26H), 1.00-0.80 (m, 12H), 0.79 (t, \( J = 7.2 \) Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 167.8, 152.6, 152.1, 152.0, 140.0, 139.1, 138.1, 131.5, 130.3, 119.3, 119.2, 113.7, 112.8, 99.1, 98.9, 85.7, 85.4, 84.9, 66.8, 41.1, 38.0, 37.4, 32.2, 32.1, 30.2, 30.1, 27.8, 27.7, 24.1, 22.9, 21.9, 21.0, 17.5, 14.3, 10.6 ppm; IR (KBr) 2929, 2870, 1720, 1615, 1468, 1448 cm\(^{-1}\); ESI-MS \( m/z: 1239.6 ([M+Na]^{+}, 100\%), 1215.7 ([M]^{+}, 40\%); \) Anal. Calcd. for \( C_{62}H_{71}Br_3O_{10} \): C, 61.24; H, 5.89; found C, 61.40; H, 6.22.
Inside-C-pentyl-(2-carbo-n-butoxyphenyl) tribromo cavitand 1.4g and outside-C-pentyl-(2-carbo-n-butoxyphenyl) tribromo cavitand 1.5g

These compounds were synthesized using the general procedure with n-butyl 2-iodobenzoate as electrophile 1.3. The reaction time was 18 h. NMR of the crude product indicated a 5:95 mixture of inside:outside isomers. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give inside isomer 1.4g (4 mg, 4%) and outside isomer 1.5g (69 mg, 66%).

The inside isomer 1.4g was obtained as a white solid: \( R_f = 0.28 \) (1:9 ethyl acetate/hexane); m.p. 88-93 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 8.02 (d, \( J = 7.8 \) Hz, 1H), 7.54 (t, \( J = 7.5 \) Hz, 1H), 7.43 (t, \( J = 7.5 \) Hz, 1H), 7.13 (s, 2H), 7.11 (s, 1H), 7.08 (s, 1H), 7.01 (d, \( J = 7.5 \) Hz, 1H), 5.94 (d, \( J = 7.5 \) Hz, 2H), 5.47 (d, \( J = 7.5 \) Hz, 2H), 4.88 (t, \( J = 8.1 \) Hz, 2H), 4.74 (t, \( J = 7.8 \) Hz, 2H), 4.66 (d, \( J = 7.5 \) Hz, 2H), 4.25 (d, \( J = 7.2 \) Hz, 2H), 3.90 (t, \( J = 6.6 \) Hz, 2H), 2.40-2.10 (m, 8H), 1.50-1.10 (m, 28H), 1.00-0.80 (m, 12H), 0.78 (t, \( J = 7.5 \) Hz, 3H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)), this compound interconverted into inside/outside mixture quickly on \(^{13}\)C-NMR timescale) \( \delta \) 167.9, 167.2, 152.8, 152.4, 152.1, 151.9, 141.5, 140.0, 139.9, 139.5, 139.1, 138.2, 137.7, 136.7, 135.3, 133.2, 132.7, 131.4, 131.1, 130.4, 129.8, 129.3, 128.6, 127.9, 120.1, 119.8, 119.3, 119.0, 114.0, 113.8, 113.4, 112.8, 99.6, 99.0, 98.9, 98.6, 65.2, 65.0, 38.0, 37.6, 37.5, 32.2, 31.0, 30.6, 30.5, 30.2, 29.9, 27.7, 22.9, 19.5, 19.2, 14.3, 14.0, 13.7 ppm; IR (KBr) 2928, 2858, 1715, 1639, 1466, 1449 cm\(^{-1}\); ESI-MS \( m/z \): 1251.5 ([M+Na]+, 100%), 1229.4 ([M]+, 40%); Anal. Calcd. for C\(_{67}\)H\(_{71}\)Br\(_5\)O\(_{10}\): C, 61.52; H, 5.98; found C, 61.67; H, 6.11.

The outside isomer 1.5g was obtained as a white solid: \( R_f = 0.16 \) (1:9 ethyl acetate/hexane); m.p. 88-93 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\))
Inside-C-pentyl-(2-carbo-i-butoxyphenyl) tribromo cavitand 1.4h

This compound was synthesized using the general procedure with i-butyl 2-iodobenzoate as electrophile 1.3. The reaction time was 18 h. NMR of the crude product indicated that the majority was the inside isomer, only trace of the outside isomer was formed. The crude product was purified by flash chromatography (100 g silica, 6:4 dichloromethane/hexane then 50 g silica, 1:9 ethyl acetate/hexane) to give the inside isomer 1.4h as a white solid (67 mg, 64%): Rf = 0.30 (1:9 ethyl acetate/hexane); m.p. 82-85 °C (dichloromethane/hexane); 1H NMR (300 MHz, CDCl3) δ 7.92 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.8 Hz, 1H), 7.42 (t, J = 7.5 Hz, 1H), 7.13 (s, 1H), 7.12 (s, 2H), 7.11 (s, 1H), 7.11 (d, J = 9.6 Hz, 1H), 6.00 (d, J = 7.2 Hz, 1H), 5.98 (d, J = 7.2 Hz, 1H), 5.42 (d,
$J = 7.5 \text{ Hz}, \ 1\text{H}$, $5.38 \ (d, \ J = 7.5 \text{ Hz}, \ 1\text{H})$, $4.88 \ (t, \ J = 8.1 \text{ Hz}, \ 2\text{H})$, $4.82 \ (t, \ J = 8.1 \text{ Hz}, \ 2\text{H})$, $4.32 \ (d, \ J = 7.5 \text{ Hz}, \ 1\text{H})$, $4.21 \ (d, \ J = 7.5 \text{ Hz}, \ 1\text{H})$, $4.18 \ (d, \ J = 6.9 \text{ Hz}, \ 1\text{H})$, $4.15 \ (d, \ J = 6.9 \text{ Hz}, \ 1\text{H})$, $3.93 \ (dq, \ J = 0.9 \text{ Hz}, \ J = 6.6 \text{ Hz}, \ 1\text{H})$, $2.40-2.10 \ (m, \ 8\text{H})$, $1.50-1.10 \ (m, \ 24\text{H})$, $1.00-0.80 \ (m, \ 12\text{H})$, $0.55 \ (m, \ 2\text{H})$, $-0.50 \ (t, \ J = 7.5 \text{ Hz}, \ 3\text{H})$, $-1.11 \ (d, \ J = 6.3 \text{ Hz}, \ 3\text{H}) \ ppm$; $^1\text{C} \text{ NMR} \ (75 \text{ MHz, CDCl}_3) \ \delta \ 167.8, \ 152.6, \ 152.3, \ 152.2, \ 151.5, \ 151.3, \ 140.0, \ 139.9, \ 139.8, \ 139.7, \ 139.4, \ 139.3, \ 138.4, \ 138.3, \ 134.7, \ 132.3, \ 131.9, \ 131.4, \ 131.2, \ 130.7, \ 128.0, \ 119.9, \ 119.7, \ 119.6, \ 119.5, \ 113.7, \ 113.6, \ 98.8, \ 98.4, \ 98.1, \ 73.2, \ 38.0, \ 37.6, \ 32.2, \ 32.1, \ 31.8, \ 30.2, \ 30.1, \ 29.3, \ 27.7, \ 27.6, \ 22.9, \ 16.1, \ 14.4, \ 14.3, \ 8.5 \ ppm$; IR (KBr) 2929, 2860, 1718, 1639, 1467, 1444 cm$^{-1}$; ESI-MS $m/z: 1251.5 \ ([M+Na]^+, 100\%)$; Anal. Calcd. for $C_{63}H_{75}Br_{10}O_{10}$: C, 61.52; H, 5.98; found C, 61.67; H, 6.11.
CHAPTER 2 - EXPERIMENTAL DATA

Aspirin

Two-point binding:
H-bonding
and C-H/π interaction
C-pentyl calix[4]resorcinarene 2.1

Prepared by modification of the procedure of Aoyama et al.\textsuperscript{226} To a stirring solution of resorcinol (132 g, 1.20 mol) and hexanal (120 g, 1.20 mol) in 95% ethanol (1.20 L) at 0 °C was added conc. HCl (190 mL). The solution was then heated to 70 °C for 24 h, allowed to cool to rt and upon addition of water (2 L) the product precipitated. The crude product was filtered and subsequent washing of the precipitate with boiling water (5 x 2 L) afforded the title compound 2.1 as a pale pink solid (210 g, 95%). Characterisation data corresponded to that reported in the literature.\textsuperscript{226}

C-pentyl tetrabromo calix[4]resorcinarene 2.2

Prepared by modification of the procedure of Cram et al.\textsuperscript{227} To a solution of calix[4]resorcinarene 2.1 (76.9 g, 100 mmol) in 2-butanone (500 mL) was added portionwise N-bromosuccinimide (107 g, 600 mmol). The resulting self-heated mixture was stirred for 8 h in the dark under \(\text{N}_2\), then cooled in an ice bath prior to filtration. The precipitate was washed with cold 2-butanone and water and dried \textit{in vacuo} to afford the title compound 2.2 (76.7 g, 71%) as an off-white powder. Characterisation data corresponded to that reported in the literature.\textsuperscript{227}
C-pentyl tetrabromo cavitand 2.3

Prepared by modification (see Section 2.2.1 for more details) of the procedure of Reinhoudt et al.\textsuperscript{228} To a slurry of tetrabromoresorcinarene 2.2 (55.0 g, 50.0 mmol) and K\textsubscript{2}CO\textsubscript{3} (210 g, 1.52 mol) in dry DMF (600 mL) was added bromochloromethane (60.0 mL, 912 mmol) and the mixture was stirred at 45 °C for 48 h under N\textsubscript{2}. The reaction mixture was then heated up to 65 °C for 48 h. Every 24 h, additional bromochloromethane (10.0 mL, 154 mmol) was added. The reaction mixture was then cooled down to rt and left in the fridge for 24 h. The liquid DMF phase was removed by filtration. Then, chloroform and 2 M aq. HCl were added dissolved the solid residue. The aqueous phase was extracted with more chloroform and the combined chloroform layers were washed with water, sat. aq. LiCl, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. The resulting brown powder was recrystallized from dichloromethane/hexane to afford an off-white solid, which was practically pure tetrabromocavitand 2.3 (43.7 g, 76%) for subsequent synthetic reactions. Higher purity could be achieved by flushing this material through a short plug of SiO\textsubscript{2} with dichloromethane. Characterisation data corresponded to that reported in the literature.\textsuperscript{228}
Prepared by modification of the procedure of Barrett et al.\(^9\) To a solution of tetrabromocavitand \(2.3\) (11.3 g, 10.0 mmol), dried according to the standard procedure, in dry THF (500 mL) at \(-78 \, ^\circ\text{C}\) was added \(n\text{-BuLi}\) (13.1 mL of a 1.60 M solution in hexanes, 21.0 mmol). After 20 min, B(OMe)\(_3\) (3.40 mL, 30.0 mmol) was added, the cooling bath was removed and the solution was stirred at rt for 1 h. The reaction mixture was then cooled to \(-78 \, ^\circ\text{C}\) and quenched with a 1:1 mixture of 30% aq. H\(_2\)O\(_2\) and 3.0 M aq. NaOH (90 mL) before stirring at rt for 18 h. The reaction mixture was again cooled to \(-78 \, ^\circ\text{C}\) and after cautious addition of 30% aq. Na\(_2\)S\(_2\)O\(_3\) (100 mL), the THF was removed \textit{in vacuo}. The organic products were extracted with ethyl acetate (3 x 150 mL). The combined organic phases were washed successively with sat. aq. NaHCO\(_3\) and sat. aq. NaCl, dried over MgSO\(_4\) and the solvent was removed \textit{in vacuo}. Purification by column chromatography (500 g SiO\(_2\), 8:2 to 6:4 hexane/ethyl acetate) afforded the title compound \(2.4\) as a white solid (7.08 g, 70%). Characterisation data corresponded to that reported in the literature.\(^9\)
Chloromethyl methyl ether (MOMCl) as solution in toluene was prepared according to the procedure of Berliner et al. A three-neck 500 mL flask fitted with a thermocouple thermometer, reflux condenser, and addition funnel was charged with dimethoxymethane (44.3 mL, 500 µmol), toluene (120 mL), and ZnBr$_2$ (9.2 mg, 0.1%). Acetyl chloride (34.8 mL, 490 µmol, 0.98 eq) was placed in the addition funnel, and was then introduced into the reaction mixture at a constant rate over 5 min. The reaction mixture self-heated slowly to 43 °C, and was then cooled to r.t over 4 h, at which time analysis of an aliquot of the reaction mixture by NMR indicated complete consumption of acetyl chloride. Solution of MOMCl in toluene prepared had molarity of approximately 2.6 M. MOMCl solution was then transferred to storage in an Ar-filled sealed flask. Characterisation data corresponded to that reported in the literature.

**C-pentyl A,C-dibromo di(methoxymethyleneoxy) cavitand 2.5** prepared by modification of the procedure of Barrett et al. To a solution of A,C-dibromo diphenol cavitand 2.4 (3.12 g, 3.10 mmol) and diisopropylethylamine (10.8 mL, 62.0 mmol) in dry THF (50 mL) was slowly added freshly-prepared solution of MOMCl (2.6 M in toluene, 12.0 mL, 31.0 mmol). The solution was stirred at rt under N$_2$ for 18 h, then quenched with sat. aq. NaHCO$_3$ and THF was remove in vacuo. Ethyl acetate (2 x 40 mL) was added to extract the products. The combined organic phases were washed with water, then sat. aq. NaCl, dried over MgSO$_4$ and the solvent was removed in vacuo. The crude product was recrystallized from ethyl acetate/hexane to afford the title compound 2.5 as a white solid (3.12 g, 92%). Characterisation data corresponded to that reported in the literature.
Prepared by modification of the procedure of Barrett et al.\textsuperscript{1,2} To a solution of cavitand 2.5 (3.01 g, 2.75 mmol), dried according to the standard procedure, in THF (140 mL) at -78 °C was added n-BuLi (1.89 mL of a 1.60 M solution in hexanes, 3.02 mmol). After 20 min, B(OMe)\textsubscript{3} (468 µL, 4.10 mmol) was added, the cooling bath was removed. The mixture was allowed to warm to rt and stirred at this temperature for 1 h. The reaction mixture was cooled to -78 °C, quenched with a 1:1 mixture of 30% aq. H\textsubscript{2}O\textsubscript{2} and 3.0 M aq. NaOH (20 mL) then stirred at rt for 12 h. After cautious addition of 30% aq. Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3} to the reaction mixture at -78 °C, the THF was removed \textit{in vacuo}. The residue was then extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed successively with sat. aq. NaHCO\textsubscript{3} and sat. aq. NaCl, dried over anhydrous MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. Purification by flash chromatography (150 g SiO\textsubscript{2}, 7:3 to 6:4 hexane/ethyl acetate) afforded the title compound 2.6 as a white solid (2.03 g, 70%). Characterisation data corresponded to that reported in the literature.\textsuperscript{1,2}
C-pentyl tetramethyl calix[4]resorcinarene 2.7

Prepared by modification of Aoyama's procedure. To a stirred solution of 2-methylresorcinol (74.4 g, 600 mmol) and hexanal (60.0 g, 600 mmol) in 95% ethanol (1.20 L) at 0 °C, was added conc. HCl (95 mL). The solution was heated at 70 °C under N₂ for 48 h. The precipitate formed was filtered, washed with boiling water (5 x 1 L) and dried in vacuo to afford the title compound 2.7 as a pale pink solid (111 g, 90%). Characterisation data corresponded to that reported in the literature.

C-pentyl tetra(bromomethyl) cavitand 2.8

Prepared according to Reinhoudt’s procedure. A solution of tetramethyl calix[4]-resorcinarene 2.7 (10.0 g, 12.0 mmol) K₂CO₃ (35.3 g, 250 mmol) and bromochloromethane (13.0 mL, 200 mmol) in DMF (450 mL) was stirred at 70 °C under N₂ for 48 h. The DMF was removed in vacuo and the residue was dissolved in dichloromethane and 2 M aq. HCl. The organic phase was separated and washed with 2 M aq. HCl, water, sat. aq. NaCl and dried over MgSO₄. The organic phase was filtered.
through a plug of SiO₂ and removal of the solvent in vacuo afforded the C-pentyl tetramethyl cavitand as a white solid (8.40 g, 80%). Characterisation data corresponded to that reported in the literature.¹⁰⁹

A solution of this tetramethyl cavitand (5.00 g, 5.75 mmol), recrystallised N-bromosuccinimide (4.60 g, 25.8 mmol) and a catalytic amount of AIBN in dichloromethane (60 mL) was radiated with a 100 W tungsten lamp for 24 h. The reaction mixture was allowed to cool to rt, the organic phase was washed several times with water and dried over MgSO₄. Removal of the solvent in vacuo afforded the crude product, which was recrystallised from dichloromethane/ethanol to furnish the title compound 2.8 (5.67 g, 83%) as a white solid. Characterisation data corresponded to that reported in the literature.²²⁹
Prepared by modification of the procedure of Barrett et al.\textsuperscript{1,2} A mixture of wall cavitand 2.6 (742 mg, 700 \(\mu\)mol), tetra(bromomethyl) cavitand 2.8 (166 mg, 140 \(\mu\)mol), and K\textsubscript{2}CO\textsubscript{3} (290 mg, 2.10 mmol) in dry acetone (15 mL) was heated to reflux under N\textsubscript{2} for 18 h. The mixture was allowed to cool to rt, the solvent was removed \textit{in vacuo} then the ethyl acetate and water were added. The mixture was acidified with 2 M aq. HCl then allowed to separate. The organic extract was then washed with sat. aq. NaHCO\textsubscript{3}, sat. aq. NaCl, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. The crude product was purified by flash chromatography (60 g SiO\textsubscript{2}, 7:3 hexane/ethyl acetate) to afford tetrabromo octa(methoxymethyleneoxy) pentamer 2.9 (637 mg, 91\%) as a white solid. Characterisation data corresponded to that reported in the literature.\textsuperscript{1,2}
Prepared by modification of the procedure of Barrett et al.\textsuperscript{1,2} A solution of tetrabromo octa(methoxymethyleneoxy) pentamer \textbf{2.9} (1.30 g, 260 \( \mu \)mol) and methanol (300 \( \mu \)L) in dichloromethane (20 mL) was stirred at rt for 10 min. 2-3 drops of 36.5\% aq. HCl solution was added and the reaction mixture was heated to reflux for 1 h. The solvents were removed \textit{in vacuo}. Purification by column chromatography (70 g SiO\textsubscript{2}, 7:3 dichloromethane/diethyl ether) afforded the octaphenol pentamer \textbf{2.10} as a white solid (1.18 g, 97\%). Characterisation data corresponded to that reported in the literature.\textsuperscript{1,2}
Prepared by modification of the procedure of Barrett et al. To a slurry of tetrabromo pentamer octaphenol 2.10 (1.16 g, 250 µmol) and Cs₂CO₃ (8.15 g, 25.0 mmol) in DMF (250 mL) was added bromochloromethane (168 µL, 2.50 mmol) and the mixture was stirred at 65 °C under N₂ for 72 h. Additional bromochloromethane (168 µL, 2.50 mmol) was added every 18 h. The solvent was removed in vacuo; the residue was dissolved in dichloromethane (40 mL) and acidified with 2 M aq. HCl. The two phases were separated and more dichloromethane (2 x 20 mL) was added to further extract the aqueous phase. The combined organic phases were washed successively with sat. aq. NaHCO₃, sat. aq. CuSO₄, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude material was purified by column chromatography (100 g SiO₂, 8:2 to 6:4 dichloromethane/hexane) to afford the title compound 2.11 as a white solid (553 mg, 47%). Characterisation data corresponded to that reported in the literature.
General method for free radical debromination of tetrabromo superbowl 2.11

To a stirred, degassed solution of tetrabromo superbowl 2.11 (94.0 mg, 20.0 μmol) in toluene (10 mL) under a nitrogen atmosphere were added tributyltin hydride (quantity as listed in Table 2.3.2). The reaction mixture was heated to 110 °C, then AIBN (2.0 mg in 1 mL toluene, 10.0 μmol) was added. The reaction mixture was stirred at that temperature for another 4 h, then cooled to rt and diluted with more toluene. The resulting solution was washed with 30% aq. ammonium hydroxide solution, sat. aq. NaCl and dried over MgSO₄ before the solvent was removed in vacuo. The crude product was filtered through a short plug of silica to remove the majority of tin by-products. The product mixture was further isolated by repeating column chromatography (50 g silica, 4:6 to 6:4 dichloromethane/hexane, 2-3 times) to obtain a family of debrominated superbowl products 2.11 to 2.16. For product ratios, analytical HPLC or ¹H NMR analyses were employed.

<table>
<thead>
<tr>
<th>Molar equivalent of Bu₃SnH</th>
<th>1.1 eq (*)</th>
<th>2.2 eq (*)</th>
<th>3.3 eq (*)</th>
<th>4.4 eq (*)</th>
<th>16 eq (#)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Br (2.11)</td>
<td>30%</td>
<td>3%</td>
<td>1%</td>
<td>trace</td>
<td></td>
</tr>
<tr>
<td>3Br1H (2.12)</td>
<td>44%</td>
<td>21%</td>
<td>12%</td>
<td>4%</td>
<td></td>
</tr>
<tr>
<td>A,B-2Br2H(2.13)</td>
<td>3%</td>
<td>18%</td>
<td>15%</td>
<td>11%</td>
<td></td>
</tr>
<tr>
<td>A,C-2Br2H(2.14)</td>
<td>7%</td>
<td>25%</td>
<td>18%</td>
<td>9%</td>
<td></td>
</tr>
<tr>
<td>1Br3H (2.15)</td>
<td>1%</td>
<td>12%</td>
<td>28%</td>
<td>12%</td>
<td>3%</td>
</tr>
<tr>
<td>4H (2.16)</td>
<td></td>
<td>3%</td>
<td>7%</td>
<td>43%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Table 2.3.2. Free radical debromination of tetrabromo superbowl 2.11. (*) Percentage ratios obtained from HPLC peak area integration. (#) Percentage ratios obtained from ¹H NMR integration.
General method for Knochel’s debromination of tetrabromo superbowl 2.11

Tetrabromo superbowl 2.11 (94.0 mg, 20.0 µmol) was dried according to the standard procedure. It was then dissolved in dry THF (10 mL). The reaction mixture was cooled down to -20 °C. Knochel’s reagent PrMgCl,LiCl (0.89 M solution in THF, quantity as listed in Table 2.3.3) was injected quickly into the reaction mixture followed by addition of dry 1,4-dioxane (1 mL). After stirring at that temperature for 50 min, sat. aq. NH₄Cl solution was added to quench the reaction mixture and the THF was removed in vacuo. The organic products were extracted with dichloromethane (3 x 15 mL). The combined organic phases were further washed with sat. aq. NaCl, dried over MgSO₄, then the solvent was removed in vacuo. The product mixture was isolated by repeating column chromatography (50 g silica, 4:6 to 6:4 dichloromethane/hexane, 2-3 times) to obtain a family of debrominated superbowl products 2.11 to 2.16. For product ratios, analytical HPLC or 1H NMR analyses were employed.

<table>
<thead>
<tr>
<th>Mol. eq. Knochel’s reagent</th>
<th>3.3 eq (#)</th>
<th>4.4 eq (*)</th>
<th>8.8 eq (*)</th>
<th>15.0 eq (*)</th>
<th>24.0 eq (*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4Br (2.11)</td>
<td>90%</td>
<td>78%</td>
<td>13%</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>3Br1H (2.12)</td>
<td>2%</td>
<td>13%</td>
<td>22%</td>
<td>9%</td>
<td>trace</td>
</tr>
<tr>
<td>A,B-2Br2H(2.13)</td>
<td>trace</td>
<td>2%</td>
<td>23%</td>
<td>14%</td>
<td>4%</td>
</tr>
<tr>
<td>A,C-2Br2H(2.14)</td>
<td>trace</td>
<td>2%</td>
<td>28%</td>
<td>15%</td>
<td>5%</td>
</tr>
<tr>
<td>1Br3H (2.15)</td>
<td></td>
<td></td>
<td>7%</td>
<td>29%</td>
<td>9%</td>
</tr>
<tr>
<td>4H (2.16)</td>
<td></td>
<td></td>
<td>2%</td>
<td>23%</td>
<td>72%</td>
</tr>
</tbody>
</table>

Scheme 2.3.3. Knochel’s debromination of tetrabromo superbowl 2.11. (*) Percentage ratios obtained from HPLC peak area integration. (#) Percentage ratios obtained from 1H NMR integration.
Tribromo monoprotio superbowl 3 was obtained as a white solid: $R_f = 0.43$ (1:1 dichloromethane/hexane); m.p. $> 310$ °C (decomp.) (dichloromethane/hexane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 (s, 4H), 7.12 (s, 1H), 7.09 (s, 3H), 6.87 (s, 2H), 6.85 (s, 2H), 6.84 (s, 2H), 6.83 (s, 6H), 6.53 (s, 1H), 6.11 (d, $J = 6.5$ Hz, 4H), 6.10 (d, $J = 5.0$ Hz, 2H), 6.06 (d, $J = 7.0$ Hz, 6H), 6.00 (d, $J = 7.5$ Hz, 2H), 5.98 (d, $J = 7.5$ Hz, 2H), 5.95 (d, $J = 7.0$ Hz, 2H), 5.91 (d, $J = 7.0$ Hz, 2H), 5.66 (d, $J = 2.0$ Hz, 2H), 5.59 (d, $J = 2.0$ Hz, 2H), 5.11-5.04 (m, 32H), 4.88 (dt, $J = 3.0$ Hz, $J = 7.5$ Hz, 4H), 4.80 (dt, $J = 4.0$ Hz, $J = 8.0$ Hz, 8H), 4.78 (dt, $J = 1.5$ Hz, $J = 7.5$ Hz, 8H), 4.74 (t, $J = 8.0$ Hz, 2H), 4.58 (dd, $J = 6.5$ Hz, $J = 6.8$ Hz, 4H), 4.55 (d, $J = 5.5$ Hz, 2H), 4.54 (m, 8H), 4.38 (d, $J = 7.0$ Hz, 2H), 4.36 (dd, $J = 2.0$ Hz, $J = 8.5$ Hz, 6H), 4.23 (dd, $J = 6.5$ Hz, $J = 6.8$ Hz, 4H), 2.30-2.10 (m, 32H), 2.20-2.05 (m, 8H), 1.50-1.20 (m, 120H), 0.98-0.85 (m, 60H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 154.9, 154.5, 154.4, 151.9, 148.9, 148.8, 147.1, 146.9 (two coincident resonances), 146.7, 146.5, 146.4, 143.7, 143.6, 141.1, 141.0, 140.9 (two coincident resonances), 139.8, 139.7, 139.5, 139.4, 139.1, 139.0, 138.6, 138.4, 129.1, 128.2, 121.9, 121.6, 119.8, 115.1, 114.2, 114.0, 112.5, 100.0, 99.7, 99.2, 97.2, 96.8, 66.3, 37.3, 37.2, 36.8, 32.2, 32.0, 31.9, 31.8, 31.6,
30.4, 27.7, 27.5, 27.4, 22.7, 14.1 ppm; IR (KBr) 2928, 2862, 1577 cm⁻¹; Nanospray ESI-MS m/z: 2305.63 ([M+2H]⁺, 100%); Anal. Calcd. for C₂₆₈H₃₁Br₅O₁₅₂: C, 69.82; H, 6.93; found C, 69.71; H, 6.89.

C-pentyl A,B-dibromo diprotio superbowl 2.13

A,B-dibromo diprotio superbowl 2.13 was obtained as a white solid: Rf = 0.37 (1:1 dichloromethane/hexane); m.p. > 310 °C (decomp.) (dichloromethane/hexane); ¹H NMR (500 MHz, CDCl₃) δ 7.26 (s, 4H), 7.12 (s, 2H), 7.09 (s, 2H), 6.87 (s, 2H), 6.86 (s, 2H), 6.85 (m, 6H), 6.85 (s, 2H), 6.51 (s, 2H), 6.12 (d, J = 6.5 Hz, 2H), 6.11 (d, J = 5.0 Hz, 2H), 6.08 (d, J = 5.5 Hz, 2H), 6.06 (d, J = 7.5 Hz, 4H), 5.98 (m, 4H), 5.90 (m, 6H), 5.69 (d, J = 2.0 Hz, 1H), 5.60 (d, J = 2.0 Hz, 1H), 5.58 (d, J = 1.5 Hz, 2H), 5.54 (s, 2H), 5.52 (d, J = 1.5 Hz, 2H), 4.88 (t, J = 8.0 Hz, 4H), 4.79 (m, 12H), 4.73 (t, J = 8.0 Hz, 4H), 4.55 (m, 16H), 4.38 (d, J = 7.0 Hz, 4H), 4.36 (d, J = 3.5 Hz, 2H), 4.35 (d, J = 4.0 Hz, 2H), 4.23 (m, 4H), 2.30-2.20 (m, 32H), 2.20-2.05 (m, 8H), 1.50-1.20 (m, 12OH), 0.98-0.85 (m, 60H) ppm; ¹³C NMR (125 MHz, CDCl₃) δ 154.8, 154.6, 152.2, 149.0, 147.3, 147.1 (two coincident resonances), 147.0, 146.9, 146.8, 146.6, 143.9, 142.2, 141.4, 141.2, 141.1, 140.9, 140.1, 139.9, 139.6, 139.3, 138.9, 138.7, 122.1, 121.9,
A,C-dibromo diprotio superbowl 2.14 was obtained as a white solid: $R_f = 0.32$ (1:1 dichloromethane/hexane); m.p. > 310 °C (decomp.) (dichloromethane/hexane); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.25 (s, 4H), 7.12 (s, 2H), 7.08 (s, 2H), 6.87 (s, 8H), 6.85 (s, 4H), 6.48 (s, 2H), 6.12 (d, $J = 6.5$ Hz, 2H), 6.09 (dd, $J = 6.0$ Hz, $J = 7.0$ Hz, 6H), 5.97 (dd, $J = 7.0$ Hz, $J = 7.5$ Hz, 4H), 5.93 (d, $J = 7.5$ Hz, 2H), 5.88 (d, $J = 6.0$ Hz, 6H), 5.56 (m, 8H), 4.88 (t, $J = 4.0$ Hz, 4H), 4.78 (t, $J = 7.0$ Hz, 8H), 4.73 (t, $J = 7.0$ Hz, 8H), 4.55 (m, 16H), 4.38 (m, 6H), 4.29 (d, $J = 6.5$ Hz, 2H), 4.23 (m, 4H), 2.30-2.10 (m, 32H), 2.20-2.05 (m, 8H), 1.50-1.20 (m, 120H), 0.98-0.85 (m, 60H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 154.7, 154.6, 152.1, 149.2, 147.3, 147.2, 147.1, 146.8, 146.7, 143.9, 142.3, 141.4, 141.2, 141.0, 140.9, 140.7, 140.1, 139.9, 139.7, 139.3, 138.9, 138.6, 122.0,
121.9, 120.1, 115.8, 114.8, 114.5, 112.8, 110.6, 100.2, 99.9, 97.3, 66.7, 66.1, 60.7, 37.6, 37.4, 37.1, 32.4, 32.1, 32.0, 30.8, 30.0, 27.9, 27.8, 27.6, 22.9, 21.3, 15.5, 14.4, 14.3 ppm; IR (KBr) 2928, 2861, 1577 cm\(^{-1}\); Nanospray ESI-MS \(m/z\): 2267.36 ([M+2H]\(^{2+}\), 35%), 2243.66 (100%); Anal. Calcd. for C\(_{268}H_{318}Br_2O_{52}\): C, 71.04; H, 7.07; found C, 70.97; H, 7.32.

**C-pentyl monobromo triprotio superbowl 2.15**

Monobromo triprotio superbowl 2.15 was obtained as a white solid: \(R_f = 0.20\) (1:1 dichloromethane/hexane); m.p. > 310 °C (decomp.) (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.26 (s, 4H), 7.13 (s, 3H), 7.10 (s, 1H), 6.90-6.80 (m, 12H), 6.50 (s, 3H), 6.14 (d, \(J = 5.1\) Hz, 2H), 6.15-6.05 (m, 6H), 6.05-5.85 (m, 12H), 5.62 (s, 2H), 5.57 (s, 2H), 5.54 (s, 4H), 4.88 (m, 4H), 4.85-4.70 (m, 16H), 4.65-4.45 (m, 16H), 4.38 (m, 8H), 4.24 (m, 4H), 2.40-2.05 (m, 4OH), 1.50-1.15 (m, 12OH), 1.00-0.85 (m, 60H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 155.0, 154.7, 154.6, 154.5, 152.0, 149.1 (two coincident resonances), 149.0, 147.2, 147.1 (two coincident resonances), 147.0, 146.8, 146.6, 143.8, 143.6, 141.1 (two coincident resonances), 141.0, 140.8, 140.0, 139.8, 139.7, 139.5, 139.2 (two coincident resonances), 138.7, 138.5 (two coincident
resonances), 122.0, 121.7, 116.1, 115.4, 114.4, 114.2, 112.7, 100.2, 99.8, 97.3, 97.1, 66.4, 60.5, 37.3, 36.9, 36.8, 32.3, 32.1, 31.9, 31.7, 30.5, 29.9, 29.8, 27.8, 27.6, 27.5, 22.8, 20.9, 14.2 (two coincident resonances) ppm; IR (KBr) 2928, 2861, 1578 cm⁻¹; Nanospray ESI-MS m/z: 2226.33 ([M+2H]⁺, 65%), 2208.42 (100%); Anal. Calcd. for C₅₀H₃₉BrO₉: C, 72.30; H, 7.22; found C, 72.04; H, 6.99.

C-pentyl tetraprotio superbowl 2.16

Tetraprotio superbowl 2.16 was obtained as a white solid: Rᵣ = 0.11 (1:1 dichloromethane/hexane). Characterisation data corresponded to that reported in the literature.¹²
Prepared by the procedure developed by Yoshida.\(^{26}\) To a slurry of tetrabromo superbowl 2.11 (94.0 mg, 20.0 \(\mu\)mol), dried according to the standard procedure, and sodium hydride (60% in mineral oil, 50.0 mg) in THF (10 mL) at \(-78\) °C was added \(t\)-BuLi (500 \(\mu\)L of a 1.6 M solution in pentanes, 800 \(\mu\)mol, 40 eq.). After 20 min, B(OMe)\(_3\) (115 \(\mu\)L, 1.00 mmol, 50 eq.) was added, the cooling bath was removed and the mixture was allowed to warm to rt and was stirred at this temperature for 1 h. The resulting solution was cooled to \(-78\) °C, cautiously quenched with a 1:1 mixture of 30% aq. \(\text{H}_2\text{O}_2\) and 3.0 M aq. \(\text{NaOH}\) (10 mL) then stirred at rt for 18 h. After cautious addition of 30% aq. \(\text{Na}_2\text{S}_2\text{O}_3\) to the reaction mixture at \(-78\) °C, the THF was removed in vacuo. The resulting aqueous phase was extracted with dichloromethane (3 x 10 mL). The combined organic phases were washed successively with sat. aq. \(\text{NaHCO}_3\) and sat. aq. \(\text{NaCl}\), dried over anhydrous \(\text{MgSO}_4\) and the solvent was removed in vacuo. Purification by flash chromatography (30 g \(\text{SiO}_2\), 9:1 to 7:3 dichloromethane/diethyl ether) afforded the title compound 2.17 as a white solid (36.0 mg, 40%). Characterisation data corresponded to that reported in the literature.\(^2\)
To a slurry of tetrabromo superbowl 2.11 (94.0 mg, 20.0 μmol), dried according to the standard procedure, and sodium hydride (40.0 mg, 60% in mineral oil, 1.00 mmol) in dry THF (10 mL) at −78 °C was rapidly added t-BuLi (500 μL of a 1.6 M solution in pentanes, 800 μmol, 40 eq.). After 20 min, ethyl iodide (100 μL, 1.25 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and stirred at this temperature for 4 h. After cautious addition of 5% aq. NH₄Cl, the organic solvents were removed in vacuo. The resulting aqueous mixture was extracted with dichloromethane (3 x 15 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed in vacuo. Purification by flash chromatography (30 g SiO₂, 7:3 dichloromethane/hexane) afforded the title compound 2.18 as a white solid (66.1 mg, 74%): Rf = 0.52 (7:3 dichloromethane/hexane); m.p. > 300 °C (decomp.) (dichloromethane/hexane); ¹H NMR (500 MHz, CDCl₃) δ 7.24 (s, 4H), 6.98 (s, 4H), 6.87 (s, 12H), 6.07 (d, J = 6.5 Hz, 8H), 6.02 (d, J = 7.5 Hz, 4H), 5.99 (d, J = 6.5 Hz, 8H), 5.61 (d, J = 1.5 Hz, 4H), 5.54 (d, J = 2.0 Hz, 4H), 4.87 (t, J = 8.0 Hz, 4H), 4.78 (t, J = 7.5 Hz, 8H), 4.74 (t, J = 8.0 Hz, 8H), 4.56 (s, 8H), 4.51 (d, J = 7.0 Hz, 8H), 4.32 (d, J = 7.0 Hz, 8H), 4.25 (d, J = 7.5 Hz, 4H), 2.44 (q, J = 7.0 Hz, 8H), 2.30-2.06 (m, 40H),
1.50-1.25 (m, 120H), 1.03 (t, J = 7.5, 12H), 0.98-0.84 (m, 60H) ppm; $^{13}$C NMR (125 MHz, CDCl$_3$) δ 154.6, 153.4, 149.0, 146.9, 146.8, 143.7, 141.0, 139.5, 139.4, 139.3, 138.5, 138.2, 129.3, 122.1, 121.6, 118.6, 115.5, 114.3, 100.3, 100.0, 99.4, 66.4, 37.2, 37.0, 32.3, 32.1, 32.0, 30.5, 30.2, 30.0, 27.8, 27.7, 27.6, 22.8, 18.8, 14.8, 14.3, 14.2 ppm; IR (KBr) 2928, 2861, 1577, 1490 cm$^{-1}$; Nanospray ESI-MS m/z: 2244.16 ([M+2H]$^{2+}$, 100%); Anal. Calcd. for C$_{276}$H$_{330}$O$_{52}$: C, 73.90; H, 7.55; found C, 73.69; H, 7.62.

C-pentyl tetramethoxy superbowl 2.19

To a solution of tetrahydroxy superbowl 2.17 (22.1 mg, 5.00 µmol), dried according to the standard procedure, in dry THF (5 mL) at 0 °C was added sodium hydride (50.0 mg, 60% in mineral oil, 1.25 mmol). The reaction mixture was stirred for 20 min at that temperature before methyl iodide (100 µL, 1.60 mmol) was added. The reaction mixture was heated at 45 °C for 12 h, cooled to rt and then diluted with ethyl acetate. The organic mixture was quenched cautiously with 2M aq. HCl. The mixture was allowed to separate. The organic extract was then washed with sat. aq. NaHCO$_3$, sat. aq. NaCl,
dried over anhydrous MgSO₄ and the solvent was removed in vacuo. Purification by flash chromatography (20 g SiO₂, 7:3 dichloromethane/hexane) afforded the title compound 2.19 as a white solid (16.1 mg, 71%): \( R_f = 0.49 \) (7:3 dichloromethane/hexane); m.p. > 300 °C (decomp.) (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta 7.26 \) (s, 4H), 6.87 (s, 4H), 6.83 (s, 12H), 6.09 (d, \( J = 6.3 \) Hz, 8H), 5.97 (d, \( J = 6.9 \) Hz, 8H), 5.94 (d, \( J = 9.3 \) Hz, 4H), 5.60 (s, 4H), 5.57 (s, 4H), 4.88 (t, \( J = 7.8 \) Hz, 4H), 4.85-4.70 (m, 16H), 4.59 (d, \( J = 6.3 \) Hz, 8H), 4.53 (s, 8H), 4.33 (d, \( J = 6.6 \) Hz, 8H), 4.22 (d, \( J = 6.9 \) Hz, 4H), 3.84 (s, 12H), 2.35-2.10 (m, 40H), 1.55-1.20 (m, 120H), 1.00-0.80 (m, 60H) ppm; \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta 154.6, 153.8, 151.3, 149.1, 148.3, 147.2, 143.8, 141.0, 139.6, 139.4, 139.2, 138.5, 136.5, 131.0, 122.4, 122.1, 115.2, 114.5, 100.1, 99.9, 97.2, 59.6, 37.1, 36.9, 32.1, 32.0, 31.4, 30.6, 29.8, 27.8, 27.7, 27.5, 26.3, 22.8, 22.6, 22.4, 14.3, 14.0 ppm; IR (KBr) 2929, 2866, 1569 cm⁻¹; Nanospray ESI-MS \( m/z: 4495.0098 \) \([M+H]^+\) 5%, 2247.6533 \([M+2H]^{2+}\) 100%; Anal. Calcd. for C₂₇₂H₃₂₈O₅₆: C, 72.70; H, 7.36; found C, 72.64; H, 7.42.
Synthesis of aspirin para and meta regioisomers

General procedure: Hydroxybenzoic acid (1.38 g, 10.0 mmol) was placed in a conical flask equipped with a magnetic stirrer. With vigorous stirring, acetic anhydride (1.13 g, 11.0 mmol) was added then concentrated H$_2$SO$_4$ (98%, 3-4 drops) was added to the reaction mixture. The reaction mixture was then left stirring for another 6 h. The crude product mixture was then taken up in diethyl ether and water. The aqueous phase was further extracted with more diethyl ether. The combined organic phases were washed with sat. aq. NaCl then dried over MgSO$_4$. The solvent was removed in vacuo and the solid residue was recrystallized from diethyl ether/hexane to obtain the pure acetoxy benzoic acid product.

![2.28](image.png)

3-Acetoxy benzoic acid 2.28 was prepared by the above general procedure from 3-hydroxy benzoic acid. It was recrystallized from the crude product as white crystals (1.67 g, 93%).

![2.29](image.png)

4-Acetoxy benzoic acid 2.29 was prepared by the above general procedure from 4-hydroxy benzoic acid. It was recrystallized from the crude product as white crystals (1.67 g, 93%).

Characterization data for compounds 2.28 and 2.29 corresponded to that reported in literature.\textsuperscript{227}
Synthesis of aspirin hybrid drug 2.30

This compound was prepared by modification of the procedures reported by Wijtmans et al.\textsuperscript{102}

![Structure of aspirin hybrid drug](image)

Acetylsalicylic acid (aspirin, 5.00 g, 28.8 mmol) was dissolved in dry dichloromethane (100 mL) followed by the addition of pyridine (2.30 mL, 28.5 mmol). The solution was cooled to 0 °C and SOCl\textsubscript{2} (3.20 mL, 43.1 mmol) was slowly added. After 20 min, the solution turned from colorless to yellow. The reaction mixture was further stirred for 4 h, after which the solvent was removed by evaporation in a well-ventilated fumehood. The resulting dark yellow solid was dissolved in dichloromethane (75 mL) followed by addition of Et\textsubscript{3}N (4.80 mL, 34.5 mmol). The solution was cooled to 0 °C and the commercially available 4-hydroxybenzaldehyde (4.20 g, 34.6 mmol) was added. After 4 h of stirring, the dark brown solution was washed with water, sat. aq. NaHCO\textsubscript{3} and sat. aq. NaCl. The organic layer was dried with MgSO\textsubscript{4} and the solvent was evaporated to afford crude product, which was purified by column chromatography (200 g SiO\textsubscript{2}, 1:4 ethyl acetate/hexane) to afford aldehyde 2.32 (6.74 g, 80% over two steps).

![Structure of aldehyde 2.32](image)

Aldehyde 2.32 (3.71 g, 13.0 mmol) was dissolved in THF (50 mL). The solution was cooled to 0 °C and NaBH\textsubscript{4} (510 mg, 13.4 mmol) was added. After 3 h stirring at that temperature, the reaction was complete according to TLC. THF was removed \textit{in vacuo} and the crude product was taken up into diethyl ether (50 mL). The mixture was washed
with sat. aq. NH₄Cl, water and sat. aq. NaCl. The organic phase was dried with MgSO₄ and the solvent was evaporated to afford practically pure benzyl alcohol 2.33 as a white solid (3.23 g, 87%).

\[
\text{OAc} \quad \begin{array}{c}
\text{O} \\
\text{Cl}
\end{array} \\
\text{OAc}
\]

\[\text{2.34}\]

Benzylalcohol 2.33 (750 mg, 2.50 mmol) was dissolved in dichloromethane (25 mL). The solution was cooled to -30 °C. Pyridine (240 μL, 2.98 mmol) was added slowly, followed by SOCl₂ (270 μL, 3.70 mmol). After 1 h, the reaction mixture was allowed to warm up to rt. After another 5 h, the reaction was complete according to TLC. The solution was washed with water and sat. aq. NaCl then dried with MgSO₄. Solvent was removed in vacuo. The crude product was purified by column chromatography (100 g SiO₂, 1:8 ethyl acetate/hexane) to afford benzyl chloride 2.34 as white crystals (590 mg, 78%).

\[
\text{OAc} \quad \begin{array}{c}
\text{O} \\
\text{ONO₂}
\end{array} \\
\text{OAc}
\]

\[\text{2.30}\]

Benzyl chloride 2.34 (140 mg, 440 μmol) was dissolved in acetonitrile (15 mL). AgNO₃ (150 mg, 880 μmol) was added to the solution. The reaction mixture was heated at reflux for 12 h in the dark. The suspension was then filtered to remove the solids and the solvent in the filtrate was evaporated. The crude product was purified using column chromatography (50 g SiO₂, 1:6 ethyl acetate/hexane) to afford compound 2.30 as a white fine solid (85.0 mg, 56%).
Characterization data for the final target compound 4-(nitrooxymethyl)phenyl 2-acetoxybenzoate 2.30 and all intermediates 2.32-2.34 corresponded to that reported in literature.\textsuperscript{102}

**Synthesis of aspirin hybrid drug 2.31**

This compound was prepared by modification of the procedures reported by Wijtmans \textit{et al.}\textsuperscript{102}

\[
\text{CHO}
\]

2.35

4-Hydroxy benzaldehyde (5.00 g, 41.1 mmol) was dissolved in THF (150 mL). The solution was cooled to 0 °C and Et₃N (8.60 mL, 61.5 mmol) then acetyl chloride (4.40 mL, 61.5 mmol) were added. After stirring at rt overnight, the reaction was complete according to TLC, THF was removed \textit{in vacuo}. The crude product was taken up into diethyl ether. The mixture was washed with sat. aq. NH₄Cl, water and sat. aq. NaCl. The organic extract was dried with MgSO₄ and the solvent was evaporated to afford practically pure aldehyde 2.35 (5.57 g, 82%) for subsequent synthetic steps.

\[
\text{HO}
\]

2.36

Aldehyde 2.35 (4.82 g, 29.0 mmol) was dissolved in THF (50 mL). The solution was cooled to 0 °C and NaBH₄ (1.69 g, 44.7 mmol) was added. After 3 h stirring at that temperature, the reaction was complete according to TLC. THF was removed \textit{in vacuo} and the crude product was taken up into diethyl ether. The mixture was washed with sat. aq. NH₄Cl, water and sat. aq. NaCl. The organic phase was dried with MgSO₄ and the
solvent was evaporated to afford practically pure benzyl alcohol 2.36 (4.13 g, 83%) for subsequent synthetic steps.

![Image of benzyl chloride 2.37](image)

Benzyl alcohol 2.36 (2.54 g, 15.3 mmol) was dissolved in dichloromethane (25 mL). The solution was cooled to -30 °C. Pyridine (1.50 mL, 18.0 mmol) was added slowly, followed by SOCl₂ (1.82 mL, 25.0 mmol). After 1 h, the reaction mixture was allowed to warm up to rt. After stirring overnight, the reaction was complete according to TLC. The solution was washed with water and sat. aq. NaCl then dried with MgSO₄. Solvent was removed in vacuo. The crude product was purified by column chromatography (200 g SiO₂, 1:9 ethyl acetate/hexane) to afford benzyl chloride 2.37 as white crystals (2.19 g, 78%).

![Image of 4-(nitrooxymethyl)phenyl acetate 2.31](image)

Benzyl chloride 2.37 (234 mg, 1.27 mmol) was dissolved in acetonitrile (15 mL). AgNO₃ (435 mg, 2.55 mmol) was then added. The reaction mixture was heated at reflux for 3 h in the dark. The suspension was filtered to remove the solids and the solvent in the filtrate was evaporated. The crude product was purified using column chromatography (50 g SiO₂, 1:6 ethyl acetate/hexane) to afford compound 2.31 as white crystals (134 mg, 50%).

Characterization data for the final target compound 4-(nitrooxymethyl)phenyl acetate 2.31 and all intermediates 2.35-2.37 corresponded to that reported in literature.¹⁰²
Synthesis of nicotine hydrochloride salt

To a solution of nicotine (162 mg, 1.00 mmol) in dry diethyl ether (15 mL) under N₂ atmosphere at 0 °C was hydrogen chloride (500 μL of a 2 M solution in diethyl ether, 1.00 mmol). The reaction mixture was stirred for 30 min, then diethyl ether was evaporated to obtain an off-white solid. This was further dried at 0.1 mmHg for 8 h. No characterization was carried out for this compound/mixture.

Synthesis of 3,3',5,5'-tetrakis(bromomethyl)biphenyl 2.38

3,5-bis(bromomethyl) bromo benzene 2.40: To a solution of 5-bromo m-xylene (1.85 g, 10.0 mmol) in carbon tetrachloride (40 mL) was added recrystallised N-bromosuccinimide (3.92 g, 22.0 mmol). The reaction mixture was heated at reflux while being radiated with a 100 W tungsten lamp until all NBS was converted to succinimide. The reaction mixture was allowed to cool to rt then filtered to removed all solids. The organic solvent in the filtrate was removed in vacuo to afford the crude product, which was purified using column chromatography (100 g SiO₂, 1:9 dichloromethane/hexane) to obtain the title compound 2.40 as a white solid (1.82 g, 53%). Characterization data corresponded to that reported in literature.²³¹
3,5-bis(methoxymethyl) bromo benzene 2.41: To a solution of 3,5-bis(bromomethyl) bromo benzene 2.40 (1.03 g, 3.00 mmol) in dry MeOH (30 mL) under N₂ atmosphere was added sodium methoxy (356 mg, 6.60 mmol). The reaction mixture was stirred overnight at 35 °C. After reaction was completed by checking TLC, the solvent was removed in vacuo. Water (40 mL) and diethyl ether (40 mL) were added to partition the crude product. The aqueous phase was extracted with more diethyl ether (2 x 10 mL). The combined organic phases were washed with sat. aq. NaHCO₃, sat. aq. NaCl, dried over MgSO₄ and solvent was removed in vacuo. The crude product was purified using column chromatography (70 g SiO₂, 3:7 dichloromethane/hexane) to afford the title compound 2.41 as a colorless oil (632 mg, 86%). Characterization data corresponded to that reported in literature.⁴³²

3,3',5,5'-tetrakis(methoxymethyl)biphenyl 2.42: To a solution of 3,5-bis(methoxymethyl) bromo benzene 2.41 (490 mg, 2.00 mmol) in DMF (3 mL) was added Pd(PPh₃)₄ (92.5 mg, 80.0 μmol) and indium (230 mg, 2.01 mmol). The resulting mixture was heated at 100 °C for 12 h. The reaction was cooled down to rt then quenched with sat. aq. NaHCO₃ and the organic products were extracted with ethyl acetate (3 x 10mL). The combined organic phases were washed with water (3 x 5 mL), sat. aq. NaCl, dried over MgSO₄ and concentrated in vacuo. The crude product was purified using column chromatography (50 g SiO₂, 2:8 ethyl acetate/hexane) to afford
the title compound 2.42 as a low-melting-point white solid (258 mg, 78%). Characterization data corresponded to that reported in literature.\textsuperscript{104}

![Chemical structure of title compound 2.38](image)

### 3,3’,5,5’-tetrakis(bromomethyl)biphenyl 2.38:

To a solution of 3,3’,5,5’-tetrakis(methoxymethyl)biphenyl 2.42 (251 mg, 760 µmol) in dry dichloromethane (15 mL) at -78 °C was added tribromo borane (6.00 mL of a 1M solution in DCM, 6.00 mmol). The reaction mixture was warmed up to rt and stirred for 12 h. After diluting the mixture with more DCM (20 mL) and cooling back down to 0 °C, water was cautiously added. The organic phase was washed with sat. aq. NaHCO\textsubscript{3}, sat. aq. NaCl, dried over MgSO\textsubscript{4} and then concentrated \textit{in vacuo}. The crude product was then filtered through a short plug of silica with hexane to obtain the title compound 2.38 as a white solid (280 mg, 70%). Characterization data corresponded to that reported in literature.\textsuperscript{104}
General method for synthesis of xylyl-bridged superbows

To a solution of tetrahydroxy superbowl 2.17 (22.1 mg, 5.00 \( \mu \)mol), dried according to the standard procedure, in dry acetone (20 mL) under \( \text{N}_2 \) atmosphere was added Cs\(_2\)CO\(_3\) (65.2 mg, 200 \( \mu \)mol) and \( \alpha,\alpha\)-dibromo xylene (26.4 mg, 100 \( \mu \)mol). The reaction mixture was stirred for 12 h at 45 \(^\circ\)C. The solvent was then removed \textit{in vacuo} and the crude product was partitioned between dichloromethane (20 mL) and 2M aq. HCl solution (20 mL). The aqueous phase was extracted with more dichloromethane (10 mL). The combined organic phases were washed with sat. aq. NaHCO\(_3\), sat. aq. NaCl, dried over MgSO\(_4\) then the solvent was removed \textit{in vacuo}. The crude product was filtered through a short plug of silica with 100% dichloromethane. The filtrate was concentrated then filtered through another short plug of silica with dichloromethane/hexane mixture (3:7, 50 mL). The target xylyl-bridged superbowl, which stayed on top of the second silica plug, was washed down again with 100% dichloromethane. The final filtrate solution was concentrated to give practically pure xylyl-bridged superbowl.

\textit{para}-Xylyl-bridged superbowl 2.43
This compound was synthesized using the general method above with α,α-dibromo p-xylene. It was obtained as a white solid (17.9 mg, 77%): R_f = 0.76 (8:2 dichloromethane/hexane); m.p. > 300 °C (decomp.) (dichloromethane/hexane); ^1^H NMR (300 MHz, CDCl_3) δ 7.33 (s, 4H), 7.31 (d, J = 11.4 Hz, 8H), 6.87 (s, 8H), 6.82 (s, 4H), 6.79 (s, 4H), 6.17 (d, J = 7.5 Hz, 4H), 6.15 (d, J = 7.5 Hz, 4H), 5.98 (d, J = 7.2 Hz, 4H), 5.94 (d, J = 7.2 Hz, 2H), 5.70 (d, J = 6.9 Hz, 2H), 5.61 (s, 2H), 5.50-5.36 (m, 6H), 5.34-5.24 (m, 4H), 5.10 (d, J = 7.2 Hz, 4H), 4.98-4.86 (m, 4H), 4.86-4.60 (m, 28H), 4.50-4.30 (m, 12H), 4.21 (d, J = 6.9 Hz, 2H), 4.15-4.04 (m, 6H), 2.35-2.00 (m, 40H), 1.55-1.20 (m, 120H), 1.00-0.80 (m, 60H) ppm; ^13^C NMR (75 MHz, CDCl_3) δ 155.0, 154.2, 149.3, 148.2, 147.6, 147.2, 145.6, 143.6, 140.8, 140.0, 139.7, 139.4, 138.7, 138.4, 125.7, 121.8, 115.2, 114.7, 99.6, 99.4, 97.4, 95.7, 66.0, 37.1, 36.8, 32.5, 32.1, 32.9, 29.7, 29.5, 27.7, 27.4, 22.8, 14.3, 14.2 ppm; IR (KBr) 2928, 2863, 1570 cm^-1_; Nanospray ESI-MS m/z: 2321.7620 ([M+2H]^2+, 100%); Anal. Calcd. for C_{284}H_{332}O_{56}: C, 73.49; H, 7.21; found C, 73.34; H, 7.12.

\textit{meta-Xylyl-bridged superbowl 2.44}
This compound was synthesized using the general method above with α,α-dibromo m-xylene. It was obtained as a white solid (17.4 mg, 75%): \( R_f = 0.75 \) (8:2 dichloromethane/hexane); m.p. > 300 °C (decomp.) (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.95 (s, 2H), 7.50-7.35 (m, 6H), 7.22 (s, 4H), 6.90 (s, 4H), 6.85 (s, 8H), 6.83 (s, 4H), 6.34 (d, \( J = 6.9 \) Hz, 2H), 6.26 (d, \( J = 7.2 \) Hz, 4H), 6.18-6.02 (m, 6H), 5.95 (d, \( J = 6.9 \) Hz, 4H), 5.79 (d, \( J = 7.2 \) Hz, 4H), 5.75-5.60 (m, 4H), 5.39 (s, 2H), 5.22 (s, 2H), 5.00-4.70 (m, 32H), 4.60-4.40 (m, 8H), 4.40-4.20 (m, 12H), 4.17 (d, \( J = 7.5 \) Hz, 2H), 2.35-2.00 (m, 40H), 1.55-1.10 (m, 120H), 1.00-0.75 (m, 60H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 154.9, 154.0, 148.9, 148.5, 147.4, 147.1, 146.3, 146.0, 144.4, 143.6, 141.6, 140.9, 139.2, 139.0, 138.7, 138.6, 138.1, 128.7, 128.2, 121.4, 114.8, 100.4, 100.2, 99.8, 97.5, 66.0, 36.9, 32.2, 32.1, 32.0, 31.8, 30.4, 28.9, 29.7, 27.6, 27.5, 27.4, 22.7, 14.2, 14.1 ppm; IR (KBr) 2929, 2865, 1572 cm\(^{-1}\); Nanospray ESI-MS \( \text{m/z} \): 2321.8503 ([M+2H]\(^{++}\), 100%); Anal. Calcd. for \( \text{C}_{284}\text{H}_{332}\text{O}_{56} \): C, 73.49; H, 7.21; found C, 73.36; H, 7.17.

**ortho-Xylyl-bridged superbowl 2.45**
This compound was synthesized using the general method above with α,α-dibromo o-xylene. It was obtained as a white solid (16.0 mg, 69%): Rf = 0.77 (8:2 dichloromethane/hexane); m.p. > 300 °C (decomp.) (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl₃) δ 7.74 (dd, J = 3.9 Hz, J = 5.7 Hz, 4H), 7.49 (dd, J = 3.6 Hz, J = 5.7 Hz, 4H), 7.22 (s, 4H), 6.89 (s, 4H), 6.86 (s, 4H), 6.83 (s, 4H), 6.80 (s, 4H), 6.50 (d, J = 7.2 Hz, 2H), 6.37 (d, J = 7.2 Hz, 4H), 6.08 (d, J = 6.6 Hz, 4H), 5.91 (d, J = 3.3 Hz, 2H), 5.85 (d, J = 6.6 Hz, 4H), 5.74 (d, J = 7.2 Hz, 2H), 5.69 (d, J = 3.6 Hz, 2H), 5.54 (d, J = 6.9 Hz, 4H), 5.55-5.40 (m, 4H), 5.14 (d, J = 2.4 Hz, 2H), 5.05-4.68 (m, 20H), 4.50-4.20 (m, 28H), 2.35-2.00 (m, 40H), 1.55-1.10 (m, 120H), 1.00-0.80 (m, 60H) ppm; $^{13}$C NMR (75 MHz, CDCl₃) δ 155.1, 154.1, 148.6, 147.6, 147.2, 146.2, 144.5, 143.8, 141.7, 141.0, 139.3, 139.2, 138.9, 138.2, 128.8, 128.3, 122.3, 121.5, 115.2, 114.9, 100.2, 99.9, 99.7, 66.1, 37.3, 37.0, 32.2, 32.1, 32.0 (two coincident resonances), 30.0, 29.9, 27.8, 27.7, 27.6, 27.5, 22.8, 14.3 (two coincident resonances) ppm; IR (KBr) 2928, 2864, 1569 cm⁻¹; Nanospray ESI-MS m/z: 2321.7085 ([M+2H]⁺, 100%); Anal. Calcd. for C₄₈H₃₂O₅₆: C, 73.49; H, 7.21; found C, 73.37; H, 7.11.
Line-broadening NMR studies of aspirin signal linewidth with additions of superbowl 2.16 (refer to Section 2.5.3)

Studies were carried out using INOVA 500 MHz NMR spectrometer at 25 °C. Linewidths of aspirin signals were measured using internal functions of Varian software installed with the spectrometer.

**Step 1:** 10 mM aspirin and 1 mM tetraprotio superbowl 2.16 solutions in CDCl₃ were prepared and degassed. The ¹H NMR spectrum of a sample of 10 mM aspirin solution (1 mL) in a standard NMR sample tube was recorded.

**Step 2:** 1 mM tetraprotio superbowl 2.16 solution (10 µL) was added to the NMR tube. The solution was throughout mixed and allowed to equilibrate over 30 min. During this time, the volume of the solution was adjusted back to 1 mL by means of evaporation by a dry nitrogen stream. This brought the ratio of aspirin/superbowl to 1000:1. The ¹H NMR spectrum of this sample was recorded.

**Step 3:** Repeating what was done in step 2 to the 1000:1 aspirin/host sample from step 2 with another aliquot (10 µL) of 1 mM tetraprotio superbowl 2.16 solution. This brought the ratio of aspirin/superbowl to 500:1.

**Step 4:** Repeating what was done in step 2 to the 500:1 aspirin/host sample from step 3 with another aliquot (20 µL) of 1 mM tetraprotio superbowl 2.16 solution. This brought the ratio of aspirin/superbowl to 250:1.

**Step 5:** Repeating what was done in step 2 to the 250:1 aspirin/host sample from step 4 with another aliquot (60 µL) of 1 mM tetraprotio superbowl 2.16 solution. This brought the ratio of aspirin/superbowl to 100:1.

Linewidths of aspirin signals were then measured and the linewidth change factor for each individual signal was calculated as:

\[
\text{Linewidth change} = \frac{\text{(Broadened) linewidth}}{\text{Original linewidth (of free aspirin)}}
\]
The linewidths and linewidth change factors are summarized below:

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<th>Aspirin Signal</th>
<th>Linewidths (Hz)</th>
<th>1st addition</th>
<th>2nd addition</th>
<th>3rd addition</th>
<th>4th addition</th>
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<tbody>
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<td>1.27825</td>
<td>1.33917</td>
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<tr>
<td></td>
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<td>2nd addition</td>
<td>3rd addition</td>
<td>4th addition</td>
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<tr>
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<td>468.995</td>
<td>505.644</td>
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<table>
<thead>
<tr>
<th>Ratio (aspirin/host)</th>
<th>Linewidth change</th>
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<tr>
<td></td>
<td>CH₃</td>
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<tr>
<td>250:1</td>
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<tr>
<td>100:1</td>
<td>1.67</td>
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</table>
Host-guest binding studies of superbows with tetraalkyl ammonium salts and aspirin

Binding studies between superbows and tetraalkyl ammonium salts and aspirin were carried out in chloroform using the general method for host-guest binding studies. ITC profiles of the binding host-guest pairs are included in the following:
Binding study between superbowl 2.16 and tetraethyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.16 (1 mM) vs Et4NBr (50 mM)

- N = 1.02 ± 0.08
- K = 317 ± 10
- ΔH = -4190 ± 60
- ΔS = -2.62

\[ \text{Data 2.16 (1 mM) vs Et}_4\text{NBr (50 mM)} \]

\[ \begin{align*}
N & = 1.02 \pm 0.08 \\
K & = 317 \pm 10 \\
\Delta H & = -4190 \pm 60 \\
\Delta S & = -2.62
\end{align*} \]
Binding study between superbowl 2.16 and tetrapropyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.16 (1 mM) vs Pr₄NB₄ (50 mM)
N 1.09 ±0.07
K 273 ±10
ΔH -2400 ±20
ΔS 310

Molar Ratio

Kcal/mole of injectant

μcal/sec

Time (min)
Binding study between superbowl 2.16 and tetrabutyl ammonium bromide (ITC, chloroform, 25 °C)

Data: 2.16 (2.5 mM) vs Bu4NBr (50 mM)

- N = 1.03 ± 0.08
- K = 329 ± 30
- ΔH = -3300 ± 110
- ΔS = 0.454
Binding study between superbowl 2.16 and tetrapentyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.16 (1 mM) vs Pent4NBr (50 mM)

N 0.97 ± 0.06
K 358 ± 15
ΔH -3840 ± 40
ΔS -1.19
Binding study between superbowl 2.16 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.16 (1 mM) vs Hex$_2$NBt (50 mM)

\[ N = 1.05 \pm 0.07 \]
\[ K = 467 \pm 16 \]
\[ \Delta H = -2240 \pm 30 \]
\[ \Delta S = 4.69 \]
Binding study between superbowl 2.16 and tetraheptyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.16 (3 mM) vs Hept4NBt (50 mM)

\[
\begin{array}{|c|c|}
\hline
\text{Parameter} & \text{Value} \\
\hline
N & 1.05 \pm 0.16 \\
K & 231 \pm 20 \\
\Delta H & -2600 \pm 290 \\
\Delta S & 203 \\
\hline
\end{array}
\]

Molar Ratio

kcal/mole of injectant

0.00 20.00 40.00 60.00 80.00 100.00 120.00 140.00

Time (min)

μcal/sec

0.00 20.00 40.00 60.00 80.00 100.00 120.00 140.00

247
Binding study between superbowl 2.16 and tetraoctyl ammonium bromide (ITC, chloroform, 25 °C)

![Graph showing the binding study between superbowl 2.16 and tetraoctyl ammonium bromide.]

Data 2.16 (1 mM) vs Oct$_2$NBr (50 mM)

- N: 1.00 ± 0.02
- K: 139 ± 3
- ΔH: -3320 ± 30
- ΔS: -133

![Graph showing the heat flow over time during the binding study.]

![Graph showing the molar ratio over time during the binding study.]

Time (min) vs Heat Flow (μcal/sec)
Binding study between superbowl 2.13 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.13 (1 mM) vs Hex$_2$NB$\text{r}$ (50 mM)

- N = 1.05 ± 0.09
- K = 79 ± 6
- $\Delta H$ = -3340 ± 140
- $\Delta S$ = -2.52
Binding study between superbowl 2.13 and aspirin (ITC, chloroform, 25 °C)

Data: 2.13 (1 mM) vs Aspirin (50 mM)
N = 1.03 ± 0.11
K = 94 ± 6
H = -3190 ± 110
S = -1.65
Binding study between superbowl 2.14 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

Data 2.14 (1 mM) vs Hex$_7$NB$\text{r}$ (50 mM)

- $N = 1.10 \pm 0.07$
- $K = 49 \pm 2$
- $\Delta H = -6640 \pm 140$
- $\Delta S = -14.5$

kcal/mole of injectant vs Molar Ratio

μcal/sec vs Time (min)
Binding study between superbowi 2.14 and aspirin (ITC, chloroform, 25 °C)

Data 2.14 (1 mM) vs Aspirin (50 mM)

\[ N = 0.96 \pm 0.08 \]
\[ K = 96 \pm 3 \]
\[ \Delta H = -6.700 \pm 100 \]
\[ \Delta S = -13.3 \]

Molar Ratio

Time (min)

\( \mu \text{cal/sec} \)
Binding study between superbowl 2.15 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

\[ N = 0.98 \pm 0.11 \]
\[ K = 147 \pm 13 \]
\[ \Delta H = -1450 \pm 50 \]
\[ \Delta S = 5.04 \]
Binding study between superbowl 2.15 and aspirin (ITC, chloroform, 25 °C)

Data 2.15 (0.5 mM) vs Aspirin (50 mM)

<table>
<thead>
<tr>
<th>Molar Ratio</th>
<th>kcal/mole of injectant</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.67</td>
<td>-0.8</td>
</tr>
<tr>
<td>0.00</td>
<td></td>
</tr>
<tr>
<td>16.67</td>
<td></td>
</tr>
<tr>
<td>33.33</td>
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<td>50.00</td>
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<tr>
<td>16.67</td>
<td></td>
</tr>
<tr>
<td>33.33</td>
<td></td>
</tr>
</tbody>
</table>

Time (min) 0.00 16.67 33.33 50.00 66.67 83.33 100.00

μcal/sec

0.00 16.67 33.33

N 1.03 ± 0.06
K 295 ± 14
ΔH -8560 ± 190
ΔS -17.4
Binding study between superbowl 2.20 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)
Binding study between superbowl 2.20 and aspirin (ITC, chloroform, 25 °C)

-0.8
-0.6
-0.4
-0.2
0.0
0.2
0.4
0.6
0.8

Molar Ratio

kcal/mole of injectant

0.00 20.00 40.00 60.00 80.00 100.00 120.00 140.00
Time (min)

30
28
26
24
22
20
18
16
14

μcal/sec

0.00 20.00 40.00 60.00 80.00 100.00 120.00 140.00
Time (min)

Data 2.20 (2 mM) vs Aspirin (50 mM)

N 1.00 ±0.04
K 485 ±10
ΔH -1870 ±20
ΔS 6.02
Binding study between superbowl 2.23 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

Data: 2.23 (0.5 mM) vs Hex$_4$NBr (50 mM)

- N: 1.12 ± 0.14
- K: 100 ± 19
- H: -1410 ± 40
- S: 4.57

Molar Ratio vs. kcal/mole of injectant

Time (min) vs. µcal/sec
Binding study between superbowl 2.23 and aspirin (ITC, chloroform, 25 °C)

Data: 2.23 (1 mM) vs Aspirin (50 mM)
N  1.04 ± 0.03
K  470 ± 12.0
H  -2330 ± 20
S  4.43
Binding study between superbowl 2.25 and aspirin (ITC, chloroform, 25 °C)

Data: **2.25** (0.5 mM) vs Aspirin (50 mM)

- N: 1.05 ± 0.09
- K: 138 ± 13
- H: -140 ± 60
- S: 5.65
Binding study between superbowl 2.27 and aspirin (ITC, chloroform, 25 °C)
Binding study between superbowl 2.43 and aspirin (ITC, chloroform, 25 °C)

Data 2.43 (0.5 mM) vs Aspirin (50 mM)
N 0.98 ±0.5
K 314 ±24
ΔH ≈-890 ±30
ΔS 8.45
CHAPTER 3 – EXPERIMENTAL DATA

\[ n = 0-2; \ X = \text{hetero atom} \]
To a solution of 2,6-dimethoxyphenol (77.1 mg, 500 μmol) in dry acetone (25 mL) was added tetra(bromomethyl) cavitand 2.8 (119 mg, 100 μmol) and potassium carbonate (1.38 g, 10.0 mmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt; acetone was removed \textit{in vacuo}. Ethyl acetate (25 mL) and water (25 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl to allow partition between two phases. The aqueous phase was further extracted with more ethyl acetate (2 x 10 mL). The combined organic phases were washed with sat. aq. NaHCO\textsubscript{3} and sat. aq. NaCl, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. The crude product was purified by column chromatography (40 g SiO\textsubscript{2}, 3:7 ethyl acetate/hexane) to obtain the title cavitand 3.1 as a white solid (118 mg, 80%): \( R_f = 0.37 \) (3:7 ethyl acetate/hexane); m.p. 213-215 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 7.21 (s, 4H), 6.76 (t, \( J = 9 \) Hz, 4H), 6.31 (d, \( J = 8.7 \) Hz, 8H), 5.77 (d, \( J = 7.5 \) Hz, 4H), 5.00-4.85 (m, 12 H), 4.33 (d, \( J = 7.2 \) Hz, 4H), 3.32 (s, 24H), 2.37-2.05 (m, 8H), 1.50-1.05 (m, 24 H), 1.00-0.80 (m, 12H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 154.5, 154.0, 138.0, 136.6, 124.5, 123.8, 120.5, 104.8, 100.6, 64.6, 55.3, 36.9, 32.2, 30.2, 27.8, 22.9, 14.3 ppm; IR (KBr) 2930, 2836, 1595 cm\(^{-1}\); ESI-MS \textit{m/z}: 1503.7 ([M+Na]\(^+\), 100%); Anal. Calcd. for C\textsubscript{88}H\textsubscript{104}O\textsubscript{20}: C, 71.33; H, 7.07; found C, 71.24; H, 6.92.
To a solution of phenol (47.1 mg, 500 µmol) in dry acetone (25 mL) was added tetra(bromomethyl) cavitand 2.8 (119 mg, 100 µmol) and potassium carbonate (1.38 g, 10.0 mmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt and acetone was removed in vacuo. Ethyl acetate (25 mL) and water (25 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl. The two phases were separated. The aqueous phase was further extracted with more ethyl acetate (2 x 10 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (40 g SiO₂, 3:7 ethyl acetate/hexane) to obtain the title cavitand 3.2 as a white solid (102 mg, 82%): Rf = 0.49 (3:7 ethyl acetate/hexane); m.p. 200-201 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.30-7.20 (m, 12H), 7.00-6.85 (m, 12H), 5.75 (d, J = 7.2 Hz, 4H), 4.90 (s, 8H), 4.86 (t, J = 8.1 Hz, 4H), 4.67 (d, J = 7.5 Hz, 4H), 2.37-2.20 (m, 8H), 1.55-1.25 (m, 24 H), 0.94 (t, J = 6.9 Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 158.8, 154.5, 138.1, 129.7, 123.0, 121.2, 121.1, 114.7, 100.3, 60.6, 37.1, 32.2, 30.3, 27.8, 22.9, 14.3 ppm; IR (KBr) 2928, 2859, 1576 cm⁻¹; ESI-MS m/z: 1279.5 ([M+K]⁺, 100%), 1263.6 ([M + Na]⁺, 50%), 1258.6 ([M+H₂O]⁺, 10%); Anal. Calcd. for C₈₀H₇₄O₁₂: C, 77.39; H, 7.14; found C, 77.14; H, 7.18.
To a solution of tetra(hydroxymethyl) cavitand 3.4 (93.7 mg, 100 μmol) in dry THF (5 mL) at 0 °C was added sodium hydride (24.0 mg of 60% in mineral oil, 600 μmol). The reaction mixture was stirred at that temperature for 30 min, then methyl iodide (50.0 μL, 800 μmol) was added. The mixture was stirred at 25 °C for 18 h; the solvent was then removed in vacuo. Ethyl acetate (25 mL) and water (25 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl to allow partition between two phases. The aqueous phase was further extracted with more ethyl acetate (2 x 10 mL). The combined organic phases were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (40 g SiO₂, 3:7 to 1:1 ethyl acetate/hexane) to obtain the title cavitand 3.3 as a white solid (90.4 mg, 91%): Rₜ = 0.25 (1:1 ethylacetate/hexane); m.p. 168-170 °C (dichloromethane/hexane; ¹H NMR (300 MHz, CDCl₃) δ 7.11 (s, 4H), 5.86 (d, J = 7.2 Hz, 4H), 4.79 (t, J = 8.1 Hz, 4H), 4.38 (d, J = 7.5 Hz, 4H), 4.26 (s, 8H), 3.33 (s, 12H), 2.35-2.15 (m, 8H), 1.50-1.25 (m, 24 H), 1.00-0.85 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 154.1, 138.0, 124.1, 120.6, 99.8, 64.6, 58.7, 37.0, 32.2, 30.2, 27.7, 22.8, 14.3 ppm; IR (KBr) 2929, 2866, 1572 cm⁻¹; ESI-MS m/z: 1016.0 ([M+Na]⁺, 100%); Anal. Calcd. for C₁₀₀H₈₀O₁₂: C, 72.55; H, 8.12; found C, 72.62; H, 8.07.
To a solution of tetra(bromomethyl) cavitand 2.8 (119 mg, 100 μmol) in THF (25 mL) was sodium acetate (65.6 mg, 800 μmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt, lithium hydroxide (500 mg, 20.8 mmol) and methanol (10 mL) were added and the reaction mixture was heated to reflux for another 12 h. The mixture was then allowed to cool to rt and the solvents were removed in vacuo. Ethyl acetate (25 mL) and water (25 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl and two phases were separated. The aqueous phase was further extracted with more ethyl acetate (2 x 10 mL). The combined organic phases were washed with sat. aq. NaHCO₃, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was recrystallized from ethyl acetate/hexane to obtain the title cavitand 3.4 as a white solid (83.4 mg, 89%): m.p. 130-132 °C (dichloromethane/hexane); ¹H NMR (500 MHz, CDCl₃) δ 7.12 (s, 4H), 5.92 (d, J = 7.0 Hz, 4H), 4.80 (br. s, 4H), 4.56 (s, 8H), 4.43 (br. s, 4H), 2.35-2.10 (m, 8H), 2.08 (br. s, 4H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 153.6, 138.2, 126.4, 120.3, 99.8, 60.4, 55.4, 36.9, 32.0, 30.0, 27.6, 22.7, 21.0, 14.1 ppm; IR (KBr) 3600-3100, 2928, 2860, 1589 cm⁻¹; ESI-MS m/z: 936.5 ([M+H]+, 60%), 935.5 ([M]+, 100%); Anal. Calcd. for C₉₅H₁₇₂O₁₂: C, 71.77; H, 7.74; found C, 71.61; H, 7.78.
C-pentyl monobromo triprotio cavitand 3.5

Prepared by modification of the procedure of Barrett et al.\(^2\) To a solution of tetrabromo cavitand 2.3 (3.40 g, 3.00 mmol), dried according to the standard procedure, in anhydrous THF (300 mL) under nitrogen atmosphere at \(-78^\circ\)C was added rapidly \(n\)-BuLi (2.06 mL of a 1.60 M solution in hexanes, 1.10 mmol). After 5 min, isopropanol (229 \(\mu\)L, 1.00 mmol) was added rapidly and stirring was continued at \(-78^\circ\)C for 1 min. These \(n\)-BuLi and isopropanol additions were repeated two more times and finally an excess of methanol was added. The solution was allowed to warm to RT and the THF was removed \textit{in vacuo}. The residue was taken up in ethyl acetate, washed successively with water and sat. aq. NaCl, dried over anhydrous MgSO\(_4\), and the solvent was removed \textit{in vacuo}. Purification by flash chromatography (250 g SiO\(_2\), 8:2 hexane/ethyl acetate) afforded monobromo triprotio cavitand 3.5 (1.88 g, 71%). Characterisation data corresponded to that reported in the literature.\(^2\)
Monobromo triprotio cavitand 3.5 (896 mg, 1.00 mmol), dried according to the standard procedure, was dissolved in anhydrous THF (50 mL). The solution was cooled to –78 °C and n-BuLi (753 μL of a 1.46 M solution in hexanes, 1.10 mmol) was added rapidly. After 20 min, dry DMF (155 μL, 2.00 mmol) was added rapidly, the cooling bath was removed and the solution was allowed to warm to rt. The solution was then cooled to 0 °C and cautiously quenched with 5% aq. NH₄Cl before THF was removed in vacuo. The product cavitands were extracted into ethyl acetate (3 x 20 mL) and the combined organic phases were washed with sat. aq. NaHCO₃ then sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. Monoaldehyde 3.6 was obtained after column chromatography (100 g SiO₂, 1:9 to 3:7 ethyl acetate/hexane) as a white solid (701 mg, 83%): Rf = 0.15 (1:9 ethyl acetate/hexane); m.p. 101-103 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 10.26 (s, 1H), 7.34 (s, 1H), 7.09 (s, 3H), 6.52 (s, 2H), 6.49 (s, 1H), 5.83 (d, J = 7.2 Hz, 2H), 5.74 (d, J = 7.2 Hz, 2H), 4.81 (t, J = 8.1 Hz, 2H), 4.72 (t, J = 8.1 Hz, 2H), 4.45 (d, J = 3.0 Hz, 2H), 4.42 (d, J = 3.0 Hz, 2H), 2.35-2.10 (m, 8H), 1.50-1.25 (m, 24H), 0.98-0.90 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 190.8, 155.2, 154.9, 154.7, 139.5, 138.9, 138.6, 138.1, 125.5, 124.0, 120.7, 116.8, 100.0, 99.6, 36.5, 36.3, 32.2, 32.1, 30.0, 29.8, 27.7, 22.8, 22.7, 14.3 ppm; IR (KBr) 2929, 2863, 1665, 1573 cm⁻¹; ESI-MS m/z: 867.2 ([M+Na]+, 100%), 843.9 ([M]⁺, 20%); Anal. Calcd. for C₃₅H₆₂O₁₀: C, 75.33; H, 7.63; found C, 75.14; H, 7.50.
Monoaldehyde cavitand 3.6 (84.5 mg, 100 μmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and NaBH₄ (19.0 mg, 500 μmol) was added. After 8 h at that temperature, the reaction was complete according to TLC. After cautious addition of sat. aq. NH₄Cl, THF was removed in vacuo and the organic products were extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with water, sat. aq. NaCl, dried with MgSO₄ and the solvent was evaporated to afford practically pure mono(hydroxymethyl) cavitand 3.7, which could be further purified by pushing through a short plug of silica to obtain a white solid (76.2 mg, 90%) after solvent removal: $R_f = 0.12$ (100% dichloromethane); m.p. 188-190 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.14 (s, 1H), 7.10 (s, 3H), 6.56 (s, 1H), 6.47 (s, 2H), 5.82 (d, $J = 7.5$ Hz, 2H), 5.72 (d, $J = 6.9$ Hz, 2H), 4.76 (t, $J = 7.5$ Hz, 2H), 4.72 (t, $J = 8.1$ Hz, 2H), 4.66 (s, 2H), 4.55 (d, $J = 7.8$ Hz, 2H), 4.41 (d, $J = 7.5$ Hz, 2H), 2.30-2.10 (m, 8H), 1.90 (br. s, 1H), 1.50-1.10 (m, 24H), 0.91 (t, $J = 11$ Hz, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl₃) $\delta$ 155.1, 154.8, 154.7, 153.9, 138.4 (two coincident resonances), 138.2, 125.8, 120.6, 120.5, 117.0, 116.6, 100.0, 99.4, 55.1, 36.7, 36.4, 32.1, 30.0, 27.7, 22.8, 14.2 ppm; IR (KBr) 3500-3100, 2929, 2866, 1574 cm⁻¹; ESI-MS $m/z$: 869.7 ([M+Na]⁺, 100%), 846.8 ([M+H]⁺, 20%); Anal. Calcd. for C₃₃H₆₆O₉: C, 75.15; H, 7.85; found C, 75.14; H, 7.82.
To a solution of tetrabromo cavitand 2.3 (1.13 g, 1.00 mmol), dried according to the standard procedure, in THF (100 mL) at −78 °C was added n-BuLi (3.13 mL of a 1.60 M solution in hexanes, 5.00 mmol). After 20 min, B(OMe)$_3$ (6.08 mL, 6.00 mmol) was added, the cooling bath was removed and the solution was stirred at rt for 1 h. The resulting solution was cooled to −78 °C, quenched with a 1:1 mixture of 30% aq. H$_2$O$_2$ and 3 M aq. NaOH (90 mL), then stirred at rt for 18 h. The solution was cooled to −78 °C and after cautious addition of 30% aq. Na$_2$S$_2$O$_3$, the THF was removed in vacuo. The resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic phases were washed successively with sat. aq. NaHCO$_3$ and sat. aq. NaCl, dried over MgSO$_4$ and the solvent was removed in vacuo. Recrystallization of the crude product from ethyl acetate/hexane afforded the title compound 3.8 as a white solid (774 mg, 88%). Characterisation data corresponded to that reported in the literature.$^{233}$
Monobromo triprotio cavitand 3.5 (89.6 mg, 100 μmol), dried according to the standard procedure, was dissolved in anhydrous THF (20 mL), cooled to -78 °C and n-BuLi (75.3 μL of a 1.46 M solution in hexanes, 110 μmol) was added rapidly. After 20 min, B(OMe)₃ (150 μL, 150 μmol) was added, the cooling bath was removed and the solution was stirred at rt for 1 h. The resulting solution was cooled to -78 °C, quenched with a 1:1 mixture of 30% aq. H₂O₂ and 3 M aq. NaOH (9 mL), then stirred at rt for 18 h. The solution was cooled to -78 °C and after cautious addition of 30% aq. Na₂S₂O₅, the THF was removed in vacuo. The resulting mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. Recrystallization of the crude product from ethyl acetate/hexane afforded the title compound 3.9 as a white solid (74.1 mg, 89%): Rᵣ = 0.18 (8:2 dichloromethane/hexane); m.p. 161 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.10 (s, 3H), 6.65 (s, 1H), 6.50 (s, 2H), 6.49 (s, 1H), 5.85 (d, J = 6.9 Hz, 2H), 5.75 (d, J = 7.8 Hz, 2H), 4.72 (t, J = 7.5 Hz, 2H), 4.70 (t, J = 8.1 Hz, 2H), 4.43 (dd, J = 1.8 Hz, J = 6.9 Hz, 4H), 2.30-2.10 (m, 8H), 1.50-1.20 (m, 24H), 0.91 (t, J = 7.2 Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 155.0, 154.9 (two coincident resonances), 142.0, 141.0, 138.7, 138.6 (two coincident resonances), 138.5, 121.0, 120.7, 116.6, 116.5, 109.7, 99.8, 99.7, 36.7, 36.5, 32.2, 30.0, 29.8, 27.7, 22.8, 14.3 ppm; IR (KBr) 3500-3100, 2931, 2860, 1572 cm⁻¹; ESI-MS m/z: 833.0 ([M+H]+, 100%); Anal. Calcd. for C₃₅H₆₄O₆: C, 74.97; H, 7.74; found C, 75.02; H, 7.82.
Monobromo triprotio cavitand 3.5 (896 mg, 1.00 mmol), dried according to the standard procedure, was dissolved in anhydrous THF (50 mL), cooled to –78 °C and n-BuLi (753 μL of a 1.46 M solution in hexanes, 1.10 mmol) was added rapidly. After 20 min, methyl chloroformate (500 μL, 6.35 mmol) was added rapidly, the cooling bath was removed and the solution was allowed to warm to rt. The solution was cooled to 0 °C and cautiously quenched with 5% aq. NH₄Cl before THF was removed in vacuo. The cavitand products were extracted into ethyl acetate (3 x 30 mL) and the combined organic phases were washed with sat. aq. NaHCO₃, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo to afford an off-white solid (726 mg, 83%). Crude product of mono(carbomethoxy) cavitand 3.10 was submitted to the next step without any further purification.

Mono(carbomethoxy) triprotio cavitand 3.10 crude (87.5 mg, 100 μmol) was dissolved in THF (15 mL). Lithium hydroxide (100 mg, 4.17 mmol) and 3-4 drops of water were added to the solution and the reaction mixture was heated at reflux for 48 h. THF was removed in vacuo and the crude product was partitioned between ethyl acetate (30 mL) and 2 M aq. HCl (30 mL). The aqueous phase was washed with more ethyl acetate (2 x 10 mL) and the combined organic extracts were washed successively with water, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (40 g SiO₂, 5:95 to 10:90 methanol/dichloromethane) to obtain the title cavitand 3.11 as a white solid (68.9 mg, 80%): Rₜ = 0.24 (1:9 methanol/dichloromethane); m.p. > 100 °C (decomp.) (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.21 (s, 1H), 7.08 (s, 3H), 6.55 (s, 1H), 6.47 (s, 2H), 5.85-5.60 (m, 4H), 4.80-4.60 (m, 4H), 4.51 (d, J = 7.8 Hz,
2H), 4.41 (d, $J = 7.2$ Hz, 2H), 2.30-2.10 (m, 8H), 1.50-1.15 (m, 24H), 1.00-0.80 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl$_3$) δ 167.8, 155.0, 154.5, 150.8, 139.0, 138.8, 138.4, 138.3, 137.7, 120.4, 116.9, 116.6, 99.6, 99.4, 36.3, 32.0, 29.9, 29.7, 27.6, 22.7, 14.1 ppm; IR (KBr) 3300-3100, 2928, 2864, 1570 cm$^{-1}$; ESI-MS $m/z$: 883.8 ([M+Na]$^+$, 80%), 861.6 ([M]$^+$, 5%), 843.7 ([M-OH]$^+$, 100%); Anal. Calcd. for C$_{53}$H$_{64}$O$_{16}$: C, 73.93; H, 7.49; found C, 73.84; H, 7.42.
To a solution of monobromo cavitand 3.5 (260 mg, 290 μmol), dried according to the standard procedure, in dry THF (25 mL) under a nitrogen atmosphere at -78 °C was rapidly added n-BuLi (190 μL of a 1.60 M solution in hexanes, 305 μmol). The reaction mixture was stirred at that temperature for 20 min then diphenyl phosphoryl azide (160 mg, 580 μmol) in dry THF (3 mL) was added. The reaction mixture was warmed to rt and stirred for 8 h. The reaction was again cooled to -78 °C, LiAlH₄ (100 mg, 2.64 mmol) was added and stirring was continued for 12 h at rt. Then, fridge-cold 2M aq. NaOH solution (30 mL) was cautiously added. THF was subsequently removed in vacuo and the organic products were extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with 1 M aq. NaOH, sat. aq. NaCl then dried over MgSO₄. The solvent was removed in vacuo. The crude product was purified by column chromatography (50 g SiO₂, 4:6 ethyl acetate/hexane) to obtain the title cavitand 3.12 as a white solid (145 mg, 60%): $R_f = 0.29$ (4:6 ethyl acetate/hexane); m.p. 190-191 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.10 (s, 3H), 6.52 (s, 1H), 6.48 (s, 3H), 5.83 (br. d, $J = 6.0$ Hz, 2H), 5.75 (d, $J = 7.2$ Hz, 2H), 4.72 (t, $J = 8.1$ Hz, 2H), 4.70 (t, $J = 7.5$ Hz, 2H), 4.48 (d, $J = 6.9$ Hz, 2H), 4.40 (d, $J = 6.9$ Hz, 2H), 3.75 (br. s, 2H), 2.30-2.05 (m, 8H), 1.50-1.20 (m, 24H), 0.91 (t, $J = 7.2$ Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 155.0, 154.8, 138.8, 138.5, 138.0, 121.0, 120.7, 116.7, 116.6, 99.6, 99.4, 36.7, 36.5, 32.2 (two coincident resonances), 30.0, 29.8, 27.8, 27.7, 22.8, 14.3 ppm; IR (KBr) 3465, 3365, 2928, 2860, 1607, 1577 cm⁻¹; ESI-MS m/z: 831.9 ([M+H]⁺, 100%); Anal. Calcd. for C₅₂H₆₅NO₈: C, 75.06; H, 7.87; found C, 74.94; H, 7.92.
C-pentyl triprotio monoboronic acid cavitand 3.13

Prepared by modification of the procedure of Barrett et al.\textsuperscript{2} To a solution of monobromo cavitand 3.5 (448 mg, 500 μmol), dried according to the standard procedure, in anhydrous THF (25 mL) under nitrogen atmosphere at –78 °C was added rapidly n-BuLi (343 μL of a 1.60 M solution in hexanes, 550 μmol). After 20 min, trimethylborate (85.0 μL, 750 μmol) was introduced, the cooling bath was removed and the solution was allowed to warm to rt and was stirred at this temperature for 1 h. The reaction was quenched with 2 M aq. HCl, then stirred at rt for 45 min. The phases were separated and the aqueous phase was then further extracted with dichloromethane. The combined organic extracts were dried over anhydrous MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. Purification by flash chromatography (50 g SiO\textsubscript{2}, 7:3 to 4:6 hexane/ethyl acetate) afforded the monoboronic acid 3.13 (327 mg, 76%). Characterisation data corresponded to that reported in the literature.\textsuperscript{2}
To a stirred suspension of (methoxymethyl)triphenylphosphonium bromide (387 mg, 1.00 mmol) in THF (2 mL) was added dropwise n-BuLi (620 μL of a 1.6 M solution in hexanes, 0.99 mmol) at 0 °C under nitrogen atmosphere. The cooling bath was removed and the mixture was stirred at rt for 2 h. A solution of monoformyl triprotio cavitand 3.6 (845 mg, 1.00 mmol) in THF (3 mL) was added dropwise and stirring was continued for 1 h at rt, then at 60 °C for 10 h. After cooling to rt, water (30 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed in vacuo. ¹H-NMR of the crude product corresponded to a mixture with majority of cavitand intermediate 3.15.

The crude product 3.15 was then dissolved in THF (30 mL) and 2 M aq. HCl solution (20 mL) was added. The reaction mixture was heated to reflux for 12 h then THF was removed in vacuo. The organic products were extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (60 g SiO₂, 3:7 ethylacetate/hexane) to afford the title cavitand 3.16 as a white solid (653 mg, 76% over two steps): Rf = 0.32 (3:7 ethyl acetate/hexane); m.p. > 160 °C (decomp.) (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 9.79 (s, 1H), 7.15-7.05 (m, 4H), 6.56 (s, 1H), 6.45 (s, 2H), 5.73 (d, J = 6.9 Hz, 2H), 5.61 (d, J = 7.5 Hz, 2H), 4.80-4.50 (m, 6H), 4.18 (d, J = 7.5 Hz, 2H), 3.82 (s, 2H), 2.30-2.10 (m, 8H), 1.50-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 200.9, 155.1, 154.9, 154.8, 153.8, 138.6, 138.5, 138.0, 137.9, 120.5, 120.1, 119.5, 116.9 (two coincident resonances), 99.9, 99.4, 41.2, 36.8, 36.5, 32.2, 30.2, 30.0, 27.7, 22.9, 14.3 ppm; IR (KBr) 2929, 2866, 1675, 1570 cm⁻¹; ESI-MS m/z: 858.9
C-pentyl mono(2-hydroxyethyl) triprotio cavitand 3.14

Cavitand 3.16 (85.9 mg, 100 μmol) was then again dissolved in THF (10 mL). The solution was cooled down to 0 °C and NaBH₄ (8.3 mg, 220 μmol) was added. The reaction mixture was stirred at that temperature for 6 h, by that time reaction was completed by TLC. After cautious addition of 5% aq. NH₄Cl, THF was removed in vacuo. Ethyl acetate (3 x 20 mL) was added to extract the organic products from the residue. The combined organic phases were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed in vacuo. Pure mono(hydroxyethylene) triprotio cavitand 3.14 was obtained after column chromatography (20 g SiO₂, 2:8 to 1:1 ethyl acetate/hexane) as a white solid (74.9 mg, 87%); Rₜ = 0.25 (1:1 ethyl acetate/hexane); m.p. 170-172 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.11 (s, 3H), 7.02 (s, 1H), 6.48 (s, 3H), 5.82 (d, J = 6.9 Hz, 2H), 5.74 (d, J = 6.9, 2H), 4.80-4.60 (m, 4H), 4.45 (d, J = 7.2 Hz, 2H), 4.38 (d, J = 7.2 Hz, 2H), 3.73 (t, J = 6.3 Hz, 2H), 2.68 (t, J = 6.6 Hz, 2H), 2.35-2.05 (m, 8H), 1.66 (s, 1H), 1.50-1.20 (m, 24H), 1.00-0.78 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 154.9, 153.7, 138.6, 138.4, 138.3, 124.5, 120.8, 120.7, 118.8, 116.8, 116.5, 99.6, 62.5, 36.8, 36.5, 32.2 (two coincident resonances), 30.1, 30.0, 27.7 (two coincident resonances), 22.8, 14.3 ppm; IR (KBr) 3500-3200, 2929, 2862, 1578 cm⁻¹; ESI-MS m/z: 883.8 ([M+Na]⁺, 100%), 860.9 ([M]⁺, 15%); Anal. Calcd. for C₅₅H₆₆Br₃O₇: C, 75.32; H, 7.96; found C, 75.25; H, 7.92.
**C-pentyl tribromo monohydroxy cavitand 3.17**

![Chemical Structure](image)

Prepared by modification of the procedure of Barrett et al.\(^2\) To a solution of tetrabromo cavitand 2.3 (1.13 g, 1.00 mmol), dried according to the standard procedure, in THF at -78 °C was added n-BuLi (688 μL of a 1.60 M solution in hexanes, 1.10 mmol). After 20 min, B(OMe)₃ (170 μL, 1.50 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and was stirred at this temperature for 1 h. The resulting solution was cooled to -78 °C, quenched with a 1:1 mixture of 30% aq. H₂O₂ and 3 M aq. NaOH (20 mL), then stirred at rt for 18 h. The solution was cooled to -78 °C and after cautious addition of 30% aq. Na₂S₂O₅, the THF was removed *in vacuo*. The resulting mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed *in vacuo*. Purification by column chromatography (100 g SiO₂, 2:8 ethyl acetate/hexane) afforded the title compound 3.17 as a white solid (832 mg, 74%). Characterisation data corresponded to that reported in the literature.\(^2\)
To a solution of tetrabromo cavitand 2.3 (1.13 g, 1.00 mmol), dried according to the standard procedure, in THF at −78 °C was added n-BuLi (1.94 mL of a 1.6 M solution in hexanes, 3.10 mmol). After 10 min, methyl iodide (193 μL, 3.10 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and stirred for 2 h. The reaction mixture was cooled to −78 °C again, n-BuLi (750 μL of a 1.6 M solution in hexanes, 1.20 mmol) was added rapidly. After 20 min, B(OMe)3 (170 μL, 1.50 mmol) was added, the cooling bath was removed and the mixture was allowed to warm to rt and was stirred at this temperature for 1 h. The resulting solution was cooled to −78 °C, quenched with a 1:1 mixture of 30% aq. H2O2 and 3 M aq. NaOH (20 mL), then stirred at rt for 18 h. The solution was cooled to −78 °C and after cautious addition of 30% aq. Na2S2O5, the THF was removed in vacuo. The resulting mixture was extracted with ethyl acetate (3 x 25 mL). The combined organic phases were washed successively with sat. aq. NaHCO3 and sat. aq. NaCl, dried over MgSO4, and the solvent was removed in vacuo. Purification by column chromatography (100 g SiO2, 2:8 to 3:7 ethyl acetate/hexane) afforded the title compound 3.18 as a white solid (481 mg, 55%): Rf = 0.32 (3:7 ethyl acetate/hexane); m.p. 151-153 °C (dichloromethane/hexane); 1H NMR (300 MHz, CDCl3) δ 7.16 (s, 3H), 6.61 (s, 1H), 5.95 (d, J = 7.2 Hz, 2H), 5.93 (d, J = 7.2 Hz, 2H), 5.60 (br. S, 1H), 4.87-4.68 (m, 4H), 4.42 (d, J = 7.2 Hz, 2H), 4.36 (d, J = 7.2 Hz, 2H), 2.35-2.05 (m, 8H), 2.04 (s, 9H), 1.50-1.20 (m, 24H), 1.00-0.78 (m, 12H) ppm; 13C NMR (75 MHz, CDCl3) δ 153.4, 142.0, 140.8, 138.7, 138.0, 136.2, 123.9, 117.9, 116.8, 110.0, 99.3, 98.8, 37.1, 36.9, 32.2, 29.9, 27.7, 22.0, 14.3 ppm; IR (KBr) 3500-3200, 2927, 2861, 1579 cm−1; ESI-MS m/z: 876.8 ([M+H]+, 100%); Anal. Calcd. for C55H70O9: C, 75.48; H, 8.06; found C, 75.32; H, 7.92.
C-pentyl tribromo monoformyl cavitand 3.19

![Diagram of C-pentyl tribromo monoformyl cavitand 3.19](image)

Tetrabromo cavitand 2.3 (1.13 g, 1.00 mmol) was dried according to the standard procedure, dissolved in dry THF (50 mL), cooled to −78 °C and n-BuLi (753 µL of a 1.46 M solution in hexanes, 1.10 mmol) was added rapidly. After 20 min, dry DMF (155 µL, 2.0 mmol) was added rapidly, the cooling bath was removed and the solution was allowed to warm to rt and stirred for another 30 min. The solution was then cooled to 0 °C and cautiously quenched with 5% aq. NH₄Cl. THF was removed *in vacuo* and the product cavitands were extracted into ethyl acetate (3 x 30 mL) and the combined organic phases were washed with sat. aq. NaHCO₃ then sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed *in vacuo*. The title cavitand 3.19 was obtained after column chromatography (100 g SiO₂, 1:1 → 4:6 → 2:8 ethyl acetate/hexane) of the crude product as a white powder (774 mg, 73%). Characterisation data corresponded to that reported in the literature.²
C-pentyl tribromo mono(hydroxymethyl) cavitand 3.20

![Chemical structure of C-pentyl tribromo mono(hydroxymethyl) cavitand 3.20](image)

Tribromo monoformyl cavitand 3.19 (108 mg, 100 μmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and NaBH₄ (19.0 mg, 500 μmol) was added. After 8 h at that temperature, the reaction was complete according to TLC. After cautious addition of sat. aq. NH₄Cl, THF was removed in vacuo and the organic products were extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed with water, sat. aq. NaCl, dried with MgSO₄ and the solvent was evaporated to afford practically pure mono(hydroxymethyl) cavitand 3.20, which could be further purified by pushing through a short plug of silica to obtain a white solid (93.2 mg, 86%) after solvent removal: Rf = 0.21 (8:2 dichloromethane/hexane); m.p. 218-219 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.11 (s, 1H), 7.04 (s, 3H) 5.94 (d, J = 7.5 Hz, 4H), 4.84 (t, J = 7.5 Hz, 2H), 4.82 (t, J = 8.1 Hz, 2H), 4.68 (s, 2H), 4.51 (d, J = 7.2 Hz, 2H), 4.38 (d, J = 7.2 Hz, 2H), 2.30-2.10 (m, 8H), 1.80 (br. s, 1H), 1.50-1.05 (m, 24H), 0.91 (t, J = 6.6 Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 153.9, 152.4, 152.2 (two coincident resonances), 139.4, 139.3, 139.1, 138.2, 126.3, 120.7, 119.2, 118.9, 113.8, 99.6, 98.5, 55.2, 37.8, 37.4, 32.1, 32.0, 30.0, 27.6 (two coincident resonances), 22.8, 14.3 ppm; IR (KBr) 3500-3200, 2929, 2866, 1565 cm⁻¹; ESI-MS m/z: 1082.2 ([M⁺], 100%); HRMS Calcd. for C₃₅H₅₉Br₂O₂: 1082.2002; found 1082.1998.
Syntheses of 2,6-dimethoxy substituted benzene 3.23 and 3.27

Although these compounds could be synthesized directly from 2,6-dimethoxy benzene, a common intermediate 3.28 was made to make the syntheses more convenient.

![Chemical structure of 3.28](image)

**2,6-dimethoxy bromo benzene 3.28:** To a stirring solution of 2,6-dimethoxy benzene (13.8 g, 100 mmol) in dry THF (400 mL) under nitrogen atmosphere at -78 °C was added rapidly n-BuLi (65.6 mL of a 1.6 M solution in hexane, 105 mmol). The reaction mixture was warmed to 0 °C. After 24 h, the reaction mixture was cooled down to -78 °C again and elemental bromine (5.41 mL, 105 mmol) was added dropwise over 5 min. The reaction mixture was then warmed to rt and stirred for another 2 h. After quenching with 10% aq. Na$_2$S$_2$O$_3$ (50 mL), THF was removed in vacuo. Diethyl ether (3 x 100 mL) was added to extract the organic products. The combined organic phases were washed with water, sat. aq. NaCl, dried over MgSO$_4$ and the solvent was removed in vacuo. The crude product was purified by column chromatography (500 g SiO$_2$, 1:9 ethyl acetate/hexane) to afford the title compound 3.28 as colorless needles (13.2 g, 61%). Characterisation data corresponded to that reported in the literature.$^{234}$

![Chemical structure of 3.23](image)

**2,6-dimethoxy phenol 3.23:** To a stirring solution of 2,6-dimethoxy bromo benzene 3.28 (217 mg, 1.00 mmol) in dry THF (30 mL) under nitrogen atmosphere at -78 °C was added rapidly n-BuLi (688 μL of a 1.6 M solution in hexane, 1.10 mmol). After 20 min, B(OMe)$_3$ (170 μL, 1.50 mmol) was added, the cooling bath was removed and the
mixture was allowed to warm to rt and was stirred at this temperature for 2 h. The resulting solution was cooled to -78 °C, quenched with a 1:1 mixture of 30% aq. H₂O₂ and 3 M aq. NaOH (10 mL), then stirred at rt for 18 h. The solution was cooled to -78 °C and after cautious addition of 30% aq. Na₂S₂O₅, the THF was removed in vacuo. The organic products were extracted with ethyl acetate (3 x 15 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. Recrystallization of the crude product in diethyl ether/hexane solution afforded the title compound 3.23 as a white solid (105 mg, 68%). Characterisation data corresponded to that reported in the literature.²³⁵

2,6-dimethoxy aniline 3.27: Prepared by modification of the procedure of Shiori et al.²³⁶ To a stirring solution of 2,6-dimethoxy bromo benzene 3.28 (217 mg, 1.00 mmol) in dry THF (30 mL) under nitrogen atmosphere at -78 °C was added rapidly n-BuLi (688 μL of a 1.6 M solution in hexane, 1.10 mmol). After 20 min, diphenyl phosphoryl azide (331 mg, 1.20 mmol) in dry THF (3 mL) was added. The reaction mixture was warmed to rt and stirred for 8 h. The reaction was again cooled to -78 °C, LiAlH₄ (150 mg, 3.96 mmol) was added to the reaction mixture, stirring continued for 12 h at rt. Then, fridge-cold 2M aq. NaOH solution (30 mL) was carefully added to the mixture. The THF was subsequently removed in vacuo; the organic products were extracted by EtOAc (3 x 15 mL). The combined organic phases were washed with 1 M aq. NaOH and sat. aq. NaCl then dried over MgSO₄. The solvent was removed in vacuo. The crude product was purified by column chromatography (50 g SiO₂, 4:6 ethyl acetate/hexane) to obtain the title compound 3.27 as a white solid (78.1 mg, 51%). Characterisation data corresponded to that reported in the literature.²³⁶
Host-guest binding studies of cavitands with aspirin

Dissociation of cavitand 3,4 dimer/oligomers was studied by titrating a concentrated solution of that cavitand into a blank chloroform solvent. Binding studies between cavitands and aspirin were carried out in chloroform using the general method for host-guest binding studies. ITC profiles of the binding host-guest pairs are included in the following:
Dissociation of cavitand 3.4 dimer/oligomer (ITC, chloroform, 25 °C)

Data: Dissociation of 3.4
Cell conc. = 0 mM
Syriene conc. = 10 mM
Volume of injection = 7 μL
ΔH (cal/mole) = 3.064E4 ± 359
K (M) = 0.0149 ± 0.0008
Binding study between cavitand 3.7 and aspirin (ITC, chloroform, 25 °C)

Data: 3.7 (5 mM) vs Aspirin (100 mM)

- N = 0.98 ± 0.07
- K = 68 ± 4
- H = -380 ± 10
- S = 7.11

Molar Ratio

Time (min)
Binding study between cavitand 3.8 and aspirin (ITC, chloroform, 25 °C)

![Graph showing the binding study between cavitand 3.8 and aspirin](image)

Data: 3.8 (5 mM) vs Aspirin (100 mM)
- N: 1.02 ± 0.06
- K: 25 ± 3
- H: -1470 ± 30
- S: 1.47

![Graph showing the change in microcalories per second over time](image)
Binding study between cavitand 3.9 and aspirin (ITC, chloroform, 25 °C)

Data: 3.9 (5 mM) vs Aspirin (100 mM)
N  1.09 ± 0.11
K  53 ± 3
H  -410 ± 10
S  6.49
Binding study between cavitand 3.12 and aspirin (ITC, chloroform, 25 °C)

Data 3.12 (5 mM) vs Aspirin (100 mM)

- N = 1.01 ± 0.04
- K = 69 ± 3
- ΔH = -1110 ± 20
- ΔS = 4.71

Molar Ratio

kcal/mole of injectant

Time (min)

µcal/sec

0.00 30.00 60.00 90.00 120.00
Binding study between cavitand 3.18 and aspirin (ITC, chloroform, 25 °C)

Data 3.18 (5 mM) vs Aspirin (100 mM)
- N = 1.01 ± 0.05
- K = 49 ± 2
- ΔH = -1460 ± 20
- ΔS = 2.86 cal/mol K

![Graph showing binding data between cavitand 3.18 and aspirin](image)
CHAPTER 4 - EXPERIMENTAL DATA
To a solution of anhydrous phloroglucinol (1.26 g, 10.0 mmol) in dry THF (50 mL) at 0 °C was added sodium hydride (400 mg, 60% in mineral oil, 10.0 mmol). The reaction mixture was stirred under N₂ for 1 h at that temperature, then benzyl bromide (1.71 g, 10.0 mmol) in dry THF (5 mL) was added. The reaction mixture was warmed to rt and stirred for another 12 h. THF was then removed in vacuo. Water (50 mL) was cautiously added and the organic products were extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with more water, then sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (100 g SiO₂, 4:6 to 6:4 ethyl acetate/hexane) to afford the title compound 4.4 as pale-pink crystals (1.10 g, 51%). Characterisation data corresponded to that reported in the literature.
Chloromethyl methyl ether (MOMCl) was prepared as described for cavitand 2.5

To a solution of phloroglucinol (12.6 g, 100 mmol) and diisopropylethylamine (34.8 mL, 200 mmol) in THF (150 mL) was slowly added freshly-prepared solution of MOMCl (76.9 mL of a 2.6 M solution in toluene, 200 mmol). The solution was stirred under nitrogen atmosphere for 8 h, additional amount of MOMCl solution (20 mL, 52.0 mmol) was added (based on appearance of reaction mixture TLC). The reaction was stirred overnight then quenched with sat. aq. NaHCO₃. THF was removed in vacuo and ethyl acetate (3 x 40 mL) was added to extract the organic products. The combined organic phases were washed with water, then sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (400 g SiO₂, 4:6 to 6:4 ethyl acetate/hexane) to afford the title compound 4.9 as a white solid (9.21 g, 43%): Rf = 0.52 (6:4 ethyl acetate/hexane); m.p. 62-63 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 6.28 (d, J = 2.4 Hz, 1H), 6.22 (d, J = 2.4 Hz, 2H), 5.10 (s, 4H), 3.45 (s, 6H), 2.4 (br. s, 1H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 158.9, 157.8, 97.5, 97.1, 94.3, 56.0 ppm; IR (KBr) 3500-3100, 2929, 2867, 1582 cm⁻¹; ESI-MS m/z: 214.1 ([M]+, 10%), 186.3 ([M]+, 100%); Anal. Calcd. for C₁₀H₁₅O₄: C, 56.07; H, 6.59; found C, 56.24; H, 6.73.
To a solution of 3,5-bis(methoxymethylenoxy) phenol 4.9 (1.07 g, 5.00 mmol) in dry acetone (50 mL) was added tetra(bromomethyl) cavitand 2.8 (1.19 g, 1.00 mmol) and potassium carbonate (13.8 g, 100 mmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt and acetone was removed in vacuo. Ethyl acetate (40 mL) and water (20 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl and allowed to separate. The aqueous phase was washed with more ethyl acetate (2 x 15 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (150 g SiO₂, 3:7 ethyl acetate/hexane) to obtain the title compound 4.10 as a white solid (1.55 g, 90%): Rf = 0.32 (3:7 ethyl acetate/hexane); m.p. > 125 °C (decomp. (dichloromethane/hexane); 1H NMR (300 MHz, CDCl₃) δ 7.23 (s, 4H), 6.34 (d, J = 1.8 Hz, 4H), 6.28 (d, J = 1.8 Hz, 8H), 5.79 (d, J = 7.2 Hz, 4H), 5.05 (s, 16H), 4.95-4.70 (m, 12H), 4.56 (d, J = 7.5 Hz, 4H), 3.40 (s, 24H), 2.40-2.10 (m, 8H), 1.55-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; 13C NMR (75 MHz, CDCl₃) δ 160.5, 158.9, 154.4, 138.1, 122.6, 121.1, 110.0, 100.0, 97.4, 96.7, 94.3, 60.8, 56.0, 36.9, 32.0, 30.1, 27.6, 22.7, 14.2 ppm; IR (KBr) 2929, 2866, 1577 cm⁻¹; ESI-MS m/z: 1744.8 ([M+Na]+, 100%); Anal. Calcd. for C₉₆H₁₂₆O₂₈: C, 66.96; H, 7.02; found C, 66.84; H, 6.92.
Prepared by modification of the procedure of Tanaka et al.\textsuperscript{192} To a solution of anhydrous phloroglucinol (1.26 g, 10.0 mmol) in dry THF (50 mL) at -78 °C was rapidly added n-BuLi (13.8 mL of a 1.6 M solution in hexane, 22.1 mmol). The reaction mixture was stirred under N\textsubscript{2} for 30 min at that temperature, then \textit{tert}-butyldimethylsilyl chloride (3.77 g, 25.0 mmol) in dry THF (5 mL) was added. The reaction mixture was warmed to rt and stirred for another 12 h. THF was then removed \textit{in vacuo}. Water (50 mL) was cautiously added and the organic products were extracted with ethyl acetate (3 x 20 mL). The combined organic phases were washed with more water, then sat. aq. NaCl, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. The crude product was purified by column chromatography (150 g SiO\textsubscript{2}, dichloromethane) to afford the title compound 4.11 as a pale-purple solid (2.23 g, 63%): R\textsubscript{f} = 0.49 (100% dichloromethane); m.p. > 50 °C (decomp.) (dichloromethane/hexane); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) \( \delta \) 5.82 (d, \( J = 1.8 \) Hz, 2H), 5.77 (s, 1H), 5.26 (br. s, 1H), 0.78 (s, 18H), 0.00 (s, 12H) ppm; \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}) \( \delta \) 157.3, 156.9, 105.2, 101.5, 25.8, 18.3, -4.3 ppm; IR (KBr) 3500-3200, 2927, 2871, 1575 cm\textsuperscript{-1}; ESI-MS \textit{m/z}: 354.6 ([M\textsuperscript{+}], 5%), 61.6 (100%); Anal. Calcd. for C\textsubscript{18}H\textsubscript{34}Si\textsubscript{2}O\textsubscript{3}: C, 60.96; H, 9.66; found C, 60.81; H, 9.42. Characterization data corresponded to that reported in literature (MS and \textsuperscript{1}H NMR).\textsuperscript{192}
Benzoyl protected phloroglucinols 4.13 and 4.14

Prepared by modification of the procedure of Nagvekar et al. To a slurry of anhydrous phloroglucinol (12.6 g, 100 mmol) in dry dichloromethane (120 mL) at 0 °C was added pyridine (17.7 mL, 220 mmol). The reaction mixture was stirred under nitrogen for 30 min at that temperature, at that point it became a clear yellowish solution, then benzoyl chloride (25.6 mL, 220 mmol) was added dropwise over 10 min. The reaction mixture was warmed to rt and stirred for another 12 h. Water (100 mL) was cautiously added and the organic phase was washed with more water (3 x 100 mL), then sat. aq. NaCl, dried over MgSO4 and the solvent was removed in vacuo. The crude product was submitted to column chromatography (400 g SiO2, 100% dichloromethane) to afford compound 4.14 (10.9 g, 24%) as a white solid. The column was further eluted with 3:7 ethyl acetate/hexane to afford compound 4.13 (18.4 g, 55%) as a white solid. Characterization data of compounds 4.13 and 4.14 corresponded to that reported in literature.

Direct recrystallization of the crude product above from dichloromethane/hexane solution afforded a practically clean 2:1 mixture of 4.13/4.14 (26.0 g, ~ 72%), which was used to synthesize compound 4.2.

Tetrakis(3,5-di(benzoyloxy)phenoxy)methyl) cavitand 4.16
To a solution of 3,5-di(benzoyloxy) phenol 4.13 (1.67 g, 5.00 mmol) in dry acetone (50 mL) was added tetra(bromomethyl) cavitand 2.8 (1.19 g, 1.00 mmol) and potassium carbonate (13.8 g, 100 mmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt and acetone was removed in vacuo. Ethyl acetate (50 mL) and water (20 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl and allowed to separate. The aqueous phase was washed with more ethyl acetate (2 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (100 g SiO₂, 3:7 to 1:1 ethyl acetate/hexane) to obtain the title compound 4.16 as a white solid (1.21 g, 55%): Rf = 0.10 (1:1 ethyl acetate/hexane); m.p. 105-107 °C (dichloromethane/hexane); 'H NMR (300 MHz, CDCl₃) δ 8.13 (d, J = 7.8 Hz, 16H), 7.58 (t, J = 6.9 Hz, 8H), 7.45 (t, J = 8.1 Hz, 16H), 7.24 (s, 4H), 6.45 (s, 4H), 6.36 (s, 8H), 5.76 (d, J = 6.9 Hz, 4H), 4.90 (s, 8H), 4.00 (s, 8H), 4.83 (t, J = 7.5 Hz, 4H), 4.65 (d, J = 7.5 Hz, 4H), 2.40-2.10 (m, 8H), 1.55-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; 'C NMR (75 MHz, CDCl₃) δ 165.6, 160.3, 157.2, 154.6, 152.6, 138.0, 133.8, 130.4, 128.7, 122.6, 103.1, 101.6, 99.4, 53.7, 37.1, 32.2, 29.2, 27.7, 22.8, 14.3 ppm; IR (KBr) 2929, 2872, 1737, 1607 cm⁻¹; ESI-MS m/z: 2220.9 ([M+H⁺], 40%), 2113.0 (100%); Anal. Calcd. for C₁₅₈H₁₂₀O₂₈: C, 74.17; H, 5.49; found C, 74.04; H, 5.42.

Tetrakis(3,5-di(hydroxy)phenoxy)methyl cavitand 4.2
To a solution of a 1:2 mixture of 1,3,5-tri(benzoyloxy) benzene 4.14/3,5-di(benzoyloxy) phenol 4.13 (2.77 g, 5.00 mmol with respect to 4.13, mixture obtained as described above) in dry acetone (50 mL) was added tetra(bromomethyl) cavitand 2.8 (1.19 g, 1.00 mmol) and potassium carbonate (13.8 g, 100 mmol). The reaction mixture was heated to reflux under a nitrogen atmosphere for 18 h. The mixture was then allowed to cool to rt and acetone was removed in vacuo. Ethyl acetate (50 mL) and water (20 mL) were added to the residue and the mixture was acidified with 2 M aq. HCl and allowed to separate. The aqueous phase was washed with more ethyl acetate (2 x 25 mL). The combined organic extracts were washed with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo to obtain the crude product as an off-white solid.

To a solution of the above crude product in THF (50 mL) was added a solution of aq. 2M NaOH (50 mL). The reaction mixture was stirred vigorously at rt for 24 h. The THF solvent was then removed in vacuo. The residue was then acidified with a solution of 2 M aq. HCl and ethyl acetate was used (3 x 30 mL) to extract the organic products. The combined organic phases were washed with sat. aq. NaCl, dried over MgSO₄ then the solvent was removed in vacuo. The crude product was then purified by flash column chromatography (100 g SiO₂, 100:0 to 96:4 diethyl ether/methanol) to afford the title compound 4.2 as a white powder (1.22 g, 89%): Rᵢ = 0.10 (96:4 diethyl ether/methanol); m.p. > 230 °C (decomp.) (diethyl ether/hexane); ¹H NMR (300 MHz, (CD₃)₂CO) δ 8.22 (br. s, 8H), 7.77 (s, 4H), 5.97 (s, 8H), 5.96 (s, 4H), 5.87 (d, J = 7.2 Hz, 4H), 4.95-4.75 (m, 12H), 4.50 (d, J = 10.2 Hz, 4H), 2.50-2.30 (m, 8H), 1.60-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; ¹³C NMR (75 MHz, (CD₃)₂CO) δ 161.8, 159.8, 155.1, 139.0, 124.2, 123.1, 100.7, 96.6, 94.7, 61.2, 37.9, 32.6, 28.4, 23.3, 14.3 ppm; IR (KBr) 3600-3100, 2929, 2856, 1605 cm⁻¹; ESI-MS m/z: 1368.6 ([M+H]⁺, 20%), 1367.6 ([M⁺, 20%), 863.1 (100%); Anal. Calcd. for C₉₀H₇₈O₇₀: C, 70.16; H, 6.48; found C, 70.20; H, 6.59.
Procedure 1: To a slurry of substituted-cavitand octol 4.2 (137 mg, 100 µmol) and cesium carbonate (652 mg, 2.00 mmol) in dry DMF (15 mL) was added α,α'-dibromo o-xylene (116 mg, 440 µmol). The reaction mixture was heated to 65 °C and stirred at that temperature under a nitrogen atmosphere for 48 h. DMF was removed in vacuo and the residue was dissolved in dichloromethane and 2 M aq. HCl. The organic phase was separated and washed with water, sat. aq. NaHCO₃, sat. aq. NaCl and dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (50 g SiO₂, 7:3 to 10:0 dichloromethane/hexane) to afford the title compound 4.19 as a white solid (44.5 mg, 25%).

Procedure 2: To a slurry of substituted-cavitand octol 4.2 (137 mg, 100 µmol) and cesium carbonate (652 mg, 2.00 mmol) in dry DMF (10 mL) was added α,α'-dibromo o-xylene (116 mg, 440 µmol). The reaction mixture was stirred at rt under a nitrogen atmosphere for 8 days. DMF was removed in vacuo and the residue was dissolved in dichloromethane and 2 M aq. HCl. The organic phase was separated and washed with water, sat. aq. NaHCO₃, sat. aq. NaCl and dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (50 g SiO₂, 7:3 to 10:0 dichloromethane/hexane) to afford the title compound 4.19 as a white solid (65.8 mg, 37%): Rf = 0.76 (100% dichloromethane); m.p. > 190 °C (decomp.) (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.48-7.40 (m, 8H), 7.36-7.26 (m, 8H), 7.21 (s, 4H), 6.28-6.22 (m, 4H), 6.22-6.15 (m, 8H), 6.04 (d, J = 7.5 Hz, 4H),
5.06 (s, 8H), 5.04 (d, \(J = 10.8\) Hz, 8H), 4.92 (d, \(J = 11.1\) Hz, 8H), 4.84 (t, \(J = 8.1\) Hz, 4H), 4.66 (d, \(J = 7.5\) Hz, 4H), 2.35-2.18 (m, 8H), 1.55-1.25 (m, 24H), 1.00-0.80 (m, 12H) ppm; \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 160.6, 160.4, 154.5, 137.9, 135.1, 129.3 (two coincident resonances), 128.7, 123.5, 121.0, 110.7, 96.9, 69.3, 61.8, 37.1, 32.2, 30.4, 27.8, 22.9, 14.3 ppm; IR (KBr) 2929, 2859, 1573 cm\(^{-1}\); ESI-MS \(m/z\): 1794.3 ([\(M+H_2O]^+, 100\%\]), 1777.8 ([\(M+H]^+, 100\%\]); Anal. Calcd. for \(C_{112}H_{112}O_{20}\): C, 75.65; H, 6.35; found C, 75.54; H, 6.42.
Host-guest binding studies between the substituted-cavitand octol and the deep-cavity cavitand with tetraalkyl ammonium salts and with aspirin

Dissociation of the substituted-cavitand octol 4.2 dimer/oligomers was studied by titrating a concentrated solution of that cavitand into a blank acetone solvent. Binding studies between the substituted-cavitand octol 4.2 and tetraalkyl ammonium salts were carried out in acetone using the general method for host-guest binding studies. Binding studies between the deep-cavity cavitand 4.19 and tetraalkyl ammonium salts or aspirin were carried out in chloroform using the general method for host-guest binding studies. ITC profiles of the binding host-guest pairs are included in the following:
Dissociation of substituted-cavitand octol 4.2 dimer/oligomers (ITC, acetone, 25 °C)

Data: Dissociation of 4.2
Cell conc. = 0 mM
Syringe conc. = 20 mM
Volume of injection = 7 mL
$\Delta H$ (cal/mole) 1263 ± 62.0
$K$ (M) 0.0014 ± 0.0002
Binding study between substituted-cavitand octol 4.2 and tetrabutyl ammonium chloride (ITC, acetone, 25 °C)

Data: 4.2 (5 mM) vs Bu$_4$NCl (50 mM)

- \( N = 0.53 \pm 0.05 \)
- \( K = 940 \pm 70 \)
- \( H = -7960 \pm 350 \)
- \( S = -13.1 \)

Time (min) vs Molar Ratio

\( \mu \text{cal/sec} \) vs Time (min)
Binding study between substituted-cavitand octol 4.2 and tetrabutyl ammonium bromide (ITC, acetone, 25 °C)

Data: 4.2 (5 mM) vs Bu₄NBr (50 mM)

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Binding study between substituted-cavitand octol 4.2 and tetrahexyl ammonium bromide (ITC, acetone, 25 °C)

Data: 4.2 (5 mM) vs Hex$_4$NBr (50 mM)

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The lower graph shows the heat output over time in $\mu$cal/sec.
Binding study between substituted-cavitand octol 4.2 and tetraoctyl ammonium bromide (ITC, acetone, 25 °C)

![Graphical representation of the binding study between substituted-cavitand octol 4.2 and tetraoctyl ammonium bromide.](image)

Data: 4.2 (5 mM) vs Oct₄NBr (50 mM)

- N = 0.48 ± 0.05
- K = 470 ± 70
- H = -7340 ± 160
- S = -12.4
Binding study between deep-cavity cavitand 4.19 and tetrabutyl ammonium bromide (ITC, chloroform, 25 °C)

Data: 4.19 (1 mM) vs Bu₄NBr (50 mM)
- N: 1.09 ± 0.12
- K: 69 ± 7
- H: -940 ± 50
- S: 5.28
Binding study between deep-cavity cavitand 4.19 and tetrahexyl ammonium bromide (ITC, chloroform, 25 °C)

Data: 4.19 (1 mM) vs Hex$_3$NBr (50 mM)
- $N = 1.05 \pm 0.07$
- $K = 50 \pm 4$
- $H = -2050 \pm 90$
- $S = 0.902$

![Graph showing binding study results](image-url)
Binding study between deep-cavity cavitand 4.19 and tetraoctyl ammonium bromide (ITC, chloroform, 25 °C)

Data: 4.19 (1 mM) vs Oct,NBr (50 mM)
N = 1.07 ± 0.13
K = 25 ± 4
H = -1500 ± 60
S = 1.38
CHAPTER 5 – EXPERIMENTAL DATA

A,C-aminoacid cavitand

\[ \text{HOOC} \text{H} \text{H} \text{O} \text{H} \text{NH}_2 \]
\[ \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \]

\[ \text{A,C-aminoacid cavitand} \]

\[ \text{COOH} \text{H} \text{H} \text{NH}_2 \]
\[ \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \quad \text{C}_5\text{H}_{11} \]
\[ \text{(± ) A,B-aminoacid cavitand} \]
C-pentyl tetraprotio cavitand 5.3

To a slurry of resorcinarene 2.1 (7.69 g, 10.0 mmol) and K₂CO₃ (138 g, 1.00 mol) in dry DMF (600 mL) was added bromochloromethane (20.0 mL, 304 mmol) and the mixture was stirred at 65 °C for 72 h under N₂. Every 24 h, additional bromochloromethane (10.0 mL, 152 mmol) was added. The reaction mixture was then cooled down to rt and left in the fridge for 24 h. The liquid DMF phase was removed by filtration. Then, chloroform and 2 M aq. HCl were added dissolved the solid residue. The aqueous phase was extracted with more chloroform and the combined chloroform layers were washed with water, sat. aq. LiCl, dried over MgSO₄ and the solvent was removed in vacuo. The resulting brown residue was purified by column chromatography (150 g SiO₂, 6:4 to 8:2 dichloromethane/hexane) to afford a white solid, which was practically pure tetraprotio cavitand 5.3 (4.08 g, 50%) for subsequent synthetic reactions. Characterisation data corresponded to that reported in the literature.²
C-pentyl monoamino triprotio cavitand 3.12

**Procedure 7:** To a solution of monobromo cavitand 3.5 (260 mg, 290 μmol), dried according to the standard procedure, in dry THF (25 mL) under a nitrogen atmosphere at -78 °C was rapidly added n-BuLi (190 μL of a 1.60 M solution in hexanes, 305 μmol). The reaction mixture was stirred at that temperature for 20 min then diphenyl phosphoryl azide (160 mg, 580 μmol) in dry THF (3 mL) was added. The reaction mixture was warmed to rt and stirred for 8 h. The reaction was again cooled to -78 °C, LiAlH₄ (100 mg, 2.64 mmol) was added and stirring was continued for 12 h at rt. Then, fridge-cold 2M aq. NaOH solution (30 mL) was cautiously added. THF was subsequently removed *in vacuo* and the organic products were extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with 1 M aq. NaOH, sat. aq. NaCl then dried over MgSO₄. The solvent was removed *in vacuo*. The crude product was purified by column chromatography (50 g SiO₂, 4:6 ethyl acetate/hexane) to obtain the title cavitand 3.12 as a white solid (145 mg, 60%).

**Procedure 2:** To a solution of tetraprotio cavitand 5.3 (237 mg, 290 μmol), dried according to the standard procedure, in anhydrous THF (25 mL) under nitrogen atmosphere at -78 °C was added quickly n-BuLi (190 μL of a 1.60 M solution in hexanes, 305 μmol). The reaction mixture was warmed to 0 °C and stirred at that temperature for 2 h then diphenyl phosphoryl azide (160 mg, 580 μmol) in dry THF (3 mL) was added. The reaction mixture was warmed to rt and stirred for 8 h. The reaction was again cooled to -78 °C, LiAlH₄ (100 mg, 2.64 mmol) was added and stirring was continued for 12 h at rt. Then, fridge-cold 2M aq. NaOH solution (30 mL) was carefully added. The THF was subsequently removed *in vacuo* and the organic product were extracted by EtOAc (3 x 15 mL). The combined organic phases were washed with 1 M aq. NaOH and sat. aq. NaCl then dried over MgSO₄. The solvent was removed in vacuo.
The crude product was purified by column chromatography (50 g SiO₂, 4:6 ethyl acetate/hexane) to obtain the title cavitand 3.12 as a white solid (142 mg, 59%): Rf = 0.29 (4:6 ethyl acetate/hexane); m.p. 190-191 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.10 (s, 3H), 6.52 (s, 1H), 6.48 (s, 3H), 5.83 (br. d, J = 6.0 Hz, 2H), 5.75 (d, J = 7.2 Hz, 2H), 4.72 (t, J = 8.1 Hz, 2H), 4.70 (t, J = 7.5 Hz, 2H), 4.48 (d, J = 6.9 Hz, 2H), 4.40 (d, J = 6.9 Hz, 2H), 3.75 (br. s, 2H), 2.30-2.05 (m, 8H), 1.50-1.20 (m, 24H), 0.91 (t, J = 7.2 Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 155.0, 154.8, 138.8, 138.5, 138.0, 121.0, 120.7, 116.7, 116.6, 99.6, 99.4, 36.7, 36.5, 32.2 (two coincident resonances), 30.0, 29.8, 27.8, 27.7, 22.8, 14.3 ppm; IR (KBr) 3465, 3365, 2928, 2860, 1607, 1577 cm⁻¹; ESI-MS m/z: 831.9 ([M]+, 100%); Anal. Calcd. for C₃₂H₆₉NO₄: C, 75.06; H, 7.87; found C, 74.94; H, 7.92.

C-pentyl A,C-dibromo diprotio cavitand 5.4

Prepared by modification of the procedure of Barrett et al.² To a solution of tetrabromocavitand 2.3 (5.66 g, 5.00 mmol), dried according to the standard procedure, in THF at −78 °C was added rapidly n-BuLi (6.56 mL of a 1.60 M solution in hexanes, 10.5 mmol). After 20 min, iso-propanol (1.00 mL) was added, the cooling bath was removed and the solution was allowed to warm to rt. The solvent was removed in vacuo and the residue was partitioned between ethyl acetate (3 x 40 mL) and water (100 mL). The combined organic phases were washed with sat. aq. NaHCO₃, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. Purification by column chromatography (250 g SiO₂, 9:1 hexane/ethyl acetate) afforded the title compound 5.4 as a white solid (3.00 g, 61%). Characterisation data corresponded to that reported in the literature.³
To a solution of A,C-dibromo cavitand 5.4 (195 mg, 200 µmol), dried according to the standard procedure, in dry THF (50 mL) at -78 °C was rapidly added n-BuLi (137 µL of 1.6 M solution in hexane, 220 µmol). After stirring at that temperature for 5 minutes, methyl chloroformate (200 µL, 2.54 mmol) was added and the reaction mixture was warmed to rt and stirred at that temperature for another 2 h. The solution was cooled to 0 °C and quenched with 5% aq. NH₄Cl before THF was removed in vacuo. The product cavitands were extracted into ethyl acetate (3 x 15 mL) and the combined organic phases were washed with sat. aq. NaHCO₃, then sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The title cavitand 5.6 was obtained after column chromatography (40 g SiO₂, 100% dichloromethane) as a white solid (128 mg, 67%): Rᵣ = 0.16 (100% dichloromethane); m.p. 116-117 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.19 (s, 1H), 7.09 (s, 2H), 7.07 (s, 1H), 6.51 (s, 2H), 5.85 (d, J = 7.5 Hz, 2H), 5.69 (d, J = 6.9 Hz, 2H), 4.81 (t, J = 8.1 Hz, 2H), 4.75 (t, J = 7.5 Hz, 2H), 4.51 (d, J = 7.2 Hz, 2H), 4.40 (d, J = 6.9 Hz, 2H), 3.63 (s, 3H), 2.35-2.10 (m, 8H), 1.50-1.20 (m, 26H), 0.91 (t, J = 6.9 Hz, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 166.7, 154.9, 154.7, 152.1, 150.8, 139.3, 138.7, 138.4, 138.0, 123.7, 121.6, 120.6, 118.6, 117.1, 113.4, 99.4, 98.8, 52.6, 37.0, 36.3, 32.0, 29.9, 29.7, 27.5, 22.7, 14.1 ppm; IR (KBr) 2929, 2862, 1725, 1590, cm⁻¹; ESI-MS m/z: 977.7 ([M+Na]+, 100%), 953.9 ([M]+, 35%); Anal. Calcd. for C₅₅H₅₆Br₃O₁₀: C, 67.99; H, 6.87; found C, 67.86; H, 6.81.
To a solution of A,C-dibromo cavitand 5.4 (195 mg, 200 μmol), dried according to the standard procedure, in dry THF (25 mL) at -78 °C was rapidly added n-BuLi (137 μL of 1.6 M solution in hexane, 220 μmol). After stirring at that temperature for 5 min, di tert-butyl dicarbonate (65.5 mg, 300 μmol) was added rapidly and the reaction mixture was warmed to rt and stirred for another 2 h. Ice water was cautiously added to the reaction mixture and then THF solvent was removed in vacuo. The residue was partitioned between ethyl acetate (3 x 15 mL) and water (30 mL). The combined organic phases were washed with sat. aq. NaHCO₃, sat. aq. NaCl then dried over MgSO₄ before the solvent was removed in vacuo. The crude product was purified by column chromatography (40 g SiO₂, 1:1 to 8:2 dichloromethane/hexane) to afford the title compound 5.8 as a white solid (102 mg, 51%): Rf = 0.21 (8:2 dichloromethane/hexane); m.p. 121-123 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.12 (s, 1H), 7.06 (s, 2H), 7.04 (s, 1H), 6.48 (s, 2H), 5.84 (d, J = 7.2 Hz, 2H), 5.68 (d, J = 7.2 Hz, 2H), 4.78 (t, J = 9.0 Hz, 2H), 4.72 (t, J = 8.1 Hz, 2H), 4.54 (d, J = 7.2 Hz, 2H), 4.38 (d, J = 7.5 Hz, 2H), 2.30-2.10 (m, 8H), 1.55 (s, 9H), 1.50-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 165.5, 154.7 (two coincident resonances), 152.1, 150.5, 139.3, 138.7, 138.3, 138.1, 125.1, 120.8, 120.6, 118.6, 117.2, 113.3, 99.36, 98.7, 83.1, 37.0, 36.3, 32.0, 29.9, 29.7, 28.1, 27.5, 22.7, 14.1 ppm; IR (KBr) 2954, 2929, 2868, 1714, 1648, 1621 cm⁻¹; ESI-MS m/z: 1060.5 (100%), 1035.4 ([M+K]⁺, 60%), 1014.5 ([M+H₂O]⁺, 50%), 997.4 ([M+H]⁺, 10%); Anal. Calcd. for C₅₇H₃₁BrO₁₀: C, 68.73; H, 7.18; found C, 68.63; H, 7.25.
To a solution of A,C-dibromo cavitand 5.4 (488 mg, 500 μmol), dried according to the standard procedure, in dry THF (25 mL) at -78 °C was rapidly added n-BuLi (344 μL of 1.60 M solution in hexane, 550 μmol). After stirring at that temperature for 5 min, dry DMF (400 μL, 5.16 mmol) was added rapidly, the cooling bath was removed and the solution was allowed to warm to rt. After stirring at that temperature for 2 h, the solution was cooled to 0 °C and cautiously quenched with 5% aq. NH₄Cl before THF was removed in vacuo. The product cavitands were extracted into ethyl acetate (3 x 25 mL) and the combined organic phases were washed with sat. aq. NaHCO₃ then sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The title cavitand 5.10 was obtained after column chromatography (80 g SiO₂, 2:8 ethyl acetate/hexane) as a white solid (282 mg, 61%): Rf = 0.30 (2:8 ethyl acetate/hexane); m.p. 130 °C (decomp.) (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 10.27 (s, 1H), 7.33 (s, 1H), 7.08 (s, 1H), 6.55 (s, 1H), 5.85 (d, J = 4.5 Hz, 1H), 5.83 (d, J = 5.4 Hz, 2H), 4.95-4.70 (m, 4H), 4.46 (d, J = 7.8 Hz, 2H), 4.40 (d, J = 7.5 Hz, 2H), 2.35-2.10 (m, 8H), 1.50-1.20 (m, 24H), 1.00-0.80 (m, 4H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 190.5, 155.1, 154.9, 154.8, 152.2, 139.4, 138.3, 125.4, 124.0, 120.8, 118.9, 117.0, 113.3, 100.0, 99.1, 37.1, 36.2, 32.1, 30.0, 29.7, 27.6, 22.8, 14.2 ppm; IR (KBr) 2929, 2866, 1665, 1571 cm⁻¹; ESI-MS m/z: 988.4 (100%), 924.4 ([M+H]⁺, 75%); Anal. Calcd. for C₅₁H₅₃BrO₆: C, 68.90; H, 6.87; found C, 68.84; H, 6.92.
To a stirred suspension of methyltriphenylphosphonium bromide (36.0 mg, 100 µmol) in THF (2 mL) was added dropwise n-BuLi (62.0 µL of a 1.60 M solution in hexanes, 99.2 µmol) at 0 °C under Ar. The cooling bath was removed and the mixture was stirred at rt for 2 h. A solution of A,C-monobromo monoformyl cavitand 5.10 (92.4 mg, 100 µmol) in THF (3 mL) was added dropwise and stirring was continued for 1 h at rt, then at 60 °C for 10 h. After cooling to rt, water (30 mL) was added and the mixture was extracted with ethyl acetate (3 x 10 mL). The combined organic phases were washed successively with sat. aq. NaHCO₃ and sat. aq. NaCl, dried over anhydrous MgSO₄ and the solvent was removed in vacuo. Pure A,C-monobromo monovinyl cavitand 5.12 was obtained after column chromatography (25 g SiO₂, 7:3 dichloromethane/hexane) as a white powder (57.2 mg, 61%): $R_f = 0.32$ (7:3 dichloromethane/hexane); m.p. 120-121 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl₃) δ 7.10 (s, 2H), 7.08 (s, 1H), 7.03 (s, 1H), 6.58 (dd, $J = 12.3$ Hz, $J = 18.3$ Hz, 1H), 6.52 (s, 2H), 5.95-5.75 (m, 5H), 5.41 (dd, $J = 1.8$ Hz, $J = 12.0$ Hz, 1H), 4.85-4.70 (m, 4H), 4.40 (d, $J = 2.7$ Hz, 2H), 4.37 (d, $J = 3.0$ Hz, 2H), 2.30-2.10 (m, 8H), 1.50-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; $^{13}$C NMR (75 MHz, CDCl₃) δ 155.1, 154.8, 153.1, 152.1, 139.6, 138.8, 138.4, 138.3, 128.1, 123.9, 121.0, 120.3, 119.3, 119.0, 116.6, 113.2, 99.2, 37.2, 36.7, 32.2, 32.1, 30.2, 30.0, 27.7 (two coincident resonances), 22.8, 14.3 ppm; IR (KBr) 2931, 2868, 1602, 1573 cm⁻¹; ESI-MS m/z: 922.4 ([M⁺], 100%); Anal. Calcd. for C₅₄H₆₀BrO₈: C, 70.35; H, 7.11; found C, 70.39; H, 7.22.
A,C-monobromo monoaldehyde cavitand 5.10 (185 mg, 200 μmol) was dissolved in THF (20 mL). The solution was cooled to 0 °C and NaBH₄ (19.1 mg, 500 μmol) was added. After stirring for 6 h at that temperature, the reaction was complete according to TLC. 5% aq. NH₄Cl was cautiously added and THF was then removed in vacuo. The organic products were washed with ethyl acetate (3 x 10 mL). The combined organic phases were washed with water and sat. aq. NaCl then dried with MgSO₄ and the solvent was evaporated to afford practically pure A,C-monobromo mono(hydroxymethyl) cavitand derivative, which was further purified by pushing through a short plug of silica (5:5 ethyl acetate/hexane). The pure A,C-monobromo mono(hydroxymethyl) cavitand 5.14 was obtained as a white solid (156 mg, 84%): \( R_f = 0.14 \) (100% dichloromethane); m.p. 163-164 °C (dichloromethane/hexane); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.14 (s, 1H), 7.11 (s, 2H), 7.08 (s, 1H), 6.50 (s, 2H), 5.84 (d, \( J = 7.2 \) Hz, 2H), 5.81 (d, \( J = 6.9 \) Hz, 2H), 4.90-4.70 (m, 4H), 4.64 (s, 2H), 4.55 (d, \( J = 7.2 \) Hz, 2H), 4.42 (d, \( J = 7.8 \) Hz, 2H), 2.42 (br. s, 1H), 2.40-2.10 (m, 8H), 1.55-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; \(^1\)C NMR (75 MHz, CDCl₃) \( \delta \) 154.8, 154.5, 153.7, 152.0, 139.3, 138.4, 138.1, 138.0, 126.1, 120.6, 120.2, 118.6, 117.0, 113.3, 99.8, 98.7, 54.9, 37.0, 36.6, 32.0 (two coincident resonances), 29.8, 27.6, 27.5, 22.7, 14.1 ppm; IR (KBr) 3500-3100, 2929, 2864, 1607, 1572 cm\(^{-1}\); ESI-MS \( m/z \): 947.2 ([M+Na]⁺, 100%), 924.5 ([M]**, 35%); Anal. Calcd. for C\(_{35}\)H\(_{65}\)BrO\(_8\): C, 68.75; H, 7.08; found C, 68.71; H, 6.92.
A,C-monobromo mono(hydroxymethyl) cavitand 5.14 (139 mg, 150 µmol) was dried at 0.1 mmHg, 50 °C for 2 h before dissolved in dry THF (20 mL) in a reaction flask under nitrogen atmosphere. Diisopropylethylamine (700 µL, 4.00 mmol) was added and the reaction mixture was stirred for 30 min. To this reaction mixture was then added solution of MOMCl (770 µL of a 2.6 M solution in toluene, 2.00 mmol, referred to compound 2.5 for more details). The reaction mixture was stirred under N₂ for 12 h, then quenched with sat. aq. NaHCO₃. The THF was removed in vacuo and ethyl acetate (3 x 10 mL) was added to extract the product from the residue. The combined organic phases was washed with water, sat. aq. NaCl, dried over MgSO₄ and the solvent was removed in vacuo. The crude product was purified by column chromatography (40 g SiO₂, 3:7 ethyl acetate/hexane) to afford the title compound 5.15 as a white solid (131 mg, 90%): R_f = 0.32 (3:7 ethyl acetate/hexane); m.p. 130-132 °C (dichloromethane/hexane); ¹H NMR (300 MHz, CDCl₃) δ 7.15 (s, 1H), 7.07 (s, 2H), 7.04 (s, 1H), 6.47 (s, 2H), 5.82 (d, J = 7.5 Hz, 2H), 5.79 (d, J = 7.8 Hz, 2H), 4.82-4.70 (m, 4H), 4.65 (s, 2H), 4.54 (d, J = 7.2 Hz, 2H), 4.52 (s, 2H), 4.37 (d, J = 7.2 Hz, 2H), 3.37 (s, 3H), 2.30-2.10 (m, 8H), 1.50-1.20 (m, 24H), 1.00-0.80 (m, 12H) ppm; ¹³C NMR (75 MHz, CDCl₃) δ 155.9, 155.2, 154.4, 138.1, 138.0, 136.5, 131.8, 122.6, 121.1, 113.5, 96.7, 96.3, 60.8, 56.0, 37.2, 36.9, 32.0, 30.1 (two coincident resonances), 27.6, 22.7, 14.2 ppm; IR (KBr) 2929, 2866, 1574 cm⁻¹; ESI-MS m/z: 991.7 ([M+Na]⁺, 100%), 970.8 ([M+H]⁺, 10%); Anal. Calcd. for C₅₅H₆₉BrO₁₀: C, 68.10; H, 7.17; found C, 68.18; H, 7.32.
To a solution of A,C-monobromo mono(methoxymethyleneoxymethyl) cavitand 5.15 (97.0 mg, 100 μmol), dried according to the standard procedure, in dry THF (15 mL) under nitrogen atmosphere at -78 °C was added quickly n-BuLi (69.0 μL, 111 μmol). The reaction mixture was stirred at that temperature for 10 minutes then diphenyl phosphoryl azide (41.4 mg, 150 μmol) in dry THF (3 mL) was added. The reaction mixture was warmed to rt and stirred for 8 h. The reaction was again cooled to -78 °C, LiAlH₄ (50 mg, 1.32 mmol) was added to the reaction mixture, stirring continued for 12 h at rt. Then, fridge-cold 2M aq. NaOH solution (10 mL) was carefully added to the mixture. The THF was subsequently removed in vacuo; ethyl acetate (3 x 10 mL) was added to extract the cavitand products. The combined organic phases were washed with 1 M aq. NaOH and sat. aq. NaCl then dried over MgSO₄. The solvent was removed in vacuo.

The crude product was dissolved in dichloromethane (5 mL) and methanol (500 μL) was added. The solution was stirred at rt for 10 min. 2 drops of 36.5% aq. HCl solution was added and the reaction mixture was heated to reflux for 1 h. The reaction mixture was quenched with 5% aq. NaOH solution (10 mL) and the organic solvents were removed in vacuo. Ethyl acetate (3 x 10 mL) was added to the residue to extract the cavitand products. The combined organic phases were washed with water and sat. aq. NaCl then dried over MgSO₄. The solvent was removed in vacuo. The crude product was purified by column chromatography (20 g SiO₂, 4:6 to 7:3 ethyl acetate/hexane) to obtain the title cavitand 5.16 as a white solid (42.2 mg, 49% over two steps): $R_f = 0.14$ (7:3 ethyl acetate/hexane); m.p. 180-182 °C (dichloromethane/hexane); $^1$H NMR (300 MHz, CDCl₃) $\delta$ 7.14 (s, 1H), 7.09 (s, 2H), 6.47 (s, 3H), 5.82 (d, $J = 6.9$ Hz, 2H), 5.77 (d, $J = 6.9$ Hz, 2H), 4.76 (t, $J = 8.1$ Hz, 2H), 4.68 (t, $J = 8.1$ Hz, 2H), 4.65 (s, 2H), 4.48
C-pentyl A,B-dibromo diprotio cavitand 5.17

Prepared by modification of the procedure of Barrett et al.\textsuperscript{2} To a solution of tetrabromocavitand 2.3 (5.66 g, 5.00 mmol), dried according to the standard procedure, in THF at –78 °C was added rapidly n-BuLi (3.44 mL of a 1.60 M solution in hexanes, 5.50 mmol). After 5 min, isopropanol (382 μL, 5.50 mmol) was added rapidly and stirring was continued at –78 °C for 5 min. Another aliquot of n-BuLi (5.50 mmol) was added and the solution was stirred at –78 °C for 10 min. Then, methanol was added, the cooling bath was removed and the solution was allowed to warm to rt. The solvent was removed \textit{in vacuo} and the residue was partitioned between ethyl acetate (3 x 30 mL) and water (100 mL). The combined organic phases were washed with sat. aq. NaHCO\textsubscript{3}, sat. aq. NaCl, dried over MgSO\textsubscript{4} and the solvent was removed \textit{in vacuo}. Purification by column chromatography (400 g SiO\textsubscript{2}, 9:1 hexane/ethyl acetate) afforded the title compound 5.17 as a white solid (1.90 g, 39%). Characterisation data corresponded to that reported in the literature.\textsuperscript{2}
Host-guest binding studies of cavitand 5.16 with aspirin

Binding studies between cavitand 5.16 and aspirin were carried out in chloroform using the general method for host-guest binding studies. ITC profile of this host-guest pairs is included in the following:
Binding study between cavitand 5.16 and aspirin (ITC, chloroform, 25 °C)

Data: **5.16** (5 mM) vs Aspirin (50 mM)

- **N**: 1.03 ± 0.02
- **K**: 58 ± 2
- **H**: -3840 ± 40
- **S**: -4.81
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